

Diagnostic criteria for peripheral neuropathy in metabolic syndrome

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Neuropathy in prediabetes/metabolic syndrome overall concepts:

- Metabolic syndrome represents a complex continuum of disorder and risk.
- Metabolic syndrome features contribute to the pathogenesis of neuropathy, and confer variable degrees of risk for neuropathy.
- Phenotypic diagnostic criteria for neuropathy in metabolic syndrome are the same as for DPN, but diagnostic certainty is comparatively reduced.

Why establish diagnostic criteria for prediabetic neuropathy?

Remarkably large risk pool; 35% of US population.
Recognition of disease early in its course allows effective treatment.

To codify prediabetic neuropathy as disease entity:

- allows diagnostic consideration in general practice.
- Is foundational to examining the consequences of the disorder
- encourages further study of the pathogenic contributions of its component parts.

Helps to define neuropathy in the spectrum of metabolic syndrome disorders

Springboard for consideration of complex genetic risk factors

Clinical phenotype of hyperglycemic neuropathy

Distal polyneuropathy indistinguishable from that seen in diabetes

Sensory first, predominant

Distal, symmetrical

Often painful

Autonomic involvement

? Small fiber predominance

Essentially any feature of diabetic neuropathy can occur in the prediabetic setting



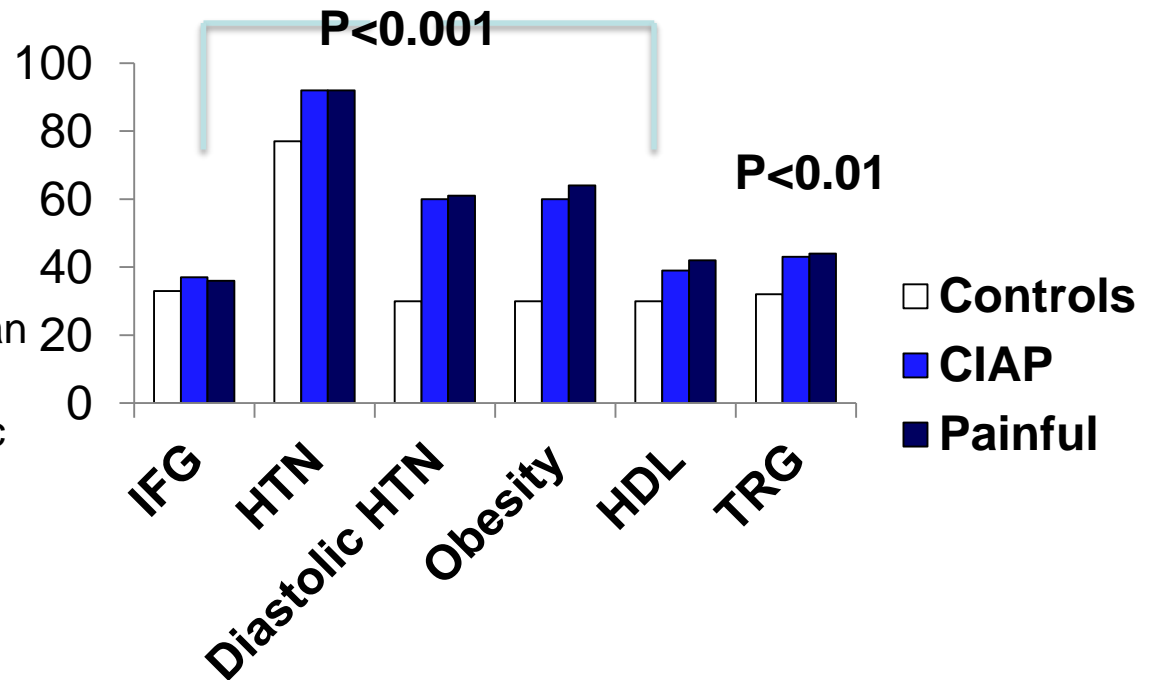
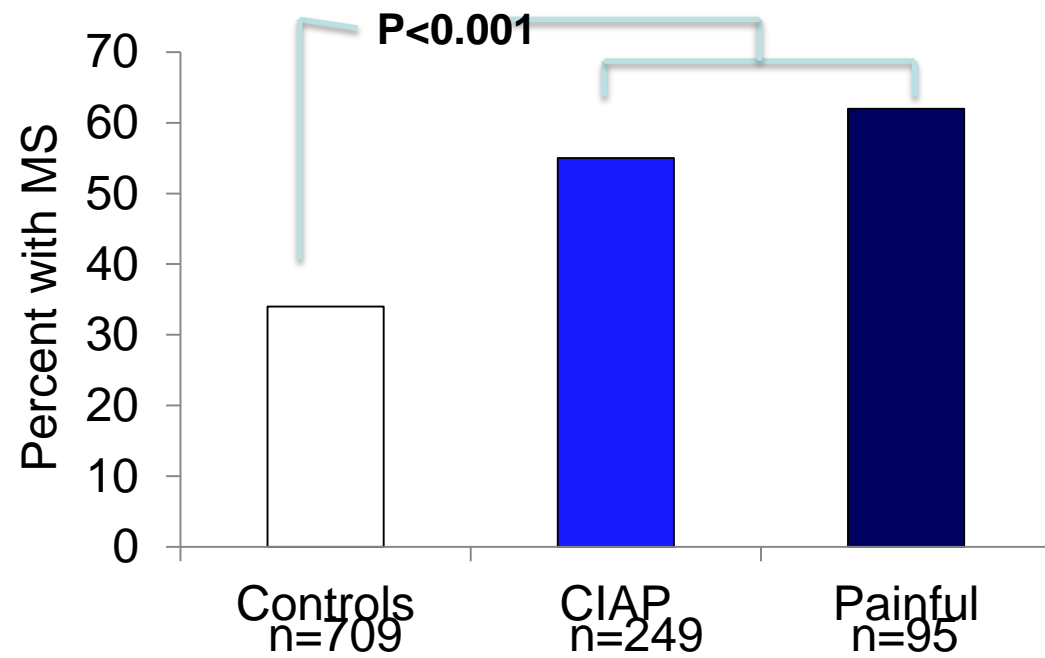
Nomenclature of the disorder

- “Prediabetic Neuropathy”
 - Ties to diabetes
 - Does not adequately recognize contribution of other features
- Impaired glucose tolerance neuropathy
- Cryptogenic Sensory Polyneuropathy (CSPN)
- Polyneuropathy in Metabolic Syndrome (PiMS)

Evidence for PiMS

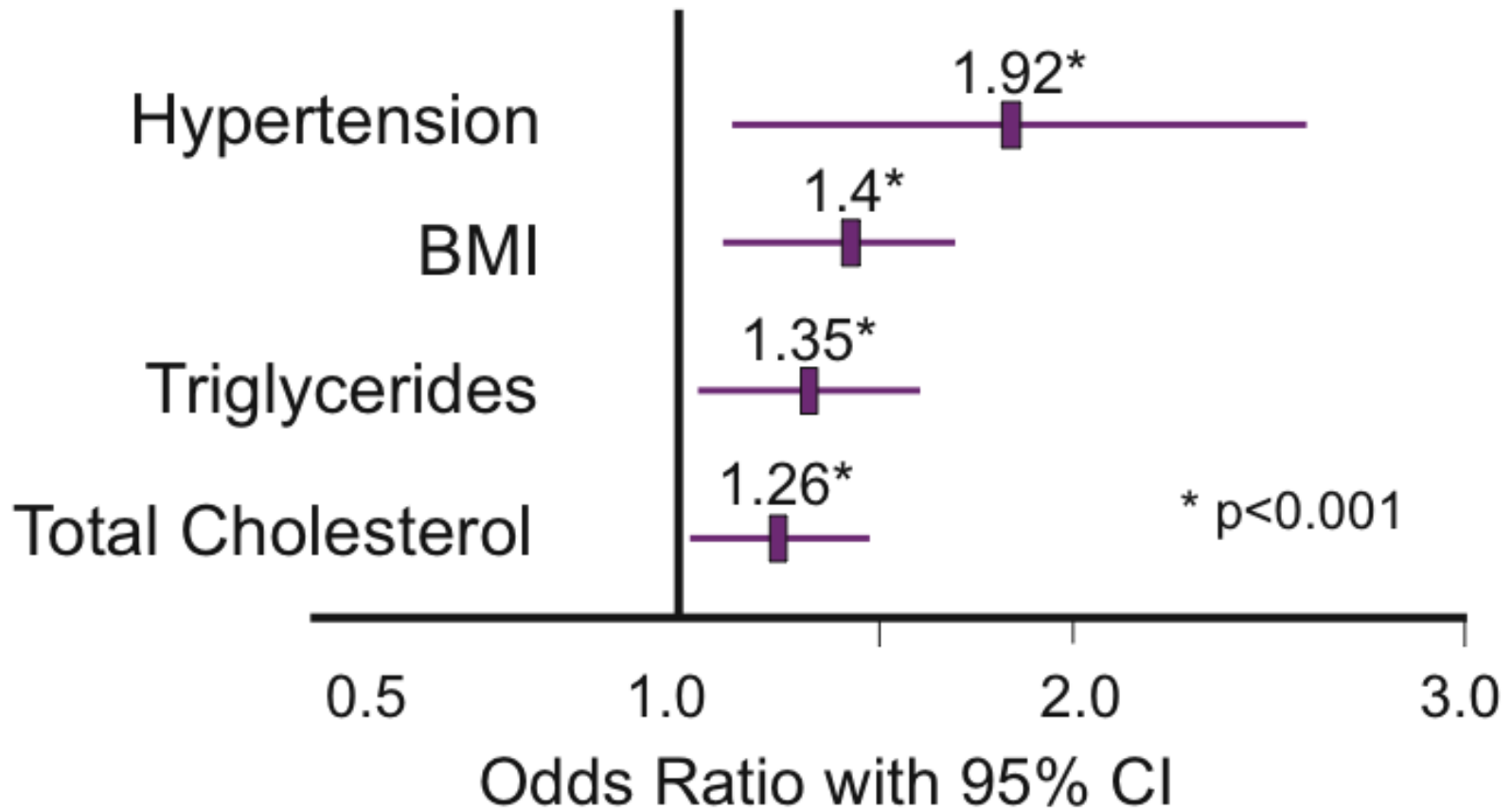
- Epidemiology
 - Effect of MS features in diabetic neuropathy
 - Risk of MS features in otherwise idiopathic neuropathy
 - Risk of neuropathy in prediabetic MS
- Animal models recapitulate PiMS
- Treatment studies in prediabetic neuropathy
- Biological research on pathogenic effects of individual MS components, particularly obesity and dyslipidemia

Metabolic syndrome is prevalent in otherwise idiopathic neuropathy



From- Visser NA, Vrancken AF, van der Schouw YT, van den Berg LH, Notermans NC. Chronic Idiopathic Axonal Polyneuropathy Is Associated With the Metabolic Syndrome. *Diabetes Care*. 2012.

