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RESEARCH REPORT

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Vitamin D levels do not correlate with severity of idiopathic peripheral neuropathy

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Abstract

Background and Aims: Peripheral neuropathy (PN) is a common neurological condition in elderly adults. Vitamin D deficiency has been associated with diabetic and chemotherapy-induced neuropathy, but its role in idiopathic PN, in which no underlying cause of neuropathy can be identified, has not been investigated.

Methods: Two hundred thirty patients with idiopathic PN enrolled in the Peripheral Neuropathy Research Registry (PNRR) at Johns Hopkins University School of Medicine had vitamin D testing information on record. Linear and logistic regressions were used to investigate the relationship between absolute vitamin D level or vitamin D insufficiency (<20 ng/mL) and both the severity of neuropathy as measured by the reduced total neuropathy score (TNSr) and severity of neuropathic pain.

Results: Sixteen (7%) patients were vitamin D insufficient (<20 ng/mL). Controlling for factors known to correlate with severity of neuropathy, there was no correlation between absolute vitamin D levels and TNSr (correlation coefficient 0.01, 95% CI −0.03 to 0.07, $p = .59$) and no association between vitamin D insufficiency and TNSr (correlation coefficient 0.3, 95% CI −2.8 to 3.4, $p = .86$). Vitamin D insufficiency was not associated with the presence of neuropathic pain (OR 4.1, 95% CI 0.6–26.0, $p = .13$), and there was no correlation between vitamin D levels and pain score (correlation coefficient 0.01, 95% CI −0.02 to 0.03, $p = .59$).

Interpretation: In a single-center cohort of patients with idiopathic PN, there was no correlation between vitamin D levels and the severity of neuropathy or neuropathic pain.

KEYWORDS
idiopathic peripheral neuropathy, neuropathic pain, vitamin D

1 | INTRODUCTION

Peripheral neuropathy (PN) is a common disease that affects 5%–10% of people over the age of 50 and its prevalence increases with age to approximately 30% over the age of 80.[1,2] Despite complete diagnostic workups, no underlying etiology can be identified for 20%–50% of patients and they are diagnosed with idiopathic PN (IPN).[2,3] Both acute and chronic vitamin deficiencies, particularly those of B

Abbreviations: BMI, body mass index; CIPN, chemotherapy-induced peripheral neuropathy; CMAP, compound motor action potential; DPN, diabetic peripheral neuropathy; HDL-C, high-density lipoprotein cholesterol; IENFD, intraepidermal nerve fiber density; IPN, idiopathic peripheral neuropathy; NCS, nerve conduction study; NCV, nerve conduction velocity; PN, peripheral neuropathy; PNRR, Peripheral Neuropathy Research Registry; SNAP, sural nerve action potential; TNSr, total neuropathy score-reduced; TSH, thyroid stimulating hormone.

vitamins,[4] are known to cause PN and patients with IPN often take vitamin supplements for nerve health. Whether additional vitamins play a role in the development and progression of IPN is unknown.

Vitamin D insufficiency is common worldwide and occurs in about 25% of the US population.[5] In addition to its canonical role in bone health, vitamin D insufficiency has been linked to an increased risk of developing several health conditions, including type 1 diabetes and multiple sclerosis.[6] In diabetic peripheral neuropathy (DPN), meta-analyses of several cohort studies have found that, on average, diabetic patients with PN have lower vitamin D levels than those without PN.[7,8] Moreover, small cross-sectional studies have shown lower levels of vitamin D in patients with painful DPN compared with those with non-painful DPN and a possible correlation between vitamin D levels and pain intensity.[9,10] In chemotherapy-induced peripheral neuropathy (CIPN), pre-treatment vitamin D deficiency has been associated with increased severity of PN.[11–13]

The role of vitamin D in IPN has never been systematically studied. To investigate if vitamin D levels are associated with the severity of IPN, we examined plasma vitamin D levels in IPN patients using cross-sectional data from the Peripheral Neuropathy Research Registry (PNRR).

2 | MATERIALS AND METHODS

2.1 | Study population

The PNRR is a multicenter database and biorepository of well-characterized patients with distal, symmetrical polyneuropathies sponsored by the Foundation for Peripheral Neuropathy.[14] The registry enrolls patients with diabetic PN, chemotherapy-induced PN, HIV-induced PN, and IPN. This study was limited to those with a diagnosis of IPN who had negative testing for other common PN etiologies.

