EPIDEMIOLOGIA CLINICA DELLA MALATTIA DI PARKINSON

Nicola Vanacore

Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Istituto Superiore di Sanità

I SEI QUESITI DELL'EPIDEMIOLOGIA CLINICA NEL CONTESTO DELLA MP

1. DIAGNOSI - Quanto sono accurati i criteri utilizzati per diagnosticare la MP ?

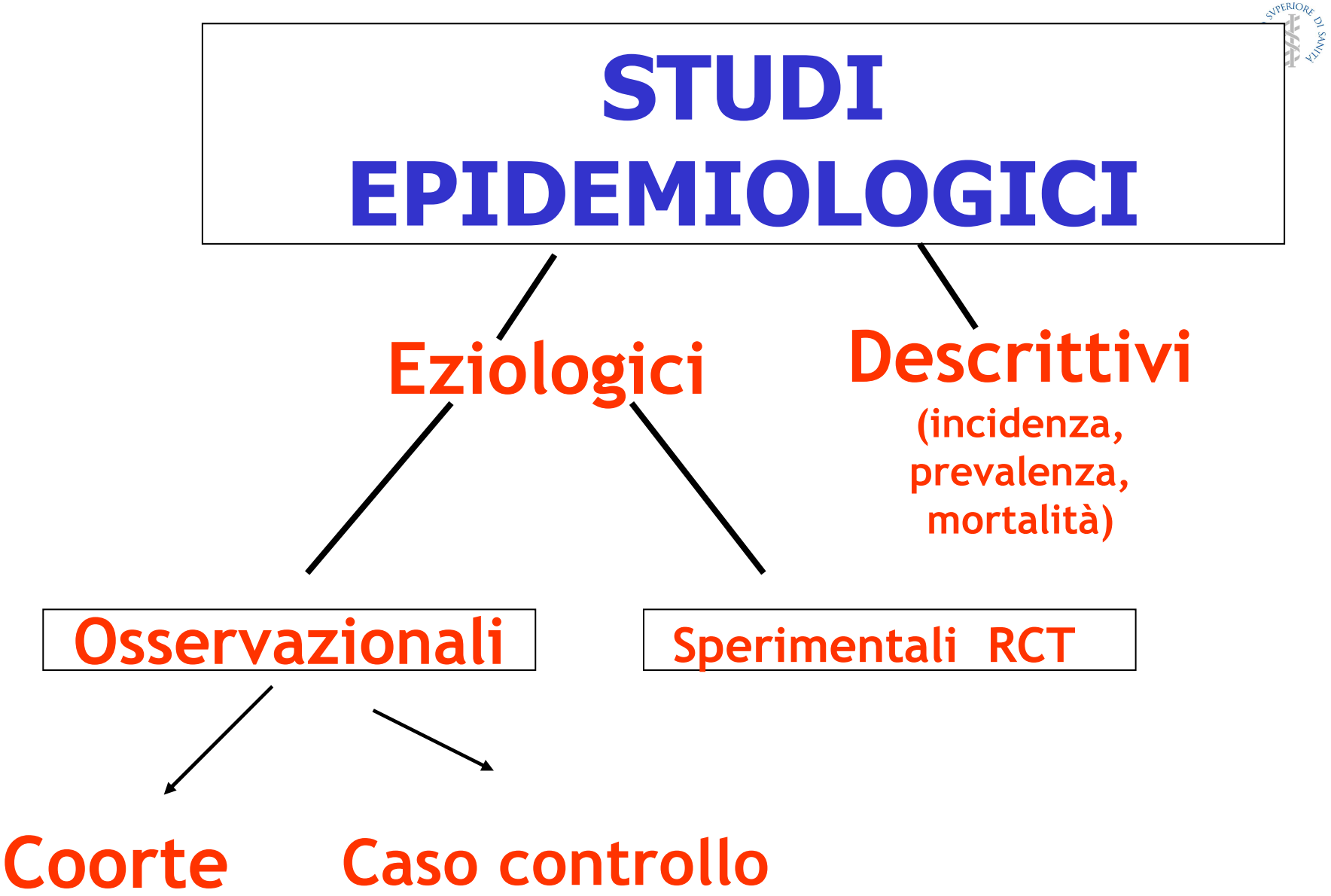
2. FREQUENZA - Quanto spesso si manifesta la MP ?

3. RISCHIO – Quali fattori sono associati con una maggiore probabilità di insorgenza alla MP ?

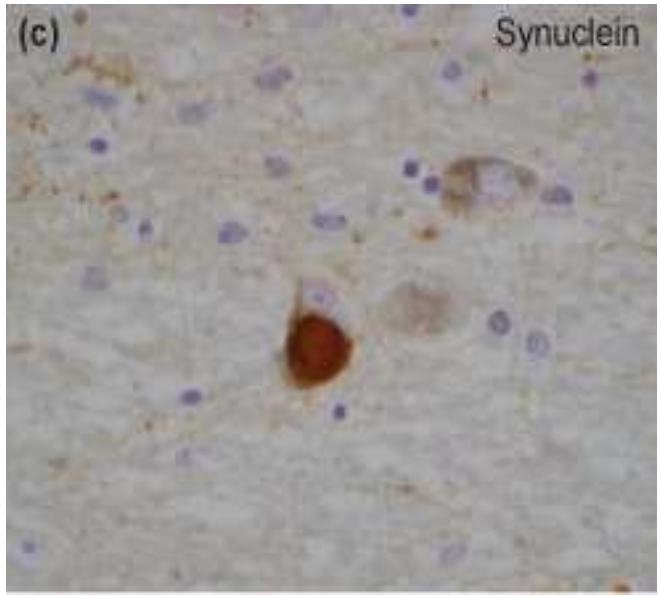
4. PROGNOSI – Quali sono le conseguenze derivanti dall'essere affetti dalla MP ?

5.TRATTAMENTO – Come cambia un trattamento il decorso della MP ?

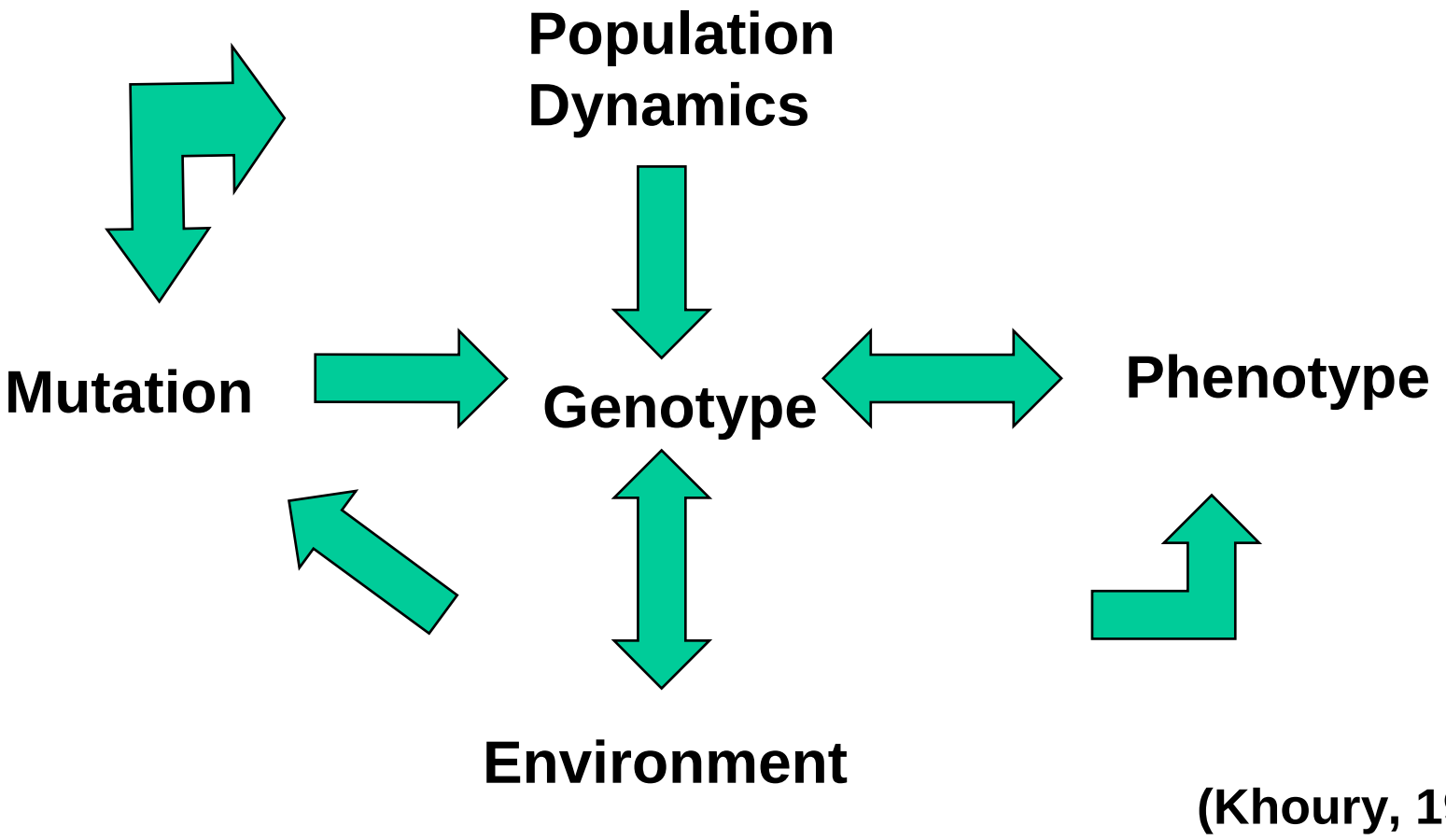
6. PREVENZIONE – L'adozione di un intervento su soggetti sani previene l'insorgenza della MP ?
Un riconoscimento ed un trattamento precoci migliorano il decorso della MP ?


STUDI EPIDEMIOLOGICI
Eziologici
Descrittivi
(incidenza, prevalenza, mortalità)
Osservazionali
Sperimentali RCT
Coorte
Caso controllo

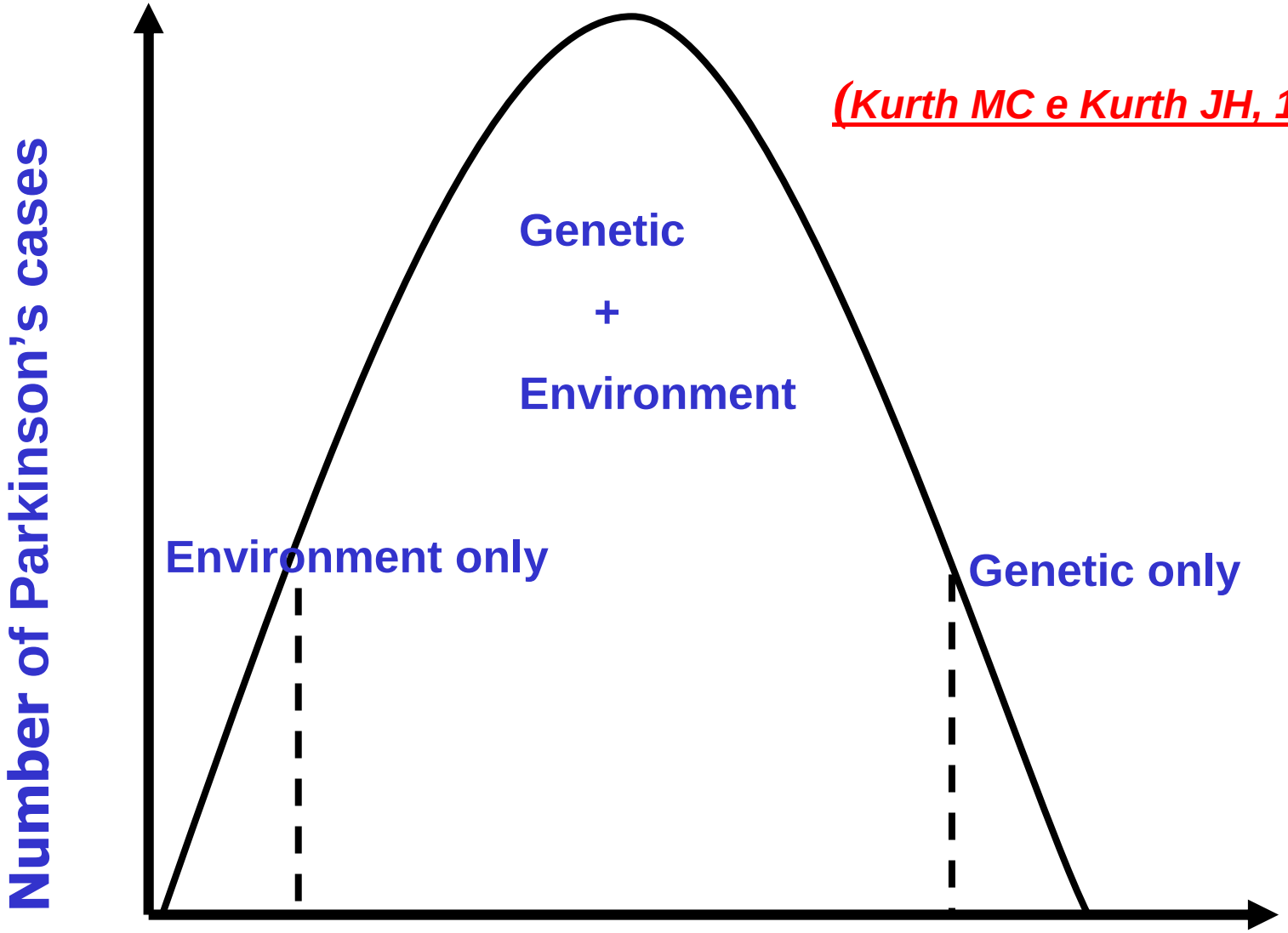
3. RISCHIO



SCOPE OF GENETIC RESEARCH



(Khoury, 1993)



(Kurth MC e Kurth JH, 1999)

