



Metabolic Syndrome Components Are Associated With Symptomatic Polyneuropathy Independent of Glycemic Status

Diabetes Care 2016;39:801–807 | DOI: 10.2337/dc16-0081

Brian C. Callaghan,¹ Rong Xia,²
Mousumi Banerjee,²
Nathalie de Rekeneire,³
Tamara B. Harris,⁴ Anne B. Newman,⁵
Suzanne Satterfield,⁶ Ann V. Schwartz,⁷
Aaron I. Vinik,⁸ Eva L. Feldman,¹ and
Elsa S. Strotmeyer,⁵ for the Health ABC
Study

OBJECTIVE

Previous studies demonstrate that the metabolic syndrome is associated with distal symmetric polyneuropathy (DSP). We aimed to determine the magnitude of this effect and the precise components involved.

RESEARCH DESIGN AND METHODS

We determined the symptomatic DSP prevalence in the Health, Aging, and Body Composition (Health ABC) study (prospective cohort study, with subjects aged 70–79 years at baseline), stratified by glycemic status (glucose tolerance test) and the number of additional metabolic syndrome components (updated National Cholesterol Education Program/Adult Treatment Panel III definition). DSP was defined as neuropathic symptoms (questionnaire) plus at least one of three confirmatory tests (heavy monofilament, peroneal conduction velocity, and vibration threshold). Multivariable logistic and linear regression evaluated the association of metabolic syndrome components with DSP in cross-sectional and longitudinal analyses.

RESULTS

Of 2,382 participants with neuropathy measures (mean age 73.5 ± 2.9 years, 38.2% black, 51.7% women), 21.0% had diabetes, 29.9% prediabetes, 52.8% metabolic syndrome, and 11.1% DSP. Stratified by glycemic status, DSP prevalence increased as the number of metabolic syndrome components increased ($P = 0.03$). Diabetes (cross-sectional model, odds ratio [OR] 1.65 [95% CI 1.18–2.31]) and baseline hemoglobin A_{1c} (longitudinal model, OR 1.42 [95% CI 1.15–1.75]) were the only metabolic syndrome measures significantly associated with DSP. Waist circumference and HDL were significantly associated with multiple secondary neuropathy outcomes.

CONCLUSIONS

Independent of glycemic status, symptomatic DSP is more common in those with additional metabolic syndrome components. However, the issue of which metabolic syndrome components drive this association, in addition to hyperglycemia, remains unclear. Larger waist circumference and low HDL may be associated with DSP, but larger studies with more precise metabolic measures are needed.

¹Department of Neurology, University of Michigan, Ann Arbor, MI

²School of Public Health, University of Michigan, Ann Arbor, MI

³University Bordeaux, ISPED, Centre INSERM U1219-Epidemiologie-Biostatistique, Bordeaux, France

⁴National Institute on Aging, Bethesda, MD

⁵School of Public Health, University of Pittsburgh, Pittsburgh, PA

⁶Department of Preventative Medicine, University of Tennessee Health Science Center, Memphis, TN

⁷Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA

⁸Strelitz Diabetes Research Institute, Norfolk, VA

Corresponding author: Brian C. Callaghan, bcallagh@med.umich.edu.

Received 12 January 2016 and accepted 13 February 2016.

© 2016 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.

The prevalence of distal symmetric polyneuropathy (DSP) is greater than 3% and is even higher in the elderly (1,2). This common condition causes significant morbidity and is associated with pain, falls, and reduced quality of life (3,4). While diabetes is by far the number one cause, enhanced glucose control is only marginally effective at reducing the incidence in patients with type 2 diabetes (5). One possible explanation for this small therapeutic effect is that other factors, such as the other components of the metabolic syndrome (MetS), may be significant contributors to nerve injury (6). The other MetS components may also be the underlying cause for some of the 30% of DSP patients currently labeled as idiopathic (7–10).

Past studies have revealed an association between the MetS and polyneuropathy (11–14). However, previous investigations have reported conflicting associations between the individual MetS components and neuropathy (15–21). For example, while diabetes is a well-established risk factor for neuropathy, population studies investigating the effect of prediabetes have reached different conclusions (16,22,23). To date, most studies investigating the association between the MetS and polyneuropathy have been performed only in patients with diabetes, used cross-sectional designs, and lacked rigorous definitions of DSP such as only evaluating one confirmatory test (6). The goal of this study is to address these limitations.

In a large cohort of older adults, we aimed to determine whether the prevalence of symptomatic DSP, utilizing a rigorous definition, increases with increasing numbers of MetS components independent of glycemic status. We also investigated the associations between the individual MetS components and symptomatic DSP in cross-sectional and longitudinal analyses.

