Experimental Gerontology 119 (2019) 14–24

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Orthostatic blood pressure variability is associated with lower visual contrast sensitivity function: Findings from The Irish Longitudinal Study on Aging

Bláithín Ní Bhuachalla[a], Christine A. McGarrigle[b,*], Neil O'Leary[b], Kwadwo Owusu Akuffo[c], Tunde Peto[d], Stephen Beatty[e], Rose Anne Kenny[a,b]

[a] Department of Medical Gerontology, School of Medicine, Trinity College Dublin, The University of Dublin, Old Stone Building, Trinity Centre for Health Sciences, St James's Hospital, James's Street, Dublin 8, Ireland
[b] The Irish Longitudinal Study on Aging (TILDA), Lincoln Gate, Trinity College Dublin, The University of Dublin, College Green, Dublin 2, Ireland
[c] Department of Optometry and Visual Science, College of Science, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana
[d] Head of Reading Centre, Department of Research and Development, National Institute of Health Research Biomedical Research Centre at Moorfields Eye Hospital National Health Service Foundation Trust and UCL Institute of Ophthalmology, London, United Kingdom
[e] Macular Pigment Research Group, Vision Research Centre, Carriganore House, Waterford Institute of Technology, Waterford, Ireland

ARTICLE INFO

Section Editor: Borg Holly M Brown

Keywords:
Eye
Contrast sensitivity
Blood pressure variability
End-organ damage
Orthostatic hypotension
Orthostatic hypertension

ABSTRACT

Background: Hypertension is established to cause vascular end-organ damage. Other forms of dysregulated blood pressure (BP) behaviour, such as orthostatic hypotension have also been associated with cardiovascular (CV) events. The eye is potentially vulnerable to dysregulated systemic BP if ocular circulation autoregulation is impaired. We investigated whether phenotypes of abnormal BP stabilisation after orthostasis, an autonomic stressor, had a relationship with contrast sensitivity (CS), an outcome measure of subtle psychophysical visual function.

Methods: This was a cross-sectional study from wave 1 of The Irish Longitudinal Study on Ageing (TILDA). From beat-to-beat orthostatic BP (BP), measured by digital photoplethysmography during active stand, 4 phenotypes have been defined 1) normal stabilisation 2) orthostatic hypotension, 3) orthostatic hypertension 4) BP variability. Contrast sensitivity was measured using a Functional Visual Analyzer. Multivariable linear regression models investigated the relationship between orthostatic BP phenotypes and contrast sensitivity in 4289 adults aged ≥50 years adjusting for, demographics, cardiovascular risk factors, self-reported eye pathologies, objective hypertension and antihypertensives. A sensitivity analysis adjusted for age-related macular degeneration, glaucoma, diabetic retinopathy and maculopathy identified on retinal photographs. Finally models were compared, adjusting for alternative measures of cataract versus not, to examine the potential effect of cataract on any associations.

Results: Systolic orthostatic BP variability was associated with worse contrast sensitivity, in the primary and the sensitivity analysis. Adjusting for alternative measures of clinical cataract attenuated the association by 18%.

Conclusions: Orthostatic BP variability is associated with worse contrast sensitivity, independent of hypertension and retinal pathology and may be a cardiovascular biomarker of early ocular pathology.

1. Introduction

Orthostasis is an established autonomic stressor; hence, evaluation of orthostatic blood pressure (BP) behaviour during active stand provides valuable data regarding dysregulation of the cardiovascular system. Age-related normograms of beat-to-beat OBP response find that in adults aged 50–59 years, orthostatic BP stabilises to resting supine BP by 30 s (Finucane et al., 2014). A pattern of non-stabilisation of orthostatic BP such as orthostatic hypotension is familiar to many physicians. Classical orthostatic hypotension, by consensus definition, is identified as a sustained reduction in systolic BP (SBP) of at least 20 mmHg and/or diastolic BP (DBP) of 10 mmHg within 3 min of standing (Freeman et al., 2011). However, this definition is based on sphygmomanometer (cuff measurement) and not beat-to-beat

* Corresponding author.
E-mail addresses: nibhuacb@tcd.ie (B. Ní Bhuachalla), Christine.McGarrigle@tcd.ie (C.A. McGarrigle), olearyne@tcd.ie (N. O'Leary), akuffokwadwoowusu@knust.edu.gh (K.O. Akuffo), Tunde.Peto@moorfields.nhs.uk (T. Peto), sbeatty@wit.ie (S. Beatty), rkenny@tcd.ie (R.A. Kenny).

https://doi.org/10.1016/j.exger.2019.01.009
Received 3 April 2018; Received in revised form 8 January 2019; Accepted 10 January 2019
Available online 22 January 2019
0531-5565/

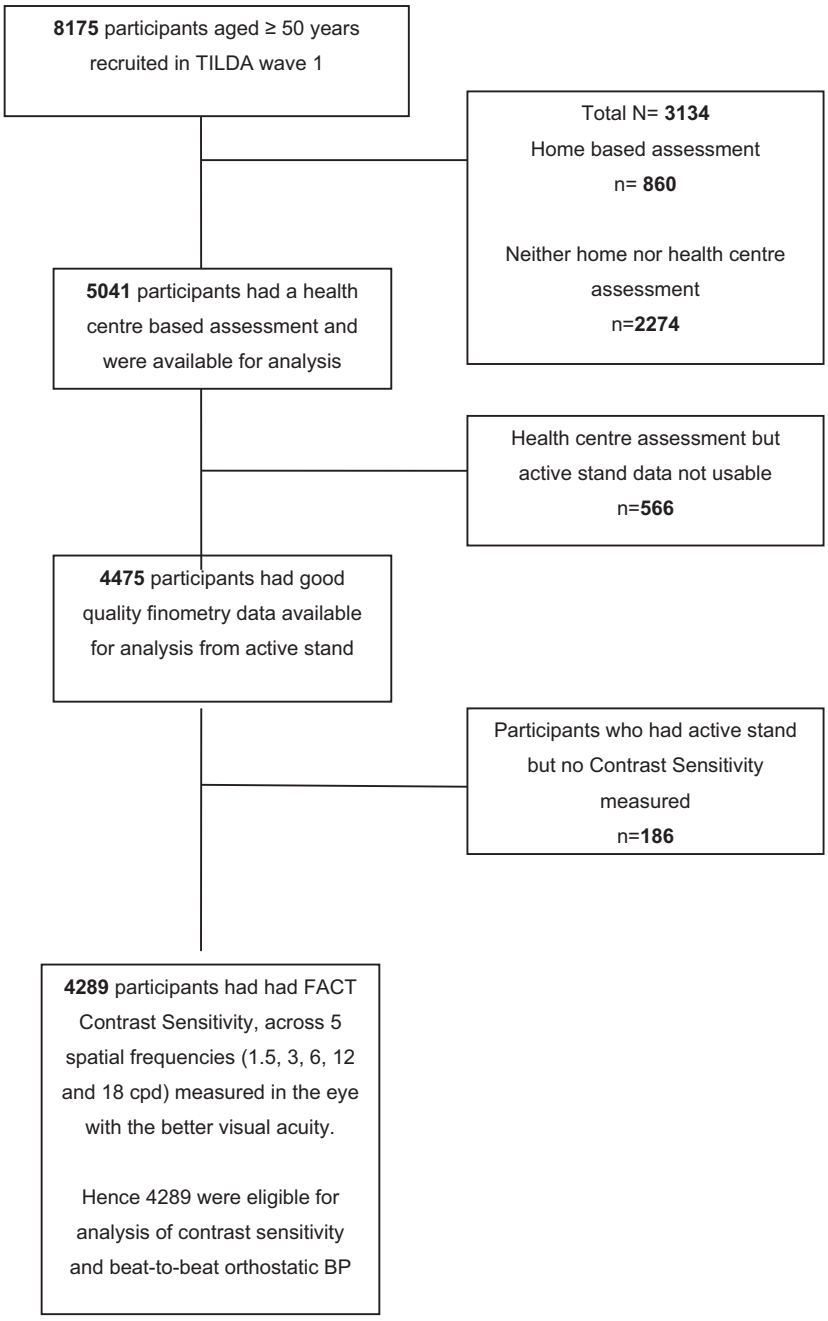


Fig. 1. Sample for analysis.
Key: TILDA, the Irish Longitudinal Study on Ageing; FACT, functional acuity contrast test; cpd, cycles per degree.

