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Original Article

Orthostatic Hypotension and Novel Blood Pressure Associated Gene Variants in Older Adults: Data From the TILDA Study

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Abstract

Orthostatic hypotension (OH) is associated with increased risk of trauma and cardiovascular events. Recent studies have identified new genetic variants that influence orthostatic blood pressure (BP). The aim of this study was to investigate the associations of candidate gene loci with orthostatic BP responses in older adults. A total of 3,430 participants aged ≥50 years from The Irish Longitudinal Study on Ageing (TILDA) with BP measures and genetic data from 12 single-nucleotide polymorphism (SNP) linked to BP responses were analyzed. Orthostatic BP responses were recorded at each 10 s interval and were defined as OH (SBP drop ≥20 mmHg or DBP drop ≥10 mmHg) at the time-points 40, 90, and 110 s. We defined sustained OH (SOH) as a drop that exceeded consensus BP thresholds for OH at 40, 90, and 110 s after standing. Logistic regression analyses modeled associations between the candidate SNP alleles and OH. We report no significant associations between OH and measured SNPs after correction for multiple comparisons apart from the SNP rs5068 where proportion of the minor allele was significantly different between cases and controls for SOH 40 (p = .002). After adjustment for covariates in a logistic regression, those with the minor G allele (compared to the A allele) had a decreased incidence rate ratio (IRR) for SOH 40 (IRR 0.45, p = .001, 95% CI 0.29–0.72). Only one SNP linked with increased natriuretic peptide concentrations was associated with OH. These results suggest that genetic variants may have a weak impact on OH but needs verification in other population studies.

Keywords: Blood pressure, Genetics, Single-nucleotide polymorphism, Aging, Cardiovascular

Orthostatic hypotension (OH) is a common chronic condition affecting nearly 30% of all community-dwelling adults aged ≥65 years (1). It is characterized as a significant drop in blood pressure (BP) upon standing and is associated with extensive adverse health outcomes including increased risk of cardiovascular events, falls, and all-cause mortality (2–4). The causes of OH are often multifactorial, complex, and secondary to other disorders such as age-related deconditioning with frailty, diabetes, and neurodegenerative diseases (5,6). Other risk factors that can also precipitate the onset of BP perturbations and/or OH in older adults include hypovolaemia and commonly prescribed medications (such as β-blockers, diuretics, and antidepressants) (7). Recently, it has been hypothesized that there could be a genetic component which could make individuals more susceptible to OH when combined with the more "traditional" risk factors (8).

Over the past decade several genome-wide studies have shown associations between genetic determinants, BP levels and susceptibility to OH (8–11). One study among 29,717 individuals found that common genetic variants at the NPPA–NPPB locus were associated with circulating natriuretic peptide (NP) concentrations and

contributed to interindividual variation in BP and hypertension (8). Other single-nucleotide polymorphisms (SNPs) that have been associated with increased circulating concentrations of NPs were also associated with lower systolic blood pressure (SBP) and diastolic blood pressure (DBP) (8). Natriuretic peptides are hypotensive cardiac hormones that regulate intravascular blood volume and vascular tone and can lower BP by increasing glomerular filtration rate, renal excretion of salt and water, and vascular permeability (12). Thus, the regulation of NP concentrations could alter the thresholds for susceptibility when the physiological and neuroendocrine systems involved in BP regulation are challenged.

A recent article from the Genetics of Postural Hemodynamics (GPH) Consortium examined 37,970 individuals from 5 large population cohorts and investigated 31 novel and common gene variants in loci associated with BP for OH occurrence (13). The associations between common gene variants in BP loci and OH were generally weak and the direction of effect was inconsistent with resting BP findings. The combined findings suggested that OH and resting BP share few genetic components but those that are associated could increase susceptibility under particular circumstances. However, the newly identified SNPs from these patient cohorts have yet to be applied to a population series data.

