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REVIEW ARTICLE

Seasonal variation in vascular function: a systematic review and recommendations for future research

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ABSTRACT

Vascular function serves as a prognostic marker for cardiovascular disease and may exhibit seasonal variations due to lifestyle and environmental factors. Our systematic review aimed to determine whether seasonal variations in vascular function are present. We conducted a search of five databases (MEDLINE via PubMed, CINAHL, Web of Science, Cochrane Library, and Biomed Central) to identify evidence of seasonal variations in vascular function. Studies were eligible for inclusion if they assessed vascular function in adult humans during two or more seasons and were published in English. Of the 20,420 studies screened, 12 were eligible and none were excluded due to bias. Nine studies reported significant seasonal variations in vascular function, whereas three studies found no significant seasonal variations. The seasonality of vascular function remains unclear. However, current literature indicates that vascular dysfunction may exhibit a seasonal pattern, with vascular function reduced in the winter. Seasonal variations in endothelial function necessitate further exploration, particularly concerning factors such as exercise, temperature, light exposure, and air pollution. Future research should adopt standardised protocols, involve diverse and larger populations, employ longitudinal designs to minimise confounding factors, systematically measure and adjust for environmental variables, and accurately assess the impact of seasonal variation on vascular function.

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Endothelium; seasonal variation; vascular function; nitric oxide; endothelial function

Introduction

Cardiovascular disease (CVD) is the leading cause of all-cause mortality globally (Mc Namara et al. 2019), and an increased incidence of cardiovascular (CV) events has been observed in the winter months (Fares 2013). The seasonality of CVD is likely attributed to the complex interaction between seasonal environmental factors, behavioural factors, and individual susceptibility factors such as age and pre-existing health conditions (Stewart et al. 2017). However, the underlying pathophysiological mechanisms are not yet well understood. The endothelium, a single-cell layer lining all the blood vessels, is crucial for maintaining vascular homeostasis and function (Poredos et al. 2021). Endothelial dysfunction, fundamentally characterised by impaired nitric oxide (NO) bioavailability (Cyr et al. 2020), is widely recognised as the first step in the pathogenic progression of CVD (Poredos et al. 2021). Indeed, the endothelium is increasingly becoming a surrogate endpoint for

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assessing cardiovascular risk (Versari et al. 2009). As such, investigating potential fluctuations in endothelial and/or vascular function may provide valuable insights into the pathophysiological mechanisms responsible for the observed seasonal variation in CVD susceptibility and inform the development of targeted preventative strategies.

Current data indicate that vascular function may be compromised during winter months compared to summer months (Widlansky et al. 2007; Iwata et al. 2012; Honda and Igaki 2021). A cross-sectional study involving 2,587 participants from the Framingham Offspring cohort demonstrated that flow mediated dilation (FMD) was highest (3.01 ± 0.09%, $n = 733$) in the warmest quartile and lowest (2.56 ± 0.10%, $n = 599$) in the coldest quartile, even after adjusting for known risk factors for endothelial dysfunction (Widlansky et al. 2007). These results are consistent with the findings of Iwata et al. (2012), who observed similar statistically significant differences in FMD responses in the same participants between winter and summer seasons (Winter: 4.74 ± 2.15%, Summer: 5.71 ± 2.15%). Conversely, Patel et al. (2011) reported no significant seasonal differences in agonist-mediated endothelium-dependent vasodilation (EDV) in their analysis of a large cross-sectional dataset (Summer: 9.95 ± 0.53%, Winter: 11.32 ± 0.53%). Nevertheless, the relationship between vascular function and seasonal variation remains unclear (Klein-Weigel et al. 2003; Patel et al. 2011; Iwata et al. 2012).

An understanding of the seasonality of endothelial function is essential given that endothelial dysfunction may manifest under specific environmental conditions (Honda and Igaki 2021), thereby placing some populations at greater risk. Furthermore, this understanding enables the development and optimisation of interventions to either prevent or mitigate adverse health outcomes associated with vascular dysfunction. To the best of our knowledge, no previous study has comprehensively reviewed existing evidence on seasonal variations in vascular function. Therefore, this study aims to systematically review and synthesise the available evidence on seasonal variations in vascular dysfunction.

Methods

Protocol registration and search strategy (literature search strategy)

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration ID: CRD42022346315) on 18 July 2022. Online databases were systematically searched on 18 July 2022 and researched on the 10th of May 2023 and 14th of March 2024 to identify all studies investigating seasonal variation in endothelial function. The search was conducted in the following electronic databases: MEDLINE (via PubMED), CINAHL, Web of Science, Cochrane Library, and Biomed Central for articles published until March 2024. The search terms consisted of keywords related to seasonal variations in meteorological conditions and vascular dysfunction (Supplementary Material S1). The results of the initial search were uploaded into EndNote (Clarivate Analytics, Philadelphia, USA) and de-duplicated according to a standardised protocol (Bramer et al. 2016). Upon removal of duplicates, the resulting papers were uploaded to Rayyan.ai (Ouzzani et al. 2016), a web-based programme for systematic reviews.

Inclusion criteria (selection criteria)

Reviewer 1 (AG) screened the titles and abstracts using the web-based tool Rayyan.ai (Ouzzani et al. 2016). Two reviewers (AG and DM) independently screened all full texts of eligible studies. After selection, the full text of the articles were studied. The reference lists of all the included studies were manually searched to identify any additional relevant studies. The inclusion criteria were as follows: (a) studies involving human adults aged ≥18 years; (b) studies including at least one measure of vascular function in at least two distinct seasons; (c) studies which included original data; and (d) studies published in English.

Justification for inclusion of assessment methods

Our systematic review aimed to broadly examine evidence of seasonal variation in vascular dysfunction. While FMD is the gold-standard technique of assessing endothelial function, we also included in our search other relevant methods that provide insight into vascular dysfunction. Supplementary file S1 provides an overview of included methods and the justification for their inclusion.

Quality assessment

The quality, selection, comparability, and outcome of cross-sectional and cohort studies were critically appraised using the Newcastle–Ottawa scale (Wells et al. 2000), and adapted Newcastle–Ottawa scale for cross-sectional research (Herzog et al. 2013). Study quality was rated as good, fair, or poor, according to the instrument. Two authors independently scored the included articles, and any discrepancies were discussed with a third reviewer (MR).

Data extraction

One reviewer (AG) performed the data extraction, and another reviewer (DM) verified it. Data from eligible full texts were collectively extracted into a standardised data extraction table prepared in Microsoft Office Excel 2021 (Microsoft Corporation, Redmond, WA, USA). The extracted information included the first author's name, publication year, study population, study design, study conditions, measure of endothelial function, outcomes, and confounding factors. Studies varied considerably in how they defined seasons. Several studies used traditional calendar month definitions with winter as December–February, spring as March–May, summer as June–August, and autumn as September–November (Honda et al. 2020; Cheng et al. 2023; Maruhashi et al. 2023). Some studies used solstice dates with winter (21 December–20 March), spring (21–March–20 June), summer (21 June–20 September), and autumn (21 September–20 December) (Widlansky et al. 2007; Patel et al. 2011). Other studies compared just two seasons, typically winter versus summer, with varying definitions of these periods (Gardner-Medwin et al. 2001; Klein-Weigel et al. 2003; Tsao et al. 2019). One study divided the year into six bimonthly periods (Kita and Kitamura 2019), while others used non-traditional seasonal definitions (Haliloğlu et al. 2016). For analysis purposes in this review, we used the seasonal classifications as defined within each individual study to compare between studies. The summary was reported in narration and a descriptive table, along with a detailed critical assessment of each study.

