ORIGINAL ARTICLE

Peripheral neuropathy and the risk of cardiovascular events in type 2 diabetes mellitus

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ABSTRACT

Aims Identifying individuals with diabetes at high risk of cardiovascular disease (CVD) remains challenging. We aimed to establish whether peripheral neuropathy (PN) is associated with incident CVD events and to what extent information on PN may improve risk prediction among individuals with type 2 diabetes.

Methods We obtained data for individuals with type 2 diabetes, and free of CVD, from a large primary care patient cohort. Incident CVD events were recorded during a 30-month follow-up period. Eligible individuals had complete ascertainment of cardiovascular risk factors and PN status at baseline. The association between PN and incident CVD events (non-fatal myocardial infarction, coronary revascularisation, congestive cardiac failure, transient ischaemic attack and stroke) was evaluated using Cox regression, adjusted for standard CVD risk factors. We assessed the predictive accuracy of models including conventional CVD risk factors with and without information on PN.

Results Among 13 043 eligible individuals, we recorded 407 deaths from any cause and 399 non-fatal CVD events. After adjustment for age, sex, ethnicity, systolic blood pressure, cholesterol, body mass index, HbA1c, smoking status and use of statin or antihypertensive medication, PN was associated with incident CVD events (HR 1.33; 95% CI 1.02 to 1.75, p=0.04). The addition of information on PN to a model based on standard CVD risk factors resulted in modest improvements in discrimination for CVD risk prediction and reclassified 6.9% of individuals into different risk categories.

Conclusions PN is associated with increased risk for a first cardiovascular event among individuals with diabetes.

INTRODUCTION

Diabetes mellitus is increasing in prevalence[1] and results in an approximately twofold higher risk of cardiovascular disease (CVD) and approximately 6–7 years of life years lost when compared with individuals without diabetes.[2] Better systematic approaches to cardiovascular risk factor modification have resulted in significant reductions in CVD mortality and morbidity during the last 10 years among individuals with diabetes,[3–5] although the absolute risk remains much higher than among individuals without diabetes. A significant clinical challenge that remains is the identification of higher-risk individuals who, despite conventional treatments, may remain at substantially higher CV risk. Currently the UKPDS risk engine is the only prognostic risk score routinely available for individuals with diabetes, which includes information on traditional risk factors in addition to diabetes-specific variables; the duration of diabetes and HbA_{1c}.[6] However, those data preceded the widespread use of statins and renin angiotensin blockade that significantly reduce the CV risk among those with diabetes.[7 8] Furthermore, the UKPDS risk engine has demonstrated, at best, moderate discrimination for CVD risk in external validation.[9 10] While HbA_{1c} is readily available in most countries worldwide but perhaps limited only by the assay cost, duration of diabetes is often difficult to ascertain. A simple routine low-cost clinical assessment that improves risk prediction therefore may be of value.

Peripheral neuropathy (PN) is present in a significant proportion of patients at the time of diagnosis of type 2 diabetes[11] and progresses with duration of disease. While evidence suggests an association between cardiovascular autonomic neuropathy and an increase in overall mortality or silent myocardial ischaemia,[12 13] data assessing the relationship between PN and CVD events are limited to a single observational study of 363 subjects that reported on 165 CVD mortality events.[14] This study did not assess purely PN, but instead assessed the association between neuropathic foot ulcers and CVD mortality among subjects attending a foot ulcer clinic, demonstrating an equivalent CVD mortality risk among those with ulcers compared with those without.

To date, no prior study has evaluated data from approximately general populations in order to evaluate the relationship between PN and CVD risk and whether the addition of this simple routine clinical test to standard measures improves CVD risk prediction. If clinically useful, PN might help identify high-risk individuals for potentially more intensive treatment or greater clinical scrutiny and monitoring. To address this issue, we obtained data from a large primary care patient database to assess whether PN diagnosed during routine diabetic follow-up was associated with incident CVD events independent of conventional risk factors and to what extent the presence or absence of PN improved risk prediction over and above conventional factors among individuals with type 2 diabetes.