The Irish Longitudinal Study on Ageing (TILDA) study has previously shown that older adults with OH detected through active stand with frequent phasic measures are more susceptible to cognitive decline, depression, injurious falls, and syncope (14–16). Therefore, investigating genetic susceptibility for OH in a population cohort such as this is of clinical and physiological relevance. Thus, the aim of this analysis was to investigate the associations of previously identified 12 candidate gene loci with BP response (OH) in older adults recruited from the TILDA study.

Materials and Methods

Study Population

Analysis was conducted on data from Wave 1 (June 2009–June 2011) of TILDA, a nationally population representative cohort of community-dwelling adults aged ≥50 years. Full details of the study design, sampling, and methodology have been published previously (17,18). The study consisted of (i) a computer-aided personal interview carried out by trained interviewers in the participant's home, (ii) a self-completion questionnaire, (iii) a health assessment carried out by research nurses in one of the two health centers. The study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin, and all participants gave informed written consent. All experimental procedures adhered to the Declaration of Helsinki and all assessments were performed by trained research nurses. Anonymized data and materials have been made publicly available at the Irish Social Science Data Archive based in University College Dublin and the Interuniversity Consortium for Political and Social Research based in the University of Michigan and can be accessed at www.tilda.ie.

Genotyping

A blood sample was collected by venipuncture into one 10 mL K2EDTA tube (BD, Becton; Dickinson Limited, Oxford, UK) by a trained phlebotomist. Samples were kept chilled and centrifuged (3,000 rpm for 15 min) with buffy coats extracted and archived at −80°C prior to DNA extraction. DNA extraction from archived buffy coats was performed by the "Salting Out" method using standard operating procedures, reagents, and equipment for the Autopure system (Qiagen, Velto, Netherlands). DNA concentrations were assessed by Qubit dsDNA HS Assay (ThermoFisher Scientific, Waltham) and normalized to 100 ng/μL using TE buffer. Subaliquots of each participant DNA sample were then adjusted to a final concentration of 5 ng/μL with TE buffer and 10 μL volumes transferred to mapped 96-well plates and stored at −20°C. Samples were sent on dry ice to Lund University, Malmo, Sweden, for SNP analysis and were genotyped for 12 SNPs (rs7221985; rs17367504; rs12568255; rs12566889; rs12561975; rs11953630; rs11191548; rs7129220; rs3013384; rs1173771; rs198358; rs5068). Further background information on these chosen SNPs are available in Supplementary Table 1. Genotyping of all selected SNPs was performed with Applied Biosystems TaqMan PCR (ThermoFisher Scientific) and by matrix-assisted, laser desorption ionization time-of-flight mass spectrometry on a MASS array platform with iPLEX genotyping technology (Sequenom, San Diego, CA) (11). The genotyping call rate for the studied SNPs was between 95.2% and 98.6% (Supplementary Figure 1).

Assessment of BP and OH

Participants who attended the health center for assessment underwent an active stand, which noninvasively measures beat-to-beat BP response to stand following 10 min of supine rest, using digital photoplethysmography (Finometer MIDI device; Finapres Medical Systems, Amsterdam, The Netherlands). A standardized protocol was followed for application of the equipment and during the active stand, to minimize artifact. Participants were asked to relax their hand down by their side, and to keep the arm and finger that had the finometer cuff attached as straight as possible during the test. All recorded readings occurred in a silent room maintained at an ambient temperature of 21–23°C under the supervision of a trained health nurse. Baseline BP was measured as the mean value between 60 and 30 s prior to standing during the rest period. Further details of this methodology have been published extensively elsewhere (19). Impaired BP stabilization was recorded at each 10 s interval and was defined as OH (SBP drop ≥20 mmHg or DBP drop ≥10 mmHg) at the time-points 40, 90, and 110 s. We defined sustained OH (SOH) as a drop that exceeded consensus BP thresholds for OH (SBP drop ≥20 mmHg or DBP drop ≥10 mmHg) at the following time points: 40, 90, and 110 s after standing. The American Autonomic Society definition of OH does not specify the length of time that the BP drop has to be sustained for, so both of these set groups would fit in within this definition, but in particular the OH110 group (who would also have OH40) as they sustain the drop throughout the entire active stand period. Baseline SBP and DBP were measured at the health assessment using traditional oscillometric methods.

