Parkinson's Disease in an Ageing Population: Epidemiological & Clinical Studies

Parkinson's Foundation
CENTER OF EXCELLENCE

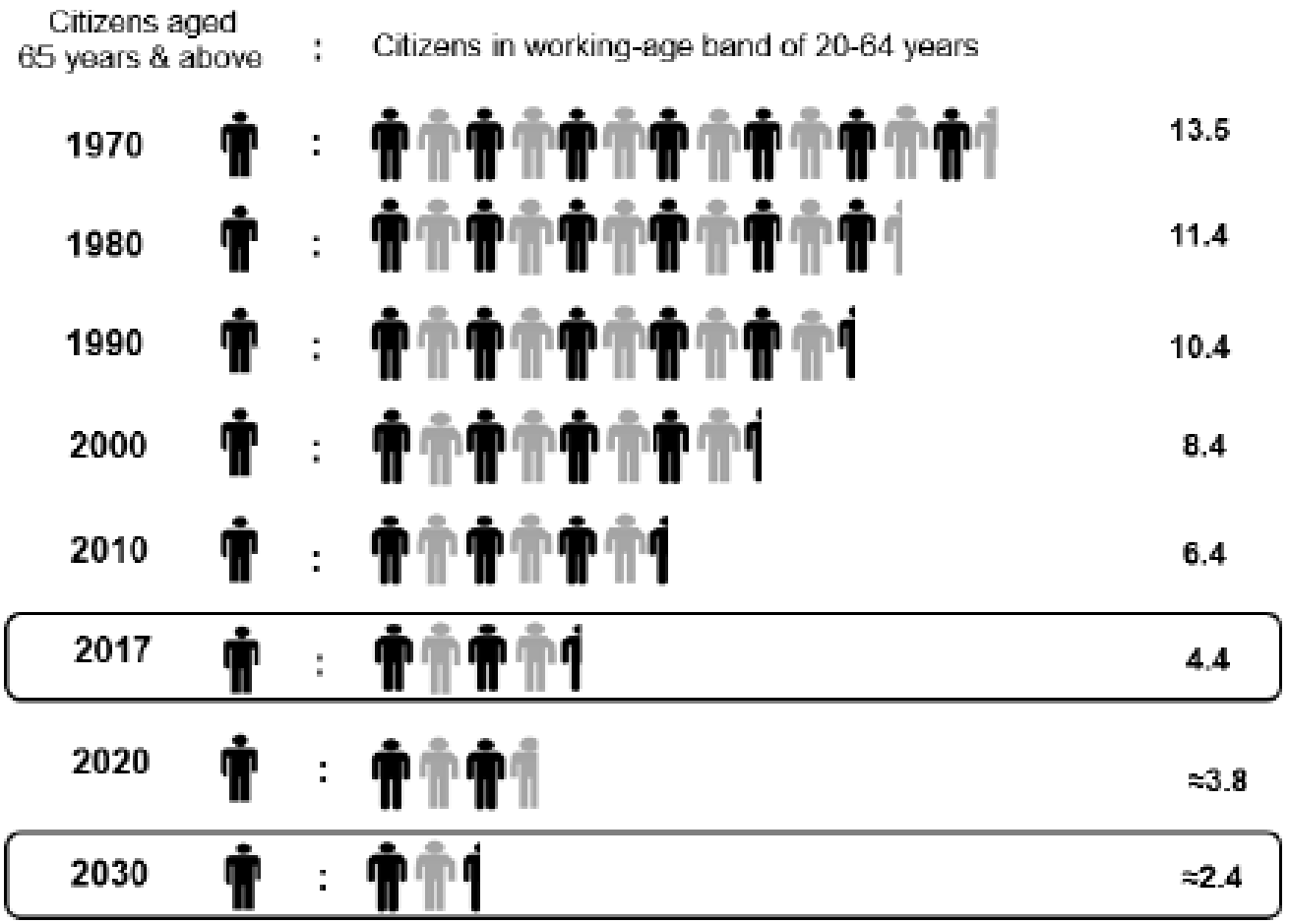
National Neuroscience Institute
SingHealth

A/Prof Louis Tan

National Neuroscience Institute, Singapore

Fewer Working-Age Citizens to Each Citizen Aged 65 and Above

Chart 5: Citizen old-age support ratio, 1970-2030



Source: Department of Statistics

Prevalence of Parkinson disease in Singapore

Chinese vs Malays vs Indians

L.C.S. Tan, MRCP(UK); N. Venketasubramanian, MMed; C.Y. Hong, FRACGP; S. Sahadevan, MRCP(UK); J.J. Chin, MRCP(UK); E.S. Krishnamoorthy, MD; A.K.Y. Tan, MRCP(UK); and S.M. Saw, PhD

Abstract—*Objective:* To investigate the prevalence of Parkinson disease (PD) in Singapore and compare the rates between Singaporean Chinese, Malays, and Indians. *Methods*: A three-phase community-based survey among a disproportionate random sample of 15,0[illegible] aged 50 years and above who live in central Singapore was [illegible] door-to-door survey using a validated 10-question questionnaire. In phase 2, medical specialists examined participants who screened positive to any of the questions. Participants suspected to have [illegible] confirmed in phase 3 by a movement disorders specialist. *Results*: The participation rate was 67% among 22,279 eligible individuals. Forty-six participants with PD were identified of which 16 were newly diagnosed cases. The prevalence rate of PD for those aged 50 and above in Singapore was 0.30% (95% CI: 0.22 to 0.41), age-adjuste[illegible] cases. [illegible]valence rates increased significantly with age. The age-adjusted prevalence rates among Chinese (0.33%, 95% CI: 0.22 to 0.48), Malays (0.29%, 95% CI: 0.13 to 0.67), and Indians (0.28%, 95% CI: 0.12 to 0.67) were the same ($p = 1.0$). *Conclusions*: The prevalence of PD in Singapore was comparable to that of Western countries. Race-specific rates were also similar to previously reported rates and similar among the three races. Environmental factors may be more important than racially determined genetic factors in the development of PD.

