

Age and sex related differences in orthostatic cerebral oxygenation: Findings from 2764 older adults in the Irish Longitudinal Study on Ageing (TILDA)

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ABSTRACT

Aims: Cerebral hypoperfusion is implicated in the pathogenesis of associations between orthostatic hypotension and adverse outcome such as falls, cognitive impairment, depression, and mortality. Although the blood pressure response to orthostasis has been well studied there is a lack of information on orthostatic cerebrovascular responses in older populations.

Methods and results: We measured cerebral hemodynamics, utilizing near infrared spectroscopy, coupled with peripheral blood pressure during an active stand in a large population of well-phenotyped older adults ($N = 2764$). Multi-level mixed effect models were utilized to investigate associations with age and sex, as well as confounders including anti-hypertensive medications. Normative cerebral oxygenation responses were also modelled utilizing generalized additive models for location, scale, and shape (GAMLSS). Older age groups experienced larger initial drops in oxygenation and a slower recovery, and responses also differed by sex. The drop after standing ranged from -1.85% (95 % confidence interval (CI): -2.02 to -1.68) in the males aged 54–59 years vs -1.15% (95 % CI: -1.31 to -1.00) in females aged 54–59 years, to -2.67% (95 % CI: -3.01 to -2.33) in males aged ≥ 80 years vs -1.97% (95 % CI: -2.32 to -1.62) females aged ≥ 80 years. Reduced oxygenation levels were also evident in those taking anti-hypertensive medications.

Conclusion: Cerebral autoregulation is impaired with age, particularly in older women and those taking anti-hypertensives. SBP during the stand explained some of the age gradient in the late recovery stage of the stand for the oldest age group. Reported orthostatic symptoms did not correlate with hypoperfusion. Therefore, measures of orthostatic cerebral flow should be assessed in addition to peripheral BP in older patients irrespective of symptoms. Further studies are required to investigate the relationship between NIRS measurements and clinical outcomes such as falls, cognitive impairment and depression.

1. Introduction

Cerebral metabolic demands are high, with $\sim 20\%$ of available energy being used for normal function. This combined with limited substrate storage capabilities means precise blood flow control is required for the adequate supply of oxygen and nutrients (Sokoloff, 1969; Brown and Ransom, 2007). Cerebral hypoperfusion can occur when cerebral autoregulation (CA) fails to maintain adequate flow to the brain in the event of large changes in systemic blood pressure (BP), such as the drop invoked upon assuming an upright position. Orthostasis is a physiological stressor, which requires a neuro-cardiovascular response to achieve

BP homeostasis due to the large shift in blood volume to the lower extremities.

Impaired BP stabilization after orthostasis, as evidenced with advancing age (Finucane et al., 2014) suggests such individuals may be at a higher risk of transient cerebral hypotensive burden. It is unclear whether this impaired BP response translates directly to episodes of insufficient cerebral perfusion, due to the non-linear nature of the CA mechanism. Chronic transient episodes of hypoperfusion may in part explain the mechanism linking the associations between orthostatic hypotension (OH) and adverse outcome such as falls (Finucane et al., 2017), cognitive impairment (McNicholas et al., 2018; Frewen et al.,

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2014), dementia (Wolters et al., 2016), depression (Briggs et al., 2018), increased cardiovascular events and mortality (Fedorowski et al., 2010). CA is less effective at higher and lower BP pressures (Willie et al., 2014). This also raises concerns regarding hypotensive burden in people with hypertension, and those who require anti-hypertensive therapies to lower BP levels, particularly those over 75 years (Sexton et al., 2017) or who are frail (O'Connell et al., 2018). A higher cerebral hypotensive burden is associated with alterations in brain structure including increased white matter hyperintensities and atrophy, which is a possible causal pathway for falls, depression, cognitive decline and dementia (Robertson et al., 2019; Briggs et al., 2019).

Although hypotensive symptoms during orthostasis such as dizziness, light-headedness, weakness, blurred vision, pre-syncope and even syncope are assumed to be due to transient cerebral hypoperfusion, the orthostatic BP response often does not correlate with symptoms (Bachus et al., 2017; Novak, 2016). An objective measure of the cerebrovascular response is required to assess the true cerebral hypotensive burden during orthostasis, as well as any effect of anti-hypertensive medications on the response.

Near infra-red spectroscopy (NIRS) is a non-invasive imaging modality enabling continuous monitoring of cerebral hemodynamics during rest or movement. Based on the translucency of the skull, it provides measurements of cerebral oxygenation, which have been shown to correlate well with MRI and transcranial Doppler approaches and measure the same phenomenon (Mehagnoul-Schippier et al., 2002; Mol et al., 2020). It is easy to use, particularly suited for older adult populations, and is being employed more frequently in the clinic to assess hypotensive symptoms (Bachus et al., 2017; Claffey et al., 2020). Several small studies have investigated the cerebrovascular response to orthostasis and CA using NIRS, but results showed varied responses between cohorts and methods used also varied (Mehagnoul-Schippier et al., 2000) (Kim et al., 2011). Novak described a drop in cerebral hemodynamics, devoid of peripheral hemodynamic changes or vascular abnormalities (Novak, 2016). Bachus et al. ascertained that cerebral oxygenation steadily decreases independently of hemodynamic changes prior to hypotensive events, and they also detected distinctive patterns of deoxygenation in their patient cohort (Bachus et al., 2017). There is a lack of NIRS reference data distinguishing the normal response to orthostasis, throughout its timecourse, as well as an absence of population data, which is useful for clinical reference and research. Also, previous studies employed basic averaged data in their statistical analysis and did not focus on the detailed cerebral response despite having sufficient sampling rate to do so.

The aim of this study was to characterize in detail the age-related cerebrovascular response to orthostasis in a large community-dwelling population of older adults. A secondary aim was to provide normative reference data from a large sample of older adults. We utilized near-infrared spectroscopy (NIRS) to monitor frontal lobe cerebral oxygenation during an active stand.

2. Methods

2.1. Study population

Cross-sectional data from Wave 3 (March 2014 to December 2015) of The Irish Longitudinal Study on Ageing (TILDA), a nationally representative sample of adults aged ≥ 50 years in Ireland was employed in this study. Randomized selection of participants and design of the study has been detailed elsewhere (Donoghue et al., 2018; Kearney et al., 2011). Participants were interviewed in their own homes via a computer-assisted personal interview (CAPI). In addition, they were asked to return a self-completed questionnaire (SCQ) and were invited to a comprehensive health assessment in a dedicated health center or a modified version in their home. This study is based on participants who attended the health center and performed an active stand. Those with a doctor's diagnosis of dementia or Parkinson's disease were excluded

from the study.

All participants provided written informed consent. Ethical approval was granted by the Research Ethics Committee at Trinity College Dublin. Experimental procedures adhered to the Declaration of Helsinki.

2.2. Orthostatic challenge measurements

The active stand was performed in a quiet, comfortably lit room maintained at an ambient temperature. Participants rested in the supine position for ~ 10 min before standing in a timely manner, aided by a nurse when required, and remained standing quietly for a further 3 min.

