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Orthostatic hypertension as a risk factor for age-related macular degeneration: Evidence from the Irish longitudinal study on ageing

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ABSTRACT

Purpose: Age related macular degeneration (AMD) is a leading cause of irreversible visual loss in developed countries. It is associated with vascular risk factors including hypertension. Dysregulated blood pressure (BP) behaviour including orthostatic hypertension (OHTN), hypotension (OH) and BP variability (BPV) are associated with end-organ damage, particularly in the brain. We investigated if abnormal orthostatic BP (OBP) was a risk factor for AMD, for which a vascular aetiology is implicated.

Methods: A nationally representative, cross-sectional study was carried out 2009/2010 in The Irish Longitudinal Study on Ageing (TILDA). Beat-to-beat BP data, measured by digital photoplethysmography during active stand, was used to characterise OBP behaviour in the 30–110 s after standing. OH, OHTN, BPV and normal stabilisation recovery phenotypes were defined. AMD was identified following masked grading of 45° monoscopic colour retinal photographs, which were centred on the macula and taken with a NIDEK AFC-210 non-mydriatic auto-fundus camera. The relationship between OBP recovery phenotypes and AMD in 3750 adults aged ≥50 years was investigated using multivariate logistic regression models, adjusted for traditional AMD risk factors.

Results: From 30 to 110 s post active stand, systolic and diastolic OHTN was associated with increased odds of AMD after adjustment for demographics, health behaviours including smoking, family history of AMD, self-report (SR) diabetes, SR cataracts, objective hypertension and prescribed antihypertensives. No evidence of heterogeneity of OHTN effect was found between those who were hypertensive to those who were normotensive.

Conclusions: This study provides evidence that OHTN may be an independent cardiovascular risk factor for AMD.

1. Introduction

Age related macular degeneration (AMD) is a progressive neurodegenerative disease that affects the macula, the part of the retina responsible for central, fine detail and colour vision. Systematic review of worldwide data between 1990 and 2010 confirm that it is the third most common cause of both blindness and moderate to severe visual impairment, after cataract and uncorrected refractive error (Bourne et al., 2013). The prevalence of overall AMD in Ireland is 7.2%, early AMD 6.6% and late AMD 0.6% (Akuffo et al., 2015). The aetiology of AMD is multifactorial, however some risk factors are established, such as increasing age, genetic background and smoking and some remain putative, such as obesity and low dietary intake of vitamins A,C and E, lutein and omega-3 fatty acids (Cheung and Wong, 2014). In addition, several genes key in inflammatory pathways have been associated with AMD risk, for example genes that code for interleukin (IL)-1, IL-6 and IL-8, other chemokines and complement (Cascella et al., 2014). Furthermore there is emerging evidence supporting a role for atherosclerosis and ischemia in pathogenesis and progression. High body mass index (BMI)(van Lookeren et al., 2014) diabetes(Vassilev et al., 2015)

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and dyslipidemia have all been associated with AMD, although a recent meta-analysis suggests that evidence for the latter is not compelling (Klein et al., 2004). A recent systematic review of thirteen population-based cohort studies that investigated links between AMD and cardiovascular disease (CVD), coronary heart disease (CHD) and stroke concluded that both early and late AMD are predictive of a small increase in risk of future CVD, while subgroup analyses limited to prospective studies demonstrate a markedly increased risk of CVD in late AMD (Wu et al., 2014).

Certain patterns of orthostatic blood pressure (OBP) behaviour, such as orthostatic hypotension (OH) and orthostatic hypertension (OHTN) have been associated with increased risk of cardiovascular events (Angelousi et al., 2014; Kario, 2013). Increased visit-to-visit SBP variability, independent of mean SBP is associated with stroke (Rothwell et al., 2010) and residual SBP variability in treated hypertension with vascular events (Rothwell et al., 2010). Orthostatic BPV is associated with poorer visual acuity (VA), independent of objective hypertension and self-report (SR) and objective eye diseases (NiBhuachalla et al., 2015). This suggests a possible direct deleterious effect of unstable OBP on the densely autonomically innervated choroidal circulation and psychophysical vision.

Given that ischemia and cardiovascular risk have been implicated in the pathogenesis of AMD and because dysregulated OBP behaviour is associated with CV events, we hypothesise that OBP behaviour may have an effect on choroidal blood flow and therefore AMD. This study aimed to investigate whether any phenotype of OBP behaviour is associated with AMD prevalence in older adults.

2. Materials and methods

2.1. Study population

The Irish Longitudinal Study on Ageing (TILDA) is a nationally representative study, that collected social, economic and health data from 8175, community dwelling adults aged ≥50 years. The methodology has been published previously (Kearney et al., 2011; Whelan and Savva, 2013). There are three components to the study; a home-based interview, delivered using computer-assisted personal interviewing (CAPI), a self-completion questionnaire (SCQ) and either a home or a health centre assessment. The CAPI included detailed questions on socio-demographic characteristics, health and health behaviours and the SCQ, questions that were more sensitive or personal. The health centre-based assessments included detailed measurements of vision and beat-to-beat BP and heart rate behaviour. Ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee of Trinity College, Dublin, and all respondents provided signed informed consent prior to participation. All experimental procedures adhered to the Declaration of Helsinki.