METHODS

Study population and data collection

Anonymised demographic, medical history and laboratory data on all registered patients were

extracted from 122 primary care practices across England using Morbidity Information Query and Export Syntax (MIQUEST) software (n=951 764). MIQUEST has been used in the national data quality programme at the Primary Care Information Services.[15] All diagnoses, laboratory data, prescribing information and incident cases are electronically recorded as Read codes, a hierarchical coding system used in UK primary care,[16] and consistent with nationally agreed definitions from the General Medical Services contract quality and outcomes framework. Contributing practices are a nationally representative sample from inner city, suburban and rural areas. Practice inclusion criteria specified the use of the same computer system for the prior 5 years with electronic laboratory links and access permission to check data quality.

Eligibility criteria for this observational study were applied to all registered patients; hence, those subjects enrolled are reflective of a contemporary UK general practice population. Eligible patients were those aged ≥18 in June 2008, with a prior diagnosis of type 2 diabetes and complete ascertainment of cardiovascular risk factors in the preceding 12 months, including age, smoking status, blood pressure (mm Hg), plasma total cholesterol (mmol/L), high-density lipoprotein (HDL) cholesterol (mmol/L) and low-density lipoprotein (LDL) cholesterol (mmol/L). For the present analysis, we excluded individuals with a prior history of myocardial infarction (MI), coronary revascularisation, congestive cardiac failure (CCF), transient ischaemic attack (TIA) or stroke. In addition, and in order to reduce systematic errors due to a detection bias that would require propensity adjustment, patients who did not undergo foot examination with a monofilament for the presence of PN were excluded. Diabetes was defined as fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), random plasma glucose ≥11.1 mmol/L (200 mg/dL) or the use of antihyperglycaemic medications. Individuals with type 2 diabetes were identified by diagnostic, investigation, treatment and process of care codes specific to type 2 diabetes. PN was defined as reduced 10 g monofilament peripheral sensation. Sensation was assessed by primary care physicians, practice nurses and podiatrists during annual foot screening examination, which forms part of the Quality Outcomes Framework for diabetes in the UK.[17] Albuminuria was defined as albumin–creatinine ratio ≥30 mg/g or dipstick-positive proteinuria.

Outcomes data were obtained for the period between July 2008 and December 2010. The composite outcome included any first incident MI, coronary revascularisation procedure, CCF, TIA or stroke. The Read codes used to identify CVD events were developed in accordance with published guidance.[18 19] Data were controlled in accordance with data protection legislation, institutional protocols of St George's University of London and National Health Service policies for research and information governance. The study was approved by the Oxford Research Ethics Committee.

Statistical analysis

Probability weighted Cox regression models were used to evaluate the relationship between PN and incident CVD events.[20] Potential confounding variables were selected on the basis of established evidence demonstrating their association with CVD events. The covariates included age, sex, ethnicity, hypertension, HDL cholesterol, LDL cholesterol, body mass index (BMI), HbA1c, cigarette smoking, lipid-lowering therapy, renal function and the use of antihypertensive medication. Multiple imputation by chained equations (MICE) in R was used to replace missing values for HbA1c; Rubin's rules were subsequently used to combine five imputations. Variables demonstrating an association with CVD events at a level of $p \leq 0.10$ were subsequently included in a multivariate model. Kaplan–Meier curves were used to compare estimated proportions of at-risk patients with and without PN.

We assessed the predictive accuracy of a model including conventional CVD risk factors (model A) and the same model incorporating PN (model B) for incident CVD events. We stratified individuals into 2.5-year risk categories of <2.5%, 2.5% to <5% and ≥5%, which approximately correspond to the 10-year Framingham risk categories. Model discrimination was assessed to determine the ability of PN to differentiate between individuals who do and do not have events. Receiver operating characteristic curves (ROC) were constructed for model A and

