

## ONLINE APPENDIX

### **Participants' classification criteria**

The American Academy of Neurology (AAN) and the American Association of Electrodiagnostic Medicine (AAEM) have published a recommended protocol for the electrodiagnosis of DSPN, commonly known as the Toronto criteria.(1) This recommendation has been supported in research to detect participant with definite DSPN.(2) The Toronto criteria for electrodiagnosis of DSPN includes unilateral studies of sural sensory, ulnar sensory, and median sensory nerves, and fibular, tibial, median, and ulnar motor nerves. The minimum case definition criterion for electrodiagnostic confirmation of distal symmetric polyneuropathy is an abnormality ( $\leq 99^{\text{th}}$  or  $\geq 1^{\text{st}}$  percentile) of any attribute of nerve conduction in two separate nerves, one of which must be the sural nerve.(2)

In our study, we used a different reference standard based on the use of corneal confocal microscopy (CCM), a measure of small nerve fibre.(3) The diagnostic thresholds in CCM for DSPN in type I and II diabetes have been determined in a large cohort study.(3) The reference standard for DSPN used in that study,(3) which was a stringent clinical criteria, required: 1) clinical symptoms or signs to be present and 2) fibular motor nerve conduction velocity  $< 42$  m/s or corneal nerve fibre length  $< 12.5$  mm/mm<sup>2</sup>. This reference was based on consensus criteria.(1,2,4) Other criteria (including the Toronto criteria) were explored in sensitivity analyses to account for imperfect reference standards. The stringent clinical criteria utilised in our study performed better than the Toronto definition for area under the curve when people with diabetes type I and II were pooled together. For this the reason, the criterion of fibular conduction velocity  $< 42$  m/s was used as the reference standard, although is not (yet) included in guidelines.

We included additional QST analyses using the Toronto criteria to reflect the common standard (Supplementary Table 1).

### **Carpal Tunnel Syndrome**

Carpal Tunnel Syndrome (CTS) is the most common peripheral nerve entrapment syndrome worldwide caused by compression of the median nerve at the wrist as it passes through a space-limited osteofibrous canal.(5) CTS occurs in 14% of diabetes patients without DSPN, and in 30% of diabetes patients with DSPN.(6) According to the AAN and AAEM,(1) the standard examination to confirm a clinical diagnosis of CTS includes exploring the median and ulnar sensory nerve across the wrist. In people with DSPN, the diagnosis of CTS is challenging. In this study, if the attributes of the median sensory nerve were abnormal but the ulnar sensory nerve appeared normal on the same limb, then CTS could not be excluded in people with DSPN.(7) The results are reported in Supplementary Table 3. Additionally, we have included a QST analysis excluding the people for whom we could not rule out CTS (Supplementary Table 5). All findings were comparable to the initial analysis.

## REFERENCES

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## SUPPLEMENTARY TABLES

**Supplementary Table 1.** Overview of medication use

	<b>Healthy participants (n=31)</b>	<b>Diabetes without DSPN (n=35)</b>	<b>DSPN FEET ONLY (n=31)</b>	<b>DSPN HANDS &amp; FEET (n=28)</b>
Hypolipidaemic medication	3 (10%)	11 (31%)	13 (42%)	11 (32%)
Antihypertensive medication	3 (10%)	12 (34%)	16 (52%)	13 (46%)
Antiasthmatic medication	0 (0%)	1 (3%)	3 (10%)	1 (4%)
Antidepressant medication:				
Tricyclic antidepressants	0 (0%)	0 (0%)	0 (0%)	1 (4%)
SNRI (duloxetine)	1 (3%)	0 (0%)	1 (3%)	3 (11%)
SSRI (citalopram)	1 (3%)	1 (3%)	2 (7%)	1 (4%)
NDRI (methylphenidate)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Anxiolytic:				
Benzodiazepines (diazepam)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Gabapentinoids				
Pregabalin	1 (3%)	2 (6%)	3 (10%)	5 (18%)
Non-opioid analgesics				
NSAIDS (ibuprofen)	1 (3%)	3 (9%)	4 (13%)	4 (14%)
Opioid analgesics				
Moderate (codeine)	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Antagonists (naloxone)	0 (0%)	0 (0%)	0 (0%)	1 (4%)

Data shown as frequencies (percentages). DSPN: distal symmetrical polyneuropathy; SSRI: Selective serotonin reuptake inhibitors; SNRI: serotonin-norepinephrine reuptake inhibitors; NDRI: norepinephrine-dopamine reuptake inhibitor; NSAIDS: nonsteroidal anti-inflammatory drugs.