RESEARCH DESIGN AND METHODS

Population

Data for our analysis came from participants in the Health, Aging, and Body Composition (Health ABC) study, which is an ongoing, prospective cohort study of 70–79 year olds ($n = 3,075$; 48.4% male; 41.6% black) followed since the baseline evaluation in 1997 or 1998. The cohort consists of a random sample

of age-eligible white Medicare beneficiaries, all black Medicare beneficiaries, and all community-dwelling black persons in Pittsburgh and Memphis. Participants had to self-report having no difficulty with walking 1/4 mile, climbing 10 steps, or any basic activity of daily living; be free of any life-threatening cancers; and plan to remain in the study area for at least 3 years. This cohort has been followed annually for the past 17 years with questionnaires, biospecimens, anthropomorphic measures, blood pressure, and neuropathy outcome assessments at differing intervals. Participants were included in the cross-sectional analysis if they had complete neuropathy outcome data from year 4 in 2000–2001. Participants were included in the longitudinal analysis if they had complete neuropathy outcome data from years 4 (2000–2001) and 11 (2007–2008). All study protocols were approved by institutional review boards at the University of Pittsburgh and University of Tennessee Health Science Center.

MetS Components

The glucose tolerance test was obtained only at year 1 (baseline). Hemoglobin A_{1c} was measured at years 4, 6, 10, and 11. Diabetes (fasting glucose ≥ 126 mg/dL or 2-h glucose ≥ 200 mg/dL) and prediabetes (fasting glucose ≥ 100 mg/dL or 2-h glucose ≥ 140 mg/dL) were defined according to the guidelines of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (24). Participants on diabetes medications were also considered to have diabetes. Lipid panels and blood pressure were measured at years 1, 2, 4, 6, 8, 10, and 11, with blood pressure also measured at years 3 and 5. Height, weight, and BMI were measured at years 1, 4, 6, 8, 10, and 11, whereas waist circumference was only measured at years 1 and 6. The updated National Cholesterol Education Program/Adult Treatment Panel III criteria were used to define the MetS and its individual components, which takes into consideration medications for the different components (25). Specifically, the MetS criteria were a waist circumference ≥ 102 cm in men and ≥ 88 cm in women, systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, triglycerides ≥ 150 mg/dL, and HDL < 40 mg/dL in men and < 50 mg/dL in women. In the

cross-sectional analysis, metabolic data from year 1 were used. In the longitudinal analysis, baseline metabolic data were obtained from year 1 with the exception of hemoglobin A_{1c}, which was only available starting in year 4.

DSP Definition

Our primary DSP outcome measure was determined by the combination of neuropathy symptoms as identified by at least one of two questionnaire items endorsed and at least one of three confirmatory neuropathy tests abnormal; therefore, our primary outcome construct was symptomatic DSP. Neuropathy outcome measures were available at years 4 and 11. The questionnaire items were as follows: “In the past 12 months, have you ever had numbness, an ‘asleep feeling,’ a prickly feeling or tingling in your legs or feet?” and “In the past 12 months, have you ever had a sudden stabbing or burning pain, or a deep aching in your legs or feet?” The three confirmatory neuropathy tests included a peroneal motor nerve conduction velocity (CV) < 40 m/s, a vibration threshold > 131 μ m, and inability to feel a 10-g (heavy) monofilament at the dorsum of the great toe in three out of four trials.

Secondary DSP outcome measures included the three confirmatory tests above. In addition, the peroneal compound motor action potential (CMAP) at the ankle and a 1.4-g (light) monofilament at the dorsum of the great toe (abnormal if unable to feel in three of four trials) were secondary outcomes. Five of the six secondary DSP outcome measures did not require symptoms; therefore, these measures had the potential to capture asymptomatic as well as symptomatic DSP. The peroneal motor nerve conduction studies were performed on a NeuroMax 8 (Xitek). Vibration detection was performed at the bottom of the great toe using the VSA-3000 Vibratory Sensory Analyzer (Medoc). Feet were warmed to 30°C, and measures were performed on the right unless contraindicated owing to knee replacement, amputation, trauma, ulcer, or recent surgery, in which case the left side was tested unless also contraindicated.

Statistical Analysis

Descriptive statistics were used to describe the characteristics of the population. One-way ANOVA (continuous

variables) and χ^2 tests (categorical variables) were used to test for differences in demographics between the three glycemic groups. We determined the prevalence of neuropathy stratified by glycemic status and the number of MetS components. We then applied the Cochran-Mantel-Haenszel test to investigate the effect of the number of MetS components on neuropathy prevalence, controlling for glycemic status.

Cross-sectional Analyses

Multivariable logistic regression was used to model the year 4 primary neuropathy outcome as a function of the year 1 MetS components (waist circumference, prediabetes, diabetes, HDL level, triglyceride level, systolic blood pressure) after adjustment for baseline demographic factors (age, sex, race, height, smoking, and alcohol consumption). Weight, hemoglobin A_{1c}, log HOMA of insulin resistance, and diastolic blood pressure were also considered as MetS component variables but were not used in the final model (Akaike information criterion was used in model selection). Secondary neuropathy outcomes including neuropathic symptoms, heavy monofilament, and light monofilament outcomes were also analyzed using multivariable logistic regression models. Multivariable linear regression was used to analyze the continuous neuropathy measurements (peroneal CV, peroneal CMAP, vibration threshold) as a function of MetS components, adjusting for the same covariates. Finally, we fit a separate multivariable logistic regression model to study the association of the number of MetS components, excluding glycemic status, with our primary neuropathy outcome, adjusting for demographic factors and glycemic status.

