

# Factors associated with diabetic polyneuropathy-related sensory symptoms and signs in patients with polyneuropathy: A cross-sectional Japanese study (JDDM 52) using a non-linear model

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## Keywords

Diabetic polyneuropathy-related symptoms, Non-linear model, Type 2 diabetes mellitus

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## ABSTRACT

**Aims/Introduction:** To assess the prevalence of diabetic polyneuropathy (DPN)-related sensory symptoms/signs and associated factors in patients with polyneuropathy, considering non-linear effects for numerical variables.

**Materials and Methods:** A cross-sectional survey of patients with type 2 diabetes mellitus from 17 primary care clinics across Japan was carried out. DPN and DPN-related sensory symptoms/signs were diagnosed according to the Diabetic Neuropathy Study Group in Japan criteria.

**Results:** Of the 9,914 patients with type 2 diabetes mellitus in this study, 2,745 had DPN and 1,689 had DPN-related sensory symptoms/signs (61.5% of patients with DPN). There were significant correlations between DPN-related sensory symptoms/signs and smoking status (odds ratio 2.04 for current and 1.64 for former;  $P < 0.001$  and  $P = 0.002$ , respectively), sex (odds ratio 0.56 for male/female;  $P < 0.001$ ) and alcohol consumption (odds ratio 2.02 for former/never;  $P = 0.004$ ). Based on the non-linear logistic regression model, significant correlations were observed between the presence of DPN-related sensory symptoms/signs and higher systolic blood pressure (SBP), longer diabetes duration, and decreasing age. The logarithm of odds for SBP increased until reaching approximately 130 mmHg, then it plateaued.

**Conclusions:** Some modifiable factors assessed in the large survey database might be associated with DPN-related sensory symptoms/signs, namely smoking, alcohol consumption and SBP. Maintaining SBP <130 mmHg was associated with lower odds of DPN-related sensory symptoms/signs in patients with DPN.

## INTRODUCTION

The number of patients with diabetes mellitus is increasing globally and is expected to reach 366 million in 2030<sup>1</sup>. In accordance with the global trend, the National Diabetes Survey between 1997 and 2007 in Japan showed that the percentage of patients with diabetes mellitus increased from 9.9 to 15.3% in males and from 7.1 to 7.3% in females<sup>2</sup>; therefore, the burden of diabetic complications is also expected to increase.

Diabetic polyneuropathy (DPN) is one of the most common complications of diabetes mellitus<sup>3,4</sup>, and is prevalent in approximately 37–45% of patients with type 2 diabetes mellitus and 54–59% of patients with type 1 diabetes mellitus<sup>5</sup>. Some patients with DPN experience positive symptoms, such as pain, and negative symptoms, such as numbness; however, it is common for the disease to progress undetected<sup>3,6,7</sup>.

DPN-related pain occurs in approximately one-quarter of patients with DPN<sup>8</sup>, and has been associated with considerable morbidity and diminished quality of life<sup>9,10</sup>. In particular,

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DPN-related pain has been shown to be associated with sleep impairment, depression and anxiety<sup>11,12</sup>. To prevent the deleterious effects of DPN-related symptoms on quality of life and complications associated with asymptomatic DPN, such as foot ulceration, early diagnosis of DPN by physicians is important<sup>9,10</sup>. Despite DPN being such a commonly encountered complication, physicians often do not recognize DPN in their patients. For example, just 36.4% of Japanese physicians were aware of painful diabetic neuropathy in their patients in a sample of Japanese outpatients<sup>10</sup>. Although DPN is common in Japan, the last large-scale report on the disease burden was in 2001<sup>13</sup>. At that time, a limited selection of treatments was available to treat DPN-related symptoms; presently, a variety of different analgesic agents are available<sup>14</sup>. Globally, there are many studies that have assessed the risk factors associated with DPN<sup>15</sup>; however, there are very few studies that have assessed the risk factors associated with DPN-related symptoms<sup>16</sup>.