Covariates

Participant information recorded included gender, age, self-reported educational attainment (primary, secondary, or third level), living alone and self-reported physican's diagnosis of common health conditions. The occurrence of cardiovascular disease (CVD) conditions (0, 1–2, ≥3) included high BP, angina, heart attack, heart failure,stroke, diabetes, high cholesterol, heart murmur, transient ischemic attack and abnormal heart rhythm. Medications taken on a daily basis including prescribed medications (all groups of medications that could affect BP including antihypertensives and antidepressants)

were recorded and assigned World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification codes and binarized to yes/no usage. Self-reported physical activity levels were assessed and classified using the International Physical Activity Questionnaire (IPAQ) categories: physically active (minimally or health enhancing physically active) versus physically inactive (inactive or insufficiently active). Obesity was measured as a body mass index (BMI) ≥30 kg/m^2. Other lifestyle information included current smoker status and problematic alcohol usage as assessed by the cut-annoyed-guilty-eye (CAGE) questionnaire (a CAGE score of ≥2 indicates problem alcohol use).

Statistical Analysis

Participants who had inadequate active stand data for analysis or were missing blood samples or SNP data were excluded from the study (Figure 1). All analyses were carried out using STATA 14 (StataCorp, College Station, TX). Hardy–Weinberg equilibrium (HWE) was calculated using the Chi-square goodness-of-fit test. Participants were allotted to either cases (yes to OH or SOH at various time-points 40, 90, 110 s) or controls (no to OH or SOH). Genotype and allele frequencies were compared across groups by Chi-square or Fishers test (for groups with ≤5 participants). Where significant differences in genotype frequency between any OH or SOH group and the control group were detected, further modeling included logistic regression analyses of alleles adjusting for age, sex, waist:hip ratio, baseline SBP, antidepressant medication use, occurrence of CVD conditions, smoking, physical activity, other medications (vasodilators, β-blockers, diuretics, etc.). These covariates have been selected as previous evidence from TILDA and the wider research literature has shown these variables to be significant predictors of OH (19). In addition, a Bonferroni correction for multiple comparisons (*P*/36 for SNP comparison tables and *P*/24 for allele comparison tables) was applied across each frequency table.

