

**Online-Only Supplemental Material**

**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**

This document presents supplemental materials cited in the text of the main manuscript.

**Supplementary Table S1.** Risk factors employed in the analyses by block

**Supplementary Table S2.** Odds ratios for DPN and CAN per unit change in each time-dependent covariate in separate longitudinal GEE models, with no additional adjustments

**Supplementary Table S3.** Multivariable GEE models for DPN and CAN as a function of baseline and time-dependent covariates, using backwards elimination

**Supplementary Table S4.** Final multivariable GEE models for DPN and CAN as a function of baseline and time-dependent covariates, including diabetic retinopathy

SUPPLEMENTARY DATA

**Supplementary Table S1. Risk factors employed in the analyses by block**

Block	Variable	Availability*
1.	<b>Design</b>	
	Treatment group (conventional vs. intensive)	B
	Cohort (secondary vs. primary)	B
	<b><u>Demographic</u></b>	
2.	<b>Physical</b>	
	Sex (men vs. women)	B
	Age (years)	B
	Adult ( $\geq 18$ years vs. $< 18$ )	B
	Height (cm)	B, C†
	Weight (kg)	B, C†, M†
	Weight gain (kg)	C†
	Body mass index ( $\text{kg}/\text{m}^2$ )	B, C†, M†
3.	<b>Behavioral</b>	
	Current cigarette smoker (yes vs. no)	B, C†
	Occasional or regular alcohol use (yes vs. none)	B, C†
	Moderate or strenuous activity (yes vs. sedentary)	B, C†
4.	<b>Family history</b>	
	Family history	
	Hypertension (yes vs. no)	B
	Myocardial infarction (yes vs. no)	B
	Type 1 diabetes (yes vs. no)	B
	Type 2 diabetes (yes vs. no)	B
	<b><u>Traditional</u></b>	
5.	<b>Blood pressure</b>	
	Systolic blood pressure (mm Hg)	B, C†, M†
	Diastolic blood pressure (mm Hg)	B, C†, M†
	Pulse pressure (mm Hg)	B, C†
	Pulse (bpm)	B, C†, M†
	Hypertension (yes vs. no)	B, C†
6.	<b>Medications</b>	
	ACE inhibitor use (yes vs. no)	C‡
	ARB use (yes vs. no)	C‡
	$\beta$ -blocker use (yes vs. no)	C‡
	Calcium channel blocker use (yes vs. no)	C‡
	Lipid-lowering agent use (yes vs. no)	C‡
7.	<b>Lipids</b>	
	Total cholesterol (mg/dl)	B, C§, M§
	Triglycerides (mg/dl)	B, C§, M§
	HDL cholesterol (mg/dl)	B, C§, M§
	LDL cholesterol (mg/dl)	B, C§, M§
	Hyperlipidemia (yes vs. no)	B, C§
	<b><u>Diabetes-related</u></b>	
8.	<b>History of diabetes</b>	
	Duration of type 1 diabetes (years)	B
	Stimulated C-peptide (nmol/L)	B
	Duration $< 5$ years	
	Duration $\geq 5$ years	
	Insulin dose (units/kg/day)	B, C†, M†

SUPPLEMENTARY DATA

**Supplementary Table S1. Risk factors employed in the analyses by block (continued)**

Block		Variable	Availability*
<b>9.</b>	<b>Kidney Disease</b>	eGFR (mL/min/1.73 m <sup>2</sup> )	B, C†
		eGFR <60 mL/min/1.73 m <sup>2</sup>	B, C†, A†
		AER (mg/24 hour)	B, C§
		Sustained AER ≥30 mg/24 hour	B, C§, A§
		AER ≥300 mg/24 hour	B, C§, A§
<b>10.</b>	<b>Hypoglycemia</b>	Coma and/or seizure	B, C†
		Requiring assistance	B, C†
<b>11.</b>	<b>Glycemia</b>	HbA1c (%)	B, C†, M†

ACE=angiotensin-converting enzyme, AER=albumin excretion rate, ARB=angiotensin II receptor blocker, eGFR=estimated glomerular filtration rate, HDL=high-density lipoprotein, LDL=low-density lipoprotein.

\*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.

†Collected annually during DCCT and EDIC.

‡Collected annually in EDIC only.

§Collected annually in DCCT, every two years in EDIC.