Data synthesis

A meta-analysis was not conducted because of the inherent complexity of the repeated-measures (within-subjects) design present in the original studies, which precludes traditional meta-analysis approaches (Higgins and Thompson 2002). Furthermore, the original studies did not report the nature of the correlation between the repeated measures in each study. Not accounting for this correlation would result in biased wide confidence intervals and potentially affect the study conclusions (Higgins and Thompson 2002). Consequently, narrative synthesis was deemed the most suitable approach for presenting and summarising the findings of this review.

Results

Included studies

A total of 20,420 studies were identified from the database search. Following duplicate removal and title and abstract screening, full-text eligibility was assessed for 98 articles

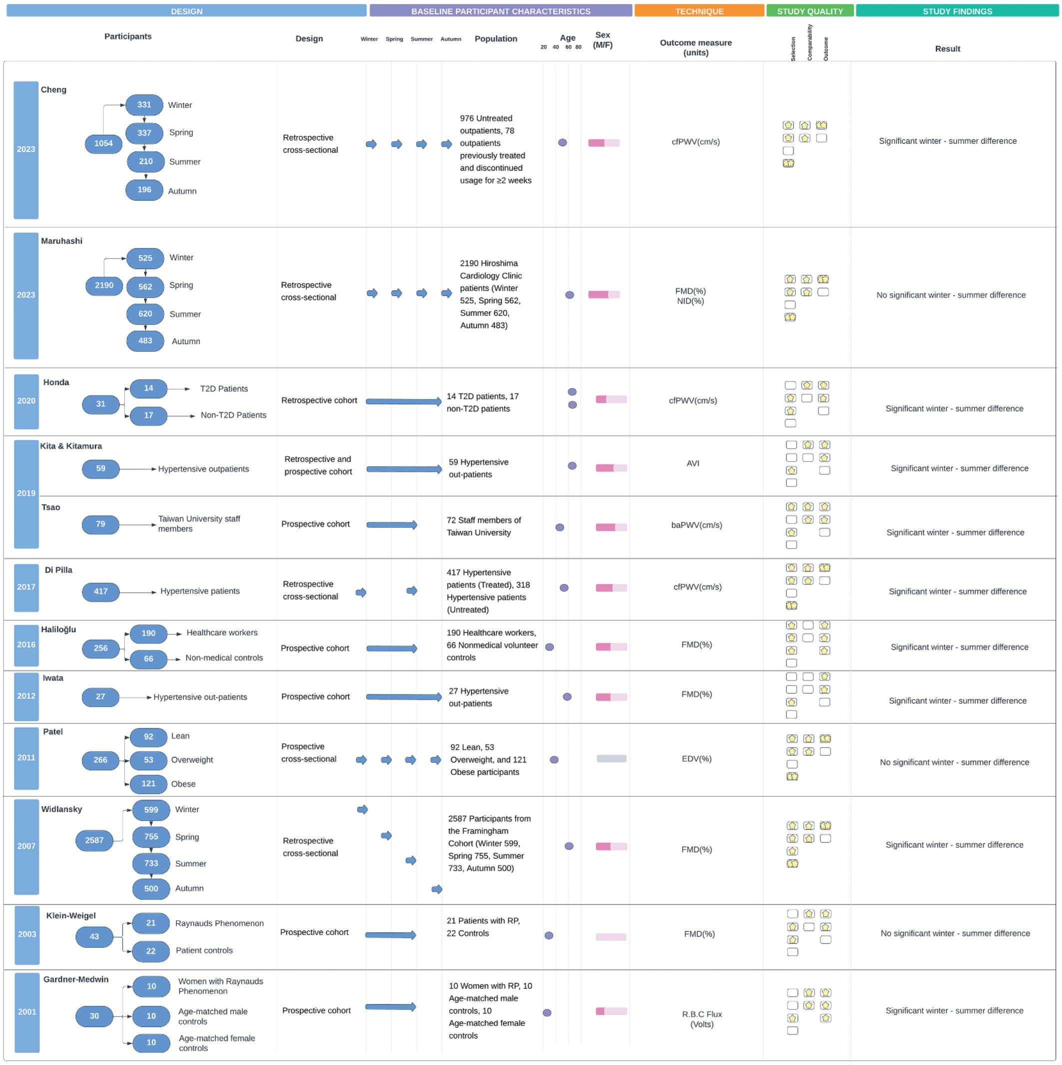

Figure 1. GoFER (graphical overview for evidence reviews) diagram summarising the study designs, participant characteristics, techniques, study quality assessments, and key findings of studies investigating seasonal variation in endothelial function. FMD, flow-mediated dilation; PWV, pulse wave velocity; NID, nitroglycerine-induced vasodilation; RBC, red blood cell; AVI, arterial velocity pulse index; EDV, endothelial-dependent vasodilation.

(Figure 1). Finally, 12 articles were included, comprising 7 cohort studies and 5 cross-sectional studies (Figure 2) (Gardner-Medwin et al. 2001; Klein-Weigel et al. 2003; Nawrot et al. 2005; Widlansky et al. 2007; Patel et al. 2011; Iwata et al. 2012; Di Pilla et al. 2017; Tsao et al. 2019; Kita and Kitamura 2019; Honda et al. 2020; Maruhashi et al. 2023).

Quality assessment

Quality assessment of cohort studies was conducted using the Newcastle–Ottawa scale for cohort studies (Wells et al. 2000) and an adapted version for cross-sectional studies (Herzog et al. 2013). The quality assessment of cohort studies revealed that six studies were rated as fair quality (score of

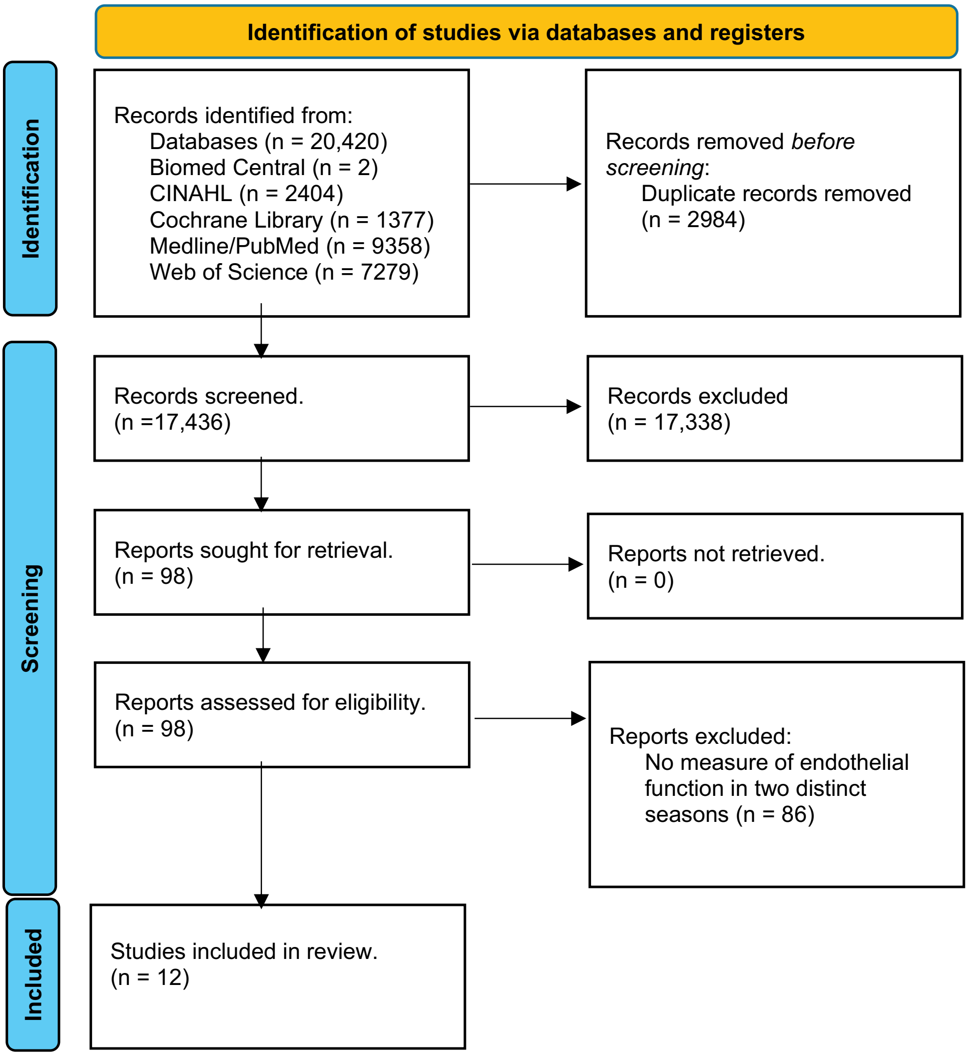

Figure 2. Prisma flow diagram for new systematic reviews detailing the study selection and screening process.