2.2.1. Cerebral oxygenation

Cerebral oxygenation was measured continuously from the left frontal lobe via a non-invasive single NIRS channel during the orthostatic challenge, at a sample rate of 50 Hz, using the Portalite (Artinis Medical Systems, Zetten, Netherlands). Through the use of multiple transmitters, two different wavelengths, and the difference in the light absorption rates of oxygenated hemoglobin (O₂Hb) and deoxygenated hemoglobin (HHb), absolute cerebral oxygenation can be calculated via the principle described by the modified Beer-Lambert law and spatial resolved spectroscopy (SRS) (Ferrari and Quaresima, 2012). O₂Hb, HHb and absolute cerebral oxygenation were recorded, with absolute cerebral oxygenation determined as O₂Hb as a percentage of the total O₂Hb and HHb, referred to as the tissue saturation index (TSI).

2.2.2. Blood pressure measurements

Continuous beat-to-beat blood pressure was measured simultaneously at a rate of 200 Hz via a Finometer (Finapres Medical Systems, Arnhem, Netherlands), which applies the volume-clamp method along with physiological calibration (Physiocal) and brachial artery waveform reconstruction (Guelen et al., 2003; Imholz et al., 1998). The Physiocal function was disabled directly prior to standing, to avoid interruption to the recording of the continuous response to orthostasis. Outputs from the Finometer included SBP and cardiac output (CO).

2.3. Covariates

Potential confounding covariates were derived from the CAPI, the SCQ and health assessment data. Covariates selected included age group (54–59, 60–69, 70–79, ≥ 80 years), sex, highest educational attainment (primary/none, secondary, tertiary), smoking history, excess alcohol intake (score ≥ 2 on the CAGE questionnaire (Bush et al., 1987)), self-reported doctor's diagnosis of diabetes, number of cardiovascular conditions, anti-hypertensive medication use, anti-depressant medication use, timed-up-and-go (TUG) test (time taken to stand up from a chair, walk 3 m, turn and sit back down), height, body mass index (BMI) and depression (Short-form of the Centre for Epidemiological Studies Depression (CES–D) scale was used (O'Halloran et al., 2014)). Medications were recorded based on the Anatomical Therapeutic Chemical (ATC) Classification System. Anti-hypertensive medication use was defined as the use of any medications with ATC codes C02, C03, C07, C08 or C09. Anti-depressant use was determined as the use of any medications with ATC code N06A. The number of cardiovascular conditions (0, 1, 2 or more) was determined by the following: self-reported physician-diagnosis of transient ischemic attack (TIA), stroke, hypertension, angina, heart attack, congestive heart failure, high cholesterol, heart murmur or abnormal heart rhythm (including atrial fibrillation). Height and weight were measured during the health assessment and BMI was calculated from these measurements. At the end of the 3 min participants were asked if they had any symptoms of dizziness, light-headedness or unsteadiness at any stage. Onset of the stand and standing speed (the time taken to transition from supine to standing), was calculated via an algorithm using the height correct unit data from the Finometer (O'Connor et al., 2020).

2.4. Data analysis

2.4.1. Signal processing

NIRS and Finometer data was processed with custom scripts in MATLAB R2016b. Data was downsampled to 1 Hz. To remove noise and allow comparison of active stand patterns an 11-point median filter and 10-point moving average filter were applied to the data. Baseline data was calculated from mean values for a duration of 30 to 60 s before standing. Active stand data recorded after standing, from 0 to 180 s, at 10 s intervals, was included in this analysis, as well as the nadir (minimum value within 40 s of standing) and delta (baseline minus nadir). Time 0 s corresponded to the onset of the stand.

2.5. Statistical analysis

Statistical analysis was carried out using Stata 14.0. The normality of covariates and their residuals was assessed with histograms and Q-Q plots. Due to repeated measurements over time multi-level mixed effect models with selected covariates were utilized to investigate the cerebral oxygenation response by age group and by sex. The data was analyzed in 10-s intervals, from 0 to 180 s, with 0 representing the onset of the stand. To model the different time phases of the response, from initial drop to recovery (i.e. 0–10 s, 10–20 s, 20–30 s, 30–50 s and 50–180 s), linear splines were fitted to the data with knots at 0 s, 10 s, 20 s, 30 s and 50 s. As adjacent time points are more strongly correlated an autoregression covariance matrix with a lag of 1 was used to model residual variance across time. Parameters were nested within participant to allow random effects (random intercept) at the participant level. The fixed effect and the interaction with each time parameter was modelled for all covariates. Thus, the varying effect of covariates on different time phases of the recovery were included.

The outcome measure was TSI change from baseline over time. Model 1 adjusted for age and sex only. Model 2 included age, sex, education, height and continuous SBP as covariates. Model 3, the fully adjusted model, additionally included standing speed, smoking history, excess alcohol intake, antihypertensive medication, antidepressant medication, diabetes, number of cardiovascular conditions, TUG, BMI, depression and CO as covariates.

2.5.1.1. Sensitivity analysis. Sensitivity tests examined associations with anti-hypertensive medication use and reported orthostatic symptoms. These models were adjusted for age, sex, education, height and continuous SBP only.

2.5.1.2. Prevalence of cerebral hypoperfusion and impaired stabilization. Prevalence of an impaired cerebrovascular response, defined as a TSI value >1 % or 2 % lower than baseline during the recovery phase, are reported with 95 % confidence intervals. These levels were selected based on the normative estimates described below. Sample weights were applied to prevalence estimates, for generalizability to the population. Results are stratified by sex and age.

2.5.1.3. Normative estimates. Generalized additive models for location, scale, and shape (GAMLSS) (Rigby and Stasinopoulos, 2005) and the Box Cox Power Exponential (BCPE) distribution with parameters for location, scale, skew, and kurtosis of the distribution (Rigby and Stasinopoulos, 2004) were derived using R software suite version 3.4.3. These parameters were utilized to estimate normative reference values for cerebral oxygenation during active stand, stratified by age and sex only. An inverse probability weight was applied to these estimates to make them generalizable to the population of those aged ≥ 54 years in Ireland. This is the same approach as used previously to estimate normative reference values for blood pressure in the same cohort (Finucane et al.,

2014).

3. Results

3.1. Participant characteristics

Cerebral oxygenation data during the active stand was available for 2764 participants. Supplementary Fig. S1 shows the sample selection criteria. The sample was 52.9 % female. Mean age was 64.8 ± 7.5 years (54–93 years). Females had a higher prevalence of high cholesterol (41 % vs 33 %), but a lower prevalence of diabetes (4 % vs 9 %) than males. Around 60 % of both males and females reported at least one cardiovascular condition. A higher proportion of males reported orthostatic symptoms (32 % vs 27 %). Full characteristics of the sample are shown in Table 1.

3.2. Cerebral oxygenation response

Fig. 1 illustrates the relationship of the TSI response during the active

Table 1

- Characteristics of the participants in the sample by sex.