Data analysed in this study is from the first wave of the study (October 2009 to July 2011).

The overall response rate in wave one was 62% (n = 8175) (Kenny, 2013). Of those, 62% participated in a health centre assessment (n = 5041), of whom 4475 had beat-to beat BP data from an active stand test collected of sufficient quality for phenotypic categorisation. A retinal photograph was taken of both eyes independently in 4343 individuals. Of these, 3750 were deemed to be of either excellent or good quality in at least one eye. Thus, the total population eligible for analysis comprised 3750 individuals (Fig. 1).

2.2. Orthostatic blood pressure measurement

The active stand is a lying-to-standing orthostatic test during which non-invasive beat-to-beat BP is measured for 3 min using digital photoplethysmography (Finometer® MIDI device, Finapres Medical Systems BV, Amsterdam, The Netherlands, http://www.finapres.com). Active stand data was pre-processed before incorporation into the final dataset. The active stand protocol has been described previously (Romero-Ortuno et al., 2013). The following measures were recorded from the active stand: supine SBP, DBP which were defined as the mean value in the time interval 60 to 30 s prior to standing; SBP, DBP and HR at the time of the nadir BP (i.e. the lowest BP value after standing); and SBP, DBP and HR at each 10 s interval post stand from 10 s to 110 s.

2.3. Orthostatic blood pressure behaviour

Thirty seconds after standing, 3 distinct phenotypes of OBP other than normal stabilisation of BP have been identified and defined (NiBhuachalla et al., 2015), orthostatic hypotension (OH), orthostatic hypertension (OHTN) and orthostatic blood pressure variability (BPV). These definitions are outlined in Fig. 2.

2.4. Retinal morphology assessment

For each eye, using a NIDEK AFC-210 non-mydriatic auto-fundus camera, one 45 monoscopic colour photograph, centred on the macula (EDTRS standard field 2), was obtained. Pupils were not dilated. A masked grader graded the photographs using standard protocols. Grading was conducted under the supervision of the MEH Reading centre lead ophthalmologist. Each retinal photograph was assessed for photographic quality and classified into one of the following 8 categories; excellent; good; fair; poor, but main features are still gradable; ungradable; wrong field definition but some features are gradable; missing. The TILDA AMD protocol has been previously described in detail (Akuffo et al., 2015) and was a modified version of the International Classification and Grading System for AMD (Bird et al., 1995). For our outcome measure we chose any evidence of AMD on either retinal photograph (i.e. both eyes were considered). We did not differentiate between early and late AMD, due to small numbers.

2.5. Other covariates

Baseline characteristics were described in the following domains: demographics, health behaviours, cardiovascular and ophthalmic variables. Demographic variables included age (categorical), gender, and highest level of education achieved (none/primary, secondary, or tertiary/higher). Health behaviours included smoking history (never smoked, previously smoked, current smoked) and problematic alcohol intake; defined as 2+ affirmative answers on the CAGE questionnaire (Mayfield et al., 1974). Body mass index (BMI) was calculated by dividing the patient's weight in kilograms by height in metres squared, both of which were objectively measured in the health centre assessment.

Objective BP was measured twice, seated, by sphygmomanometer and the average calculated of the two recordings (OMRON™ digital automatic BP monitor). Objective hypertension was defined as SBP > 140 mmHg or DBP > 90 mmHg (Mancia et al., 2007). All medications taken by a participant were recorded by interviewers after viewing medication packages and assigning WHO Anatomic Therapeutic Chemical (ATC) classification codes (WHO Collaborating Centree for Drug Statistics Methodology, 2010). Antihypertensives adjusted for were anti-adrenergic agents, agents acting on arteriolar smooth muscle and combination antihypertensive including those with diuretics (C02); diuretics (C03); beta blocking agents (C07); calcium channel blockers (C08) and agents acting on the renin-angiotensin system (C09)(WHO Collaborating Centree for Drug Statistics Methodology, 2010).

