

Supplementary Table 1. Summary of included studies.

| Painful DSPN vs DSPN | | | | | | |
|---------------------------------|--------------|---------------|--|--|--|---------------------|
| Author | Study design | Pain modality | Painful DSPN | Diagnose of neuropathy | DSPN | Downs & Black score |
| Krämer 2004 | Case-control | HPT | n = 15, age: 51.8 (3.3), M/F: 26/7, BMI: NR, HRQoL: NR. Diabetes type I/II: 7/8, years with diabetes: NR | Electrophysiological studies and clinical results (VAS diary and neurological examination). | n = 15, age: 57.5 (10.8), M/F: 11/4, BMI: NR. HRQoL: NR. Diabetes type I/II: 5/10, years with diabetes: 25.5 (12.7) | 7 |
| Raputova 2017* | Cohort | CPT, HPT, PPT | n = 158, age: 61.1(12.1), M/F: 87/71, BMI: 29.9(5.6), HRQoL: NR. Diabetes type I/II: 35/123, years with diabetes: 15.2(10.0) | Nerve conduction studies or intra-epidermal nerve fibre density + combination of symptoms and signs. | n = 74, age: 58.5 (15.7), M/F: 53/21, BMI: 29.0(4.7), HRQoL: NR. Diabetes type I/II: 25/49 Years with diabetes: 14.4(10.7) | 11 |
| Themistocleus 2106 [†] | Cohort | CPT, HPT, PPT | n = 111, age: 68.8 (10.9), M/F: 60/35, BMI: 31.5(7.4) Diabetes type I/II: 12/99, years with diabetes: 14.7(10.9) | Nerve conduction studies or intra-epidermal nerve fibre density + combination of symptoms and signs. | n = 80, age: 67.6 (9.3), M/F: 53/27, BMI: 30.5(6.6), HRQoL: NR. Diabetes type I/II: 5/75 Years with diabetes: 15.3(9.1) | 9 |
| DSPN vs diabetes | | | DSPN | Diagnose of neuropathy | DSPN | |
| Guo 2013* | Cohort | CPT, HPT | n = 124, age: NR, M/F: NR, BMI: NR, HRQoL: NR. Diabetes type I/II: 0/124, years with diabetes: NR | American Diabetes Association criteria (2009). | n = 184, age: NR, M/F: NR, BMI: NR, HRQoL: NR. Diabetes type I/II: 0/124, years with diabetes: NR | 8 |
| Levy 1989* | Case-control | HPT | n = 128, age: 52.1 (10.6), M/F: NR, BMI: NR, HRQoL: NR. | Presence of one or more of the following: symmetrical lower | n= 182, age: 50.2(11.4), M/F: NR, BMI: NR, HRQoL: NR. | 8 |

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| | | | Diabetes type I/II: NR, years with diabetes: NR | limb numbness, paraesthesia, contact sensitivity, spontaneous pain or burning. | Diabetes type I/II: NR | |
| Petropoulos 2015 | Case-control | CPT, HPT | n = 25, age: 60.1 (10.2), M/F: 14/11, BMI: 28.6(6), HRQoL: Neuropathic disability score: 3.9(2.5). Diabetes type I/II: 14/11, years with diabetes: 42.7(17.2) | Toronto criteria for confirmed DSPN | n = 28, age: 42.4 (14.7), M/F: 19/9, BMI: 28.6(6), HRQoL: Neuropathic disability score: 1.7(1.5). Diabetes type I/II: 20/8, years with diabetes: 16.2 (9.3) | 8 |
| Quattrini 2007 [‡] | Cohort | HPT | n = 44, age: 59.3(10.0), M/F: 36/8, BMI: NR, HRQoL: NR. Diabetes type I/II: 13/31, years with diabetes: 20.4(3.1) | Neuropathic Disability Score, Cold Detection Threshold and heat-as-pain visual analogue scale, autonomic function and electrodiagnostic studies. | n= 10, age: 53.5(10.2), M/F: 6/4, BMI:NR, HRQoL: NR. Diabetes type I/II: 3/7, years with diabetes: 16.7(14.0) | 10 |
| Rage 2011 | Case-control | HPT | n= 5, age: 55.4(3.3), M/F: 5/0, BMI: 28.2(2.6), HRQoL: NR. Diabetes type I/II: NR | Toronto Clinical Scoring System (symptom scores, reflex scores, sensory test scores) ⁷⁹ | n = 23, age: 44.4 (3.2), M/F: 15/8 BMI: 27.5(3.7), HRQoL: NR. Diabetes type I/II: 10/13, years with diabetes: 14.8(4) | 9 |
| Redmond 1992 | Case-control | CPT, HPT | n= 27, age: NR, M/F: NR, BMI:NR, HRQoL: NR. Diabetes type I/II: NR | Sensory symptoms | n= 9, age: NR, M/F: NR, BMI:NR, HRQoL: NR. Diabetes type I/II: NR | 8 |
| Suzuki 2016 | Case-control | EST | n = 7, age: 56.2 (14.6), M/F: NR BMI: NR, HRQoL: NR. Diabetes type I/II: NR, years with diabetes: NR | Loss of ankle reflexes and/or reduced vibrationdetection sense at the ankles | n= 13, age:56.5(9.8), M/F: NR, BMI: NR, HRQoL: NR. Diabetes type I/II: NR, years with diabetes: NR | 9 |