	Males	Females	Statistical test
	N	N	
	1301	1463	p-value
Age (years), mean (SD)	65.0 (7.6)	64.7(7.3)	0.169
Highest educational attainment			
Primary/none, n (%)	258(20)	203(14)	
Secondary, n (%)	534(41)	588(40)	<0.001*
Tertiary, n (%)	509(39)	672(46)	
	173.3		
Height (cm), mean (SD)	(6.4)	159.9(6.2)	<0.001*
BMI	28.8(4.1)	27.9(5.1)	<0.001*
Smoking history			
Never	528(41)	795(54)	
Past	646(50)	531(36)	<0.001*
Current	127(10)	137(9)	
Alcohol excess, n (%)			
	977 (75 %)	1171 (80 %)	
CAGE <2	193 (15 %)		
CAGE ≥2	131 (10 %)	139 (10 %)	<0.001*
Did not complete		153 (11 %)	
Diabetes, n (%)	121(9)	61(4)	<0.001*
Stroke, n (%)	25(2)	12(1)	0.012*
Transient ischaemic attack, n (%)	38(3)	35(2)	0.387
Hypertension, n (%)	437(34)	444(30)	0.068
High cholesterol, n (%)	430(33)	600(41)	<0.001*
Angina, n (%)	51(4)	32(2)	0.008*
Heart attack, n (%)	87(7)	26(2)	<0.001*
Congestive heart failure, n (%)	7(<1)	4(<1)	0.270
Heart murmur, n (%)	39(3)	73(5)	0.008*
Abnormal heart rhythm, n (%)	118(9)	107(7)	0.092
CVD conditions			
none, n (%)	533(41)	567(39)	
=1, n (%)	443(34)	565(39)	0.041*
≥ 2, n (%)	325(25)	331(22)	
Baseline (supine) SBP (mmHg), mean (SD)	138 (20)	144 (23)	<0.001*
Taking antihypertensive medications, n (%)	547(42)	475(33)	<0.001*
Taking antidepressant medications, n (%)	63(5)	140(10)	<0.001*
CESD	3.3(3.3)	4.2(3.8)	<0.001*
TUG (s), mean (SD)	9.0(1.7)	9.0(2.8)	0.605
Reported OI symptoms	407(32)	395(27)	0.014*
Standing speed (s), mean (SD)	6.9(2.6)	7.6(3.1)	<0.001*

* $p < 0.05$.

^ Categorical variables were examined via the chi-square test, and continuous variables were compared via the student *t*-test.

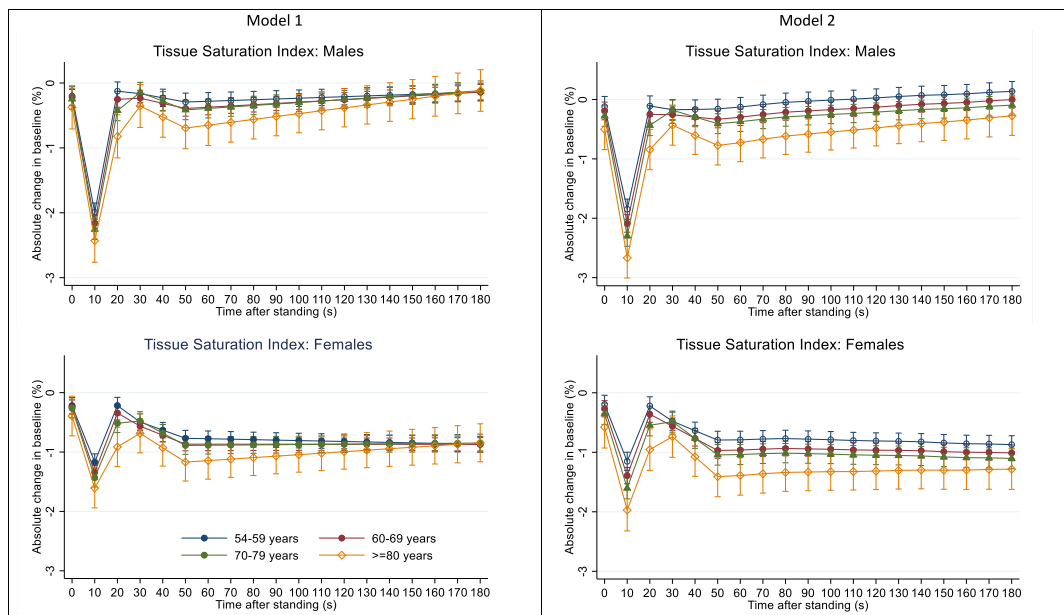


Fig. 1. Conditional means and 95 % confidence intervals for tissue saturation index (TSI) stratified by age groups for males and females, estimated from mixed effect models. Model 1 is adjusted for age and sex only. Model 2 is additionally adjusted for education, height and systolic blood pressure during the stand.

stand with age and sex. The pattern of responses differed by both age and sex, with a graded association between older age and slower recovery. When the basic model (model 1) was additionally adjusted for education, height and SBP (model 2) the age gradient in later stages of recovery became more apparent, particularly in the later stages of recovery. This caused the main effect for the oldest age group to become statistically significant. This change was driven by adding SBP during the stand to the model, suggesting that SBP recovery explains some of

the difference observed for the oldest age group. Females demonstrated a different pattern of response to males, including a smaller drop at 10 s, which ranged from -1.85% (95 % confidence interval (CI): -2.02 to -1.68) in the youngest males vs -1.15% (95 % CI: -1.31 to -1.00) in the youngest females, to -2.67% (95 % CI: -3.01 to -2.33) in the oldest males vs -1.97% (95 % CI: -2.32 to -1.62) in the oldest females (model 2). After 180 s females had still not returned to baseline levels, and females stabilized at significantly lower levels than males, -1.28%

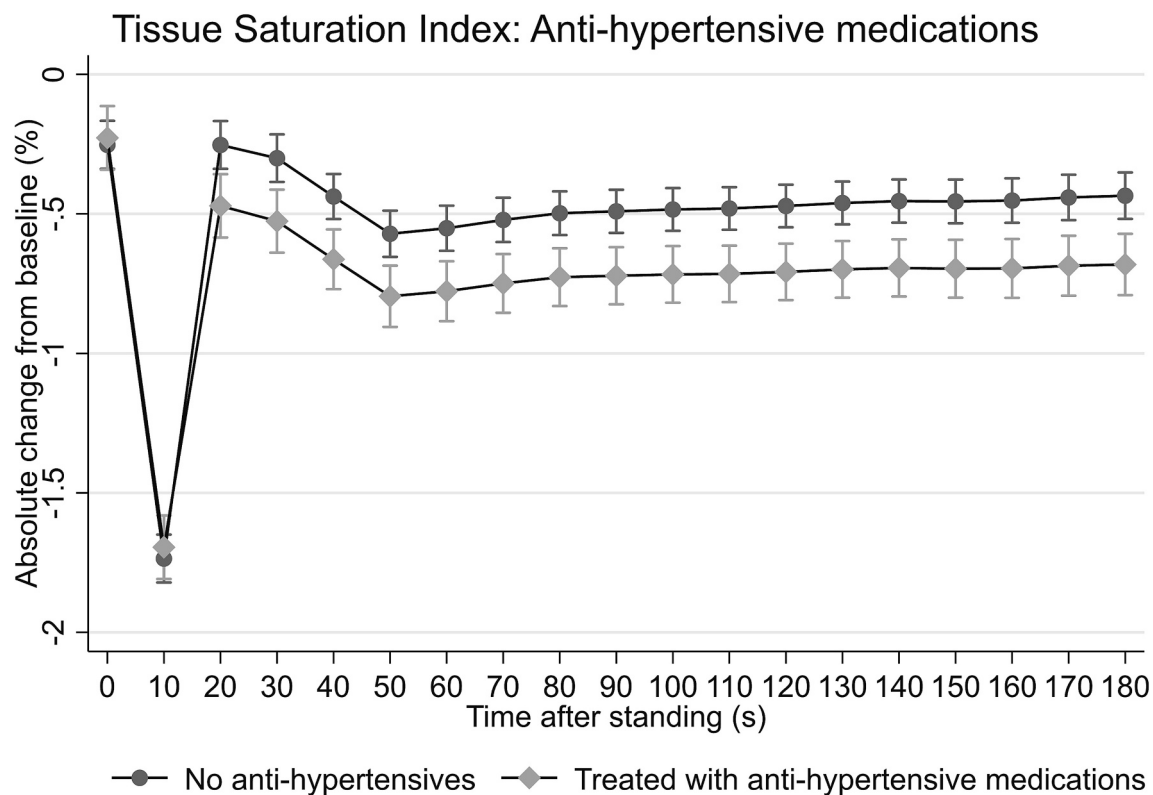


Fig. 2. Conditional means and 95 % confidence intervals for tissue saturation index (TSI) by anti-hypertensive treatment, estimated from mixed effect models. Models are adjusted for age, sex, education, height and systolic blood pressure during the stand.

