Risk-Factor Trajectories Preceding Diabetic Polyneuropathy: ADDITION-Denmark

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OBJECTIVE

To study cardiometabolic risk-factor trajectories (in terms of levels and changes over time) preceding diabetic polyneuropathy (DPN) 13 years after a screen-detected diagnosis of type 2 diabetes.

RESEARCH DESIGN AND METHODS

We clinically diagnosed DPN in a nested case-control study of 452 people in the Danish arm of the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION). By linear regression models, we estimated preceding risk-factor trajectories during 13 years. Risk of DPN was estimated by multivariate logistic regression models of each individual's risk-factor trajectory intercept and slope adjusting for sex, age, diabetes duration, height, and trial randomization group.

RESULTS

Higher baseline levels of HbA_{1c} (odds ratio [OR] 1.76 [95% CI 1.37; 2.27] and OR 1.68 [95% CI 1.33; 2.12] per 1% and 10 mmol/mol, respectively) and steeper increases in HbA_{1c} over time (OR 1.66 [95% CI 1.21; 2.28] and OR 1.59 [95% CI 1.19; 2.12] per 1% and 10 mmol/mol increase during 10 years, respectively) were associated with DPN. Higher baseline levels of weight, waist circumference, and BMI were associated with DPN (OR 1.20 [95% CI 1.10; 1.31] per 5 kg, OR 1.27 [95% CI 1.13; 1.43] per 5 cm, and OR 1.24 [95% CI 1.12; 1.38] per 2 kg/m^2, respectively).

CONCLUSIONS

Both higher levels and slopes of HbA_{1c} trajectories were associated with DPN after 13 years. Our findings indicate that the rate of HbA_{1c} increase affects the development of DPN over and above the effect of the HbA_{1c} level. Furthermore, this study supports obesity as a risk factor for DPN.

Hyperglycemia is considered the most important risk factor for the development of diabetic polyneuropathy (DPN) in type 1 diabetes (1,2). A more complex risk factor profile exists for DPN in type 2 diabetes, as intervention trials have failed to show a clear effect of enhancing glucose control on the risk of DPN (3–5). Besides hyperglycemia, age, diabetes duration, height, obesity, hypertension, dyslipidemia, and smoking have been proposed as risk factors for DPN in type 2 diabetes (6–9). Still, intervention trials targeting many of these risk factors have failed to demonstrate a clear effect on the risk of DPN (3,10,11).

Previous studies have assessed potential risk factors concurrently with DPN in cross-sectional studies and as baseline or mean levels of risk factors over time in longitudinal

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studies (6,9,12–17). The velocity of risk factor changes during the course of diabetes may reflect distinct pathophysiological mechanisms. Thus, risk-factor trajectories (both the levels and changes in risk factors over time) may influence the development of DPN. Identification of effects of changes in risk factors over time on the development of DPN (over and above the effects of risk factor levels) could reveal a need for stratification and intensification of the prevention efforts in the care for type 2 diabetes, and this could potentially bring new insight into the pathogenesis of DPN.

In our previous prospective study of risk factors associated with incident DPN assessed longitudinally by the Michigan Neuropathy Screening Instrument (MNSI) questionnaire in the Danish arm of the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION-Denmark), higher baseline levels of obesity and methylglyoxal and lower levels of HDL and LDL cholesterol were associated with a higher risk of incident DPN (17). Yet, clinically confirmed DPN is a more robust definition of DPN as outlined in the Toronto criteria for DPN (18). Clinically confirmed DPN requires the combination of abnormal nerve conduction (or a validated measure of small-fiber neuropathy) and symmetrical symptoms and/or signs of DPN to diagnose DPN (18). The point-of-care DPNCheck device (NeuroMetrix Inc., Waltham, MA), measuring sural nerve conduction, offers a rapid and clinically accessible method for diagnosing DPN (19,20). At the 13-year follow-up examination in ADDITION-Denmark, a thorough clinical examination for DPN was conducted, including DPNCheck measures. Additionally, conventional nerve conduction studies (NCSs) were conducted in a subgroup. In this nested case-control study of participants attending the 13-year follow-up examination, we aim to determine the impact of risk-factor trajectories from the onset of screen-detected type 2 diabetes preceding clinically confirmed DPN after 13 years.