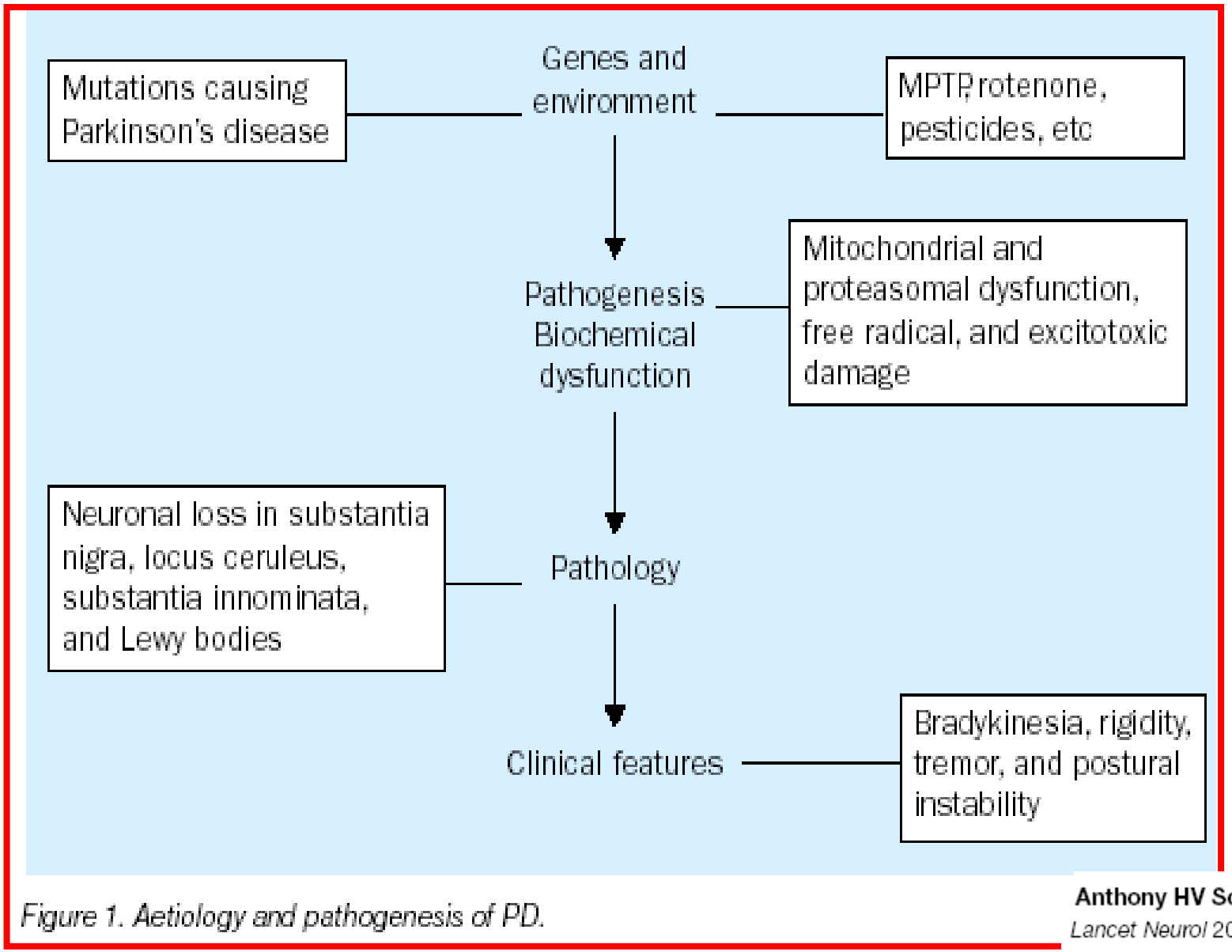


Figure 1. Aetiology and pathogenesis of PD.

Anthony HV Schapira
Lancet Neurol 2004; **3:** 362–68

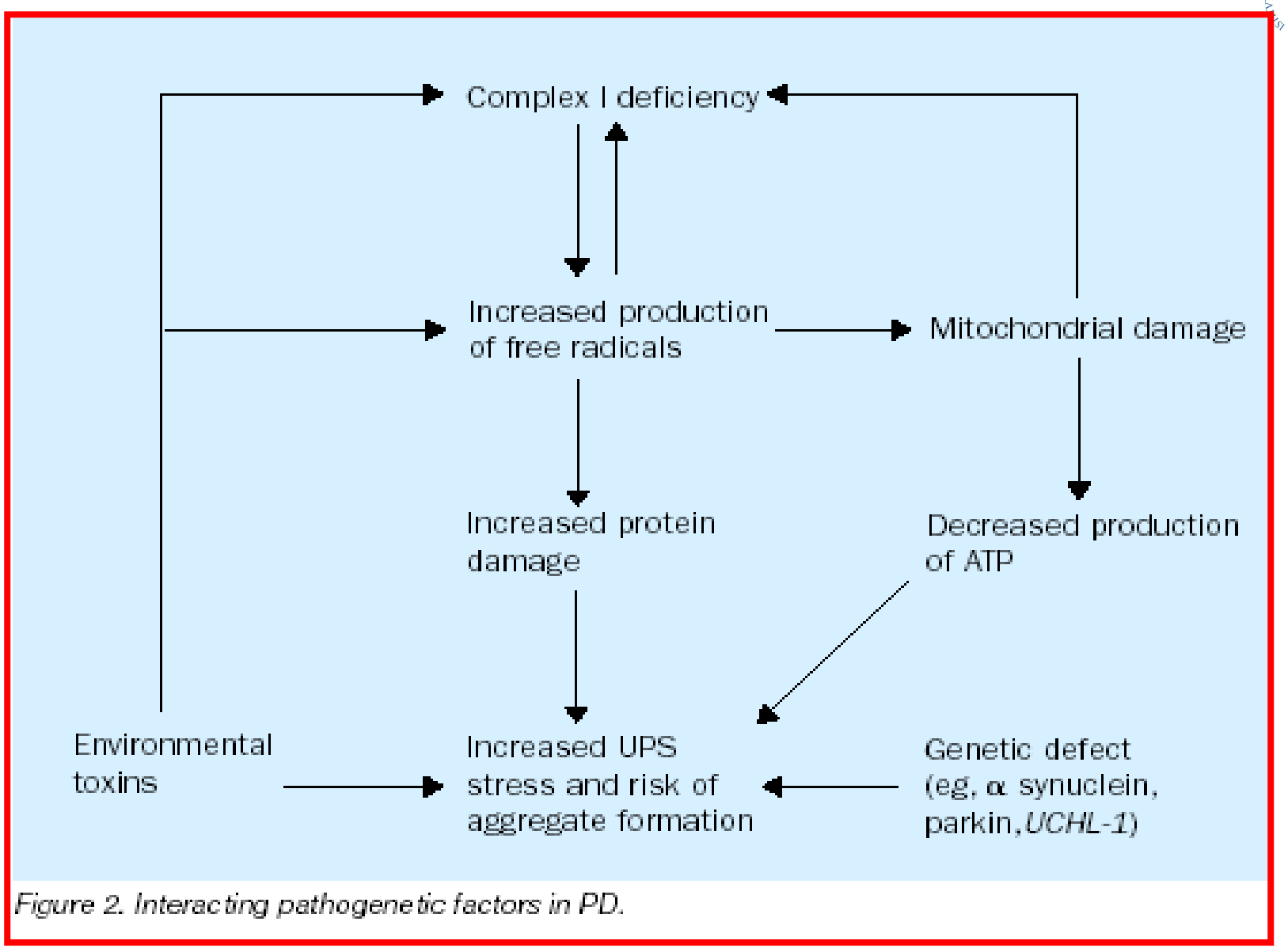


Figure 2. Interacting pathogenetic factors in PD.

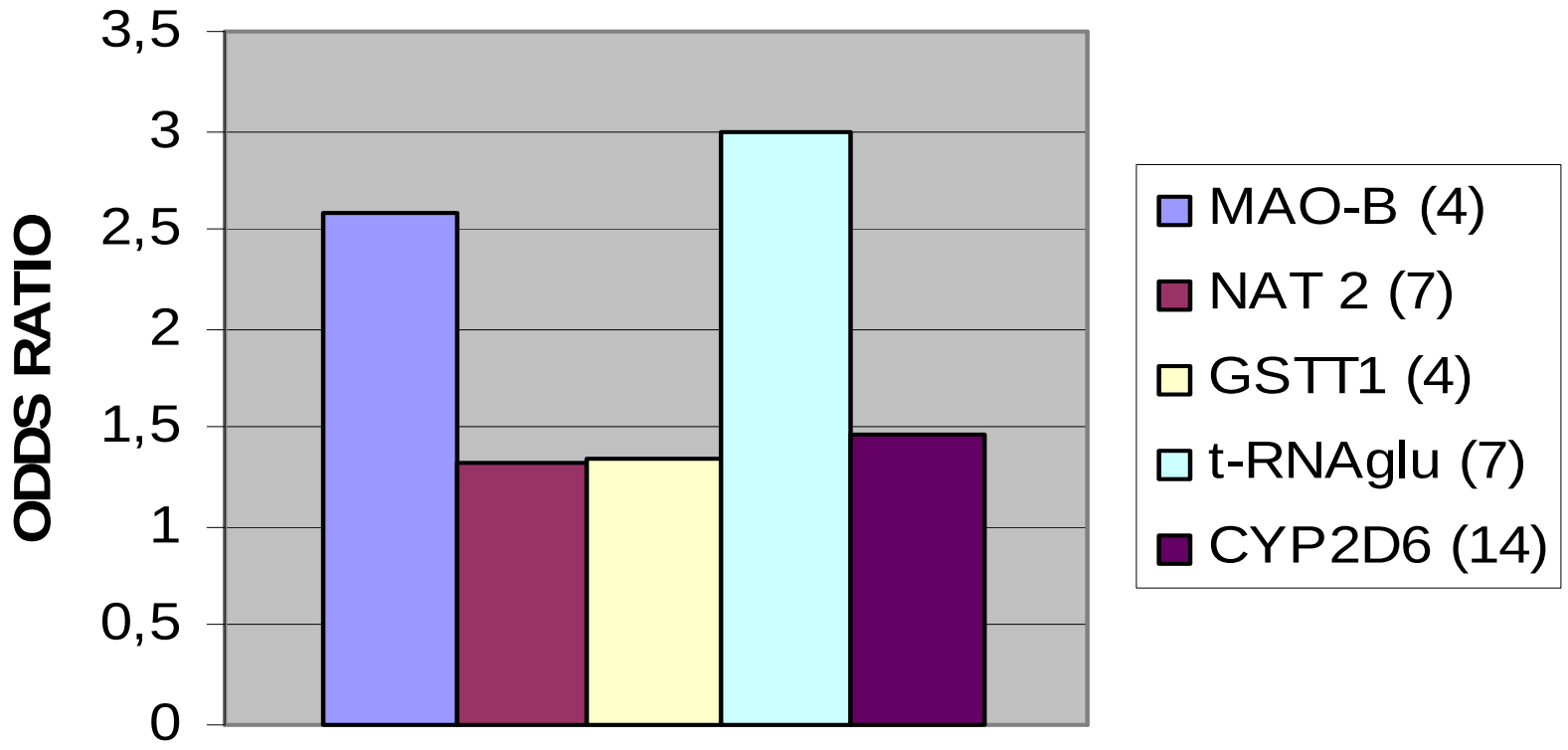
STUDI DI ASSOCIAZIONE ALLELICA NELLA MALATTIA DI PARKINSON

GENI	MP vs Controlli
Citocromo P450 2D6	lenti metaboliz. vs veloci
Glutatione transferasi	GSTT1
	delezioni vs non delezioni
N.-acetiltransferasi 2	lenti acetilatori vs veloci
MAO-B	GTn dinucleotide repeat polymorphism
	allele > 188 vs > 188
tRNA ^{glu}	mutaz.puntiforme A4336G

STUDI DI ASSOCIAZIONE ALLELICA

(STUDI DI META-ANALISI)

(Tan EK 2000, McCann SJ 1997)



DOPAMINE D_2 RECEPTOR GENE POLYMORPHISM AND THE RISK OF LEVODOPA INDUCED DYSKINESIAS IN PD (Neurology 1999;53:1425-430)

The intronic short tandem (STR) polymorphism of the DRD2 gene

	136 PD	224 control subjects	
Allele 15	172/272 (63.2%)	249/448 (55.6%)	p = 0.04

COMMENTO (6)

Update TRENDS in Genetics Vol.xx No.xx Monthxxxx
Full text provided by www.sciencedirect.com
Letters Response

Response to Manly: Statistical stringency in tests of genetic association – implications for sample size and study design

Marcus R. Munafò[1], E. Paul Wileyto[2] and Jonathan Flint[3]

Table 1. Total study sample size required to achieve 80% power[a]

True effect size[b] (odds ratio)	Critical *P*-value[c]		
	0.05	0.001	0.0001
1.1	14 812	32 225	42 265
1.2	4006	8718	11 434
1.3	1919	4176	5477
1.4	1158	2522	3309
1.5	793	1728	2267

Negli studi di associazione allelica è molto elevata la probabilità di commettere un errore statistico di I tipo (falso positivo).

Per tali ragioni vengono oggi richiesti studi con elevata numerosità e con evidenze scientifiche con un p di almeno 0.001

Potenza 80%; p =0.001

Table 2 | **Approximate sample sizes needed to detect a significantly increased allelic odds ratio***

Disease allele frequency	Marker allele frequency	Allelic odds ratio of disease gene					
		3.0		2.0		1.3	
		No. cases (= no. controls)	No. cases: no. controls (= 1:4)	No. cases (= no. controls)	No. cases: no. controls (= 1:4)	No. cases (= no. controls)	No. cases: no. controls (= 1:4)
0.05	0.05	360	210:840	1110	650:2600	9500	5600:22400
	0.1	600	350:1400	2000	1200:4800	19000	11500:46000
	0.2	1170	700:2800	4150	2500:10000	40000	25000:100000
	0.3	1900	1200:4800	6800	4300:13200	70000	43000:172000
	0.5	4200	2700:10800	15000	9500:38000	160000	100000:400000
0.2	0.05	710	420:1680	1900	1090:4360	14000	8500:34000
	0.1	350	200:800	900	500:2000	6600	4400:13600
	0.2	150	85:340	360	220:880	2900	1750:7000
	0.3	210	130:520	530	360:1440	4800	3000:12000
	0.5	430	270:1080	1250	800:3200	11000	6950:27800
0.5	0.05	3150	1870:7480	6800	4000:16000	40000	25000:100000
	0.1	1500	900:3600	3200	2000:8000	19000	12000:48000
	0.2	640	390:1560	1350	850:3400	8500	5300:21200
	0.3	360	220:880	800	500:2000	5000	3100:12400
	0.5	140	90:360	320	200:800	2100	1300:5200

*Using diallelic markers with varying allele frequency and allowing linkage disequilibrium between marker and disease allele down to $D' = 0.7$, odds ratio (power ≈ 80%; $\alpha = 0.001$).

