BMJ Open Diabetes Research & Care

# Association of arterial stiffness and neuropathy in diabetes: a systematic review and meta-analysis

Angela Beros , John Sluyter , Robert Keith Rhodes Scragg

**To cite:** Beros A, Sluyter J, Scragg RKR. Association of arterial stiffness and neuropathy in diabetes: a systematic review and meta-analysis. *BMJ Open Diab Res Care* 2023;**11**:e003140. doi:10.1136/bmjdrc-2022-003140

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2022-003140).

Received 21 September 2022
Accepted 8 January 2023



School of Population Health, University of Auckland, The University of Auckland Faculty of Medical and Health Sciences, Auckland, New Zealand

**Correspondence to**
Dr Robert Keith Rhodes Scragg; r.scragg@auckland.ac.nz

## ABSTRACT

Evidence is still emerging on the relationships of arterial stiffness with cardiac autonomic neuropathy (CAN) and peripheral neuropathy (PN). To our knowledge no systematic reviews or meta-analyses of these associations have been published. The purpose of our review was to assess the association of arterial stiffness with each type of neuropathy. Medline and Embase were systematically searched for observational studies of arterial stiffness and neuropathy.

The systematic review of 60 studies (25 for CAN and 37 for PN), 59 including people with diabetes, showed arterial stiffness overall was higher in people with neuropathy than people without neuropathy. Forty-three studies were included in the meta-analysis. For CAN (19 studies), arterial stiffness was increased in people with neuropathy compared with without, as measured by pulse wave velocity (PWV) (mean difference: 1.32 m/s, 95% CI 0.82 to 1.81, p<0.00001), pulse pressure (PP) (mean difference: 6.25 mmHg, 95% CI 4.51 to 7.99, p<0.00001) or augmentation index (mean difference: 5.52%, 95% CI 3.46 to 7.58, p<0.0001). For PN (26 studies), arterial stiffness was increased in people with neuropathy compared with those without, as measured by PWV (mean difference: 1.22 m/s, 95% CI 0.87 to 1.58, p<0.00001) or PP (mean difference: 4.59 mmHg, 95% CI 2.96 to 6.22, p<0.00001). Only two cohort studies were located so the temporality of the association between arterial stiffness and neuropathy remains unclear. Increased arterial stiffness is associated with CAN and PN.

PROSPERO registration number: CRD42019129563.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There are an increasing number of studies in people with diabetes that investigate the association of arterial stiffness with cardiac autonomic neuropathy (CAN) and peripheral neuropathy (PN). The evidence, however, as far as we are aware, has not been assessed by way of systematic review and meta-analysis.

### WHAT THIS STUDY ADDS

⇒ This review identifies, in people with diabetes, clear evidence of an association of arterial stiffness with CAN and PN and indicates that arterial stiffness could be associated with the development of each type of neuropathy. The review also reveals that further research is required to establish the temporality of the relationship.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Arterial stiffness, which is inexpensive and easily able to be assessed in clinical practice, is not usually evaluated in people with diabetes. Incorporation of this measure may help to identify people who are at increased risk of CAN and PN. The reduction of arterial stiffness may also form a new research avenue for therapeutics that prevent and treat each type of neuropathy. Further investigation, however, is first required to understand the temporality of the relationships of arterial stiffness with CAN and PN.

Neuropathy is a common complication of diabetes. The most usual type of neuropathy is distal symmetric peripheral polyneuropathy, also referred to as peripheral neuropathy (PN), defined in people with diabetes as the presence of symptoms or signs of peripheral damage to nerves (sensory or motor) after the exclusion of other causes.[1] The incidence and prevalence of PN is uncertain but is estimated to occur in at least 20% of people who have had type 1 diabetes for at least 20 years[2 3] and 50% of people who have had type 2 diabetes for at least 10 years.[4 5] PN can lead to foot ulceration and is a major contributor to falls and fractures.[1]

Cardiac autonomic neuropathy (CAN), which results from damage to the autonomic nerve fibers to the heart, is also prevalent in populations who have had diabetes for many years. CAN was found in 30% of one cohort of people who had type 1 diabetes for at least 20 years[3 6] and is present in 60% of people who had type 2 diabetes for 15 years.[7 8] CAN is associated with significantly increased risk of cardiovascular mortality as well as progression of diabetic nephropathy and chronic kidney disease.[1]

CAN and PN are for the most part irreversible though treatments do exist to alleviate

patient symptoms. Historically, diagnosis of neuropathy requires examination by skilled personnel and can involve specialized equipment.[9] In its early stages, CAN is often asymptomatic and can only be detected by decreased heart rate variability (HRV).[1]

The identification of modifiable risk factors for neuropathy could assist in the diagnosis of neuropathy, as well as provide new research avenues for the prevention and treatment of the condition. An emerging modifiable risk factor is arterial stiffness, which is the loss of compliance in the more elastic arteries. This leads to reduced cushioning of the cardiac pulse when blood is ejected from the heart and enhanced systolic blood pressure (SBP). This in turn, results in an increase in pulsatile stress in the microcirculation, leading to tearing of endothelial and smooth muscle cells in the smaller arteries that supply blood to the peripheral and cardiac nerves.[10]

Arterial stiffness can be measured by waveform analysis. The most common measures are pulse wave velocity (PWV), with carotid-femoral PWV considered the "gold standard," augmentation index (AIx), and the cruder measure of pulse pressure (PP). With advances in technology, devices that measure arterial stiffness with waveform analysis have become increasingly inexpensive, non-invasive, easy to use, and portable.[11]

An increasing number of studies have measured the relationship between arterial stiffness and neuropathy. To our knowledge, these studies have yet to be assessed by way of systematic review or meta-analysis. Accordingly, we conducted a systematic review and meta-analysis of observational studies that examined the association between arterial stiffness and neuropathy (limited to CAN or PN). We hypothesized that, compared with people who have lower arterial stiffness, people with higher arterial stiffness were more likely to have neuropathy or experience a progression in neuropathy.

## METHODS

### Data sources and searches

We conducted our systematic review and meta-analyses in accordance with both the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[12] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines.[13] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on August 27, 2019 (registration number CRD42019129563).

AB searched Medline and Embase up to June 13, 2022. The search strategy for Medline, which was adapted for Embase, is set out in online supplemental table 1. In addition, AB searched the reference lists of eligible articles and previous reviews for additional studies, and the gray literature using Google and Web of Science, as well as PROSPERO for any ongoing or recently completed systematic reviews. Studies reported in abstracts were included. There was no restriction on language with non-English articles translated using Google Translate. For cohort studies, there was no restriction on length of follow-up.

### Study selection

We included observational studies, namely, cross-sectional, case-control, or cohort studies. We excluded case series and case reports. There was no restriction on participants, including age, sex, blood pressure level, diabetes status, type, or duration.

Neuropathy studies were limited to those that investigated CAN or PN. We included studies where participants were classified as having neuropathy either through a recorded history of neuropathy, or the use of a validated screening instrument (with any adaptations) including for CAN, the Ewing battery of tests[14] and for PN, the Michigan Neuropathy Screening Instrument (MNSI),[15] and the Neuropathy Disability Score (NDS).[16] We also included studies that employed one or more validated tests used to help diagnose neuropathy (such tests may also be incorporated into screening instruments), which included for CAN, measures of HRV, and for PN, included self-report, nerve conduction velocity (NCV), quantitative sensory testing (QST), vibration perception with a tuning fork, pinprick sensation using a monofilament, and ankle reflexes tested with a hammer.[1 9]

Studies were further limited to those that used waveform analysis, including PWV, AIx, and PP, to measure arterial stiffness. In relation to cross-sectional and case-control studies, we included studies where the exposure was arterial stiffness and the outcome was neuropathy and vice versa. In relation to cohort studies, we included studies where the exposure was arterial stiffness and the outcome was the development or progression of neuropathy.