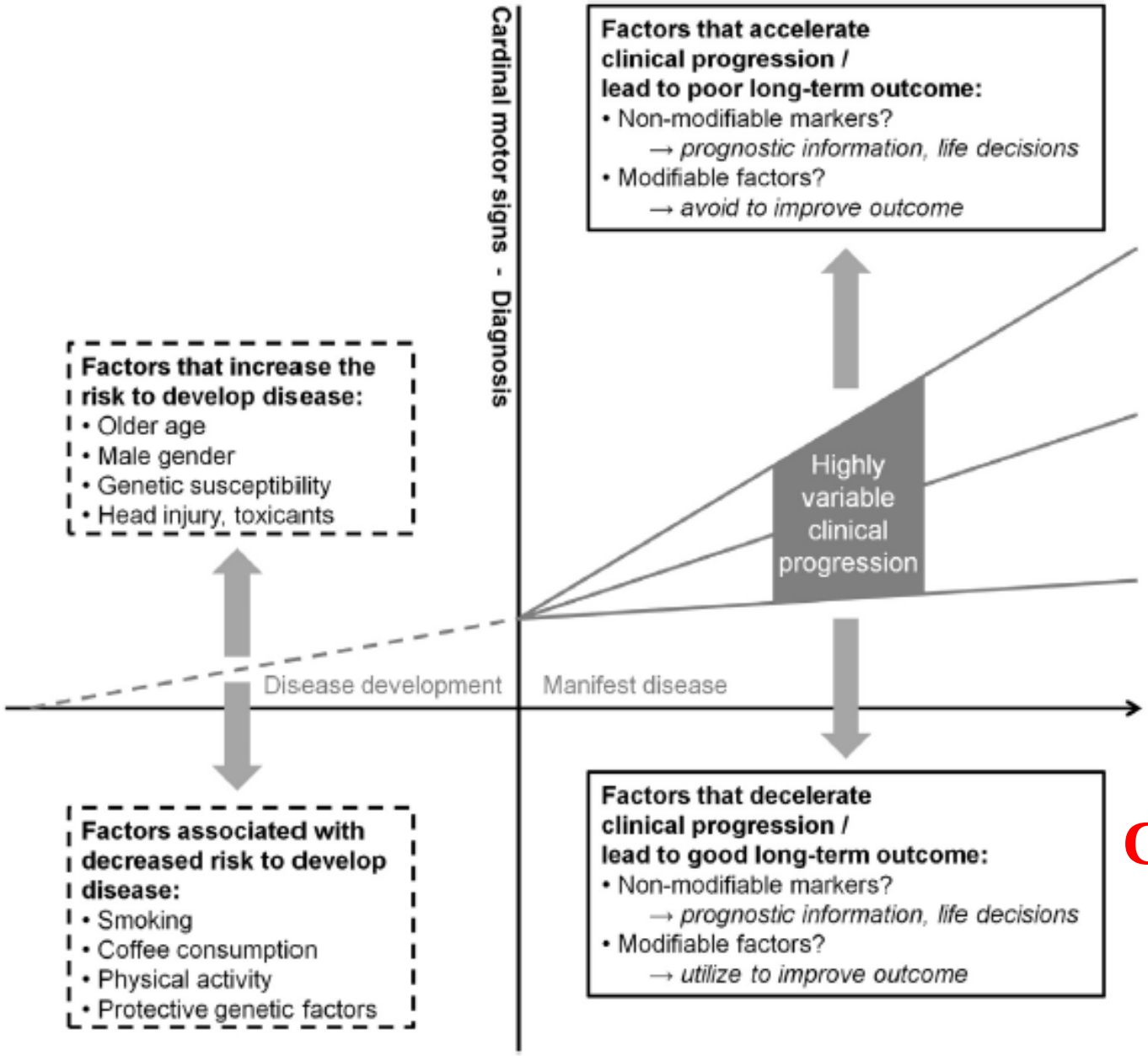
NEUROLOGY 2004;62:1999–2004

Singapore PD Population

2016: 6,070

2030: 12,121

http://www.populationpyramid.net/singapore/2030/



Clinical Course of PD

Puschmann, et al. PRD 2015;21:675-682

Tea & PD

- 11 case-control and 1 cohort study
- Pooled OR 0.83 (95% CI: 0.74-0.92)
- Significant heterogeneity across studies
- Chinese: OR 0.73 (95% CI: 0.6-0.9), homogeneity present (3 case-control studies)

Quintana, et al. J of Am College of Nutrition 2009;28:1-6

Black Tea & PD

Singapore Chinese Health Cohort Study

Characteristics	Cases	HR (95% CI)	Adjusted for smoking status HR (95% CI)
Black tea			
Non-drinker	120	1.00	1.00
T1 (< 5 cups/mth)	20	0.89 (0.55-1.42)	0.87 (0.54-1.40)
T2 (5–23 cups/mth)	11	0.55 (0.30-1.03)	0.53 (0.29-1.00)
T3 (23+ cups/mth)	6	0.29 (0.13-0.65)	0.28 (0.12-0.64)
P for trend		0.0006	0.0004

- Green tea was not associated with ↓ PD risk
- Black tea effect present even after correction for caffeine

Tan, et al. Am J of Epidemiology 2008;167(5):553-60

Cholesterol, Fats & PD

Movement disorders JNNP 2016;87:86-92

RESEARCH PAPER

Dietary cholesterol, fats and risk of Parkinson's disease in the Singapore Chinese Health Study

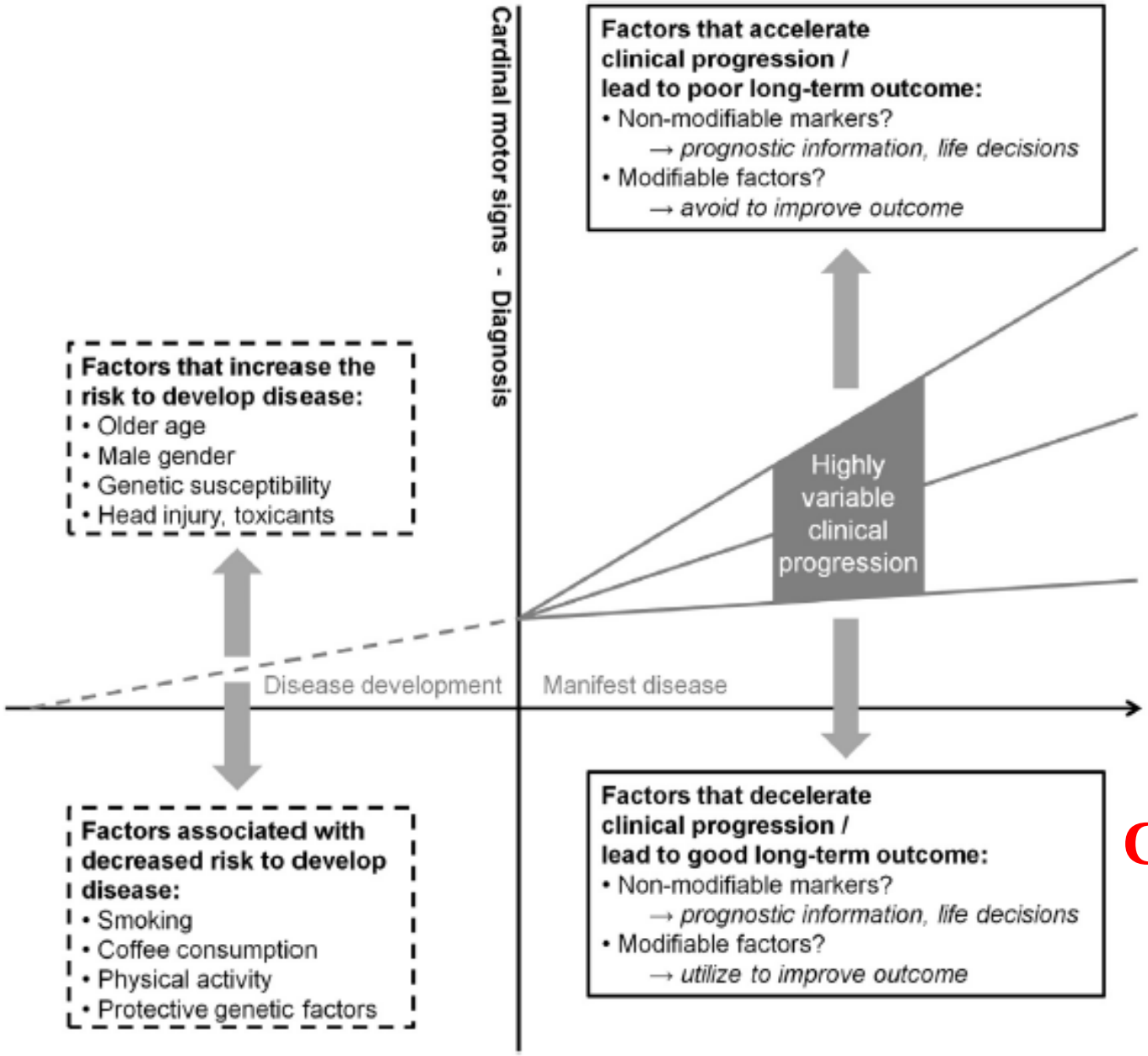
Louis C Tan,[1,2] Kulthida Methawasin,[1] Eng-King Tan,[1,2] June H Tan,[3] Wing-Lok Au,[1,2] Jian-Min Yuan,[4,5] Woon-Puay Koh[2,6]

Table 3 Dietary cholesterol and fatty acids in relation to risk of Parkinson's disease, The Singapore Chinese Health Study 1993–2010

Energy-adjusted intake by quartile	Total Cases	HR (95% CI)	Men Cases	HR (95% CI)	Women Cases	HR (95% CI)
Cholesterol (mg/day)						
1st (<130.7)	130	1.00	82	1.00	48	1.00
2nd (130.7–166.5)	115	0.96 (0.74 to 1.23)	56	0.94 (0.67 to 1.32)	59	1.00 (0.68 to 1.47)
3rd (166.5–206.4)	91	0.84 (0.64 to 1.10)	44	0.83 (0.57 to 1.19)	47	0.87 (0.58 to 1.31)
4th (>206.4)	75	0.77 (0.58 to 1.02)	36	0.62 (0.42 to 0.93)	39	0.98 (0.64 to 1.5)
P for trend		0.046		0.018		0.72
Monounsaturated fatty acids (g/day)						
1st (<12.8)	116	1.00	69	1.00	47	1.00
2nd (12.8–14.9)	121	1.10 (0.85 to 1.42)	63	1.27 (0.9 to 1.79)	58	0.88 (0.6 to 1.29)
3rd (14.9–17.0)	102	1.01 (0.77 to 1.33)	45	1.05 (0.72 to 1.53)	57	0.90 (0.61 to 1.33)
4th (>17.0)	72	0.80 (0.60 to 1.08)	41	1.03 (0.7 to 1.52)	31	0.57 (0.36 to 0.90)
P for trend		0.16		0.99		0.029

