Metabolic Factors, Lifestyle Habits, and Possible Polyneuropathy in Early Type 2 Diabetes: A Nationwide Study of 5,249 Patients in the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) Cohort

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OBJECTIVE

To investigate the association of metabolic and lifestyle factors with possible diabetic polyneuropathy (DPN) and neuropathic pain in patients with early type 2 diabetes.

RESEARCH DESIGN AND METHODS

We thoroughly characterized 6,726 patients with recently diagnosed diabetes. After a median of 2.8 years, we sent a detailed questionnaire on neuropathy, including the Michigan Neuropathy Screening Instrument questionnaire (MNSIq), to identify possible DPN (score ≥4) and the Douleur Neuropathique en 4 Questions (DN4) questionnaire for possible associated neuropathic pain (MNSIq ≥4 + pain in both feet + DN4 score ≥3).

RESULTS

Among 5,249 patients with data on both DPN and pain, 17.9% (n = 938) had possible DPN, including 7.4% (n = 386) with possible neuropathic pain. In regression analyses, central obesity (waist circumference, waist-to-hip ratio, and waist-to-height ratio) was markedly associated with DPN. Other important metabolic factors associated with DPN included hypertriglyceridemia ≥1.7 mmol/L, adjusted prevalence ratio (aPR) 1.36 (95% CI 1.17; 1.59); decreased HDL cholesterol <1.0/1.2 mmol/L (male/female), aPR 1.35 (95% CI 1.12; 1.62); hs-CRP ≥3.0 mg/L, aPR 1.66 (95% CI 1.42; 1.94); C-peptide ≥1,550 pmol/L, aPR 1.72 (95% CI 1.43; 2.07); HbA_{1c} ≥78 mmol/mol, aPR 1.42 (95% CI 1.06; 1.88); and antihypertensive drug use, aPR 1.34 (95% CI 1.16; 1.55). Smoking, aPR 1.50 (95% CI 1.24; 1.81), and lack of physical activity (0 vs. ≥3 days/week), aPR 1.61 (95% CI 1.39; 1.85), were also associated with DPN. Smoking, high alcohol intake, and failure to increase activity after diabetes diagnosis associated with neuropathic pain.

CONCLUSIONS

Possible DPN was associated with metabolic syndrome factors, insulin resistance, inflammation, and modifiable lifestyle habits in early type 2 diabetes.

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Diabetic polyneuropathy (DPN) affects 25–50% of patients with type 2 diabetes (1,2). DPN increases the risk of falls, foot ulcers, and lower-extremity amputations (1,2), and up to 38% of patients experience neuropathic pain (1,3,4). Current preventive measures for DPN are mainly limited to strict glycemic control, which exerts a limited effect against DPN risk in type 2 diabetes patients (5).

Increasing evidence supports an association between the degree of obesity and risk of DPN in type 2 diabetes (6–10), but the exact biological mechanisms remain unclear. Visceral fat accumulation associates with metabolic dysfunction, e.g., low-grade inflammation, insulin resistance, and dyslipidemia. Some individuals who are obese by BMI criteria (BMI >30 kg/m^2) can be metabolically healthy (11), which can possibly be attributed to less visceral fat distribution (12). Accordingly, central obesity has been shown to be a stronger predictor of some diabetes complications than—and independently of—BMI (13). However, it is not known whether central obesity associates with DPN independently of BMI in type 2 diabetes. Results are mixed and conflicting from studies examining other possible DPN risk factors in diabetes populations, such as metabolic syndrome–related factors, including dyslipidemia, hypertension, and hyperglycemia as well as low-grade inflammation and lifestyle habits like smoking and physical activity (3,7–9,14,15). Large-scale studies on DPN in type 2 diabetes patients are scarce, and existing DPN studies have often included patients with long-standing diabetes rather than newly diagnosed diabetes where the potential to prevent complications may be largest. Specifically, little knowledge is available on risk factors that may underlie the presence of neuropathic pain in type 2 diabetes (16).

In a recent cross-sectional analysis of the nationwide Danish Centre for Strategic Research in Type 2 Diabetes (DD2) cohort, we investigated the association of DPN and painful DPN with mental health comorbidities and with a few selected patient characteristics including age, sex, and BMI, assessed concurrently with DPN (17,18). In the current study, we linked the DD2 cohort with a range of other medical databases to comprehensively investigate the association of various metabolic and lifestyle factors at diabetes diagnosis with occurrence of DPN and neuropathic pain at a median of 2.8 years later. We examined the hypothesis that central obesity markers are strongly—and independently of general obesity—associated with DPN (12,13,19). We also investigated whether higher levels or rates of a range of other metabolic and lifestyle risk factors would associate with higher DPN prevalence. Finally, we explored the hypothesis that distinct metabolic factors associate with painful DPN compared with nonpainful DPN.

RESEARCH DESIGN AND METHODS

Setting

The DD2 cohort is a nationwide cohort of individuals with newly or recently diagnosed type 2 diabetes (median diagnosed diabetes duration at enrollment time 1.3 years [interquartile range (IQR) 0.3–2.9]) enrolled from hospital specialist outpatient clinics and from general practitioners' offices in Denmark since November 2010. The enrollment process, implementation, logistics, DD2 biobank, and characteristics of this cohort have previously been described (18). Briefly, interview and clinical examination data for each patient are recorded at the DD2 enrollment date, and fasting blood and urine samples are obtained and stored in the DD2 biobank. The unique civil personal registration number assigned to all Danish citizens links the DD2 cohort to other Danish health registries, including a complete hospital contact history from the Danish National Patient Registry, filled drug prescriptions from the Danish National Health Service Prescription Database, and information on vital status and migration from the Danish Civil Registration System. For a subcohort of DD2 patients (69%), additional detailed clinical data can be retrieved from the nationwide quality-of-care database, the Danish Diabetes Database for Adults (DDDA) (18).

