The Contemporary Prevalence of Diabetic Neuropathy in Type 1 Diabetes: Findings From the T1D Exchange

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OBJECTIVE

To evaluate the contemporary prevalence of diabetic peripheral neuropathy (DPN) in participants with type 1 diabetes in the T1D Exchange Clinic Registry throughout the U.S.

RESEARCH DESIGN AND METHODS

DPN was assessed with the Michigan Neuropathy Screening Instrument Questionnaire (MNSIQ) in adults with ≥5 years of type 1 diabetes duration. A score of ≥4 defined DPN. Associations of demographic, clinical, and laboratory factors with DPN were assessed.

RESULTS

Among 5,936 T1D Exchange participants (mean ± SD age 39 ± 18 years, median type 1 diabetes duration 18 years [interquartile range 11, 31], 55% female, 88% non-Hispanic white, mean glycated hemoglobin [HbA_{1c}] 8.1 ± 1.6% [65.3 ± 17.5 mmol/mol]), DPN prevalence was 11%. Compared with those without DPN, DPN participants were older, had higher HbA_{1c}, had longer duration of diabetes, were more likely to be female, and were less likely to have a college education and private insurance (all $P < 0.001$). DPN participants also were more likely to have cardiovascular disease (CVD) ($P < 0.001$), worse CVD risk factors of smoking ($P = 0.008$), hypertriglyceridemia ($P = 0.002$), higher BMI ($P = 0.009$), retinopathy ($P = 0.004$), reduced estimated glomerular filtration rate ($P = 0.02$), and Charcot neuroarthropathy ($P = 0.002$). There were no differences in insulin pump or continuous glucose monitor use, although DPN participants were more likely to have had severe hypoglycemia ($P = 0.04$) and/or diabetic ketoacidosis ($P < 0.001$) in the past 3 months.

CONCLUSIONS

The prevalence of DPN in this national cohort with type 1 diabetes is lower than in prior published reports but is reflective of current clinical care practices. These data also highlight that nonglycemic risk factors, such as CVD risk factors, severe hypoglycemia, diabetic ketoacidosis, and lower socioeconomic status, may also play a role in DPN development.

Diabetic neuropathy is a prevalent complication in patients with diabetes and a major cause of morbidity and mortality (1). Among the various forms of diabetic neuropathy, distal symmetric polyneuropathy (DPN) and diabetic autonomic neuropathies are by far the most studied (1).

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DPN is one of the most important causes of foot ulceration (2) and lower extremity amputations in the U.S. Patients with DPN and prior lower-extremity amputations have a 50% higher risk for losing a second limb within the next 2 years and 5-year survival rates that are substantially lower than age- and sex-matched patients with diabetes without DPN (1–3). DPN has multiple other consequences, such as major impact on impaired daily function through small- and large-nerve fiber dysfunction, as well as loss of sensory perception, including proprioception, temperature discrimination, and pain, all of which ultimately lead to unsteadiness; recurrent minor injuries, with an increased risk of falls and fractures (1,4); impact on daily function (1,4); impaired control of the accelerator pedal while driving (5); poor oral health (6); and poor quality of life (1,7). Thus, the clinical and socioeconomic costs of DPN are staggering.

Prior estimates of the incidence and prevalence of DPN in the adult population with type 1 diabetes have been obtained through interventional and observational studies, including the follow-up of the Diabetes Control and Complications Trial/Epidemiology and Diabetes Interventions and Complications (DCCT/EDIC) or the Epidemiology of Diabetes Complications Study (EDC) cohorts, and these estimates vary greatly (1,8,9). Yet, there are continuous changes in the standard of care and differences in the access to medical care across the U.S. (10). Thus the objectives of this study were to assess the contemporary prevalence of and potential risk factors and comorbidities for DPN in U.S. adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Participants and Data Source

The T1D Exchange Clinic Network includes >80 U.S.-based pediatric and adult endocrinology practices. Details on eligibility criteria, the informed consent process, and data collection have been published previously (11). More than 25,000 individuals with type 1 diabetes were enrolled between September 2010 and August 2012. Core data were updated annually from medical record data extraction. This study targeted U.S. adults ≥18 years with ≥5 years type 1 diabetes duration, participating and receiving care from a clinic participating in the T1D Exchange Clinic Network. This report includes data on all adult participants from those sites in the T1D Exchange Clinic Network who met inclusion criteria and who completed the Michigan Neuropathy Screening Instrument questionnaire (MNSIQ) between April 2016 and April 2018.