Cholesterol, Fats & PD: biological plausibility

- **Cholesterol** levels highest in brain (25%)
- chol turnover ↑ in neurodegen disorders
- α-synuclein binds to chol with high affinity, aggregation modified by chol
- **MUFA** has anti-inflammatory and immune-modulatory, anti-oxidant
- **Gender differences** in lipoprotein metabolism



Clinical Course of PD

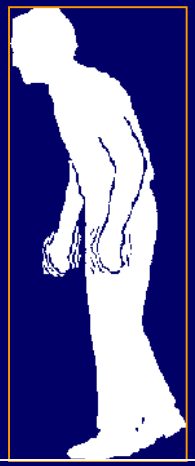
Puschmann, et al. PRD 2015;21:675-682

Clinical Measures of PD Progression

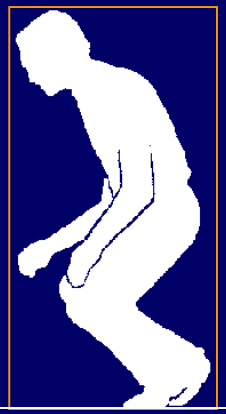
- UPDRS – motor, ADL, total score
- H&Y – time to stage 3, transition times
- Other motor/disability scales - Columbia score, Northwestern Disability scale, UCLA scale
- Levodopa therapy – time to levodopa use
- Quality of life measures

Stages of PD
Modified Hoehn & Yahr Staging

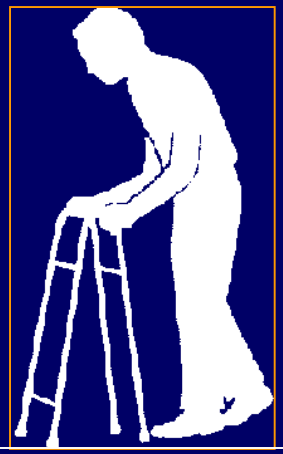
Stage 1 & 1.5
Unilateral disease
1.5: + axial involvement



Stage 2 & 2.5
Bilateral disease without impairment of balance
2.5: recovery on pull test



Stage 3
Mild-mod bilateral disease, some postural instability, physically independent



Stage 4
Severe disability; still able to walk or stand unassisted

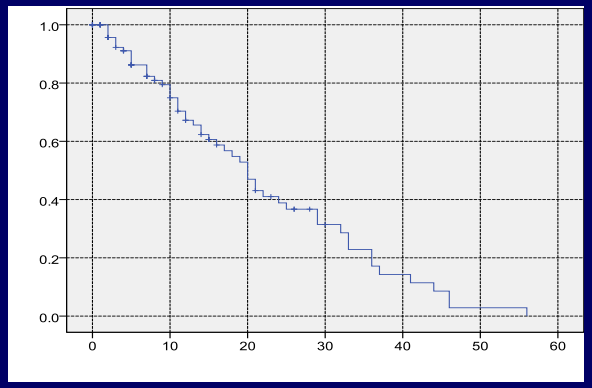
Stage 5
Wheelchair bound or bedridden unless aided

Progression of PD Study
Analyses

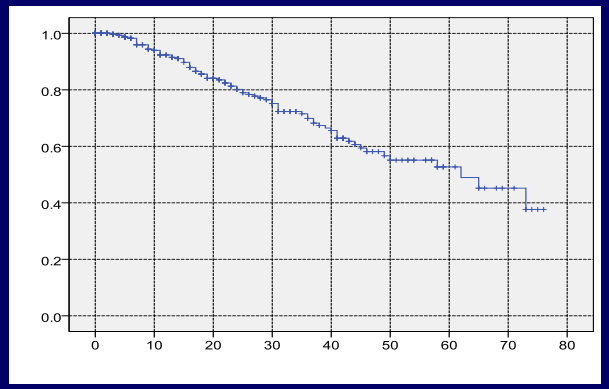
- Kaplan-Meier survival analysis in view of unequal follow-up times
- Entry requirement:
  - At H&Y stage at or within 1 year from PD diagnosis, or
  - clear documentation of entry from a prior H&Y stage
- Failure/transition event:
  - Progression to next H&Y stage
- 695 patients analysed

