Idiopathic Neuropathy Workup: *What to Exclude?*

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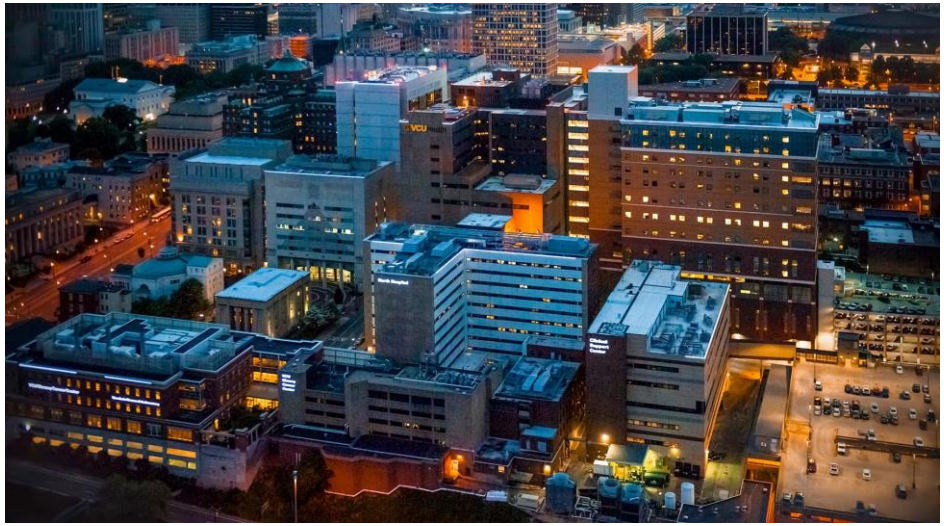

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Disclosures

Consulting

Alexion
CSL
Grifols
Allergan
Celgene
Regenesis

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Clinical Laboratory

Utah Cutaneous Nerve Lab

Editorial

American Academy of Neurology

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of the National Institutes of Health

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Idiopathic Neuropathy

Idio (unknown) + Pathic (the cause of)

"You must be an idiot because you cant figure out what I have"

Idiopathic Neuropathy

Chronic Idiopathic Axonal Polyneuropathy (CIAP)

Cryptogenic Sensory Peripheral Neuropathy (CSPN)

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Chronic Cryptogenic Sensory Polyneuropathy

Clinical and Laboratory Characteristics

Gil I. Wolfe, MD; Noel S. Baker, MD; Anthony A. Amato, MD; Carlayne E. Jackson, MD; Sharon P. Nations, MD; David S. Saperstein, MD; Choon H. Cha, MD; Jonathan S. Katz, MD; Wilson W. Bryan, MD; Richard J. Barohn, MD

Distal symmetric pain numbness and tingling > 3 months

B12, TFT, RPR, SPEP/IFE (MGUS allowed), 'significant abnormalities on other laboratory studies".

Diabetes, ETOH, metabolic disturbances, endocrine abnormalities, CTD, cancer, HIV, Toxic exposure, hereditary neuropathy, amyloidosis

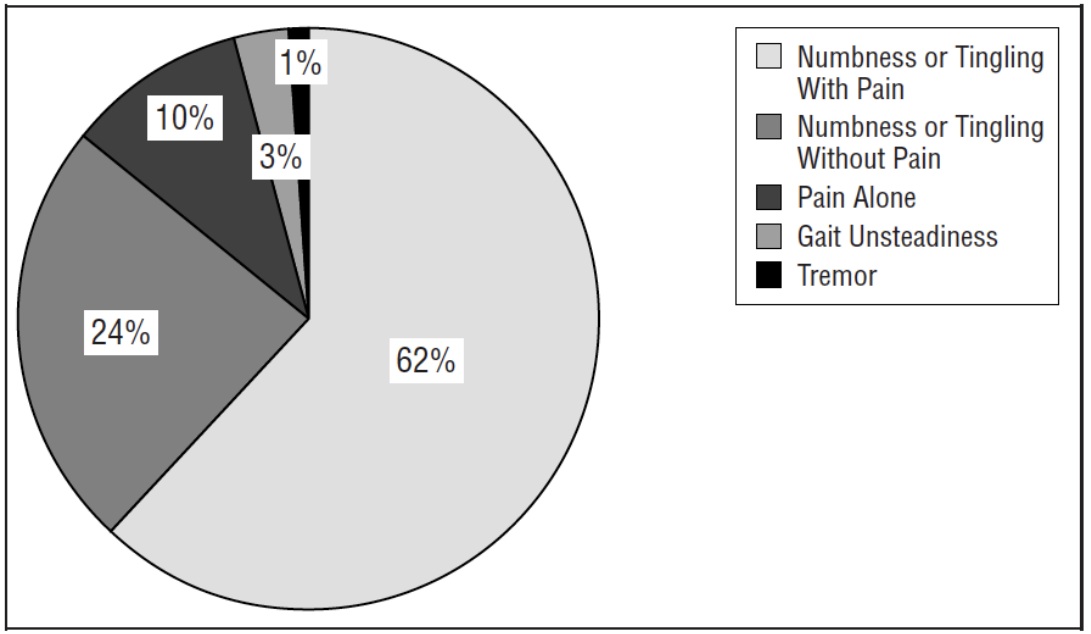

Figure 1. *Presenting symptoms in patients with cryptogenic sensory polyneuropathy (N = 93).*

Wolfe, G. I., et al. (1999). "Chronic cryptogenic sensory polyneuropathy: clinical and laboratory characteristics." Arch Neurol **56**(5): 540-547.

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CSPN Clinical Features

Table 2. Percentage of CSPN Patients With Abnormal Results*

Abnormal QST	84.6
Abnormal sensory NCS	77.0
Abnormal motor NCS	59.6
Abnormal needle EMG	70.3
Fibrillation potentials	42.2
Neurogenic motor units	63.1

**CSPN indicates cryptogenic sensory polyneuropathy; QST, quantitative sensory testing; NCS, nerve conduction studies; and EMG, electromyography.*

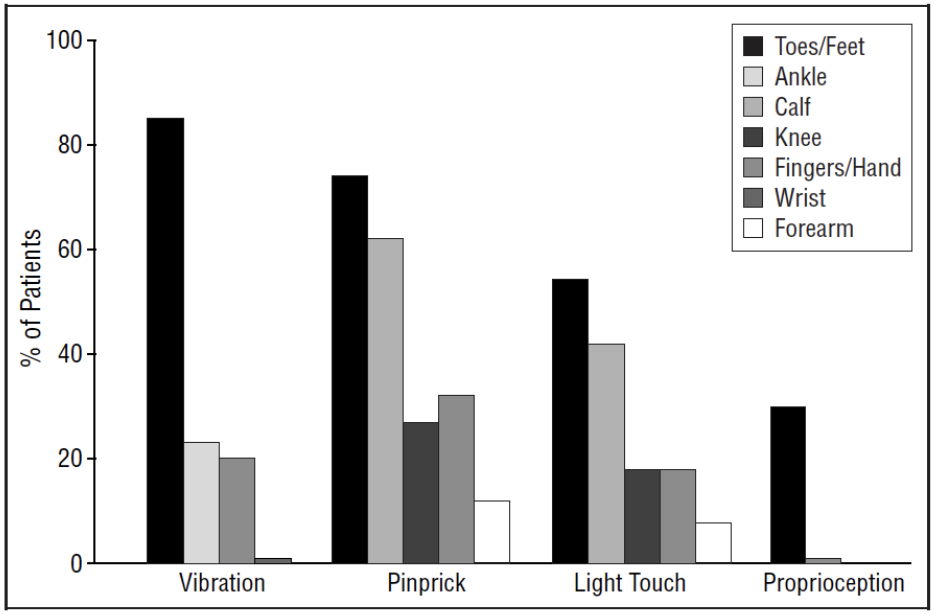

Figure 2. *Percentage of patients with cryptogenic sensory polyneuropathy with sensory loss on initial examination (N = 93). Anatomic extent of the deficit for each sensory modality is represented by bar graphs.*

<5% had isolated small fiber neuropathy based on physical examination and EDX studies

Wolfe, G. I., et al. (1999). "Chronic cryptogenic sensory polyneuropathy: clinical and laboratory characteristics." Arch Neurol **56**(5): 540-547.

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Epidemiology

Table 1 Characteristics of papers included in the review

Number of CIAP patients studied	
Total number of CIAP patients	3904
Range	3–381
Mean number of patients per study (SD)	81.3 (82.4)
Median	56
Demographics	
Male:female	3:2
Mean age	60.4 years
Year of publication	
Range	1985–2015
Number of publications per decade	
Until 1990	4
1991–2000	13
2001–2010	24
2011–2015	7

Zis, P., et al. (2016). "Chronic idiopathic axonal polyneuropathy: a systematic review." J Neurol **263**(10): 1903-1910.

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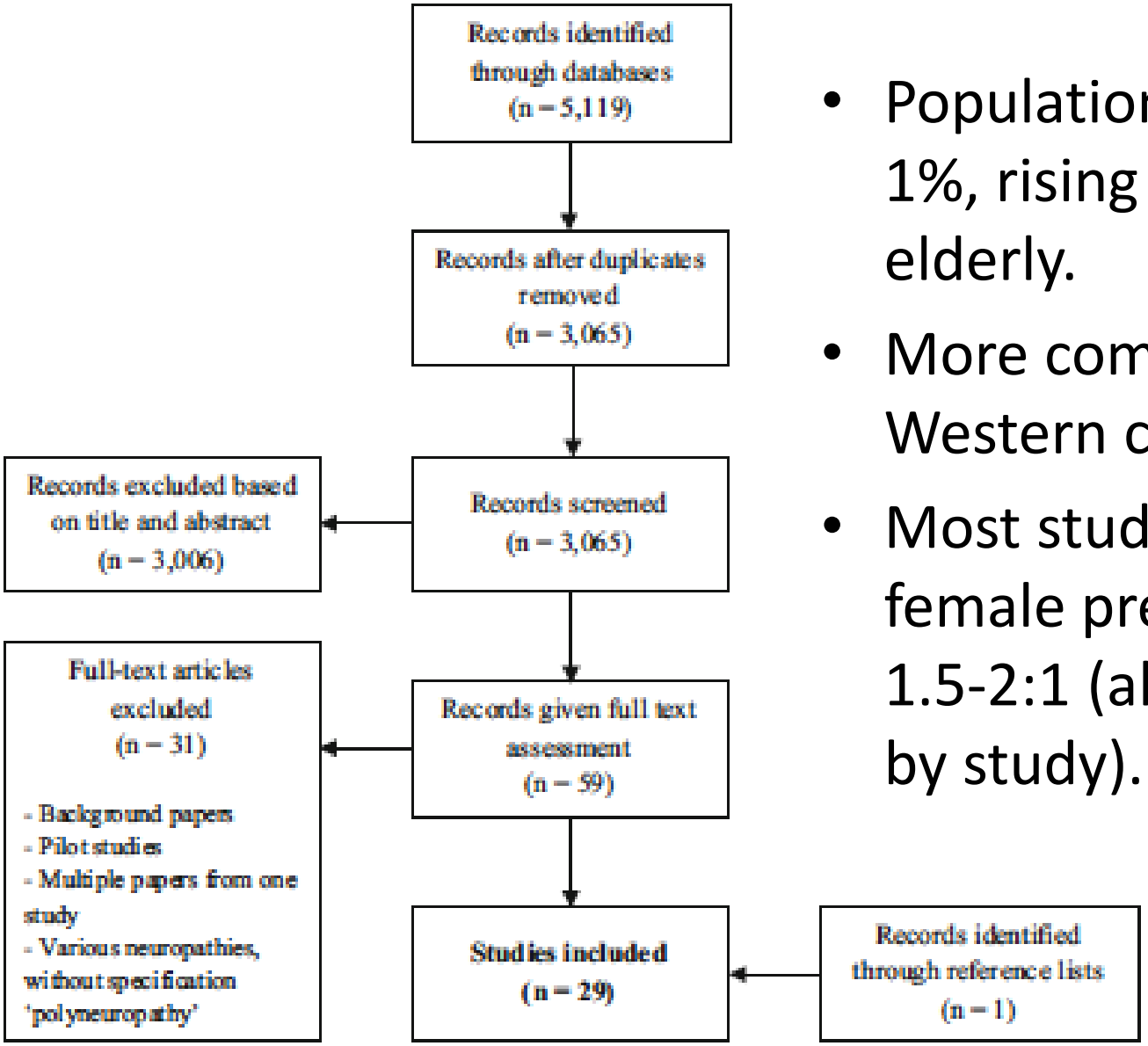

- Population prevalence of 1%, rising to 7% in the elderly.
- More common in Western countries.
- Most studies reported a female preponderance 1.5-2:1 (although varies by study).

