Peripheral Vascular Disease and Peripheral Neuropathy in Individuals With Cardiometabolic Clustering and Obesity

National Health and Nutrition Examination Survey 2001–2004

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OBJECTIVE—Two lower-extremity diseases (LEDs), including peripheral neuropathy and peripheral vascular disease (PVD), are leading causes of disability in the U.S. Although LEDs can be complications of diabetes, their prevelances and risk factors apart from diabetes are poorly described. This study describes the prevalence of LEDs and examines the association of obesity and cardiometabolic clustering in a population-based sample.

RESEARCH DESIGN AND METHODS—Adults aged ≥40 years (n = 2,514) were evaluated in the 2001–2004 National Health and Nutrition Examination Survey for clustering of two or more cardiometabolic characteristics, including elevated triglycerides or plasma glucose, low HDL cholesterol levels, increased waist circumference, or hypertension. Clustering was combined with BMI (dichotomized at ≥30 kg/m^2) to generate three groups: obese (with or without clustering); nonobese with clustering; and nonobese without clustering. Multivariate logistic regression procedures incorporated the complex survey sampling design.

RESULTS—Overall, 9.0% of individuals had peripheral neuropathy alone, 8.5% had PVD alone, and 2.4% had both LEDs. The obese group was more likely to have peripheral neuropathy (odds ratio 2.20 [95% CI 1.43–3.39]), PVD (3.10 [1.84–5.22]), and both LEDs (6.91 [2.64–18.06]) compared with nonobese subjects without clustering. Within the nonobese group, clustering increased the odds of peripheral neuropathy (1.50 [1.00–2.25]) and PVD (2.48 [1.38–4.44]) compared with no clustering.

CONCLUSIONS—Obesity and clustering markedly increased the likelihood of LEDs in this sample and identified a group for whom preventive activities may reduce the risk of future disability.

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Peripheral vascular disease (PVD) and peripheral neuropathy, both lower-extremity diseases (LEDs), are the leading cause of non–injury-related amputations and disabilities in the U.S. (1). Declines in physical functioning and loss of independence later in life are additional complications of these conditions and speak to their public health importance (2,3).

Peripheral neuropathy was traditionally thought to develop in the diabetic patient after many years of persistent hyperglycemia. However, it is increasingly recognized that many individuals with diabetes have neuropathy at the time of their diagnosis (4), which suggests that idiopathic neuropathy may be a marker for prediabetes and thus may precede, rather than follow, overt type 2 diabetes (5–7). Considering measurement of LEDs in the general population rather than in diabetic-only populations acknowledges that the general population may include those with the transient hyperglycemia of prediabetes. Transient hyperglycemia is associated with increased reactive oxygen species and impaired nitric oxide–mediated vasodilatation (6,8,9). Because neuropathy is a microvascular condition, structural damage to the microvasculature can ultimately lead to nerve dysfunction, which is central to the pathogenesis of peripheral nerve injury (6).

The etiological link between the lower-extremity conditions and metabolic disorders, such as obesity, diabetes, or cardiovascular disorders, may be a function of insulin action on vascular tone (10). It is generally accepted that chronic exposure to abnormal plasma insulin levels from chronic hyperglycemia leads to vascular resistance in the larger vasculature. However, there is growing appreciation that smaller vessels may become similarly damaged giving rise to poor circulation in the extremities and ultimately to peripheral neuropathy. In addition, this process may begin well before the diagnosis of diabetes, which suggests the utility of examining prediabetic individuals for LEDs.

Apart from prediabetes, other important metabolic abnormalities that may predispose individuals to LEDs include obesity, increased visceral or peripheral fat, hypertension, elevated serum triglycerides, and dyslipidemia, alone or in combination (6,11–13). Although each of these components in itself is a risk factor for cardiovascular disease and other related outcomes such as PVD, their aggregation or "clustering" may result in a greater overall disease risk (14,15). Independent of hyperglycemia, there may be a relationship between lipid abnormalities, hypertension, and LEDs through their shared contribution to the pathogenesis of micro- and macrovascular dysfunction

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(6,16,17). The relative contribution of cardiometabolic clustering to the development of LEDs is poorly characterized, particularly in the general population.

