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Diabetic neuropathy is a substantial burden in people with Type I diabetes and is strongly associated with socioeconomic disadvantage: A population representative study from Scotland

Anita Jeyam[1], Stuart J McGurnaghan[1], Luke AK Blackbourn[1], John M McKnight[2], Fiona Green[3], Andrew Collier[4], Paul M McKeigue[5], Helen M Colhoun[1,6]; on behalf of the SDRNT1BIO Investigators

Author affiliations:

[1]MRC Institute of Genetic and Molecular Medicine, University of Edinburgh, Edinburgh, UK
[2]Western General Hospital, NHS Lothian, Edinburgh, UK
[3]Research & Development Support Unit, Dumfries & Galloway Royal Infirmary, Dumfries, UK
[4]Diabetic Day Centre University Hospital, Ayr, UK
[5]Usher Institute of Population Health Sciences and Informatics, Centre for Population Health Sciences, School of Molecular, Genetic and Population Health Sciences, University of Edinburgh, Edinburgh, UK
[6] Department of Public Health, NHS Fife, Kirkcaldy, Scotland, UK

Corresponding author:

Anita Jeyam, Institute of Genetic and Molecular Medicine Crewe Road South Edinburgh EH4 2XU UK email: anita.jeyam@igmm.ed.ac.uk

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ABSTRACT

Objective: To assess the contemporaneous prevalence of diabetic peripheral neuropathy (DPN) in people with type 1 diabetes (T1D) in Scotland and study its cross-sectional association with risk factors and other diabetic complications.

Research design and methods: We analyzed data from a large representative sample of adults with T1D (N=5,558). We assessed the presence of symptomatic neuropathy using the dichotomized (≥4) Michigan Screening Instrument Patient Questionnaire score. Logistic regression models were used to investigate associations between DPN and risk factors, as well as with other complications.

Results: The burden of DPN is substantial with 13% prevalence overall. Adjusting for attained age, diabetes duration and sex, the odds of DPN increased mainly with waist-hip ratio, lipids, poor glycemic control (OR 1.51 95% CI [1.21 - 1.89] for levels of 75 vs 53 mmol/mol), ever vs. never smoking (1.67 [1.37-2.03]), worse renal function (1.96 [1.03-3.74] for eGFR levels <30 vs. ≥90 ml/min/1.73m²). The odds significantly decreased with HDL-cholesterol (0.77 [0.66-0.89] per mmol/L). Living in more deprived areas was associated with DPN, (2.17 [1.78, 2.65]) for more vs. less deprived areas adjusted for other risk factors). Finally, individuals with prevalent DPN were much more likely than others to have other diabetes complications.

Conclusions: Diabetic neuropathy remains substantial, particularly affecting those in the most socioeconomically deprived groups. Those with clinically manifest neuropathy also have a higher burden of other complications and elevated levels of modifiable risk factors. These data suggest that there is considerable scope to reduce neuropathy rates and narrow the socioeconomic differential by better risk factor control.

Keywords: type 1 diabetes; SDRNT1BIO; DPN; Michigan Neuropathy Screening Instrument; SIMD; logistic regression

Introduction

Neuropathy is a major complication of diabetes that results from nerve damage and has diverse manifestations (1). One of the most common manifestations is diabetic peripheral neuropathy (DPN), the symptoms of which depend on the class of sensory fibers involved. The typical DPN is distal symmetrical polyneuropathy, which is defined by the Toronto Diabetic Neuropathy Expert Group as “a symmetrical length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure (diabetes) and cardiovascular risk covariates” (2). The majority of patients with DPN may remain asymptomatic (1); others experience pain, loss of sensation, which in turn increases the risk of injury, falls, fractures, foot ulceration and thereby amputation. Hence, patients suffering from DPN experience a deterioration of their quality of life (1,3,4).

Current guidelines recommend testing for temperature or pinprick sensation, vibration perception and using the 10-g monofilament to test for risk of foot ulceration (5–7). The tests only detect neuropathy at an advanced stage (8,9).

There is currently no approved treatment specifically targeted at prevention of DPN. Current guidelines such as the American Diabetes Association’s 2019 Standards of Care (7) only recommend tight glycemic control in patients with Type 1 diabetes. This recommendation mainly stems from the results of the Diabetes Control and Complications Trial (DCCT) (10,11). Drug treatment of DPN mainly comprises symptom control using anticonvulsants and antidepressants (7,12,13), with duloxetine and pregabalin being among the first-line therapies indicated in the major guidelines (14). There are no neuropathy specific preventive or curative drugs.

Risk factor management has changed over the past decade with new tools of glycemic control being available such as pumps and continuous glucose monitoring; the landscape of complications has also changed. For example, diabetes is no longer the leading cause of blindness in England and Wales (15); the incidence of lower extremity amputations in Scotland has reduced (16). Therefore, in order to have up-to-date guidelines and policy, it is important to capture a current picture of the burden of clinically manifest neuropathy as well as of the risk factors and other diabetes complications associated with neuropathy. Neuropathy is one of the most difficult complications to define epidemiologically since the clinical screening examination is time consuming to conduct at epidemiological scale. Here we used the Michigan Neuropathy Screening Instrument Patient Questionnaire (MNSIQ) (17) to derive a picture of the current burden of symptomatic DPN across age and sociodemographic strata in a large nationally representative sample of people with type 1 diabetes. Finally, we explored the association of symptomatic DPN with potential risk factors and its clustering with other diabetes complications.