Study Population

In June 2016, a median of 2.8 years (IQR 1.8–3.7) after the DD2 enrollment date, a detailed questionnaire on neuropathy and pain was sent out to all 6,726 living DD2 participants enrolled from November 2010 to February 2016 (17). The questionnaire included the 15-item Michigan Neuropathy Screening Instrument questionnaire (MNSIq), the 7-item Douleur Neuropathique en 4 Questions (DN4) questionnaire, questions about pain location (e.g., whether the person experienced pain in both feet), anthropometric data, and lifestyle factors.

Our main study population consisted of the 5,249 (78%) DD2 patients, who provided information on both polyneuropathy and neuropathic pain status from the questionnaire survey (Supplementary Fig. 1). Characteristics of all 5,514 DD2 patients who returned a fully or partly filled questionnaire have previously been described (17).

Diabetic Polyneuropathy and Neuropathic Pain: Definitions

The MNSIq tool was developed to screen for and identify DPN (20,21). We used the validated cutoff score of ≥ 4 (specificity 92%, sensitivity 40%) to assess possible DPN (21,22). Neuropathic pain was evaluated according to NeuroPPIC (Neuropathic pain phenotyping by international consensus for genetic studies) (23), and the updated NeuPSIG (Neuropathic Pain Special Interest Group) neuropathic pain grading system (24) defining possible neuropathic pain as *1*) pain with neuropathic characteristics, *2*) an anatomically plausible pain distribution (here, pain in both feet), and *3*) a history of a relevant underlying somatosensory lesion or disease (here, diabetes) (24). We used the DN4 questionnaire (25), which has specifically been validated in DPN (specificity and sensitivity 84%) (26), and defined neuropathic pain as the presence of pain in both feet together with a DN4 score of ≥ 3. It was emphasized in the questionnaire that the DN4 questions specifically related to pain in the feet and should only be answered if there was pain in both feet. Thus, DPN was defined as MNSIq ≥ 4; painful DPN as MNSIq ≥ 4 + pain in both feet + DN4 ≥ 3, and nonpainful DPN as MNSIq ≥ 4 in combination with either DN4 <3 or no pain in the feet (Supplementary Fig. 2*A*).

Obesity Measures

We used information on BMI (weight in kilograms divided by the square of height in meters) as a measure of general obesity at three different time points: at 20 years of age (based on recall at the time of DD2 enrollment), at time of DD2 enrollment (subcohort: based on DDDA data, i.e., recorded as part of routine clinical diabetes care [18]), and at time of the questionnaire survey in 2016 (based on self-reported data). We then calculated changes in BMI from age 20 years to the time of questionnaire in 2016.

Waist and hip circumference were measured as part of the DD2 enrollment process and were used to assess central obesity with three different measures: waist circumference, waist-to-hip ratio, and waist-to-height ratio (13).

The timeline of obesity measures, nonobesity metabolic risk factors, lifestyle factors (see below), and DPN status is shown in Fig. 1. For further definitions and categories, see Supplementary Table 1.

Other Metabolic and Lifestyle Factors

Information on other patient characteristics and metabolic and lifestyle factors at time of DD2 enrollment (from here on referred to as "baseline") was extracted from the DD2 cohort data and linked health registers. Patient characteristics and metabolic factors of particular interest that were available for the entire population included C-peptide level (insulin resistance surrogate), low-grade inflammation assessed by hs-CRP (excluding hs-CRP values $\geq$10 mg/L to exclude patients with ongoing infections) (27), physical activity (days per week with $>$30 min of physical activity), alcohol consumption ($\leq$ or $>$21/14 units per week for males/females— the recommended safe dose in 2010 when the DD2 was initiated), and diabetes duration (at the time of questionnaire survey [2016]). Metabolic risk factors available for the subcohort linked via the DDDA included hemoglobin A1$_c$ (HbA_{1c}), lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), smoking habits (current, former [$>$6 months ago], and never), and blood pressure.

Some patients may have had normal blood pressure, HbA_{1c}, and lipid levels at baseline due to relevant treatment. Thus, we also retrieved information on antihypertensive, glucose-lowering, and lipid-lowering drug usage within 1 year prior to baseline.

In contrast to the focus of our previous publication based solely on data at the time of the questionnaire survey (17), our main focus was the lifestyle and metabolic risk factor profile in patients around the time of type 2 diabetes diagnosis, i.e., at baseline. For smoking and physical activity, however, we also used follow-up data from the neuropathy questionnaire a median of 2.8 years later to assess the role of risk factor changes.

