Diabetic Polyneuropathy Early in Type 2 Diabetes Is Associated With Higher Incidence Rate of Cardiovascular Disease: Results From Two Danish Cohort Studies

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OBJECTIVE

Symptoms indicative of diabetic polyneuropathy (DPN) early in type 2 diabetes may act as a marker for cardiovascular disease (CVD) and death.

RESEARCH DESIGN AND METHODS

We linked data from two Danish type 2 diabetes cohorts, the Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes in Primary Care (ADDITION-Denmark) and the Danish Centre for Strategic Research in Type 2 Diabetes (DD2), to national health care registers. The Michigan Neuropathy Screening Instrument questionnaire (MNSIq) was completed at diabetes diagnosis in ADDITION-Denmark and at a median of 4.6 years after diagnosis of diabetes in DD2. An MNSIq score ≥4 was considered as indicative of DPN. Using Poisson regressions, we computed incidence rate ratios (IRRs) of CVD and all-cause mortality comparing MNSIq scores ≥4 with scores <4. Analyses were adjusted for a range of established CVD risk factors.

RESULTS

In total, 1,445 (ADDITION-Denmark) and 5,028 (DD2) individuals were included in the study. Compared with MNSIq scores <4, MNSIq scores ≥4 were associated with higher incidence rate of CVD, with IRRs of 1.79 (95% CI 1.38–2.31) in ADDITION-Denmark, 1.57 (CI 1.27–1.94) in the DD2, and a combined IRR of 1.65 (CI 1.41–1.95) in a fixed-effect meta-analysis. MNSIq scores ≥4 did not associate with mortality; combined mortality rate ratio was 1.11 (CI 0.83–1.48).

CONCLUSIONS

The MNSIq may be a tool to identify a subgroup within individuals with newly diagnosed type 2 diabetes with a high incidence rate of subsequent CVD. MNSIq scores ≥4, indicating DPN, were associated with a markedly higher incidence rate of CVD, beyond that conferred by established CVD risk factors.

Diabetic polyneuropathy (DPN) is a serious manifestation of microvascular complications and occurs in nearly half of individuals with type 2 diabetes (1). Early assessment and intervention for individuals with DPN are strongly advocated (2,3), as a substantial fraction of individuals with diabetes have signs of DPN at the time of

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or briefly after diabetes diagnosis (4,5). In addition, studies have identified DPN as an important risk factor for lower-limb amputations (2). Also, prior research has indicated higher mortality (6,7) and up to 30% higher cardiovascular disease (CVD) risk in patients with signs of DPN (8). However, previous studies have been limited in size and conducted in individuals with long diabetes duration or in individuals with foot ulcers and/or lower-limb amputations (6–9).

Most CVD guidelines recommend multifactorial risk assessment and management of individuals with type 2 diabetes (10,11), due to their elevated CVD risk. There is an increasing focus on identifying individuals with diabetes who are likely to benefit the most from intensive multifactorial treatment to reduce the risk of diabetes-related complications and mortality. Those with higher risk of CVD and death should be identified as early as possible after diagnosis in order to maximize their benefit from early and/or more aggressive multifactorial CVD risk factor management (12). In this study, we investigate whether symptoms indicative of DPN, assessed by the Michigan Neuropathy Screening Instrument questionnaire (MNSIq) (13), at the time of or shortly after diagnosis of type 2 diabetes are associated with higher incidence rate (IR) of subsequent CVD and mortality.

RESEARCH DESIGN AND METHODS

Setting

This cohort study was based on two well-described Danish cohorts: the Danish arm of the Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes in Primary Care (ADDITION-Denmark) cohort and the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) cohort (14,15). Both cohorts have clinical and self-reported questionnaire data available. We linked these data to individual-level data obtained from Danish administrative and health registries using the unique personal registration number assigned to all residents of Denmark (16).