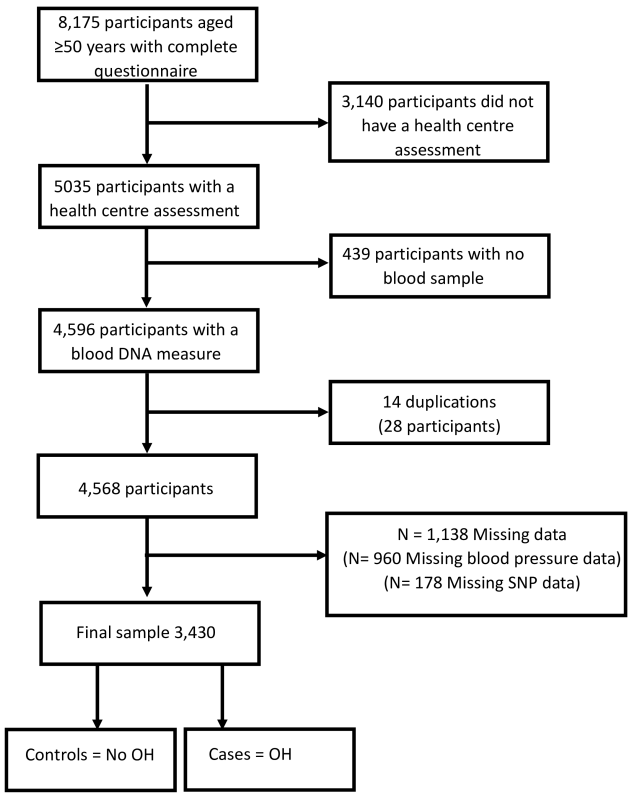

Figure 1. Study design

Results

At baseline, 8,175 adults completed a computer-aided personal interview, representing a response rate of 62%. Of those, 72.1% (*n* = 5,895) consented to, and participated in, a health assessment. From those who participated in the health assessment, 439 participants had no blood stored whereas a further 14 were removed due to duplicate SNP results. Of these, 1,138 participants were excluded due to either not having a BP measure or were missing a SNP result leaving a final sample (*n* = 3,430) to analyze for cases (yes to OH) versus controls (no to OH), Figure 1, at the various time-points. The demographic characteristics of TILDA participants genotyped are reported in Table 1. The mean age was 61.5 years, 32.2% were obese, and 31.4% reported antihypertensive medication use. The prevalence of OH 40, OH 90, and OH 110 was 13.0%, 10.7%, and 11.6%, respectively, whereas the prevalence of SOH 40, SOH 90, and SOH 110 was 9.7%, 4.5%, and 4.1%, respectively.

All SNPs were assessed for HWE in the total population and separately in cases and controls. In the total population, all measured SNPs were within HWE (Supplementary Table 2). For each SNP, allele frequencies were calculated and checked against the published literature and genetic databases. For all SNPs, the minor allele frequencies were within the range found for the British and combined European population (Supplementary Table 2). In addition, our reported minor allele frequencies closely match those reported for the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, the Framingham Heart Study, the Malmö Preventive Project, and the Rotterdam Study (13).

Table 1. Demographic Characteristics of the Study Population

Characteristic (*N* = 3,430)	Value
Age (years)	61.5 (8.2)
Sex, % female	53.5 (51.8–55.1)
Education, % primary	20.7 (19.4–22.1)
Smoking status, % current	15.1 (14.0–16.4)
Body mass index, kg/m^2	28.4 (4.7)
Obese, % yes	32.2 (30.7–33.8)
Alcohol use, % >2 CAGE	13.7 (12.5–14.9)
Physical activity, % active	72.6 (71.1–74.0)
Living alone, % yes	16.7 (15.5–18.0)
Hypertension, %	40.3 (38.6–41.9)
Diabetes, %	5.8 (5.0–6.6)
No CVD conditions, %	39.3 (37.7–41.0)
CVD conditions 1–2, %	51.3 (49.6–52.9)
CVD conditions ≥3, %	9.4 (8.4–10.3)
Arthritis, %	25.9 (24.5–27.4)
Polypharmacy, %	16.6 (15.4–17.9)
Antihypertensives, %	31.4 (29.9–33.0)
Antidepressants, %	5.5 (4.8–6.3)

Notes: Values are mean ± *SD* for continuous variables or % (95% confidence interval) for binary variables. The 95% confidence interval defines the precision of the sample estimate of proportion.

CAGE = cut-annoyed-guilty-eye alcohol questionnaire score; CVD = cardiovascular disease.

Associations of Genotype With OH

All participants included in the analysis were assigned to either cases (yes OH) or controls (no OH) based on the defined OH or SOH time-points and the frequency distribution of each genotype was tabulated. Genotype frequencies by OH at 40, 90, and 110 s poststand are displayed in Supplementary Tables 4–6. Genotype frequencies by SOH at 40, 90, and 110 s are displayed in Tables 2 and 3 (SOH 40, SOH 110) and in Supplementary Table 7 (SOH 90). SNP genotype frequencies that were initially significantly different ($p \leq .05$) between case and controls included rs5068 (OH 40, SOH 40, SOH 90, SOH 110); rs1173771 (OH 110, SOH 110); rs7129220 (OH 40, SOH 40, SOH 110); rs11953630 (OH 90); rs17367504 (SOH 40, SOH 90, SOH 110).

As per the genotype frequency comparison, the allele frequencies of each SNP were compared across cases and controls by OH definition. SNP allele frequencies that were initially significantly ($p \leq .05$) different between case and controls included rs5068 (OH 40, SOH 40, SOH 90, SOH 110); rs719220 (OH 40, SOH 40); rs11953630 (OH 90); rs17367504 (SOH 40); rs7221985 (OH 40).