Demographic data on sex, race/ethnicity, insurance, annual household income, education level, smoking status, the occurrence of severe hypoglycemia (SH), defined as seizure and/or loss of consciousness, in the prior 3 months, and the occurrence of diabetic ketoacidosis (DKA) in the prior 3 months were collected through comprehensive participant questionnaires. Information about age, diabetes duration, diabetes control as estimated from the HbA_{1c} levels, insulin treatment (insulin pump or multiple daily injections), use of a continuous glucose monitor (CGM), blood pressure, height, weight, smoking status, chronic complications, serum creatinine level, retinopathy, cardiovascular disease (CVD), lipid levels, and use of medications were obtained as part of usual care and were collected from clinic medical records.

Assessment of DPN

Evaluation of the presence of DPN was performed with the MNSIQ, which includes 15 self-administered "yes" or "no" questions on foot sensation, including pain, numbness, and temperature sensitivity, that is scored by summing responses that show an abnormality (12). A score of ≥4, which has been validated to be specific and sensitive for the presence of DPN (13), was used to define the presence of DPN. A secondary outcome of painful DPN was defined as selection of "yes" to the MNSIQ question: "Do you ever have any burning pain in your legs and/or feet?" Calculation of estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration equation (14).

Statistical Analysis

Stepwise logistic regression models were used to assess the association between DPN and age, sex, race/ethnicity, diabetes duration, HbA_{1c}, education level, insurance type, smoking status, geographical region, BMI, height, diastolic and systolic blood pressure, total daily insulin, CGM use, insulin pump use, LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and triglycerides. Logistic regression models were used to assess the association between DPN and the following medications, medical conditions, measurements and events, adjusting for covariates that remain in the above stepwise regression model: statin medication use; ACE inhibitor/angiotensin II receptor blocker (ARB) medication use; presence of retinopathy, foot ulcers, Charcot neuroarthropathy, carpal tunnel, and CVD (defined as history of coronary artery disease, myocardial infarction, atherosclerotic peripheral vascular disease and heart failure); eGFR; occurrence of one or more SH events; and occurrence of one or more DKA events.

Stepwise logistic regression models were used to assess the association between painful DPN and sex, HbA_{1c}, BMI, LDL-C, HDL-C, and triglycerides. The association between painful DPN and the following medical conditions, measurements, and events were assessed through logistic regression models adjusted for covariates that remain in the prior stepwise regression model: presence of foot ulcers, Charcot arthropathy, carpal tunnel, CVD, eGFR, occurrence of one or more SH events, and occurrence of one or more DKA events.

If a lipid or blood pressure covariate was selected from stepwise regression, then statin medication use also was included as a covariate in the respective logistic regression model. Multiple comparisons were corrected using the adaptive Benjamini-Hochberg false discovery rate correction method (15). Results are expressed as mean ± SD for normally distributed variables or median and interquartile range (IQR) for nonnormally distributed variables. Data analyses were performed using SAS 9.4 software. All *P* values are two-sided.

RESULTS

Baseline Characteristics

Data were obtained from 5,936 eligible T1D Exchange participants from 63 sites across the U.S. As reported in Table 1, mean age of responders was 39 ± 18 years, 55% were women, and 88% were non-Hispanic white. The median duration of type 1 diabetes was 18 (IQR 11, 31) years, and the mean HbA_{1c} was 8.1 ± 1.6% (65.3 ± 17.7 mmol/mol). An insulin pump was used by 66% of participants and a CGM by 31%. In this cohort, 67% had at least an associate degree, 56% had an annual income of ≥$75,000, and 80% had access to private insurance (Table 1).