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| Telli 2006 | Case-control | EST | n= 57, age: 48.3(10), M/F: 21/36, BMI: 26.4(3.0), HRQoL: NR. Diabetes type I/II: 0/57, years with diabetes: 19.2(4.9) | Michigan Neuropathy Screening Index | n = 22, age: 49.8 (5.5), M/F: 12/11, BMI: 28.8(2.6), HRQoL: NR. Diabetes type I/II: 0/22, years with diabetes: 8.5(3.5) | 10 |
| Wong 2011 | Case-control | CHEPs | n = 10, age: 55.1 (4.6), M/F: 13/17, BMI: 24.0(4.3), HRQoL: NR. Diabetes type I/II: NR, years with diabetes: 6.6(7.7) | Presence of lower limb symptoms | n= 19, age: 52.2(5.3), M/F: 5/14, BMI: 23.9(3.6), HRQoL: NR. Diabetes type I/II: 0/57, years with diabetes: 6.7(5.9) | 9 |
| Yildiz 2010 | Case-control | CPT, HPT | n = 10, age: 55.1 (8.5), M/F: 2/8 BMI: NR, HRQoL: NR. Diabetes type I/II: 0/10, years with diabetes: 6.3 (0.6) | LANSS | n= 40, age: 55.5(8.4), M/F: 17/23, BMI: NR, HRQoL: NR. Diabetes type I/II: 0/40, years with diabetes: 6.3(0.6) | 8 |
| Diabetes vs healthy | | | Diabetes | Diagnose of diabetes | Healthy | |
| Krishnan 2004 | Case-control | HPT | n = 18, age: 67 (9.4), M/F: NR BMI: NR, HRQoL: NR. Diabetes type I/II: 0/18, years with diabetes: 8.2 (10) | No diagnosis criteria specified. | n= 20, age: 52.2(11.5), M/F: NR, BMI: NR, HRQoL: NR. | 11 |
| Petropoulos 2015 | Case-control | CPT, HPT | n = 28, age: 42.4 (14.7), M/F: 19/9, BMI: 28.6(6), HRQoL: Neuropathic disability score: 1.7(1.5). Diabetes type I/II: 20/8, years with diabetes: 16.2 (9.3) | No diagnosis criteria specified. | n= 15, age: 41.9 (14.6), M/F: NR, BMI: NR, HRQoL: NR. | 8 |
| Quattrini 2007 | Cohort | HPT | n= 10, age: 53.5(10.2), M/F: 6/4, BMI:NR, HRQoL: NR. | No diagnosis criteria specified. | n= 15, age: 55.0 (18.5), M/F: 6/9, BMI: NR, HRQoL: NR. | 10 |

