Supplementary material

Diabetic polyneuropathy early in type 2 diabetes is associated with higher incidence rate of cardiovascular disease: Results from two Danish cohort studies

Short running title: Diabetic polyneuropathy and cardiovascular disease

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Supplemental table S1

Michigan neuropathy screening instrument questionnaire (MNSIq)

Frequency (%) of positive answers indicating diabetic peripheral neuropathy in each cohort separately by MNSIq score.

In line with the validated MNSIq, questions 4 and 10 were not included in the total score.

Participants were asked to answer the following questions about the feeling in legs and feet based on how they usually feel.

		ADDITION-Denmark		DD2	
		MNSIq < 4 (n= 1,256)	MNSIq ≥ 4 (n= 189)	MNSIq < 4 (n= 4,210)	MNSIq ≥ 4 (n= 818)
1	Are your legs and/or feet numb?†	42 (3.3)	92 (48.7)	116 (3.0)	339 (41.4)
2	Do you ever have any burning pain in your legs and/or feet?†	105 (8.4)	159 (84.1)	368 (8.7)	586 (71.6)
3	Are your feet too sensitive to touch?†	128 (10.2)	98 (51.9)	520 (12.4)	448 (54.8)
4	Do you get muscle cramps in your legs and/or feet?*	-	-	1,746 (41.5)	586 (71.6)
5	Do you ever have any prickling feelings in your legs or feet?†	183 (14.6)	164 (86.8)	1,156 (27.5)	728 (89.0)
6	Does it hurt when the bed covers touch your skin?†	11 (0.9)	35 (18.5)	50 (1.2)	187 (22.9)
7	When you get into the tub or shower, are you able to tell the hot water from the cold water?	137 (10.9)	14 (7.4)	384 (9.1)	121 (15.0)
8	Have you ever had an open sore on your foot?	22 (1.8)	26 (13.8)	444 (10.6)	259 (31.7)
9	Has your doctor ever told you that you have diabetic neuropathy?	≤ 5	6 (3.2)	217 (5.2)	239 (29.2)
10	Do you feel weak all over most of the time?	111 (17.5)	108 (57.4)	372 (8.9)	351 (42.9)
11	Are your symptoms worse at night?	66 (5.3)	91 (48.1)	320 (7.6)	305 (37.3)
12	Do your legs hurt when you walk?	102 (8.1)	148 (78.3)	681 (16.2)	586 (71.6)
13	Are you able to sense your feet when you walk?	167 (13.3)	26 (13.8)	465 (11.1)	115 (14.1)
14	Is the skin on your feet so dry that it cracks open?	71 (5.7)	76 (40.2)	502 (11.9)	326 (39.9)
15	Have you ever had an amputation?	≤ 5	6 (3.2)	26 (0.6)	26 (3.2)

Data are expressed as n (%) for answers indicating diabetic peripheral neuropathy.

† Diabetic peripheral neuropathy was defined as a score ≥ 4, with the additional requirement that one of question 1, 2, 3, 5, or 6 had to be answered positively.

*Was not asked in the ADDITION-study.

Supplemental Table S2

Codes from the *International Classification of Diseases, 10th revision* and surgery codes used in the study to identify

outcomes.

Outcome	ICD-10 codes	Surgery codes
Ischaemic heart disease	DI20-DI25	KFNA-KFNG (except: KFNG20, KFNG22
Stroke	DI61, DI63-DI66, DI69.3, DI69.4	KAAL10, KAAL11
Peripheral arterial disease/amputation	DI70, DI74, DI73.9, DZ89.4-DZ89.7	KPDH, KPDQ, KPAE, KPBE, KPDE, KPFE, KNGQ19, KNGQ29, KNFQ19, KNFQ29
Heart failure	DI50,DI11.0 , DI13.0 , DI13.2	-

Supplemental Table S3

Table of variables included in the imputation models, pattern of missing data in both cohorts, and variables included in the regression models.

	Missing data, n (%)		Included in the outcome analyses
	ADDITION-Denmark	DD2	
Number of individuals	1,448	5,028	
HbA1$_c$ (%)	51 (3.5%)	1120 (22.3%)	X
BMI (kg/m^2)	56 (3.9%)	64 (1.3%)	X
Waist (cm)	59 (4.1%)	8 (0.2%)	
SBP (mmHg)	56 (3.9%)	1296 (25.8%)	X
DBP (mmHg)	56 (3.9%)	1296 (25.8%)	
Total cholesterol (mmol/L)	111 (7.7%)	2891 (57.5%)	
Triglycerides (mmol/L)	128 (8.9%)	1365 (27.1%)	
HDL cholesterol (mmol/L)	144 (10.0%)	2882 (57.3%)	
LDL cholesterol (mmol/L)	186 (12.9%)	1198 (23.8%)	X
Albumine-creatinine ratio (mg/g)	115 (8.0%)	1425 (28.3%)	X
Smoking	18 (1.2%)	15 (0.3%)	X
Alcohol	150 (10.4%)	64 (1.3%)	X
MNSIq	-	-	
Sex	-	-	X
Age (years)	-	-	X
Duration of diabetes_(years)	-	-	
Antihypertensive medication	-	-	X
Lipid-lowering medication	-	-	X
Aspirin	-	-	
History of CVD	-	-	X
Treatment group	-	-	X
Outcome status	-	-	
Nelson–Aalen estimate of cumulative hazard	-	-	