Statistical Analyses

Descriptive data were median (IQR) for continuous variables and proportions (*n* [%]) for categorical variables. We examined the proportion of overall DPN, nonpainful DPN, and painful DPN. We then calculated prevalence ratios (PRs) with 95% CIs of DPN associated with obesity measures and other metabolic and lifestyle factors using log-binomial and Poisson (with robust error variance) regression models (28). Continuous risk factors were investigated both as categorical and continuous variables. All PRs were adjusted for age, biological sex, and diabetes duration. We did not make further adjustments in our main analysis because the obesity measures and other metabolic and lifestyle factors may act as intermediates and clusters in the same incompletely understood pathophysiological pathways. The associations between obesity measures and DPN were also evaluated with the use of restricted cubic spline regressions with five knots (29). To elaborate on the associations of central obesity measures with DPN independently of BMI, we additionally adjusted for BMI in these models. The analyses of change of physical activity level were stratified according to baseline physical activity level.

Next, we restricted the cohort to those with DPN (MNSIq $\geq$4) and calculated the adjusted PR of painful DPN for each risk factor under study.

In sensitivity analyses, we restricted the population to individuals with a short registered diabetes duration ($<$1 year and $<$0.5 years) at DD2 enrollment. Since having diabetes and neuropathic pain (DN4 $\geq$3) in both feet may be considered to fulfill the NeuroPPIC/NeuPSIG criteria for possible painful DPN (23,24) despite a MNSIq score $<$4, we did a sensitivity analysis including these patients in the painful DPN group, as we did in our previous publication (17) (Supplementary Fig. 2*B*). In another sensitivity analysis, we excluded patients with alcohol overconsumption because peripheral neuropathy may result from DPN, alcoholic polyneuropathy, or a mixture in these patients. Because central obesity may precede other metabolic risk factors, we performed additional analyses in which we adjusted the DPN analyses for waist-to-hip ratio. We also did analyses controlling for HbA_{1c} level.

Finally, we examined presence of the metabolic syndrome as one entity as a risk factor for DPN and painful DPN (definition in Supplementary Table 1).

We tested for effect measure modification by sex using the likelihood ratio test.

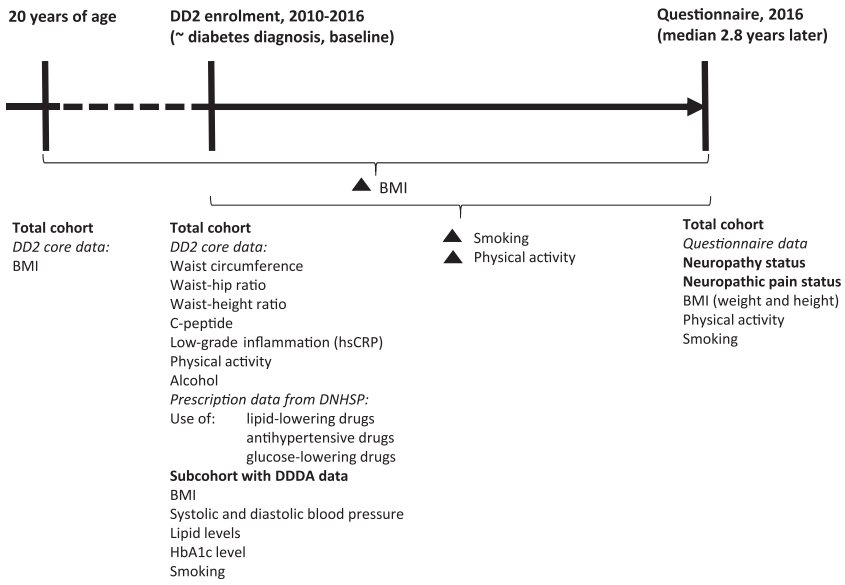

Figure 1—Time line of assessment of obesity measures, other metabolic and lifestyle factors, and DPN status. DD2, The Danish Centre for Strategic Research in Type 2 Diabetes; DNHSP, Danish National Health Service Prescription Database.

Research Ethics and Informed Consent

The Danish National Committee on Health Research Ethics (record number

S-20100082) and the Danish Data Protection Agency (record number 2008-58-0035) approved the DD2 study. All DD2 patients volunteered to participate in the DD2 study and gave written informed consent.

RESULTS

Descriptive Data

We included 5,249 patients, of whom 938 (17.9%) had DPN, including 386 (7.4%) with painful DPN (17). Median age was 65 years (IQR 57–72), 42% were female, and median diabetes duration was 4.6 years (IQR 3.5–5.7) at DPN assessment (Supplementary Table 2).

Obesity Measures and DPN

Higher BMI at baseline and at the questionnaire date, as well as larger waist circumference, waist-to-hip ratio, and waist-to-height ratio were all associated with a higher DPN prevalence (Fig. 2). Similar results were observed when the obesity measures were analyzed as continuous variables (Supplementary Table 3). The magnitude of the association with DPN for 1 SD increase was similar for the general and central obesity measures (Supplementary Table 3). Spline regression analyses yielded approximate linear relations with DPN for general and central obesity measures, except for a J-shaped association observed with BMI at age 20 years and with BMI change since age 20 years (Supplementary Fig. 3).

When we additionally adjusted central obesity for BMI, all central obesity measures remained positively associated with DPN (Supplementary Fig. 4). For example, for a given BMI, DPN prevalence increased by a factor of 1.86 (95% CI 1.32; 2.61) for individuals with a waist circumference of ≥102/88 cm (male/female) vs. <94/80 cm. In these analyses, BMI persistently associated with DPN.