continuous (phasic) measurement of BP. Other patterns of orthostatic BP behaviour are less often considered, such as orthostatic hypertension (OHTN) and orthostatic blood pressure variability (BPV) and do not have consensus definitions. Orthostatic hypertension is defined by elevation in BP on standing ranging from 5 to 20 mmHg from supine BP or by the development of hypertension on standing i.e. a change in SBP from < 140 mmHg to ≥ 140 mmHg after adopting upright posture (Kario, 2013). Blood pressure variability is defined according to different time periods: a) very short intervals (beat-to-beat variability), b) short intervals over 24 h, c) diurnal variation over 24 h and longer time intervals, including d) day-to-day variability and e) visit-to-visit variability, typically over months to years (Eguchi, 2014). Orthostatic hypotension, orthostatic hypertension and some forms for BP variability, although not orthostatic BP variability, have all been associated with cardiovascular disease. Orthostatic hypotension has been associated with an increased risk of cardiovascular events and overall

mortality (Angelousi et al., 2014); orthostatic hypertension with lacunar stroke (Yatsuya et al., 2011) and coronary artery events (Nardo et al., 1999) and there is accumulating evidence that BP variability predicts risk of stroke and other vascular events independent of mean BP (Rothwell, 2011).

In an earlier study, we have identified and defined four distinct phenotypes of orthostatic BP behaviour in the 30 s–110 s after standing; 1) normal stabilisation (recovery of SBP/DBP back to within 20/10 mmHg of supine SBP/DBP pre-stand (70%) 2) persistent orthostatic hypotension (4%) 3) persistent orthostatic hypertension (2%) and 4) orthostatic BP variability (25%). In a sample with excellent or good quality retinal photographs, BP variability was associated with worse visual acuity (logMAR scale) independent of demographics, health behaviours, existing eye pathology, objective hypertension and prescribed antihypertensives (Ní Bhuachalla et al., 2015). This relationship between visual acuity and abnormal orthostatic BP behaviour has not been previously reported, although it is biologically plausible that fluctuations and instability in systemic BP could affect choroidal blood flow given that the choroid circulation itself is predominantly regulated by the autonomic nervous system. Furthermore, orthostatic hypertension was also found to be associated with age related macular degeneration (AMD) (Ní Bhuachalla et al., 2018).

Contrast sensitivity is a measure of how faded an image can become, before it is indistinguishable from the uniform field. It is dependent on the ocular optics, the retina and the brain (Wong and Hyman, 2008). In many ocular diseases, Contrast sensitivity is impaired earlier than visual acuity. Contrast sensitivity was found to have high specificity as a tool for diagnosis of early glaucoma in patients with good visual acuity (Onal et al., 2008). The independent association of orthostatic BP variability with worse visual acuity suggests instability in orthostatic BP may influence the eye (Ní Bhuachalla et al., 2015). In this study, we aimed to establish if abnormal stabilisation of orthostatic BP, namely any of the phenotypes: orthostatic hypotension, orthostatic hypertension or BP variability, was associated with contrast sensitivity, a more subtle measure of psychophysical visual function, following adjustment for confounders including clinical evidence of hypertension, self-reported and clinical eye pathology. We also aimed to characterise the cardiovascular profile associated with these orthostatic BP phenotypes.

2. Methods

2.1. Study design and participants

This study is based on data from the first wave (October 2009 to July 2011) of the Irish Longitudinal Study on Ageing (TILDA) (TILDA, http://www.tcd.ie./tilda/). In Wave 1, social, economic and health data from 8175, nationally representative, community dwelling adults aged ≥50 years (Kenny, 2013) was collected. The methodology has been published previously (Kearney et al., 2011), but briefly, participants were selected using a multi-stage stratified random sampling methodology using the Irish Geodirectory of all residential houses in Ireland as a sampling frame. In total, 640 geographical areas, stratified by socio-economic characteristics were selected and 40 households within each area. All household residents aged over 50 years, and their spouse/partner were eligible to participate. The overall response rate in Wave one was 62% (Kenny, 2013).The study has three components; a home-based computer-assisted personal interview (CAPI) administered by trained social researchers, a self-completion questionnaire (SCQ) and either a home or a health centre assessment administered by trained research nurses. The CAPI included questions on socio-demographic characteristics, health and health behaviours. The health centre-based assessments included detailed measurements of vision and beat-to-beat BP and heart rate behaviour. In total, 62% participated in a health centre assessment (n = 5041), of whom 4475 had beat-to beat BP data collected during active stand. Visual acuity was measured in both eyes independently in 4907 individuals. In the eye with the better vision, contrast sensitivity was then measured, across five spatial frequencies. Thus, the total sample eligible for analysis, including both data from active stand and contrast sensitivity was 4289 individuals (Fig. 1). Ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee of Trinity College, Dublin. All respondents provided signed informed consent prior to participation. All experimental procedures adhered to the Declaration of Helsinki.

2.2. Visual function measures

2.2.1. LogMAR visual acuity

In the health centre assessment, 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. From a fixed distance of 4 m away, different ETDRS charts were read for each eye, under standardised illumination. Participants were asked to wear their glasses if they usually wore glasses for distance vision and this was documented (Ní Bhuachalla et al., 2015).

2.2.2. Contrast sensitivity

Spatial contrast sensitivity was assessed at five spatial frequencies [1.5, 3, 6, 12 and 18 cycles per degree (cpd)] in the eye with the better VA using the Optec® Functional Vision Analyzer™ (Stereo Optical Co. Inc., Chicago, IL) which utilises the Functional Acuity Contrast Test (FACT). The device presented sinusoidal gratings in the form of Gabor patches to the respondent. For each spatial frequency, a series of nine patches were presented with a 0.15 log unit or 50% loss of contrast between consecutive patches. Gratings were tilted to the left (+15°), right (−15°) or upright (0°) to keep them within the bandwidth of the visual channel. The respondent indicated the direction of grating tilt for each patch without guessing. The test was conducted under mesopic or nighttime conditions (3.0 cd per meter square [cd/m^2]) without glare. Impairment in contrast sensitivity, detected under mesopic conditions, may not be evident under photopic conditions; hence this lighting condition was chosen to optimally detect more subtle impairment in contrast sensitivity (Hertenstein et al., 2016). The contrast sensitivity score corresponds to the contrast of the last grating that was accurately identified on each row. If a participant could identify no grating on a particular row, the FACT numerical score was zero for that row. Thus, for each individual, we collected 5 contrast sensitivity measures, one for each spatial frequency.

From the contrast sensitivity, the area under the log contrast sensitivity function was determined, using a previously described methodology (Applegate et al., 1998). Each contrast sensitivity score was converted to $\log_{10}$ contrast sensitivity score (representing a participant's threshold contrast sensitivity for that spatial frequency). The $\log_{10}$ contrast sensitivity score was plotted as a function of log spatial frequency at each of the 5 spatial frequencies (1.5–18 cpd), and generated a contrast sensitivity function (CSF) curve for each participant. The CSF maps out the threshold between visible and invisible across the 5 spatial frequencies and therefore represents global visual function for that individual. The fitted function was integrated between the fixed limits of log spatial frequencies of 0.18 (corresponding to 1.5 cpd) and 1.26 (corresponding to 18 cpd), and the resultant value was defined as the area under the log CSF (AULCSF). Hence, all 5 available contrast sensitivity scores for each participant were utilised, creating a single contrast sensitivity measure representing all 5 spatial frequencies, which was easier to analyse and interpret.

2.2.3. Retinal morphology assessment

One 45° monoscopic colour photograph, centred on the macula (EDTRS standard field 2), was obtained for each eye, using a NIDEK AFC-210 non-mydriatic auto-fundus camera, through a non-dilated pupil. The retinal photographs were graded in a masked fashion using standard protocols by a grader (K.O.A.), trained and certified at the Moorfields Eye Hospital (MEH) Reading Centre, London, United

Table 1
Demographics and health characteristics of study sample.