SUPPLEMENTARY DATA

**Supplementary Table S2. Odds ratios for DPN and CAN per unit change in each time-dependent covariate in separate longitudinal GEE models, with no additional adjustments**

		DPN		CAN	
	*	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
<b>Physical</b>					
Height (per 5 cm)	C	1.21 (1.14,1.28)	<0.0001	0.98 (0.94,1.04)	0.5400
Weight (per 5 kg)	C	1.09 (1.06,1.12)	<0.0001	1.03 (1.00,1.06)	0.0481
Mean weight (per 5 kg)	M	1.13 (1.09,1.17)	<0.0001	1.04 (1.00,1.08)	0.0319
Body mass index (per 1 kg/m <sup>2</sup> )	C	1.02 (1.00,1.04)	0.0814	1.02 (1.01,1.04)	0.0081
Mean body mass index (per 1 kg/m <sup>2</sup> )	M	1.04 (1.01,1.07)	0.0040	1.04 (1.01,1.07)	0.0063
<b>Behavioral</b>					
Current cigarette smoker (yes vs. no)	C	1.21 (0.93,1.56)	0.1545	1.49 (1.19,1.86)	0.0005
Occasional or regular alcohol use (yes vs. none)	C	1.11 (0.91,1.36)	0.3028	0.86 (0.74,1.01)	0.0605
Moderate or strenuous activity (yes vs. sedentary)	C	1.04 (0.87,1.26)	0.6507	0.85 (0.74,0.98)	0.0212
<b>Blood pressure</b>					
Systolic blood pressure (per 5 mm Hg)	C	1.10 (1.06,1.14)	<0.0001	1.12 (1.09,1.15)	<0.0001
Mean systolic blood pressure (per 5 mm Hg)	M	1.18 (1.12,1.25)	<0.0001	1.29 (1.22,1.36)	<0.0001
Diastolic blood pressure (per 5 mm Hg)	C	1.06 (1.01,1.12)	0.0304	1.03 (0.99,1.07)	0.1493
Mean diastolic blood pressure (per 5 mm Hg)	M	1.23 (1.13,1.34)	<0.0001	1.24 (1.14,1.35)	<0.0001
Pulse pressure (per 5 mm Hg)	C	1.10 (1.06,1.15)	<0.0001	1.14 (1.11,1.18)	<0.0001
Pulse rate (per 1 bpm)	C	1.02 (1.01,1.03)	<0.0001	1.03 (1.03,1.04)	<0.0001
Mean pulse rate (per 1 bpm)	M	1.04 (1.03,1.05)	<0.0001	1.07 (1.06,1.09)	<0.0001
Hypertension (yes vs. no)	C	2.23 (1.75,2.83)	<0.0001	2.15 (1.80,2.57)	<0.0001
<b>Medications</b>					
ACE inhibitor use (yes vs. no)	C	1.64 (1.29,2.09)	<0.0001	1.59 (1.33,1.91)	<0.0001
ARB use (yes vs. no)	C	1.43 (1.01,2.02)	0.0425	1.59 (1.25,2.04)	0.0002
β-blocker use (yes vs. no)	C	3.73 (2.38,5.85)	<0.0001	3.14 (2.26,4.36)	<0.0001
Calcium channel blocker use (yes vs. no)	C	1.68 (1.06,2.67)	0.0259	1.92 (1.40,2.64)	<0.0001
Lipid-lowering agent use (yes vs. no)	C	1.39 (1.09,1.76)	0.0068	1.60 (1.34,1.93)	<0.0001
<b>Lipids</b>					
Total cholesterol (per 10 mg/dl)	C	1.01 (0.98,1.04)	0.4893	1.01 (0.99,1.03)	0.4554
Mean total cholesterol (per 10 mg/dl)	M	1.09 (1.06,1.13)	<0.0001	1.11 (1.08,1.15)	<0.0001
Triglycerides (per 20% increase mg/dl)	C	1.10 (1.06,1.13)	<0.0001	1.08 (1.05,1.11)	<0.0001
Mean triglycerides (per 20% increase mg/dl)	M	1.15 (1.10,1.20)	<0.0001	1.16 (1.11,1.20)	<0.0001
HDL cholesterol (per 10 mg/dl)	C	0.91 (0.84,0.98)	0.0089	0.97 (0.92,1.02)	0.2050

SUPPLEMENTARY DATA

**Supplementary Table S2. Odds ratios for DPN and CAN per unit change in each time-dependent covariate in separate longitudinal GEE models, with no additional adjustments (continued)**

