Metabolic factors, lifestyle habits, and possible polyneuropathy in early type 2 diabetes: A nationwide study of 5,249 patients in the Danish DD2 cohort

Authors:
Diana H. Christensen,[1,2] Søren T. Knudsen,[3] Sandra S. Gylfadottir,[2,4,5] Lotte B. Christensen,[1] Jens S. Nielsen,[6] Henning Beck-Nielsen,[6] Henrik T. Sørensen,[1] Henning Andersen,[2,5] Brian C. Callaghan,[2,7] Eva L. Feldman,[2,7] Nanna B. Finnerup,[2,4,5] Troels S. Jensen,[2,4,5] Reimar W. Thomsen,[1]

Author affiliations:
[1]Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark
[2]International Diabetic Neuropathy Consortium, Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark
[3]Steno Diabetes Center Aarhus (SDCA), Aarhus University Hospital, Aarhus, Denmark
[4]Department of Clinical Medicine, Danish Pain Research Center, Aarhus University, Aarhus, Denmark
[5]Department of Neurology, Aarhus University Hospital, Aarhus, Denmark
[6]Danish Center for Strategic Research in Type 2 Diabetes (DD2), Steno Diabetes Center Odense, Odense, Denmark
[7]Department of Neurology, University of Michigan, Ann Arbor, MI, 48109, USA

Corresponding author:
Diana Christensen, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200, Aarhus N, Denmark. Tel: +45 8716 8248. Fax: +45 8716 7215. Email: dhcr@clin.au.dk

Supplemental material

The main focus of this study is the association of metabolic and lifestyle factors measured at baseline around time of type 2 diabetes diagnosis with possible DPN and neuropathic pain at a median of 2.8 years later, as well as the association of changes in some factors from age 20 (BMI) or baseline (smoking and physical activity) to possible DPN/pain assessment median 2.8 years after baseline.

Results for the most important baseline risk factors are presented in the table/figures in the main manuscript.

In this supplementary material, we present results for a few additional baseline risk factors; stratified analyses results; analyses of risk factors measured at the time of questionnaire in 2016; additionally adjusted analyses; and analyses of continuous risk factor data.

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Supplementary Table 1: Definitions and codes used in this study	
Variable	Definition and codes
DDDA/DD2/IDNC variables	
DDDA variables -Blood pressure -Lipids -HbA1c -Smoking baseline -BMI (see anthropometric data)	Categories: Systolic blood pressure: </≥130 Diastolic blood pressure: </≥80 Lipids LDL: <1.8/1.8-2.6, ≥2.6 HDL (male/female): <1.0/1.2, ≥1.0/1.2 Triglycerides: </≥1.7 Total cholesterol: </≥4.3 HbA1c, mmol/mol: < 48, 48-57, 58-67, 68-77, ≥78 HbA1c, %: <6.5, 6.5-7.4, 7.5-8.4, 8.5-9.4, ≥9.5 Smoking: Never, former, current (daily + occasionally) <u>References:</u> https://www.nbv.cardio.dk/dyslipidaemi American Diabetes Association 2003 BMI: see below
DD2 core variables -low-grade inflammation/hsCRP -C-peptide -Physical activity, baseline -Alcohol, baseline -Waist circumference -Waist-hip ratio -Waist-height ratio -BMI age 20 (see anthropometric data)	Low-grade inflammation: excluding measures of hsCRP ≥10mg/L in order to exclude values related to potential ongoing infection. Physical activity: "number of days with minimum 30 minutes of physical activity per week". Categories Low-grade inflammation: <1.0, 1.0-2.9, ≥3.0 mg/L Physical activity: 0, 1-2, ≥3 days/week Alcohol: </≥21/14 units/week for male/female, which was the recommended safe dose in 2010, where the DD2 began enrollment Waist circumference: see below Waist-hip ratio: see below Waist-height ratio: see below
Questionnaire 2016 variables -Smoking -Physical activity -BMI	Physical activity: "number of days with minimum 30 minutes of physical activity per week". Categories: Smoking: Never, former, current (daily + occasionally) Physical activity: 0, 1-2, ≥3 days/week BMI: see below
Anthropometric data	
Height	Data on height is available from 3 different sources: DD2 enrollment (2016 onwards), DDDA data (repeated measures), questionnaire data 2016 (self-reported). Regarding DDDA data: a mean height based on all available DDDA heights where calculated for all patients 18 years or older. Heights below 130 cm and above 220 were considered outliers and not included in any calculations. See variables below for hierarchically order of the height

BMI age 20 years	Weight: Recalled at DD2 enrollment. Weights below 35 and above 300 kg were considered outliers and not included in the BMI calculation. Height: We do not expect height to change over time among these adults. Thus, we used the available heights in a hierarchically order; height from questionnaire survey in 2016, DD2 enrollment, DDDA. That is, if a patient has a height recorded from the questionnaire, we will use that height. If not, we will use the DD2 enrollment height (measured by health personal, but only a few available measures [not part of the DD2 core data initially]) and if no DD2 enrollment height is available, we will use DDDA height. Categories: BMI age 20 years: <25, 25-29, 30-34, ≥35 kg/m^2
BMI baseline	Weight: If weight recorded as part of the DD2 enrollment process is available (few [not part of the DD2 core data initially]), we used that weight measure, otherwise the DDDA weight. Weights below 35 and above 300 kg were considered outliers and not included in the BMI calculation. Height: We do not expect height to change over time among these adults. Thus, we used the available heights in a hierarchically order; height from questionnaire survey in 2016, DD2 enrollment, DDDA. That is, if a patient has a height recorded from the questionnaire, we will use that height. If not, we will use the DD2 enrollment height (measured by health personal, but only a few available measures [not part of the DD2 core data initially]) and if no DD2 enrollment height is available, we will use DDDA height. Categories: BMI at DD2 enrollment: <25, 25-29, 30-34, ≥35 kg/m^2
BMI questionnaire 2016	Will be based solely on the weight and height data from the 2016 questionnaire survey in order to report the exact same number of missing as in other paper based solely on the neuropathy questionnaire data. (That means 90 missing vs. 73 with if we instead had used the height variable that was used in calculation of the other anthropometric variables) Categories: BMI at DD2 enrollment: <25, 25-29, 30-34, ≥35 kg/m^2
Waist circumference	Categories: Male/female: < 94/80 cm, 94-101/80-87 cm, ≥102/88 cm Reference: WHO: World health Organ Tech Rep Ser 2000;894:i-xii, 1-253 IDF: Diabet Med 2006;23:469-480

Waist-hip ratio	Categories: Male/female: < 0.95/0.85 0.95 - 0.99/0.85 - 0.89 1.00 - 1.04/0.90 - 0.94 ≥1.05/0.95 References: We based our categories on often used waist-hip ratio classifications in the scientific literature together with observations of baseline WHR distributions in our cohort.
Waist-height ratio	Categories: <0.5, 0.5-0.6, ≥0.6 Reference: Schneider et al. J Clin Endocrinol Metab 2007;92(2):589-594
Prescription data	For all prescription data the relevant time period is around baseline = DD2 enrollment. Thus, lookback period is 1 year prior to DD2 enrollment date
Lipidlowering drugs	ATC: C10
Antihypertensives	ATC: C02, C03, C07, C08, C09
Glucose-lowering drugs	ATC: A10 Categories: No GLD: no A10 prescription redemption Non-insulin only: ≥1 prescription redemption of A10B and NO prescription redemption of A10A Insulin only: ≥1 prescription redemption of A10A and NO prescription redemption of A10B Non-insulin + insulin: ≥1 prescription redemption of A10B and ≥1 prescription redemption of A10A
Diabetes duration	Determined as the period time following either i) a first-time prescription redemption of a glucose-lowering drug, ii) a hospital record of diabetes, iii) an HbA1c ≥48 mmol/mol (DDDA data), or iv) time of DD2-enrolment.
Metabolic syndrome	Defined using the International Diabetes Federation metabolic syndrome definition: Metabolic syndrome: Central obesity (defined as waist circumference ≥94/80 cm [male/female], i.e. European ethnic specific value)) AND any two of the following: a) Raised triglycerides ≥ 1.7 mmol/L, or treatment for this lipid abnormality. b) Reduced HDL cholesterol < 1.03 mmol/L (males)/1.29 mmol/mol (females), or treatment for this lipid abnormality. c) Raised blood pressure: systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg, or treatment for hypertension. d) Raised fasting plasma glucose ≥ 5.6 mmol/L or diagnosed type 2 diabetes. Reference:

	International Diabetes federation, https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome.html

Supplementary Table 2: Patient characteristics of the total cohort of 5,249 DD2 patients and of the subcohort of 3,623 DD2 patients that could be linked to the DDDA