Patients from a single consortia site (Johns Hopkins University School of Medicine) met the following inclusion criteria: (a) diagnosis of IPN, (b) plasma 25-hydoxy vitamin D [25(OH)D] value available within 2 years of study enrollment date, and (c) complete PNRR dataset, including demographics, body mass index (BMI), smoking history, drinking history, and metabolic disease history. A diagnosis of IPN was made by the enrolling neuromuscular physician based on the presence of large or small fiber sensory or motor deficits on exam, axonal physiology on nerve conduction studies (if large fiber involvement was present), and the exclusion of diabetes, autoimmune disease, chemotherapy, HIV, toxins, B12 deficiency, and hereditary neuropathies.

Nine hundred fourteen patients with IPN were enrolled in the PNRR prior to December 31, 2023. After excluding 580 patients without a recorded vitamin D level, 3 without a recorded TNSr, 3 without a known date of neuropathy onset, 97 without complete data for determination of metabolic syndrome, and 1 without information on drinking history, 230 patients met the inclusion criteria. PNRR is approved by the Institutional Review Board of Johns Hopkins University, and all study participants provided written consent.

2.2 | PNRR dataset

The data collected from each patient in the PNRR database includes the following: (a) neurological examination capturing muscular strength, deep tendon reflexes, sensory examination findings, gait evaluations, and Romberg test; (b) nerve conduction study (NCS) evaluations of major motor and sensory nerves; (c) laboratory testing results to evaluate for common underlying etiologies for PN as recommended by the American Academy for Neurology that included HIV, vitamin B12, hemoglobin A1c, and serum protein electrophoresis[15]; and (d) a history questionnaire that asks patients to evaluate the nature and severity of their PN symptoms (pain, numbness, weakness, balance, and autonomic symptoms). The questionnaire also captures their medical history and medication intake. Additional testing for vitamins B1, B6, D, and E was performed in selected patients at the discretion of the treating physicians or was available in the medical record.

Vitamin D laboratory results were performed in CLIA-approved commercial laboratories and recorded as plasma 25(OH)D. Vitamin D deficiency was defined as 25(OH)D <12 ng/mL (30 nmol/L) and insufficiency was defined as 25(OH)D of 12–<20 ng/mL (30–<50 nmol/L) per the Institute of Medicine.[16] Dyslipidemia was defined as serum triglycerides >150 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, taking medication to lower triglycerides, or taking medication to lower low-density lipoprotein. Metabolic syndrome was defined as any 3 of 5 criteria: BMI > 30 kg/m^2 (in place of increased waist circumference), elevated triglycerides, reduced HDL-C, elevated blood pressure, or elevated fasting glucose per AHA guidelines.[17] A documented history of taking fibrates, ezetimibe or icosapent ethyl or taking niacin or omega-3 fatty acids for the purposes of lowering triglycerides fulfilled criteria for elevated triglycerides. A documented history of taking a statin fulfilled criteria for reduced HDL-C. Isolated small fiber neuropathy was defined as presence of small fiber involvement on exam (reduced pinprick or cold temperature sensibility) or reduced intraepidermal nerve fiber density (IENFD) on skin biopsy, normal sural sensory response, normal vibratory response at the toes, and normal Achilles tendon reflex. A significant alcohol intake history was defined as drinking more than 2 drinks per day for more than 10 years. Painful IPN was determined by patient response to the question "Do you have pain or painful discomfort from your polyneuropathy?" and graded on a scale of 0–10 with 0 representing no pain and 10 representing the most intense pain sensation imaginable. Exercise was determined by patient report and categorized in a binary fashion. The total neuropathy score-reduced (TNSr),[18] which includes pinprick sensibility, vibration sensibility, muscular strength, absence of deep tendon reflexes, degree of paresthesia extension as measured by pain and numbness, peroneal compound muscle action potential (CMAP) amplitude, and sural sensory nerve action potential (SNAP) amplitude, was used as a measure of overall neuropathy severity. Vitamin D supplementation was determined by patient report and any supplement with vitamin D was included regardless of the vitamin D dose.