The ADDITION study is a cluster-randomized study designed to investigate the effect of intensive multifactorial treatment in primary care among individuals with screen-detected type 2 diabetes (14). Using a stepwise screening protocol, the ADDITION-Denmark study screened 160,000 individuals in general practice in the period 2001–2006. In total, 1,533 individuals were enrolled in ADDITION-Denmark. The participating general practices were randomized to deliver either target-driven intensive multifactorial care or routine care until the end of clinical trial follow-up in 2009 (mean follow-up time 5.3 years), after which the study transitioned to an observational posttrial follow-up study (17).

The ongoing DD2 study has enrolled individuals with recently diagnosed type 2 diabetes since November 2010. Its overall aim is to establish a large and data-rich cohort to serve as a platform for type 2 diabetes research (15). Individuals with newly or recently diagnosed type 2 diabetes are eligible for participation. Enrollment can take place either in general practices or at hospital outpatient clinics (53% and 47%, respectively, up to 2016) throughout Denmark (15).

Determinant

DPN was assessed using the MNSIq (13), which is based on 15 questions (Supplementary Table 1). DPN was defined according to the validated cutoff point of an MNSIq score $\geq$4 (18), with the additional requirement that at least one out of five specific questions was answered positively. The five specific questions were: are your legs and/or feet numb? Do you ever have any burning pain in your legs and/or feet? Are your feet too sensitive to touch? Do you ever have any prickling feelings in your legs or feet? Does it hurt when the bedcovers touch your skin? The MNSIq was completed at enrollment in ADDITION-Denmark, while the DD2 study administered a neuropathy questionnaire survey including the MNSIq to all enrolled DD2 participants in 2016 (median diabetes duration at that time point was 4.6 years [interquartile range 3.5–5.7]) (5). In the current study, the ADDITION-Denmark enrollment date and the date of the DD2 neuropathy questionnaire survey served as index dates. Only individuals with valid data on the MNSIq were included in the current study.

Covariates

We had access to the following descriptive data: anthropometric data, smoking habits (current, former, or never), alcohol consumption (more or less than 7 out of 14 units per week [female/male]), systolic and diastolic blood pressure, and biochemistry measures including HbA_{1c}, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, and urinary albumin-to-creatinine ratio (u-ACR). The descriptive data were either collected directly for the two cohorts on the index date or, for the DD2 cohort, additionally obtained through linkage with the Danish Diabetes Database for Adults (DDDA) (19). The DDDA variables included HbA_{1c}, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, u-ACR, and systolic and diastolic blood pressure. For the DDDA variables, we used the data measured closest to the index date, but we searched within a time window up to 5 years before and 90 days after the index date. In total, 14% of included individuals had HbA_{1c} measured within 1 year prior to the index date. The percentages of included individuals with a measurement within 1 year prior to the index date were 12%, 20%, and 14% for cholesterols, u-ACR, and blood pressure, respectively. The mean time from the last assessment to the index date for variables from the DDDA included in the main analyses was between 25 and 28 months. In ADDITION-Denmark, general practitioners provided records of prescribed medications (glucose-lowering medication, lipid-lowering medication, antihypertensive medication, and aspirin) at the index date. For the DD2 population, complete information on prescriptions was obtained from the Danish National Health Service Prescription Database for the period 180 days prior to the index date (20).

Outcomes

The outcomes of interest were CVD and all-cause mortality. Information on CVD was obtained from the Danish National Patient Registry. The Danish National Patient Registry has collected data on all nonpsychiatric inpatient hospitalizations since 1977 and all nonpsychiatric emergency room and outpatient hospital contacts since 1995 (21), including date of admission/discharge and one primary diagnosis and any number of secondary diagnoses, coded according to the ICD-8 until the end of 1993 and the ICD-10 thereafter (21). We defined CVD as an

inpatient or outpatient hospital clinic contact for ischemic heart disease, stroke, heart failure, or peripheral arterial disease using both primary and secondary ICD-10 diagnoses and surgery codes (Supplementary Table 2). The first registration of CVD after the index date was used as outcome in the analysis of CVD incidence. Information on mortality was extracted from the Danish Civil Registration System, which maintains complete status of death and migration, with daily electronic updates. All individuals were followed until 15 April 2016 for the ADDITION-Denmark cohort and 10 August 2018 for the DD2 cohort, respectively.