No statistically significant effect measure modification by sex was found; however, PRs tended to be higher among males for central obesity measures (Supplementary Table 4).

Other Metabolic Risk Factors and DPN

Figure 3 shows risk estimates for baseline nonobesity metabolic risk factors and lifestyle habits. Metabolic factors markedly associated with DPN included low HDL cholesterol, high triglycerides, low-grade inflammation, higher C-peptide, and higher HbA_{1c} (Supplementary Table 5). Antihypertensive drug treatment was associated with DPN but not systolic and diastolic blood pressure. Finally, insulin treatment was associated with DPN (Supplementary Table 6). No statistically significant effect measure modification by sex was found.

Lifestyle Factors and DPN

Lower physical activity level and a current smoker status or former smoker status at baseline were clearly associated with DPN. Of note, continued smoking compared with smoking cessation between baseline and questionnaire date was also associated with DPN (adjusted PR [aPR] 1.24 [95% CI 0.80; 1.92]), yet with limited statistical precision. In contrast, no clear association was observed with change in physical activity level in the main analyses (Fig. 3). However, in the analyses stratified by baseline activity, DPN prevalence was low in patients whose activity level was low at baseline but had increased at DPN assessment time (aPR 0.67 [95% CI 0.52; 0.85]). Conversely, DPN prevalence was high in patients whose activity was high at baseline but had decreased at DPN assessment (aPR 1.20 [95% CI 1.00; 1.46]) (Supplementary Table 5). No statistically significant effect measure modification by sex was found.

Risk Factors and Neuropathic Pain

Among DPN patients, we did internal analyses of risk factors associated with neuropathic pain (i.e., factors associated with painful vs. nonpainful DPN) shown in Table 1 and Supplementary Tables 7–10. Several risk factors appeared to associate with increased prevalence of painful DPN, yet often with limited statistical precision. These included central obesity (waist circumference and waist-to-hip ratio), high systolic blood pressure, high total cholesterol, high LDL cholesterol, and high triglycerides. In analyses of continuous data (Supplementary Tables 8 and 9), some of these factors reached statistical significance, e.g., total cholesterol (unit = 0.5 mmol/L, aPR 1.07 [95% CI 1.01; 1.13]). Neuropathic pain was associated with alcohol overconsumption at baseline and with smoking at baseline (current smoking, aPR 1.17 [95% CI 0.90; 1.51]) and at the questionnaire date (current smoking, aPR 1.29 [95% CI 1.03; 1.62]) ($n = 608$ vs. $n = 938$, respectively), with the latter in agreement with our previous study using a slightly different painful DPN definition (17). Increased physical activity from baseline to questionnaire date was associated with lower painful DPN prevalence (aPR 0.82 [95% CI 0.67; 0.99]).

Sensitivity Analyses

Of the 5,249 patients, 130 (2.5%) had pain in both feet and DN4 ≥3 but MNSIq <4 (17). For the majority of risk factors, these patients were more similar to patients without DPN than to patients with painful DPN. Including these 130 patients in the painful DPN group yielded an overall prevalence of painful DPN of 10% as reported in our previous study (17). This inclusion marginally reduced most risk estimates for DPN and for neuropathic pain but did not change our conclusions (data not shown).

Restricting the cohort to individuals with diabetes duration ≤1 year and ≤0.5 year generally supported the main analyses but with lower precision (data not shown). Excluding DPN patients with alcohol overconsumption from the analyses did not change conclusions (data not shown).

Of note, most risk factor–DPN associations were robust to further adjustment for central obesity and for hyperglycemia (Supplementary Tables 11 and 12). For example, the strong association of high C-peptide with DPN (≥1,550 pmol/L, aPR 1.72 [95% CI 1.43; 2.07]) attenuated only moderately when we adjusted both for central obesity as a potential cause of insulin resistance and for HbA_{1c} as a potential effect of insulin resistance: aPR 1.49 (95% CI 1.19; 1.85).

The metabolic syndrome associated strongly with DPN (aPR 2.19 [95% CI 1.58; 3.02]) but not with painful DPN (aPR 1.09 [95% CI 0.70; 1.70) (Supplementary Tables 5 and 7).

CONCLUSIONS

This is the largest study to date to investigate in detail multiple obesity measures and several metabolic and lifestyle factors with both DPN and painful DPN in patients with early type 2 diabetes. We found that both general and central obesity are strongly—and independently of each other—associated with DPN prevalence. Other metabolic and lifestyle factors that clearly associated with DPN prevalence included low-grade inflammation, hypertriglyceridemia, hyperglycemia, high C-peptide levels, low HDL