Self-reported (SR) health measures relating either to the cardiovascular system or vision were collected on CAPI by the following question 'has a doctor ever told you that you have any of the conditions on this card?' and conditions were then listed. SR health measures included in analyses were diabetes and cataract. Family history of AMD was also recorded. Family history was defined as having a first-degree

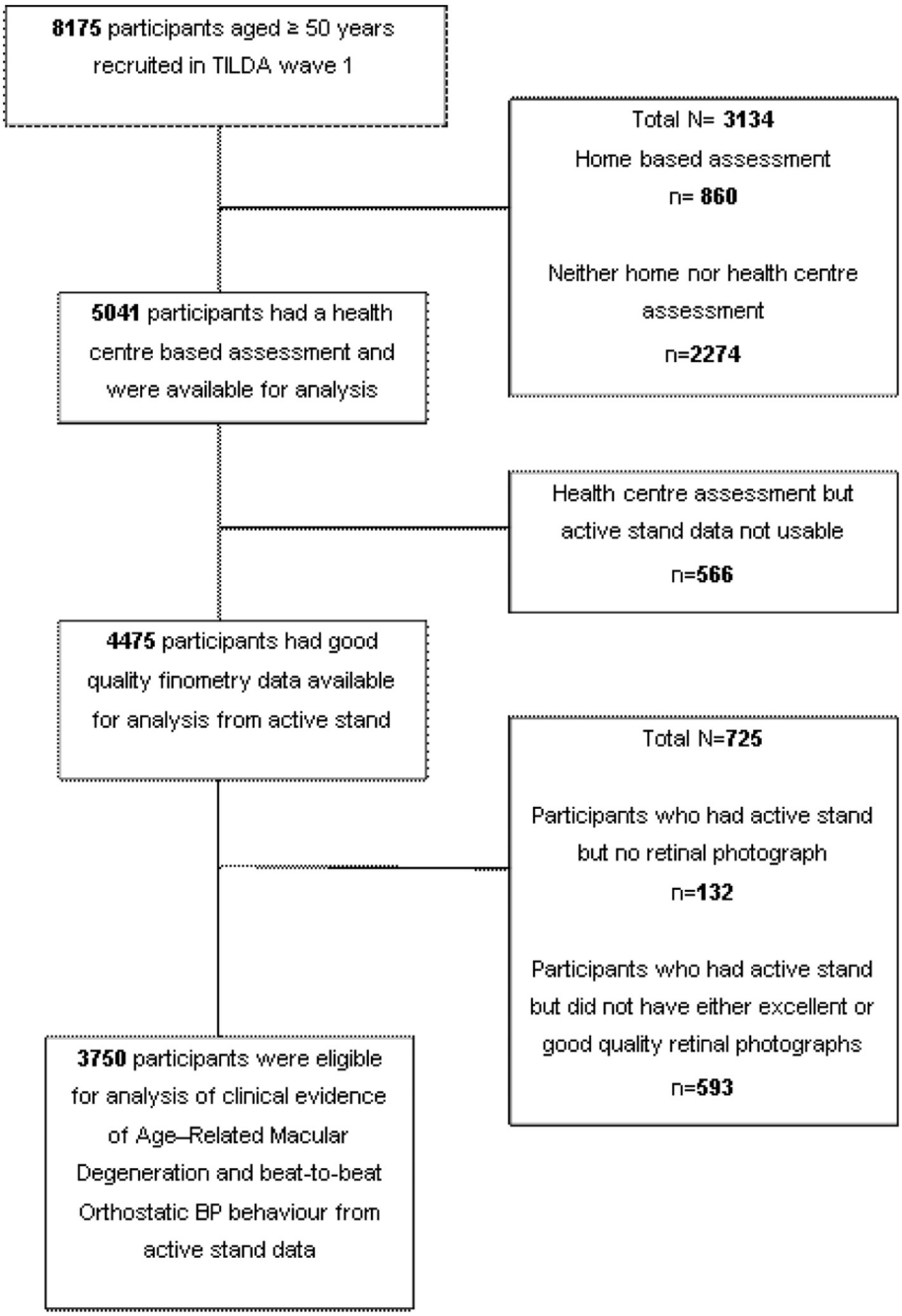


Fig. 1. Population for Analysis
Key: TILDA; The Irish Longitudinal Study on Ageing; BP, blood pressure.

relative, i.e. parent or sibling with AMD. Visual Acuity was measured separately in both eyes using an Early Treatment Diabetic Retinopathy Study (ETDRS) Logarithm of the minimal angle of resolution (logMAR) chart. Spatial contrast sensitivity (CS) was assessed in the eye with the better VA, using a Functional Vision Analyser™ (Stereo Optical Co. Inc., Chicago, IL) under mesopic (3 cd/m^2) background illumination conditions, without glare. Area under the log_{10} Contrast Sensitivity function (CSF) curve (AULCSF) was calculated which represented overall CS function across five spatial frequencies.

