Risk Factors for Diabetic Peripheral Neuropathy and Cardiovascular Autonomic Neuropathy in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study

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COMPLICATIONS

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study demonstrated that intensive glucose control reduced the risk of developing diabetic peripheral neuropathy (DPN) and cardiovascular autonomic neuropathy (CAN). We evaluated multiple risk factors and phenotypes associated with DPN and CAN in this large, well-characterized cohort of participants with type 1 diabetes, followed for >23 years. DPN was defined by symptoms, signs, and nerve conduction study abnormalities in ≥2 nerves; CAN was assessed using standardized cardiovascular reflex tests. Generalized estimating equation models assessed the association of DPN and CAN with individual risk factors measured repeatedly. During DCCT/EDIC, 33% of participants developed DPN and 44% CAN. Higher mean HbA_{1c} was the most significant risk factor for DPN, followed by older age, longer duration, greater height, macroalbuminuria, higher mean pulse rate, β-blocker use, and sustained albuminuria. The most significant risk factor for CAN was older age, followed by higher mean HbA_{1c}, sustained albuminuria, longer duration of type 1 diabetes, higher mean pulse rate, higher mean systolic blood pressure, β-blocker use, estimated glomerular filtration rate <60 mL/min/1.73 m^2, higher most recent pulse rate, and cigarette smoking. These findings identify risk factors and phenotypes of participants with diabetic neuropathy that can be used in the design of new interventional trials and for personalized approaches to neuropathy prevention.

Diabetic peripheral neuropathy (DPN) and cardiovascular autonomic neuropathy (CAN) are prevalent and costly complications of diabetes affecting up to 50% of patients with diabetes worldwide (1,2). DPN and CAN are also most challenging chronic complications given the independent risk for mortality, foot complications including lower limb amputations, severe pain, falls and fractures, arrhythmia, heart failure, and direct impact on daily function and quality of life (1,3–6). Although the increase in diabetes prevalence is largely driven by the increase in type 2 diabetes, type 1 diabetes prevalence and incidence has also increased worldwide, as evidenced in recent U.S. reports from the National Health and Nutrition Examination Survey (NHANES) and the SEARCH for Diabetes in Youth study (7–9). With the persistent increase in diabetes prevalence and incidence (10), neuropathy impacts medical care across a spectrum of providers, yet, to date, disease-modifying therapies are not available. Furthermore, the field has witnessed a decline in the interest of pharmaceutical companies to develop novel and effective therapies for neuropathy.

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The Diabetes Control and Complications Trial (DCCT) study demonstrated in participants with type 1 diabetes that intensive glucose control, with lower hemoglobin A_{1c} (HbA_{1c}) levels, reduced the risk of DPN and CAN by 64% and 45%, respectively, over an average follow-up of 6.5 years (11). Moreover, the prevalence and incidence of DPN and CAN increased in both treatment groups through 14–17 years of observational follow-up in the Epidemiology of Diabetes Interventions and Complications (EDIC) study; however, these remained significantly lower in the intensive group compared with the conventional group (11,12).

The objective of the current study was to identify clinical and biochemical risk factors for DPN and CAN, independent of glycemia, in the large, well-characterized DCCT/EDIC cohort of participants with type 1 diabetes. Through its unparalleled wealth of clinical and biochemical evaluations obtained continuously for over 30 years, including sensitive and standardized DPN and CAN assessments, the DCCT/EDIC study provides a unique opportunity to comprehensively identify risk factors and phenotypes, associated both independently and jointly, with DPN and CAN.

RESEARCH DESIGN AND METHODS

Participants

The DCCT enrolled 1,441 participants with type 1 diabetes who were randomly assigned to either intensive or conventional diabetes therapy and followed for a mean of 6.5 years (13). Intensive therapy ($n = 711$) aimed to achieve near-normal glucose and HbA_{1c} levels while conventional therapy ($n = 730$) was designed to prevent symptoms of hypo- or hyperglycemia with no glucose targets but an HbA_{1c} target level <13.5% (13). Two parallel cohorts were recruited: the primary prevention cohort ($n = 726$, no retinopathy or kidney disease at baseline) and the secondary intervention cohort ($n = 715$, with mild-to-moderate nonproliferative retinopathy and urinary albumin excretion <200 mg/24 h). Baseline exclusion criteria included hypertension, hyperlipidemia, cardiovascular disease, neuropathy requiring medical intervention, and recurrent severe hypoglycemia.

Participants who were originally assigned to receive conventional therapy were taught and encouraged to adopt intensive therapy, and both original treatment groups returned to their own health care providers for ongoing diabetes care. In 1994, 96% of the surviving DCCT cohort enrolled in the EDIC observational study, an ongoing, long-term follow-up (14) of the DCCT cohort. The present analyses focus on the data obtained during the combined DCCT and EDIC study, up to the last complete DPN and CAN evaluations conducted in EDIC year 16/17 (2009/2010), for a mean total DCCT/EDIC study period of 23 years.

Risk Factors

Risk factors were assessed by standardized methods during DCCT and EDIC (14,15). Annual visits included a detailed medical history assessing demographic and behavioral risk factors and medical outcomes, and a physical examination with measurements of height, weight, waist circumference (only during EDIC), sitting blood pressure, and pulse rate (14,15). Insulin doses were self-reported and expressed as the average total daily dose in units per kilogram of body weight. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, documented hypertension, or the use of antihypertensive medications, and hyperlipidemia as LDL cholesterol ≥130 mg/dL or the use of lipid-lowering medications. Concurrent medication usage was collected during EDIC but not during the DCCT. Therefore, during the DCCT, hypertension and hyperlipidemia were defined using only elevated blood pressures and lipids.