Research design and methods

The Scottish Diabetes Research Network Type 1 Bioresource (SDRNT1BIO) is a large cohort (N=6,127) of adults aged 16 years and older, recruited between December 2010 and November 2013 across Scotland. The Bioresource consists of patients with type 1 diabetes (T1DM), MODY (Maturity Onset diabetes of the Young) or LADA (Latent autoimmune diabetes of adults. The patients were current insulin users and had started insulin within 1 year of diagnosis. This cohort and its representativeness of the national adult population with Type 1 diabetes has been previously described: the SDRNT1BIO cohort was shown to have similar characteristics to those of the national population with

Type 1 diabetes for whom we also have data on many clinical characteristics but unfortunately not on the MNSI (18). Baseline data including a self-report questionnaire were collected at study date, and linked, both retrospectively and prospectively, to routine electronic health care data. The questionnaire included the MNSIQ. These linked data included diabetes related information from the Scottish Care Information-Diabetes Mellitus (SCI-DM) database (19), the Scottish Renal Registry and routine data from Information Services Division Scotland such as hospital admissions data (Scottish Morbidity Record SMR01). The data linkage and these data sources have been described in detail in Akbar et al (18). In brief, SCI-DM captures routine clinical encounters (>99%) of those with a diagnostic code of diabetes nationally. This includes the Scottish foot screening program which aims to assess the risk of developing foot ulceration in diabetes patients. The annual screening involves the use of a 10-g monofilament test plus the evaluation of the foot for ulceration and the possible development of a Charcot joint. (20). However, due to high levels of absence of data available at this time, it was not possible to use these to help define DPN.

Assessment of symptomatic DPN

We defined symptomatic DPN based on the MNSIQ (17), using the validated threshold of a MNSIQ score of 4 or more (21) as evidence of the presence of symptomatic DPN; this criterion was also used in a recent study to define DPN (22). We also estimated the proportion of patients with painful neuropathy, defined as a MNSIQ score of 4 or more combined with a positive answer to the MNSIQ item: *"Do you ever have any burning pain in your legs and/or feet?"*

We evaluated the proportion of patients who had been hospitalized for diabetic neuropathy, using ICD-10 and ICD-9 codes for diabetes with neurological complications. We also evaluated the proportion of those who had ever had Charcot joint based on the foot screening records.

Risk factors

We explored associations with known risk factors for microvascular disease and other factors previously reported as potentially related to DPN.

Height (cm), weight (Kg), waist (cm) and hip (cm) measures were taken on study date as described in Akbar et al. (18). The albuminuria status on study day was derived as described in Bermingham et al. (23). Information on alcohol consumption was self-reported in a patient questionnaire, the typical weekly consumption of alcohol was used in our analyses. Measurements for other risk factors were obtained through the linked data: HbA1c (mmol/mol), triglycerides (mmol/L), total Cholesterol (mmol/L), HDL Cholesterol (mmol/L), LDL Cholesterol (mmol/L), smoking status (ever smoker); eGFR levels (mL/min/1.73m^2) were computed using the CKD Epidemiology Collaboration formula eGFR (24). Baseline measure was taken as the closest measure to study date within a one year window (from 365 days pre to 365 days post study date). Due to the high variability in blood pressure measurements, we used the mean value within this window for both systolic and diastolic blood pressure (mmHg).

Complications

Retinopathy status at baseline was obtained from the Scottish Diabetic Retinopathy Screening Programme (DRS) records, plus via SCI-DC, retaining the closest measurable

screening record within the time-frame set above. The grades measured and their meaning were described previously in Looker et al. (25), with the grading of the worst eye being used. Finally, for the purposes of the analyses, all stages of retinopathy were grouped together (mild, moderate or any of the referable states). A history of prior cardiovascular disease (CVD) at baseline was extracted from linked hospital admissions data having occurred before the study date and involving ICD-9 and ICD-10 codes for: ischemic heart disease, cerebrovascular disease, transient cerebral ischemic attacks, heart failure, cardiac arrhythmia, hypertensive disease, diabetes with circulatory complications. A history of prior peripheral vascular disease (PVD) at baseline was extracted from linked hospital admissions data having occurred before the study date and involving ICD-9 and ICD-10 codes for: amputations below the knee (leg, foot or toe), peripheral arterial disease, OPCS3 and OPCS4 codes for revascularization procedures, as well as any ulceration or below-knee amputation recorded prior to consent date in the SCI-DC foot screening.

The acute complications of diabetes considered were severe hypoglycemia and diabetic ketoacidosis (DKA). We combined information from the patient questionnaire and SMR01 data to define a recent history (within 12 months preceding study date), thus replicating the timeframe used by Tesfaye et al. (26) for DKA or hypoglycemia: any self-reported history or hospital admissions involving the ICD-10 codes: E10.1 to E14.1 for DKA; E16.0 to E16.2 and E15 for hypoglycemia (in SMR01 data). Finally, nephropathy was crudely defined as the presence of micro or macroalbuminuria or eGFR levels lower than 60 mL/min/1.73m^2.