2–5) and one was rated good/high quality (score of 6–9) (Wells et al. 2000). For cross-sectional studies, all five were rated as good/high quality (score of 6–9) (Herzog et al. 2013). No study was excluded due to risk of bias.

Characteristics of included studies

The characteristics of the 12 included studies are presented in Table 1. The 12 studies were published between 2001 and 2024 and conducted in various temperate countries, including Turkey, the USA, Italy, Taiwan, Japan, Austria, China, and the United Kingdom. The sample sizes ranged from 27 to 2587, with 7211 participants across all the studies. The mean age of the participants ranged from 21 to 67 years. Six studies utilised the FMD technique to assess vascular function, one utilised the brachial-ankle pulse wave velocity (baPWV) technique, two utilised the

Table 1. Main characteristics of included studies.

Author (year)	Country, city, latitude (degrees)	Study design	Participants	Sex distribution (M/F)	Age (mean years)	Outcome measure (units)	Observed seasons	Confounders	Newcastle–Ottawa Scale Score
Cheng et al. (2023)	Shangai, China (31.23)	Retrospective-cross sectional	976 Untreated outpatients, 78 outpatients previously treated and discontinued usage for ≥2 weeks	522/532	51.0	cfPWV (m/s)	Winter, Spring, Summer, Autumn	Age, Sex, BMI, smoking, alcohol intake, serum total cholesterol, and nighttime pulse rate.	8*
Di Pilla et al. (2017)	Pisa, Italy (43.72°N)	Retrospective cross-sectional	417 hypertensive patients (treated), 318 hypertensive patients (untreated)	425/306	55.7	cfPWV (m/s)	Winter, Summer	Hypertension, hypertensive medication, dietary habits, selection bias, season, physical activity, age, sex, sunlight exposure	8*
Gardner-Medwin et al. (2001)	Birmingham, England (52.45°N)	Prospective cohort	10 Women with RP, 10 Age-matched male controls, 10 Age-matched female controls	10/20	28.3	R.B.C. Flux (Volts)	Winter, Summer	RP, Sample size, clothing, temperature, season, dietary habits, selection bias, sunlight exposure, climate	5
Haliloğlu et al. (2016)	Istanbul, Turkey (40.99°N)	Prospective cohort	190 healthcare workers, 66 nonmedical volunteer controls	133/123	34.7, 32.5	FMD (%)	Winter, Summer	Selection bias, ethnicity, socioeconomic status, sunlight exposure, physical activity, sample size, vitamin D supplements, climate	5
Honda et al. (2020)	Higashioda, Japan (34.84°N)	Retrospective cohort	14 T2DM patients, 17 non-T2DM patients	12/19	65.9, 66.7	FMD (%)	Winter, Spring, Summer, Autumn	Diabetes Mellitus, medication usage, dietary habits, physical activity, climate, sunlight exposure	5
Iwata et al. (2012)	Shizuoaka, Japan (35.20°N)	Prospective cohort	27 hypertensive out-patients	14/13	60	FMD (%)	Winter, Summer	Hypertension, diabetes mellitus and hyperlipidaemia, medication usage, measurement clinic site, sample size	3
Kita and Kitamura (2019)	Miyazaki, Japan (31.83°N)	Retrospective and prospective cohort	59 hypertensive out-patients	32/27	66.5	AVI	Winter, Spring, Summer, Autumn	Hypertension, hypertension medication, dietary habits, physical activity, air pollution, sunlight exposure	3
Klein-Weigel et al. (2003)	Innsbruck, Austria (47.26°N)	Prospective cohort	21 Patients with RP, 22 controls	0/43	31.1; 27.8	FMD (%)	Winter, Summer	RP, dietary habits, physical activity, medication, air pollution, smoking, sample size, sex	5
Maruhashi et al. (2023)	Hiroshima, Japan (34.39°N)	Retrospective cross-sectional	2190 hiroshima Cardiology Clinic patients (Winter 525, Spring 562, Summer 620, Autumn 483)	1355/835	61.1	FMD (%), NID (%)	Winter, Spring, Summer, Autumn	Age, Sex, BMI, SBP, HR, Dyslipidemia, Diabetes mellitus, Smoking, Cardiovascular disease, Hypertensive drug use, Statin use	8*
Patel et al. (2011)	Indianapolis, USA (39.78°N)	Prospective cross-sectional	92 Lean, 53 overweight, 121 obese	Not reported	37	EDV (%)	Winter, Spring, Summer, Autumn	Ethnicity, smoking, BMI, dietary habits, physical activity, mediation usage	8*

(*Continued*)

Table 1. (Continued).

Author (year)	Country, city, latitude (degrees)	Study design	Participants	Sex distribution (M/F)	Age (mean years)	Outcome measure (units)	Observed seasons	Confounders	Newcastle–Ottawa Scale Score
Tsao et al. (2019)	Nantou, Taiwan (23.96°N)	Prospective cohort	72 Staff members of Taiwan University	49/23	46	baPWV (cm/s)	Winter, Summer	Age, gender, BMI, smoking and alcohol habits, physical activity, hypertension and hypertension medications	6
Widlansky et al. (2007)	Boston, USA (42.49°N)	Retrospective cross-sectional	2587 Participants from the Framingham Cohort (Winter 599, Spring 755, Summer 733, Autumn 500)	1216/1371	61	FMD (%)	Winter, Spring, Summer, Autumn	Ethnicity, clinic attendance, dietary habits, residual Inter-individual variation, vasoactive medication	9*

AVI, ankle vascular index; baPWV, brachial-ankle pulse wave velocity; cfPWV, carotid-femoral pulse wave velocity; EDV, endothelial-dependent vasodilation; FMD, flow-mediated dilation; Nitroglycerine-induced vasodilation (NID), RBC, red blood cell; RP, Raynaud's phenomenon. *Denotes use of an adapted Newcastle-Ottawa Scale suitable for cross-sectional studies (Herzog et al. 2013).

carotid-femoral pulse wave velocity (cfPWV) technique, one utilised thermodilution, one utilised arterial velocity pulse index (AVI), one utilised nitroglycerine-induced vasodilation (NID), and one utilised red blood cell (RBC) flux to assess vascular function (Table 1). The study designs included six prospective cohort studies, one retrospective cohort study, four retrospective cross-sectional studies and one prospective cross-sectional study (Table 1).

All included studies were conducted in the Northern Hemisphere, and the latitudes of the included studies ranged from 23.96° to 52.45° (Table 1). Nine of the 12 studies recruited participants with pre-existing medical conditions, including Raynaud's phenomenon, Type-2 Diabetes Mellitus (T2DM), hypertension, and dyslipidaemia. All studies measured endothelial function in at least two seasons and six studies measured endothelial function during all four seasons (Table 1). Of the 11 studies that reported sex data, the sex split was 3768 males and 3312 females (53% male, 47% female) (Table 1). One study did not report sex (Table 1) (Patel et al. 2011).