	All, N = 5,249	MNSIq < 4, N = 4,311	MNSI≥4, N = 938	MNSIq≥4	
				No pain or DN4 <3, N = 552	Pain and DN4 ≥3, N = 386
	Total	No DPN	DPN	Non-painful DPN	Painful DPN
Total cohort, N = 5249					
Total, N	5249	4311 (82.1)	938 (17.9)	552 (10.5)	386 (7.4)
Age, questionnaire 2016, N=5249	65.4 (56.6; 71.5)	65.8 (57.2; 71.7)	63.1 (54.9; 70.3)	62.8 (54.9; 70.0)	64.0 (55.3; 70.8)
Female sex, N=5249	2216 (42.2)	1770 (41.1)	446 (47.5)	258 (46.7)	188 (48.7)
Diabetes duration, questionnaire 2016, years, N=5247	4.6 (3.5; 5.7)	4.5 (3.4; 5.7)	4.8 (3.7; 6.0)	4.7 (3.6; 5.9)	4.9 (3.8; 6.1)
Height, N=5220	173 (166; 180)	173 (166; 179)	172 (165; 180)	172 (165; 180)	173 (166; 180)
BMI, age 20 years, kg/m2, N=4542	23.2 (21.0; 25.5)	23.2 (21.0; 25.5)	23.2 (20.9; 25.7)	23.3 (21.1; 25.8)	23.1 (20.5; 25.2)
BMI, questionnaire 2016, kg/m2, N=5159	29.7 (26.4; 33.6)	29.4 (26.2; 33.1)	31.2 (27.7; 35.7)	31.2 (27.8; 35.5)	31.5 (27.5; 35.7)
Waist circumference, cm, baseline, N=5239	106 (97; 116)	105 (96; 115)	110 (100; 119)	110 (100; 120)	110 (100; 119)
Waist-hip ratio, baseline, N=5237	0.98 (0.92; 10.4)	0.98 (0.92; 1.04)	0.98 (0.92; 1.04)	0.98 (0.92; 1.04)	0.99 (0.93; 1.04)
Waist-height ratio, N=5210	0.61 (0.56; 0.67)	0.61 (0.56; 0.66)	0.63 (0.58; 0.69)	0.63 (0.58; 0.70)	0.64 (0.58; 0.69)
Low-grade inflammation (hsCRP),* mg/L, N=4722	1.7 (0.8; 3.4)	1.6 (0.7; 3.1)	2.2 (1.0; 4.2)	2.2 (0.9; 4.2)	2.2 (1.0; 4.2)
C-peptide, pmol/L, N=4353	1149 (856; 1553)	1128 (841; 1516)	1266 (958; 1701)	1256 (927; 1691)	1276 (978; 1717)
Physical activity,† baseline, days/week, N=5247	4 (2; 7)	4 (2; 7)	3 (1;7)	3 (1; 7)	3 (1; 7)
Physical activity,† questionnaire 2116, days/week, N=5189	4 (2; 6)	4 (2; 6)	3 (1; 6)	3 (2; 5)	3 (1; 6)
Alcohol, baseline, N=5247					
> 21/14 units/week (male/female)	343 (6.5)	277 (6.4)	66 (7.0)	32 (5.8)	34 (8.8)
Smoking, questionnaire 2016, N=5231					
Never	1850 (35.4)	1584 (36.9)	266 (28.4)	174 (31.5)	92 (23.8)
Former	2361 (45.1)	1909 (44.5)	452 (48.2)	253 (45.8)	199 (51.6)
Current	1020 (19.5)	800 (18.6)	220 (23.5)	125 (22.6)	95 (24.6)
Antihypertensive drug use, N=5247	3874 (73.8)	3147 (73,0)	727 (77.5)	426 (77.2)	301 (78.0)
Lipid lowering drug use, N=5247	3764 (71,7)	3102 (72.0)	662 (70.6)	396 (71.7)	266 (68.9)
Glucose-lowering drug use, N=5247					
Any glucose-lowering drug	4460 (85.0)	3640 (84.5)	820 (87.4)	477 (86.4)	343 (88.9)
Non-insulin glucose-lowering drug only	4143 (79.0)	3408 (79.1)	735 (78.4)	432 (78.3)	303 (78.5)
Insulin only	53 (1.0)	39 (0.9)	14 (1.5)	7 (1.3)	7 (1.8)
Both insulin + non-insulin glucose-lowering drug	264 (5.0)	193 (4.5)	71 (7.6)	38 (6.9)	33 (8.6)
Subcohort, N = 3,623					
BMI, baseline, kg/m2, N=3263	30.3 (27.1; 34.3)	30.0 (26.8; 34.0)	31.8 (28.1; 36.0)	32.0 (28.4; 36.0)	31.5 (27.7; 36.0)
Systolic blood pressure, mmHg, N=3387	130 (124; 140)	130 (124; 140)	130 (124; 140)	130 (123; 140)	130 (124; 142)
Diastolic blood pressure, mmHg, N=3387	80 (75; 86)	80 (74; 85)	80 (75; 86)	80 (75; 87)	80 (75; 86)
Dyslipidemia					
Total cholesterol, mmol/L, N=2267	4.3 (3.7; 5.1)	4.3 (3.7; 5.1)	4.4 (3.8; 5.1)	4.3 (3.7; 5.0)	4.5 (3.9; 5.3)
HDL cholesterol, mmol/L, N=2274	1.2 (1.0; 1.5)	1.2 (1.0; 1.5)	1.2 (1.0; 1.4)	1.2 (1.0; 1.4)	1.2 (1.0; 1.4)
LDL, mmol/L, N=3433	2.2 (1.7; 2.8)	2.2 (1.7; 2.8)	2.2 (1.7; 2.9)	2.2 (1.7; 2.8)	2.3 (1.8; 2.9)
Triglycerides, mmol/L, N=3302	1.6 (1.1; 2.3)	1.6 (1.1; 2.3)	1.9 (1.3; 2.6)	1.8 (1.2; 2.5)	1.9 (1.3; 2.9)
Glycemic control (HbA1c), mmol/mol, N=3536	47 (43; 53)	47 (43; 53)	48 (42; 56)	47 (42; 57)	48 (43; 55)
Glycemic control (HbA1c), %, N=3536	6.5 (6.1; 7.0)	6.5 (6.1; 7.0)	6.5 (6.0; 7.3)	6.5 (6.0; 7.4)	6.5 (6.1; 7.2)
Smoking, baseline, N=3437					
Never	1643 (47.8)	1398 (49.4)	245 (40.3)	154 (42.9)	91 (36.6)
Former	1189 (34.6)	960 (33.9)	229 (37.7)	128 (35.7)	101 (40.6)
Current	605 (17.6)	471 (16.7)	134 (22.0)	77 (21.5)	57 (22.9)

Abbreviations: MNSIq; Michigan Neuropathy Screening Instrument questionnaire, DN4; Douleur Neuropathique en 4 questions, DPN; diabetic polyneuropathy, DD2; The Danish Centre for Strategic Research in Type 2 Diabetes, DDDA; Danish Diabetes Database for Adults, BMI; body mass index, hsCRP; high-sensitivity C-reactive protein, HbA1c; hemoglobin A1c.

*Of note, CRP value was available for 5111, of which 389 had hsCRP ≥10 mg/L

†Days per week with minimum 30 minutes of physical activity

Missing data in the total cohort (n = 5249); height (n = 29 missing); BMI at 20 years (n = 707 missing); BMI at questionnaire 2016 (n = 90); waist circumference (n = 10 missing); waist-hip ratio (n = 12 missing), waist-height ratio (n = 39 missing), low-grade inflammation (n = 138 missing hsCRP, 389 with hsCRP ≥10 mg/L); C-peptide (n = 896 missing); physical activity at baseline (n = 2 missing); physical activity at questionnaire 2016 (n = 60), alcohol at baseline (n = 2 missing), alcohol at questionnaire 2016 (n = 70), smoking at questionnaire (n= 0 18), remaining variables (n = 0 missing)

Missing data in the DDDA-subcohort (n = 3623): BMI at baseline (n = 360); blood pressure (n = 236 missing); total cholesterol (n = 1356 missing); HDL cholesterol (n = 1,349 missing); LDL cholesterol (n = 190 missing); triglycerides (n = 321 missing); HbA1c (n = 87 missing); albumin/creatinine ratio (n = 0 missing), smoking at baseline (n = 186 missing).