HbA_{1c} was measured by high-performance liquid chromatography quarterly during DCCT and annually during EDIC. Fasting lipids and albumin excretion rates (AER) were measured annually during DCCT and on alternate years during EDIC. AER was measured from 4-h urine samples using fluoroimmunoassay from DCCT baseline to EDIC year 18 and subsequently from spot urine samples, with AER estimated using the ratio of urine albumin and creatinine concentrations (16). The DCCT/EDIC central biochemistry laboratory performed all laboratory measurements with standardized methods and long-term controls to guard against assay drift. LDL cholesterol was calculated using the Friedewald equation (17).

Estimated glomerular filtration rates (eGFR) were calculated from serum creatinine measured annually using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Kidney disease was defined as an eGFR <60 mL/min/1.73 m^2, microalbuminuria (AER ≥30 mg/24 on ≥2 consecutive visits), or macroalbuminuria (AER ≥300 mg/24). Standardized stereoscopic seven-field fundus photographs were obtained every 6 months during DCCT, and in one-fourth of the cohort annually during EDIC and graded centrally using the final Early Treatment of Diabetic Retinopathy Study (ETDRS) severity grading scale (18). Proliferative diabetic retinopathy was defined as 61/<61 or greater on the ETDRS scale or pan-retinal photocoagulation and clinically significant macular edema as focal photocoagulation or treatment with anti–vascular endothelial growth factor at any point during the DCCT/EDIC study.

Neuropathy Outcomes

DPN was formally assessed twice during the DCCT (baseline, year 5) and once during EDIC (year 13/14). The primary outcome for DPN was confirmed clinical neuropathy, requiring at least two abnormal findings among symptoms, sensory signs, or reflex changes consistent with a distal symmetrical polyneuropathy as assessed by a qualified neurologist, plus abnormal nerve conduction studies involving two or more nerves among the median (motor or sensory), peroneal, and sural nerves (11). The DPN outcome was sensitive to detection of primarily large- or mixed small- and large-fiber neuropathies. CAN was assessed up to five times during DCCT (baseline, years 2, 4, 6, and 8) and twice

during EDIC (years 13/14 and 16/17) with R-R response to paced breathing, Valsalva maneuver, and postural changes in blood pressure under standardized conditions, as previously described (3,12). All subjects were required to fast and avoid caffeine and tobacco products, as well as prescription and over-the-counter medications (except for their usual insulin regimen), for at least 8 h prior to CAN testing. Presence of CAN was defined as either an R-R variation <15 or an R-R variation 15–19.9 in combination with a Valsalva ratio ≤ 1.5 or a decrease of >10 mmHg in DBP during 10 min of standing (3). Participants with at least two DPN ($n = 1{,}386$) or two CAN ($n = 1{,}434$) assessments during DCCT/EDIC were included in the analyses. DPN and CAN measurements overlapped twice during the study: DCCT baseline and EDIC year 13/14.

Statistical Considerations

Candidate risk factors were grouped into 11 blocks (Supplementary Table 1) as performed in other DCCT/EDIC studies of risk factors (19–21). All covariates were measured either concurrently with the neurology assessment or within the closest visit window preceding the respective DPN or CAN assessment. For these analyses, given the known association with DPN, height was added to the second block of candidate risk factors (Demographic Physical). Generalized estimating equation (GEE) models were used to evaluate the association of neuropathy (DPN or CAN) with individual risk factors over repeated time points.

A comprehensive multivariable GEE regression model was evaluated for both DPN and CAN using similar model-building techniques previously described by the DCCT/EDIC study (19). Given the large number of risk factors, variables were entered into the GEE model one block at a time in the order displayed in Supplementary Table 1. After each block was added, a variable was deleted if it was not nominally significant ($P < 0.10$) (19). After the last block was entered, the final multivariable model was fit using the selected covariates and variables significant at $P < 0.05$ were retained. Height and weight were more strongly associated with DPN than BMI in both unadjusted and minimally adjusted models. Given its strong dependence on height and weight, BMI was not entered into the model with the second block of candidate risk factors. Similarly, pulse pressure was not entered into the model with the fifth block of variables since it is a function of both SBP and DBP.

A sensitivity analysis was conducted, using a backward elimination modeling technique, where variables significant at $P < 0.10$ were retained at each step (see Supplementary Data). The odds ratios (ORs) and unsigned covariate Z-test value are presented, the latter to differentiate covariate effects with $P < 0.0001$ (two-sided), equivalent to a $|Z| \geq 3.89$.

Each risk factor could be included in the model as a fixed baseline covariate (e.g., baseline HbA_{1c}), time-dependent covariate using the most recent measurement (e.g., current HbA_{1c}), or time-dependent covariate using the updated mean of all follow-up values since randomization (e.g., updated mean HbA_{1c} representing the cumulative mean of prior HbA_{1c} values up to each visit). To account for different measurement frequencies of HbA_{1c} during DCCT (every 3 months) and EDIC (every 12 months), the updated mean was computed by weighting each value by the time interval since the last measurement. All analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

Data and Resource Availability

Data collected for the study are available to the public through the National Institute of Diabetes and Digestive and Kidney Disease repository (https://repository.niddk.nih.gov/home/).

RESULTS

Over 23 years of mean follow-up, 33% of participants developed DPN and 44% CAN. At baseline, 90% of the cohort had neither DPN nor CAN; 5% had DPN only, 4% had CAN only, and 1% had both. By EDIC year 13/14, 54% of the cohort had no neuropathy; 13% had DPN only, 16% had CAN only, and 16% had both.

At DCCT baseline, 53% of the participants were men, median age was 27 years, duration of diabetes was 4 years, HbA_{1c} was 8.80% (73 mmol/mol), and 18% were smokers. The baseline characteristics of the DCCT/EDIC cohort among those who did and did not develop DPN at any time during the study are shown in Table 1. The baseline characteristics for participants who did and did not develop CAN are presented in Table 2. Nominally significant baseline factors that were associated with higher odds of DPN at any time during DCCT/EDIC included male sex, older age, greater height, weight, and BMI in both men and women, moderate or strenuous physical activity, family history of type 2 diabetes, higher SBP and DBP, higher pulse rate, higher total cholesterol, triglycerides, and LDL cholesterol levels, longer duration of type 1 diabetes, higher HbA_{1c} levels independent of treatment assignment, as well as randomization to conventional versus intensive treatment and inclusion in the secondary prevention versus primary intervention cohort. Most of these risk factors were also associated with higher odds of CAN at any time during DCCT/EDIC, with the exception of sex, height, physical activity, and HDL cholesterol. In addition, cigarette smoking and occasional or regular alcohol use (Table 2) at the onset of the DCCT were associated with CAN.