RESEARCH DESIGN AND METHODS

This nested case-control study is based on data from participants attending the clinical 13-year follow-up examination in the Danish arm of ADDITION. ADDITION has been described in detail elsewhere (21). ADDITION-Denmark enrolled participants (aged 40–69 years) with screen-detected previously undiagnosed diabetes via stepwise screening in primary care between 2001 and 2006. In Denmark, the trial enrolled 1,533 patients from 190 general practices. The general practices were randomized to deliver either routine care for diabetes or intensive multifactorial target-driven care until the trial was concluded in 2009 (11,22). After the closure of ADDITION, participants have been followed observationally via questionnaires and registers and by a clinical follow-up examination in 2015–2016 (i.e., 13 years after the trial baseline).

Risk factors were evaluated at the diagnosis of diabetes and at the 6- and 13-year follow-up examinations assessing anthropometrics, blood pressure, and metabolic measures from blood and urine samples (HbA_{1c}, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, creatinine, and albumin-to-creatinine ratio), as previously described (21). Additional metabolic measures were obtained at the 13-year examination, including vitamin B12, alanine aminotransferase, thyrotropin (TSH), triiodothyronine, thyroxine (T4), and T4 uptake. Estimated glomerular filtration rate was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation (23). From self-administered questionnaires, records of alcohol consumption (units of alcohol per week) and smoking habits (current smoking or nonsmoker) were obtained. The general practitioners provided records on prescribed medication (glucose-lowering drugs, statins, antihypertensives, and aspirin).

The assessment of DPN was performed fulfilling the Toronto criteria for a confirmed diagnosis of DPN (18). Participants were interviewed about symptoms in the feet and/or the legs that could indicate DPN using the MNSI and Douleur Neuropathique en 4 Questions (DN4) questionnaire (24,25).

Clinical signs (deficits) of DPN were evaluated in both feet by *1*) activity of ankle reflexes with reinforcement applied if the reflex did not appear, *2*) vibration sensation at the dorsal aspect of the great toes using a 125-Hz tuning fork and the on-off method, and *3*) light touch sensation by a 10-g monofilament on the dorsal aspect of the great toes. These examinations were performed as outlined for the MNSI physical examination (24). Signs of DPN were defined as present if at least one of these examinations was graded as decreased or absent bilaterally.

All included participants underwent sural nerve assessments by DPNCheck (19,20). An internal validation has been performed in an unselected subgroup of 168 participants to validate DPNCheck measures against conventional NCS, including a binary outcome of NCS indicating DPN present or not by criteria outlined by Dyck et al. (26) (i.e., criteria number 8 of sum scores of *Z*-scores of six nerve parameters as described below) (A.M. Kural, S.T.A., N.T. Andersen, H.A., M.C., N.B.F., T.S.J., H.T., unpublished observations). Abnormal results from the DPNCheck had a sensitivity of 78%, specificity of 89%, positive predictive value of 71%, and negative predictive value of 92% for NCS indicating DPN (A.M. Kural, S.T.A., N.T. Andersen, H.A., M.C., N.B.F., T.S.J., H.T., unpublished observations). We considered DPNCheck results abnormal by bilateral values below the cutoff levels provided for the device (amplitude $\leq$4 μV or conduction velocity $\leq$40 m/s). We regarded a unilateral result valid if no measures were obtained from the other leg (e.g., due to discomfort from the examination or a bandage obstructing the examination; n = 23). Yet, we regard the requirement of bilateral abnormalities appropriate and likely to enhance the specificity of the DPNCheck for diagnosing DPN.

Participants with other potential causes of neuropathy were excluded: a history of cancer and chemotherapy treatment, excessive alcohol intake ($>$5 units alcohol/day), vitamin B12 deficiency ($<$125 mmol/L), hypothyroidism (TSH $>$10 mIU/L or TSH $>$4 mIU/L and T4 below the reference value), chronic renal failure (estimated glomerular filtration rate $<$15 mL/min/1.73 m^2), or acute liver failure (alanine aminotransferase $>$100 units/L).

We defined DPN by the combination of abnormal DPNCheck measures and the presence of symptoms and/or symmetrical signs of DPN. Participants with an abnormal DPNCheck but no symptoms and/or signs were considered to have subclinical DPN (n = 22), and participants with symptoms and/or signs of DPN but normal DPNCheck were considered

to have possible or probable DPN (n = 193) (18). We pooled the participants with subclinical and possible or probable DPN together with the DPN-free control subjects in our analyses and performed a sensitivity analysis that excluded these participants from the control group.