Statistical Analysis

All analyses were conducted separately for each cohort.

We tabulated characteristics of included individuals on the index date by MNSIq score $\geq 4/<4$ (as medians [interquartile range] and *n* [%]).

We followed both cohorts from index date until the date of outcome, death, emigration, or end of follow-up, whichever occurred first. We plotted the crude cumulative incidence curves for CVD and mortality for each cohort based on the total follow-up time in the DD2 study (2.2 years). Also, for ADDITION-Denmark, we plotted the crude cumulative incidence curves for CVD and mortality based on the longer follow-up period available. We used Poisson regression models to estimate crude IRs, mortality rates (MRs), adjusted IR ratios (IRRs), and MR ratios (MRRs) with associated 95% CIs, comparing individuals with MNSIq scores ≥ 4 to those with MNSIq scores <4. The models were adjusted for age, sex, HbA_{1c}, BMI, smoking status, alcohol consumption, LDL cholesterol, systolic blood pressure, lipid-lowering medication, antihypertensive medication, u-ACR, and history of CVD. Furthermore, we adjusted for randomization group in the ADDITION-Denmark cohort and for diabetes duration in the DD2 cohort. We stratified the analyses in each cohort by sex and stratified by randomization group in the ADDITION-Denmark cohort.

We imputed missing data on covariates using the multiple imputation by chained equations (MICE). We imputed data sets for each cohort and each outcome separately. Data were missing for up to 13% of individuals for variables used in the main analyses in ADDITION-Denmark and for up to 28% of individuals in DD2. Supplementary Table 3 lists variables used in the imputation models and shows the patterns of missingness in the two cohorts. We performed Poisson regression in 60 imputed data sets for each cohort and summarized the obtained estimates using Rubin's rules.

Based on data similarity and ascertainment of outcomes from the same data sources, we assumed a homogeneous underlying effect of DPN in both cohorts and used a fixed-effect meta-analysis to combine the estimated IRRs and MRRs.

We performed a sensitivity analysis to assess any potential bias arising from prevalent CVD and repeated the analyses after excluding individuals with a history of CVD up to 10 years before the index date.

Data management and analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC) and R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org) using the Epi package for data handling and analyses, MICE package for multiple imputation, and metafor package for conducting fixed-effect meta-analyses.

Research Ethics and Informed Consent

ADDITION-Denmark was approved by the Committee on Health Research Ethics in the Central Denmark Region (approval numbers 20000183 and 1-10-72-63-15) and by the Danish Data Protection Agency (approval number 2005–57–0002, ID185). The Danish National Committee on Health Research Ethics (record number S-20100082) and the Danish Data Protection Agency (record number 2008-58-0035) approved the DD2 study. All participants in ADDITION-Denmark and DD2 gave written informed consent.

RESULTS

Study Population

The ADDITION-Denmark study enrolled 1,533 individuals. We excluded 88 individuals with missing MNSIq information on the index date, leaving 1,445 for inclusion in the study. Of these, 189 (13.1%) individuals had an MNSIq score ≥ 4. Among the 6,276 individuals in DD2 who received a questionnaire in 2016, 5,028 returned valid data (response rate 80.1%) for the MNSIq (according to the MNSIq criteria described above) and constituted the DD2 study population. Of these, 818 (16.2%) had an MNSIq score ≥ 4. Supplementary Table 4 provides the number and percentage of individuals by MNSIq scores for each cohort separately. For CVD, total follow-up was 13,097 person-years (PY) in the ADDITION-Denmark study and 10,259 PY in DD2 (median follow-up was 11.4 years and 2.2 years, respectively). Total follow-up for all-cause mortality was slightly longer (totaling 15,370 PY in ADDITION-Denmark and 10,801 PY in DD2). Characteristics of included individuals on their index date are shown in Table 1 separately for each cohort and by MNSIq score $\geq 4/<4$. The sex distribution was similar in the ADDITION-Denmark cohort and the DD2 cohort, but individuals in DD2 were slightly older. Furthermore, the percentage of individuals prescribed antihypertensive medication, lipid-lowering medication, and aspirin at index date was higher in the DD2 cohort. In both cohorts, the percentage of individuals who had a history of CVD prior to the index date was larger among those with MNSIq score ≥ 4. Supplementary Table 1 shows the percentage of positive answers (i.e., indicating DPN, for each question item of the MNSIq in individuals with and without MNSIq ≥ 4 for each cohort separately).