Study outcomes

Table 2 presents a summary of the seasonal variation in vascular dysfunction outcome measures from the 12 published papers. Nine studies reported significant seasonal variation in vascular dysfunction, while three studies found no significant seasonal variation (Table 2).

Seasonal variation of FMD and NID

Four of the six studies that utilised the FMD technique reported that endothelial function was significantly higher during summer than during winter (Widlansky et al. 2007; Iwata et al. 2012; Haliloğlu et al. 2016; Honda et al. 2020). The study by Haliloğlu et al. (2016) observed a decrease in FMD% of 2.74% points from summer to winter in healthcare workers and a 4.2% point decrease in non-medical volunteers (11.53 ± 6.07% and 8.79 ± 4.75%, $p = 0.008$ in healthcare workers versus 11.2 ± 5.1% and 7.0 ± 3.3%, $p = 0.001$ in non-medical volunteers). In this study, subgroup analysis revealed that seasonality varied by occupation, with medical doctors demonstrating a significant seasonal difference in FMD% (11.65 ± 6.28% vs 8.83 ± 4.95%, $p = 0.01$), whereas no statistically significant difference was observed in other subgroups ($p > 0.05$). Iwata et al. (2012) observed a significant decline between summer and winter measurements (5.71 ± 2.17% vs. 4.74 ± 2.15%), and this association was not associated with biological sex gender, age, body mass index, alcohol consumption, or smoking.

In the study by Widlansky et al. (2007), FMD% was lowest in winter (2.56 ± 0.10% winter, 3.01 ± 0.09% summer, $p = 0.02$), with sex an independent predictor of brachial artery diameter ($R^2 = 0.32$). Furthermore, Honda et al. (2020) observed that in participants with T2DM, FMD % was greater in the summer months (T2DM summer group: 4.5 ± 0.8%) compared to the winter months (T2DM winter group: 3.5 ± 1.1% $p < 0.01$). Similarly, in participants without T2DM, FMD% was greater in the summer months (non-T2DM summer group: 4.6 ± 0.7%) compared to the winter months (non-T2DM winter group: 3.9 ± 0.6%, $p < 0.01$). In contrast to these findings, a large cross-sectional study by Maruhashi et al. (2023) found no significant seasonal difference in FMD% (spring: 3.9 ± 3.1%, summer: 3.5 ± 3.0%, autumn: 3.7 ± 3.0%, winter: 3.6 ± 3.2%, $p = 0.14$). Furthermore, Klein-Weigel et al. (2003), observed no significant changes in FMD% between summer (12.5 ± 8.2%) and winter (14.7 ± 9.0%) ($p = 0.09$) (Klein-Weigel et al. 2003). The Maruhashi et al. (2023) study also included NID as a measure of endothelium independent vasodilation. They reported significant seasonal differences in NID (spring: 12.8 ± 6.3%, summer: 12.0 ± 6.1%, autumn: 11.7 ± 6.1%, winter: 12.3 ± 5.9%; $p = 0.02$). However, after adjusting for confounding factors in a multivariate analysis, season was not significantly associated with NID ($\beta = -0.012$, $p = 0.56$).

Table 2. Vascular dysfunction measures by group across seasons.

Author (year)	Outcome Measure (units)	Group	N	Winter	Spring	Summer	Autumn	Sig	Winter – summer statistically significant difference
Cheng et al. (2023)	cfPWV (m/s)	Untreated outpatients	976	7.9 ± 1.5	7.6 ± 1.2	7.8 ± 1.4	7.9 ± 1.3	*P = 0.040*	Y
Di Pilla et al. (2017)	cfPWV (m/s)	Hypertensive outpatients	731	9.28 ± 2.04	–	7.99 ± 1.47	–	*P* < 0.01	Y
Gardner-Medwin et al. (2001)	R.B.C Flux (Volts)	RP patients	10	Hotbox: 2.61 ± 0.10 Coldbox: 0.71 ± 0.08,	– –	Hotbox: 2.17 ± 0.11 Coldbox: 1.08 ± 0.08	– –	*p* < 0.0001 *P* < 0.0001	Y
Gardner-Medwin et al. (2001)	R.B.C Flux (Volts)	Male healthy controls	10	Hotbox: 2.03 ± 0.10 Coldbox: 1.07 ± 0.13	– –	Hotbox: 2.51 ± 0.12 Coldbox: 1.33 ± 0.10	– –	*P* < 0.0001 *P* < 0.0001	
Gardner-Medwin et al. (2001)	R.B.C Flux (Volts)	Female healthy controls	10	Hotbox: 2.11 ± 0.10 Coldbox: 0.52 ± 0.07	– –	Hotbox: 2.48 ± 0.10 Coldbox: 1.15 ± 0.07	– –	*P* < 0.0001 *P* < 0.0001	
Haliloğlu et al. (2016)	FMD (%)	Healthcare workers	190	8.79±4.75	–	11.53±6.07	–	*P* = 0.008	Y
Haliloğlu et al. (2016)	FMD (%)	Non-medical volunteers	66	7.0±3.3	–	11.20±5.10	–	*P* = 0.001	Y
Honda et al. (2020)	FMD (%)	Non-type-2 diabetes	17	3.9 ± 0.6	4.5 ± 1.1	4.6 ± 0.7	4.4 ± 0.9	*P* < 0.01	Y
Honda et al. (2020)	FMD (%)	Type-2 diabetes	14	3.5 ± 1.1	4.3 ± 1.0	4.5 ± 0.8	4.1 ± 1.1	*P* < 0.01	Y
Iwata et al. (2012)	FMD (%)	Hypertensive outpatients	27	4.74 ± 2.15	–	5.71 ± 2.17	–	*P* = 0.03	Y
Kita and Kitamura (2019)	AVI (%)	Hypertensive outpatients	59	22.6 ± 6.9	24.3 ± 8.3	25.1 ± 7.6	24.4 ± 7.6	*P* < 0.01	Y
Klein-Weigel et al. (2003)	FMD (%)	RP patients	21	14.7 ± 9.0	–	15.2 ± 6.2	–	None reported	N
Klein-Weigel et al. (2003)	FMD (%)	Healthy controls	22	12.5 ± 8.2	–	10.6 ± 9.0	–	*P* = 0.09	N
Maruhashi et al. (2023)	FMD (%)	Cardiology outpatients	2190	3.6 ± 3.2	3.9 ± 3.1	3.5 ± 3.0	3.7 ± 3.0	*P* = 0.14	N
Maruhashi et al. (2023)	NID (%)	Cardiology outpatients	2190	12.3 ± 5.9	12.8 ± 6.3	12.0 ± 6.1	11.7 ± 6.1	*P = 0.02*	N^{-}
Patel et al. (2011)	EDV (%)	Healthy general population	266	11.32 ± 0.53	11.79 ± 0.53	9.95 ± 0.59	11.01 ± 0.51	*P* = 0.123	N^{+}
Tsao et al. (2019)	baPWV (cm/s)	Forest workers	72	1481.8 ± 236.0	–	1425.1 ± 209.5	–	*P* < 0.01	Y
Widlansky et al. (2007)	FMD (%)	Framingham offspring cohort	2587	2.56 ± 0.10	2.79 ± 0.09	3.01 ± 0.09	2.87 ± 0.11	*P* = 0.02 (winter–summer)	Y

AVI, ankle vascular index; baPWV, brachial-ankle pulse wave velocity; cfPWV, carotid-femoral pulse wave velocity; EDV, endothelial-dependent vasodilation; FMD, flow-mediated dilation; R.B.C, red blood cell; Nitroglycerine-induced vasodilation (NID); RP, Raynaud's phenomenon. Note. $^{+}$after adjusting for the unequal distribution of obesity grouping. Patel different participant numbers for each season (winter, $n = 70$; spring, $n = 68$; summer, $n = 54$; and autumn, $n = 74$). Widlansky different participant numbers each season: winter, $n = 599$; spring, $n = 755$; summer, $n = 733$; autumn, $n = 500$). $^{-}$Multiple linear regression analysis revealed not significantly associated (*p = 0.56*)