(95 % CI: -1.62 to -0.94) in the oldest females vs -0.28 % (95 % CI: -0.60 to 0.05) in the oldest males (model 2). Larger differences were seen between the sexes than between age groups, Supplementary Fig. S2. These patterns remained after further adjusting for the full set of selected covariates, Supplementary Fig. S3 (model 3). Model parameters for age and sex for all three models are provided in Supplementary Table S5.

3.2.1.1. Sensitivity analysis. Those treated with anti-hypertensive medications had reduced cerebral oxygenation levels in the recovery phase from 20 s post-standing, although there was no difference in the initial response at 10 s, Fig. 2. Reported orthostatic symptoms did not correlate with an effect on cerebral oxygenation, Fig. 3.

3.2.1.2. Prevalence estimates. The percentage of those who experienced reduced cerebral oxygenation in the recovery phase is shown in Table 2. Estimates are given for a TSI value ≥ 2 % or 1 % below baseline. After an initial peak in recovery mean TSI levels decrease again. Thus, a greater percentage experience hypoperfusion at 180 s, e.g. at 30s 9.8 % of women had a TSI value ≥ 2 % below baseline vs 24.1 % at 180 s. Women in the oldest age group had the highest prevalence of reduced oxygenation at all timepoints.

3.2.1.3. Normative estimates. Normative estimates for the cerebral oxygenation response to an orthostatic challenge, stratified by sex, are presented in Supplementary Fig. S4, with median data shown in Fig. 4. A full set of reference values is provided in Supplementary Tables S6 and S7. There was no difference in supine baseline TSI levels across the age groups, and a small difference between women and men (72.44 % vs 73.06 % respectively). In men a graded pattern of a lower nadir value (lowest value in first 40 s) with increasing age was observed, decreasing

from 71.12 % (interquartile range [IQR]: 67.89 to 74.2) in the youngest (54–59 years) to 69.81 % (IQR: 66.05 to 73.42) in the oldest (those aged ≥ 80 years). Similarly, in women the nadir decreased from 71.12 % (IQR: 68.14 to 74.05) in the youngest group to 69.81 % (IQR: 66.35 to 73.20) in the oldest. Delta TSI (baseline minus nadir) was smaller in women compared to men across all age groups. Delta increased with advancing years in both genders (Supplementary Tables S6–S7), ranging from -2.02 % (IQR: -3.01 to -1.13) in the youngest men to -2.75 % (IQR: -4.23 to -1.48) in the oldest men, and from -1.56 % (IQR: -2.21 to -0.98) in the youngest women to -1.81 % (IQR: -2.80 to -0.95) in the oldest females.

Overall (Fig. 4), cerebral oxygenation remained high at all ages. There is a range of responses, with the mean response in women failing to return to supine baseline values after 180 s, and stabilizing below baseline supine values.

4. Discussion

This large population study reports an age gradient and sex-specific differences in the dynamic orthostatic cerebral oxygenation response, as measured from the frontal lobe by NIRS, in older community-dwelling adults across a continuum of ages. Older age groups experienced larger drops in cerebral oxygenation, as well as a slower recovery. Men experienced a larger drop compared to women, with women failing to stabilize to supine baseline values for all age groups. Women in the oldest age group experienced the most impaired recovery pattern, and a higher proportion of women at all ages experienced cerebral hypoperfusion in the recovery phase. SBP recovery during the stand explained some of the delayed recovery observed in the oldest age group. In addition, we report age and sex-specific normative TSI reference values over the time course of the response in this nationally representative cohort for those aged ≥ 54 years. There was a broad distribution of responses indicated by the wide limits of the normative

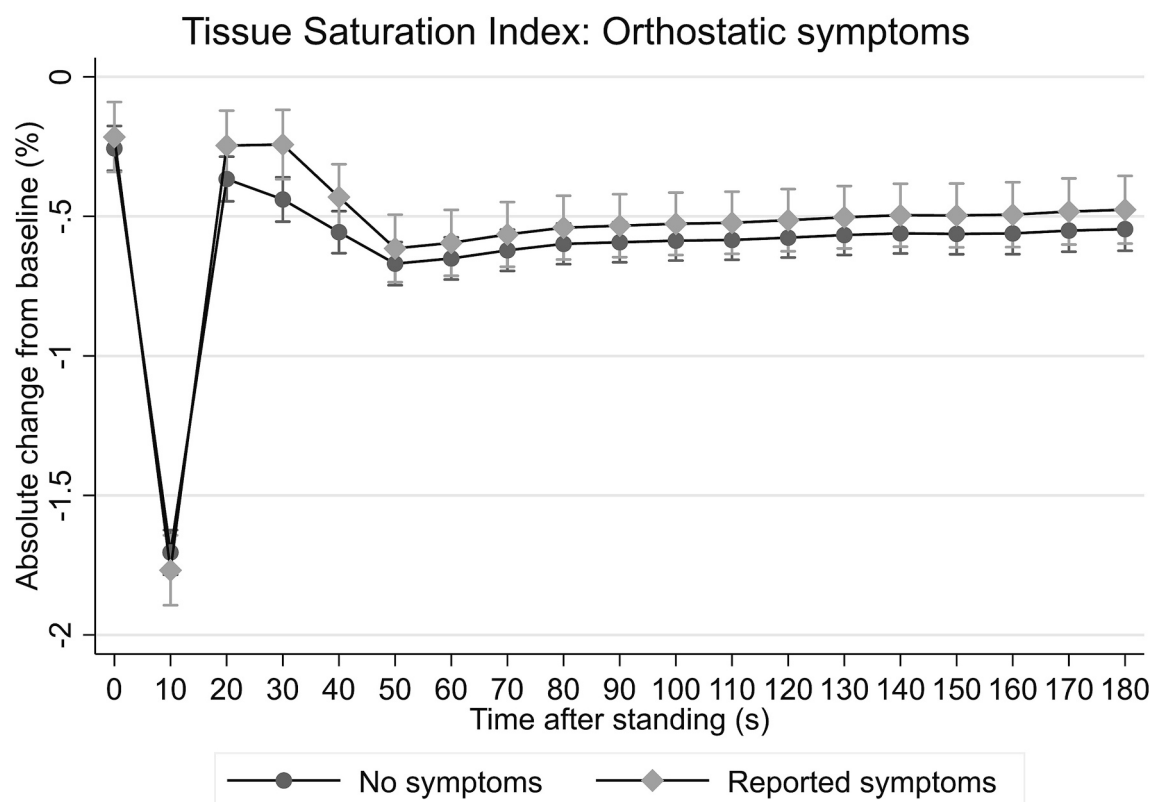


Fig. 3. – Conditional means and 95 % confidence intervals for tissue saturation index (TSI) by reported orthostatic symptoms, estimated from mixed effect models. Models are adjusted for age, sex, education, height and systolic blood pressure during the stand.