3. Statistical analyses

All statistical analyses were performed with STATA (version 12.0). Baseline characteristics of the population for analysis were identified. In addition baseline characteristics of those with and without AMD on retinal photographs were determined and compared, as were baseline characteristics of those who were normotensive and not on antihypertensives, those with objective hypertension and those on antihypertensives. Descriptives for categorical variables were given as total number (N) and percentage (%) of total population. Continuous variables were described as the mean with standard deviation (SD). Continuous and categorical variables were compared with the one way analysis of variance (ANOVA) and the Chi-squared test respectively. Multivariate logistic regression was used to determine whether different phenotypes of OBP behaviour at 30–110 s, namely BPV, OH and OHTN, were associated with increased rates of objective AMD (outcome variable). The predictor variable for OBP phenotypes was categorical, with normal BP stabilisation set as base reference (Fig. 2). Separate

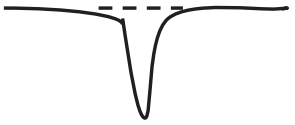
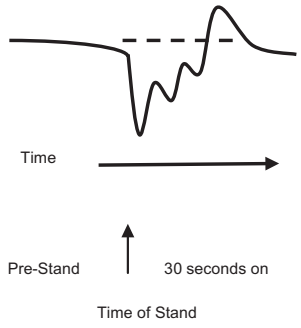
Definitions of Phasic OBP Recovery Phenotypes, 30-110s after Standing				
	Delta BP = Standing BP - Supine BP pre-AS (at Time 30s-110s after standing)			Schematic
Phenotype				
Delta SBP	<-20mmHg	-20mmHg ≤ Delta SBP ≤ 20mmHg	> 20mmHg	
Delta DBP	<-10mmHg	-10mmHg ≤ Delta DBP ≤ 10mmHg	> 10mmHg	
Normal stabilisation		✓ ✓		
OH	✓ ✓			
OHTN			✓ ✓	
BPV	✓ ✓	✓ ✓	✓ ✓	

Fig. 2. Definitions of phasic OBP recovery phenotypes, 30–110 s after standing.

analyses were conducted for SBP and DBP. The model included adjustments for socio-demographics, health behaviours and BMI, family history of AMD, diabetes and cataract, in addition to an interaction term between objective hypertension and antihypertensives. Moderator effects were examined separately by adding interaction terms between the OPB phenotypes and 1) age 2) objective hypertension 3) antihypertensive use and 4) the interaction term objective hypertension/antihypertensives. A series of reduced models were fitted to establish if the different covariates controlled for, significantly altered the findings of the final fully adjusted model. The continuous covariate BMI was centred on the group mean for improved interpretability of odds ratios.

Finally a new categorical variable that combined the objective hypertension measure and antihypertensive use was created. This variable divided the population for analysis into the following three groups: 1) those with no objective hypertension and not on antihypertensives 2) those with objective hypertension but not on anthypertensives and 3) those on antihypertensives. These three groups represent a gradient from no hypertensive disease to those on antihypertensives for either established hypertension or previous CV events. To investigate if there was any heterogeneity of the effect of OHTN on risk of AMD, between those with no hypertension and these other subgroups, a multivariate logistic model was fitted as before with an additional interaction term between this new variable and the OBP predictor variable.

4. Results

4.1. Demographics and health characteristics of study population

The mean age of the population was 61 years with 55% female. Cardiovascular risk factors were BMI (mean 29 kg/m^2; overweight range), objective hypertension (38%), prescribed antihypertensives (31%), hypercholesteremia (41%), diabetes (6%) and current smoking (15%). Details of other cardiovascular diseases are given in Table 1. The prevalence of SR glaucoma, cataract and AMD were 2%, 7% and 1%

Table 1
Baseline characteristics of population for analysis and comparison of those with and without AMD on retinal photographs.

	Overall $N = 3750$	No AMD $N = 3497$	AMD $N = 253$
Demographics			
Age, mean (SD)	60.9 (7.9)	60.7(7.8)	64.3 (9.0)***
Female, N (%)	2073 (55)	1934 (55)	139 (55)
Received Tertiary Education, N (%)	1414 (38)	1321 (38)	93 (37)
Health behaviours			
Current smoker, N (%)	553 (15)	517 (15)	36 (14)
Alcohol problem, N (%)	484 (14)	445 (14)	225 (17)
BMI in kg/m^2, mean (SD)	28.5 (4.8)	28.5 (4.9)	28.2 (4.9)
Cardiovascular conditions			
Hypertension, N (%)	1425 (38)	1320 (38)	105 (42)
On any antihypertensive (ATC code C02, CO3, CO7-CO9), N (%)	1180 (32)	1084 (31)	96 (38)*
Beta Blockers, N (%)	397 (11)	362 (10)	35 (14)
Ace Inhibitors, N (%)	339 (9)	303 (9)	36 (14)**
SR Diabetes, N (%)	233 (6)	208 (6)	25 (10)*
SR Hypercholesteraemia, N (%)	1544 (41)	1419 (41)	125 (49)**
SR Angina, N (%)	152 (4)	131 (4)	21 (8)***
SR Myocardial Infarct, N (%)	132 (4)	115 (3)	17 (7)**
SR Heart Failure, N (%)	26 (0.7)	22 (0.6)	4 (1.6)
SR TIA, N (%)	61 (2)	52 (2)	9 (4)*
SR stroke, N (%)	42 (1)	39 (1)	3 (1)
SR syncope past year, N (%)	171 (5)	160 (5)	11 (4)
Eye disease related conditions			
SR glaucoma, N (%)	71 (2)	64 (2)	7 (3)
SR cataract, N (%)	260 (7)	229 (7)	31 (12)**
SR AMD, N (%)	60 (2)	36 (1)	24 (10)***
Self-rated impaired vision, N (%)	284 (8)	255 (7)	29 (12)*
Wore glasses for VA, N (%)	1374 (64)	1273 (64)	101 (65)
Family history of AMD, N (%)	202 (5)	179 (5)	23 (9)*
Better eye: VA, mean (SD)	0.06 (0.18)	0.05 (0.18)	0.09 (0.19)**
Area $\log_{10}$ CSF curve, mean (SD)	1.28 (0.36)	1.29 (0.36)	1.21 (0.35)**
Systolic OBP phenotypes			
Normal Stabilisation, N (%)	2652 (70)	2493 (71)	159 (63)
BPV, N (%)	897 (24)	826 (24)	71 (28)
OH, N (%)	133 (3.6)	120 (3.4)	13 (5.1)
OHTN, N (%)	68 (1.8)	58 (1.7)	10 (4.0)**

