

1 **Impaired Orthostatic Blood Pressure Recovery, but not Initial Orthostatic**

2 **Hypotension, is associated with Unexplained and Injurious Falls**

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38 Abstract

39 **Background/Objectives:** Cardiovascular disorders are recognised as important modifiable
40 risk factors for falls. However the association between falls and orthostatic hypotension (OH)
41 remains ambivalent, particularly because of poor measurement methods of previous studies.
42 Our goal was to determine for the first time to what extent OH (and variants) are risk factors
43 for incident falls, unexplained falls (UF), injurious falls (IF) and syncope using dynamic blood
44 pressure (BP) measurements in a population study.

45 **Design:** Nationally Representative Longitudinal Cohort Study - The Irish Longitudinal Study
46 on Ageing (TILDA) – wave 1 (2009-2011) with 2 year follow-up at wave 2 (2012-2013).

47 **Setting:** Community dwelling adults.

48 **Participants:** 4127 participants were randomly sampled from the population of older adults
49 aged ≥ 50 years resident in Ireland.

50 **Measurements:** Continuous BP recordings measured during active stands were analysed.
51 OH and variants (initial OH and impaired orthostatic BP stabilisation OH(40)) were defined
52 using dynamic BP measurements. Associations with the number of falls, UF, IF and syncope
53 reported two years later were assessed using negative binomial and modified Poisson
54 regression.

55 **Results:** Participants had a mean age 61.5(8.2) years (54.2% female). OH(40) was associated
56 with increased relative risk of UF (RR:1.52 95%CI:1.03-2.26). OH was associated with all-
57 cause falls (IRR:1.40 95%CI:1.01-1.96), UF(RR:1.81 95%CI:1.06-3.09), and IF(RR:1.58
58 95%CI:1.12-2.24). IOH was not associated with any outcome.

59 **Conclusion:** With the exception of initial orthostatic hypotension, beat-to-beat measures of
60 impaired orthostatic BP recovery (delayed or incomplete stabilisation) are independent risk
61 factors for future falls, unexplained falls, and injurious falls.

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77 INTRODUCTION

78 Falls are the leading cause of injury in older people (1,2). One in three people over the age
79 of 65 will suffer a fall each year (3) with healthcare costs associated with falls rising (4). With
80 40% of falls preventable, evidence for causative, treatable factors is essential (5).

81 Cardiovascular disorders are among several risk factors which have been identified to cause
82 falls; in particular unexplained falls (UF) (defined as those for which no attributable
83 mechanical cause such as a trip or slip can be found) and recurrent falls (6). Syncope
84 secondary to underlying cardiovascular disease is more common with advancing years and
85 may lead to injurious falls (IF) (7,8).

86 In a recent systematic review from our group (9), whereas a strong association between
87 many cardiovascular disorders (10) and falls was reported the association between falls and
88 OH was ambivalent. This was attributed to varied quality of reviewed studies which
89 employed several different assessment methods to detect OH, inadequate details to enable
90 adjustment for relevant confounders and sample populations which varied in size, most of
91 which were convenience samples. In addition, recent findings from the TILDA study (11)
92 note a high prevalence of OH variants among older adults, as defined using continuous beat-
93 to-beat BP measurements. The clinical relevance of these findings are unknown (12).

94 Furthermore no previous cohort studies have examined the association between OH and UF
95 where the associations might be greatest (9,13,14).

96 This paper provides an opportunity to redress these shortcomings by presenting continuous
97 orthostatic BP measurements in a randomly selected community population of well
98 characterised cognitively normal adults, followed longitudinally to capture details of falls,

99 injurious events and syncope. Here we test the hypothesis that failure of orthostatic BP to
100 stabilise after standing is associated with incident all-cause falls and more specifically UF, IF
101 and syncope in older adults.

102 **METHODS**

103 **Setting and Participants**

104 Analysis was performed on data obtained from wave 1 (Sept 2009-July 2011) and wave
105 2 (April 2012-July 2013) of The Irish Longitudinal Study on Ageing (TILDA), a nationally
106 representative longitudinal cohort study of adults aged 50 and over resident in the Republic
107 of Ireland. Ethical approval was obtained for the study from Trinity College Research Ethics
108 committee and written informed consent was obtained prior to participation. The cohort
109 was recruited based on the RANSAM sampling framework with a wave 1 household
110 response rate of 62% (15).

111 **Assessments**

112 The TILDA study design has been described previously (16, 17). Briefly, data collection at
113 wave 1 involved a computer-assisted personal interview (CAPI) carried out in the
114 respondents' homes that included questions on socioeconomic and health circumstances, a
115 self-completion questionnaire, and a research nurse led health assessment in a study centre.
116 The second interview took place approximately 2 years after the first and included a
117 detailed falls and syncope history.

118 **Inclusion and Exclusion Criteria**

119 Every member of the population of Ireland aged 50 and over living in the community
120 (excluding long-term care or other institutions) was equally likely to be invited to participate.
121 All participants who had orthostatic BP measured at wave 1 of the study were eligible for
122 inclusion. Participants with moderate to severe cognitive difficulties (because of likelihood
123 of poor recall and therefore inaccuracy of falls and syncope details), those who had been
124 institutionalized between waves or whose falls data was missing or was provided by a proxy
125 at wave 2 were excluded.