Longitudinal Analysis

We first estimated the longitudinal change in each MetS component (hemoglobin A_{1c}, weight, systolic blood pressure, triglycerides, and HDL) by fitting a simple linear regression model over time for each subject. Then, the estimated subject-specific slopes, along with the baseline measurements for each MetS component, were incorporated into a multivariable logistic regression model to investigate the association of longitudinal change in MetS components and incident symptomatic neuropathy

(those with neuropathy in year 11 but not at year 4) after adjustment for baseline demographics as described above.

All analyses were performed with SAS 9.3 (Cary, NC).

RESULTS

Of participants in the Health ABC cohort, 2,382 had complete neuropathy outcome data and were included in our cross-sectional analysis. Of these 2,382, 1,263 participants also had complete neuropathy outcome data at year 11 and were included in our longitudinal analysis. In a comparison of year 4 with year 11, 184 subjects developed symptomatic neuropathy (incident neuropathy), 948 remained neuropathy free, 67 continued with neuropathy, and 64 became neuropathy free. Population demographics and metabolic phenotyping measures at year 1 are presented in Table 1. The mean (SD) age was 73.5 (2.9), and 51.7% were female. Participants with normoglycemia accounted for 49.1% of the population, prediabetes 29.9%, and diabetes 21.0%. MetS was present in 52.8%, and DSP was present in 11.1%.

The prevalence of symptomatic DSP was significantly higher in participants with higher number of MetS components ($P = 0.03$), controlling for glycemic status (Fig. 1). In the entire population, the DSP prevalence was 8.5% in those with no MetS components (excluding hyperglycemia) compared with 12.9% in those with four MetS components. In those with normoglycemia, the DSP prevalence was 8.6% in those with no MetS components compared with 11.4% in those with four MetS components. In those with prediabetes, the DSP prevalence was 5.6% in those with no additional MetS components compared with 10.6% in those with four additional MetS components. In contrast, the DSP prevalence in participants with diabetes was similar between those with no additional MetS components (16.7%) and those with four additional MetS components (17.1%).

Cross-sectional Analyses

In a multivariable logistic regression model investigating the individual MetS components, diabetes (odds ratio [OR] 1.65 [95% CI 1.18–2.31]), height (OR 1.39 [95% CI 1.24–1.54], unit = 5 cm), and male sex (OR 0.59 [95% CI

0.39–0.92]) were significantly associated with the DSP primary outcome (Table 2). Prediabetes, waist circumference, systolic blood pressure, triglycerides, and HDL were not significantly associated with DSP. In a separate multivariable logistic regression model investigating the association of the number of MetS components in addition to glycemic status, the number of MetS components (OR 1.20 [95% CI 1.06–1.37]) was significantly associated with symptomatic DSP.

In investigation of the association of MetS components and the 6 secondary neuropathy outcomes, diabetes was significantly associated with all outcomes (Tables 2 and 3). Increasing age and height were significantly associated with all neuropathy outcome measures with the exception of neuropathic symptoms. Increasing waist circumference was significantly associated with four of the six neuropathy outcomes. Decreasing HDL was significantly associated with two of the six neuropathy outcomes. Prediabetes was not associated with any of the neuropathy outcome measures. While systolic blood pressure and triglycerides were significantly associated with one and two neuropathy outcomes, respectively, the association was in the opposite direction of what was expected (lower blood pressure and lower triglycerides).

Longitudinal Analysis

In a multivariable logistic regression model evaluating the longitudinal change of MetS components, only the baseline hemoglobin A_{1c} (year 4 OR 1.42 [95% CI 1.15–1.75]) and height (OR 1.26 [95% CI 1.09–1.46]) were significantly associated with incident symptomatic neuropathy. Baseline weight (OR 0.99 [95% CI 0.92–1.07]), systolic blood pressure (OR 1.06 [95% CI 0.97–1.17]), triglycerides (OR 0.99 [95% CI 0.84–1.16]), and HDL (OR 0.94 [95% CI 0.81–1.09]) were not significantly associated with incident neuropathy. Similarly, the slopes of the MetS components (hemoglobin A_{1c} OR 1.91 [95% CI 0.28–12.95], weight OR 0.71 [95% CI 0.20–2.55], systolic blood pressure OR 1.54 [95% CI 0.62–3.86], triglyceride OR 0.79 [95% CI 0.13–4.85], and HDL OR 0.87 [95% CI 0.13–5.88]) were not significantly associated with incident neuropathy.