H&Y Progression

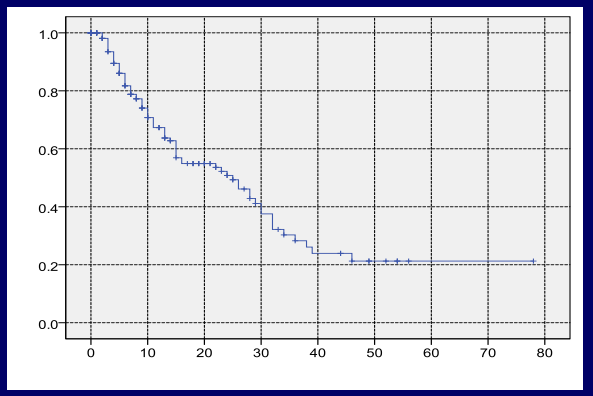
Median time to transitions



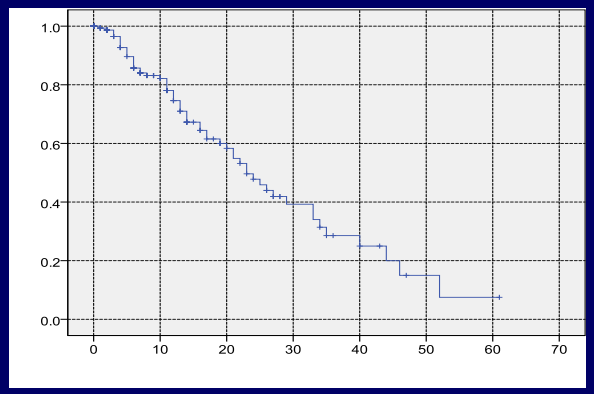
Stage 1 to 2, n=106
20.0 (1.7) mths



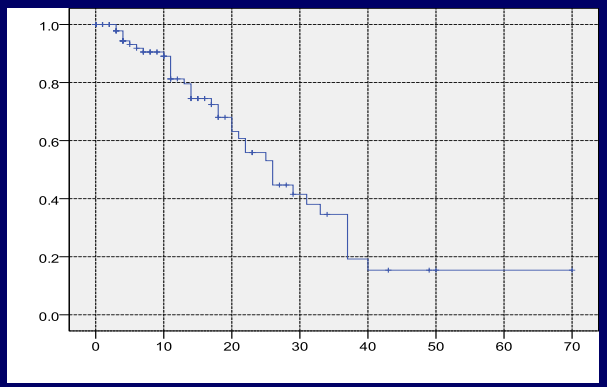
Stage 2 to 2.5, n=359
62.0 (7.7) mths



Stage 2.5 to 3, n=194
25.0 (4.6) mths



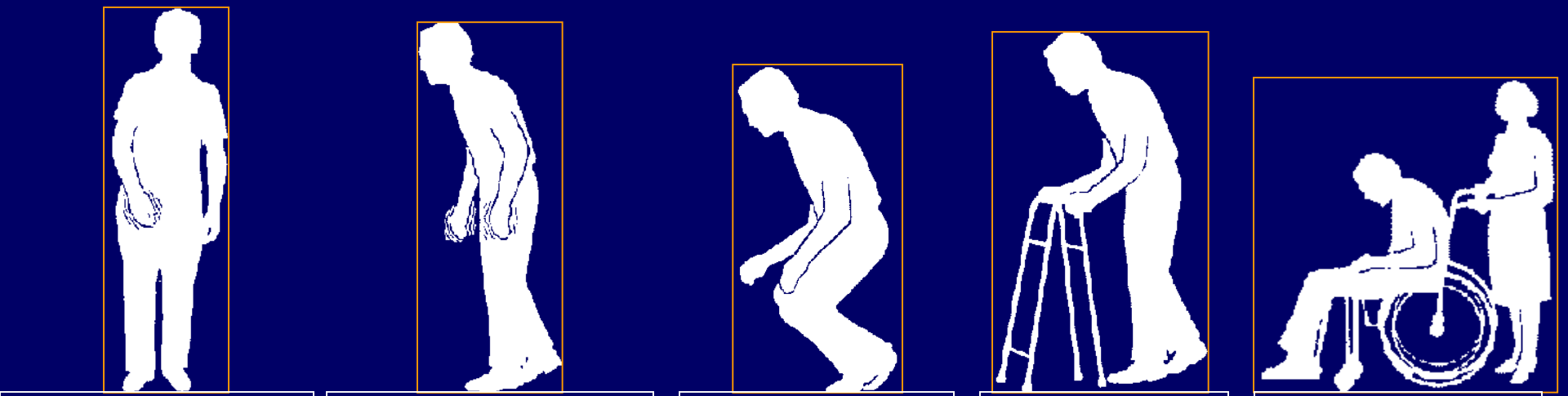
Stage 3 to 4, n=185
24.0 (2.7) mths



Stage 4 to 5, n=114
26.0 (2.7) mths

Movement Disorders
2010, 25:710-716

Modified Hoehn & Yahr Staging
Measuring Disease Progression



20 mths/1.7 yrs

25 mths/2.1 yrs

24 mths/2 yrs

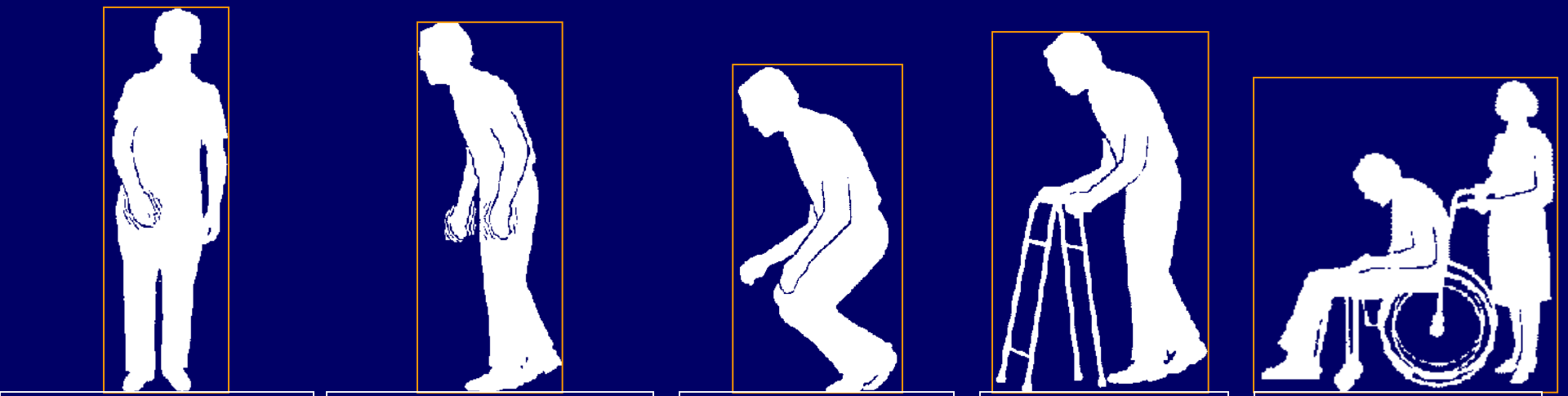
26 mths/2.2 yrs

62 mths/5.2 yrs

Zhao, Tan, et al. Movement Disorders 2010, 25:710-716

Modified Hoehn & Yahr Staging

Factor Affecting Disease Progression



Stage 1 & 1.5 | Stage 2 & 2.5 | Stage 3 | Stage 4 | Stage 5

↑ UPDRS motor

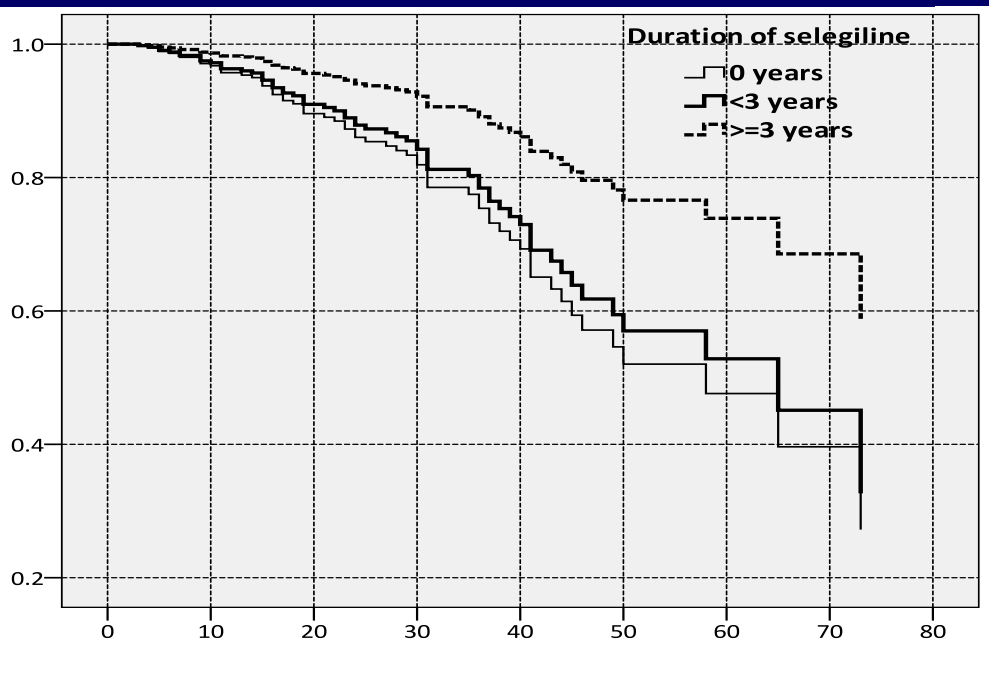
↑ disease duration

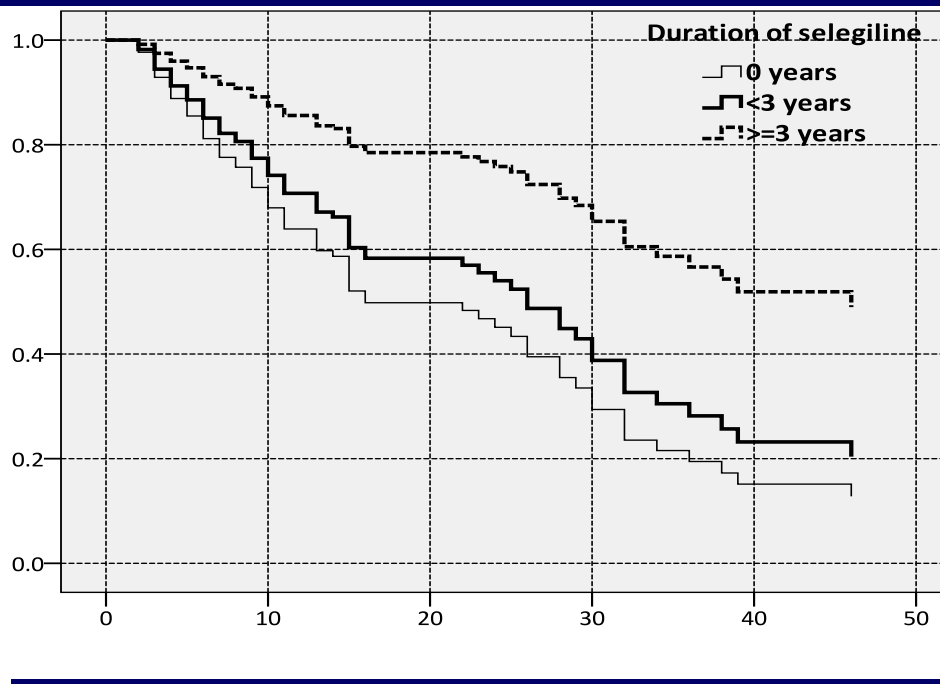
↑ UPDRS motor

Older age at diagnosis, ↑ disease duration, ↑ UPDRS motor

Zhao, Tan, et al. Movement Disorders 2010, 25:710-716

Effect of Selegiline on PD Progression





Transition from stage 2 to 2.5 (*p=0.03*)

Transition from stage 2.5 to 3 (*p=0.002*)

Tan et al, Parkinsonism and Related Disorders 2011;17:194-197

ORIGINAL ARTICLE

Clinical evolution of Parkinson's disease and prognostic factors affecting motor progression: 9-year follow-up study