Time-Dependent Characteristics

The longitudinal ORs for DPN and CAN per unit change in the current or the updated mean value of each time-dependent covariate, without adjustments, are shown in Supplementary Table 2. During follow-up, greater weight and BMI, higher SBP and DBP and pulse pressure, higher pulse rate, higher total cholesterol, triglycerides, and LDL cholesterol levels, higher HbA_{1c}, and a higher prevalence of

Table 1—DCCT baseline characteristics of participants according to the presence or absence of any DPN over the duration of the DCCT/EDIC study, through EDIC year 13/14

	Overall	No	Yes	Per unit change	OR (95% CI)	*P* value
N	1,386	931	455			
Design						
Treatment group (% conventional)	51	48	57	Conventional vs. intensive	1.56 (1.26, 1.93)	0.0001
Cohort (% secondary)	51	45	61	Secondary vs. primary	1.90 (1.53, 2.36)	<0.0001
Physical						
Sex (% men)	52	49	60	Men vs. women	1.51 (1.21, 1.88)	0.0002
Age (years)	27 (22, 32)	26 (21, 32)	29 (24, 34)	5 years	1.30 (1.21, 1.41)	<0.0001
Adult (% ≥18 years)	87	84	91	≥18 vs. <18 years	1.83 (1.28, 2.63)	0.0009
Height (cm)	171 (164, 179)	170 (163, 177)	174 (167, 182)	5 cm	1.20 (1.13, 1.27)	<0.0001
Weight men (kg)	74 (67, 82)	73 (66, 80)	78 (70, 85)	5 kg	1.19 (1.11, 1.27)	<0.0001
Weight women (kg)	62 (56, 69)	61 (55, 68)	64 (58, 70)	5 kg	1.20 (1.10, 1.32)	<0.0001
BMI men (kg/m^2)	24 (22, 25)	23 (21, 25)	24 (22, 26)	1 kg/m^2	1.08 (1.02, 1.14)	0.0052
BMI women (kg/m^2)	23 (21, 25)	23 (21, 25)	23 (22, 25)	1 kg/m^2	1.09 (1.03, 1.15)	0.0021
Behavioral						
Cigarette smoker (%)	18	18	20	Yes vs. no	1.23 (0.94, 1.60)	0.1358
Occasional or regular alcohol use (%)	22	20	24	Yes vs. none	1.23 (0.95, 1.59)	0.1107
Moderate or strenuous activity (%)	70	68	74	Yes vs. sedentary	1.31 (1.03, 1.66)	0.0264
Family history						
Hypertension (%)	56	54	58	Yes vs. no	1.16 (0.93, 1.44)	0.1872
Myocardial infarction (%)	49	47	52	Yes vs. no	1.18 (0.95, 1.46)	0.1366
Type 1 diabetes (%)	14	14	15	Yes vs. no	1.22 (0.90, 1.66)	0.2041
Type 2 diabetes (%)	9	8	12	Yes vs. no	1.44 (1.04, 2.00)	0.0292
Blood pressure						
SBP (mmHg)	114 (106, 122)	112 (106, 120)	116 (110,124)	5 mmHg	1.11 (1.06, 1.17)	<0.0001
DBP (mmHg)	72 (68, 80)	70 (66, 78)	76 (68, 80)	5 mmHg	1.16 (1.09, 1.24)	<0.0001
Pulse pressure (mmHg)	40 (34, 48)	40 (34, 48)	40 (36, 48)	5 mmHg	1.03 (0.98, 1.09)	0.2658
Pulse rate (bpm)	76 (68, 84)	76 (68, 82)	76 (70, 84)	1 bpm	1.02 (1.01, 1.03)	<0.0001
Lipids						
Total cholesterol (mg/dL)	174 (152, 196)	172 (152, 194)	176 (155, 202)	10 mg/dL	1.05 (1.02, 1.08)	0.0038
Triglycerides (mg/dL)	70 (55, 93)	69 (54, 92)	73 (57, 98)	10 mg/dL	1.03 (1.01, 1.05)	0.0032
HDL cholesterol (mg/dL)	49 (42, 57)	50 (42, 58)	47 (41, 56)	10 mg/dL	0.92 (0.84, 1.00)	0.0614
LDL cholesterol (mg/dL)	106 (90, 127)	104 (89, 125)	110 (92, 131)	10 mg/dL	1.06 (1.02, 1.10)	0.0011
History of diabetes						
Duration of type 1 diabetes (years)	4 (2, 9)	4 (2, 8)	6 (3, 10)	1 year	1.08 (1.06, 1.11)	<0.0001
Stimulated C-peptide (nmol/L·100)						
Duration <5 years	12 (4, 25)	12 (4, 26)	13 (4, 24)	1 year	0.99 (0.98, 1.01)	0.3172
Duration ≥5 years	3 (3, 4)	3 (3, 4)	3 (3, 3)	1 year	1.01 (0.97, 1.05)	0.6864
Insulin dose (units/kg/day)	0.64 (0.50, 0.80)	0.64 (0.50, 0.81)	0.63 (0.49, 0.77)	1 unit/kg/day	0.88 (0.57, 1.35)	0.5552
HbA_{1c} (%)	8.80 (7.84, 10.08)	8.63 (7.70, 9.74)	9.20 (8.23, 10.60)	1%	1.31 (1.22, 1.40)	<0.0001
HbA_{1c} (mmol/mol)	72.7 (62.2, 86.7)	70.8 (60.7, 83.0)	77.1 (66.5, 92.4)	1 mmol/mol	1.31 (1.22, 1.40)	<0.0001

Data are based on 1,386 participants with at least two DPN assessments during DCCT/EDIC. Medians (first quartile, third quartile) or % are presented. ORs and *P* values were generated using GEE models with no adjustment for other factors.

hypertension and hyperlipidemia, medication use, and kidney disease were all significantly associated with higher odds of DPN and CAN. DPN was also significantly associated with greater height and lower HDL cholesterol while CAN was associated with cigarette smoking, sedentary activity, and higher daily insulin dose.

