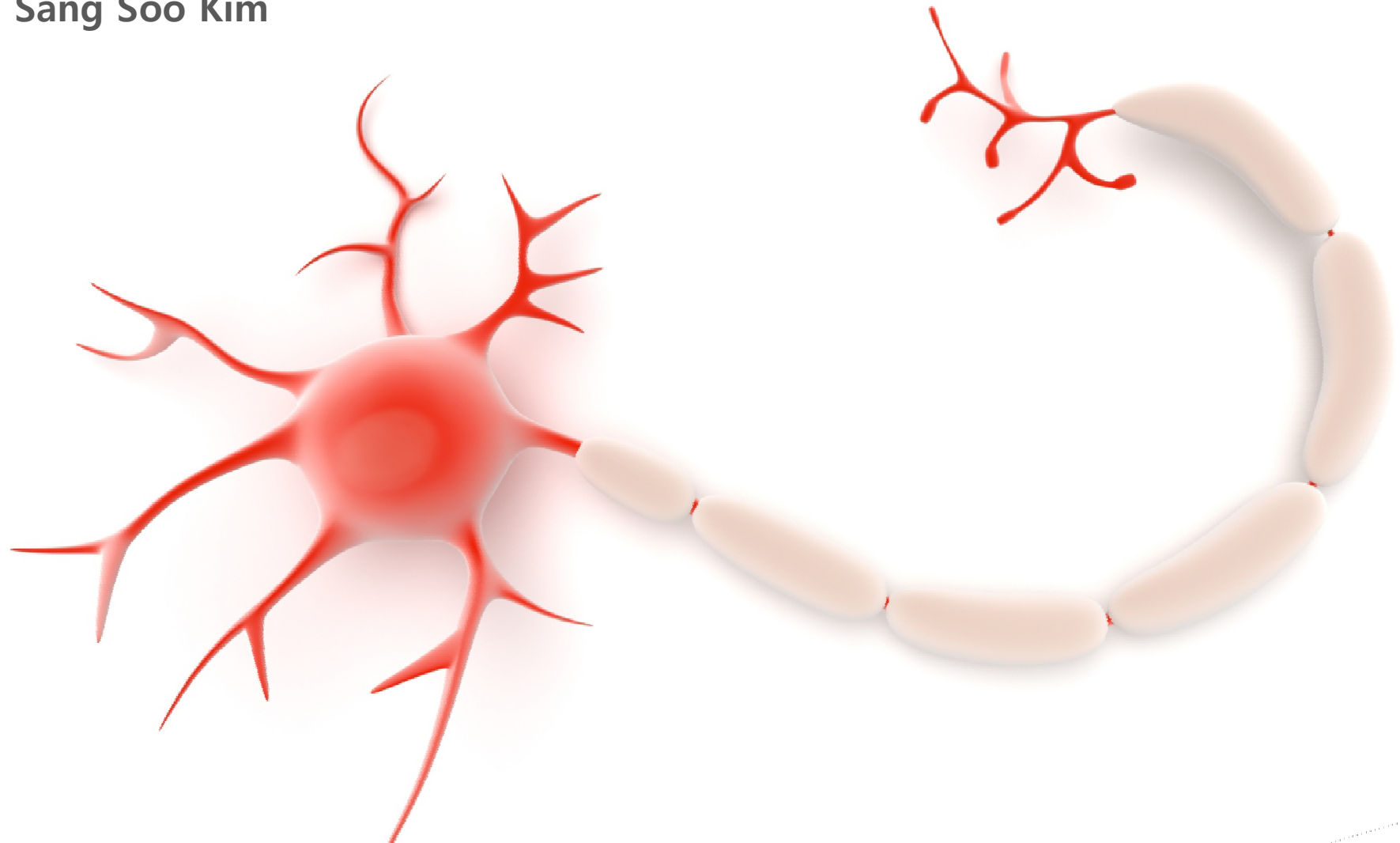


Overview of painful and painless DPN - Epidemiology & QoL

Pusan National University Hospital

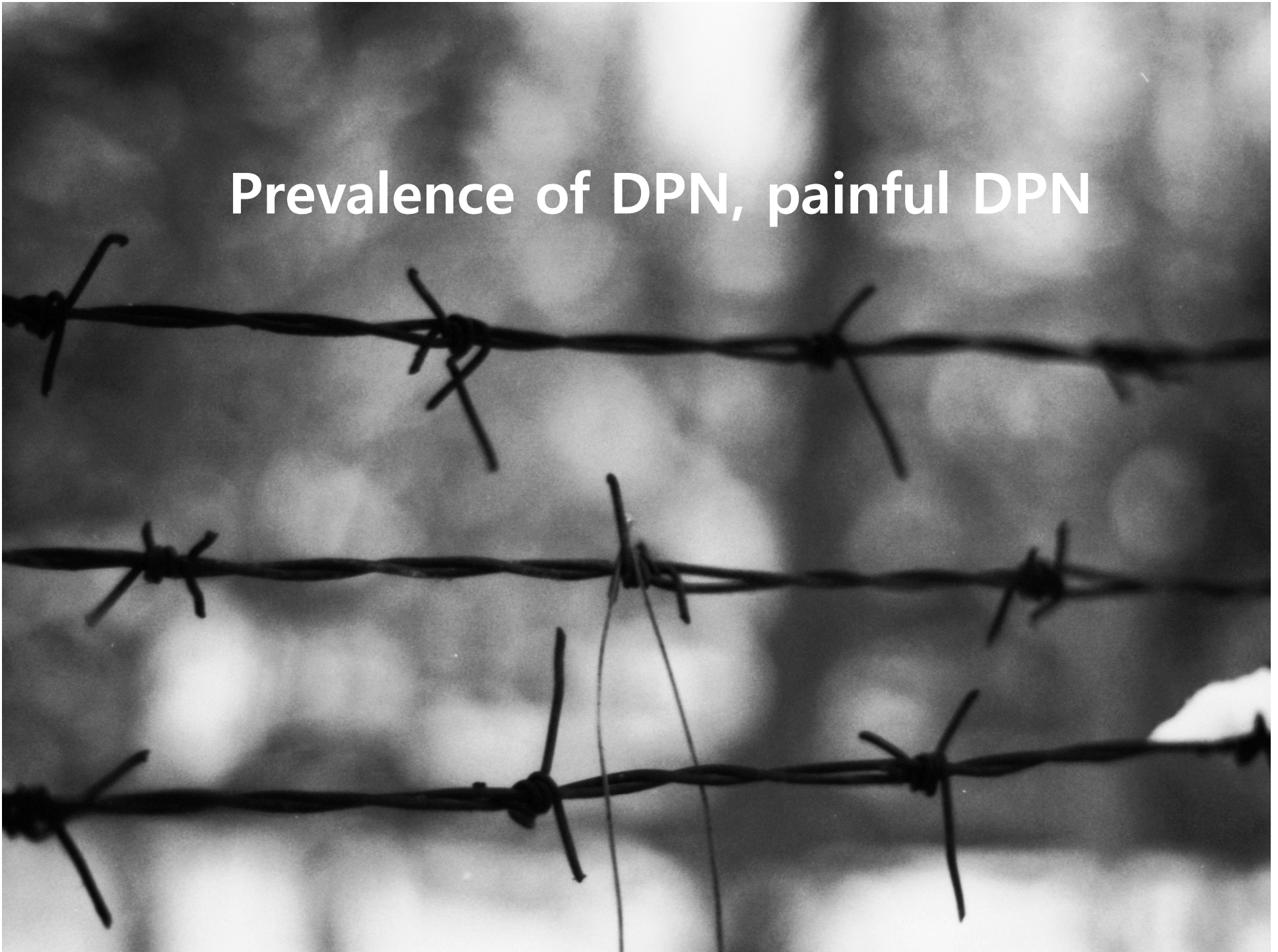
Sang Soo Kim



Contents

- Prevalence of DPN, painful DPN
- Risk factors for Painful/painless DPN
- Are two forms (painful and painless DPN) mutually exclusive?
: In epidemiological aspects
- QoL for Painful/painless DPN

Prevalence of DPN, painful DPN



Prevalence of DPN

10%

?

23% - Primary/hospital in Spain (2,644) | Diabetologia 1998

28% - EURODIAB (16 countries / 3,250) | Diabetologia 1996

29% - Multi-center hospital in UK (6,487) | Diabetologia 1993

51% - BARI 2D + CAD (2,368) | J Pheriph Nerv Syst 2009

?