Seasonal variation of pulse wave velocity (PWV)

Three studies utilised PWV as the outcome measure, and all three studies reported that PWV values were significantly higher in winter than summer (Di Pilla et al. 2017; Tsao et al. 2019) In the study by Tsao et al. (2019), which estimated PWV from the brachial-ankle recording site, the authors observed a significant decrease in mean baPWV from winter (1481.8 ± 236.0 cm/s) to summer (1425.1 ± 209.5 cm/s) ($p < 0.0001$). Di Pilla et al. (2017) utilised the carotid-femoral recording sites, and the authors demonstrated an inverse correlation between daylight hours and cfPWV ($r = -0.18$, $p < 0.0001$). Furthermore, they also report that the median monthly cfPWV values were highest in winter, with January and November recording the highest values of 9.28 ± 2.04 m/s and 9.18 ± 2.35 m/s, respectively (Di Pilla et al. 2017). Conversely, the lowest values were observed during the summer months, with June and July recording values of 7.99 ± 1.47 m/s and 8.03 ± 2.02 m/s, respectively (Di Pilla et al. 2017). Cheng et al. (2023) also observed significant seasonal variation in cfPWV, with the lowest values in spring (7.6 ± 1.2 m/s) and the highest values in summer (7.8 ± 1.4 m/s), autumn (7.9 ± 1.3 m/s) and winter (7.9 ± 1.5 m/s) ($p = 0.040$).

Seasonal variation of EDV, AVI, and RBC flux

Three studies used alternative methods to vascular function (Table 1). Patel et al. (2011) observed a significant seasonal variation in unadjusted EDV values for healthy individuals ($p = 0.019$). However, after adjusting for the unequal distribution of obesity grouping, no significant seasonal variation in EDV was observed ($p = 0.123$). Kita and Kitamura (2019) observed a significant seasonal variation in a novel AVI, with AVI significantly higher in the summer compared to the winter (22.6 ± 6.9 vs 25.1 ± 7.6, $p < 0.01$). Furthermore, in the study by Gardner-Medwin et al. (2001), the authors observed that R.B.C. flux was significantly lower during winter compared to summer under identical conditions ($p < 0.0001$).

Discussion

To the best of our knowledge, this is the first systematic review of the literature investigating the impact of seasonal changes on vascular dysfunction. The key finding of our review is that it supports the notion that endothelial function follows a seasonal pattern in adults. In this systematic review of 12 studies the majority of studies (9/12) demonstrate a seasonal pattern in vascular function, with a significant decrease in function observed during the winter months (Gardner-Medwin et al. 2001; Widlansky et al. 2007; Iwata et al. 2012; Haliloğlu et al. 2016; Di Pilla et al. 2017; Tsao et al. 2019; Kita and Kitamura 2019; Honda et al. 2020; Cheng et al. 2023). Three studies did not demonstrate any significant seasonal variation in vascular function (Klein-Weigel et al. 2003; Patel et al. 2011; Maruhashi et al. 2023). Klein-Weigel et al. (2003) observed no statistically significant difference in FMD between participants, however, it is noteworthy that they observed a change in FMD in the expected direction, with higher FMD values in the summer compared to winter. Likewise, Maruhashi et al. (2023) reported a non-significant change in FMD that followed the anticipated seasonal pattern, suggesting the presence of a trend consistent with the majority of studies, despite the absence of statistical significance.

A key finding of our review is that the quality of the included studies varied, with five studies (Widlansky et al. 2007; Patel et al. 2011; Di Pilla et al. 2017; Cheng et al. 2023; Maruhashi et al. 2023) receiving a high-quality score and seven studies (Gardner-Medwin et al. 2001; Klein-Weigel et al. 2003; Iwata et al. 2012; Haliloğlu et al. 2016; Tsao et al. 2019; Kita and Kitamura 2019; Honda et al. 2020) receiving a lower quality score based on their respective Newcastle–Ottawa scale score. The studies that scored the lowest on the Newcastle–Ottawa scale consistently lacked a non-exposed cohort for comparison and did not adequately control for confounding factors in their analyses. Indeed, the Newcastle–Ottawa scale presents certain limitations, one of which is its reliance on the evaluator's judgement, which could potentially introduce bias. Furthermore, the scale assesses a limited number of study characteristics and does not provide guidance on handling missing data. Consequently, further research with larger sample sizes and rigorous methodologies are needed to support the evidence base for the seasonal variation of vascular function.

A common limitation among the included studies was the lack of control for confounding variables such as diet, physical activity levels, exercise habits, disease status, age, biological sex, and BMI. Additionally, the assessment frequency of vascular function varied considerably, ranging from 2 to 4 time points. Of the 12 studies, six employed the gold standard technique (FMD) for measuring endothelial function, and one utilised multiple methods. Studies were evenly split between cohort-based design and cross-section design. The cross-sectional study design does not allow for understanding how an individual's vascular function measurements correlate with each other across different seasons. Longitudinal studies that observe vascular function in the same individuals across different seasons offer more robust insights into potential cause-and-effect relationships compared to cross-sectional designs.

Seasonal changes in environmental conditions and lifestyle behaviours may affect endothelial function through several mechanisms (Stewart et al. 2017). Endothelial dysfunction is a complex pathology characterised by reduced NO production, increased oxidative stress, increased inflammation, altered angiogenesis, and increased leukocyte adhesion (Poredos et al. 2021). The mechanisms associated with endothelial dysfunction appear to converge on complex and multifactorial pathways (Cyr et al. 2020; Poredos et al. 2021). The observed seasonal variations in endothelial function in our systematic review may result from alterations in environmental conditions, lifestyle adaptations, or other confounding factors that influence one or more mechanistic pathways.

Environmental and lifestyle influences on vascular dysfunction

Our systematic review reveals conflicting findings regarding the relationship between average external temperature and endothelial function. Widlansky et al. (2007) reported a significant positive association between temperature and FMD. In line with this, Iwata et al. (2012) reported an increased resting brachial artery diameter in the warm season compared to the cold season. However, the underlying mechanisms for this observation remain unclear and warrant further investigation. In contrast, a study by Nawrot et al. (2005) demonstrated that for each 10°C increase in average daily temperature, the odds of developing endothelial dysfunction rises by 58%. Importantly, Widlansky et al. (2007) employed a multivariate model to examine the relationship between temperature and endothelial function. After adjusting for potential risk factors, they found no statistically significant association between temperature and FMD% suggesting a single focus on temperature may oversimplify the complex interplay of factors influencing endothelial function.

The complexity of this relationship is accentuated by the multiple converging mechanisms that influence endothelial function. Other mechanisms, such as NO bioavailability, might also play a role, as temperature changes can increase NO production via NO synthase (NOS) enzymes (Venturini et al. 1999). Additionally, endothelial function, assessed using the FMD technique, is partially mediated by shear rate (Poredos et al. 2021). Furthermore, heat exposure may increase the production of reactive oxygen species (ROS), directly impairing endothelial function (Shaito et al. 2022) or indirectly influencing NO production (Cyr et al. 2020). Di Pilla et al. (2017) showed a negative correlation between PWV and mean outdoor temperature, however when they employed a multiple linear regression model to examine the relationship between seasonal changes and PWV, only daylight hours remained independently associated with PWV (Di Pilla et al. 2017). This finding indicates that light exposure may be a crucial determinant of arterial stiffness in this population.