Table 1—Demographics of the Health ABC cohort at year 1 stratified by glycemic status

	Total	Normoglycemia	Prediabetes	Diabetes	<i>P</i>
Subjects, <i>N</i> (%)	2,382 (100)	1,145 (49.1)	699 (29.9)	490 (21.0)	
Age (years), mean (SD)	73.5 (2.9)	73.4 (2.8)	73.6 (3.0)	73.6 (2.7)	0.18
Male, <i>N</i> (%)	1,151 (48.3)	528 (46.1)	326 (46.6)	275 (56.1)	<0.001
Race, <i>N</i> (%)					<0.001
White	1,472 (61.8)	746 (65.2)	460 (65.8)	245 (50.0)	
Black	910 (38.2)	399 (34.8)	239 (34.2)	245 (50.0)	
Smoking, <i>N</i> (%)					0.05
Current	206 (8.7)	104 (9.1)	57(8.2)	36 (7.4)	
Former	1,100 (46.2)	509 (44.5)	320 (45.8)	257 (52.6)	
Never	1,073 (45.1)	531 (46.4)	321 (45.9)	196 (40.0)	
Alcohol (drinks per week), mean (SD)	2.1 (1.5)	2.2 (1.5)	2.2 (1.7)	1.9 (1.4)	<0.001
Height (cm), mean (SD)	165.6 (9.4)	165.4 (9.5)	165.2 (9.1)	166.8 (9.4)	0.008
Fasting glucose (mg/dL), mean (SD)	103.4 (32.5)	88.6 (6.3)	99.4 (9.9)	144.5 (51.6)	<0.001
2-h glucose (mg/dL), mean (SD)	133.7 (56.0)	102.7 (21.1)	146.8 (28.8)	254.7 (65.9)	<0.001
BMI (kg/m ²), mean (SD)	27.4 (4.7)	26.3 (4.4)	28.0 (4.9)	29.0 (4.6)	<0.001
Waist circumference (cm), mean (SD)	99.5 (12.8)	96.9 (12.8)	100.9 (12.1)	103.9 (12.3)	<0.001
SBP (mmHg), mean (SD)	135.3 (20.5)	133.6 (20.3)	135.9 (20.3)	138.0 (20.7)	<0.001
DBP (mmHg), mean (SD)	71.2 (11.6)	71.0 (11.6)	71.8 (11.4)	70.8 (11.7)	0.29
Triglycerides (mg/dL), mean (SD)	139.5 (80.0)	123.9 (62.3)	147.9 (81.3)	164.7 (104.0)	<0.001
HDL (mg/dL), mean (SD)	53.8 (16.8)	55.6 (16.5)	53.6 (17.1)	49.8 (16.5)	<0.001
LDL (mg/dL), mean (SD)	122.0 (34.4)	122.0 (33.3)	123.8 (34.8)	119.4 (36.1)	0.10
MetS, <i>N</i> (%)	1,224 (52.8)	295 (25.8)	520 (74.4)	406 (82.9)	<0.001

DBP, diastolic blood pressure; SBP, systolic blood pressure.

CONCLUSIONS

In our large cohort of older black and white men and women, 21.0% of the population had diabetes and 52.8%

met criteria for MetS at baseline. These numbers are comparable with those in previous studies using National Health and Nutrition Examination Survey

(NHANES) data, which have estimated a diabetes prevalence of ~20% in those over 65 years of age and a MetS prevalence of 47–58% in those over 70 years of age (26,27). In our well-functioning older cohort, the baseline symptomatic DSP prevalence was 11.1%. A previous NHANES study revealed similar results with a symptomatic DSP prevalence of 3.1% in those over 40 years of age, which was three times higher in those age 70–79 years (2). A study in Italy in those over the age of 55 years revealed a symptomatic DSP prevalence of 7–8% with an even higher prevalence in those >75 years (1). Similarly, others have estimated a clinical neuropathy prevalence of 6–9% in those >70–79 years old (28). In concert with previous studies, we demonstrate that the prevalence of diabetes, MetS, and DSP is incredibly high in even a well-functioning older population. As a result, any causal link between MetS and neuropathy, regardless of diabetes status, would have potential therapeutic implications for a large proportion of older adults. Furthermore, previous studies have demonstrated that the peripheral nerve measures used in this study are associated with important functional outcomes in older populations including