However, no tests survived Bonferroni multiple test correction for genotype ($p \leq .0001$) while a single SNP (rs5068) survived correction for allele frequencies ($p \leq .002$) for SOH 40. A linear regression with Poisson distribution (with vce robust option to give relative risk) was utilized to investigate rs5068 alleles as a risk factor for SOH 40 (Table 4). After adjustment for covariates, those with the G allele (compared to the A allele) had a decreased incidence rate ratio (IRR) for SOH 40 (IRR 0.45, $p = .001$, 95% CI 0.28–0.71). In examining associations of alleles with continuous SBP and DBP, there was no association of any SNP including rs5068 (data not shown).

Finally, in Supplementary Table 8, we compared baseline characteristics between rs5068 G allele carriers and noncarriers. Carriership of the G allele was positively associated with less antihypertensive use (25.4% vs 32.3%, $p = .004$). There were no other associations observed.

Discussion

In this large population study of older adults, we observed little association of novel gene loci with the prevalence of OH. However,

Table 2. Cases Versus Controls for Sustained SOH 40

Polymorphism	Genotype	Controls frequency *N* (%)	Cases (SOH 40) frequency *N* (%)	HWE control	HWE cases	Overall $\chi 2$	SNP test	*p* value
rs5068	A:A	2,715 (87.7)	311 (93.4)	0.987	0.9999	0.003	A:A/A:G	.002
	A:G	364 (11.7)	20 (6.0)				A:A/G:G	.661
	G:G	18 (0.6)	2 (0.6)				A:G/G:G	.298
rs198358	T:T	1,734 (56.0)	200 (60.1)	0.9978	0.9999	0.282	T:T/C:T	.252
	C:T	1,167 (37.7)	117 (35.1)				T:T/C:C	.199
	C:C	196 (6.3)	16 (4.8)				C:T/C:C	.458
rs11737771	G:G	1,114 (36.0)	114 (34.2)	0.9986	0.9998	0.101	G:G/A:G	.206
	A:G	1,440 (46.5)	173 (52.0)				G:G/A:A	.300
	A:A	543 (17.5)	46 (13.8)				A:G/A:A	.043
rs3013384	T:T	1,379 (44.5)	157 (47.2)	0.9969	0.9998	0.659	T:T/G:T	.387
	G:T	1,367 (44.2)	140 (42.0)				T:T/G:G	.591
	G:G	351 (11.3)	36 (10.8)				G:T/G:G	.994
rs7129220	G:G	2,348 (75.8)	271 (81.4)	0.9768	0.9999	0.026	G:G/A:G	.011
	A:G	704 (22.7)	55 (16.5)				G:G/A:A	.467
	A:A	45 (1.5)	7 (2.1)				A:G/A:A	.103
rs11191548	T:T	2,676 (86.4)	290 (87.1)	0.9973	0.9999	0.773	T:T/C:T	.660
	C:T	399 (12.9)	40 (12.0)				T:T/C:C	.449
	C:C	22 (0.7)	3 (0.9)				C:T/C:C	.414
rs11953630	C:C	1,158 (37.4)	133 (39.9)	0.9996	0.9998	0.634	C:C/C:T	.447
	C:T	1,446 (46.7)	151 (45.4)				C:C/T:T	.410
	T:T	493 (15.9)	49 (14.7)				C:T/T:T	.774
rs12561975	T:T	1,810 (58.4)	205 (61.6)	0.9921	0.9999	0.504	T:T/A:T	.353
	A:T	1,109 (35.8)	112 (33.6)				T:T/A:A	.393
	A:A	178 (5.8)	16 (4.8)				A:T/A:A	.676
rs12566889	G:G	1,777 (57.4)	200 (60.1)	0.9997	0.9999	0.624	G:G/A:G	.409
	A:G	1,131 (36.5)	115 (34.5)				G:G/A:A	.516
	A:A	189 (6.1)	18 (5.4)				A:G/A:A	.805
rs12568255	T:T	1,773 (57.3)	200 (60.1)	0.9961	0.9999	0.596	T:T/C:T	.387
	C:T	1,134 (36.6)	115 (34.5)				T:T/C:C	.498
	C:C	190 (6.1)	18 (5.4)				C:T/C:C	.797
rs17367504	A:A	2,171 (70.1)	254 (76.3)	0.9852	0.9999	0.059	A:A/A:G	.018
	A:G	844 (27.3)	71 (21.3)				A:A/G:G	.629
	G:G	82 (2.6)	8 (2.4)				A:G/G:G	.704
rs7221985	C:C	2,069 (66.8)	209 (62.8)	0.994	0.9999	0.332	C:C/C:G	.153
	C:G	903 (29.2)	109 (32.7)				C:C/G:G	.542
	G:G	125 (4.0)	15 (4.5)				C:G/G:G	.984