Hanewinckel, R., et al. (2016). "The epidemiology and risk factors of chronic polyneuropathy." Eur J Epidemiol **31**(1): 5-20.

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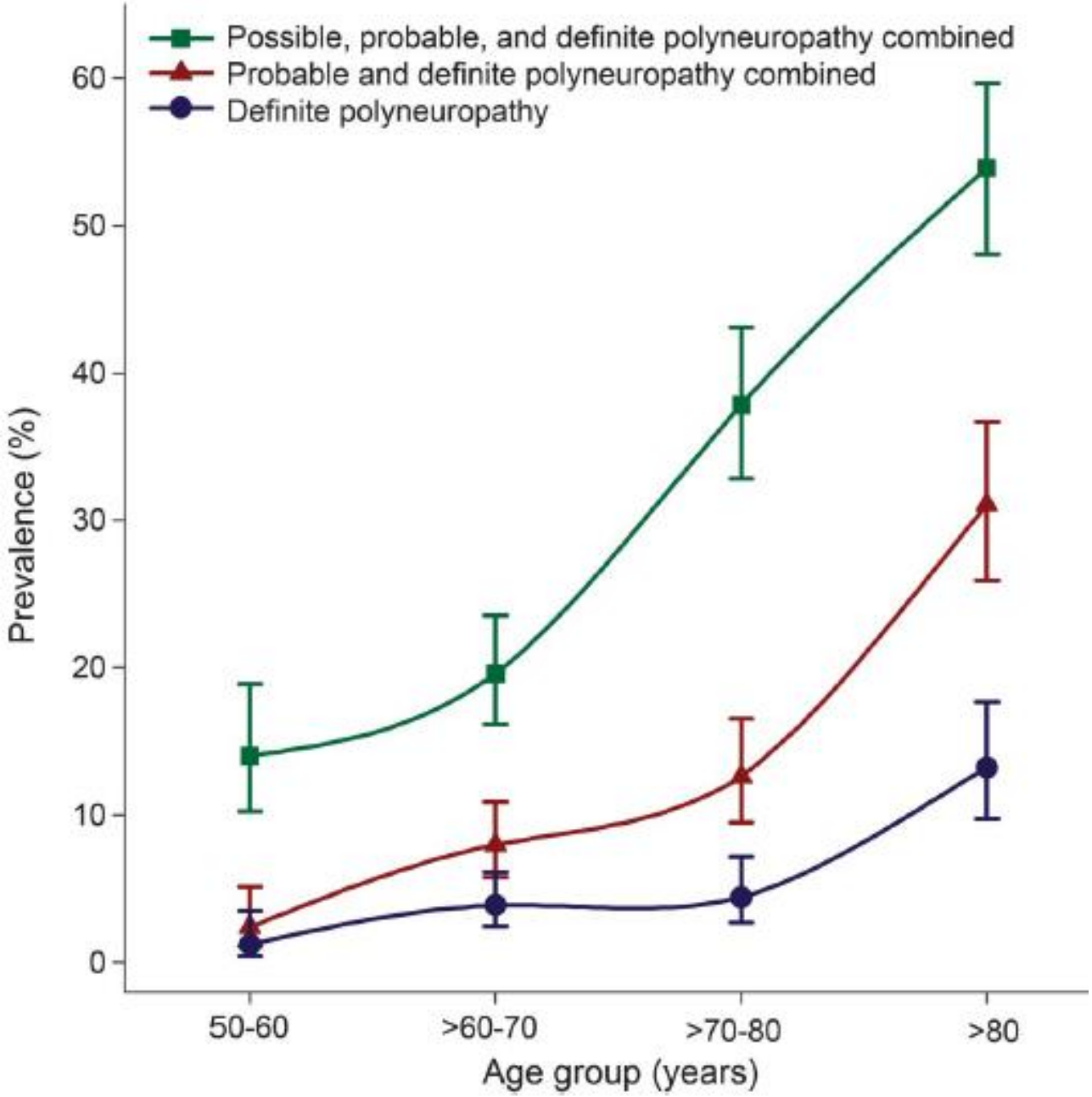
Rotterdam Study

- Prospective population based (1310 participants)
- Prevalence of definite neuropathy 5.5% (6.7% men, 4.5% women), probable/definite 9.4%
- 46% Idiopathic, 31% DM
- Over half of cases were newly reported, suggesting this is an underestimate.
- Screened for vitamin deficiency (B1 and B12), TFT, gammopathy, diabetes, ETOH, medical record review for other causes

Hanewinckel, R., et al. (2016). "Prevalence of polyneuropathy in the general middle-aged and elderly population." Neurology **87**(18): 1892-1898.



Hanewinckel, R., et al. (2016). "Prevalence of polyneuropathy in the general middle-aged and elderly population." Neurology **87**(18): 1892-1898.

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Table 3 Potential causes in cases with definite polyneuropathy

Associated risk factor present	Cases with a previous diagnosis (n = 37), n (%)	Cases with a new diagnosis (n = 35), n (%)	All cases (n = 72), n (%)
Diabetes	17 (46)	5 (14)	22 (31)
Vitamin deficiency[a]	4 (11)	6 (17)	10 (14)
Possible alcohol abuse[b]	2 (5)	1 (3)	3 (4)
Toxic	3 (8)	1 (3)	4 (6)
Hereditary	1 (3)	—	1 (1)
Immune-mediated[c]	4 (11)	3 (9)	7 (10)
Thyroid dysfunction	2 (5)	3 (9)	5 (7)
Renal failure	4 (11)	1 (3)	5 (7)
Systemic disease[d]	2 (5)	—	2 (3)
No risk factor present/CIAP	13 (35)	20 (57)	33 (46)
Total	52 (141)	40 (114)	92 (128)

Hanewinckel, R., et al. (2016). "Prevalence of polyneuropathy in the general middle-aged and elderly population." Neurology **87**(18): 1892-1898.

Diagnostic Yield of Commonly Ordered Blood Tests

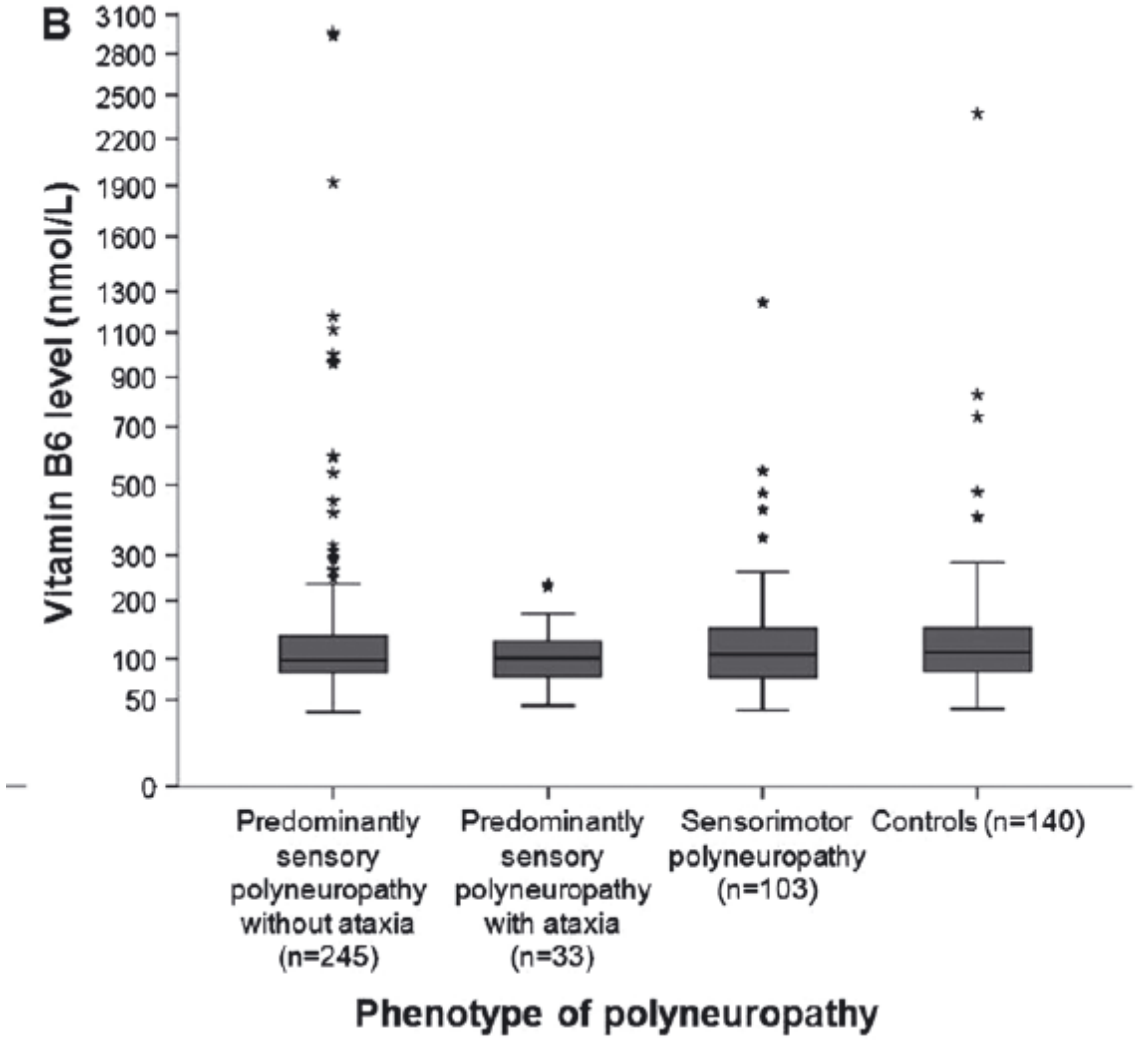
Test	No. (%) of Patients With a Positive Result	No. (%) of Patients Tested
OGT	53 (61)	87 (63)
HbA_{1c}	16 (26)	61 (44)
Fasting plasma glucose	12 (11)	106 (77)
ANA	2 (3)	65 (47)
SPEP/IFIX	3 (2.8)	104 (75)
Vitamin B_{12}	2 (1.6)	120 (87)
WESR	0	65 (47)
Folate	0	51 (37)
TSH	0	112 (81)

Abbreviations: ANA, antinuclear antibody; HbA_{1c}, hemoglobin A_{1c}; OGT, oral glucose tolerance; SPEP/IFIX, serum protein electrophoresis pattern and immunofixation; TSH, thyroid-stimulating hormone; WESR, Westergren erythrocyte sedimentation rate.