Given the high and increasing burden of type 2 diabetes mellitus globally and, specifically, in Japan<sup>1,2</sup>, plus the impact DPN-related symptoms have on the quality of life of patients with DPN<sup>9,10</sup>, it is important to understand the factors that are associated with DPN and DPN-related symptoms. A cross-sectional study found that specific markers for vascular wall properties, as well as the albumin-to-creatinine ratio, retinopathy, systemic blood pressure, duration of diabetes and glycated hemoglobin (HbA1c), are associated with diabetic neuropathy, suggesting that the interplay of vascular and metabolic factors might contribute to the pathogenesis of neuropathy<sup>16</sup>. The identification of associated factors could facilitate screening for DPN and DPN-related symptoms at an early stage of the disease. A better understanding of the factors associated with DPN and related symptoms would also improve the care provided by physicians for patients with DPN. Therefore, the objective of the present study was to assess the prevalence of DPN-related sensory symptoms/signs and to evaluate associated factors among Japanese patients with DPN, with consideration of non-linear effects for numerical variables.

## METHODS

### Study design and population

A cross-sectional nationwide survey was designed to determine the prevalence of microvascular complications and rates of achieving treatment targets among Japanese patients with type 2 diabetes mellitus; the study design and primary findings have been reported previously<sup>17</sup>. Patients with type 2 diabetes mellitus were enrolled from 17 primary care clinics across various regions of Japan<sup>17</sup>. These clinics consisted of physicians who specialize in diabetes, and they were responsible for recording the clinical data from the patients<sup>17</sup>. Of the overall population of 13,039 patients who attended the medical clinics between January 2013 and December 2015, and had urinary albumin and serum creatinine measured within 1 year of attendance<sup>17</sup>, a total of 9,914 patients had neuropathy evaluated within 1 year of attendance at the clinic and were registered in the present study.

The diagnosis of diabetes mellitus and treatment targets were based on the Japan Diabetes Society guidelines<sup>18</sup>. All patients provided informed consent, and the study was carried out in accordance with the Declaration of Helsinki. This study was approved by the Japan Diabetes Clinical Data Management Study Group (JDDM 52) ethics committee, Osaka City University ethics committee and the ethics committee of Shionogi & Co., Ltd.

### Measurements and definitions

Demographic characteristics, including age, sex, bodyweight, smoking status, alcohol consumption, duration of diabetes, medical history (diabetic retinopathy and diabetic nephropathy, defined as albumin-to-creatinine ratio  $\geq 30$  mg/g Cr) and anti-hypertensive medication use, were collected from patient medical records<sup>17</sup>. Body mass index (BMI), serum and urinary creatinine, HbA1c, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides (TG), systolic blood pressure (SBP) and estimated glomerular filtration rate (eGFR) were assessed as described previously<sup>17</sup>.

The diagnosis of DPN was established based on two or more of the following three criteria from The Diabetic Neuropathy Study Group in Japan<sup>17,19,20</sup>: (i) subjective symptoms in the bilateral lower limbs or feet; (ii) loss of or decreased ankle jerk reflex; and (iii) decreased vibration perception, assessed using a C128 tuning fork and bilaterally measured at the medial malleoli. Neuropathic sensory symptoms/signs were defined as bilateral spontaneous pain; hypoesthesia, including decreased perception to pinprick and temperature (cold tuning fork); or paresthesia of the legs<sup>20</sup>.

### Statistical analysis

Patient demographic and clinical characteristics were summarized using medians and interquartile ranges for continuous variables, and as counts and percentages for categorical variables.

To assess the association between various factors and the occurrence of DPN-related sensory symptoms/signs, we carried out a multivariable logistic regression analysis that included the following factors as independent variables: age, sex, BMI, disease duration, SBP, HbA1c, eGFR, HDL-c, LDL-c, TG, alcohol consumption status (current, former, never), smoking status (current, former, never), use of antihypertensive medicine, and the presence/absence of nephropathy and retinopathy. This regression model contained restricted cubic splines for all continuous variables to examine the non-linear association between each factor and the occurrence of DPN-related sensory symptoms/signs. All missing data were imputed by the multiple imputation method using the "aregImpute" function in the "rms" package of R software version 3.3.0 (<https://www.r-project.org/foundation/>).

All statistical analyses were carried out with a two-sided significance level of 5%, and carried out with R software version 3.3.0 using the "rms" package.