	N = 4289
Demographics	
Age, mean (SD)	61.5 (8.2)
Female, N (%)	2306 (54)
Received tertiary education, N (%)	1608 (38)
Health behaviours	
Current smoker N (%)	629 (15)
Alcohol problem, 'CAGE', N (%)	562 (14)
BMI in kg/m^2, mean (SD)	28.5 (4.9)
Cardiovascular conditions	
Hypertension, N (%)	1665 (39)
On any antihypertensive (ATC code C02, CO3, CO7-CO9), N (%)	1389 (32)
Self-report diabetes, N (%)	271 (6)
Self-report hypercholesteraemia, N (%)	1757 (41)
Self-report angina, N (%)	185 (4)
Self-report myocardial infarct, N (%)	164 (4)
Self-report Heart Failure, N (%)	33 (0.8)
Self-report TIA, N (%)	70 (2)
Self-report stroke, N (%)	47 (1)
NCVI related conditions	
Self-report ever fainted/LOC, N (%)	838 (20)
Self-report any LOC past year, N (%)	194 (5)
Self-report any fall in the past year, N (%)	834 (20)
Orthostatic intolerance, N (%)	1640 (38)
Eye disease related conditions	
Self-report glaucoma, N (%)	80 (2)
Self-report cataract, N (%)	340 (8)
Self-report AMD, N (%)	66 (2)
Self-Rated Impaired Vision, N (%)	323 (8)
Wore prescribed glasses during assessment of visual acuity, N (%)	1622 (66)
Better eye: LogMAR VA, mean (SD)	0.06 (0.18)
Area $\log_{10}$ CSF curve, mean (SD)	1.28 (0.36)
$\log_{10}$ contrast sensitivity at spatial frequency 1.5 cpd,mean (SD)	1.51(0.25)
$\log_{10}$ contrast sensitivity at spatial frequency 3 cpd,mean (SD)	1.78 (0.27)
$\log_{10}$ contrast sensitivity at spatial frequency 6 cpd,mean (SD)	1.29 (0.59)
$\log_{10}$ contrast sensitivity at spatial frequency 12 cpd,mean (SD)	0.51 (0.59)
$\log_{10}$ contrast sensitivity at spatial frequency 18 cpd, mean (SD)	0.10 (0.26)

Key: SD, standard deviation; CI, confidence interval; CAGE, Cut down, Annoyed, Guilty, Eye-opener; BMI, body mass index; kg, kilograms; ATC; Anatomical Therapeutic Classification; TIA, transient ischemic attack; NCVI, Neurocardiovascular Instability; LOC, loss of consciousness; AMD, age-related macular degeneration; VA, visual acuity; logMAR, Logarithm of the Minimum Angle of Resolution; $\log_{10}$, logarithm to the base 10; CSF, contrast sensitivity function.

Kingdom (www.readingcentre.org). Grading was conducted under the supervision of the MEH Reading centre lead ophthalmologist (T.P). Photographs were assessed and classified by quality (Akuffo et al., 2015). Objective evidence of the following conditions was identified: age-related macular degeneration (AMD), glaucoma, diabetic retinopathy and diabetic maculopathy. The TILDA AMD protocol has been previously described (Akuffo et al., 2015). DR/DM was graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) classification (Early Treatment Diabetic Retinopathy Study Research Group, 1991). Glaucoma was graded as normal or suspicious based on the presence of notching, disc haemorrhage, or vertical cup to disc ratio > 0.6.

2.3. Orthostatic blood pressure measurement

The active stand is a lying-to-standing test during which non-invasive beat-to-beat BP is measured using digital photoplethysmography (Finometer® MIDI device, Finapres Medical Systems BV, Amsterdam, The Netherlands, http://www.finapres.com). The active stand protocol has been described previously (Romero-Ortuno et al., 2013). Respondents first rested supine for 10 min. Then immediately after prompting, independently stood, the monitored arm extended by the side, remaining still and silent. Systolic BP (SBP), diastolic BP (DBP) and heart rate were monitored for 3 min. The following measures were recorded from the active stand: supine SBP and DBP, which were defined as the mean value in the time interval 60 to 30 s prior to standing; SBP, DBP and heart rate at the time of the nadir BP (i.e. the lowest BP value after standing); and SBP, DBP and heart rate at each

Table 2
Differences in area under the $\log_{10}$ contrast sensitivity function integrated across five spatial frequencies (1.5, 3, 6, 12 and 18 cycles per degree) within different subgroups of demographic and of health characteristics of the sample for analysis.

	Area under the $\log_{10}$ contrast sensitivity function mean (standard deviation)	
Full sample	1.28 (0.36)	†
Demographics		
Gender		***
Male	1.31 (0.37)	
Female	1.25 (0.35)	
Age-group		***
50–64 years	1.34 (0.35)	
65–74 years	1.21 (0.35)	
≥75 years	1.01 (0.34)	
Highest level of education achieved		***
Primary	1.20 (0.36)	
Secondary	1.28 (0.36)	
Tertiary	1.32 (0.36)	
Health behaviours		
Smoking status		
Never smoked	1.28 (0.36)	
Ex smoker	1.28 (0.36)	
Current smoker	1.25 (0.35)	
Alcohol problem (CAGE 2+)		**
No	1.27 (0.36)	
Yes	1.32 (0.35)	
Vision related variables		
Visual acuity (logMAR)		***
Normal visual acuity	1.35 (0.33)	
Mild visual acuity loss	1.05 (0.36)	
Moderate/severe visual acuity loss	0.92 (0.45)	
Self-report glaucoma		**
No	1.28 (0.36)	
Yes	1.17 (0.36)	
Self-report cataract		***
No	1.29 (0.36)	
Yes	1.08 (0.36)	
Self-report age-related macular degeneration		***
No	1.28 (0.36)	
Yes	1.09 (0.38)	
Self-report visual function		***
Good	1.29 (0.36)	
Impaired	1.16 (0.39)	
Wore glasses for visual acuity		***
No	1.15 (0.39)	
Yes	1.29 (0.34)	
Cardiovascular conditions		
Clinical hypertension		**
No	1.30 (0.36)	
Yes	1.25 (0.37)	
On antihypertensives		**
No	1.30 (0.36)	
Yes	1.23 (0.37)	
Self-report diabetes		***
No	1.28 (0.36)	
Yes	1.18 (0.36)	

† Oneway ANOVA,Testing for Differences in area under the $\log_{10}$CSF curve (integrated across 5 spatial frequencies 1.5, 6,8,12 and 18 cycles per degrees) across subgroups within demographics, health behaviours, vision and cardiovascular conditions.
Key: FACT, Functional Acuity Contrast Test; $\log_{10}$,logarithm to the base 10; CAGE, Cut down, Annoyed, Guilty, Eye-opener; VA, visual acuity; logMAR, Logarithm of the Minimum Angle of Resolution.
** $P < 0.01$.
*** $P < 0.001$.

Table 3
Prevalence of orthostatic blood pressure phenotypes including predicted prevalence in Irish population ≥50 years (after applying appropriate sampling weights).

	N *N* = 4355	Prevalence of orthostatic BP phenotypes in sample analysed in study	Predicted prevalence of orthostatic BP phenotypes in Irish population ≥50 years
		Proportion of population % (95% CI)	Proportion of population % (95% CI)
SBP			
Normal stabilisation	2993	69.78 (68.42, 71.16)	67.70 (65.64, 69.75)
BP variability	1054	24.57 (23.29, 25.86	25.58 (23.70, 27.46)
Orthostatic hypotension (OH)	159	3.71 (3.14, 4.27)	4.71 (3.58, 5.85)
Orthostatic hypertension (OHTN)	83	1.94 (1.52, 2.35)	2.02 (1.43, 2.60)
DBP			
Normal stabilisation	2979	69.46 (68.08, 70.84)	68.69 (66.69, 70.70)
BP variability	1065	24.83 (23.54, 26.12)	24.89 (23.03, 26.75)
Orthostatic hypotension (OH)	167	3.89 (3.31, 4.47)	4.77 (3.73, 5.80)
Orthostatic Hypertension (OHTN)	78	1.82 (1.42, 2.22)	1.65 (1.23, 2.06)

Key: SBP, systolic blood pressure; BP, Blood pressure; DBP, diastolic blood pressure.

Table 4
Characteristics of systolic orthostatic blood pressure phenotypes in sample for analysis.