Table 2

Prevalence of cerebral hypotension (i.e. reduced cerebral oxygenation), stratified by age, sex and time after standing, in the recovery phase.

	30 s	40 s	50 s	60 s	90 s	180 s
	% (95 % CI)	% (95 % CI)	% (95 % CI)	% (95 % CI)	% (95 % CI)	% (95 % CI)
TSI ≥ 2 % below baseline						
Sex						
Men	12.1 (10.2 14.2)	15.1 (13.0 17.5)	15.5 (13.3 17.9)	16.0 (13.8 18.4)	16.5 (14.4 18.9)	16.5 (14.3 18.9)
Women	9.8 (8.1 11.8)	13.6 (11.7 15.8)	16.4 (14.2 18.7)	18.4 (16.1 20.9)	20.8 (18.5 23.4)	24.1 (21.4 26.9)
Age group						
54–59	8.0 (6.0 10.6)	11.6 (9.2 14.4)	14.1 (11.5 17.2)	16.7 (13.9 19.9)	17.8 (15.0 21.0)	20.7 (17.5 24.4)
60–69	12.8 (10.8 15.1)	15.9 (13.7 18.3)	15.6 (13.5 18.0)	16.6 (14.4 19.0)	18.5 (16.3 21.1)	19.6 (17.1 22.3)
70–79	9.7 (7.3 12.8)	14.7 (11.6 18.4)	16.8 (13.6 20.7)	16.8 (13.5 20.6)	19.4 (15.9 23.6)	20.5 (16.7 24.9)
≥ 80	18.8 (11.7 28.8)	18.6 (11.9 27.9)	25.6 (17.5 35.7)	26.3 (18.2 36.5)	22.4 (15.1 32.0)	22.2 (15.0 31.5)
Men						
Age group						
54–59	7.5 (4.7 11.6)	10.8 (7.5 15.2)	12.5 (9.0 17.0)	14.9 (11.1 19.6)	15.5 (11.9 19.9)	15.2 (11.4 20.0)
60–69	15.4 (12.4 19.1)	17.7 (14.5 21.4)	16.1 (13.1 19.7)	15.9 (12.9 19.3)	18.5 (15.1 22.4)	19.1 (15.6 23.2)
70–79	11.9 (8.2 17.0)	17.0 (12.6 22.5)	18.0 (13.4 23.7)	17.0 (12.6 22.4)	15.5 (11.2 21.0)	14.7 (10.6 20.0)
≥ 80	15.8 (6.9 32.0)	15.5 (7.4 29.5)	21.4 (11.3 36.8)	21.1 (11.1 36.5)	10.9 (4.5 23.9)	9.6 (3.7 22.7)
Women						
Age group						
54–59	8.5 (5.8 12.3)	12.4 (9.2 16.5)	15.8 (12.2 20.4)	18.5 (14.5–23.3)	20.2 (16.1 25.0)	26.5 (21.5 32.3)
60–69	10.0 (7.7 13.0)	14.0 (11.3 17.4)	15.1 (12.1 18.6)	17.3 (14.3 20.9)	18.6 (15.4 22.2)	20.0 (16.6 24.0)
70–79	7.7 (4.9 11.8)	12.5 (8.7 17.8)	15.7 (11.5 21.2)	16.6 (12.2 22.1)	23.0 (17.8 29.1)	25.7 (20.0 32.5)
≥ 80	20.9 (11.7 34.5)	20.8 (11.9 33.9)	28.4 (17.6 42.4)	29.9 (18.9 43.9)	30.5 (19.5 44.2)	30.6 (19.4 44.7)
TSI ≥ 1 % below baseline						
Sex						
Men	29.8 (27.0 32.7)	34.2 (31.4 37.2)	32.3 (29.6 35.1)	32.4 (29.7 35.3)	33.2 (30.4 36.1)	31.7 (28.9 34.6)
Women	33.8 (31.0 36.8)	41.4 (38.4 44.4)	44.5 (41.5 47.5)	45.1 (42.1 48.2)	47.9 (44.9 51.0)	44.7 (41.6 47.9)
Age group						
54–59	32.8 (29.1 36.6)	37.4 (33.7 41.3)	37.9 (34.2 41.7)	39.2 (35.5 43.0)	41.8 (37.9 45.8)	39.5 (35.6 43.5)
60–69	32.1 (29.1 35.3)	37.2 (34.1 40.4)	38.4 (35.4 41.6)	38.4 (35.3 41.6)	39.2 (36.2 42.4)	36.2 (33.1 39.5)
70–79	27.9 (23.8 32.4)	36.3 (31.7 41.0)	36.2 (31.7 41.0)	35.7 (31.3 40.5)	40.6 (35.9 45.5)	38.9 (34.2 43.9)
≥ 80	38.7 (29.4 49.0)	50.5 (40.1 60.8)	49.4 (39.3 59.6)	51.1 (40.9 61.3)	43.8 (34.1 54.1)	43.6 (34.4 53.3)

Table 2 (continued)

	30 s	40 s	50 s	60 s	90 s	180 s
	% (95 % CI)	% (95 % CI)	% (95 % CI)	% (95 % CI)	% (95 % CI)	% (95 % CI)
Age group						
54–59	28.6 (23.7 34.0)	31.2 (26.2 36.7)	28.8 (24.0 34.0)	31.4 (26.5 36.8)	34.1 (28.8 39.8)	31.6 (26.5 37.1)
60–69	32.6 (23.7 37.2)	35.9 (31.7 40.4)	34.8 (30.7 39.2)	33.7 (29.6 38.2)	34.6 (30.5 39.0)	33.7 (29.5 38.2)
70–79	24.9 (23.7 31.0)	33.8 (28.0 40.2)	31.5 (25.8 37.8)	29.8 (24.3 36.0)	29.7 (24.0 36.2)	30.0 (24.2 36.5)
≥ 80	34.9 (23.7 50.0)	42.7 (28.0 58.9)	39.0 (25.2 54.8)	38.8 (24.9 54.7)	27.9 (16.9 42.3)	22.2 (12.3 36.8)
Women						
Age group						
54–59	37.0 (31.6 42.8)	43.8 (38.3 49.4)	47.2 (41.7 52.8)	47.1 (41.6 52.7)	49.6 (43.9 55.3)	47.7 (41.8 53.7)
60–69	31.6 (27.6 35.9)	38.5 (34.2 43.0)	42.2 (37.9 46.6)	43.3 (38.9 47.8)	44.0 (39.5 48.6)	38.8 (34.5 43.3)
70–79	30.6 (24.8 37.2)	38.5 (32.0 45.3)	40.5 (33.9 47.5)	41.0 (34.5 47.9)	50.4 (43.6 57.2)	47.1 (40.2 54.0)
≥ 80	41.4 (28.8 55.3)	55.9 (42.0 68.9)	56.7 (42.7 69.7)	59.8 (45.6 72.5)	55.0 (41.1 68.1)	58.0 (44.1 70.6)

response, with many stabilizing below baseline levels.

