Diabetes and Metabolism 52 (2026) 101773

Contents lists available at ScienceDirect

Diabetes & Metabolism

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

Original article

# Blood oxygen saturation and its associations with autonomic and peripheral neuropathy in diabetes

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ARTICLE INFO

*Keywords:*
Autonomic neuropathy
Peripheral neuropathy
Type 1 diabetes
Type 2 diabetes
Oxygen saturation

ABSTRACT

*Aim:* Individuals with diabetes have lower blood oxygen saturation ($SpO_2$), and hypoxia is suggested to play a role in the pathophysiology of diabetic complications, including diabetic polyneuropathy (DPN). This study investigated whether lower $SpO_2$ was associated with DPN.

*Methods:* The study involves participants with type 1 and type 2 diabetes from a cross-sectional study. $SpO_2$ was measured in the supine position with fingertip pulse oximetry. To assess multiple domains of peripheral and autonomic nerve function, several different standardized tests were used, including autonomic tests, sensory measures, nerve conduction and symptom scores. Odds ratios (OR) were adjusted for relevant covariates and calculated as a function of a 1%-point decrease in $SpO_2$ for type 1 diabetes and type 2 diabetes, respectively. In addition, ORs were calculated between participants with low (< 96%) and high (≥ 96%) SpO2 levels.

*Results:* Among 1,515 participants with diabetes, lower $SpO_2$ was associated with markers of DPN. In type 1 diabetes (n = 753), each 1%-point lower $SpO_2$ was associated with higher odds of abnormal sudomotor function in the hands and feet and impaired vibration perception, independent of conventional risk factors. In type 2 diabetes (n = 762), lower $SpO_2$ was associated with cardiovascular autonomic neuropathy and neuropathic pain. Results were largely similar when $SpO_2$ was analyzed categorically (< 96% vs ≥ 96%).

*Conclusion:* Lower blood oxygen saturation was associated with sudomotor dysfunction and impaired vibration perception threshold in type 1 diabetes, and with cardiovascular autonomic neuropathy and neuropathic pain in type 2 diabetes.

## Introduction

Diabetic polyneuropathy (DPN) is a heterogeneous complication that includes peripheral neuropathy and autonomic neuropathy. Peripheral neuropathy primarily affects distal sensory and motor neurons, and can lead to sensory loss, paresthesia and pain [1]. In contrast, autonomic neuropathy can affect cardiovascular, gastrointestinal, and urogenital systems as well as sudomotor function [2,3].

DPN develops in up to 20% of individuals with type 1 diabetes and up to 50% of those with type 2 diabetes. Neuropathic pain affects 13 – 35% of patients [1] and is often poorly responsive to current treatments. Both peripheral and autonomic neuropathy are associated with increased morbidity and mortality, underscoring the severe and often progressive burden of the condition.

Individuals with type 1 diabetes have lower levels of $SpO_2$ compared with healthy individuals [4–6]. Evidence suggests that multiple organs and tissues in diabetes are exposed to hypoxia, which may promote the development and progression of diabetic complications [7]. Tissue hypoxia can impair mitochondrial metabolism, promote oxidative stress, and trigger inflammation — all processes implicated in neuronal injury and microvascular dysfunction [1,8,9]. Although the causal relationship remains uncertain, these findings suggest that hypoxia could play a role in the pathogenesis of DPN.

Reduced baroreflex sensitivity, an early indicator of autonomic

*Abbreviations:* SpO2, Blood oxygen saturation; DPN, Diabetic polyneuropathy; VPT, Vibration perception threshold; CAN, Cardiovascular autonomic neuropathy; CART, Cardiovascular autonomic reflex test; CART: L-S, Lying to standing test (30:15 ratio); CART: EI, Deep breathing test (expiration to inspiration ratio), CART: V, Valsalva ratio; HRV, Heart rate variability; MNSI-E, Michigan Neuropathy Screening Instrument Examination; DN4i, Douleur Neuropathique 4 interview.

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https://doi.org/10.1016/j.diabet.2026.101773
Received 1 April 2026; Received in revised form 6 May 2026; Accepted 18 May 2026
Available online 23 May 2026

dysfunction [10,11], has been associated with lower blood oxygen saturation in type 1 diabetes [12]. Similarly, a previous study from a subset of the same cohort demonstrated that blood oxygen saturation below 96% in individuals with type 1 diabetes was associated with the presence of DPN, defined as vibration perception threshold (VPT) > 25 volts [13]. Whether similar associations exist in type 2 diabetes and extend to a broader range of neuropathy measures remains unclear. We therefore examined these associations across both diabetes types, hypothesizing that lower levels of $SpO_2$ would be associated with a higher prevalence of both autonomic and peripheral neuropathy.