Socio-economic status

An area-level indicator of socioeconomic status, the Scottish Index of Multiple Deprivation quintiles (SIMD2012) (27) was used, based on the patient's postcode from SCI-DC database extract performed in 2014. The first and fifth SIMD quintiles represent the most and least deprived areas respectively.

Statistical analysis

All analyses were conducted using R version 3.3.3-64 bit (28). Significance was based on a level of 0.05.

We presented the crude overall prevalence rate of symptomatic DPN, using as denominator the overall study cohort size or the age-sex stratum size as appropriate. In order to allow for international comparisons we also presented directly age-standardized prevalences, by applying our age and sex specific prevalence estimates to the European Standard Population 2013. Both overall and strum specific age-standardized prevalences and associated 95% confidence intervals were calculated using the R *epitools* package version 0.5-10 (29). Finally, we performed simple sensitivity analyses, using MNSIQ thresholds of 2 and 3 to define symptomatic DPN, and presented the crude overall prevalence obtained. We used multivariable logistic regression models to investigate the associations between potential risk factors and symptomatic DPN, entering all clinically relevant risk factors simultaneously and adjusting for age at baseline, diabetes duration at baseline and sex. We performed complete-case analyses, including only variables with less than 10% missingness (model M1), we then performed sensitivity analyses setting the missingness threshold for variable inclusion to 20% (model M2). Non-linearity of the relationship between continuous covariates and the log-odds of symptomatic DPN was investigated using restricted cubic spines, implemented through the R *rms* package

version 5.1-3 (30). A gradual step-up approach was used to complexify the model, first including only the adjustment variable and then using all the variables from model M1: a spline was considered for each continuous variable in turn and the best model retained at each stage was selected based on the AIC criterion, using the rules of thumb from Burnham et al. (31). The more complex model was only retained if the corresponding drop in AIC was of more than two compared to the best model from the previous stage. We used four knots for fitting the splines, located at Harrell's recommended quantiles (30).

The association between having symptomatic DPN and presenting with other diabetes complications was examined using a multinomial logistic regression (R package *nnet* version 7.3-12) with the number of other complications as outcome and symptomatic DPN as covariate, adjusting for age at baseline, diabetes duration at baseline and sex.

Results of the logistic regression models are presented in terms of odds-ratios (OR) and associated 95% Confidence Intervals (CI).

Results

Prevalence

The analyzed cohort consisted of 5,558 individuals with T1D and an available dichotomized MNSIQ score. At baseline, they had a median age of 44.7 years and a median diabetes duration of 20.5 years, 44.1% were female. None of the patients were recorded as having had Charcot on the foot screening program (data not shown), 11.2% of those with symptomatic DPN had ever had a hospital admission for neuropathy whilst 46.7% of them were taking one of the drugs recommended by guidelines for DPN symptom control (32,33) - amitriptyline, duloxetine, gabapentin, pregabalin or capsaicin

cream 0.075% (Table 1). Finally, amongst the 715 patients with symptomatic DPN, 483 patients (67.6%) met the definition of painful neuropathy (data not shown).

The age-standardized prevalence rates of symptomatic DPN by age band and sex are illustrated in Figure 1 and detailed in Supplementary Table S1.The overall crude prevalence rate was estimated as 12.9%, the age-standardized prevalence did not differ: 12.9% (95%CI 11.8-16.0). When using thresholds of 3 and 2 to define symptomatic DPN, the overall crude prevalence rates rose to respectively 19.4% and 35.2%.Figure 1 shows that the prevalence based on MNSIQ is higher for females than males in the younger age bands and higher for males in the higher age bands (from 45 years onwards). Overall, the prevalence of symptomatic DPN generally increased with age, apart from the oldest age band, where it decreased The lower point prevalence estimate over 75 years, particularly in women, may reflect higher death rates in those with DPN since of course prevalence rates will reflect a combination of age-specific incidence rates and death rates. Also, as shown in Supplementary Table S1, there is uncertainty around estimates in the oldest age band.

Risk factors

The baseline cohort characteristics are presented by symptomatic DPN status, and overall in Table 1. Those with symptomatic DPN were more likely to be older, have longer diabetes duration and live in more deprived areas. Being on a long-term prescription for aspirin, statin or anti-hypertensive drugs was more common in those with symptomatic DPN and the crude levels of many cardiovascular risk factors were higher. As shown in Table 2, age and diabetes duration were significantly associated with symptomatic DPN.

Adjusted for age and diabetes duration, the odds of symptomatic DPN for females vs. males was 1.0.