An unselected subgroup of 161 participants (at one of five study sites) who completed conventional NCS was used for another sensitivity analysis of the diagnostic strategy applied using DPNCheck measures as a proxy for the gold standard of NCSs. NCSs were performed using Keypoint.NET equipment (Dantec, Skovlunde, Denmark). We evaluated NCSs by the criteria defined by Dyck et al. (26) (i.e., criteria number 8 from Z-scores of in-house age- and height-matched normative material). Sum scores were calculated from six Z-scores of the following parameters: the conduction velocity of the peroneal, tibial, and median (or ulnar) nerves; minimum F-wave latencies of the tibial and median (or ulnar) nerves; and sensory nerve action potential amplitude of the sural nerve. NCS sum scores $>$2.0 were considered abnormal and indicating DPN. Thus, in this sensitivity analysis, we defined DPN by abnormal NCS combined with symptoms and/or symmetrical signs of DPN. Participants with subclinical DPN (n = 10) or possible or probable DPN (n = 66) were pooled together with the DPN-free control subjects in this analysis.

Ethics

The study was approved by the Committee on Health Research Ethics in the Central Denmark Region (file numbers 20000183 and 1-10-72-63-15) and the Danish Data Protection Agency (file number 2005-57-0002, ID185). The study was conducted in accordance with the principles of the Declaration of Helsinki, 1996 version, and all study participants gave written informed consent.

Statistical Analysis

We performed a nested case-control analysis comparing risk-factor levels and changes (trajectories) between those who had developed DPN at 13-year follow-up (case subjects) and those without DPN (control subjects). The characteristics of participants (at baseline, 6-year follow-up, and 13-year follow-up) were reported by DPN status at the 13-year follow-up. Data were represented as median and interquartile range for continuous variables and as frequencies and proportions for categorical variables. Covariates were compared using Kruskal-Wallis and χ^2 tests as appropriate. The prevalence of DPN was reported.

To obtain individual indicators for risk factor levels and change, a set of linear regression models were fitted separately for each participant from levels of risk factors assessed at the diagnosis of diabetes and at the 6- and 13-year examinations. These models used the individual participant's time from the diagnosis of diabetes to the three risk-factor assessments as the explanatory variable, and respective outcomes were weight, waist circumference, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA_{1c}, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Only participants with all three assessments for a risk factor had a linear regression fitted. Each of these models yielded an individual intercept and a slope subsequently used as indicators of risk-factor levels and change, respectively. We reported the medians and interquartile range of intercepts and slopes of risk-factor trajectories for the entire study sample. An example of risk-factor trajectories by status of DPN is depicted (Fig. 1).

The risk of DPN was estimated for each risk-factor trajectory (for intercept and slope, respectively) by multivariate logistic regression models. All models were adjusted for sex, age, diabetes duration, height, and trial randomization group. We also adjusted the intercept for the slope and conversely adjusted the slope for the intercept. We reported the risk of DPN by odds ratios (ORs) per clinically relevant differences of each risk factor at baseline and per clinically relevant changes in risk factors over time (calculated per 10 years of follow-up). To express the outcome of ORs on our analyses, we chose a clinically achievable scale that expressed clinically relevant differences and changes rather than OR per unit of each parameter.

Effect modification by sex and other covariates under study was tested using a Wald test. We confirmed the linearity of the associations between risk-factor levels and changes and the risk of DPN by testing the statistical significance of quadratic terms.

A sensitivity analysis was performed excluding the participants with subclinical, possible, or probable DPN from the control group.