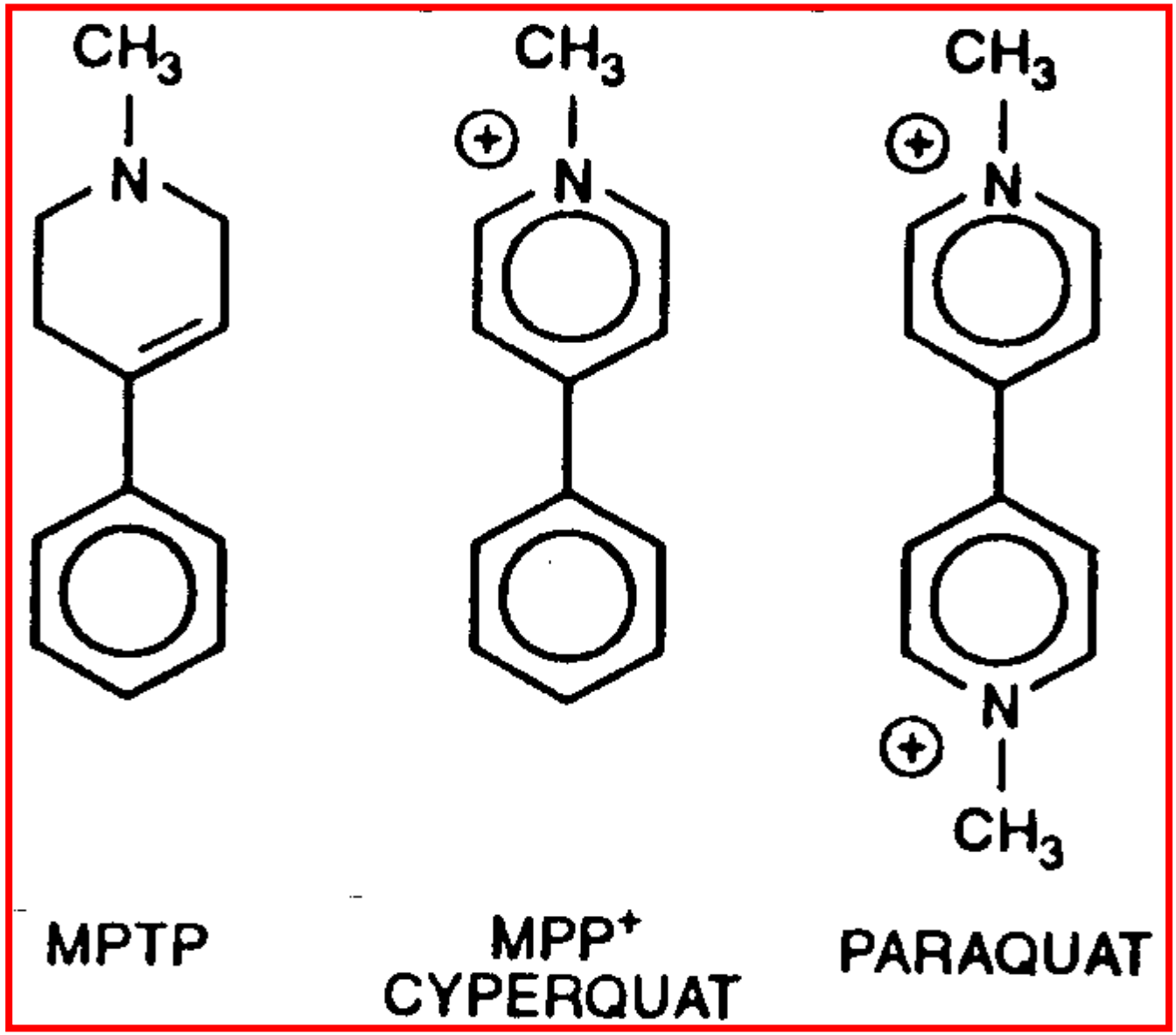
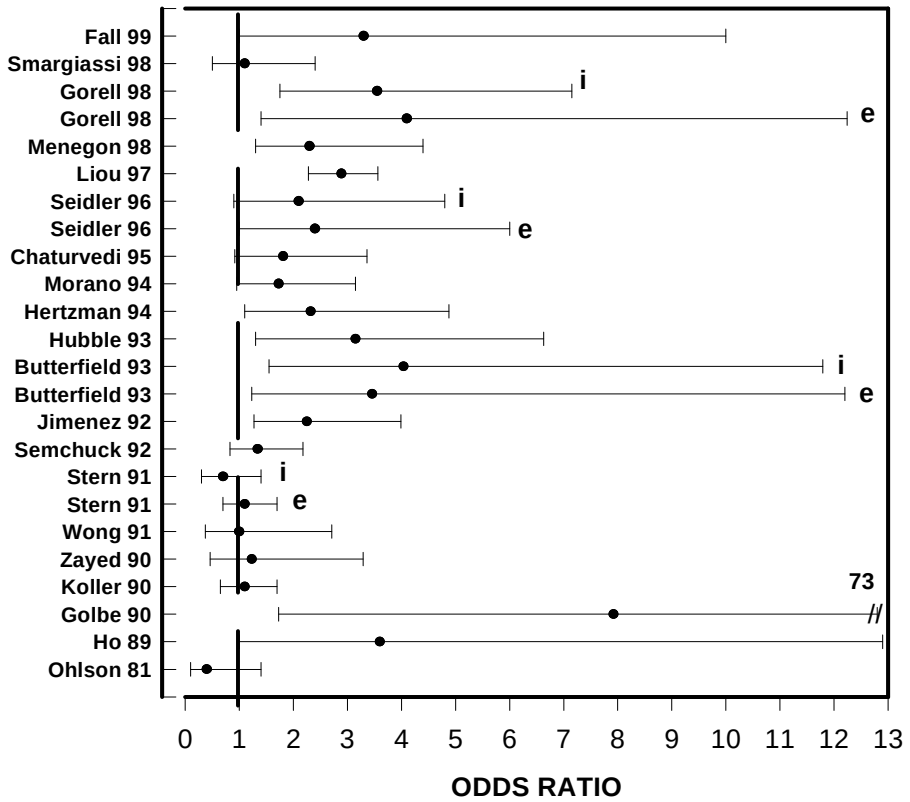

CH3
N
MPTP
CH3
N
MPP+
CYPERQUAT
CH3
N
N
CH3
PARAQUAT

FIGURA 1

ASSOCIAZIONE TRA ESPOSIZIONE A PESTICIDI E MALATTIA DI PARKINSON

Studi caso-controllo



i: esposizione ad insetticidi *e: esposizione ad erbicidi*

19 studi
OR=1.94
(IC95% 1.49-2.53)

NeuroToxicology® 21(4): 435-440, 2000

A Meta-Analysis of Parkinson's Disease And Exposure to Pesticides

ANUMEET PRIYADARSHI[1], SADIK A. KHUDER[1,2], ERIC A. SCHAUB[1,2], AND SNIGDHA SHRIVASTAVA

[1]*Department of Public Health, Medical College of Ohio, Toledo, OH;* [2]*Department of Medicine, Medical College of Ohio, Toledo, OH, USA*

Abstract: *This study examined the association between Parkinson's disease (PD) and exposure to pesticides. A series of meta-analysis of peer-reviewed studies were performed, using 19 studies published between 1989 and 1999. Prior to the meta-analysis, all studies were reviewed and evaluated for heterogeneity and publication bias. Significant heterogeneity among studies was detected and combined odds ratio (OR) was calculated using the random effect model. The majority of the studies reported consistent elevation in the risk of PD with exposure to pesticides. The combined OR studies was 1.94 [95% confidence interval (95% CI) 1.49-2.53] for all the studies, and 2.15 (95% CI 1.14—4.05) for studies performed in United States. Although the risk of PD increased with increased duration of exposure to pesticides, no significant dose-response relation was established, and no specific type of pesticide was identified. Our findings suggest that exposure to pesticides may be a significant risk factor for developing PD. © 2000 Intox Press, Inc.*

Key Words: Parkinson's Disease, Pesticides Exposure, Meta-Analysis

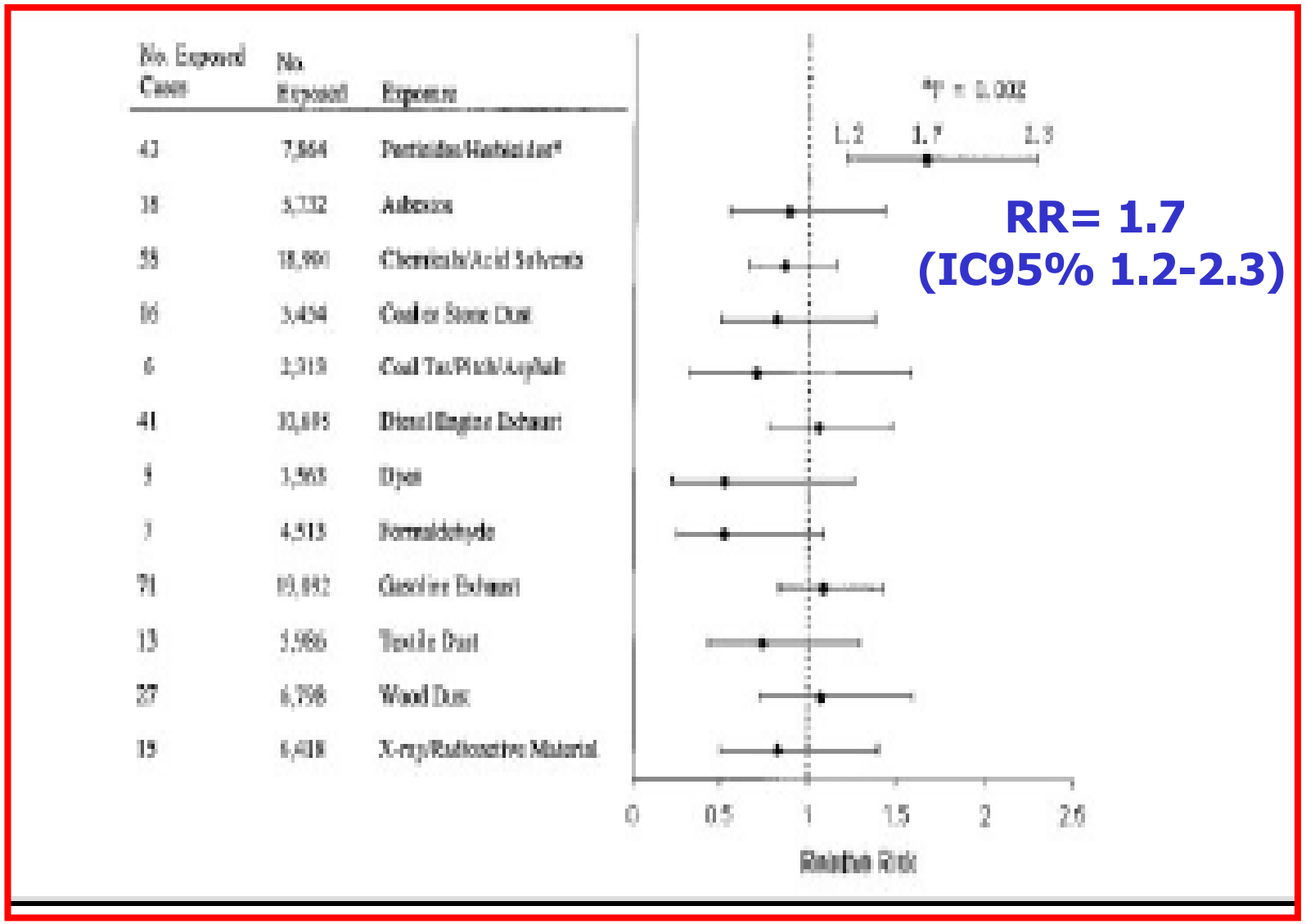
PARKINSON'S DISEASE AND EXPOSURE TO AGRICULTURAL WORK AND PESTICIDE CHEMICALS (Semchuck et al, 1992)

The estimated population attributable risk (i.e. percent of PD cases in this study that can be explained by the exposure factor) associated with previous occupational herbicide use is 10% .

Pesticide Exposure and Risk for Parkinson's Disease

Alberto Ascherio, MD, DrPH,[1,2] Honglei Chen, MD, PhD,[3] Marc G. Weisskopf, PhD,[1] Eilis O'Reilly, MSc,[1] Marjorie L. McCullough, ScD,[4] Eugenia E. Calle, PhD,[4] Michael A. Schwarzschild, MD, PhD,[5] and Michael J. Thun, MD[4]

Ann Neurol 2006;60:197–203



RR= 1.7
(IC95% 1.2-2.3)

Ascherio 2006

FEBS 25011

FEBS Letters 500 (2001) 105–108

Pesticides directly accelerate the rate of α-synuclein fibril formation: a possible factor in Parkinson's disease

Vladimir N. Uversky, Jie Li, Anthony L. Fink*

Department of Chemistry and Biochemistry, University of California, Santa Cruz, CA 95064, USA

Received 23 May 2001; revised 7 June 2001; accepted 7 June 2001

First published online 19 June 2001

Edited by Jesus Avila

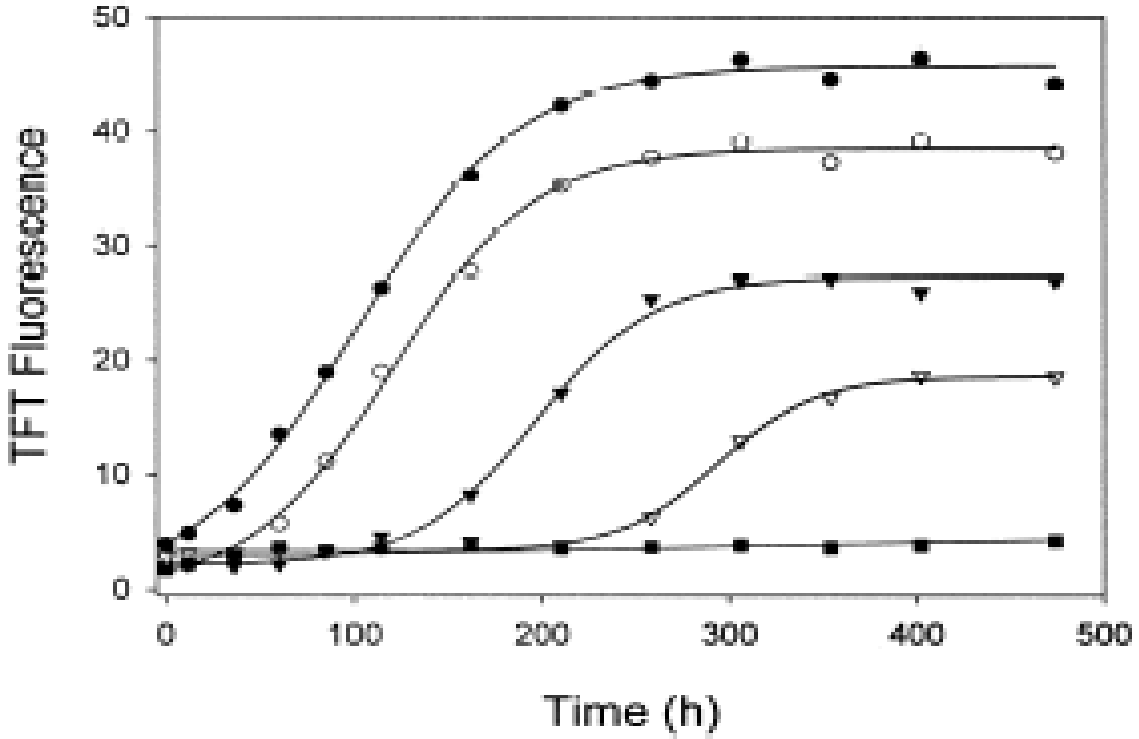


Fig. 1. Kinetics of α-synuclein fibril formation in the presence of pesticides. Solutions of α-synuclein (35 μM) were incubated with stirring at 37°C, in 10 mM phosphate buffer, pH 7.5, in the presence of the indicated pesticides (100 μM) as described in the text. Fibril formation was monitored by the increase in TFT fluorescence. Key: control, ■; DDC, ●; dieldrin, ○; paraquat, ▼; rotenone, ▽. The lag times (h) and rate constants for fibril growth (elongation) (h^{-1}) were as follows: DDC (9.9, 0.023), dieldrin (42.5, 0.026), rotenone (137.2, 0.035), and paraquat (241.2, 0.038).