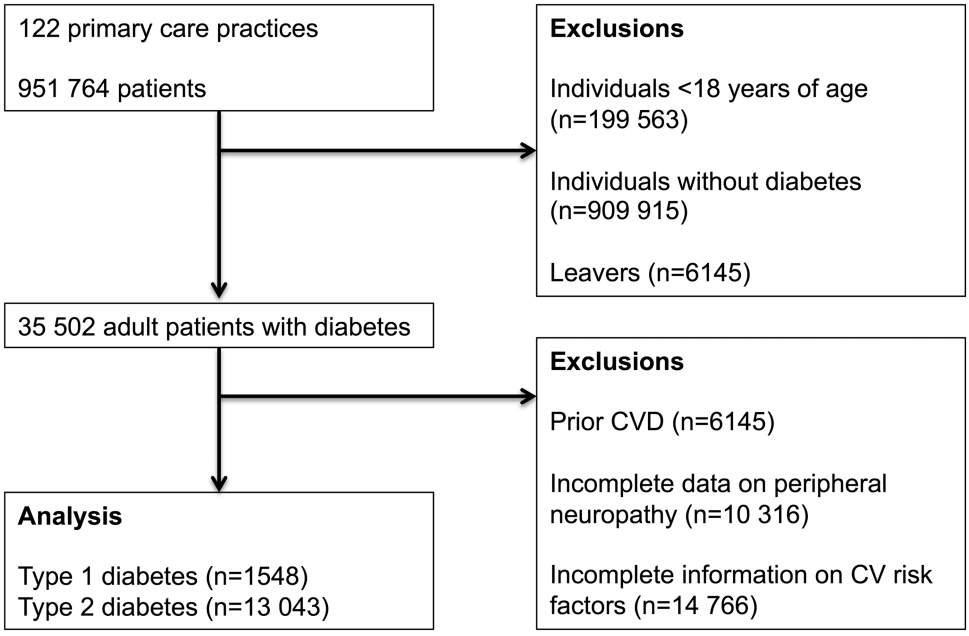

Figure 1 Consolidated Standards on Reporting Trials (CONSORT) diagram of the study population.

model B, and the areas under the ROC curves were compared. Model fit was assessed using the Akaike information criterion (AIC)[21] and the Bayes information criterion (BIC),[22] a likelihood-based measure that penalises for an increasing number of model variables. The integrated discrimination index (IDI) was estimated,[23] measuring the improvement in the average sensitivity with the new variable, while subtracting any increase in the mean 1-specificity. We calculated the proportion of participants who were reclassified into higher-risk or lower-risk categories using model A and model B. Net reclassification improvement (NRI) was calculated to evaluate any improvement in performance of model B with respect to risk stratification into low-risk, intermediate-risk and high-risk groups.[23] The clinical NRI (CNRI) was calculated to evaluate any equivalent improvement in patients considered to be at intermediate risk.[24] Statistical analyses were performed in R V.3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) and Stata release 11 (Stata corp, Texas, USA).

RESULTS

After the exclusion of individuals with prevalent CVD and type 1 diabetes, data for 13 043 patients were included in this analysis (figure 1). Patients had a mean age of 63.8 years (SD 12.8, range 20–103), 6761 (51.8%) were men and the prevalence of PN was 9.9% (1296/13 043). During a total of 32 608 person-years of follow-up, 399 incident CVD events were reported (table 1). Compared with patients who remained event free during follow-up, patients who experienced a CVD event were more likely to be older, with a history of smoking, hypertension and PN (eTable 1). Individuals with PN were more likely to be older, white, with higher HbA1c and current smokers. In contrast, those with PN had lower mean total and LDL cholesterol readings, likely related to the greater use of lipid-lowering therapy. When compared with individuals with complete data, those with incomplete data were significantly younger, had higher HDL cholesterol levels and were more likely to be a current smoker. We observed no significant differences in

Table 1 Patient characteristics and cardiovascular disease (CVD) events by presence of neuropathy