90%

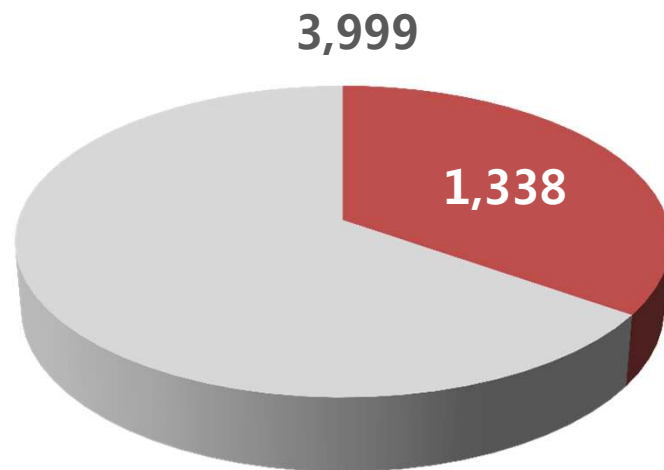
Prevalence of DPN in Korea (1957-1994)

Study site and year	Neuropathy diagnosis	Subjects, <i>n</i>	Prevalence, %
Seoul, 1957-1977	NA	5,601	32.7
Seoul, 1963-1973	NA	1,332	22.9
Nationwide, 1976	NA	3,076	28.9
Kwangju, 1976-1981	NA	779	14.1
Seoul, 1981-1983	Symptoms, signs, NCV	300	54.5
Seoul, 1982	Symptoms, signs, NCV	224	45.5
Seoul, 1990	Symptoms, signs, NCV	837	48.9
Seoul, 1993	Symptoms, signs, NCV	1,301	39.0
Seoul, 1994	Symptoms, signs, NCV	668	19.0
Seoul, 1994	Symptoms, signs, NCV	235	37.5
Taegu, 1999	Symptoms, signs, NCV	1,270	47.6

NA, not available; NCV, nerve conduction velocity

Prevalence of DPN in Korea 2009

- 3,999 / Nationwide 40 centers
- Diabetic Neuropathy Study Group of the KDA
- Typical Sn & Sx or MNSI (≥ 3) + Monofilament (2/10)



33.5%

Symptoms in DPN

- Typical “glove and stocking” distribution

“Positive” Symptoms

- Persistent burning or dull pain
- Paroxysmal electric, shooting, stabbing pain
- Dysesthesias (painful paresthesias)
- Evoked pain (hyperalgesia, allodynia)
- Numbness

“Negative” Symptoms (deficits)

- Hypoalgesia, analgesia
- Hypoesthesia, anesthesia
- ↓ Thermal, vibration, pressure sensation, reflexes

Epidemiological studies on prevalence of **Painful** DPN

Author, yr	Study setting	N	Type	Diagnostic criteria	Prevalence, %
Chan, 1990	Hospital clinic, UK	962	T1, T2	Neuropathic pain in the lower limbs	7.4
Harris, 1993	Population, US	2,392	T1, T2	Painful sensation or tingling in hands/feet	26.8
Partanen, 1995	Hospital, Finland	132	T2	+4 NCS abnormalities	6 (at Dx) 20 (at 10 yrs)
Sorensen, 2002	Hospital, Australia	2610	T2	VPT \geq 30 for DPN	3.3
Daousi, 2004	Community, UK	350	T1, T2	Typical neuropathic pain >1 yr + PSS \geq 3 + (NDS \geq 6) or (NDS \geq 3 + NSS \geq 5)	16.2
Davies, 2006	Population, UK	353	T2	Typical neuropathic pain (History and examination + TCSS)	26.4
Wu, 2007	Population, France	1023	T1, T2	Neuropathic Symptoms and pain (MNSI-Q + average pain on BPI)	8
Ziegler, 2009	Population, Germany	195	T1, T2	MNSI-Q (+ to Q2,Q6 / score \geq 2)	13.3

Epidemiological studies on prevalence of **Painful** DPN

Author, yr	Study setting	N	Type	Diagnostic criteria	Prevalence, %
Ziegler, 2009	Population, Germany	214	T1, T2	MNSI-Q (+ to Q2, Q6 / score ≥ 2)	21
Van Acker, 2009	40 outpatient clinic, Belgium	344	T1, T2	DN4 ≥ 4 + 10g monofilament / pinprick	14.1
Miralles-Garcia, 2010	20 hospital outpatient, Spain	1,011	T1, T2	DN4 ≥ 4 + Von Frey filaments or VPT or TT or NCS	21.1
Halawa, 2010	100 outpatient, Saudi Arabia	1,020	T1, T2	DN4 ≥ 4	65.3
Erbas, 2011	14 Hospital, Turkish	1,113	T1, T2	LANSS ≥ 12	14.0
Jambart, 2011	Outpatient, Middle East	3,989	T1, T2	DN4 ≥ 4	53.7
Abbott, 2011	Community, UK	15,544	T1, T2	NSS ≥ 5 and NDS ≥ 3	21
Kim & Won, 2014	40 Hospital, Korea	3,999	T2	Daily pain intensity ≥ 4 or Taking medication for pain	14.4

Prevalence of **Painful** DPN

1. When based on the presence of both neuropathic pain and DPN,
the median value was **17.5%** for prevalence of painful DPN
2. **10-20%** in patients with all DM,
40-50% in those with neuropathy
3. **14%** in all DM; **17.9% (T2DM)** vs. 5.8% (T1DM)

1. *Curr Diab Rep* 2013;13:533-549
2. *Pain Med* 2008;140:441-451
3. *Diabetes Metab* 2009;35:206-213

Pain

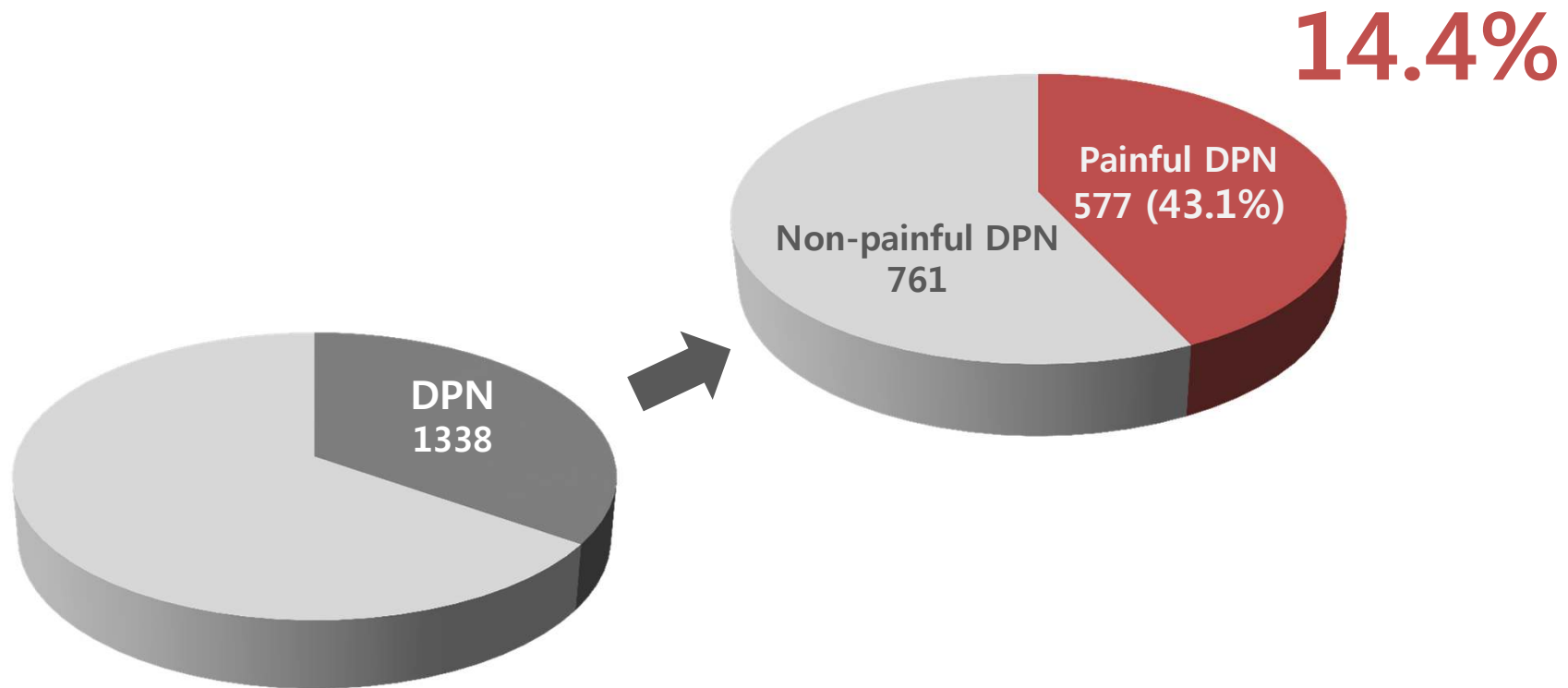
Socio-cultural and ethnic differences

A very personal experience

Marked variation in the description of symptoms

Prevalence of **Painful** DPN in Korea

- Diabetic Neuropathy Study Group of the KDA (3,999)
- Painful DPN – Daily pain intensity ≥ 4 (VAS) or
if patients were taking medication for their current pain



**Risk factors for
Painful/painless DPN**



Risk factors for DPN

Age

Diabetic duration

Glycemic control

Microvascular complications

hypertension

Smoking

Obesity - BMI, WC

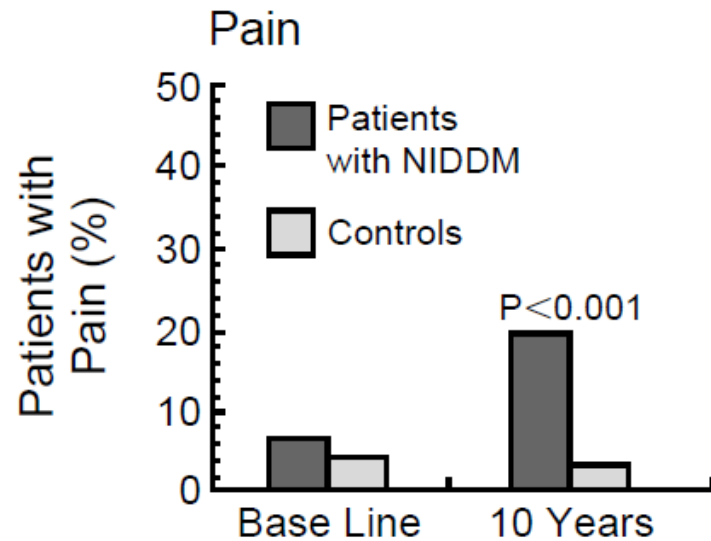
Hypoinsulinemia (T2DM), low levels of C-peptide (T1DM)

Metabolic dyslipidemia

Cardiovascular disease (including PAD)

...