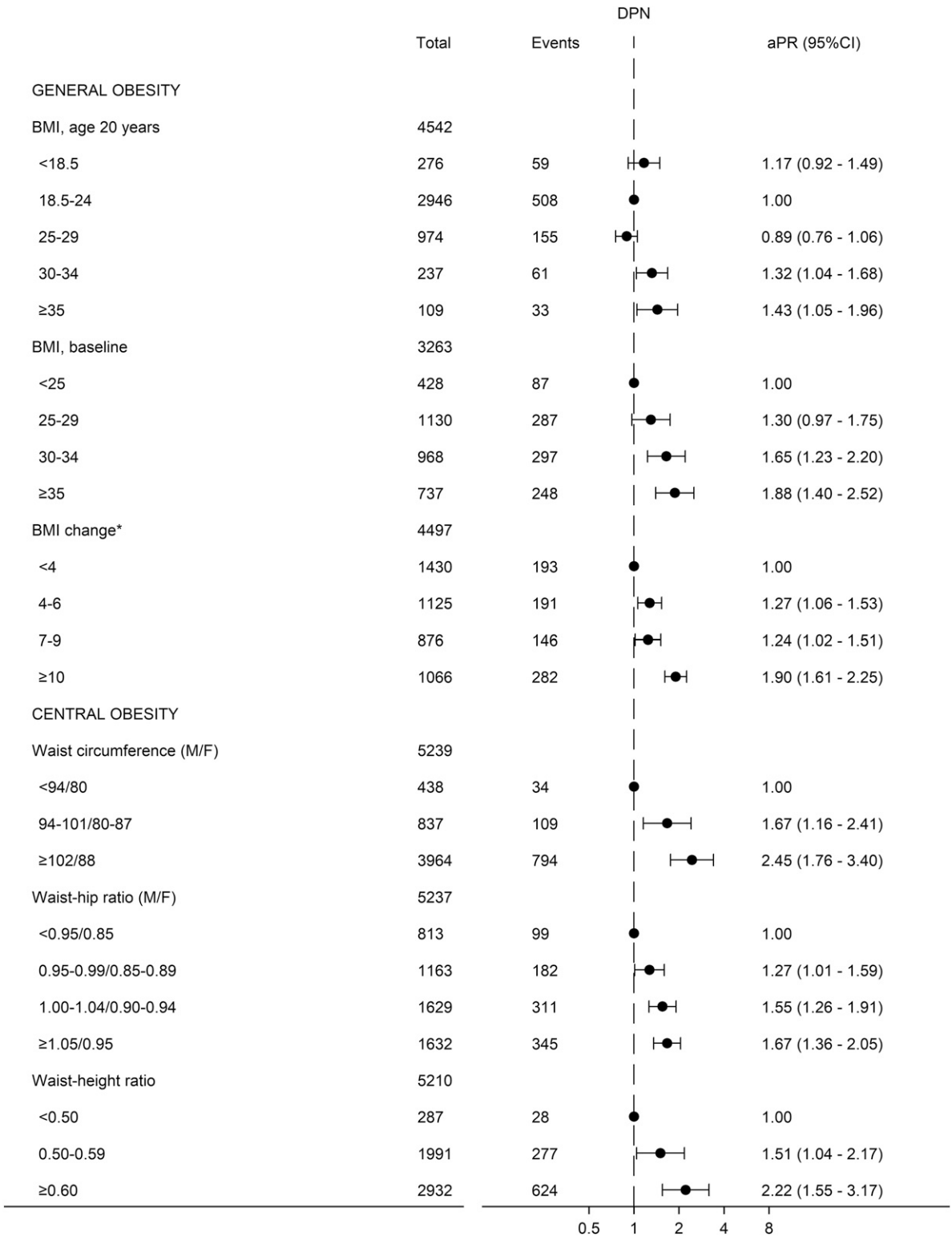

Figure 2—PRs of DPN associated with general obesity measures (BMI: kg/m^2) and central obesity measures (waist circumference: cm). All estimates are adjusted for age, sex, and diabetes duration. *BMI change from age 20 years to questionnaire 2016. M/F, male/female.

levels, antihypertensive drug use, tobacco smoking, and low physical activity. These findings suggest that controlling metabolic factors through weight loss and medications as well as lifestyle interventions, including smoking cessation and increased physical activity, may potentially reduce DPN risk.

Even within this large study, statistical precision was limited for the analyses of painful DPN. While metabolic syndrome metrics (central obesity, increased lipids, and hypertension) seemed to associate with neuropathic pain, these results generally did not reach statistical significance