## RESULTS

## Patient characteristics and demographics

Of the 9,914 patients who had type 2 diabetes mellitus, 2,745 patients had DPN and 1,689 had DPN-related sensory symptoms/signs (61.5% of patients with DPN) (Table 1). The demographic and clinical characteristics of the cohort are shown in Table 1. The median age for all participants was 66 years, and 62.3% of patients were male with a median BMI of 24.5 and median SBP of 127 mmHg (Table 1). The median duration of diabetes for all patients was 13.0 years, with a median HbA1c of 6.9. The median age, sex distribution, BMI, SBP, smoking status, alcohol consumption status and median eGFR were similar in the subgroups of patients with DPN and DPN-related sensory symptoms/signs. The median HbA1c was also similar between the subgroups of patients with DPN (7.0) and those with DPN-related sensory symptoms/signs (7.1). The duration of diabetes mellitus in patients with DPN (15.9 years) and DPN-related sensory symptoms/signs (16.5 years) was longer

when compared with all patients (13.0 years) and patients without DPN (11.8 years). The frequency of retinopathy in patients with DPN (43.1%) and DPN-related sensory symptoms/signs (44.3%) was higher when compared with all patients (25.8%) and patients without DPN (19.2%).

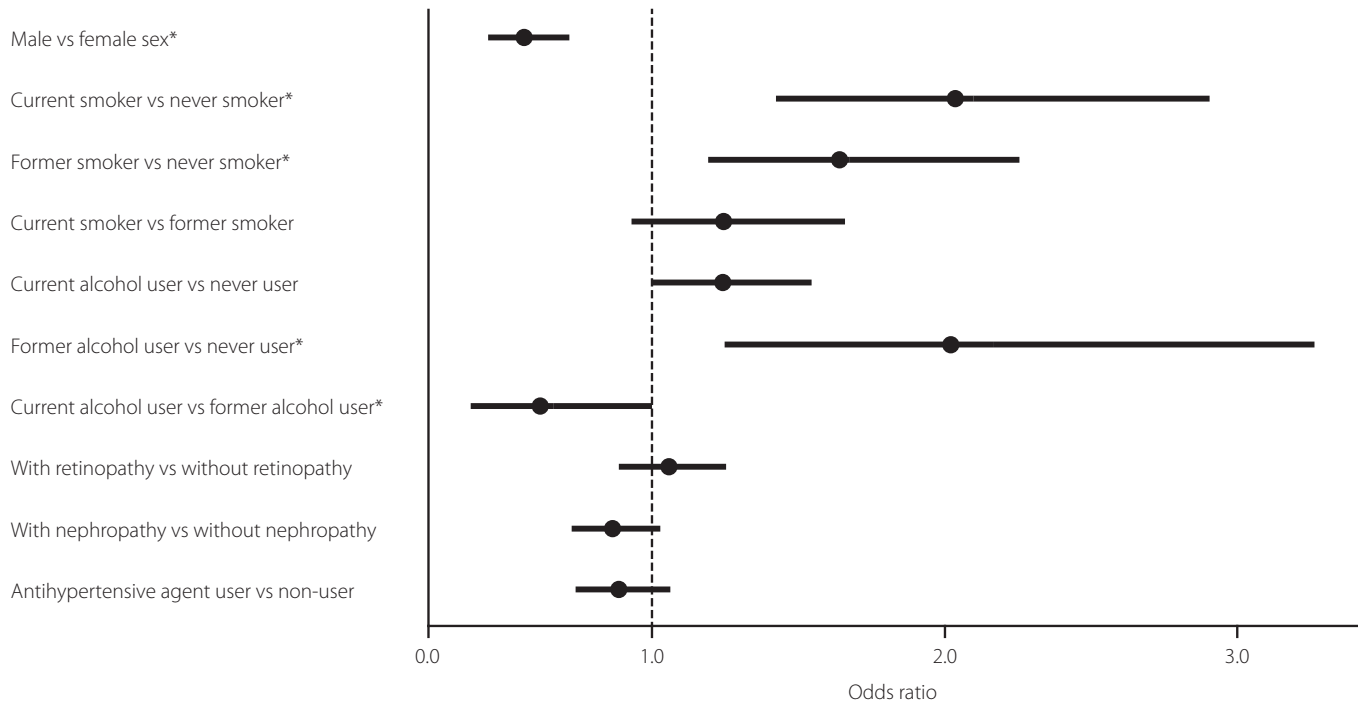
## Correlations between patient characteristics and DPN-related sensory symptoms/signs