Prevalence and Characteristics of Participants With and Without DPN

The overall prevalence of MNSIQ-defined DPN based on a score of ≥4 was 11%. Compared with participants without DPN, participants with DPN were older (51 ± 17 vs. 37 ± 17 years, $P < 0.001$), had longer type 1 diabetes duration (median 32 vs. 17 years, $P < 0.001$), and had a higher mean HbA_{1c} (8.4 ± 1.7% vs. 8.1 ± 1.6% [68.4 ± 18.6 vs. 64.9 ± 17.6 mmol/mol], $P < 0.001$), as reported in Table 1. Within different age strata, DPN prevalence increased with age, ranging from 4% in those 18–25

Table 1—Characteristics of T1D Exchange Registry cohort

Characteristic	Overall (N = 5,936)	No DPN (n = 5,306)	MNSIQ-DPN (n = 630)	P value†
Age (years)	39 ± 18	37 ± 17	51 ± 17	<0.001
Female*	55	54	60	<0.001
Race/ethnicity*				0.05
Non-Hispanic white	88	88	89	
Non-Hispanic black	3	3	5	
Hispanic/Latino	5	6	3	
Other race/ethnicity	3	3	3	
Highest education level*				<0.001
Less than high school graduate	3	2	5	
High school graduate/GED	31	29	40	
Associate or bachelor degree	42	43	37	
Master, professional, or doctorate degree	25	25	17	
Annual household income*				
<$50,000	29	27	47	
$50,000 to <$75,000	15	15	15	
≥$75,000	56	59	38	
Insurance*				<0.001
Private insurance	80	83	58	
Other insurance	19	17	42	
No insurance	<1	<1	<1	
Type 1 diabetes duration (years)*	18 (11, 31)	17 (11, 29)	32 (17, 43)	<0.001
HbA_{1c} (%)*	8.1 ± 1.6	8.1 ± 1.6	8.4 ± 1.7	<0.001
HbA_{1c} (mmol/mol)*	65.3 ± 17.7	64.9 ± 17.6	68.4 ± 18.6	<0.001
Total daily insulin use (units/kg)*	0.7 ± 0.3	0.7 ± 0.3	0.6 ± 0.3	0.93
BMI (kg/m^2)*	27.2 ± 5.3	27.0 ± 5.2	28.5 ± 6.1	0.009
Systolic blood pressure (mmHg)*	123 ± 14	123 ± 14	127 ± 17	0.40
Diastolic blood pressure (mmHg)*	73 ± 10	73 ± 9	71 ± 10	0.54
eGFR ($mL \cdot min^{-1}/1.73\ m^2$)*	94.8 ± 28.5	97.0 ± 27.6	79.3 ± 30.3	0.02
Triglycerides (mg/dL)*	98 ± 68	96 ± 65	115 ± 86	0.002
HDL-C (mg/dL)*	62 ± 19	63 ± 19	61 ± 18	0.49
LDL-C (mg/dL)*†	92 ± 29	93 ± 29	89 ± 33	0.38
Total cholesterol (mg/dL)*	173 ± 36	173 ± 36	173 ± 39	
Medication use				
ACE inhibitor/ARB*	26	24	45	0.74
Statin	35	32	62	0.009
Smokers*	4	4	8	0.008
Retinopathy	24	21	47	0.004
Charcot neuroarthropathy	<1	<1	4	0.002
CVD	7	5	24	0.002
Insulin pump use*	66	67	62	0.70
CGM use*	31	32	27	0.10
Subjects with ≥1 SH events‡	7	7	14	0.04
Subjects with ≥1 DKA events*§	3	3	7	<0.001

All data are presented as the mean ± SD, median (25th, 75th quartiles), or percentage of participants. *Sex missing for 8 participants, race/ethnicity missing for 15 participants, education level missing for 314 participants, annual household income missing for 1,435 participants, insurance missing for 159 participants, type 1 diabetes duration missing for 1 participant, HbA_{1c} missing for 988 participants, total daily insulin use missing for 2,682 participants, BMI missing for 720 participants, systolic and diastolic blood pressure missing for 136 participants, eGFR missing for 2,326 participants, triglycerides missing for 2,465 participants, HDL-C missing for 2,436 participants, LDL-C missing for 2,180 participants, total cholesterol missing for 3,118 participants, ACE inhibitor/ARB use missing for 15 participants, smoking status missing for 216 participants, pump use status missing for 82 participants, CGM use status missing for 156 participants, and DKA events missing for 5 participants. †From a logistic regression model adjusting for age, sex, HbA_{1c}, diabetes duration, level of education, insurance, smoking status, BMI, height, triglycerides, and statin use. P values were adjusted for multiple comparisons via the adaptive false discovery rate correction procedure. ‡Defined as self-report of a severe hypoglycemia event in the past 3 months. §Defined as self-report of a DKA event in the past 3 months.

