CLINICAL RESEARCH ARTICLE

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Which combined nerve conduction study scores are best suited for polyneuropathy in diabetic patients?

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Abstract

Introduction/Aims: Nerve conduction studies (NCS) are widely used in diagnosing diabetic polyneuropathy. Combining the Z scores of several measures (Z-compounds) may improve diagnostics by grading abnormality. We aimed to determine which combination of nerves and measures is best suited for studies of diabetic polyneuropathy.

Methods: Sixty-eight patients with type 1 diabetes and 35 controls were included in this study. NCS measurements were taken from commonly investigated nerves in one arm and both legs. Different Z-compounds were calculated and compared with reference material to assess abnormality. A sensitivity proxy, the accuracy index (AI), and Cohen's d were calculated.

Results: Z-compounds with the highest AI consisted of the tibial and peroneal motor, and the sural, superficial peroneal, and tibial medial plantar sensory nerves in one or two legs. All Z-compounds were able to discriminate between diabetic subjects and nondiabetic controls (mean Cohen's $d = 1.42$ [range, 1.03-1.63]). The association between AI and number of measures was best explained logarithmically ($R^2 = 0.401$), with diminishing returns above approximately 14 or 15 measures. F-wave inclusion may increase the AI of the Z compounds. Although often clinically useful among the non-elderly, the additional inclusion of medial plantar NCS into Z-compounds in general did not improve AI.

Discussion: Performing unilateral NCS in several motor and sensory lower extremity nerves is suited for the evaluation of polyneuropathy in diabetic patients. The use of Z-compounds may improve diagnostic accuracy in diabetic polyneuropathy and may

be particularly useful for follow-up research studies as single summary measures of NCS abnormality development over time.

KEYWORDS

F waves, medial plantar nerve, nerve conduction studies, neurography, Z-compound

1 | INTRODUCTION

For clinical purposes, nerve conduction studies (NCS) may give a quantifiable and objective indication of polyneuropathy,[1] and are recommended for research studies on diabetic neuropathy.[2] Normally, several measures are obtained from each nerve, and each measure is compared with reference values to determine abnormality in a dichotomous manner. An alternative approach, in which Z scores from several measures are combined (Z-compounds), has been shown to be more sensitive than single measures in diabetic polyneuropathy[3,4] without loss of specificity.[5] Recently, it has also been suggested that amplitude-based Z-compounds may be predictive of long-term nerve fiber loss and disability in chronic inflammatory demyelinating polyneuropathy.[6] Averaging many measures also eliminates statistical issues regarding multiple testing of several NCS variables, minimizes the effect of nonsystematic errors, and leads to low inter- and intrasubject variance.[4,5,7,8] Accordingly, Z-compounds should be particularly suitable for following the progression of neuropathies over time. Furthermore, it has been shown that Z-compounds are correlated with clinical impairment and the severity of neuropathy,[4] which highlights a distinct and clinically important feature of Z-compounds: they allow for the grading of abnormality on a continuous scale in an easy-to-interpret manner.

Despite these advantages, adoption of Z-compounds for diabetic neuropathy has not been widely accepted. Besides requiring a valid reference material and some mathematical manipulation of data, a critical contributor may be that it is not known which Z-compound is optimal for screening or follow-up, or even which nerves or measures should be included. It is likely that the accuracy of the Z-compound depends on both the nature and number of included measures.[5,8] Suggested measures of importance include sural amplitude and peroneal motor conduction velocity,[3,5] as well as F waves in general.[9,10] Recordings from the medial plantar nerve may be a sensitive addition,[11,12] but have not yet been assessed as part of a Z-compound.

Our aim was to explore which combination of nerves and measures best facilitates the evaluation of polyneuropathy in diabetic patients. This would help the clinician to plan for sufficient and tolerable NCS protocols with a reasonable balance between resource limitations and completeness. Our specific objectives were to: (a) calculate and compare a diagnostic accuracy index for several Z-compounds, categorized to reflect either axonal, demyelinating or mixed nerve pathophysiology, arm vs leg involvement, or motor vs sensory involvement; (b) evaluate whether the medial plantar nerve, as well as F waves in general, are major determinants of Z-compound accuracy; and (c) determine the optimal number of measures to be included in the Z-compounds, beyond which gains in accuracy diminish rapidly.