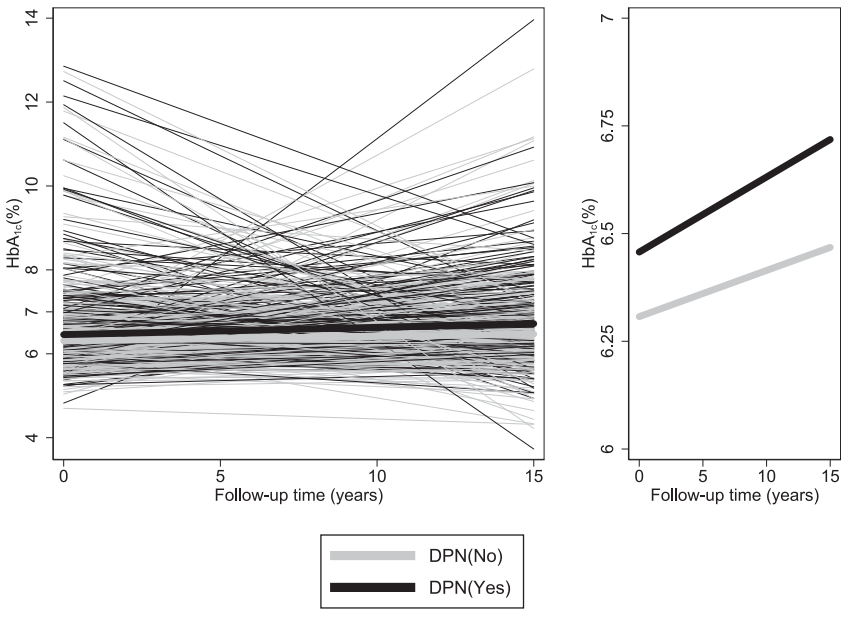

Figure 1—Example of risk-factor trajectories by status of DPN at the 13-year follow-up examination, ADDITION-Denmark. The trajectories of HbA_{1c} (%) for each participant (N = 452) by status of DPN after 13 years of diabetes. The left panel shows the trajectories for individuals (thin lines) and the trend for groups by DPN status (thick lines). The right panel shows the trends for the trajectories of HbA_{1c} on a narrow scale around the intercept for HbA_{1c} by DPN status. DPN(No), no DPN clinically confirmed at the 13-year follow-up examination; DPN(Yes), a diagnosis of clinically confirmed DPN at the 13-year follow-up examination.

Another sensitivity analysis was performed in the subgroup of 161 participants who had DPN additionally diagnosed by conventional NCS.

RESULTS

Of the total cohort of 585 participants attending the 13-year follow-up examination, we excluded 79 participants in accordance with the exclusion criteria: 26 had a history of cancer and chemotherapeutic treatment, 25 had excessive alcohol intake, 3 had renal failure, 23 had vitamin B12 deficiency, and 2 had acute liver failure. DPNCheck assessment was not completed in 54 participants, which left 452 participants for analysis (median age 70.9 years [25th percentile; 75th percentile (p25; p75): 65.9; 75.6], 281 [62.2%] men, and 427 [94.5%] white Caucasians). The prevalence of DPN was 27.0%, and subclinical DPN was seen in 4.9%. In the control group, 193 (59%) had possible or probable DPN.

The characteristics of participants by DPN status at the 13-year follow-up are shown in Table 1. DPN case subjects were more often males, tended to be taller, and had higher levels of obesity (weight, waist circumference, and BMI), higher levels of HbA_{1c}, and a higher proportion of albuminuria and treatment by insulin or aspirin than control subjects. In contrast, DPN case subjects had lower levels of total cholesterol and LDL cholesterol, and a lower proportion of case subjects were currently smoking than control subjects.

We found no effect modification by sex. The calculated intercepts (modeled baseline levels) and slopes (changes per year) characterizing each individual's trajectory for each risk factor are summarized in Table 2. An example of risk-factor trajectories is depicted in Fig. 1.

No difference was seen in the risk of DPN comparing sexes (OR 0.46 [95% CI 0.46; 1.13] for men compared with women) and trial randomization groups (OR 1.15 [95% CI 0.76; 1.73]; i.e., for the intensive group compared with the routine group). A higher risk of DPN was associated with increasing age (OR 1.08 [95% CI 1.04; 1.13] per year of age), longer duration of diabetes (OR 1.14 [95% CI 1.00; 1.30] per year), and greater height (OR 1.06 [95% CI 1.03; 1.10] per centimeter).

Table 3 summarizes the ORs per clinically relevant differences in the modeled baseline levels (intercepts) and per changes during 10 years (slopes) for each risk factor.

Both higher modeled baseline levels of HbA_{1c} (OR 1.76 [95% CI 1.37; 2.27] and OR 1.68 [95% CI 1.33; 2.12] per 1% and 10 mmol/mol, respectively) and steeper increase in HbA_{1c} over time (OR 1.66 [95% CI 1.21; 2.28] and OR 1.59 [95% CI 1.19; 2.12] per 1% and 10 mmol/mol increase during 10 years, respectively) were associated with a higher risk of DPN. Higher baseline levels of weight, waist circumference, and BMI were also associated with higher risk of DPN (OR 1.20 [95% CI 1.10; 1.31] per 5 kg, OR 1.27 [95% CI 1.13; 1.43] per 5 cm, and OR 1.24 [95% CI 1.12; 1.38] per 2 kg/m^2, respectively). In contrast, a steeper increase in total cholesterol over time was associated with a lower risk of DPN (OR 0.83 [95% CI 0.70; 0.99] per 0.5 mmol/L increase during 10 years).

Sensitivity analyses excluding participants with subclinical, possible, or probable DPN from the control group are shown in Supplementary Table 1. Similar results were produced, except that no association appeared for change in total cholesterol, and a somewhat larger magnitude of ORs was found for the significant associations.