Previous studies using NIRS to assess orthostatic hemodynamics report outcomes based on small participant numbers, lack of adjustment for confounders and limited age ranges, making it difficult to draw age-related conclusions. For example, in a study of 30 participants a smaller drop in oxygenation in older adults (52–65 years) compared to younger adults (27–33 years) was reported, and this smaller drop was also reflected in their transcranial Doppler measurements (Kim et al., 2011). In another study of 27 participants no age gradient was found (Gatto et al., 2007), but the upper age was just 60 years. Our results are consistent with Mehagnoul-Schipper et al. who found a large drop in oxygenated hemoglobin in older participants (70–83 years, $N = 18$) compared to younger participants (22–45 years, $N = 10$) (Mehagnoul-Schipper et al., 2000). As their analysis was based on an averaged one-minute period, this reduction was most likely due to a combination of a large drop and slow recovery. In the younger group no reduction was detected which is likely due to a quick recovery. The one-minute averaged data would conceal such nuances in the response. The mixed effect models in our study also allowed us to examine the response in more detail, and also allowed us to control for a comprehensive set of covariates and confounders such as standing speed, which were not included in other studies. Our large sample size also allowed us to detect such differences.

Given degradations in compensatory elements of the cardiovascular system with age including reduced baroreflex sensitivity, increased BP leading to reduced arterial compliance and microvascular stiffness, reduced CO, and less efficacy of the muscle pump (Lieshout et al., 2001), it is expected that age-related changes in the cerebral oxygenation response would be present. As the muscle pump is the main component of the response, we accounted for this in the fully adjusted model by including TUG time as a covariate. However, the age differences remained. Our findings were also independent of the change in cardiac output.

The findings in relation to sex differences are consistent with a large transcranial Doppler study ($N = 544$, 236 males) by Deegan et al. who reported a greater drop in indexes of cerebral perfusion in men compared to women (Deegan et al., 2011). An MRI sub-study in this TILDA cohort reported higher cerebral perfusion in women (Leidhin

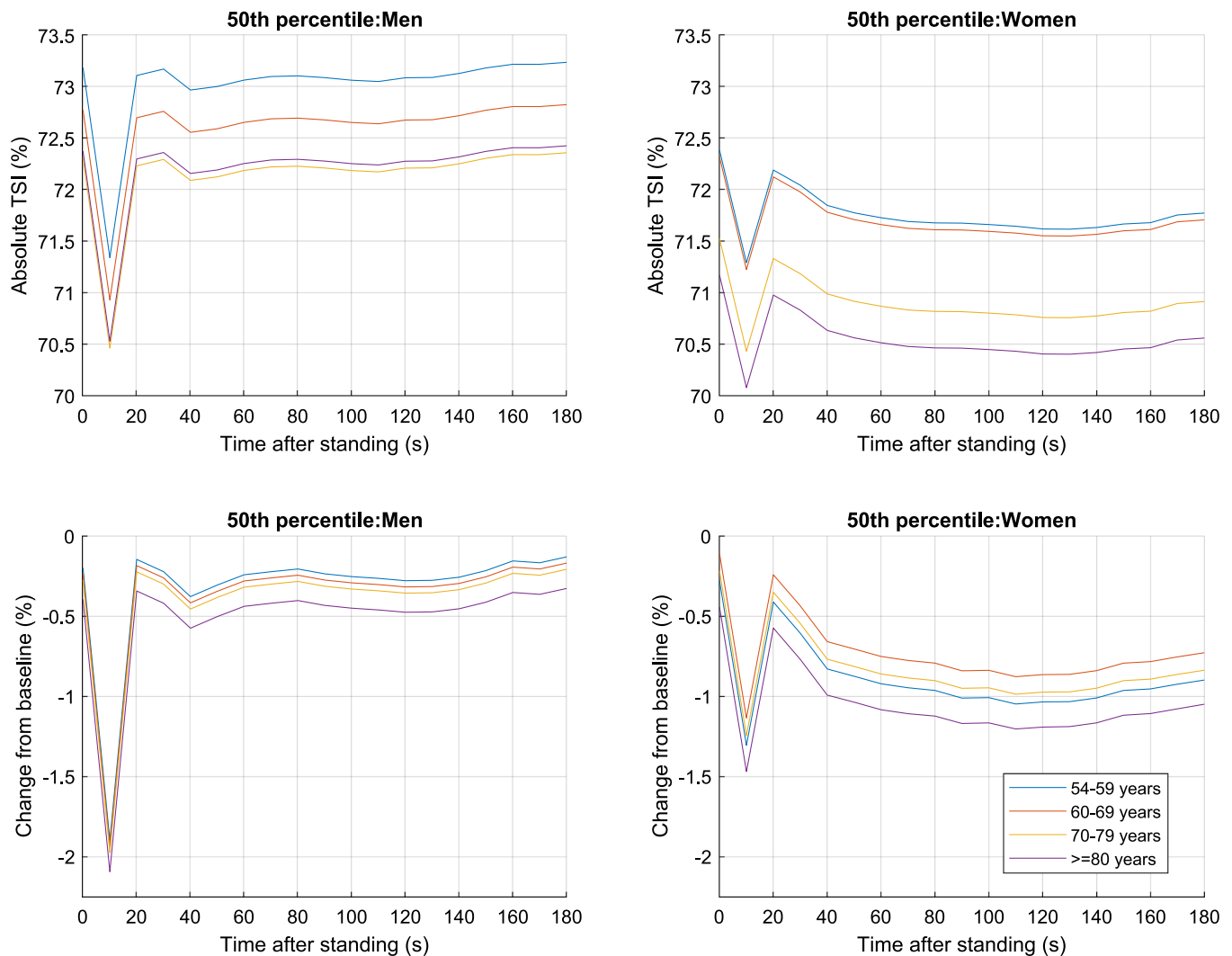


Fig. 4. Age-related cerebral oxygenation response to orthostasis. Median normative values for change in tissue saturation index (TSI) from baseline, stratified by age and sex. (See Data Supplementary for Fig. S4 and Tables S6 and S7 for 5th to 95th percentiles).

et al., 2021) also indicating evidence of sex differences in this group. However, many studies utilizing NIRS did not report sex differences, or had imbalance in genders (Mol et al., 2019) making the effects difficult to separate.

A potential source of sex differences could be the variation in CO, however we adjusted for CO in the final model, and it did not explain the differences. Mol et al. also found that CO did not account for the drops in postural cerebral oxygenation (Mol et al., 2019). Lower hematocrit and blood viscosity (Parkes et al., 2004) and increased metabolic rates (Hazlett et al., 2010; Lu et al., 2011) in women may in part explain why we found women stabilizing below baseline values, but we were not able to determine this in our study.

The maximum change in cerebral oxygenation detected was small compared to our previous report on the change in peripheral blood pressure (Finucane et al., 2014) (maximum drop was ~2 % vs ~25 % of the baseline) which may also explain discrepancies in other studies with low numbers. They may have been insufficiently powered to detect such differences across age ranges and sexes, particularly when initial responses were averaged over 15, 30 or 60 s periods as previously described the rapid and transient elements would be obscured. In this study we have taken a more granular approach and revealed differences in the early stages of the cerebrovascular response. Transcranial Doppler studies also measure the cerebral response in large arteries (e.g. middle cerebral artery), compared to NIRS which was measured in the frontal

lobe microvasculature which could also explain some of the differences observed.