Risk factors for Painful DPN – Duration of DM



N Engl J Med 1995;333:89-94

Consistent

Diabetes Metab 2009;35:206–213

J Int Med Res 2011;39:366–377

Diabetes Res Clin Pract 2002;57:45–51

Diabetes Care 1993;16:1446–1452

Eur J Pain 2011;15:153–160

Opposite

Diabet Med 2004;21:976–982

Pain Med 2009;10:393–400

Diabetes Care 2011;34:2220–2224

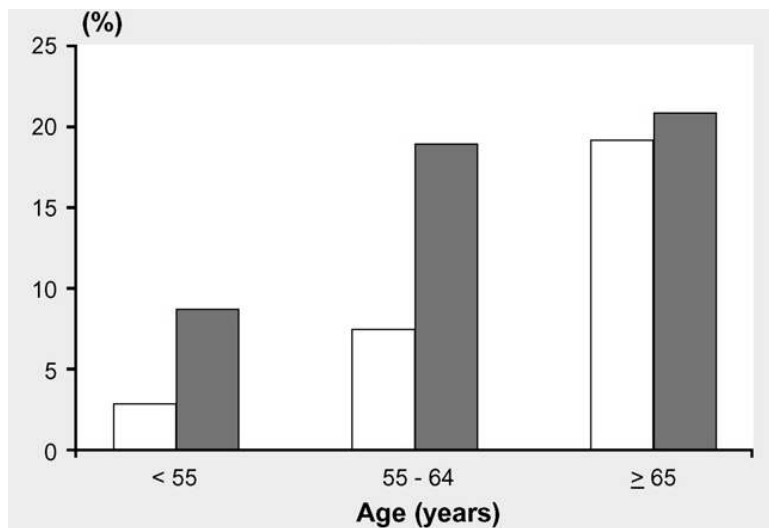
Endocrinol Nutr 2010;57:414–420

Diabetes Care 2008;31:464–469

J Clin Neurophysiol 2011;28:51–55

Risk factors for Painful DPN – Age

Prevalence of Painful DPN



Diabetes Metab 2009;35:206-213

Consistent

Pain Med 2009;10:393-400
Curr Med Res Opin 2010;26:337-343
J Int Med Res 2011;39:366-377
Curr Med Res Opin 2007;23:2035-2042

Opposite

Risk factors for Painful DPN – PAD

	OR (95% CI)	P value
All subjects (N = 393)		
Age (years)	1.08 (1.02–1.14)	0.0085
Weight (kg)	1.03 (1.00–1.05)	0.0415
Diabetes	2.61 (1.09–6.24)	0.0305
Peripheral arterial disease (ABI < 0.9)	5.72 (2.44–13.39)	<0.0001
Diabetic subjects (N = 195)		
Age (years)	1.08 (1.00–1.16)	0.0389
Weight (kg)	1.03 (1.00–1.06)	0.0539
Peripheral arterial disease (ABI < 0.9)	9.27 (3.44–25.0)	<0.0001
Albuminuria (mg/L)	1.19 (0.95–1.51)	0.1378

Pain Med 2009;10:393–400

Consistent

Opposite

Eur J Pain 2011;15:153–160
Diabet Med 1994;11:17–21

Risk factors for Painful DPN – Obesity (BMI, WC)

Variables	OR	95% CI	P
	∴		
BMI (kg/m ²)	1.22	1.08– 1.37	0.0012
Abdominal obesity	0.60	0.12–2.99	0.38

Eur J Pain 2011;15:153–160

Consistent

Pain Med 2009;10:393–400
Diabetes Metab 2009;35:206–213
J Int Med Res 2011;39:366–377