The second sensitivity analysis using conventional NCS instead of the proxy measure of NCS by DPNCheck consisted of 161 participants (median age 70.0 years [p25; p75: 65.3; 74.9], 102 [63.4%] men, and 142 [88.2%] white Caucasians). The prevalence of DPN was 19.3%, and 6.2% had subclinical DPN. In the control group, 66 (51%) had possible or probable DPN.

The characteristics of participants by status of DPN defined by including NCS are shown in Supplementary Table 2. Similar patterns as for the main analysis were seen. The risk of DPN for risk-factor trajectories of DPN defined by including NCS are summarized in Supplementary Table 3. Similar results as for the main analysis were seen, with the additional finding that a steeper increase in LDL cholesterol over time was associated with a lower risk of DPN (OR 0.83 [95% CI 0.69; 0.99] per 0.25 mmol/L increase during 10 years). In contrast to the results from the main analysis, none of the modeled baseline levels of risk factors were associated with the risk of DPN.

CONCLUSIONS

This study is the first to evaluate both levels and changes in risk factors from the onset of screen-detected type 2 diabetes associated with a confirmed diagnosis of DPN after 13 years of diabetes. We performed a case-control analysis based on 452 participants clinically examined for DPN. A higher risk of DPN was associated with greater height, increasing age, and longer diabetes duration. Both higher baseline levels of HbA_{1c} and a steeper increase in HbA_{1c} over time were seen in case subjects with DPN than in control subjects without DPN. Higher baseline levels of obesity (weight, waist circumference, and BMI) were associated with a higher risk of DPN, and a steeper increase in total cholesterol was associated with a lower risk of DPN.

The novel nature of this study prevents a direct comparison of our findings with previous reports. We find a relatively low prevalence of DPN of 27% after a median of 13 years of type 2 diabetes (15,27,28). Yet, little evidence exists on the prevalence of DPN in people with diabetes detected at an early stage, and comparison of prevalence between studies applying different definitions of DPN and conducted in different time windows is not straightforward (7). The ADDITION study included participants identified through screening, which means that their baseline examination is likely to have preceded the clinical presentation of diabetes by 3–5 years (29).

We identified increasing age, greater height, and longer diabetes duration as risk factors for DPN, which is in line with previous studies (6,7,12,27).

We defined DPN by abnormal DPNCheck and fulfilling the Toronto criteria for confirmed DPN. We used conventional NCS in an unselected subgroup for sensitivity analyses of the diagnostic strategy. Similar DPN prevalence, participant characteristics, and risk factors associated with the development of DPN were seen using either DPNCheck or conventional NCS. However, a relatively large proportion of control subjects had subclinical, possible, or probable DPN using either measure of nerve conduction. One explanation for this could be that we overlooked cases of isolated small-fiber neuropathy, yet less is known about the prevalence of isolated small-fiber neuropathy in type 2 diabetes (30). Also, cases of early-stage DPN that were more distally located than the anatomical site for

Table 1—Characteristics of participants by DPN status at 13-year follow-up with characteristics of participants shown by data from baseline, 6-year, and 13-year follow-up, ADDITION-Denmark