This investigation examines the relationship between LEDs, including PVD and peripheral neuropathy, and cardiometabolic clustering, presuming that LEDs would be positively associated with cardiometabolic clustering among nonobese adults aged ≥40 years. In addition, it was hypothesized that obese individuals would have a higher prevalence of LEDs compared with nonobese individuals, in those with and without diabetes.

RESEARCH DESIGN AND METHODS

The National Health and Nutrition Examination Survey (NHANES) III is an ongoing survey of the National Center for Health Statistics that includes both interview and physical examination components. Approximately 10,000 nationally representative civilian adults and children are sampled annually, with an oversampling of subjects aged ≥60 years, African Americans, and Hispanics. Additional documentation about the NHANES survey sampling is available at the National Center for Health Statistics Web site (18).

This investigation is based on data from men and women aged ≥40 years from two combined NHANES survey cycles, 2001–2002 and 2003–2004. The unweighted response rates for individuals who participated in the exam portion of the survey cycles were 80 and 76%, respectively. The study population for this investigation consisted of 2,514 individuals aged ≥40 years who were fasted at the time of their examination.

LEDs include both PVD and peripheral neuropathy. All individuals aged ≥40 years were eligible to participate in the LED examination component of the NHANES. Exclusion criteria included individuals >400 lb (because of equipment limitations); those with bilateral leg amputations; any rash, open wounds, casts, or dressings that interfered with testing; or those who could not understand the testing instructions. In addition, approximately one-half of the individuals who participated in the examination component of the NHANES had a morning appointment time and were fasted for at least 8 h. Individuals who were not fasted were excluded from this report to obtain interpretable and comparable values.

Outcome variables

PVD was characterized using the systolic blood pressure in the lower legs, measured in the posterior tibial vessel of both ankles in ratio to the systolic blood pressure measured in the brachial vessel of the right arm. The resulting ankle-brachial blood pressure index (ABPI) ratio was used to characterize PVD, with an ABPI ratio <0.9 considered to be PVD.

Peripheral neuropathy was assessed using Semmes-Weinstein monofilament standardized testing at three different locations on the bottom of each foot. A 10-g filament force was applied, and the participant was asked to indicate to the examiner when they felt pressure. A location was defined as sensate if the first participant response was affirmative or if two of three tests at a particular location yielded affirmative responses. A location was defined as insensate if there was no response from two administrations of the monofilament, two "unable to determine" responses, or one nonresponse and one "unable to determine" response for the site. Peripheral neuropathy was defined as one or more insensate locations on either foot.

Exposure variables

Obesity status and the clustering of cardiovascular/metabolic measures were the independent variables. Height (meters) and weight (kilograms) were used to calculate BMI (weight [in kilograms] divided by the square of height [in meters]), and a BMI ≥30 kg/m^2 was used to define obesity. The individual factors contributing to potential cardiometabolic clustering included measures of blood pressure, lipids, carbohydrate metabolism, and a proxy measure for visceral fat. These factors and their corresponding risk cut points have been used previously (15,19). Four blood pressure measurements were averaged. Hypertension was defined as having an average systolic blood pressure ≥130 mmHg, an average diastolic blood pressure ≥85 mmHg, or taking prescription medication for high blood pressure. Risk-level cut points for HDL cholesterol and triglycerides were <50 mg/dL in women (<40 mg/dL in men) and ≥200 mg/dL, respectively. Diabetes was defined as a fasting plasma glucose of ≥126 mg/dL or the current use of diabetes medications. The risk cut point for impaired fasting plasma glucose was ≥110 mg/dL; impaired fasting glucose or current use of diabetes medications determined dysfunctional carbohydrate metabolism The risk level for waist circumference was >88 cm in women and >102 cm in men.

In this investigation, the presence of at least two of the abnormal cardiometabolic measures were used to characterize cardiometabolic clustering and classify individuals into one of three subgroups: *1*) nonobese without clustering; *2*) nonobese with clustering; and *3*) obese with and without clustering. Because of the small number of obese individuals without dysfunctional cardiometabolic clustering, we included all obese individuals (with and without dysfunctional cardiometabolic clustering) in one group.