**Supplementary Table 2.** Electrodiagnostic and in vivo corneal confocal microscopy results.

	Healthy participants (n=31)	Diabetes without DSPN (n=35)	DSPN FEET ONLY (n=31)	DSPN HANDS & FEET (n=28)	ANOVA results	Pairwise differences
Electrodiagnostic studies						
Sural SNAP (µV)	Mean (SD) Abnormal (<4 µV)	8.5 (6.1) 5 (16%)	8.0 (3.7) 4 (11%)	4.8 (1.9) 11 (36%)	4.8 (2.8) 15 (57%)	<0.001 1-3**, 1-4**, 2-3*, 2-4*
Sural SCV (m/s)	Mean (SD) Abnormal (<37 m/s)	43.2 (8.1) 6 (19%)	39.5 (9.0) 11 (29%)	35.2 (8.1) 20 (65%)	25.1 (11.6) 19 (68%)	<0.001 1-3**, 1-4*
Fibular CMAP (mV)	Mean (SD) Abnormal (<4.0 mV)	- -	- -	- -	- -	
Fibular MCV (m/s)	Mean (SD) Abnormal (<42 m/s)	54.6 (6.4) 0 (0%)	52.2 (9.6) 3 (9%)	40.9 (7.9) 16 (52%)	41.6 (5.3) 14 (50%)	<0.001 1-3***, 1-4***, 2-3***, 2-4***
Tibial CMAP (mV)	Mean (SD) Abnormal (<4.4mV)	11.3 (3.7) 0 (0%)	9.1 (3.9) 5 (9%)	5.0 (3.9) 15 (49%)	4.2 (2.8) 16 (57%)	<0.001 1-3***, 1-4***, 2-3***, 2-4***
Tibial MCV (m/s)	Mean (SD) Abnormal (<39 m/s)	51.4 (5.1) 0 (0%)	49.2 (7.6) 3 (8.6%)	42.4 (9.1) 13 (42%)	42.6 (8.0) 8 (29%)	<0.001 1-3***, 1-4***, 2-3**, 2-4**
Median CMAP (mV)	Mean (SD) Abnormal (<4.1 mV)	7.5 (2.2) 1 (3%)	5.3 (1.3) 3 (9%)	5.1 (1.9) 9 (29%)	4.6 (1.9) 13 (46%)	<0.001 1-2**, 1-3**, 1-4**
Median MCV (m/s)	Mean (SD) Abnormal (<49 m/s)	73.7 (7.0) 0 (0%)	70.3 (7.3) 0 (0%)	63.9 (6.2) 0 (0%)	63.2 (8.7) 1 (3.6%)	<0.001 1-3**, 1-4***, 2-4*
Median SNAP (µV)	Mean (SD) Abnormal (<10 µV)	33.3 (18.3) 2 (7%)	18.5 (14.1) 4 (11%)	9.6 (6.7) 21 (68%)	5.4 (2.5) 27 (96%)	<0.001 1-2**, 1-3***, 1-4***, 2-4**
Median SCV (m/s)	Mean (SD) Abnormal (<44 m/s)	44.0 (6.9) 6 (19%)	47.5 (6.5) 3 (9%)	40.5 (7.7) 21 (68%)	36.1 (8.7) 22 (79%)	<0.001 1-4*, 2-4***
Ulnar SNAP (µV)	Mean (SD) Abnormal (<10.0 mV)	33.5 (17.0) 1 (3%)	23.4 (14.4) 2 (6%)	15.7 (10.8) 9 (29%)	10.8 (7.8) 17 (61%)	<0.001 1-3***, 1-4***, 2-4*
Ulnar SCV (m/s)	Mean (SD) Abnormal (<45 m/s)	48.6 (8.7) 4 (13%)	50.7 (5.5) 2 (6%)	41.9 (9.6) 15 (48%)	39.9 (13.3) 18 (64%)	0.002 2-4*
Probable CTS	Presence	0 (0%)	0 (0%)	0 (0%)	4 (15%)	0.058
In vivo corneal confocal microscopy						
CNFL (mm/mm <sup>2</sup> )	Abnormal (<12.5 mm/mm <sup>2</sup> )	0 (0%)	13 (37%)	20 (65%)	19 (68%)	<0.001 1-2*, 1-3***, 1-4***, 2-3**, 2-4**

Data shown as mean (standard deviation) and analysed by a one-way ANOVA (ANOVA results), with Bonferroni post-hoc tests (pairwise differences). Categorical data are reported as frequencies (percentages). Pairwise differences indicate significant  $p$  values between group pairs: 1: Healthy participants; 2: diabetes without DSPN; 3: DSPN in feet only; 4: DSPN in hands & feet. \*:  $p < 0.05$ ; \*\*:  $p < 0.01$ ; \*\*\*:  $p < 0.001$ . DSPN: distal symmetrical polyneuropathy; SNAP: sensory nerve action potential;  $\mu$ V, microvolts; SCV: sensory conduction velocity; m/s: metres per second; CMAP: compound muscle action potentials; MCV: motor conduction velocity; CTS: carpal tunnel syndrome; CNFL: corneal nerve fibre length; mm/mm<sup>2</sup>. Due to a technical error, the fibular CMAP could not be determined accurately. Presence of CTS was considered as having any abnormal attributes in the median sensory nerve without any changes on the ulnar sensory nerve of the same hand.

