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INSTITUTE FOR RISK ASSESSMENT SCIENCES

Radboudumc university medical center

EXPERTISECENTRUM PARKINSON

Veroorzaakt onze werkomgeving Parkinson?

Pesticiden en overige risico's in kaart brengen

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NVvA symposium
Zeist, 5 april 2023

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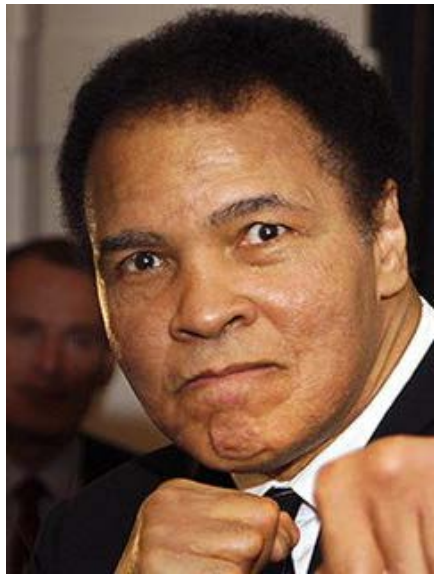

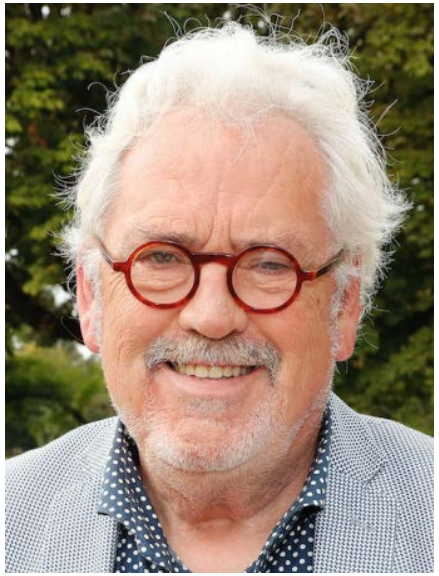

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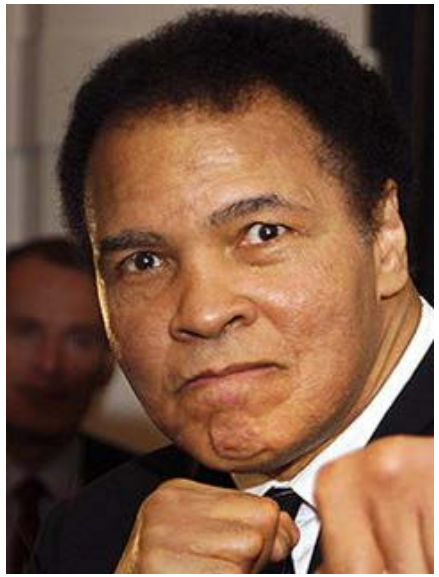
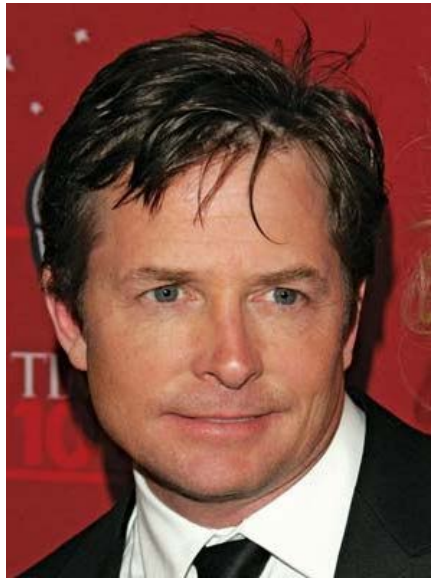
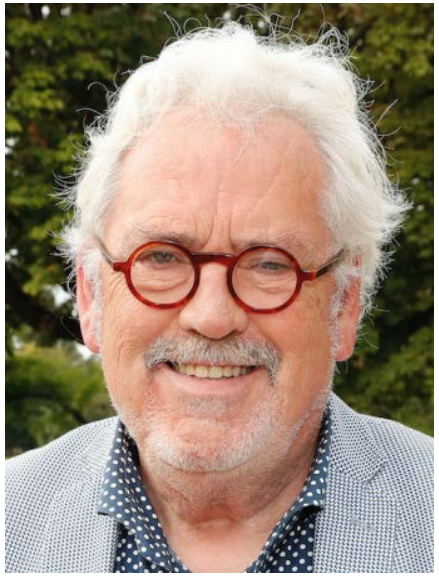