Smith, A. G. and J. R. Singleton (2004). "The diagnostic yield of a standardized approach to idiopathic sensory-predominant neuropathy." Archives of internal medicine **164**(9): 1021-1025.

Chronic idiopathic axonal polyneuropathy and vitamin B6: a controlled population-based study

Nora A. Visser[1], Nicolette C. Notermans[1], Lieveke A. R. Degen[2], Jelle R. de Kruijk[3], Leonard H. van den Berg[1], and Alexander F. J. E. Vrancken[1]



Visser, N. A., et al. (2014). "Chronic idiopathic axonal polyneuropathy and vitamin B6: a controlled population-based study." J Peripher Nerv Syst **19**(2): 136-144.

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Idiopathic Small Fiber Neuropathy

- Retrospective study of patients with small fiber neuropathy based on IENFD, autonomic testing or nerve biopsy.
- 213 patients
- Prevalence of abnormalities in numerous laboratory tests was compared to published control data.

Lang, M., et al. (2016). "Diagnostic value of blood tests for occult causes of initially idiopathic small-fiber polyneuropathy." J Neurol **263**(12): 2515-2527.

Table 2 Prevalence of abnormal test results (ABTR) in the iiSFPN cohort and in comparator populations

Test (definition of abnormal result)	Medical condition tested for	Prevalence of ABTR in sample (*n*)	Population prevalence of ABTR and source of population data
ACE (high)	Sarcoidosis [24]	44.6% (83)	Not evaluated due to positive predictive value = 0
ESR (high)	Inflammation/infection [12, 43]	28.0% (157)	5.0% in Norway [70]
ANA (≥ 1:160)	Lupus/rheumatic disease [43]	27.5% (153)	8.9% in Brazil [21]
2-hr OGTT value for prediabetes (140-149 mg/dL)	Impaired glucose tolerance (prediabetes) [5]	25.0% (8)	44.9% in US adults 45-64y from A1C , FPG, or 2-hr OGTT value NHANES [40]
Fasting plasma glucose for prediabetes (100-125 mg/dl)	Impaired fasting plasma glucose (prediabetes) [5]	25.0% (20)	44.9% in US adults 45-64y from A1C, FPG, or 2-hr OGTT value NHANES [40]
Triglycerides (high)	Hypertriglyceridemia [28]	24.7% (97)	30% NHANES [66]
Complement C4 (low)	Inflammation/vasculitis [43]	15.7% (115)	10.4% WHS [31]
Liver AST/ALT (high)	Fatty liver, alcoholism, hepatitis [73]	14.8% (162)	10% NHANES [29]
A1C for prediabetes (≥ 5.7%, <6.5)	Recent hyperglycemia (prediabetes) [5]	14.7% (109)	44.9% in US adults 45-64y from A1C, FPG, or 2-hr OGTT value [40]
C-reactive protein (high)	Injury/inflammation [25]	12.6% (95)	7.1% WHS [30]
Complement C3 (low)	Autoimmunity/vasculitis [43]	11.0% (118)	2.7% WHS [31]
AntiRo/SS-A	Sjögren's syndrome [49, 56]	9.2% (98)	0.7% WHS [31], 3.9% NHANES [54]
AntiLa/SS-B	Sjögren's syndrome [49, 56]	9.2% (98)	1.2% WHS [31], 2.4% NHANES [54]
Lyme (IgG Western Blot)	Lyme disease [25]	8.7% (104)	No data found on immunoblot positivity
A1C for diabetes (≥6.5%)	Recent hyperglycemia/diabetes [60]	5.5% (109)	5.8% occult DM by A1C or OGTT age 45-64 NHANES [40]
Thyroid stimulating hormone (TSH) (high)	Hyperthyroidism [1]	4.1% (145)	0.5% NHANES [27]
SPEP/IFIX	Monoclonal gammopathy [74]	3.9% (128)	3.2% for age > 50y [35]
IgA TTG antibody (high)	Celiac sprue [9]	3.5% (109)	0.5-1.0% U.S. estimate [20]
Creatinine (high)	Renal disease, Fabry [67]	2.5% (162)	No data found
Thyroid stimulating hormone (TSH) (low)	Hypothyroidism [47]	2.1% (144)	0.3% NHANES [27]
Folate (low)	Folate deficiency [33]	2.0% (49)	0.1% [44]
Vitamin B12 (low)	Vitamin B12 deficiency [60]	1.5% (135)	3.8% [52]
Hepatitis C antibodies	Hepatitis C [10]	1.1% (88)	1.6% NHANES [4]
Fasting glucose for diabetes including OGTT (≥ 126 mg/dl)	Diabetes mellitus [5]	0.0% (20)	5.8% occult DM by A1C or OGTT age 45-64 NHANES [40]
2-hr value from OGTT for diabetes (≥ 200 mg/dL)	Diabetes mellitus [5]	0.0% (8)	5.8% occult DM by A1C or OGTT age 45-64 NHANES [40]

Lang, M., et al. (2016). "Diagnostic value of blood tests for occult causes of initially idiopathic small-fiber polyneuropathy." J Neurol **263**(12): 2515-2527.

ORIGINAL ARTICLE

Associated conditions in small fiber neuropathy – a large cohort study and review of the literature

B. T. A. de Greef[a], J. G. J. Hoeijmakers[a], C. M. L. Gorissen-Brouwers[a], M. Geerts[a], C. G. Faber[a] and I. S. J. Merkies[a,b]

[a]*Department of Neurology, School of Mental Health and Neuroscience, Maastricht University Medical Center+, Maastricht, The Netherlands; and* [b]*Department of Neurology, St Elisabeth Hospital, Willemstad, Curaçao*

- 921 patients with 'pure small fiber neuropathy' defined as abnormal IENFD or thermal testing with normal large fiber examination and NCS.
- Standardized evaluation

de Greef, B. T. A., et al. (2018). "Associated conditions in small fiber neuropathy - a large cohort study and review of the literature." Eur J Neurol **25**(2): 348-355.

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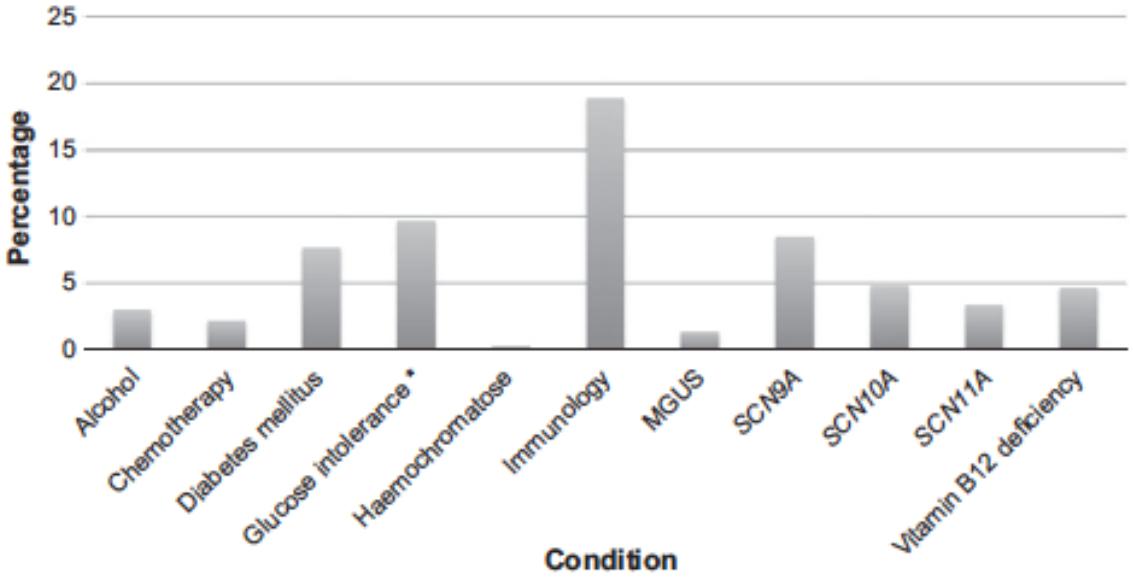
Table 1 Diagnostic tests performed in patients referred to the SFN Center

Kind of test		Disease investigated	Abnormal values
X-ray	Chest X-ray	Sarcoidosis	
Blood samples	Glucose	Diabetes mellitus	Two sober plasma levels of ≥ 7.0 mmol/l or the combination of a sober plasma glucose level of ≥ 7.0 mmol/l, a random plasma glucose level of ≥ 11.1 mmol/l with complaints of hyperglycemia, or a level of ≥ 11.1 mmol/l after 120 min
	Glucose tolerance test	Impaired glucose tolerance	Sober level of < 7.0 mmol/l and a level of ≥ 7.8 and < 11.1 mmol/l after 120 min
	Cholesterol	Hypercholesterolemia	Low density lipoprotein value above 3.1 mmol/l, high density lipoprotein value lower than 0.9 mmol/l and triglyceride value above 2.1 mmol/l
	Liver function	Hepatic impairment	Increased liver functions
	Kidney function	Renal insufficiency	Glomerular filtration rate < 30
	Thyroid function	Hypothyroid or hyperthyroid function	Increased or decreased thyroid stimulating hormone/thyroxin
	Vitamin B1	Vitamin B1 deficiency	<100 nmol/l
	Vitamin B6	Vitamin B6 toxicity	>200 nmol/l
	Vitamin B12	Vitamin B12 deficiency	<148 pmol/l
	Anti-tissue transglutaminase	Coeliac disease	Present
	Anti-extractable nuclear antigen antibodies	Sjogren's disease	Present
	Antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, and soluble Interleukin-2 receptor	Other autoimmune diseases	Present or soluble IL-2 receptor above 700 U/l
	Monoclonal gammopathy	Monoclonal gammopathy of undetermined significance	Present
	Borrelia burgdorferi (immunoglobulin I and M)	Lyme's disease	Present
	Anti-human immunodeficiency virus 1 and 2	Human immunodeficiency virus	Present
	Alpha-galactosidase A activity and alpha-galactosidase A gene	Fabry disease	< 30 nmo/l and variants class 3, 4 or 5.
	SCN9A, SCN10A and SCN11A gene	Sodium channel gene mutations	Variants with uncertain clinical significance, possibly pathogenic, probably pathogenic or pathogenic variants
Urine sample	Lysosomal globotriaosylceramide	Fabry disease	>0 nmol/mmol creatinine

SCN, sodium voltage-gated channels.

de Greef, B. T. A., et al. (2018). "Associated conditions in small fiber neuropathy - a large cohort study and review of the literature." Eur J Neurol **25**(2): 348-355.



- 53% were idiopathic (no abnormality)
- Most common abnormalities were B12 deficiency, diabetes/prediabetes, NaV mutations and autoimmune disorders (sarcoidosis 3%, Sjogren 1.3%, celiac 0.5%, other 8.5%).
- In those with a known risk factor, 27% had another identified.

de Greef, B. T. A., et al. (2018). "Associated conditions in small fiber neuropathy - a large cohort study and review of the literature." Eur J Neurol **25**(2): 348-355.