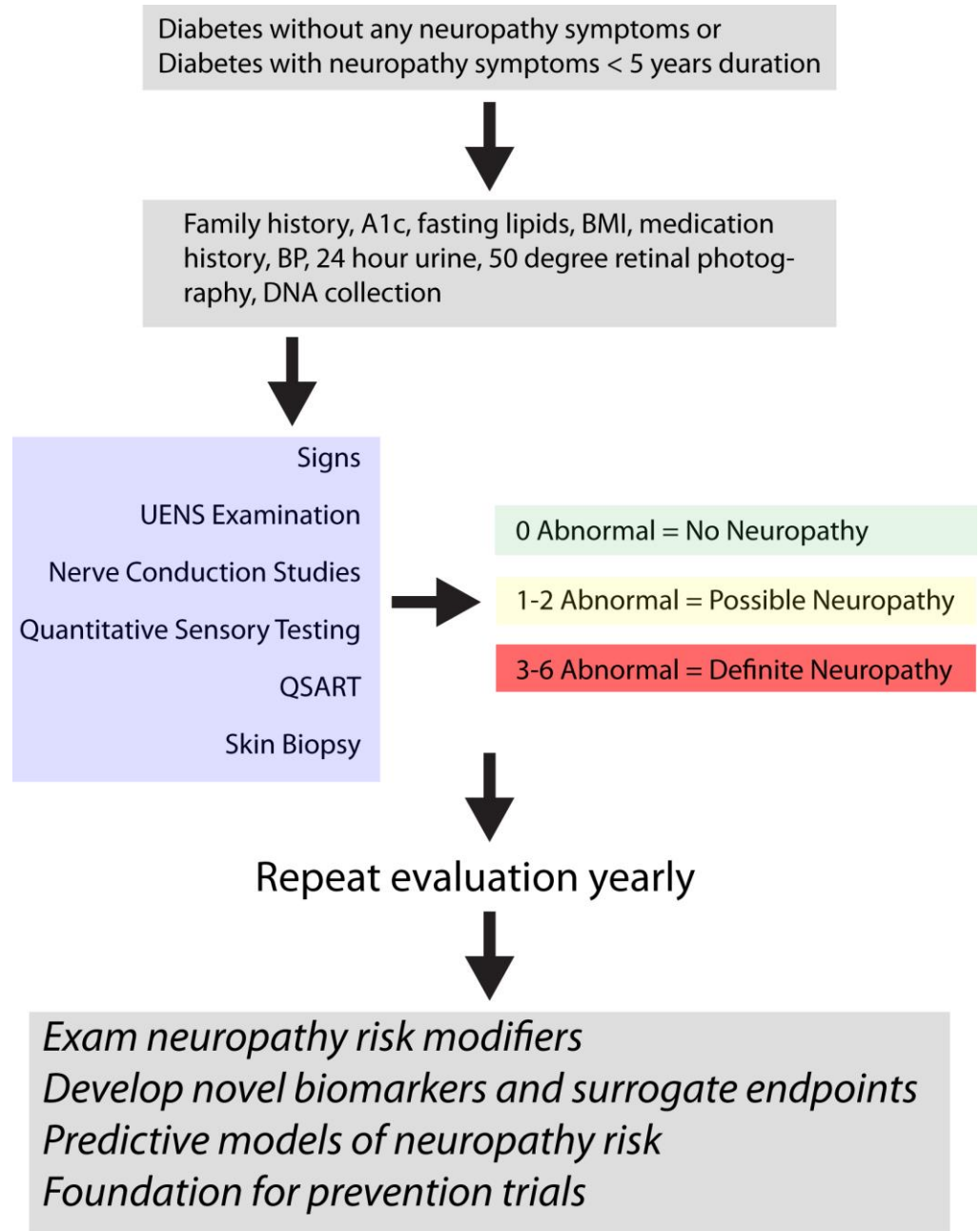
Neuropathy associated with metabolic syndrome



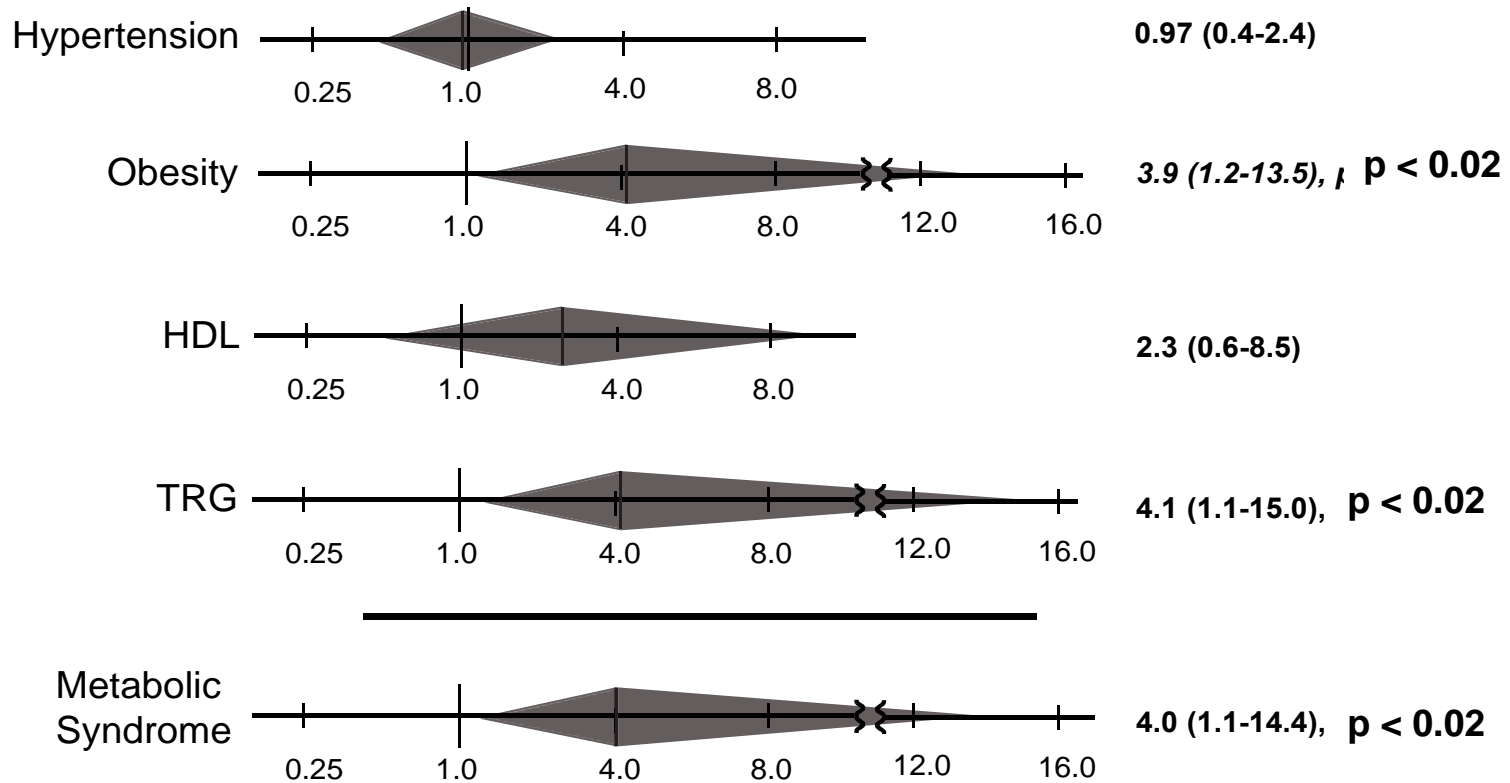
Solomon Tesfaye, M.D., Nish Chaturvedi, M.D., Simon E.M. Eaton, D.M., John D. Ward, M.D., Christos Manes, M.D., Constantin Ionescu-Tirgoviste, M.D., Daniel R. Witte, Ph.D., and John H. Fuller, M.A. for the EURODIAB Prospective Complications Study Group. *N Engl J Med* 2005

Cutaneous Measures of Neuropathy in Diabetes

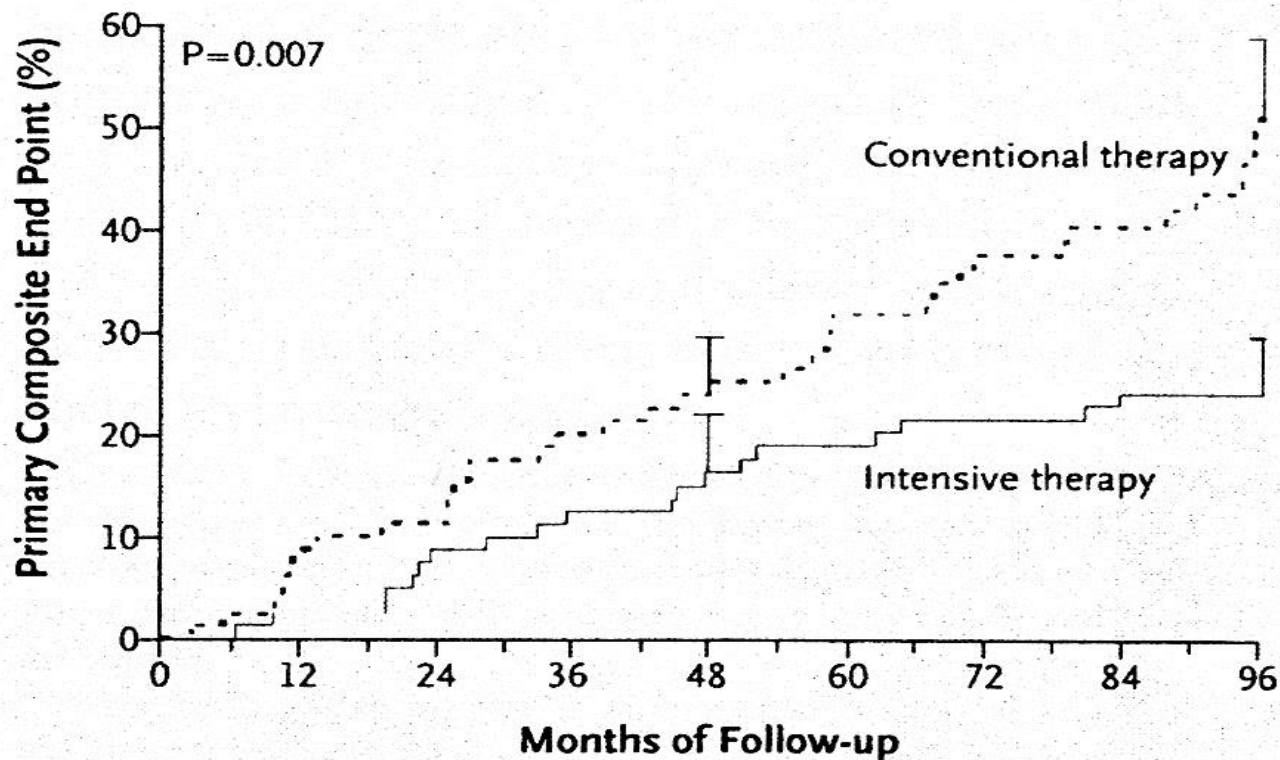
- 221 Subjects (48% female)
- 57 +/- 9 years old
- Diabetes duration 87 +/- 79 months.
- Hemoglobin A1c 6.8 +/- 1.5
- Body mass index 33.6 +/- 7.8.
- 17% no, 45% possible, 38% definite neuropathy