Key: AMD, age related macular degeneration; SD, standard deviation; CI, confidence interval; BMI, body mass index; ATC, anatomical therapeutic classification; SR, self-report; TIA, transient ischemic attack; VA, visual acuity; LogMAR, logarithm of the minimal angle of resolution; $\log_{10}$, logarithm to base 10; CSF, contrast sensitivity function; BPV, impaired blood pressure variability; OH, orthostatic hypotension; OHTN, orthostatic hypertension.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

respectively. The prevalence of AMD by retinal photograph assessment (objective) in our sample was 6.8% ($N = 253$). The prevalence of AMD in the right and left eyes were similar; 7% and 6%. In Table 1, demographics by AMD are also described and differences between those with and without AMD are compared. Those with objective evidence of AMD were older, more likely to be taking antihypertensive medication and have a higher prevalence of SR diabetes, hypercholesteraemia, angina, MI and TIA, a family history of AMD, report visual impairment, have lower VA (logMAR) and a lower AULCSF. Participants with AMD also had a higher prevalence of BPV, OH and OHTN (Table 1).

4.2. Prevalence of orthostatic BP recovery phenotypes

The majority of participants achieved BP stabilisation to within 20/10 mm Hg of supine BP within 30 s, and maintained this throughout the AS to 110 s; (SBP/DBP$_{Normal}$; 70%, 69%). The prevalence of persistent OH and persistent OHTN was SBP / DBP$_{OH}$ (4%, 4%) and SBP /DBP$_{OHTN}$ (2%, 2%), respectively. The prevalence of orthostatic BPV or SBP / DBP$_{BPV}$ was 25% and 25% respectively.

Table 2
Multivariate logistic regression of the association between age-related macular degeneration (AMD) and phenotypes of orthostatic BP behaviour adjusted for demographics, health behaviours, family history of AMD, self-reported diabetes, self-reported cataract, objective hypertension and antihypertensives.

Orthostatic recovery BP phenotype	N (%)	AMD	P
		Model 1[a]	
		Odds ratio (95% CI)	
Systolic blood pressure (SBP)			
Normal stabilisation	2734 (70)	Base Reference	
BPV	937 (24)	1.14 (0.83, 1.57)	0.416
OH	140 (4)	1.22(0.63, 2.38)	0.550
OHTN	71 (2)	2.49(1.18, 5.23)	**0.016**
Diastolic blood pressure (DBP)			
Normal stabilisation	2703 (70)	Base Reference	
BPV	974 (25)	1.06 (0.77, 1.47)	0.702
OH	134 (4)	1.41(0.74, 2.68)	0.299
OHTN	71 (2)	2.57 (1.23, 5.41)	**0.013**

Key: AMD, age related macular degeneration; SR, self-report; CVD, cardiovascular diseases; CI, confidence interval; BP, blood pressure; BPV, impaired BP variability; OH, orthostatic hypotension; OHTN, orthostatic hypertension, BMI, body mass index.
Bold data statistically significant at the 5% level.
[a] Adjusted for age, sex, level of education, smoking, alcohol problem, bmi (centred at group mean of 28.5 kg/m^2) family history of age-related macular degeneration, self-reported diabetes and self-reported cataract an interaction term between objective hypertension/on antihypertensives.