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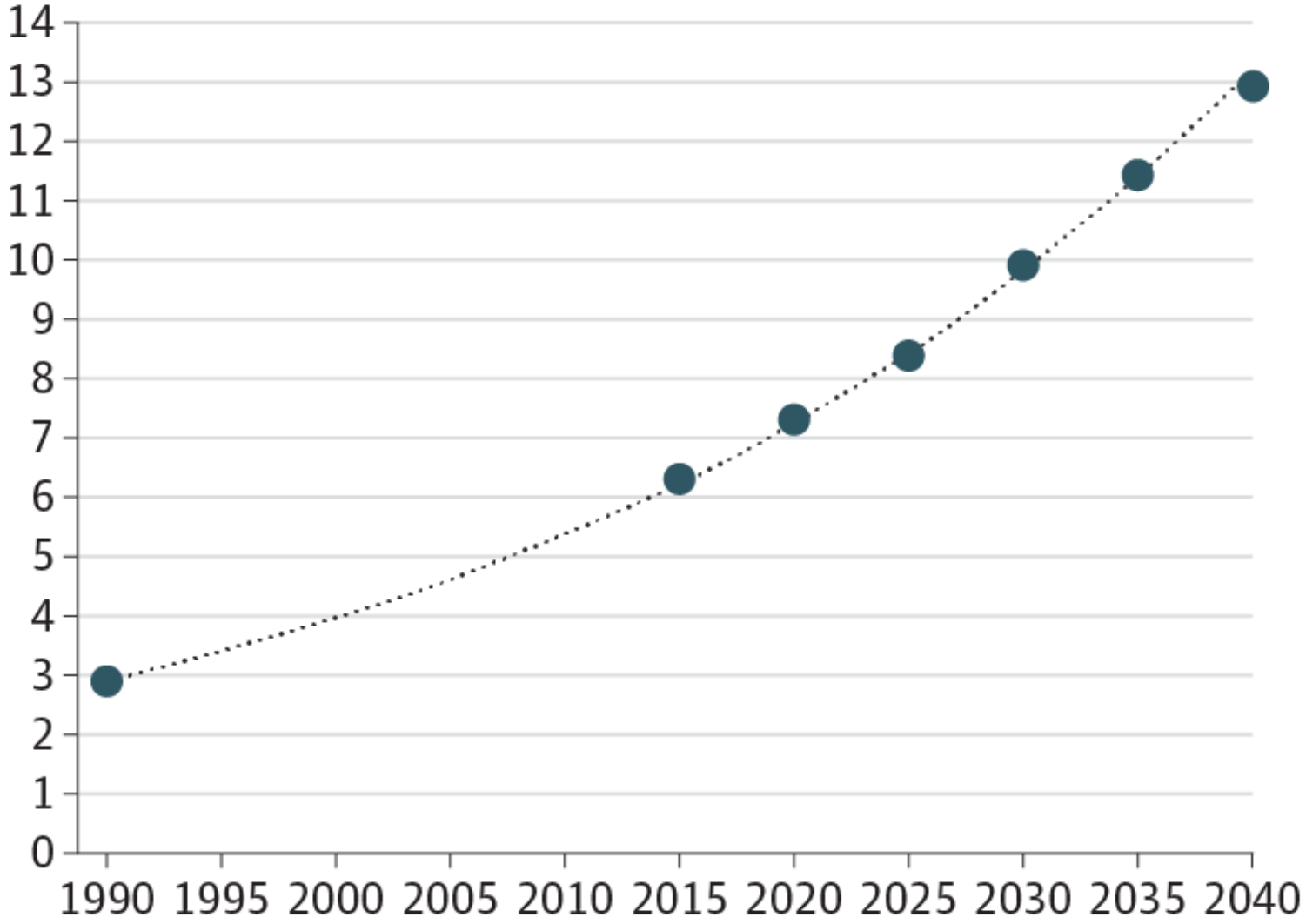
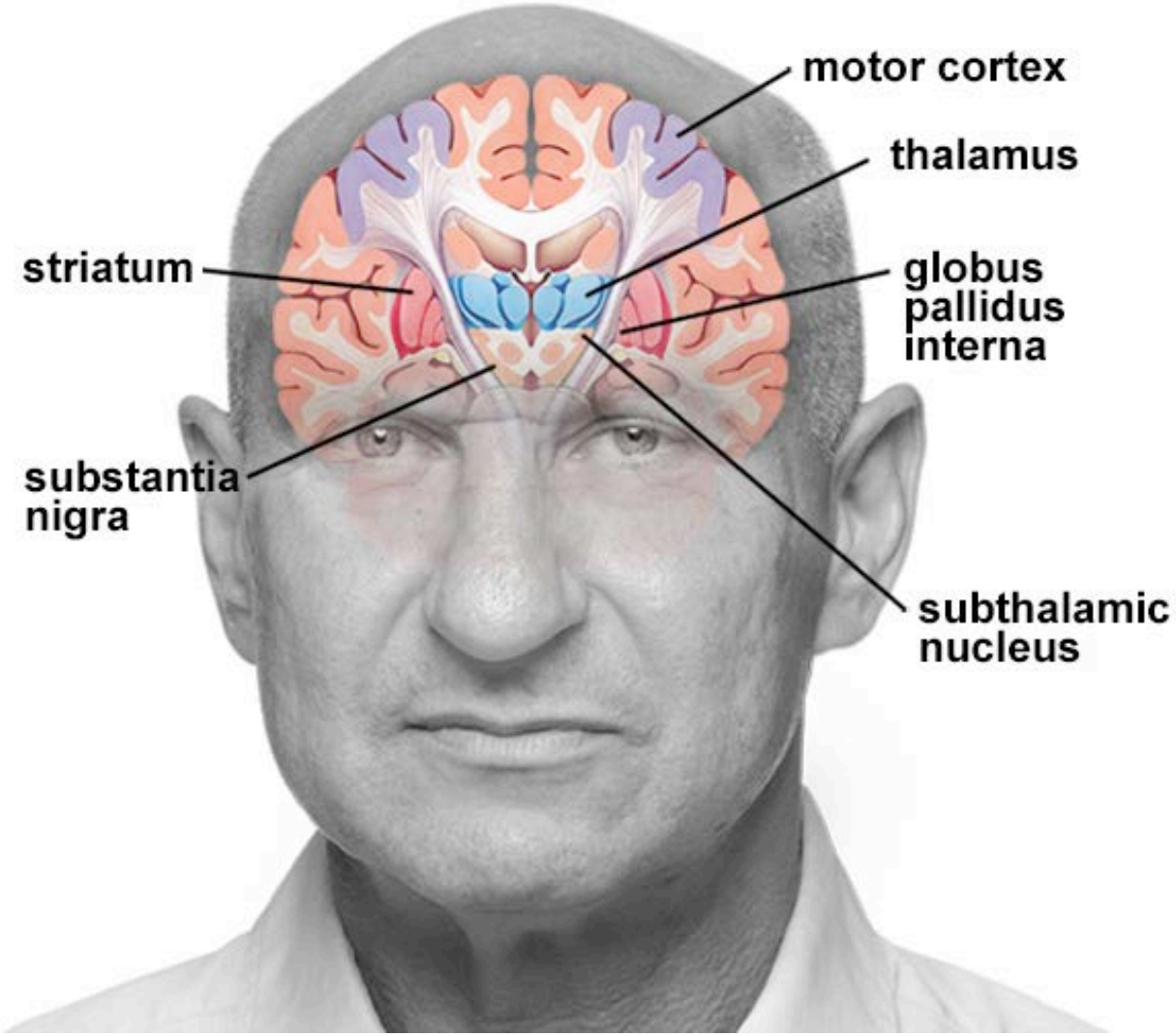