Following the search, duplicates were removed. Titles and abstracts were screened by AB and JS who also undertook the final study selection, based on the inclusion criteria and the full-text articles. Rayyan software was used for both parts of the screening process.[17] Any discrepancies were resolved by consensus and discussion with any disagreements between the authors resolved through discussion with RKRS.

### Data extraction and quality assessment

Data were extracted by AB and checked by JS. Any calculations using the study data were conducted by AB. The quality of each included study was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) for case-control and cohort studies.[18] NOS was also adapted for cross-sectional studies. There were five criteria for cross-sectional studies, with a study able to obtain a maximum of six points; and eight criteria for case-control or cohort studies, with a study able to obtain a maximum of nine points. Studies were judged to be of high quality (≥3 for cross-sectional studies or ≥5 for case-control or cohort studies) or low quality (<3 for cross-sectional studies or <5 for case-control or cohort studies).

### Data synthesis and analysis

For the systematic review, a qualitative summary was used to summarize and explain the characteristics and outcomes of the included studies. We further performed a meta-analysis if we identified at least two studies with results that could be combined into such an analysis. For the meta-analysis, studies were separated into CAN and PN. Case-control and cross-sectional studies were combined in the same meta-analyses. The vast majority of results suitable for meta-analysis (which may not be the only results presented) reported the number of people with and without neuropathy, likely due to the ease of categorization. Arterial stiffness was predominantly recorded as a continuous measure. To perform a meta-analysis in these studies, therefore, we also treated neuropathy as the exposure and arterial stiffness as the outcome. We extracted the number of people with and without neuropathy, as recorded by the study investigators, and the mean and SD of the different measures of arterial stiffness for each exposure group. The few studies that split participants into people with high and low arterial stiffness differed in their measures of arterial stiffness, as well as the cut-points applied to such measures, and hence were unable to be combined into a meta-analysis where arterial stiffness was the exposure and neuropathy was the outcome.

Weighted mean differences and 95% CIs were calculated for each continuous exposure. When the outcome measure was reported as mean and SEM, SDs were estimated using Review Manager V.5.4 software (https://training.cochrane.org/online-learning/core-software/revman). If the outcome measures were reported as the median and IQR, mean and SD values were estimated using formulas published by Luo *et al*[19] and Wan *et al*.[20] Where a study separated out an exposure or non-exposure group into two or more groups, such as when participants with neuropathy were grouped by severity of neuropathy (ie, participants may be grouped as having early stage neuropathy or manifest neuropathy based on the number of abnormal tests), where possible, we combined those groups into one exposure or non-exposure group. If a study, while using a measure of arterial stiffness, determined that measure at more than one site, such as carotid-femoral PWV and brachial-ankle PWV, the most central measure was used. Random-effects models were used in the meta-analyses to provide the most conservative estimates. We assessed heterogeneity with Cochran's Q test and the $I^2$ statistic, with an $I^2$ >50% taken to indicate substantial heterogeneity.[21]

When we detected substantial heterogeneity, and there were at least 10 studies,[21] we conducted subgroup analyses in relation to type of PWV (central or peripheral), age, diabetes duration and SBP as well as meta-regression, where each subgroup had at least four studies,[22] in relation to other potential sources of heterogeneity including sex and study size. Sensitivity analyses were conducted by excluding the one low-quality study (as assessed using NOS), by excluding the two studies published only by way of abstract and by assessing whether the review conclusions would have been different if a fixed effect model had been used. Where there were at least 10 studies in a meta-analysis, we also generated funnel plots for the visual assessment of publication bias,[23] and performed Egger's test.[24] All tests were two-tailed and a p value <0.05 was considered statistically significant. We undertook the meta-analysis using Review Manager V.5.4 software and R statistical software package V.4.0.5 (https://www.r-project.org/).

We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to evaluate the overall certainty of the body of evidence for each outcome.[25] GRADE has four levels: high, moderate, low, or very low, with observational studies initially classified as providing low quality of evidence.

## RESULTS

### Study characteristics

In total, 60 studies were included in the systematic review,[26–85] with 43 of those studies including at least one arterial stiffness measurement suitable for meta-analysis.[29–31 33–35 37–39 41 42 46 47 52 53 55 57 59–77 79–85] Although various studies adjusted for age, sex, diabetes duration, or SBP in data analysis, the values used in the meta-analyses were not adjusted for, other than those studies that only included participants of one sex.[65 75] Aso *et al*[29] and Yokoyama *et al*[83] investigated both CAN and PN (figure 1). Characteristics of the studies included in the meta-analysis are summarized in table 1 in respect of those measures included in the meta-analysis. More detailed characteristics, as well as results, for all studies included in the systematic review are set out in online supplemental table 2 (CAN) and online supplemental table 3 (PN). Those articles that fit the inclusion criteria but were excluded, as they were not the primary article, are set out in online supplemental table 4.

For the purposes of investigating arterial stiffness and neuropathy, we classified 53 of the studies as cross-sectional,[26 28–31 33–36 38–62 64–67 69 71 73–85] 5 as case-control[37 63 68 70 72] and 2 as cohort.[27 32] For cross-sectional studies, all participants had diabetes, except Allison *et al*[26] and Kuo *et al*,[46] who included participants regardless of diabetes status, as well as Cho *et al*,[35] who alongside participants with diabetes, also separately analyzed those with no history of disease known to cause PN. Amione-Guerra and Prasad[28] did not state diabetes status. In case-control studies, we only analyzed participants with diabetes (to avoid confounding where cases had diabetes and neuropathy and controls were healthy). All participants in cohort studies had diabetes.

Of the 59 studies specifying inclusion of participants with diabetes, 38 were carried out in people with type 2 diabetes,[27 29 30 32–34 36 39 41–43 45 48 49 51 54–56 59 60 62 64–67 70–72 75–77 79–85] 11 in people with type 1 diabetes[37 40 44 47 50 53 58 63 69 74 78] and 4 in people with either type 1 or type 2 diabetes[31 38 57 73]

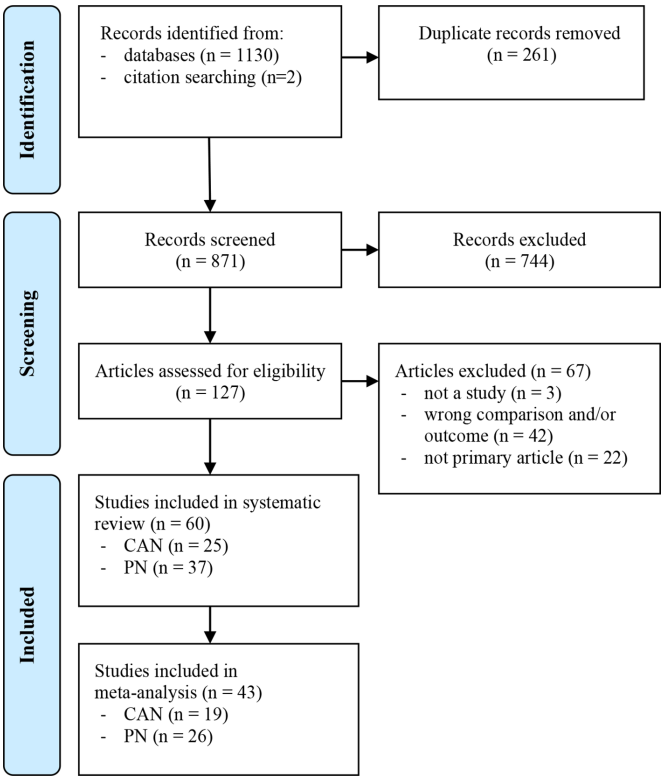


**Figure 1** Flowchart diagram for study selection of systematic review and meta-analysis (based on PRISMA guideline). CAN, cardiac autonomic neuropathy; PN, peripheral neuropathy.

with Fleischer *et al*[38] and Moţăţăianu *et al*[57] reporting separate results for type 1 and type 2 diabetes. Six studies did not specify diabetes type.[26 35 46 52 61 68] Of the 49 studies that reported mean diabetes duration, 26 had a mean diabetes duration of at least 10 years[29 31 33 34 36–38 40 41 44 48 50 53 54 56 58 59 62 63 67–69 74 76 78 82] and 22 had a mean diabetes duration of less than 10 years.[27 30 32 39 42 43 47 49 55 60 64 65 70 71 73 75 79–81 83–85] Moţăţăianu *et al*[57] reported mean diabetes duration of 16 years for type 1 diabetes and mean diabetes duration of 7 years for type 2 diabetes.