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| | | | Diabetes type I/II: 3/7, years with diabetes: 16.7(14.0) | | | |
| Rage 2011 ¹ | Case-control | HPT | n = 23, age: 44.4 (3.2), M/F: 15/8 BMI: 27.5(3.7), HRQoL: NR. Diabetes type I/II: 10/13, years with diabetes: 14.8(4) | No diagnosis criteria specified. | n= 18 [§] , age: 42.5 (9.1), M/F: 12/6, BMI: 25.3(4.0), HRQoL: NR. | 9 |
| Redmond 1992 | Case-control | CPT, HPT | n= 9, age: NR, M/F: NR, BMI:NR, HRQoL: NR. Diabetes type I/II: NR | No diagnosis criteria specified. | n= 91, age: NR, M/F: NR, BMI:NR, HRQoL: NR. Diabetes type I/II: NR | 8 |
| Suzuki 2016 | Case-control | EST | n = 13, age: 56.5 (9.8), M/F: NR BMI: NR, HRQoL: NR. Diabetes type I/II: NR, years with diabetes: NR | Glycosylated hemoglobin (HbA1c) test. | n= 18, age: 55.2(10.4), M/F: NR, BMI: NR, HRQoL: NR. | 9 |
| Telli 2006 | Case-control | EST | n = 22, age: 49.8 (5.5), M/F: 12/11, BMI: 28.8(2.6), HRQoL: NR. Diabetes type I/II: 0/22, years with diabetes: 8.5(3.5) | No diagnosis criteria specified. | n= 32, age: 46.3(7.1), M/F: 15/17, BMI: 24.9(3.0), HRQoL: NR. | 10 |
| Wong 2011 | Case-control | CHEPs | n= 19, age: 52.2(5.3), M/F: 5/14, BMI: 23.9(3.6), HRQoL: NR. Diabetes type I/II: 0/57, years with diabetes: 6.7(5.9) | Glycosylated hemoglobin (HbA1c) ≤ 7.5% within the previous 3 months. | n= 13, age: 51.4(4.2), M/F: 6/7, BMI: 22.8(4.5), HRQoL: NR. | 9 |
| Yildiz 2010 | Case-control | CPT, HPT | n = 40, age: 55.5 (8.4), M/F: 17/23, BMI: NR, HRQoL: NR. Diabetes type I/II: 0/40, years with diabetes: 6.3 (0.6) | No diagnosis criteria specified. | n= 60, age: 54.7(8.4), M/F: NR, BMI: NR, HRQoL: NR. | 8 |

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| Yin 2015* | Case-control | CPT, HPT | n = 20, age: 55.4(11.4), M/F:NR BMI: NR, HRQoL: NR. Diabetes type I/II: 0/20, years with diabetes: < 1 year | Criteria set by the Diabetes Society of China. | n= 20, age: NR, M/F: NR, BMI: NR, HRQoL: NR. | 7 |
| Ziegler 1988 | Case-control | CPT, HPT | n = 30, age: 37.8 (11), M/F: 16/14, BMI: NR, HRQoL: NR. Diabetes type I/II: 30/0, years with diabetes: 19.2 (4.9) | Glycosylated hemoglobin (HbA1c) | n= 70, age: 35.2(11.7), M/F: NR, BMI: NR, HRQoL: NR. | 11 |
| Other comparisons | | | | | | |
| Painful DSPN vs Healthy | | | Painful DSPN | Diagnose of neuropathy | Healthy | |
| Chao 2010 | Case-control | CHEP | n = 32, age: 51.6 (10.9), M/F: 20/12, BMI: NR, HRQoL: NR. Diabetes type I/II: 0/32, years with diabetes: 8.3(6.6) | Intra-epidermal nerve fibre density | n = 3, age: 47.3 (14.9), M/F: NR, BMI: NR, HRQoL: NR. | 9 |
| Granovsky 2017 | Case-control | CPM, TS | n= 35, age: 37.8(11), M/F: 16/14, BMI: NR, HRQoL: NR. Diabetes type I/II: 30/0, years with diabetes: 19.2(4.9) | Sensory detection thresholds were measured at the dorsum of the foot to assess neuropathy severity | n= 29, age:53.9(6.7), M/F: 12/17, BMI: NR, HRQoL: NR. | 10 |
| Krämer 2004 | Case-control | HPT | n = 15, age: 51.8(3.3), M/F: 26/7, BMI: NR, HRQoL: NR. Diabetes type I/II: 7/8, years with diabetes: NR | Electrophysiological studies and clinical results (VAS diary and neurological examination). | n= 34, age: 50.6(2.2), M/F: 19/15, BMI: NR, HRQoL: NR. | 7 |
| Ziegler 1988 | Case-control | CPT, HPT | n= 30, age: 43.2(12.1), M/F: 13/17, BMI: NR, HRQoL: NR. Diabetes type I/II:NR, years with | Sensory symptoms | n= 70, age: 35.2(11.7), M/F: NR, BMI: NR, HRQoL: NR. | 11 |