## Methods

### *Study design & population*

This study was a substudy of the cross-sectional DANES study, conducted at Steno Diabetes Center Copenhagen, Denmark, which screened for DPN among consecutive patients with type 1 and type 2 diabetes attending their annual status examination. Patients from the outpatient clinic who fulfilled the inclusion criteria were invited to participate in the study between October 1st 2019 and December 23rd 2022 [14]. Eligible participants were adults (≥ 18 years) with a diagnosis of type 1 or type 2 diabetes. Exclusion criteria were current cancer, pregnancy, or lower extremity amputation. The present analysis excluded individuals with chronic obstructive pulmonary disease or missing SpO2 data (Fig S1; see supplementary material associated with this article online). The study was approved by the Research Ethics Committee of the Capital Region of Denmark (H-19029796) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

### *Study aim*

This study aimed to evaluate whether lower supine $SpO_2$ levels were associated with a higher prevalence of peripheral and autonomic neuropathy outcomes in people with type 1 and type 2 diabetes.

### *Study procedures*

Demographic characteristics, BMI, smoking status (current, previous, or never), alcohol consumption, information on physical activity defined as any exercise that increases the heart rate (> 30 minutes per day, < 30 minutes per day, or none), current medication, and a detailed medical history were obtained at the study visit. Standard laboratory measurements were collected, including HbA1c, lipids, and plasma creatinine. Blood pressure and heart rate were measured three times in the supine position and averaged using the last two measurements. $SpO_2$ reflects the percentage of hemoglobin saturated with oxygen and was measured with fingertip pulse oximetry in the supine position three times, separated by 1 minute. The mean value was calculated as the average of available measurements. Previous analyses, including a subset of participants with type 1 diabetes from this cohort [13], found no associations between supine $SpO_2$ and diabetic complications, including DPN defined by vibration perception threshold > 25 V. The present analysis included the full cohort with both diabetes types, applied a broader set of standardized DPN measures, and focused on supine $SpO_2$ only.

### *Autonomic neuropathy measurements*

Cardiovascular autonomic neuropathy (CAN) was determined using an autonomic test device (Vagus device, Medicus Engineering, Aarhus, Denmark), and assessed by cardiovascular autonomic reflex tests (CARTs) and resting heart rate variability (HRV) indices. The test consisted of a 5-minute HRV measurement, followed by the three CARTs: heart rate response to standing (CART: L-S), deep breathing (CART: EI), and the Valsalva maneuver (CART: V). CARTs were assessed by age-dependent cut-off values [15], and two or three pathological CARTs constituted CAN. Patients were instructed to fast for at least 2 hours prior to the test, including avoiding caffeine and refraining from strenuous exercise 24 hours before the test. Patients rested for 5 minutes in the supine position before testing. Patients with arrhythmia or pacemakers were not tested for CAN, and patients undergoing laser eye treatment were not tested with the Valsalva maneuver. If a patient was taking beta-blockers, they were instructed to pause treatment at least 24 hours prior to examination. Patients with missing data were classified as having unknown CAN status, unless only one test was missing and the remaining tests were either all normal or all abnormal, in which case they were classified as CAN or no CAN, respectively.

Sudomotor function was assessed indirectly using electrochemical skin conductance of the hands and feet (Sudoscan, Impeto Medical, Paris, France). Two measurements were performed and averaged. Results were interpreted according to age- and sex-specific reference values [16]. Sudomotor dysfunction was classified as pathological only if pathological findings were observed bilaterally.

### *Peripheral neuropathy measurements*

The Michigan Neuropathy Screening Instrument Examination (MNSI-E) was used to classify participants according to neuropathy status, using a cut-off score > 2. One point per extremity was assigned for foot ulcers, foot abnormalities, absent ankle reflexes, or vibration perception threshold (VPT) above the age-, sex-, and height-specific reference limits [17,18].

### *Large fiber measurements*

Vibration perception threshold (VPT) was measured on the distal end of the 1st toe, bilaterally (Biothesiometer, Bio-medical instruments, Ohio, USA). A 25-volt cut-off was used [19], consistent with previous large cohort studies. The measurements were repeated three times and averaged per side. The test was classified as pathological only if pathological findings were present on both sides.

Sural nerve conduction velocity and amplitude were measured using a point-of-care nerve conduction device (DPNCheck, NeuroMetrix Inc., Waltham, USA). Measurements were repeated three times and averaged. For both tests, perception thresholds were stratified for age and height [20]. To be classified as pathological, pathological findings had to be present bilaterally in nerve conduction velocity, amplitude or both.

### *Small fiber measurements*

Pinprick (Neuropen, Owen Mumford Ltd., Oxford, UK) was used to assess pain sensation at the distal dorsal part of the 1st, 3rd, and 5th toes on each foot. The test was considered abnormal with the absence of pain sensation in all tested locations.

### *Painful diabetic neuropathy measurement*

Painful DPN was evaluated using the 7-item interview component of the *Douleur Neuropathique 4 questionnaire* (DN4i), with a cut-off of ≥ 3 [21].

### *Statistical analysis*

All analyses were stratified by diabetes type. In baseline comparisons, DPN measures were compared between participants with low (< 96%) and high (≥ 96%) peripheral oxygen saturation ($SpO_2$) using Pearson's $\chi^2$ or Fisher's exact tests as appropriate.