Nine studies reported mean SBP ≥140 mmHg,[32 33 35 36 38 41 54 57 76] but for Fleischer *et al*[38] and Moţăţăianu *et al*[57] this was only in respect of participants with type 2 diabetes. Fourteen studies did not report mean SBP[28 44–46 48 51 52 61 68 70–73 77] with the remainder of studies reporting mean SBP <140 mmHg. Five studies reported participants with a mean age of ≤30 years,[40 44 47 50 71] 34 studies reported participants with a mean age of between 31 and 59 years,[30–32 34 37 39 42 43 45 49 52 53 55 57 58 60–66 68–70 72–74 78 81–85] and 18 studies reported participants with a mean age of ≥60 years.[26 27 29 33 35 36 41 46 48 54 56 59 67 75–77 79 80] Fleischer *et al*[38] reported participants with a mean age of 50 in the type 1 diabetes group and 64 in the type 2 diabetes group. Two studies did not report mean age.[28 51] Refaie[65] only included women. Morimoto *et al*[56] and Tanaka *et al*[75] only included men. Scarpello *et al*[68] did not report sex. All other studies included men and women.

Arterial stiffness was measured by way of PWV in 32 studies,[29 30 32–34 36 37 39 40 46 47 50–52 60–62 66 68 70–79 81–83] PP in 27 studies,[30 31 33–35 38 39 41 42 53–55 57 59 60 63–65 67 69 75 76 80 82–85] AIx in 6 studies,[34 47 66 69–71] AIx adjusted to a heart rate of 75 bpm in 4 studies,[30 40 56 78] ankle-brachial index (ABI) in 5 studies,[26–28 49 58] cardio ankle vascular index (CAVI) in 4 studies,[43–45 82] pulsatility index in 1 study,[74] stiffness index in 1 study,[48] and the subendocardial viability ratio in 1 study.[69]

## Association of CAN and arterial stiffness

There were 25 studies that investigated the association between CAN and arterial stiffness.[29 31 33 36 38 40 44 47 50 53 55 57 58 60 63–66 69–71 78 79 83 85] Seventeen reported a positive association of CAN with at least one measure of arterial stiffness without adjusting for age, sex, diabetes duration, or SBP.[29 31 36 38 47 50 53 55 58 60 66 69–71 78 79 83] Four other studies did not find a relationship.[33 57 64 85] Of those studies that adjusted for age, sex, diabetes duration, or SBP, eight studies reported a positive association of CAN with at least one measure of arterial stiffness.[29 40 44 50 65 66 69 79] Five studies did not find a relationship[33 36 63 78 85] (table 1 and online supplemental table 2).

There were 19 studies with sufficient data to be included in the meta-analysis to estimate the association of CAN with arterial stiffness[29 31 33 38 47 53 55 57 60 63–66 69–71 79 83 85] (figure 2). Eight studies measured arterial stiffness by way of PWV with a total number of 1629 participants: 400 with CAN and 1229 without CAN[29 33 47 60 66 71 79 83] (figure 2A). Overall, PWV was higher in participants with CAN than those without CAN (mean difference: 1.32 m/s, 95% CI 0.82 to 1.81, p<0.00001).

Thirteen studies measured arterial stiffness by way of PP, with Fleischer *et al*[38] and Moţăţăianu *et al*[57] reporting separate results for type 1 and type 2 diabetes.[31 33 38 53 55 57 60 63–65 69 83 85] There was a total number of 2776 participants: 1065 with CAN and 1711 without CAN (figure 2B). PP was higher in participants with CAN than those without CAN (mean difference: 6.25 mmHg, 95% CI 4.51 to 7.99, p<0.0001).

Five studies measured arterial stiffness by way of AIx with a total number of 866 participants: 216 with CAN and 650 with no CAN[47 66 69–71] (figure 2C). AIx was higher in participants with CAN than those with no CAN (mean difference: 5.52%, 95% CI 3.46 to 7.58, p<0.0001).

## Association of PN with arterial stiffness

There were 37 studies that investigated the association between PN and arterial stiffness.[26–30 32 34 35 37 39 41–43 45 46 48 49 51 52 54 56 59 61 62 67 68 72–77 80–84] Twenty-three studies reported a positive association of PN with at least one measure of arterial stiffness without adjusting for age, sex, diabetes duration, or SBP.[27 29 30 32 34 37 39 41 46 48 51 54 59 62 67 68 72 76 77 81–84] Seven other studies did not find a relationship.[35 42 52 61 73 74 80] Of those studies that controlled for age, sex, diabetes duration, or SBP, 11 reported a positive association of PN with at least one measure of arterial stiffness.[26 28 29 32 43 45 46 62 75 76 82]

**Table 1** Characteristics of observational studies included in meta-analysis on the association between arterial stiffness and neuropathy

| | | Neuropathy | Diabetes | Arterial stiffness | Arterial stiffness and neuropathy association, p<0.05 | |
|---|---|---|---|---|---|---|
| Study | Study design | Type | Type | Measure(s) | No adjustments | Adjustments for age, sex, diabetes, duration, and/or SBP |
| Aso 2003[29] | CS | CAN | 2 | PWV, cf | X | – |
| | | PN | | PWV, cf | X | – |
| Avci 2014[30] | CS | PN | 2 | PP | X | – |
| | | | | PWV, central | ✓ | X |
| Cabezas-Cerrato 2009[31] | CS | CAN | 1&2 | PP | ✓ | – |
| Cardoso 2014[33] | CS | CAN | 2 | PP | X | – |
| | | | | PWV, cf | X | X |
| Chen 2015[34] | CS | PN | 2 | PP | ✓ | – |
| | | | | PWV, cf | ✓ | – |
| Cho 2006[35] | CS | PN | DM | PP | X | – |
| | | | No DM | PP | X | – |
| Edmonds 1982[37] | CC | PN | 1 | PWV, femoral-tibial | ✓ | – |
| Fleischer 2014[38] | CS | CAN | 1 | PP | ✓ | – |
| | | | 2 | PP | ✓ | – |
| Ha 2012[39] | CS | PN | 2 | PP | ✓ | – |
| | | | | PWV, ba | ✓ | X |
| Jarmuzewska 2005[41] | CS | PN | 2 | PP | ✓ | – |
| Jung 2014[42] | CS | PN | 2 | PP | X | – |
| Kuo 2020[46] | CS | PN | DM & no DM | PWV, ba | ✓ | ✓ |
| Laptev 2015[47] | CS | CAN | 1 | AIx | X | – |
| | | | | PWV, ba | ✓ | – |
| Matsuto 1998[52] | CS | PN | DM | PWV, central | X | – |
| Mogensen 2012[53] | CS | CAN | 1 | PP | ✓ | – |
| Moon 2010[55] | CS | CAN | 2 | PP | ✓ | – |
| Moţăţăianu 2018[57] | CS | CAN | 1 | PP | X | – |
| | | | 2 | PP | X | – |
| Nguyen 2013[59] | CS | PN | 2 | PP | ✓ | – |
| Ohisa 2006[60] | CS | CAN | 2 | PP | ✓ | – |
| | | | | PWV, ba | ✓ | – |
| Okada 1992[61] | CS | PN | DM | PWV, aortic | X | – |
| Pek 2015*[62] | CS | PN | 2 | PWV, cf | ✓ | ✓ |
| Philips 2012[63] | CC | CAN | 1 | PP | – | X |
| Philips 2017[64] | CS | CAN | 2 | PP | X | – |
| Refaie 2014[65] | CS | CAN | 2 | PP | – | ✓ |
| Sacre 2012[66] | CS | CAN | 2 | AIx | ✓ | X |
| | | | | PWV, aortic | ✓ | ✓ |
| Salvotelli 2015[67] | CS | PN | 2 | PP | ✓ | X |