	13-year follow-up		6-year follow-up		Diabetes diagnosis	
Characteristics	No DPN	DPN	No DPN	DPN	No DPN	DPN
Number of participants	330 (73.0)	122 (27.0)				
Male sex	194 (58.8)	87 (71.3)*				
Age (years)	70.1 (65.0; 74.5)	73.8 (68.5; 77.0)*				
Diabetes duration (years)	12.7 (11.3; 13.4)	12.9 (12.2; 13.7)*				
Height (cm)	169.4 (163.0; 175.8)	172.0 (167.0; 177.5)*				
HbA_{1c} (%)	6.5 (6.2; 7.0)	6.8 (6.4; 7.5)*	6.3 (6.0; 6.7)	6.6 (6.0; 7.2)*	6.3 (6.0; 6.8)	6.5 (6.1; 7.4)*
HbA_{1c} (mmol/mol)	48.0 (43.9; 53.0)	51.0 (46.0; 58.0)*	45.4 (42.1; 49.7)	48.6 (42.1; 55.2)*	45.4 (42.1; 50.8)	47.5 (43.2; 57.4)
Weight (kg)	84.7 (74.1; 94.2)	91.0 (82.3; 106.8)*	86.0 (75.6; 96.6)	91.6 (84.2; 106.2)*	86.6 (77.2; 97.1)	93.3 (85.5; 105.8)*
Waist circumference (cm)	103.0 (95.5; 111.0)	110.5 (101.6; 118.0)*	101.5 (94.3; 109.6)	106.2 (99.6; 116.4)*	102.0 (95.5; 109.5)	107.3 (100.7; 114.8)*
BMI (kg/m^2)	29.1 (26.2; 32.2)	31.1 (28.1; 35.2)*	29.1 (26.5; 32.8)	31.2 (28.2; 34.8)*	29.0 (27.0; 33.0)	31.0 (28.0; 35.0)*
SBP (mmHg)	137.0 (127.0; 149.0)	138.0 (130.0; 149.0)	132.7 (122.0; 144.3)	135.2 (124.3; 145.7)	145.3 (133.0; 158.0)	146.7 (134.3; 158.3)
DBP (mmHg)	82.0 (77.0; 88.0)	82.0 (74.0; 89.0)	83.0 (77.3; 92.0)	83.8 (77.3; 90.7)	88.3 (80.7; 95.7)	86.5 (80.7; 93.5)
Total cholesterol (mmol/L)	4.3 (3.7; 5.0)	4.0 (3.5; 4.7)*	4.4 (3.8; 4.9)	3.9 (3.5; 4.7)*	5.5 (4.9; 6.3)	5.6 (4.9; 6.3)
HDL cholesterol (mmol/L)	1.4 (1.1; 1.6)	1.3 (1.1; 1.6)	1.3 (1.1; 1.6)	1.3 (1.1; 1.6)	1.4 (1.2; 1.6)	1.3 (1.1; 1.6)
LDL cholesterol (mmol/L)	2.1 (1.7; 2.6)	1.9 (1.5; 2.4)*	2.1 (1.7; 2.7)	1.9 (1.4; 2.4)*	3.3 (2.7; 4.0)	3.4 (2.8; 4.0)
Triglycerides (mmol/L)	1.5 (1.1; 2.1)	1.5 (1.1; 2.2)	1.4 (1.1; 2.0)	1.3 (1.0; 2.0)	1.6 (1.1; 2.2)	1.6 (1.1; 2.3)
Any albuminuria†	76 (23.5)	50 (41.7)*	61 (18.8)	39 (32.2)*	41 (13.9)	22 (20.2)
Alcohol (units/week)	3.0 (0.0; 9.0)	3.0 (0.0; 12.0)	5.0 (1.0; 12.0)	5.0 (1.0; 14.0)	5.0 (2.0; 12.0)	7.0 (1.0; 14.0)
Current smoking	46 (15.5)	10 (8.8)*	69 (21.4)	18 (15.8)*	81 (24.7)	33 (27.0)
Former smoking	129 (43.3)	70 (61.4)*	119 (37.0)	62 (54.4)*	109 (33.2)	52 (42.6)
Treatment with insulin	31 (11.4)	28 (26.9)*	21 (6.8)	13 (10.9)	—	—
Treatment with metformin	170 (62.5)	74 (71.2)	136 (43.7)	61 (51.3)	—	—
Treatment with statins	220 (80.9)	78 (75.0)	242 (77.8)	91 (76.5)	48 (15.0)	14 (11.6)
Treatment with aspirin	130 (47.8)	67 (64.4)*	201 (64.6)	88 (73.9)	37 (11.5)	17 (14.0)
Treatment with antihypertensives	231 (84.9)	94 (90.4)	247 (79.4)	98 (82.4)	127 (39.6)	48 (39.7)

Categorical data are frequencies (percentage of participants with data on the particular characteristic), and continuous data are medians (p25; p75). DPN, a diagnosis of clinically confirmed DPN at 13-year follow-up; No DPN, no DPN clinically confirmed at 13-year follow-up. *$P < 0.05$. †Albumin-to-creatinine ratio ≥3.5 mg/mmol for women and albumin-to-creatinine ratio ≥2.5 for men.

Table 2—Calculated intercepts (modeled baseline levels) and slopes (changes per year) of risk factors in the entire study sample of 452 participants, ADDITION-Denmark

Risk factors	Median of modeled baseline values	p25; p75	Median of change per year	p25; p75
HbA_{1c} (%)	6.4	6.0; 6.9	0.01	−0.03; 0.05
HbA_{1c} (mmol/mol)	45.9	41.9; 51.8	0.13	−0.30; 0.57
Weight (kg)	89.1	79.3; 99.3	−0.17	−0.54; 0.18
Waist circumference (cm)	102.9	96.5; 111.6	0.10	−0.29; 0.80
BMI (kg/m^2)	29.9	27.2; 33.5	−0.02	−0.16; 0.10
SBP (mmHg)	143.2	132.4; 154.6	−0.63	−1.68; 0.39
DBP (mmHg)	87.7	81.3; 94.1	−0.44	−1.08; 0.09
Total cholesterol (mmol/L)	5.3	4.7; 5.9	−0.10	−0.17; −0.03
LDL cholesterol (mmol/L)	3.1	2.6; 3.7	−0.10	−0.16; −0.03
HDL cholesterol (mmol/L)	1.3	1.2; 1.6	0.00	−0.02; 0.02
Triglycerides (mmol/L)	1.6	1.1; 2.2	0.00	−0.04; 0.03