years old, to 8% in those 26–49 years old, and to 21% in participants >50 years. DPN participants were also more likely to be women (60% vs. 54%, $P < 0.001$), have lower eGFR (79.3 ± 30.3 vs. 97.0 ± 27.6 mL • min^{-1}/1.73 m^2, $P = 0.02$), and have higher BMI (28.5 ± 6.1 vs. 27.0 ± 5.2, $P = 0.009$) than non-DPN participants (Table 1). Women had a DPN prevalence of 12% compared with 9% in men. There were no differences in insulin pump or CGM use between the two groups (Table 1). Occurrence of an SH event (14% in participants with DPN vs. 7% in those without, $P = 0.04$) and a DKA event (7% in participants with DPN vs. 3% in those without, $P < 0.001$) in the past 3 months were both more common in DPN participants compared with non-DPN participants (Table 1). Prevalence of gastroparesis was higher in participants with DPN than in participants with no DPN regardless of whether or not they had a DKA or SH event (data not shown).

DPN participants had a high prevalence of comorbid CVD compared with non-DPN participants (24% vs. 5%, $P = 0.002$). Several cardiovascular risk factors were associated with DPN, including higher triglycerides (115 ± 86 vs. 96 ± 65 mg/dL, $P = 0.002$) and higher rates of smoking (8% vs. 4%, $P = 0.008$), as reported in Table 1. Odds ratios (OR) of the association of various factors with DPN are shown in Fig. 1.

Novel findings in these analyses highlight the impact of socioeconomic factors on the risk of DPN, including race/ethnicity (black vs. white, OR 1.95 [95% CI 1.11–3.42]), lower education (OR 1.15, [95% CI 1.08–1.23]), and lack of private insurance (other insurance vs. private insurance; OR 1.89 [95% CI 1.46–2.44]) (Fig. 1). Income was evaluated but not included as a possible covariate in the stepwise regression model due to the presence of missing responses and moderate correlation with education.

Painful DPN and Neuropathy Pain Medication Use

Lastly, we evaluated the phenotypes of painful DPN in this cohort. Of the 630 participants with DPN, 427 (68%) reported burning foot pain and were designated as painful DPN. Compared with painless DPN, participants with painful DPN had higher HbA_{1c} (8.5 ± 1.8% vs 8.2 ± 1.6% [69.3 ± 19.2 vs. 66.4 ± 17.1 mmol/mol], $P = 0.04$) (Table 2) but no other differences between groups were found.

Of the 630 MNSIQ-defined DPN participants, 182 (29%) were taking medications for neuropathy (data not shown). Evaluated medications included amitriptyline, gabapentin, duloxetine, and nortriptyline.

CONCLUSIONS

In this study we assessed the prevalence of DPN and painful DPN in a large cohort of patients with type 1 diabetes in the U.S. By using a validated survey questionnaire, we found a DPN prevalence of 11% after a median of 32 years of diabetes duration. Risk factors for DPN in this cohort include traditional DPN risk factors such as older age, longer duration of diabetes, poor glycemic control, female sex, other microvascular complications, established CVD, and CVD risk factors, including BMI, smoking history, and high triglycerides. However, the analyses also unveiled a strong association of DPN with acute diabetes complications, including SH events and DKA events, as well as a correlation between DPN and several socioeconomic factors. Neither of these associations was described before. To our knowledge, this study, which includes >5,900 participants, is the largest study of DPN prevalence in a contemporary population of adults with type 1 diabetes.