Continued

Table 1 Continued

| Study | Study design | Neuropathy Type | Diabetes Type | Arterial stiffness Measure(s) | Arterial stiffness and neuropathy association, p<0.05 No adjustments | Adjustments for age, sex, diabetes, duration, and/or SBP |
|---|---|---|---|---|---|---|
| Scarpello 1980[68] | CC | PN | DM | PWV, lower limb | ✓ | – |
| Secrest 2011[69] | CS | CAN | 1 | AIx | ✓ | X |
| | | | | PP | ✓ | – |
| Serhiyenko 2013[70] | CC | CAN | 2 | AIx | ✓ | – |
| Shah 2019[71] | CS | CAN | 2 | AIx | X | – |
| | | | | PWV, cf | ✓ | – |
| Shi 2012[72] | CC | PN | 2 | PWV, carotid | ✓ | – |
| Suh 2010[73] | CS | PN | 1&2 | PWV, ba | X | – |
| Szczyrba 2015[74] | CS | PN | 1 | PWV, cf | X | – |
| Tanaka 2018[75] | CS | PN | 2 | PP | – | ✓ |
| | | | | PWV, ba | – | ✓ |
| Tentolouris 2017[76] | CS | PN | 2 | PP | ✓ | – |
| | | | | PWV, cf | ✓ | ✓ |
| Teoh 2011*[77] | CS | PN | 2 | PWV, carotid-radial | ✓ | X |
| Wu 2014[79] | CS | CAN | 2 | PWV, ba | ✓ | ✓ |
| Yan 2020[80] | CS | PN | 2 | PP | X | – |
| Yang 2014[81] | CS | PN | 2 | PWV, ba | ✓ | X |
| Yeboah 2018[82] | CS | PN | 2 | PP | ✓ | X |
| Yokoyama 2007[83] | CS | CAN | 2 | PP | ✓ | – |
| | | | | PWV, ba | ✓ | – |
| | | PN | | PP | ✓ | – |
| | | | | PWV, ba | ✓ | – |
| ZZhao 2021 (reference 84) | CS | PN | 2 | PP | ✓ | – |
| Zoppini 2015[85] | CS | CAN | 2 | PP | X | X |

✓ association found between arterial stiffness and neuropathyx no association found between arterial stiffness and neuropathy; - not reported.
*only reported by way of abstract; values included in meta-analysis do not control for age, sex, diabetes duration or SBP, other than those that included participants of one sex.[65 75]
1, type 1 diabetes; 2, type 2 diabetes; AIx, augmentation index; ba, brachial-ankle; CAN, cardiac autonomic neuropathy; CC, case-control; cf, carotid-femoral; CS, cross-sectional; DM, diabetes mellitus; PN, peripheral neuropathy; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

Seven studies did not find a relationship[30 39 49 56 67 77 81] (table 1 and online supplemental table 3).

There were 26 studies with sufficient data to be included in the meta-analysis to estimate the association of PN with arterial stiffness[29 30 34 35 37 39 41 42 46 52 59 61 62 67 68 72–77 80–84] (figure 3). Eighteen studies measured arterial stiffness by way of PWV with a total number of 6137 participants: 1634 with PN and 4503 with no PN[29 30 34 37 39 46 52 61 62 68 72–77 81 83] (figure 3A). Overall, arterial stiffness, as measured by PWV, was higher in participants with PN than those with no PN (mean difference: 1.22 m/s 95% CI 0.87 to 1.58, p<0.00001).

Fourteen studies measured arterial stiffness by way of PP, with Cho *et al*[85] reporting separate results for people with and without diabetes[30 34 35 39 41 42 59 67 75 76 80 82–84] (figure 3B). There was a total number of 7909 participants: 2555 with PN and 5354 without PN. PP was higher in participants with PN than without PN (mean difference: 4.59 mmHg, 95% CI 2.96 to 6.22, p<0.00001).

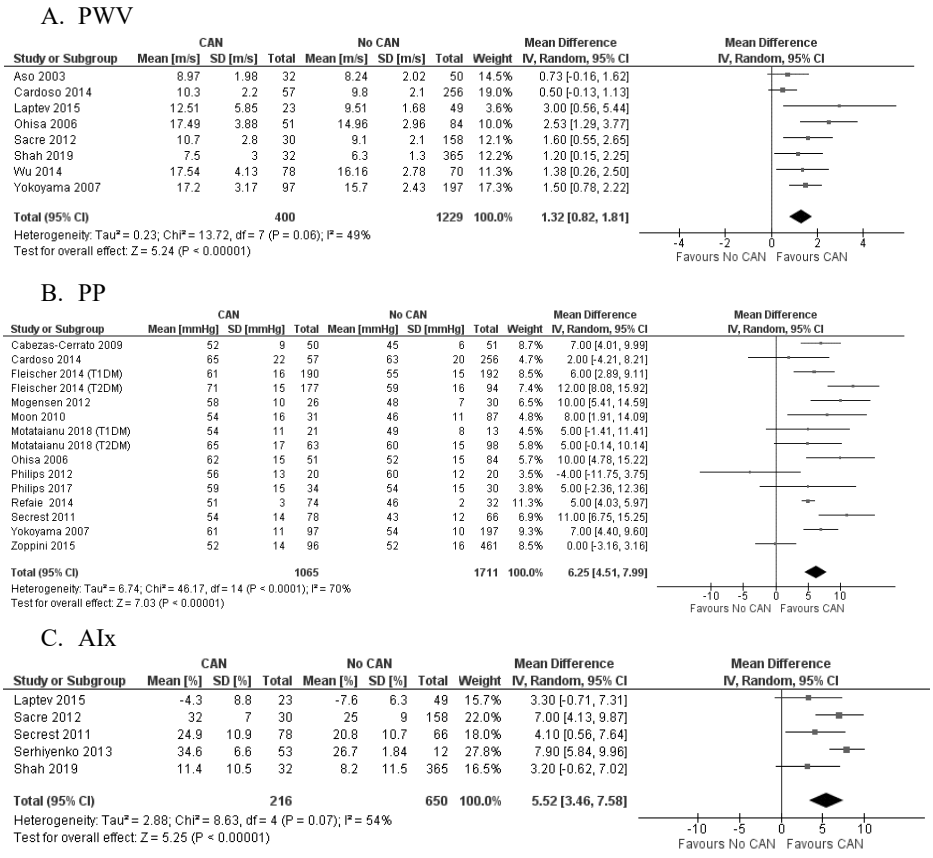


**Figure 2** Forest plot of the association of cardiac autonomic neuropathy (CAN) with arterial stiffness. AIx, augmentation index; PP, pulse pressure (mmHg); PWV, pulse wave velocity (m/s); T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

The two longitudinal studies included found arterial stiffness was predictive of PN in people with type 2 diabetes. That is, Cardoso *et al*[32] reported that increased aortic stiffness (carotid-femoral PWV≥10 m/s) was associated with new PN or a progression in PN over a median follow-up period of 6.2 years (incidence rate ratio: 2.04, 95% CI 1.28 to 3.23) and Alves-Cabratosa *et al*[27] reported that increased aortic stiffness (1.3≤ABI<3) was associated with the development of PN over a median follow-up period of 6.0 years (HR=1.44, 95% CI 1.08 to 1.92; reference group: 1.1≤ABI< 1.3).