Analyses of factors associated with DPN-related sensory symptoms/signs among patients with DPN are shown in Figure 1. There were significant correlations between the presence of DPN-related sensory symptoms/signs and current smoking (odds ratio [OR] 2.036, confidence interval [CI] 1.423–2.911;  $P < 0.001$ ), former smoking (OR 1.639, CI 1.190–2.257;  $P = 0.002$ ), sex (OR 0.559, CI 0.437–0.715;  $P < 0.001$ ) and former alcohol consumption (OR 2.019, CI 1.247–3.271;  $P = 0.004$ ). Based on the non-linear model, significant correlations between the presence of DPN-related sensory symptoms/

Table 1 | Clinical characteristics and demographics

	Patients with T2DM ( <i>n</i> = 9,914)				
	Overall population ( <i>n</i> = 9,914)	Patients without DPN ( <i>n</i> = 6,180)	Patients with DPN ( <i>n</i> = 2,745)		Patients with unknown status of DPN ( <i>n</i> = 989)
			Overall ( <i>n</i> = 2,745)	With DPN-related sensory symptoms/signs ( <i>n</i> = 1,689)	
Median age, years (IQR)	66.0 (59.0–73.0)	65.0 (57.0–71.0)	70.0 (63.0–77.0)	69.0 (63.0–76.0)	67.0 (59.0–75.0)
Male, <i>n</i> (%)	6,139 (62.3)	3,904 (63.2)	1,705 (62.1)	1,025 (60.7)	530 (57.2)
Median BMI, kg/m <sup>2</sup> (IQR)	24.5 (22.1–27.2)	24.4 (22.1–27.1)	24.7 (22.3–27.3)	24.7 (22.3–27.3)	24.6 (22.1–27.4)
Smoking, <i>n</i> (%)					
Current	1,511 (18.4)	951 (18.5)	419 (17.0)	308 (20.5)	141 (22.7)
Former	1,686 (20.5)	982 (19.1)	557 (22.5)	378 (25.2)	147 (23.7)
Never	5,024 (61.1)	3,197 (62.3)	1,495 (60.5)	814 (54.3)	332 (53.5)
Alcohol use, <i>n</i> (%)					
Current	2,477 (31.6)	1,530 (31.8)	703 (29.3)	475 (32.7)	244 (39.9)
Former	264 (3.4)	157 (3.3)	95 (4.0)	74 (5.1)	12 (2.0)
Never	5,087 (65.0)	3,128 (65.0)	1,604 (66.8)	905 (62.2)	355 (58.1)
Median DM duration, years (IQR)	13.0 (7.5–19.7)	11.8 (6.8–18.5)	15.9 (9.8–23.4)	16.5 (10.4–24.1)	12.6 (7.2–19.6)
Median HbA1c, % (IQR)	6.9 (6.5–7.4)	6.9 (6.5–7.4)	7.0 (6.6–7.5)	7.1 (6.6–7.6)	6.8 (6.4–7.3)
Median SBP, mmHg (IQR)	127.0 (118.0–134.0)	126.0 (118.0–134.0)	129.0 (119.0–134.0)	130.0 (120.0–134.0)	127.0 (119.0–135.0)
Retinopathy, <i>n</i> (%)					
No	7,290 (74.2)	4,986 (80.8)	1,554 (56.9)	935 (55.7)	750 (81.1)
Yes	2,539 (25.8)	1,187 (19.2)	1,177 (43.1)	743 (44.3)	175 (18.9)
Nephropathy, <i>n</i> (%)					
Stage 1	7,037 (71.9)	4,725 (76.9)	1,664 (61.1)	1,043 (62.2)	648 (70.4)
Stage ≥2	2,750 (28.1)	1,417 (23.1)	1,061 (38.9)	633 (37.8)	272 (29.6)
Median eGFR, mL/min/1.73 m <sup>2</sup> (IQR)	78.4 (64.4–94.7)	80.5 (67.2–96.8)	74.1 (59.5–89.9)	74.8 (59.8–91.1)	74.9 (60.8–91.7)
Median HDL-c, mg/dL (IQR)	53.0 (45.0–64.0)	54.0 (45.0–65.0)	51.0 (43.0–61.0)	51.0 (43.0–61.0)	53.0 (45.0–63.0)
Median LDL-c, mg/dL (IQR)	104.0 (86.7–122.6)	105.0 (88.0–124.0)	102.4 (85.0–121.6)	102.0 (85.0–122.0)	98.0 (84.0–116.0)
Median TG, mg/dL (IQR)	118.0 (81.0–172.0)	117.0 (80.0–173.0)	119.0 (83.0–171.0)	118.0 (83.0–169.0)	116.0 (80.0–166.8)
Antihypertensive agents, <i>n</i> (%)	5,259 (53.4)	3,051 (49.4)	1,652 (60.2)	983 (58.2)	556 (60.0)