Statistical analysis

Fasting exam weights were used to calculate weighted descriptive statistics for the total eligible sample (n = 2,514), with continuous variables reported as means and SEs and categorical variables reported as percentages and SEs. Disease classifications used in these analyses were peripheral neuropathy alone (without PVD), PVD alone (without peripheral neuropathy), and the co-occurrence of both LEDs.

After the development of descriptive statistics by the three disease classifications using a weighted subpopulation analysis, bivariate logistic regression models were used to provide comparisons of independent variables within each disease classification. Next, unadjusted logistic regression models were developed for LEDs and clustering groups, using the nonobese group without clustering as the referent group. Multivariate logistic regression models were used to assess the associations between the cardiometabolic clustering group and LEDs while accounting for sex, age, and race/ethnicity covariates determined using a priori evidence. First-order interactions between cardiometabolic clustering groups and covariates were considered but not retained in the final multivariate models because the interaction terms were not statistically significant at the $\alpha = 0.05$ level.

SAS version 9.2 software was used for statistical analysis to correctly specify complex survey sampling weights, stratification, and clustering for the two combined NHANES cycles. As recommended by the NHANES data documentation, fasting examination weights from the 2001–2002 and 2003–2004 cycles were each down weighted by 0.5 to account for combining the survey cycles.

RESULTS—The prevalence of peripheral neuropathy was 11.5% (unweighted prevalence 14.9%) and the prevalence of PVD was 11.0% (unweighted prevalence 15.1%). A total of 9% (unweighted prevalence 11.3%) of individuals had peripheral neuropathy alone (Table 1), 8.5% (unweighted prevalence 11.3%) had PVD alone (Table 1), and 2.4% (unweighted prevalence 3.6%) had a combination of peripheral neuropathy and PVD (Table 2).

A total of 15% of individuals were classified as having diabetes. Individuals without diabetes had a 9.7% prevalence of peripheral neuropathy and a 9.4% prevalence of PVD. The prevalence of peripheral neuropathy alone and PVD alone was 8.2 and 7.8%, respectively, among individuals without diabetes. The average age of the study sample was 56 years. Over 75% of participants were white, and 55% reported more than a high school education. Mean body weight was 75.3 kg for women and 88.7 kg for men. Mean fasting plasma glucose was 105.60 mg/dL. More than 50% of individuals were hypertensive.

In comparison with individuals without peripheral neuropathy, individuals with peripheral neuropathy alone were significantly more likely to be older, to be men, to be African American or black, and to be less educated. They had higher waist circumference, BMI, glucose, systolic blood pressure, triglyceride levels and greater prevalence of diabetes and hypertension. They had lower LDL cholesterol. Results are shown in Table 1.

Compared with those without PVD, individuals with PVD alone were more likely to be older, to be women, to be African American or black, and to be less educated. They had higher waist circumference, BMI, glucose, and systolic and diastolic blood pressure and greater prevalence of diabetes and hypertension.

Individuals with both peripheral neuropathy and PVD were more likely to be older, to be male, and to be heavier. They had higher waist circumference, glucose, and diastolic blood pressure but lower LDL cholesterol levels. They also had a higher prevalence of diabetes.

Influence of obesity cardiometabolic clustering

Progressively greater prevalence of peripheral neuropathy alone was observed with the three obesity-clustering groups. The obese group and the nonobese group with cardiometabolic clustering had increased odds of peripheral neuropathy alone compared with the nonobese group without clustering. This association remained even after adjusting for sex, age, and race/ethnicity (Table 3). Compared with the nonobese group without clustering, the nonobese group with clustering had 1.5 times the adjusted odds of peripheral neuropathy alone (odds ratio [OR] 1.50 [95% CI 1.00–2.25]). Compared with the nonobese group without clustering, the obese group was two times more likely to have peripheral neuropathy alone (2.20 [1.43–3.39]) after adjusting for sex, age, and race/ethnicity.