The primary analyses examined the associations between $SpO_2$ and DPN measures using logistic regression. First, $SpO_2$ was analyzed as a continuous variable (per 1%-point decrease) to estimate odds ratios

(ORs) for DPN measures. Second, analyses were repeated with $SpO_2$ categorized as low (< 96%) versus high (≥ 96%). The cutoff of 96% was based on a Norwegian study showing higher mortality with $SpO_2$ < 96% [22] and applied for consistency with Laursen *et al.* [13].

Each model was run with four levels of adjustment:

Model 1: unadjusted,
Model 2: adjusted for age and sex,

**Table 1**
Clinical characteristics.

| Variable | Type 1 Diabetes | | | | Type 2 Diabetes | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | SpO2 < 96% | SpO2 ≥ 96% | *P* -value | Total | SpO2 < 96% | SpO2 ≥ 96% | *P*-value |
| N | 753 | 26 | 727 | | 762 | 80 | 682 | |
| Age (years) | 54 ± 16 | 65 ± 13 | 54 ± 16 | < 0.001 | 67 ± 12 | 68 ± 10 | 67 ± 12 | 0.215 |
| Female sex | 334 (44.4) | 17 (65.4) | 317 (43.6) | 0.046 | 226 (29.7) | 28 (35) | 198 (29) | 0.329 |
| Body mass index | 26.2 ± 4.5 | 28.1 ± 4.3 | 26.2 ± 4.5 | 0.031 | 29.8 ± 5.5 | 31.1 ± 6.1 | 29.6 ± 5.4 | 0.037 |
| Systolic blood pressure (mmHg) | 129 ± 16 | 136 ± 15 | 128 ± 16 | 0.015 | 131 ± 17 | 127 ± 18 | 132 ± 16 | 0.024 |
| Diastolic blood pressure (mmHg) | 72 ± 10 | 71 ± 9 | 72 ± 9 | 0.517 | 76 ± 11 | 74 ± 9 | 76 ± 11 | 0.010 |
| Heart rate (bpm) | 67 ± 11 | 71 ± 10 | 67 ± 11. | 0.092 | 73 ± 12 | 76 ± 11 | 73 ± 12 | 0.085 |
| Supine SpO2 (%) | 99.0 [98.0; 99.7] | 94.5 [93.8; 95.3] | 99.0 [98.0; 99.7] | - | 98.0 [97.3; 99.0] | 94.7 [93.7; 95.3] | 98.3 [97.7; 99.0] | - |
| EGFR (ml/min/1.73 m2) | 92.3 ± 21.2 | 82.9 ± 20.2 | 92.6 ± 21.1 | 0.029 | 64.4 ± 21.3 | 68.5 ± 19.0 | 63.8 ± 21.6 | 0.092 |
| Blood hemoglobin (mmol/mol) | 8.7 ± 0.8 | 8.4 ± 0.8 | 8.7 ± 0.8 | 0.041 | 8.8 ± 1.0 | 8.8 ± 0.9 | 8.8 ± 1.0 | 0.433 |
| Urine albumin creatinine ratio (mg/g) | 6.0 [4.0; 13.0] | 15.5 [7.2; 46.8] | 6.0 [4.0; 13.0] | < 0.001 | 14.0 [6.0; 52.8] | 14.5 [7.0; 56.8] | 14.0 [6.0; 51.8] | 0.428 |
| HbA1c (mmol/mol) | 58 [51; 65] | 60 [57; 65] | 58 [51; 65] | 0.215 | 55 [48; 64] | 56 [48; 67] | 55 [48; 63] | 0.229 |
| HbA1c (%) | 7.5 [6.8;8.1] | 7.6 [7.4;8.1] | 7.5 [6.8;8.1] | 0.215 | 7.2 [6.5;8.0] | 7.3 [6.5;8.3] | 7.2 [6.5;7.9] | 0.229 |
| Total cholesterol (mmol/l) | 4.3 [3.9; 4.9] | 4.2 [3.9; 4.6] | 4.3 [3.8; 5.0] | 0.352 | 3.6 [3.1; 4.3] | 3.5 [3.1; 3.9] | 3.7 [3.1; 4.3] | 0.055 |
| LDL cholesterol (mmol/l) | 2.1 [1.7; 2.6] | 1.9 [1.5; 2.2] | 2.1 [1.7; 2.6] | 0.041 | 1.6 [1.2; 2.2] | 1.5 [1.1; 1.9] | 1.6 [1.2; 2.2] | 0.099 |
| Triglycerides (mmol/l) | 0.9 [0.7; 1.2] | 1.0 [0.8; 1.4] | 0.9 [0.7; 1.2] | 0.230 | 1.7 [1.2; 2.5] | 1.7 [1.2; 2.5] | 1.7 [1.2; 2.5] | 0.743 |
| Diabetes duration (years) | 27 [17; 42] | 38 [24; 47] | 27 [17; 42] | 0.015 | 17 [11; 23] | 18 [12; 24] | 17 [11; 23] | 0.487 |
| Smoking status | - | - | - | 0.880 | - | - | - | 0.747 |
| Never | 413 (54.9) | 16 (61.5) | 397 (54.7) | - | 347 (45.6) | 35 (44.3) | 312 (45.7) | - |
| Former | 252 (33.5) | 8 (30.8) | 244 (33.6) | - | 310 (40.7) | 31 (39.2) | 279 (40.9) | - |
| Current | 87 (11.6) | 2 (7.7) | 85 (11.7) | - | 104 (13.7) | 13 (16.5) | 91 (13.3) | - |
| Physical activity | - | - | - | 0.852 | - | - | - | 0.061 |