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Gain of Function $Na_V1.7$ Mutations in Idiopathic Small Fiber Neuropathy

8/28 patients with confirmed idiopathic small fiber neuropathy had Nav 1.7 mutations

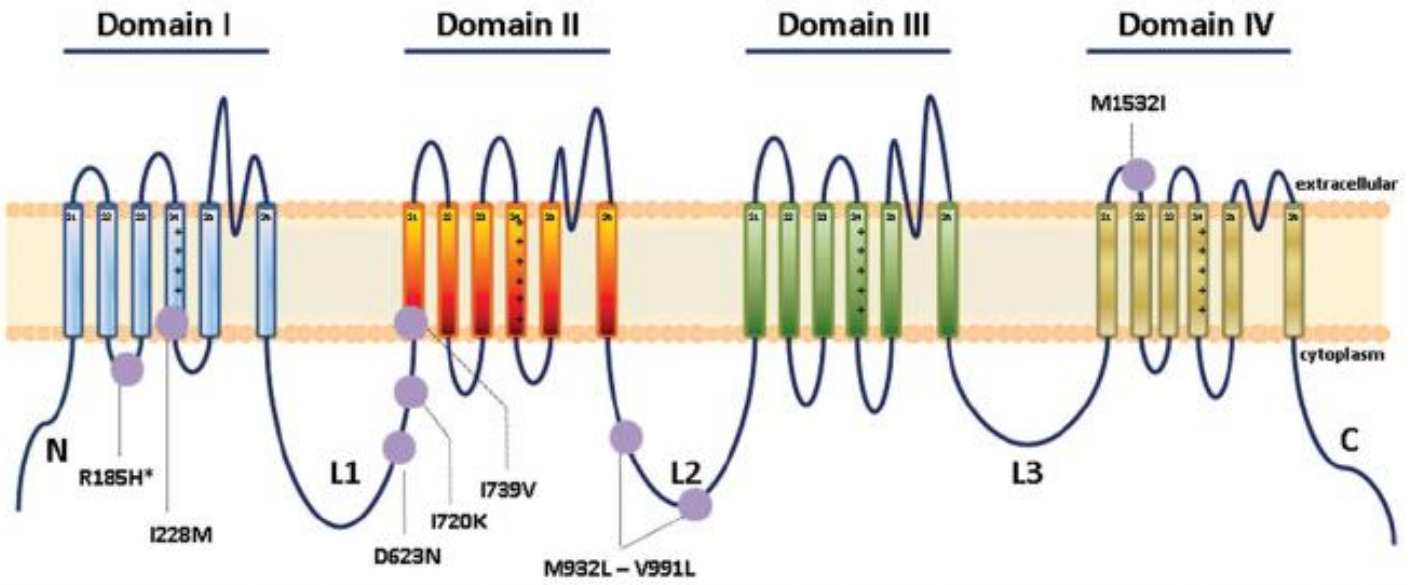

FIGURE 2: Schematic sodium channel showing the locations of the $Na_V1.7$ mutations found in patients with idiopathic small nerve fiber neuropathy. Mutation R185H was found in 2 patients.

Faber, C. G., Hoeijmakers, J. G., Ahn, H. S., Cheng, X., Han, C., Choi, J. S., et al. (2011). Gain of function Na(V) 1.7 mutations in idiopathic small fiber neuropathy. Ann Neurol, 71(1), 26–39. doi:10.1002/ana.22485

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Peripheral Neuropathy Research Registry

- 457 patients: 278 CSPN (67% painful), and 179 DPN.
- Next generation sequencing and haplotype analysis.
- 36 SCN9A, 31 SCN10A and 15 SCN11A nonsynonymous missense variants, with 47.7% carrying low frequency missense variants in at least one gene.
- Previously reported gain of function mutations were rare (<3%) and were seen in those with and without pain.
- No differences between CSPN and DPN, or those with and without pain.
- Variant frequencies were no different from existing normative databases:
  - NHLBI Exome Sequencing Project Exome Variant Server, European American (EVS-EA) population
  - 1000 Genomes Project16 global or European (EUR) populations.

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Target-enrichment sequencing and copy number evaluation in inherited polyneuropathy

Wei Wang, MD

ABSTRACT

- 93 patients with possible inherited neuropathy.
- 197 gene panel.
- 18 mutations in 17 cases (18%).
- No mutations or VUS in 6 CIAP patients evaluated

Groups by onset age and family history		Positive genetic test rate	Total positive genetic test rate
Onset age ≤ 40 n=47	With family history n=27	9/27 = 33%	13/47=27%
	Without family history n=20	4/20 = 20%	
Onset age >40 n=46	With family history n=24	3/24 = 12.5%	4/46 = 9%
	Without family history n=22	1/22 = 5%	
With family history n=51	Onset Age ≤ 40 n=27	9/27 = 33%	12/51 =24%
	Onset age >40 n=24	3/24 = 12.5%	
Without family history n=42	Onset age ≤ 40 n=20	4/20 = 20%	5/42 = 12%
	Onset age >40 n=22	1/22 = 5%	

Wang, W., et al. (2016). "Target-enrichment sequencing and copy number evaluation in inherited polyneuropathy." Neurology **86**(19): 1762-1771.

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DOI: 10.1093/brain/awh192 *Brain* (2004), **127**, 1723–1730

A controlled investigation of the cause of chronic idiopathic axonal polyneuropathy

R. A. C. Hughes,[1] T. Umapathi,[1] I. A. Gray,[1] N. A. Gregson,[1] M. Noori,[1] A. S. Pannala,[1] A. Proteggente[2] and A. V. Swan[1]

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E-mail: richard.a.hughes@kcl.ac.uk

- 50 patients and controls from the same region
- Prior evaluation: UA, CBC, WESR, renal and liver tests, TFT's, random glucose, A1c and folate, SPEP, ANA and CXR.
- OGTT, vitamin C and E, ganglioside antibodies

Hughes, R. A., et al. (2004). "A controlled investigation of the cause of chronic idiopathic axonal polyneuropathy." Brain **127**(Pt 8): 1723-1730.

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Table 4 *Glucose tolerance in patients and control subjects*

	All patients	Patients with pain	Patients without pain	Controls	*P* (all patients versus controls)	*P* (patients with pain versus controls)
HbA1c (mmol/l)	5.28 (0.37)	5.26 (0.42)	5.30 (0.34)	5.31 (0.71)	0.91	0.83
Fasting glucose (mmol/l)	5.23 (0.76)	5.24 (0.97)	5.22 (0.54)	5.18 (0.80)	0.85	0.98
2-h glucose (mmol/l)	6.59 (2.14)	7.28 (2.15)	5.97 (1.98)	5.85 (2.62)	0.14	0.016
Normal glucose tolerance (*n*)	33	11	22	42	0.88*	0.74*
IFG (*n*)	2	2	0	1		
IGT (*n*)	12	8	4	5		
Diabetes mellitus (*n*)	2	1	1	1		
IGT, IFG or diabetes mellitus	16/49	11/22	5/27	7/49	0.45	0.27

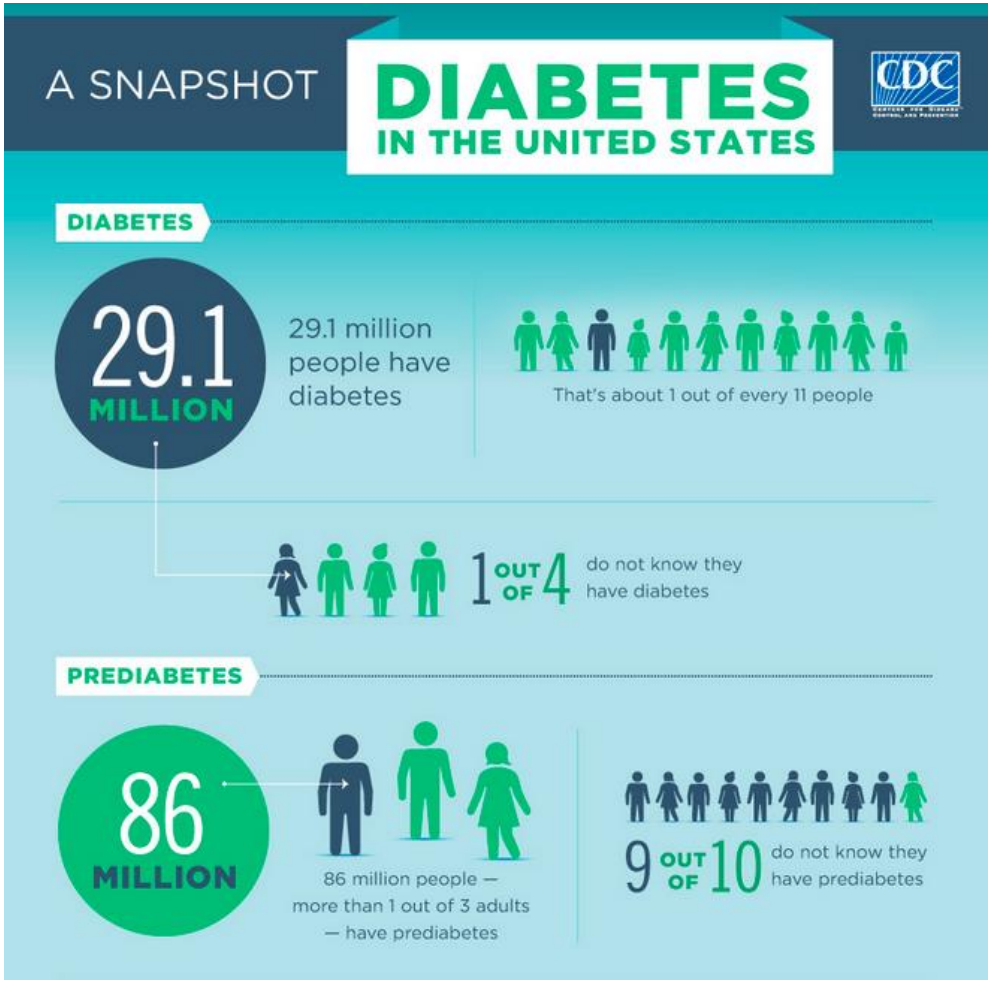
Figures are numbers or means (standard deviations) and *P* values have been adjusted for age and sex.
*This test compares the distribution of the subcategories of glucose tolerance between the patients and the controls.

Table 5 *Insulin, insulin resistance and lipid concentrations in patients and control subjects*

	Patients	Patients with pain	Patients without pain	Controls	*P* (all versus controls)	*P* (painful versus controls)
Fasting insulin (mmol/l)	75.85 (44.37)	92.21 (37.10)	61.73 (46.03)	47.28 (37.93)	0.01	<0.0001
Number with increased fasting insulin >75 mmol/l	17/41	12/19	5/22	10/43	0.60	0.32
Insulin resistance (HOMA formula)	2.61 (1.63)	3.18 (1.58)	2.12 (1.53)	1.86 (2.28)	0.18	0.04
Number with insulin resistance	15/41	9/19	6/22	7/43	0.58	0.39
Serum cholesterol	5.64 (1.15)	5.911.33)	5.43 (0.95)	5.91 (1.07)	0.74	0.48
Serum triglycerides	1.90 (1.41)	2.37 (1.72)	1.53 (1.01)	1.25 (0.79)	0.02	0.003

Figures are numbers or means (standard deviations). *P* values have been adjusted for age, sex and BMI.

Hughes, R. A., et al. (2004). "A controlled investigation of the cause of chronic idiopathic axonal polyneuropathy." Brain **127**(Pt 8): 1723-1730.