126 **Outcome Variables Measured during Wave 2**

127 At wave 2, participants were asked: i) Have you fallen since your last interview?; (ii) How
128 many times have you fallen since your last interview?; (iii) Were any of these falls non-
129 accidental, i.e. with no apparent or obvious reason? (unexplained falls, UF); (iv) Did you
130 injure yourself seriously enough to need medical treatment? (injurious falls, IF). Questions (i)
131 and (ii) were repeated for syncope. Note those with prior syncope were asked a modified
132 version of question ii) How many times have you fainted or blacked out in the last year?
133 Four outcome variables were derived for longitudinal analyses in keeping with our
134 hypotheses: number of falls (0-5+), any UF (binary variable), any IF (binary variable), any
135 reported faint (binary variable).

136 **Baseline Predictor Variables Measured during Wave 1**

137 *Orthostatic BP Measurement*

138 BP responses to orthostasis were measured at wave 1 (16). In brief continuous BP responses
139 were recorded using a calibrated volume clamp method (Finometer®, Finapres Medical
140 Systems BV, Amsterdam, The Netherlands). Participants rested in the supine position for 10

141 minutes and when requested stood quickly and remained standing for 2 minutes. Beat-to-
142 beat systolic BP(SBP), diastolic BP(DBP) was monitored throughout . Subjects were then
143 asked to report postural symptoms i.e. dizziness, light-headedness or unsteadiness.

144 *Orthostatic BP Analysis*

145 We applied the following data pre-processing steps to BP data using custom written
146 software (MATLAB® v13.0, The MathWorks Inc., Natick, MA, 2000): a) artefact rejection; b)
147 10-second moving average filtering; and c) feature extraction, as described in detail
148 previously (18).

149 *Definitions of predictor variables*

150 Supine SBP, DBP and HR were derived from the average of values occurring 30-60 seconds
151 prior to standing. BP behaviour was characterised by (i) initial transient drop, and (ii) the
152 recovery phase at fixed times after stand as per (11). *Initial orthostatic hypotension (IOH)*
153 was defined as an initial drop in SBP \geq 40mmHg and/or drop in DBP \geq 20mmHg occurring
154 within 15 seconds of standing (with or without symptoms)¹⁹. Note beat-to-beat data was
155 used to identify the minimum BP values. *Impaired orthostatic BP stabilisation*, denoted here
156 as *OH(t)*, was defined (11) by failure to return to within SBP \geq 20mmHg and/or DBP
157 \geq 10mmHg of supine levels at 40s after standing. *OH* was defined as sustained failure of SBP
158 or DBP to stabilise to within 20mmHg SBP or 10mmHg DBP of supine levels throughout the
159 active stand (11). The selection of these thresholds was based on current clinical guidelines
160 and recent population normative data indicating that these values represent the 5th
161 percentile of orthostatic BP responses in the over 50's population (11).

162 **Covariates**

163 Confounding factors selected on the basis of known interactions with falls or CV risk were
164 recorded at wave 1: age, gender, self-reported educational attainment (primary, secondary
165 or tertiary), living alone, health insurance, self-reported doctor's diagnosis of common
166 health conditions (HTN, angina, heart attack, heart failure, diabetes, stroke, transient
167 ischaemic attack (TIA), irregular heart rhythm, heart murmur, high cholesterol, cataracts,
168 glaucoma, age-related macular degeneration (ARMD), cancer, arthritis, osteoporosis, or
169 fractures). Medication use was coded using the Anatomical Therapeutic Chemical (ATC)
170 Classification codes for the following medication classes: (a) beta-blockers (ATC code C07),
171 (b) calcium channel blockers (C08), (c) diuretics (C03), (d) angiotensin-converting enzyme
172 inhibitors (C09) (e) angiotensin II receptor antagonists (C09), (f) psychotropics including
173 benzodiazepines (N05B or N05C), antipsychotics (N05A), psychostimulants (N06B),
174 psycholeptics (N06C), anti-depressants (N06A), (g) alpha-blockers (C02CA, C02LE). Mean
175 usual gait speed (cm/sec), mean grip strength (both hands) (kg), cognitive function
176 (Montreal Cognitive Assessment (MOCA) and Mini-mental state examination (MMSE)),
177 mental health (20-item Centre for Epidemiological Studies Depression (CES-D)) scale were
178 also collected. Further study details are published elsewhere (15, 16, 17). Two resting
179 (seated) SBP and DBP measurements were obtained, separated by 1 minute, using an
180 automatic digital oscillometric BP monitor (Model M10-IT, OMRON, Kyoto, Japan). The
181 mean of both SBP and DBP were calculated. Individuals were classified as having
182 hypertension (HTN) if SBP \geq 140mmHg and/or DBP \geq 80mmHg (20).

183 **Statistical Analysis**

184 Statistical analysis was performed using Stata version 12 (StataCorp. 2011. Stata Statistical
185 Software: Release 12. College Station, TX: StataCorp LP).