Obesity, hypertriglyceridemia and metabolic syndrome associated with increased neuropathy prevalence



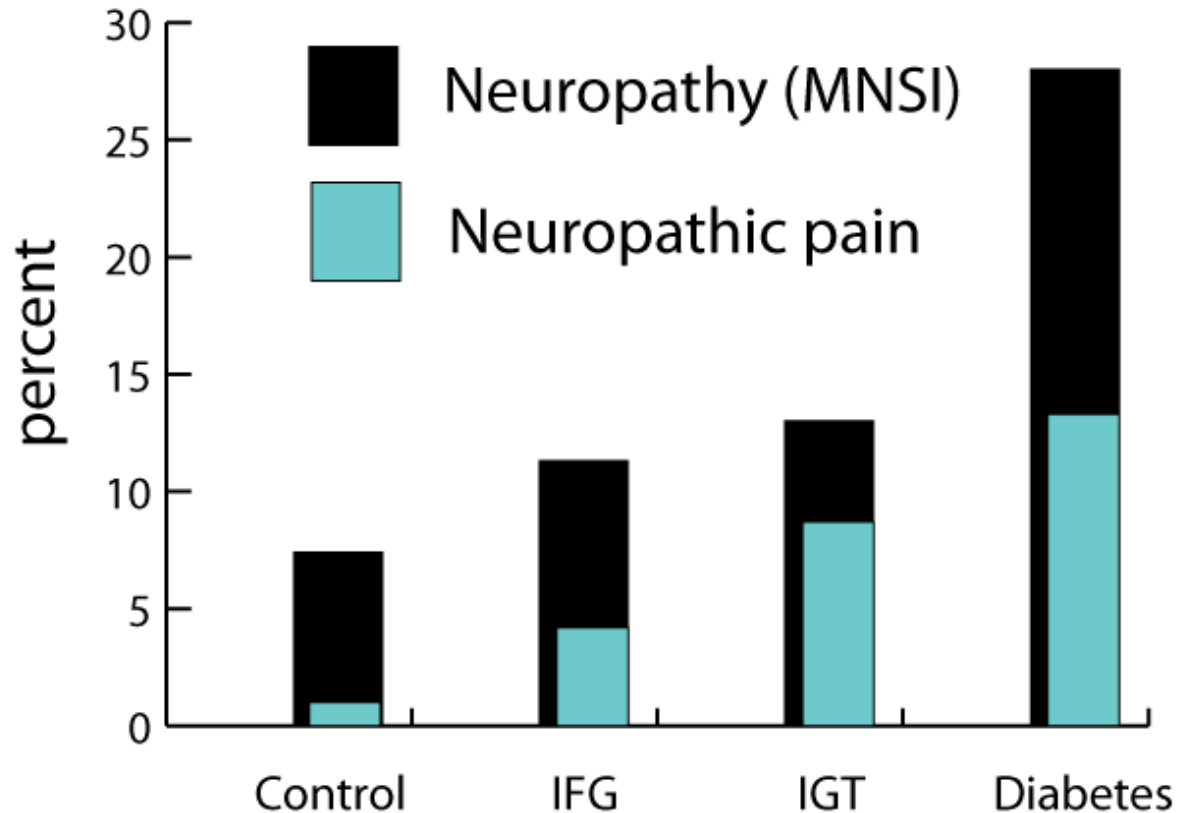
Targeted metabolic syndrome therapy reduces diabetic complications in Steno 2



No. at Risk

Conventional therapy	80	72	70	63	59	50	44	41	13
Intensive therapy	80	78	74	71	66	63	61	59	19

Neuropathy and neuropathic pain are more common in prediabetic patients than controls



Ziegler et al. *Diabetes Care*, 2008

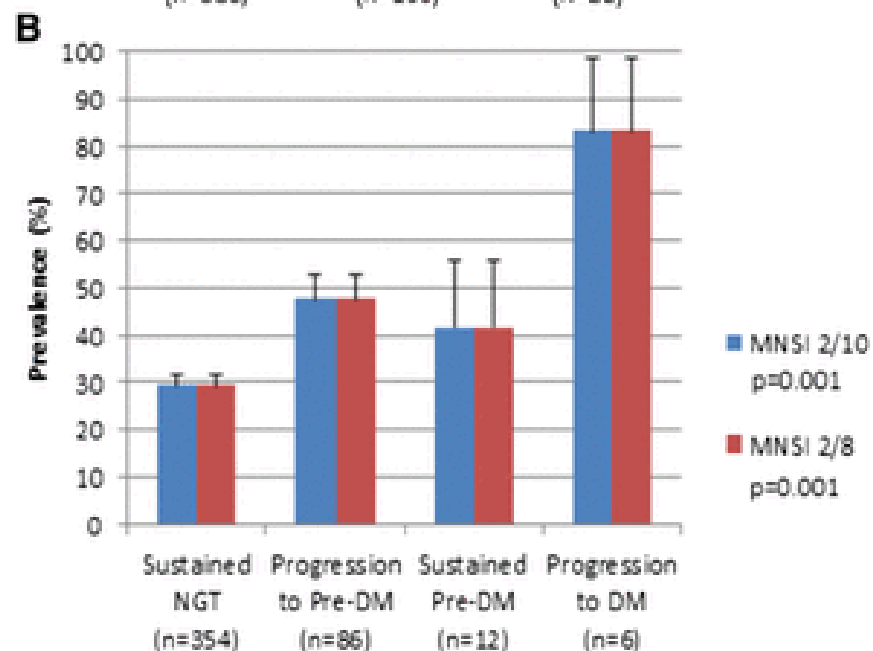
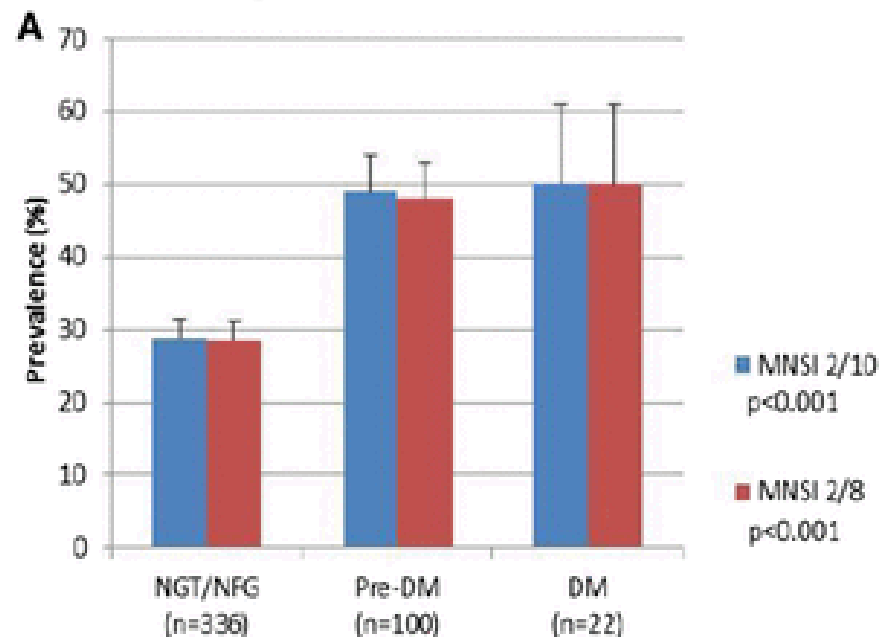
Ziegler et al. *Pain Med*, 2009

Neuropathy is associated with prediabetes

497 members of the
Prospective Pancreatic
Metabolism and Islet
Cell Evaluation
(PROMISE) cohort who
had 3 year follow-up.

Neuropathy symptoms
based on MNSI of 2 (or
3) of 10 questions.

Neuroesthesiometer use to
measure vibration
sensation threshold.



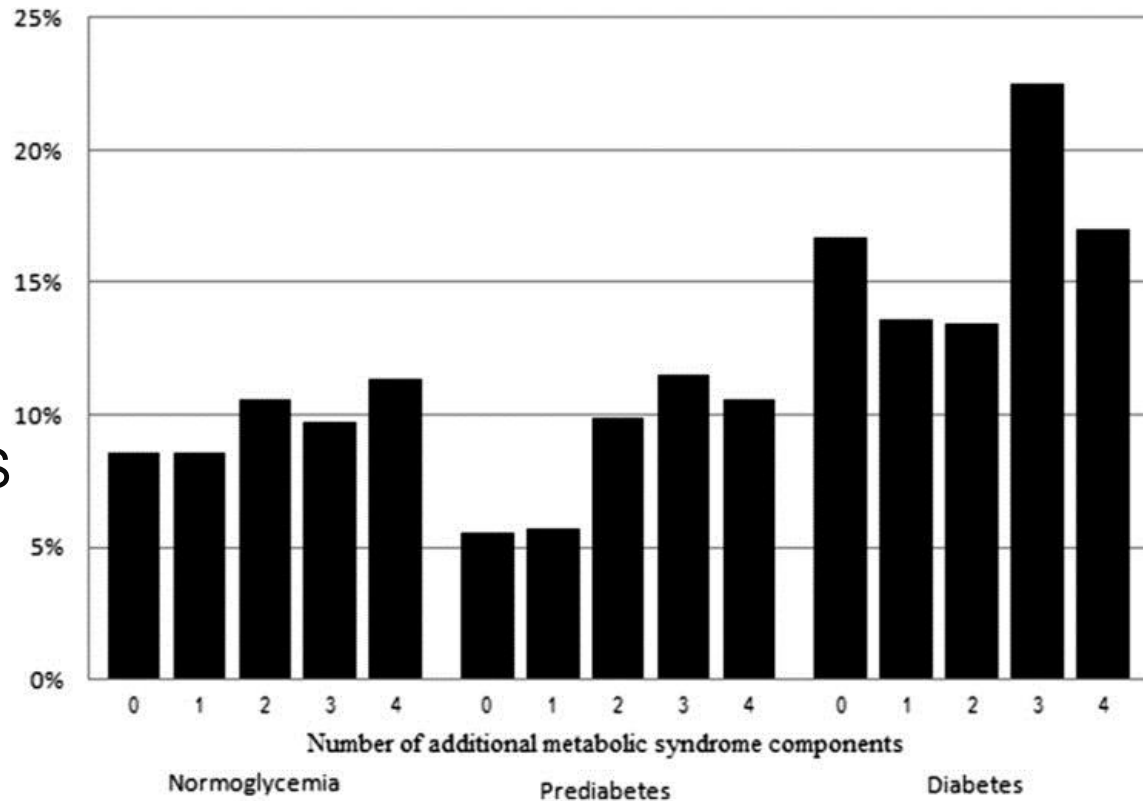
Neuropathy is associated with metabolic syndrome features