	No PN (n=11 747)	PN (n=1296)	p Value	Overall (n=13 043)
Demographics				
Age, years	63.1±12.7	70.1±12.1	0.000	63.8±12.8
Male sex, n (%)	6060 (51.6)	701 (54.1)	0.09	6761 (51.8)
Ethnicity, n (%)				
Caucasian	5337 (45.4)	730 (56.3)		6067 (46.5)
Mixed	144 (1.2)	16 (1.2)		160 (1.2)
Asian	2228 (19.0)	150 (11.6)		2378 (18.2)
Black	936 (8.0)	64 (4.9)	0.000	1000 (7.7)
Other	166 (1.4)	5 (0.4)		171 (1.3)
Not stated	462 (3.9)	29 (2.2)		491 (3.8)
Missing	2474 (21.1)	302 (23.3)		2776 (21.3)
Body mass index, kg/m^2	30.5±6.5	30.4±6.8	0.70	30.5±6.5
HbA1c	8.5±2.1	8.7±2.1	0.01	8.5±2.1
Systolic blood pressure, mm Hg	137.4±17.0	138.2±17.1	0.09	137.5±17.0
Diastolic blood pressure, mm Hg	79.3±10.2	77.3±10.1	0.000	79.1±10.2
Cholesterol, mmol/L				
Total	4.72±1.10	4.56±1.03	0.000	4.70±1.09
HDL	1.27±0.37	1.29± 0.38	0.14	1.28±0.37
LDL	2.38±0.85	2.25±0.78	0.000	2.37±0.85
eGFR, mL/min/1.73 m^2	75.5±19.6	69.0±18.5	0.000	74.9±19.6
Cigarette smoking, n (%)				
Never	7092 (60.4)	702 (54.2)	0.000	7794 (59.8)
Past	2040 (17.4)	280 (21.6)		2320 (17.8)
Current	2615 (22.3)	314 (24.2)		2929 (22.5)
HMG-CoA use, n (%)	9013 (76.7)	1033 (79.7)	0.02	10 046 (77.0)
ACE/ARB, n (%)	7315 (62.3)	881 (68.0)	0.000	8196 (62.8)
Other antihypertensive, n (%)	4219 (35.9)	564 (43.5)	0.000	4783 (36.7)
Antiplatelet, n (%)	3371 (28.7)	403 (31.1)	0.07	3774 (28.9)
Outcomes				
Myocardial infarction	68 (0.6)	11 (0.8)	0.24	79 (0.6)
Coronary revascularisation	88 (0.7)	14 (1.1)	0.20	102 (0.8)
Heart failure	90 (0.8)	21 (1.6)	0.001	111 (0.9)
Stroke	76 (0.6)	15 (1.2)	0.04	91 (0.7)
TIA	62 (0.5)	7 (0.5)	0.95	69 (0.5)
All-cause mortality	333 (2.8)	74 (5.7)	0.000	407 (3.1)

Values are mean±SD or n (%). HbA1c indicates glycated haemoglobin.
Missing values: HbA1c values were missing for 73/11 747 (6.2%) individuals in the 'No PN' group.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockade; eGFR, estimated glomerular filtration rate; HbA1c values were missing for 4/1296 (3.1%) individuals in the 'PN' group; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein; PN, peripheral neuropathy; TIA, transient ischaemic attack.

gender, systolic blood pressure and total cholesterol among those with complete and incomplete data (eTable 2).

During follow-up, 65 (5.0%) individuals with PN experienced a cardiovascular event compared with 334 (2.8%) of those without PN at baseline. Crude mortality was 22.8 per 1000 person-years for those with PN compared with 11.3 per 1000 person-years for those without (p<0.001). The cumulative event-free survival after 30 months was 94.4% among participants without PN and 89.4% among those with PN (p<0.001) (figure 2). When compared with individuals with incomplete data, those with complete data had no significant differences in any component of the composite outcome measure. No significant differences were observed in components of the composite endpoint between individuals with type 1 and type 2 diabetes, with the exception of heart failure, which occurred more often in those with type 2 diabetes (p=0.03) (eTable 3).

PN was a significant predictor of death or CVD events in univariate Cox regression (HR, 1.78; 95% CI 1.37–2.32; p<0.001), but was somewhat attenuated after adjustment for conventional risk factor covariates (HR, 1.38; 95% CI 1.05 to 1.80; p=0.02, n=13 043). After further adjustment for HbA1c using both complete and imputed data, the results were qualitatively similar (HR 1.33; 95% CI 1.02 to 1.75, p=0.04 in both analyses).

Although crude event rates for all components of the composite endpoint were higher among those with PN, the differences were not significant for any single endpoint (eTable 4). PN was associated with an increased cardiovascular risk consistently across all major subgroups (eFigure 1), with no evidence of effect modification (interaction p>0.10). Cardiovascular event rates were greater among those with PN irrespective of conventional risk factor status, including smoking, systolic blood pressure and LDL levels (figure 3, eFigures 2–5).