	Normal stabilisation N (%) 2993 (70)	BP variability N (%) 1054 (24)	Orthostatic hypotension N (%) 159 (4)	Orthostatic hypertension N (%) 83 (2)	
Age, mean (SD)	60 (8)	64 (8)	66 (9)	64 (8)	***
Female, N (%)	1540 (52)	617 (59)	105 (66)	44 (53)	***
Tertiary level education, N (%)	1145 (38)	381 (36)	49 (31)	33 (40)	***
Current smoker, N (%)	445 (15)	147 (14)	26 (16)	11 (13)	
Objective hypertension, N (%)	1055 (35)	489 (47)	75 (48)	46 (55)	***
Baseline heart rate, mean (SD)	66 (10)	64 (10)	63 (10)	66 (10)	**
Increase in heart rate at 10s, mean (SD)	15 (7)	13 (7)	10 (6)	15 (6)	***
Beta blockers, N (%)	283 (9)	154 (15)	26 (16)	9 (11)	***
Calcium channel blockers, N (%)	203 (7)	85 (8)	10 (6)	4 (5)	
Thiazide, N (%)	70 (2)	48 (5)	2 (1)	3 (4)	**
ACE inhibitor, N (%)	259 (9)	112 (11)	17 (11)	11 (13)	
ARB, N (%)	172 (6)	83 (8)	8 (5)	11 (13)	**
Frusemide, N (%)	29 (1)	22 (2)	2 (1)	1 (1)	*
Combined tablet: two antihypertensives, N (%)	87 (3)	47 (5)	9 (6)	4 (5)	*
Self-report diabetes, N (%)	168 (6)	86 (8)	10 (6)	7 (8)	*
Self-report myocardial infarction, N (%)	115 (4)	45 (4)	3 (2)	1 (1)	
Self-report stroke, N (%)	26 (1)	16 (2)	3 (2)	2 (2)	
Self-report angina, N (%)	122 (4)	53 (5)	8 (5)	2 (2)	
Self-report TIA, N (%)	34 (1)	24 (2)	9 (6)	3 (4)	***

Key: BP, blood pressure; SD, standard deviation; CI, confidence interval; ACE, angiotensin-converting-enzyme; ARB, angiotension receptor blocker; TIA, transient ischemic attack.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

10 s interval post stand from 10 s to 110 s.

2.3.1. Orthostatic blood pressure behaviour

Beat-to-beat orthostatic BP behaviour from the active stand data from TILDA participants was analysed as previously described (Ní Bhuachalla et al., 2015). We investigated 4 distinct phenotypes 30 s after standing as previously defined (Ní Bhuachalla et al., 2018), 1) normal stabilisation: BP stabilisation (to within 20/10 mmHg of baseline BP) achieved within 30 s, and persisted up to 110 s, 2) orthostatic hypotension: BP between 30 and 110 s of 20 mmHg SBP or 10 mmHg DBP, 3) orthostatic hypertension: an increase from baseline BP between 30 and 110 s of 20 mmHg SBP or 10 mmHg DBP, and 4) orthostatic blood pressure variability: a combination of 20/10 mmHg SBP/DBP overshoot and/or Deficit and/or within 20/10 mmHg of original baseline SBP/DBP pre-stand at 30, 60, 90 or 110 s.

2.4. Other covariates

In multivariable linear regression analyses we controlled for socio-demographic and health behaviour variables, in addition to specific diseases pertinent to the cardiovascular system and the eye. Demographic variables included age, 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). Self-reported health measures included: glaucoma, cataracts, AMD and diabetes, 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. If a participant that usually wore glasses didn't wear them for visual acuity assessment, this was recorded and coded as a binary variable 'wore glasses' yes/no.

Objective BP was measured from sphygmomanometer seated recordings (OMRON™ digital automatic BP monitor) average of two readings. Objective hypertension was defined as SBP > 140 mmHg or DBP > 90 mmHg (Mancia et al., 2007). Vascular risk has been implicated in the pathogenesis of cataract. Cataract would be a confounder of the relationship with reduced contrast sensitivity. We had no clinical measure of cataract in our study. However, we used three alternative measures of clinical cataract to examine potential

Table 5
Multivariable linear regression analyses of the association between phenotypes of orthostatic blood pressure, and area under the $\log_{10}$ contrast sensitivity function, adjusting for demographics, health behaviours, self-report eye diseases, known uncorrected refractive error, self-report diabetes, objective hypertension and individual antihypertensive classes.

	Total sample N = 4289 N (%)	Coefficient[a] (95% CI)	Likelihood ratio test *P* value	*P*
Systolic BP			0.058	
Normal stabilisation	2993 (70)	Base reference		
BP variability	1054 (24)	−0.046 (−0.079, −0.012)		0.008
Orthostatic hypotension	159 (4)	−0.036 (−0.112, 0.040)		0.356
Orthostatic hypertension	83 (2)	−0.010 (−0.105, 0.086)		0.844
Diastolic BP			0.290	
Normal stabilisation	2979 (70)	Base reference		
BP variability	1065 (24)	−0.032 (−0.065, 0.001)		0.060
Orthostatic hypotension	167 (4)	−0.025 (−0.099, 0.049)		0.509
Orthostatic hypertension	78 (2)	−0.007 (−0.110, 0.096)		0.892

Key: N, number of participants; Coefficient, estimated coefficient; CI, confidence interval; BP, blood pressure.
Note: Separate models for Systolic BP and Diastolic BP.
[a] Both models adjusted for age, sex, education, smoking, alcohol intake, SR Glaucoma, self-report Cataracts and self-report Age-Related Macular Degeneration and whether the participant wore glasses for the measurement of logMAR visual acuity if they usually wore glasses for distance vision; Self-Report Diabetes, Objective Hypertension, Beta blockers, Calcium channel blockers, ACE inhibitors, Angiotension receptor blockers, Thiazide, Doxazosin, Frusemide and dual antihypertensive agents.

Table 6
Restricted sample (sensitivity analysis) multivariable linear regression analyses of the association between phenotypes of orthostatic blood pressure, and area under the log contrast sensitivity function, adjusted for demographics, health behaviours, SR cataract, clinical evidence of AMD, glaucoma, diabetic retinopathy and maculopathy, known uncorrected refractive error, objective hypertension and individual antihypertensive classes.

	Total sample *N* = 3731 N (%)	Coefficient[a] (95% CI)	Likelihood ratio test *P* value	*P*
Systolic BP			0.05	
Normal stabilisation	2634 (71)	Base reference		
BP variability	891 (24)	−0.047 (−0.084, −0.010)		0.012
Orthostatic hypotension	137 (4)	−0.031 (−0.115, 0.053)		0.471
Orthostatic hypertension	69 (2)	0.044 (−0.060, 0.148)		0.408
Diastolic BP			0.651	
Normal stabilisation	2604 (70)	Base reference		
BP variability	928 (25)	−0.022 (−0.058, 0.014)		0.230
Orthostatic hypotension	129 (4)	−0.018 (−0.105, 0.068)		0.679
Orthostatic hypertension	70 (2)	0.011 (−0.097, 0.120)		0.839

Key: N, number of participants; Coefficient, estimated coefficient; CI, confidence interval; BP, blood pressure.
Separate models for Systolic BP and Diastolic BP.
[a] Both models adjusted for age, sex, education, smoking, alcohol intake, self-report cataracts and clinical evidence on retinal photographs of glaucoma, age-related macular degeneration, diabetic retinopathy, diabetic maculopathy and whether the participant wore glasses for the measurement of logMAR visual acuity if they usually wore glasses for distance vision; Objective Hypertension, Beta blockers, Calcium channel blockers, ACE inhibitors, Angiotension receptor blockers, Thiazide, Doxazosin, Frusemide and dual antihypertensive agents.

confounding of cataract on any relationship between orthostatic BP and contrast sensitivity and to measure any attenuation of effect following adjustment for these alternative measures. The alternative measures chosen were 1) self-reported cataract 2) abnormal visual acuity ($< 6/6$ or logMAR ≤ 0) and 3) poor quality retinal photographs (one cause of which could be dense cataract).