Supplementary Table 3: Prevalence ratios of DPN for different obesity measures, continuous data		
		DPN (MNSIq ≥4)
	Total	aPR (95% CI)
General obesity		
BMI, baseline (unit = 2 kg/m^2)	3263	1.07 (1.04; 1.09)
BMI, questionnaire 2016, 2016 (unit = 2 kg/m^2)	5159	1.07 (1.06; 1.09)
Central obesity		
Waist circumference (unit = 5 cm)	5239	1.08 (1.06; 1.10)
Waist-hip ratio (unit = 0.1 cm/cm)	5237	1.16 (1.09; 1.24)
Waist-height ratio (unit = 0.1 cm/cm)	5210	1.29 (1.22; 1.37)
Per 1 SD increase*		
BMI, baseline	3259	1.22 (1.14; 1.30)
Waist circumference	3259	1.27 (1.20; 1.35)
Waist-hip ratio	3259	1.15 (1.07; 1.23)
Waist-height ratio	3259	1.23 (1.16; 1.31)

Abbreviations: DPN; diabetic polyneuropathy, MNSIq; Michigan Neuropathy Screening Instrument questionnaire, aPR; adjusted prevalence ratio, CI; confidence interval, DD2; The Danish Centre for Strategic Research in Type 2 Diabetes, BMI; body mass index.

*The analyses with a unit of 1 SD were restricted to the 3259 patients with available data on all four obesity measures at baseline = DD2 enrollment. This restriction was applied in order to be able to compare the magnitude of the effect across obesity measures.

All analyses are adjusted for age, sex, and diabetes duration.

Supplementary Table 4: Sex-stratified: Prevalence ratios of DPN for different obesity measures		
	DPN (MNSIq ≥4)	
	aPR (95% CI)	
	Female	Male
General obesity = BMI measures		
BMI, age 20 years, kg/m^2		
< 18.5	1.24 (0.95; 1.62)	0.92 (0.48; 1.75)
18.5 - 24	1 (ref)	1 (ref)
25 - 29	1.05 (0.81; 1.36)	0.82 (0.66; 1.02)
30 - 34	1.40 (0.97; 2.02)	1.27 (0.93; 1.75)
≥35	1.40 (0.88; 2.22)	1.40 (0.92; 2.14)
BMI, baseline, kg/m^2		
< 25	1 (ref)	1 (ref)
25 - 29	1.29 (0.85; 1.96)	1.26 (0.83; 1.92)
30 - 34	1.74 (1.16; 2.60)	1.54 (1.01; 2.34)
≥35	1.84 (1.22; 2.77)	1.88 (1.22; 2.88)
BMI, questionnaire 2016, kg/m^2		
< 25	1 (ref)	1 (ref)
25 - 29	1.42 (1.02; 1.95)	1.35 (0.99; 1.85)
30 - 34	1.80 (1.32; 2.47)	1.73 (1.26; 2.38)
≥35	2.23 (1.62; 3.07)	2.09 (1.50; 2.91)
BMI change*, kg/m^2		
< 4	1 (ref)	1 (ref)
4 – 6	1.48 (1.09; 2.01)	1.17 (0.93; 1.48)
7 - 9	1.38 (1.00; 1.90)	1.17 (0.91; 1.51)
≥10	2.13 (1.63; 2.78)	1.77 (1.42; 2.22)
Central obesity measures		
Waist circumference (M/F), cm		
< 94/80 cm	1 (ref)	1 (ref)
94-102/80-88	1.53 (0.83; 2.83)	1.71 (1.08; 2.70)
≥102/88	1.90 (1.10; 3.25)	2.73 (1.81; 4.13)
Waist-hip ratio (M/F)		
< 0.95/0.85	1 (ref)	1 (ref)
0.95 - 0.99/0.85 - 0.89	1.11 (0.82; 1.51)	1.41 (1.00; 1.98)
1 - 1.04/0.90 - 0.94	1.25 (0.94; 1.66)	1.89 (1.39; 2.55)
≥1.05/0.95	1.27 (0.96; 1.69)	2.13 (1.57; 2.89)
Waist-height ratio		
< 0.5	1 (ref)	1 (ref)
0.5 - 0.6	1.38 (0.87; 2.18)	1.78 (0.96; 3.29)
≥0.6	1.85 (1.19; 2.88)	2.84 (1.55; 5.20)

Abbreviations: DPN; Diabetic polyneuropathy, MNSIq; Michigan Neuropathy Screening Instrument questionnaire
aPR; adjusted prevalence ratio, CI; confidence interval, DD2; The Danish Centre for Strategic Research in Type 2
Diabetes, BMI; body mass index, M/F; male/female
*BMI change from age 20 to questionnaire 2016.
All analyses are adjusted for age, sex, and diabetes duration

Supplementary Table 5: Prevalence ratios of DPN for additional risk factors measured at baseline and at questionnaire 2016, categorical data

		DPN (MNSIq ≥4)	
	Total	N events (%)	aPR (95% CI)
Total, N (%)	5249	938 (17.9)	
BMI, questionnaire 2016, kg/m2	5159		
<25	792	87 (11.0)	1 (ref)
25-29	1899	287 (15.1)	1.39 (1.11; 1.74)
30-34	1493	297 (19.9)	1.78 (1.02; 1.51)
≥35	975	248 (25.4)	1.90 (1.61; 2.25)
HbA1c, %	3536		
< 6.5	1848	307 (16.6)	1 (ref)
6.5 – 7.4	1119	188 (16.8)	1.00 (0.85; 1.18)
7.5 – 8.4	299	66 (22.1)	1.26 (1.00; 1.60)
8.5 – 9.4	124	38 (30.7)	1.71 (1.29; 2.27)
≥9.5	146	31 (21.2)	1.23 (0.88; 1.71)
Glucose-lowering drug use	5249		
No	789	118 (15.0)	1 (ref)
Yes	4460	820 (18.4)	1.15 (0.96; 1.38)
Insulin use*			
No	4143	735 (17.7)	1 (ref)
Yes	317	85 (26.8)	1.43 (1.18; 1.75)
Physical activity, questionnaire 2016†	5189		
0	539	150 (27.8)	1.67 (1.43; 1.96)
1 – 2	1076	195 (18.1)	1.09 (0.94; 1.26)
≥3	3574	581 (16.9)	1 (ref)
Physical activity, change, stratified‡			
Baseline, activity level = 0 days	756		
2016: no change	226	76 (33.6)	1 (ref)
2016: more active	530	118 (22.3)	0.67 (0.52; 0.85)
Baseline, activity level = 1-2 days	1035		
2016: less active	223	49 (22.0)	1.08 (0.75; 1.56)
2016: no change	218	44 (20.2)	1 (ref)
2016: more active	594	113 (19.0)	0.94 (0.69; 1.29)
Baseline, activity level ≥3 days	3396		
2016: less active	1694	282 (16.7)	1.20 (1.00; 1.46)
2016: no change	999	133 (13.3)	1 (ref)
2016: more active	703	111 (15.8)	1.14 (0.91; 1.45)
Smoking, questionnaire 2016	5231		
Never	1850	266 (14.4)	1 (ref)
Former	2361	452 (19.1)	1.43 (1.25; 1.65)
Current	1020	220 (21.6)	1.52 (1.30; 1.79)
Metabolic syndrome	4941		
No	425	35 (8.2(	1 (ref)
Yes	4516	848 (18.8)	2.19 (1.58; 3.02)

Abbreviations: DPN; diabetic polyneuropathy, MNSIq; Michigan Neuropathy Screening Instrument questionnaire, DN4; Douleur Neuropathique en 4 questions, aPR; adjusted prevalence ratio, CI; confidence interval, DD2; The Danish Centre for Strategic Research in Type 2 Diabetes, hsCRP; high-sensitivity C-reactive protein, HbA1c; hemoglobin A1c. All analyses are adjusted for age, and diabetes duration

*Among those who use glucose-lowering drugs

†Days per week with minimum 30 minutes of physical activity

‡Stratified according to activity level at baseline = DD2 enrollment

Supplementary Table 6: Prevalence ratios of DPN for non-obesity risk factors, continuous data		
		DPN
		MNSIq ≥4
	Total	aPR(95% CI)
Systolic blood pressure (unit = 10 mmHg)	3387	1.00 (0.95; 1.05)
Diastolic blood pressure (unit = 5 mmHg)	3387	1.02 (0.98; 1.05)
Total cholesterol (unit = 0.5 mmol/l)	2267	0.99 (0.95; 1.04)
LDL cholesterol (unit = 0.25 mmol/l)	3433	1.01 (0.99; 1.03)
HDL cholesterol (unit = 0.25 mmol/l)	2274	0.92 (0.86; 0.98)
Triglycerides (unit = 0.5 mmol/l)	3302	1.04 (1.02; 1.06)
Low-grade inflammation, hsCRP (unit = 1)	4722	1.08 (1.06; 1.11)
C-peptide (Unit = 25 pmol/l)	4353	1.01 (1.00; 1.01)
HbA1c (unit = 10 mmol/mol)	3536	1.05 (1.01; 1.09)
HbA1c (unit = 1%)	3536	1.06 (1.01; 1.10)
Physical activity, baseline (unit = 1 day)	5247	0.95 (0.93; 0.97)

Abbreviations: DPN; diabetic polyneuropathy, MNSIq; Michigan Neuropathy Screening Instrument questionnaire, aPR; adjusted prevalence ratio, CI; confidence interval, hsCRP; high-sensitivity C-reactive protein, HbA1c; hemoglobin A1c.