Table 1—*Mean demographic and cardiometabolic factors of individuals aged ≥40 years by peripheral neuropathy* and PVD† status, NHANES III, 2001–2004*

	Total	Peripheral neuropathy	No peripheral neuropathy	*P*‡	PVD	No PVD	*P*‡
Proportion (%)	100	9.0 (0.7)	91.0 (0.7)		8.5 (0.8)	91.5 (0.8)	
Age (years)	56.4 (0.3)	63.2 (0.7)	55.8 (0.4)	<0.0001	62.2 (1.2)	55.4 (0.3)	<0.0001
Sex (%)							
Male	47.9 (1.0)	65.5 (3.1)	46.2 (1.0)	<0.0001	37.6 (3.8)	49.7 (1.2)	0.01
Female	52.1 (1.0)	34.5 (3.1)	53.8 (1.0)	<0.0001	62.4 (3.8)	50.3 (1.2)	0.01
Race/ethnicity (%)							
White	77.8 (2.2)	78.8 (3.2)	77.7 (2.2)	Reference	75.0 (3.8)	78.4 (2.1)	Reference
Black	9.4 (1.2)	11.5 (2.0)	9.2 (1.2)	0.04	15.1 (2.8)	8.6 (1.1)	<0.0001
Other	12.8 (1.8)	9.7 (2.6)	13.1 (1.8)	0.06	9.9 (26)	12.9 (1.8)	0.01
Education (%)							
Less than high school	18.9 (1.0)	22.2 (3.6)	18.5 (1.0)	0.7	27.6 (4.1)	17.1 (1.1)	0.4
High school or equivalent	25.7 (1.0)	25.0 (3.6)	25.8 (1.2)	Reference	25.4 (3.1)	25.9 (1.2)	Reference
More than high school	55.4 (1.5)	52.8 (4.8)	55.7 (1.5)	0.5	47.1 (3.5)	57.0 (1.7)	0.009
Weight (kg)	81.8 (0.5)	88.3 (1.6)	81.1 (0.5)	<0.0001	82.3 (1.6)	81.6 (0.6)	0.6
Waist circumference (cm)	99.0 (0.4)	105.5 (0.9)	98.4 (0.4)	<0.0001	102.5 (1.0)	98.5 (0.4)	<0.0001
BMI (kg/m^2)	28.5 (0.2)	29.4 (0.4)	28.4 (0.2)	0.01	29.8 (0.6)	28.3 (0.2)	0.0009
Glucose (mg/dL)	105.6 (0.8)	111.8 (2.4)	105.0 (0.8)	0.0005	110.2 (2.4)	104.8 (0.8)	0.002
Diabetes (%)	15.5 (0.9)	23.6 (3.1)	14.7 (1.0)	0.003	21.2 (3.0)	14.4 (0.9)	0.008
Lipid levels (mg/dL)							
HDL cholesterol	52.9 (0.7)	50.3 (1.6)	53.1 (0.7)	0.2	53.3 (2.3)	52.7 (0.7)	0.8
LDL cholesterol	123.3 (1.2)	117.4 (3.5)	123.9 (1.1)	0.05	119.9 (2.7)	123.7 (1.2)	0.2
Triglycerides	161.1 (5.8)	187.0 (22.2)	158.5 (5.4)	0.05	167.2 (12.8)	160.1 (6.2)	0.5
Blood pressure (mmHg)							
Systolic	127.6 (0.6)	131.4 (1.7)	127.2 (0.6)	0.02	136.7 (1.5)	126.2 (0.6)	<0.0001
Diastolic	72.6 (0.4)	70.9 (1.1)	72.8 (0.4)	0.1	69.7 (1.0)	73.2 (0.4)	<0.0001
Hypertension (%)	56.4 (1.5)	66.9 (3.9)	55.3 (1.6)	0.007	76.3 (3.3)	53.7 (1.6)	<0.0001

Data are means (SE) for continuous variables and percentage (SE) for categorical variables. *Peripheral neuropathy defined as one or more insensate sites on either foot. †PVD defined as an ABPI <0.90. ‡*P* values obtained from bivariate logistic regression. Statistical significance considered *P* value <0.05.