Minimally Adjusted Baseline and Time-Dependent Covariate Effects

After adjustment for age and updated mean HbA_{1c}, the following risk factors were significantly associated with higher odds of DPN: secondary prevention versus primary intervention cohort, male sex, greater height, weight, and BMI, higher SBP and DBP and pulse pressure, higher pulse rate, higher triglycerides, lower HDL cholesterol, longer duration of type 1 diabetes, higher daily insulin dose, a higher prevalence of hypertension, and any kidney disease (Table 3). Total cholesterol, LDL cholesterol, and hyperlipidemia were no longer significantly associated with odds of DPN after adjustment for age and updated mean HbA_{1c}.

For CAN, secondary prevention versus primary intervention cohort, greater BMI, behavioral risk factors (cigarette smoking, alcohol use, sedentary activity), higher SBP and DBP and pulse pressure, higher pulse rate, higher total cholesterol and triglycerides levels, longer duration of type 1 diabetes, higher daily insulin dose, a higher prevalence of hypertension and hyperlipidemia, and any kidney disease were associated with higher odds of CAN after adjustment for age and updated mean HbA_{1c} (Table 3). LDL cholesterol was no longer significant after adjustment for age and updated mean HbA_{1c}.

The use of ACE inhibitors and β-adrenoceptor blocking medications (β-blockers) during EDIC was significantly associated with higher odds of DPN and CAN.

Final Multivariate Models

The final multivariable GEE models for DPN and CAN, with covariates listed in order of the unsigned covariate *Z*-test values (or *P* values) to designate relative importance in the models, are shown in Table 4. For DPN, higher mean HbA_{1c} was the most significant risk factor (OR = 1.63 per 1 HbA_{1c} percentage point, 95% CI 1.51, 1.77, $Z = 11.81$, $P < 0.0001$), followed closely by older age (OR = 1.42 per 5 years, 95% CI 1.30, 1.55, $Z = 8.05$, $P < 0.0001$). Other nominally significant factors, in order of significance, were longer duration of type 1 diabetes ($Z = 7.66$, $P < 0.0001$), greater height ($Z = 7.31$, $P < 0.0001$), presence of any AER ≥300 mg/24 hour ($Z = 4.12$, $P < 0.0001$), higher mean pulse rate ($Z = 3.92$, $P < 0.0001$), β-blocker use ($Z = 3.38$, $P = 0.0007$), and presence of any sustained AER ≥30 mg/24 hour ($Z = 2.76$, $P = 0.0058$).

In the multivariable GEE model for CAN (Table 4), older age (OR 1.50 per 5 years, 95% CI 1.39, 1.62, $Z = 10.43$, $P < 0.0001$) was the most significant risk factor, followed by higher mean HbA_{1c} (OR 1.27 per 1 HbA_{1c} percentage point, 95% CI 1.17, 1.37, $Z = 6.04$, $P < 0.0001$). Other nominally significant factors, in order of significance, were presence of any sustained AER ≥30 mg/24 h ($Z = 5.96$, $P < 0.0001$), longer duration of type 1 diabetes ($Z = 5.73$, $P < 0.0001$), higher mean pulse rate ($Z = 4.62$, $P < 0.0001$), higher mean SBP ($Z = 3.75$, $P = 0.0002$), β-blocker use ($Z = 3.60$, $P = 0.0003$), presence of eGFR <60 mL/min/1.73 m^2 ($Z = 3.51$, $P = 0.0005$), higher pulse rate ($Z = 2.84$, $P = 0.0045$), and cigarette smoking ($Z = 2.28$, $P = 0.0226$).

A sensitivity analysis was conducted starting with the complete set of variables in the model and using a backward elimination approach to select covariates (Supplementary Table 3). This technique selected a similar set of covariates for the DPN with the exception that mean pulse rate and any sustained AER ≥30 mg/24 h were not included in the backward elimination model while mean daily insulin dose and sex were marginally significant. For CAN, mean SBP was not included in the backward elimination model whereas the most recent AER was as a continuous measurement.

Supplementary Table 4 presents the final model build for DPN and CAN including variables for diabetic retinopathy. In both models, a similar set of risk factors was retained in the final selection in addition to any proliferative diabetic retinopathy for both DPN and CAN and any clinically significant macular edema for CAN.

DISCUSSION

These analyses provide a thorough evaluation of numerous clinical features and risk factors, considered alone and jointly, associated with DPN and CAN in a large cohort of participants with type 1 diabetes who have been phenotyped with detailed and standardized neuropathy evaluations and risk factors obtained longitudinally over more than 20 years. Retention has been extremely high, and we have demonstrated high prevalence rates for both DPN (33%) and CAN (44%), which continued to rise over the duration of the study. Given the persistent increase in diabetes prevalence and incidence, these findings impact medical care across a spectrum of providers including general practitioners, internal medicine physicians, endocrinologists, neurologists, cardiologists, gastroenterologists, and pain specialists.

We have previously reported that intensive diabetes therapy achieving lower glucose control markedly reduced the risk of DPN and CAN during the DCCT compared with conventional therapy (13,22), an effect that persisted through much of EDIC follow-up (3,11). In concert with these prior reports, the data reported here underscore the important role of ongoing glycemic management. In multivariable models, higher mean HbA_{1c} was the most significant risk factor for DPN and strongly associated with CAN.