## Subgroup and sensitivity analysis

There was substantial heterogeneity in relation to CAN when arterial stiffness was measured by way of PP ($I^2$=70%, p<0.0001) and AIx ($I^2$=54%, p=0.07) (figure 2B,C). For PP, heterogeneity may have arisen due to various factors with subgroup analysis suggesting age may have played a role ($I^2$ for subgroup differences=87.7%, p=0.004) (online supplemental figure 1) and meta-regression indicating diabetes duration, diabetes type, sex, and study setting may have also have contributed to heterogeneity (online supplemental table 5).

For AIx, heterogeneity no longer appeared to be substantial when Serhiyenko *et al*,[70] the only study in the analysis which was case-control was removed from the analysis ($I^2$=17%, p<0.00001) (online supplemental figure 2).

There was substantial heterogeneity in relation to PN when arterial stiffness was measured by way of PWV ($I^2$=75%, p<0.00001) and PP ($I^2$=75%, p<0.00001) (figure 3). For PWV, heterogeneity was partially explained by whether PWV was measured centrally (mean difference: 0.88 m/s, 95% CI 0.41 to 1.35, p=0.0003) or peripherally (mean difference: 1.68, 95% CI 1.38 to 1.99, p<0.00001) ($I^2$ for subgroup differences=87.2%, p=0.005) (figure 3A). No heterogeneity was indicated between studies using peripheral measures ($I^2$=0%, p=0.90) with six[39 46 73 75 81 83] out of the eight studies employing brachial-ankle PWV. Heterogeneity remained substantial for studies using central measures ($I^2$=81%, p<0.00001) and there appeared to be more variation in the types of central measures used, although at least half of the studies[29 34 62 74 76] relied on carotid-femoral PWV. Meta-regression indicated mean SBP, PWV type, and study size may have contributed to the differences in association (online supplemental table 6) but was unable to further explain potential sources of heterogeneity for PP (online supplemental table 7). In respect of both CAN and PN, studies often used differing tests to evaluate a participant's neuropathy status. This may also have contributed

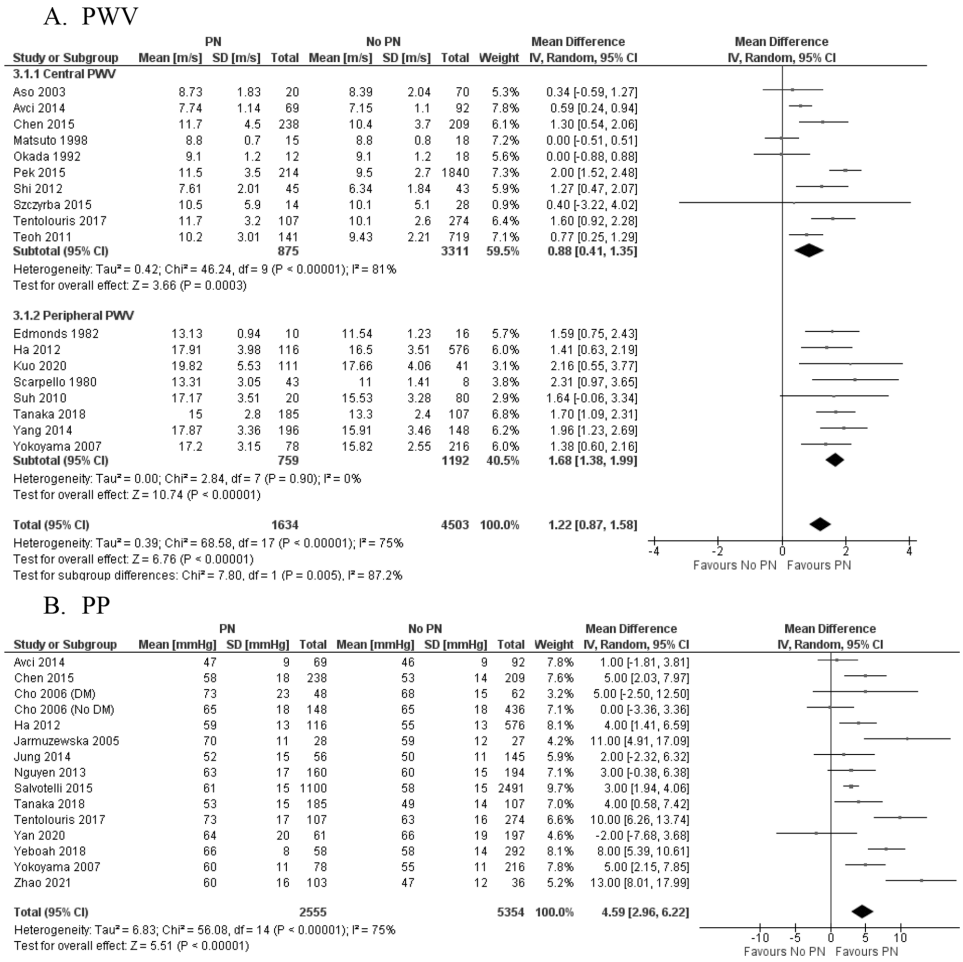


**Figure 3** Forest plot of association of peripheral neuropathy (PN) with arterial stiffness. Forest plot A is stratified by type of PWV. DM, diabetes mellitus; PP, pulse pressure (mmHg); PWV, pulse wave velocity (m/s).

toward heterogeneity but was unable to be investigated as studies could not be placed into sufficiently similar subgroups.

For both CAN and PN, we would not have changed our review conclusions based on sensitivity analyses where we used a fixed effect model, where we excluded Shi *et al*,[72] the only study of low quality, or where we excluded Pek *et al*[62] and Teoh *et al*,[77] which were only reported by way of abstract.

### Assessment of bias

As assessed by the NOS, all of the studies, other than Shi *et al*,[72] were of high quality (online supplemental tables 8–10). This was predominantly due to participants with diabetes being assessed as being somewhat representative of people with neuropathy, the review's wide parameters around the acceptability of measures used to assess arterial stiffness and CAN or PN, and studies controlling for confounders in data analysis. When we investigated meta-analyses of more than 10 studies, there was little evidence of publication bias from funnel plots, nor from Egger's test (online supplemental figure 3).

### Grade assessment

Following the GRADE approach, we are moderately confident the effect estimates for CAN and arterial stiffness measured by PWV, PP, and AIx, as well as the effect estimate for PN and PWV, are correct (ie, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different). Our confidence that the effect estimate for PN and arterial stiffness measured by PP is correct is low, due to high inconsistency (ie, the true effect may be substantially different from the estimate of effect). Although all outcomes were initially rated as low quality, they were all upgraded to moderate, due to the large magnitude of effect for each outcome, with the association for PN and PP being downgraded due to unexplained heterogeneity (online supplemental table 11).

## DISCUSSION

As far as we know, this is the first systematic review and meta-analysis of the association between arterial stiffness and neuropathy. We have shown that arterial stiffness is increased in people with CAN and PN regardless of how arterial stiffness was measured (table 1, online supplemental tables 2 and 3, figures 2 and 3). All but one of the

studies, as assessed by NOS, were of high quality (online supplemental tables 8–10) and there was little evidence of reporting bias including publication bias (online supplemental figure 3).