2 | METHODS

Patients 19 to 65 years of age with type I diabetes mellitus were invited from the outpatient population at St. Olavs Hospital, Trondheim, Norway. Exclusion criteria were pregnancy, breastfeeding, former or present addiction to alcohol or other substances, serious mental or neurological illness, seriously reduced vision or hearing, daily use of medication that could influence the results of the tests (β-blockers, α-blockers, tricyclic antidepressants, antiepileptic drugs, antihistamines, or analgesics), or other plausible causes identified through history that could affect the NCS results. Signs and symptoms of peripheral neuropathy were recorded through a structured history and clinical examination by one of the coauthors (S.E.O.) to describe the patient group. The Neuropathy Impairment Score (NIS) and the Neurological Symptom Score (NSS) were calculated. These scores provide a standardized assessment of the peripheral neuropathy and its severity, including muscle weakness, reflex loss and decreased sensation, as well as positive and negative sensory symptoms.[13,14] Further details regarding inclusion and disease severity of the patients assessed in this study have been described elsewhere.[15]

Age- and sex-matched control subjects without diabetes were recruited by announcement at the intranet of St. Olavs Hospital and the Norwegian University of Science and Technology.

Standard NCS were performed with the Keypoint G4 electromyography apparatus, utilizing Keypoint Classic version 5.13 (Medtronic, Copenhagen, Denmark). Pre-gelled adhesive surface electrodes with a recording area of 9 mm × 6 mm were used (Alpine Biomed ApS, Skovlunde, Denmark). Room temperature was kept between 22° and 24°C, and skin temperature was kept at at least 33°C by heat packs and an infrared lamp. Recordings were made of both legs and the left arm. Motor amplitude (baseline to peak), distal latency, conduction velocity, and F responses (F-M latency) of the median, ulnar, peroneal, and posterior tibial nerves were recorded, as well as orthodromic sensory amplitude and conduction velocity (sensory nerve action potential (SNAP) onset at initial positive peak) of the median nerve (finger III), ulnar nerve (finger V), sural nerve (lateral ankle–calf segment), and medial plantar nerve (foot sole metatarsal 1-2 interspace to medial ankle segment). Antidromic sensory studies from the radial and superficial peroneal nerves in the left arm and both legs were also performed. Sensory amplitudes were measured from the negative peak to the intersection of a line drawn between the first and last positive peak ("tilted amplitude option") to reduce the effects of occasional stimulus artifacts. Fractionated conduction velocity and amplitude from proximal stimulation were obtained from the ulnar nerve in the elbow region (stimulation above the elbow, 10-cm distance) and

peroneal nerve in the lateral knee region (popliteal stimulation behind the knee). If a traumatic neuropathy was suspected, the values from that extremity were not analyzed. All NCS were performed by technicians with more than 5 years of experience, and later evaluated by a senior consultant clinical neurophysiologist (T.S.).

Reference data (n = 568) were gathered over several years, mainly between 2012 and 2017, partly from healthy subjects and partly from patients referred to one of two Departments of Neurology in Mid-Norway (Trondheim or Ålesund) for nonspecific symptoms without known disease (malignancy, diabetes, connective tissue disease, etc), and found to be free any neurological diagnosis after examination. Both laboratories were supervised by the same senior electrodiagnostic physician and used identical guidelines and standards for the NCS. Mean age was 44 years (standard deviation [SD], 14.8 years; range, 13-86 years), mean height was 171 cm (SD, 8.6 cm; range, 149-190 cm), and 71% were women.

We included a wide variety of Z-compounds. The selection of nerves to be included in the different Z-compounds was based on pathophysiology (eg, conduction velocity-based Z-compounds were compiled in order to represent dominating demyelinating pathophysiology and amplitude-based Z-compounds to represent dominating axonal pathology), anatomy (eg, lower extremities compared to upper extremities, and unilateral compared to bilateral lower extremity), previously published combinations,[3-5,7,16,17] or the authors' own experience ("clinical guess"–based Z-compounds). Six different "clinical guess" variants were created, with a mixture of different measures emphasizing amplitudes, F responses, and one or more nerves from the upper extremity. Because diabetes polyneuropathy can have components of both axonal degeneration and demyelination,[18-20] some Z-compounds were made up of combinations of amplitude and conduction velocities that were expected to perform well in detecting mixed diabetes polyneuropathy. In addition, we employed a principal component analysis (PCA) as a data reduction tool, and we included a Z-compound based on the findings. To reduce the multicollinearity of the NCS measures (R > 0.8) in the PCA, only one amplitude or conduction velocity measure was kept where several existed, and only

F_{mean} was included. Direct oblimin rotation was selected due to correlation between factors.