Beyond glycemia and diabetes duration, our results confirm strong associations with kidney disease and elevated blood pressure for both DPN and CAN, in age and glucose adjusted models. Thirty years ago, the Pittsburgh Epidemiology of Diabetes Complications study, involving 400 participants with type 1 diabetes, reported a cross-sectional

Table 2—DCCT baseline characteristics of participants according to the presence or absence of any CAN over the course of the DCCT/EDIC study, through EDIC year 16/17

	Overall	No	Yes	Per unit change	OR (95% CI)	*P* value
N	1,434	803	631			
Design						
Treatment group (% conventional)	51	49	53	Conventional vs. intensive	1.36 (1.11, 1.66)	0.0025
Cohort (% secondary)	50	44	57	Secondary vs. primary	1.72 (1.41, 2.10)	<0.0001
Physical						
Sex (% men)	53	54	52	Men vs. women	0.92 (0.75, 1.13)	0.4286
Age (years)	27 (22, 32)	26 (21, 31)	29 (23, 34)	5 years	1.39 (1.29, 1.50)	<0.0001
Adult (% ≥18 years)	86	83	91	≥18 vs. <18 years	2.03 (1.45, 2.85)	<0.0001
Height (cm)	171 (164, 179)	171 (164, 178)	171 (164, 180)	5 cm	1.02 (0.97, 1.07)	0.4951
Weight men (kg)	74 (67, 82)	73 (66, 81)	76 (69, 84)	5 kg	1.14 (1.07, 1.21)	<0.0001
Weight women (kg)	62 (56, 69)	61 (55, 68)	63 (57, 69)	5 kg	1.09 (1.01, 1.18)	0.0251
BMI men (kg/m^2)	24 (22, 25)	23 (21, 25)	24 (22, 26)	1 kg/m^2	1.10 (1.04, 1.15)	0.0004
BMI women (kg/m^2)	23 (21, 25)	23 (21, 25)	23 (21, 25)	1 kg/m^2	1.07 (1.02, 1.12)	0.0107
Behavioral						
Cigarette smoker (%)	18	16	21	Yes vs. no	1.77 (1.38, 2.28)	<0.0001
Occasional or regular alcohol use (%)	22	19	24	Yes vs. none	1.31 (1.03, 1.65)	0.0261
Moderate or strenuous activity (%)	70	67	73	Yes vs. sedentary	1.23 (0.98, 1.53)	0.0698
Family history						
Hypertension (%)	56	55	58	Yes vs. no	1.22 (1.00, 1.50)	0.0528
Myocardial infarction (%)	49	49	49	Yes vs. no	1.00 (0.81, 1.22)	0.9666
Type 1 diabetes (%)	14	14	15	Yes vs. no	1.07 (0.80, 1.43)	0.6297
Type 2 diabetes (%)	9	8	11	Yes vs. no	1.54 (1.12, 2.11)	0.0073
Blood pressure						
SBP (mmHg)	114 (106, 122)	112 (106, 120)	116 (108, 122)	5 mmHg	1.07 (1.03, 1.12)	0.0021
DBP (mmHg)	72 (68, 80)	72 (66, 80)	74 (68, 80)	5 mmHg	1.13 (1.07, 1.20)	<0.0001
Pulse pressure (mmHg)	40 (34, 48)	40 (35, 48)	40 (34, 48)	5 mmHg	1.00 (0.95, 1.05)	0.9673
Pulse rate (bpm)	76 (68, 84)	74 (68, 80)	78 (72, 84)	1 bpm	1.03 (1.02, 1.04)	<0.0001
Lipids						
Total cholesterol (mg/dL)	174 (152, 196)	171 (150, 195)	177 (156, 201)	10 mg/dL	1.09 (1.06, 1.12)	<0.0001
Triglycerides (mg/dL)	70 (55, 94)	68 (54, 90)	72 (56, 98)	10 mg/dL	1.04 (1.02, 1.06)	0.0002
HDL cholesterol (mg/dL)	49 (42, 58)	50 (42, 58)	48 (42, 57)	10 mg/dL	0.99 (0.91, 1.07)	0.7660
LDL cholesterol (mg/dL)	107 (91, 127)	104 (88, 125)	110 (92, 130)	10 mg/dL	1.10 (1.06, 1.13)	<0.0001
History of diabetes						
Duration of type 1 diabetes (years)	4 (2, 9)	4 (2, 8)	5 (2, 10)	1 year	1.07 (1.05, 1.10)	<0.0001
Stimulated C-peptide (nmol/L·100)						
Duration <5 years	12 (4, 25)	12 (4, 24)	13 (5, 27)	1 year	1.00 (0.99, 1.01)	0.4487
Duration ≥5 years	3 (3, 4)	3 (3, 4)	3 (3,3)	1 year	0.99 (0.95, 1.03)	0.6122
Insulin dose (units/kg/day)	0.64 (0.50, 0.80)	0.65 (0.50, 0.82)	0.63 (0.50, 0.79)	1 unit/kg/day	0.79 (0.52, 1.20)	0.2679
HbA_{1c} (%)	8.80 (7.82, 10.10)	8.64 (7.70, 9.81)	9.00 (8.01, 10.30)	1%	1.25 (1.18, 1.33)	<0.0001
HbA_{1c} (mmol/mol)	72.7 (62.0, 86.9)	70.9 (60.7, 83.7)	74.9 (64.7, 89.1)	1 mmol/mol	1.25 (1.18, 1.33)	<0.0001

Data are based on 1,434 participants with at least two CAN assessments during DCCT/EDIC. Medians (first quartile, third quartile) or % are presented. ORs and *P* values were generated using GEE models with no adjustment for other factors.

association of hypertension with DPN (23) and CAN (24). This was later confirmed in prospective analyses (25,26). Other studies of individuals with type 1 diabetes including the European Diabetes Prospective Complications Study (EURODIAB) (27) and the SEARCH for Diabetes in Youth study (28) have reported similar findings for DPN and/or CAN. In addition, hypertension is closely linked with kidney disease in type 1 diabetes (26). The current analyses suggest that hypertension and kidney disease (higher AER and lower eGFR) are independently associated with DPN and CAN. The mechanisms linking hypertension to DPN are unclear but may involve a complex set of pathways interlinking nerve function and energy production with a dysfunctional neural vascular supply (29).