2382 Health ABC study participants

“Neuropathy” if + to 1 of 2 questions and had abnormality of PCV or 10g monofilament

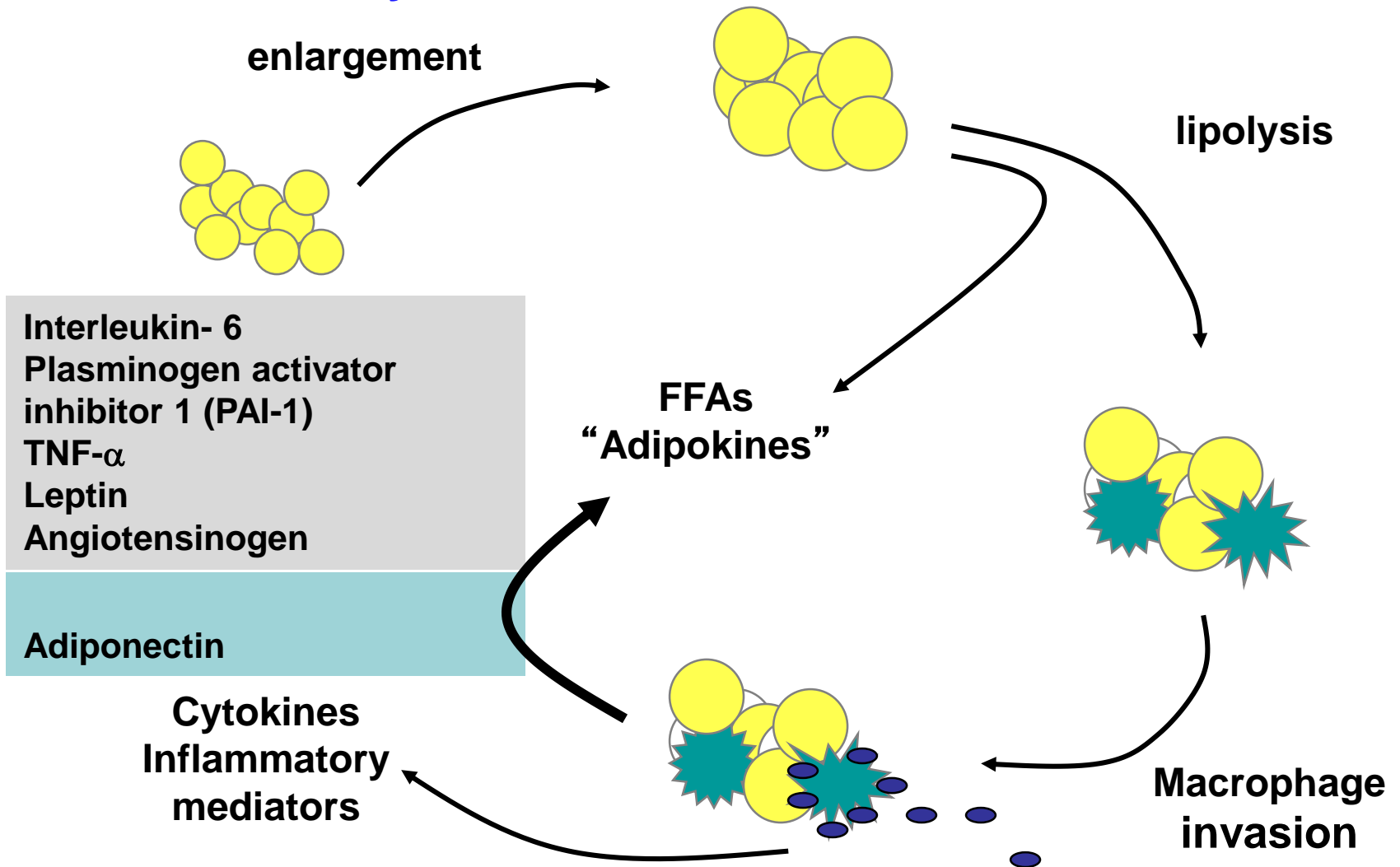
1.1% increase in neuropathy for each MS component

Waist circumference and HDL associated with DSP secondary measures

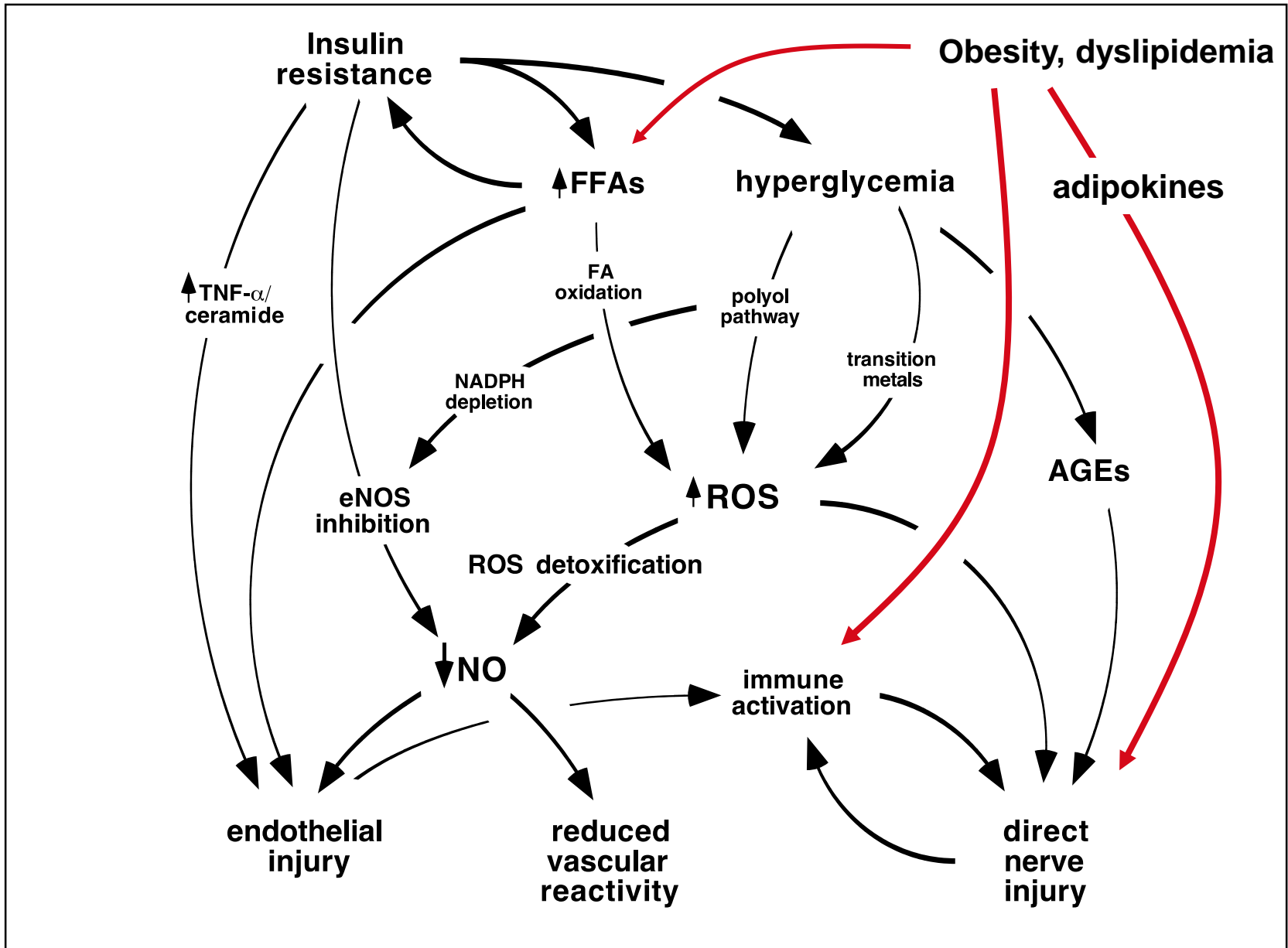


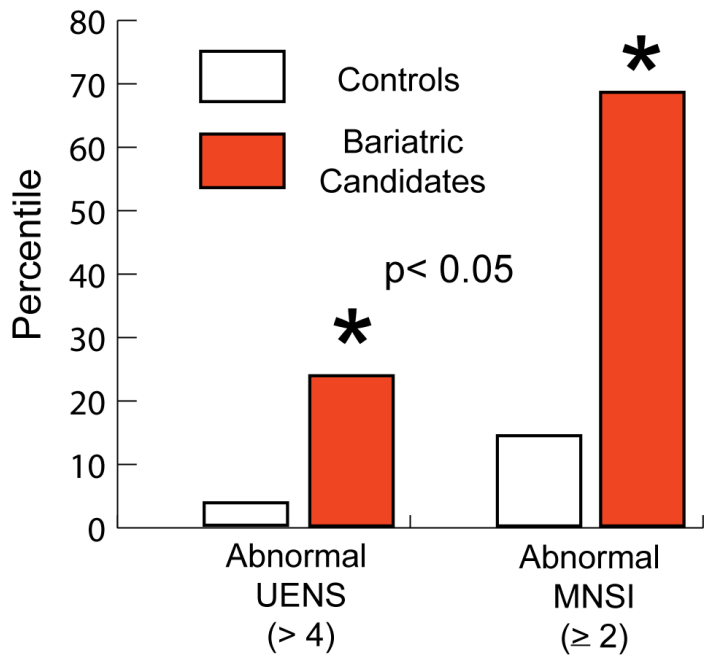
Proinflammatory, neurotoxic adipokines

An inflammatory disease:



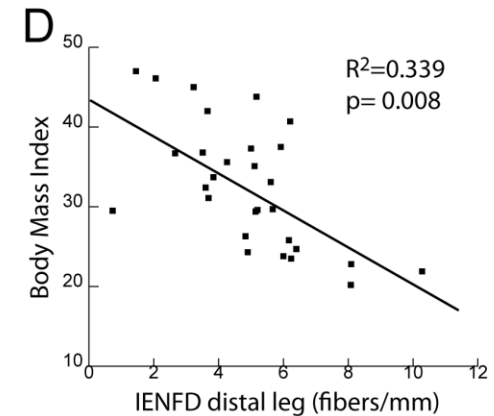
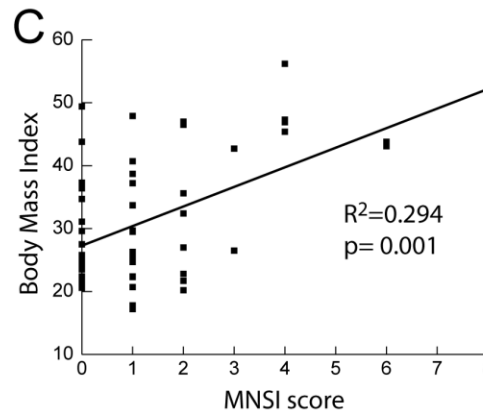
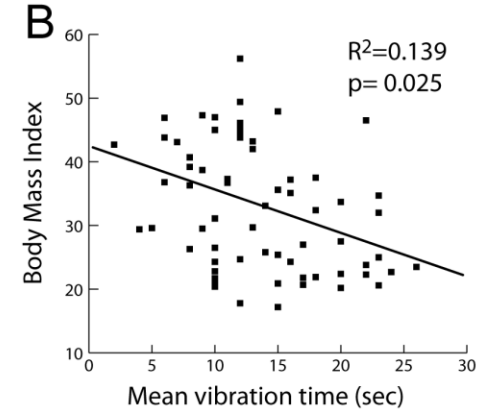
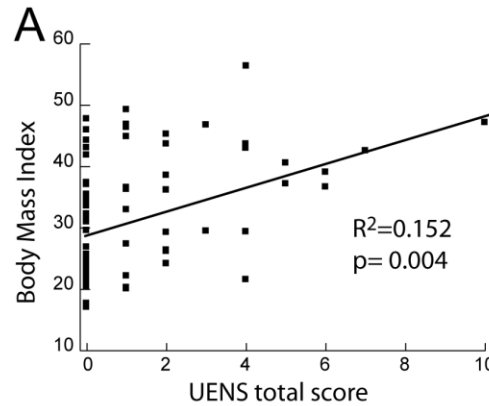
Neuropathy pathogenesis





Bariatric candidates are more likely to meet symptomatic and exam thresholds of neuropathy

Body mass index correlates with features of distal peripheral axonal injury



Rodent Models of Prediabetes

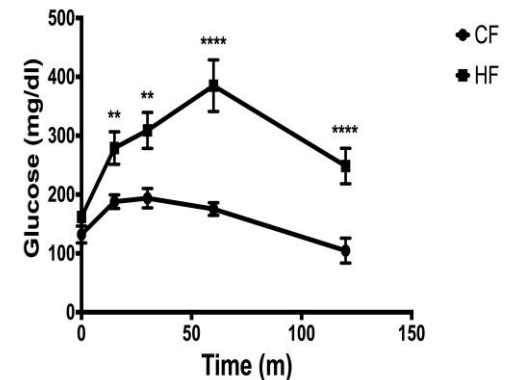
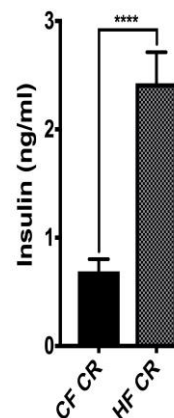
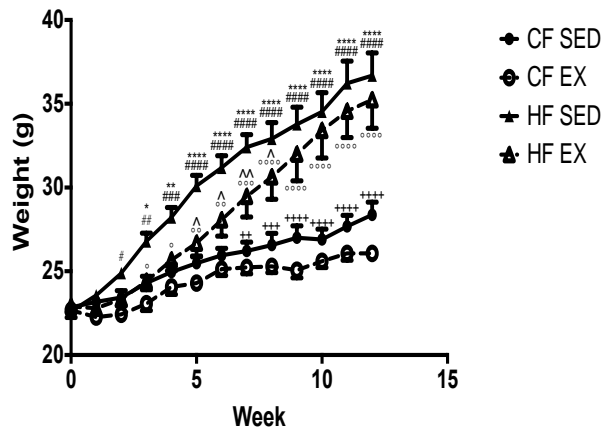


Approaches:

- Western diets (45% fat, high sucrose)
- High Fat diets (50—60% fat; lard)
- Standard American Diet (flour, sucrose)

Metabolic Abnormalities

- Increased body weight
- Mild hyperglycemia
- Increased serum insulin
- Impaired glucose tolerance
- Insulin resistance
- Increased cholesterol

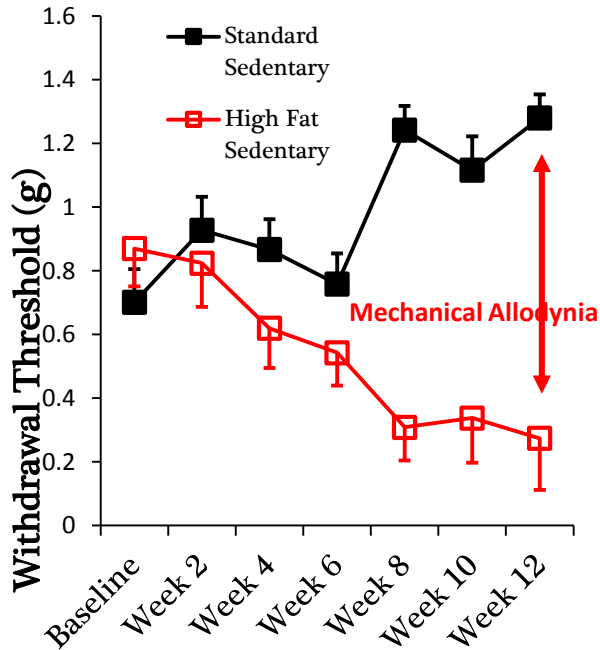
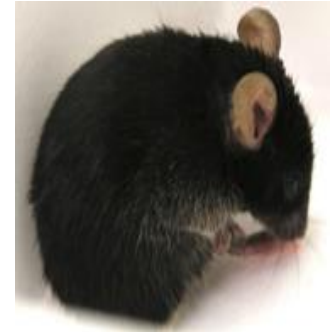


Rodent Models of Prediabetes



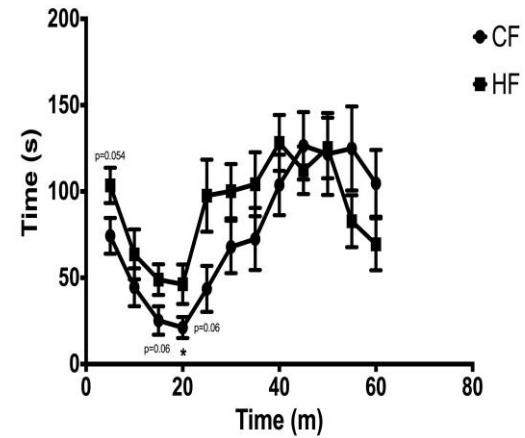
Behavioral Abnormalities

- Mechanical allodynia
- Thermal hypersensitivity
- Cognition and memory deficits
- Chemogenic hypersensitivity



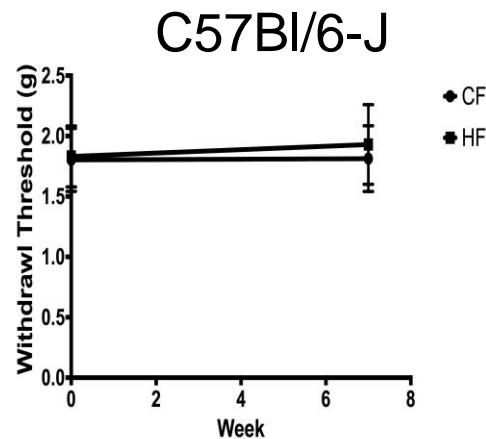
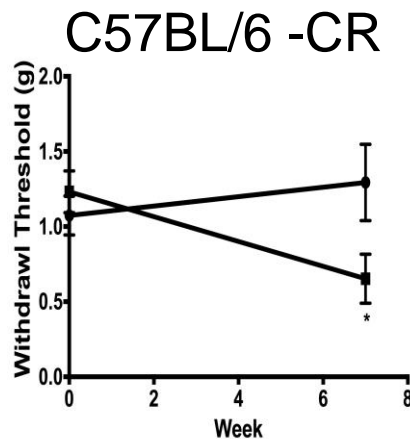
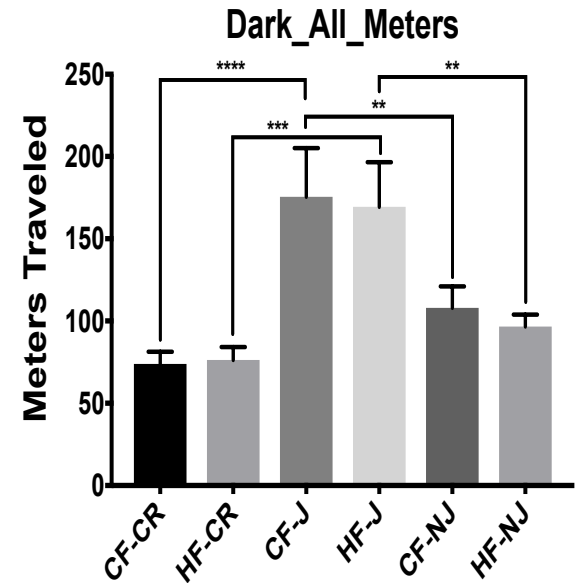
Neuropathy Changes

- Decreased SNCV (longterm)
- Decreased MNCV (longterm)
- Mild to no IENF changes