In our meta-analysis, we compensated for potential heterogeneity by using a random-effects model. For CAN, heterogeneity was not evident when arterial stiffness was measured by way of PWV. For PN, subgroup analysis and meta-regression showed a difference between central and peripheral measures of PWV. PWV can be measured at various arterial sites, with varying levels of elasticity and levels of pulsatility, with more peripheral sites resulting in higher PWV values than more central sites.[86] Although subgroup analyses for PN showed no heterogeneity for studies that used peripheral measures, remaining heterogeneity for central measures may have reflected variation between studies in the choice of central arterial sites used to assess PWV. We were unable to ascertain any sources of heterogeneity for PP. It is possible, however, as PP can be measured centrally and peripherally, that the site of PP measurement could be a cause of heterogeneity in these studies (figures 2 and 3). As studies investigating CAN and PN often employed differing tests to identify neuropathy status, this may also have contributed to heterogeneity. This source of heterogeneity was unable to be investigated further.

Following our GRADE assessment, we are moderately confident that the effect estimate observed for CAN and arterial stiffness measured by PWV, PP, and AIx, and for PN and arterial stiffness measured by PWV, is correct. Our confidence that the effect estimate observed in studies of arterial stiffness measured by PP and PN was correct, however, is low. This suggests that PWV may be preferable to PP in assessing whether a person's arterial stiffness is indicative of neuropathy, at least in respect of PN.

Our review suggests increased arterial stiffness may lead to the development of neuropathy, particularly in relation to PN. The direction of causation is supported by Alves-Cabratosa *et al*[27] and Cardoso *et al*,[32] the two cohort studies in the review, which both found an association between increased arterial stiffness at baseline and the future development or progression of PN. The direction is also biologically plausible as arterial stiffness can damage the small vessels that supply blood to the peripheral nerves and nerves surrounding the heart, as it impairs the aortic buffering function which prevents the transmission of harmful pulsatile pressure waves into the microcirculation.[10] For CAN, it has been hypothesized that stiffening of the carotid arteries and the aorta may affect the function of stretch-sensitive baroreceptors, which, in turn, impacts on HRV.[87]

Conversely, neuropathy may increase arterial stiffness as it may lead to calcification of the tunica media of the arterial wall, which, in turn, impacts on vascular tone and vasomotion.[36 88] The relationship may also be causal in either direction resulting in a vicious cycle where each condition sustains the other. It also cannot be ruled out that the association seen with arterial stiffness and neuropathy may be non-causal and due only to the sharing of a common pathway. For example, hyperglycemia may result in the formation of advanced glycation end products that result in the stiffening of elastic arteries,[89] as well as neural inflammation which may ultimately lead to neuropathy.[90]

Furthermore, as the data in most of our studies came from patients with diabetes, our results are only generalizable to people with this condition. For people with diabetes, our results suggest that arterial stiffness could potentially be used to identify people at higher risk of neuropathy. This is practical as devices to measure arterial stiffness, including PWV, are increasingly accessible and easy to use. People identified as being at increased risk could then be referred for more accurate diagnostics and provided with preventative measures such as glucose control and lifestyle changes. The reduction of arterial stiffness may well also be a focal point for research investigating therapeutics for the prevention and treatment of neuropathy. This could include exploration of the effectiveness of existing medications which may improve arterial stiffness, such as angiotensin-converting enzyme (ACE) inhibitors and advanced glycation end product (AGE) cross-link breakers.[91] Before arterial stiffness can be considered as a tool to combat neuropathy, however, steps first need to be taken to more firmly establish the temporality of the relationship of neuropathy and arterial stiffness, particularly in relation to CAN, where we were unable to locate any cohort studies.

In conclusion, the summary evidence from this review indicates that neuropathy is associated with increased arterial stiffness, particularly when measured by way of PWV. The identification of this modifiable risk factor could assist in the diagnosis of neuropathy and provide new research avenues for the treatment of the latter condition. Further longitudinal research is first required to determine the temporality of the association of arterial stiffness and neuropathy.

**Contributors** AB designed the study, registered the protocol, and searched databases. AB and JS performed the selection of studies with the assistance of RKRS. AB analyzed the data. JS checked the data analysis. AB wrote the manuscript. JS and RKRS critically evaluated the protocol, systematic review, and meta-analysis. All authors reviewed and approved the final manuscript. AB is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information.

**ORCID iDs**
Angela Beros http://orcid.org/0000-0003-3154-744X
John Sluyter http://orcid.org/0000-0002-9722-139X
Robert Keith Rhodes Scragg http://orcid.org/0000-0003-0013-2620