G. Reinoso[a], J. C. Allen Jr[a], W.-L. Au[b,c], S.-H. Seah[b,c], K.-Y. Tay[b,c] and L. C. S. Tan[b,c]

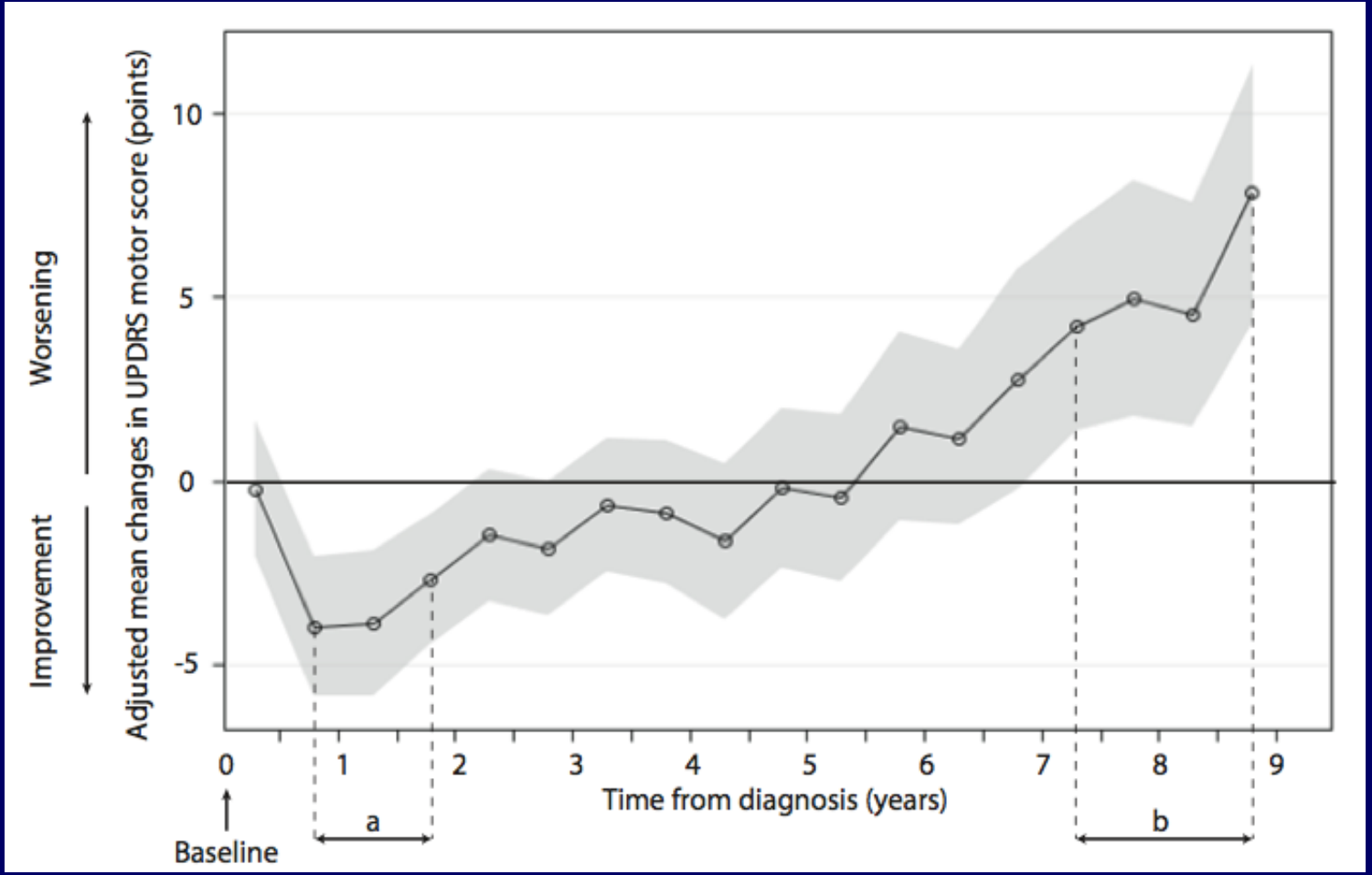
[a]*Duke – NUS Graduate Medical School, Singapore;* [b]*Department of Neurology, National Neuroscience Institute, Singapore; and* [c]*Parkinson's Disease and Movement Disorders Centre, USA National Parkinson Foundation Centre of Excellence, National Neuroscience Institute, Singapore, Singapore*

576 patients derived from the NNI Movement Disorders Database (2002-2012) were selected with the following criteria:

- Idiopathic PD (based on NINDS criteria)
- Did not undergo DBS surgery
- Baseline assessment done within 2 years of diagnosis
- Followed up for at least 3 years

Reinoso, Tan, et al. Eur J Neurol 2015;22(3):457-63

Progression was non-linear

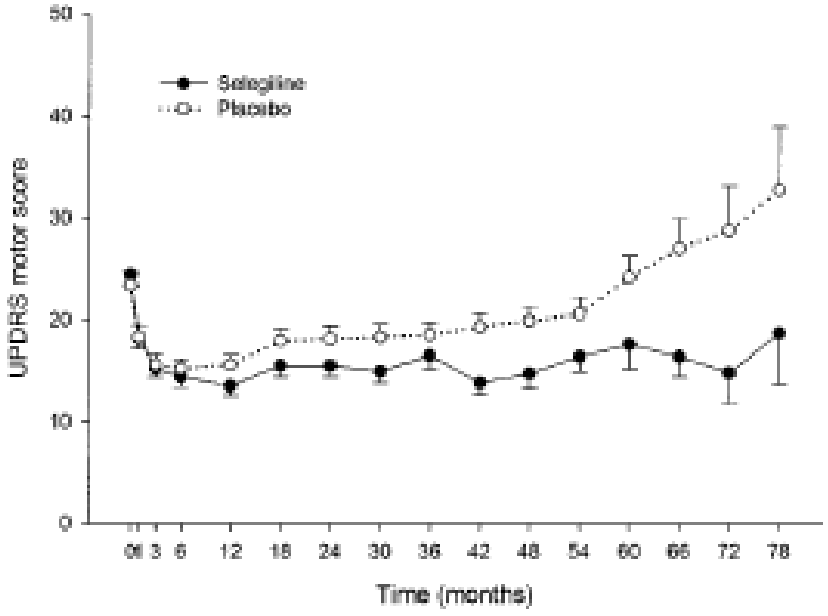


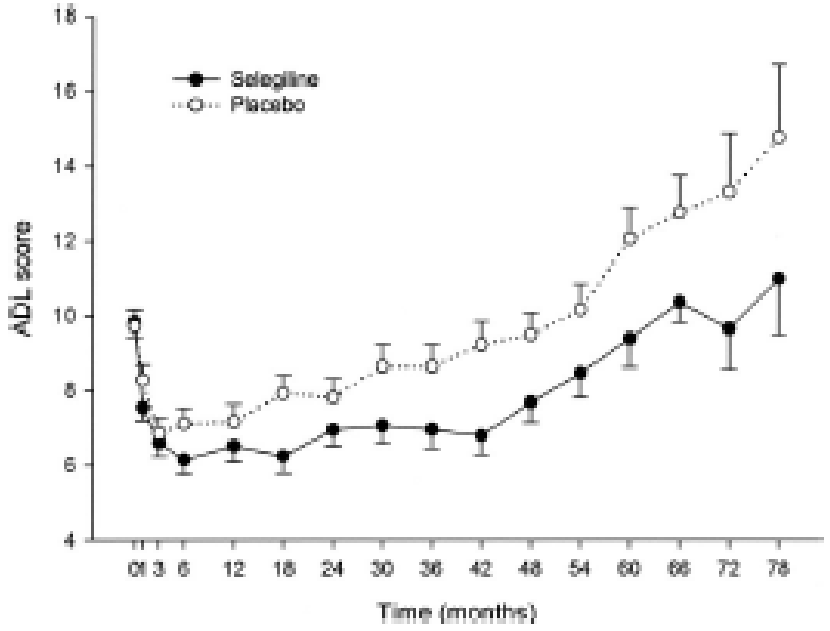
Reinoso, Tan, et al. Eur J Neurol 2015;22(3):457-63

Selegiline slows the progression of the symptoms of Parkinson disease

S. Pålhagen, MD; E. Heinonen, MD; J. Hägglund, MD; T. Kaugesaar, MD; O. Mäki-Ikola, MD; R. Palm, MD; and the Swedish Parkinson Study Group*