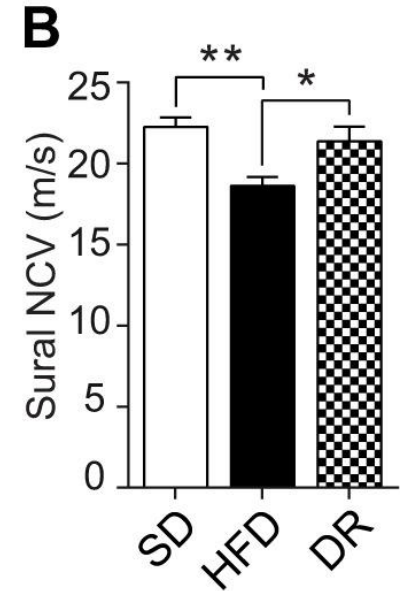
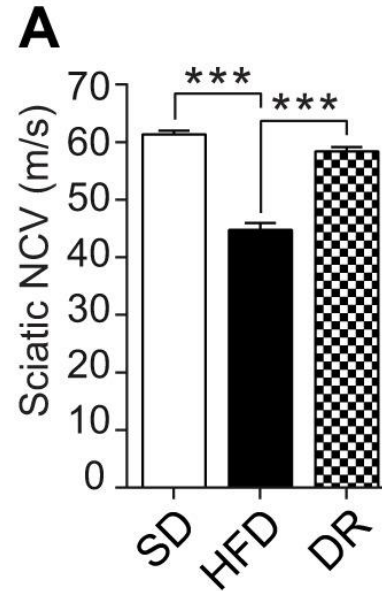
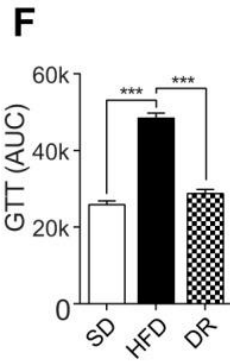
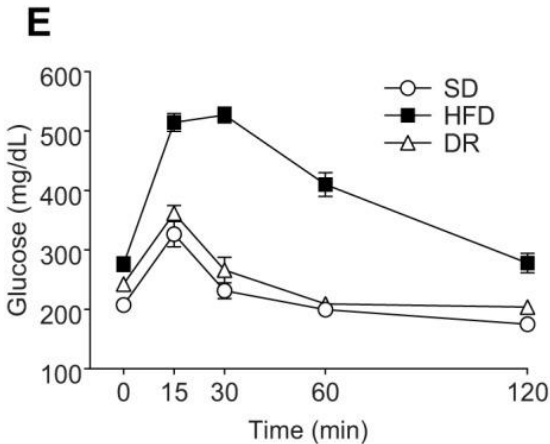
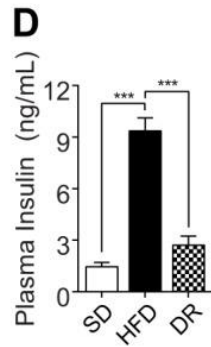
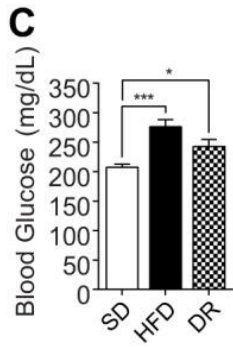
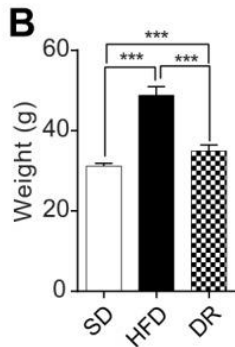


Rodent Models of Prediabetes

- Highly strain-, vendor-, and species-dependent
- Sensitive to fat and carbohydrate levels
- Pain behavior appears earlier than PNS pathology
- CNS and PNS likely impacted
- Strongly impacted by activity levels



High fat diet produces DSP in B6wt mice...



..and dietary change reverses it

IGTN subject characteristics

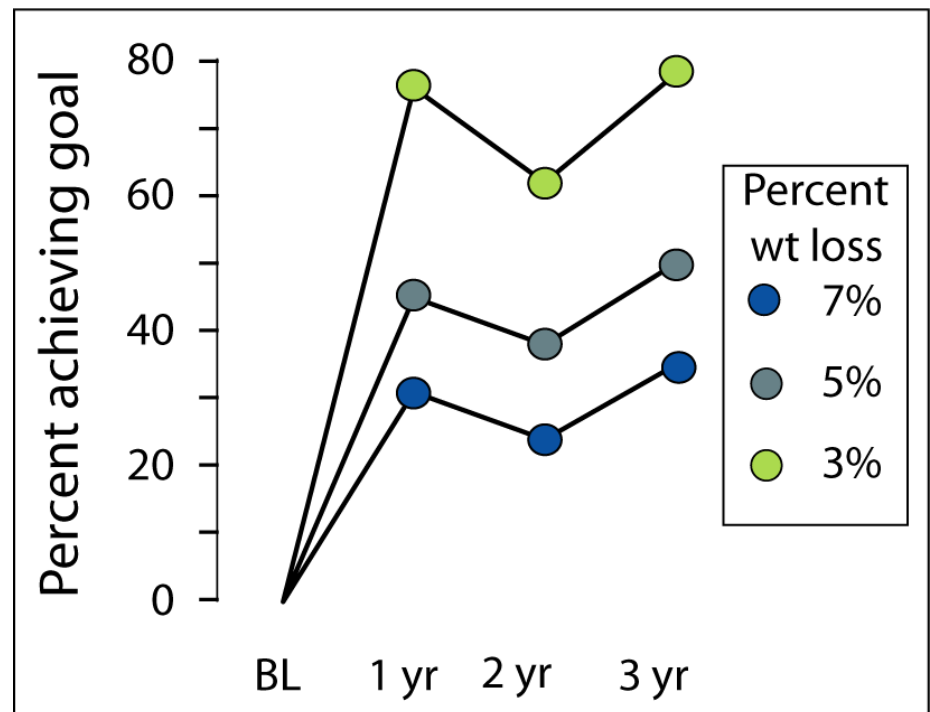
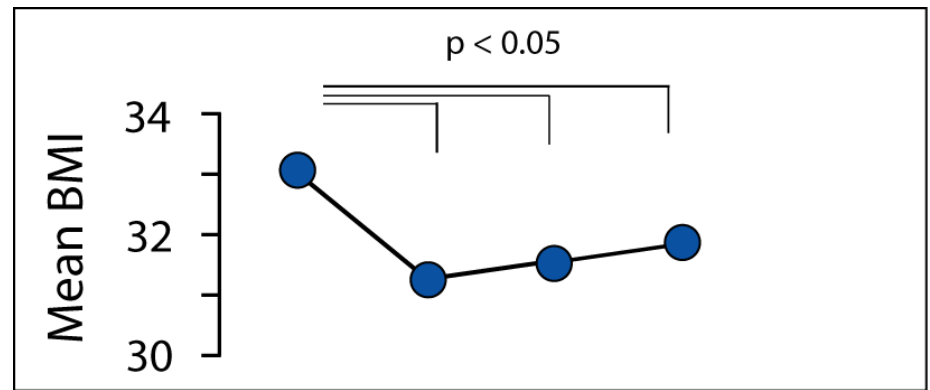
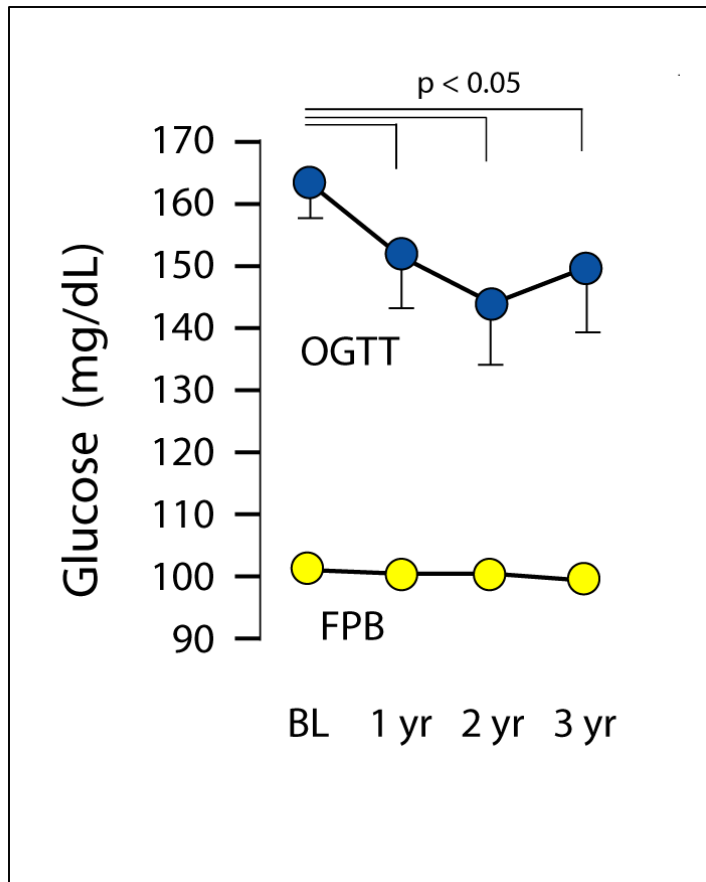
Subjects: 71, 29 followed for up to three years

Percent Female: 62

	Mean	Range
Age	56	41-75
Body mass index	32.8	23- 41.5
Reported minutes of exercise	15	0- 120
Months of neuropathy	54	12- 180
OGTT glucose (0/2h)	101/ 166	142- 199 (2h)