Prior interventional and observational studies evaluating DPN in type 1 diabetes, including the DCCT/EDIC, EDC, and EURODIAB, found prevalence rates up to 34% after an average of 25 years of diabetes duration (1,8,9,16,17). The DCCT/EDIC played a pivotal role in our understanding of metabolic memory, which highlighted the importance of early tight glycemic control in patients with type 1 diabetes (9). However, no recent studies have looked at the contemporary prevalence of DPN in a large cohort of adults with type 1 diabetes in the post-DCCT era reflecting contemporary practices of clinical care. Using the MNSIQ, a survey tool previously found to be reliable for assessment of DPN symptoms in patients with type 1 diabetes, we found a prevalence of 11%, which is lower than prior reported prevalence rates for similar diabetes duration, including the DCCT/EDIC cohort. This may be related to the younger age of the cohortg with type 1 diabetes in the T1D Exchange Clinic Registry or to the lower sensitivity of this screening instrument, considering that DPN in the DCCT and EDIC studies was defined using either a comprehensive outcome that included symptoms, clinical signs as documented by a board-certified neurologist and electrodiagnostic criteria in several peripheral nerves, or the entire MNSI that included the questionnaire and the clinical examination (9). The more recent SEARCH for Diabetes in Youth Study, evaluating the prevalence and risk factors for DPN in youth and adolescents with type 1 diabetes, found a DPN prevalence of 7% in participants with an average age of 21 years, which is in line with our age-stratified DPN prevalence of 4% in 18–25-year-olds (18).

Similar to DCCT/EDIC or other prior observational cohorts, including the Pittsburgh EDC and the EURODIAB Prospective Complications studies, we found that DPN prevalence rates were associated with traditional risk factors including age, duration of diabetes, and glucose control as documented by glycosylated hemoglobin (8,9,16). Additionally, we found associations between DPN and several CVD risk factors, including higher BMI, triglycerides, and cigarette use as well as a clear association between CVD and DPN. The role of traditional CVD risk factors, including higher BMI, triglycerides, and smoking, in the development of DPN in people with type 1 diabetes was first observed in the EURODIAB cohort (19). In later studies, including in cohorts with type 1 diabetes and available sural nerve biopsy specimens, higher triglycerides in particular were shown to be associated with rapid DPN progression as documented by loss of sural nerve myelinated fibers, independent of other DPN risk factors including age, glycemic control, and duration (20). Higher BMI, weight and waist circumference play a pivotal role as risk factors for DPN in patients with metabolic syndrome, prediabetes, and type 2 diabetes as well (18,21). In contrast to the findings in EURODIAB, the Pittsburgh EDC, and SEARCH, we found no association between other lipid parameters and DPN in this cohort (8,18,19). Similarly, we found no associations between systolic or diastolic blood pressure and DPN, although prior studies of cohorts with type 1

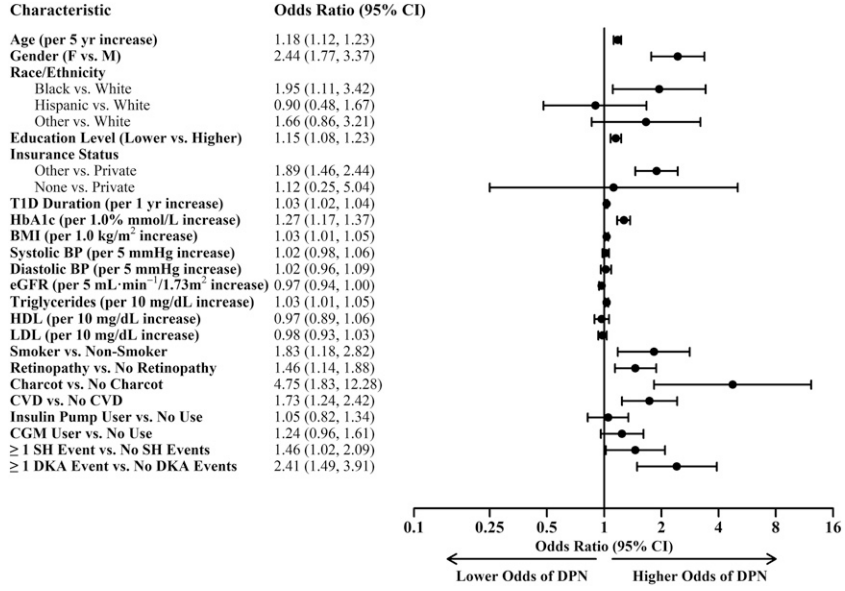

Figure 1—ORs ratios of MNSIQ-defined DPN risk factors were calculated from a logistic regression model adjusting for age, sex, level of education, insurance, diabetes duration, HbA_{1c}, BMI, height, triglycerides, statin use, and smoking status. BP, blood pressure; F, female; M, male; T1D, type 1 diabetes.

diabetes have found associations between hypertension and DPN (8,18,19). Not unexpectedly, we also found associations between DPN and other microvascular complications, including retinopathy and Charcot arthropathy, which is also in concert with the findings reported by Tesfaye et al. (16) in the EURODIAB cohort.