Note: Values are *N* (%). Genotype frequencies were compared across groups by Chi-square or Fishers Test with a Bonferroni correction for multiple comparisons (*P*/36).

HWE = Hardy–Weinberg equilibrium; SNP = single-nucleotide polymorphism.

the minor G allele of the SNP rs5068 was associated with a decreased risk for SOH 40. Rs5068 is located on chromosome 1 in the 3′ untranslated region of the atrial natriuretic peptide (ANP) gene. Previous work has demonstrated that the minor allele has been associated with a minor decrease in SBP (0.9–1.5 mmHg) and DBP (0.3–0.8 mmHg) in addition to a stepwise increase in the concentration of ANP (8). ANP is secreted upon detection of atrial stretch and can decrease SBP by two main mechanisms. Initially, it can increase vasodilation via relaxing vascular smooth muscle and increasing vascular permeability through the microvascular endothelium (20). The second mechanism is through increasing renal perfusion and renal clearance of both sodium and water, thereby decreasing fluid blood volume and pressure (21). Therefore, given the ability of ANP to reduce BP, any SNP increasing ANP concentrations has been hypothesized to increase the risk of OH. One previous study—the GPH Consortium (13)—had observed a significant increased risk of OH with the minor allele of rs5068, which is in contrast to our study results. Within the analysis of the GPH Consortium study, the effects appear to be driven by the largest of the five cohorts studied—the Malmö Preventive Project (13). Interestingly, the Malmö Preventive Project participants were on average 14 years younger than the participants in the current study (47.5 y vs 61.5 y) while OH was detected in 2.1% within Malmö Preventive Project compared with 4.1%–13.0% in TILDA. These differences in age and OH prevalence may account for some of the divergence in the direction of the relationship observed with rs5068. It is also possible that, in older participants, the allele could be protective while in younger adults it carries an adverse risk though more population-based study data are needed to explore these associations.

In healthy human individuals, the full effects of minor NP variations on BP stability are unknown (22). Individuals carrying the minor allele of rs5068 may have been exposed to higher concentrations of ANP for decades and the cardiovascular system may have adapted to these elevated levels. In explanation of a potential OH-protective effect, it is known that the minor G allele may also have other important cardio-protective benefits. It has been associated with higher HDL concentrations, lower diabetes risk, enhanced insulin sensitivity lower BMI, and a lower prevalence of