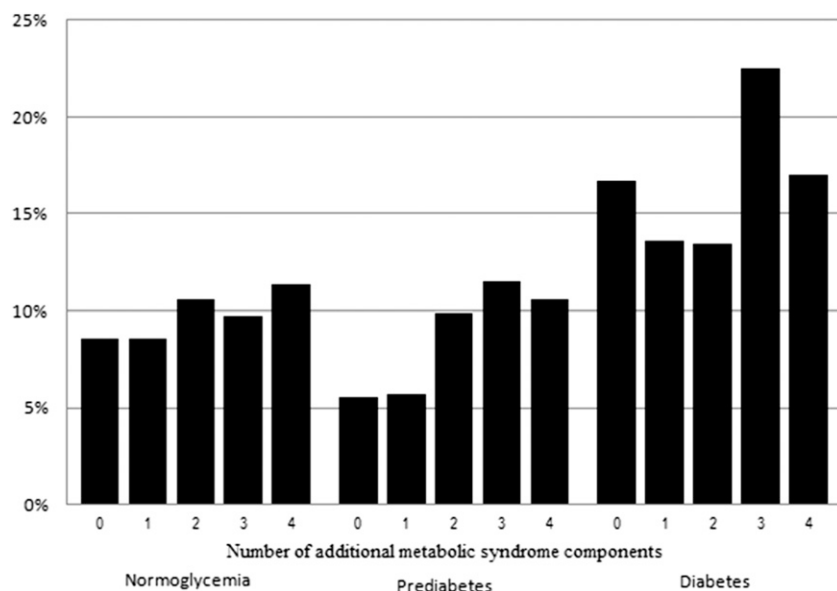


Figure 1—The prevalence of DSP with increasing MetS components stratified by glycemic status. DSP was defined as those with neuropathic symptoms (questionnaire) plus at least 1 of 3 confirmatory tests (heavy monofilament, peroneal CV, or vibration threshold) in year 4 of the study. Glycemic status was determined by the glucose tolerance test according to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus in year 1. MetS components were defined using the updated National Cholesterol Education Program/Adult Treatment Panel III definition.

Table 2—Multivariable logistic regression evaluating the association of MetS components (year 1) and neuropathy (year 4) (cross-sectional)

	Neuropathy primary outcome	Neuropathic symptoms	Heavy monofilament	Light monofilament
Demographics				
Age	1.04 (0.99, 1.09)	1.01 (0.98, 1.04)	1.14 (1.08, 1.20)*	1.08 (1.05, 1.12)*
Male (reference female)	0.59 (0.39, 0.92)*	0.54 (0.41, 0.71)*	0.78 (0.48, 1.29)	1.12 (0.86, 1.47)
Black (reference white)	1.10 (0.81, 1.49)	1.48 (1.22, 1.80)*	1.18 (0.84, 1.66)	1.16 (0.95, 1.40)
Current smoker (reference never)	1.35 (0.82, 2.21)	1.22 (0.88, 1.71)	0.87 (0.47, 1.59)	0.78 (0.56, 1.09)
Former smoker (reference never)	1.18 (0.87, 1.59)	1.15 (0.95, 1.40)	0.90 (0.65, 1.26)	0.94 (0.78, 1.14)
Alcohol (drinks per week)	0.99 (0.90, 1.09)	0.99 (0.93, 1.05)	1.02 (0.92, 1.12)	0.95 (0.90, 1.01)
Height (unit 5 cm)	1.39 (1.24, 1.54)*	1.05 (0.98, 1.13)	1.39 (1.23, 1.57)*	1.13 (1.06, 1.22)*
MetS components				
Diabetes	1.65 (1.18, 2.31)*	1.52 (1.20, 1.92)*	1.98 (1.36, 2.88)*	1.57 (1.24, 1.99)*
Prediabetes (reference normal)	0.94 (0.67, 1.31)	0.98 (0.80, 1.20)	1.16 (0.80, 1.68)	1.06 (0.87, 1.30)
Waist circumference (unit 5 cm)	1.04 (0.98, 1.10)	1.07 (1.03, 1.11)*	1.10 (1.03, 1.17)*	1.02 (0.99, 1.06)
SBP (unit 10 mmHg)	0.97 (0.91, 1.04)	0.97 (0.93, 1.02)	0.93 (0.87, 1.01)	0.95 (0.91, 0.99)*
Triglycerides (unit 50 mg/dL)	1.01 (0.93, 1.10)	1.02 (0.96, 1.08)	1.02 (0.92, 1.12)	0.93 (0.88, 0.99)*
HDL (unit 10 mg/dL)	0.91 (0.81, 1.01)	0.91 (0.85, 0.97)*	0.94 (0.83, 1.06)	0.92 (0.86, 0.98)*

Data are OR (95% CI). SBP, systolic blood pressure. * $P < 0.05$.

mobility, quadriceps strength, and other physical performance measures (29–31). Therefore, therapeutic interventions to prevent and/or ameliorate DSP in this population may have a clinically meaningful effect.

We found a statistically significant association between the number of MetS components and symptomatic DSP when adjusting for glycemic status in two separate analyses. In fact, the DSP prevalence increased from 8.5 to 12.9% when we compared subjects with no MetS components, excluding hyperglycemia, with those with all four components. The implication is that MetS components may be important risk factors for the development of DSP

independent of glycemic status. The magnitude of the effect of additional MetS components on DSP prevalence (1.1% difference per component) is not as high as the effect of diabetes (8.6%). However, given the high prevalence of MetS components individually and in combination, this effect may be clinically important. Our results are comparable with those of the recent Prospective Metabolism and Islet Cell Evaluation (PROMISE) study in patients at high risk of diabetes that demonstrated that the vibration threshold increased as the number of MetS components increased (32). However, in contrast to our analysis, this association did not persist after adjustment for participant demographics.