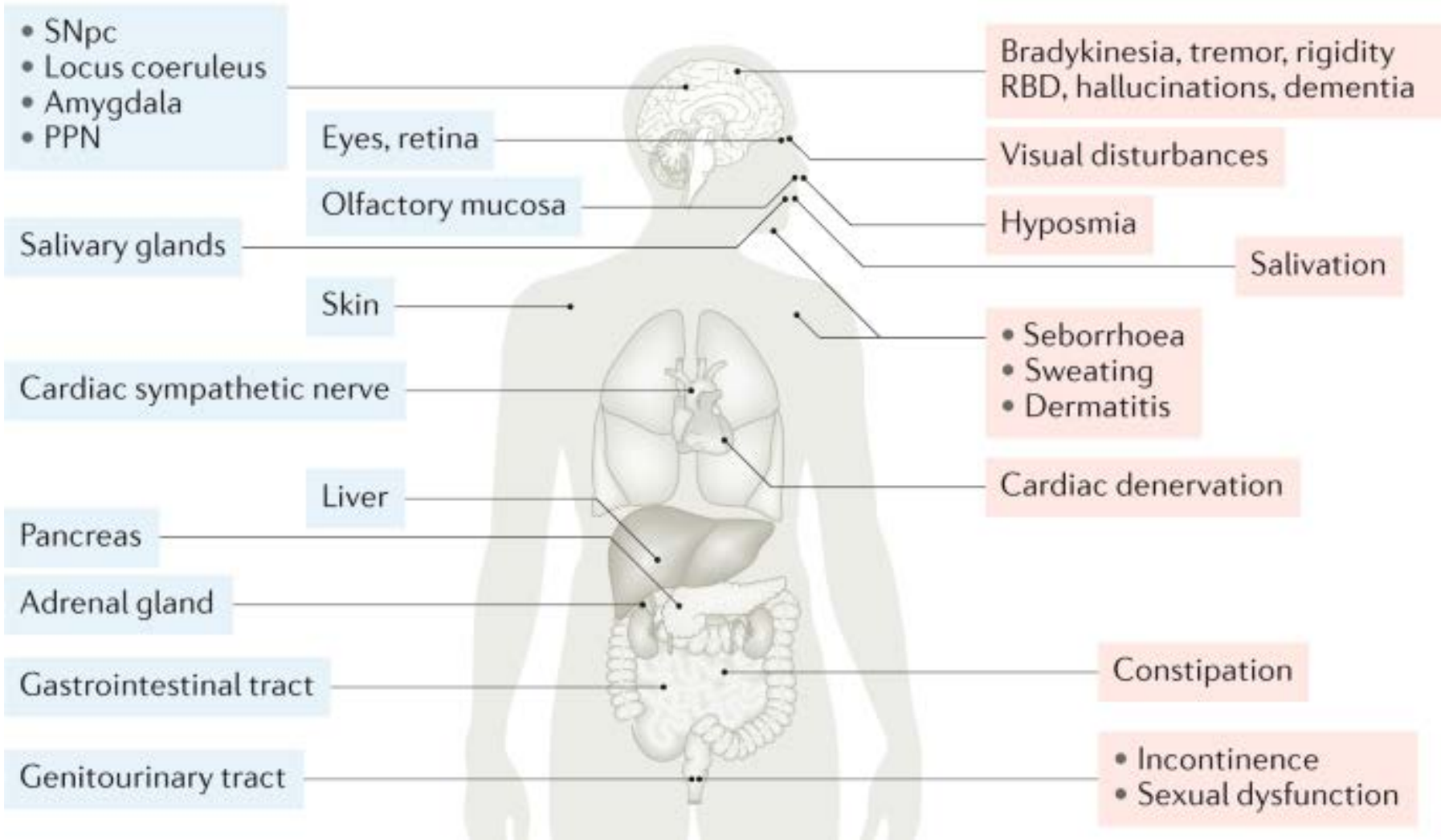
Aantal mensen met Parkinson (miljoen)