All medications taken by a participant, were recorded by interviewers after viewing medication packages and assigning WHO Anatomic Therapeutic Chemical (ATC) classification codes (WHO, 2011). Thus each participant's use of antihypertensives were adjusted for in analyses using the following classifications; beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (CO9AA), angiotension receptor blockers (C09CA), frusemide (C03CA01), doxazosin (C02CA04), thiazide diuretics (C03AA), and combination antihypertensive agents i.e. beta blocker/calcium channel blocker combined with a thiazide diuretic (C07, C09).

2.5. Statistical analyses

All statistical analyses were performed with STATA (version 12.0). The data was analysed in five main steps. Firstly, baseline characteristics of the total sample were described. Area under the $\log_{10}$ CSF (AULCSF) was compared between different demographic and health subgroups. Phenotypes of orthostatic BP were characterised for demographics, smoking status, cardiovascular diseases including objective hypertension and individual antihypertensives. Descriptives for dichotomous variables were given as total number (N) and percentage (%). Continuous variables were described as the mean with standard deviation (SD). Continuous variables were compared with the one-way ANOVA test and Chi-square and Fishers exact for categorical data. Prevalence estimates included inverse probability weights (at population level) created by comparing age, sex, education and marital status and geography of participants to their distribution in the Irish census 2011, to account for non-differential selection into the cohort. These weights were modified further to account for probability of taking part in the health assessment. This was necessary as the 4475 individuals

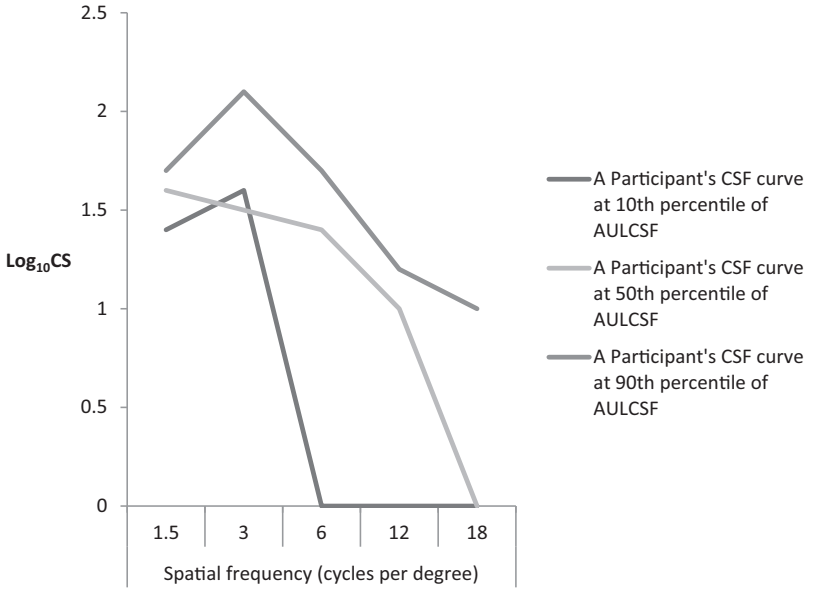


Fig. 2. Exemplar contrast sensitivity function curves across five spatial frequencies, illustrating the contrast sensitivity curves of a participants at the 10th, 50th and 90th percentiles of the area under the log contrast sensitivity function.
Key: Log, logarithm; CSF, contrast sensitivity function; AULCSF, area under the log contrast sensitivity function.

Key: Log, logarithm; CSF, contrast sensitivity function; AULCSF, area under the log contrast sensitivity function

who had good quality active stand data from the health assessment were younger and had less morbidity than those excluded because they could attend the health assessment (Finucane et al., 2014).

Secondly, multivariable linear regression models were used to examine the associations between orthostatic BP phenotypes and contrast sensitivity function (CSF) which is summarised using area under the log CSF scores. The outcome variable was the AULCSF. Orthostatic BP phenotypes variable was categorical with normal BP stabilisation set as the base reference and the model was adjusted for the covariates. Separate analyses were carried out for SBP and DBP. A series of reduced models were fitted initially to achieve the most parsimonious model (data not shown). The final fully adjusted model, was adjusted for socio-demographics, health behaviours (smoking and problematic alcohol intake), self-reported diabetes and self-reported eye pathologies (cataract, glaucoma, AMD), uncorrected refractive error, objective hypertension and individual hypertensive drug classes (beta-blockers, calcium channel blockers, ACE-inhibitors, angiotension receptor blockers, frusemide, doxazosin, thiazide diuretics and combined antihypertensives).

Thirdly, to assess if these associations were moderated by age, objective hypertension and a binary variable 0 “no antihypertensive use” 1 “taking any antihypertensive”, we ran a series of models including the interaction terms to examine whether the association between orthostatic BP phenotypes and area under the log CSF differed significantly by age, objective hypertension or antihypertensive use.

Fourthly, a sensitivity analysis was next carried out to examine if the association between orthostatic BP and area under the log CSF remained when the model was additionally adjusted for clinical evidence of retinal pathology on retinal photographs rather than self-reported measures of ocular disease. The model adjusted for clinical evidence of diabetic retinopathy and maculopathy, AMD and glaucoma in place of self-report diagnoses. This sensitivity analysis also excluded participants without excellent or good quality retinal photograph, thereby excluding significant media opacities. It should be noted that poor quality photographs could also have been due to operator error or poor patient tolerance of the test.

Finally, to assess if the association between orthostatic BP and area under the log CSF remained with the presence of cataract, a final multivariable linear regression model additionally adjusted for our alternative measures of clinical cataract (self-reported cataract, visual acuity logMAR ≤ 0 and poor quality retinal photographs) was compared with the first multivariable model.

All models were checked for variance inflation factors. The likelihood ratio test initially tested across all phenotypes of the categorical orthostatic BP variable for an association with area under the log CSF; then the association of each individual orthostatic BP phenotype, with contrast sensitivity was examined. Statistical significance was set as $P < 0.05$.

3. Results

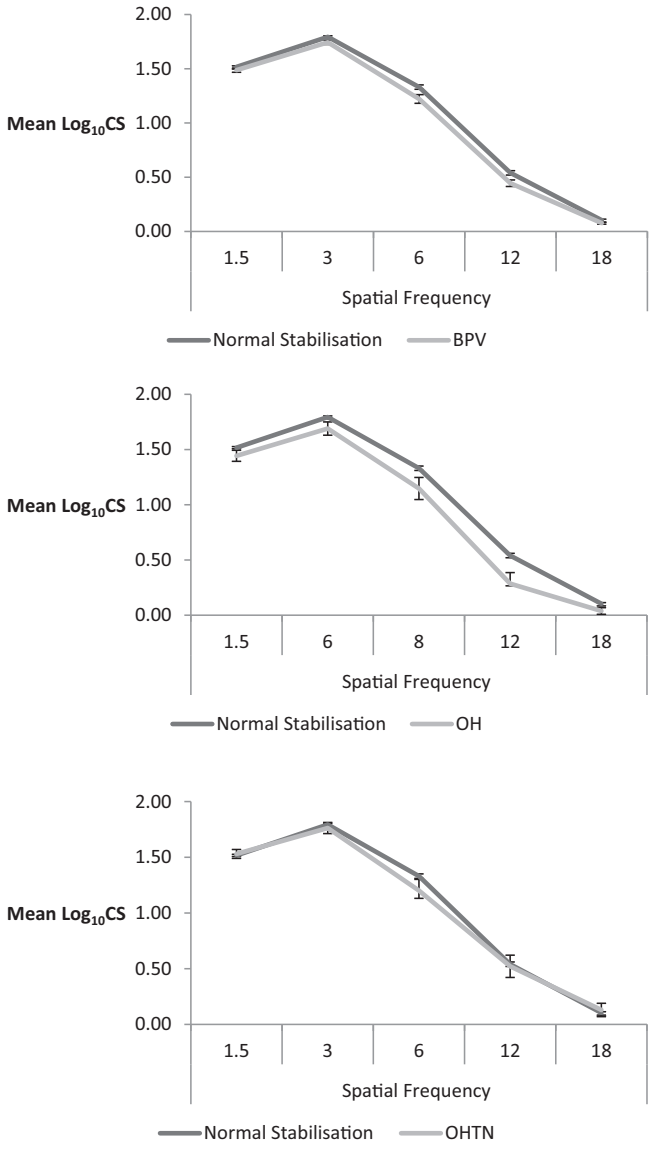
3.1. Demographic and health characteristics of sample

Of 4289 people aged ≥ 50 years the mean (SD) area under the log CSF was 1.28 (0.36) with a range of 0.00 to 2.16. Fifty-seven percent of participants reported they wore glasses for distance vision. Of those 2447, 1622 (66%) wore their glasses during measurement of logMAR visual acuity. The prevalence of self-reported glaucoma, cataracts and AMD in the sample was 2%, 8% and 2% respectively. The demographic, and health characteristics of the sample are described in Table 1.