Seasonal changes in ultraviolet (UV) light exposure have been demonstrated to affect vitamin D synthesis, with office workers exhibiting lower vitamin D levels during winter than during summer (Cinar et al. 2014). Vitamin D plays a role in the renin-angiotensin system and influences NO production (Legarth et al. 2018). Insufficient vitamin D levels are also associated with increased oxidative stress in endothelial cells (Victor et al. 2009). Interestingly, UVA exposure to healthy human skin (i.e. vitamin D-independent exposure) can increase NO and S-nitrosothiol concentrations, inducing vasodilation and reducing blood pressure by 11% (Opländer et al. 2009), independent of endothelial NOS (eNOS) enzymes and temperature changes (Liu et al. 2014). Liddle et al. (2022) observed that NO bioavailability follows a seasonal pattern, with enhanced NO synthesis during the summer months potentially resulting from increased UV-A exposure on the skin, activating dermal stores of NO precursors (Paunel et al. 2005; Opländer et al. 2009; Liddle et al. 2022). However, in our review, Haliloğlu et al. (2016) reported no statistically significant differences in UV indices despite observing a seasonal variation in FMD%, indicating that UV exposure may not influence endothelial function. In our review, only Haliloğlu et al. (2016) and Di Pilla et al. (2017) specifically addressed UV exposure in relation to endothelial function. This highlights the need for more focused research in this area to understand it's potential influence.

Increased physical activity is associated with improvements in endothelial function (Moyna and Thompson 2004), and physical activity levels exhibit seasonal fluctuations for both males and females (Shephard and Aoyagi 2009). Nevertheless, in a recent mini-review by Honda and Igaki (2021), the authors concluded that there is no definitive evidence supporting the hypothesis that seasonal fluctuations in physical activity levels directly result in alterations in endothelial function among males. This statement was based on the findings three studies (Widlansky et al. 2007; Iwata et al. 2012; Honda et al. 2020), all of which were included in our systematic review of the literature. In our review, two studies included measures of physical activity in their analysis (Haliloğlu et al. 2016; Honda et al. 2020). Honda et al. (2020) investigated the seasonal impact on FMD and exercise in adults with and without T2DM. They reported that FMD was significantly greater in spring, summer, and autumn than in winter regardless of regular exercise participation (Honda et al. 2020). Haliloğlu et al. (2016) corroborate this finding by observing a seasonal variation in FMD, despite the absence of a significant variation in physical activity. From the reviewed literature it is unclear how exercise habits interact with season to affect vascular function.

A study in Japan demonstrated that types and amounts of certain dietary nutrients consumed change throughout the seasons (Suga et al. 2014). Furthermore, alterations in specific nutrient intakes such as omega-3, antioxidants, fibre, flavanols, nitrate-containing foods, and sodium intake can influence endothelial function (Cuevas and Germain 2004). Given the role of nitrate in NO production, it is essential to consider the potential influence of seasonal variations in nitrate intake on endothelial function (Lundberg et al. 2008). Notably, none of the included studies reported dietary intake data. However, a cohort study involving healthy adults observed reduced NO bioavailability in winter compared to summer, despite vitamin D and dietary nitrate intake remaining consistent across both seasons (Liddle et al. 2022).

Di Pilla et al. (2017) employed a univariate analysis to investigate the association between air pollution and PWV and observed that certain air pollutants, such as carbon monoxide (CO), nitrous oxide (N_2O), and nitrogen oxides (NOx), were positively correlated with PWV. However, further analysis using a multiple linear regression model that accounted for confounding variables revealed no significant association between air pollution and PWV (Di Pilla et al. 2017). Analogous to the effects of light exposure and temperature, increased exposure to air pollutants can generate ROS, increase inflammation, and reduce NO bioavailability, consequently affecting vascular function (Rao et al. 2018). Furthermore, exposure to air pollution may increase sympathetic activity, leading to increased vasoconstriction and contributing to the development of vascular dysfunction (Rao et al. 2018).

Confounding factors

Several studies investigating the potential determinants of seasonal changes in vascular function have indicated that vascular function may be significantly influenced by confounding factors, such as weight status, age, biological sex, and disease status (Widlansky et al. 2007; Man et al. 2020; Cheng et al. 2023). Obesity is associated with low-grade chronic inflammation and insulin resistance, which can disrupt production of NO via reduced activation of eNOS (Engin 2017). Interestingly, Patel et al. (2011) adjusted for the unequal distribution of obesity groups in their analysis and found no significant seasonal variations in the EDV percentage (Patel et al. 2011). In support of this, Haliloğlu et al. (2016) reported no statistically significant differences in BMI despite showing seasonal variation in FMD%.

Honda et al. (2020) observed significant differences in FMD% values between seasons irrespective of disease status (T2DM vs. non-T2DM). Interestingly, Klein-Weigel et al. (2003) reported no seasonal variation in FMD% of patients with Raynaud's phenomenon. At present, it is unclear whether the presence of certain diseases influenced the observed seasonal variations in vascular function in the studies included in this review, and thus, there is a need to investigate whether those with established disease demonstrate differing seasonal variations in vascular function. The mean age of the participants included in the studies in our review ranged between 21 and 67 years. In older adults, a decrease in the production of NO via eNOS is observed (Toda 2012). As such, the observed variations in vascular function could, in part, be attributed to the age-related changes in vascular health (Toda 2012).

Furthermore, biological sex may have confounded the results, as variations in sex hormones, such as oestrogen and testosterone, can affect vascular function by promoting NO bioavailability, reducing inflammation, and inhibiting atherosclerosis (Stanhewicz et al. 2018). Indeed, smoking can influence vascular function through mechanisms similar to those of previous confounders by influencing NO bioavailability, oxidative stress, and inflammation (Hashimoto et al. 2021). Furthermore, excessive alcohol consumption is associated with endothelial dysfunction via inflammatory and oxidative stress mechanisms (Tanaka et al. 2016).

Clinical implications

A previous meta-analysis of 14 studies demonstrated that an increase in FMD by 1% point was associated with a 13% reduction in the risk of CV events (Inaba et al. 2010). In our review, studies that utilised the FMD technique to assess endothelial function observed an average 20% increase in FMD value (~1.0% point) from winter to summer (Klein-Weigel et al. 2003; Widlansky et al. 2007; Iwata et al. 2012; Haliloğlu et al. 2016; Honda et al. 2020; Maruhashi et al. 2023). Therefore, interventions aimed at augmenting FMD% could be beneficial to offset impairment in the winter months. It is also important to note that while the seasonal changes in FMD% may be statistically significant, they may not translate into clinically relevant health outcomes. Indeed, in our review, FMD% ranged from $2.56 \pm 0.1\%$ to $15.2 \pm 6.2\%$ across the included studies, highlighting that for some populations (e.g. where high baseline FMD% is reported) any changes may not be of practical/clinical importance.

At present, a cut-off value for normal PWV is set between 8 and 12 m/s (Reference Values for Arterial Stiffness' Collaboration 2010). Di Pilla et al. (2017) observed a PWV of 9.28 m/s in the winter and 7.99 m/s in the summer, indicating that winter conditions may reduce vascular function. Despite the lack of clarity around cut-off values, the current data hold clinical utility, as increased PWV of any magnitude indicates that endothelial function is reduced (Jadhav and Kadam 2005). The growing evidence of winter-associated endothelial dysfunction may elucidate the mechanistic causes of this impairment. Consequently, interventions targeting endothelial function may improve public health outcomes, may help reduce elevated winter CVD peaks and potentially influence public health policies regarding winter physical activity, dietary advice, and sunlight exposure.

Limitations

Our review has several limitations. Initially, a meta-analysis was intended; however, due to the high heterogeneity between study protocols and outcome measures, synthesising pooled data was deemed inappropriate. The included studies feature a mix of designs, with some opting for cross-sectional design, as such, paired comparisons could not be made in these studies. Furthermore, some studies only measured endothelial function in two seasons rather than four. Additionally, the studies used various methods for assessing endothelial function. While the most common method utilised was the gold standard FMD assessment, others employed PWV, an indirect measure of arterial stiffness that is influenced by endothelial dysfunction, AVI, or RBC flux. Furthermore, controlling for potential confounding factors in this type of research is challenging, and most studies had sample sizes < 50 without controlling for confounding risk factors.