Table 3—ORs for DPN and CAN per unit change in each baseline or time-dependent covariate in separate longitudinal GEE models, minimally adjusted for age and updated mean HbA_{1c}

		DPN		CAN	
	*	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Design					
Treatment group (conventional vs. intensive)	B	1.05 (0.83, 1.32)	0.7022	1.12 (0.91, 1.38)	0.2883
Cohort (secondary vs. primary)	B	2.07 (1.66, 2.57)	<0.0001	1.81 (1.49, 2.21)	<0.0001
Physical					
Sex (men vs. women)	B	1.51 (1.21, 1.88)	0.0003	0.85 (0.70, 1.04)	0.1164
Adult (≥18 vs. <18 years)	B	1.05 (0.66, 1.67)	0.8291	0.76 (0.50, 1.16)	0.1997
Height (per 5 cm)	C	1.21 (1.14, 1.28)	<0.0001	0.96 (0.91, 1.01)	0.1134
Weight (per 5 kg)	C	1.09 (1.06, 1.13)	<0.0001	1.02 (0.99, 1.05)	0.1299
Mean weight (per 5 kg)	M	1.12 (1.08, 1.17)	<0.0001	1.02 (0.98, 1.06)	0.2686
BMI (per 1 kg/m^2)	C	1.02 (1.00, 1.05)	0.0612	1.03 (1.01, 1.04)	0.0079
Mean BMI (per 1 kg/m^2)	M	1.04 (1.01, 1.07)	0.0090	1.03 (1.01, 0.106)	0.0174
Behavioral					
Cigarette smoker (yes vs. no)	C	0.98 (0.75, 1.29)	0.8932	1.39 (1.10, 1.76)	0.0057
Occasional or regular alcohol use (yes vs. none)	C	1.14 (0.93, 1.41)	0.2158	0.85 (0.72, 1.00)	0.0462
Moderate or strenuous activity (yes vs. sedentary)	C	1.08 (0.89, 1.31)	0.4471	0.86 (0.74, 1.00)	0.0543
Family history					
Hypertension (yes vs. no)	B	1.17 (0.94, 1.46)	0.1514	1.25 (1.03, 1.53)	0.0276
Myocardial infarction (yes vs. no)	B	1.17 (0.94, 1.45)	0.1503	0.97 (0.80, 1.19)	0.7897
Type 1 diabetes (yes vs. no)	B	1.15 (0.83, 1.57)	0.4048	0.95 (0.71, 1.28)	0.7468
Type 2 diabetes (yes vs. no)	B	1.22 (0.87, 1.73)	0.2544	1.22 (0.89, 1.66)	0.2164
Blood pressure					
SBP (per 5 mmHg)	C	1.08 (1.04, 1.12)	0.0003	1.09 (1.06, 1.13)	<0.0001
Mean SBP (per 5 mmHg)	M	1.17 (1.10, 1.24)	<0.0001	1.24 (1.17, 1.30)	<0.0001
DBP (per 5 mmHg)	C	1.07 (1.01, 1.13)	0.0184	1.05 (1.00, 1.09)	0.0462
Mean DBP (per 5 mmHg)	M	1.21 (1.11, 1.32)	<0.0001	1.21 (1.11, 1.31)	<0.0001
Pulse pressure (per 5 mmHg)	C	1.07 (1.02, 1.12)	0.0035	1.11 (1.07, 1.14)	<0.0001
Pulse rate (per 1 bpm)	C	1.01 (1.00, 1.02)	0.0048	1.03 (1.03, 1.04)	<0.0001
Mean pulse rate (per 1 bpm)	M	1.03 (1.02, 1.04)	<0.0001	1.07 (1.06, 1.09)	<0.0001
Hypertension (yes vs. no)	C	2.03 (1.56, 2.64)	<0.0001	1.94 (1.61, 2.34)	<0.0001
Medications					
ACE inhibitor use (yes vs. no)	C	1.54 (1.20, 1.97)	0.0008	1.51 (1.25, 1.82)	<0.0001
ARB use (yes vs. no)	C	1.24 (0.87, 1.77)	0.2438	1.45 (1.13, 1.87)	0.0038
β-Blocker use (yes vs. no)	C	2.88 (1.79, 4.64)	<0.0001	2.77 (1.95, 3.92)	<0.0001
Calcium channel blocker use (yes vs. no)	C	1.41 (0.88, 2.26)	0.1524	1.70 (1.21, 2.40)	0.0022
Lipid-lowering agent use (yes vs. no)	C	1.15 (0.89, 1.48)	0.2740	1.36 (1.12, 1.65)	0.0020
Lipids					
Total cholesterol (per 10 mg/dL)	C	0.98 (0.95, 1.01)	0.1607	1.00 (0.98, 1.02)	0.9612
Mean total cholesterol (per 10 mg/dL)	M	1.02 (0.98, 1.05)	0.4334	1.06 (1.02, 1.10)	0.0027
Triglycerides (per 20% increase mg/dL)	C	1.06 (1.02, 1.10)	0.0054	1.07 (104, 1.10)	<0.0001
Mean triglycerides (per 20% increase mg/dL)	M	1.09 (1.04, 1.15)	<0.0001	1.14 (1.09, 1.18)	<0.0001
HDL cholesterol (per 10 mg/dL)	C	0.89 (0.83, 0.93)	0.0034	0.96 (0.91, 1.01)	0.1113
Mean HDL cholesterol (per 10 mg/dL)	M	0.88 (0.81, 0.96)	0.0052	0.95 (0.88, 1.03)	0.2238
LDL cholesterol (per 10 mg/dL)	C	0.98 (0.95, 1.01)	0.1804	0.99 (0.96, 1.02)	0.4320
Mean LDL cholesterol (per 10 mg/dL)	M	1.02 (0.98, 1.06)	0.4137	1.04 (1.00, 1.08)	0.0719
Hyperlipidemia (yes vs. no)	C	1.02 (0.83, 1.26)	0.8568	1.27 (1.08, 1.51)	0.0052
History of diabetes					
Duration of type 1 diabetes (per 1 year)	B	1.11 (1.08, 1.13)	<0.0001	1.09 (1.06, 1.12)	<0.0001
Stimulated C-peptide (per 1 nmol/L*100)					
Duration <5 years	B	0.99 (0.98, 1.00)	0.1345	1.00 (0.98, 1.01)	0.7650
Duration ≥5 years	B	1.00 (0.96, 1.05)	0.8726	0.98 (0.94, 1.02)	0.3685
Insulin dose (per 1 unit/kg/day)	C	1.19 (0.82, 1.73)	0.3718	1.26 (0.99, 1.62)	0.0648
Mean insulin dose (per 1 unit/kg/day)	M	2.07 (1.25, 3.43)	0.0046	1.88 (1.18, 3.00)	0.0083
Kidney disease					
eGFR (per 5 mL/min/1.73 m^2)	C	0.93 (0.90, 0.97)	<0.0001	0.92 (0.90, 0.95)	<0.0001
eGFR <60 mL/min/1.73 m^2 (yes vs. no)	C	2.56 (1.36, 4.80)	0.0034	5.95 (3.36, 10.52)	<0.0001
Any eGFR <60 mL/min/1.73 m^2 (yes vs. no)	A	2.44 (1.45, 4.10)	0.0007	3.24 (2.12, 4.99)	<0.0001