Previous cohort and population studies have established associations between anti-hypertensive medications and OH, syncope, and falls (Canney et al., 2016; Group SR et al., 2015; Juraschek et al., 2019). Our observation of those using anti-hypertensives having lower cerebral oxygenation in the recovery phase, and thus being less likely to return to baseline may explain this association which warrants further investigation.

In patient studies there are clear associations between postural symptoms, syncope and cerebral oxygenation levels e.g. during head-up tilt (Bachus et al., 2017; Novak, 2016), however it is likely that the levels induced in this study during orthostasis were insufficient to cause such symptoms.

European Society of Cardiology guidelines (Brignole et al., 2018) recommend that for the investigation of orthostatic symptoms that BP is measured supine and standing. This work suggests the addition of measures of cerebral perfusion may be useful to detect patients at risk from syncope or falls from hypoperfusion changes.

We utilized NIRS to measure cerebral oxygenation as a proxy for cerebral perfusion. This study adds to the interpretation of these measures and adds to the evidence supporting its usefulness as a clinical tool in monitoring cerebral hemodynamics. Given that it is non-invasive, portable and requires minimal training to use it is well-suited to

monitoring clinical populations, as well as large cohorts. Previous work from the TILDA group has also shown associations between these NIRS measurements and clinical outcomes such as depression (Briggs et al., 2019), generalized anxiety disorder (McDowell et al., 2021) and cardiovascular risk factors (Newman et al., 2020).

4.1. Strengths and limitations

Strengths of this study include the large population cohort, which has extensive health and behavioral data, enabling adjustment of important covariates. Survey weights were applied to the normative and prevalence data to control for biases in those attending the health center. NIRS overcomes some of the disadvantages associated with transcranial Doppler technology (e.g. acoustic window availability in older participants, training, assumption of constant vessel diameter during measurement). However, there are limitations to the study. CO₂ partial pressure and blood hemoglobin were not measured due to practicalities for such a large cohort in a population study. The cross-sectional nature of the study limits causality interpretation.

5. Conclusions

Cerebral autoregulation is impaired with age, particularly in older women and those taking anti-hypertensives. SBP during the stand explained some of the age gradient in the late recovery stage of the stand for the oldest age group. Reported orthostatic symptoms did not correlate with hypoperfusion. Therefore, measures of orthostatic cerebral flow should be assessed in addition to peripheral BP in older patients irrespective of symptoms. Further studies are required to investigate the relationship between NIRS measurements and clinical outcomes such as falls, cognitive impairment and depression.

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Data availability statement

The data underlying this article will be shared on reasonable request to The Irish Longitudinal study on Ageing, Trinity College Dublin, Dublin 2 via email at tilda@tcd.ie.

CRediT authorship contribution statement

Louise Newman: Conceptualization, Methodology, Software, Formal analysis, Data curation, Resources, Writing – original draft, Writing – review & editing, Visualization. **John D. O'Connor:** Methodology, Writing – review & editing, Visualization. **Hugh Nolan:** Methodology, Writing – review & editing. **Richard B. Reilly:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Rose Anne Kenny:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors report no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.exger.2022.111903>.

References

- Bachus, E., Holm, H., Hamrefors, V., Melander, O., Sutton, R., Magnusson, M., et al., 2017. Monitoring of cerebral oximetry during head-up tilt test in adults with history of syncope and orthostatic intolerance. *Europace* 20 (9), 1535–1542.
- Briggs, R., Carey, D., Kennelly, S.P., Kenny, R.A., 2018. Longitudinal association between orthostatic hypotension at 30 seconds post-standing and late-life depression. *Hypertension* 71 (5), 946–954.
- Briggs, R., Carey, D., Claffey, P., McNicholas, T., Newman, L., Nolan, H., et al., 2019. The association between frontal lobe perfusion and depressive symptoms in later life. *Br. J. Psychiatry* 214 (4), 230–236.
- Brignole, M., Moya, A., de Lange, F.J., Deharo, J.C., Elliott, P.M., Fanciulli, A., et al., 2018. 2018 ESC guidelines for the diagnosis and management of syncope. *Eur. Heart J.* 39 (21), 1883–1948.
- Brown, A.M., Ransom, B.R., 2007. Astrocyte glycogen and brain energy metabolism. *Glia* 55 (12), 1263–1271.
- Bush, B., Shaw, S., Cleary, P., Delbanco, T.L., Aronson, M.D., 1987. Screening for alcohol abuse using the CAGE questionnaire. *Am. J. Med.* 82 (2), 231–235.
- Canney, M., O'Connell, M.D., Murphy, C.M., O'Leary, N., Little, M.A., O'Seaghdha, C.M., et al., 2016. Single agent antihypertensive therapy and orthostatic blood pressure behaviour in older adults using beat-to-beat measurements: the Irish longitudinal study on ageing. *PLoS One* 11 (1), e0146156.
- Claffey, P., Pérez-Denia, L., Rivasi, G., Finucane, C., Kenny, R.A., 2020. Near-infrared spectroscopy in evaluating psychogenic pseudosyncope—a novel diagnostic approach. *QJM* 113 (4), 239–244.
- Deegan, B.M., Sorond, F.A., Galica, A., Lipsitz, L.A., O'Laughlin, G., Serrador, J.M., 2011. Elderly women regulate brain blood flow better than men do. *Stroke* 42 (7), 1988–1993.
- Donoghue, O.A., McGarrigle, C.A., Foley, M., Fagan, A., Meaney, J., Kenny, R.A., 2018. Cohort profile update: the Irish longitudinal study on ageing (TILDA). *Int. J. Epidemiol.* 47 (5), 1398–1.
- Fedorowski, A., Stavenow, L., Hedblad, B., Berglund, G., Nilsson, P.M., Melander, O., 2010. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmö Preventive Project). *Eur. Heart J.* 31 (1), 85–91.
- Ferrari, M., Quaresima, V., 2012. Near infrared brain and muscle oximetry: from the discovery to current applications. *J. Near Infrared Spectrosc.* 20 (1), 1–14.
- Finucane, C., O'Connell, M.D.L., Fan, C.W., Savva, G.M., Soraghan, C.J., Nolan, H., et al., 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.
- Finucane, C., O'Connell, M.D., Donoghue, O., Richardson, K., Savva, G.M., Kenny, R.A., 2017. Impaired orthostatic blood pressure recovery is associated with unexplained and injurious falls. *J. Am. Geriatr. Soc.* 65 (3), 474–482.
- 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.
- Gatto, R., Hoffman, W., Paisansathan, C., Mantulin, W., Gratton, E., Charbel, F.T., 2007. Effect of age on brain oxygenation regulation during changes in position. *J. Neurosci. Methods* 164 (2), 308–311.
- Group SR, Wright Jr., J.T., Williamson, J.D., Whelton, P.K., Snyder, J.K., Sink, K.M., et al., 2015. A randomized trial of intensive versus standard blood-pressure control. *N. Engl. J. Med.* 373 (22), 2103–2116.
- Guelen, I., Westerhof, B.E., Van Der Sar, G.L., Van Montfrans, G.A., Kiemeneij, F., Wesseling, K.H., et al., 2003. Finometer, finger pressure measurements with the possibility to reconstruct brachial pressure. *Blood Press Monit.* 8 (1), 27–30.
- Hazlett, E.A., Byne, W., Brickman, A.M., Mitsis, E.M., Newmark, R., Haznedar, M.M., et al., 2010. Effects of sex and normal aging on regional brain activation during verbal memory performance. *Neurobiol. Aging* 31 (5), 826–838.
- Imholz, B.P., Wieling, W., van Montfrans, G.A., Wesseling, K.H., 1998. Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. *Cardiovasc. Res.* 38 (3), 605–616.
- Juraschek, S.P., Simpson, L.M., Davis, B.R., Beach, J.L., Ishak, A., Mukamal, K.J., 2019. Effects of antihypertensive class on falls, syncope, and orthostatic hypotension in older adults: the ALLHAT trial. *Hypertension* 74 (4), 1033–1040.
- Kearney, P.M., Cronin, H., O'Regan, C., Kamiya, Y., Savva, G.M., Whelan, B., et al., 2011. Cohort profile: the Irish longitudinal study on ageing. *Int. J. Epidemiol.* 40 (4), 877–884.
- Kim, Y.S., Bogert, L.W., Immink, R.V., Harms, M.P., Collier, W.N., van Lieshout, J.J., 2011. Effects of aging on the cerebrovascular orthostatic response. *Neurobiol. Aging* 32 (2), 344–353.
- Leidhin, C.N., McMorrough, J., Carey, D., Newman, L., Williamson, W., Fagan, A.J., et al., 2021. Age-related normative changes in cerebral perfusion: data from the Irish longitudinal study on ageing (TILDA). *NeuroImage* 117741.
- Lieshout, J.J.V., Pott, F., Madsen, P.L., Goudoever, J.V., Secher, N.H., 2001. Muscle tensing during standing. *Stroke* 32 (7), 1546–1551.
- Lu, H., Xu, F., Rodrigue, K.M., Kennedy, K.M., Cheng, Y., Flicker, B., et al., 2011. Alterations in cerebral metabolic rate and blood supply across the adult lifespan. *Cereb. Cortex* 21 (6), 1426–1434.