Although the associations of DPN with the more traditional risk factors described above was expected, this study unveiled several important new findings. The first is a higher prevalence (68%) of painful DPN in this cohort. This is in contrast with prior reports showing in general only up 20–30% of DPN is painful (1,22,23). However, this relatively higher prevalence of painful DPN in this cohort could be due to bias associated with both the self-selection of participants involved in our study as well as the instrument used to diagnose DPN, given that the foot burning pain question is one of the four questions used in outcome definition. As expected, medication use for neuropathic pain was common in this cohort, with 29% of MNSIQ-defined DPN participants using at least one agent for pain.

The next interesting finding is a slightly higher prevalence of DPN in women, irrespective of pain, which has not been found in other large cohorts with type 1 diabetes (8,16,18,24). However, there was a higher rate of responders among women with type 1 diabetes in this survey, which may have contributed. Somewhat unexpectedly, we did not find a female sex predominance of painful DPN. Higher prevalence of pain in general was described in women in many disease states, including in diabetes (25), and prior studies report that women with diabetes experience more severe pain despite milder nerve injury (26). Our findings are also in contrast to prior reports in cohorts with diabetes in the U.K. and Canada (27,28).

Another important finding that has emerged is the association between DPN and acute diabetes complications, including both SH and DKA events within the past 3 months. This finding highlights a potential relationship between DPN and glycemic variability, which was suggested by prior findings in smaller cohorts (29,30), although not documented in DCCT/EDIC (31). However, glucose variability in the DCCT/EDIC study was derived from the 7-point glucose profile, because no CGM data were available. A more recent study evaluating CGM-derived indices of glycemic variability in relationship to DPN as measured by nerve conduction studies demonstrated that the mean amplitude of glycemic excursions was strongly associated with medial plantar neuropathy (32). Larger observational studies with more stringent measures of glycemic variability are needed to confirm these observations. Interestingly, participants with DPN were also more likely to have gastroparesis. Although correlations DPN and forms of autonomic neuropathy, including gastroparesis, may

Table 2—Characteristics of participants with and without painful DPN

	Painful DPN (n = 427)	Painless DPN (n = 203)	P value*
Age (years)	52 ± 16	51 ± 19	
Female sex	62	57	0.21
HbA_{1c} (%)†	8.5 ± 1.8	8.2 ± 1.6	0.04
HbA_{1c} (mmol/mol)†	69.3 ± 19.2	66.4 ± 17.1	0.04
BMI (kg/m^2)†	28.6 ± 6.2	28.2 ± 5.9	0.55
Triglycerides (mg/dL)†	122 ± 95	100 ± 57	0.11
HDL-C (mg/dL)†	61 ± 18	62 ± 18	0.64
LDL-C (mg/dL)†	91 ± 35	83 ± 28	0.47
Total cholesterol (mg/dL)†	177 ± 40	163 ± 35	
eGFR (mL • min^{-1}/1.73 m^2)†	81.1 ± 29.2	75.2 ± 32.3	0.24
Foot ulcers	<1	2	0.56
Charcot neuroarthropathy	3	6	0.47
CVD	22	28	0.08
Subjects with ≥1 SH events‡	14	14	0.77
Subjects with ≥1 DKA events†§	8	4	0.12

All data are presented as mean ± SD or percentage of participants. *From a logistic regression model adjusting for HbA_{1c}, triglycerides, and statin medications. P values were corrected for multiple comparisons via the adaptive false discovery rate correction procedure. †HbA_{1c} missing for 115 participants, BMI and weight missing for 98 participants, triglycerides missing for 242 participants, HDL-C missing for 245 participants, LDL-C missing for 211 participants, total cholesterol missing for 355 participants, eGFR missing for 173 participants, and DKA missing for 1 participant. ‡Defined as self-eport of a severe hypoglycemia event in the past 3 months. §Defined as self-report of a DKA event in the past 3 months.

reflect a more advanced disease associated with both small-and large-fiber dysfunction, fluctuations in blood glucose levels in both hypo- and hyperglycemic range have been shown to directly affect gastric emptying (33), potentially explaining these findings.