Modeled baseline levels and changes per year of risk factors calculated from linear regression models for each participant of each risk factor with the time since diabetes diagnosis as the underlying timescale.

nerve conduction assessments might have been overlooked (18,27). The stronger risk-factor associations observed in the sensitivity analysis excluding participants with subclinical, possible, or probable DPN from the control group could be owing to the exclusion of false-negative participants from the control group. In contrast, symptoms and signs assessed could reflect unspecific age-related abnormalities or comorbidities that are likely to be more prevalent in this cohort of elderly people; for example, it has been reported that the prevalence of abnormal ankle reflexes increases during the course of life (31). We do not consider age in the definition of DPN, as it is also not accounted for in the Toronto criteria for DPN. Importantly, the mean age of this cohort at diabetes diagnosis was 60 years, which is highly applicable to a large part of people with type 2 diabetes, as prevalence and incidence of diabetes peaks just around this age (32). In summary, to some extent, we might underestimate the prevalence of DPN and the strength of associations between risk factors and DPN by the applied definition of DPN. Nevertheless, we consider the definition of DPN applicable to a real-life setting in the care for diabetes and likely to enhance the specificity of the definition of DPN in this cohort of elderly people.

We showed that higher baseline levels of HbA_{1c} were associated with the risk of DPN. This finding supports the comprehensive body of evidence pointing to hyperglycemia as an important risk factor for DPN (6,12,27). In addition, we showed that a steeper increase in HbA_{1c} over time was associated with a higher risk of DPN independently of the baseline level of HbA_{1c}. This is a novel and noteworthy finding. The associations between HbA_{1c} and DPN were found despite the fact that we studied a group of patients with very little variation in HbA_{1c} at baseline and very little change in HbA_{1c} over time, remaining very close to normal levels. Our findings indicate that the impact of HbA_{1c} is important for the development of DPN, even at near-normal levels, and that a small steady increase in HbA_{1c}, even within a near-normal range and over a long period of time, warrants clinical attention.

Table 3—Risk of DPN after 13 years of screen-detected diabetes per clinically relevant differences in modeled baseline levels (intercepts) and changes during 10 years (slopes) of risk factors by multivariate logistic regression models, ADDITION-Denmark

Risk factors	OR of DPN by baseline value	95% CI	OR of DPN by change during 10 years	95% CI
HbA_{1c} (unit = 1%)	1.76*	1.37; 2.27	1.66*	1.21; 2.28
HbA_{1c} (unit = 10 mmol/mol)	1.68*	1.33; 2.12	1.59*	1.19; 2.12
Weight (unit = 5 kg)	1.20*	1.10; 1.31	1.17	0.97; 1.42
Waist circumference (unit = 5 cm)	1.27*	1.13; 1.43	1.16	0.94; 1.42
BMI (unit = 2 kg/m^2)	1.24*	1.12; 1.38	1.23	0.99; 1.53
SBP (unit = 10 mmHg)	1.03	0.86; 1.23	1.08	0.89; 1.31
DBP (unit = 5 mmHg)	0.95	0.81; 1.11	1.02	0.86; 1.20
Total cholesterol (unit = 0.5 mmol/L)	0.91	0.76; 1.09	0.83*	0.70; 0.99
LDL cholesterol (unit = 0.25 mmol/L)	0.95	0.85; 1.06	0.91	0.81; 1.01
HDL cholesterol (unit = 0.25 mmol/L)	0.88	0.70; 1.12	0.94	0.73; 1.22
Triglycerides (unit = 0.5 mmol/L)	1.05	0.89; 1.25	0.93	0.75; 1.14

The risk of DPN is expressed by OR (95% CI) from multivariate logistic regression models adjusted for sex, age, diabetes duration, and trial randomization group, besides slope for the intercept estimate and intercept for the slope estimate. ORs expressed per clinically relevant difference in baseline levels and changes during 10 years. The ORs can be converted from OR per x-units (e.g., per 5 kg in weight) to OR per y-units (e.g., per 1 kg weight) using the following equation: $OR^{(y/x)}$. For example, the OR for weight per 1 kg is $(1.22)^{1/5} = 1.04$. The same equation applies to the CI. The χ^2 test and P values are unchanged by a change of scale. *$P < 0.05$.