All analyses are adjusted for age, sex, and diabetes duration.

Supplementary Table 7: Prevalence ratios of neuropathic pain occurrence (pain in both feet + DN4 ≥3) among the 938 patients with DPN defined as MNSIq ≥4 for additional risk factors measured at baseline and at questionnaire 2016

		Painful DPN MNSIq ≥4 and pain in feet + DN4 ≥3	
	Total	N events (%)	aPR (95% CI)
Total, N (%)	938	386 (41.2)	
BMI, questionnaire 2016	919		
< 25	87	37 (42.5)	1 (ref)
25 - 29	287	115 (40.1)	0.95 (0.72; 1.26)
30 - 34	297	123 (41.4)	1.00 (0.75; 1.32)
≥35	248	107 (43.2)	1.05 (0.79; 1.40)
HbA1c, %	630		
< 6.5	307	121 (39.4)	1 (ref)
6.5 – 7.4	188	85 (45.2)	1.16 (0.94; 1.44)
7.5 – 8.4	66	28 (42.4)	1.10 (0.80; 1.51)
8.5 – 9.4	38	12 (31.6)	0.86 (0.52; 1.42)
≥9.5	31	13 (41.9)	1.13 (0.73; 1.76)
Glucose-lowering drug use	938		
No	118	43 (36.4)	1 (ref)
Yes	820	343 (41.8)	1.15 (0.90; 1.49)
Insulin use*	820		
No	735	303 (41.2)	1 (ref)
Yes	85	40 (47.1)	1.18 (0.92; 1.53)
Physical activity, questionnaire 2016†	926		
0	150	68 (45.3)	1.12 (0.91; 1.37)
1 - 2	195	76 (39.0)	0.96 (0.78; 1.17)
≥3	581	235 (40.5)	1 (ref)
Physical activity, change‡			
Baseline, activity level = 0 days	194		
2016: no change	76	36 (47.4)	1 (ref)
2016: more active	118	46 (39.0)	0.83 (0.60; 1.15)
Baseline, activity level = 1-2 days	206		
2016: less active	49	20 (40.8)	1.19 (0.70; 2.02)
2016: no change	44	15 (34.1)	1 (ref)
2016: more active	113	39 (34.5)	1.01 (0.62; 1.64)
Baseline, activity level ≥3 days	526		
2016: less active	282	119 (42.2)	0.89 (0.71; 1.11)
2016: no change	133	63(47.4)	1 (ref)
2016: more active	111	41 (36.9)	0.78 (0.57; 1.05)
Smoking, questionnaire 2016	938		
Never	266	92 (34.6)	1 (ref)
Former	452	199 (44.0)	1.28 (1.05; 1.56)
Current	220	95 (43.2)	1.29 (1.03; 1.62)
Metabolic syndrome	883		
No	35	13 (37.1)	1 (ref)
Yes	848	345 (40.7)	1.09 (0.70; 1.70)

Abbreviations: DPN; diabetic polyneuropathy, MNSIq; Michigan Neuropathy Screening Instrument questionnaire, DN4; Douleur Neuropathique en 4 questions, aPR; adjusted prevalence ratio, CI; confidence interval, hsCRP; high-sensitivity C-reactive protein, HbA1c; hemoglobin A1c.

All analyses are adjusted for age, and diabetes duration

*Among those who use glucose-lowering drugs

†Days per week with minimum 30 minutes of physical activity

‡Stratified according to activity level at baseline = DD2 enrollment

Supplementary Table 8: Prevalence ratios of neuropathic pain occurrence (pain in both feet + DN4 ≥3) among the 938 patients with DPN defined as MNSIq ≥4: continuous obesity data

	Painful DPN MNSIq ≥4 and pain in feet + DN4 ≥3	
General obesity	Total	aPR (95% CI)
BMI, age 20 years (unit = 2 kg/m^2)	816	0.97 (0.94; 1.01)
BMI, baseline (unit = 2 kg/m^2)	581	0.98 (0.95; 1.01)
BMI, questionnaire, 2016 (unit = 2 kg/m^2)	919	1.00 (0.98; 1.03)
BMI change* (unit = 2 kg/m^2)	812	1.02 (0.99; 1.04)
Central obesity		
Waist circumference (unit = 5 cm)	937	1.01 (0.98; 1.03)
Waist-hip ratio (unit = 0.1 cm/cm)	937	1.09 (0.98; 1.21)
Waist-height ratio (unit = 0.1 cm/cm)	929	1.02 (0.93; 1.12)
Per 1 SD increase†		
BMI, baseline	581	0.95 (086; 1.04)
Waist circumference	581	1.01 (0.91; 1.10)
Waist-hip ratio	581	1.09 (0.97; 1.23)
Waist-height ratio	581	0.98 (0.89; 1.08)

Abbreviations: DPN; diabetic polyneuropathy, MNSIq; Michigan Neuropathy Screening Instrument questionnaire, DN4; Douleur Neuropathique en 4 questions, aPR; adjusted prevalence ratio, CI; confidence interval BMI; body mass index.

All analyses are adjusted for age, sex, and diabetes duration

*BMI change from age 20 years to questionnaire 2016.

†For the analyses with a unit of 1 SD, we restricted the population to the 581 patients that had available obesity data at time of enrollment in order to be able to compare the magnitude of the effect across obesity measures.

Supplementary Table 9: Prevalence ratios of neuropathic pain occurrence (pain in both feet + DN4 ≥3) for different metabolic risk factors measures among the 938 patients with DPN defined as MNSIq≥4, continuous data

| | Painful DPN | |
| | MNSIq ≥4 and pain in feet + DN4 ≥3 | |
	Total	aPR (95% CI)
Systolic blood pressure (unit = 10 mmHg)	599	1.03 (0.97; 1.09)
Diastolic blood pressure (Unit 5 mmHg)	599	0.98 (0.94; 1.03)
Total cholesterol (unit 0.5 mmol/l)	417	1.07 (1.01; 1.13)
LDL cholesterol (unit = 0.25 mmol/l)	594	1.02 (0.99; 1.04)
HDL cholesterol (unit = 0.25 mmol/l)	417	1.01 (0.93; 1.10)
Triglycerides (unit = 0.5 mmol/l)	585	1.03 (1.00; 1.06)
Lowgrade inflammation, hsCRP (unit = 1)	833	1.01 (0.97; 1.04)
C-peptide (unit = 25 pmol/l?)	790	1.00 (1.00; 1.00)
HbA1c (unit = mmol/mol)	630	1.01 (0.94; 1.07)
HbA1c (unit = 1%)	630	1.01 (0.94; 1.08)
Physical activity, baseline	938	1.01 (0.98; 1.04)

Abbreviations: DPN; diabetic polyneuropathy, MNSIq; Michigan Neuropathy Screening Instrument questionnaire, DN4; Douleur Neuropathique en 4 questions, aPR; adjusted prevalence ratio, CI; confidence interval, hsCRP; high-sensitivity C-reactive protein, HbA1c; hemoglobin A1c.

All analyses are adjusted for age, sex, and diabetes duration.

Supplementary Table 10: Sex-stratified analyses: Prevalence ratios of neuropathic pain occurrence (pain in both feet + DN4 ≥3) among the 938 patients with DPN defined as MNSIq ≥4 for obesity measures.

	Female aPR (95% CI)	Male aPR (95% CI)
General obesity = BMI measures		
BMI, age 20 years, kg/m^2		
< 18.5	1.13 (0.81; 1.57)	0.84 (0.34; 2.09)
18.5 - 24	1 (ref)	1 (ref)
25 - 29	1.01 (0.71; 1.43)	0.78 (0.58; 1.06)
30 - 34	0.93 (0.55; 1.58)	0.80 (0.49; 1.29)
≥35	0.64 (0.27; 1.53)	0.90 (0.51; 1.68)
BMI, baseline, kg/m^2		
< 25	1 (ref)	1 (ref)
25 - 29	0.69 (0.44; 1.07)	0.82 (0.50; 1.34)
30 - 34	0.68 (0.45; 1.04)	0.88 (0.54; 1.44)
≥35	0.66 (0.43; 1.02)	0.86 (0.51; 1.43)
BMI, questionnaire, 2016, kg/m^2		
< 25	1 (ref)	1 (ref)
25 - 29	0.91 (0.61; 1.34)	1.00 (0.66; 1.52)
30 - 34	0.94 (0.64; 1.37)	1.06 (0.70; 1.61)
≥35	1.00 (0.68; 1.34)	1.12 (0.72; 1.73)
BMI change*, kg/m^2		
< 4	1 (ref)	1 (ref)
4 - 6	1.05 (0.68; 1.62)	1.15 (0.85; 1.56)
7 - 9	1.33 (0.88; 2.01)	1.12 (0.80; 1.58)
≥10	1.14 (0.78; 1.67)	1.16 (0.86; 1.58)
Central obesity		
Waist circumference (M/F), cm		
< 94/80 cm	1 (ref)	1 (ref)
94-102/80-88 cm	1.24 (0.51; 3.02)	1.56 (0.75; 3.24)
≥102/88 cm	1.27 (0.57; 2.85)	1.50 (0.75; 3.00)
Waist-hip ratio (M/F)		
< 0.95/0.85	1 (ref)	1 (ref)
0.95 - 0.99/0.85 - 0.89	0.82 (0.54; 1.26)	1.85 (1.09; 3.15)
1 - 1.04/0.90 - 0.94	1.00 (0.69; 1.46)	1.50 (0.89; 2.52)
≥1.05/0.95	1.16 (0.81; 1.66)	1.61 (0.96; 2.70)
Waist-height ratio		
< 0.5	1 (ref)	1 (ref)
0.5 - 0.6	0.76 (0.46; 1.27)	1.36 (0.52; 3.59)
≥0.6	0.87 (0.54; 1.41)	1.37 (0.53; 3.57)