Recruitment and data collection were approved by the Regional Committee for Medical and Health Research Ethics (REC, 2012/439). The current study is a quality assurance project based on these data and approved by the hospitals' data protection officers through use of a data transfer agreement.

2.1 | Statistics

Each NCS variable was assessed for normality and transformed with power or logarithmic functions as necessary to fit a normal distribution, before age- and height-corrected reference ranges were calculated by linear regression. A small constant (0.1) was added to all values to ensure proper transformation. Z scores, that is, the standardized deviation from the expected age- and height-corrected reference value, were calculated for every NCS variable. The Z-score sign was adjusted to ensure that abnormality (low amplitudes, low conduction velocities, high distal and F-wave latencies) always produced positive Z values.

TABLE 1   Characteristics of patients and controls

	Patients (n = 68)	Controls (n = 35)
Sex, female, n (%)	39 (57%)	22 (58%)
Age, years, median (IQR)	47 (15.0)	47 (17.5)
Diabetes duration, years, median (IQR)	31 (13.3)	—
Current HbA$_{1c}$, mmol/mol, median (IQR)	64.0 (19.7)	—
Total NSS, median (IQR)	1.0 (3.0)	0
Total NIS, median (IQR)	10 (12.0)	0

Abbreviations: HbA$_{1c}$, glycated hemoglobin; IQR, interquartile range; NSS, Neurological Symptom Score; NIS, Neuropathy Impairment Score.
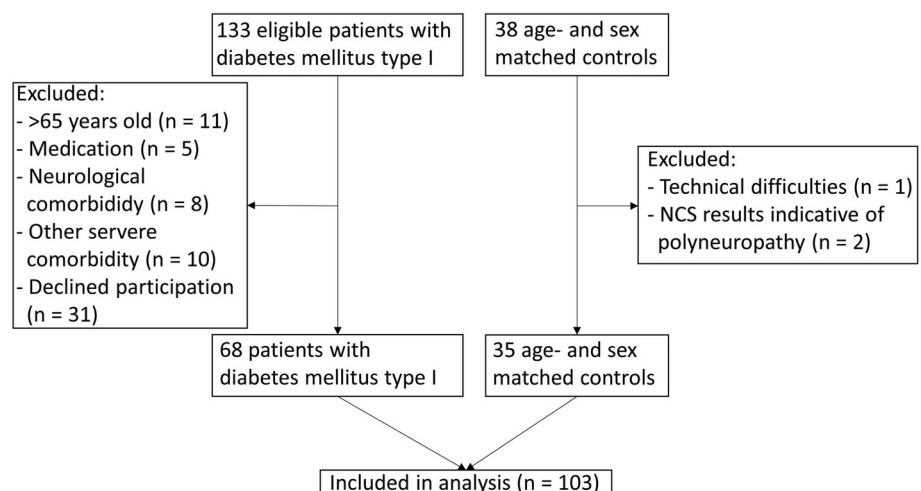