## REFERENCES

1 Pop-Busui R, Boulton AJM, Feldman EL, *et al*. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:136–54.
2 Albers JW, Herman WH, Pop-Busui R, *et al*. Effect of prior intensive insulin treatment during the diabetes control and complications trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *Diabetes Care* 2010;33:1090–6.
3 Martin CL, Albers JW, Pop-Busui R, *et al*. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care* 2014;37:31–8.
4 Ang L, Jaiswal M, Martin C, *et al*. Glucose control and diabetic neuropathy: lessons from recent large clinical trials. *Curr Diab Rep* 2014;14:528.
5 Pop-Busui R, Lu J, Brooks MM, *et al*. Impact of glycemic control strategies on the progression of diabetic peripheral neuropathy in the bypass angioplasty revascularization investigation 2 diabetes (BARI 2D) cohort. *Diabetes Care* 2013;36:3208–15.
6 Pop-Busui R, Low PA, Waberski BH, *et al*. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: the diabetes control and complications trial/epidemiology of diabetes interventions and complications study (DCCT/EDIC). *Circulation* 2009;119:2886–93.
7 Low PA, Benrud-Larson LM, Sletten DM, *et al*. Autonomic symptoms and diabetic neuropathy: a population-based study. *Diabetes Care* 2004;27:2942–7.
8 Spallone V, Ziegler D, Freeman R, *et al*. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. *Diabetes Metab Res Rev* 2011;27:639–53.
9 Tesfaye S, Boulton AJM, Dyck PJ, *et al*. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010;33:2285–93.
10 Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J Appl Physiol (1985)* 2008;105:1652–60.
11 DeLoach SS, Townsend RR. Vascular stiffness: its measurement and significance for epidemiologic and outcome studies. *Clin J Am Soc Nephrol* 2008;3:184–92.
12 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
13 Stroup DF, Berlin JA, Morton SC, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12.
14 Ewing DJ, Martyn CN, Young RJ, *et al*. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care* 1985;8:491–8.
15 Herman WH, Pop-Busui R, Braffett BH, *et al*. Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in Type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. *Diabet Med* 2012;29:937–44.
16 Young MJ, Boulton AJ, MacLeod AF, *et al*. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom Hospital clinic population. *Diabetologia* 1993;36:150–4.
17 Ouzzani M, Hammady H, Fedorowicz Z, *et al*. Rayyan—a web and mobile APP for systematic reviews. *Syst Rev* 2016;5:210.
18 Wells GA, Shea B, O'Connell D, *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. 2000. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 10 Dec 2021].
19 Luo D, Wan X, Liu J, *et al*. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018;27:1785–805.
20 Wan X, Wang W, Liu J, *et al*. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135.
21 Deeks JJ, Higgins JPT, Altman DG. Chapter 10: analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane, 2022. Available: www.training.cochrane.org/handbook
22 Fu R, Gartlehner G, Grant M, *et al*. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the effective health care program. *J Clin Epidemiol* 2011;64:1187–97.
23 Page MJ, Higgins JPT, Sterne JA. Chapter 13: assessing risk of bias due to missing results in a synthesis. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane, 2022. Available: www.training.cochrane.org/handbook
24 Egger M, Smith GD. Bias in location and selection of studies. *BMJ* 1998;316:61–6.
25 Schünemann HJ, Higgins JPT, Vist GE, *et al*. Chapter 14: completing "summary of findings" tables and grading the certainty of evidence. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Intervention*. Cochrane, 2022. Available: www.training.cochrane.org/handbook
26 Allison MA, Hiatt WR, Hirsch AT, *et al*. A high ankle-brachial index is associated with increased cardiovascular disease morbidity and lower quality of life. *J Am Coll Cardiol* 2008;51:1292–8.
27 Alves-Cabratosa L, Comas-Cufí M, Ponjoan A, *et al*. Levels of ankle-brachial index and the risk of diabetes mellitus complications. *BMJ Open Diabetes Res Care* 2020;8:e000977.
28 Amione-Guerra J, Prasad A. The prevalence, clinical characteristics, and functional significance of ankle brachial index defined peripheral arterial disease in patients with heart failure. *Journal of Cardiac Failure* 2019;25:S46.
29 Aso K, Miyata M, Kubo T, *et al*. Brachial-ankle pulse wave velocity is useful for evaluation of complications in type 2 diabetic patients. *Hypertens Res* 2003;26:807–13.
30 Avci A, Demir K, Kaya Z, *et al*. Arterial stiffness and carotid intima-media thickness in diabetic peripheral neuropathy. *Med Sci Monit* 2014;20:2074–81.
31 Cabezas-Cerrato J, Hermida RC, Cabezas-Agricola JM, *et al*. Cardiac autonomic neuropathy, estimated cardiovascular risk, and circadian blood pressure pattern in diabetes mellitus. *Chronobiol Int* 2009;26:942–57.
32 Cardoso CRL, Moran CBM, Marinho FS, *et al*. Increased aortic stiffness predicts future development and progression of peripheral neuropathy in patients with type 2 diabetes: the Rio de Janeiro type 2 diabetes cohort study. *Diabetologia* 2015;58:2161–8.
33 Cardoso CR, Moraes RA, Leite NC, *et al*. Relationships between reduced heart rate variability and pre-clinical cardiovascular disease in patients with type 2 diabetes. *Diabetes Res Clin Pract* 2014;106:110–7.
34 Chen Q, Chiheb S, Fysekidis M, *et al*. Arterial stiffness is elevated in normotensive type 2 diabetic patients with peripheral neuropathy. *Nutr Metab Cardiovasc Dis* 2015;25:1041–9.
35 Cho DY, Mold JW, Roberts M. Further investigation of the negative association between hypertension and peripheral neuropathy in the elderly: an Oklahoma Physicians Resource/Research Network (OKPRN) study. *J Am Board Fam Med* 2006;19:240–50.
36 Chorepsima S, Eleftheriadou I, Tentolouris A, *et al*. Pulse wave velocity and cardiac autonomic function in type 2 diabetes mellitus. *BMC Endocr Disord* 2017;17:27.
37 Edmonds ME, Roberts VC, Watkins PJ. Blood flow in the diabetic neuropathic foot. *Diabetologia* 1982;22:9–15.
38 Fleischer J, Yderstraede K, Gulichsen E, *et al*. Cardiovascular autonomic neuropathy is associated with macrovascular risk factors in type 2 diabetes: new technology used for routine large-scale screening adds new insight. *J Diabetes Sci Technol* 2014;8:874–80.
39 Ha BK, Kim BG, Kim DH, *et al*. Relationships between brachial-ankle pulse wave velocity and peripheral neuropathy in type 2 diabetes. *Diabetes Metab J* 2012;36:443–51.
40 Jaiswal M, Urbina EM, Wadwa RP, *et al*. Reduced heart rate variability is associated with increased arterial stiffness in youth with type 1 diabetes: the search CVD study. *Diabetes Care* 2013;36:2351–8.
41 Jarmuzewska EA, Mangoni AA. Pulse pressure is independently associated with sensorimotor peripheral neuropathy in patients with type 2 diabetes. *J Intern Med* 2005;258:38–44.