BMI, body mass index; DM, diabetes mellitus; DPN, diabetic polyneuropathy; eGFR, estimate glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TG, triglyceride.



**Figure 1** | Factors associated with diabetic polyneuropathy-related sensory symptoms/signs in patients with diabetic polyneuropathy using a logistic regression model. \* $P \leq 0.05$ .

signs and SBP ( $P < 0.001$ ), diabetes mellitus duration ( $P = 0.012$ ) and age ( $P < 0.001$ ) were observed (Figure 2); the logarithm of odds decreased in a linear manner for age and, in contrast, it increased linearly for diabetes duration. The logarithm of odds increased with increasing SBP, until it reached approximately 130 mmHg, above which it did not increase further. In non-linear models, both the trend of the graph and the  $P$ -value are informative. Although the  $P$ -value was  $>0.05$  for HbA1c, the logarithm of odds increased with higher HbA1c, until HbA1c reached approximately 7%, above which the slope was less steep. In contrast, the  $P$ -value for triglycerides was  $<0.05$ , and the logarithm of odds decreased with increasing triglyceride levels until reaching approximately 200 mg/dL. Although the logarithm of odds  $>200$  mg/dL tended to slightly increase, the CI widened with increasing triglyceride levels, so this result was considered less reliable and is unlikely to be clinically relevant. Only minor changes in OR were detected between DPN-related sensory symptoms/signs and BMI, LDL-c, HDL-c, TG or eGFR.