FIGURE 1   Flowchart of the inclusion process

TABLE 2 Accuracy index, Cohen's *d*, and prevalence of PN-NCS

	Z-compounds	NCS measures, n	Prevalence of PN-NCS (%) patients controls		Cohen's *d*	Accuracy index
Extremities	Lower extremity, unilateral	14	72	2.9	1.48	0.81
	Lower extremity, bilateral	28	74	5.7	1.46	0.81
	Upper extremities, unilateral	13	57	8.6	1.43	0.69
Clinical guesses	All measures	41	76	5.7	1.58	0.83
	Clinical guess 4	14	74	5.7	1.41	0.81
	Clinical guess 5	21	75	8.6	1.61	0.81
	Clinical guess 3	8	74	8.6	1.41	0.80
	Clinical guess 1	19	75	11.4	1.62	0.80
	Clinical guess 2	15	72	8.6	1.53	0.79
Motor NCV and amplitudes	Motor, all	22	63	2.9	1.50	0.75
	Motor, short	4	59	2.9	1.36	0.72
	Lower extremities motor, unilateral	8	59	5.7	1.46	0.71
Sensory NCV and amplitudes	All sensory measures, unilateral	13	68	11.4	1.44	0.75
	All sensory measures	19	71	17.1	1.40	0.75
	Sensory, short	4	66	20.0	1.03	0.71
All amplitudes	Amplitudes, all	16	59	8.6	1.19	0.70
	Amplitudes, unilateral	10	54	11.4	1.20	0.66
Nerve conduction speed	Conduction velocity, F and latency, 3 extremities	26	69	2.9	1.63	0.79
	Clinical guess 6	12	69	5.7	1.61	0.78
Previously published	Heise variant	5	63	2.9	1.47	0.75
	Solders variant	13	66	8.6	1.46	0.75
	Dyck variant 3	2	59	2.9	1.50	0.72
	Dyck variant 5	6	56	0.0	1.45	0.71
	Dyck variant 1	2	56	5.7	1.47	0.69
	Dyck variant 2	7	50	5.7	1.24	0.65
	Tankisi variant	7	49	8.6	1.10	0.63
	Dyck variant 4	5	40	2.9	1.31	0.59
	Lee variant	2	38	2.9	1.20	0.58
Principal component analysis	PCA variant	18	63	2.9	1.51	0.75

Note: Z-compounds were sorted by accuracy index within type group.
Abbreviations: NCS, nerve conduction study; PN-NCS, polyneuropathy indicated by nerve conduction study; PCA, principal component analysis; Z-compound, aggregate of the Z scores of certain NCS measures.

Missing data resulting from technical errors or unmeasurable conduction velocities or latencies were imputed with single imputation. Single imputation was chosen over multiple imputation for practical reasons; that is, a complete data set was necessary for the Z-compound analyses, and because the amount of missing data was limited. The method of single imputation was based on fully conditional specification (chained equations) with predictive mean matching (SPSS version 25; IBM Corp, Armonk, NY): the imputation was run 20 times and the average imputed value was entered into the final data set for analysis. Non-recordable sensory and motor amplitudes were scored as 0 μV (giving a high positive single Z score).

The Z scores for each variable were averaged into Z-compounds. SDs for every Z-compound were estimated from a subset of 197 of the reference subjects with complete data on the included NCS variables (mean age, 48 years; SD, 15.6 years; mean height, 171 cm; SD, 8.4 cm; 46% women). The limit of abnormality was defined as over 2 SDs from the mean. Using 197 subjects with normal NCS, the estimated reference limits should be sufficiently precise with 95% confidence intervals equal to [11%, -9%] calculated from the chi-square (degrees of freedom = 196) distribution.

Exploratory Student *t* tests with Bonferroni correction were performed to first assess whether different Z-compounds could discriminate between patients and the control group. As the true prevalence of polyneuropathy depends in part on the NCS data under study, "true" sensitivity and receiver-operating curves (ROCs) could not be calculated. We have instead employed a purely NCS-based definition