ELSEVIER

Neurobiology of Disease

www.elsevier.com/locate/ynbdi
Neurobiology of Disease xx (2006) xxx – xxx

Intersecting pathways to neurodegeneration in Parkinson's disease: Effects of the pesticide rotenone on DJ-1, α-synuclein, and the ubiquitin–proteasome system

Ranjita Betarbet,[a,*] Rosa M. Canet-Aviles,[b] Todd B. Sherer,[a] Pier G. Mastroberardino,[a,f] Chris McLendon,[b] Jin-Ho Kim,[a] Serena Lund,[a] Hye-Mee Na,[a,f] Georgia Taylor,[a] Neil F. Bence,[c] Ron Kopito,[c] Byoung Boo Seo,[d] Takao Yagi,[d] Akemi Yagi,[d] Gary Klinefelter,[e] Mark R. Cookson,[b] and J. Timothy Greenamyre [a,f]

REVIEW

Review

Epidemiological methods for studying genes and environmental factors in complex diseases

David Clayton, Paul M McKelgue

Environmental exposure	Positive genotype		Negative genotype	
	Cases	Controls	Cases	Controls
Yes	*a*	*b*	*e*	*f*
No	*c*	*d*	*g*	*h*
Odds ratio	$\frac{ad}{bc}$		$\frac{eh}{fg}$	

Table 2: **Odds ratios for association of disease with environmental exposure, by genotype**

OR int = OR susc/OR non susc

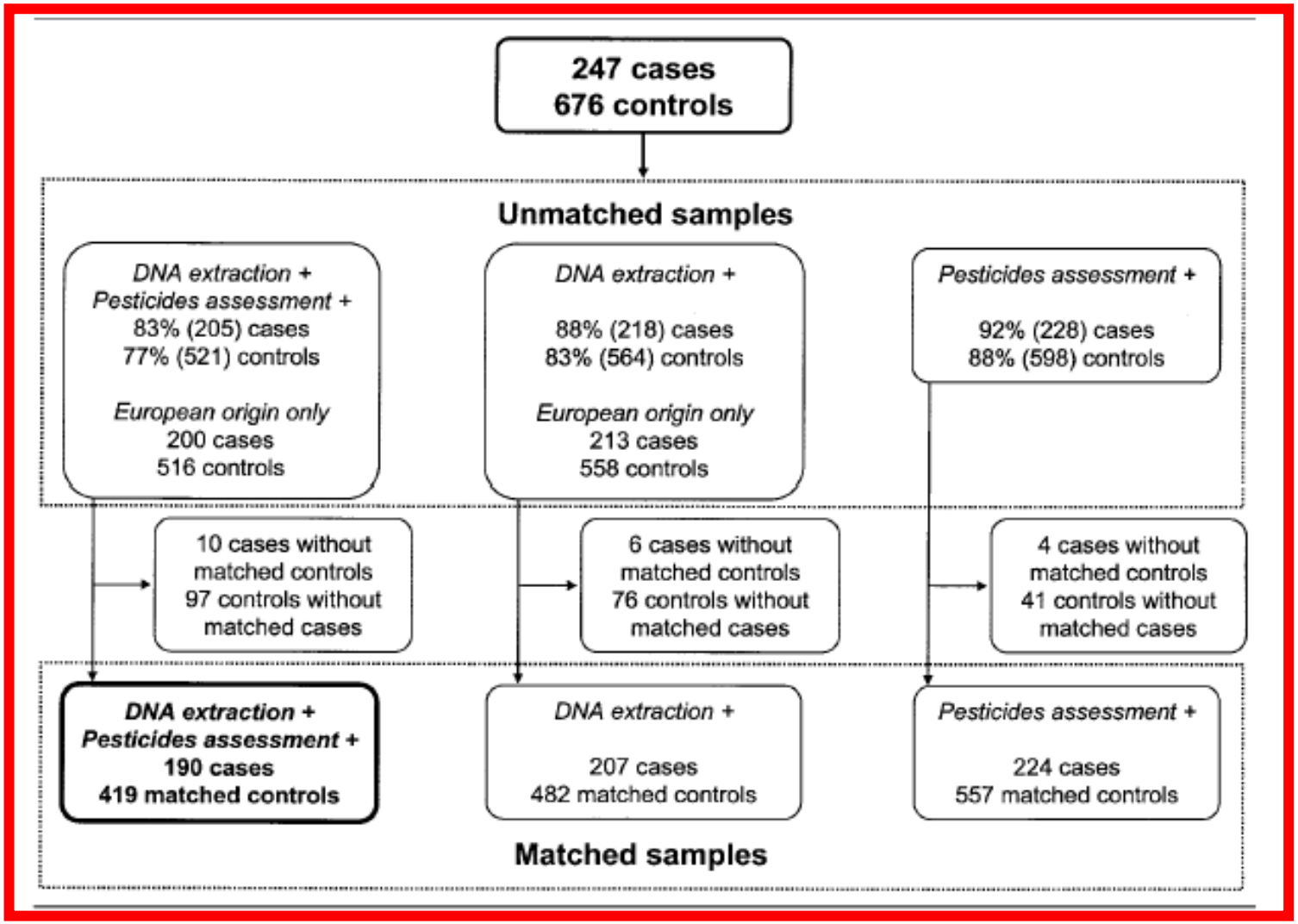
39 PD vs 26 controlli
(Distribuzione di uno specifico polimorfismo della glutatione transferasi in esposti a pesticidi (p= 0.009)
(Menegon, Lancet 1998)

7 PD vs 12 controlli
(CYP2D6 poor metabolizer ed esposti a solventi)
(OR = 14.47 , IC95% 1.16-185.23)
(De Palma, Lancet 1998)

CYP2D6 Polymorphism, Pesticide Exposure, and Parkinson's Disease

Alexis Elbaz, MD, PhD,[1] Clotilde Levecque, MSc,[2]
Jacqueline Clavel, MD, PhD,[3] Jean-Sébastien Vidal, MD,[4]
Florence Richard, MD, PhD,[2]
Philippe Amouyel, MD, PhD,[2]
Annick Alpérovitch, MD, MSc,[1]
Marie-Christine Chartier-Harlin, PhD,[2] and
Christophe Tzourio, MD, PhD[1]

Ann Neurol 2004;55:430–434

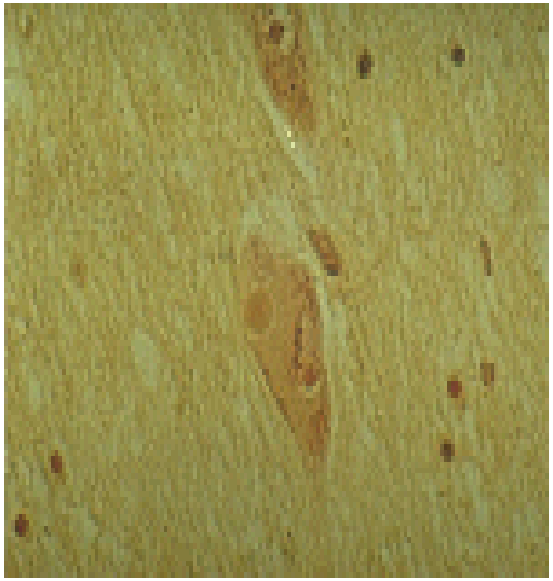

247 cases
676 controls
Unmatched samples
DNA extraction +
Pesticides assessment +
83% (205) cases
77% (521) controls
European origin only
200 cases
516 controls
DNA extraction +
88% (218) cases
83% (564) controls
European origin only
213 cases
558 controls
Pesticides assessment +
92% (228) cases
88% (598) controls
10 cases without matched controls
97 controls without matched cases
6 cases without matched controls
76 controls without matched cases
4 cases without matched controls
41 controls without matched cases
DNA extraction +
Pesticides assessment +
190 cases
419 matched controls
DNA extraction +
207 cases
482 matched controls
Pesticides assessment +
224 cases
557 matched controls
Matched samples

Elbaz 2004

*Table 2. The Relation between CYP2D6*4, Pesticide Exposure, and Parkinson's Disease*

	Exposure to Pesticides					
	None		Gardening Use		Professional Use	
Model	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Model 1 (−2 log likelihood = 406.288)						
0 CYP2D6*4 allele	1.00	—	1.73 (0.86–3.48)	0.12	1.85 (0.96–3.55)	0.06
1 CYP2D6*4 allele	1.39 (0.70–2.76)	0.35	1.17 (0.49–2.77)	0.72	1.83 (0.84–3.95)	0.13
2 CYP2D6*4 alleles (PMs)	0.41 (0.04–3.99)	0.44	2.75 (0.55–13.74)	0.22	4.74 (1.29–17.45)	0.02
Model 2 (−2 log likelihood = 407.859)						
0 or 1 CYP2D6*4 allele	1.00	—	1.34 (0.76–2.35)	0.31	1.65 (0.91–2.98)	0.10
2 CYP2D6*4 alleles (PMs)	0.35 (0.04–3.46)	0.37	2.45 (0.50–11.98)	0.27	4.18 (1.17–14.96)	0.03
Model 3 (−2 log likelihood = 409.604)						
0 or 1 CYP2D6*4 allele	1.00	—	1.50 (0.92–2.43)	0.10		
2 CYP2D6*4 alleles (PMs)	1.00	—	3.28 (1.16–9.27)	0.02		
Model 4 (−2 log likelihood = 412.298)						
0 or 1 CYP2D6*4 allele	1.00	—	1.00	—		
2 CYP2D6*4 alleles (PMs)	1.00	—	2.39 (0.92–6.24)	0.07		

5. TRATTAMENTO



(Am J Cardiol 1999;83:897–902)

Prevalence and Clinical Determinants of Mitral, Tricuspid, and Aortic Regurgitation (The Framingham Heart Study)

Jagmeet P. Singh, MD, DPhil, Jane C. Evans, MPH, Daniel Levy, MD, Martin G. Larson, ScD, Lisa A. Freed, MD, Deborah L. Fuller, RDCS, Birgitta Lehman, RDCS, and Emelia J. Benjamin, MD, ScM

TABLE IIa Prevalence of Valvular Regurgitation Stratified by Age and Severity in Men

	Age (yr)				
	26–39	40–49	50–59	60–69	70–83
Mitral regurgitation	(n = 91)	(n = 351)	(n = 432)	(n = 372)	(n = 90)
None (%)	14.4	13.3	11.3	12.7	9.0
Trace (%)	76.7	72.9	74.6	60.3	51.7
Mild (%)	8.9	13.5	12.5	24.6	28.1
≥Moderate (%)	0.0	0.3	1.6	2.4	11.2
Tricuspid regurgitation	(n = 77)	(n = 289)	(n = 320)	(n = 260)	(n = 66)
None (%)	14.3	17.8	19.0	18.3	16.7
Trace (%)	72.7	72.5	71.5	59.8	47.0
Mild (%)	13.0	9.4	9.2	21.9	25.8
≥Moderate (%)	0.0	0.3	0.3	0.0	1.5
Aortic regurgitation	(n = 91)	(n = 352)	(n = 433)	(n = 359)	(n = 91)
None (%)	96.7	95.4	91.1	74.3	75.6
Trace (%)	3.3	2.9	4.7	13.0	10.0
Mild (%)	0.0	1.4	3.7	12.1	12.2
≥Moderate (%)	0.0	0.3	0.5	0.6	2.2

TABLE IIb Prevalence of Valvular Regurgitation Stratified by Age and Severity in Women

	Age (yr)				
	26–39	40–49	50–59	60–69	70–83
Mitral regurgitation	(n = 93)	(n = 452)	(n = 515)	(n = 395)	(n = 90)
None (%)	14.0	8.6	9.0	7.2	5.6
Trace (%)	76.3	75.0	74.0	66.5	70.8
Mild (%)	9.7	15.5	16.0	24.0	23.6
≥Moderate (%)	0.0	0.9	1.0	2.3	0.0
Tricuspid regurgitation	(n = 84)	(n = 371)	(n = 414)	(n = 300)	(n = 71)
None (%)	20.5	16.0	14.5	10.4	14.1
Trace (%)	65.1	70.0	70.7	62.2	56.4
Mild (%)	13.2	13.5	14.1	25.7	23.9
≥Moderate (%)	1.2	0.5	0.7	1.7	5.6
Aortic regurgitation	(n = 93)	(n = 451)	(n = 515)	(n = 390)	(n = 90)
None (%)	98.9	96.6	92.4	86.9	73.0
Trace (%)	1.1	2.7	5.5	6.3	10.1
Mild (%)	0.0	0.7	1.9	6.0	14.6
≥Moderate (%)	0.0	0.0	0.2	0.8	2.3

Data are presented as percentage of subjects.