	*	DPN		CAN	
		Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Mean HDL cholesterol (per 10 mg/dl)	M	0.91 (0.84,1.00)	0.0403	0.99 (0.92,1.07)	0.7708
LDL cholesterol (per 10 mg/dl)	C	1.00 (0.98,1.04)	0.7969	1.00 (0.97,1.02)	0.8175
Mean LDL cholesterol (per 10 mg/dl)	M	1.10 (1.05,1.14)	<0.0001	1.10 (1.06,1.14)	<0.0001
Hyperlipidemia (yes vs. no)	C	1.30 (1.07,1.59)	0.0087	1.50 (1.29,1.76)	<0.0001
<b>History of diabetes</b>					
Insulin dose (per 1 unit/kg/day)	C	1.22 (0.88,1.71)	0.2370	1.35 (1.06,1.72)	0.0152
Mean insulin dose (per 1 unit/kg/day)	M	1.35 (0.86,2.11)	0.1960	1.41 (0.92,2.16)	0.1199
<b>Kidney Disease</b>					
eGFR (per 5 mL/min/1.73 m <sup>2</sup> )	C	0.91 (0.89,0.94)	<0.0001	0.91 (0.89,0.93)	<0.0001
eGFR <60 mL/min/1.73 m <sup>2</sup> (yes vs. no)	C	3.39 (1.96,5.85)	<0.0001	5.95 (3.67,9.65)	<0.0001
Any eGFR <60 mL/min/1.73 m <sup>2</sup> (yes vs. no)	A	3.23 (2.05,5.10)	<0.0001	3.53 (2.40,5.19)	<0.0001
AER (per 20% increase mg/24 hour)	C	1.07 (1.05,1.08)	<0.0001	1.06 (1.05,1.07)	<0.0001
Sustained AER ≥30 mg/24 hour (yes vs. no)	C	2.98 (2.34,3.78)	<0.0001	2.56 (2.06,3.18)	<0.0001
Any sustained AER ≥30 mg/24 hour (yes vs. no)	A	2.75 (2.21,3.42)	<0.0001	2.75 (2.26,3.36)	<0.0001
AER ≥300 mg/24 hour (yes vs. no)	C	4.72 (3.08,7.25)	<0.0001	3.36 (2.28,4.95)	<0.0001
Any AER ≥300 mg/24 hour (yes vs. no)	A	4.45 (3.17,6.25)	<0.0001	3.22 (2.34,4.42)	<0.0001
<b>Hypoglycemia</b>					
Coma and/or seizure (yes vs. no)	C	0.86 (0.52,1.44)	0.5671	0.91 (0.68,1.23)	0.5503
Requiring assistance (yes vs. no)	C	1.01 (0.74,1.36)	0.9691	0.98 (0.79,1.21)	0.8601
<b>Glycemia</b>					
HbA1c (per 1 %)	C	1.32 (1.24,1.40)	<0.0001	1.11 (1.05,1.17)	0.0004
Mean HbA1c (per 1 %)	M	1.59 (1.48,1.71)	<0.0001	1.36 (1.26,1.46)	<0.0001

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 generalized estimating equation (GEE) models, unadjusted. Triglyceride and AER values were log transformed and the odds ratios are presented per 20% increase in the covariate (1.2<sup>b</sup>). ACE=angiotensin-converting enzyme, AER=albumin excretion rate, ARB=angiotensin II receptor blocker, eGFR=estimated glomerular filtration rate, HDL=high-density lipoprotein, LDL=low-density lipoprotein.

<sup>a</sup> 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.

SUPPLEMENTARY DATA

**Supplementary Table S3. Multivariable GEE models for DPN and CAN as a function of baseline and time-dependent covariates, using backwards elimination**