All variables listed in this table were used for the imputation of missing covariates.

We imputed datasets for each cohort and each outcome separately.

Supplemental Table S4

Number (N) (both histogram and table) and percentage of MNSIq scores at index date for both cohorts.
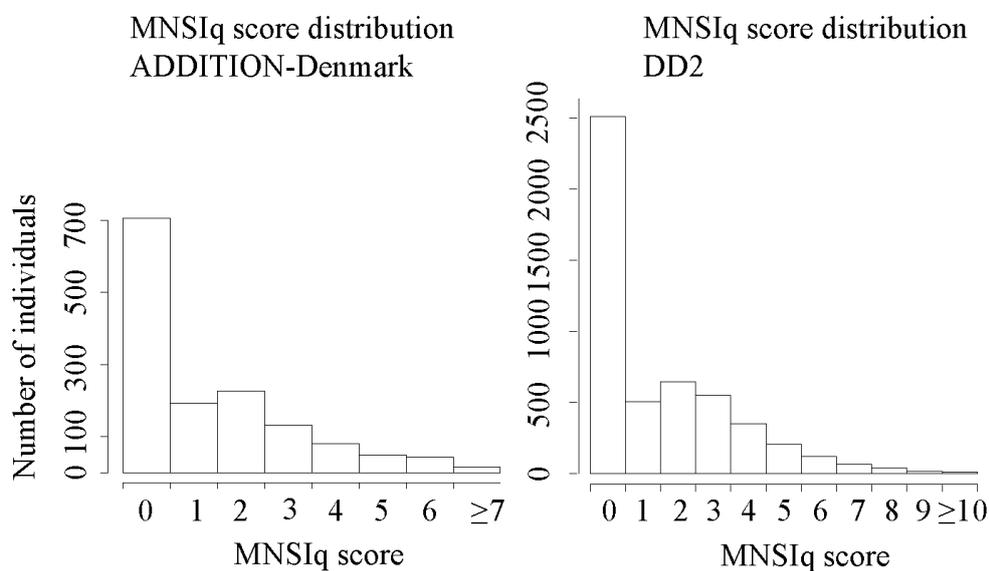
	ADDITION-Denmark	DD2
MNSIq score	N (%)	N (%)
0	705 (48.8%)	2510 (49.9%)
1	193 (13.4%)	504 (10.0%)
2	226 (15.6%)	645 (12.8%)
3	132 (9.1%)	551 (11.0%)
4	80 (5.5%)	349 (6,.9%)
5	50 (3.5%)	208 (4.1%)
6	43 (3.0%)	121 (2.4%)
7	16 (1.1%)*	67 (1.3%)
8	-	43 (0.9%)
9	-	17 (0.3%)
10	-	13 (0.3%)**
11	-	-
12	-	-
13	-	-
14	-	-
15	-	-

* Individuals at or above MNSIq score of 7

** Individuals at or above MNSIq score of 10

Supplemental table S5

Panel a shows incidence rate ratios of CVD and mortality comparing individuals with MNSIq ≥ 4 with individuals with MNSIq < 4 stratified by sex for each cohort separately.

Panel b shows incidence rate ratios of CVD and mortality comparing individuals with MNSIq ≥ 4 with individuals with MNSIq < 4 stratified by randomization group for the ADDITION cohort.

Panel a	Incidence rate ratio (95% CI)	
	Male	**Female**
Cardiovascular disease		
ADDITION-Denmark	1.75 (1.26-2.44)	1.98 (1.30-3.02)
DD2	1.80 (1.40-2.31)	1.22 (0.83-1.79)
Mortality		
ADDITION-Denmark	1.05 (0.65-1.70)	1.00 (0.54-1.87)
DD2	1.33 (0.77-2.31)	0.90 (0.38-2.09)

Panel b	Incidence rate ratio (95% CI)	
	Intensive treatment	**Routine care**
Cardiovascular disease	1.57 (1.13-2.18)	2.40 (1.58-3.64)
Mortality	1.03 (0.64-1.67)	1.07 (0.58-1.96)

Adjusted incidence rate ratios of CVD and all-cause mortality in individuals with MNSIq scores ≥ 4 compared with individuals with MNSIq scores < 4 stratified by sex (panel a) and by randomization group in ADDITION (panel b) Models are adjusted for age, sex (panel b), HbA_{1c}, BMI, smoking status, alcohol consumption, LDL-cholesterol, systolic blood pressure, lipid-lowering medication, antihypertensive medication, albumin-creatinine ratio, history of CVD, and randomization group (ADDITION-Denmark, panel a) or duration of diabetes (DD2). Pooled estimates from 60 datasets using Rubin's Rules.