4.3. Multivariate association between AMD and phenotypes of orthostatic BP behaviour

4.4. Multivariate logistic regression: phenotypes of sustained OBP response (30–110s)

Table 2 presents the fully adjusted multivariate logistic regression model of the association between OPB phenotypes and AMD. After 30 s, examining the 3 distinct phenotypes of BPV, OH and OHTN compared to normal response, individuals with either SBP or DBP OHTN have more than twice the odds of having AMD than those with normal stabilisation. The reduced models which were fitted, although not presented, showed there was no attenuation of the association for either SBP$_{OHTN}$ or DBP$_{OHTN}$, after adjusting for family history of AMD in addition to demographics and heath behaviours, nor after additionally adjusting for SR cataract and diabetes and in particular, no attenuation after adjustment for the interaction term objective hypertension and antihypertensives. There was no evidence of an interaction between the OBP phenotypes and 1) age either as a categorical or continuous variable 2) objective hypertension or 3) prescribed antihypertensives 4) the interaction term between objective hypertension and antihypertensives.

4.5. Multivariate logistic regression: examining for heterogeneity of effect of OHTN between normotensive participants and those with systolic hypertension

In those who were normotensive and not taking antihypertensives, OHTN was strongly associated with increased odds of AMD; SBP$_{OHTN}$ OR, 4.9; 95% CI, 1.6–15; p, 0.006 and DBP$_{OHTN}$ OR, 3.7; 95% CI, 1.4–10; p, 0.011. This finding was independent of demographics, health behaviours, family history of AMD, SR diabetes and cataract. Comparing then 1) the group who had objective hypertension in the health assessment but were not taking antihypertensives and 2) those taking antihypertensives to this reference normotensive group, the relative odds ratios were not statistically significant. Thus, there was no evidence of heterogeneity of effect of OHTN across groups with

Table 3
Comparing baseline characteristics of those not on antihypertensives and clinically normotensive to those with objective hypertension but not on antihypertensives and those on antihypertensives in the study population.

	No objective hypertension	Objective hypertension No antihypertensives	On antihypertensives (with and without objective hypertension)
Total $N = 3739$	$N = 1686$	$N = 881$	$N = 1172$
Demographics			
Age, mean (SD)	58 (7)	61 (8)	64 (8)***
Female, N (%)	1070 (64)	409 (46)	588 (50)***
Tertiary education, N (%)	708 (42)	405 (46)	471 (40)***
Health behaviours			
Previous smoker, N (%)	600 (36)	338 (38)	512 (44)
Current smoker, N (%)	274 (16)	141 (16)	137 (12)***
Alcohol problem, N (%)	211 (14)	127 (16)	144 (14)
BMI in kg/m^2, mean (SD)	27 (4)	29 (5)	30 (5)***
Cardiovascular conditions			
Self-reported diabetes, N (%)	50 (3)	27 (3)	153 (13)***
Self-reported high cholesterol, N (%)	583 (35)	303 (34)	650 (56)***
Self-reported angina, N (%)	13 (1)	5 (1)	134 (11)***
Self-reported myocardial infarction, N (%)	18 (1)	4 (1)	110 (9)***
Self-reported transient ischemic attack, N (%)	15 (1)	5 (1)	40 (3)***
Self-reported stroke, N (%)	9 (1)	1 (0.1)	32 (3)***
Supine systolic blood pressure pre stand	128 (18)	149 (21)	137 (23)***
Supine diastolic blood pressure pre stand	71 (10)	79 (11)	73 (11)***
Systolic OBP phenotypes			
Normal Stabilisation, N (%)	1293 (77)	596 (68)	758 (65)
Impaired blood pressure variability, N (%)	330 (20)	239 (27)	323 (28)
Orthostatic hypotension, N (%)	41 (2)	32 (4)	59 (5)
Orthostatic hypertension, N (%)	22 (1)	14 (2)	32 (3)***

Key N, number of participants; SD, standard deviation; CI, confidence interval; BMI, body mass index; kg, kilograms.
*** $P < 0.001$.

differing burdens of hypertensive disease. The baseline characteristics of these groups are presented in Table 3.

5. Discussion & conclusions

Individuals with systolic OHTN, defined as ≥20 mm Hg above supine SBP at 30 s–110 s after standing, had more than twice the odds of having AMD compared to those with normal BP stabilisation. Diastolic OHTN from 30 s onwards, defined as ≥10 mm Hg above supine DBP, was also associated with a similarly increased rate of AMD. To our knowledge, no such association has been reported in the literature previously. However, there is research that asserts that OHTN may be a new haemodynamic cardiovascular risk factor (Kario, 2013). Equally there is research investigating the role of vascular risk factors and atherosclerosis in pathogenesis of AMD (Feigl, 2009). OHTN has to date been associated with lacunar stroke (Yatsuya et al., 2011), coronary artery disease (Nardo et al., 1999), peripheral artery disease (Fan et al., 2010) and chronic kidney disease; and now AMD. Whether OHTN is an independent cause of target organ pathology or a biomarker of CV risk or early CVD disease requires and warrants further study. Nevertheless, this study supports the contention that BP dysregulation and vascular risk have an important role in AMD.