3.2. Visual performance measured by contrast sensitivity within different demographic and health subgroups for analysis

Table 2 compares mean area under the $\log_{10}$ CSF within different demographic and health subgroups.

The measure of contrast sensitivity was lower in women, reduced with increasing age, lower levels of education and with worsening visual acuity (logMAR). A lower measure of contrast sensitivity was found in those who reported impaired vision or had self-reported eye disease, self-reported diabetes, objective hypertension or were taking antihypertensives (Table 2). Comparing variance in contrast sensitivity between those with perfect and abnormal visual acuity: Area under the $\log_{10}$ CSF was 1.42 (0.31) in those with normal visual acuity (logMAR ≤ 0), mean (SD) and 1.16 (0.36) for those with abnormal visual acuity (logMAR > 0). In the overall sample mean visual acuity



Key; log, logarithm; CS, contrast sensitivity; BPV, blood pressure variability; OH, orthostatic hypotension; OHTN, orthostatic hypertension

Fig. 3. Exemplar unadjusted contrast sensitivity function curves (mean $\log_{10}$ contrast sensitivity with error bars representing 95% CI) comparing those with normal stabilisation to BP variability, orthostatic hypotension and orthostatic hypertension.
Key; log, logarithm; CS, contrast sensitivity; BPV, blood pressure variability; OH, orthostatic hypotension; OHTN, orthostatic hypertension.

(logMAR) was 0.06 (0.18).

3.3. Prevalence of phenotypes of orthostatic BP behaviour

Table 3 presents the unweighted prevalence of the phenotypes of orthostatic BP. At 30 s–110 s after standing 70% of participants achieved steady state BP recovery to within 20/10 mmHg of baseline BP. After applying appropriate sampling weights (Whelan and Savva, 2013), the predicted prevalence of normal stabilisation in the Irish population ≥ 50 years was 68% for both SBP and DBP.

3.4. Characterisation of phenotypes of orthostatic BP behaviour 30 s after standing

Characteristics of participant's with each of the systolic phenotypes BP variability, orthostatic hypotension, orthostatic hypertension and normal stabilisation were compared and are presented in Table 4. Those with normal stabilisation were younger, had a lower prevalence of objective hypertension and prescribed beta-blockers compared to all of the other three phenotypes. Those with persistent orthostatic hypotension were the oldest, most likely to be female, and had the highest prevalence of report self- TIA. Participants with BP variability and orthostatic hypertension had a higher prevalence of self-reported diabetes at 8% compared to the other two phenotypes (Table 4).

3.5. Multivariable association between orthostatic BP phenotypes and contrast sensitivity

3.5.1. Multivariable linear regression

Table 5 shows the fully adjusted models of the association of orthostatic BP phenotypes with area under the log CSF adjusted for sociodemographics, health behaviours and self-reported eye pathology. Systolic orthostatic BP phenotypes were associated with variation in area under the $\log_{10}$ CSF scores ($P = 0.058$), with BP variability

significantly associated with reduced contrast sensitivity scores relative to those with normal stabilisation. There was no evidence of an association between diastolic orthostatic BP phenotypes and area under the $\log_{10}$ CSF ($P = 0.290$).

3.5.2. Sensitivity analysis: restricted sample adjusting for objective retinal pathology

In the sensitivity analysis (Table 6) which was restricted to those with excellent or good retinal photographs and adjusted for clinical evidence of disease on retinal photographs rather than self-reported measures, systolic BP variability remained associated with reduced contrast sensitivity scores.

Systolic orthostatic BP across all phenotypes was associated with variation in the contrast sensitivity measure ($P = 0.05$). Systolic BP variability compared to normal stabilisation remained associated with a reduced contrast sensitivity ($P = 0.012$); the adjusted difference (95%) was −0.047 (−0.084, −0.010). Again, there was no evidence that diastolic orthostatic BP was associated with area under the $\log_{10}$ CSF in the total population ($P = 0.651$). There was no evidence of an interaction between age, objective hypertension or prescribed antihypertensives and the orthostatic BP phenotypes on the measure of contrast sensitivity. Variance inflation factors for all models were < 10.

3.5.3. Multivariable linear regression analysis: models comparing the potential effect of cataract on association between orthostatic blood pressure and log contrast sensitivity

When no adjustment was made for cataract the BP variability phenotype relative was associated with an estimated mean decrease (95% CI) in area under the log CSF of −0.044 (−0.078, −0.011) for SBP (see Supplementary table 1). Adjusting for the three alternative measures of clinical cataract in addition to the other usual covariates, BP variability remained associated with a reduction in area under the log CSF of −0.036 (−0.068, −0.003) and the coefficient was attenuated by 18%, indicating a small indirect or distorting effect of cataract on the relationship. There was no change in the cataract adjusted and unadjusted estimated relationship between BP variability and log contrast sensitivity for DBP (−0.032 vs. -0.032 units AULCSF).

3.6. Contrast sensitivity function curves

To aid clinical interpretation of the outcome measure, the Area under the log CSF, Fig. 2 presents exemplar curves of participants at the 10th, 50th and 90th percentiles of area under the log CSF for the study sample. For these individuals the $\log_{10}$ contrast sensitivity at each of the spatial frequencies 1.5, 3, 6, 12 and 18 cycles is plotted and graphed, generating a function curve. The area under this curve (AULCSF) represents global CSF (CSF) across 5 spatial frequencies from low to high for that individual. Also presented are unadjusted CSF curves for participants with BP variability, Orthostatic Hypotension and Orthostatic Hypertension compared to those with Normal Stabilisation (Fig. 3).

4. Discussion & conclusions

Our previous work was the first to establish an association between BP variability and visual acuity (Ní Bhuachalla et al., 2015). We build on these findings and present some initial evidence on the relationship between BP variability and visual function, examining the more sensitive measure of contrast sensitivity. We observed that systolic BP variability or labile SBP 30 s after standing, when compared to normal stabilisation, was associated with poorer CSF represented by reduced area under the log CSF. All associations were independent of objective hypertension, individual antihypertensive drug classes and self-reported eye pathology, as well as other demographic and health characteristics. Furthermore, findings were confirmed when adjusted for clinical evidence of retinal pathology rather than just self-reported measures. The findings concur with research that suggests that fluctuating systemic BP may have consequences downstream in the microcirculation of the eye, despite that organ having its own tight autoregulatory mechanisms. Impaired choroidal autoregulation with age, which has been found in animal and human studies, may be an influencing factor (Grunwald et al., 1998; Reiner et al., 2011).

The retinal circulation is intrinsically regulated by several mechanisms; flow-medicated dilatation in response to changes in perfusion pressure and most importantly by the phenomenon of neurovascular coupling. The release of nitric oxide and lactate by metabolising glial and neuronal cells is detected by the retinal endothelium with consequent, appropriate alteration in vascular tone to maintain circulatory homeostasis. Retinal vascular tone is influenced also by levels of hypoxia and hypercapnia and uniquely light-dark transition and the flicker stimulation (Kur et al., 2012). In contrast, the choroidal circulation is predominantly under the extrinsic control of the autonomic nervous system, the choroidal vasculature being densely innervated by sympathetic and parasympathetic fibres. The highly permeable, fenestrated choriocapillaris is influenced by large molecules such as hormones (e.g. angiotension II) unlike the retinal circulation. The occurrence of intrinsic autoregulation in the choroidal circulation was previously controversial, but is thought to exist. Although evidence is limited, studies have suggested that there may be a local myogenic/neuronal response to changing perfusion pressure; however light stimulation has been found to have little effect and there is insensitivity to arterial levels of oxygen (Kur et al., 2012).