Supplemental Figure S1

Panel A

Cumulative incidence of CVD
ADDITION-Denmark

Cumulative incidence of CVD
DD2

Cumulative mortality
ADDITION-Denmark

Cumulative mortality
DD2

Panel B

Cumulative incidence of CVD
ADDITION-Denmark

Cumulative mortality
ADDITION-Denmark
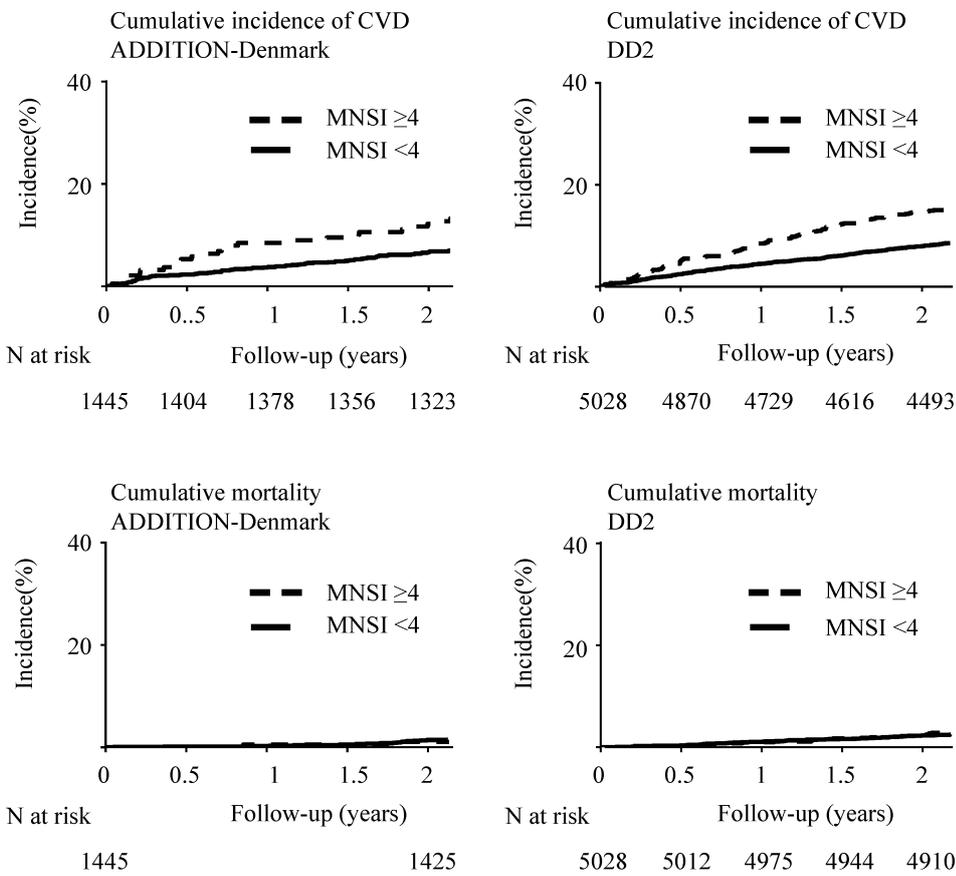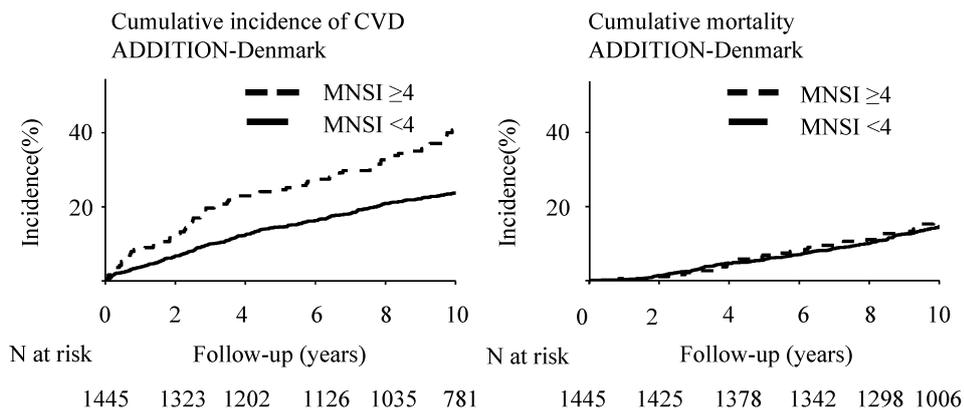
Panel A: Crude cumulative incidence curves in ADDITION-Denmark and DD2. CIP of cardiovascular disease and mortality by MNSIq scores ≥ 4 and MNSIq scores < 4 during the follow-up period in DD2.