**Supplementary Table 3.** Raw quantitative sensory testing values

Test location: Hand		Healthy participants N = 31	Diabetes without DSPN N = 35	DSPN FEET ONLY N = 31	DSPN HANDS & FEET N = 28	p value
CDT (Z-score)		0.05 (-0.66, 0.60)	-0.02 (-1.26, 0.56)	-0.66 (-1.52, 0.44)	-1.81 (-2.79, -0.43)	< 0.001 <sup>1-4,2-4,3-4</sup>
CDT	Normal	30 (96.8%)	32 (91.4%)	25 (80.7%)	17 (60.2%)	< 0.001 <sup>1-4,2-4</sup>
	Abnormal (loss: <-2)	1 (3.2%)	3 (8.6%)	6 (19.3%)	11 (39.8%)	
WDT (Z-score)		0.06 (-0.57, 0.81)	-0.01 (-0.90, 0.44)	-1.42 (-1.83, 0.62)	-1.45 (-2.34, 0.40)	< 0.001 <sup>1-3,1-4,2-3,2-4</sup>
WDT	Normal	30 (96.8%)	31 (88.6%)	25 (80.7%)	14 (64.3%)	0.0077 <sup>1-4</sup>
	Abnormal (loss: <-2)	1 (3.2%)	4 (11.4%)	6 (19.3%)	10 (35.7%)	
TSL (Z-score)		-0.08 (-0.60, 0.88)	-0.17 (-1.11, 0.36)	-1.47 (-2.10, 0.43)	-1.84 (-2.57, 0.79)	< 0.001 <sup>1-3,1-4,2-3,2-4</sup>
TSL	Normal	31 (100%)	31 (88.6%)	21 (64.7%)	13 (46.4%)	< 0.001 <sup>1-2,1-3,1-4,2-3,2-4</sup>
	Abnormal gain (>2)	0 (0%)	0 (0%)	0 (0%)	1 (3.6%)	
	Abnormal (loss: <-2)	0 (0%)	4 (11.4%)	10 (32.3%)	14 (50%)	
CPT (Z-score)		0.27 (-0.83, 0.88)	0.48 (-0.38, 1.01)	0.09 (-0.95, 1.17)	-0.43 (-1.14, 0.60)	0.13
CPT	Normal	31 (100%)	35 (100.0%)	31 (100%)	28 (100%)	0.99
HPT (Z-score)		0.11 (-0.85, 0.95)	0.18 (-0.25, 1.14)	-0.86 (-1.29, 0.04)	-1.08 (-1.56, 0.12)	< 0.001 <sup>1-3,1-4,2-3,2-4</sup>
HPT	Normal	31 (100%)	33 (94.3%)	31 (100%)	28 (100%)	0.25
	Abnormal gain (>2)	0 (0%)	2 (5.7%)	0 (0%)	0 (0%)	
MDT (Z-score)		0.18 (-0.71, 0.72)	-1.20 (-2.18, 0.47)	-2.18 (-2.38, 1.34)	-2.18 (-2.40, 1.84)	< 0.001 <sup>1-2,1-3,1-4,2-3,2-4</sup>
MDT	Normal	29 (93.5%)	24 (68.6%)	12 (38.7%)	8 (28.6%)	< 0.001 <sup>1-2,1-3,1-4,2-3,2-4</sup>
	Abnormal loss (<-2)	2 (6.5%)	11 (31.4%)	19 (61.3%)	20 (71.4%)	
MPT (Z-score)		-0.07 (-0.52, 0.29)	0.01 (-0.35, 0.51)	-0.33 (-0.84, 0.19)	-0.33 (-1.17, 0.71)	0.18
MPT	Normal	31 (100%)	35 (100.0%)	30 (96.8%)	27 (96.4%)	0.47
	Abnormal loss (<-2)	0 (0%)	0 (0%)	1 (3.2%)	1 (3.6%)	
MPS (Z-score)		-0.08 (-0.81, 0.44)	0.91 (-0.67, 2.28)	0.02 (-0.69, 0.84)	0.26 (-0.70, 1.06)	0.037 <sup>1-2</sup>
MPS	Normal	30 (96.8%)	23 (65.7%)	25 (80.7%)	23 (82.1%)	0.012 <sup>1-2</sup>
	Abnormal gain (>2)	1 (3.2%)	12 (34.3%)	6 (19.3%)	5 (17.9%)	
PPT TE (Z-score)		-0.04 (-0.64, 0.86)	0.32 (-0.71, 1.29)	0.49 (-0.81, 0.85)	-0.39 (-1.44, 0.50)	0.31
PPT TE	Normal	29 (93.5%)	31 (88.6%)	29 (93.5%)	22 (78.6%)	0.40
	Abnormal (gain: >2)	2 (6.5%)	3 (8.6%)	2 (6.5%)	3 (10.7%)	
	Abnormal loss (<-2)	0 (0%)	1 (2.9%)	0 (0%)	3 (10.7%)	
PPT UT (Z-score)		0.17 (-0.75, 0.58)	-0.00 (-0.77, 1.22)	-0.32 (-0.69, 0.21)	-0.73 (-1.41, 0.10)	0.003 <sup>1-4,2-3,2-4</sup>
PPT UT	Normal	29 (93.6%)	30 (85.7%)	31 (100%)	25 (89.3%)	
	Abnormal (gain: >2)	1 (3.2%)	5 (14.3%)	0 (0%)	0 (0%)	0.0055 <sup>2-4</sup>
	Abnormal (loss: <-2)	1 (3.2%)	0 (0%)	0 (0%)	3 (10.7%)	
VDT MCP III (Z-score)		0.18 (0.18, 0.18)	0.18 (0.18, 0.18)	0.18 (-9.82, 0.18)	0.18 (-9.82, 0.18)	< 0.001 <sup>1-3,1-4,2-3,2-4</sup>
VDT MCP III	Normal	31 (100%)	30 (85.7%)	18 (58.1%)	25 (53.6%)	< 0.001 <sup>1-3,1-4,2-3,2-4</sup>
	Abnormal (loss: <-2)	0 (0%)	5 (14.3%)	13 (41.9%)	13 (46.4%)	
VDT US (Z-score)		0.16 (0.16, 0.16)	0.16 (0.16, 0.16)	0.16 (-9.08, 0.16)	0.16 (0.16, 0.16)	0.012 <sup>1-3,2-3</sup>
VDT US	Normal	30 (96.8%)	27 (77.1%)	19 (61.3%)	22 (78.6%)	0.0095 <sup>1-3</sup>
	Abnormal (loss: <-2)	1 (3.2%)	8 (22.9%)	12 (38.7%)	6 (21.4%)	
DMA	Normal (absent)	31 (100%)	33 (94.3%)	26 (83.9%) <sup>b</sup>	26 (92.9%)	0.061