The multivariable model 1 for symptomatic DPN fitted risk factors simultaneously. Model 2 further included triglycerides and albuminuria in those in whom these data were available. LDL-C was not evaluated as almost 50% were missing these data. As shown in Table 2 adjusted for age, diabetes duration and gender, higher BMI, waist-hip ratio, total cholesterol, triglycerides, ever smoked, lower levels of eGFR (vs levels ≥90), albuminuria, current used of aspirin, statin and anti-hypertensive were associated with higher odds of symptomatic DPN. Higher levels of HDL-cholesterol, and higher weekly consumption of alcohol (vs consumption <2 units/week) were associated with lower odds of symptomatic DPN. When these risk factors were entered into a model simultaneously, the associations with DPN remained similar, apart from current use of statin therapy which was no longer associated with DPN.

As shown in Figure S1 using restricted cubic splines, the relationship between HbA1c levels and the odds of having DPN was found to be non-linear, with odds of DPN becoming significantly higher only with very elevated HbA1c levels (from around 65 mmol/mol i.e. 8.1%), compared to controlled levels of 53 mmol/mol (7.0%).

A non-linear relationship was also found between the odds of having DPN and systolic blood pressure: the odds were higher only for lower systolic blood pressure (compared to a median of 130.2 mmHg).

Socio-economic status

Adjusted for age, gender and diabetes duration, individuals who lived in more deprived areas had significantly higher odds of having DPN than those living in less deprived areas (2.61 [2.21 – 3.08]). Following adjustment for other risk factors, this association remained (2.17[1.78 – 2.65]).

Complications

The distribution of other diabetic complications by DPN status is presented in supplementary Table S2: for each of the complications considered, the proportion of individuals with each complication was consistently higher among those with DPN. We examined the clustering of diabetic complications in relation to neuropathy in the N=4,514 for whom information on all complications was available. Figure 2 shows the distribution of the number of other diabetic complications by age band and neuropathy status. At all ages, multiple complications were more common in those with neuropathy and the number of multiple complications increased with age.

The multinomial logistic regression model adjusting for age, sex and diabetes duration confirmed that patients with DPN were more likely to present with other diabetes complications compared to those without neuropathy: (2.62 [2.00; 3.42] for one other diabetes complication versus none and 10.53 [8.08; 13.71] for 2 or more other complications versus none).

Conclusions

In this study we found that symptomatic diabetic peripheral neuropathy is a common problem in those with type 1 diabetes despite modern standards of care. We found a large

socioeconomic gradient with those in the more deprived groups being at almost three times the risk. Moreover we found very strong associations with modifiable risk factors. We also found that symptomatic DPN clusters strongly with other complications since those with DPN are much more likely than those without to also have retinopathy, CVD, renal disease and be at risk of acute complications.

This study is, to the best of our knowledge, the largest contemporaneous study of symptomatic DPN in adults with Type 1 diabetes. The prevalence of DPN amongst this representative sample of adults with Type 1 diabetes in Scotland, was estimated as 12.9%. We have had to rely on symptomatic measures in our large epidemiological setting, with the dichotomized MNSIQ score used having a reported sensitivity of 40% (21). This definition was likely to underestimate the prevalence of symptomatic DPN and we performed sensitivity analyses using MNSIQ thresholds of 3 and 2, leading to the higher crude prevalence estimates of 19.4% and 35.2%, respectively. Hence, the key message is that symptomatic neuropathy which is only the tip of the iceberg, remains common.

DPN prevalence estimates reported in the literature are highly variable as different studies assessed the presence of neuropathy using different methods, and focus on different populations (e.g. youth, community-based or hospital based-settings) (1,4,14,34). Jaiswal et al. (35) reported a prevalence of 7% in youth with T1D from the SEARCH for Diabetes youth study using the clinical examination from the Michigan Neuropathy Screening Instrument, which is comparable to our estimated prevalence of 5.6% in the lowest age band (16 to 25 years old). Tesfaye et al. (26) reported, a 28% prevalence in the EURODIAB IDDM Complications study. They measured neuropathy based on a

combination of symptoms, clinical and neurophysiological assessments in a group of clinic-attending insulin-dependent patients aged 15 to 60 (36). The prevalence identified using our methodology are therefore consistent with the data from these studies.

We investigated the clinical risk factors cross-sectionally associated with prevalent DPN and found similar results to findings from the literature (1,4,26,37,38). DPN was cross-sectionally associated with poor glycemic control, smoking, higher lipids and poor renal function whilst HDL-Cholesterol was inversely associated. We did not find a linear association with glycaemia in our data but the risks of DPN rose steeply above HbA1c levels of 65 mmol/mol (8.1%), and we note that 63% of our cohort was above these levels. We did not replicate previous associations with higher blood pressures but antihypertensive usage was high and was highest in those with DPN. We also found counter-intuitive results with lower weekly alcohol consumption being associated to higher odds of DPN, we believe this is because about half of the individuals with DPN are on drugs used for neuropathy, and avoidance of alcohol consumption is often recommended with these.

Our associations are cross-sectional and do not demonstrate causality per se. However, they are very similar to prospective studies such as Tesfaye et al. (11) that have highlighted such a causal role. Indeed, although current guidelines mainly focus on tight glycemic control (7), others such as Tesfaye et al. (11,35) have also emphasized the control of other risk factors and smoking cessation in preventing and ameliorating DPN. A key message from our data is that even in people with symptomatic disease, there remains inadequate control of risk factors and therefore that opportunities for reducing disease burden are being missed.