CVD and Mortality

In ADDITION-Denmark, a total of 394 individuals experienced a CVD outcome (27.3%) and 253 died (17.5%) during a median of 11.4 years of follow-up. The corresponding numbers in DD2 were 480 (9.5%) and 127 (2.5%) during a median of 2.2 years of follow-up. Of note, cumulative incidence of CVD and mortality during the first few years of follow-up were very similar in the ADDITION-Denmark and DD2 cohorts (Supplementary Fig. 1). The curves for CVD separated after some months, while the curves for mortality were highly similar in those with and without MNSIq scores ≥ 4. In ADDITION-Denmark, the same patterns were seen after longer follow-up (Supplementary Fig. 1).

During the total follow-up period, crude IRs of CVD per 1,000 PY were

Table 1—Characteristics of study participants on their index date by MNSIq scores ≥4/<4 in the ADDITION-Denmark and DD2 cohorts

	ADDITION-Denmark (*N* = 1,445)		DD2 (*N* = 5,028)	
	MNSIq <4	MNSIq ≥4	MNSIq <4	MNSIq ≥4
Number of individuals	1,256	189	4,210	818
Female sex	521 (41.5)	93 (49.2)	1,731 (41.1)	386 (47.2)
Age (years)	61 (56–66)	60 (56–65)	66 (57–72)	63 (55–70)
HbA_{1c} (%)	6.3 (6.0–6.90)	6.4 (5.9–7.1)	6.5 (6.1–7.1)	6.7 (6.2–7.4)
HbA_{1c} (mmol/mol)	45 (42–52)	46 (41–54)	48 (43–54)	50 (44–57)
BMI (kg/m^2)	30 (27–33)	31 (29–34)	29 (26–33)	31 (27–36)
Waist (cm)	104 (96–113)	108 (99–116)	105 (96–115)	110 (100–119)
Systolic blood pressure (mmHg)	148 (135–163)	143 (131–153)	130 (123–140)	130 (122–140)
Diastolic blood pressure (mmHg)	87 (81–95)	85 (78–93)	80 (74–85)	80 (74–86)
Total cholesterol (mmol/L)	5.6 (4.9–6.4)	5.4 (4.8–6.0)	4.3 (3.7–5.0)	4.3 (3.7–5.0)
Triglycerides (mmol/L)	1.6 (1.1–2.3)	1.6 (1.1–2.3)	1.6 (1.1–2.3)	1.9 (1.3–2.8)
HDL cholesterol (mmol/L)	1.3 (1.1–1.6)	1.3 (1.1–1.5)	1.2 (1.0–1.5)	1.1 (1.0–1.4)
LDL cholesterol (mmol/L)	3.4 (2.7–4.0)	3.2 (2.6–3.7)	2.1 (1.6–2.6)	2.1 (1.6–2.7)
u-ACR (mg/g)	7.3 (2.5–19.7)	8.2 (2.9–19.7)	8.0 (3.0–18.0)	10.0 (4.0–22.0)
Antihypertensives*	531 (42.3)	92 (48.7)	3,060 (72.7)	620 (75.8)
ACE/ARB blockers	251 (20.0)	37 (19.6)	2,635 (62.6)	527 (64.4)
β-Blockers	226 (18.0)	34 (18.0)	985 (23.4)	221 (27.0)
Calcium antagonists	145 (11.5)	21 (11.1)	1184 (28.1)	242 (29.6)
Diuretics	297 (23.6)	70 (37.0)	1,828 (43.4)	436 (53.3)
Statins*	153 (12.2)	29 (15.3)	3,044 (72.3)	579 (70.8)
Aspirin*	152 (12.1)	38 (20.1)	923 (21.9)	213 (26.0)
Smoking				
Nonsmoker	347 (27.9)	63 (34.1)	778 (18.5)	184 (22.5)
Former smoker	472 (38.0)	58 (31.4)	1,858 (44.3)	390 (47.7)
Current smoker	423 (34.1)	64 (34.6)	1,559 (37.2)	244 (29.8)
Alcohol use†	349 (30.8)	39 (24.2)	673 (16.2)	121 (15.1)
History of CVD‡	180 (14.3)	43 (22.8)	829 (19.7)	248 (30.3)
Follow-up time by end of study (years)	11.4 (9.4–12.2)	11.4 (9.1–12.1)	2.2 (2.2–2.2)	2.2 (2.2–2.2)
Intensive treatment group	730 (58.1)	124 (65.6)	—	—
Duration of diabetes (years)	—	—	4.5 (3.4–5.7)	4.8 (3.7–6.0)