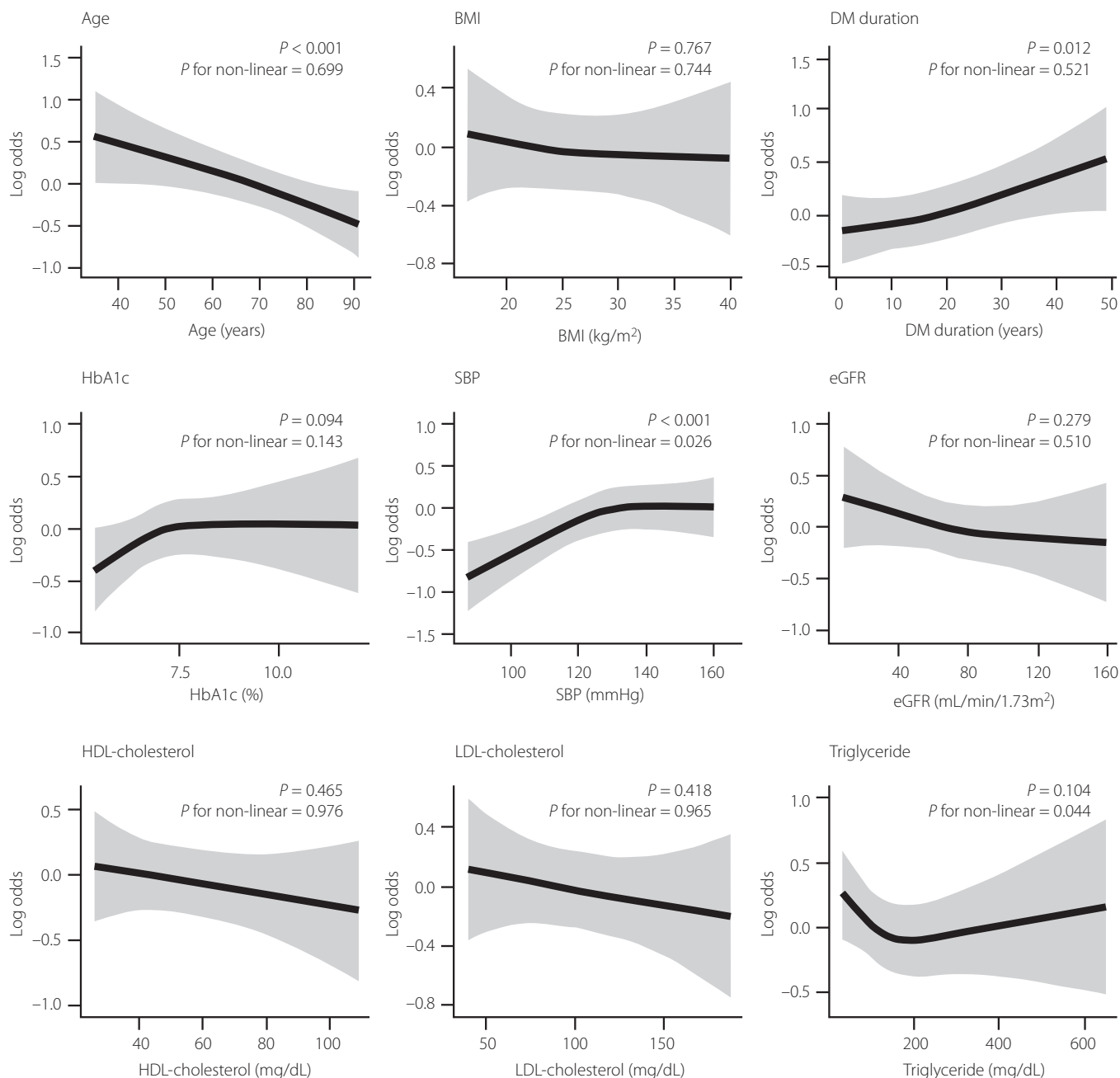
**DISCUSSION**

DPN-related symptoms can cause considerable morbidity and diminished quality of life for patients with diabetes, and it is, therefore, important to determine the factors associated with DPN-related symptoms. In the present cross-sectional Japanese study using a large survey database, the factors associated with DPN-related sensory symptoms/signs within a population of patients with DPN were analyzed<sup>17</sup>. Diabetes

mellitus duration, age, smoking status (current and former), alcohol consumption (former), sex and SBP were all identified as candidate factors potentially associated with the development of DPN-related sensory symptoms/signs in patients with DPN.

In accordance with multiple previous studies, diabetes mellitus duration was identified as a factor associated with DPN-related sensory symptoms/signs in patients with DPN in the present study<sup>15</sup>. In addition, increasing age was associated with reduced DPN-related sensory symptoms/signs in patients with DPN; however, previous studies have yielded varying reports with regard to the link between increasing age and DPN. Some studies have suggested that increasing age is associated with a greater risk for DPN with increasing age<sup>15</sup>. In the present study, it is possible that the apparent decrease in DPN-related sensory symptoms/signs observed with age might be due to an increase in pain threshold with age<sup>21-23</sup>. DPN-related symptoms do not necessarily coincide with the severity of DPN (i.e., extent of fiber reduction), as subjective symptoms might improve while DPN worsens.

Smoking appeared to have the strongest association with DPN-related sensory symptoms/signs in the present study, which is consistent with previous studies that reported smoking to be a risk factor for DPN-related symptoms and DPN<sup>15</sup>. In the present study, former alcohol consumption was associated with increased DPN-related sensory symptoms/signs in patients with DPN; however, previous studies have reported mixed results regarding the association between alcohol consumption



**Figure 2** | Factors associated with diabetic polyneuropathy-related sensory symptoms/signs in patients with diabetic polyneuropathy using a non-linear regression model. BMI, body mass index; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

and development of DPN-related symptoms. Some studies have suggested that alcohol consumption was associated with DPN<sup>15,24,25</sup>, whereas others have not shown an association between alcohol consumption and DPN<sup>15,26,27</sup>. Alcohol consumption has been associated with an inability to sense vibrations from a tuning fork (serves as a measure of peripheral neuropathy), and it has been suggested that alcohol and diabetes mellitus can work synergistically to cause nerve damage<sup>25</sup>.

As no similar association was observed with current alcohol consumption in the present study, the association between DPN-related sensory symptoms/signs and former alcohol consumption might be an artifact due to the small number of patients in this subgroup, a causal relationship reversal or another confounding variable not detected.