186 For descriptive analysis, the 'number of falls' outcome variable was divided into 3 groups
187 (for ease of tabulation): 0 falls; 1 fall; ≥ 2 falls while for multivariate analysis, this was coded
188 as 0, 1, 2, 3, 4, or '5 or more falls'. Separate binary variables were constructed for UF, IF and
189 syncope. Wave 1 baseline characteristics of those who reported 0, 1, and 2 or more falls
190 during follow up period were compared using ANOVA, Kruskal-Wallis, or Chi-squared test
191 statistics for continuous (normal and non-normal) and categorical variables respectively.

192 Prevalence of IOH, OH(40), and OH were reported by age category. Weights were applied
193 to these prevalence estimates to ensure applicability to the whole population (15). Kappa (K)
194 statistics assessed the level of agreement between definitions of OH. Chi-squared test
195 statistics were used to assess the association between each of the OH variables considered
196 (IOH, OH(40), and OH) and each outcome variable.

197 Separate multiple regression analyses were used to estimate the effect of each OH variant
198 on each outcome, controlling for baseline confounding factors. Negative binomial regression
199 was applied to estimate the effect of OH and its variants on the incidence rate of falls.

200 Modified Poisson regression was used to calculate the effect of OH variants on the risk of IF,
201 UF and syncope (21). Regression models were estimated for each outcome variable
202 adjusting for socio-demographic variables (age, sex, education), and all health-related
203 covariates (See Figure 1). The number of days between interviews was included as an
204 exposure variable to account for the fact that participants with more time between
205 assessments had longer to accrue falls.

206 To estimate the moderating effects of age, gender, orthostatic symptoms and HTN on these
207 associations, a stratified analysis was performed. The fully adjusted model was re-estimated

208 having stratified the whole population by each of these factors individually. Significance at
209 $p < 0.05$ was assumed.

210 **RESULTS**

211 **Sample**

212 4475 participants completed an active stand at wave 1, and 4167 (93%) of these had
213 complete data on incident falls outcomes at wave 2. After applying the exclusion criteria,
214 4127 participants remained for analyses. The mean (SD) time between waves was 743(83.9)
215 days \approx 24(3) months.

216 **Participant characteristics**

217 The mean (SD) age at wave 1 was 61.5(8.2) years and 54.2% were female. Participants had a
218 mean (SD) MOCA score of 25.4(3.1). Overall 902(21.9%) participants reported one or more
219 falls during follow-up, a total of 1532 falls; 174(4.2%) reported an UF, 369(8.9%) IF, and
220 196(4.8%) syncope (Table 1). There was a marked age related increase in all events –
221 comparing 50 to 59 year olds to participants 80 and older: falls increased from 17.8 to 39.0%;
222 UF from 3.2 to 8.7%; IF from 7.2 to 18.1%; syncope from 3.7 to 9.5% (Table 1).

223 [Insert Table 1]

224 Fallers were older, and more likely to be female and living alone and reported a higher
225 prevalence of chronic eye conditions, previous hip or wrist fractures, poorer baseline
226 physical and mental health (Table 2).

227 [Insert Table 2]

228 **Prevalence of OH Variants, their Agreement and Age Dependence**

229 The prevalence of OH variants ranges from 6.9%(95% CI:5.9-7.8) for OH to 32.9%(95% CI:
230 31.2-34.6) for IOH as reported in (11).

231 The level of agreement between IOH and both OH(40) (K = 0.007) and OH (K = 0.011) was
232 low, while a higher but still moderate level of agreement was detected between OH(40) and
233 OH (K = 0.481) (See Table A1.1).

234 The prevalence of all OH variants, with the exception of IOH increase with age (11). For
235 example, OH(40) is present in 9.2%(95% CI:7.8-10.7) of those aged 50-64 compared to
236 37.2%(95% CI: 25.7-48.7) of those aged over 80 years.

237 **Characteristics of those with Orthostatic Hypotension and its Variants**

238 Table 3 details characteristics of individuals with or without OH (and its variants). Those with
239 IOH are younger, have higher levels of education, have better physical health (higher gait
240 speed), and are taking less medication but have marginally higher levels of anxiety and
241 depressive symptoms. On the other hand, those with OH(40), and OH are older, more likely
242 female, have lower levels of education, higher levels of chronic health conditions and
243 medication use.

244 [Insert Table3]

245 **Prospective Associations between Falls, Syncope and Variants of Orthostatic Hypotension**

246 At a univariate level, the prevalence of all-cause falls ($p < 0.001$), UF($p = 0.007$), IF($p < 0.001$)
247 increased significantly in those with OH(40). Similar patterns existed for OH, with OH ($p =$
248 0.015) also associated with increased prevalence of syncope. IOH was not associated with
249 any falls outcome considered (Table 4).

250 [Insert Table4]

251 Fully adjusted models reveal that OH was associated with the highest risk of all-cause falls
252 (IRR:1.495%CI:1.01–1.96; p=0.044), UF(RR:1.8195%CI:1.06–3.09; p=0.029), and IF(RR:1.58
253 95%CI:1.12–2.24; p=0.010). Similar trends were also noted for OH(40). No associations with
254 IOH or syncope were evident (Figure 1).

255 Additional sensitivity analysis suggests these multivariate models are quite robust to the
256 selection of model covariates (although there was some variation in significance across
257 models), with our fully adjusted model reflecting a conservative estimate of the effects
258 between these variables and the outcomes of interest.