<b>Test location: Hand</b>		<b>Healthy participants</b>	<b>Diabetes without DSPN</b>	<b>DSPN FEET ONLY</b>	<b>DSPN HANDS &amp; FEET</b>	<b>p value</b>
PHS	Abnormal (present)	0 (0%)	2 (5.7%)	5 (16.1%)	2 (7.1%)	0.093
	Normal (absent)	31 (100%)	33 (91.4%)	26 (80.6%)	26 (77.4%)	0.059
	Abnormal (at least one abnormality)	0 (0%)	2 (8.6%)	5 (19.4%)	2 (22.6%)	<b>0.018<sup>1-4</sup></b>
QST summary*	Normal (no abnormalities)	23 (74.2%)	8 (22.9%)	3 (9.7%)	1 (3.6%)	<b>&lt;0.001<sup>1-2,1-3,1-4</sup></b>
	Abnormal (at least one abnormality)	8 (25.8%)	27 (77.1%)	28 (90.3%)	27 (96.4%)	

Continuous parameters are summarised as median (5<sup>th</sup>-95<sup>th</sup> percentile range). Categorical parameters are expressed as absolute and relative frequencies. P-values represent the comparison between the groups (for continuous variables: one-way ANOVA and post-hoc LSD tests; for categorical variables: Fisher's exact test with pairwise tests of independence). 1: healthy controls; 2: people with diabetes without DSPN; 3: people with DSPN in feet; 4: people with DSPN in hands and feet. \*Hypoesthesia to thermal or mechanical stimuli (i.e., loss of detection in CDT, WDT, TSL, MDT and VDT) and/or hyperalgesia or hypoalgesia to thermal or mechanical stimuli (i.e., both gain or loss of function in HPT, CPT, MPT, MPS, DMA or PPT) and/or gain in PHS was taken into account in the definition of abnormality. DSPN: distal symmetrical polyneuropathy; QST: quantitative sensory testing; CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; PPT: pressure pain threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; MDT: mechanical detection threshold; VDT: vibration detection threshold; US: ulnar styloid; DMA: dynamic mechanical allodynia; PHS: paradoxical heat sensation; TE: thenar eminence; UT: upper trapezius muscle; MCP III: third metacarpophalangeal joint.

**Supplementary Table 4.** Raw quantitative sensory testing values using the AAN/AAEM (Toronto) criteria to classify participants.

Parameters in hand		Healthy participants N = 31	Diabetes without DSPN N = 35	DSPN FEET ONLY N = 30	DSPN HANDS & FEET N = 26	p value
CDT (Z-score)		0.047 (- 0.66,0.60)	-0.017 (- 1.3,0.56)	-0.68 (- 1.6,0.38)	-1.8 (-2.9,-0.35) 4,3-4	<0.001 <sup>1-3,1-4,2-</sup>
CDT	Normal	30 (96.8%)	32 (91.4%)	24 (80 %)	15 (58 %)	<0.001 <sup>4,1-3,1-</sup>
	Abnormal (loss: <-2)	1 (3.2%)	3 (8.6%)	6 (20 %)	11 (42 %)	4,2-4
WDT (Z-score)		0.056 (- 0.57,0.81)	-0.013 (- 0.90,0.44)	-1.5 (-1.9,-0.74)	-1.4 (-2.4,-0.45) 3,2-4	<0.001 <sup>1-3,1-4,2-</sup>
WDT	Normal	30 (96.8%)	31(88.6%)	24 (80 %)	16 (62 %)	0.0041 <sup>1-4,2-4</sup>
	Abnormal (loss: <-2)	1 (3.2%)	4 (11.4%)	6 (20 %)	10 (38 %)	
TSL (Z-score)		-0.080 (- 0.60,0.88)	-0.17 (- 1.1,0.36)	-1.6 (-2.1,-0.49)	-2.1 (-2.7,-0.90) 3,2-4	<0.001 <sup>1-3,1-4,2-</sup>
TSL	Normal	31(100%)	31(88.6%)	20 (67 %)	12 (46 %)	<0.001 <sup>1-2,1-3,1-</sup>
	Abnormal (loss: <-2)	0(0%)	0(0%)	10 (33 %)	14 (54 %)	4,2-3,2-4,3-4
CPT (Z-score)		0.27 (- 0.83,0.88)	0.48 (-0.38,1.0)	0.30 (-0.97,1.2)	-0.40 (- 0.94,0.63)	0.28
CPT	Normal	31 (100 %)	35 (100 %)	30 (100 %)	26 (100 %)	0.99
HPT (Z-score)		0.11 (- 0.85,0.95)	0.18 (-0.25,1.1)	-0.72 (- 1.3,0.048)	-1.1 (-1.6,0.33) 3,2-4	0.0011 <sup>1-3,1-4,2-</sup>
HPT	Normal	31 (100 %)	33 (94 %)	30 (100 %)	26 (100 %)	0.25
	Abnormal gain (>2)	0 (0 %)	2 (6 %)	0 (0 %)	0 (0 %)	
MDT (Z-score)		0.18 (- 0.71,0.72)	-1.2 (-2.2,0.47)	-2.2 (-2.4,-1.3)	-2.2 (-2.4,-1.9) 4,2-3,2-4	<0.001 <sup>1-2,1-3,1-</sup>
MDT	Normal	29 (94 %)	24 (69 %)	11 (37 %)	7 (27 %)	<0.001 <sup>1-2,1-3,1-</sup> 4,2-3,2-4,3-4
	Abnormal loss (<-2)	2 (6 %)	11 (31 %)	19 (63 %)	19 (73 %)	
MPT (Z-score)		-0.067 (- 0.52,0.29)	0.011 (- 0.35,0.51)	-0.33 (- 0.78,0.23)	-0.33 (- 1.0,0.71)	0.4
MPT	Normal	31 (100 %)	35 (100 %)	29 (97 %)	25 (96 %)	0.35
	Abnormal loss (<-2)	0 (0 %)	0 (0 %)	1 (3 %)	1 (4 %)	
MPS (Z-score)		-0.084 (- 0.81,0.44)	0.91 (-0.67,2.3)	0.036 (- 0.64,0.84)	-0.0030 (- 0.72,1.3)	0.040 <sup>1-2</sup>
MPS	Normal	30 (97 %)	23 (66 %)	24 (80 %)	21 (81 %)	0.012 <sup>1-2</sup>
	Abnormal gain (>2)	1 (3 %)	12 (34 %)	6 (20 %)	5 (19 %)	
PPT TE (Z-score)		-0.043 (- 0.64,0.86)	0.32 (-0.71,1.3)	0.25 (- 0.83,0.77)	-0.39 (- 1.4,0.46)	0.49
PPT TE	Normal	29 (94 %)	31 (89 %)	28 (93 %)	20 (77 %)	0.34
	Abnormal (gain: >2)	2 (6 %)	3 (9 %)	2 (7 %)	3 (12 %)	
	Abnormal loss (<-2)	0 (0 %)	1 (3 %)	0 (0 %)	3 (12 %)	
PPT UT (Z-score)		0.17 (- 0.75,0.58)	-0.0043 (- 0.77,1.2)	-0.33 (- 0.70,0.30)	-0.73 (-1.6,- 0.15)	0.0065 <sup>1-4,2-3,2-4</sup>
PPT UT	Normal	29 (94 %)	30 (86 %)	30 (100 %)	23 (88 %)	
	Abnormal (gain: >2)	1 (3 %)	5 (14 %)	0 (0 %)	0 (0 %)	0.0061 <sup>2-4</sup>
	Abnormal (loss: <-2)	1 (3 %)	0 (0 %)	0 (0 %)	3 (12 %)	
VDT III-MCP (Z-score)		0.18 (0.18,0.18)	0.18 (0.18,0.18)	0.18 (-9.8,0.18)	0.18 (-9.8,0.18)	<0.001 <sup>1-3,1-4,2-</sup> 3,2-4
VDT III-MCP	Normal	31 (100 %)	30 (86 %)	17 (57 %)	15 (58 %)	<0.001 <sup>1-2,1-3,1-</sup>
	Abnormal (loss: <-2)	0 (0 %)	5 (14 %)	13 (43 %)	11 (42 %)	4,2-3,2-4,3-4
VDT US (Z-score)		0.16 (0.16,0.16)	0.16 (0.16,0.16)	0.16 (-9.1,0.16)	0.16 (0.16,0.16)	<0.001 <sup>1-3,2-3,3-4</sup>
VDT US	Normal	1 (3 %)	8 (23 %)	12 (40 %)	4 (15 %)	0.0031 <sup>1-2,1-3</sup>
	Abnormal (loss: <-2)	30 (97 %)	27 (77 %)	18 (60 %)	22 (85 %)	
DMA	Normal (absent)	31 (100 %)	33 (94 %)	25 (83 %)	24 (92 %)	0.079
	Abnormal (present)	0 (0 %)	2 (6 %)	5 (17 %)	2 (8 %)	
PHS	Normal (absent)	31 (100 %)	32 (91 %)	24 (80 %)	19 (73 %)	0.059
	Abnormal (at least one abnormality)	0 (0 %)	3 (9 %)	6 (20 %)	7 (27 %)	0.0089 <sup>1-3,1-4</sup>