SIMD was strongly associated with symptomatic DPN, with individuals living in deprived areas having much higher odds of having DPN. This association remained strong even after including the clinical risk factors in the model. Hence, possible poor risk factor control in the more deprived population would not suffice to explain the disparity in the odds of DPN. This emphasizes the need to tackle the unmet burden of risk factors in those with poorer social circumstances. It is also important to consider that conditional upon the presence or absence of disease, the responses to the MNSIQ could vary by social deprivation, levels of education and the quality of local service-provision. If clinical detection rates were lower, for example, in the most deprived, then the response to question 9 from the MNSIQ “Has your doctor ever told you that you have diabetic neuropathy” could be biased downwards; hence the true association between symptomatic DPN and deprivation could be stronger than what we were able to capture in our study. Our findings regarding the cross-sectional risk factor associations with DPN demonstrate that neuropathy risk is not some fixed inevitable consequence of diabetes in particular individuals but rather is highly subject to modifiable factors.

The clustering of symptomatic DPN with other chronic complications was striking in our data. This demonstrates the importance of not just considering one complication at a time but the importance of the overall management of risk and the potential interplay of complications on life quality in the individual with diabetes. The data reinforce previous findings (26) and give support to the idea of a holistic, comprehensive approach to diabetes management.

We found a higher prevalence of recent DKA and hypoglycemia in those with DPN. These data suggest that diagnosed neuropathy identifies a group at higher risk of acute

metabolic complications. Hence, structured education, which has been shown to be beneficial in terms of DKA and hypoglycemia (39), might be targeted at this group.

The main limitation of the study is that we did not have resources or the fieldwork time to carry out extensive clinical examination for more subtle levels of neuropathy. Also, our risk factor association analysis is cross-sectional since we only have the MNSIQ score at a single time point. The strengths of our study are the use of a standardized questionnaire instrument, its contemporaneous nature, its population representativeness and the wide range of risk factors measured.

In summary, the burden of neuropathy remains substantial in this population of adults with Type 1 diabetes, and there is substantial scope for risk factor modification in those with DPN. Patients need to have a comprehensive support which is holistic in terms of diabetes care as they are likely to present several concurrent complications. Finally, the significant association of socio-economic status in the likelihood of having DPN indicates an urgent need to tackle inequalities in health within Type 1 diabetes patients.

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Data availability

We do not have governance permissions to share individual level data on which these analyses were conducted since they derive from clinical record data. However, for any

bona fide requests to audit the validity of the analyses, the verifiable research pipeline which we operate means that one can request to view the analyses being run and the same tabulations resulting. We are also happy to share summary statistics for those wishing to conduct meta-analyses with other studies.

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Duality of interest

HMC receives research support and honorarium and is also a member of the advisory panels and speaker's bureaus for Sanofi Aventis, Regeneron and Eli Lilly. HMC has been a member of Data and Safety Monitoring Board of the Advisory Panel for the CANTOS Trial (Novartis Pharmaceuticals). HMC also receives or has recently received a non-binding research support from Pfizer Inc. and AstraZeneca LP. HMC is a shareholder of Roche Pharmaceuticals and Bayer.

The other co-authors declare that there is no duality of interest associated with their contribution to this manuscript.

Contribution statement

AJ carried out the primary statistical analyses and reviewed/edited the manuscript. SJM undertook quality control of the clinical diabetes data sets and reviewed the manuscript. LAKB contributed to the cleaning-up, harmonization and databasing of data and contributed to manuscript revision. FG, JMM, AC commented on data and manuscript drafts. PMM contributed to study design, analysis and drafting of the manuscript. HMC contributed to study conception and design, analysis and data interpretation and drafting of the manuscript. All authors approved the manuscript for publication. AJ is the guarantor of this work.

Guarantor

Helen M Colhoun is responsible for the integrity of the work as a whole.

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Table 1 – Baseline characteristics of the study population by DPN status