Vibration sense was recorded using a Rydel-Seiffer graduated tuning fork and normal values were as follows: ≥4.5 if age ≤40 years, ≥4.0 if age 41–60 years, ≥3.5 if age 61–85 years, ≥3.0 if age >85 years.[19] For nerve conduction studies, the applied normative values were as follows: peroneal motor nerve conduction velocity (NCV) > 39 m/s; peroneal CMAP amplitude ≥2 mV; sural sensory NCV > 39 m/s; sural SNAP amplitude ≥5 μV if patient age ≥65 or ≥9 μV if patient age <65. IENFD in skin biopsies was determined by counting the number of nerve fibers crossing the epidermal basement membrane and excluding isolated nerve fragments in epidermis that do not cross the basement membrane.[20] IENFD was deemed abnormal if it was <5th percentile based on age and sex-matched controls at our institution.

2.3 | Outcomes

The primary outcome was the linear correlation between vitamin D levels and TNSr adjusting for age, sex, duration of PN, significant alcohol history, metabolic syndrome, and exercise. Secondary outcomes were (1) the difference in TNSr between patients with normal vitamin D and vitamin D insufficiency by multiple linear regression adjusting for age, duration of PN, sex, significant alcohol history, metabolic syndrome, and exercise; (2) the odds ratio of abnormality on each TNSr component by vitamin D insufficiency adjusting for age, sex, and duration of neuropathy; (3) the odds ratio of painful neuropathy by vitamin D insufficiency adjusting for age, duration of PN, sex, significant alcohol history, metabolic syndrome, and exercise; and (4) the linear correlation between numerical neuropathic pain score and vitamin D level adjusting for age, duration of PN, sex, significant alcohol history, metabolic syndrome, and exercise, and use of neuropathic pain medication. For the odds of neuropathic pain, individual covariates were tested individually, and the three significant covariates were added to vitamin D in the multivariable model.

2.4 | Statistical analysis

Baseline characteristics were summarized using STATA descriptive statistics. The correlation between TNSr and vitamin D levels and the relationship between TNSr and vitamin D cutoffs were performed using multiple linear regression. Logistic regression was used to evaluate the relationship between vitamin D levels and individual components of the exam. Firth's penalized maximum likelihood logistic regression was performed to assess the relationships between vitamin D levels and the presence of neuropathic pain because low event frequency led to collinearity with standard models.[21] All analyses were performed using Stata IC version 15.1 (StataCorp).

3 | RESULTS

A total of 230 patients were included, of whom two (1%) were vitamin D deficient (<12 ng/mL) and 14 (6%) were vitamin D insufficient (12–<20 ng/mL). Due to the low number of patients with vitamin D deficiency, vitamin D deficiency and insufficiency were pooled and vitamin D <20 ng/mL was termed "vitamin D insufficiency." The median age was 63 (IQR 54–72), 124 (54%) patients were male, 220 patients (96%) identified as white, and 150 (65%) patients were taking vitamin D-containing supplements, of whom 126 (84%) were taking isolated vitamin D and 24 (16%) were taking a multivitamin. The median daily vitamin D dose among those taking supplements was 2000 international units (IU) and 58/141 (42%) of patients with a known vitamin D dose were taking ≤1000 IU per day (Table S1). The median duration of neuropathy was 3.6 years (IQR 2–8) and the median TNSr was 7 (IQR 4–12). Patients with vitamin D insufficiency were younger (median [IQR] age, insufficiency: 50 [42–61.5] vs. sufficiency 64.5 [56–72]), more likely to have smoked (insufficiency 9/16 [56%] vs. sufficiency 70/214 [33%]), and less likely to have a significant alcohol use history (insufficiency 0/16 [0%] vs. sufficiency 11/214 [5%]) than those with normal vitamin D (Table 1). Isolated small fiber neuropathy (insufficiency 7/16 [44%] vs. sufficiency 48/214 [22%]) and painful neuropathy (insufficiency 15/16 [94%] vs. sufficiency 139/214 [65%]) were more common in patients with vitamin D insufficiency. Metabolic risk factors and levels of serum B vitamins, thyroid stimulating hormone (TSH), and hemoglobin A1c were similar in patients with vitamin D sufficiency and insufficiency (Table 1).