If autonomic dysregulation of the macro-circulation contributes to an individual clinically demonstrating systemic BP variability, choroidal blood flow within the microcirculation may be unstable either as a consequence or a manifestation of the same thing, given it is predominantly under autonomic system control. Intrinsic choroidal autoregulation with increasing age may not be able to compensate for BP variability, if extrinsic regulation is impaired. Age-related impairment in choroidal blood flow has been demonstrated both in animal and human studies (Grunwald et al., 1998; Kergoat and Lovasik, 2005; Reiner et al., 2011). Hence, the association of BP variability with reduced measures of contrast sensitivity is biologically plausible.

What this study adds to our earlier study's findings (Ní Bhuachalla et al., 2015) relates to the key question: is the association between BP variability and contrast sensitivity more likely 1) a direct effect on the choroidal microcirculation and the photoreceptors it supplies? or 2) interplay with antecedents of eye diseases, many of which have vascular aetiology? The pathogenesis of cataracts, AMD and glaucoma has been linked to atherosclerosis and ischemia (He et al., 2011; Wong and Hyman, 2008; Wu et al., 2014). Cataract would be a confounder of impaired contrast sensitivity. In TILDA, we did not collect a clinical measure that assessed for cataract specifically, such as slit lamp biomicroscopy or retro-illumination photographic grading. However, we did adjust for self-reported cataract and in the sensitivity analysis excluded poor quality retinal photographs, which precludes dense cataract. Additionally, as we had data on both contrast sensitivity and visual acuity in this study, we used abnormal visual acuity as one of our alternative measures of clinical cataract to assess for the change in effect of BP variability on contrast sensitivity scores. The rationale for this was that if one had perfect visual acuity, it follows that one had less undiagnosed eye pathology, such as early cataract. In this way some limited inferences could be drawn, regarding whether a relationship between orthostatic BP and contrast sensitivity was more likely due to a direct effect on the choroidal microcirculation or interplay with early eye disease of potential vascular aetiology (Prokofyeva et al., 2013). We found, adjusting for cataract in as robust a manner as possible with our available measures, attenuation of the association coefficient was only 18%. Therefore, while cataract may modulate the relationship between BP variability and contrast sensitivity, our findings suggest that a direct effect on the autonomically regulated choroidal microcirculation is also feasible.

Associations with BP variability and pathology have largely been

investigated in the context of stroke (Rothwell, 2011). It is established however that abnormal diurnal variability on ambulatory BP monitoring A increases risk of target organ damage (White and Gulati, 2015). More recently the ADVANCE trial found that visit-to-visit variability in SBP was an independent risk factor for macrovascular and microvascular complications in type 2 diabetes mellitus, following adjustment for mean SBP and other confounders (Hata et al., 2013). As contrast sensitivity (FACT) is a measure of the composite and respective contributions of ocular optics, retinal function and the brain, it is possible the association of BP variability with reduced measures of contrast sensitivity scores may be a finding that relates to cerebral function rather than simply the peripheral sensory organ. Our definition of BP variability encompasses some participants demonstrating orthostatic hypotension and orthostatic hypertension after 30 s. Literature has associated orthostatic hypotension and orthostatic hypertension with cerebral end-organ pathology. Orthostatic hypotension has been associated to the burden of white matter disease in Alzheimer's disease (Andin et al., 2007), dementia (Hayakawa et al., 2015) and cognitive impairment (Frewen et al., 2014). Orthostatic hypertension has been associated with greater incidence of lacunar stroke (Yatsuya et al., 2011) and age related macular degeneration (Ní Bhuachalla et al., 2018). Orthostatic stress has been found to evoke regional differences in cerebral blood flow, dynamic cerebral autoregulation being attenuated on head –up tilt, both in the internal carotid and vertebral arteries, but to a greater extent in the latter (Sato et al., 2012). Given that the occipital lobe is supplied by the posterior circulation, this supports the argument that the association of BP variability with reduced contrast sensitivity scores may be due to some influence of BP variability centrally.

An important clinical finding of this study was the clear differences in baseline characteristics between those participants with normal stabilisation of orthostatic BP versus orthostatic hypotension, orthostatic hypertension and BP variability (Table 3). Furthermore characteristics of orthostatic hypotension, orthostatic hypertension and BP variability differed in themselves suggesting they are unique entities, despite some participants defined as BP variability possibly have largely orthostatic hypotension or orthostatic hypertension over 30–110 s.

Our study has some limitations. It is a cross-sectional study. Participants were not fasting prior to the digital photoplethysmography BP measurements, and were not asked to abstain from smoking, alcohol, caffeine, or exercise before assessment. While such factors could affect orthostatic BP behaviour, recent work suggests they are unlikely to alter our results significantly (Fan et al., 2012). Our study has several strengths. We used a large subset of a large nationally representative population sample with objective health measures of both cardiovascular and ocular disease. Retinal photographs allowed us to control for objective retinal pathology, although were taken through undilated pupils. In addition, the diagnosis of glaucoma requires data on intraocular pressure and visual field measurement to be definitive. Contrast sensitivity is a robust measure of psychophysical visual function. The availability of contrast sensitivity data across five spatial frequencies for 4289 individuals was a key strength of this study. This was capitalised upon by choosing the area under the $\log_{10}$ CSF curve, integrated across all of those spatial frequencies as our outcome measure of global CSF.

In conclusion, this study provides evidence that abnormal BP variability, readily identifiable by active stand in a clinical setting, has an independent association with reduced visual contrast sensitivity scores. This is the first such study to our knowledge that has reported such an association and in relation to a vascular end organ, typically subserved by tight autoregulatory mechanisms and independent of objective hypertension. This study is clinically important as 1) BP variability is modifiable and 2) after applying appropriate weights, the predicted prevalence of systolic BP variability in Irish adults ≥50 years was 25%. As we have previously hypothesised, orthostatic BP variability may modulate cardiovascular risk or may be an independent biomarker of cardiovascular risk but this area warrants further research particularly as cardiovascular disease is the leading cause of morbidity and mortality worldwide.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2019.01.009.

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 (research grant), Irish Life plc and the Irish Government (research grant). 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.

References

Akuffo, K.O., Nolan, J., Stack, J., Moran, R., Feeney, J., Kenny, R.A., ... Beatty, S., 2015. Prevalence of age-related macular degeneration in the Republic of Ireland. Br. J. Ophthalmol. 99 (8), 1037–1044. https://doi.org/10.1136/bjophthalmol-2014-305768.

Andin, U., Passant, U., Gustafson, L., Englund, E., 2007. Alzheimer's disease (AD) with and without white matter pathology-clinical identification of concurrent cardiovascular disorders. Arch. Gerontol. Geriatr. 44 (3), 277–286. https://doi.org/10.1016/j.archger.2006.06.002.

Angelousi, A., Girerd, N., Benetos, A., Frimat, L., Gautier, S., Weryha, G., Boivin, J.M., 2014. Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis. J. Hypertens. 32 (8), 1562–1571. discussion 1571. https://doi.org/10.1097/hjh.0000000000000235.

Applegate, R.A., Howland, H.C., Sharp, R.P., Cottingham, A.J., Yee, R.W., 1998. Corneal aberrations and visual performance after radial keratotomy. J. Refract. Surg. 14 (4), 397–407.

Early Treatment Diabetic Retinopathy Study Research Group, E, 1991. Grading diabetic retinopathy from stereoscopic color fundus photographs–an extension of the modified Airlie House classification. ETDRS report number 10. Ophthalmology 98 (5 Suppl), 786–806 (Early Treatment Diabetic Retinopathy Study Research Group).

Eguchi, K., 2014. Blood pressure variability/dipper/non-dipper in hypertension and diabetes. Curr. Hypertens. Rev [Epub ahead of print].

Fan, C.W., Savva, G.M., Finucane, C., Cronin, H., O'Regan, C., Kenny, R.A., 2012. Factors affecting continuous beat-to-beat orthostatic blood pressure response in community-dwelling older adults. Blood Press. Monit. 17 (4), 160–163. https://doi.org/10.1097/MBP.0b013e328356821f.

Finucane, C., O'Connell, M.D., Fan, C.W., Savva, G.M., Soraghan, C.J., Nolan, H., ... Kenny, R.A., 2014. Age related normative changes in phasic orthostatic blood pressure in a large population study: findings from the Irish Longitudinal Study on Ageing (TILDA). Circulation 130 (20), 1780–1789. https://doi.org/10.1161/CIRCULATIONAHA.114.009831.