Furthermore, here we report associations between elements of socioeconomic status and DPN. Not surprisingly, we found that DPN prevalence was associated with markers of lower socioeconomic status, including lower education levels and more reliance on public insurance options. The impact of the social determinants on diabetes self-management and glycemic control in diabetes is emerging as an important theme, particularly in the U.S., due to the rising costs of insulin and the resulting deliberate underuse of insulin (34). The association between the social determinants of health and markers of microvascular and cardiovascular complications has been explored in pediatric poulations with type 1 diabetes and in a Scottish cohort of adults with type 1 diabetes, and there appears to be an adverse relationship (35–37); however, this topic needs further exploration in the adult population with type 1 diabetes in the U.S. The prospective German Diabetes Study, which aims to evaluate nonglycemic risk factors for progression of complications, including socioeconomic and psychosocial factors, may provide more clarity in the future (38).

Our study has several limitations. The first is that the T1D Exchange is not a true population-based cohort of all patients with type 1 diabetes, a limitation that has been well-described in prior publications (11), although >63 U.S. diabetes clinics, both academic and private, are represented in this current study, reflective of contemporary diabetes care practices across the U.S. This has the potential to underestimate the MSNIQ-defined DPN prevalence found in these analyses because certain demographics may not be adequately represented. This study, for example, found that the lack of private insurance is associated with MNSIQ-defined DPN; however, 80% of this survey's participants had private insurance, which is higher than other cohorts of patients with type 1 diabetes that reported insurance information (39,40). Furthermore, the MNSIQ survey responders were self-selected to participate in this study, which also limits the generalizability of our findings. However, even though estimated frequencies and prevalence of MNSIQ-defined DPN and various factors could be over- or underestimates, this is unlikely to affect the interpretation of associations between one variable and another (11).

Another limitation is the measurement of DPN in this cohort. While the MNSIQ has been found to be a reliable screening method for DPN in DCCT/EDIC and other large cohorts, prior studies reported only 40% sensitivity for the ≥4 threshold on the survey for detecting DPN (13). Indeed, based on a sensitivity analysis using cutoffs of ≥2 and ≥3 on the MNSIQ, the prevalence may be as high as 17–39%; however, the number of false positives likely also rises. Furthermore, being a symptom-based questionnaire, it is possible that we missed individuals with DPN with less severe neuropathy symptoms or those who may present with clinical findings in the absence of any symptoms that would have been picked up with the examination portion of the full MNSI instrument. This is the rationale behind referring to MNSI-defined DPN as MNSI questionnaire or "MNSIQ-defined DPN," although it may be more appropriate to call these participants "symptomatic DPN" participants (13). In terms of classification of painful and painless DPN, the symptom-based MSNIQ questionnaire also has the ability to overestimate painful neuropathy, which may be contributing to the high prevalence of painful DPN in this cohort. Although we found that the use of several medications, including duloxetine, pregabalin, gabapentin, or tricyclic antidepressants commonly prescribed for neuropathic pain, was high in MNSIQ-defined DPN participants, we recognize that these agents may be used for a variety of different conditions, including treatment of depression or seizure disorders, so the frequency of use of these agents may be overestimated in our cohort.

Finally, this current study is cross-sectional, and therefore, we cannot assume any causality for our associations between the risk factors reported and the presence of DPN. Nonetheless, this study of >5,900 participants is the largest study to date to evaluate the prevalence of DPN in type 1 diabetes.

In summary, in this large cohort with type 1 diabetes, a DPN prevalence of 11% is markedly lower compared with prior published studies in earlier cohorts, suggesting potential beneficial effects of the improvement in the clinical care and risk factor control in the U.S. adult population with type 1 diabetes. Although we confirmed expected associations between DPN and traditional glycemic and vascular risk factors, we have also found associations with novel nonglycemic DPN risk factors, such as CVD risk factors, both SH and DKA, potentially reflecting effects of glycemic variability, and lower socioeconomic status, highlighting the importance of social determinants of health in patients with type 1 diabetes. This emphasizes the importance of ongoing research for more disadvantaged populations with type 1 diabetes.

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