FIGURE 2 Association between number of measures included in the nerve conduction study Z-compound and either accuracy index (Prevalence PN-NCS in diabetes group + Prevalence non−PN-NCS in control group) / Total number of subjects, or Cohen's *d* for studies of diabetic polyneuropathy. Abbreviation: PN-NCS, polyneuropathy as indicated by nerve conduction study
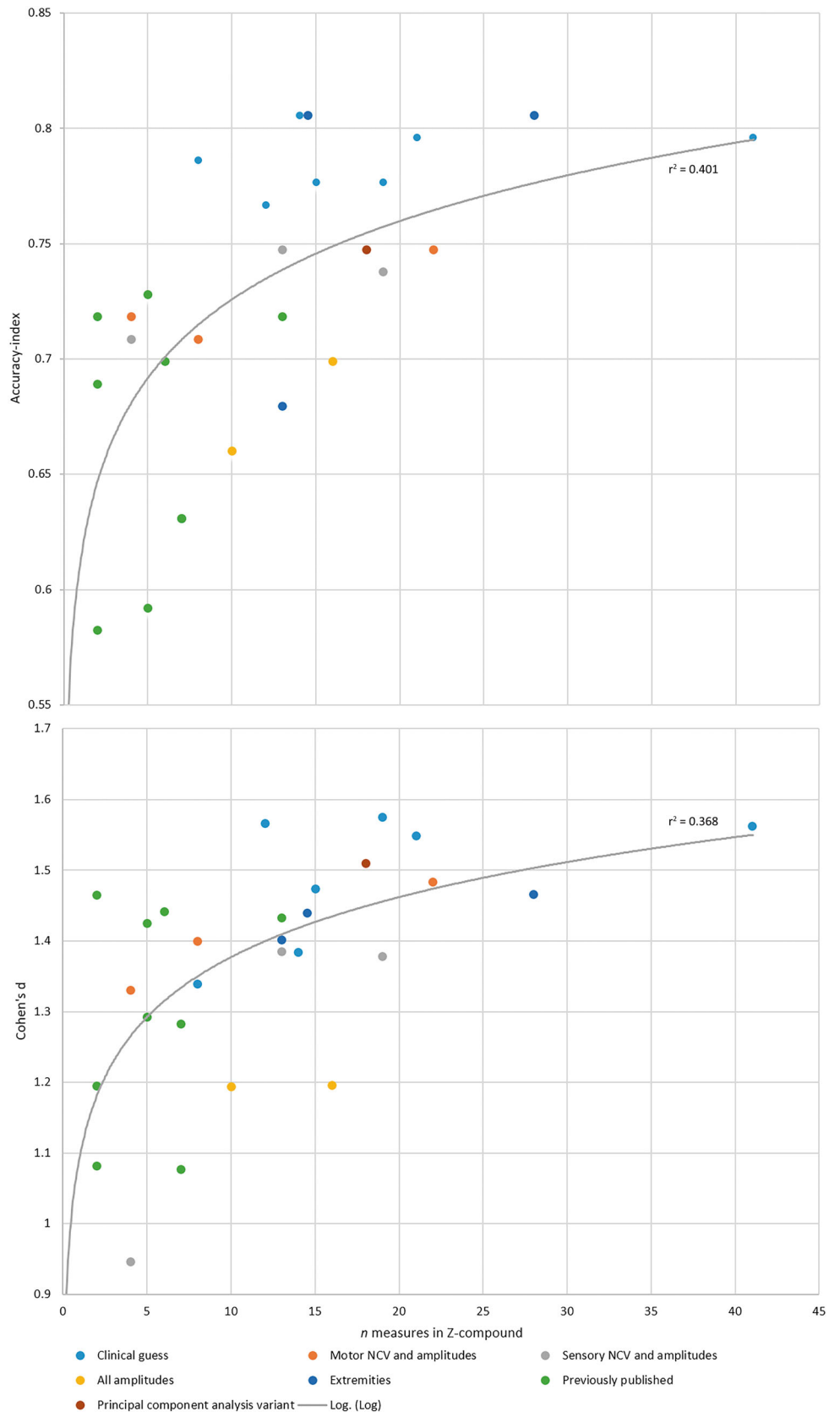
of polyneuropathy (PN-NCS), wherein we classify NCS measurements exceeding 2 SDs of the reference material as abnormal, and measure the prevalence of this abnormality in our two groups, for all different Z-compounds. Abnormality was one-sided, meaning that supranormal controls were classified as normal. Our primary outcome was a proxy measure defined as the "accuracy index" (AI) = (Prevalence of

TABLE 3 The impact of F latencies and the medial plantar nerve on Z-compound accuracy index