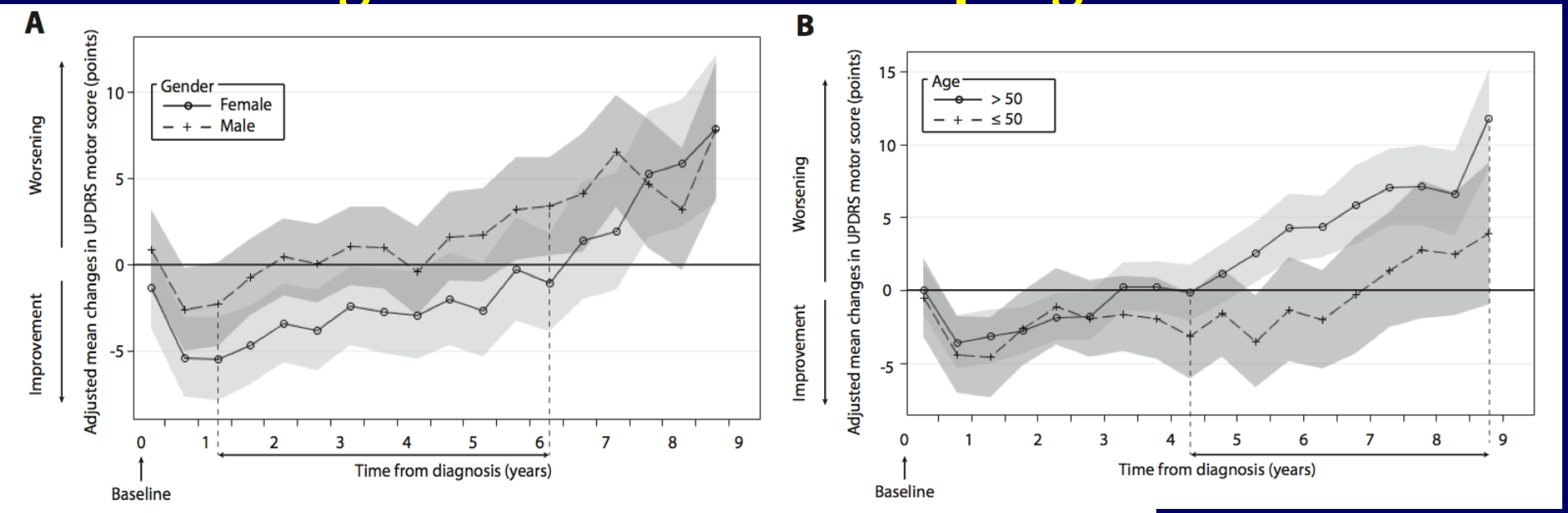
Abstract—*Objective:* To study the long-term effects of selegiline in monotherapy and in combination with levodopa in the early phase of Parkinson disease (PD). *Methods:* One hundred fifty-seven de novo PD patients were randomized in a double-blind, placebo-controlled study of 7 years' duration. In the monotherapy part, selegiline significantly delayed the initiation of levodopa therapy vs placebo. The authors now report the results from the combination part of the study, in which 140 patients received selegiline or placebo in addition to individually tailored levodopa therapy. *Results:* Compared with placebo, selegiline slowed the progression of disease disability as measured by the Unified Parkinson Disease Rating Scale (UPDRS) total score ($p = 0.003$) or by motor ($p = 0.002$) and Activities of Daily Living ($p = 0.0002$) subscores. After 5 years in combination therapy, the mean difference in the UPDRS total score was nearly 10 points, with patients

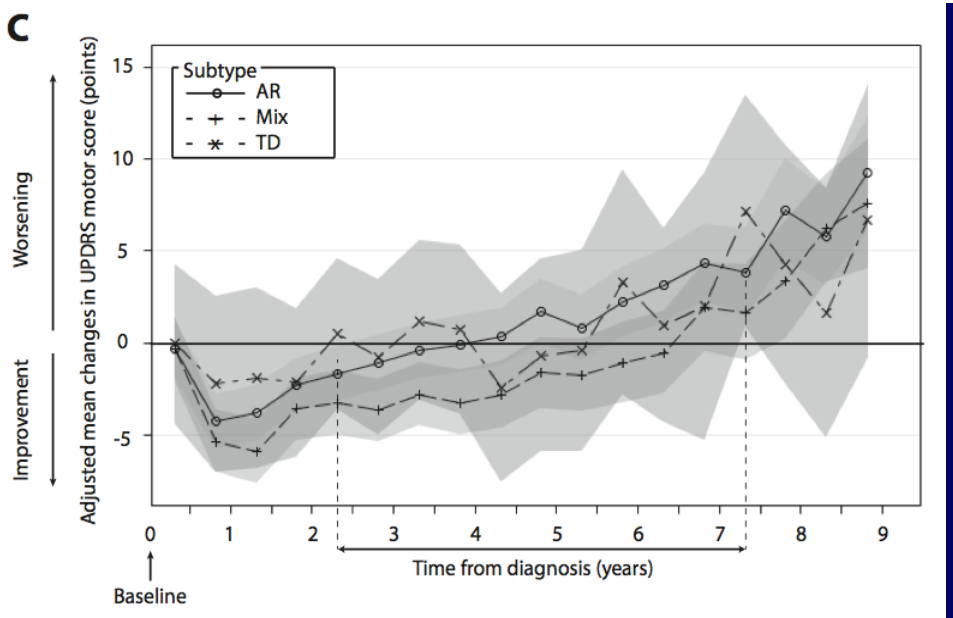




Palhagen et al, Neurology 2006;66:1200-6

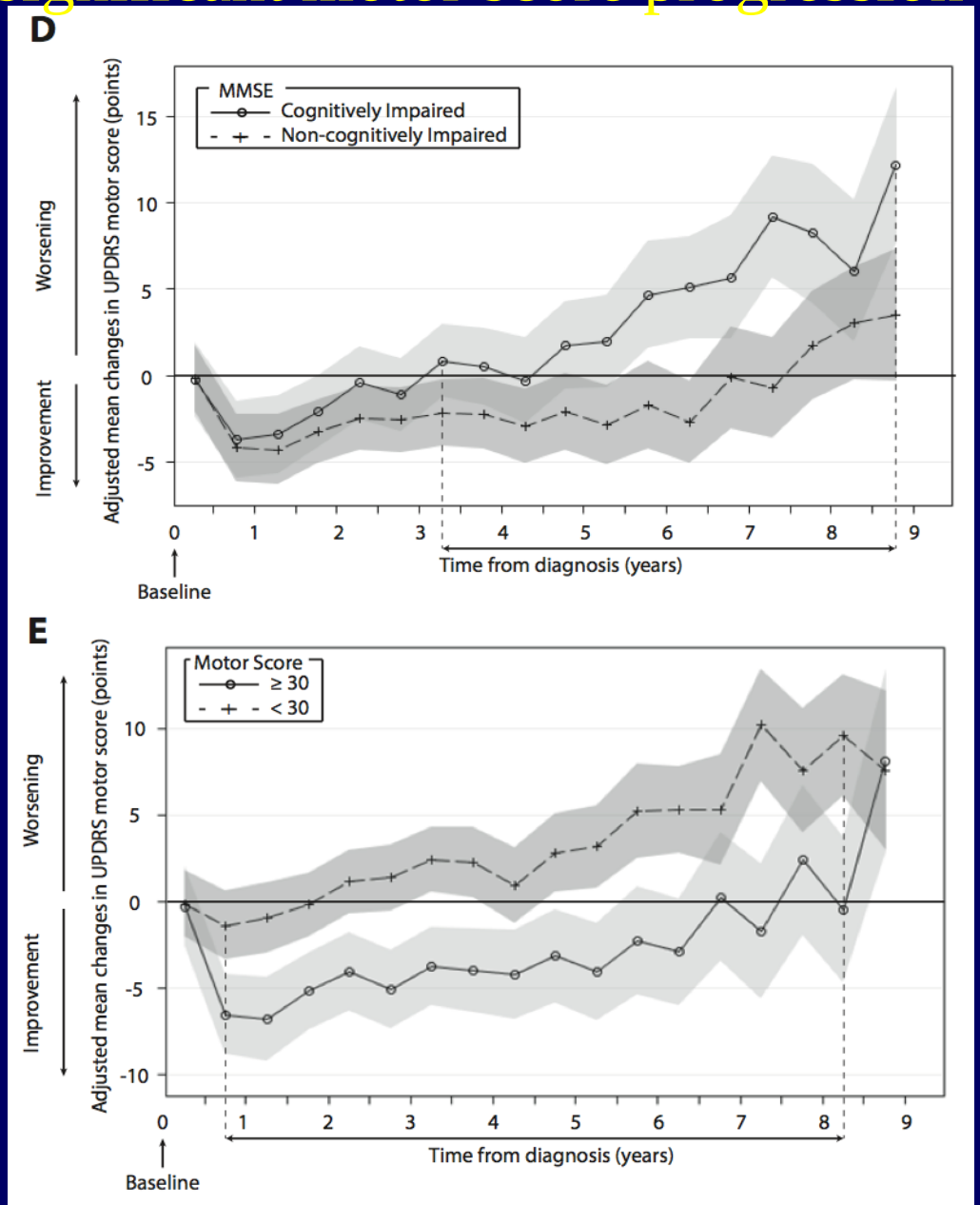
Male, Older age at diagnosis, AR subtype had significant motor score progression