Opposite

Risk factors for Painful DPN – **Other** factors

HT ¹

Physical inactivity ²

Low HDL-C / High TG ³

Female ⁴⁻⁶

1. Diabetes Care 1993;16:1446–1452

2. Eur J Pain 2009;13:582–587

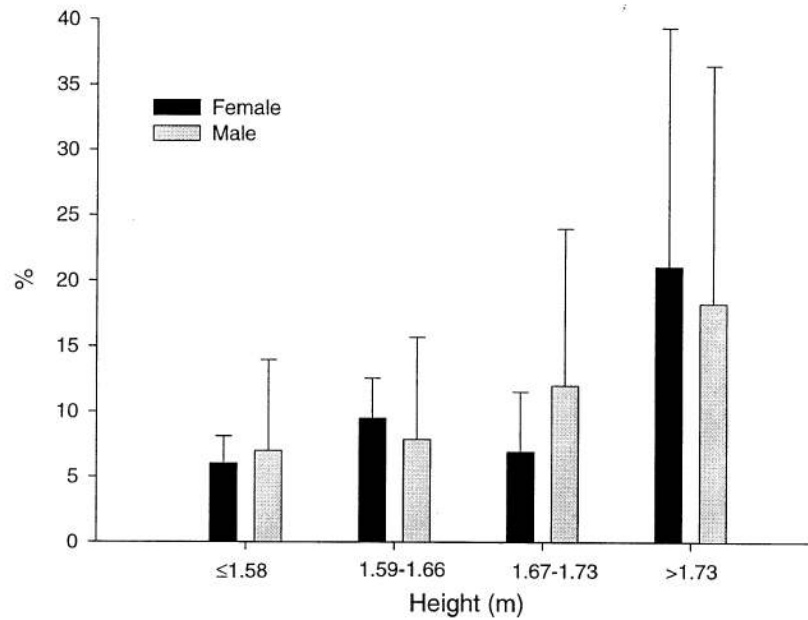
3. Diabetes Metab 2009;35:206–213

4. Diabetes Care 2011;34:2220–2224

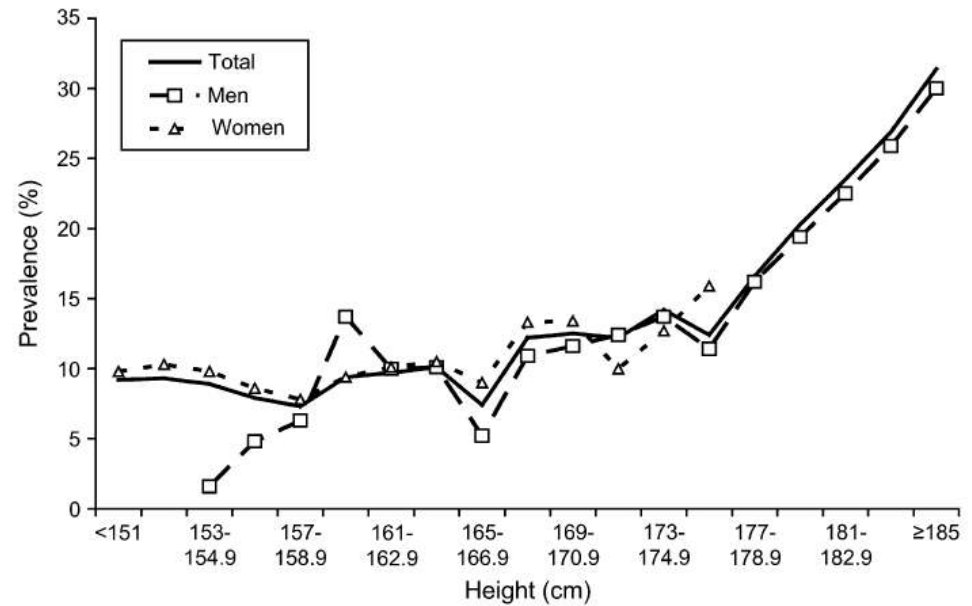
5. J Int Med Res 2011;39:366–377

6. J Clin Neurophysiol 2011;28:51–55

Risk factors for Painless DPN – Height



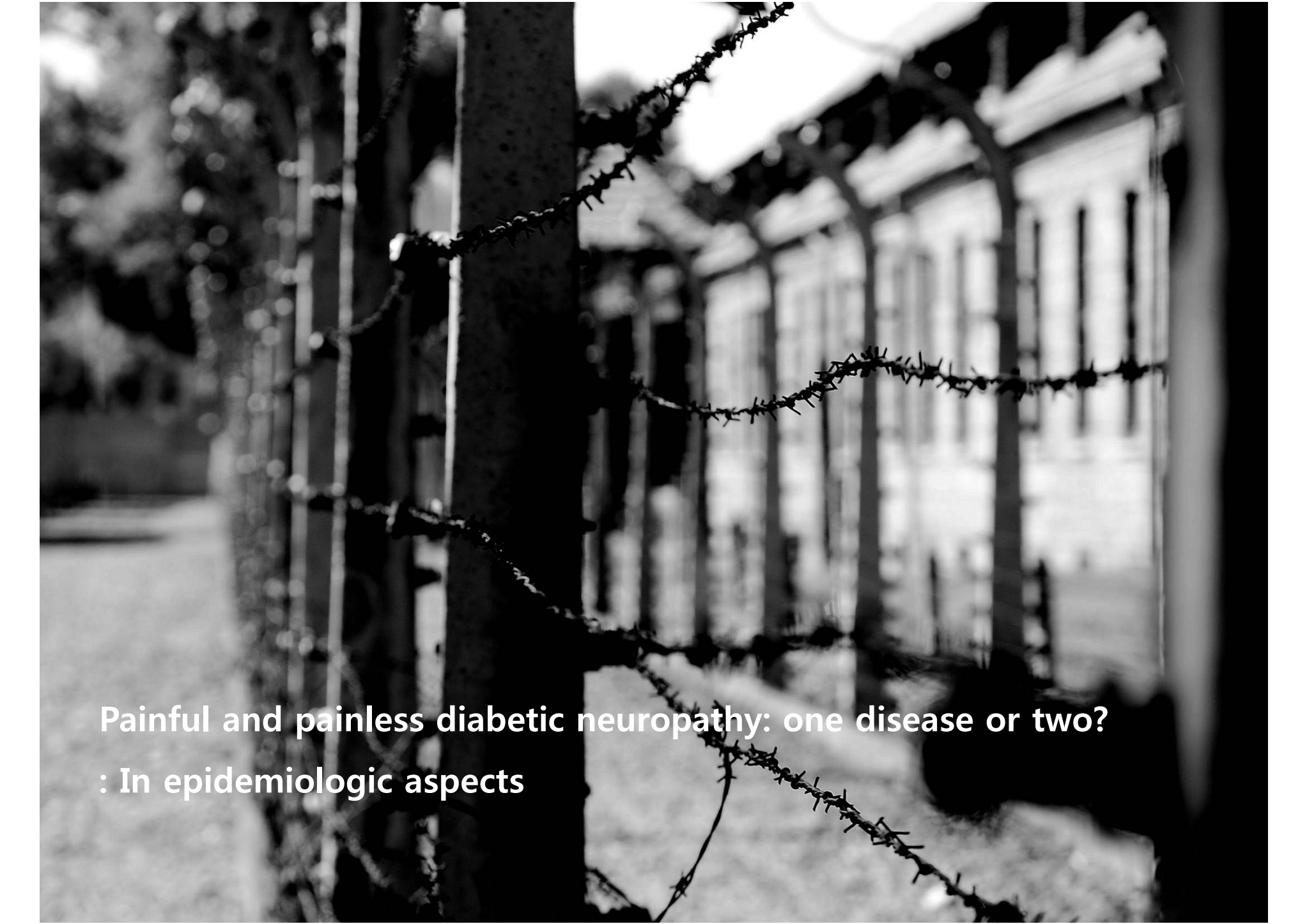
Diabetes Res Clin Pract 2002;57:45–51



Am J Epidemiol 2006;164:873–880

Risk factor of **Painful** DPN vs. Painless

Variable	OR (95% CI)
Age	1.02 (1.00–1.03)
Gender, female	1.49 (1.08–2.07)
Fasting glucose	1.00 (1.00–1.01)
Cerebrovascular accident	1.81 (1.02–3.22)
Hypertension	1.59 (1.14–2.23)

A black and white photograph of a barbed wire fence in the foreground, with a building visible in the background. The fence is made of several strands of barbed wire, with the most prominent one in sharp focus. The building in the background has a series of vertical supports and a roof, possibly a covered walkway or a structure in an industrial or institutional setting. The overall mood is somber and restrictive.

Painful and painless diabetic neuropathy: one disease or two?
: In epidemiologic aspects

Paradoxical condition

50%

Painful/uncomfortable

Pavy in 1887

“Burning and unremitting character”

QoL

50%

No pain

Dr. Paul Brand

“The gift of pain”

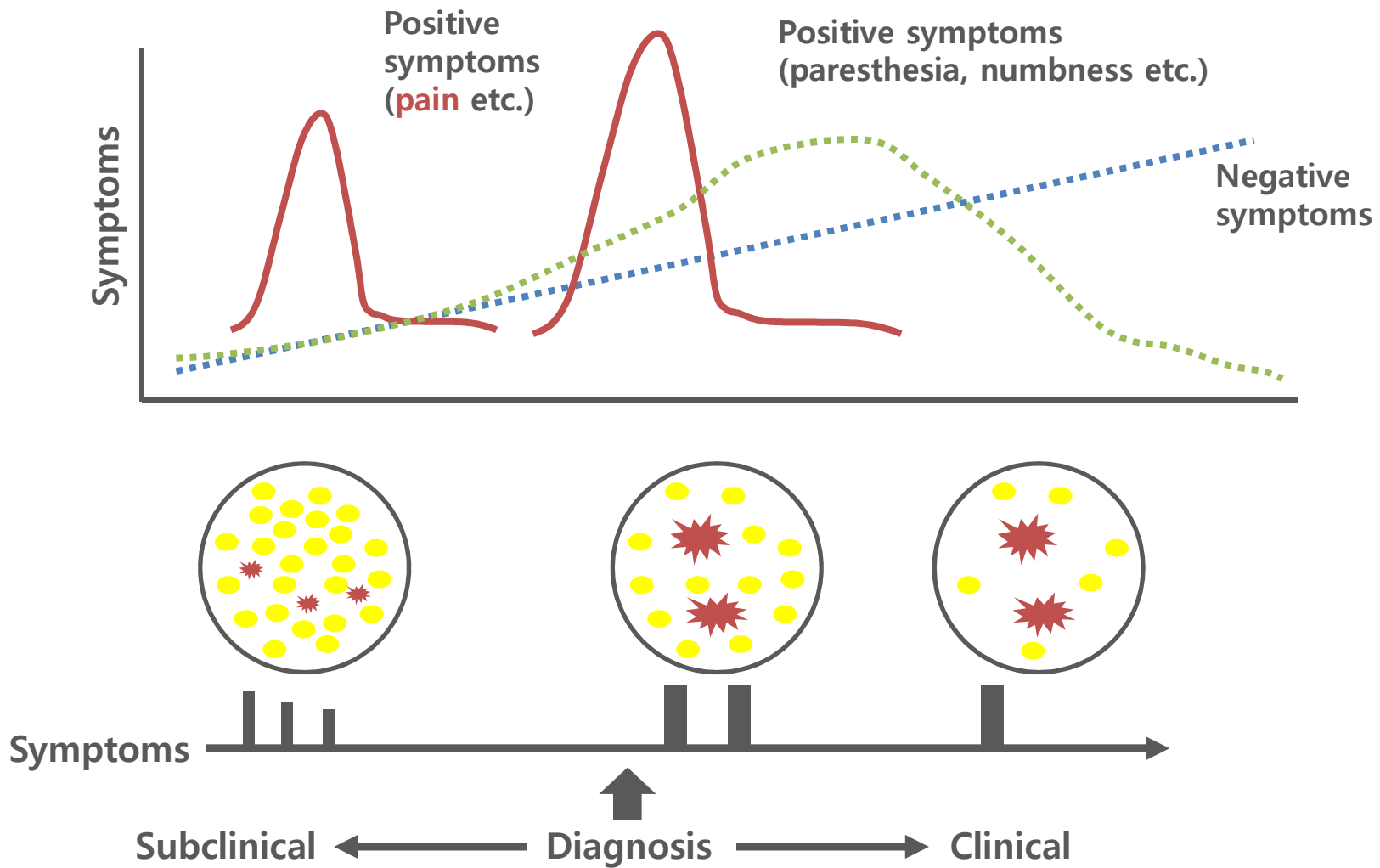
Foot ulceration / Charcot neuroarthropathy

Painful-painless leg

Spontaneous painful symptomatology

**On examination, marked loss of pain vibration,
and other sensory modalities**

Clinical Course of Diabetic Neuropathy



Natural history of Painful Sx. in Painful DPN

50 diabetic patients with chronic painful DPN

Pain – VAS 0-10

Small fiber function – Thermal limen, heat-pain threshold, weighted pinprick threshold

3.6 years of follow-up

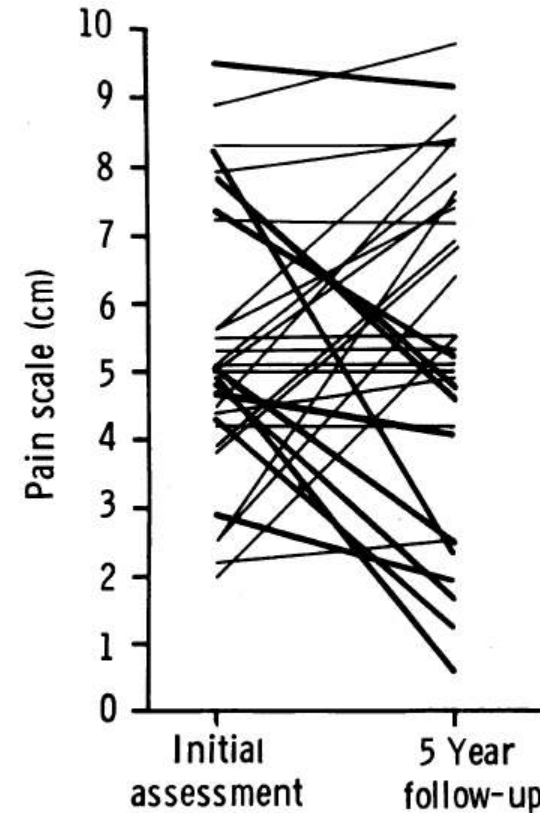
- An improvement of positive symptoms occurred in 88%
- Despite this symptomatic improvement,
small-fiber function generally deteriorated.