Abbreviations: DPN; Diabetic polyneuropathy, MNSIq; Michigan Neuropathy Screening Instrument questionnaire

aPR; adjusted prevalence ratio, CI; confidence interval, BMI; body mass index, M/F; male/female

All analyses are adjusted for age, sex, and diabetes duration

*BMI change from age 20 years to questionnaire 2016.

Supplementary Table 11: Prevalence ratios of DPN associated with metabolic risk factors and lifestyle factors at baseline with additional adjustment for central obesity and HbA1c

	Main results adjusted for age, sex, and diabetes duration	Additional adjusted for waist-hip ratio	Additional adjusted for HbA1c	Additional adjusted for waist-hip ratio and HbA1c
	aPR (95% CI)	aPR (95% CI)	aPR (95% CI)	aPR (95% CI)
NON-OBESITY METABOLIC AND LIFESTYLE FACTORS AT BASELINE				
Blood pressure (systolic) mmHg				
< 130	1 (ref)	1 (ref)	1 (ref)	1 (ref)
≥130	0.95 (0.82; 1.10)	0.93 (0.80; 1.08)	0.94 (0.81; 1.09)	0.93 (0.80; 1.08)
Blood pressure (diastolic) mmHg				
< 80	1 (ref)	1 (ref)	1 (ref)	1 (ref)
≥80	1.10 (0.95; 1.29)	1.09 (0.94; 1.27)	1.09 (0.93; 1.27)	1.08 (0.92; 1.25)
Antihypertensive drug use				
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	1.34 (1.16; 1.55)	1.30 (1.12; 1.50)	1.34 (1.12; 1.61)	1.31 (1.09; 1.58)
Total cholesterol, mmol/L				
< 4.3	1 (ref)	1 (ref)	1 (ref)	1 (ref)
≥4.3	1.04 (0.87; 1.24)	1.04 (0.88; 1.25)	1.04 (0.87; 1.24)	1.05 (0.88; 1.25)
LDL cholesterol				
< 1.8	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1.8 - 2.6	0.97 (0.80; 1.16)	0.96 (0.80; 1.16)	0.97 (0.81; 1.17)	0.97 (0.81; 1.17)
≥2.6	1.09 (0.91; 1.32)	1.10 (0.91; 1.33)	1.10 (0.91; 1.32)	1.10 (0.91; 1.33)
HDL cholesterol (M/F))				
< 1.0/1.2	1.35 (1.12; 1.62)	1.30 (1.07; 1.57)	1.28 (1.06; 1.55)	1.24 (1.03; 1.50)
≥1.0/1.2	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Triglycerides				
< 1.7	1 (ref)	1 (ref)	1 (ref)	1 (ref)
≥1.7	1.36 (1.17; 1.59)	1.33 (1.14; 1.55)	1.34 (1.15; 1.56)	1.31 (1.12; 1.53)
Lipid-lowering drug use				
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	0.97 (0.86; 1.11)	0.95 (0.84; 1.09)	0.89 (0.76; 1.04)	0.87 (0.74; 1.02)
Low-grade inflammation (hsCRP)*, mg/L				
< 1.0	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1.0 - 2.9	1.12 (0.95; 1.31)	1.10 (0.93; 1.29)	1.23 (1.01; 1.50)	1.21 (0.99; 1.48)
≥3.0	1.66 (1.42; 1.94)	1.61 (1.37; 1.88)	1.71 (1.41; 2.08)	1.66 (1.37; 2.02)
C-peptide				
< 850	1 (ref)	1 (ref)	1 (ref)	1 (ref)
850 - 1550	1.29 (1.08; 1.53)	1.25 (1.04; 1.49)	1.20 (0.98; 1.47)	1.16 (0.94; 1.42)
≥1550	1.72 (1.43; 2.07)	1.65 (1.36; 2.00)	1.57 (1.27; 1.95)	1.49 (1.19; 1.85)
HbA1c, mmol/mol				
< 48	1 (ref)	1 (ref)	-	-
48 - 57	1.00 (0.85; 1.19)	0.99 (0.84; 1.17)	-	-
58 - 67	1.28 (1.01; 1.62)	1.24 (0.98; 1.58)	-	-
68 - 77	1.61 (1.20; 2.17)	1.58 (1.17; 2.13)	-	-
≥78	1.42 (1.06; 1.88)	1.35 (1.02; 1.81)	-	-
Physical activity, baseline†				
0	1.60 (1.39; 1.85)	1.58 (1.37; 1.82)	1.72 (1.44; 2.04)	1.68 (1.41; 2.00)
1 – 2	1.26 (1.09; 1.46)	1.25 (1.08; 1.45)	1.24 (1.04; 1.48)	1.22 (1.02; 1.46)
≥3	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Physical activity, change‡				
Decreased activity	0.97 (0.83; 1.12)	0.97 (0.83; 1.12)	0.95 (0.79; 1.13)	0.94 (0.79; 1.13)
No change	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Increased activity	1.05 (0.91; 1.22)	1.05 (0.91; 1.22)	0.98 (0.81; 1.17)	0.97 (0.81; 1.16)
Smoking, baseline				
Never	1 (ref)	1 (ref)	1 (ref)	1 (ref)

Former	1.39 (1.18; 1.64)	1.38 (1.17; 1.63)	1.39 (1.18; 1.65)	1.39 (1.17; 1.64)
Current	1.50 (1.24; 1.81)	1.48 (1.22; 1.79)	1.51 (1.25; 1.83)	1.50 (1.23; 1.81)
Smoking change§				
Questionnaire 2016: discontinued	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Questionnaire 2016: continued	1.24 (0.80; 1.92)	1.23 (0.79; 1.90)	1.27 (0.81; 1.98)	1.24 (0.80; 1.94)
Alcohol (M/F), baseline‖				
≤21/14	1 (ref)	1 (ref)	1 (ref)	1 (ref)
>21/14	1.19 (0.95; 1.49)	1.18 (0.94; 1.48)	1.25 (0.96; 1.63)	1.25 (0.96; 1.63)

Abbreviations: aPR; adjusted prevalence ratio, DPN; diabetic polyneuropathy, CI; confidence interval, hsCRP; high-sensitivity C-reactive protein, HbA1c; hemoglobin A1c, M/F; male/female.

*hsCRP values above 10 mg/L were excluded in order to exclude values reflecting ongoing infections.

†Days per week with minimum 30 minutes of physical activity.

‡Change from baseline to questionnaire 2016 in the number of days per week with minimum 30 minutes of physical activity; Decreased: at least 1 day less per week with more than 30 minutes of physical activity, Increased activity: at least 1 day more per week with minimum 30 minutes of physical activity.

§Among those who were current users at baseline.

‖Units of alcohol (male/female), which was the maximum safe amount recommended by the Danish Health Authority, when the DD2 began enrollment.