Interestingly, we found that the rise in DSP prevalence with additional MetS components was most evident in those with normoglycemia and prediabetes. The number of MetS components did not affect the DSP prevalence in those with diabetes. Of note, the PROMISE study investigators did not stratify their results by glycemic status. Future studies investigating the effect of treatment of MetS components on the prevention or treatment of DSP may need to target the normoglycemic populations and populations with prediabetes.

The prevalence of symptomatic DSP in those with prediabetes (9.3%) was comparable with the prevalence in those with normoglycemia (9.7%). Furthermore,

Table 3—Multivariable linear regression evaluating the association of MetS components (year 1) and continuous outcomes of neuropathy (year 4) (cross-sectional)

	Peroneal CV parameter estimate, m/s (95% CI)	Peroneal CMAP parameter estimate, mV (95% CI)	Vibration threshold parameter estimate, μ m (95% CI)
Demographics			
Age	-0.10 (-0.19, -0.02)*	-0.08 (-0.11, -0.05)*	2.01 (1.53, 2.48)*
Male (reference female)	-0.87 (-1.62, -0.11)*	0.12 (-0.16, 0.40)	-5.20 (-9.52, -0.88)*
Black (reference white)	0.93 (0.39, 1.46)*	0.51 (0.31, 0.71)*	-5.52 (-8.59, -2.45)*
Current smoker (reference never)	-0.18 (-1.10, 0.75)	0.12 (-0.22, 0.47)	4.86 (-0.33, 10.06)
Former smoker (reference never)	-0.16 (-0.69, 0.37)	0.09 (-0.11, 0.29)	1.36 (-1.63, 4.35)
Alcohol (drinks per week)	0.25 (0.08, 0.42)*	0.02 (-0.04, 0.08)	-1.00 (-1.96, -0.05)*
Height (unit 5 cm)	-0.98 (-1.17, -0.79)*	-0.22 (-0.29, -0.15)*	6.92 (5.83, 8.02)*
MetS components			
Diabetes	-1.07 (-1.74, -0.40)*	-0.40 (-0.64, -0.15)*	8.17 (4.41, 11.93)*
Prediabetes (reference normal)	0.25 (-0.30, 0.81)	-0.04 (-0.24, 0.17)	0.86 (-2.31, 4.03)
Waist circumference (unit 5 cm)	0.05 (-0.05, 0.15)	-0.05 (-0.09, -0.01)*	0.58 (0.01, 1.14)*
SBP (unit 10 mmHg)	-0.03 (-0.15, 0.09)	0.02 (-0.02, 0.07)	-0.42 (-1.09, 0.25)
Triglycerides (unit 50 mg/dL)	0.06 (-0.12, 0.23)	0.07 (0.005, 0.14)*	0.09 (-0.87, 1.06)
HDL (unit 10 mg/dL)	-0.03 (-0.20, 0.15)	0.03 (-0.04, 0.09)	0.28 (-0.72, 1.28)

SBP, systolic blood pressure. * $P < 0.05$.

prediabetes was not associated with any of our neuropathic outcome measures in multivariable regression models. These observations add to other conflicting studies on the importance of prediabetes as a cause of DSP. The MONICA/KORA (Multinational Monitoring of trends and determinants in Cardiovascular disease/Cooperative Health Research in the Region of Augsburg), San Luis Valley, and PROMISE (all with DSP defined by neurologic examination) studies all revealed an increased prevalence of DSP in those with impaired glucose tolerance compared with normoglycemia (16,23,32). However, investigators using NHANES data reported a DSP prevalence (based on monofilament testing) comparable with that in our population with no significant difference between those with normoglycemia (10.5%) and those with impaired fasting glucose (11.9%) (22). All of these studies used different definitions of DSP, were conducted in different populations, and included subjects of different ages. One possible explanation for the discrepant results is that the effect of prediabetes in older adults is less than in younger adults. Alternatively, the neuropathy definition used in this study was insufficient to capture small fiber predominant neuropathy, which is typically seen in those with either prediabetes and/or MetS (33). Another possibility is that prediabetes is not as important as the other MetS components that tend to cluster with this condition. Future studies are needed to further understand the role of prediabetes in DSP. A clinical trial investigating the effects of the treatment of prediabetes on neuropathy outcomes may be the only way to definitely address this question.

Diabetes was the only MetS component that was significantly associated with the primary DSP outcome in both cross-sectional and longitudinal analyses. However, waist circumference (four of six) and HDL (two of six) were associated with some of the secondary neuropathy outcome measures. One potential reason for the lack of associations between MetS components and DSP is that we did not have enough power to detect the associations, which likely have smaller effect sizes. The power of our secondary outcomes may

have been more robust because most had the potential to capture asymptomatic DSP as well as symptomatic DSP. Furthermore, we did not have adequate power to investigate interactions between glycemic status and the other MetS components. Interactions are likely important, as the prevalence of DSP only increased as the number of MetS components increased in those with normoglycemia and prediabetes. Another possibility is that the main drivers of DSP are not the MetS components themselves but, rather, other factors that are associated with them. For example, perhaps abdominal obesity is not one of the main drivers of DSP and, instead, adipose tissue-derived inflammatory markers, such as interleukin-6 levels or adiponectin-to-leptin ratios, are the true mediators (34). Further studies with larger samples sizes and more precise MetS and neuropathy measurements are needed to further delineate the role of MetS components in the development of DSP.