Natural history of Painful Sx. in Painful DPN

39 Painful DPN

Symptoms, MCV, ankle pressure indices

4.7 years of follow-up



- No significant change in pain was observed during 5 years of FU.
- There was a significant fall in median nerve MCV

Natural history of Painful Sx. in Painful DPN

105 patients participating in clinical trials for the treatment of painful DPN

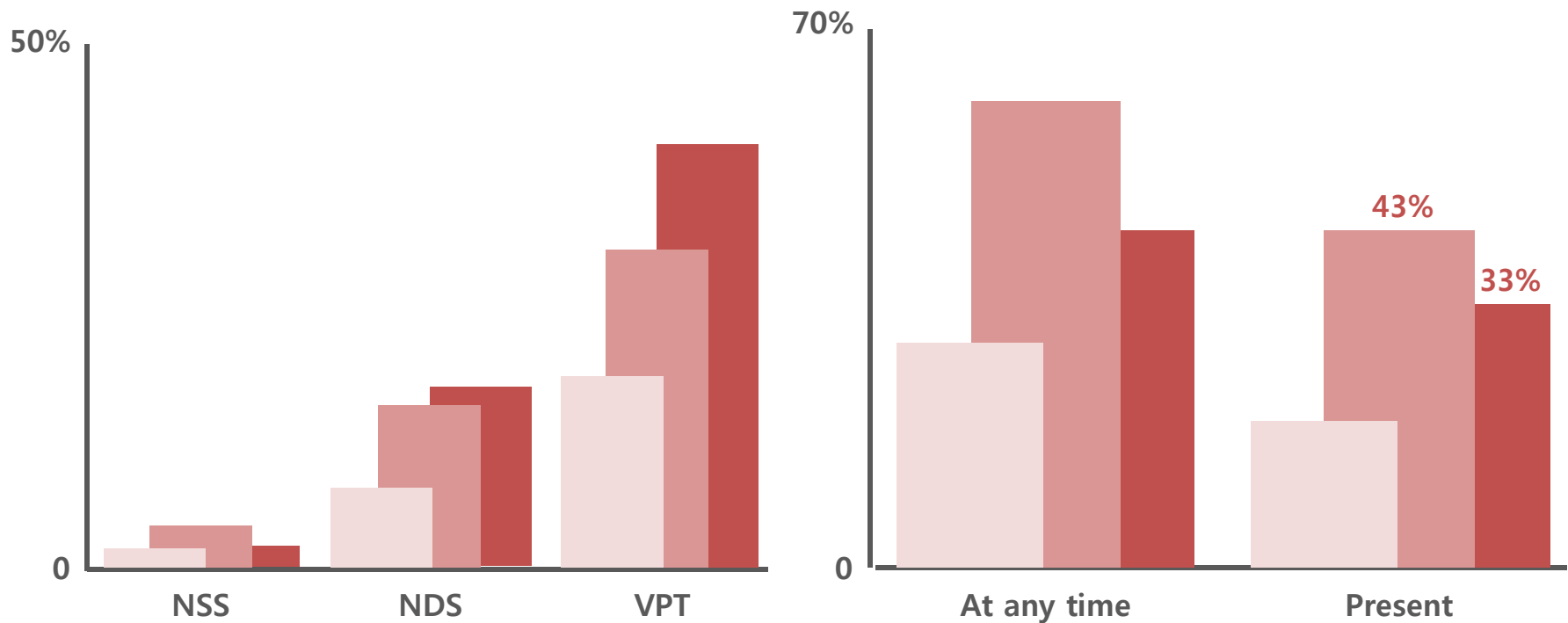
Survey

Pain since painful DPN onset

- 72% worsening
- 12% improvement
- 15% no change

Painful-painless leg

	Nonneuropathic	Neuropathic	Foot ulcer
N	24	30	40
Age	56.1 (38-76)	55.3 (21-73)	58.1 (41-72)
Diabetes duration	12.6 (0.4-40)	17.3 (0.2-61)	18.5 (1-46)

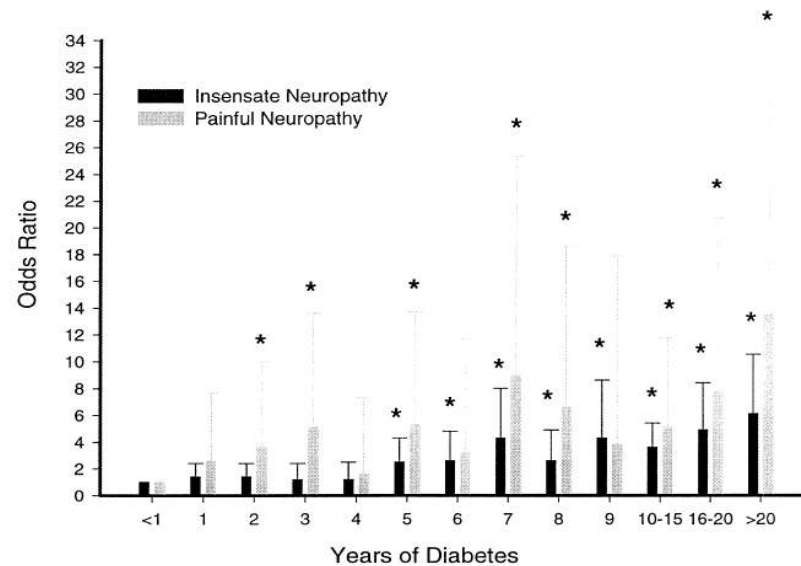


Relationships between neuropathic pain & DPN severity

	DPN (-)	Painless DPN	Painful DPN
	38	32	52
NSS	0.2±0.5	0.5±0.8	6.8±2.7
NDS	0.8±1.7	8.6±6.8	12.6±6.4
VPT (great toe, volts)	14.3±7.0	27.0±12.6	31.2±12.0
TDT (hand, °C)	0.26±0.15	0.6±0.9	0.5±0.6
TDT (Foot, °C)	1.0±2.6	6.9±7.7	6.3±7.8
PMCV (m/s)	44.3±5.3	36.6±5.7	36.0±7.5
Orthostatic hypotension (mmHg)	2.6±5.1	8.0±9.1	9.2±13.8
RR variation during deep breath (beat/min)	14±8.1	8.7±6.0	8.4±6.7
30:15 ratio	1.1±0.1	1.08±0.1	1.08±0.1

Two presentations of DPN - 'Not' mutually exclusive

	Pain	No pain	Odds ratio (OR)	P
Age (years)	55.5 (49.4–61.4)	53.8 (46.8–59.4)	1.03 (1.003–1.06)	NS
Years of Diabetes	7.1 (3.1–12.6)	2.3 (0.2–7.1)	1.09 (1.06–1.1)	<0.0001
Sex (%)	Males 60.0	Males 59.1	1.04 (0.7–1.6)	NS
Ethnicity (%)	Anglo 40.0 Other 60.0	Anglo 35.0 Other 65.0	1.2 (0.8–1.9)	NS
Treatment (%)	Diet 14.4 Tablets 64.7 Tabs/Insulin 21.1	Diet 31.6 Tablets 59.3 Tabs/Insulin 9.0	1.0 1.7 (0.9–2.8) 3.0 (1.4–6.3)	NS 0.005
Height (cm)	169 (161–177)	167 (159–174)	1.03 (1.003–1.05)	NS
HbA _{1c} (%)	8.2 (7.0–10.0)	8.0 (6.7–9.8)	1.03 (0.9–1.1)	NS
VPT (V)	26 (12.3–38)	14 (10–21)	1.06 (1.04–1.07)	<0.0001