| Yes (> 30 min/d) | 476 (64.2) | 16 (61.5) | 460 (64.2) | - | 309 (40.7) | 31 (39.2) | 278 (40.9) | - |
| Yes (< 30 min/d) | 212 (28.6) | 8 (30.8) | 204 (28.5) | - | 240 (31.6) | 18 (22.8) | 222 (32.6) | - |
| None | 54 (7.3) | 2 (7.7) | 52 (7.3) | - | 210 (27.7) | 30 (38) | 180 (26.5) | - |
| Excess alcohol consumption* | 23 (3.1) | 1 (3.8) | 22 (3) | 0.560 | 14 (1.8) | 0 (0) | 14 (2.1) | 0.383 |
| Hypertension | 297 (39.8) | 14 (53.8) | 283 (39.3) | 0.197 | 568 (74.6) | 60 (75) | 508 (74.6) | 1.000 |
| Any cardiovascular disease | 85 (11.3) | 4 (15.4) | 81 (11.2) | 0.524 | 241 (31.7) | 27 (33.8) | 214 (31.5) | 0.774 |
| Congenital heart disease | 5 (0.7) | 0 (0) | 5 (0.7) | 1.000 | 14 (1.9) | 1 (1.3) | 13 (2) | 1.000 |
| Acute myocardial infarction | 23 (3.2) | 0 (0) | 23 (3.3) | 1.000 | 80 (10.8) | 11 (14.1) | 69 (10.4) | 0.414 |
| Percutaneous coronary intervention | 26 (3.6) | 1 (4) | 25 (3.6) | 0.603 | 89 (12) | 14 (18.2) | 75 (11.3) | 0.114 |
| Coronary artery bypass grafting | 16 (2.2) | 1 (4) | 15 (2.1) | 0.431 | 63 (8.5) | 5 (6.5) | 58 (8.7) | 0.649 |
| Stroke or transient ischemic attack | 29 (3.9) | 2 (8) | 27 (3.8) | 0.259 | 64 (8.6) | 10 (12.5) | 54 (8.2) | 0.275 |
| Deep venous thrombosis | 6 (0.8) | 0 (0) | 6 (0.9) | 1.000 | 16 (2.2) | 3 (3.9) | 13 (2) | 0.229 |
| Medication | | | | | | | | |
| Metformin | 35 (4.7) | 2 (7.7) | 33 (4.6) | 0.344 | 589 (77.5) | 62 (77.5) | 527 (77.5) | 1.000 |
| GLP-1 receptor agonists | 22 (2.9) | 2 (7.7) | 20 (2.8) | 0.174 | 461 (60.7) | 52 (65) | 409 (60.1) | 0.472 |
| SGLT2 inhibitors | 9 (1.2) | 0 (0) | 9 (1.2) | 1.000 | 430 (56.6) | 46 (57.5) | 384 (56.5) | 0.955 |
| DPP-4 inhibitors | 0 (0) | 0 (0) | 0 (0) | 1.000 | 92 (12.1) | 10 (12.5) | 82 (12.1) | 1.000 |
| Sulfonylureas | 0 (0) | 0 (0) | 0 (0) | 1.000 | 26 (3.4) | 0 (0) | 26 (3.8) | 0.099 |
| Insulin | 751 (100) | 26 (100) | 725 (100) | 1.000 | 429 (56.4) | 54 (67.5) | 375 (55.1) | 0.047 |
| Betablocker | 67 (8.9) | 5 (19.2) | 62 (8.6) | 0.127 | 271 (35.7) | 30 (37.5) | 241 (35.4) | 0.810 |
| Antihypertensive treatment | 230 (30.6) | 13 (50) | 217 (29.9) | 0.049 | 437 (57.5) | 52 (65) | 385 (56.6) | 0.188 |
| RAAS blocade | 343 (45.7) | 17 (65.4) | 326 (45) | 0.064 | 592 (77.9) | 60 (75) | 532 (78.2) | 0.605 |
| Lipid lowering treatment | 416 (55.4) | 22 (84.6) | 394 (54.3) | 0.002 | 681 (89.6) | 74 (92.5) | 607 (89.3) | 0.482 |
| Neuropathy outcomes | | | | | | | | |
| CAN | 100 (17.3) | 2 (12.5) | 98 (17.5) | 1.000 | 113 (22.7) | 20 (39.2) | 93 (20.8) | 0.005 |
| Sudo hands | 201 (27.1) | 11 (45.8) | 190 (26.5) | 0.062 | 210 (33.3) | 25 (38.5) | 185 (32.7) | 0.425 |
| Sudo feet | 335 (45.1) | 16 (66.7) | 319 (44.4) | 0.052 | 408 (64.7) | 42 (64.6) | 366 (64.7) | 1.000 |
| VPT > 25 volts | 214 (28.5) | 18 (69.2) | 196 (27.1) | <0.001 | 408 (54.1) | 45 (56.2) | 363 (53.9) | 0.774 |
| DPNCheck bilat. | 363 (61.2) | 9 (69.2) | 354 (61) | 0.775 | 332 (62.8) | 35 (60.3) | 297 (63.1) | 0.795 |
| Pinprick bilat. | 54 (7.3) | 0 (0) | 54 (7.5) | 0.248 | 165 (22.3) | 19 (24.1) | 146 (22.1) | 0.795 |
| MNSI-E > 2 | 520 (69.1) | 20 (76.9) | 500 (68.8) | 0.505 | 623 (81.8) | 67 (83.8) | 556 (81.5) | 0.738 |
| DN4i ≥ 3 | 55 (8.3) | 4 (19) | 51 (8) | 0.088 | 117 (18.5) | 18 (27.3) | 99 (17.4) | 0.075 |