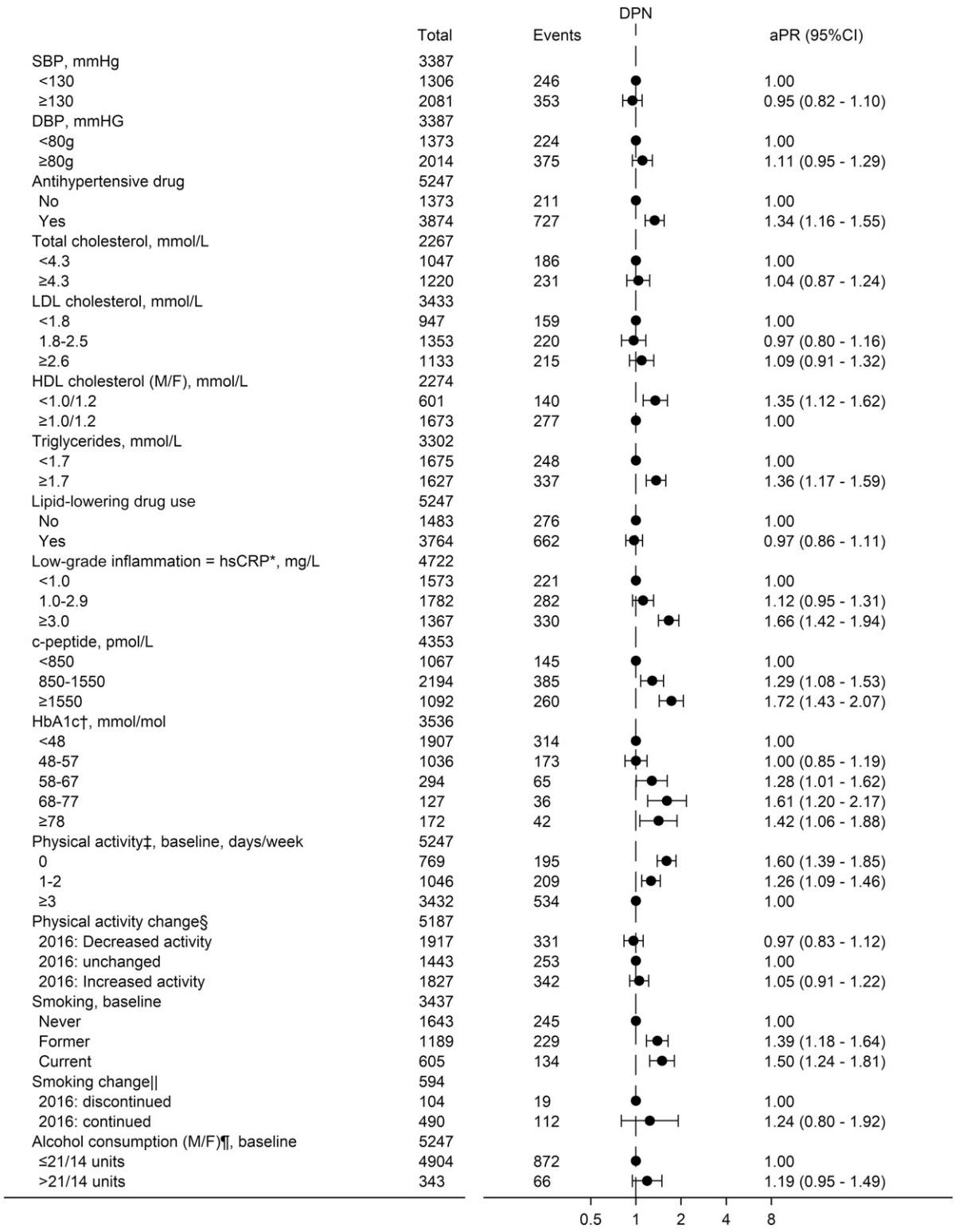

Figure 3—PRs of DPN associated with metabolic risk factors and lifestyle factors at baseline. All estimates are adjusted for age, sex, and diabetes duration. *hs-CRP values >10 mg/L were excluded in order to exclude values reflecting ongoing infections. †Results for HbA_{1c} (%) are available in Supplementary Table 5. ‡Days per week with minimum 30 min of physical activity. §Change from baseline to questionnaire 2016 in the number of days per week with minimum 30 min of physical activity: decreased activity, at least 1 day less per week with >30 min of physical activity; increased activity, at least 1 day more per week with minimum 30 min 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. M/F, male/female.

Table 1—PRs of neuropathic pain occurrence (pain in both feet + DN4 ≥3) among the 938 patients with DPN

	DPN, total *n*	Painful DPN, *n* (%)	aPR (95% CI)
Total	938	386 (41.2)	
Obesity			
General obesity measures: BMI, kg/m^2			
BMI at age 20 years	816		
<18.5	59	27 (45.8)	1.06 (0.78; 1.43)
18.5–24	508	221 (43.5)	1 (ref)
25–29	155	58 (37.4)	0.87 (0.69; 1.09)
30–34	61	22 (36.1)	0.85 (0.60; 1.22)
≥35	33	11 (33.3)	0.80 (0.48; 1.31)
BMI at baseline	581		
<25	50	26 (52.0)	1 (ref)
25–29	170	66 (38.8)	0.74 (0.54; 1.03)
30–34	190	76 (40.0)	0.78 (0.57; 1.07)
≥35	171	66 (38.6)	0.76 (0.55; 1.06)
BMI change*	812		
<4	193	72 (37.3)	1 (ref)
4–6	191	79 (41.4)	1.10 (0.86; 1.41)
7–9	146	66 (45.2)	1.21 (0.94; 1.56)
≥10	282	120 (42.6)	1.14 (0.91; 1.44)
Central obesity measures at baseline			
Waist circumference (M/F), cm	937		
<94/80	34	10 (29.4)	1 (ref)
94–102/80–88	109	46 (42.2)	1.42 (0.81; 2.51)
≥102/88	794	329 (41.4)	1.40 (0.83; 2.37)
Waist-to-hip ratio (M/F)	937		
<0.95/0.85	99	34 (34.3)	1 (ref)
0.95–0.99/0.85–0.89	182	74 (40.7)	1.18 (0.86; 1.64)
1–1.04/0.90–0.94	311	124 (39.9)	1.17 (0.87; 1.59)
≥1.05/0.95	345	153 (44.3)	1.31 (0.97; 1.76)
Waist-to-height ratio	929		
<0.5	28	12 (42.9)	1 (ref)
0.5–0.6	277	109 (39.4)	0.92 (0.59; 1.45)
≥0.6	624	262 (42.0)	0.99 (0.64; 1.54)
Nonobesity metabolic lifestyle factors at baseline			
Systolic blood pressure, mmHg	599		
<130	246	91 (37.0)	1 (ref)
≥130	353	152 (43.1)	1.16 (0.94; 1.42)
Diastolic blood pressure, mmHg	599		
<80	224	96 (42.9)	1 (ref)
≥80	375	147 (39.2)	0.94 (0.76; 1.16)
Antihypertensive drug use	938		
No	211	85 (40.3)	1 (ref)
Yes	727	301 (41.4)	1.00 (0.82; 1.21)
Total cholesterol, mmol/L	417		
<4.3	186	63 (33.9)	1 (ref)
≥4.3	231	97 (42.0)	1.25 (0.97; 1.62)
LDL cholesterol, mmol/L	594		
<1.8	159	59 (37.1)	1 (ref)
1.8–2.6	220	89 (40.5)	1.09 (0.84; 1.42)
≥2.6	215	93 (43.3)	1.17 (0.90; 1.52)
HDL cholesterol (M/F))	417		
<1.0/1.2	140	53 (37.9)	1 (ref)
≥1.0/1.2	277	108 (39.0)	1.02 (0.79; 1.32)
Triglycerides, mmol/L	585		
<1.7	248	93 (37.5)	1 (ref)
≥1.7	337	146 (43.3)	1.17 (0.96; 1.44)
Lipid-lowering drug use	938		
No	276	120 (43.5)	1 (ref)
Yes	662	266 (40.2)	0.91 (0.77; 1.08)
Low-grade inflammation (hs-CRP), mg/L†	833		
<1.0	221	89 (40.3)	1 (ref)
1.0–2.9	282	112 (39.7)	0.98 (0.79; 1.22)
≥3.0	330	137 (41.5)	1.03 (0.84; 1.27)