Continued on p. 1007

Table 3—Continued

	*	DPN		CAN	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
AER (per 20% increase mg/24 h)	C	1.06 (1.04, 1.07)	<0.0001	1.06 (1.04, 1.07)	<0.0001
Sustained AER ≥30 mg/24 h (yes vs. no)	C	2.45 (1.89, 3.17)	<0.0001	2.36 (1.86, 3.00)	<0.0001
Any sustained AER ≥30 mg/24 h (yes vs. no)	A	2.50 (1.98, 3.15)	<0.0001	2.87 (2.32, 3.53)	<0.0001
AER ≥300 mg/24 h (yes vs. no)	C	3.81 (2.42, 6.01)	<0.0001	3.25 (2.17, 4.87)	<0.0001
Any AER ≥300 mg/24 h (yes vs. no)	A	4.02 (2.81, 5.75)	<0.0001	3.30 (2.36, 4.59)	<0.0001
Hypoglycemia					
Coma and/or seizure (yes vs. no)	C	1.09 (0.61, 1.97)	0.7636	1.03 (0.73, 1.45)	0.8697
Requiring assistance (yes vs. no)	C	1.36 (0.96, 1.92)	0.0837	1.13 (0.88, 1.45)	0.3264

Data are based on 1,386 participants with at least two DPN assessments or 1,434 participants with at least two CAN assessments during DCCT/EDIC. ORs and *P* values were generated using GEE models, adjusting for age and updated mean HbA_{1c}. Triglyceride and AER values were log transformed, and the ORs are presented per 20% increase in the covariate (1.2^{β}). ARB, angiotensin II receptor blocker. *B, baseline value; C, current value; M, updated mean value; A, cumulative incidence (e.g., any use). Covariates classified as C, M, and A enter into the analyses as time-dependent covariates.

In our multivariable GEE regression analyses, height was retained in the final model. The unadjusted and minimally adjusted associations between height and weight, separately, with DPN ($P < 0.0001$ for both) were much stronger than the association between BMI and DPN ($P = 0.0497$) (Table 3). We therefore decided to keep both height and weight in the second block during the multivariable modeling process, and we removed BMI. The adverse influence of increasing height on peripheral nerve function is well known and attributed in part to the tapering of axon diameter at a given distance from the cell body (30,31).

After adjusting for age and glucose control, elevated triglycerides were a risk factor for DPN and CAN, while lower HDL cholesterol levels increased DPN risk and higher total cholesterol levels increased CAN risk. Our findings are in agreement with other studies identifying dyslipidemia as a risk factor in the development and progression of CAN (24,27,28) and DPN (23,27). Traditionally, elevated triglycerides, in concert with low HDL cholesterol, are highly prevalent in type 2 diabetes. However, with the contemporary changes in clinical phenotypes in individuals with type 1 diabetes, particularly with the increase in overweight and obese individuals, metabolic syndrome and associated dyslipidemia are now more prevalent in type 1 diabetes as well (28). Observational evidence also suggests that lowering triglyceride levels with fibrates may delay development of DPN (32). The role of dyslipidemia is further supported by recent work in experimental diabetes where tissue-specific changes in fatty acid metabolism are associated with DPN, independent of glycemic control (33).

Occasional or regular alcohol use did not increase the risk of DPN over the course of the DCCT/EDIC study in any of the models despite previous research demonstrating that alcohol is a peripheral neurotoxicant (34). One study of the relationship between peripheral neuropathy and nutritional status in individuals with chronic alcohol abuse demonstrated that the total lifetime dose of alcohol is an essential independent factor for acquiring an alcohol-related peripheral neuropathy, usually after a cumulative exposure exceeding about 15 kg alcohol/kg body weight (34). In the DCCT/EDIC, the measure of alcohol use was likely imprecise to determine an effect on DPN.