A significant limitation across the included studies was the lack of consistent adjustment for environmental variables that could influence vascular function. While some studies considered outdoor temperature (Widlansky et al. 2007; Iwata et al. 2012) or UV exposure (Haliloğlu et al. 2016; Di Pilla et al. 2017), there was no standardised approach to measuring or adjusting for important environmental factors. Key variables such as humidity, indoor temperature, use of air conditioning or heating, and time spent indoors versus outdoors were rarely reported or controlled for. This inconsistency in accounting for environmental variables makes it challenging to determine whether observed seasonal variations are due to direct environmental effects, behavioural adaptations to these conditions, or other seasonal factors.

Recommendations for future research

Our review highlights the significance of understanding and considering the seasonality of vascular function and its implications for vascular health. Recommendations for future research include employing the FMD technique to assess endothelial function and evaluating its function across all four seasons. Future studies should involve larger and more diverse populations to minimise individual differences and identify confounding factors. Longitudinal studies following the same participants would provide a more accurate understanding of the effects of seasonal variations on vascular function. Additionally, future research should examine the impact of environmental factors such as light exposure, temperature, and air pollution on vascular function. Personal exposure to these conditions should be measured and analysed to determine their influence on seasonal variation in vascular function. Future studies should implement standardised protocols for measuring and adjusting for environmental variables including environmental variables including indoor and outdoor temperature, humidity, sunlight exposure hours, use of heating and air conditioning, air pollution levels, altitude and atmospheric pressure. Collecting detailed information on participants' comorbidities, exercise habits, diet, and other lifestyle factors will aid in controlling for potential confounding factors. Standardised protocols for measuring FMD, as per Thijssen et al. (2019), should be followed, encompassing factors such as cuff placement, occlusion duration, and measurement timing. Future studies should also explore sex differences and their impact on vascular function.

Conclusion

In conclusion, our review highlights the potential influence of seasonality on vascular function and its implications for vascular health. The observed seasonal decline in vascular function during winter warrants further investigation, particularly in relation to environmental factors such as light exposure, temperature, and air pollution. To better understand these associations and inform public health policies, future research should employ standardised protocols, involve diverse and larger populations, adopt longitudinal designs to minimise confounding factors, and accurately assess the effects of seasonal variation on vascular function. Moreover, considering the potential impact of participants' comorbidities, exercise habits, diet, and other lifestyle factors will contribute to the development of targeted interventions aimed at reducing seasonal CVD peaks and improving overall vascular health.

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Authors contributions

AG, DM, MR and LN conceptualised the study. All authors were involved in the development of the design of the methods. AG and DM conducted the formal analysis. AG prepared an initial draft of the manuscript. All authors contributed to reviewing and editing the final manuscript.

References

Bramer WM, Giustini D, de JG, Holland L, Bekhuis T. 2016. De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc. 104(3):240–243. doi: 10.5195/jmla.2016.24.

Cheng Y, Sheng C-S, Huang J-F, Zhang D-Y, M-X L, Cheng Y-B, D-W A, Guo Q-H, Wang Y, Huang Q-F. 2023. Seasonality in nighttime blood pressure and its associations with target organ damage. Hypertens Res. 46(6):1433–1441. doi: 10.1038/s41440-023-01201-5.

Cinar N, Harmanci A, Yildiz BO, Bayraktar M. 2014. Vitamin D status and seasonal changes in plasma concentrations of 25-hydroxyvitamin D in office workers in Ankara, Turkey. Eur J Intern Med. 25(2):197–201. doi: 10.1016/j.ejim.2013.11.004.

Cuevas AM, Germain AM. 2004. Diet and endothelial function. Biol Res. 37(2):225–230. doi: 10.4067/s0716-97602004000200008.

Cyr AR, Huckaby LV, Shiva SS, Zuckerbraun BS. 2020. Nitric oxide and endothelial dysfunction. Crit Care Clin. 36 (2):307–321. doi: 10.1016/j.ccc.2019.12.009.

Di Pilla M, Bruno RM, Stea F, Massetti L, Taddei S, Ghiadoni L, Modesti PA, Li Volti G. 2017. Impact of seasonality and air pollutants on carotid-femoral pulse wave velocity and wave reflection in hypertensive patients. PLOS ONE. 12(2):e0172550. doi: 10.1371/journal.pone.0172550.

Engin A. 2017. Endothelial dysfunction in obesity. Adv Exp Med Biol. 960:345–379. doi: 10.1007/978-3-319-48382-5_15.

Fares A. 2013. Winter cardiovascular diseases phenomenon. N Am J Med Sci. 5(4):266–279. doi: 10.4103/1947-2714.110430.

Gardner-Medwin JM, Macdonald IA, Taylor JY, Riley PH, Powell RJ. 2001. Seasonal differences in finger skin temperature and microvascular blood flow in healthy men and women are exaggerated in women with primary Raynaud's phenomenon. Br J Clin Pharmacol. 52(1):17–23. doi: 10.1046/j.0306-5251.2001.01405.x.

Haliloğlu Ö, Kasaci T, Yavuz D. 2016. Seasonal vitamin D status and endothelial function in healthcare workers. Turk J Med Sci. 46(1):72–78. doi: 10.3906/sag-1403-114.

Hashimoto H, Maruhashi T, Yamaji T, Harada T, Han Y, Takaeko Y, Kihara Y, Chayama K, Goto C, Aibara Y, et al. 2021. Smoking status and endothelial function in Japanese men. Sci Rep. 11(1):95. doi: 10.1038/s41598-020-80012-x.

Herzog R, Mj Á-P, Díaz C, Del Barrio JL, Estrada JM, Á G. 2013. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Public Health. 13(1):154. doi: 10.1186/1471-2458-13-154.

Higgins JPT, Thompson SG. 2002. Quantifying heterogeneity in a meta-analysis. Stat Med. 21(11):1539–1558. doi: 10.1002/sim.1186.

Honda H, Igaki M. 2021. Seasonal variations in vascular endothelial function and physical activity in men. J Mens Health. 18(2):47. doi: 10.31083/jomh.2021.136.