Continued on p. 8

Table 1—Continued

	DPN, total *n*	Painful DPN, *n* (%)	aPR (95% CI)
C-peptide, pmol/L	790		
<850	145	59 (40.7)	1 (ref)
850–1,550	385	160 (41.6)	1.03 (0.82; 1.29)
≥1,550	260	106 (40.8)	1.00 (0.79; 1.28)
HbA_{1c}, mmol/mol‡	630		
<48	314	126 (40.1)	1 (ref)
48–57	173	77 (44.5)	1.13 (0.91; 1.40)
58–67	65	29 (44.6)	1.13 (0.83; 1.54)
68–77	36	10 (27.8)	0.73 (0.42; 1.27)
≥78	42	17 (40.5)	1.08 (0.72; 1.62)
Physical activity, baseline, days/week§	938		
0	195	83 (42.6)	1.00 (0.83; 1.21)
1–2	209	76 (36.4)	0.85 (0.69; 1.04)
≥3	534	227 (42.5)	1 (ref)
Physical activity, change‖	926		
Decreased activity	331	139 (42.0)	0.93 (0.77; 1.12)
No change	253	114 (45.1)	1 (ref)
Increased activity	342	126 (36.8)	0.82 (0.67; 0.99)
Smoking, baseline	608		
Never	245	91 (37.1)	1 (ref)
Former	229	101 (44.1)	1.18 (0.95; 1.47)
Current	134	57 (42.5)	1.17 (0.90; 1.51)
Smoking change¶	131		
Questionnaire 2016: discontinued	19	7 (36.8)	1 (ref)
Questionnaire 2016: continued	112	49 (43.8)	1.26 (0.67; 2.36)
Alcohol (M/F), baseline#	938		
≤21/14	872	352 (40.4)	1 (ref)
>21/14	66	34 (51.5)	1.31 (1.01; 1.69)

All estimates are adjusted for age, sex, and diabetes duration. M/F, male/female; ref, reference. *BMI change from age 20 years to questionnaire 2016. †hs-CRP values >10 mg/L were excluded in order to exclude values reflecting ongoing infections. ‡Results for HbA_{1c}, unit %, are available in Supplementary Table 7. §Days per week with minimum 30 min of physical activity. ‖Change from baseline to questionnaire 2016 in the number of days per week with minimum 30 min of physical activity: decreased activity, at least 1 day less per week with >30 min of physical activity; increased activity, at least 1 day more per week with minimum 30 min of physical activity. ¶Among those who were current users at baseline. #Units of alcohol (male/female); the maximum safe amount recommended by the Danish Health Authority when the DD2 began enrollment.

and we observed no clear association of neuropathic pain with the metabolic syndrome. Notably, we found clear evidence that high alcohol intake, tobacco smoking, and failure to increase activity after diabetes diagnosis associated with higher prevalence of painful DPN. These results are extremely important, as all three risk factors are modifiable without requiring medications.

Compared with previous studies of obesity (6,8,9,17,30), we additionally found that central fat distribution is associated with DPN independent of BMI. In line with this observation, we found increased DPN prevalence with metabolic factors closely associated with central obesity, including low-grade inflammation and C-peptide as a marker of insulin resistance (12,31). On the contrary, other studies have linked insulin deficiency with DPN (32,33). A recent study by Zaharia et al. (33) suggested that a diabetes phenotype with less obesity, higher HbA_{1c} values, and more insulin deficiency but without autoimmunity (severe insulin-deficient diabetes) ($n = 28$) associated with increased DPN risk compared with four other clusters, paradoxically including also that of insulin deficiency with coexisting autoimmunity. Further studies are thus needed to clarify the exact association between insulin levels and DPN. Although associated with DPN, insulin resistance, HbA_{1c}, and low-grade inflammation did not seem to associate with neuropathic pain in our study, whereas Doupis et al. (15) previously reported an association of increased CRP in painful versus nonpainful DPN. Also, studies of diabetic animal populations and of human populations without diabetes have suggested a role of inflammatory markers in painful polyneuropathy (34). Future studies of painful DPN in type 2 diabetes should investigate a broader range of inflammatory markers in addition to hs-CRP.