Reinoso, Tan, et al.
Eur J Neurol
2015;22(3):457-63

Cognitively impaired and low baseline motor score had significant motor score progression

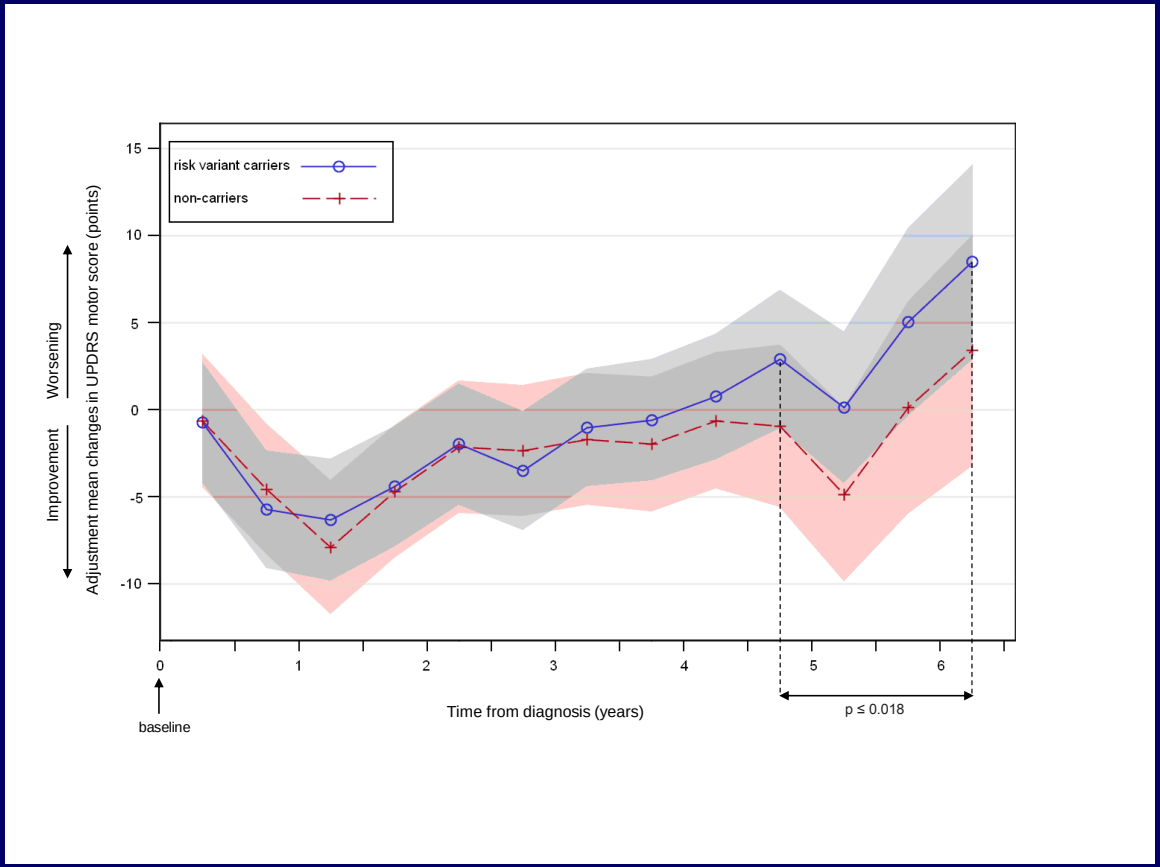


Reinoso, Tan, et al.
Eur J Neurol 2014

Clincal Evolution of PD
Conclusions

- When measured clinically, disease progression was non-linear, and occurred in distinct phases
- Factor associated with ↑ disease progression:
  - male gender
  - older age at diagnosis
  - cognitive impairment
  - akinetic-rigid subtype
  - low baseline motor score

LRRK2 risk variant carriers vs non-carriers



risk variant carriers had a greater rate of motor progression than non-carriers after 4 years from the date of diagnosis ($p \leq 0.018$)

Oosterveld, Tan, et al. Neurology 2015;85:1039–1042

Parkinsonism and Related Disorders 21 (2015) 226–230

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Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Prognostic factors for early mortality in Parkinson's disease

Linda P. Oosterveld [a, b, 1], John C. Allen Jr. [c], Giselle Reinoso [a, b, c], Soo-Hoon Seah [a, b], Kay-Yaw Tay [a, b], Wing-Lok Au [a, b], Louis C.S. Tan [a, b, *]

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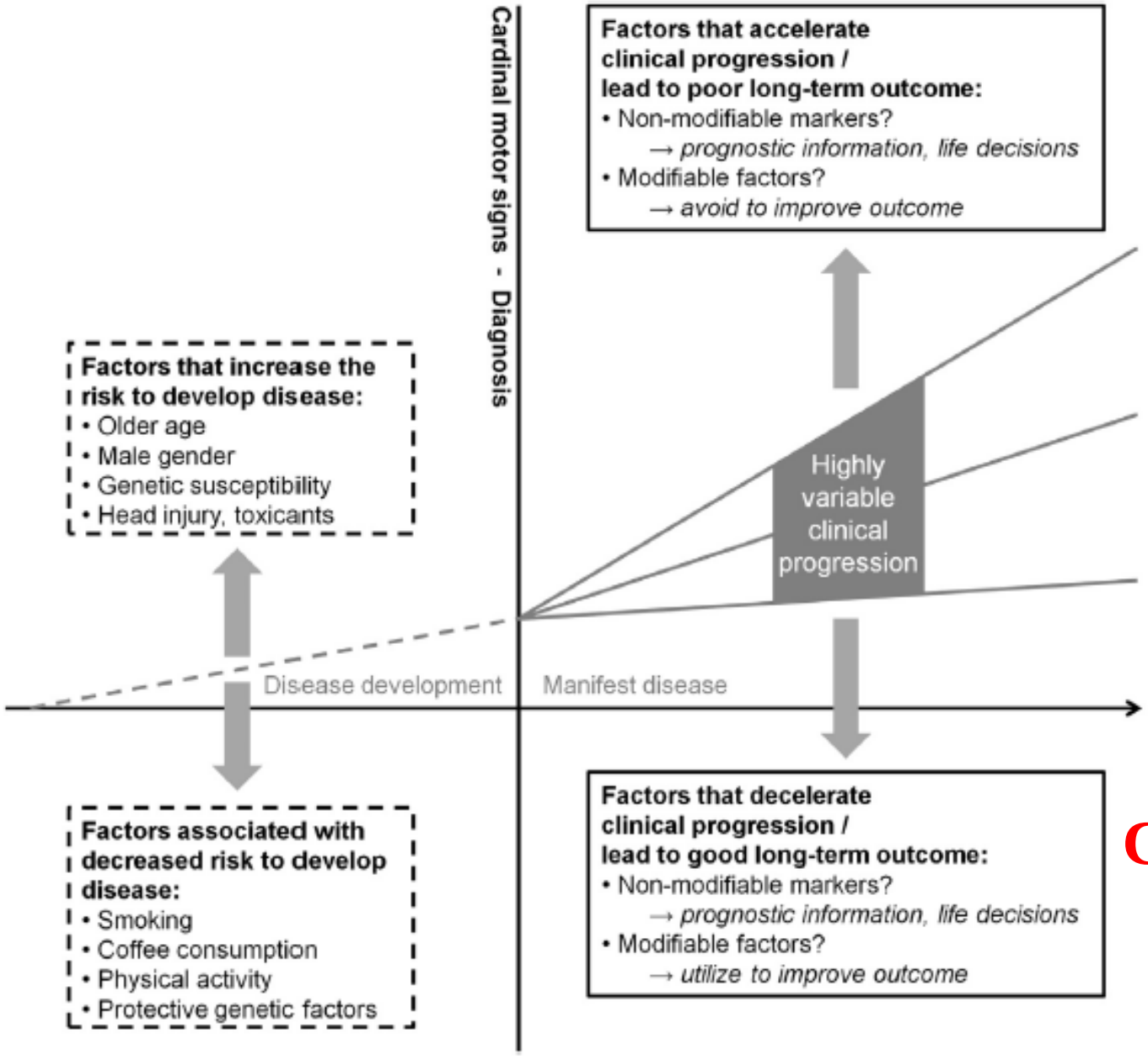
ABSTRACT

Introduction: There are few large studies that have evaluated prognostic factors for mortality in Parkinson's disease (PD). This large study aimed to identify demographic and clinical features associated with early mortality in PD.