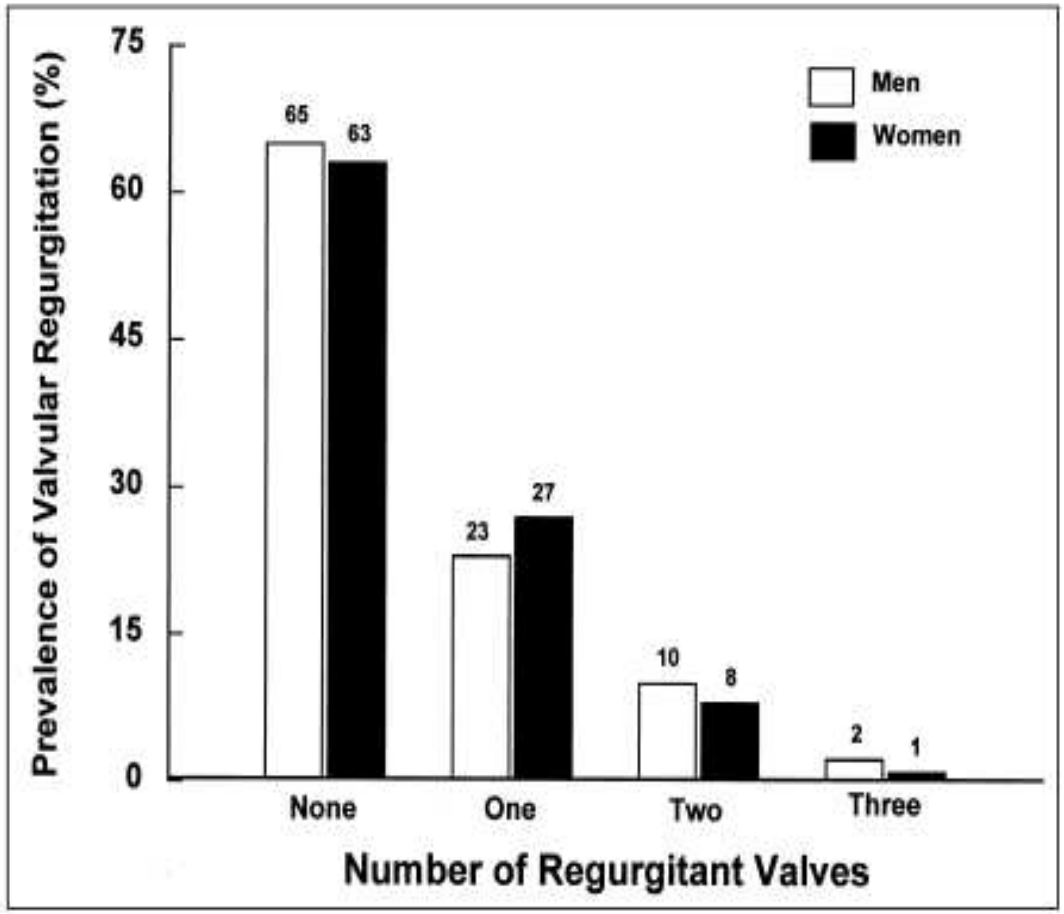


FIGURE 1. Histogram showing prevalence of valvular regurgitation by number of regurgitant valves. One indicates any single regurgitant valve; Two, any 2 regurgitant valves; Three, combined aortic, mitral, and tricuspid regurgitation. Regurgitation was defined as ≥mild severity for mitral and tricuspid regurgitation and ≥trace severity for aortic regurgitation.

Articles

Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease

Guy Van Camp, Anja Flamez, Bernard Cosyns, Caroline Weytjens, Luc Muyldermans, Michel Van Zandijcke, Johan De Sutter, Patrick Santens, Pierre Decoodt, Christian Moerman, Danny Schoors

Lancet 2004; **363:** 1179–83

Methods 78 patients with Parkinson's disease treated with pergolide and 18 never treated with an ergot-derived dopamine agonist (controls) were evaluated by echocardiography. A valvular scoring system was used, ranging from 1 (proven ergot-like restrictive valvular heart disease) to 4 (no disease). For the mitral valve, tenting areas and tenting distances were measured. Systolic pulmonary artery pressures were derived from the tricuspid regurgitant jet.

19% nei pts con pergolide

0% nei pts senza pergolide

CME

Pergolide use in Parkinson disease is associated with cardiac valve regurgitation

D.G. Baseman, BS; P.E. O'Suilleabhain, MBBCh; S.C. Reimold, MD; S.R. Laskar, MD; J.G. Baseman, MPH; and R.B. Dewey, Jr., MD

2

NEUROLOGY 2004;63:301–304

Table 2 Number of patients and controls with abnormal and concerning regurgitation with calculated odds ratios and p values*

	Pergolide, n = 46	Controls, n = 46	Odds ratio (95% CI)	*p* Value
Abnormal† mitral regurgitation	22.5	12.4	2.6 (1.1–6.2)	0.03
Abnormal aortic regurgitation	20	9.7	3.0 (1.3–7.7)	0.01
Abnormal tricuspid regurgitation	22	10	3.3 (1.3–8.2)	0.02
Concerning‡ mitral regurgitation	6.5	2	3.7 (0.7–19.2)	0.13
Concerning aortic regurgitation	15	5	4.0 (1.3–12.2)	0.04
Concerning tricuspid regurgitation	8.5	0.6	18.4 (1.2–283)	0.02

* Fractional number of patients resulted from adding fractional valve scores.
† Abnormal regurgitation = AR ≥ trace severity, MR ≥ mild severity, and TR ≥ mild severity.
‡ Concerning regurgitation = AR ≥ mild severity, MR ≥ moderate severity, and TR ≥ moderate severity.

AR = aortic regurgitation; MR = mitral regurgitation; TR = tricuspid regurgitation.

Movement Disorders
Vol. 20, Suppl. 10, 2005, pp. S57–S113

POSTER SESSION 2

Monday, March 7, 2005
8:30 AM–5:00 PM
Poster numbers 188–383
Authors present: 12:30 PM–2:15 PM

3

P383

Valvular heart disease in Parkinson's disease versus controls—An echocardiographic study

C.M. Peralta, E. Wolf, K. Seppi, H. Alber, S. Mueller, W. Poewe
(Innsbruck, Austria)

Results: There were 33 patients in the non-ergot (NE) group (25 PD/PXP, 8 PD/ROP), 53 in the ergot group (29 PD/PERG, 14 PD/CAB, 10 PD/MIX), and 51 in the control group.

31% of PD/PERG patients had VR II–III vs. 14% of controls ($P = 0.06$), while 43% of PD/CAB patients showed VR II–III vs. 14% of controls ($P = 0.01$). PD/MIX patients also had higher prevalences of VR II–III than controls (40% vs. 14%, $P = 0.04$).

VR II–III prevalences did not differ between NE and controls (10% vs. 14%, $P = 0.52$), while PD/CAB and PD/PERG patients showed higher prevalences than NE patients (43% vs. 10%, $P = 0.007$ and 31% vs. 10%, $P = 0.02$).

Clear-cut fibrotic changes with leaflet thickening and/or retraction were evident only in 2 cases, both on Pergolide.

Valvulopatie cardiache e trattamento cronico con dopamino-agonisti.

Gemma Gatto
Angelo Antonini

Cardiologia Riabilitativa
Centro Parkinson

DOI 10.1007/s00702-005-0289-1
J Neural Transm (2005) 112: 661–668

Journal of Neural Transmission
Printed in Austria

5

Retrospective evaluation of cardio-pulmonary fibrotic side effects in symptomatic patients from a group of 234 Parkinson's disease patients treated with cabergoline

V. Dhawan[1,2], P. Medcalf[4], F. Stegie[1], G. Jackson[1], S. Basu[1], P. Luce[1], P. Odin[5], and K. Ray Chaudhuri[1,2,3]

Solo 3 casi con fibrosi valvolare (1.3%)

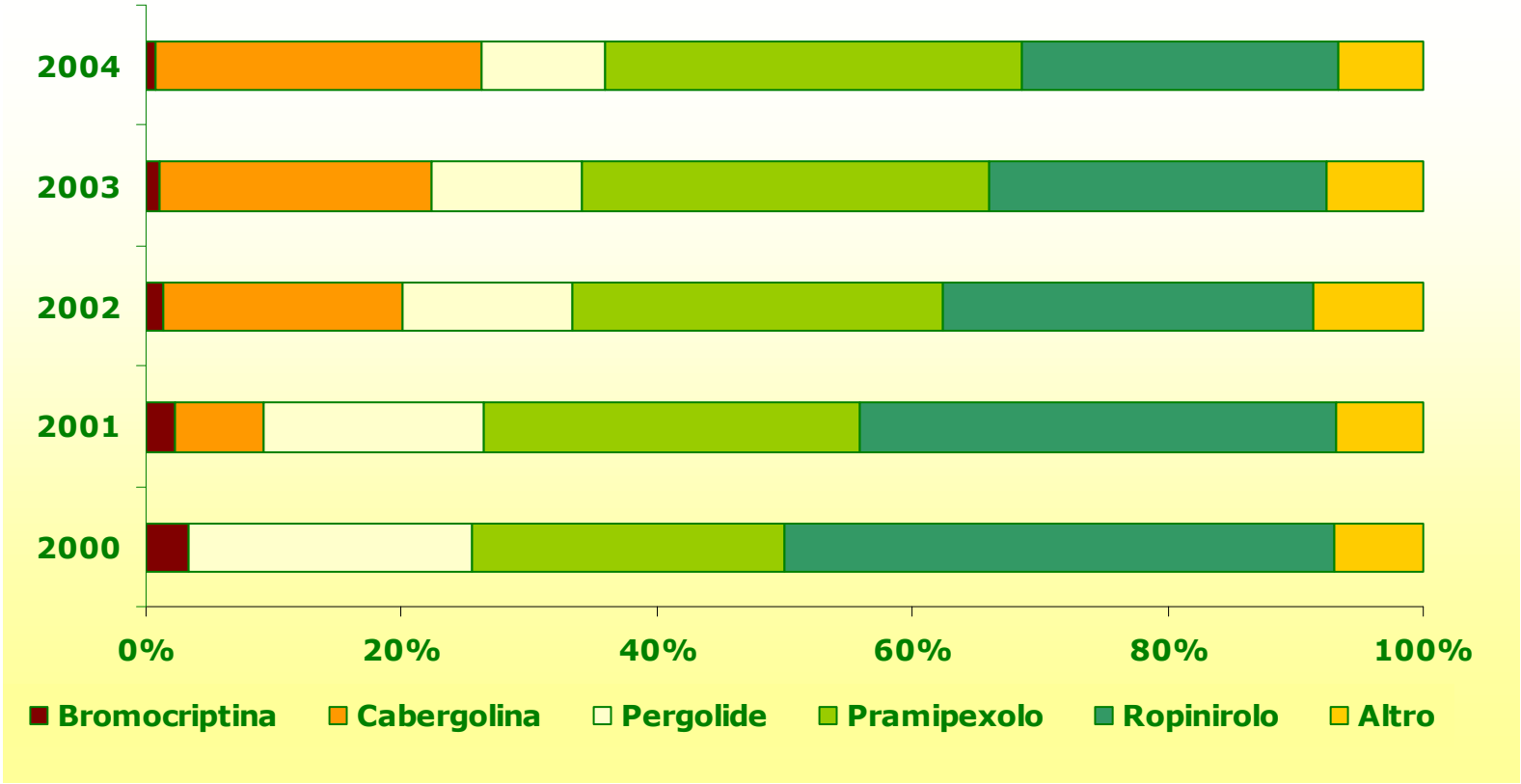
NOTA INFORMATIVA IMPORTANTE CONCORDATA CON L'AIFA

NOPAR (pergolide):
IMPORTANTI INFORMAZIONI DI SICUREZZA RELATIVE ALLA POSSIBILE COMPARSA DI VALVULOPATIE CARDIACHE

20 Dicembre 2004

- Pergolide deve essere utilizzata come farmaco di seconda linea, dopo che sia stato impiegato senza successo un dopamino-agonista non derivato dell'ergotamina.
- La dose di pergolide non deve superare i 5 mg/giorno
- Pergolide è controindicata in tutti i pazienti con anamnesi positiva per fibrosi a carico di un qualunque tessuto corporeo
- Prima di iniziare un trattamento con pergolide è necessario effettuare un ecocardiogramma

COMSUMO DI DOPAMINOAGONISTI IN ITALIA



Fonte OSMED 2005

Non vi sono studi RCT di confronto del profilo rischio-beneficio fra le diverse molecole dei dopaminoagonisti

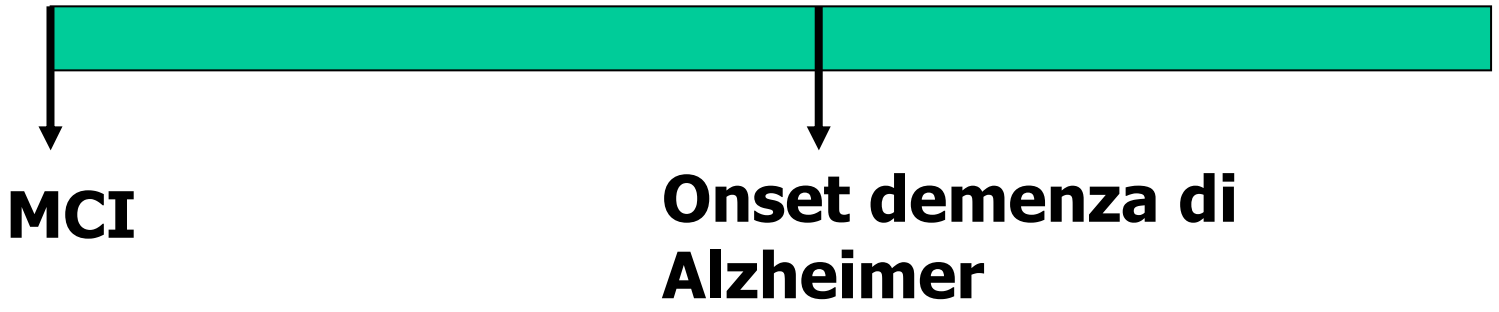
Gli studi finora condotti sulla relazione tra DA-tipo ergot e fibrosi valvolare non consentono di trarre delle conclusioni in termini di imputabilità del farmaco

La pergolide è stata declassata a farmaco di seconda scelta

Quale decisione verrà assunta dall'EMEA per la cabergolina ?