	Z-compounds	Original	All F values removed	$F_{mean} \rightarrow F_{min}$	Medial plantar nerve added	Medial plantar nerve removed
Extremities	Lower extremity, unilateral	0.806	0.786	0.806	—	0.796
	Lower extremity, bilateral	0.806	0.786	0.806	—	0.816
	Upper extremities, unilateral	0.689	0.680	0.689	0.680	—
Clinical guesses	All measures	0.825	0.806	0.796	—	0.816
	Clinical guess 4	0.806	0.786	0.806	—	0.786
	Clinical guess 5	0.806	0.796	0.786	—	0.786
	Clinical guess 3	0.796	0.757	0.767	—	—
	Clinical guess 1	0.796	0.786	0.786	—	—
	Clinical guess 2	0.786	0.777	0.786	—	—
Motor NCV and amplitudes	Motor, all	0.748	0.767	0.718	0.757	—
	Motor, short	0.718	0.680	0.680	0.689	—
	Lower extremities motor, unilateral	0.709	0.689	0.709	0.709	—
Sensory NCV and amplitudes	All sensory measures, unilateral	0.748	—	—	—	0.738
	All sensory measures	0.748	—	—	—	0.777
	Sensory, short	0.709	—	—	—	—
All amplitudes	Amplitudes, all	0.699	—	—	—	—
	Amplitudes, unilateral	0.660	—	—	—	—
Nerve conduction speed	Conduction velocity, F and latency, 3 extremities	0.786	0.767	0.767	—	—
	Clinical guess 6	0.777	0.748	0.777		—
Previously published	Heise variant	0.748	0.709	0.728	0.728	
	Solders variant	0.748	0.767	0.748	0.718	—
	Dyck variant 3	0.718	—	—	0.728	—
	Dyck variant 5	0.709	0.728	0.709	0.718	—
	Dyck variant 1	0.689	—	—	0.689	—
	Dyck variant 2	0.650	0.641	0.660	0.621	—
	Tankisi variant	0.631	0.631	0.631	-	—
	Dyck variant 4	0.592	—	—	0.689	—
	Lee variant	0.583	—	—	0.621	—
Principal component analysis	PCA variant	0.748	0.777	0.738		—
	Mean difference from original accuracy	—	−0.011	−0.010	0.004	−0.004

Note: Z-compounds were sorted by accuracy index within type group. Dashed entries indicate change not possible due to measure(s) already included or excluded in original Z-compound.

Abbreviations: NCS, nerve conduction study, PCA, principal component analysis; Z-compound, aggregate of the Z scores of certain NCS measures.

PN-NCS in diabetes group + Prevalence of non–PN-NCS in control group) / Total number of subjects. AI was chosen to combine the two prevalence scores, while best reflecting the sensitivity of the Z-compounds in the patient group and still allowing false positives in the control group to impact the score negatively. Simulations show that a Z-compound capable of detecting two additional (of 40) polyneuropathy (PNP) patients (5%) will increase AI from 0.72 to 0.74. Consequently, quite small AI changes (±0.02) are treated as reflecting a clinically meaningful difference.

To gauge the effect of specific, preselected measures on AI, we performed the following "sensitivity" analyses: (a) F values were omitted; (b) F_{mean} values were substituted with F_{min} values; and (c) the amplitude and conduction velocity of the medial plantar nerve was included in or excluded from the Z-compounds. Explorative binomial tests were used to determine whether AI tended to increase or decrease after these exclusions/inclusions. Explorative two-sample *t* tests were used to confirm the statistical difference between groups.

As a secondary outcome, we calculated Cohen's *d* to compare the ability to detect group differences between diabetic patients and nondiabetic controls in research studies. Cohen's *d* effect sizes were interpreted as: 0.2 = small, 0.5 = medium, 0.8 = large, 1.2 = very large, and 2.0 = huge.[21] Curve estimation (SPSS version 25) was utilized to model the association between number of measures included in the Z-compounds and AI or Cohen's *d*.

3 | RESULTS

Sixty-eight patients and 35 age- and sex-matched controls were recruited (Figure 1). Table 1 lists patient and control characteristics, whereas the composition and weighting of each of the 29 Z-compounds are presented in Table S1.

In total, 4.5% of the data were missing in a random pattern (Little's MCAR, $P = .282$), and were imputed. Using exploratory *t* tests, all Z-compounds differentiated patients from controls ($P < .001$ after Bonferroni correction). Prevalence of PN-NCS in the patient group ("sensitivity") varied between 38% and 76%, depending on the Z-compound, with a median prevalence of 63% (Table 2). The PN-NCS prevalence in the patient group was logarithmically associated with number of measures included in the Z-compound ($R^2 = 0.401$).