Parameters in hand		Healthy participants	Diabetes without DSPN	DSPN FEET ONLY	DSPN HANDS & FEET	p value
QST summary*	Normal (no abnormalities)	23(74.2%)	8(22.9%)	3(10%)	1(3.8%)	<0.001 <sup>1-2,1-3,1-4,2-3,2-4,3-4</sup>
	Abnormal (at least one abnormality)	8(25.8%)	27(77.1%)	27(90%)	25(96.2%)	

Continuous parameters are summarised as median (5<sup>th</sup>-95<sup>th</sup> percentile range). Categorical parameters are expressed as absolute and relative frequencies. P-values represent the comparison between the groups (for continuous variables: one-way ANOVA and post-hoc LSD tests; for categorical variables: Fisher's exact test with pairwise tests of independence). 1: healthy controls; 2: people with diabetes without DSPN; 3: people with DSPN in feet; 4: people with DSPN in hands and feet. \*Hypoesthesia to thermal or mechanical stimuli (i.e., loss of detection in CDT, WDT, TSL, MDT and VDT) and/or hyperalgesia or hypoalgesia to thermal or mechanical stimuli (i.e., both gain or loss of function in HPT, CPT, MPT, MPS, DMA or PPT) and/or gain in PHS was taken into account in the definition of abnormality. DSPN: distal symmetrical polyneuropathy; QST: quantitative sensory testing; CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; PPT: pressure pain threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; MDT: mechanical detection threshold; VDT: vibration detection threshold; US: ulnar styloid; DMA: dynamic mechanical allodynia; PHS: paradoxical heat sensation; TE: thenar eminence; UT: upper trapezius muscle; MCP III: third metacarpophalangeal joint.

Note: one participant from DSPN in feet and two participants from DSPN in feet and hands were excluded using the Toronto criteria for not presenting abnormalities in any of the sural nerve attributes.

**Supplementary Table 5.** Raw quantitative sensory testing values in sensitivity analysis excluding participants with potential presence of carpal tunnel syndrome.