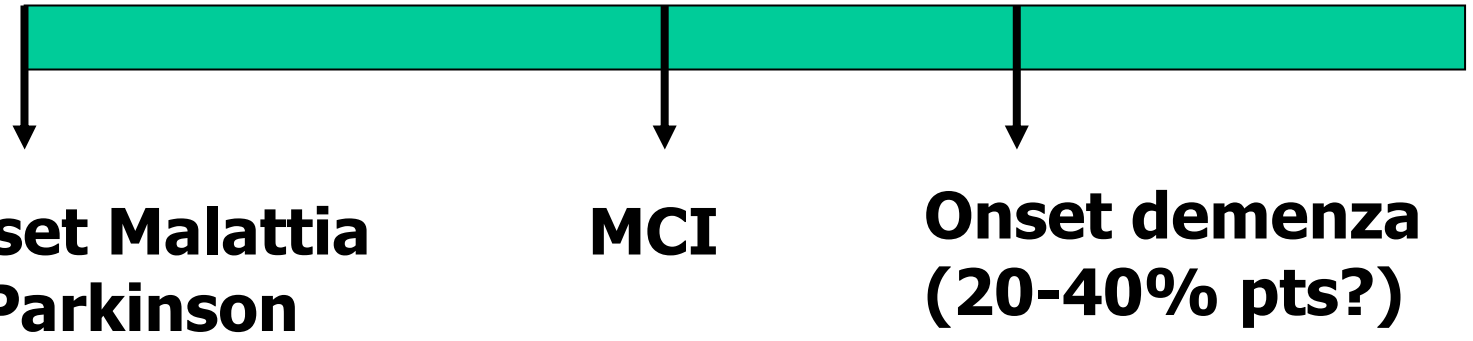
Malattia di Alzheimer

1



2 **Il MCI è un fattore di rischio per la demenza di Alzheimer ?**

Malattia di Parkinson



PAPER

Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study

D Aarsland, K Laake, J P Larsen, C Janvin

J Neurol Neurosurg Psychiatry 2002;**72**:708–712

See end of article for authors' affiliations

Correspondence to: Dr D Aarsland, Section of Geriatric Psychiatry, Psychiatric Hospital of Rogaland, Arm. Hansen v 20, 4095 Stavanger, Norway; aarsland@netpower.no

Received 9 August 2001
In revised form 19 November 2001
Accepted 14 December 2001

Objective: To study the safety and efficacy of the cholinesterase inhibitor donepezil in patients with Parkinson's disease (PD) and cognitive impairment.
Methods: This was a double blind, randomised and placebo controlled, crossover study in which 14 patients with PD and cognitive impairment received donepezil (5 or 10 mg per day) or matching placebo during two sequential periods lasting 10 weeks each. The primary outcome measures were the mini mental state examination (MMSE) score, the clinician's interview based impression of change plus caregiver input (CIBIC+) score, and the motor subscale of the unified Parkinson's disease rating scale (UPDRS).
Results: Two patients on donepezil (14%) dropped out after one and four weeks of the first treatment period because of peripheral cholinergic side effects, otherwise the adverse effects were few and not severe. Carryover or residual effects were not observed. Parkinsonism did not increase during donepezil treatment. After 10 weeks of treatment, the mean MMSE score was increased by 2.1 (SD 2.7) points on donepezil and 0.3 (SD 3.2) points on placebo, and the CIBIC+ score was 3.3 (SD 0.9) on donepezil and 4.1 (SD 0.8) on placebo. Statistical analysis of the repeated measurements and crossover study design showed significant effects of donepezil compared with placebo for MMSE ($p=0.013$) and CIBIC+ ($p=0.034$). Five (42%) patients on donepezil and two (17%) on placebo were rated as improved on the basis of the CIBIC+ score.
Conclusions: Donepezil improves cognition, and seems to be well tolerated and not to worsen parkinsonism in patients with cognitive impairment.

BMJ 2005;330:276 (5 February), 276-b

News extra

Regulatory authorities review use of galantamine in mild cognitive impairment

London Susan Mayor

The studies combined included 2048 people aged 50 years and over with mild cognitive impairment (insufficient impairment to be diagnosed as dementia). The participants were randomly assigned to receive 8 mg or 12 mg twice daily **galantamine** or placebo for 24 months to see if the drug slowed progression to dementia**.**

Initial results showed more deaths in those treated with the drug (13/1026) than with placebo (2/1022) (hazard ratio for death 4.86 (95% confidence interval 1.76 to 13.40) during the double blind phase of the studies

The NEW ENGLAND JOURNAL of MEDICINE

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., David Bennett, M.D., Rachelle Doody, M.D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D., Shelia Jin, M.D., M.P.H., Jeffrey Kaye, M.D., Allan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D., Christopher H. van Dyck, M.D., and Leon J. Thal, M.D., for the Alzheimer's Disease Cooperative Study Group*

Totale decessi n = 23
Fase in doppio cieco (n= 17)

Donepezil (n= 7/253)
Vit. E (n=5/257)
Placebo (n=5/259)

Fase open-label (n = 6)

Jelic et al 2005

Donepezil (n= 10)	**(3,9%)**
Vit. E (n=6)	**(2,3%)**
Placebo (n=7)	**(2,7%)**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivastigmine for Dementia Associated with Parkinson's Disease

Murat Emre, M.D., Dag Aarsland, M.D., Ph.D., Alberto Albanese, M.D., E. Jane Byrne, F.R.C.Psych., M.B., Ch.B., Günther Deuschl, M.D., Peter P. De Deyn, M.D., Ph.D., Franck Durif, M.D., Ph.D., Jaime Kulisevsky, M.D., Ph.D., Teus van Laar, M.D., Ph.D., Andrew Lees, M.D., Werner Poewe, M.D., Alain Robillard, M.D., F.R.C.P.C., Mario M. Rosa, M.D., Erik Wolters, M.D., Ph.D., Peter Quarg, M.Sc., Sibel Tekin, M.D., and Roger Lane, M.D.

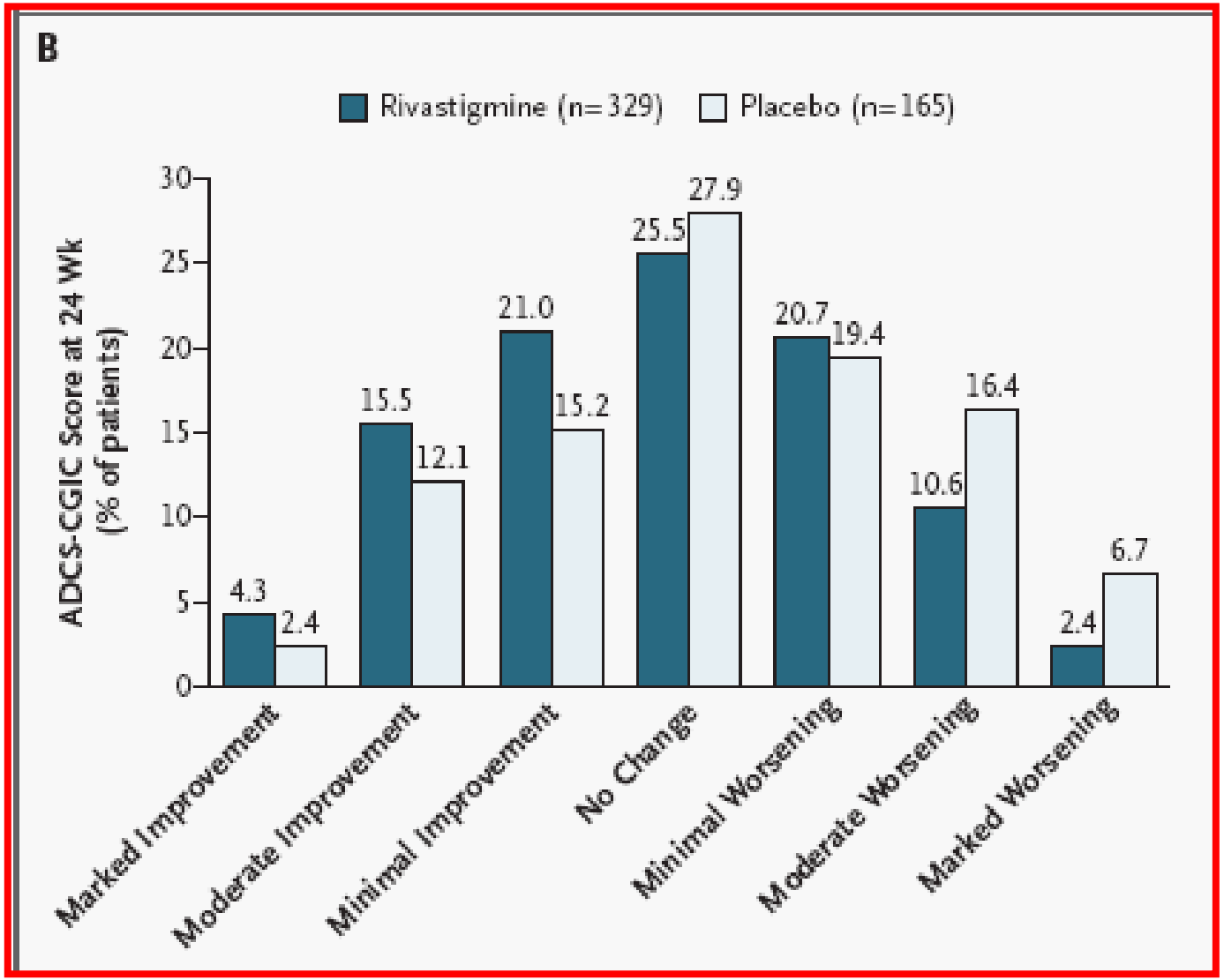
Table 1. Baseline Characteristics of All Randomized Patients.*

Characteristic	Rivastigmine Group (N=362)	Placebo Group (N=179)
Age — yr	72.8±6.7	72.4±6.4
Sex — no. (%)		
Male	234 (64.6)	117 (65.4)
Female	128 (35.4)	62 (34.6)
Race or ethnic group — no. (%)†		
White	360 (99.4)	179 (100)
Other	2 (0.6)	0
Years of education	8.8±4.1	9.2±3.9
CNS medications — no. (%)‡		
Antipsychotic agents	100 (27.6)	47 (26.3)
Antidepressants	102 (28.2)	42 (23.5)
Benzodiazepines, sedatives, hypnotics	74 (20.4)	35 (19.6)
Levodopa	346 (95.6)	169 (94.4)
Dopamine agonists	165 (45.6)	83 (46.4)

Time since diagnosis of Parkinson's disease — yr	8.7±5.7	9.5±5.9
Modified Hoehn and Yahr stage — no. (%)§		
0	1 (0.3)	0
1.0–2.5	181 (50.0)	85 (47.5)
3.0	114 (31.5)	63 (35.2)
4.0	51 (14.1)	28 (15.6)
5.0	15 (4.1)	2 (1.1)
UPDRS part III (motor function score)¶	34.0±14.6	32.2±13.2
Time since diagnosis of dementia — yr	1.1±1.4	1.3±1.9
Time between diagnosis of Parkinson's disease and first symptoms of dementia — yr	6.6±5.2	7.3±5.2
MMSE score	19.4±3.8	19.2±4.1

Table 2. Results of the Efficacy Analysis.*

Variable	No. of Patients	Baseline Score	Change at Week 24	Between-Group Difference at Week 24	
				Value	P Value
		mean ±SD			
Primary efficacy variables					
ADAS-cog score					
Rivastigmine	329	23.8±10.2	-2.1±8.2	2.90†	
Placebo	161	24.3±10.5	0.7±7.5		<0.001
ADCS-CGIC score					
Rivastigmine	329	—	3.8±1.4	0.5	
Placebo	165	—	4.3±1.5		0.007


B
Rivastigmine (n=329)
Placebo (n=165)
ADCS-CGIC Score at 24 Wk
(% of patients)
30
25
20
15
10
5
0
4.3
2.4
15.5
12.1
21.0
15.2
25.5
27.9
20.7
19.4
10.6
16.4
2.4
6.7
Marked Improvement
Moderate Improvement
Minimal Improvement
No Change
Minimal Worsening
Moderate Worsening
Marked Worsening

A videotaped CIBIC for dementia patients

Validity and reliability in a simulated clinical trial

J. Quinn, MD; M. Moore, BS; D.F. Benson, MD†; C.M. Clark, MD; R. Doody, MD, PhD; W. Jagust, MD; D. Knopman, MD; and J.A. Kaye, MD

NEUROLOGY 2002;58:433–437

Inter-rater reliability of the neurologists was poor when measured by absolute agreement on a 7-point scale (kappa = 0.18)

Kappa	Forza dell'associazione
<0	Poor
0,0 – 0,2	Slight
0,21 – 0,40	Fair
0,41 – 0,60	Moderate
0,61 – 0,80	Substantial
>0,80	Almost perfect

Che cosa è il MCI nella demenza di Alzheimer e nella Malattia di Parkinson ?

Lo studio della rivastigmina nella malattia di Parkinson pone una serie di questioni:

-tipologia di paziente

- efficacia nell'ADAS-cog
(statisticamente significativo vs clinicamente rilevante)

-nessuna valutazione delle funzioni esecutive

- efficacia nell'ADCS- CGIC
(541 pts arruolati in 12 paesi da 68 centri ?)
-analisi LOCF (Last– Observation- Carried Forward)

U.S. Food and Drug Administration

FDA Talk Paper

FDA Issues Public Health Advisory for Antipsychotic Drugs used for Treatment of Behavioral Disorders in Elderly Patients (1)

The Food and Drug Administration (FDA) today issued a public health advisory to alert health care providers, patients, and patient caregivers to new safety information concerning an unapproved (i.e., "off-label") use of certain drugs called "atypical antipsychotic drugs." These drugs are approved for the treatment of schizophrenia and mania, but clinical studies of these drugs to treat behavioral disorders in elderly patients with dementia have shown a higher death rate associated with their use compared to patients receiving a placebo (sugar pill).

Today's advisory applies to such antipsychotic drugs as Abilify (aripiprazole), Zyprexa (olanzapine), Seroquel (quetiapine), Risperdal (risperidone), Clozaril (clozapine) and Geodon (ziprasidone). Symbyax, which is approved for treatment of depressive episodes associated with bipolar disorder is also included in the agency's advisory.