A SNAPSHOT
DIABETES
IN THE UNITED STATES
CDC
DIABETES
29.1
MILLION
29.1 million people have diabetes
That's about 1 out of every 11 people
1 OUT OF 4 do not know they have diabetes
PREDIABETES
86
MILLION
86 million people — more than 1 out of 3 adults — have prediabetes
9 OUT OF 10 do not know they have prediabetes

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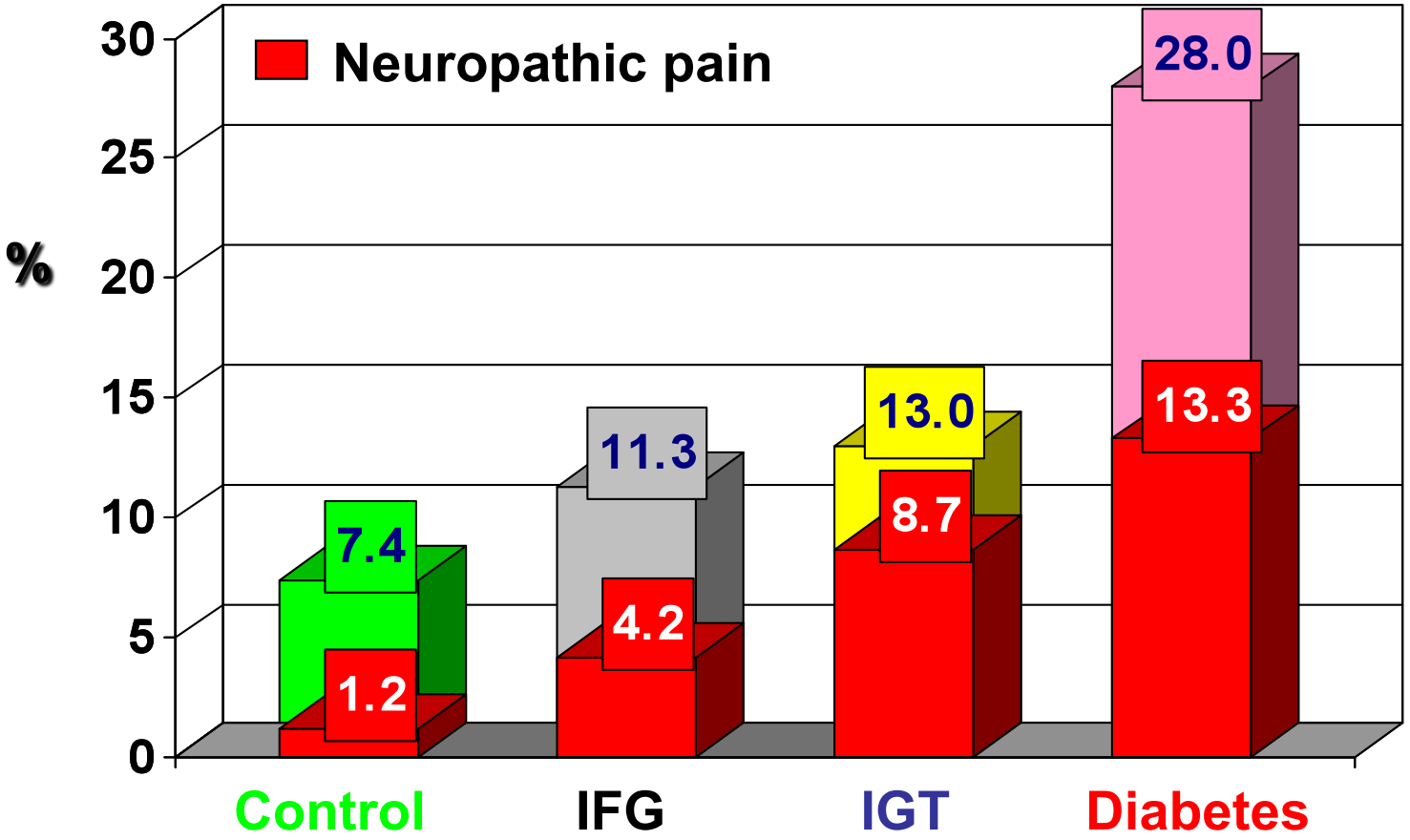
Neuropathy (esp. painful) is more common in prediabetic patients than controls



IFG = impaired fasting glucose; IGT = impaired glucose tolerance

Ziegler et al . Papanas, Vinik and Ziegler Nature reviews. Endocrinology 2011;7(11):682-90.

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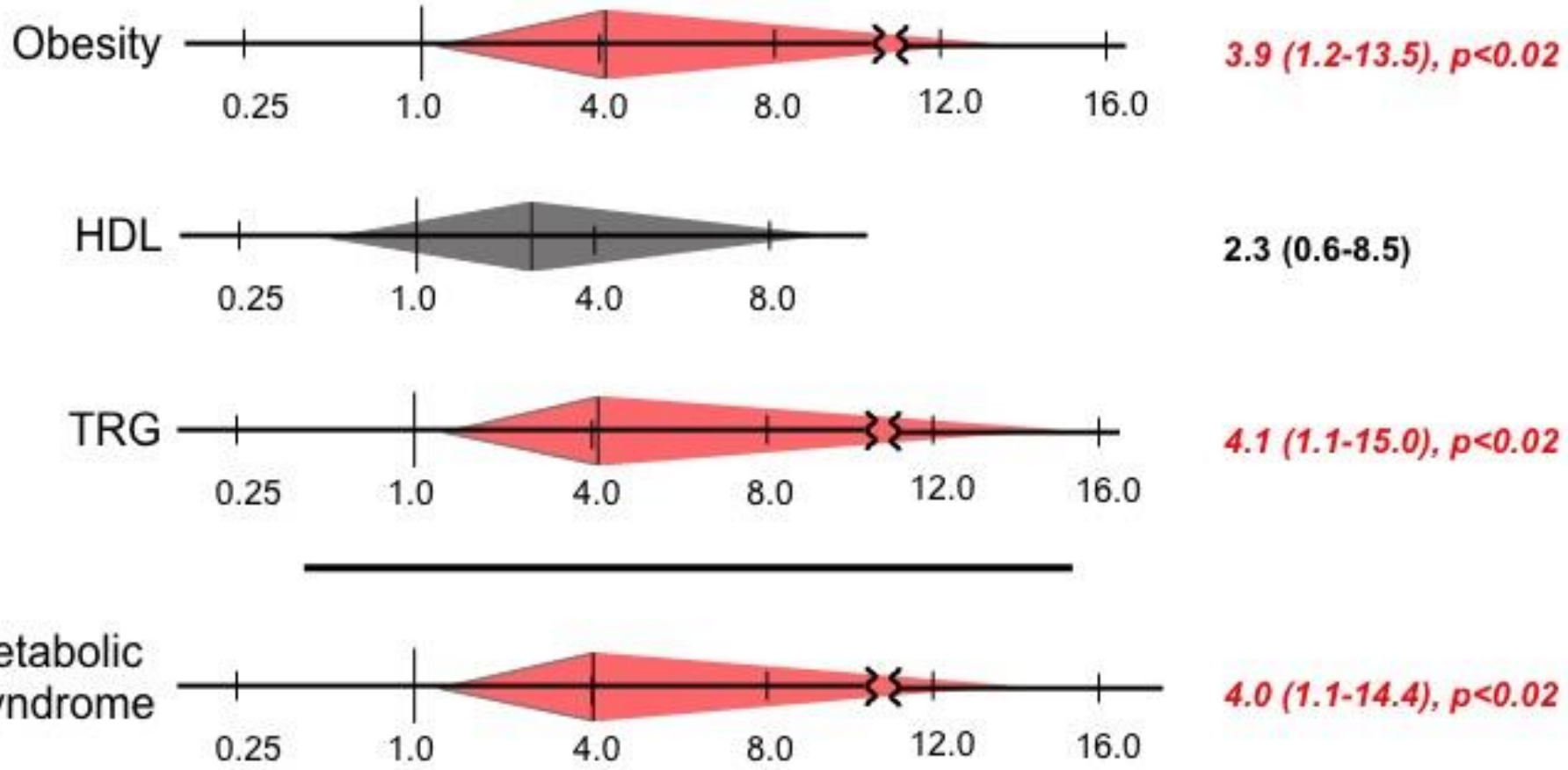
Obesity, Hypertriglyceridemia and Metabolic Syndrome Increase Neuropathy Risk



Smith, A. G. and J. R. Singleton (2013). "Obesity and hyperlipidemia are risk factors for early diabetic neuropathy." Journal of Diabetes and Its Complications.

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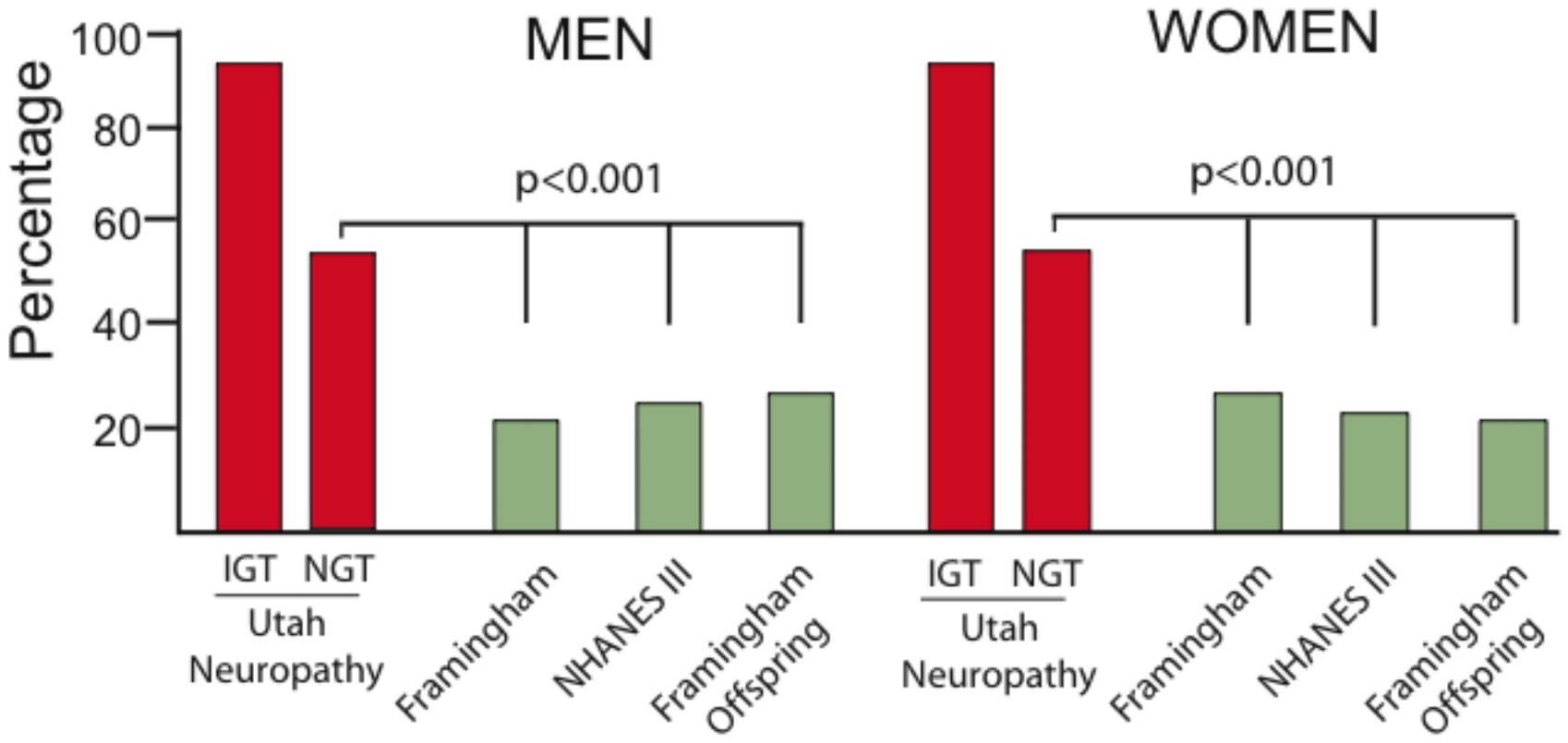
Metabolic syndrome is more prevalent among NGT and IGT neuropathy subjects.