Parameters in hand		Healthy participants (N=31)	Diabetes without DSPN (N=35)	DSPN FEET ONLY (N=31)	DSPN HANDS & FEET (N=24)	p value
CDT (Z-score)		0.047 (- 0.66,0.60)	-0.017 (- 1.3,0.56)	-0.66 (- 1.5,0.44)	-1.9 (-3.0,- 0.63)	< 0.001 <sup>1-4,2-4,3- 4</sup>
CDT	Normal	30 (96.8%)	32 (91.4%)	25 (81 %)	14 (58 %)	< 0.001 <sup>1-4,2-4</sup>
	Abnormal (loss: <-2)	1 (3.2%)	3 (8.6%)	6 (19 %)	10 (42 %)	
WDT (Z-score)		0.056 (- 0.57,0.81)	-0.013 (- 0.90,0.44)	-1.4 (-1.8,- 0.62)	-1.4 (-2.2,- 0.40)	< 0.001 <sup>1-3,1-4,2- 3,2-4</sup>
WDT	Normal	30 (96.8%)	31(88.6%)	25 (81 %)	16 (77 %)	0.018 <sup>1-4</sup>
	Abnormal (loss: <-2)	1 (3.2%)	4 (11.4%)	6 (19 %)	8 (33 %)	
TSL (Z-score)		-0.080 (- 0.60,0.88)	-0.17 (- 1.1,0.36)	-1.5 (-2.1,- 0.43)	-1.8 (-2.6,- 0.79)	< 0.001 <sup>1-3,1-4,2- 3,2-4</sup>
TSL	Normal	31(100%)	31(88.6%)	21 (65 %)	11 (46 %)	< 0.001 <sup>1-2,1-3,1- 4,2-3,2-4,3-4</sup>
	Abnormal gain (>2)	0(0%)	0(0%)	0(0%)	1 (4%)	
	Abnormal (loss: <-2)	0(0%)	0(0%)	10 (32 %)	12 (50 %)	
CPT (Z-score)		0.27 (- 0.83,0.88)	0.48 (- 0.38,1.0)	0.085 (- 0.95,1.2)	-0.52 (- 1.4,0.26)	0.063
CPT	Normal	31 (100 %)	35 (100 %)	31 (100 %)	24 (100 %)	0.99
HPT (Z-score)		0.11 (- 0.85,0.95)	0.18 (- 0.25,1.1)	-0.86 (- 1.3,0.044)	-1.2 (- 1.6,0.45)	0.0018 <sup>1-3,1-4,2- 3,2-4</sup>
HPT	Normal	31 (100 %)	33 (94 %)	31 (100 %)	26 (100 %)	0.25
	Abnormal gain (>2)	0 (0 %)	2 (6 %)	0 (0 %)	0 (0 %)	
MDT (Z-score)		0.18 (- 0.71,0.72)	-1.2 (- 2.2,0.47)	-2.2 (-2.4,- 1.3)	-2.2 (-2.6,- 1.9)	< 0.001 <sup>1-2,1-3,1- 4,2-3,2-4</sup>
MDT	Normal	29 (94 %)	24 (69 %)	12 (39 %)	6 (25 %)	< 0.001 <sup>1-2,1-3,1- 4,2-3,2-4,3-4</sup>
	Abnormal loss (<-2)	2 (6 %)	11 (31 %)	19 (61 %)	18 (75 %)	
MPT (Z-score)		-0.067 (- 0.52,0.29)	0.011 (- 0.35,0.51)	-0.33 (- 0.84,0.19)	-0.33 (- 1.2,0.27)	0.25
MPT	Normal	31 (100 %)	35 (100 %)	30 (97 %)	23 (96 %)	0.45
	Abnormal loss (<-2)	0 (0 %)	0 (0 %)	1 (3 %)	1 (4 %)	
MPS (Z-score)		-0.084 (- 0.81,0.44)	0.91 (- 0.67,2.3)	0.021 (- 0.69,0.84)	0.30 (- 0.67,1.5)	0.036 <sup>1-2</sup>
MPS	Normal	30 (97 %)	23 (66 %)	25 (81 %)	19 (79 %)	0.013 <sup>1-2</sup>
	Abnormal gain (>2)	1 (3 %)	12 (34 %)	6 (19 %)	5 (21 %)	
PPT TE (Z-score)		-0.043 (- 0.64,0.86)	0.32 (- 0.71,1.3)	0.49 (- 0.81,0.85)	-0.16 (- 1.5,0.64)	0.61
PPT TE	Normal	29 (94 %)	31 (89 %)	29 (93 %)	18 (74 %)	0.25
	Abnormal (gain: >2)	2 (6 %)	3 (9 %)	2 (7 %)	3 (13 %)	
	Abnormal loss (<-2)	0 (0 %)	1 (3 %)	0 (0 %)	3 (13 %)	
PPT UT (Z-score)		0.17 (- 0.75,0.58)	-0.0043 (- 0.77,1.2)	-0.32 (- 0.69,0.21)	-0.54 (- 1.4,0.019)	0.0065 <sup>1-4,2-3,2-4</sup>
PPT UT	Normal	29 (94 %)	30 (86 %)	31 (100 %)	21 (87 %)	
	Abnormal (gain: >2)	1 (3 %)	5 (14 %)	0 (0 %)	0 (0 %)	0.0046 <sup>2-4</sup>
	Abnormal (loss: <-2)	1 (3 %)	0 (0 %)	0 (0 %)	3 (13 %)	
VDT III-MCP (Z-score)		0.18 (0.18,0.18)	0.18 (0.18,0.18)	0.18 (- 9.8,0.18)	0.18 (- 9.8,0.18)	< 0.001 <sup>1-3,1-4,2- 3,2-4</sup>
VDT III-MCP	Normal	31 (100 %)	30 (86 %)	18 (58 %)	14 (58 %)	< 0.001 <sup>1-3,1-4,2- 3,2-4</sup>
	Abnormal (loss: <-2)	0 (0 %)	5 (14 %)	13 (42 %)	10 (42 %)	
VDT US (Z-score)		0.16 (0.16,0.16)	0.16 (0.16,0.16)	0.16 (- 9.1,0.16)	0.16 (0.16,0.16)	0.020 <sup>1-3,2-3</sup>
VDT US	Normal	30 (97 %)	27 (77 %)	19 (61 %)	20 (83 %)	0.0043 <sup>1-3</sup>
	Abnormal (loss: <-2)	1 (3 %)	8 (23 %)	12 (39 %)	4 (17%)	
DMA	Normal (absent)	31 (100 %)	33 (94 %)	26 (84 %)	22 (92 %)	0.093
	Abnormal (present)	0 (0 %)	2 (6 %)	5 (16 %)	2 (8 %)	
PHS	Normal (absent)	31 (100 %)	32 (91 %)	26 (81 %)	18 (75%)	0.058
	Abnormal (at least one abnormality)	0 (0 %)	3 (9 %)	5 (19 %)	6 (25%)	0.010 <sup>1-4</sup>