FDA Issues Public Health Advisory for Antipsychotic Drugs used for Treatment of Behavioral Disorders in Elderly Patients (2)

FDA is requesting that the manufacturers of all of these kinds of drugs add a boxed warning to their drug labeling describing this risk and noting that these drugs are not approved for the treatment of behavioral symptoms in elderly patients with dementia. Patients receiving these drugs for treatment of behavioral disorders associated with dementia should have their treatment reviewed by their health care providers. In analyses of seventeen placebo-controlled studies of four drugs in this class, the rate of death for those elderly patients with dementia was about 1.6 to 1.7 times that of placebo. Although the causes of death were varied, most seemed to be either heart-related (such as heart failure or sudden death) or from infections (pneumonia). The atypical antipsychotics fall into three drug classes based on their chemical structure. Because the increase in mortality was seen with atypical antipsychotic medications in all three chemical classes, the agency has concluded that the effect is probably related to the common pharmacologic effects of all atypical antipsychotic medications, including those that have not been studied in the dementia population.

U.S. Food and Drug Administration

Department of Health and Human Services

FDA Issues Public Health Advisory for Antipsychotic Drugs used for Treatment of Behavioral Disorders in Elderly Patients (3)

The agency is considering adding a warning to the labeling of older antipsychotic medications because limited data also suggest a similar increase in mortality for these drugs. The review of the data on these older drugs, however, is still on-going.

HEALTH AND DRUG ALERTS

Increased mortality among elderly patients with dementia using atypical antipsychotics

Published at www.cmaj.ca on July 13, 2005.

Sonal Singh
Department of Medicine
Wake Forest University
Winston Salem, NC
Eric Wooltorton
CMAJ

17 trials con 5106 pazienti (placebo o olanzapina, aripiprazolo, risperidone o quetiapina).

Durata media dei trials 10 settimane

Decesssi : gruppo trattati 4,5%
gruppo placebo 2,6%
diff. 1,9 %
rischio relativo 1.7

Risk of Death With Atypical Antipsychotic Drug Treatment for Dementia

Meta-analysis of Randomized Placebo-Controlled Trials

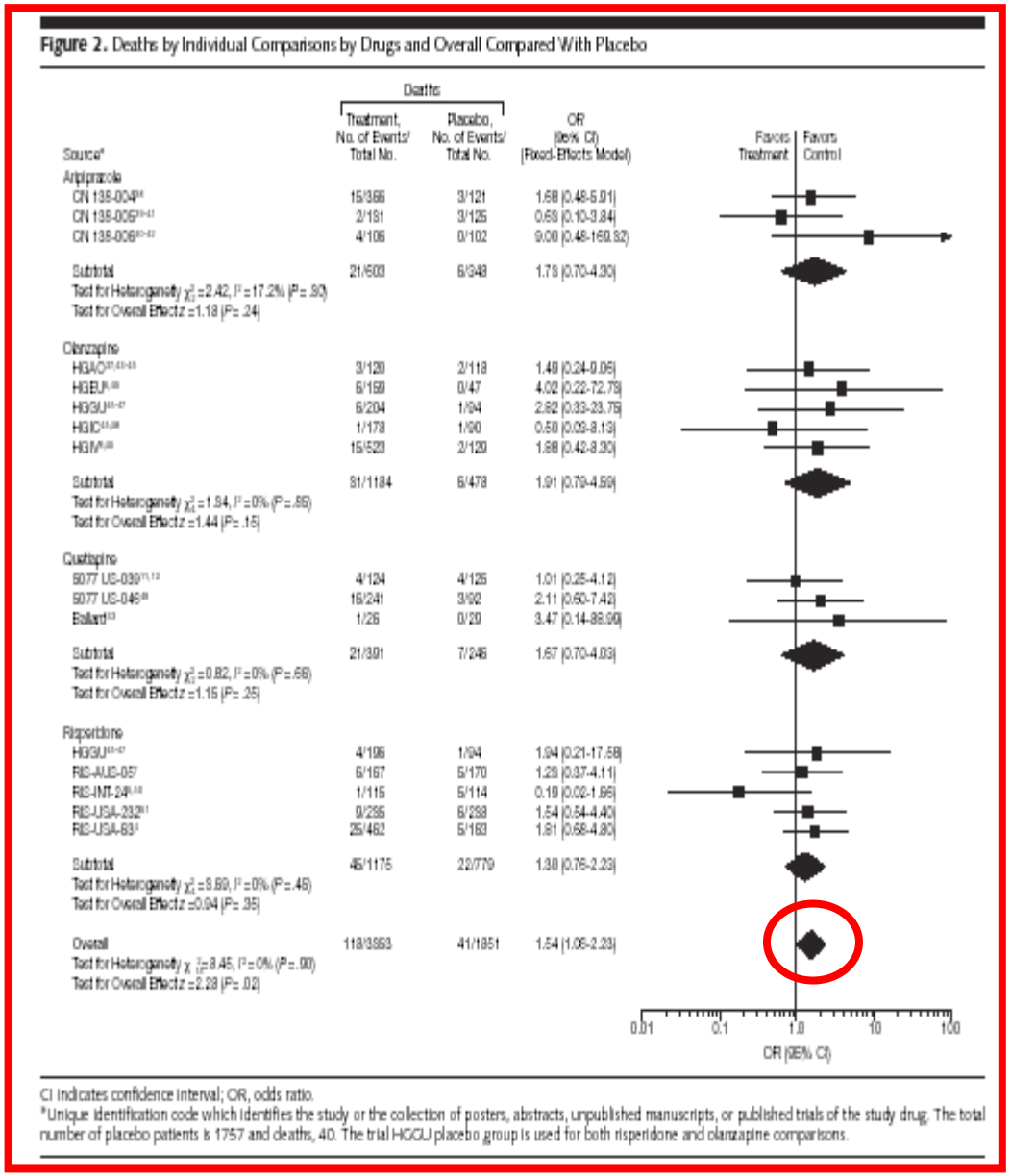
Lon S. Schneider, MD, MS
Karen S. Dagerman, MS
Philip Insel, MS

Context Atypical antipsychotic medications are widely used to treat delusions, aggression, and agitation in people with Alzheimer disease and other dementia; however, concerns have arisen about the increased risk for cerebrovascular adverse events, rapid cognitive decline, and mortality with their use.

(Reprinted) JAMA, October 19, 2005—Vol 294, No. 15

Decessi

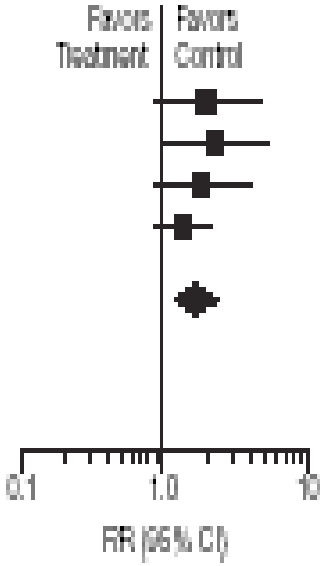
Figure 2. Deaths by Individual Comparisons by Drugs and Overall Compared With Placebo



CI indicates confidence interval; OR, odds ratio.
*Unique identification code which identifies the study or the collection of posters, abstracts, unpublished manuscripts, or published trials of the study drug. The total number of placebo patients is 1757 and deaths, 40. The trial HGGU placebo group is used for both risperidone and olanzapine comparisons.

Figure 4. Deaths Based on Total Drug and Placebo Exposures Pooled by Drug

Drug	Death: Treatment, No. of Events/ Total No.	Death: Placebo, No. of Events/ Total No.	RR [95% CI] [Random-Effects Model]
Aripiprazole	21/95	6/54	1.99 [0.86-4.62]
Olanzapine	31/217	6/97	2.31 [1.00-5.35]
Quetiapine	21/58	7/35	1.85 [0.88-3.93]
Risperidone	45/201	22/133	1.35 [0.85-2.14]
Overall	118/571	41/320	1.55 [1.10-2.20]
Test for Heterogeneity $\chi^2_3 = 1.83$, $I^2 = 0\%$ ($P = .65$)			
Test for Overall Effect $z = 3.01$ ($P = .003$)			



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications

Philip S. Wang, M.D., Dr.P.H., Sebastian Schneeweiss, M.D., Jerry Avorn, M.D., Michael A. Fischer, M.D., Helen Mogun, M.S., Daniel H. Solomon, M.D., M.P.H., and M. Alan Brookhart, Ph.D.

Table 2. Relative Risk of Death within 180 Days after Beginning Therapy with Conventional as Compared with Atypical Antipsychotic Medications.*

Model	Hazard Ratio (95% CI)
Unadjusted analysis	1.51 (1.43–1.59)
Adjusted analysis†	
Use of any conventional APM	1.37 (1.27–1.49)
Low dose of conventional APM (<median)	1.14 (1.04–1.26)
High dose of conventional APM (>median)	1.73 (1.57–1.90)
Adjusted analysis of death†	
<40 Days after beginning therapy	1.56 (1.37–1.78)
40–79 Days after beginning therapy	1.37 (1.19–1.59)
80–180 Days after beginning therapy	1.27 (1.14–1.41)
Adjusted analysis of patient subgroups†	
With dementia	1.29 (1.15–1.45)
Without dementia	1.45 (1.30–1.63)
In a nursing home	1.26 (1.08–1.47)
Not in a nursing home	1.42 (1.29–1.56)

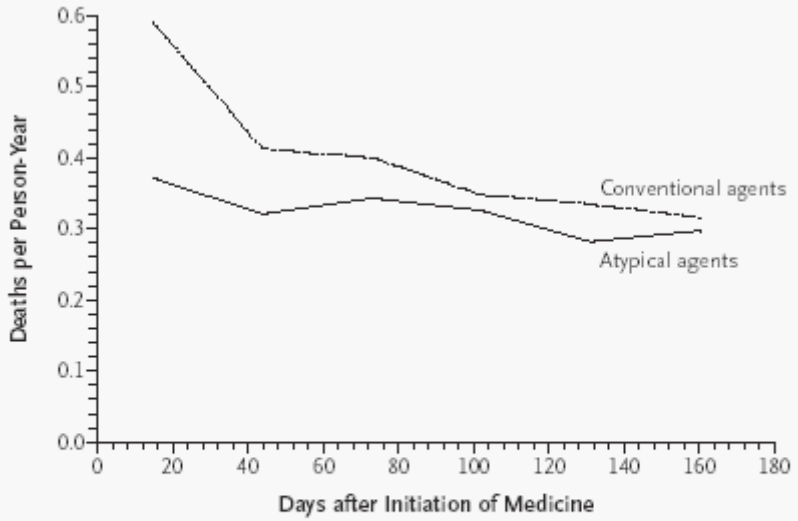


Figure 1. Rates of Death after the Initiation of Conventional and Atypical Antipsychotic Medications.

The rate of death before 10 days was not calculated, owing to insufficient data.

La questione degli antipsicotici nella demenza dimostra tutta la fragilità del sistema del farmaco

Quali antipsicotici utilizzare nella MP ?

Tra l'uso off-label e le decisioni degli ultimi anni delle Autorità Regolatorie quale strada intraprendere ?

Gli studi osservazionali sono sufficienti per prendere una decisione di sanità pubblica ?

E' etico condurre uno studio RCT di confronto tra gli antipsicotici tipici ed atipici con le evidenze disponibili ?

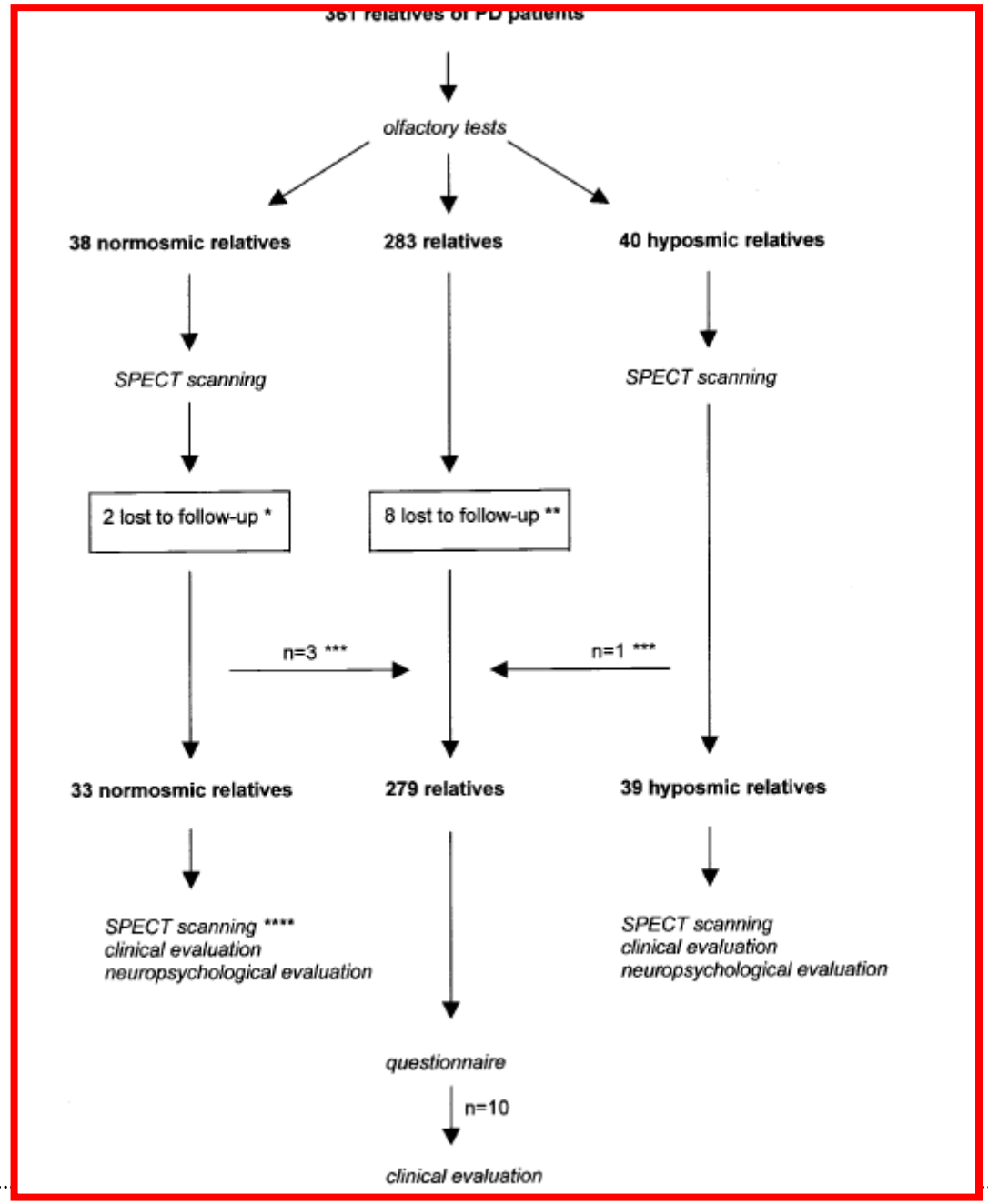
6. PREVENZIONE

Idiopathic Hyposmia As a Preclinical Sign of Parkinson's Disease

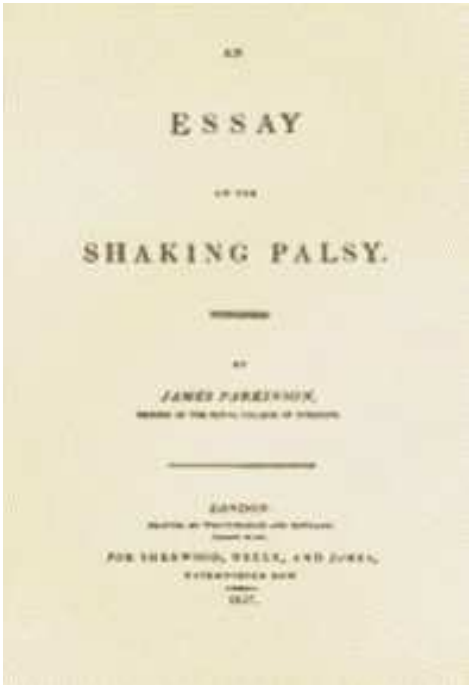
Mirthe M. Ponsen, MD,[1] Diederick Stoffers, MA,[1,2] Jan Booij, MD, PhD,[3]
Berthe L. F. van Eck-Smit, MD, PhD,[3] Erik Ch. Wolters, MD, PhD,[1] and Henk W. Berendse, MD, PhD[1]