259 Stratification analysis suggests that in those with HTN, OH(40) is a significant risk factor for
260 each falls outcome considered with similar patterns for OH. Similarly the presence of OH in
261 women was associated with an increased relative risk of all-cause falls, UF, IF. The results
262 associated with age and orthostatic symptoms were less consistent (Table A1.2).

263 **DISCUSSION**

264 Our results suggest that impaired orthostatic BP recovery characterised by incomplete or
265 delayed stabilisation is associated with an increased relative risk of future all-cause falls, UF,
266 and IF while IOH is not associated with any of these outcomes.

267 This is the first cohort study to report associations between beat-to-beat phasic BP
268 measures, falls and syncope risk. Although there are no prior studies of this nature using
269 phasic BP, our results are consistent with a number of studies (based on standard
270 sphygmomanometer measurements) that indicate that OH is associated with an increased
271 risk of all-cause falls (13, 14). Heitterachi et al., (22) using head-up tilt testing, detected a

272 relative risk of 1.7 for OH in fallers versus non-fallers in a small convenience sample (n=70)
273 of older adults. Other longitudinal studies using the sit-to-stand test report no association
274 between falls and OH (23). We would suggest that our large sample size, combined with a
275 more strenuous postural supine-stand challenge and more sensitive phasic BP measurement
276 methods contributed to detection of this positive relationship.

277 It appears that the prevalence of OH variants does not follow a uniform distribution in the
278 population, and intermittent measurements (such as those with a standard
279 sphygmomanometer) may underestimate the true prevalence and significance of impaired
280 orthostatic BP behaviour. OH as measured using beat-to-beat approaches were associated
281 with higher absolute risks of falls, UF, IF compared to single point measurements. OH(40)
282 has shown consistent associations with known correlates of falls i.e. increases in mortality
283 (24), impaired cognition (25), and frailty (26,27) which further supports our assertion of the
284 importance of beat-to-beat biomarkers.

285 This is also the first cohort study to consider the role of UF. In this sample we report a
286 stronger association between variants of OH and UF than all-cause falls. This may explain
287 the conflicting results of previous studies with the prevalence of UF varying from study to
288 study. UF are often associated with CV events (28) and may be associated with orthostatic
289 BP impairments either because an individual has amnesia for loss of consciousness coupled
290 with unwitnessed syncopal events or because covert cerebral hypoperfusion causes balance
291 instability and resultant falls (13). Repeated subclinical bouts of hypoperfusion in localised
292 centres governing gait and balance, could lead to neurodegenerative changes and ultimately,
293 impaired gait, balance, and UF (28). Additional comorbidities may compound this risk and
294 the likelihood of amnesia for loss of consciousness (30, 31). Finally impaired BP stabilisation

295 and falls have been associated with frailty in older adults (26, 27). Our results are however
296 independent of many frailty criteria (gait speed, grip strength), and a wide range of co-
297 morbidities.

298 The result that IOH is of limited use in falls risk stratification in older adults warrants further
299 discussion. We suggest the following explanation. Firstly IOH i.e. large BP drops within 15
300 seconds of standing has a very high prevalence in our sample (over 30%). Secondly it's
301 prevalence does not increase with age. Such a high prevalence and lack of association with
302 age effects the ability of IOH to predict adverse outcomes. Secondly, the cut-off time used in
303 the IOH definition selects individuals with nadirs occurring within 15 seconds of standing.
304 These individual tend have a quicker orthostatic BP recovery profile since they are younger,
305 healthier individuals, that stand more quickly during testing (See Table 3). IOH is therefore
306 not associated with poorer clinical sequelae. Conversely OH(40), which was not correlated
307 with IOH, captures individuals with slower initial drops and a slower recovery and is
308 associated with poorer outcomes. It is likely that these individuals are similar to the frailer
309 older adults attending a post-fall clinical assessment. IOH does not capture these. Finally,
310 our definition of IOH does not include since reporting of symptoms can be unreliable
311 especially in older adults. In light of these observations, an alternative to the current IOH
312 definition maybe sought for use in older community dwelling cohorts to reflect age-related
313 variations in the morphology and timing of the complex BP waveform, patterns of cerebral
314 perfusion and symptom expression. OH(40) maybe a suitable alternative.

315 Miller et al. (12) recently noted the clinical dilemma faced regarding management of OH and
316 its variants in the face of coexisting hypertension. Our stratified analysis suggests that
317 coexisting OH(40) and HTN is a risk factor for all-cause falls, UF and IF and is particularly

318 important given that over 50% of the over 70's have OH and HTN in this sample. These
319 results may also support previous findings reported by Gangavati et al.(13), the ACCORD (32)
320 and SANDs trials (33) indicating that lower BP (<140/80) does not necessarily increase falls
321 risk. The recent SPRINT study (34) suggests that aggressive treatment of hypertension below
322 120/80mmHg decreases rates of major cardiovascular events, death, and OH, while
323 increasing rates of hypotension, syncope with the rate of injurious falls not changing.

324 From the full analysis OH is clearly associated with increased falls risk. However stratification
325 analysis did not lead to a consistent conclusion regarding the role of symptoms. OH tends to
326 be present in older groups often with neurodegenerative disorders and is therefore more
327 likely linked to falls, UF and amnesia for loss of consciousness (30, 31). Self-reported
328 postural symptoms maybe an unreliable marker of cerebral hypoperfusion (35, 36, 37) and
329 therefore restricting testing to older adults with overt postural symptoms may miss those
330 with silent cerebral hypoperfusion and increased falls risk.