The finding that lower HDL cholesterol associates with DPN was also recently reported in the Anglo-Danish-Dutch study of Intensive Treatment of Diabetes in Primary Care (ADDITION) cohort with screen-detected type 2 diabetes (8) and in most studies of long-standing diabetes (3,9,14). In contrast to our results, lower LDL cholesterol also predicted DPN in the ADDITION cohort (8) and was associated with peripheral nerve damage in another type 2 diabetes study (35). The authors speculated whether this might result from statin treatment (8) or impaired peripheral nerve regeneration with insufficient cholesterol supply (35).

Previous smaller studies of patients with type 2 diabetes have not found an association of hypertension and DPN (6,8,9,14,36). Well-controlled blood pressure in our cohort may have masked an association between DPN and hypertension, which might be supported by our higher DPN prevalence seen among patients on antihypertensive drugs.

Current, former, and continued smoking versus cessation associated with both DPN and neuropathic pain. The latter may possibly reflect detrimental effects from higher cumulative smoke exposure (dose and time), whereas cessation could

possibly reverse smoke-induced nerve damage. A recent meta-analysis reported only low-grade evidence for smoking as a DPN risk factor (37); however, previous studies often merged former and never smokers as reference group, which may have masked any association (37). Since peripheral arterial disease is smoking related and may also cause pain and positive answers to some of the MNSIq questions, we cannot exclude that we overestimate the associations with smoking due to a mix of DPN with peripheral arterial disease. Thus, a post hoc analysis showed that smoking was strongly associated with MNSIq question 12, "Do your legs hurt when you walk?" with aPRs of 1.84 (95% CI 1.59; 2.13) for current and 1.44 (95% CI 1.26; 1.65) for former smokers (data not shown). On the other hand, post hoc restriction of our DPN analyses to patients without a prior history of peripheral arterial disease, or alternatively adjusting for peripheral arterial disease in the model, only reduced the associations of smoking with DPN and painful DPN very slightly (data not shown). Finally, we cannot exclude that reverse causation, i.e., tobacco smoking as self-medication for pain, may explain part of the association with painful DPN.

The fact that high alcohol intake at baseline (defined as >21/14 units for males/females) but not as defined at the later questionnaire (>14/7 units for males/females) (17) associated with neuropathic pain may suggest a dose-response relationship.

New and promising research advocates physical exercise for preventing and treating DPN (38). This is in line with our observation that DPN associated with low baseline physical activity and that increased physical activity after baseline related to reduced DPN prevalence among those with low baseline level and with reduced neuropathic pain prevalence. We cannot exclude the possibility of reverse causation, i.e., that absence of DPN symptoms may have led to more physical activity. Future intervention studies are needed to clarify any preventive or therapeutic role of physical activity against DPN.

This study included patients with early diabetes, which is relevant when determining correlative features that might emerge as possible preventive measures. The median 2.8 years time frame from baseline cohort enrollment until DPN assessment implies that DPN cases were a mixture of new incident and preexisting prevalent DPN. Of note, our findings were robust in the subcohort with very short diabetes duration at baseline, who more likely had new incident DPN at later follow-up, thus more closely mimicking a longitudinal study. This strengthens our conclusions and suggests potential interventional measures.

Our study also has limitations. First, DPN and painful DPN assessment relied on the MNSIq and DN4 questionnaires and not on neurological examinations, nerve conduction studies, or validated small-fiber measures. This leads to a DPN and neuropathic pain assessment at the level of "possible" (22–24). However, both tools are validated (21,26). Although MNSIq sensitivity is rather low (40% in a study of long-standing type 1 diabetes patients [21]) for measures of relative risk, high specificity leads to unbiased results in comparative analyses and is thus more important than sensitivity (39). Overlap of pain-related questions in the MNSIq (i.e., question 2, "Do you ever have any burning pain in your legs and/or feet?") with questions on pain in the DN4 may have mitigated our possibility of discrimination between nonpainful and painful DPN (17). This may have impeded our ability to identify risk factors specifically associated with painful DPN. Second, despite the time elapse since patient characteristics were determined at baseline until DPN assessment a median of 2.8 years later, our main analyses reflect a cross-sectional study design due to the unknown DPN and pain status at baseline. This leads to intrinsic uncertainty about temporal relationships and the possibility for reverse causality for some associations. Third, self-reported BMI and other factors may be subject to recall errors. There is evidence that self-reported anthropometric data are reasonably accurate and adequate for use in large epidemiological studies (40). Finally, it is a limitation that some variables were only available for a subcohort of patients.

In conclusion, these data provide evidence that DPN in early type 2 diabetes is closely associated with specific risk factors in addition to hyperglycemia, including metabolic syndrome factors, insulin resistance, and low-grade inflammation. Moreover, unhealthy lifestyle habits, including smoking and physical inactivity, are modifiable factors strongly associated with DPN. Pain occurrence in DPN may share some, but not all, of these modifiable risk factors. Future longitudinal studies should further investigate specific risk factors for DPN and painful DPN and the clinical effects of improving such factors.

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