Table 1: Clinical characteristics stratified by diabetes type and low vs. high $SpO_2$ within each type. Data are presented as mean ± SD, median [IQR], number (%). P values represent comparisons between low and high $SpO_2$ groups using t-test or Mann-Whitney U test for continuous variables, and Pearson's chi-square test or Fisher's exact test for categorical variables. Neuropathy outcomes are presented as n (%) of pathological tests. Outcome abbreviations: CAN = Cardiovascular Autonomic Neuropathy, CART = Cardiovascular Autonomic Reflex Test, CART: L-S = Lying-to-standing test, CART: EI = Expiration to inspiration ratio, CART: V = Valsalva, VPT = Vibration Perception Threshold, DPNCheck bilat. = DPNCheck bilateral, Pinprick bilat. = Pinprick bilateral, MNSI-E = Michigan Neuropathy Screening Instrument Examination, DN4i = Douleur Neuropathique 4 interview.
*Defined as > 21 units of alcohol per week for men, and > 14 units of alcohol per week for women.

Model 3: adjusted for age, sex, hemoglobin, LDL cholesterol, systolic blood pressure, smoking, alcohol consumption, physical activity, and BMI, and
Model 4: additionally adjusted for UACR and eGFR

Model 3 was considered the primary model. In Model 4, renal outcomes were added as surrogate markers of microvascular disease to explore if these could be confounding associations between hypoxia and DPN. Adjustment for diabetes duration in sensitivity analyses did not materially change the estimates (Tables S1 and S2; see supplementary materials associated with this article on line).

Results are reported as ORs with 95% confidence intervals. A two-sided $P < 0.05$ was considered statistically significant. All analyses were performed using R (version 4.4.2).

## Results

### *Participant characteristics*

A total of 1,720 participants were included in the study. Of these, 64 had COPD, 138 had missing $SpO_2$ data, and 3 had both, resulting in 1,515 participants available for analysis. Baseline characteristics of the study population are summarized in Table 1.

Among participants with type 1 diabetes (n = 753), those with lower $SpO_2$ (< 96%, n = 26) were older and had higher BMI and systolic blood pressure, as well as lower eGFR and hemoglobin levels, compared to those with higher $SpO_2$ (≥ 96%, all $P < 0.05$). They also showed higher urinary albumin-to-creatinine ratio and a greater prevalence of elevated VPT ($P < 0.001$).

For participants with type 2 diabetes (n = 762), individuals with lower $SpO_2$ (n = 80) had higher BMI and lower blood pressure compared to those with higher $SpO_2$ ($P < 0.05$). Age, kidney function, and metabolic profile were similar across groups. The prevalence of CAN was higher in the low $SpO_2$ group (39% vs 21%, $P = 0.005$).

### *$SpO_2$ assessed as a continuous variable*

In participants with type 1 diabetes, lower $SpO_2$ was associated with higher odds of sudomotor dysfunction, vibration perception loss and neuropathic pain (Fig. 1). Full model estimates are provided in Table S3 (see supplementary material associated with this article online).

In the primary adjusted model (Model 3), each 1%-point decrease in $SpO_2$ was associated with higher odds of abnormal sudomotor function in the hands (OR 1.24, 95% CI 1.08–1.44, $P = 0.003$) and feet (OR 1.22, 95% CI 1.06–1.41, $P = 0.007$), as well as VPT >25 V (OR 1.30, 95% CI 1.11–1.52, $P = 0.001$). Associations remained largely consistent after additional adjustment for UACR and eGFR (Model 4), although the association with sudomotor function in the feet was no longer significant($P = 0.036$).

No significant associations were found for autonomic function (CARTs or CAN) or other DPN measures.

In type 2 diabetes, lower $SpO_2$ was associated with cardiovascular autonomic neuropathy (Fig. 1), with detailed results available in Table S3 (see supplementary materials associated with this article online).