331 This study has a number of clinical implications especially in the context of assessing falls
332 risk in older adults. Here we identify a novel beat-to-beat risk factors i.e. delayed and/or
333 incomplete BP recovery for injurious and unexplained falls risk. We also note the current
334 definition of IOH is limited in falls risk stratification in community dwelling older adults with
335 refinements warranted in fallers and non-fallers. Furthermore this study highlights the
336 clinical perils of measuring OH in the context of falls where adherence to strict
337 measurement protocol is imperative, with errors easily made that can lead to patient
338 mismanagement. The use of beat-to-beat BP measurement approaches present the clinician
339 with a tool to clearly differentiate between IOH and other important variants of OH,
340 avoiding such issues. Once a subtype of OH is clearly identified these risk factors can be

341 managed as per international falls and syncope guidelines. The next step in respect of
342 clinical practice is to ascertain in future intervention trials whether inclusion of these phasic
343 BP measures in clinical practice and targeted intervention for same will reduce subsequent
344 events.

345 A number of study limitations must be noted. A regular falls diary was not collected and
346 therefore our falls data relies on the recollection capacity of frailer older adults. However to
347 maximise reliability of our self-reported information, we excluded participants with
348 moderate cognitive impairment and controlled for well-accepted falls risk factors. Given the
349 repeated-measure nature of the BP measurements, multiple statistical tests (n=16 in main
350 effects model) were performed. However, it is unlikely that our results are a chance finding
351 given that 7/16 tests were positive in the main-effects model. The sample considered here is
352 relatively young and healthy and is representative of the over 50's community dwelling
353 population. It does however under-represent older frail individuals, although our sample
354 does capture a similar proportion of fallers and injurious falls to that which occurs in the
355 total population. In addition, the age stratification analysis presented in the appendix
356 suggests that the effects detected in the whole sample are still present (albeit without
357 statistical significance) in the older sample. The selection of the 20mmHg/10mmHg
358 threshold for defining OH (and variants) although based on population normative data and
359 clinical guidelines may still not be optimum as it is dependent on baseline BP, and age as we
360 have shown previously (11). Assigning a single threshold value to describe such a complex
361 waveform morphology is also a likely limited analytical approach. In addition, the duration
362 of stand was limited to two minutes. It is therefore likely that we have underestimated the
363 effects of delayed OH on falls risk. Exploration of how falls risk varies with waveform

364 morphology and key factors that drive differences in these waveforms (e.g. duration of
365 stand, age, gender, resting BP) would be key future considerations in this area.

366 In addition to the use of UF and beat-to-beat BP data, this study has a number of significant
367 strengths. Use of the Finometer for measuring changes in BP has been shown to be accurate
368 in a number of studies, although the accuracy of its absolute values has been questioned (37,
369 38). To overcome this, we used baseline measurements from a validated oscillometric
370 device to identify HTN and used changes in beat-to-beat BP only. All measures were
371 collected using internationally standardised protocols and processing of active stand data
372 was objectively performed.

373 **CONCLUSION**

374 With the exception of initial orthostatic hypotension, beat-to-beat measures of impaired
375 orthostatic BP recovery (delayed or incomplete stabilisation) are independent risk factors
376 for future falls, unexplained falls, and injurious falls.

377 **COMPETING INTERESTS**

378 None.

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391 **Conflicts of Interest:**

Elements of Financial/Person I Conflicts	*CF		MOC		OD		KR		GS		RAK	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X		X		X
Grants/Funds		X		X		X		X		X		X
Honoraria		X		X		X		X		X		X
Speaker Forum		X		X		X		X		X		X
Consultant		X		X		X		X		X		X

Stocks		X		X		X		X		X		X
Royalties		X		X		X		X		X		X
Expert Testimony		X		X		X		X		X		X
Board Member		X		X		X		X		X		X
Patents		X		X		X		X		X		X
Personal Relationship		X		X		X		X		X		X

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393 **Authors Contributions:** CF, MOC, KR, OD made substantial contributions to the study design.

394 RAK is the Principal Investigator of the TILDA study and originally conceived the study and its

395 design. CF, OD, MOC contributed to acquisition of data. CF, MOC analysed the data. GS, KR

396 contributed to the statistical design of the study. CF, GS, RAK, KR, MOC, OD contributed to

397 the interpretation of the data. CF wrote each draft of the manuscript. All authors critically

398 reviewed and contributed significantly to the intellectual content of the manuscript. CF and

399 MOC had full access to all the data in the study and all authors had final responsibility for

400 the decision to submit for publication.

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402 The funders had no role in the study design, data collection, data analysis, data
403 interpretation, writing of the report or decision to publish.