Smith AG, Rose K, Singleton JR. J Neuro Sci. 2008

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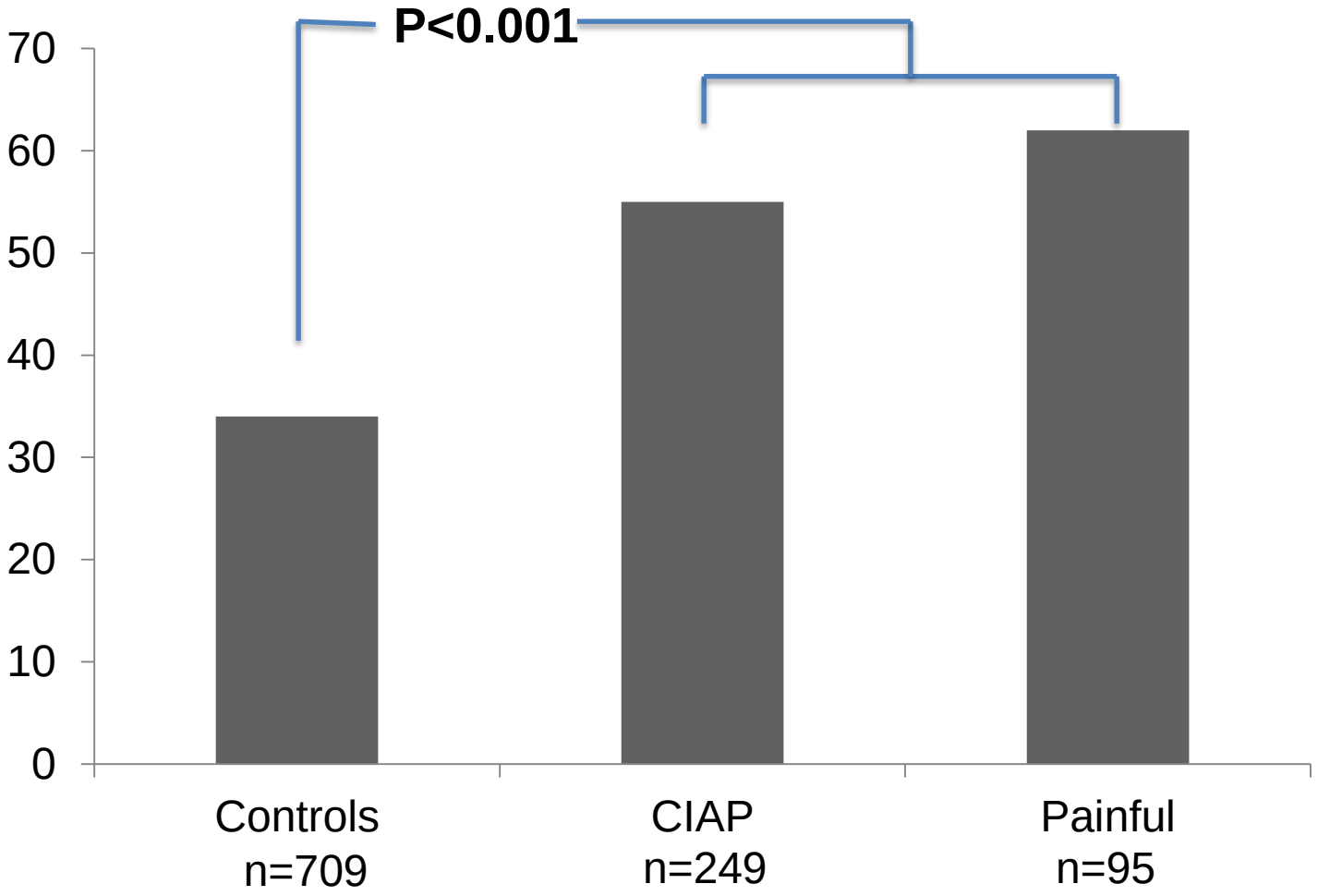
Metabolic Syndrome is Prevalent in CSPN



Visser, N. A., Vrancken, A. F. J. E., van der Schouw, Y. T., van den Berg, L. H., & Notermans, N. C. (2013). Chronic idiopathic axonal polyneuropathy is associated with the metabolic syndrome. Diabetes Care, 36(4), 817–822. doi:10.2337/dc12-0469

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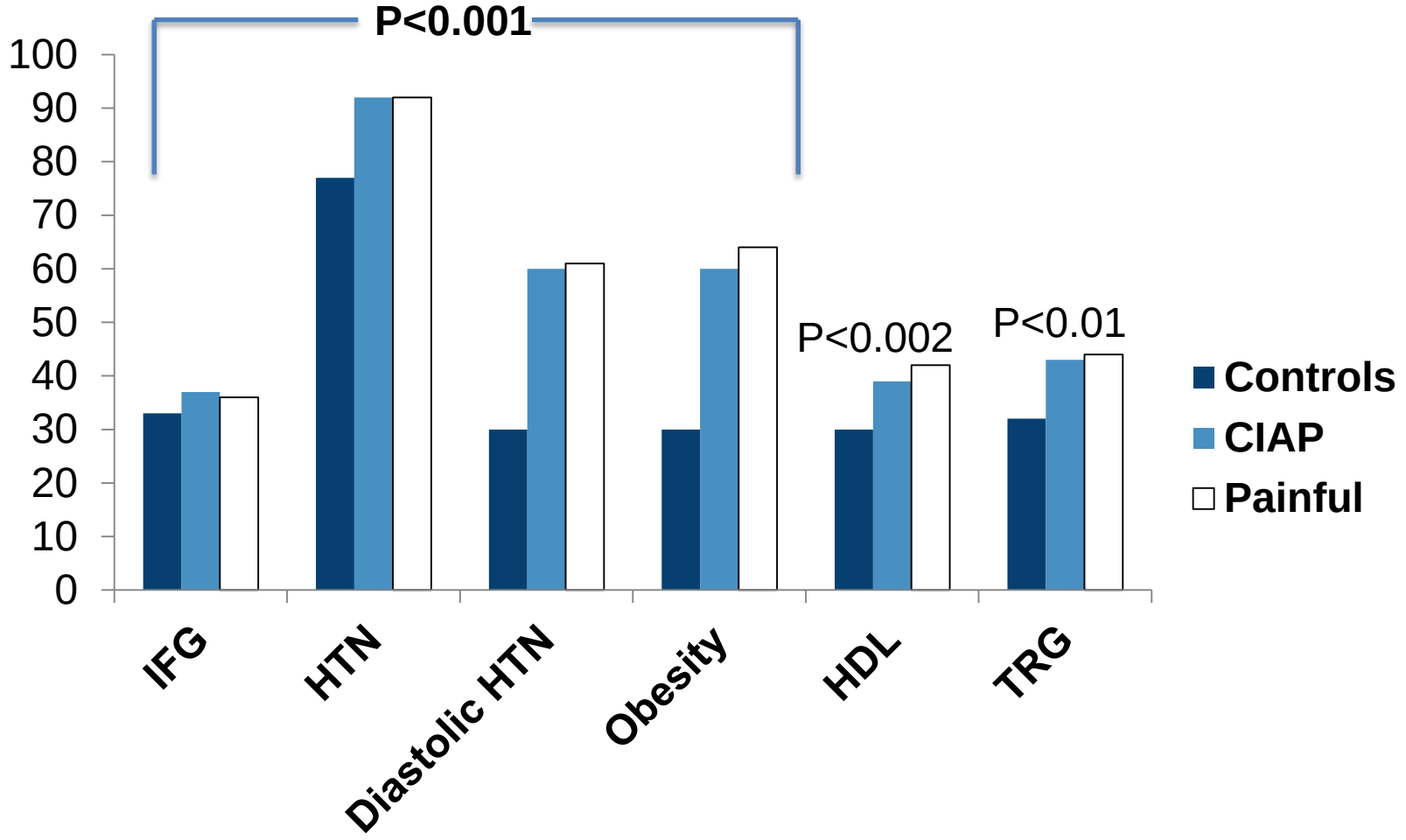
MS Features in CSPN



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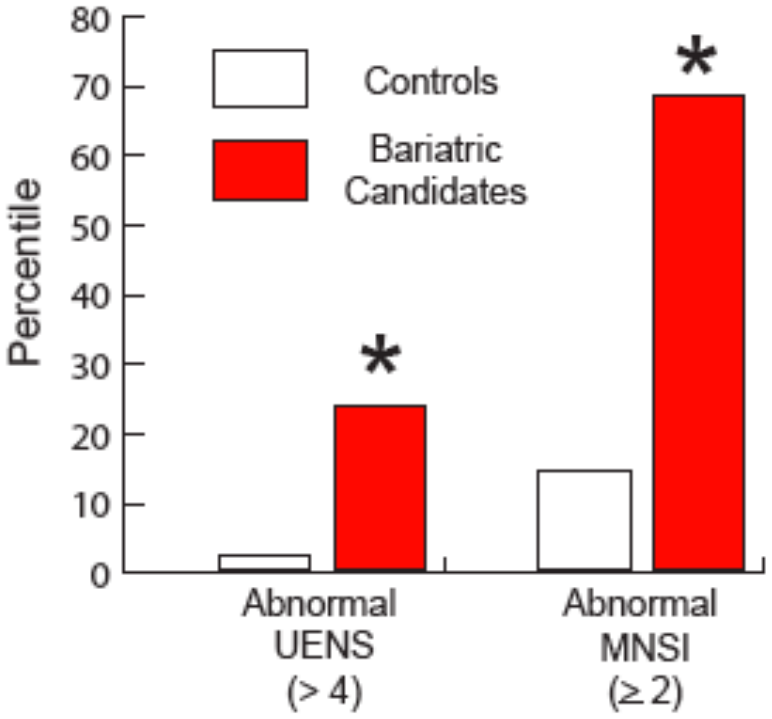
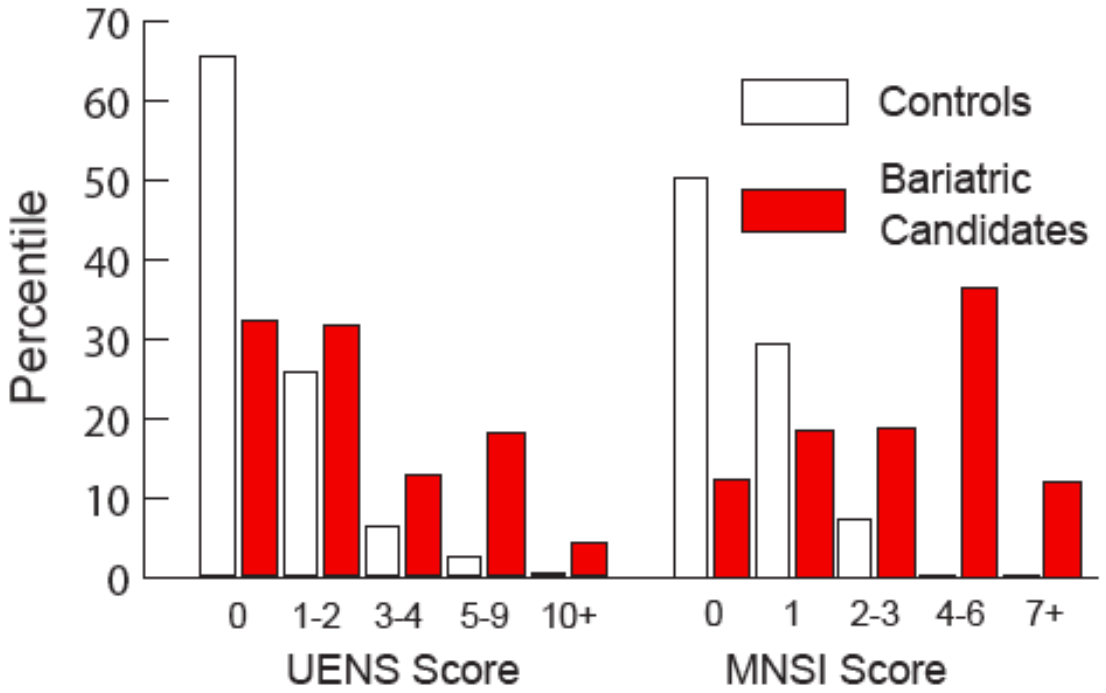
Obese individuals are at risk for neuropathy