This is the first population study to define OHTN using digital photoplethysmography. Nevertheless our 2% prevalence of $OHTN_{SBP}$ (≥20 mm Hg), is comparable to the 2.4% prevalence of $OHTN_{SBP}$ (> 20 mm Hg) in the largest population study to date (BP measured oscillometrically) which investigated epidemiology of OBP dysregulatory behaviour (Yatsuya et al., 2011). Mechanisms of OHTN are not fully elucidated, however it has been postulated that cardiopulmonary or arterial baroreceptor reflex hyperactivity in response to the transient drop in BP caused by orthostasis and consequent reduced renal blood flow, triggers hyperactivation of the sympathetic nervous system. Predominant alpha adrenergic over beta-adrenergic activation increases vasoconstriction of resistance arteries and the result is OHTN (Kario, 2013).

OHTN may represent pre-hypertension (Kario, 2013). In the CARDIA study (ages18–30 yrs), those who were normotensive but had OHTN, had increased odds of developing hypertension during an 8 year follow-up (Thomas et al., 2003). In the HARVEST study, diastolic OHTN in those with stage 1 hypertension was associated with higher daytime BP (Vriz et al., 1997). OHTN has also been linked to other variants of dysregulated BP such as exaggerated morning BP surge (Kario et al., 2003) and extreme nocturnal dipping of BP (Kario et al., 1998) both which have been associated with increased stroke risk in the morning waking hours (Yano and Kario, 2012; Cohen and Townsend, 2014). Traditional CV risk factors that contribute to developing hypertension and indeed hypertension itself are also considered risk factors for AMD, namely smoking, diabetes, hypertension, obesity, dyslipidemia, previous cardiovascular disease and stroke (Vassilev et al., 2015; Klein et al., 2004; Wong and Mitchell, 2007; Jonasson et al., 2014; Ikram et al., 2012). Hence, it is clinically plausible that OHTN, a potential CV risk factor, would be implicated in risk of AMD.

This study suggests OHTN and objective hypertension may not be on the same pathway for increased AMD risk. Neither objective hypertension (which could partially be a measurement of white coat hypertension as well as untreated hypertension) nor antihypertensives were independently associated with increased risk of AMD in our fully adjusted models. Although the interaction term between the two was significant (OR 0.5; 95% CI 0.3, 0.9; $p = 0.016$) it did not attenuate the association between OHTN and individuals' increased risk of AMD. Furthermore, there was no evidence of heterogeneity of OHTN effect, between those participants who were normotensive, compared to those with white coat or untreated hypertension and those taking antihypertensives. It is important to consider however, that we obtained only imprecise relative odds ratio estimates in these subgroups, due to small numbers as demonstrated by the wide 95% CI's (Table 4). This suggests that both OHTN and AMD may develop before CV events such as stroke or MI which is consistent with research that has found an

Table 4
Multivariate logistic regression of the association between age-related macular degeneration (AMD) and phenotypes of OBP behaviour, adjusting for demographics, health behaviours, family history of AMD, SR diabetes and cataracts; and examining an interaction between subgroups of hypertensive disease and OBP.[a]

	AMD								
	No objective hypertension not on antihypertensives $N = 1734$			Objective hypertension Not on antihypertensives $N = 912$			On antihypertensives (with or without objective hypertension) $N = 1220$		
	N (%)	Odds ratio (95% CI)	P	N (%)	Relative odds ratio (95% CI) vs. those with neither objective hypertension nor taking antihypertensives.	P (heterogeneity)	N (%)	Relative Odds Ratio (95% CI) vs. those with neither objective hypertension nor taking antihypertensives	P (heterogeneity)
Orthostatic recovery BP phenotype									
Systolic blood pressure (SBP)									
Normal stabilisation	1325 (76)	Base reference		612 (67)	1.37 (0.88, 2.14)	0.164	787 (65)	1.37 (0.89, 2.10)	0.149
BPV	343 (20)	1.27 (0.74, 2.19)	0.390	250 (27)	1.00 (0.45, 2.22)	0.999	339 (28)	0.74 (0.35, 1.57)	0.429
OH	44 (3)	0.53 (0.07, 3.98)	0.539	34 (4)	3.19 (0.32, 31.90)	0.324	61 (5)	2.21 (0.24, 20.2)	0.481
OHTN	22 (1)	4.91 (1.56, 15.44)	0.006	16 (2)	0.21 (0.02, 2.26)	0.198	33 (3)	0.37 (0.08, 1.85)	0.229
Diastolic blood pressure (DBP)									
Normal stabilisation	1280 (74)	Base Reference		264 (29)	1.15 (0.73, 1.80)	0.545	809 (66)	1.19 (0.78, 1.80)	0.422
BPV	376 (22)	0.75 (0.40, 1.38)	0.351	605 (66)	1.78(0.76, 4.17)	0.182	327 (27)	1.54 (0.69, 3.42)	0.289
OH	47 (3)	0.84 (0.20, 3.61)	0.818	25 (3)	3.19 (0.48, 21.03)	0.228	62 (5)	1.46 (0.26, 8.11)	0.667
OHTN	31 (2)	3.72(1.36, 10.23)	0.011	18 (2)	1.04 (0.20, 5.46)	0.961	22 (2)	0.17 (0.02, 1.75)	0.137

Key: AMD, age related macular degeneration; CVD, cardiovascular diseases; CI, confidence interval; BP, blood pressure; BPV, impaired BP variability; OH, orthostatic hypotension; OHTN, orthostatic hypertension, BMI, body mass index.