- McDowell, C.P., Newman, L., Monroe, D.C., O'Connor, J.D., Knight, S.P., Kenny, R.A., et al., 2021. The association between generalized anxiety disorder and resting-state prefrontal cortex oxygenation is modified by self-reported physical activity: results from the Irish longitudinal study on ageing. *J. Gerontol. Ser. A* 76 (8), 1391–1397.
- McNicholas, T., Tobin, K., Carey, D., O'Callaghan, S., Kenny, R.A., 2018. Is baseline orthostatic hypotension associated with a decline in global cognitive performance at 4-year follow-up? Data from TILDA (The Irish Longitudinal Study on Ageing). *J. Am. Heart Assoc.* 7 (19), e008976.
- Mehagnoul-Schipper, D.J., Vloet, L.C., Colier, W.N., Hoefnagels, W.H., Jansen, R.W., 2000. Cerebral oxygenation declines in healthy elderly subjects in response to assuming the upright position. *Stroke* 31 (7), 1615–1620.
- Mehagnoul-Schipper, D.J., van der Kallen, B.F., Colier, W.N., van der Sluijs, M.C., van Erning, L.J., Thijssen, H.O., et al., 2002. Simultaneous measurements of cerebral oxygenation changes during brain activation by near-infrared spectroscopy and functional magnetic resonance imaging in healthy young and elderly subjects. *Hum. Brain Mapp.* 16 (1), 14–23.
- Mol, A., Woltering, J.H.H., Colier, W.N.J.M., Maier, A.B., Meskers, C.G.M., van Wezel, R. J.A., 2019. Sensitivity and reliability of cerebral oxygenation responses to postural changes measured with near-infrared spectroscopy. *Eur. J. Appl. Physiol.* 119 (5), 1117–1125.
- Mol, A., Maier, A.B., van Wezel, R.J.A., Meskers, C.G.M., 2020. Multimodal monitoring of cardiovascular responses to postural changes. *Front. Physiol.* 11, 168.
- Newman, L., Nolan, H., Carey, D., Reilly, R.B., Kenny, R.A., 2020. Age and sex differences in frontal lobe cerebral oxygenation in older adults—normative values using novel, scalable technology: findings from the Irish longitudinal study on ageing (TILDA). *Arch. Gerontol. Geriatr.* 87, 103988.
- Novak, P., 2016. Orthostatic cerebral hypoperfusion syndrome. *Front. Aging Neurosci.* 8, 22.
- O'Connor, J.D., O'Connell, M.D.L., Nolan, H., Newman, L., Knight, S.P., Kenny, R.A., 2020. Impact of standing speed on the peripheral and central hemodynamic response to orthostasis. *Hypertension* 75 (2), 524–531.
- O'Halloran, A.M., Kenny, R.A., King-Kallimanis, B.L., 2014. The latent factors of depression from the short forms of the CES-D are consistent, reliable and valid in community-living older adults. *Eur. Geriatr. Med.* 5 (2), 97–102.
- O'Connell, M.D., Savva, G.M., Finucane, C., Romero-Ortuno, R., Fan, C.W., Kenny, R.A., 2018. Impairments in hemodynamic responses to orthostasis associated with frailty: results from the Irish longitudinal study on ageing (TILDA). *J. Am. Geriatr. Soc.* 66 (8), 1475–1483.
- Parkes, L.M., Rashid, W., Chard, D.T., Tofts, P.S., 2004. Normal cerebral perfusion measurements using arterial spin labeling: reproducibility, stability, and age and gender effects. *Magn. Reson. Med.* 51 (4), 736–743.
- Rigby, R.A., Stasinopoulos, D.M., 2004. Smooth centile curves for skew and kurtotic data modelled using the Box-Cox power exponential distribution. *Stat. Med.* 23 (19), 3053–3076.
- Rigby, R.A., Stasinopoulos, D.M., 2005. Generalized additive models for location, scale and shape. *J. R. Stat. Soc.: Ser. C: Appl. Stat.* 54 (3), 507–554.
- Robertson, A.D., Udow, S.J., Espay, A.J., Merola, A., Camicioli, R., Lang, A.E., et al., 2019. Orthostatic hypotension and dementia incidence: links and implications. *Neuropsychiatr. Dis. Treat.* 15, 2181–2194.
- Sexton, D.J., Canney, M., O'Connell, M.L., et al., 2017. Injurious falls and syncope in older community-dwelling adults meeting inclusion criteria for sprint. *JAMA Intern. Med.* 177 (9), 1385–1387.
- Sokoloff, L., 1969. The Metabolism of the Central Nervous System In Vivo. American Physiological Society, Washington, D.C.
- Willie, C.K., Tzeng, Y.C., Fisher, J.A., Ainslie, P.N., 2014. Integrative regulation of human brain blood flow. *J. Physiol.* 592 (5), 841–859.
- Wolters, F.J., Mattace-Raso, F.U., Koudstaal, P.J., Hofman, A., Ikram, M.A., 2016. Heart brain connection collaborative research G. Orthostatic hypotension and the long-term risk of dementia: a population-based study. *PLoS Med.* 13 (10), e1002143.