Table 2—*Mean demographic and cardiometabolic factors of individuals aged ≥40 years by both peripheral neuropathy* and PVD† statuses combined, NHANES III, 2001–2004*

	Both	Neither	*P*‡
Proportion (%)	2.4 (0.3)	97.6 (0.3)	
Age (years)	66.4 (2.5)	56.2 (0.3)	<0.0001
Sex (%)			
Male	74.1 (6.5)	47.3 (0.9)	0.0006
Female	25.9 (6.5)	52.7 (0.9)	
Race/ethnicity (%)			
White	82.4 (5.4)	77.7 (2.2)	Reference
Black	9.2 (3.1)	9.4 (1.2)	0.6
Other	8.4 (3.7)	12.9 (1.8)	0.3
Education (%)			
Less than high school	31.3 (7.4)	18.6 (1.0)	0.09
High school or equivalent	15.9 (5.7)	25.9 (1.0)	Reference
More than high school	52.8 (8.0)	55.5 (1.5)	0.8
Weight (kg)	88.1 (3.4)	81.6 (0.6)	0.05
Waist circumference (cm)	105.9 (2.6)	98.9 (0.4)	0.006
BMI (kg/m^2)	29.4 (1.1)	28.5 (0.2)	0.4
Glucose (mg/dL)	114.6 (6.1)	105.4 (0.7)	0.02
Diabetes (%)	48.2 (8.9)	14.6 (0.9)	<0.0001
Lipid levels (mg/dL)			
HDL cholesterol	47.9 (2.5)	53.0 (0.7)	0.1
LDL cholesterol	110.1 (4.5)	123.6 (1.2)	0.01
Triglycerides	174.2 (17.7)	160.7 (5.9)	0.4
Blood pressure (mmHg)			
Systolic	128.6 (2.9)	127.6 (0.6)	0.7
Diastolic	64.6 (2.3)	72.8 (0.4)	<0.0001
Hypertension (%)	68.8 (6.7)	56.1 (1.6)	0.08

Data are means (SE) for continuous variables and percentage (SE) for categorical variables. *Peripheral neuropathy defined as one or more insensate sites on either foot. †PVD defined as an ABPI <0.90. ‡*P* values obtained from bivariate logistic regression. Statistical significance considered *P* value <0.05.

A progressively greater prevalence of PVD alone also was observed across the obesity-clustering groups. Compared with the nonobese group without cardiometabolic clustering, the nonobese group with cardiometabolic clustering had 2.5 times the adjusted odds of having PVD alone (OR 2.48 [95% CI 1.38–4.44]). Compared with the nonobese group without cardiometabolic clustering, the obese group was three times more likely to have PVD alone (3.10 [1.84–5.22]) after adjustment.

The strongest associations with cardiometabolic clustering-obesity phenotypes were observed for a combination of both peripheral neuropathy and PVD (Table 3). Even after adjustment, the nonobese group with clustering was 2.6 times more likely to have LEDs (OR 2.62 [95% CI 0.95–7.25]) and the obese group was almost 7 times more likely to have LEDs (6.91 [2.64–18.06]) compared with the nonobese group without clustering.

Even after excluding individuals with diabetes, progressively greater prevalence of LEDs was observed across the obesity-clustering group. Adjusting for sex, age, and race/ethnicity, the nonobese group with clustering was 1.5 times more likely to have peripheral neuropathy alone (OR 1.51 [95% CI 1.00–2.27]), and the obese group was almost twice as likely to have peripheral neuropathy alone (1.92 [1.27–2.92]) compared with the nonobese group without clustering. The nonobese group with clustering was over twice as likely to have PVD alone (2.36 [1.31–4.25]) and the obese group was three times more likely to have PVD alone (3.16 [1.73–5.75]) compared with the nonobese group without clustering. The nonobese group with clustering also was more likely to have both LEDs (1.57 [0.47–5.21]) and the obese group was 4.5 more likely to have both LEDs (4.55 [1.60–12.99]) compared with the nonobese group without clustering.

CONCLUSIONS—Prevalences of LEDs in excess of 10% were identified in this representative sample of the U.S. population, with 2.4% of the population having a combination of both peripheral neuropathy and PVD. In addition, although diabetes was more frequent in those with LEDs compared with the general population, LEDs occurred apart from a diagnosis of diabetes. Thus, although the occurrence of LEDs is well described in diabetic populations (12,20), their frequency in the general population indicates that these conditions deserve greater clinical and public health attention.