American Diabetes Association.
Cure • Care • Commitment

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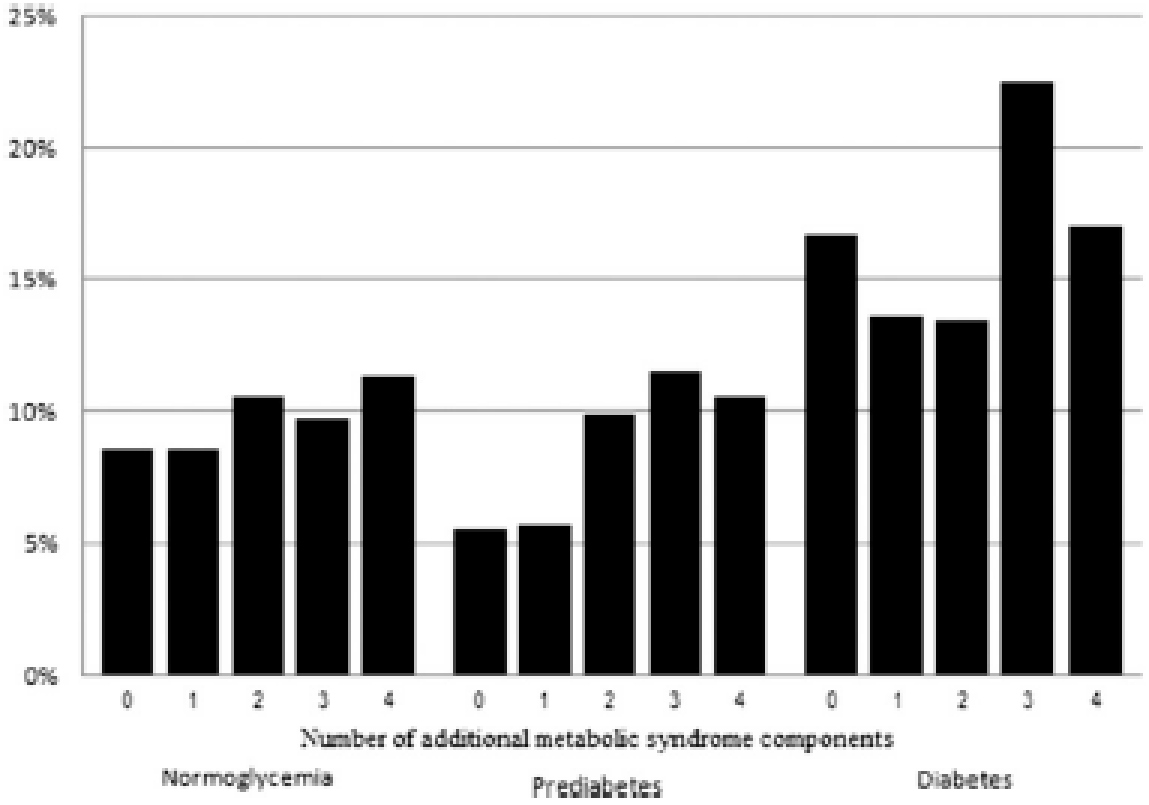
Health ABC Study



Callaghan, B. C., et al. (2016). "Metabolic Syndrome Components Are Associated With Symptomatic Polyneuropathy Independent of Glycemic Status." Diabetes Care **39**(5): 801-807.

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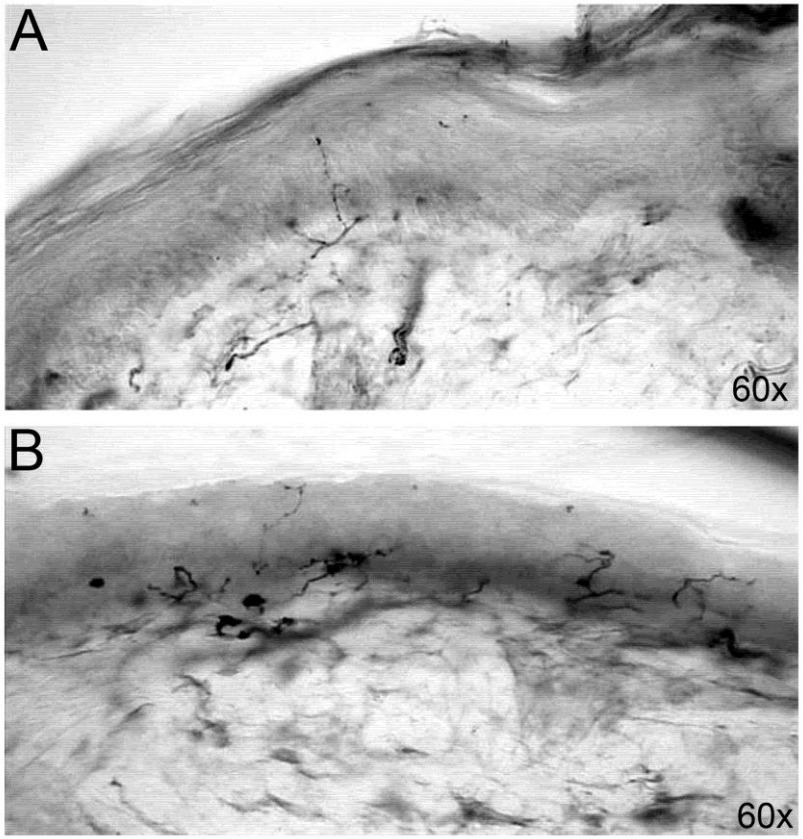
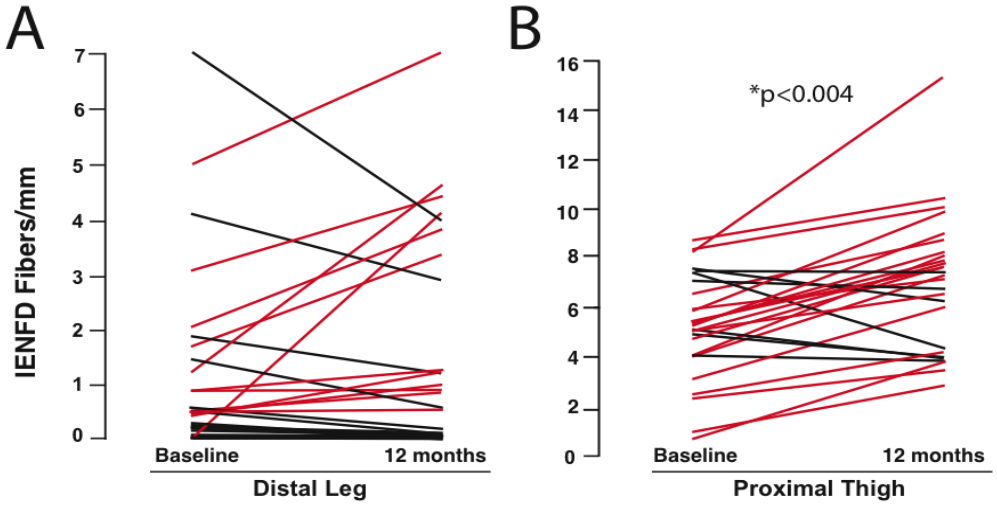
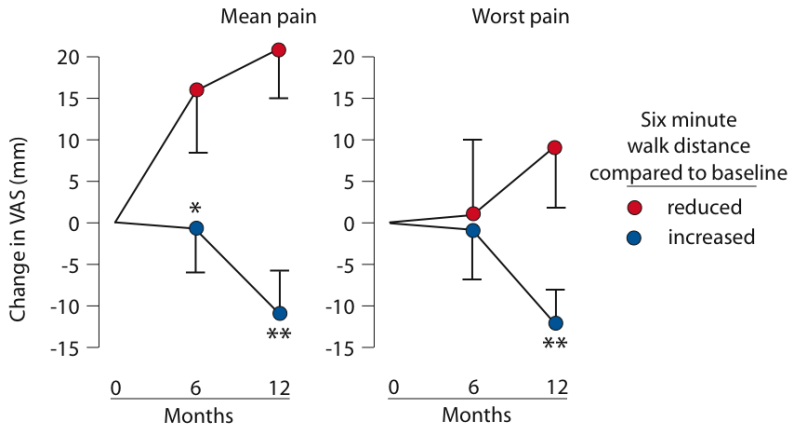
Diet and Exercise are associated with reinnervation and improved pain in IGTN







Smith, Singleton, Diabetes Care, 2006

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The Utah Diabetic Neuropathy Study (UDNS)

Exercise results in cutaneous reinnervation

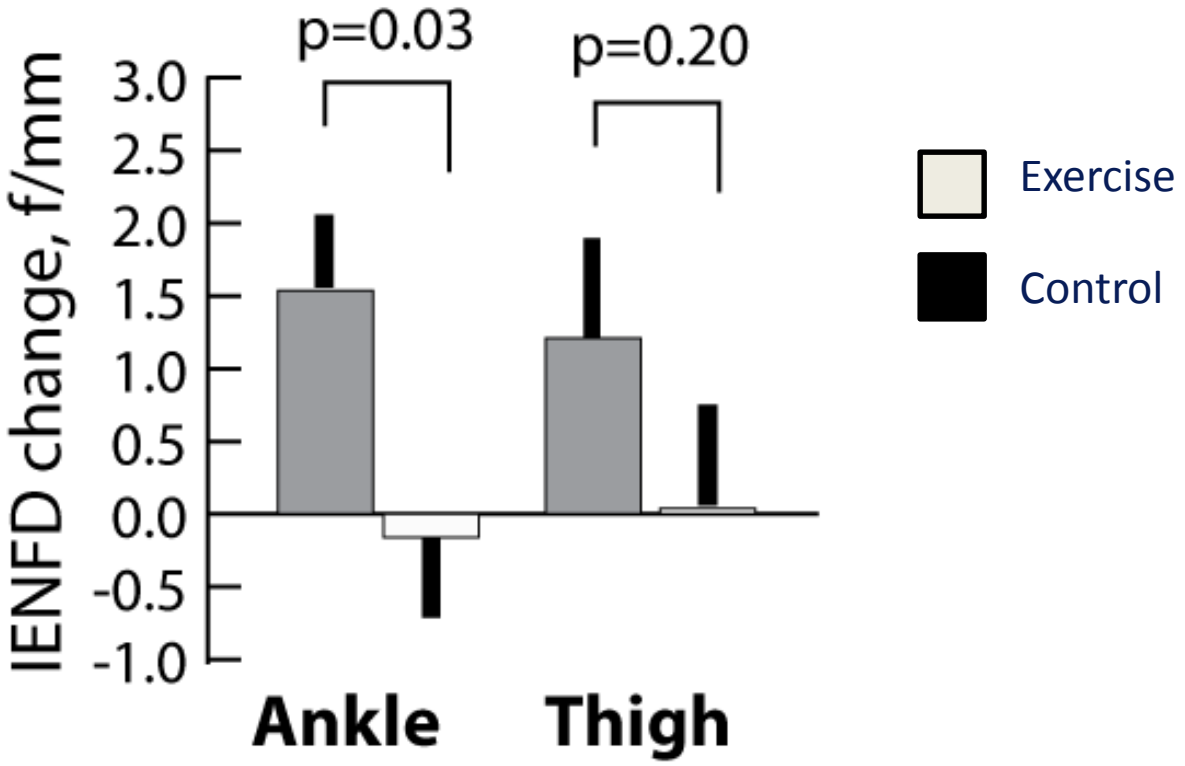

Figure 2. Supervised exercise over 12 months improves intraepidermal nerve fiber density (IENFD) in non-neuropathic patients with diabetes. Bars represent change in IENFD 0-12 months +/- SEM for exercise (filled bar) or control (unfilled) participants. Participants receiving standard-of-care counseling showed stasis or slow decline in fiber density.