To assess for a relationship between vitamin D levels and the severity of neuropathy, we performed multiple linear regression comparing vitamin D levels to the TNSr while controlling for several factors known to influence the severity of neuropathy, including age, duration of neuropathy, sex, alcohol use, metabolic syndrome, and exercise. After controlling for confounders, there was no relationship between vitamin D levels and TNSr (correlation coefficient 0.01 [−0.03 to 0.07], $p = .59$, Table 2, Figure 1). To ensure that vitamin D insufficiency was not a reflection of nutritional insufficiency, which is a known risk factor for neuropathy, we checked for correlations between vitamin D and vitamins B1, B6, B12, and E and found no correlation between vitamin D levels and levels of these vitamins (Table S2).

In bone health, the relationship between vitamin D levels and fracture risk is nonlinear. Patients with vitamin D insufficiency have an increased fracture risk but there is no relationship between vitamin D levels and fracture risk in vitamin D sufficient patients.[16] To see if there was a similar vitamin D threshold below which the severity of neuropathy increases, we compared the TNSr of patients who were vitamin D insufficient with those who were sufficient. The median TNSr was 6 (IQR 4–12) in vitamin D insufficient patients and 7 (IQR 4–13) in vitamin D sufficient patients. Using multiple linear regression to adjust for confounders as before, vitamin D insufficiency was not associated with a change in TNSr (correlation coefficient 0.3, 95% CI −2.8 to 3.4, $p = .86$). As there is some debate in the literature regarding the optimal cutoff for vitamin D insufficiency and the Endocrine Society has suggested defining vitamin D insufficiency as a vitamin D level <30 ng/mL,[22] we repeated the analysis using a vitamin D cutoff of <30 ng/mL to define insufficiency and there remained no difference in TNSr between patients with vitamin D sufficiency and insufficiency (correlation coefficient −0.65, 95% CI −1.1 to 2.4, $p = .47$).

TABLE 1 Patient characteristics.

	All patients ($N = 230$)	Vitamin D ≥20 ng/mL ($N = 214$)	Vitamin D <20 ng/mL ($N = 16$)
Age, median (IQR)	63 (54, 72)	64.5 (56, 72)	50 (42, 61.5)
Sex, male, *n* (%)	124 (54%)	116 (54%)	8 (50%)
Race, white, *n* (%)	220 (96%)	206 (96%)	14 (88%)
BMI, kg/m^2, median (IQR)	27.5 (24.1, 31.7)	27.5 (24.3, 31.5)	29.1 (23.9, 33.1)
Years since onset of PN, median (IQR)	3.6 (2, 8)	4.0 (2, 8)	2.0 (1.6, 4.5)
Smoking, current or former, *n* (%)	79 (34%)	70 (33%)	9 (56%)
Significant alcohol history, *n* (%)	11 (5%)	11 (5%)	0 (0%)
Hypertension, *n* (%)	127 (55%)	120 (56%)	7 (44%)
Dyslipidemia, *n* (%)	120 (52%)	113 (52%)	7 (44%)
Metabolic syndrome, *n* (%)	74 (32%)	67 (31%)	7 (44%)
TNSr, median (IQR)	7 (4, 12)	7 (4, 13)	6 (4, 12)
Isolated small fiber PN, *n* (%)	55 (24%)	48 (22%)	7 (44%)
Large fiber sensory PN, *n* (%)	130 (57%)	122 (57%)	8 (50%)
Sensory-motor PN, *n* (%)	43 (19%)	42 (20%)	1 (6%)
Motor PN, *n* (%)	2 (1%)	2 (1%)	0 (0%)
Sural SNAP amplitude, μV, median (IQR)	4.8 (0, 9.8)	4.8 (0, 9.8)	4.2 (0, 12.1)
Painful, *n* (%)	154 (67%)	139 (65%)	15 (94%)
Taking vitamin D containing supplements, *n* (%)	150 (65%)	141 (66%)	9 (56%)
Vitamin B1, nmol/L, median (IQR)	141 (114, 164)	141 (114, 164)	159 (120, 166)
Vitamin B6, μg/L, median (IQR)	27 (13, 55)	27 (13, 59)	27 (8, 44)
Vitamin B12, pg/mL, median (IQR)	652 (493, 1000)	659 (505, 1001)	539 (430, 788)
Hemoglobin A1c, %, mean ± SD	5.5 ± 0.5	5.5 ± 0.4	5.4 ± 0.6
TSH, mU/mL, median (IQR)	1.9 (1.3, 2.7)	1.9 (1.3, 2.8)	1.7 (1.2, 2.2)
Monoclonal gammopathy, *n* (%)	14 (6%)	14 (7%)	0 (0%)