To our knowledge, this is the first investigation of the association between LEDs and the clustering of dysfunctional cardiometabolic factors in the general population and the potential exacerbation generated by their co-occurrence with obesity. Our results indicate that even among the nonobese subjects, the clustering of dysfunctional cardiometabolic factors was associated with the increased likelihood of having peripheral neuropathy alone, PVD alone, and both LEDs. The magnitude and direction of our findings are similar to those of a clinical study among people with diabetes in which there was a linear increase (*P* value for trend <0.05) in PVD and peripheral neuropathy as cardiometabolic clustering increased (14). Identifying LED risk factors beyond glycemic control, like cardiometabolic clustering, has important ramifications for future disease prevention.

In our study, the aggregation of obesity with cardiometabolic dysfunction was associated with a modest increase in the odds of both LEDs. However, the most notable difference occurred in those who presented simultaneously with both LEDs. Being obese more than doubled the odds of having PVD and peripheral neuropathy compared with being lean with cardiometabolic clustering. These findings suggest that obesity confers an additional risk of individual LEDs over and above the risk of LEDs present with cardiometabolic dysfunction in the absence of obesity, but the magnitude of the obesity contribution with the co-occurring LEDs suggests a particularly vulnerable population to the obesity environment. Even after the exclusion of individuals with diabetes, results for the associations of LEDs with cardiometabolic clustering-obesity phenotypes remained virtually unchanged for peripheral neuropathy alone and PVD alone and only slightly attenuated for the combination of both peripheral neuropathy and PVD.

Table 3—*Unadjusted and adjusted prevalence ratios (95% CIs) of having peripheral neuropathy, PVD, or both by cardiometabolic clustering and obesity categories in individuals aged ≥40 years, NHANES III, 2001–2004*

	Nonobese (BMI <30 kg/m^2)		Obese (BMI ≥30 kg/m^2)
	Without clustering	With clustering	With and without clustering
n	503	1,148	809
Peripheral neuropathy (alone)*			
Proportion [% (SE)]	4.9 (0.9)	9.7 (0.8)	10.9 (1.3)
Unadjusted prevalence ratio	1 (Reference)	2.07 (1.41–3.02)	2.35 (1.55–3.56)
Adjusted prevalence ratio†	1 (Reference)	1.50 (1.00–2.25)	2.20 (1.43–3.39)
PVD (alone)‡			
Proportion [% (SE)]	3.2 (0.8)	9.6 (1.0)	10.3 (1.6)
Unadjusted prevalence ratio	1 (Reference)	3.25 (1.84–5.72)	3.52 (2.08–5.94)
Adjusted prevalence ratio†	1 (Reference)	2.48 (1.38–4.44)	3.10 (1.84–5.22)
LEDs (peripheral neuropathy and PVD combined)			
Proportion [% (SE)]	0.6 (0.2)	2.3 (0.4)	3.9 (0.8)
Unadjusted prevalence ratio	1 (Reference)	4.06 (1.62–10.18)	7.05 (2.67–18.57)
Adjusted prevalence ratio†	1 (Reference)	2.62 (0.95–7.25)	6.91 (2.64–18.06)

*Peripheral neuropathy defined as one or more insensate sites on either foot. †Adjusted for sex, age, and race/ethnicity. ‡PVD defined as an ABPI <0.90.

The mechanisms by which obesity confers a greater risk of LEDs await full elucidation. Varying individual responses to the levels and effects of the metabolic products of adiposity, the adipocytokines, may confer differing disease risks. Adipocytokines may act as inflammatory mediators in systemic inflammation and vascular resistance in diabetes and cardiovascular disease (21,22). Research involving adiponectin, leptin, and resistin, or the cytokines interleukin-6 and tumor necrosis factor-α, may explain the epidemiologic observation that obesity may be associated with LEDs; thus, BMI alone may be an incomplete proxy to represent the obesity metabolic environment (22), particularly considering the proportion of unhealthy nonobese individuals (15).