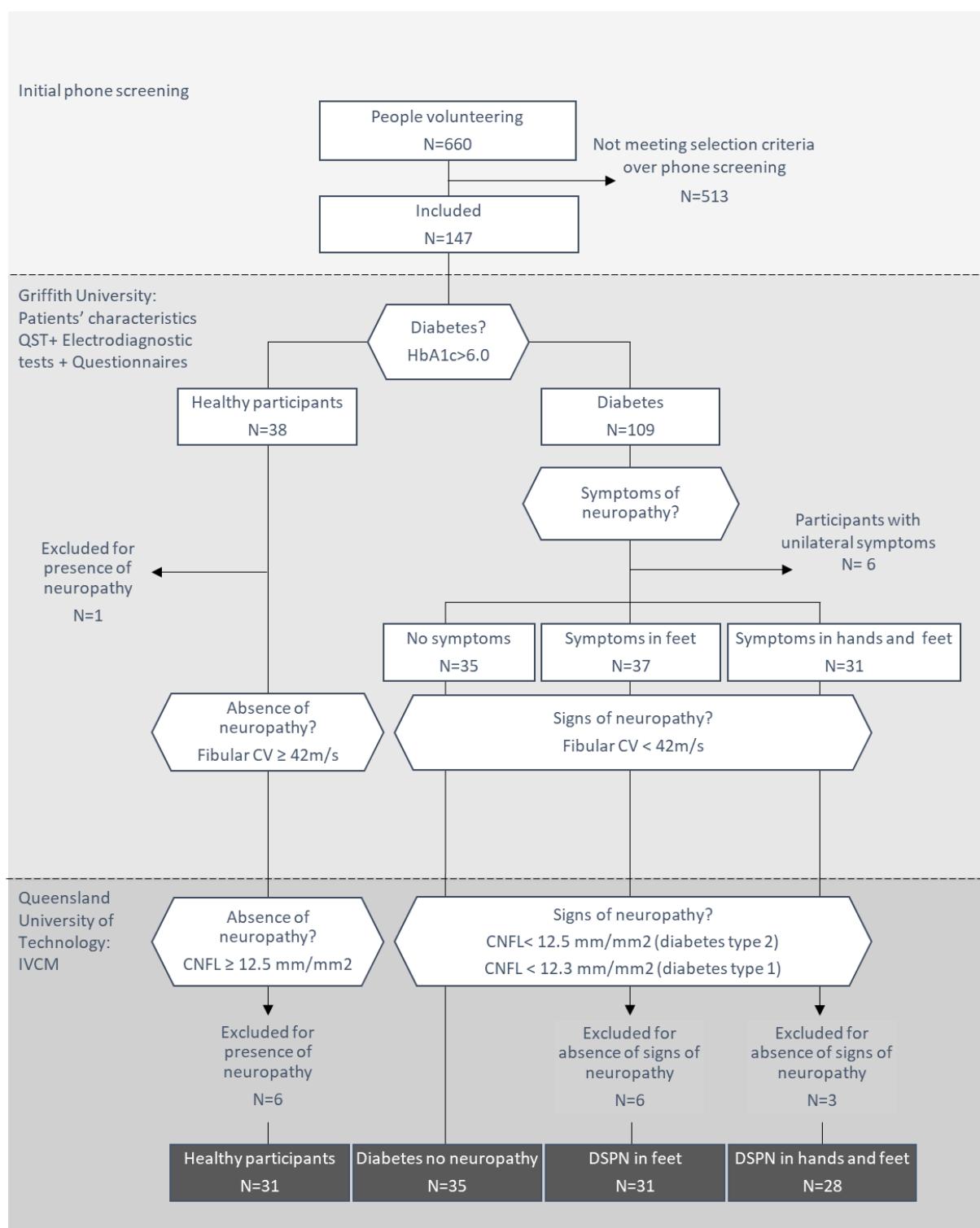
QST summary*	Normal (no abnormities)	23(74.2%)	8(22.9%)	3(10%)	0 (0%)	$< 0.001^{1-2,1-3,1-}$ $_{4,2-3,2-4,3-4}$
	Abnormal (at least one abnormality)	8(25.8%)	27(77.1%)	28 (90%)	24 (100%)	

Continuous parameters are summarised as median (5th–95th percentile range). Categorical parameters are expressed as absolute and relative frequencies. P-values represent the comparison between the groups (for continuous variables: one-way ANOVA and post-hoc LSD tests; for categorical variables: Fisher's exact test with pairwise tests of independence). 1: healthy controls; 2: people with diabetes without DSPN; 3: people with DSPN in feet; 4: people with DSPN in hands and feet.

\*Hypoesthesia to thermal or mechanical stimuli (i.e., loss of detection in CDT, WDT, TSL, MDT and VDT) and/or hyperalgesia or hypoalgesia to thermal or mechanical stimuli (i.e., both gain or loss of function in HPT, CPT, MPT, MPS, DMA or PPT) and/or gain in PHS was taken into account in the definition of abnormality. DSPN: distal symmetrical polyneuropathy; QST: quantitative sensory testing; CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; PPT: pressure pain threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; MDT: mechanical detection threshold; VDT: vibration detection threshold; US: ulnar styloid; DMA: dynamic mechanical allodynia; PHS: paradoxical heat sensation; TE: thenar eminence; UT: upper trapezius muscle; MCP III: third metacarpophalangeal joint.