Note: Significant alcohol history defined as >2 drinks a day for >10 years. $N = 61$ for vitamin B1, $N = 101$ for vitamin B6, $N = 225$ for vitamin B12, $N = 199$ for hemoglobin A1c, $N = 205$ for TSH.

TABLE 2 Multiple linear regression for TNSr.

Variable	Correlation coefficient	95% CI	*p*
Vitamin D, ng/mL	.01	−0.03 to 0.06 = 7	.59
Age	.10	0.04–0.17	<.01
Years since onset of PN	.10	−0.02 to 0.22	.02 = 9
Sex, male	2.60	1.00–4.20	<.01
Significant alcohol history	−3.81	−7.44 to −0.18	.04
Metabolic syndrome	.42	−1.24 to 2.08	.62
Exercise	.08	−4.87 to 3.65	.94

Because the TNSr is a composite of several clinical findings, we assessed whether vitamin D insufficiency was associated with abnormalities in any individual components of the physical exam or electrophysiology. Using logistic regression controlling for age, sex, and duration of neuropathy, we found no association between vitamin D insufficiency and abnormalities in any individual component of the TNSr, though the absolute prevalence of weakness was lower in patients with vitamin D insufficiency (Table S3). Given the increased frequency of isolated small fiber neuropathy in patients with vitamin D insufficiency we compared the IENFD in the distal leg between patients with vitamin D insufficiency and sufficiency who had a skin biopsy and found no difference (median [IQR] IENFD: vitamin D sufficient 4.3 fibers/mm [1.4–8.1] vs. insufficient 2.5 fibers/mm [0.3–6.2], $p = .4$).

We next investigated whether there was any relationship between vitamin D levels and neuropathic pain. Fifteen of 16 (94%) patients with vitamin D insufficiency had painful neuropathy compared to 139/214 (67%) patients who were vitamin D sufficient (unadjusted χ^2 $p = .02$). Using penalized maximum likelihood logistic regression to control for age, sex, and metabolic syndrome, which

were significantly associated with the presence of pain in univariate logistic regression, the odds ratio for painful neuropathy among patients with vitamin D insufficiency was elevated but not statistically different from 1 (OR 4.1, 95% CI 0.6–26.0, $p = .13$, Table 3). Finally, we investigated whether vitamin D levels are related to pain severity among patients who have painful IPN. In a multiple linear regression of pain intensity with vitamin D levels controlling for age, sex, exercise, and whether patients were taking neuropathic pain medication there was no correlation between vitamin D levels and pain intensity (coefficient 0.01, 95% CI −0.02 to 0.03, $p = .59$, Table S4).

4 | DISCUSSION

In this study, we evaluated the relationship between vitamin D and severity of neuropathy in patients with idiopathic PN. Using the TNSr to measure severity, we found no relationship between vitamin D levels or vitamin D insufficiency and severity of neuropathy. A numerically greater number of patients with vitamin D insufficiency had neuropathic pain, though after adjusting for confounders this did not meet statistical significance and there was no relationship between vitamin D levels and pain severity among patients with neuropathic pain.

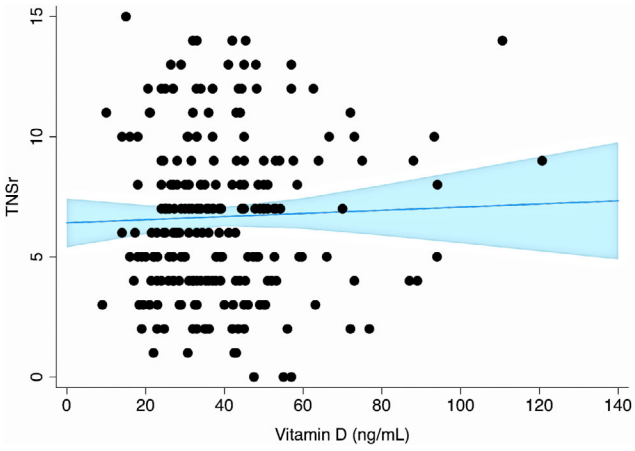

FIGURE 1 Correlation between vitamin D level and TNSr. Each dot represents a single patient. Blue line represents prediction from multiple linear regression. Blue shaded region represents 95% confidence interval.