In Model 3, lower $SpO_2$ was significantly associated with CAN (OR 1.25, 95% CI 1.09–1.43, $P = 0.001$) but lost significance in Model 4 ($P = 0.083$). Similarly, $SpO_2$ was significantly associated with CART: L-S in Model 3 (OR 1.15, 95% CI 1.01-1.31, $P = 0.036$), but not in Model 4 ($P = 0.759$). Lower $SpO_2$ was also associated with neuropathic pain, defined as DN4i ≥3 (OR 1.14, 95% CI 1.00-1.30, $P = 0.0498$).

No consistent associations were observed for other DPN measures.

### *$SpO_2$ assessed as a binary variable (low vs high)*

When $SpO_2$ was analyzed as a categorical variable (< 96% vs ≥ 96%), results were generally consistent with those obtained when $SpO_2$ was analyzed as a continuous variable (Fig 2; Table S4; see supplementary material associated with this article online).

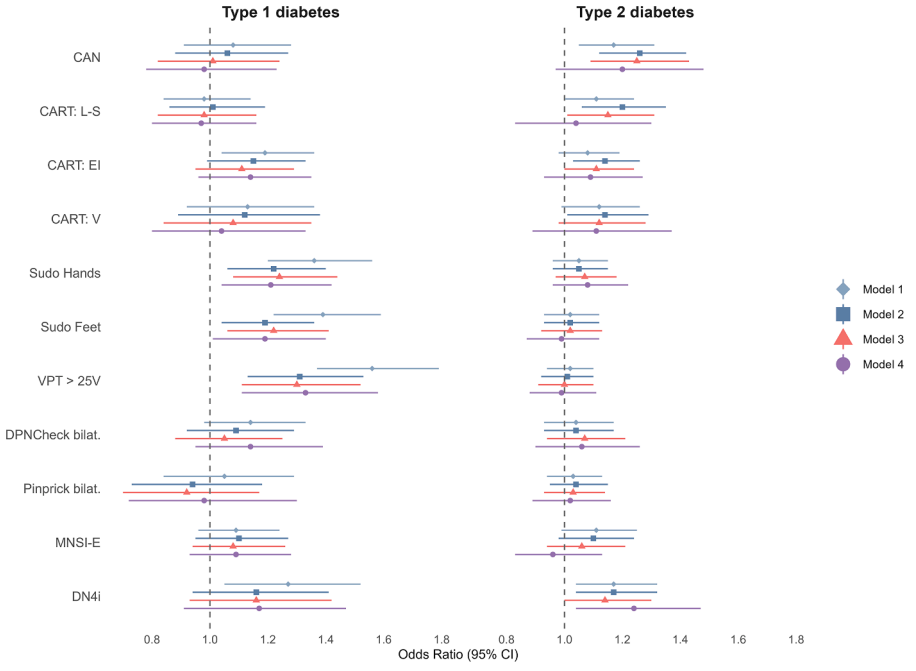


**Fig. 1.** ORs pr 1%-point decrease in $SpO_2$.
Fig. 1: Odds ratios per 1%-point decrease in SpO2. Error bars indicate 95% confidence intervals. Adjustments: Model 1, none; Model 2, age and sex; Model 3, Model 2 plus hemoglobin, LDL, sBP, smoking, alcohol, physical activity, BMI; Model 4, Model 3 plus UACR and eGFR. Outcome abbreviations: CAN = Cardiovascular Autonomic Neuropathy, CART = Cardiovascular Autonomic Reflex Test, CART: L-S = Lying-to-standing test, CART: EI = Expiration to inspiration ratio, CART: V = Valsalva, VPT = Vibration Perception Threshold, DPNCheck bilat. = DPNCheck bilateral, Pinprick bilat. = Pinprick bilateral, MNSI-E = Michigan Neuropathy Screening Instrument Examination, DN4i = Douleur Neuropathique 4 interview.