| | | | diabetes: 15·1(10·0) | | | |
|-------------------------|--------------|-----|---|---|--|----|
| DSPN vs healthy | | | DSPN | Diagnose of DSPN | Healthy | |
| Chanteleau 2012 | Cohort | PPT | n = 13, age: 69·5(19·2), M/F: 11/2, BMI: 27·6(4·6), HRQoL: NR. Diabetes type I/II:9/4, years with diabetes: 28·5(19·2) | VPT <5/8 at the first metatarsal head, 64 Hz tuning fork | n = 20, age: 52·0(18·1), M/F: 9/11, BMI: 25·9(4·6), HRQoL: NR. | 8 |
| Chanteleau 2016 | Cohort | PPT | n = 11, age: 66·2 (8·2), M/F: 7/4, BMI: 32·9 (11·5), HRQoL: NR. Diabetes type I/II: 8/3, years with diabetes: 32·9 (11·5) | Vibration perception threshold <5/8 at the first metatarsophalangeal joint | n = 10, age: 51·5·0 (8·7), M/F: 5/5, BMI: 24·0 (2·9), HRQoL: NR. | 10 |
| Claus 1987 [§] | Cohort | HPT | n = 11, age: 52·0 (16·2), M/F: NR, BMI: 32·9 (11·5), HRQoL: NR. Diabetes type I/II: 3/8, years with diabetes: NR | Decreased motor and/or sensory nerve conduction in the lower leg or Achilles jerk tendon diminished | n = 77, age: 40·0 (14·7), M/F: NR, BMI: NR, HRQoL: NR. | 6 |
| Diemel 1999 | Case-control | HPT | n = 19, age: 45·5 (15), M/F: 15/4, BMI: NR, HRQoL: NR. Diabetes type I/II: 10/9, years with diabetes: 16·7 (7·9) | Sensory symptoms | n = 24, age: 44·5 (14·2), M/F: NR, BMI: NR, HRQoL: NR. | 8 |
| Krämer 2004 | Case-control | HPT | n = 15, age: 57·5 (10·8), M/F: 11/4, BMI: NR, HRQoL: NR. Diabetes type I/II: 5/10, years with diabetes:25·5 (12·7) | Electrophysiological studies and clinical results (VAS diary and neurological examination). | n = 34, age: 50·6 (2·2), M/F: 19/15, BMI: NR, HRQoL: NR. | 7 |
| Levy 1989* | Case-control | HPT | n = 128, age: 52·1 (10·6), M/F: NR, BMI: NR, HRQoL: NR. | Presence of one or more: symmetrical lower limb | n = 78, age: 56·0 (14·2), M/F: NR, BMI: NR, HRQoL: NR. | 8 |