This study had several strengths and limitations. Although additional cardiometabolic-obesity phenotypes were of interest to us, the sample size (n <50) precluded a determination of whether LEDs and obesity are associated independently of clustering among individuals with an LED exam. Therefore, we included all obese individuals, with and without dysfunctional cardiometabolic clustering, in one group. It also is possible that individuals were misclassified with regard to diabetes status, particularly in the obesity group. The cross-sectional nature of this investigation not only precludes inferences of causality but also precludes us from understanding the temporal order of the LEDs in those with co-occurrence of both peripheral neuropathy and PVD.

It is important to note that this report may substantially underestimate the true prevalence of peripheral neuropathy and PVD because of the exclusion criteria used by the NHANES. Individuals with bilateral amputations, lesions, casts, or dressings that interfered with testing procedures were ineligible for LED assessments, as were individuals who weighed >400 lb. Because the NHANES protocol precludes the use of individual identifiers, it is unclear how many individuals were excluded from the LED examination. The presence of bilateral amputation, extreme obesity, and a lesion or dressing is likely to be causally related to LEDs. In addition, individuals with bilateral amputations are more likely to have advanced disease because peripheral neuropathy and PVD are the leading causes of noninjury amputations. Likewise, the presence of lesions or dressings also could be an indication of advanced disease. Although there may be a potential for misclassification of LEDs beyond the exclusionary criteria, monofilament testing is a commonly used screening tool in epidemiologic studies (4,20). It is possible that other factors, such as inattention, temperature of the feet, and thickness of the skin, may have influenced the monofilament results. For example, obesity may increase the plantar skin thickness of the feet, resulting in differential misclassification of peripheral neuropathy by obesity status in this population, despite attempts by examiners to avoid thickened or callus areas (18). Nevertheless, compared with nerve conduction studies, monofilament testing has demonstrated sensitivities ranging from 57 to 93% and specificities ranging from 75 to 100% (23).

The large age range (40 to ≥85 years) in our study may have led to residual confounding by age despite the inclusion of age in our statistical models. In addition, for confidentiality, the NHANES protocol dictates that any individual over the age of 85 years be considered "85" for the continuous age variable available in public use datasets. Therefore, although the maximum age was reported to be 85 years in this sample, the true maximum age was likely quite older and the reported mean ages for the total eligible sample and for the mean ages by disease status are likely underestimates of the true means. Therefore, it is likely that the association between age and LEDs would be strengthened by including the true ages over 85 years.

It is a strength to consider three different disease outcomes: peripheral neuropathy alone (without PVD); PVD alone (without peripheral neuropathy); and the presence of both peripheral neuropathy and PVD. The peripheral neuropathy (alone) and PVD (alone) groups are mutually exclusive. The benefit of these mutually exclusive groups precludes the possibility that insensate neuropathy, as assessed by the monofilament testing in the NHANES III, is a consequence of PVD or vice versa. When peripheral neuropathy and PVD groups were not mutually exclusive (results not shown), results were of increased magnitude compared with the results presented here.

The early diagnosis of both PVD and peripheral neuropathy has important prognostic value because it may delay the development of more debilitating disease consequences (24,25). The utility of the current study was the population-based sampling scheme in identifying the substantial prevalence of LEDs both with and without the co-occurrence of diabetes. To our knowledge, this is the first study to consider the association between cardiometabolic clustering and obesity with LEDs using a sample and study design representative of the U.S., enhancing our ability to generalize these results to individuals aged ≥40 years in the U.S.

PVD and peripheral neuropathy are prevalent among individuals aged ≥40 years in the U.S., and the odds of having LEDs increase with the presence of cardiometabolic-obesity clustering. The high prevalence of LEDs in the general population may warrant disease screening outside of traditionally diabetic-only populations because of the importance of early detection. Future research using longitudinal studies would allow characterization of temporal relationships of PVD, peripheral neuropathy, diabetes, and increasing obesity. In addition, the use of multiple obesity phenotypes should be considered particularly for studies of LEDs, because disease risk appears to be nonuniform across groups. Understanding this phenomenon could contribute to promoting the need for clinical and public health screening as well as multifactorial interventions beyond glycemic control.

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K.R.Y. wrote the manuscript and analyzed data. M.F.S. guided data analysis and interpretation, contributed to discussion, and reviewed and edited the manuscript. S.H. reviewed the manuscript and guided the incorporation of the sampling design into data analysis.

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