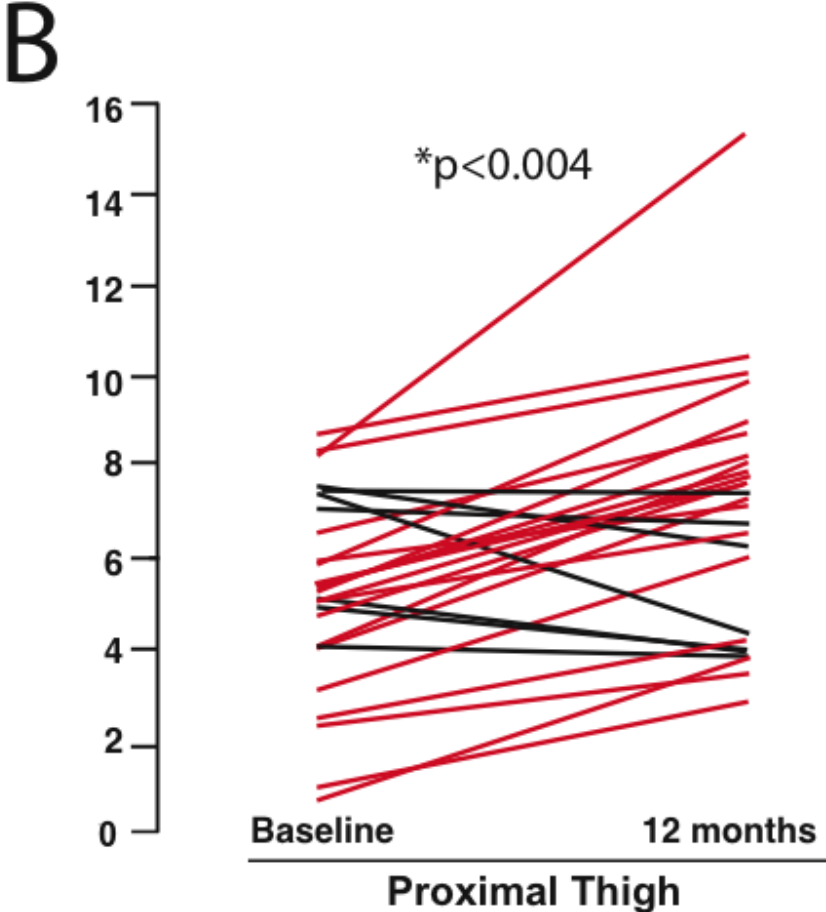
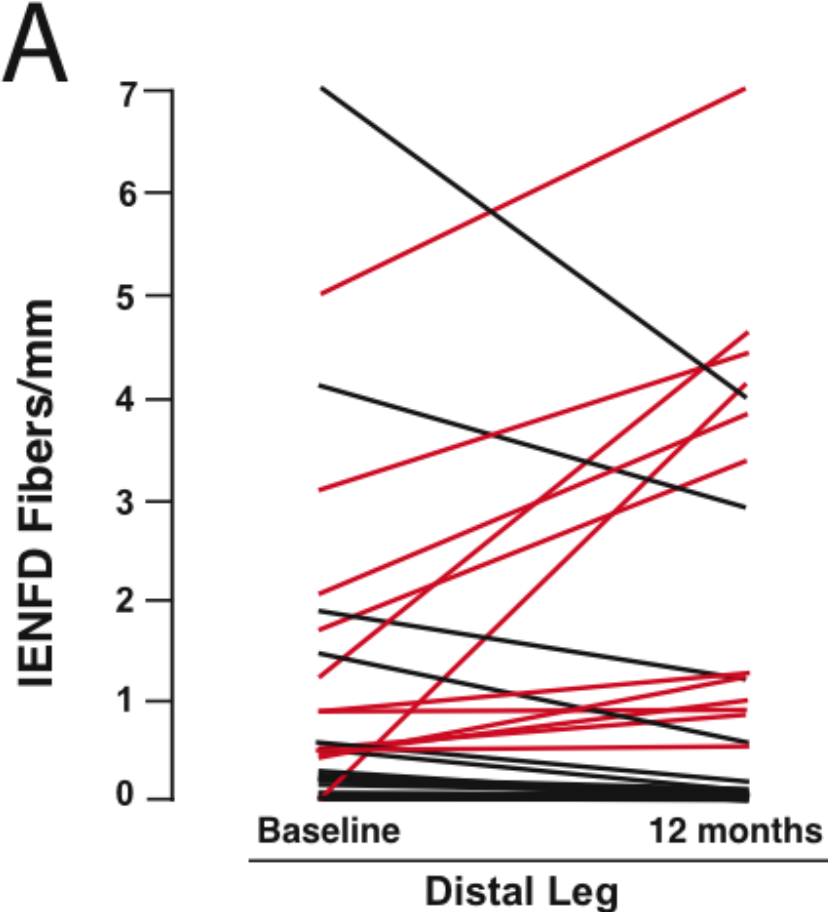
Percent with:	- hypertension	86
	- hyperlipidemia	81
	- metabolic syndrome	73
	- microalbuminuria	10

Sustained improvement in glucose and weight...

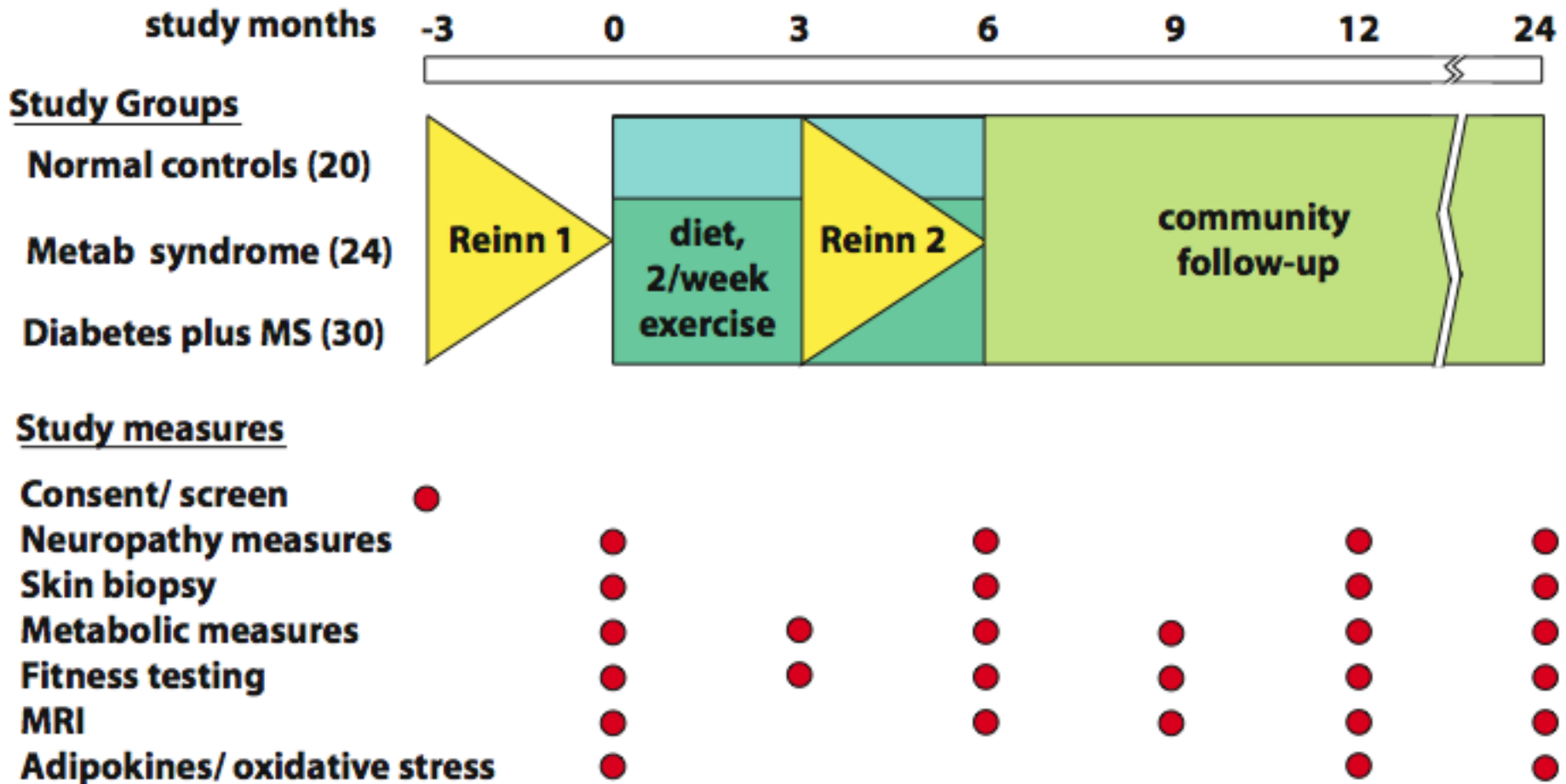


71 patients with IGT and neuropathy offered diet and exercise counseling based on the DPP, followed up to 3 years.

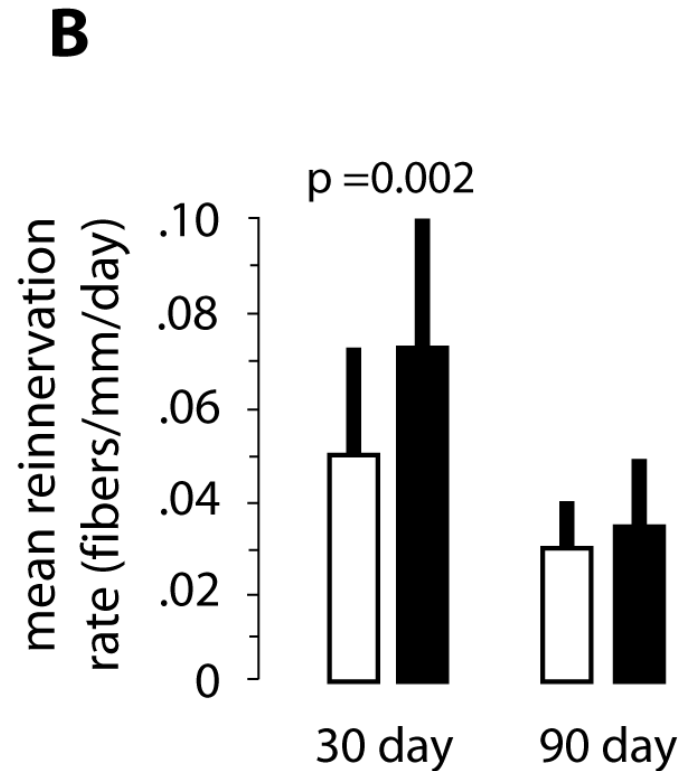
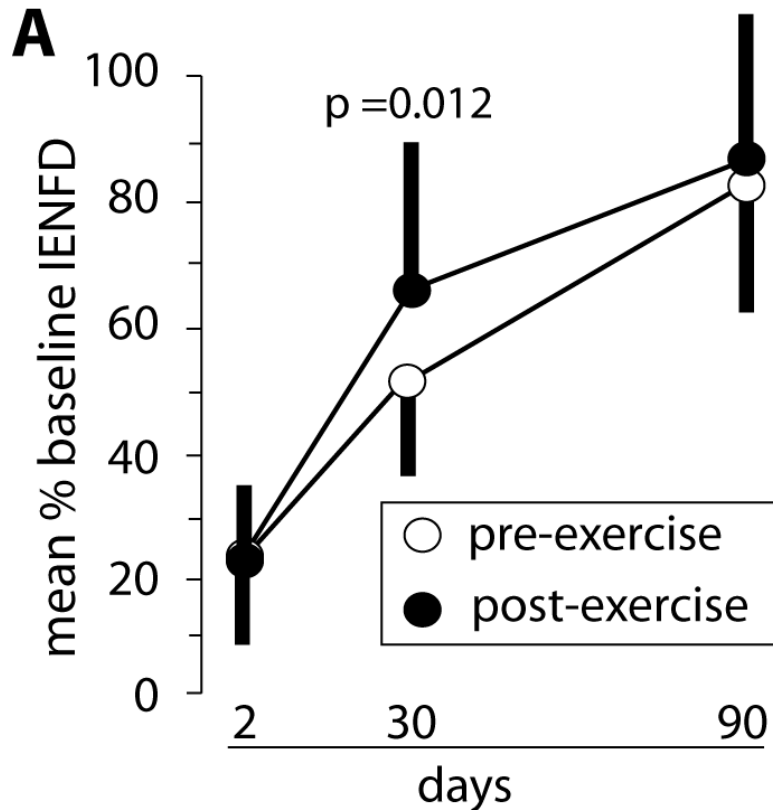
Improved metabolic function results in significant improvement in intraepidermal nerve fiber density (IENFD)