As anticipated, PN and microalbuminuria demonstrated close statistical associations, likelihood ratio χ^2 test results (32.1) were above the suggested threshold (<10). When substituted for PN

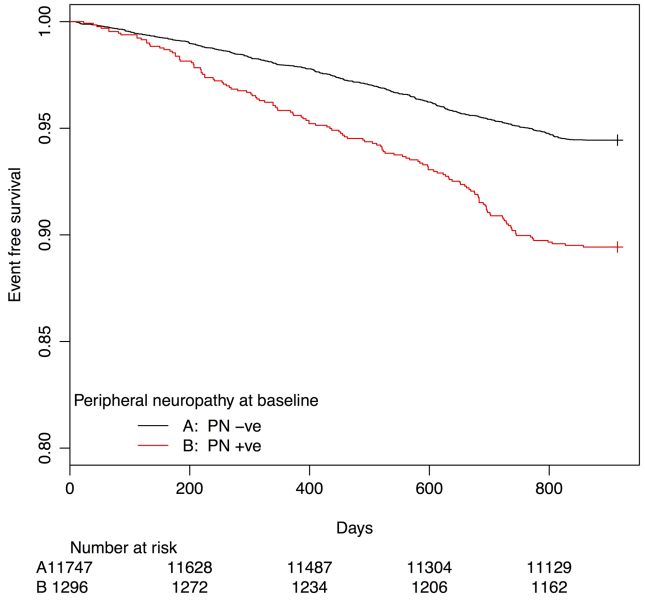

Figure 2 Unadjusted Kaplan–Meier estimates of event free survival with and without peripheral neuropathy (PN). Composite event includes myocardial infarction, coronary revascularisation, congestive cardiac failure, stroke and transient ischaemic attack. HRs for PN as compared with no PN are HR 1.78; 95% CI 1.37 to 2.32; p<0.001.

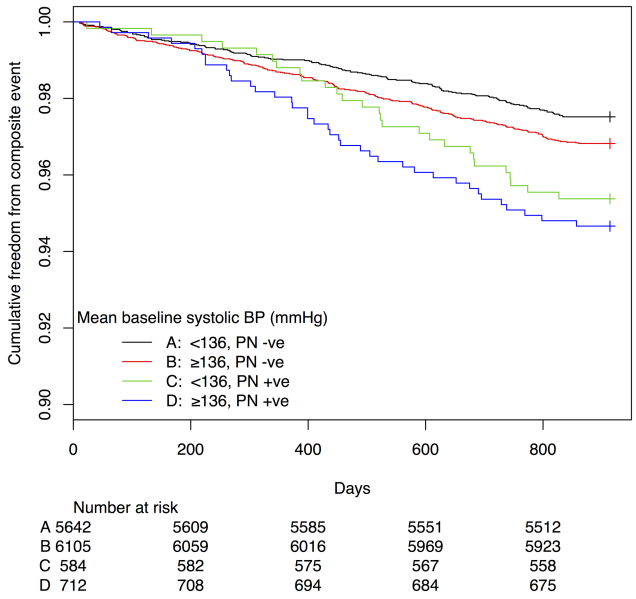

Figure 3 Kaplan–Meier estimates of the probability of the composite event by blood pressure status with and without peripheral neuropathy (PN). Composite event includes myocardial infarction, coronary revascularisation, congestive cardiac failure, stroke and transient ischaemic attack. BP, blood pressure. HRs for PN as compared with no PN are systolic BP <136 mm Hg, HR 1.92 (1.30–2.84), p=0.001; systolic BP ≥136 mm Hg, HR 1.66 (1.15–2.38) p=0.006.

in a multivariable Cox regression model, microalbuminuria was associated with CVD events (HR, 1.32; 95% CI 1.03 to 1.70; p=0.03). On inclusion of both PN and microalbuminuria in the same model, the positive relationship between PN and CVD events remained (HR 1.39; 95% CI 1.03 to 1.90; p=0.03), as did the corresponding relationship for microalbuminuria (HR 1.31; 95% CI 1.02 to 1.68; p=0.04).

The presence of PN (model B) reclassified 6.9% (894/13 043) of the study population into higher-risk or lower-risk categories, with 56.7% correct reclassification (table 2). Table 3 presents a comparison of overall fit and discrimination between models A and B. The IDI was 0.005 (p<0.001), with the relative IDI

Table 2 Reclassification of subjects based on traditional risk factors+PN versus traditional risk factors alone

	Model B (+ PN) risk category			
	Low <2.5%	Intermediate 2.5 to <5%	High ≥5%	Total
Participants with an incident CVD event				
Model A risk category				
Low	81	4	0	85
Intermediate	9	195	19	223
High	0	9	82	91
Total	90	208	101	399
Participants with no incident CVD event				
Model A risk category				
Low	5592	146	0	5738
Intermediate	262	4805	223	5290
High	0	222	1394	1616
Total	5854	5173	1617	12 644

CVD, cardiovascular disease; PN, peripheral neuropathy.