Parameter	No DPN	DPN	Total	Completeness N (%)
Total Included	4843 (87.1)	715 (12.9)	5558	
Attained age (years) at baseline	43.7 (32.0, 54.4)	50.6 (41.0, 59.3)	44.7 (33.0, 55.2)	5558(100.0)
Diabetes duration (years)	19.8 (10.7, 30.1)	26.9 (16.1, 37.4)	20.5 (11.1, 31.0)	5558(100.0)
Sex: Female	2129 (44.0)	320 (44.8)	2449 (44.1)	5558(100.0)
SIMD quintile: Q1-Q2 (most deprived)	1419 (29.5)	346 (48.7)	1765 (32.0)	5518(99.3)
HbA1c (mmol/mol)	68.0 (60.0, 79.0)	76.0 (66.0, 89.0)	69.0 (60.0, 80.0)	5499(98.9)
HbA1c (%)	8.4 (7.6, 9.4)	9.1 (8.2, 10.3)	8.5 (7.6, 9.5)	5499(98.9)
Systolic blood pressure (mmHg)	129.9 (121.8, 138.7)	132.8 (122.1, 143.8)	130.2 (121.9, 139.4)	5524(99.4)
Diastolic blood pressure (mmHg)	75.5 (70.6, 80.5)	75.0 (70.2, 80.1)	75.5 (70.6, 80.4)	5525(99.4)
Weight (kg)	76.5 (66.9, 87.4)	77.9 (66.5, 91.0)	76.7 (66.8, 87.8)	5456(98.2)
Height (cm)	171.0 (164.0, 178.0)	170.0 (163.0, 175.1)	170.8 (164.0, 177.5)	5517(99.3)
BMI (kg/m^2)	26.1 (23.4, 29.2)	26.9 (23.7, 31.2)	26.2 (23.4, 29.5)	5448(98.0)
Waist-hip ratio	0.9 (0.8, 0.9)	0.9 (0.9, 1.0)	0.9 (0.8, 0.9)	5498(98.9)
Total Cholesterol (mmol/L)	4.5 (4.0, 5.2)	4.6 (3.9, 5.3)	4.5 (4.0, 5.2)	5413(97.4)
Triglycerides (mmol/L)	1.0 (0.7, 1.5)	1.3 (0.9, 2.0)	1.1 (0.8, 1.6)	4607(82.9)
LDL Cholesterol (mmol/L)*	2.4 (1.9, 3.0)	2.4 (1.9, 3.0)	2.4 (1.9, 3.0)	2855(51.4)
HDL Cholesterol (mmol/L)	1.5 (1.2, 1.8)	1.4 (1.1, 1.7)	1.5 (1.2, 1.8)	5283(95.1)
Ever smoked: Yes	1675 (34.6)	352 (49.3)	2027 (36.5)	5555(99.9)
Weekly alcohol consumption: units/week				5253 (94.5%)
<2	930 (20.2)	234 (35.9)	1164 (22.2)	
2 — 6	1272 (27.6)	184 (28.3)	1456 (27.7)	
6 — 14	1310 (28.5)	133 (20.4)	1443 (27.5)	
14 — 21	607 (13.2)	40 (6.1)	647 (12.3)	
21 — 32	301 (6.5)	27 (4.1)	328 (6.2)	
≥32	182 (4.0)	33 (5.1)	215 (4.1)	
CKDEpi eGFR ($ml/min/1.73m^2$)				5354(96.3)
≥ 90	3242 (69.7)	348 (49.7)	3590 (67.1)	
60 — 90	1168 (25.1)	242 (34.6)	1410 (26.3)	
30 — 60	201 (4.3)	79 (11.3)	280 (5.2)	
<30	43 (0.9)	31 (4.4)	74 (1.4)	
Albuminuria: micro or macro-albuminuria	380 (9.1)	153 (26.1)	533 (11.2)	4775(85.9)
Ongoing long-term aspirin prescription(>1 yr at consent date)	604 (12.5)	190 (26.6)	794 (14.3)	5558(100.0)
Ongoing statin prescription	1863 (38.5)	404 (56.5)	2267 (40.8)	5558(100.0)
Ongoing anti-hypertensive prescription	1605 (33.1)	403 (56.4)	2008 (36.1)	5558(100.0)
Ever hospitalized for diabetic neuropathy	24 (0.5)	80 (11.2)	104 (1.8)	5558(100.0)
Current drug prescription for neuropathy (first-line, as listed in text)	334 (8.7)	419 (46.7)	753 (13.5)	5558 (100.0)

Data are presented as median (Interquartile range - IQR: 25^{th}, 75^{th} percentile) or as N (%)

* LDL-Cholesterol has 49.6% missing data, hence is not used in the rest of the analyses

Table 2 – Logistic regression results for associations between clinical risk factors and DPN