## SUPPLEMENTARY FIGURES

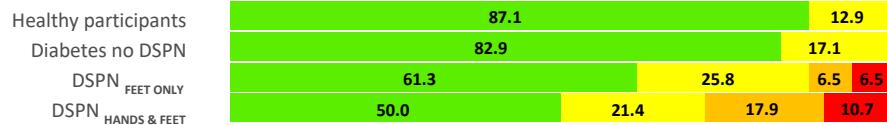
**Supplementary Figure 1.** Flow chart of participants.



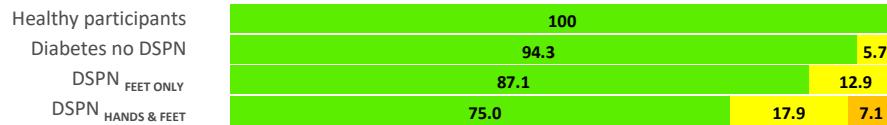
CV: conduction velocity; CNFL: corneal nerve fibre length; DSPN: distal symmetrical polyneuropathy; QST: quantitative sensory testing; IVCM: corneal confocal microscopy

**Supplementary Figure 2.** Comparison of the quality of life domains in EQ-5D-5L in healthy participants, people with diabetes without DSPN, people with DSPN in feet only, and people with DSPN in hands and feet.

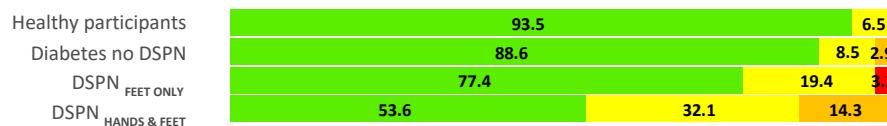
### A. Mobility



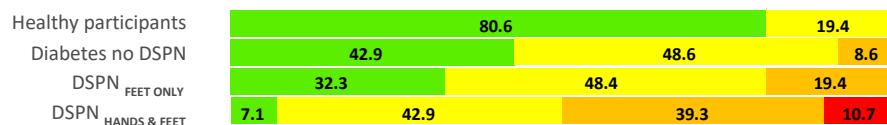
### B. Self-care



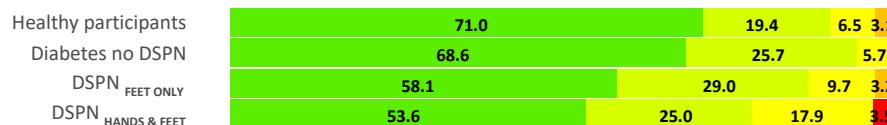
### C. Usual activities



### D. Pain/discomfort



### E. Anxiety/depression



No problem    Slight problem    Moderate problem    Severe problem    Unable  
 No pain    Slight pain    Moderate pain    Severe pain    Extreme pain  
 No anxiety    Slight anxiety    Moderate anxiety    Severe anxiety    Extremely anxious

DSPN: distal symmetrical polyneuropathy

Domain	Response category	Healthy participants (n=31)	Diabetes without DSPN (n=35)	DSPN FEET ONLY (n=31)	DSPN HANDS & FEET (n=28)	p value
Mobility	No problem	27 (87.1%)	29 (82.9%)	19 (61.3%)	14 (50.0%)	0.006
	Slight problem	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Moderate problem	4 (12.9%)	6 (17.1%)	8 (25.8%)	6 (21.4%)	
	Severe problem	0 (0.0%)	0 (0.0%)	2 (6.5%)	5 (17.9%)	
	Unable	0 (0.0%)	0 (0.0%)	2 (6.5%)	3 (10.7%)	
Self-care	No problem	31 (100.0%)	33 (94.3%)	27 (87.1%)	21 (75.0%)	0.016
	Slight problem	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Moderate problem	0 (0.0%)	2 (5.7%)	4 (12.9%)	5 (17.9%)	
	Severe problem	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (7.1%)	
	Unable	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Usual activities	No problem	29 (93.5%)	31 (88.6%)	24 (77.4%)	15 (53.6%)	0.002
	Slight problem	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Moderate problem	2 (6.5%)	3 (8.6%)	6 (19.4%)	9 (32.1%)	
	Severe problem	0 (0.0%)	1 (2.9%)	0 (0.0%)	4 (14.3%)	
	Unable	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	
Pain/discomfort	No pain/discomfort	25 (80.6%)	15 (42.9%)	10 (32.3%)	2 (7.1%)	<0.001
	Slight pain/discomfort	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Moderate pain/discomfort	6 (19.4%)	17 (48.6%)	15 (48.4%)	12 (42.9%)	
	Severe pain/discomfort	0 (0.0%)	3 (8.6%)	6 (19.4%)	11 (39.3%)	
	Extreme pain/discomfort	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (10.7%)	
Anxiety/depression	Not anxious/depressed	22 (71.0%)	24 (68.6%)	18 (58.1%)	15 (53.6%)	0.68
	Slightly anxious/depressed	6 (19.4%)	9 (25.7%)	9 (29.0%)	7 (25.0%)	
	Moderately anxious/depressed	2 (6.5%)	2 (5.7%)	3 (9.7%)	5 (17.9%)	
	Severely anxious/depressed	1 (3.2%)	0 (0%)	1 (3.2%)	0 (0%)	
	Extremely anxious/depressed	0 (0%)	0 (0%)	0 (0%)	1 (3.6%)	