Table 3 Measures of model fit, discrimination, calibration and reclassification for cardiovascular disease (CVD) event models

	Model fit			Discrimination			Calibration		Reclassification	
Model	−2 Log likelihood	BIC	AIC	IDI	Relative IDI, %	C statistic	χ^2	p Value	NRI, %	CNRI, %
Age, systolic blood pressure, smoking status, LDL-C and HDL-C	3429	3486	3441			0.657 (0.632–0.682)	113.9	<0.001		
Add PN	3424	3490	3438	0.0005	0.01	0.661 (0.636–0.686)	121.2	<0.001	2.2	5.3

AIC, Akaike information criterion; BIC, Bayes information criterion; CNRI, clinical net reclassification improvement; HDL-C, high-density lipoprotein cholesterol; IDI, integrated discrimination index; LDL-C, low-density lipoprotein cholesterol; NRI, net reclassification improvement; PN, peripheral neuropathy.

showing a 0.01% improvement in the discrimination slope. The NRI associated with the addition of PN was 2.2% (p<0.001) and the CNRI was 5.3% (p<0.001). Models A and B had a similar overall model fit (likelihood ratio test), AIC and BIC; and model B had a modest improvement in the C-index.

DISCUSSION

In this study of 13 043 individuals with type 2 diabetes from the general population who were free from CVD at study entry, PN was a significant and independent predictor of incident CVD events over 30 months. The addition of PN to a model based on conventional CVD risk factors resulted in modest improvements in discrimination for prediction of CVD events. Moreover, compared with models derived from conventional CVD risk factors, the addition of PN demonstrated improvements in reclassification of patients for an incident CVD event in the short term.

Among those with diabetes, accumulating evidence has linked the presence of PN to an excess risk of mortality from any cause,[25 26] which in part may simply reflect a deterioration of glycaemic control as suggested by the EURODIAB Prospective Complications Study,[27] or the development of more severe complications such as sepsis among those with neuropathy. Levels of advanced glycation end products (AGEs) are higher in people with diabetes because hyperglycaemia and oxidative stress increase their accumulation. Advanced glycation end products have been shown to play a role in the development of neuropathy, and their presence in the skin correlates with both autonomic and sensory diabetic neuropathy.[28] Accumulating evidence suggests that AGEs and their corresponding receptor activity are not only implicated in the complications of diabetes but also in the development of inflammation, atherosclerosis and neurodegenerative disorders,[28] which may contribute to excess risk in cardiovascular and all-cause mortality. Alternatively, PN may be a marker of sicker individuals with a greater prevalence of risk factors associated with CVD, including hypertension and higher levels of atherogenic lipids that might explain any excess risk.[29] However, in the present analysis, we observed that even after controlling for standard cardiovascular risk factors, PN remained a significant independent predictor of CVD, and moreover provided improvements (although modest over the short term) on CVD risk prediction over and above conventional factors. These observations support the suggestion that PN may reflect underlying, as yet unidentified, pathways linked to vascular disease, although further scientific research is needed to elucidate the possible mechanisms underlying the relationship between PN and cardiovascular events.

The performance of PN in short-term risk prediction limits its role in risk algorithms; however, further validation in other cohorts and in the longer term is needed to evaluate whether its inclusion can further improve existing CVD risk scores and whether interventions to aggressively target risk factor control might attenuate the excess CV risk among those with PN. If these data are replicated, testing for PN may offer a simple clinical tool to identify a cohort of higher-risk individuals with diabetes for more intensive monitoring or treatment who are currently perceived to be at lower absolute risk using contemporary risk prediction tools. Individuals with PN were more frequently prescribed lipid-lowering therapy and an angiotensin receptor blocker or angiotensin-converting enzyme (ACE) inhibitor, which follows evidence to suggest that ACE inhibition can slow progression of diabetic microvascular disease.[8]

The assessment of PN is a quick and routine test performed in primary care by physicians, practice nurses and podiatrists. In UK primary care, remuneration exists to encourage best practice in the management of chronic disease through the Quality Outcomes Framework.[17] Presently, data captured on the presence of PN are used to stratify patients with diabetes according to their risk of developing foot complications. In addition to providing important information on foot risk, our findings suggest that there may be opportunity to use these data for identifying individuals at increased cardiovascular risk.

