Impaired Orthostatic Blood Pressure Recovery, but not Initial Orthostatic Hypotension, is associated with Unexplained and Injurious Falls

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Abstract

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

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

Setting: Community dwelling adults.

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

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

Results: Participants had a mean age 61.5(8.2) years (54.2% female). OH(40) was associated with increased relative risk of UF (RR:1.52 95%CI:1.03-2.26). OH was associated with all-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 95%CI:1.12-2.24). IOH was not associated with any outcome.

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

INTRODUCTION

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

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

In a recent systematic review from our group (9), whereas a strong association between many cardiovascular disorders (10) and falls was reported the association between falls and OH was ambivalent. This was attributed to varied quality of reviewed studies which employed several different assessment methods to detect OH, inadequate details to enable adjustment for relevant confounders and sample populations which varied in size, most of which were convenience samples. In addition, recent findings from the TILDA study (11) note a high prevalence of OH variants among older adults, as defined using continuous beat-to-beat BP measurements. The clinical relevance of these findings are unknown (12). Furthermore no previous cohort studies have examined the association between OH and UF where the associations might be greatest (9,13,14).

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

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

METHODS

Setting and Participants

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

Assessments

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

Inclusion and Exclusion Criteria

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

Outcome Variables Measured during Wave 2

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

Baseline Predictor Variables Measured during Wave 1

Orthostatic BP Measurement

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

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

Orthostatic BP Analysis

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

Definitions of predictor variables

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

Covariates

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

Statistical Analysis

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

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

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

Separate multiple regression analyses were used to estimate the effect of each OH variant on each outcome, controlling for baseline confounding factors. Negative binomial regression was applied to estimate the effect of OH and its variants on the incidence rate of falls. Modified Poisson regression was used to calculate the effect of OH variants on the risk of IF, UF and syncope (21). Regression models were estimated for each outcome variable adjusting for socio-demographic variables (age, sex, education), and all health-related covariates (See Figure 1). The number of days between interviews was included as an exposure variable to account for the fact that participants with more time between assessments had longer to accrue falls.

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

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

RESULTS

Sample

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

Participant characteristics

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

[Insert Table 1]

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

[Insert Table 2]

Prevalence of OH Variants, their Agreement and Age Dependence

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

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

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

Characteristics of those with Orthostatic Hypotension and its Variants

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

[Insert Table3]

Prospective Associations between Falls, Syncope and Variants of Orthostatic Hypotension

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

[Insert Table4]

Fully adjusted models reveal that OH was associated with the highest risk of all-cause falls (IRR:1.4 95%CI:1.01–1.96; p=0.044), UF(RR:1.81 95%CI:1.06–3.09; p=0.029), and IF(RR:1.58 95%CI:1.12–2.24; p=0.010). Similar trends were also noted for OH(40). No associations with IOH or syncope were evident (Figure 1).

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSION

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

COMPETING INTERESTS

None.

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Conflicts of Interest:

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

	Age, years				
	50-59	**60-69**	**70-79**	**80+**	**Total**
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)

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

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**

Table 2. Participant characteristics reported at wave 1 stratified by the number of falls reported at wave 2 (n=4122). 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. Bold and stars indicate a significant difference between fallers and non-fallers; * = P<0.05; ** = P<0.01 *** = P<0.001.

Table 3: Sample characteristics stratified by those individuals with or without OH and its variants.												
	IOH				OH(40)				OH			
	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 %(N)***	13.9 (376)	8.3 (223)	4.6 (124)	9.3 (252)	**5.4 (146)**
	Yes %(N)	12.8 (180)	8.2 (115)	3.6 (50)	8.2 (116)	**3.5 (49)****
OH(40)	***No %(N)***	**12.8 (459)**	**7.9 (282)**	**3.9 (139)**	**8.3 (297)**	4.5 (162)
	Yes %(N)	**18.2 (100)**	**10.2 (56)*****	**6.4 (35)****	**13.1 (72)*****	6.2 (34)
OH	***No %(N)***	13.4 (523)	8.0 (313)	**4.0 (157)**	**8.6 (334)**	**4.6 (178)**
	Yes %(N)	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.

	IRR/RR *(95% CI)*	P
All-Cause Falls		
IOH	1.10 (0.93-1.31)	0.250
OH(40)	1.23 (0.98-1.55)	0.074
OH	**1.40 (1.01-1.96)**	**.044***
Unexplained falls		
IOH	0.92 (0.65-1.32)	0.657
OH(40)	**1.52 (1.03-2.26)**	**0.039***
OH	**1.81 (1.06-3.09)**	**0.029***
Injurious Falls		
IOH	0.94 (0.75-1.18)	0.582
OH(40)	1.29 (0.98-1.7)	0.068
OH	**1.58 (1.12-2.24)**	**0.010****
Syncope		
IOH	0.75 (0.53-1.06)	0.101
OH(40)	0.94 (0.63-1.41)	0.774
OH	1.20 (0.70-2.06)	0.505

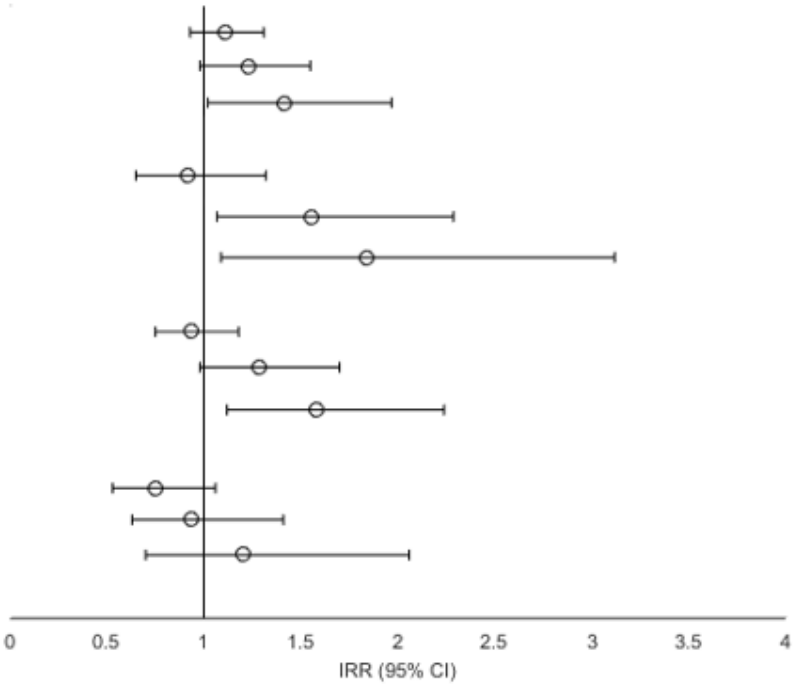

Figure 1. Multivariate models examining the relationship between variants of OH and syncope and falls. UF = Unexplained falls; IOH = initial orthostatic hypotension; OH(40) =impaired blood pressure stabilisation at 40 seconds after standing; OH = . Bold = P<0.05. Cut-off values used for OH(40), and OH 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.