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Table 1: Prevalence of all-cause falls, unexplained falls, injurious falls and syncope stratified by age (n=4127)

	Age, years				Total
	50-59	60-69	70-79	80+	
Outcomes	% (N)	% (N)	% (N)	% (N)	% (N)
Number of participants by age band	46.4 (1,916)	35.5 (1,463)	15.6 (643)	2.5 (105)	100 (4,127)
All-cause falls***	17.8 (340)	23.9 (349)	26.7 (172)	39.0 (41)	21.9 (902)
Unexplained Falls (UF)**	3.2 (61)	4.7 (69)	5.5 (35)	8.7 (9)	4.2 (174)
Injurious Falls (IF) ***	7.2 (137)	9.3 (136)	12.0 (77)	18.1 (19)	8.9 (369)
Syncope ***	3.7 (71)	4.7 (69)	7.2 (46)	9.5 (10)	4.8 (196)

539 **Table 1.** Prevalence of all-cause falls (≥ 1 fall), unexplained falls, injurious falls and syncope stratified by age
540 occurring between Wave1 and Wave 2 in longitudinal sample (N=4127). Stars indicate a significant difference
541 across age groups, * = $P < 0.05$; ** = $P < 0.01$ *** = $P < 0.001$.

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Table 2: Cohort characteristics stratified by the number of falls reported at wave 2 (n=4122)						
	Number of Falls Reported between Baseline (Wave 1) and Follow-Up (Wave 2)					
	No Falls		One Fall		Two or More Falls	
	Mean(SD) or %	N	Mean(SD) or %	N	Mean(SD) or %	N
Age (years) ***	61.1(8.1)	3,225	63.0(8.3)	559	63.4(8.7)	338
Gender (Female) ***	52.7	1,700	62.8	351	53.8	182
Education (Primary/none only)	19.9	643	19.5	109	23.4	79
Living alone ***	15.5	500	22.4	125	17.5	59
Any Cardiovascular Conditions (1 or more)	60.5	1,951	63.5	355	64.8	219
Any Chronic Eye Conditions (1 or more) ***	9.7	314	14.2	79	14.3	48
Osteoporosis ***	8.8	285	12.3	69	14.8	50
Hip or wrist fracture ***	10.2	322	13.9	76	18.7	62
History of Falls ***	14.8	476	30.2	169	44.4	150
History of Syncope ***	3.6	115	6.3	35	9.2	31
Health Measures						
MOCA	25.5(3.1)	3,218	25.5(3.1)	557	25.1(3.2)	337
MMSE	28.7 (1.6)	3224	28.7(1.5)	559	28.6(1.5)	338
HADS-A***	5.3(3.5)	2,958	5.6(3.6)	515	6.2(3.7)	293
CESD ***	4.2(3.8)	3,222	4.5(4.1)	558	5.6(4.5)	336
Gait Speed (cm/sec) ***	137.8(19.3)	3,197	135(19.2)	554	127.8(24.2)	332
Grip Strength (kg) ***	26.6(9.5)	3,180	24.6(9.2)	541	24.8(9.7)	329
Seated Blood Pressure (mmHg)	135.5(22.1)	3,225	138.9(22.4)	559	136.9(23.2)	338
Medication Use						
Antihypertensives **	31.4	1013	33.6	188	39.6	134
Anti-depressants ***	4.6	147	7.5	42	12.7	43
Polypharmacy ***	15.3	491	17.5	98	30.7	103

550 **Table 2.** Participant characteristics reported at wave 1 stratified by the number of falls reported at wave 2
551 (n=4122). Hip or wrist fracture = ever fractured a hip or wrist; History of Falls = 1 or more falls in the year
552 (prior to wave 1 interview); History of Syncope = 1 or more faints in the last year (prior to wave 1 interview);
553 MOCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Exam; HADS-A = Hospital Anxiety and
554 Depression Scale – Anxiety subscale, CESD = Centre of Epidemiological Studies Depression Scale;
555 Cardiovascular Conditions = Presence of 1 or more of the following cardiovascular conditions: Hypertension,
556 Angina, Heart Attack, Heart Failure, Diabetes, High Cholesterol, Heart Murmur, Transient Ischemic Attack,
557 Stroke. Chronic Eye Conditions = Presence of 1 or more of the following eye conditions: Age-related Macular

558 Degeneration, Cataracts, Glaucoma. Bold and stars indicate a significant difference between fallers and non-

559 fallers; * = $P < 0.05$; ** = $P < 0.01$ *** = $P < 0.001$.

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Table 3: Sample characteristics stratified by those individuals with or without OH and its variants.

	IO H				OH(40)				O H			
	No		Yes		No		Yes		No		Yes	
	Mean(SD)	N	Mean(SD)	N	Mean(SD)	N	Mean(SD)	N	Mean	N	Mea	N
Age (years)	62.3(8.3)	2704	60.0(7.9)	1408***	60.9(7.9)	3,577	65.5(9.3)	550***	61.3(8.1)	3,893	65.2(9.2)	221***
Gender (Female)	55.2	1491	52.5	739	53.5	1,915	58.4	321*	53.4	2,083	67.0	148***
Education (Primary/none only)	21.7	588	17.0	240***	19.0	681	28.0	154***	19.8	772	27.6	61*
Living alone	17.2	464	15.3	215***	15.5	555	23.5	129***	16.2	631	23.5	52***
Any Cardiovascular Conditions (1 or more)	63.1	1707	57.6	811**	60.5	2,163	66.4	365**	61.2	2,387	62.0	137
Any Chronic Eye Conditions (1 or more)	11.6	313	9.0	126*	9.8	348	17.3	95***	10.4	404	16.7	37**
Osteoporosis	10.2	276	9.0	127	9.4	337	12.2	67*	9.4	368	15.4	34**
Hip or wrist fracture	12.3	326	9.8	135*	11.0	386	13.8	75	11.3	432	12.4	27
History of Falls	19.4	525	19.2	270	18.6	665	24.5	135***	19.0	742	24.9	55*