Cigarette smoking has generally been considered a risk factor for DPN (35). However, we did not establish smoking as a major risk factor for DPN over the course of DCCT/EDIC study. This observation differs from the results of several other investigations (23,25,27,36) but is consistent with our earlier report that smoking was not associated with confirmed clinical neuropathy during DCCT (11). It is unclear why our results differ from these previous studies; however, our analyses may be limited since the cigarette smoking measurement available in DCCT/EDIC did not quantify pack-years of exposure. However, smoking has been consistently associated with CAN (23,25,27), in line with our current findings.

Other interesting findings of these analyses include the strong associations between both DPN and CAN and the use of β-blocking medications. Among the various classes of medications used to treat individuals with diabetes, β-blockers may directly affect measures of CAN, given their reported blunting effect on heart rate. As such, improvement in heart rate variability would be expected, particularly with β1-selective drugs that may augment vagally mediated heart rate variability (3,37). Although evidence for the benefit of β-blockers in modulating the impaired cardiac autonomic regulation during high sympathetic stress advocates for their use in patients with heart failure and/or post myocardial infarction (38), these agents are not currently recommended for the treatment of CAN (1). The strong association between use of β-blockers and DPN, demonstrated in this study, was not expected. β-Blockers are not first-line drugs in the treatment of hypertension in individuals with type 1 diabetes. Therefore, it is reasonable to assume that these associations do not actually reflect a direct adverse effect on autonomic or peripheral nerve

Table 4—Final multivariable GEE models for DPN and CAN as a function of baseline and time-dependent covariates

DPN	OR (95% CI)	*Z*-test value	*P* value
Mean HbA_{1c} (per 1%)	1.63 (1.51, 1.77)	11.81	<0.0001
Age (per 5 years)	1.42 (1.30, 1.55)	8.05	<0.0001
Duration of type 1 diabetes (per 1 year)	1.10 (1.08, 1.13)	7.66	<0.0001
Height (per 5 cm)	1.27 (1.19, 1.35)	7.31	<0.0001
Any AER ≥300 mg/24 h (yes vs. no)	2.44 (1.60, 3.73)	4.12	<0.0001
Mean pulse rate (per 1 bpm)	1.03 (1.01, 1.04)	3.92	<0.0001
β-Blocker use (yes vs. no)	2.50 (1.47, 4.24)	3.38	0.0007
Any sustained AER ≥30 mg/24 h (yes vs. no)	1.48 (1.12, 1.96)	2.76	0.0058
CAN	**OR (95% CI)**	***Z*-test value**	***P* value**
Age (per 5 years)	1.50 (1.39, 1.62)	10.43	<0.0001
Mean HbA_{1c} (per 1%)	1.27 (1.17, 1.37)	6.04	<0.0001
Any sustained AER ≥30 mg/24 h (yes vs. no)	1.95 (1.57, 2.43)	5.96	<0.0001
Duration of type 1 diabetes (per 1 year)	1.07 (1.05, 1.10)	5.73	<0.0001
Mean pulse rate (per 1 bpm)	1.04 (1.02, 1.06)	4.62	<0.0001
Mean SBP (per 5 mmHg)	1.11 (1.05, 1.17)	3.75	0.0002
β-Blocker use (yes vs. no)	2.01 (1.37, 2.93)	3.60	0.0003
eGFR <60 mL/min/1.73 m^2 (yes vs. no)	2.88 (1.59, 5.19)	3.51	0.0005
Pulse rate (per 1 bpm)	1.02 (1.00, 1.03)	2.84	0.0045
Cigarette smoker (yes vs. no)	1.31 (1.04, 1.66)	2.28	0.0226

Data are based on 1,386 participants with at least two DPN assessments or 1,434 participants with at least two CAN assessments during DCCT/EDIC. Odds ratios and *P* values were generated using GEE models. Covariates are listed in the order of significance as indicated by the *Z*-test value.

function but are likely driven by participants with more advanced disease states and/or overall worse risk factor profiles (e.g., cardiovascular disease, heart failure, coronary artery disease, more severe hypertension) who are prescribed β-blocking agents as second- or third-line therapy. In our multivariable model, many of the same factors were also shown to contribute to DPN and CAN risk, supporting a potential confounding effect of use of β-blocker agents.

One limitation of this study is that during EDIC we only collected information on the use of major classes of medication agents (i.e., β-blockers, ACE inhibitors, angiotensin receptor blockers, statins, etc.). Unfortunately, information on the specific type of agents from each class is not available, preventing more in-depth analyses that could take into account the differential effects of β-blocker groupings. Another study limitation is that in contrast with CAN, DPN was only assessed twice during the DCCT and once again in EDIC. In addition, the concept of small-fiber neuropathy was not well established at the start of the DCCT, and thus currently accepted methods to assess primarily small-fiber dysfunction were not available.

Strengths of the current study include the detailed phenotypic characteristics, including demographics and multiple traditional and diabetes-related risk factors, in addition to the extensive, sensitive, and standardized evaluations of DPN and CAN available longitudinally in this large cohort of participants with type 1 diabetes spanning more than 20 years of follow-up. Different than many other studies of shorter duration and with smaller sample sizes, the DCCT/EDIC study has allowed for a comprehensive multifactorial evaluation of risk factors simultaneously, which is unique.

In summary, in these comprehensive analyses, we found that higher mean HbA_{1c} and older age were the strongest risk factors for both DPN and CAN. Although hyperglycemia is strongly associated with the development of DPN and CAN, we found that other risk factors may be associated as well. Given the oberservational nature of our analyses, the risk factors we have identified are not necessarily causal in their relationship with DPN or CAN. However, we have demonstrated that individuals with more favorable risk factor profiles had lower prevalence of DPN and CAN in this type 1 diabetes population. Beyond the insights into underlying biological mechanisms described above, these findings provide critical information on the spectrum of risk factors and the phenotypes of patients with neuropathy, one of the most challenging diabetes complications. These data can be used in the design of new interventional trials, to stimulate actions to overcome a paradoxical lag in neuropathy-related drug discovery, as well as for

personalized approaches to neuropathy prevention and treatment among individuals with type 1 diabetes.

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