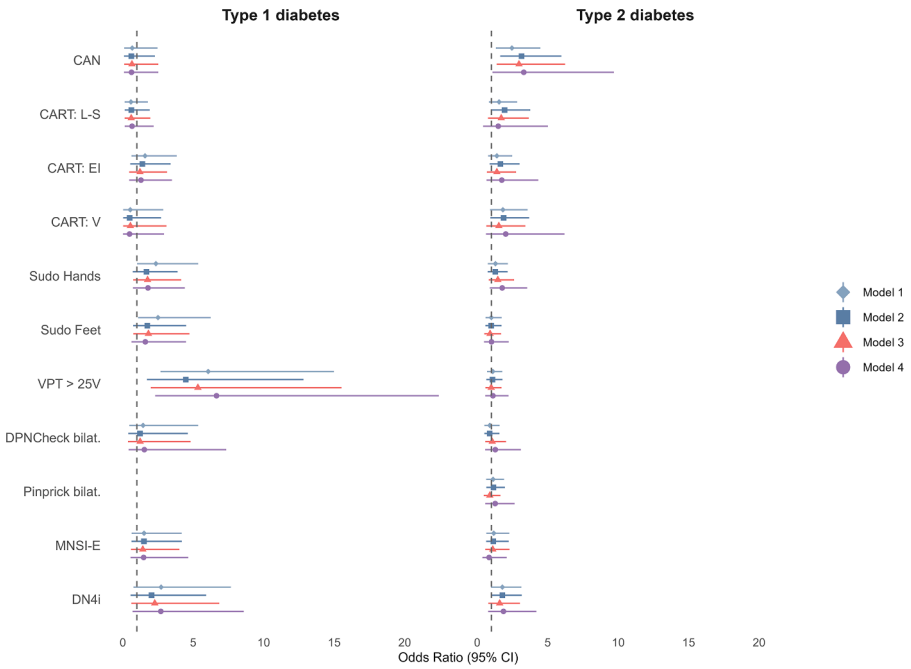


**Fig. 2.** ORs of low vs high $SpO_2$.

Fig. 2: Odds ratios from low $SpO_2$ vs high $SpO_2$. Circle Error bars indicate 95% confidence intervals. Adjustments: Model 1, none; Model 2, age and sex; Model 3, Model 2 plus hemoglobin, LDL, sBP, smoking, alcohol, physical activity, BMI; Model 4, Model 3 plus UACR and eGFR. Outcome abbreviations: CAN = Cardiovascular Autonomic Neuropathy, CART = Cardiovascular Autonomic Reflex Test, CART: L-S = Lying-to-standing test, CART: EI = Expiration to inspiration ratio, CART: V = Valsalva, VPT = Vibration Perception Threshold, DPNCheck bilat. = DPNCheck bilateral, Pinprick bilat. = Pinprick bilateral, MNSI-E = Michigan Neuropathy Screening Instrument Examination, DN4i = Douleur Neuropathique 4 interview.

In type 1 diabetes, lower $SpO_2$ was associated with higher odds of VPT >25 V (OR 5.33, 95% CI 1.99-15.52, $P = 0.001$). Associations between $SpO_2$ and sudomotor dysfunction in the hands and feet were observed only in the unadjusted model. No other associations were identified.

In type 2 diabetes, lower $SpO_2$ was associated with higher odds of CAN across all adjusted models (OR 2.96, 95% CI 1.38–6.23, $P = 0.005$), but we did not find an association with DN4i or other DPN measures.

## Discussion

### *Principal findings*

In this cross-sectional study, lower $SpO_2$ was associated with multiple measures of DPN. Among individuals with type 1 diabetes, lower $SpO_2$ was associated with sudomotor dysfunction and higher vibration perception thresholds. In contrast, in type 2 diabetes, associations were primarily observed with measures of CAN and neuropathic pain. However, causality cannot be established from this cross-sectional design.

### *Comparison with existing literature*

Patients with type 1 diabetes have been shown to have lower $SpO_2$ levels compared to healthy controls [4], but evidence directly linking hypoxia to DPN remains scarce. Existing studies from our group have demonstrated associations between lower $SpO_2$ and autonomic impairment as well as other microvascular complications, including DPN, in type 1 diabetes [12,13]. To our knowledge, no prior work has examined specific domains of DPN or included individuals with type 2 diabetes.

Obstructive sleep apnea, a cause of intermittent hypoxia, has been associated with neuropathy in type 1 diabetes but not in type 2 diabetes [23], suggesting that hypoxia-related mechanisms may be particularly relevant in type 1 diabetes.

### *Possible biological mechanisms*

Human studies have demonstrated clear microvascular pathology in DPN – including basement membrane thickening, pericyte loss, and endothelial hyperplasia in endoneurial vessels. These changes correlate closely with clinical and structural nerve abnormalities [9]. Both clinical and experimental data further demonstrate reduced nerve blood flow, increased endoneurial vascular resistance, and consequent endoneurial hypoxia, providing a well-established biological basis for hypoxia-driven nerve injury [24,25]. Importantly, one human study directly measured endoneurial oxygen tension and reported significantly lower levels in individuals with DPN compared to those without [26], providing direct physiological evidence of local hypoxia in affected nerves. While reduced nerve blood flow can directly limit oxygen delivery, impaired microvascular function may additionally restrict effective oxygen extraction. Experimental models demonstrate that altered capillary flow patterns can lead to endoneurial hypoxia despite preserved overall blood flow [8]. Given these mechanisms, reduced systemic blood oxygen saturation may further reduce the oxygen supply to the nerves, thereby amplifying endoneurial hypoxia.

These mechanisms may not affect all neural structures equally. Our results showed a difference in patterns between diabetes types, with associations to large fiber neuropathy and sudomotor dysfunction in type 1 diabetes and to small fiber neuropathy and cardiovascular autonomic dysfunction in type 2 diabetes. The reasons for these differences remain unclear and require further investigation. However, the observed differences in age, diabetes duration, and complication burden may help explain the findings.

### *Hypoxia as a target for treatment*

Modulation of tissue oxygenation has emerged as a plausible therapeutic approach for nerve damage. Improvements in baroreflex function and heart rate variability after hyperoxia [5,27,28] as well as beneficial

effects of hyperbaric oxygen therapy on neuropathic pain and nerve conduction [29–31], support further evaluation of oxygenation-targeted interventions in DPN [7]. However, high-quality randomized trials and safety data in this population remain limited.