Freeman, R., Wieling, W., Axelrod, F.B., Benditt, D.G., Benarroch, E., Biaggioni, I., ... van Dijk, J.G., 2011. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin. Auton. Res. 21 (2), 69–72. https://doi.org/10.1007/s10286-011-0119-5.

Frewen, J., Savva, G.M., Boyle, G., Finucane, C., Kenny, R.A., 2014. Cognitive performance in orthostatic hypotension: findings from a nationally representative sample. J. Am. Geriatr. Soc. 62 (1), 117–122.

Grunwald, J.E., Hariprasad, S.M., DuPont, J., 1998. Effect of aging on foveolar choroidal circulation. Arch. Ophthalmol. 116 (2), 150–154.

Hata, J., Arima, H., Rothwell, P.M., Woodward, M., Zoungas, S., Anderson, C., ... Chalmers, J., 2013. Effects of visit-to-visit variability in systolic blood pressure on macrovascular and microvascular complications in patients with type 2 diabetes mellitus: the ADVANCE trial. Circulation 128 (12), 1325–1334. https://doi.org/10.1161/circulationaha.113.002717.

Hayakawa, T., McGarrigle, C.A., Coen, R.F., Soraghan, C.J., Foran, T., Lawlor, B.A., Kenny, R.A., 2015. Orthostatic blood pressure behavior in people with mild cognitive impairment predicts conversion to dementia. J. Am. Geriatr. Soc. 63 (9), 1868–1873. https://doi.org/10.1111/jgs.13596.

He, Z., Vingrys, A.J., Armitage, J.A., Bui, B.V., 2011. The role of blood pressure in glaucoma. Clin. Exp. Optom. 94 (2), 133–149. https://doi.org/10.1111/j.1444-0938.2010.00564.x.

Hertenstein, H., Bach, M., Gross, N.J., Beisse, F., 2016. Marked dissociation of photopic and mesopic contrast sensitivity even in normal observers. Graefes Arch. Clin. Exp. Ophthalmol. 254 (2), 373–384. https://doi.org/10.1007/s00417-015-3020-4.

Kario, K., 2013. Orthostatic hypertension-a new haemodynamic cardiovascular risk factor. Nat. Rev. Nephrol. 9 (12), 726–738. https://doi.org/10.1038/nrneph.2013.

224.
Kearney, P.M., Cronin, H., O'Regan, C., Kamiya, Y., Savva, G.M., Whelan, B., Kenny, R., 2011. Cohort profile: the Irish longitudinal study on ageing. Int. J. Epidemiol. 40 (4), 877–884. https://doi.org/10.1093/ije/dyr116.
Kenny, R.A., 2013. An introduction to the Irish Longitudinal Study on Ageing. J. Am. Geriatr. Soc. 61 (Suppl. 2), S263–S264. https://doi.org/10.1111/jgs.12200.
Kergoat, H., Lovasik, J.V., 2005. Seven-degree head-down tilt reduces choroidal pulsatile ocular blood flow. Aviat. Space Environ. Med. 76 (10), 930–934.
Kur, J., Newman, E.A., Chan-Ling, T., 2012. Cellular and physiological mechanisms underlying blood flow regulation in the retina and choroid in health and disease. Prog. Retin. Eye Res. 31 (5), 377–406. https://doi.org/10.1016/j.preteyeres.2012.04.004.
Mancia, G., De Backer, G., Dominiczak, A., Cifkova, R., Fagard, R., Germano, G., ... Zanchetti, A., 2007. 2007 ESH-ESC practice guidelines for the management of arterial hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. J. Hypertens. 25 (9), 1751–1762. https://doi.org/10.1097/HJH.0b013e3282f0580f.
Mayfield, D., McLeod, G., Hall, P., 1974. The CAGE questionnaire: validation of a new alcoholism screening instrument. Am. J. Psychiatry 131 (10), 1121–1123.
Nardo, C.J., Chambless, L.E., Light, K.C., Rosamond, W.D., Sharrett, A.R., Tell, G.S., Heiss, G., 1999. Descriptive epidemiology of blood pressure response to change in body position. The ARIC study. Hypertension 33 (5), 1123–1129.
Ní Bhuachalla, B., McGarrigle, C.A., Akuffo, K.O., Peto, T., Beatty, S., Kenny, R.A., 2015. Phenotypes of orthostatic blood pressure: association with visual acuity. Clin. Auton. Res. 25 (6), 373–381. https://doi.org/10.1007/s10286-015-0315-9.
Ní Bhuachalla, B., McGarrigle, C.A., O'Leary, N., Akuffo, K.O., Peto, T., Beatty, S., Kenny, R.A., 2018. Orthostatic hypertension as a risk factor for age-related macular degeneration: evidence from the Irish longitudinal study on ageing. Exp. Gerontol. 106, 80–87. https://doi.org/10.1016/j.exger.2018.02.029.
Onal, S., Yenice, O., Cakir, S., Temel, A., 2008. FACT contrast sensitivity as a diagnostic tool in glaucoma: FACT contrast sensitivity in glaucoma. Int. Ophthalmol. 28 (6), 407–412. https://doi.org/10.1007/s10792-007-9169-z.
Prokofyeva, E., Wegener, A., Zrenner, E., 2013. Cataract prevalence and prevention in Europe: a literature review. Acta Ophthalmol. 91 (5), 395–405. https://doi.org/10.1111/j.1755-3768.2012.02444.x.
Reiner, A., Del Mar, N., Zagvazdin, Y., Li, C., Fitzgerald, M.E., 2011. Age-related impairment in choroidal blood flow compensation for arterial blood pressure fluctuation in pigeons. Invest. Ophthalmol. Vis. Sci. 52 (10), 7238–7247. https://doi.org/10.1167/iovs.10-6464.
Romero-Ortuno, R., O'Connell, M.D., Finucane, C., Soraghan, C., Fan, C.W., Kenny, R.A., 2013. Insights into the clinical management of the syndrome of supine hypertension–orthostatic hypotension (SH-OH): the Irish Longitudinal Study on Ageing (TILDA). BMC Geriatr. 13, 73. https://doi.org/10.1186/1471-2318-13-73.
Rothwell, P.M., 2011. Does blood pressure variability modulate cardiovascular risk? Curr. Hypertens. Rep. 13 (3), 177–186. https://doi.org/10.1007/s11906-011-0201-3.
Sato, K., Fisher, J.P., Seifert, T., Overgaard, M., Secher, N.H., Ogoh, S., 2012. Blood flow in internal carotid and vertebral arteries during orthostatic stress. Exp. Physiol. 97 (12), 1272–1280. https://doi.org/10.1113/expphysiol.2012.064774.
Whelan, B.J., Savva, G.M., 2013. Design and methodology of the Irish Longitudinal Study on Ageing. J. Am. Geriatr. Soc. 61 (Suppl. 2), S265–S268. https://doi.org/10.1111/jgs.12199.
White, W.B., Gulati, V., 2015. Managing hypertension with ambulatory blood pressure monitoring. Curr. Cardiol. Rep. 17 (2), 556. https://doi.org/10.1007/s11886-014-0556-6.
WHO, 2011. Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment. WHO Collaborating Centre for Drug Statistics Methodology, Oslo (2010).
Wong, T.Y., Hyman, L., 2008. Population-based studies in ophthalmology. Am J. Ophthalmol. 146 (5), 656–663. https://doi.org/10.1016/j.ajo.2008.07.048.
Wu, H., Zhang, H., Li, P., Gao, T., Lin, J., Yang, J., ... Ye, J., 2014. Association between dietary carbohydrate intake and dietary glycemic index and risk of age-related cataract: a meta-analysis. Invest. Ophthalmol. Vis. Sci. 55 (6), 3660–3668. https://doi.org/10.1167/iovs.13-13695.
Yatsuya, H., Folsom, A.R., Alonso, A., Gottesman, R.F., Rose, K.M., 2011. Postural changes in blood pressure and incidence of ischemic stroke subtypes: the ARIC study. Hypertension 57 (2), 167–173. https://doi.org/10.1161/hypertensionaha.110.161844.