Honda H, Igaki M, Komatsu M, Tanaka S. 2020. Seasonal variations on endothelium-dependent flow-mediated vasodilation in adults with type 2 diabetes and nondiabetic adults with hypertension and/or dyslipidaemia who perform regular exercise. Endocrinol Diabetes Metab. 4(1). doi: 10.1002/edm2.168.
Inaba Y, Chen JA, Bergmann SR. 2010. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. Int J Cardiovasc Imag. 26(6):631–640. doi: 10.1007/s10554-010-9616-1.
Iwata M, Miyashita Y, Kumagai H. 2012. Seasonal variation of endothelium-dependent flow-mediated vasodilation measured in the same subjects. Am J Cardiovasc Dis. 2(2):111–115.
Jadhav UM, Kadam NN. 2005. Non-invasive assessment of arterial stiffness by pulse-wave velocity correlates with endothelial dysfunction. Indian Heart J. 57(3):226–232.
Kita T, Kitamura K. 2019. Seasonal variation of novel arterial stiffness indexes in Japanese hypertensive patients. Clin Exp Hypertens. 41(7):670–674. doi: 10.1080/10641963.2018.1539092.
Klein-Weigel P, Krall K, Falkensammer J, Heinz-Erian P, Ulmer H, Fraedrich G. 2003. Lack of seasonal variation in flow-mediated dilatation of the brachial artery in women with primary Raynaud's phenomenon and healthy controls. Vasa. 32(2):69–73. doi: 10.1024/0301-1526.32.2.69.
Legarth C, Grimm D, Wehland M, Bauer J, Krüger M. 2018. The impact of vitamin D in the treatment of essential hypertension. Int J Mol Sci. 19(2):455. doi: 10.3390/ijms19020455.
Liddle L, Monaghan C, Burleigh M, Baczynska KA, Muggeridge DJ, Easton C. 2022. Reduced nitric oxide synthesis in winter: a potential contributing factor to increased cardiovascular risk. Nitric Oxide. 127:1–9. doi: 10.1016/j.niox.2022.06.007.
Liu D, Fernandez BO, Hamilton A, Lang NN, Gallagher JMC, Newby DE, Feelisch M, Weller RB. 2014. UVA irradiation of human skin vasodilates arterial vasculature and lowers blood pressure independently of nitric oxide synthase. J Invest Dermatol. 134(7):1839–1846. doi: 10.1038/jid.2014.27.
Lundberg JO, Weitzberg E, Gladwin MT. 2008. The nitrate–nitrite–nitric oxide pathway in physiology and therapeutics. Nat Rev Drug Discov. 7(2):156–167. doi: 10.1038/nrd2466.
Man AWC, Li H, Xia N. 2020. Impact of lifestyles (diet and exercise) on vascular health: oxidative stress and endothelial function. Oxid Med Cell Longev. 2020:1–22. doi: 10.1155/2020/1496462.
Maruhashi T, Kajikawa M, Kishimoto S, Yamaji T, Harada T, Hashimoto Y, Mizobuchi A, Tanigawa S, Yusoff FM, Nakano Y, et al. 2023. Seasonal variations in endothelium-dependent flow-mediated vasodilation and endothelium-independent nitroglycerine-induced vasodilation. Hypertens Res. 47(4):910–920. doi: 10.1038/s41440-023-01504-7.
Mc Namara K, Alzubaidi H, Jackson JK. 2019. Cardiovascular disease as a leading cause of death: how are pharmacists getting involved? Integr Pharm Res Pract. 8:1–11. doi: 10.2147/IPRP.S133088.
Moyna NM, Thompson PD. 2004. The effect of physical activity on endothelial function in man. Acta Physiol Scand. 180(2):113–123. doi: 10.1111/j.0001-6772.2003.01253.x.
Nawrot TS, Staessen JA, Fagard RH, Bortel LMV, Struijker-Boudier HA. 2005. Endothelial function and outdoor temperature. Eur J Epidemiol. 20(5):407–410. doi: 10.1007/s10654-005-1068-x.
Opländer C, Volkmar CM, Paunel-Görgülü A, van Faassen EE, Heiss C, Kelm M, Halmer D, Mürtz M, Pallua N, Suschek CV. 2009. Whole body UVA irradiation lowers systemic blood pressure by release of nitric oxide from intracutaneous photolabile nitric oxide derivates. Circ Res. 105(10):1031–1040. doi: 10.1161/CIRCRESAHA.109.207019.
Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. 2016. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 5(1):210. doi: 10.1186/s13643-016-0384-4.
Patel YR, Han KA, Lteif AA, Wallace JP, Mather KJ. 2011. A cross-sectional evaluation of seasonality as a determinant of endothelial function. Nitric Oxide. 25(3):282–287. doi: 10.1016/j.niox.2011.05.010.
Paunel AN, Dejam A, Thelen S, Kirsch M, Horstjann M, Gharini P, Mürtz M, Kelm M, de Groot H, Kolb-Bachofen V, et al. 2005. Enzyme-independent nitric oxide formation during UVA challenge of human skin: characterization, molecular sources, and mechanisms. Free Radic Biol Med. 38(5):606–615. doi: 10.1016/j.freeradbiomed.2004.11.018.
Poredos P, Poredos AV, Gregoric I. 2021. Endothelial dysfunction and its clinical implications. Angiology. 72(7):604–615. doi: 10.1177/0003319720987752.
Rao X, Zhong J, Brook RD, Rajagopalan S. 2018. Effect of particulate matter air pollution on cardiovascular oxidative stress pathways. Antioxid Redox Signal. 28(9):797–818. doi: 10.1089/ars.2017.7394.
Reference Values for Arterial Stiffness' Collaboration. 2010. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: "establishing normal and reference values." Eur Heart J. 31(19):2338–2350. doi: 10.1093/eurheartj/ehq165.
Shaito A, Aramouni K, Assaf R, Parenti A, Orekhov A, Yazbi AE, Pintus G, Eid AH. 2022. Oxidative stress-induced endothelial dysfunction in cardiovascular diseases. Front Biosci-Landmark. 27(3):0105. doi: 10.31083/j.fbl2703105.
Shephard RJ, Aoyagi Y. 2009. Seasonal variations in physical activity and implications for human health. Eur J Appl Physiol. 107(3):251–271. doi: 10.1007/s00421-009-1127-1.

Stanhewicz AE, Wenner MM, Stachenfeld NS. 2018. Sex differences in endothelial function important to vascular health and overall cardiovascular disease risk across the lifespan. Am J Physiol Heart Circ Physiol. 315(6):H1569–H1588. doi: 10.1152/ajpheart.00396.2018.

Stewart S, Keates AK, Redfern A, Jjv M. 2017. Seasonal variations in cardiovascular disease. Nat Rev Cardiol. 14 (11):654–664. doi: 10.1038/nrcardio.2017.76.

Suga H, Asakura K, Sasaki S, Nojima M, Okubo H, Hirota N, Notsu A, Fukui M, Date C. 2014. Effect of seasonality on the estimated mean value of nutrients and ranking ability of a self-administered diet history questionnaire. Nutr J. 13(1):51. doi: 10.1186/1475-2891-13-51.

Tanaka A, Cui R, Kitamura A, Liu K, Imano H, Yamagishi K, Kiyama M, Okada T, Iso H. 2016. Heavy alcohol consumption is associated with impaired endothelial function: the circulatory risk in communities study (CIRCS). J Atheroscler Thromb. 23(9):1047–1054. doi: 10.5551/jat.31641.

Thijssen DHJ, Bruno RM, van Mil ACCM, Holder SM, Faita F, Greyling A, Zock PL, Taddei S, Deanfield JE, Luscher T, et al. 2019. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. Eur Heart J. 40(30):2534–2547. doi: 10.1093/eurheartj/ehz350.

Toda N. 2012. Age-related changes in endothelial function and blood flow regulation. Pharmacol Ther. 133(2):159–176. doi: 10.1016/j.pharmthera.2011.10.004.

Tsao T-M, Tsai M-J, Hwang J-S, Su T-C. 2019. Health effects of seasonal variation in cardiovascular hemodynamics among workers in forest environments. Hypertens Res. 42(2):223–232. doi: 10.1038/s41440-018-0136-z.

Venturini G, Colasanti M, Fioravanti E, Bianchini A, Ascenzi P. 1999. Direct effect of temperature on the catalytic activity of nitric oxide synthases types I, II, and III. Nitric Oxide Biol Chem. 3(5):375–382. doi: 10.1006/niox.1999.0250.

Versari D, Daghini E, Virdis A, Ghiadoni L, Taddei S. 2009. Endothelial dysfunction as a target for prevention of cardiovascular disease. Diabetes Care. 32(Suppl 2):S314–S321. doi: 10.2337/dc09-S330.

Victor VM, Rocha M, Sola E, Banuls C, Garcia-Malpartida K, Ah- M. 2009. Oxidative stress, endothelial dysfunction and atherosclerosis. Curr Pharm Des. 15(26):2988–3002. doi: 10.2174/138161209789058093.

Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. 2000. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.

Widlansky ME, Vita JA, Keyes MJ, Larson MG, Hamburg NM, Levy D, Mitchell GF, Osypiuk EW, Vasan RS, Benjamin EJ. 2007. Relation of season and temperature to endothelium-dependent flow-mediated vasodilation in subjects without clinical evidence of cardiovascular disease (from the Framingham heart study). Am J Cardiol. 100 (3):518–523. doi: 10.1016/j.amjcard.2007.03.055.