<b>Diabetic Peripheral Neuropathy (DPN)</b>	<b>Odds Ratio (95% CI)</b>	<b>Z-value</b>	<b>p-value</b>
Mean HbA1c (per 1%)	1.71 (1.58,1.86)	12.86	<0.0001
Duration of type 1 diabetes (per 1 year)	1.12 (1.09,1.15)	8.68	<0.0001
Age (per 5 years)	1.44 (1.32,1.57)	7.99	<0.0001
Any AER $\geq$ 300 mg/24 hour (yes vs. no)	3.52 (2.40,5.17)	6.42	<0.0001
Height (per 5 cm)	1.35 (1.23,1.48)	6.30	<0.0001
$\beta$ -blocker use (yes vs. no)	2.57 (1.50,4.41)	3.43	0.0006
Mean insulin dose (per 1 unit/kg/day)	2.05 (1.16,3.60)	2.48	0.0130
Sex (men vs. women)	0.67 (0.47,0.94)	2.31	0.0207
<b>Cardiac Autonomic Neuropathy (CAN)</b>	<b>Odds Ratio (95% CI)</b>	<b>Z-value</b>	<b>p-value</b>
Age (per 5 years)	1.55 (1.44,1.67)	11.50	<0.0001
Duration of type 1 diabetes (per 1 year)	1.07 (1.05,1.10)	5.83	<0.0001
Mean HbA1c (per 1%)	1.25 (1.15,1.35)	5.49	<0.0001
Mean pulse rate (per 1 bpm)	1.04 (1.03,1.06)	4.79	<0.0001
Any sustained AER $\geq$ 30 mg/24 hour (yes vs. no)	1.80 (1.39,2.32)	4.52	<0.0001
$\beta$ -blocker use (yes vs. no)	2.15 (1.48,3.14)	3.99	<0.0001
eGFR $<$ 60 mL/min/1.73 m <sup>2</sup> (yes vs. no)	2.51 (1.37,4.60)	2.98	0.0029
Pulse rate (per 1 bpm)	1.02 (1.00,1.03)	2.82	0.0048
AER (per 20% increase mg/24 hour)	1.02 (1.00,1.03)	2.39	0.0169
Current cigarette smoker (yes vs. no)	1.28 (1.01,1.62)	2.08	0.0379

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 generalized estimating equation (GEE) models. AER values were log transformed and the odds ratios are presented per 20% increase in the covariate (1.2<sup>β</sup>). Covariates are listed in the order of significance as indicated by the Z-value. AER=albumin excretion rate, eGFR=estimated glomerular filtration rate.

SUPPLEMENTARY DATA

**Supplementary Table S4. Final multivariable GEE models for DPN and CAN as a function of baseline and time-dependent covariates, including diabetic retinopathy**

<b>Diabetic Peripheral Neuropathy (DPN)</b>	<b>Odds Ratio (95% CI)</b>	<b>Z-value</b>	<b>p-value</b>
Mean HbA1c (per 1%)	1.58 (1.46,1.72)	10.89	<0.0001
Age (per 5 years)	1.41 (1.30,1.54)	7.89	<0.0001
Height (per 5 cm)	1.27 (1.19,1.35)	7.26	<0.0001
Duration of type 1 diabetes (per 1 year)	1.09 (1.07,1.12)	6.73	<0.0001
Any proliferative diabetic retinopathy or worse (yes vs. no)	2.14 (1.56,2.93)	4.74	<0.0001
AER (per 20% increase mg/24 hour)	1.04 (1.02,1.05)	4.36	<0.0001
Mean pulse rate (per 1 bpm)	1.03 (1.01,1.04)	3.74	0.0002
β-blocker use (yes vs. no)	2.44 (1.44,4.14)	3.30	0.0010
<b>Cardiac Autonomic Neuropathy (CAN)</b>	<b>Odds Ratio (95% CI)</b>	<b>Z-value</b>	<b>p-value</b>
Age (per 5 years)	1.51 (1.40,1.63)	10.63	<0.0001
Any sustained AER ≥30 mg/24 hour (yes vs. no)	1.79 (1.42,2.25)	5.01	<0.0001
Mean HbA1c (per 1%)	1.21 (1.12,1.31)	4.86	<0.0001
Duration of type 1 diabetes (per 1 year)	1.06 (1.03,1.08)	4.53	<0.0001
Mean pulse rate (per 1 bpm)	1.04 (1.02,1.06)	4.40	<0.0001
β-blocker use (yes vs. no)	1.96 (1.33,2.89)	3.39	0.0007
Systolic blood pressure (per 5 mm Hg)	1.05 (1.02,1.08)	3.19	0.0014
Any proliferative diabetic retinopathy or worse (yes vs. no)	1.58 (1.19,2.10)	3.18	0.0015
Any clinically significant macular edema (yes vs. no)	1.48 (1.15,1.90)	3.04	0.0023
eGFR <60 mL/min/1.73 m <sup>2</sup> (yes vs. no)	2.44 (1.37,4.36)	3.01	0.0026
Pulse rate (per 1 bpm)	1.02 (1.00,1.03)	2.83	0.0047
Current cigarette smoker (yes vs. no)	1.33 (1.06,1.69)	2.43	0.0152

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 generalized estimating equation (GEE) models. AER values were log transformed and the odds ratios are presented per 20% increase in the covariate (1.2<sup>β</sup>). Covariates are listed in the order of significance as indicated by the Z-value. AER=albumin excretion rate, eGFR=estimated glomerular filtration rate.