Furthermore, female sex was associated with an approximately 50% increased risk of DPN-related sensory symptoms/



signs when compared with male sex. This result is similar to previous studies<sup>28–30</sup>.

Many previous studies have reported HbA1c to be an important risk factor for DPN<sup>15</sup> and DPN-related symptoms in patients with type 2 diabetes mellitus<sup>31–33</sup>. However, no significant association was detected between DPN-related sensory symptoms/signs and HbA1c in the present study. In a non-linear model analysis, both the trend of the graph and the *P*-value are informative. In this study, the logarithm of odds increased until HbA1c reached approximately 7%. This result is consistent with clinical practice, and indicates that it might be necessary to maintain HbA1c <7% to reduce the odds of developing DPN-related symptoms in patients with DPN. Although the mechanism by which changes in glucose might impact the development of DPN and related symptoms are not completely defined, preclinical studies have shown that high glucose levels can induce apoptosis and biochemical alterations in various cell types and organs<sup>34–36</sup>.

Previous studies have linked hypertension with DPN-related symptoms<sup>31,32</sup>; however, in the present study, only SBP was correlated with DPN-related sensory symptoms/signs in patients with DPN. To mitigate cardiovascular risk, the American Diabetes Association guidelines recommend that most patients with diabetes mellitus and hypertension be treated to a blood pressure target of <140 mmHg/90 mmHg, but guidelines also recommend that lower targets (e.g., <130/80 mmHg) might be appropriate for those at high risk of cardiovascular disease, if treatment is well tolerated<sup>37</sup>. Japanese guidelines recommend a SBP target of <130 mmHg<sup>38</sup>. The present findings suggest that maintaining SBP <130 mmHg might also have a beneficial effect on the emergence of DPN-related symptoms in Japanese patients.

Although the mechanism by which changes in blood pressure might impact the development of DPN and related symptoms are not completely defined, preclinical studies have shown that hypertension induces nerve ischemia, thermal hyperalgesia, nerve conduction slowing and axonal atrophy at the sensory nerve fibers<sup>39,40</sup>. HDL-c, LDL-c and TG are not reported risk factors for DPN, although a dyslipidemic profile is known to increase the risk of peripheral vascular disease<sup>41,42</sup>. Although a statistically significant association was detected between DPN-related sensory symptoms/signs and triglyceride levels in non-linear analyses in the present study, the observed trend (i.e., decreasing logarithm of odds with increasing triglyceride levels ≤200 mg/dL, followed by a slight increase in the logarithm of odds >200 mg/dL) is not likely to be clinically relevant and is not easily explained. This observation could be the result of a reverse causal relationship, due the cross-sectional study design.

The present study included a large sample size and standardized data collection procedures. In addition, a non-linear regression analysis was used in the study, which has been previously shown to be a more favorable method than linear regression<sup>43</sup>. Study limitations include the cross-sectional design and the fact that patients are from Japan only, which might limit the generalizability of the study. In addition, the present study did not

consider the effect of patients' current medications in relation to SBP, HbA1c and lipid measurements. These limitations could be considered in future, prospectively designed studies.

Some of the modifiable factors assessed in the large survey database might be associated with DPN-related sensory symptoms/signs, namely smoking, alcohol consumption and SBP. Maintaining HbA1c and SBP at <7% and <130 mmHg, respectively, was associated with lower odds of developing DPN-related sensory symptoms/signs in patients with DPN. In addition, cessation of smoking and alcohol consumption might be associated with lower odds of developing DPN-related sensory symptoms/signs in patients with DPN.

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## DISCLOSURE

TT is a full-time employee of Shionogi & Co., Ltd., and a stockholder in Shionogi & Co., Ltd. and Takeda Pharmaceutical Company Limited. SH is a full-time employee of and stockholder in Shionogi & Co., Ltd. DK and AS were employees of Osaka City University Graduate School of Medicine, which received an honorarium for consulting and data analysis from Shionogi & Co., Ltd. DK and AS had been employees of Department of Clinical Epidemiology and Biostatistics, Osaka University Graduate School of Medicine which donated by Shionogi & Co., Ltd, until October 2016. HY declares no conflict of interest.

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