Olfactory dysfunction is an early and common symptom in Parkinson's disease (PD). In an effort to determine whether otherwise unexplained (idiopathic) olfactory dysfunction is associated with an increased risk of developing PD, we designed a prospective study in a cohort of 361 asymptomatic relatives (parents, siblings, or children) of PD patients. A combination of olfactory detection, identification, and discrimination tasks was used to select groups of hyposmic (n = 40) and normosmic (n = 38) individuals for a 2-year clinical follow-up evaluation and sequential single-photon emission computed tomography (SPECT), using [^{123}I]β-CIT as a dopamine transporter ligand, to assess nigrostriatal dopaminergic function at baseline and 2 years from baseline. A validated questionnaire, sensitive to the presence of parkinsonism, was used in the follow-up of the remaining 283 relatives. Two years from baseline, 10% of the individuals with idiopathic hyposmia, who also had strongly reduced [^{123}I]β-CIT binding at baseline, had developed clinical PD as opposed to none of the other relatives in the cohort. In the remaining nonparkinsonian hyposmic relatives, the average rate of decline in dopamine transporter binding was significantly higher than in the normosmic relatives. These results indicate that idiopathic olfactory dysfunction is associated with an increased risk of developing PD of at least 10%.

Ann Neurol 2004;56:173–181


361 relatives of PD patients
olfactory tests
38 normosmic relatives
283 relatives
40 hyposmic relatives
SPECT scanning
SPECT scanning
2 lost to follow-up *
8 lost to follow-up **
n=3 ***
n=1 ***
33 normosmic relatives
279 relatives
39 hyposmic relatives
SPECT scanning ****
clinical evaluation
neuropsychological evaluation
SPECT scanning
clinical evaluation
neuropsychological evaluation
questionnaire
n=10
clinical evaluation

PROSPETTIVE


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

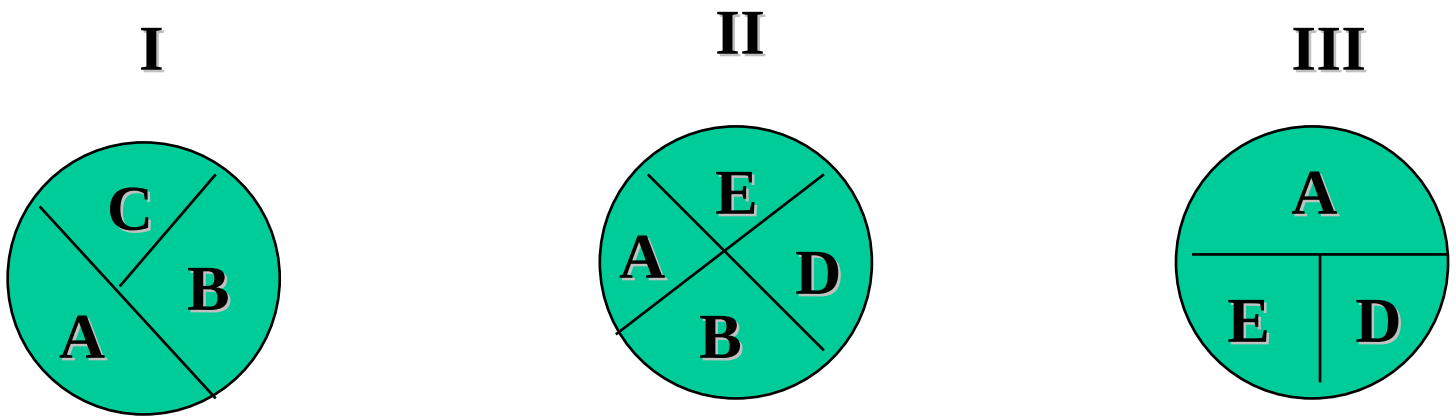
PRINTED BY WHITTINGHAM AND ROWLAND,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

A GENERAL MODEL OF CAUSATION

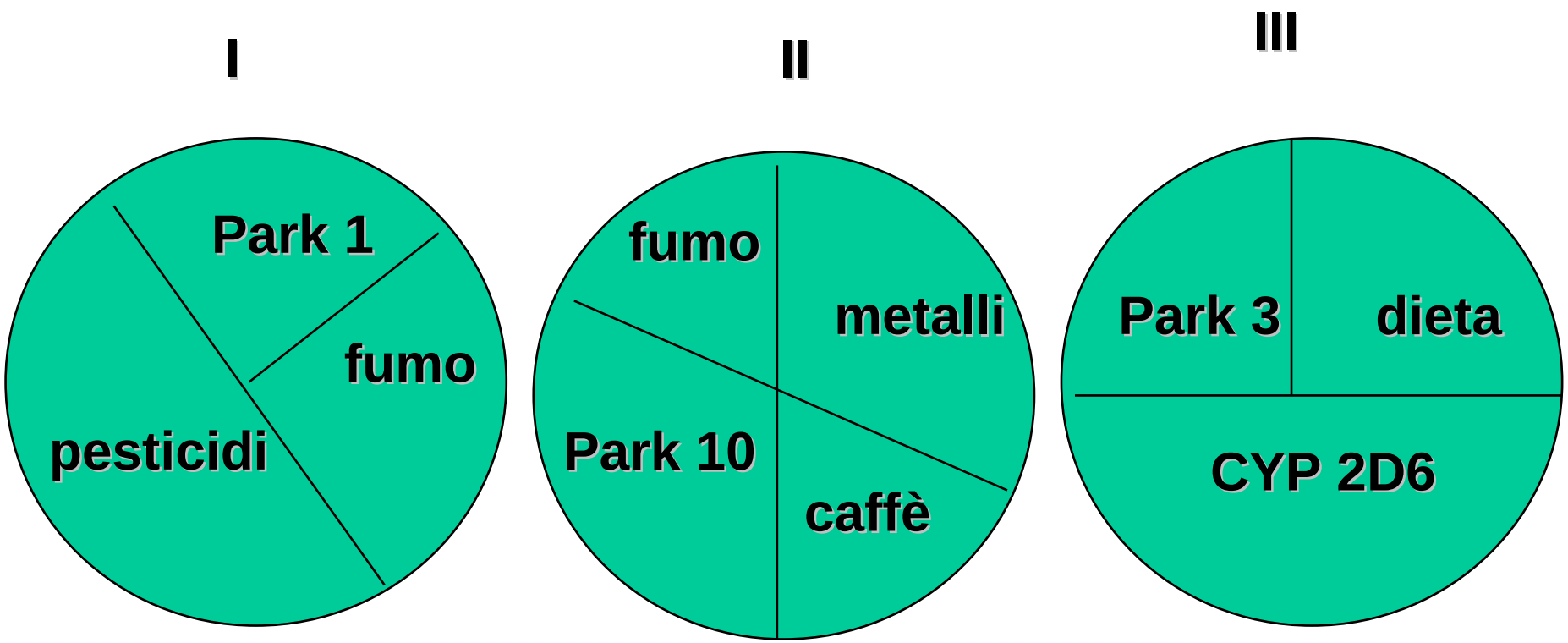


Three sufficient causes of a disease

A "sufficient" cause which means a complete causal mechanism, can be defined as a set of minim conditions and events that inevitably produce disease; "minimal" implies that all conditions or events are necessary

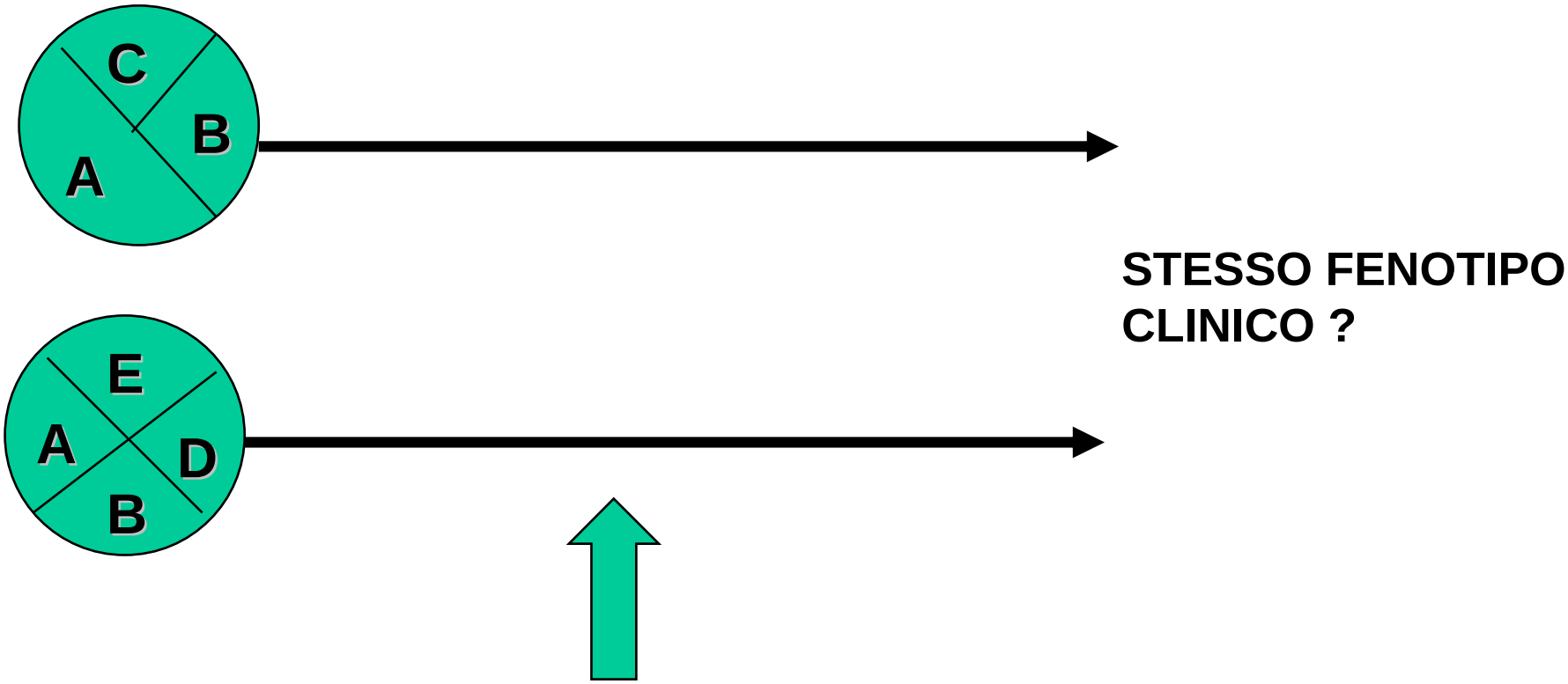
(KY Rothman and S Greenland 1998)

A GENERAL MODEL OF CAUSATION



Three sufficient causes of PD

STORIA NATURALE DELLA MALATTIA DI PARKINSON



The Rational Clinical Examination

Evidence-Based Medicine

A New Approach to Teaching the Practice of Medicine

Evidence-Based Medicine Working Group

JAMA 1992

Un medico rileva una crisi di grande male in un uomo di 43 anni e si chiede la prognosi di una prima crisi… consulta un data-base e trova 25 articoli…

L'EBM sostiene che la valutazione dell'evidenze scientifiche aiuta a prendere una decisione in ambito medico

DEFINIZIONE EBM

La medicina basata sulle evidenze "è il coscienzioso, esplicito e accorto uso delle migliori evidenze disponibili per decidere l'assistenza sanitaria da fornire. La pratica dell'EBM implica l'integrazione dell'esperienza clinica individuale con le migliori evidenze disponibili ricercate in modo sistematico"

La pratica medica basata sull'EBM richiede quindi l'integrazione delle evidenze scientifiche con l'esperienza clinica e con le preferenze del paziente.

LE DIVERSE "SIGNIFICATIVITA'"

(Liberati et al.2005)

Significatività statistica	**E' la misura della probabilità di sbagliare respingendo l'ipotesi che l'intervento sperimentati sia equivalente a quello con cui è stato confrontato**	**L'intervento dovrebbe sempre essere valutato non solo sulla base della significatività statistica ma anche alla luce della sua plausibilità biologica**
Significatività clinica	**E' la valutazione dell'importanza del risultato della sperimentazione per la pratica clinica in generale**	**Dipende alla prospettiva di giudizio; è culturalmente mediata, mutevole nel tempo e per definizione opinabile**
Significatività personale	**Esprime l'interesse del paziente per il risultato che potrebbe ottenere mediante l'intervento sperimentato**	**Rappresenta il punto di vista soggettivo del paziente (o anche del medico) per il risultato della sperimentazione**