Covariate	Univariable	Multivariable
Attained age at baseline (years): 44.7 (median)		
35	0.61 (0.55, 0.69)*	0.75 (0.63, 0.89)*
55	1.46 (1.29, 1.67)*	1.22 (1.00, 1.48)*
65	1.50 (1.26, 1.78)*	1.16 (0.87, 1.53)
Diabetes duration at baseline (years)	1.03 (1.03, 1.04)*	1.02 (1.02, 1.03)*
Sex: Female (ref: Male)	1.04 (0.88, 1.22)	1.19 (0.88, 1.60)
HbA1c: 53.0 mmol/mol (7%)		
50.0 mmol/mol (6.7%)	1.07 (0.99, 1.14)	1.04 (0.96, 1.13)
60.0 mmol/mol (7.6%)	0.94 (0.83, 1.07)	0.97 (0.84, 1.13)
75.0 mmol/mol (9.0%)	1.79 (1.48, 2.17)*	1.51 (1.21, 1.89)*
Height (cm)	0.98 (0.97, 1.00)	1.00 (0.98, 1.01)
Weight (kg)	1.01 (1.00, 1.01)	1.08 (0.91, 1.28)
BMI	1.03 (1.02, 1.05)*	
Waist-hip ratio	1.50 (1.36, 1.66)*	1.24 (1.08, 1.42)*
Diastolic Blood Pressure	1.00 (1.00, 1.02)	1.13 (0.94, 1.35)
Systolic Blood Pressure (mmHg): *130.2 (median)*	ref	ref
110	1.91 (1.49, 2.44)*	2.03 (1.43, 2.88)*
150	1.52 (1.28, 1.80)*	1.23 (0.98, 1.55)
HDL Cholesterol (mmol/L)	0.43 (0.34, 0.53)*	0.77 (0.66, 0.89)*
Total Cholesterol (mmol/L)	1.15 (1.07, 1.24)*	1.11 (1.01, 1.22)*
Triglycerides (mmol/L)	1.41 (1.31, 1.51)*	1.17 (1.04, 1.31)*
Albuminuria: Normal	ref	ref
Micro or macro-albuminuria	3.26 (2.62, 4.05)*	1.92 (1.41, 2.63)*
Typical weekly alcohol consumption (units/week) :<2 units/week	ref	ref
2 -6	0.63 (0.50, 0.78)*	0.72 (0.56, 0.92)*
6-14	0.41 (0.32, 0.52)*	0.54 (0.41, 0.71)*
14-21	0.28 (0.20, 0.40)*	0.32 (0.21, 0.49)*
21-32	0.29 (0.19, 0.44)*	0.47 (0.29, 0.75)*
≥32	0.68 (0.45, 1.02)*	0.88 (0.56, 1.38)
Ever smoked: Yes (ref: No)	1.73 (1.47, 2.05)*	1.67 (1.37, 2.03)*
CKDEpi eGFR (ml/min/1.73m²) :≥ 90	ref	ref
60 — 90	1.53 (1.25, 1.89)*	1.16 (0.92, 1.46)
30 — 60	2.79 (2.03, 3.83)*	1.78 (1.22, 2.59)*
<30	4.68 (2.86, 7.66)*	1.96 (1.03, 3.74)*
Ongoing long-term aspirin prescription: Yes (ref: No)	1.73 (1.41, 2.13)*	1.39 (1.07, 1.79)*
Ongoing long-term statin prescription: Yes (ref: No)	1.34 (1.11, 1.62)*	0.91 (0.71, 1.17)
Ongoing long-term anti-hypertensive prescription: Yes (ref: No)	1.89 (1.58, 2.27)*	1.60 (1.26, 2.04)*
SIMD Q1-Q2 vs Q3-Q5	2.61 (2.21, 3.08)*	2.17 (1.78, 2.65)*

Odds-ratio estimates and associated 95% Confidence Intervals obtained from multivariable logistic regression.
Statistical significance is denoted by *; ref denotes the reference.
M1 included all variables with less than 10% missingness whilst M2 included variables with less than 20% missingness.
Covariates modelled using splines are indicated in italics. All multivariable results from M1, apart from triglycerides and albuminuria (M2)

Figure 1 – Directly age-standardized DPN prevalence, by age band and sex, using the European Standard Population ESP2013*.
(*As obtained from https://www.opendata.nhs.scot/dataset/standard-populations/resource/29ce4cda-a831-40f4-af24-636196e05c1a [accessed on 30 Sept 2019])

Figure 2 – Number of diabetic complications other than neuropathy: distributions by age band (years) and DPN status. *The complications considered were: nephropathy, prior CVD at baseline, prior PVD at baseline, recent history of severe hypoglycemia, recent history of DKA and any retinopathy at baseline.*

Online-only Supplemental Material for: Diabetic neuropathy is a substantial burden in people with Type I diabetes and is strongly associated with socioeconomic disadvantage: A population representative study from Scotland

Anita Jeyam[1], Stuart J McGurnaghan[1], Luke AK Blackbourn[1], John M McKnight[2], Fiona Green[3], Andrew Collier[4], Paul M McKeigue[5], Helen M Colhoun[1,6]; on behalf of the SDRNT1BIO Investigators

Author affiliations:

[1]MRC Institute of Genetic and Molecular Medicine, University of Edinburgh, Edinburgh, UK
[2]Western General Hospital, NHS Lothian, Edinburgh, UK
[3]Research & Development Support Unit, Dumfries & Galloway Royal Infirmary, Dumfries, UK
[4]Diabetic Day Centre University Hospital, Ayr, UK
[5]Usher Institute of Population Health Sciences and Informatics, Centre for Population Health Sciences, School of Molecular, Genetic and Population Health Sciences, University of Edinburgh, Edinburgh, UK
[6] Department of Public Health, NHS Fife, Kirkcaldy, Scotland, UK

Corresponding author:

Anita Jeyam, Institute of Genetic and Molecular Medicine Crewe Road South Edinburgh EH4 2XU UK email: anita.jeyam@igmm.ed.ac.uk

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Table S1 – Crude and age-standardized[1] symptomatic DPN prevalence rates (%) by age band and sex

Age band (years)	Sex	N	Crude rate	Age-standardized rate (95% CI)
<25	Female	283	7.07	6.89 (4.11 11.00)
	Male	306	4.25	3.75 (1.83 7.30)
25-45	Female	987	11.25	11.15 (9.17 13.45)
	Male	1242	7.89	7.78 (6.30 9.50)
45-65	Female	951	16.09	16.12 (13.65 18.95)
	Male	1289	17.46	17.87 (15.58 20.43)
65-75	Female	175	17.14	17.03 (11.40 24.65)
	Male	215	21.40	20.63 (14.62 28.66)
≥75	Female	53	11.32	9.21 (3.22 39.64)
	Male	57	22.81	19.18 (9.59 84.93)
Overall		5558	12.86	12.91 (11.78, 16.00)