Limitations include the lack of a neurologic examination to determine neuropathy status and neuropathic symptoms based on a questionnaire. However, we were able to combine questionnaire items pertaining to neuropathic symptoms in the feet with well-validated neuropathy confirmatory studies. Our sample size was not adequate to address small effect sizes or interaction between MetS components and glycemic status. Similarly, the sample size in the longitudinal analysis was smaller than the cross-sectional analysis. Nevertheless, our study is one of the largest to date to investigate the association between MetS components and DSP. Our analysis was confined to those well-functioning 70–79 year olds at the start of the study. How our results apply to other populations is unclear.

MetS components are significantly associated with DSP independent of glycemic status, although the effect is less than that of the presence of diabetes. The precise components, or combinations of components, that drive the development of DSP remain unclear. Larger studies with more precise metabolic measures are needed to guide the development of future intervention studies. Given the high prevalence of both the MetS and DSP, particularly in older adults, even small causal effects

have the potential for a large impact on population health.

Funding. B.C.C. and E.L.F. are supported by the Taubman Medical Institute. B.C.C. is supported by a National Institute of Neurological Disorders and Stroke, National Institutes of Health (NIH), K23 grant (NS079417). E.L.F. is supported by National Institute of Diabetes and Digestive and Kidney Diseases grants DP3DK094292 and R24 082841. This research was supported by the National Institute on Aging (NIA) contracts N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106; NIA grant R01-AG028050 (to E.S.S.); and National Institute of Nursing Research grant R01-NR12459. This research was also supported in part by the Intramural Research Program of the NIH, the National Institute on Aging, and the University of Pittsburgh Claude D. Pepper Older Americans Independence Center Pilot grant P30-AG024827 (to E.S.S.).

Duality of Interest. B.C.C. receives research support from Impeto Medical, Inc., and honorarium from *BMJ*. B.C.C. certifies ALS centers for the ALS Association, performs medical consultations for Advance Medical, and consults for a Patient-Centered Outcomes Research Institute grant. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. B.C.C. was involved in the study design and interpretation of the statistical analysis and wrote the manuscript. R.X. and M.B. were involved in the study design, statistical analyses, interpretation of data, and critical revisions of the manuscript. N.d.R., T.B.H., A.B.N., S.S., A.V.S., and A.I.V. were involved in the study design and critical revisions of the manuscript. E.L.F. and E.S.S. were involved in the study design, interpretation of data, and critical revisions of the manuscript. B.C.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Italian General Practitioner Study Group (IGPSG). Chronic symmetric symptomatic polyneuropathy in the elderly: a field screening investigation in two Italian regions. I. Prevalence and general characteristics of the sample. *Neurology* 1995;45:1832–1836
2. Gregg EW, Sorlie P, Paulose-Ram R, et al.; 1999–2000 national health and nutrition examination survey. Prevalence of lower-extremity disease in the US adult population ≥ 40 years of age with and without diabetes: 1999–2000 national health and nutrition examination survey. *Diabetes Care* 2004;27:1591–1597
3. Callaghan B, Kerber K, Langa KM, et al. Longitudinal patient-oriented outcomes in neuropathy: importance of early detection and falls. *Neurology* 2015;85:71–79
4. Veresiu AI, Bondor CI, Florea B, Vinik EJ, Vinik AI, Găvan NA. Detection of undisclosed neuropathy and assessment of its impact on quality of life: a survey in 25,000 Romanian patients with diabetes. *J Diabetes Complications* 2015;29:644–649