[a] Adjusted for age, sex, level of education, smoking, alcohol problem, BMI, self-report (SR) diabetes, cataract, family history of AMD and an interaction term between OBP phenotypes and the categorical variable which divided the population for analysis into groups of normotensive and hypertensive disease.

association between a diagnosis of AMD and risk of future vascular events, such as stroke (Ikram et al., 2012) and myocardial infarction (Duan et al., 2007).

Apart from shared risk factors, an association between OHTN and AMD is credible for other reasons. It has been found that there is age-related impairment in autoregulation of the choroidal circulation (Grunwald et al., 1998), which is under the control of the autonomic nervous system (Kur et al., 2012). In both exudative and non-exudative AMD, impairment in the choroidal circulation has been identified (Mori et al., 2001; Xu et al., 2010). In exudative AMD, neovascularisation has been found to preferentially occur within submacular choroidal watershed zones (WZ) (Mendrinos and Pournaras, 2009). Therefore the suboptimally regulated choroidal circulation may vulnerable to dysregulated BP behaviour, included OHTN, particularly in WZ's, with increasing age.

AMD may be a localized ocular manifestation of a wider systemic process, suggested by associations between AMD and chronic kidney disease and neurodegenerative conditions (Cheung and Wong, 2014) such as Alzheimer's disease (AD). AD patients have poorer vision and a higher occurrence of AMD when compared to controls (Nolan et al., 2014). Both pathologies involve amyloid deposition, inflammation and oxidative stress (Sivak, 2013) and share risk factors and genetic polymorphisms. Of note, OH is three to five times more frequent in AD and vascular dementia compared to healthy age-matched controls (Mehrabian et al., 2010) leading to speculation that unstable blood pressure and impaired cerebral autoregulation may play a role in pathogenesis of cognitive impairment and dementia (Kennelly et al., 2012; Hayakawa et al., 2015). Now this study links OHTN and AMD. Such multidirectional connections between OBP, AMD and AD, supports our hypothesis that age related CV dysregulation may be a key component of a wider systemic process influencing age-related end–organ pathology.

Our study had some limitations, predominantly the cross-sectional design; hence, casual inferences cannot be made. Secondly there may be some selection bias for those identified with AMD, as those TILDA participants who did not attend the health assessment and therefore excluded from this study, were older and frailer (Akuffo et al., 2017). Retinal photographs were taken through undilated pupils. In our sample prevalence of late AMD was low (< 1%) hence we did not have enough power to examine potential differences in relationship between early and late AMD and OHTN. Limitations relating to the objective beat-to-beat BP measurement have previously been described (NiBhuachalla et al., 2015; Finucane et al., 2014) for example those participants were not fasting. However, this is unlikely to have significantly influenced our results (Fan et al., 2012). Our study has several strengths. We used a large nationally representative population sample with detailed clinical cardiovascular health and ophthalmic measures, not available in other longitudinal studies, in particular beat-to-beat OBP data from digital photoplethysmography, retinal photographs, VA and CS.

In conclusion, individuals with systolic and diastolic OHTN had increased rates of AMD compared to those with normal stabilisation with odds ratios (OR) of 2.5 and 2.6 respectively, independent of objective hypertension and other recognised risk factors for the AMD. The increased risk was greatest in normotensive individuals not taking antihypertensives. OHTN is potentially modifiable and easily assessed in an outpatient clinical setting while AMD is the primary cause of blindness in industrialised countries (World Health Organisation, 2010). Hence, we argue this is an area that warrants further research. A case control study in a clinical setting that had available measures, such as fluorescein and indocyanine green angiography, optical coherence tomography and fundus autofluorescence, would help inform any

associations between OHTN, changes in the choroidal and retinal circulation and AMD.

Conflicts of interest statement and acknowledgements

The authors report no conflicts of interest. Informed consent was obtained for all participants, and all protocols and procedures were approved by the institutional review board. TILDA is funded by The Atlantic Philanthropies, Irish Life Plc and the Irish Government. Dr Peto was funded by the NIHR BMRC at Moorfields Eye Hospital Foundation Trust and the UCL Institute of Ophthalmology. No funder played a role in the design, execution, analysis and interpretation of data or in the writing of this paper. The authors would like to thank all the participants in the study, the TILDA research, the team of interviewers and the study nurses and administrators.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2018.02.029.

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