Categorical data are expressed as *n* (%) and continuous data as medians (interquartile range). ARB, angiotensin receptor blocker. *In DD2, the look-back period for prescription register data were 180 days prior to index date. †Weekly alcohol consumption exceeding recommended intake (>7 units in women and >14 units in men). ‡History of CVD: CVD diagnosis up to 10 years prior to the index date.

slightly higher in the DD2 cohort than in the ADDITION-Denmark cohort, while MRs were higher in ADDITION-Denmark than in DD2 (Table 2).

The main driver for the CVD end point was ischemic heart disease, which accounted for 58% of events in ADDITION-Denmark and for 51% of events in DD2. The percentages of each of the other cardiovascular events encompassed by our CVD outcome definition were 15–20% in both cohorts (Table 3). A few individuals were registered with more than one cardiovascular event on the same day (e.g., ischemic heart disease and heart failure).

After adjustment for the full set of variables described in the RESEARCH DESIGN AND METHODS section, MNSIq scores ≥4 were associated with higher IR of CVD in both cohorts, with a 79% higher IR (IRR 1.79 [95% CI 1.38–2.31]) in the ADDITION-Denmark cohort, a 57% higher IR (IRR 1.57 [95% CI 1.27–1.94]) in the DD2 cohort, and a combined higher excess IR of 65% (IRR 1.65 [95% CI 1.41–1.95]) in the fixed-effect meta-analysis (Fig. 1). With a combined MRR of 1.11 (95% CI 0.83–1.48), we found that MNSIq scores ≥4 did not associate with mortality overall or in either of the two cohorts, separately: the MRR was 1.05 (95% CI 0.73–1.52) and 1.20 (95% CI 0.76–1.89) in ADDITION-Denmark and DD2, respectively (Fig. 1). Stratification by randomization group in the ADDITION-Denmark cohort indicated a higher IRR between individuals with and without MNSIq ≥4 in the routine care group than in the intensive treatment group, whereas no clear pattern was observed in the analyses stratified by sex in the two cohorts (Supplementary Table 5).

Restricting the analyses to individuals without a history of CVD increased the IRR of CVD to 1.9 (95% CI 1.5–2.4) and the MRR to 1.2 (95% CI −0.9 to 1.8) (Supplementary Fig. 2).

DISCUSSION

In this combined study of two Danish cohorts including a total of 6,473 individuals with type 2 diabetes, we find that individuals with symptoms indicative of DPN (i.e., MNSIq score ≥4) at the time

Table 2—Number of events, follow-up, and crude IRs by MNSIq scores ≥4/<4 separately for each cohort

	ADDITION-Denmark			DD2		
	Number of events, *n* (%)	Total follow-up (years)	Crude IR (95% CI) (per 1,000 PY)	Number of events, *n* (%)	Total follow-up (years)	Crude IR (95% CI) (per 1,000 PY)
CVD						
MNSIq <4	317 (25.2)	11,583	27.4 (24.5–30.6)	356 (8.5)	8,652	41.1 (37.1–45.7)
MNSIq ≥4	77 (40.7)	1,514	50.9 (40.7–63.6)	124 (15.2)	1,607	77.2 (64.7–92.0)
Mortality						
MNSIq <4	219 (17.4)	13,384	16.4 (14.3–18.7)	103 (2.4)	9,045	11.4 (9.4–13.8)
MNSIq ≥4	34 (18.0)	1,986	17.1 (12.2–24.0)	24 (2.9)	1,756	13.7 (9.2–20.4)

of or shortly after diabetes diagnosis have a markedly higher IR of subsequent CVD compared with those without symptoms indicative of DPN. We find no evidence of an association between MNSIq scores ≥4 and mortality.