The PCA revealed five factors (Kaiser-Meyer-Olkin test (KMO) = 0.827; Bartlett Test of Sphericity, $P < .001$) to explain 57% of the total variance (Table S2). The factor that accounted for the most variability consisted of conduction velocities and F_{mean} waves from the tibial and peroneal nerves. The tibial and peroneal nerves dominated four of five factors, whereas the remainder consisted of measures from the median nerve.

The AI ranged from 0.58 to 0.83, and 22 of 29 Z-compounds had values greater than or equal to 0.70. AI was not increased by including bilateral leg NCS, but AI was considerably larger for leg than arm NCS. All "clinical-guess" compounds had a high AI of at least 0.75, whereas maximal AI among the nine previously published compounds was 0.75 (Table 2). Sensitivity was higher for sensory compared with motor NCS. However, the opposite trend was noted for AI and Cohen's *d*, reflecting the lower specificity for sensory NCS variables (larger prevalence among controls in Table 2). Z-compounds consisting of pure amplitudes had moderately low sensitivity (54%-59%) and AI (0.66-0.70).

Cohen's *d* values for all Z-compounds ranged from 0.95 to 1.61, with a median of 1.4. Twenty-six of 29 Z-compounds had very high Cohen's *d* values. The Z-compounds with the highest Cohen's *d* (≥ 1.5) represented a combination of all conduction velocity measures, all measures, the PCA variant, and four of the six "clinical guess" compounds (Table 2).

The association between number of measures included in the Z-compound and AI or Cohen's *d* was best explained logarithmically (Figure 2), with rapidly diminishing rate of gain of approximately above 14 or 15 included measures in both models.

Removing all F values from Z-compounds led to decreased AI in 16 and increased AI in 3 of the Z-compounds (binomial, $P = .012$) and

a mean decrease in AI of 0.015 (Table 3), due to a small decrease in average PN-NCS prevalence in the patient group (lower "sensitivity") and a small increase in the control group (lower "specificity"). Similarly, substituting F_{mean} values with F_{min} decreased AI in nine and increased AI in one Z-compound (binomial, $P = .021$), with a mean decrease in AI of 0.012. Including or excluding the medial plantar nerve in the Z-compounds had no consistent impact on AI (Table 3).

4 | DISCUSSION

The Z-compounds with the highest AI consisted of a high number of nerves and measures ("all measures" and "lower extremities, bilateral" without the medial plantar nerve). Although these two had the highest absolute score, other Z-compounds came close with fewer nerves and measures tested. "Lower extremities, unilateral" has the advantage of only including five nerves, and this Z compound may represent the best compromise between lowest possible prevalence in the control group (high specificity), maintaining high prevalence in the patient group (high sensitivity), while minimizing the number of necessary NCS. Interestingly, this somewhat brute force approach of merely testing one leg outperformed previously suggested Z-compounds by Dyck et al,[3,4] Heise et al,[5] Solders et al,[7] Lee et al,[16] and Tankisi et al,[17] although some of the difference may be explained by the lower number of NCS measures included in most published Z-compounds.

We found that including more NCS measures in the Z-compound led to a rather high rate of AI gain up until approximately 14 or 15 measures, followed by diminishing returns above this number. Perhaps not entirely by chance, "Lower extremities, unilateral" lie just on the border for rapidly diminishing returns for number of measures in the Z-compound, where composition becomes increasingly more important. With the exception of "all measures," the best-performing Z-compounds consist mainly of measures from the lower extremities, which reflects the components identified by the PCA, and is in line with previous reports that the most sensitive measures can be found primarily in the legs and feet.[3,5,17] As one may expect from the relationship between number of NCS measures in the Z-compound and AI, shorter Z-compounds of four or fewer nerves did not perform well in the present study. Among the shorter Z-compounds, "Heise variant"[5] had the highest AI, surpassing some of the longer Z-compounds. However, the gain in sensitivity and specificity of "Lower extremities, unilateral," is probably large enough to warrant the testing of two additional nerves in the lower extremities.