Panel B: Crude cumulative incidence curves in ADDITON-Denmark. CIP of cardiovascular disease and mortality by MNSIq scores ≥ 4 and MNSIq scores < 4 during follow-up in ADDITION-Denmark

Supplemental Figure S2

Adjusted incidence rate ratios of CVD and death, comparing individuals with MNSIq scores ≥ 4 with individuals with MNSIq scores < 4, restricted to those without CVD at index date.

Incidence rate ratios in individuals without CVD at inclusion

Panel a   Cardiovascular disease

ADDITION   2.1 (1.6-2.9)

DD2   1.5 (1.0-2.2)

Combined   1.9 (1.5-2.4)

0.7   0.8   0.9   1.0   1.1   1.3   1.5   1.7   1.9   2.1

IRR, MNSIq ≥ 4 vs. MNSIq <4

Panel b   Mortality

ADDITION   1.1 (0.7-1.7)

DD2   1.5 (0.8-2.7)

Combined   1.2 (0.9-1.8)

0.7   0.8   0.9   1.0   1.1   1.3   1.5   1.7   1.9   2.1

MRR, MNSIq ≥ 4 vs. MNSIq <4
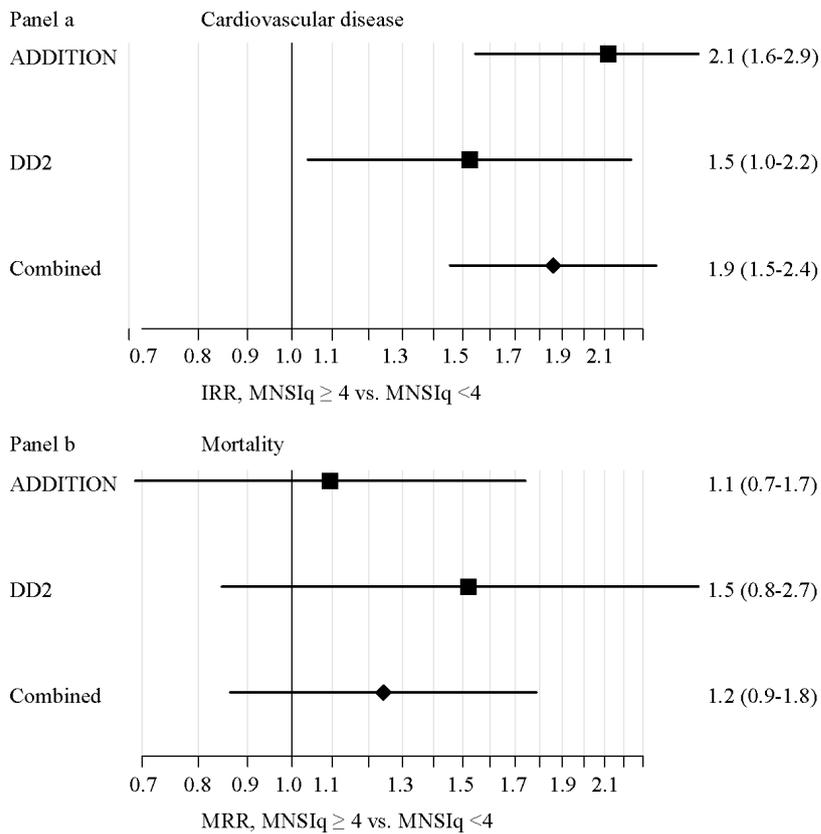
IRR for individuals without a history of CVD at index date (up to 10 years prior the index date).

Adjusted incidence rate ratios of CVD (panel a) and all-cause mortality (panel b) in individuals with MNSIq scores ≥4 compared with individuals with MNSIq scores <4.

Models are adjusted for age, sex, HbA_{1c}, BMI, smoking status, alcohol consumption, LDL-cholesterol, systolic blood pressure, lipid-lowering medication, antihypertensive medication, albumin-creatinine ratio, history of CVD, and randomization group (ADDITION-Denmark) or duration of diabetes (DD2). Pooled estimates from 60 datasets using Rubin's Rules