History of Syncope	4.6	124	4.1	58	4.3	155	5.1	28	4.3	169	6.4	14
Health Measures												
MOCA	25.3(3.2)	2699	25.6(3.0)	1404**	25.5(3.1)	3,569	25.1(3.2)	549**	25.4(3.1)	3,8990	25.5(3.0)	221
MMSE	28.6(1.7)	2703	28.9(1.4)	1408***	28.8(1.6)	3,576	28.5(1.7)	550***	28.7(1.6)	3,898	28.7(1.5)	221
HADS	5.3(3.5)	2461	5.6(3.6)	1296**	5.4(3.5)	3,278	5.2(3.7)	491	5.4(3.5)	3,566	5.3(3.3)	199
CESD	4.4(4.0)	2701	4.3(3.9)	1405	4.3(3.9)	3,572	4.6(4.0)	550*	4.3(3.9)	3,894	4.6(4.1)	220
Gait Speed (cm/sec)	135.3(20.4)	2675	139.2(18.7)	1398***	137.6(19.6)	3,551	130.4(20.9)	537***	136.9(19.8)	3,861	130.8(21.2)	220***
Grip Strength (kg)	26.0(9.6)	2652	26.7(9.4)	1388*	26.6(9.6)	3,517	24.0(8.9)	538***	26.4(9.5)	3,830	23.2(8.6)	218***
Supine Blood Pressure (mmHg)	136.1(22.6)	2704	136.1(21.3)	1408	135.1(21.5)	3,577	143.5(25.1)	550***	135.5(21.8)	3,899	146.6(26.1)	221***
Medication Use												
Antihypertensives	35.4	957	26.5	373***	31.1	1,112	40.9	225***	32.1	1,252	37.1	82
Anti-depressants	5.4	147	6.0	85	5.0	180	9.6	53***	5.5	213	9.0	20*
Polypharmacy	18.8	507	13.0	183***	15.5	554	25.7	140***	16.5	642	22.4	49*

Table 3. Sample characteristics stratified by those individuals with or without OH and its variants. Hip or wrist fracture = ever fractured a hip or wrist; History of Falls = 1 or more falls in the year (prior to wave 1 interview); History of Syncope = 1 or more faints in the last year (prior to wave 1 interview); MOCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Exam; HADS-A = Hospital Anxiety and Depression Scale - Anxiety subscale, CESD = Centre of Epidemiological Studies Depression Scale;

Cardiovascular Conditions = Presence of 1 or more of the following cardiovascular conditions: Hypertension, Angina, Heart Attack, Heart Failure, Diabetes, High Cholesterol, Heart Murmur, Transient Ischemic Attack, Stroke. Chronic Eye Conditions = Presence of 1 or more of the following eye conditions: Age-related Macular Degeneration, Cataracts, Glaucoma. IOH = initial orthostatic hypotension; OH(40) = impaired blood pressure stabilisation at 40 seconds after standing; after standing. Cut-off values used for OH(40), and OH are drops of 20mmHg SBP and/or 10mmHg DBP, while IOH is based on a drop of 40mmHg SBP and/or 20mmHg DBP. Bold and stars indicate a significant difference between OH and non-OH groups; * = $P < 0.05$; ** = $P < 0.01$ *** = $P < 0.001$.

Table 4: Proportion of participants experiencing falls and syncope by variants of orthostatic hypotension.						
		Wave 2				
OH Variant		Falls		Unexplained Falls	Injurious Falls	Syncope
		1 Fall	2+ Falls			
IOH	No %(<i>N</i>)	13.9 (376)	8.3 (223)	4.6 (124)	9.3 (252)	5.4 (146)
	Yes %(<i>N</i>)	12.8 (180)	8.2 (115)	3.6 (50)	8.2 (116)	3.5 (49)**
OH(40)	No %(<i>N</i>)	12.8 (459)	7.9 (282)	3.9 (139)	8.3 (297)	4.5 (162)
	Yes %(<i>N</i>)	18.2 (100)	10.2 (56)***	6.4 (35)**	13.1 (72)***	6.2 (34)
OH	No %(<i>N</i>)	13.4 (523)	8.0 (313)	4.0 (157)	8.6 (334)	4.6 (178)
	Yes %(<i>N</i>)	15.8 (35)	11.3 (25)	7.7 (17)**	15.4 (34)***	8.1 (18)*

Table 4. Proportion of participants experiencing falls and syncope by variants of orthostatic hypotension. Univariate associations between number of falls, unexplained falls (UF), injurious falls (IF), and syncope at wave 2 and variants of orthostatic hypotension. Results for IOH, OH(40), OH are shown. Significance and p value indicates an association between categorical variables tested using a Chi squared test. IOH = initial orthostatic hypotension; OH(40) = impaired blood pressure stabilisation at 40 seconds after standing; OH = orthostatic hypotension. Cut-off values used for OH(40), and OH are defined by drops of 20mmHg SBP and/or 10mmHg DBP, while IOH is based on a drop of 40mmHg SBP and/or 20mmHg DBP within 15 seconds of standing.