[1] Using the European Standard Population 2013

Table S2 – Description of complications by DPN status

Parameter	No DPN	DPN	Total
Total Included	4843 (87.1)	715 (12.9)	5558
Any ketoacidosis episodes in the past 12 months	234 (4.8)	91 (12.7)	325 (5.8)
Any severe hypoglycaemia episodes in the past 12 months	934 (19.3)	249 (34.8)	1183 (21.3)
Prior CVD	341 (7.0)	199 (27.8)	540 (9.7)
Retinopathy status at baseline	2232 (55.2)	337 (67.7)	2569 (56.5)
Mild/Moderate/Referable			
Peripheral vascular disease history at baseline	361 (7.5)	259 (36.2)	620 (11.2)
Nephropathy at baseline	548 (11.4)	227 (31.8)	775 (14.0)

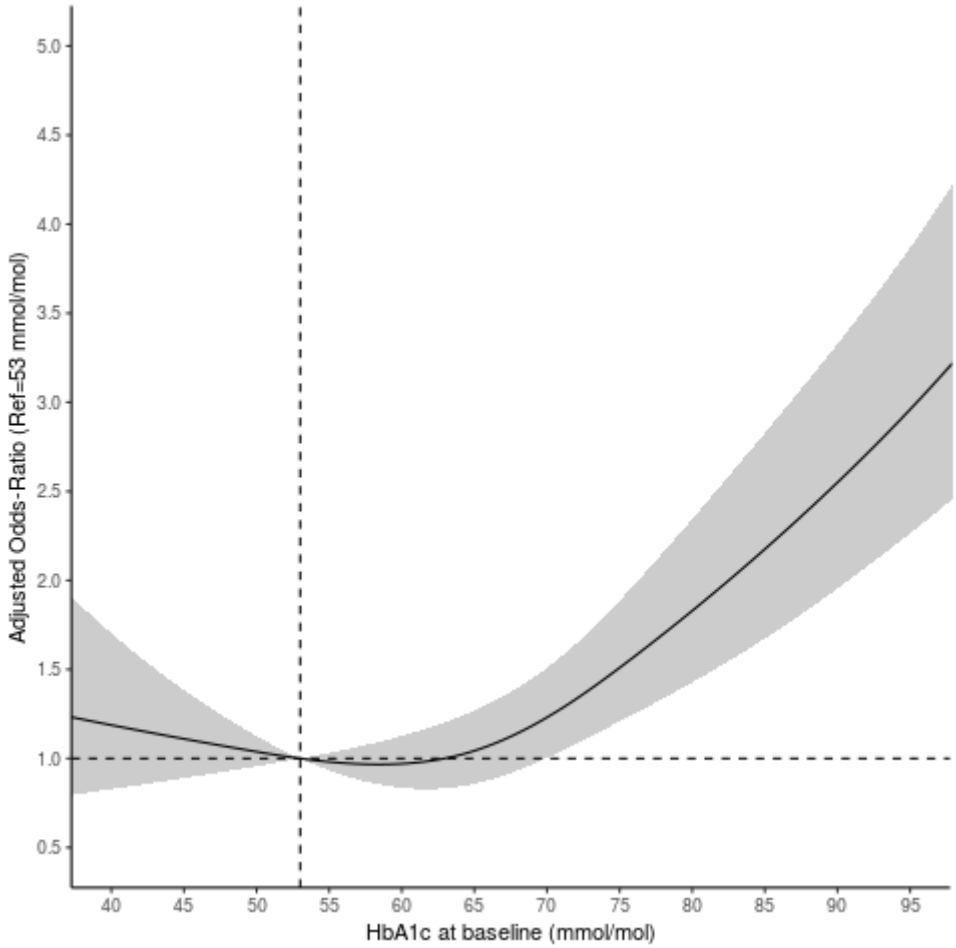

Figure S1 – Adjusted Odds-ratio for having DPN, by HbA1c at baseline (reference: 53 mmol/mol) and associated 95% Confidence Interval Bands – model M1.
Model M1 is adjusted for all other risk factors, set at representative levels.
M1 is adjusted for age at baseline (44.7 years), diabetes duration at baseline (20.6 years), sex (male),HbA1c (53 mmol/mol), weight (76.9 kg), height(171 cm), waist-hip ratio (0.9), frequency of alcohol consumption exceeding 8 units in one day (never), ever smoked (no), CKDEPI-eGFR (≥90 ml/min/1.73m²), systolic blood pressure (13.0.3 mm Hg), diastolic blood pressure (75.7 mm Hg), HDL-Cholesterol (1.5 mmol/L), total cholesterol (4.6 mmol/L), ongoing long-term aspirin prescription (no), ongoing long-term statin prescription (no) and ongoing long-term anti-hypertensive prescription (no).