Although diabetic polyneuropathy is most typically characterized by sensory symptoms, it has been suggested that F waves are the most sensitive measures.[9,10] When removing F values completely, the PN-NCS prevalence was overall reduced in the patient group, suggesting lower diagnostic sensitivity. Based on our data, this sensitivity loss would, on average across the best-performing Z-compounds, equate to roughly two false negatives per 100 patients. An argument for including F waves may be that they are generally subject to less variance than other NCS measures, which increases the sensitivity when comparing

with reference material.[9,10] As such, although amplitudes may theoretically better represent the common pathophysiology of axonal loss in diabetic polyneuropathy, the large variance owing to additional experimental sources of error makes these measures less sensitive in practice.[9] A possible explanation for F_{mean} tending to perform better than F_{min} in the Z-compounds could be that, in patients with diabetic polyneuropathy, it is sufficient that a single large myelinated axon is spared to produce a F_{min} value within normal limits. The F_{mean} value, however, is the average of nerves with both normal and abnormal function, which, in patients with diabetic polyneuropathy, results in a reduced F_{mean} value, thereby increasing the chance of detecting pathology when comparing with reference material. In addition, employing the mean of many repeated tests reduces the variance, leading to narrower normal limits and increased sensitivity. Consequently, our findings support that F waves should be included in Z-compounds for the evaluation of diabetic polyneuropathy, and the results further suggest that F_{mean} values may be the most suitable option.

The dorsal sural and superficial peroneal nerve are more commonly used in routine investigations and suggested for inclusion in Z-compounds, but the medial plantar nerve has not received the same attention, despite indications of being sensitive to diabetic polyneuropathy.[11,12,22,23] Nevertheless, the sensitivity of a stand-alone NCS measure does not necessarily make it a valuable addition to a Z-compound. Based on our data, including the medial plantar nerve in Z-compounds for diabetic polyneuropathy cannot be advocated as obligatory, perhaps because the response can be difficult to record in some healthy elderly subjects.[11]

The large effect sizes for Cohen's *d* seen for our Z-compounds suggests that they may be suited for scientific studies where small changes in nerve function between groups (eg, after treatment) need to be detected. Although the number of measures included in the Z-compound was associated with the Cohen's *d* score, the best model only explained 37% of the variance, indicating that Z-compound composition may also play an important part. Because most Z-compounds seem relatively sensitive, and isolated nerve lesions (eg, carpal tunnel syndrome or traumatic nerve lesions) may affect compound scores, the clinician should choose the most clinically suitable Z-compound for follow-up of individual patients. We recommend that the ability of Z-compounds to detect small changes over time, both for groups (for research) and for individual follow-up (after treatment), should be validated by studies with designs better suited to determine test-retest reliability and the smallest detectable change of the Z-compounds.

4.1 | Limitations

Because the true prevalence of polyneuropathy in the groups depended on the NCS data under study, we could not calculate exact sensitivity and specificity values, and instead used AI as a proxy measure. Our definition of AI entailed that the prevalence of PN-NCS in the patient group (sensitivity) was the main determinant of the score. The close correlation between sensitivity and AI means that we could have used sensitivity as our main outcome variable. Although this may

have been more intuitive, it was ultimately decided that the specificity score should also impact our recommendation to some degree. Thus, when assessing the best-performing Z-compounds in the present study, specificity comprised a small part of the AI, and ties or close calls were mostly decided by gauging the actual prevalence of PN-NCS in the patient group.

In this study we did not assess the Z-compounds' ability to discriminate between symptomatic diabetic patients with or without clinically diagnosed peripheral polyneuropathy. Z-compounds should also be studied further in other patient populations with and without symptoms and/or clinical signs, including patient groups with other PN types.

Although we studied a large number of Z-compounds, additional studies are needed to search for optimal Z-compounds for different etiological and pathophysiological types of polyneuropathy.

5 | CONCLUSIONS

We found that the Z-compound that best facilitates evaluation of diabetic polyneuropathy, while avoiding excessive testing, consisted of the tibial and peroneal motor, and the sural, superficial peroneal, and tibial medial plantar sensory nerves in one leg. The optimal number of measures included in the Z-compound was approximately 14 or 15. The inclusion of F waves in Z-compounds for diabetic polyneuropathy is important, and F_{mean} may be a better choice than F_{min}. Inclusion of the medial plantar nerve is clinically useful for evaluation of polyneuropathy in young and middle-aged subjects, but this did not improve the general diagnostic accuracy of the Z-compounds.

CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

ETHICAL PUBLICATION STATEMENT
We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.