Figure 1: Multivariate models examining the relationship between variants of OH and syncope and falls.

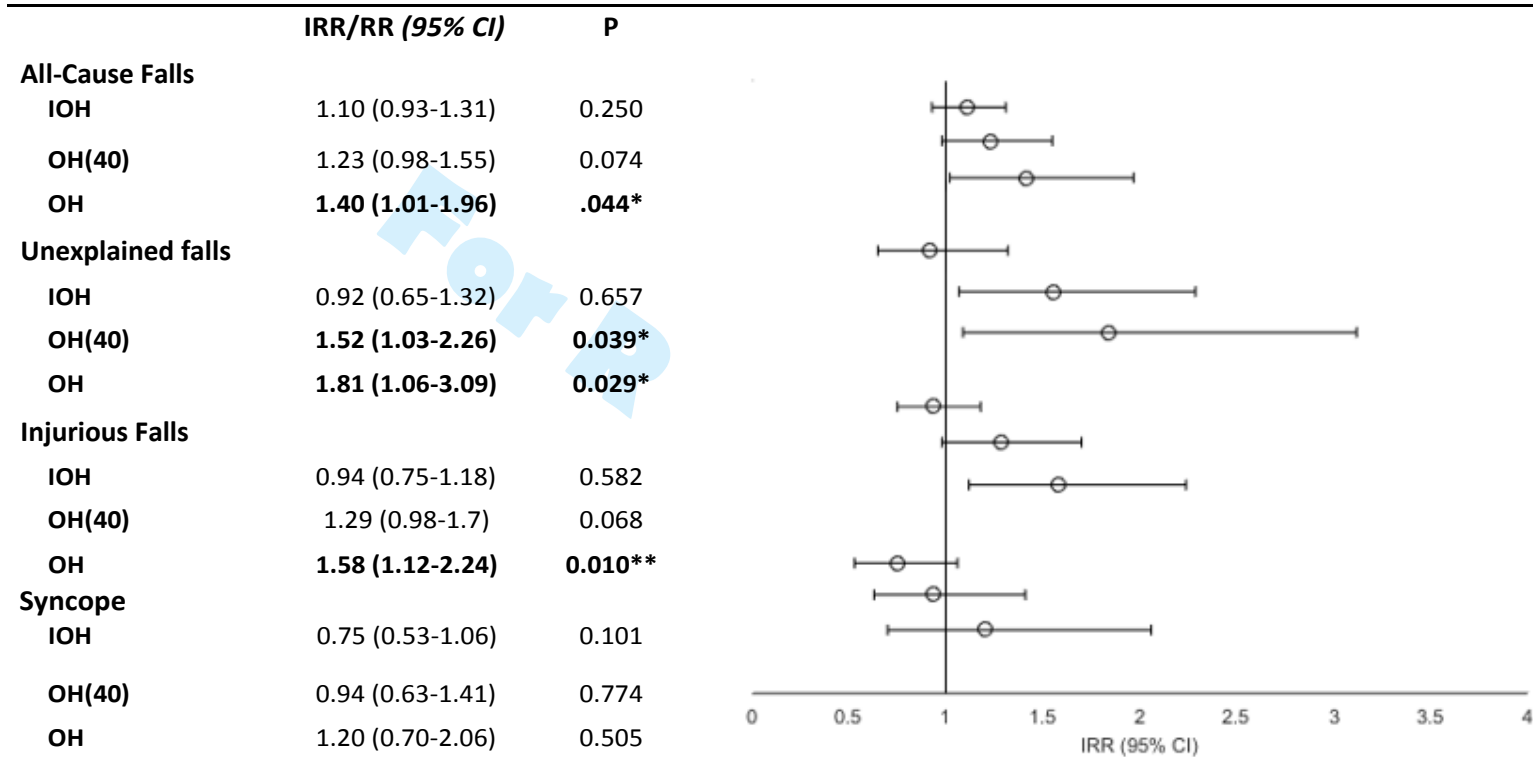


Figure 1. Multivariate models examining the relationship between variants of OH and syncope and falls. UF = Unexplained falls; IOH = initial orthostatic hypotension; OH(40) =impaired blood pressure stabilisation at 40 seconds after standing; OH = . Bold = P<0.05. Cut-off values used for OH(40), and OH are drops of 20mmHg SBP or 10mmHg DBP. IOH is based on a drop of 40mmHg SBP and/or 20mmHg DBP within 15 seconds of standing. Models are adjusted for Age, Gender, Education, Time between interviews, Living alone, Angina, Heart Attack, Heart Failure, Diabetes, Trans Ischemic Attack, High Cholesterol, Heart Murmur, Stroke, Health Insurance, Orthostatic Intolerance, Baseline SBP, Baseline HR, Cataracts, Glaucoma, ARMD, Cancer, Arthritis,

Irregular rhythm, Gait speed, BMI, Grip Strength, Disability, Osteoporosis, Fractures, MOCA score, HADSA score, CESD score, Alpha blockers, Beta blockers, Calcium channel blockers,
Diuretics, ACE Inhibitors, Angiotensin-Renin Blockers, Antidepressants.