We suggest this effect may be even stronger in populations with clinically detected diabetes likely to show higher baseline levels of HbA_{1c}, greater variation of HbA_{1c} levels, and a greater change in HbA_{1c} over time.

Higher baseline levels of obesity were associated with DPN. This is consistent with the findings from our prospective study of incident DPN in ADDITION-Denmark (17,24). A number of other studies have also reported obesity as a risk factor for DPN (9,13,33,34).

In contrast to other studies (6,12,27), we found no associations between baseline levels of total cholesterol, LDL cholesterol, and triglycerides and DPN. We observed that a steeper increase in total cholesterol over time was associated with a lower risk of DPN, as was a steeper increase in LDL cholesterol in the sensitivity analyses with DPN defined by NCS. Yet, the change in lipids over time is likely to be influenced by statin treatment initiated in a great proportion of individuals in this study after the diagnosis of diabetes (83%). Controlling our analysis for statin treatment takes away the statistical significance of associations for change in total cholesterol and LDL cholesterol (data not shown). Likewise, these associations disappeared in the sensitivity analyses excluding participants with subclinical, possible, or probable DPN from the control group. The explanation for our findings of associations between lipids and DPN is complicated, as our study is observational and lacks information on class of statin prescribed, exact onset or cessation of statin treatment, or dosage of treatment, as well as lacking related repeated measures of DPN. Moreover, the literature has shown conflicting results for the effect of statin treatment and the development of DPN (35–37). In summary, repeated measures of lipid levels and DPN assessments together with exact information on lipid-lowering treatment would be useful to further clarify whether a change in lipid levels is associated with the development of DPN.

In contrast to our previous study and others reporting low levels of HDL cholesterol as a risk factor for DPN (13,17), HDL cholesterol was not associated with DPN in the present analysis. High blood pressure and smoking did not appear as risk factors for DPN in the current study, which is in contrast to reports from others (6,7,12,38).

We found no difference in the prevalence of DPN when comparing trial randomization groups. Likewise, no difference was seen in our prospective study of DPN (17). This supports the observations made in many other trials on DPN (3). We propose that this is explained by the minor differences in treatment intensity that were achieved in this pragmatic trial. Additionally, this could reflect a limited effect of the multifactorial treatment on the development of DPN.

The key strengths of our study are the large size, longitudinal study design, and relatively long follow-up of 13 years. Despite these strengths, our study also has a number of limitations. First, our definition of DPN requires large-fiber abnormalities, as no validated measure of small nerve fiber abnormality was included. This might imply overlooking cases of small-fiber neuropathy mainly representing early-stage DPN. This possibly causes underestimation of both the prevalence of DPN and the strength of associations between risk factors and DPN in our study, as outlined above. Second, we do not know the exact timing of the onset of DPN and thus cannot claim to have studied predictive risk factors for the development of DPN. However, as the cases of DPN in our cohort are less severe DPN with little impact on the health status of the participants, we consider it unlikely that DPN influences the risk factors studied, and thus, we consider reverse causation unlikely. Third, we calculated rough estimates of changes in risk factors based on three measures for each risk factor holding a risk of imprecision in the estimated trajectories.

The generalizability of our observations to the total ADDITION-Denmark cohort (n = 1,533) is likely to be influenced by selection bias due to nonattendance in the 13-year follow-up examination with a competing risk of mortality and other diseases. We consider it likely that this selection process caused an underestimation of the true risk of DPN rather than an overestimation because nonattending participants were older at baseline and more had a history of cardiovascular disease (data not shown). Our results may not apply to patients with clinically diagnosed type 2 diabetes identified at a later time point in the course of diabetes; this group is likely to have higher baseline levels of HbA_{1c} and greater change in HbA_{1c} over time and to be less compliant in following the treatment for diabetes. In addition, risk factors may influence the development of DPN differently in elderly people compared with younger people.

In conclusion, this study indicates that the rate of increase in HbA_{1c} affects the development of DPN over and above the effect of the baseline level of HbA_{1c} even within ranges considered well controlled. Higher baseline levels of HbA_{1c} and higher obesity levels (weight, waist circumference, and BMI) were associated with higher risk of DPN. Additionally, participants who were older, had a longer duration of diabetes, or were male had higher risk of DPN 13 years after a screen-detected diagnosis of type 2 diabetes. Studies combining risk-factor trajectories with prospective assessments of DPN and including both measures of small and large nerve fiber dysfunction are called for to enhance the evidence of risk-factor trajectories identified in this study.

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