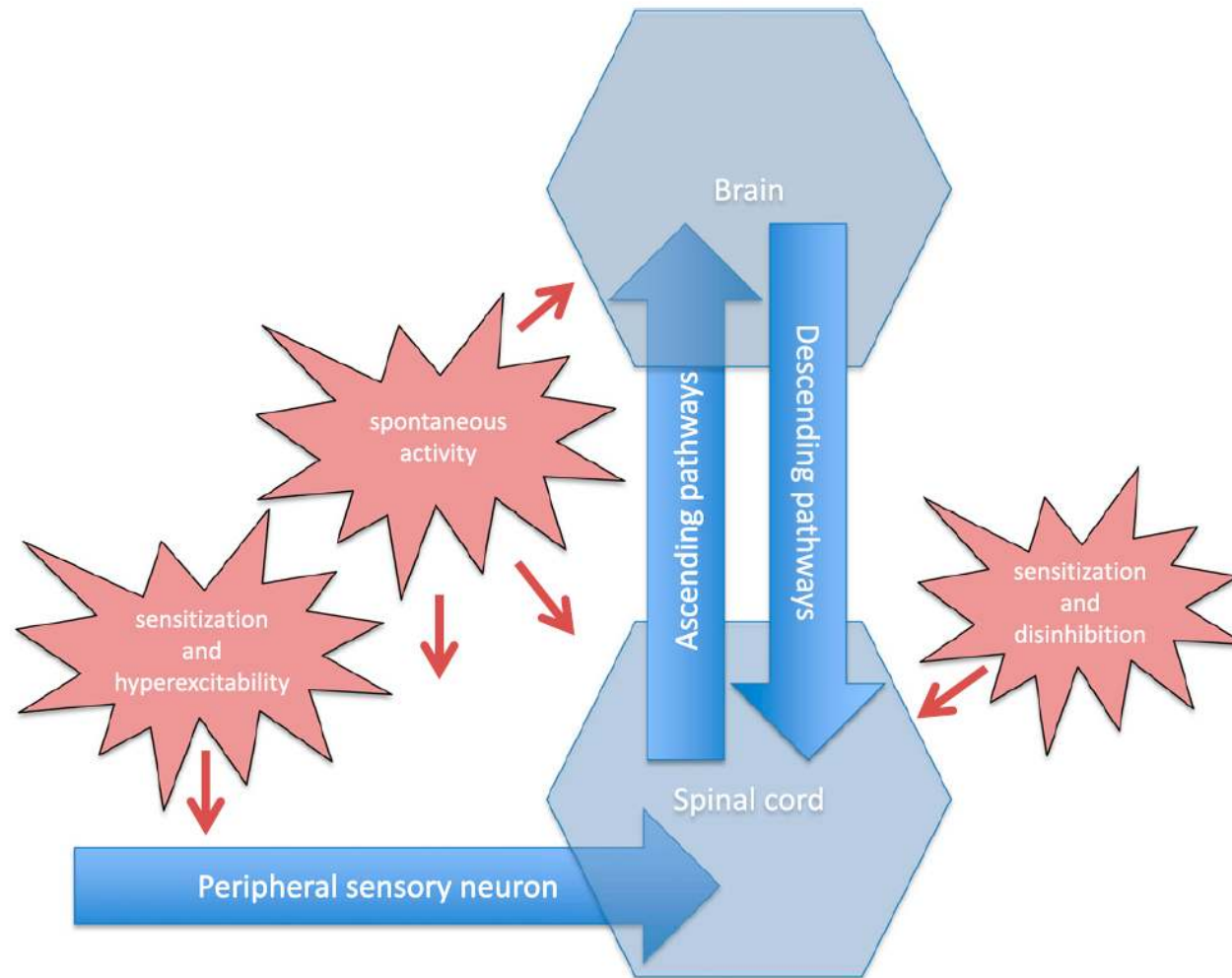


Relationship between neuropathic pain & severity of sensory loss

Degree of neuropathy assessed by the TCCS	N (%) with painful DPN or mixed pain	A1C, %	Duration of diabetes, yrs
No neuropathy (0-5)	8 (7.4)	6.9±1.3	6.1±5.6
Mild neuropathy (6-8)	20 (20.1)	7.3±1.3	8.8±6.5
Moderate neuropathy (9-11)	24 (64.9)	7.5±1.3	9.1±8.5
Severe neuropathy (≥12)	19 (67.9)	8.1±1.9	11.6±8.4
Total	71 (26.4)	7.3±1.4	8.0±6.9

Location, Location, Location?

Is the pain of DPN generated by hyperactive sensory neurons?