Singleton, J. R., Marcus, R. L., Jackson, J. E., K Lessard, M., Graham, T. E., & Smith, A. G. (2014). Exercise increases cutaneous nerve density in diabetic patients without neuropathy. Annals of Clinical and Translational Neurology, 1(10), 844–849. doi:10.1002/acn3.125

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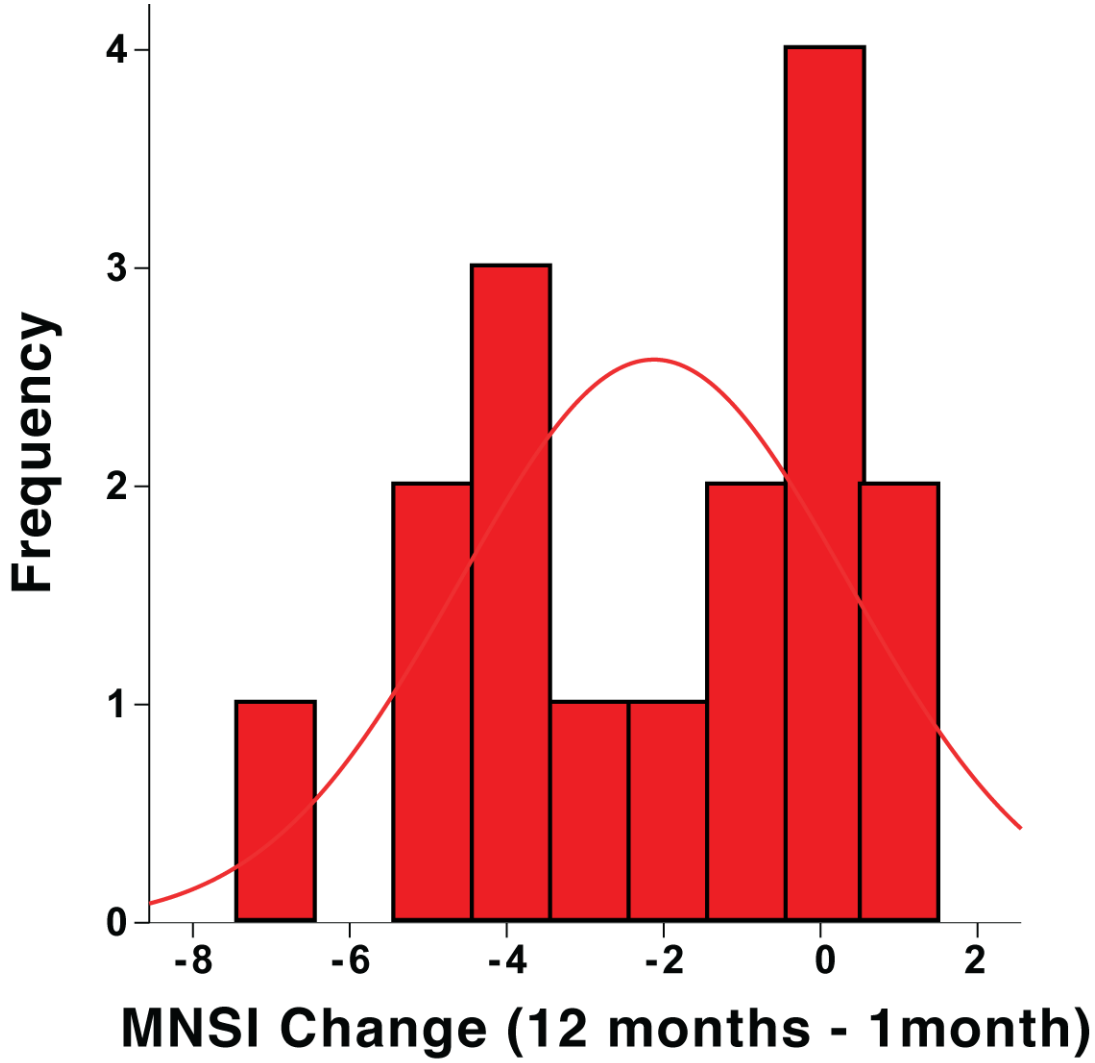

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Exercise improves nerve regenerative capacity

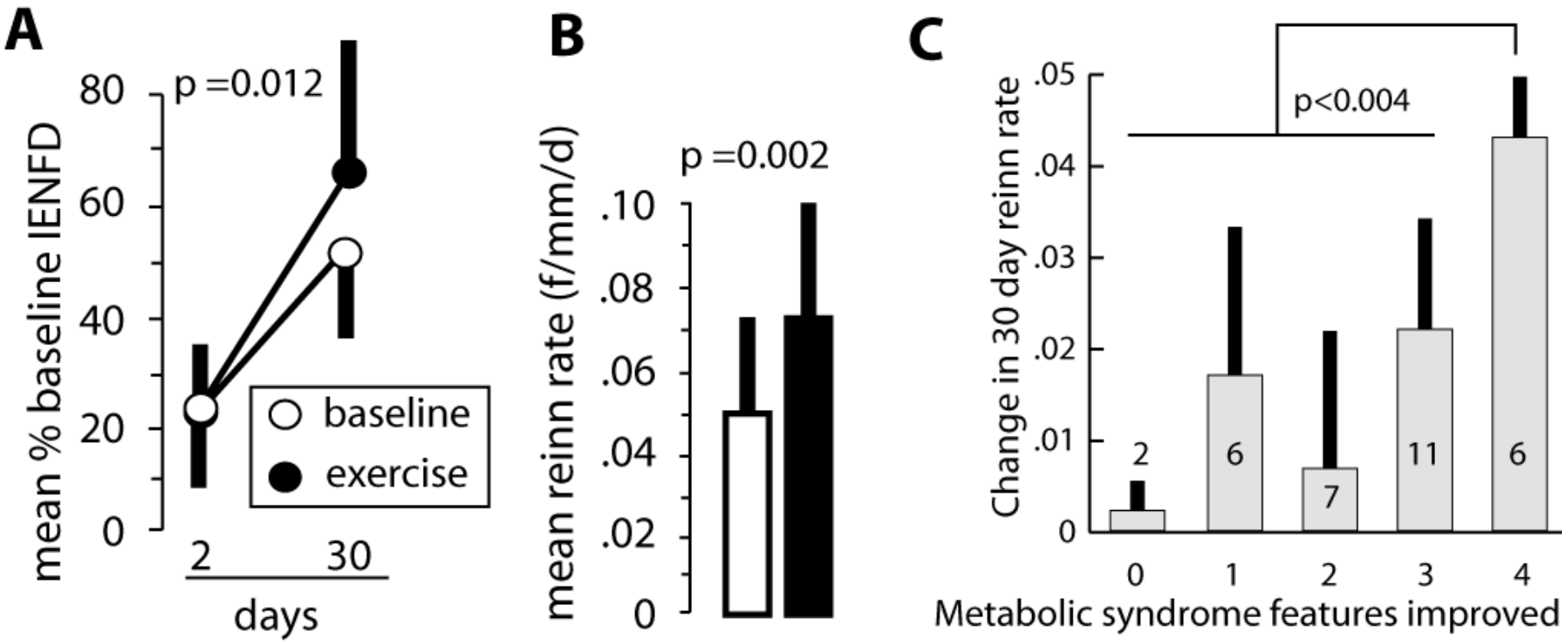

Figure 4. Exercise intervention is associated with significantly greater 30 day cutaneous reinnervation, expressed either as percentage of baseline IENFD (A), or as reinnervation rate (fibers/mm/day) (B). Dividing participants by metabolic response (C), those who improved the greatest number of metabolic syndrome features showed significantly greater reinnervation rate than those achieving fewer.

Singleton, J. R., Marcus, R. L., Lessard, M. K., Jackson, J. E., & Smith, A. G. (2014). Supervised exercise improves cutaneous reinnervation capacity in metabolic syndrome patients. Ann Neurol, n/a–n/a. doi:10.1002/ana.24310

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TABLE 8-1 Basic Laboratory Investigation of Distal Symmetric Polyneuropathy

- **High-yield Initial Investigations**
  - Complete blood count
  - Complete metabolic panel
  - Vitamin B_{12} with/without methylmalonic acid
  - Serum glucose (fasting blood glucose, 2-hour oral glucose tolerance, hemoglobin A_{1c})
  - Serum protein immunofixation
- **Low-yield Initial Investigation**
  - Thyroid function test
  - Erythrocyte sedimentation rate or C-reactive protein
  - Antinuclear antibody
  - Folate
  - Urinalysis

Li, Y. (2017). "Axonal Sensorimotor Polyneuropathies." Continuum (Minneap Minn) **23**(5, Peripheral Nerve and Motor Neuron Disorders): 1378-1393.

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of laboratory and genetic testing (an evidence-based review)

Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation

Level C Evidence that the following tests have the highest yield

- Vitamin B 12 and metabolites
- SPEP
- Testing for IGT

Level A evidence for utility of genetic testing for hereditary neuropathy, but insufficient evidence to determine usefulness in cryptogenic neuropathy

England, J. D., et al. (2009). "Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation." Neurology **72**(2): 185-192.

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Idiopathic Neuropathy

What to exclude:

- A diagnosis of CSPN is predicated on a careful history and examination.
- All patients with suspected CSPN should have the following tests in a clinical setting:
  - B12 and metabolites
  - SPEP/IFE
  - Metabolic evaluation for diabetes, prediabetes, dyslipidemia.
- Clinical trial enrollment criteria may require more explicit evaluation for other diagnoses.
- Genetic and immunologic testing in suspected CSPN is of low diagnostic yield.

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”Since polyneuropathy probably is a multifactorial disease, it is not entirely appropriate to attribute the development of polyneuropathy to only one factor. These factors should be considered as *component causes*, and not as one sufficient cause.”

Hanewinckel, R., et al. (2016). "The epidemiology and risk factors of chronic polyneuropathy." Eur J Epidemiol **31**(1): 5-20.

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TopCSPN

Neuro NEXT
The NEXT Generation of Neurologic Treatments
NIH-Network for Excellence in Neuroscience Clinical Trials

Topiramate as a Disease Modifying Therapy for Cryptogenic Sensory Peripheral Neuropathy: *The "TopCSPN Study" (NN108)*

Inclusion

- Metabolic syndrome based on ATP III
- BMI > 25 kg/m^2

Exclusion:

- Any identified alternative cause for peripheral neuropathy (including but not limited to rheumatological disorders, Hepatitis B or C, Breast Cancer treated with neurotoxic chemotherapy within the past 15 years). All potential subjects will have screening neuropathy labs including assessment for diabetes (Hemoglobin A1c, oral glucose tolerance test), vitamin B12 level, and immunofixation[47].
- Family history of a non-diabetic neuropathy in a first-degree relative.
- History of alcohol or drug abuse.

Biobank for future exploration of mechanisms or predictors of treatment response.

National Institute of Neurological Disorders and Stroke
HEALTH University of Utah
VCU Health
The University of Iowa
MGH Massachusetts General Hospital