Table 3. Cases Versus Controls for Sustained SOH 110

Polymorphism	Genotype	Controls frequency *N* (%)	Cases (SOH 110) frequency *N* (%)	HWE control	HWE cases	Overall $\chi 2$	SNP test	*p* value
rs5068	A:A	2,891 (88.0)	135 (93.7)	0.9844	0.9997	0.054	A:A/A:G	.029
	A:G	376 (11.4)	8 (5.6)				A:A/G:G	.600
	G:G	19 (0.6)	1 (0.7)				A:G/G:G	.370
rs198358	T:T	1,842 (56.1)	92 (63.9)	0.9955	0.9997	0.177	T:T/C:T	.085
	C:T	1,239 (37.7)	45 (31.2)				T:T/C:C	.338
	C:C	205 (6.2)	7 (4.9)				C:T/C:C	.881
rs11737771	G:G	1183 (46.6)	45 (31.3)	0.9993	0.9999	0.064	G:G/A:G	.082
	A:G	1,532 (36.0)	81 (56.2)				G:G/A:A	.507
	A:A	571 (17.4)	18 (12.5)				A:G/A:A	.049
rs3013384	T:T	1,466 (44.6)	70 (48.6)	0.8254	0.9999	0.621	T:T/G:T	.330
	G:T	1,449 (44.1)	58 (40.3)				T:T/G:G	.719
	G:G	371 (11.3)	16 (11.1)				G:T/G:G	.796
rs7129220	G:G	2,506 (76.3)	113 (78.5)	0.989	0.9997	0.082	G:G/A:G	.278
	A:G	733 (22.3)	26 (18.0)				G:G/A:A	.077
	A:A	47 (1.4)	5 (3.5)				A:G/A:A	.042
rs11191548	T:T	2,846 (86.6)	120 (83.3)	0.9999	0.9999	0.248	T:T/C:T	.345
	C:T	417 (12.7)	22 (15.3)				T:T/C:C	.272
	C:C	23 (0.7)	2 (1.4)				C:T/C:C	.376
rs11953630	C:C	1,234 (37.6)	57 (39.6)	0.9984	0.9999	0.666	C:C/C:T	.836
	C:T	1,529 (46.5)	68 (47.2)				C:C/T:T	.373
	T:T	523 (15.9)	19 (13.2)				C:T/T:T	.444
rs12561975	T:T	1,930 (58.7)	85 (59.0)	0.9991	0.9998	0.913	T:T/A:T	.956
	A:T	1,169 (35.6)	52 (36.1)				T:T/A:A	.685
	A:A	187 (5.7)	7 (4.9)				A:T/A:A	.674
rs12566889	G:G	1,895 (57.6)	82 (56.9)	0.9932	0.8878	0.921	G:G/A:G	.798
	A:G	1,192 (36.3)	54 (37.5)				G:G/A:A	.845
	A:A	199 (6.1)	8 (6.6)				A:G/A:A	.757
rs12568255	T:T	1,891 (57.5)	82 (56.9)	0.9984	0.9997	0.941	T:T/C:T	.818
	C:T	1,195 (36.4)	54 (37.5)				T:T/C:C	.831
	C:C	200 (6.1)	8 (5.6)				C:T/C:C	.752
rs17367504	A:A	2,314 (70.4)	111 (77.1)	0.9988	0.9998	0.121	A:A/A:G	.050
	A:G	887 (27.0)	28 (19.4)				A:A/G:G	.402
	G:G	85 (2.6)	5 (3.5)				A:G/G:G	.166
rs7221985	C:C	2,190 (66.6)	88 (61.1)	0.9972	0.9998	0.519	C:C/C:G	.155
	C:G	962 (29.3)	50 (34.7)				C:C/G:G	.802
	G:G	134 (4.1)	6 (4.2)				C:G/G:G	.736

Note: Values are *N* (%). Genotype frequencies were compared across groups by Chi-square or Fishers Test with a Bonferroni correction for multiple comparisons (*P*/36).

HWE = Hardy–Weinberg equilibrium; SNP = single-nucleotide polymorphism.

Table 4. Predicators of OH S40 Risk in the TILDA Cohort by rs5068 Genotype

				95% confidence interval	
	IRR	*SE*	*p* value	Lower	Upper
rs5068 (G allele)	0.44	0.105	.001	0.27	0.70
Age (y)	1.07	0.068	<.0001	1.05	1.08
Waist:hip ratio (cm)	0.26	0.140	.012	0.09	0.74
Mean SBP (mmHg)	1.00	0.002	<.0001	1.00	1.01
Height (cm)	1.01	0.009	.066	0.99	1.03
Antidepressants (yes)	2.15	0.388	<.0001	1.51	3.07
CVD conditions (1–2)	1.11	0.140	.401	0.86	1.42
CVD conditions (≥3)	0.81	0.173	.341	0.53	1.23
Sex (female)	1.30	0.233	.134	0.92	1.85
Smoking status (current)	1.43	0.214	.015	1.07	1.92
CAGE score 1	1.11	0.193	.540	0.79	1.56
CAGE score 2	0.81	0.199	.405	0.50	1.31
CAGE score 3	0.95	0.290	.883	0.52	1.73
CAGE score 4	0.53	0.344	.330	0.15	1.88
Physically active	1.04	0.124	.705	0.82	1.32
Vasodilator (yes)	1.60	0.560	.174	0.81	3.18
ß-Blocker (yes)	1.30	0.194	.075	0.97	1.74
Antipsych meds (yes)	1.40	0.553	.392	0.64	3.04
Alphablockers (yes)	1.94	0.513	.012	1.15	3.26
Diuretics (yes)	1.19	1.365	.874	0.12	11.1