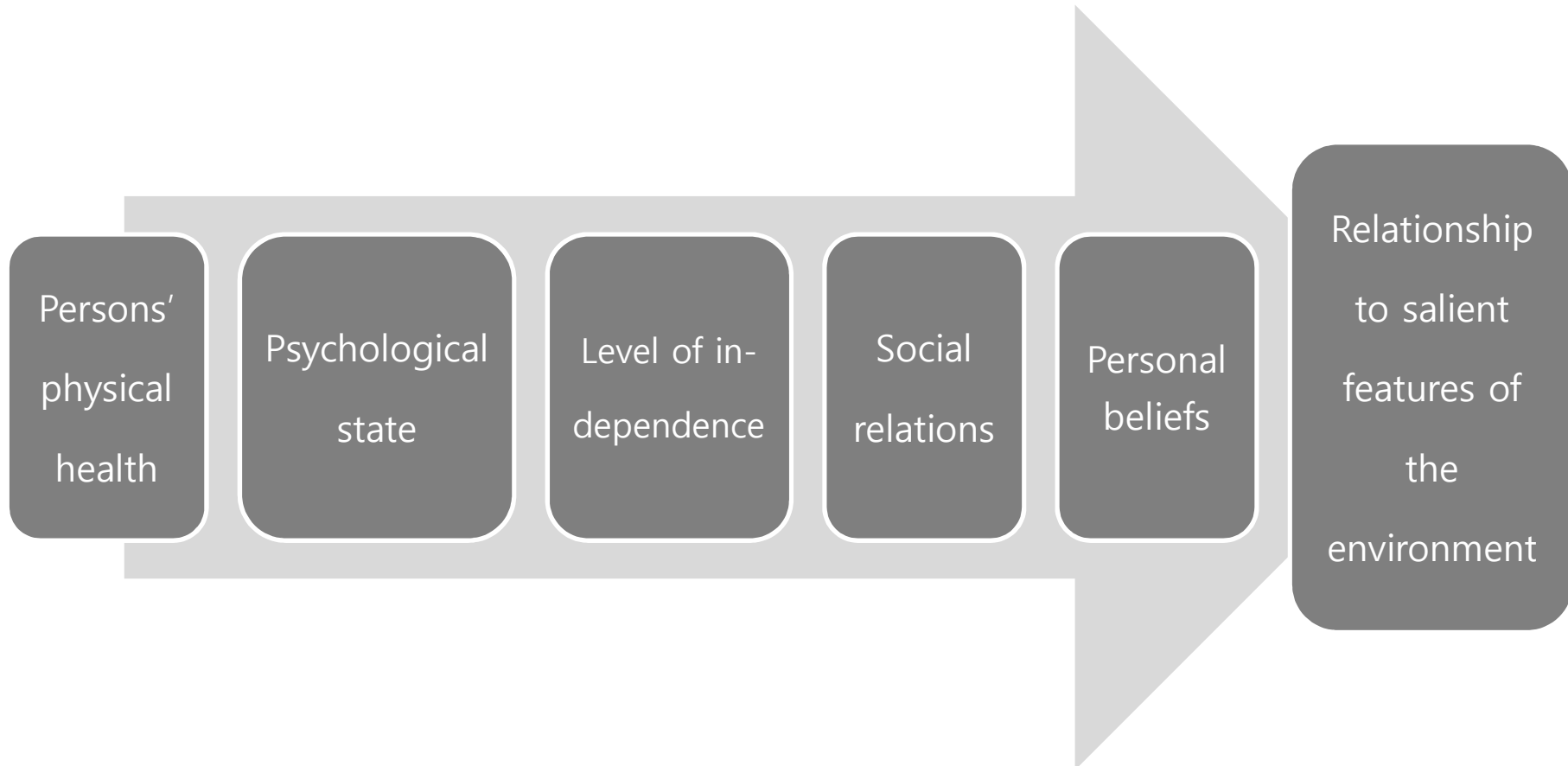


QoL for Painful/painless DPN



Quality of Life

Broad ranging concept, incorporating in a complex way



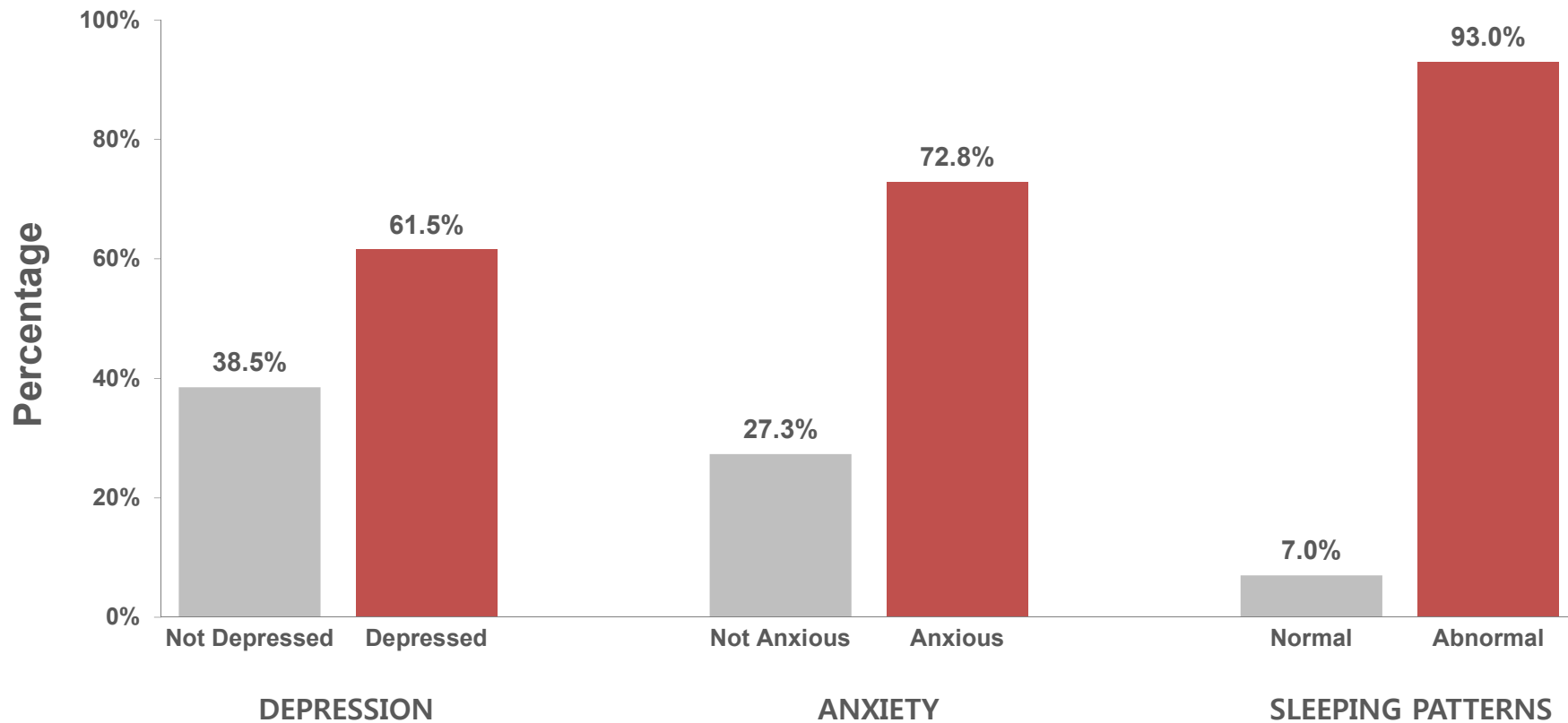
Pain in DPN & QoL

T1 & T2DM – 1,298
 NTSS-6-DN
 EQ5D, SF36, QoL-DN

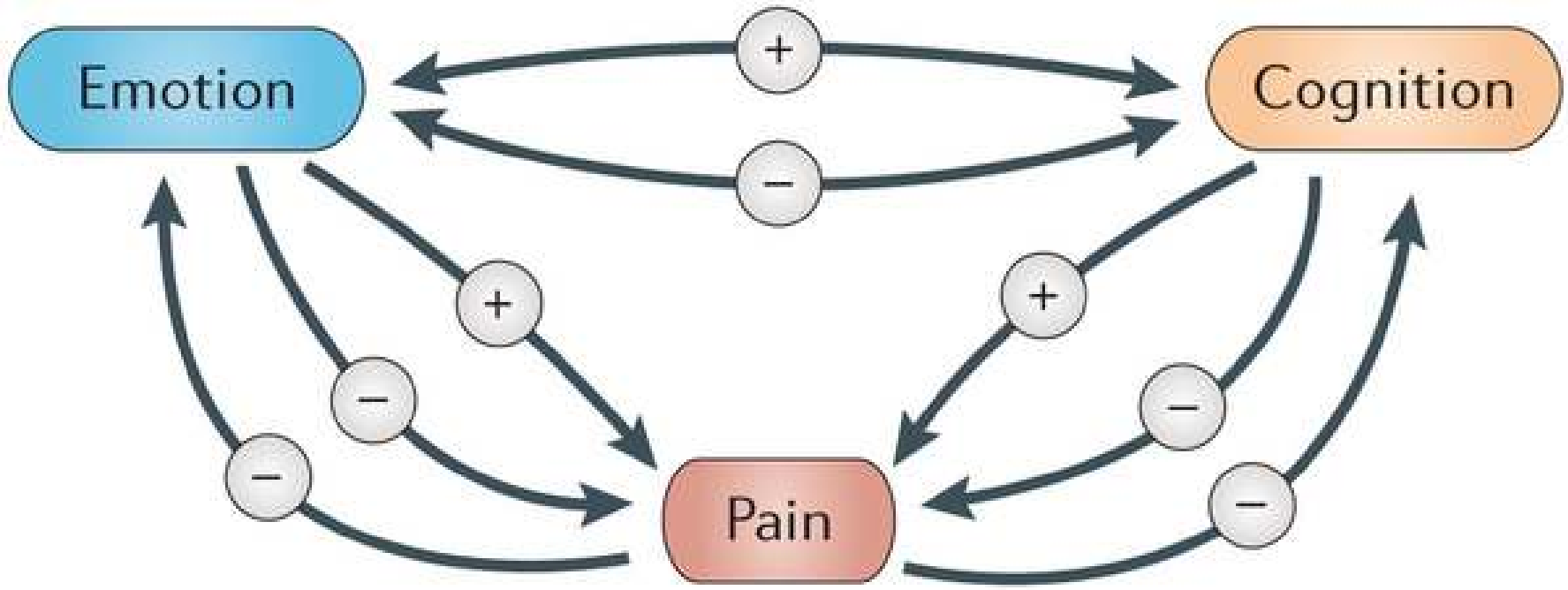
Parameter	β (95% CI)	<i>p</i>
EQ5D _{index} (patients with no diabetes-related complication): <i>n</i> =453		
Intercept	1.271 (1.116 to 1.426)	<0.001
NTSS-6-SA score	-0.043 (-0.048 to -0.037)	<0.001
Age (years)	-0.003 (-0.005 to -0.001)	<0.001
BMI	-0.010 (-0.014 to -0.006)	<0.001
EQ5D _{index} (patients with diabetes-related complication/s): <i>n</i> =177		
Intercept	1.196 (1.002 to 1.389)	<0.001
NTSS-6-SA score	-0.044 (-0.025 to -0.036)	<0.001
BMI	-0.016 (-0.022 to -0.009)	<0.001
QoL-DN: <i>n</i> =758		
Intercept	24.23 (21.17 to 27.29)	<0.001
NTSS-6-SA score	1.845 (1.697 to 1.993)	<0.001
Age (years)	0.080 (0.032 to 0.128)	<0.001
Sex (male)	-1.381 (-2.748 to -0.14)	0.048

Depression, Anxiety, Sleep – More Commonly Present With Pain Than Not

- Patients who had chronic pain for at least 3 months (N=400)