The reason we found no relationship between vitamin D levels and severity of neuropathy in IPN when a relationship has been seen in DPN and CIPN may be that distinct vitamin D dependent and independent processes are at play in these conditions. In diabetic PN, a small, randomized trial showed improved pancreatic β cell function after vitamin D supplementation[23] and a meta-analysis of several randomized trials[24–26] found a lower rate of progression from prediabetes to diabetes with vitamin D supplementation.[27] This suggests that the role of vitamin D in DPN may be related to insulin metabolism. In addition, most of the literature on the role of vitamin D in DPN has focused on the presence of neuropathy or neuropathic pain[8,9,28] rather than severity of neuropathy, which limits direct comparisons. In CIPN, vitamin D has been shown abrogate the severity of CIPN in several rodent models, but the mechanism has not been elucidated.[11,29]

The high prevalence of painful neuropathy among patients with vitamin D insufficiency is of interest given clinical and preclinical studies showing an association between vitamin D deficiency and severity of DPN and CIPN have used pain as a primary endpoint.[9–12,29] Outside of neuropathy, observational studies in end-stage cancer,[30] postoperative pain,[31–33] and headache[34] have found that patients with vitamin D deficiency are more likely to develop pain. However, randomized, double-blind trials in generalized pain,[35–37] statin-induced myalgia,[38] and fibromyalgia[39] have failed to find a treatment effect from vitamin D supplementation. This may indicate that vitamin D deficiency is a risk factor for the development but not propagation of pain. Alternatively, vitamin D may be correlated with other factors that modulate pain. For example, several studies have suggested exercise, which has been associated with lower levels of pain,[40,41] can increase vitamin D levels.[42]

There are several limitations to our study. As a single-center study in which 96% of patients were white, the generalizability to a different population is limited. The rate of vitamin D insufficiency in our cohort (8%) was much lower the general US population, in which >20% of people are estimated to be vitamin D insufficient by the most recent NHANES survey,[43] which may have limited our power to detect a significant effect. Moreover, because only 2 patients in our cohort had vitamin D deficiency, we were unable to assess the relationship

TABLE 3 Logistic regression of variables predicting painful neuropathy ($N = 196$).

	Univariate			Multivariate		
Variable	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Vitamin D <20 ng/mL	8.1	1.1–62.5	.04	4.1	0.6–26.0	.13
Age, per 10-year increase	0.6	0.5–0.8	<.01	0.6	0.4–0.8	<.01
Years since onset of PN	1.0	0.9–1.0	.4	-	-	-
Sex, male	0.3	0.2–0.6	<.01	0.3	0.1–0.5	<.01
Significant alcohol history	1.3	0.3–5.2	.7	-	-	-
Metabolic syndrome	2.8	1.5–5.5	<.01	4.2	2.0–8.8	<.01
Exercise	0.4	0.2–1.0	.06	-	-	-

between vitamin D deficiency and neuropathy severity. The low rates of vitamin D deficiency and insufficiency are likely in part due to the underrepresentation of non-white patients, in whom the prevalence of vitamin D insufficiency is more than twofold higher than in white patients,[43] and in part due to a high rate of vitamin D supplementation in our cohort. Notably the most recent NHANES survey found that about 50% of US adults over the age of 60 report taking vitamin D supplements,[44] suggesting that high rates of vitamin D supplementation are likely to be found in most US-based cohorts of patients with IPN. Additionally, vitamin D testing was not systematically performed in all patients our cohort, which may have biased our study population. Our study did not include any healthy controls and thus cannot comment on the relationship between vitamin D and the development of IPN. Further studies investigating the relationship between vitamin D and severity of neuropathy in a more diverse population that includes healthy controls are indicated.

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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 can be found online in the Supporting Information section at the end of this article.

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