Methods: PD patients at the National Neuroscience Institute were identified from the Movement Disorders Database from which demographic information and prospectively collected baseline disease characteristics were obtained. All study patients were linked to the Singapore Registry of Birth and Death to obtain information on vital status through December 31, 2012. The prognostic variables analyzed include patient demographics, baseline disease characteristics, and type of PD medication used. Multivariate Cox regression analysis was carried out to identify factors associated with the risk of mortality in PD.

Results: Of the 1786 PD patients identified, 363 (20.3%) had died during the 11-year study period. Median survival time from diagnosis was 15.8 years (range 0.3–31). Factors associated with higher mortality (HR, 95% CI) were older age at diagnosis (1.06, 1.03–1.08), male gender (2.29, 1.57–3.35), Hoehn & Yahr (HY) stage ≥2.5 (1.54, 1.07–2.22), UPDRS motor score ≥30 (1.63, 1.13–2.35), higher bradykinesia subscores (1.05, 1.01–1.09) and cognitive impairment (2.30, 1.55–3.41).

Conclusions: In the largest study to date evaluating baseline disease characteristics prognostic of mortality risk in PD, we found that male gender, older age at diagnosis, higher baseline HY stage, higher baseline UPDRS motor scores, higher bradykinesia subscores and baseline cognitive impairment were associated with early mortality in PD.



Clinical Course of PD

Puschmann, et al. PRD 2015;21:675-682

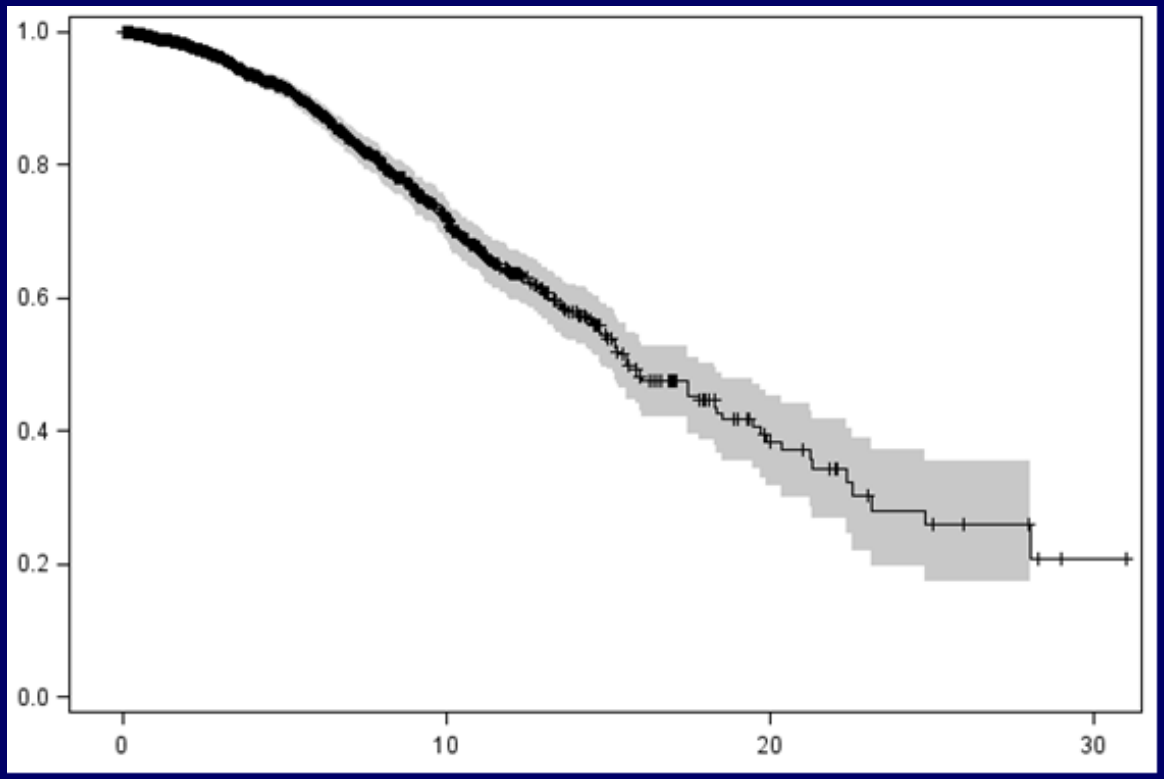
PD Mortality

- 1986 patients derived from the NNI Movement Disorders Database (2002-2012) were selected with the following criteria:
  - Idiopathic PD (based on NINDS criteria)
  - Did not undergo DBS surgery
  - Baseline assessment done within 2 years of diagnosis
- Linkage with Singapore Registry of Birth and Death

PD Mortality

- 1786 PD patients
- 363 (20.3%) died
- Most common primary causes of death:
  - infection or sepsis (197, 54.3%)
  - cardiac disease (63, 17.4%)
  - malignancy (35, 9.6%)
  - stroke (29, 8%)

Kaplan-Meier cumulative survival curve



Median survival from time of diagnosis: 15.8 years (0.3 – 31 years)

Oosterveld, Tan, et al. Parkinsonism Rel Disord 2015;12:226-230

Table 2
Prognostic factors for increased mortality risk in Parkinson's disease.

Parameter	Univariate			Multivariate Cox regression[c]		Multivariate Cox regression[d]	
	Hazard ratio (95% confidence interval)	P-value[b]		Hazard ratio (95% confidence interval)	P-value[b]	Hazard ratio (95% confidence interval)	P-value[b]
		Cox reg.	Log-rank (K–M)				
Age at diagnosis[a]	1.092 (1.079–1.104)	**<0.0001**		1.056 (1.029–1.084)	**<0.0001**	1.067 (1.044–1.090)	**<0.0001**
Gender (male vs. female)	1.099 (0.889–1.358)	0.3812	0.3811	2.292 (1.570–3.345)	**<0.0001**	2.598 (1.736–3.889)	**<0.0001**
Ethnicity (other vs. Chinese)	1.240 (0.926–1.660)	0.1489	0.1484	1.226 (0.741–2.030)	0.4277	1.222 (0.740–2.018)	0.4337
Education (<10 vs. ≥10)	1.949 (1.468–2.586)	**<0.0001**	**<0.0001**	0.983 (0.631–1.530)	0.9389	0.971 (0.625–1.507)	0.8954
MMSE (CI vs. no CI)	3.205 (2.291–4.483)	**<0.0001**	**<0.0001**	2.301 (1.552–3.411)	**<0.0001**	2.225 (1.484–3.336)	**0.0001**
HY stage (≥2.5 vs. <2.5)	2.484 (1.823–3.383)	**<0.0001**	**<0.0001**				
UPDRS motor score (≥30 vs. <30)	2.267 (1.659–3.098)	**<0.0001**	**<0.0001**	1.632 (1.132–2.351)	**0.0086**		
Tremor subscore[a]	1.042 (0.981–1.107)	0.1816				0.975 (0.910–1.045)	0.4728
Rigidity subscore[a]	1.070 (1.022–1.121)	**0.0040**				0.957 (0.894–1.023)	0.1971
Bradykinesia subscore[a]	1.060 (1.038–1.082)	**<0.0001**				1.051 (1.012–1.093)	**0.0105**
PIGD subscore[a]	1.153 (1.114–1.193)	**<0.0001**				1.036 (0.938–1.144)	0.4846
Use of levodopa (yes vs. no)	3.006 (0.958–9.428)	0.0592	**0.0473**	0.945 (0.228–3.913)	0.9383		
Use of amantadine (yes vs. no)	0.914 (0.375–2.231)	0.8436	0.8436	2.275 (0.904–5.724)	0.0808		
Use of trihexyphenidyl (yes vs. No)	0.479 (0.303–0.759)	**0.0017**	**0.0013**	1.026 (0.601–1.750)	0.9252		
Use of dopamine agonist (yes vs. no)	0.270 (0.179–0.407)	**<0.0001**	**<0.0001**	0.768 (0.460–1.282)	0.3129		
Use of selegiline (yes vs. no)	0.336 (0.229–0.492)	**<0.0001**	**<0.0001**	0.727 (0.461–1.147)	0.1710		

Oosterveld, Tan, et al. Parkinsonism Rel Disord 2015;12:226-230

PD Mortality

Independent predictors of mortality

- older age at diagnosis
- male gender
- baseline cognitive impairment
- ↑ baseline Hoehn and Yahr stage
- ↑ baseline UPDRS motor score
- ↑ baseline bradykinesia subscore

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Summary

1. Burden of PD will rise with ageing population
2. Epidemiological risk factors for PD
3. H&Y transition times and factors that increase transition times
4. UPDRS motor progression and predictors of progression
5. Predictors of PD mortality

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