There is an increasing focus on early detection of symptoms and signs of DPN, as this may open an opportunity for early intervention to prevent irreversible nerve damage, foot ulcers, amputations, and subsequent CVD and mortality (2,22). One cohort study, in the setting of the U.K.'s primary health care system, evaluated the association between DPN as assessed by monofilament and incidence of a subsequent CVD event (8). The investigators found an ~30% higher IR of CVD in those with signs of DPN compared with those without, while we found a 65% higher CVD IR in those with signs of DPN. Unknown diabetes duration and different definitions of DPN may explain some of this discrepancy (i.e., monofilament assessment detects large fiber neuropathy, while the MNSIq also includes questions that may detect small fiber neuropathy and vascular disease to some extent). Our findings corroborate those from a study that evaluated three questions from the MNSIq as a prognostic instrument for future CVD (i.e., Are your legs numb? Have you ever had an open sore on your foot? Do your legs hurt when you walk?) (23). The study population comprised of individuals with long diabetes duration (80% >5 years) and prevalent CVD and/or diabetic kidney disease at inclusion. Although that study was based on a high-risk population, in which much risk is conferred by comorbidities, they found that respondents providing a positive answer to all three questions had a 69% higher risk of a major adverse cardiovascular event than individuals without any positive answers.

Evidence suggests an association between late stages of DPN (i.e., foot ulcers and amputations) and an increased risk of CVD and mortality (6,7,9). Also, individuals diagnosed with DPN based on nerve conduction studies have been shown to have higher mortality than individuals without DPN (24). However, these studies were conducted in individuals with ~10 years of diabetes duration at inclusion. The short diabetes duration at the index date, the use of the MNSIq, which does not feature objective measures of DPN, and the low absolute MR, especially in the DD2 cohort, may to some extent explain why we find no evidence of higher MR in individuals with MNSIq score ≥4 compared with individuals with MNSIq score <4.

The mechanisms underlying our findings are unclear. Deterioration of blood glucose control and other cardiovascular risk factors (e.g., obesity and dyslipidemia) may accelerate in the years leading up to the clinical diagnosis of diabetes (25,26). As risk factors for CVD and DPN to some extent overlap, one might expect that diagnostic tools designed to detect DPN might also predict CVD, especially as some of the questions in the MNSIq focus on the vascular profile. However, a large fraction of individuals with an MNSIq score ≥4 had positive responses to questions regarded more specific for DPN (e.g., numbness, burning pain, and prickling feeling) than other questions. The associations between MNSIq ≥4 and CVD and mortality were slightly stronger among individuals without a history of CVD at inclusion. Clearly, MNSIq scores ≥4 may identify a high cardiovascular risk subpopulation among individuals without preexisting CVD. By carrying out this subanalysis restricted to individuals without CVD at inclusion, we could demonstrate that our main findings are not driven by second or subsequent CVD events.

Currently, CVD risk stratification tools for individuals with diabetes are based mainly on general CVD risk factors, complemented by some diabetes-specific items such as duration of diabetes, glycemic control, and urinary albumin levels (27). The excess IR of CVD in individuals with DPN remained well >50% even after adjustment for a wide range of established CVD risk factors. This supports the notion that DPN may act as a marker for CVD (8). However, we can only speculate that this information might add in predicting CVD over and above established risk scores. We believe it is plausible that the questions included in the MNSIq represent a more

Table 3—Number and percentage of each cardiovascular end point during follow-up in the two cohorts

	ADDITION-Denmark	DD2
CVD	394 (100)	480 (100)
Ischemic heart disease	230 (58.4)	245 (51.0)
Stroke	66 (16.8)	100 (20.8)
Peripheral arterial disease	56 (14.2)	81 (16.9)
Heart failure	53 (13.5)	81 (16.9)

The percentages do not sum to 100%, as some individuals are diagnosed with more than one condition on the same date.