Supplementary able 12. Prevalence ratios of DPN associated with obesity measures, additionally adjusted for HbA1c

|	Main results adjusted for age, sex, and diabetes duration	Additional adjusted for HbA1c
	aPR (95% CI)	aPR (95% CI)
BMI at age 20 years		
< 18.5	1.17 (0.92; 1.49)	1.23 (0.90; 1.66)
18.5 - 24	1 (ref)	1 (ref)
25 - 29	0.89 (0.76; 1.06)	0.91 (0.74; 1.12)
30 - 34	1.32 (1.04; 1.68)	1.31 (0.97; 1.76)
≥35	1.43 (1.05; 1.96)	1.43 (0.98; 2.08)
BMI, baseline		
< 25	1 (ref)	1 (ref)
25 - 29	1.30 (0.97; 1.75)	1.28 (0.95; 1.72)
30 - 34	1.65 (1.23; 2.20)	1.65 (1.23; 2.21)
≥35	1.88 (1.40; 2.52)	1.84 (1.36; 2.47)
BMI, questionnaire date		
< 25	1 (ref)	1 (ref)
25 - 29	1.39 (1.11; 1.74)	1.30 (1.00; 1.70)
30 - 34	1.78 (1.42; 2.22)	1.59 (1.22; 2.08)
≥35	2.17 (1.72; 2.73)	2.16 (1.65; 2.83)
BMI change*, kg/m^2		
< 4	1 (ref)	1 (ref)
4 - 6	1.27 (1.06; 1.53)	1.32 (1.05; 1.66)
7 - 9	1.24 (1.02; 1.51)	1.29 (1.01; 1.64)
≥10	1.90 (1.61; 2.25)	2.03 (1.65; 2.49)
Waist circumference (M/F)		
< 94/80 cm	1 (ref)	1 (ref)
94-102/80-88 cm	1.67 (1.16; 2.41)	1.58 (1.02; 2.44)
≥102/88 cm	2.45 (1.79; 3.40)	2.35 (1.60; 3.45)
Waist-hip ratio (M/F)		
< 0.95/0.85	1 (ref)	1 (ref)
0.95 - 0.99/0.85 - 0.89	1.27 (1.01; 1.59)	1.17 (0.89; 1.53)
1.00 - 1.04/0.90 - 0.94	1.55 (1.26; 1.91)	1.40 (1.09; 1.79)
≥1.05/0.95	1.67 (1.36; 2.05)	1.53 (1.20; 1.95)
Waist-height ratio		
< 0.5	1 (ref)	1 (ref)
0.5 - 0.6	1.51 (1.04; 2.17)	1.28 (0.86; 1.92)
≥0.6	2.20 (1.55; 3.17)	1.90 (1.29; 2.80)

Abbreviations: DPN; diabetic polyneuropathy, MNSIq; Michigan Neuropathy Screening Instrument questionnaire, DN4; Douleur Neuropathique en 4 questions, aPR; adjusted prevalence ratio, CI; confidence interval BMI; body mass index.

All analyses are adjusted for age, sex, and diabetes duration

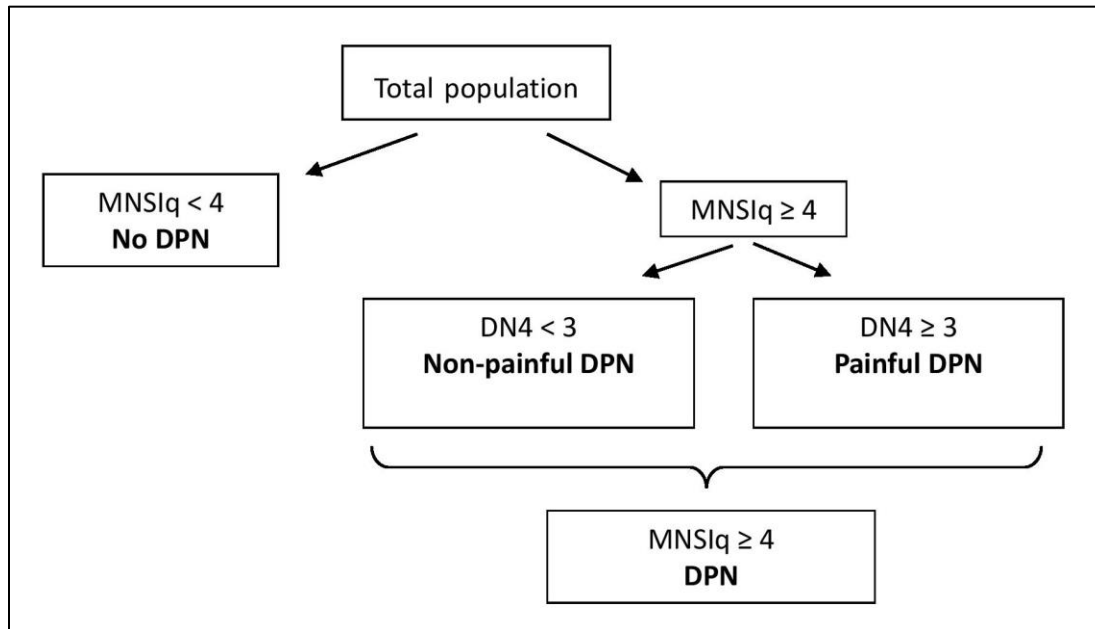*BMI change from age 20 years to questionnaire 2016.
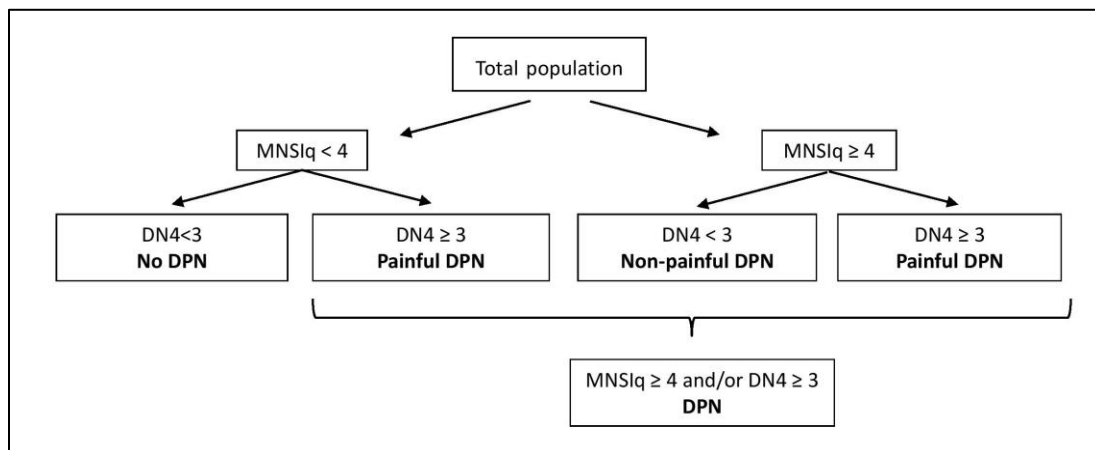
Figures:

Supplementary Figure 1: Flowchart
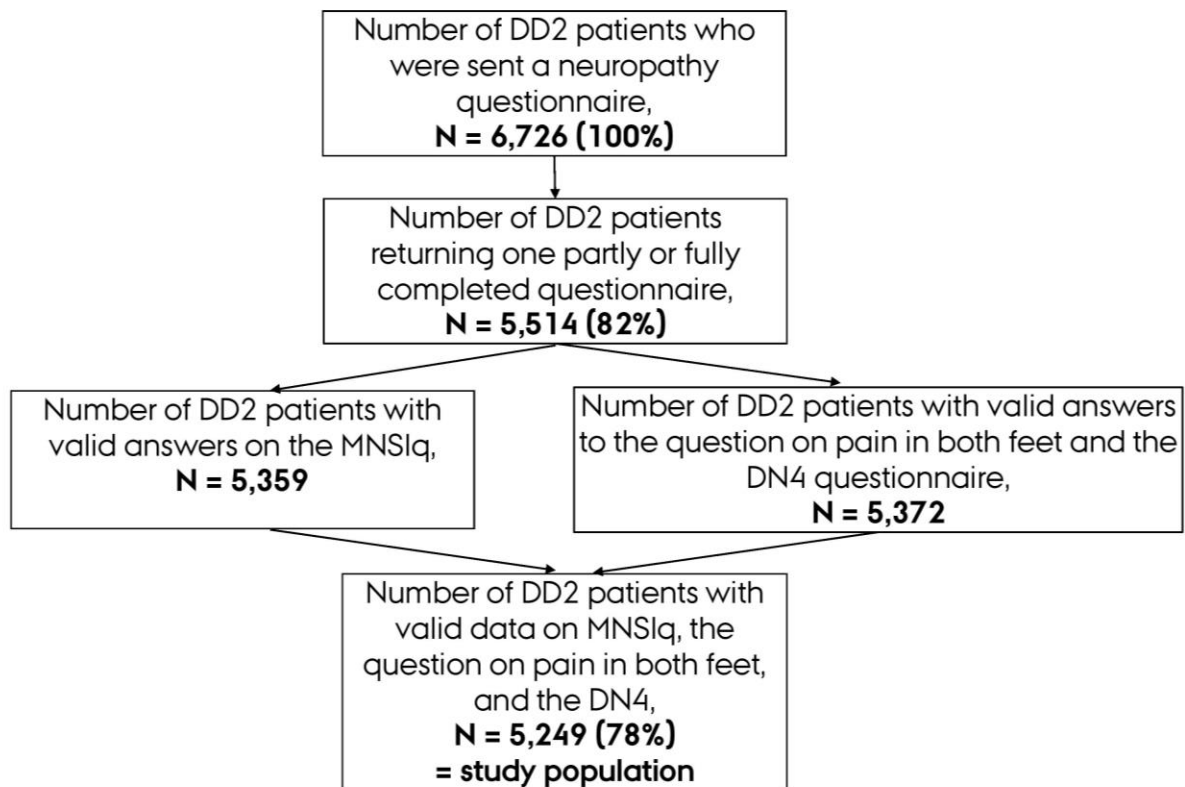
Supplementary Figure 2: Schematic overview of the definition of DPN and the division into non-painful DPN and painful DPN in A) main analyses and B) sensitivity analyses.
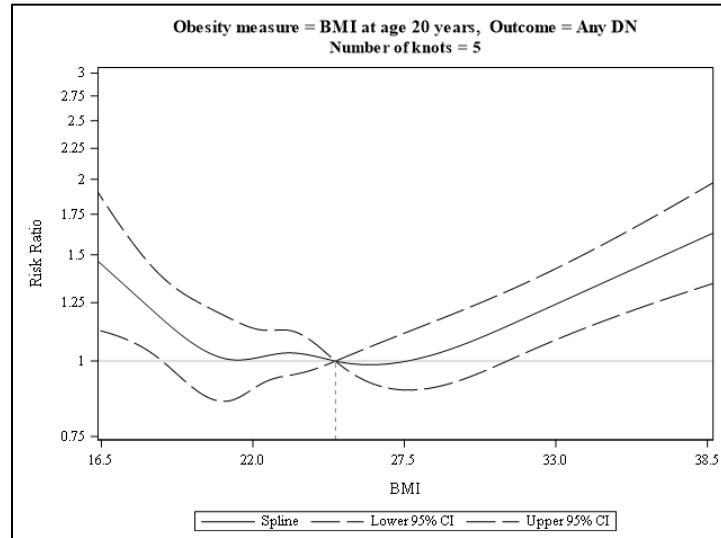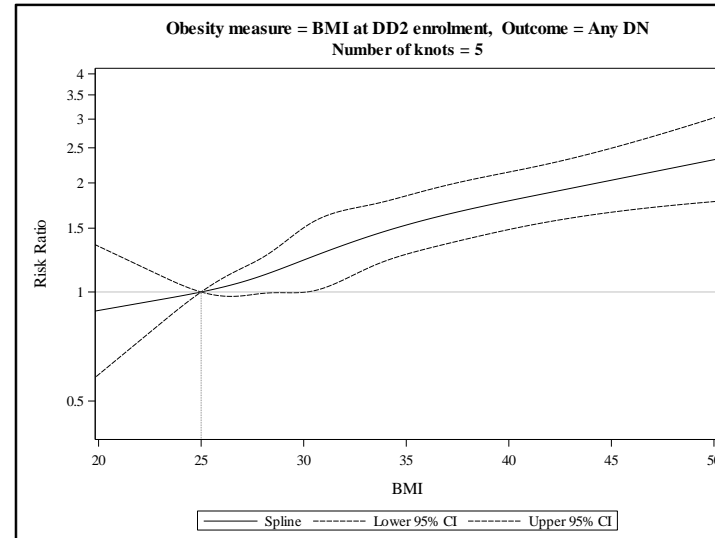
A)

B)

Of note, the DN4 score related specifically to pain in both feet and the DN4 questionnaire was only to be filled if pain in the feet was present. Thus, DN4 <3 means either no pain in feet or pain in both feet but DN4 <3.

Supplementary Figure 3: Restricted cubic spline regression of DPN for central and general obesity measures.
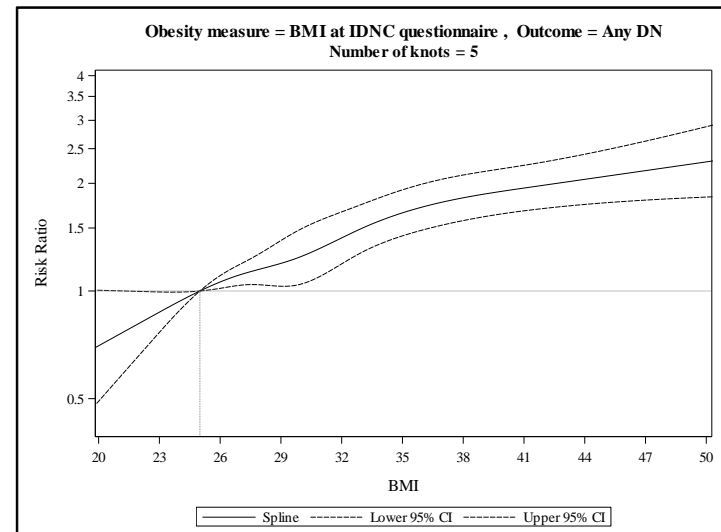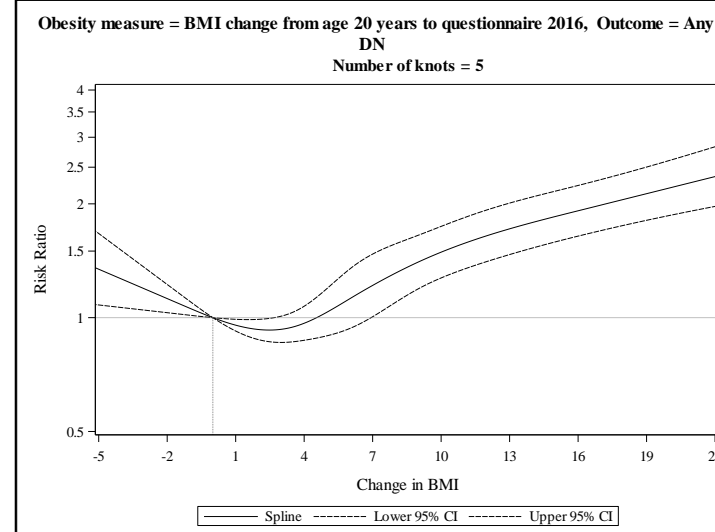
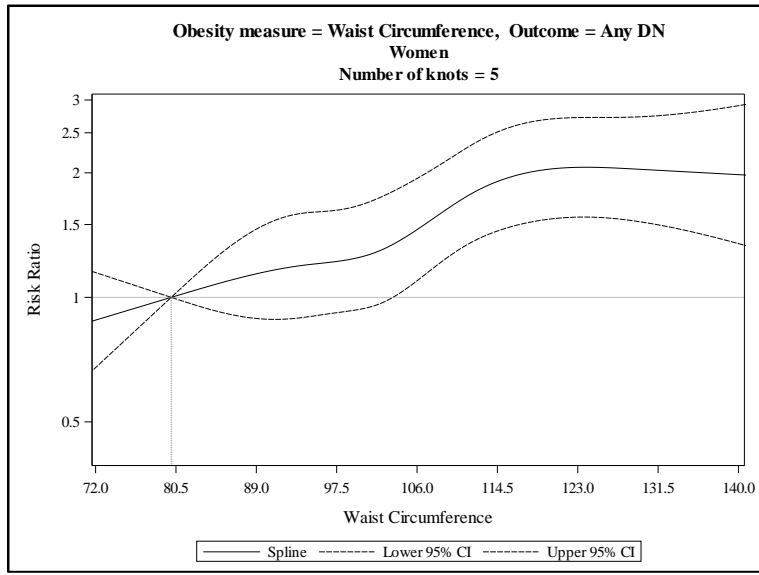Panel A: BMI, 20 years

Panel B: BMI, baseline

Panel C: BMI, questionnaire date

Panel D: BMI change (baseline -> questionnaire)

Panel E: Waist circumference, female

Obesity measure = Waist Circumference, Outcome = Any DN
Women
Number of knots = 5

Panel F: Waist circumference, male

Obesity measure = Waist Circumference, Outcome = Any DN
Men
Number of knots = 5
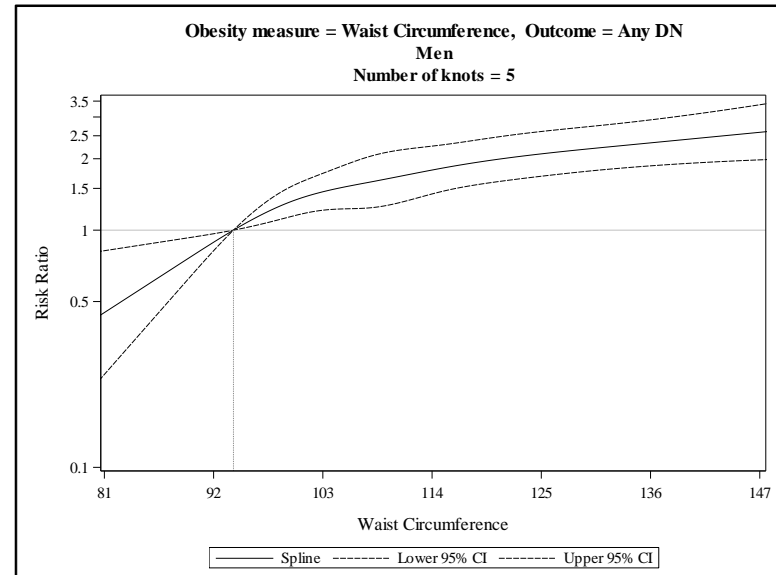
Panel G: Waist-hip ratio, female