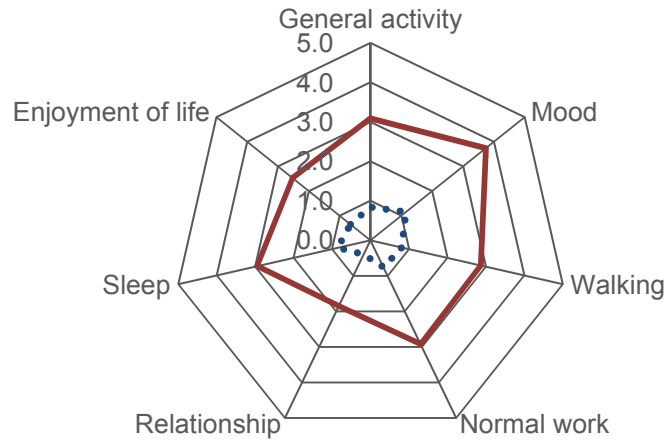


Feedback loops between pain, emotions and cognition

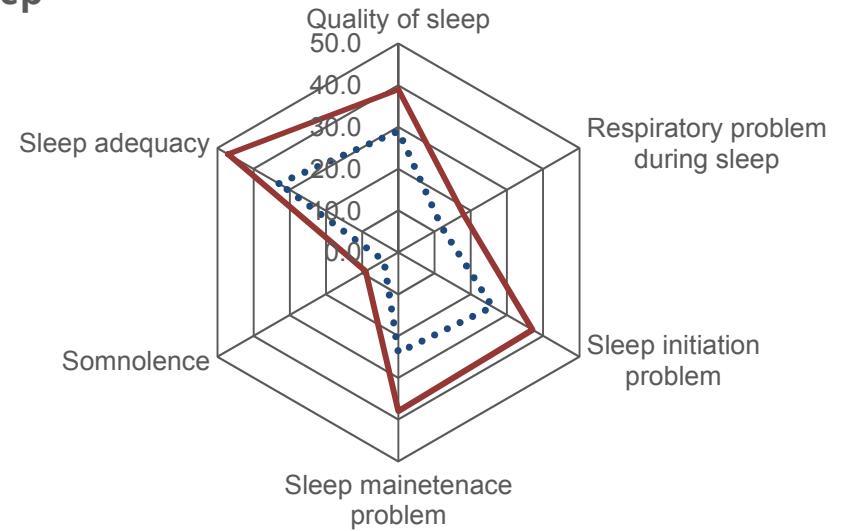


QoL in Painful vs. Non-painful DPN

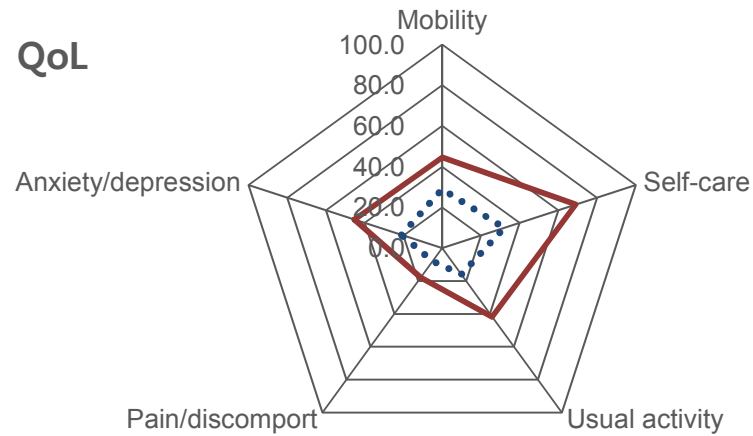
Pain Interference



Sleep

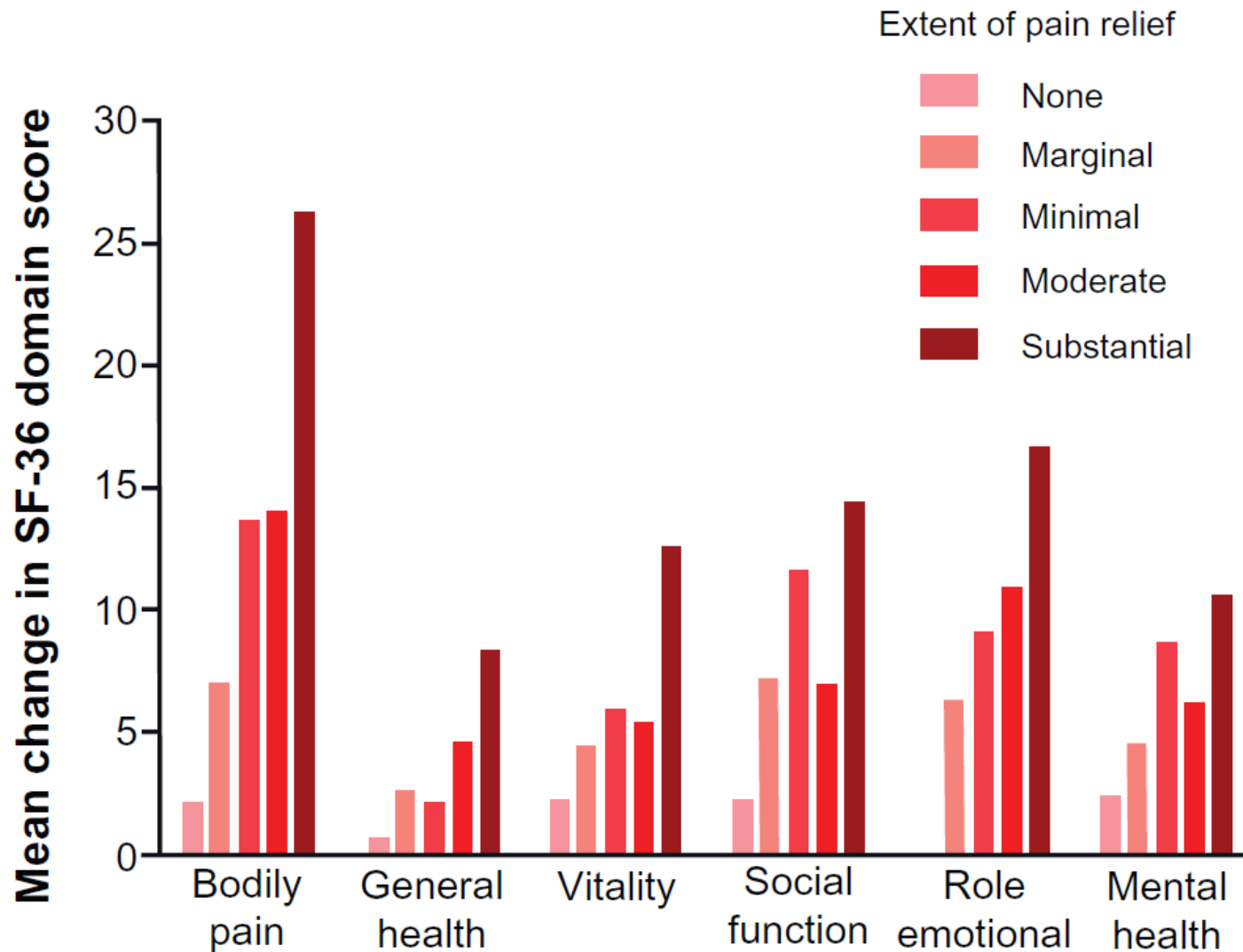


QoL



— Painful DPN
 Non-painful DPN

Changes in SF-36 scores with pregabalin



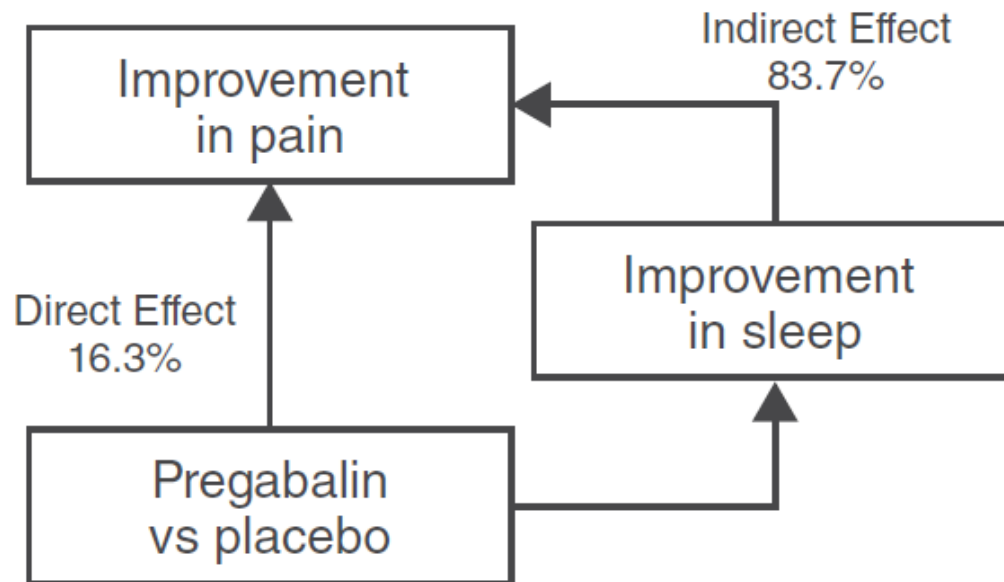
Sleep impairment in painful DPN

	MOS-1	MOS-2	MOS-3	MOS-4	MOS-5	MOS-6	SPI
Average Pain Score	0.21*	0.28*	0.28*	0.28*	0.22*	0.20*	0.34*
Pain interference score	0.40*	0.33*	0.39*	0.36*	0.29*	0.35*	0.50*

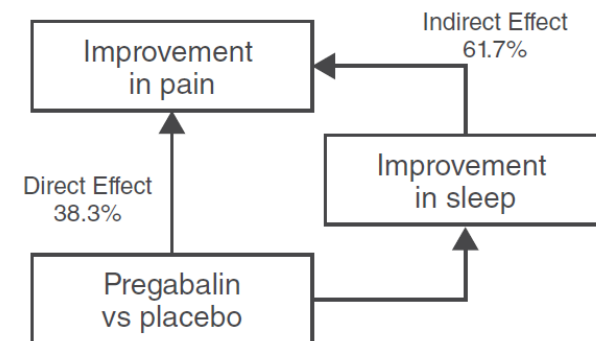
*All $P < 0.001$. †derived from MOS Sleep Scales. ‡derived from Brief pain index-short form. MOS-1, Sleep Adequacy; MOS-2, Respiratory Problem during Sleep; MOS-3, Sleep Initiation Problem; MOS-4, Sleep Maintenance Problem; MOS-5, Somnolence; MOS-6, Sleep Adequacy. MOS, medical outcome study; SPI, sleep problem index.

Prediction of Pregabalin-Mediated Pain Response by Severity of Sleep Disturbance

(A) DPN



(B) PHN



Summary

- Overall, we might estimate that 10-20% of all diabetes and 40-50% in patients with DPN have painful DPN.
- Age, female gender, glucose (especially, fasting), history of hypertension and cerebrovascular accident were risk factors for painful DPN versus painless DPN.
- Neuropathic pain can develop or persist also at advanced stages of DPN, and an increasing severity of sensory deficits is associated with an increased risk of developing neuropathic pain.
- Although they could develop in a dichotomous way with different predictors and imperfect overlapping, the clinical manifestations of painful and painless DPN was not mutually exclusive.
- As Painful DPN can significantly affect QoL, including sleep patterns, more attention is needed to assess and manage painful symptoms in diabetic patients.

Thank you for your attention!