*Interpretation of microvascular adjustments*

Adjustment for UACR and eGFR in Model 4 may influence the observed associations through several mechanisms. Prior work has demonstrated an association between lower $SpO_2$ and macroalbuminuria in type 1 diabetes [12], suggesting a link between systemic oxygenation and renal microvascular injury. Because hypoxia is implicated in both renal and neural microvascular injury [32], these variables could lie on the causal pathway, and adjustment might therefore represent overadjustment. Alternatively, attenuation of the associations could reflect shared pathophysiology or confounding by the overall burden of microvascular disease rather than mediation through renal dysfunction alone.

*Strengths and limitations*

Strengths of this study include the large, well-characterized cohort with standardized assessments of both peripheral and autonomic neuropathy, enabling evaluation of distinct DPN phenotypes in type 1 and type 2 diabetes. The simultaneous assessment of $SpO_2$ and multiple DPN modalities allowed a comprehensive evaluation of hypoxia-related associations.

Several limitations should be considered. The cross-sectional design precludes any conclusions about the directionality of the observed associations. While we hypothesize that reduced oxygen saturation may contribute to the development of DPN, alternative explanations cannot be excluded. $SpO_2$ provides only a crude estimate of systemic oxygenation and does not capture nocturnal or intermittent hypoxia. Despite extensive adjustment, shared microvascular pathology may influence the observed associations. We did not apply statistical correction for multiple testing because the analyses were exploratory and aimed to characterize patterns across the different DPN phenotypes; however, given the number of outcomes examined, chance findings cannot be excluded.

Skin pigmentation may affect the accuracy of $SpO_2$ measurements, but this was not recorded in the present study. As most participants were Caucasian and recruited from a single center, the generalizability of the findings may be limited. Furthermore, data on peripheral arterial disease were not available. Because peripheral ischemia can cause pain, we cannot exclude the possibility that the association observed between $SpO_2$ and DN4i may partly reflect ischemic rather than neuropathic pain.

## Conclusion

Lower blood oxygen saturation was associated with sudomotor dysfunction and impaired vibration perception in type 1 diabetes and with cardiovascular autonomic neuropathy and neuropathic pain in type 2 diabetes. These cross-sectional findings highlight distinct DPN patterns across diabetes types, but longitudinal studies are needed to determine causality.

## Data availability statement

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

## Funding

This study was supported by internal sources at Steno Diabetes Center Copenhagen.

## Authors' relationships and activities

P.R. has received honoraria to his institution for consultancy and/or speaking fees from Astellas, Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Gilead, MSD, Mundipharma, Novo Nordisk, and Sanofi Aventis and research grants from AstraZeneca and Novo Nordisk (to the institution). All other authors report no conflicts of interest related to this work.

## Prior presentation

Preliminary results from this study were presented in abstract form at NEURODiab 2023, Thessaloniki, Greece, September 2023 & EASD 2023, Hamburg, Germany, October 2023.

Appendix supplementary material

Supplementary materials (Fig. S1 and Tables S1-S4) associated with this article can be found at http://www.scincedirect.com at doi . . .

## CRediT authorship contribution statement

**Rasmus Budde Brødsgaard:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Jens Christian Laursen:** Writing – review & editing, Formal analysis, Data curation. **Hatice Isik Mizrak:** Writing – review & editing, Project administration, Investigation, Data curation. **Huda Kufaishi:** Writing – review & editing, Data curation. **Sofie Korsgaard Hecquet:** Writing – review & editing, Data curation. **Birgitte Brock:** Writing – review & editing. **Peter Rossing:** Writing – review & editing. **Christian Stevns Hansen:** Writing – review & editing, Supervision, Investigation, Conceptualization.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Peter Rossing reports a relationship with Astellas Pharma Inc that includes: consulting or advisory and speaking and lecture fees. Peter Rossing reports a relationship with Abbott that includes: consulting or advisory and speaking and lecture fees. Peter Rossing reports a relationship with AstraZeneca that includes: consulting or advisory, funding grants, and speaking and lecture fees. Peter Rossing reports a relationship with Bayer Corporation that includes: consulting or advisory and speaking and lecture fees. Peter Rossing reports a relationship with Boehringer Ingelheim Pharma GmbH & Co KG that includes: consulting or advisory and speaking and lecture fees. Peter Rossing reports a relationship with Eli Lilly that includes: consulting or advisory and speaking and lecture fees. Peter Rossing reports a relationship with Gilead Sciences Inc that includes: consulting or advisory and speaking and lecture fees. Peter Rossing reports a relationship with Merck Sharp & Dohme Corp that includes: consulting or advisory and speaking and lecture fees. Peter Rossing reports a relationship with Mundipharma that includes: consulting or advisory and speaking and lecture fees. Peter Rossing reports a relationship with Novo Nordisk that includes: consulting or advisory, funding grants, and speaking and lecture fees. Peter Rossing reports a relationship with Sanofi Aventis SA that includes: consulting or advisory and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

We thank all participants of the DANES study for their valuable contribution. We also acknowledge the clinical staff at Steno Diabetes Center Copenhagen for their support in data collection.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2026.101773.

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