42 Jung C-H, Jung S-H, Kim K-J, *et al*. Differential associations of central and brachial blood pressure with carotid atherosclerosis and microvascular complications in patients with type 2 diabetes. *BMC Cardiovasc Disord* 2014;14:23.
43 Kim ES, Moon S, Kim H-S, *et al*. Diabetic peripheral neuropathy is associated with increased arterial stiffness without changes in carotid intima-media thickness in type 2 diabetes. *Diabetes Care* 2011;34:1403–5.
44 Kim HY, Jung HW, Lee GM, *et al*. Is reduced heart rate variability associated with arterial stiffness in youth with childhood-onset type 1 diabetes mellitus? *Horm Res Paediatr* 2015;84:79–80.
45 Kim KJ, Lee B-W, Kim H-M, *et al*. Associations between cardio-ankle vascular index and microvascular complications in type 2 diabetes mellitus patients. *J Atheroscler Thromb* 2011;18:328–36.
46 Kuo M-C, Huang J-C, Wu P-Y, *et al*. Associations of small fiber neuropathy with geriatric nutritional risk index and arterial stiffness in hemodialysis. *Dis Markers* 2020;2020:1694218.
47 Laptev DN. n.d. Arterial stiffness and cardiovascular autonomic neuropathy relationship in children and adolescents with type 1 diabetes mellitus. *Diabetes Mellitus*18:94–100. 10.14341/DM2015194-100 Available: https://dia-endojournals.ru/dia/issue/view/578
48 Lasschuit JWJ, Greenfield JR, Tonks KTT. Contribution of peripheral neuropathy to poor bone health in the feet of people with type 2 diabetes mellitus. *Acta Diabetol* 2022;59:217–24.
49 Li X, Ren H, Wang Y, *et al*. Association of a high ankle brachial index with microvascular diseases of diabetes. *Zhonghua Yi Xue Za Zhi* 2012;92:236–9.
50 Liatis S, Alexiadou K, Tsiakou A, *et al*. Cardiac autonomic function correlates with arterial stiffness in the early stage of type 1 diabetes. *Exp Diabetes Res* 2011;2011:957901.
51 Ma B, Chen YAO, Wang X, *et al*. 177-lb: low 25-hydroxy vitamin D is associated with arterial stiffness in type 2 diabetes mellitus. *Diabetes* 2020;69:177–LB.
52 Matsuto T, Inano K, Miida T, *et al*. Assessment of diabetic cardiovascular autonomic neuropathy by heart rate variability and pulse wave velocity. *Rinsho Byori* 1998;46:1037–42.
53 Mogensen UM, Jensen T, Køber L, *et al*. Cardiovascular autonomic neuropathy and subclinical cardiovascular disease in normoalbuminuric type 1 diabetic patients. *Diabetes* 2012;61:1822–30.
54 Monami M, Vivarelli M, Desideri CM, *et al*. Pulse pressure and prediction of incident foot ulcers in type 2 diabetes. *Diabetes Care* 2009;32:897–9.
55 Moon S-S, Choi Y-K, Seo H-A, *et al*. Relationship between cardiovascular autonomic neuropathy and coronary artery calcification in patients with type 2 diabetes. *Endocr J* 2010;57:445–54.
56 Morimoto S, Iwase M, Kikuchi Y, *et al*. Radial augmentation index and diabetic complications in patients with type 2 diabetes mellitus. *Diabetol Int* 2011;2:127–33.
57 Moţăţăianu A, Maier S, Bajko Z, *et al*. Cardiac autonomic neuropathy in type 1 and type 2 diabetes patients. *BMC Neurol* 2018;18:126.
58 Nattero-Chávez L, Redondo López S, Alonso Díaz S, *et al*. Association of cardiovascular autonomic dysfunction with peripheral arterial stiffness in patients with type 1 diabetes. *J Clin Endocrinol Metab* 2019;104:2675–84.
59 Nguyen MT, Pham I, Chemla D, *et al*. Decreased stroke volume–brachial pulse pressure ratio in patients with type 2 diabetes over 50 years: the role of peripheral neuropathy. *Nutr Metab Cardiovasc Dis* 2013;23:1093–100.
60 Ohisa N, Yoshida K, Kaku M, *et al*. The relationship of autonomic functional disturbance and atherosclerosis in type 2 diabetes. *Rinsho Byori* 2006;54:453–7.
61 Okada M, Matsuto T, Sugita O, *et al*. Use of heart rate variability and pulse wave velocity for diagnosing cardiovascular autonomic neuropathy. *Rinsho Byori* 1992;40:655–9.
62 Pek SLT, Tavintharan S, Woon K, *et al*. Independent risk factors of diabetic peripheral neuropathy in type 2 diabetes (abstract). *Diabetes* 2015;70:A617.
63 Philips JC, Marchand M, Scheen AJ. Haemodynamic changes during a squat test, pulsatile stress and indices of cardiovascular autonomic neuropathy in patients with long-duration type 1 diabetes. *Diabetes Metab* 2012;38:54–62.
64 Philips JC, Marchand M, Scheen AJ. Relationships between baroreflex gain and other risk factors in patients with type 2 diabetes. *Ann Cardiol Angeiol (Paris)* 2017;66:1–6.
65 Refaie W. Assessment of cardiac autonomic neuropathy in long standing type 2 diabetic women. *The Egyptian Heart Journal* 2014;66:63–9.
66 Sacre J, Jellis C, Coombes J. Effects of cardiac autonomic neuropathy on blood pressure, aortic stiffness, and central pressure loading in patients with type 2 diabetes. *Heart, Lung and Circulation* 2012;21:S14.
67 Salvotelli L, Stoico V, Perrone F, *et al*. Prevalence of neuropathy in type 2 diabetic patients and its association with other diabetes complications: The Verona Diabetic Foot Screening Program. *J Diabetes Complications* 2015;29:1066–70.
68 Scarpello JHB, Martin TRP, Ward JD. Ultrasound measurements of pulse-wave velocity in the peripheral arteries of diabetic subjects. *Clin Sci (Lond)* 1980;58:53–7.
69 Secrest AM, Marshall SL, Miller RG, *et al*. Pulse wave analysis and cardiac autonomic neuropathy in type 1 diabetes: a report from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Technol Ther* 2011;13:1264–8.
70 Serhiyenko VA, Serhiyenko AA, Mankovsky BN. Correlation between arterial wall stiffness, N-terminal prohormone of brain natriuretic peptide, functional and structural myocardial abnormalities in patients with type 2 diabetes mellitus and cardiac autonomic neuropathy. *Diabetes Mellitus* 2013;16:72–7. 10.14341/DM2013472-77 Available: https://dia-endojournals.ru/dia/issue/view/344
71 Shah AS, El ghormli L, Vajravelu ME, *et al*. Heart rate variability and cardiac autonomic dysfunction: prevalence, risk factors, and relationship to arterial stiffness in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study. *Diabetes Care* 2019;42:2143–50.
72 Shi SS, Zhang YH, Su BL. Assessment of carotid artery wall elasticity using wave intensity in patients of type 2 diabetes mellitus with diabetic peripheral neuropathy. *Zhongguo Yi Xue Ying Xiang Ji Shu* 2012;28:2141–4.
73 Suh BC, Chung P-W, Moon H-S, *et al*. Association between pulse wave velocity and nerve conduction study in diabetic patients. *Eur Neurol* 2010;64:219–23.
74 Szczyrba S, Kozera GM, Neubauer-Geryk J, *et al*. Diabetic symmetric polyneuropathy is associated with increased aortal stiffening but not cerebral angiopathy in type 1 diabetes. *J Diabetes Complications* 2015;29:73–6.
75 Tanaka S, Kanazawa I, Sugimoto T, *et al*. Nerve conduction velocity is negatively associated with intima-media thickness and brachial-ankle pulse wave velocity in men with type 2 diabetes mellitus. *PLoS ONE* 2018;13:e0209503.
76 Tentolouris A, Eleftheriadou I, Grigoropoulou P, *et al*. The association between pulse wave velocity and peripheral neuropathy in patients with type 2 diabetes mellitus. *J Diabetes Complications* 2017;31:1624–9.
77 Teoh WL, Price JF, Williamson RM, *et al*. Relationship of arterial stiffness to microvascular complications of type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabet Med* 2011;1:165.
78 Theilade S, Lajer M, Hansen TW, *et al*. Pulse wave reflection is associated with diabetes duration, albuminuria and cardiovascular disease in type 1 diabetes. *Acta Diabetol* 2014;51:973–80.
79 Wu N, Cai X, Ye K, *et al*. Association between brachial-ankle pulse wave velocity and cardiac autonomic neuropathy in type 2 diabetes. *Diabetol Metab Syndr* 2014;6:82.
80 Yan P, Wan Q, Zhang Z, *et al*. Association between circulating B-type natriuretic peptide and diabetic peripheral neuropathy: a cross-sectional study of a Chinese type 2 diabetic population. *J Diabetes Res* 2020;2020:3436549.
81 Yang L, Li R, Li QF, *et al*. Correlation between the brachial-ankle pulse wave velocity and peripheral neuropathy in patients with type 2 diabetes. *Jie Fang Jun Yi Xue Za Zhi* 2014;39:882–7.
82 Yeboah K, Agyekum JA, Owusu Mensah RNA, *et al*. Arterial stiffness is associated with peripheral sensory neuropathy in diabetes patients in Ghana. *J Diabetes Res* 2018;2018:2320737.
83 Yokoyama H, Yokota Y, Tada J, *et al*. Diabetic neuropathy is closely associated with arterial stiffening and thickness in type 2 diabetes. *Diabet Med* 2007;24:1329–35.
84 Zhao Y, Huang L, Zhou X, *et al*. The early diagnostic value of ankle-brachial index combined with feet electrochemical skin conductance for peripheral artery disease in type 2 diabetes. *J Diabetes Investig* 2022;13:525–31.
85 Zoppini G, Cacciatori V, Raimondo D, *et al*. Prevalence of cardiovascular autonomic neuropathy in a cohort of patients with newly diagnosed type 2 diabetes: the Verona Newly Diagnosed Type 2 Diabetes Study (VNDS). *Diabetes Care* 2015;38:1487–93.
86 Laurent S, Cockcroft J, Van Bortel L, *et al*. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27:2588–605.
87 Mattace-Raso FUS, van den Meiracker AH, Bos WJ, *et al*. Arterial stiffness, cardiovagal baroreflex sensitivity and postural blood

pressure changes in older adults: the Rotterdam study. *J Hypertens* 2007;25:1421–6.
88 Jeffcoate WJ, Rasmussen LM, Hofbauer LC, *et al*. Medial arterial calcification in diabetes and its relationship to neuropathy. *Diabetologia* 2009;52:2478–88.
89 Aronson D. Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. *J Hypertens* 2003;21:3–12.
90 Papachristou S, Pafili K, Papanas N. Skin ages and diabetic neuropathy. *BMC Endocr Disord* 2021;21:28.
91 Janić M, Lunder M, Sabovič M. Arterial stiffness and cardiovascular therapy. *Biomed Res Int* 2014;2014:621437.