Note: Logistic regression analyses of rs5068 allele and OH S40 risk with covariates.

CAGE = cut-annoyed-guilty-eye alcohol questionnaire score; CVD = cardiovascular disease; SBP = systolic blood pressure; IRR = incidence rate ratio.

obesity and metabolic syndrome (23–25), all of which decrease the risk of OH (26–28) and could override the minor increased risk of OH associated with elevated ANP. In addition, higher concentrations of ANP may have specific benefits for heart structural integrity through antihypertrophic and antifibrotic actions resulting in these individuals being better placed to manage a challenged BP system and, therefore, have an increased resistance to developing OH (29). However, we have no direct measure of ANP or any NP concentration in our population and thus we can only hypothesis potential mechanisms. In addition, there could be unknown environmental or other genetic factors that have an epistatic effect on rs5068 and OH risk that we are unaware of and thus larger population-based studies are needed to explore these associations.

Surprisingly, no other SNP was associated with BP despite previous population studies reporting associations (7,11). It is possible that these specific genetic variants are simply not involved in dynamic BP responses in the assessed age segment of older adults, or the impact is so small that the study was underpowered to detect the association despite it being the largest study yet conducted in Ireland. Furthermore, because our study utilized a potentially more accurate BP measure, we were perhaps able to record and account for more subtle signals in the data compared with previous reports. Reassuringly in our analysis, we also observed the same other determinants (nongenetic) of OH as in previous TILDA work. For instance, age, smoking, and antidepressants significantly increased the risk of OH. This is in addition to raised BP (40% of the TILDA cohort have hypertension) which is a well-established risk factor for OH (30,31).

Our study has some important strengths. The data are derived from a nationally representative population study and is genetically homogenous in terms of ethnicity, with >99% of TILDA participants reported as white Caucasian, of whom 95% claim Irish descent. Additionally, we used beat-to-beat measurement of BP response to stand using a finometer, which allowed a precise assessment of BP behavior in response to orthostasis. Finometer measurements are not as reliable as brachial cuffs when looking at absolute values of BP; in our study, for the purposes of controlling baseline measurements, we used traditional oscillometric BP measurements. However, the use of the finometer for measurement of beat-to-beat BP response to stand allows for a more accurate measurement of changes in BP that occur on stand, and is more sensitive in identifying cases of OH. In addition, we recognize that these measurements are prone to artifact and therefore the way in which cuffs are applied, hands are positioned and so forth are standardized for the purposes of the study.

All measured SNPs were within HWE and the proportions of allele frequencies were within the range found for British and combined European populations in addition to other previous reported studies. Our study also has some limitations. We did not measure CYP17A1 activity, NPR-C function, or NP concentrations within the study population. Furthermore, because of the sampling criteria, our findings may not be applicable to non-Caucasians, older adults in institutional care or those with severe cognitive impairment. In addition, although every effort has been made to control for potential confounders, we cannot rule out the occurrence of some residual confounding and thus cautious interpretation of the findings is warranted.

In conclusion, we observed a little association of novel gene loci with OH, with only one SNP (rs5068) associated with a lower risk of OH at a single specific time-point. This finding needs to be replicated in other population cohorts with similar BP measures and, optimally, with NP concentrations for the SNP to be considered an additional screening marker to identify individuals at risk of OH.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None reported.

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