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|-----------------------------|--------------|----------|---|--|--|----|
| | | | Diabetes type I/II: NR, years with diabetes: NR | numbness, paraesthesia, contact sensitivity, spontaneous pain or burning | | |
| Parson 2103 | Case-control | CHEP | n = 30, age: 62.0 (1.1), M/F: 18/12, BMI: 32.5 (0.7), HRQoL: NR. Diabetes type I/II: 0/30, years with diabetes: 13.4 (1.4) | Toronto criteria for confirmed DSPN ⁴ | n= 31, age: 59.0 (1.3), M/F: 16/15, BMI: 27.1 (0.9), HRQoL: NR. | 9 |
| Petropoulos 2015 | Case-control | CPT, HPT | n = 28, age: 42.4 (14.7), M/F: 19/9, BMI: 28.6(6), HRQoL: Neuropathic disability score: 1.7(1.5). Diabetes type I/II: 20/8, years with diabetes: 16.2 (9.3) | Toronto criteria for confirmed DSPN | n= 15, age: 41.9 (14.6), M/F: NR, BMI: NR, HRQoL: NR. | 8 |
| Quattrini 2007 [‡] | Cohort | HPT | n = 44, age: 59.3(10.0), M/F: 36/8, BMI: NR, HRQoL: NR. Diabetes type I/II: 13/31, years with diabetes: 20.4(3.1) | Neuropathic Disability Score, Cold Detection Threshold and heat-as-pain visual analogue scale, autonomic function and electrodiagnostic studies. | n= 15, age: 55.0 (18.5), M/F: 6/9, BMI: NR, HRQoL: NR. | 10 |
| Rage 2011 | Case-control | HPT | n= 5, age: 55.4(3.3), M/F: 5/0, BMI: 28.2(2.6), HRQoL: NR. Diabetes type I/II: NR | Toronto Clinical Scoring System (symptom scores, reflex scores, sensory test scores) ⁷⁹ | n= 18 [§] , age: 42.5 (9.1), M/F: 12/6, BMI: 25.3(4.0), HRQoL: NR | 9 |
| Redmond 1992 | Case-control | CPT, HPT | n= 27, age: NR, M/F: NR, BMI:NR, HRQoL: NR. Diabetes type I/II: NR | Sensory symptoms | n= 91, age: NR, M/F: NR, BMI:NR, HRQoL: NR. Diabetes type I/II: NR | 8 |
| Suzuki 2016 | Case-control | EST | n = 7, age: 56.2 (14.6), M/F: NR BMI: NR, HRQoL: NR. | Loss of ankle reflexes and/or reduced vibrationdetection sense | n= 18, age: 55.2(10.4), M/F: NR, BMI: NR, HRQoL: NR. | 9 |

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|----------------|--------------|----------|--|--|---|----|
| | | | Diabetes type I/II: NR, years with diabetes: NR | at the ankles | | |
| Telli 2006 | Case-control | EST | n= 57, age: 48.3(10), M/F: 21/36, BMI: 26.4(3.0), HRQoL: NR. Diabetes type I/II: 0/57, years with diabetes: 19.2(4.9) | Michigan Neuropathy Screening Index | n= 32, age: 46.3(7.1), M/F: 15/17, BMI: 24.9(3.0), HRQoL: NR. | 10 |
| Wienemann 2012 | Case-control | PPT | n = 18, age: 60.0 (14.0), M/F: 14/4, BMI: 31.8 (10.5), HRQoL: NR. Diabetes type I/II: 11/7, years with diabetes: 30.5 (10.5) | Vibration perception threshold <5/8 at the first metatarsal head | n= 20, age: 50 (9.9), M/F: 9/11, BMI: 27.2 (6.2), HRQoL: NR. | 9 |
| Wong 2011 | Case-control | CHEPs | n = 10, age: 55.1 (4.6), M/F: 13/17, BMI: 24.0(4.3), HRQoL: NR. Diabetes type I/II: NR, years with diabetes: 6.6(7.7) | Presence of lower limb symptoms | n= 13, age: 51.4(4.2), M/F: 6/7, BMI: 22.8(4.5), HRQoL: NR. | 9 |
| Yildiz 2010 | Case-control | CPT, HPT | n = 10, age: 55.1 (8.5), M/F: 2/8, BMI: NR, HRQoL: NR. Diabetes type I/II: 0/10, years with diabetes: 6.3 (0.6) | LANSS | n= 60, age: 54.7(8.4), M/F: NR, BMI: NR, HRQoL: NR. | 8 |

DSPN: Diabetic Symmetrical Peripheral Neuropathy; NR: Not Reported; M/F: male/female; BMI: Body Mass Index; HRQoL: Health Related Quality of Life.

HPT: Heat Pain Threshold; CPT: Cold Pain Threshold; PPT: Pain Pressure Threshold; EST: Electrical Stimulation Threshold; CHEPs: Contact Heat-Evoked Potentials; CPM: Conditioned Pain Modulation; TS: Temporal Summation, VAS: Visual Analogue Scale, LANSS: Leeds Assessment of Neuropathic Symptoms and Signs.

*Values are reported for all the participants in the study, but not for individual groups.

†Groups with moderate and severe pain were averaged as painful DSPN group for this systematic review.

‡Group of patients with different levels of severity of neuropathy were averaged for this systematic review.

§Only group A was used, group B had patients with no symptoms of neuropathy.

‡Groups with diabetes type I and II combined for this systematic review.

¥Number of participant in this group differs from amount of participants explored for pain thresholds.