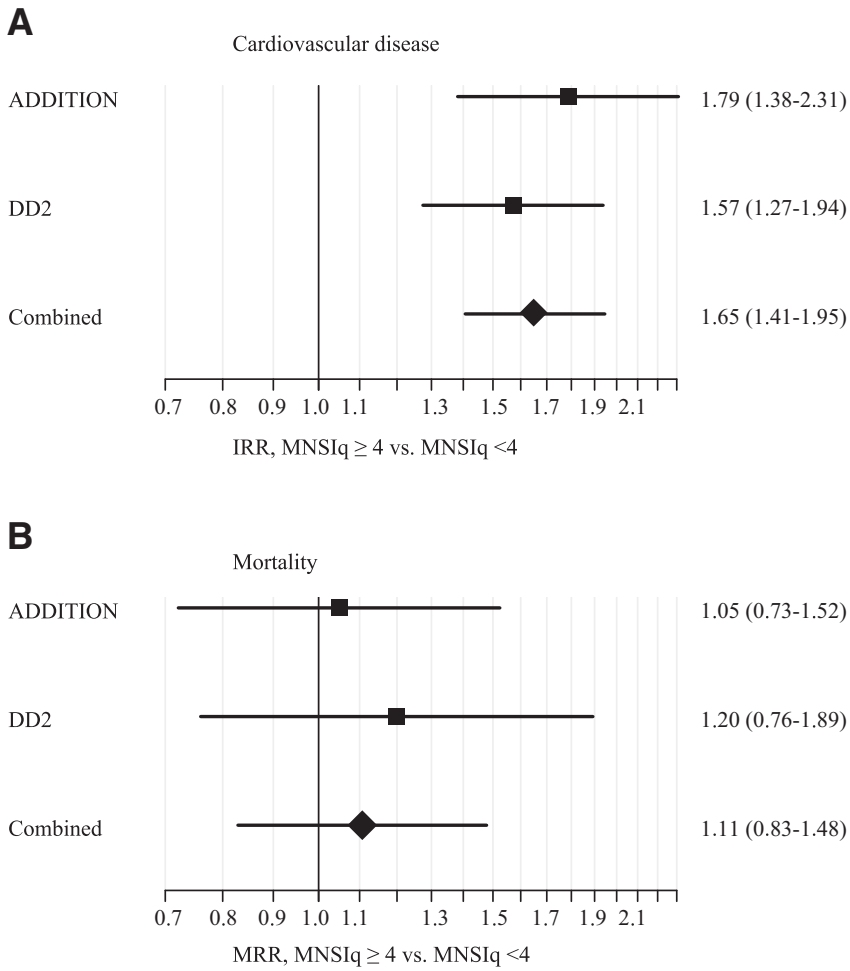

Figure 1—Adjusted cardiovascular and mortality IRRs comparing individuals with MNSIq scores ≥4 to those with MNSIq scores <4. Adjusted IRR of CVD (*A*) and adjusted all-cause MRRs (*B*) in individuals with MNSIq scores ≥4 compared with individuals with MNSIq scores <4. Models were adjusted for age, sex, HbA_{1c}, BMI, smoking status, alcohol consumption, LDL cholesterol, systolic blood pressure, lipid-lowering medication, antihypertensive medication, u-ACR, history of CVD, and randomization group (ADDITION-Denmark) or duration of diabetes (DD2). Combined estimates were obtained using fixed-effect meta-analyses.

complete summary of total lifetime exposure to CVD risk factors than the most recent levels of established CVD risk factors. The questions in the MNSIq may also represent markers of undefined mechanisms in the causal pathways of both DPN and CVD (e.g., physical activity level, obesity, cardiac, global vascular damage, or autonomic neuropathy) (28). Thus, our data suggest that the MNSIq could enhance identification of individuals who stand to gain the most from more aggressive CVD risk assessment and/or preventive CVD treatment early in diabetes. Further research is needed to evaluate whether aggressive cardiovascular risk factor management in high-risk patients additionally identified by MNSIq score can successfully attenuate the excess CVD incidence.