5. Callaghan BC, Little AA, Feldman EL, Hughes RA. Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev* 2012;6:CD007543
6. Callaghan B, Feldman E. The metabolic syndrome and neuropathy: therapeutic challenges and opportunities. *Ann Neurol* 2013;74:397–403
7. Callaghan BC, Kerber KA, Lisabeth LL, et al. Role of neurologists and diagnostic tests on the management of distal symmetric polyneuropathy. *JAMA Neurol* 2014;71:1143–1149
8. Dyck PJ, Oviatt KF, Lambert EH. Intensive evaluation of referred unclassified neuropathies yields improved diagnosis. *Ann Neurol* 1981;10:222–226
9. Johannsen L, Smith T, Havsager AM, et al. Evaluation of patients with symptoms suggestive of chronic polyneuropathy. *J Clin Neuromuscul Dis* 2001;3:47–52
10. Lubec D, Müllbacher W, Finsterer J, Mamoli B. Diagnostic work-up in peripheral neuropathy: an analysis of 171 cases. *Postgrad Med J* 1999;75:723–727
11. Bonadonna R, Cucinotta D, Fedele D, Riccardi G, Tiengo A; Metascreen Writing Committee. The metabolic syndrome is a risk indicator of microvascular and macrovascular complications in diabetes: results from Metascreen, a multicenter diabetes clinic-based survey. *Diabetes Care* 2006;29:2701–2707
12. Costa LA, Canani LH, Lisbôa HR, Tres GS, Gross JL. Aggregation of features of the metabolic syndrome is associated with increased prevalence of chronic complications in type 2 diabetes. *Diabet Med* 2004;21:252–255
13. Isomaa B, Henricsson M, Almgren P, Tuomi T, Taskinen MR, Groop L. The metabolic syndrome influences the risk of chronic complications in patients with type II diabetes. *Diabetologia* 2001;44:1148–1154
14. Ylitalo KR, Sowers M, Heeringa S. Peripheral vascular disease and peripheral neuropathy in individuals with cardiometabolic clustering and obesity: National Health and Nutrition Examination Survey 2001–2004. *Diabetes Care* 2011;34:1642–1647
15. De Block CE, De Leeuw IH, Van Gaal LF. Impact of overweight on chronic microvascular complications in type 1 diabetic patients. *Diabetes Care* 2005;28:1649–1655
16. Franklin GM, Kahn LB, Baxter J, Marshall JA, Hamman RF. Sensory neuropathy in non-insulin-dependent diabetes mellitus. The San Luis Valley Diabetes Study. *Am J Epidemiol* 1990;131:633–643
17. Novella SP, Inzucchi SE, Goldstein JM. The frequency of undiagnosed diabetes and impaired glucose tolerance in patients with idiopathic sensory neuropathy. *Muscle Nerve* 2001;24:1229–1231
18. Singleton JR, Smith AG, Bromberg MB. Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. *Diabetes Care* 2001;24:1448–1453
19. Straub RH, Thum M, Hollerbach C, Palitzsch KD, Schölermerich J. Impact of obesity on neuropathic late complications in NIDDM. *Diabetes Care* 1994;17:1290–1294
20. Tesfaye S, Chaturvedi N, Eaton SE, et al.; EURODIAB Prospective Complications Study Group. Vascular risk factors and diabetic neuropathy. *N Engl J Med* 2005;352:341–350
21. Van Acker K, Bouhassira D, De Bacquer D, et al. Prevalence and impact on quality of life of peripheral neuropathy with or without neuropathic pain in type 1 and type 2 diabetic patients attending hospital outpatients clinics. *Diabetes Metab* 2009;35:206–213
22. Gregg EW, Gu Q, Williams D, et al. Prevalence of lower extremity diseases associated with normal glucose levels, impaired fasting glucose, and diabetes among U.S. adults aged 40 or older. *Diabetes Res Clin Pract* 2007;77:485–488
23. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A; KORA Study Group. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. *Diabetes Care* 2008;31:464–469
24. Genuth S, Alberti KG, Bennett P, et al.; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26:3160–3167
25. Grundy SM, Cleeman JI, Daniels SR, et al.; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735–2752
26. Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care* 2005;28:2745–2749
27. Selvin E, Parrinello CM, Sacks DB, Coresh J. Trends in prevalence and control of diabetes in the United States, 1988–1994 and 1999–2010. *Ann Intern Med* 2014;160:517–525
28. Baldereschi M, Inzitari M, Di Carlo A, Farchi G, Scafato E, Inzitari D; ILSA Working Group. Epidemiology of distal symmetrical neuropathies in the Italian elderly. *Neurology* 2007;68:1460–1467
29. Strotmeyer ES, de Rekeneire N, Schwartz AV, et al. The relationship of reduced peripheral nerve function and diabetes with physical performance in older white and black adults: the Health, Aging, and Body Composition (Health ABC) study. *Diabetes Care* 2008;31:1767–1772
30. Ward RE, Boudreau RM, Caserotti P, et al.; Health ABC study. Sensory and motor peripheral nerve function and longitudinal changes in quadriceps strength. *J Gerontol A Biol Sci Med Sci* 2015;70:464–470
31. Ward RE, Boudreau RM, Caserotti P, et al.; Health, Aging and Body Composition Study. Sensory and motor peripheral nerve function and incident mobility disability. *J Am Geriatr Soc* 2014;62:2273–2279
32. Lee CC, Perkins BA, Kayaniyl S, et al. Peripheral neuropathy and nerve dysfunction in individuals at high risk for type 2 diabetes: the PROMISE cohort. *Diabetes Care* 2015;38:793–800
33. Pittenger GL, Mehrabian A, Simmons K, et al. Small fiber neuropathy is associated with the metabolic syndrome. *Metab Syndr Relat Disord* 2005;3:113–121
34. Lieb DC, Parson HK, Mamikunian G, Vinik AI. Cardiac autonomic imbalance in newly diagnosed and established diabetes is associated with markers of adipose tissue inflammation. *Exp Diabetes Res* 2012;2012:878760