Capsaicin axotomy protocol applied to patients with prediabetes and metabolic syndrome



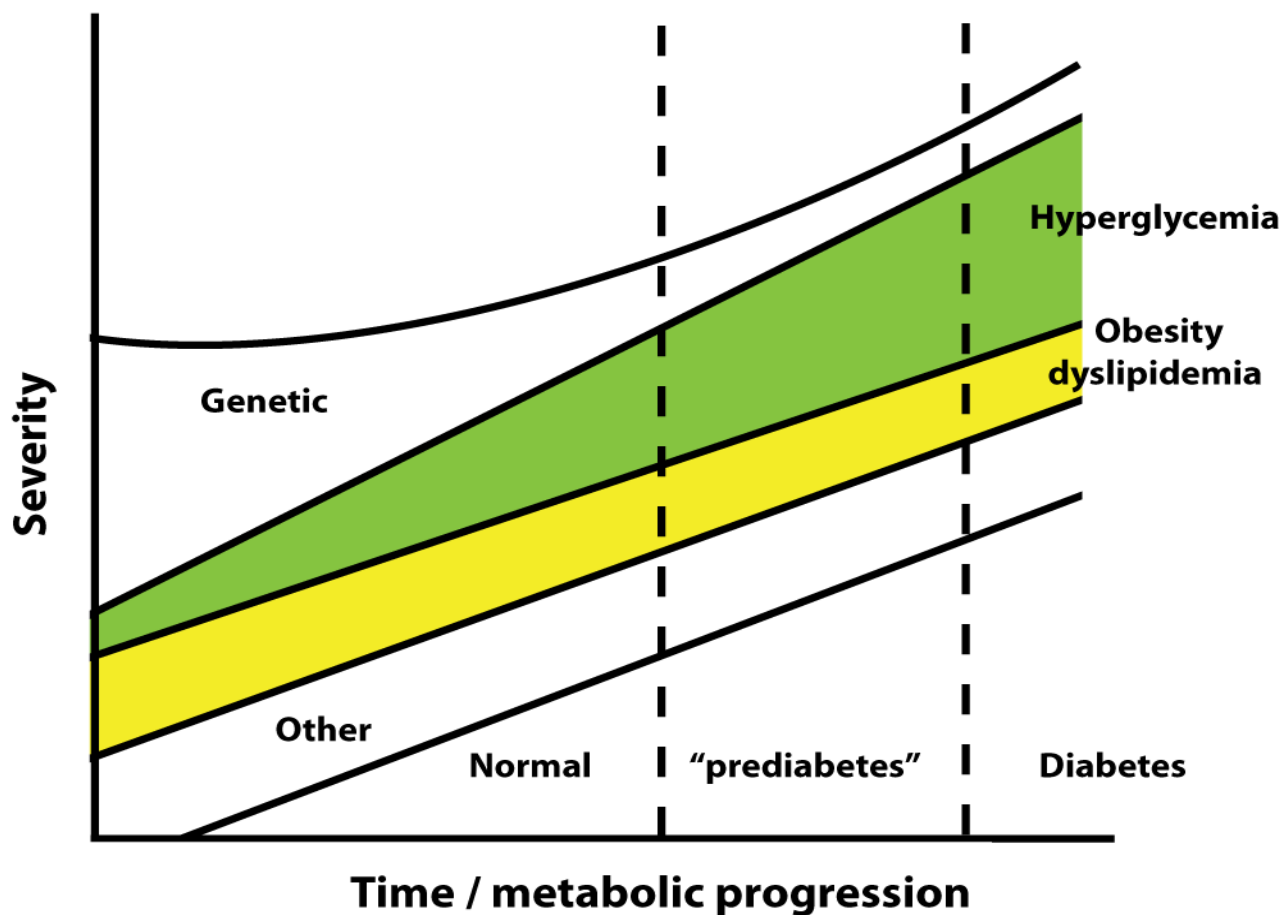
Lifestyle intervention results in improved cutaneous nerve regenerative capacity



Neuropathy in Metabolic Syndrome summary

Metabolic syndrome represents a complex continuum of disorder and risk. Metabolic syndrome features contribute to the pathogenesis of neuropathy, and confer variable degrees of risk for neuropathy.

Phenotypic diagnostic criteria are the same as for DPN, but diagnostic certainty is comparatively reduced.



Diagnostic criteria for PiMS

No authoritative diagnostic criteria have been established

Recommended:

Symptoms and exam findings of neuropathy + confirmatory testing as promulgated for diabetic neuropathy

Presence of metabolic syndrome by ATPIII criteria

Features not better ascribed to another neuropathic disorder

Recognition that neuropathy etiology may be multifactorial

Competing metabolic syndrome diagnostic criteria

WHO definition (fasting hyperinsulinemia or impaired glucose regulation plus > 2 more factors)

Also (a) fasting insulin in the upper quartile in non-diabetic or

(b) fasting blood glucose \geq 110 mg/dL plus \geq 2 of the following:

Systolic blood pressure \geq 140/ and/or diastolic \geq 90 mmHg

Dyslipidemia: triglyceride \geq 150 mg/dL or HDL < 35 in men or < 39 m/dL in women

Central obesity, waist-to-hip ratio > 0.90 in men or > 0.85 in women and/or BMI > 30 kg/m²

Microalbuminuria (\geq 20 μ g/min or albumine/creatinine \geq 30 mg/g)

ATPIII definition (\geq 3 of 5 risk factors)

Waist circumference

102 cm in men

88 cm in women

Blood pressure

\geq 130 mmHg systolic and/or

\geq 85 mmHg diastolic

Plasma glucose

\geq 110 mg/dL

Triglyceride

150 mg/dL

HDL-cholesterol

< 40 mg/dL in men

< 50 mg/dL in women

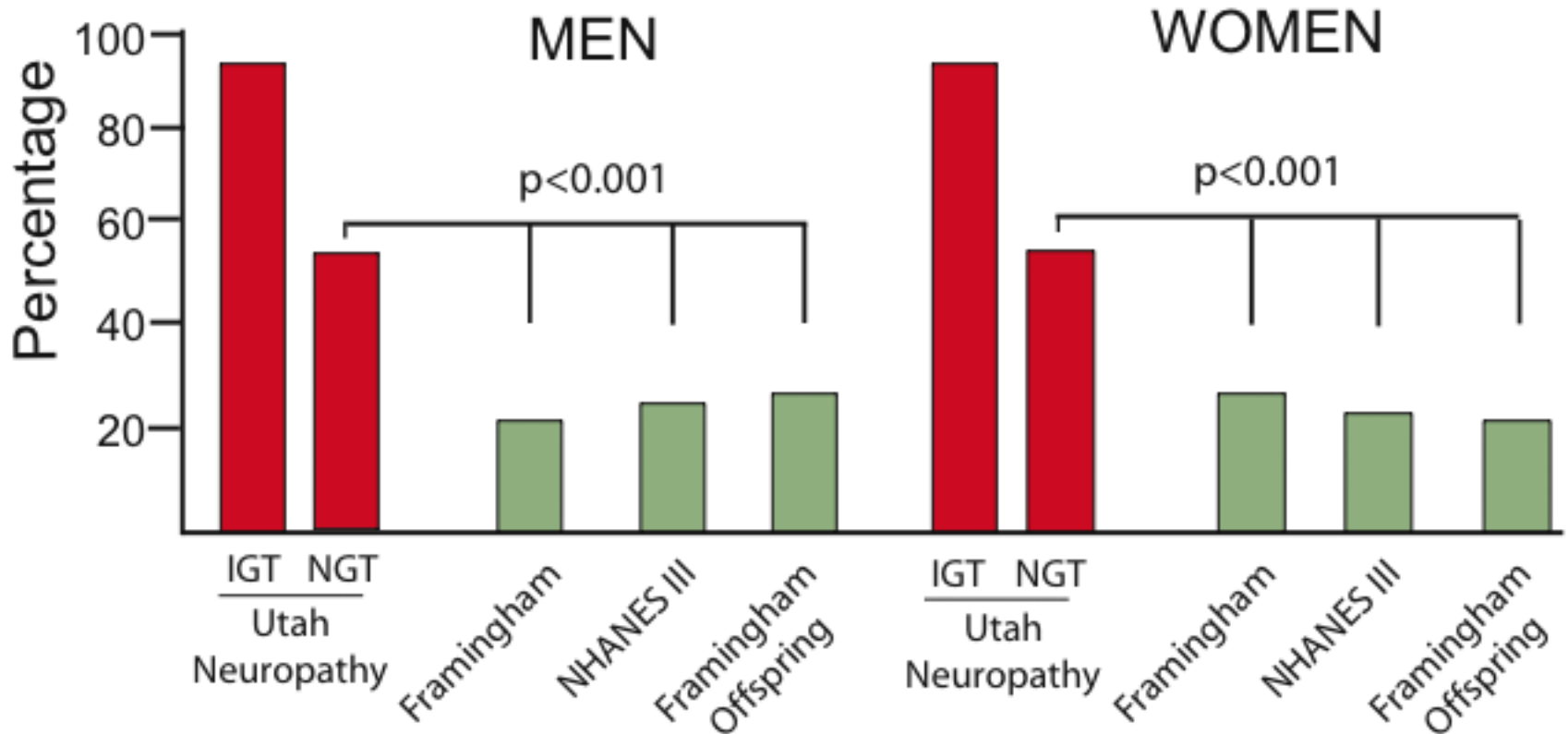
Table 1 - Clinical criteria defining metabolic syndrome

Diagnostic criteria for PiMS

Questions/ controversies

- Should small fiber involvement be emphasized?
- Should some MS criteria be given greater diagnostic weight?
- Can PiMS be present with partial fulfillment of MS?
- Establish “early” vs. “advanced” neuropathy criteria?
- Which specific MS criteria (e.g. ATP III) are most appropriate, responsive?
- Does a considered diagnosis of PiMS mandate more intensive evaluation for other causes of neuropathy than does diabetes?
- Need for genetic analysis to identify genetic features associated with increased risk for early hyperglycemic/ MS associated neuropathy.

Metabolic syndrome is more prevalent among both IGT and NGT patients with neuropathy



- 238 sequential idiopathic neuropathy patients seen between 1997-2003 who underwent an OGTT.
- Hereditary and inflammatory neuropathy excluded.
- Other common causes of neuropathy excluded (B12, TSH, SPEP/IFIX, ANA).