Strengths and Limitations

Main strengths of this study are its large sample size, inclusion of two cohorts from the same country with a similar age, sex distribution, and short diabetes duration, and the availability of detailed clinical data combined with register-based outcomes assessment. Our results are generalizable to other countries with similar demographic populations and health care systems. The positive predictive values of cardiovascular outcome diagnoses in the National Patient Registry are high (29). However, we might miss a small percentage of patients with CVD who were not hospitalized, reducing the power of the study marginally. The adjusted model included several confounders with various missingness, which, for some variables in our outcome analyses, exceeded 20%. We handled missing data by the MICE framework, which limits the loss of statistical precision and avoids the assumption of missing completely at random inherent in a complete case analysis.

We used a fixed-effect meta-analysis to combine estimates from both cohorts. The described similarity in population, data collection protocols, and ascertainment of outcomes combined with similar shapes of the cumulative incidence curves and point estimates for each outcome in the cohorts provided reassurance that the underlying effect of DPN was homogenous across both cohorts.

It is necessary to stress that the MNSIq is not the gold standard for evaluating DPN. The MNSIq was developed to facilitate an easy screening of DPN (18). In type 1 diabetes, the cutoff point of an MNSIq score ≥4 has been validated with a specificity of 92% and sensitivity of 40%, compared with clinically detected DPN (18). In a subgroup of 389 individuals in the DD2 cohort, an MNSIq score ≥4 was validated, and the reported specificity and sensitivity were 85% and 26%, respectively (30). As we expect the misclassification to be nondifferential, its impact would be an underestimation of the associations. The gold standard in that analysis was based on the definition of definite DPN as proposed by the Toronto Diabetic Neuropathy Expert Group (31). In addition to sensory symptoms, signs, or reduced ankle reflexes, the definition includes an abnormal nerve conduction study or reduced intraepidermal nerve fiber density.

We selected confounding variables on the basis of established evidence of an association of the variable with both DPN and CVD. Some variables may theoretically be caused by DPN (e.g., obesity if DPN leads to inactivity) and thus be intermediate factors rather than confounders; however, as the included individuals have short diabetes duration, we believe this is rarely the case. Finally, we cannot rule out uncontrolled and residual confounding by imperfectly measured, unmeasured, or unknown factors in our study.

CONCLUSIONS

Although the MNSIq was developed as a tool for detecting DPN, we found that symptoms indicative of DPN defined by MNSIq scores ≥4 also may serve as a marker of high IR of subsequent CVD in addition to

conventional risk factors in individuals with short diabetes duration. We found no evidence for an association between MNSIq scores ≥4 and mortality. Thus, a diagnostic workup for symptoms of DPN using the MNSIq early in the course of type 2 diabetes may offer an opportunity to identify a subpopulation for whom intensive risk factor management could potentially reduce the IR of CVD.

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Author Contributions. L.B. analyzed the data and drafted the manuscript. S.K.N. analyzed data. L.B., S.K.N., D.H.C., D.R.W., R.W.T., and M.C. conceived the idea, designed the study, provided input on statistical analysis, and participated in the drafting of the manuscript. L.B., S.K.N., D.H.C., J.S.N., S.T.A., M.E.J., T.S.J., A.S., H.A., H.B.-N., H.T.S., D.R.W., R.W.T., and M.C. contributed to data collection and interpretation of results. The presented study is based on a meta-analysis of two separate cohorts. Due to restrictions imposed by data sharing policies, full data access to each cohort's individual-level data was restricted: L.B., S.T.A., M.E.J., A.S., D.R.W., and M.C. had full access to the ADDITION-Denmark data. S.K.N., D.H.C., J.S.N., T.S.J., H.A., H.B.-N., H.T.S., and R.W.T. had full access to the DD2 study data. All authors had access to the full data that constitute the meta-analyzed results. All authors reviewed and edited the manuscript and accepted the final version for publication. L.B. had the final responsibility for the decision to submit for publication. L.B. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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