The excess mortality observed among patients with PN supports previous observations of increased mortality among patients with a history of diabetic foot ulceration compared with patients with diabetes and no history of ulceration. A meta-analysis of eight studies reporting on 17 830 individuals showed an excess risk of mortality among patients with a history of diabetic foot ulceration. However, it could not sufficiently separate the association of foot ulceration with cardiovascular versus non-cardiovascular endpoints, and to what extent a greater number of cardiovascular events were explained by the burden of conventional risk factors.[30] This study adds to previous research by studying signs that manifest themselves long before foot ulceration; and after controlling for conventional risk factors is able to demonstrate that the presence of PN is a harbinger for incident cardiovascular events and not just foot ulceration. Although the present data derive from a nationally representative sample of the population of England, the results should not be extrapolated to dissimilar population samples. This analysis is restricted to individuals in whom complete information was available, with the exception of HbA1c, and may reflect selection bias. Examination of variables among individuals with missing data suggests this group were younger, with less favourable cholesterol profiles; however, these differences were modest. Our analyses were also limited by the absence of data on cause-specific mortality; the inclusion of CVD deaths in our composite endpoint may have increased power and provided information on the relative contribution of

CVD death to all-cause mortality. The effect of diet was not considered in our analyses as these data were unavailable, which may result in residual confounding. A further limitation of the present study is the relatively short duration of follow-up and lack of data on duration of diabetes. Ten-year follow-up data would have been preferable as risk prevention guidelines generally quote risk strata at this period and a greater number of accrued events would have improved precision and power. Similar studies are needed among larger cohorts with longer follow-up duration to validate our findings using a range of endpoints. Finally, the diagnosis of PN is observer dependent and could be prone to subjectivity. As previously discussed, PN was diagnosed by a range of healthcare professionals including physicians and practice nurses. This is both a strength and a weakness of our study. While the diagnostic accuracy of neuropathy testing cannot be verified, our data reflect routine clinical practice that currently informs management of patients with diabetes in primary care in the UK. Finally, the data presented are observational in nature and although we have aimed to reduce confounding by statistical adjustment we cannot exclude the possibility of residual confounding as a potential explanation for our findings.

PN is associated with an increased risk of cardiovascular events among individuals with diabetes and no prior history of CVD. Assessment of PN among patients with diabetes is routine and provides additional information on cardiovascular risk to that of conventional risk factors, although modestly in the short term.

Key messages

What is already known on this subject?
Our search identified no studies separately reporting on incident cardiovascular events among individuals with diabetes, with and without peripheral neuropathy. Currently the UKPDS risk engine is the only prognostic risk score routinely available for individuals with diabetes that includes information on traditional risk factors in addition to diabetes-specific variables; the duration of diabetes and HbA_{1c}. However, the UKPDS risk engine has demonstrated, at best, moderate discrimination for cardiovascular disease (CVD) risk in external validation.

What might this study add?
Our results suggest that even after controlling for standard cardiovascular risk factors, peripheral neuropathy is a significant independent predictor of CVD among patients with diabetes free of CVD at baseline.

How might this impact on clinical practice?
In addition to providing important information on foot risk, there may be opportunity to use data on peripheral neuropathy for identifying individuals at increased cardiovascular risk for potentially more intensive preventative strategies.

Contributors JRWB and SdeL contributed equally and were joint first authors, and KKR and RJH contributed equally and were joint senior authors. JRWB, SdeL, KKR and RJH developed the original idea for the report. JRWB and AM wrote the first draft that was revised by MMT. JRWB and AM performed the literature search. JRWB and AM did the statistical analyses, and SdeL coordinated the analyses. All authors contributed to interpretation of results and drafting of the first submission. JRWB had full access to all of the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis and the overall content as guarantor.

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Competing interests None.

Ethics approval The study was approved by the Oxford Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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Notes