Obesity measure = Waist-hip ratio, Outcome = Any DN
Women
Number of knots = 5
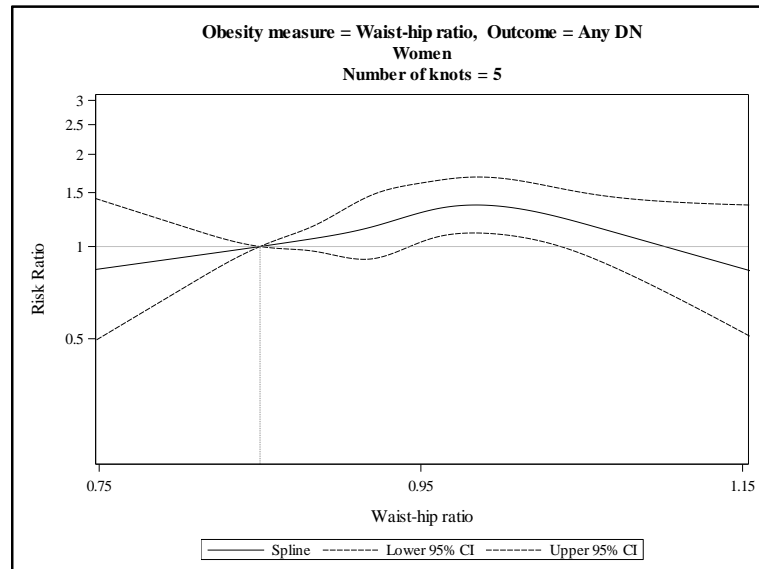
Panel H: waist-hip ratio, male

Obesity measure = Waist-hip ratio, Outcome = Any DN
Men
Number of knots = 5

25
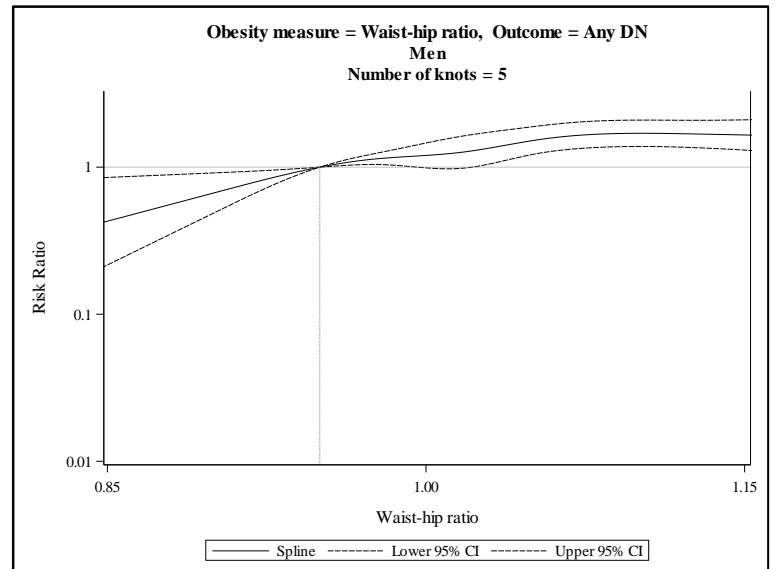
Panel I: waist-heigth ratio, female

Obesity measure = Waist-height ratio, Outcome = Any DN
Women
Number of knots = 5
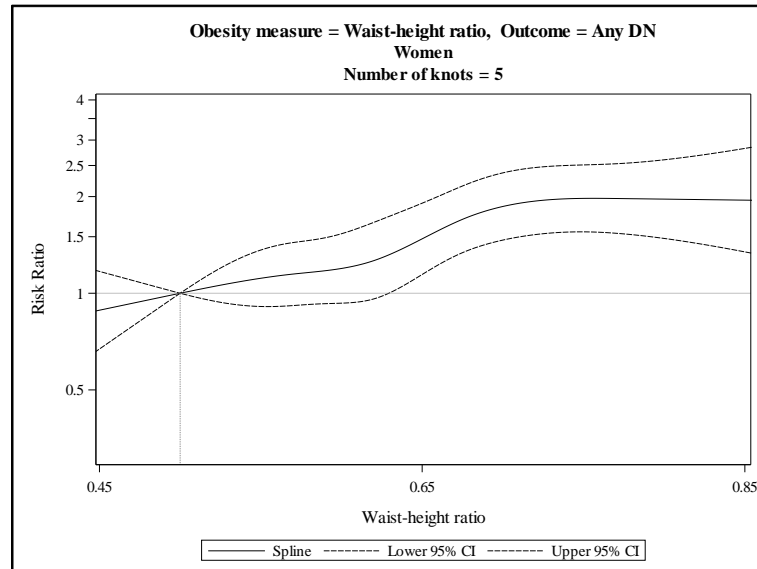
Panel J: Waist-heigth ratio ratio, male

Obesity measure = Waist-height ratio, Outcome = Any DN
Men
Number of knots = 5
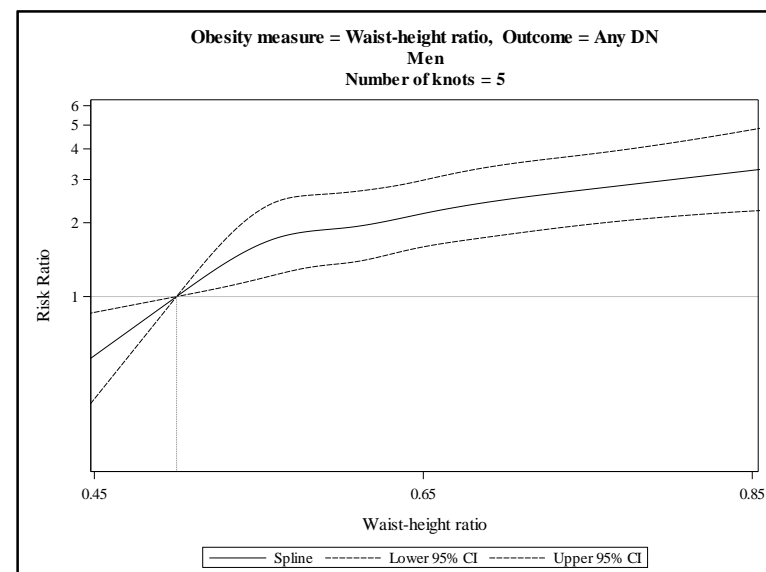
Supplementary Figure 4: Prevalence ratios of DPN for different obesity measures, without and with additional adjustment for BMI.

	Total	Events	DPN	aPR (95%CI)
Waist circumference (M/F)	5239			
<94/80	438	34		1.00
94-101/80-87	837	109		1.67 (1.16 - 2.41)
94-101/80-87, BMI-adjusted				1.52 (1.05 - 2.20)
≥102/88	3964	794		2.45 (1.76 - 3.40)
≥102/88, BMI-adjusted				1.86 (1.32 - 2.61)
Waist-hip ratio (M/F)	5237			
<0.95/0.85	813	99		1.00
0.95-0.99/0.85-0.89	1163	182		1.27 (1.01 - 1.59)
0.95-0.99/0.85-0.89, BMI-adjusted				1.20 (0.96 - 1.51)
1.00-1.04/0.90-0.94	1629	311		1.55 (1.26 - 1.91)
1.00-1.04/0.90-0.94, BMI-adjusted				1.41 (1.14 - 1.74)
≥1.05/0.95	1632	345		1.67 (1.36 - 2.05)
≥1.05/0.95, BMI-adjusted				1.44 (1.17 - 1.78)
Waist-height ratio	5210			
<0.50	287	28		1.00
0.50-0.60	1991	277		1.51 (1.04 - 2.17)
0.50-0.60, BMI-adjusted				1.32 (0.91 - 1.92)
≥0.60	2932	624		2.22 (1.55 - 3.17)
≥0.60, BMI-adjusted				1.62 (1.11 - 2.37)

Scale axis: 0.5 1 2 4 8

Abbreviations: aPR; adjusted prevalence ratio, DPN; diabetic polyneuropathy, CI; confidence interval; BMI; body mass index.
Of note: BMI from questionnaire 2016 is used for adjustment because this BMI measure is available for N=5159, whereas BMI at baseline = DD2 enrollment is available only for N=3263. Only a minor difference in BMI was observed between these two time points (median change: -0.4 kg/m [IQR: -1.6; 0.6]) and central obesity measures were also associated with DPN independent of BMI if adjusted for BMI at baseline instead of BMI at questionnaire.
All estimates are adjusted for age, sex, and diabetes duration.