Dorsey & Bloem. JAMA Neurol 2018


motor cortex
thalamus
striatum
globus pallidus interna
substantia nigra
subthalamic nucleus

© Mayfield



Blesa et al. Nat Rev Neur 2022

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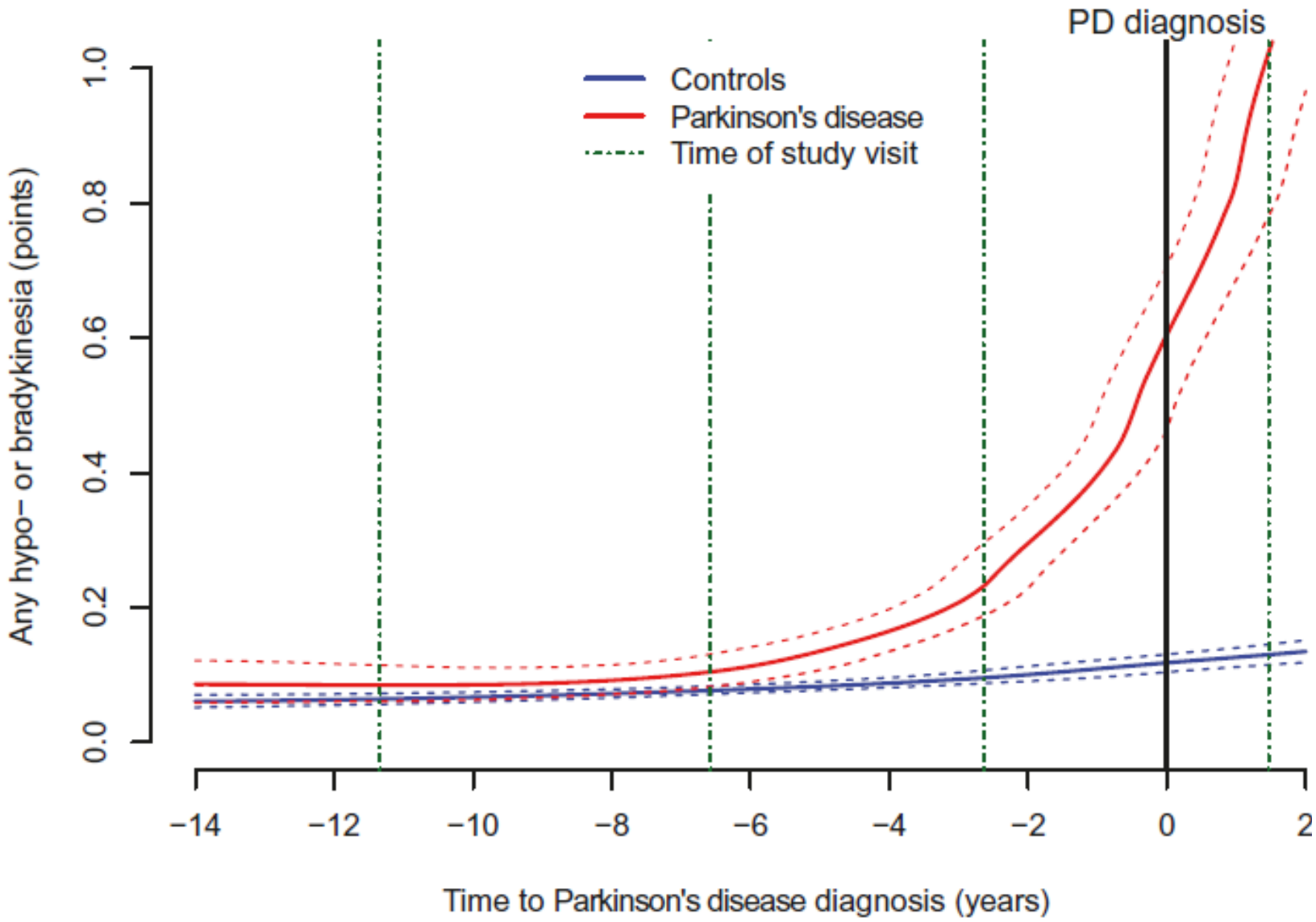
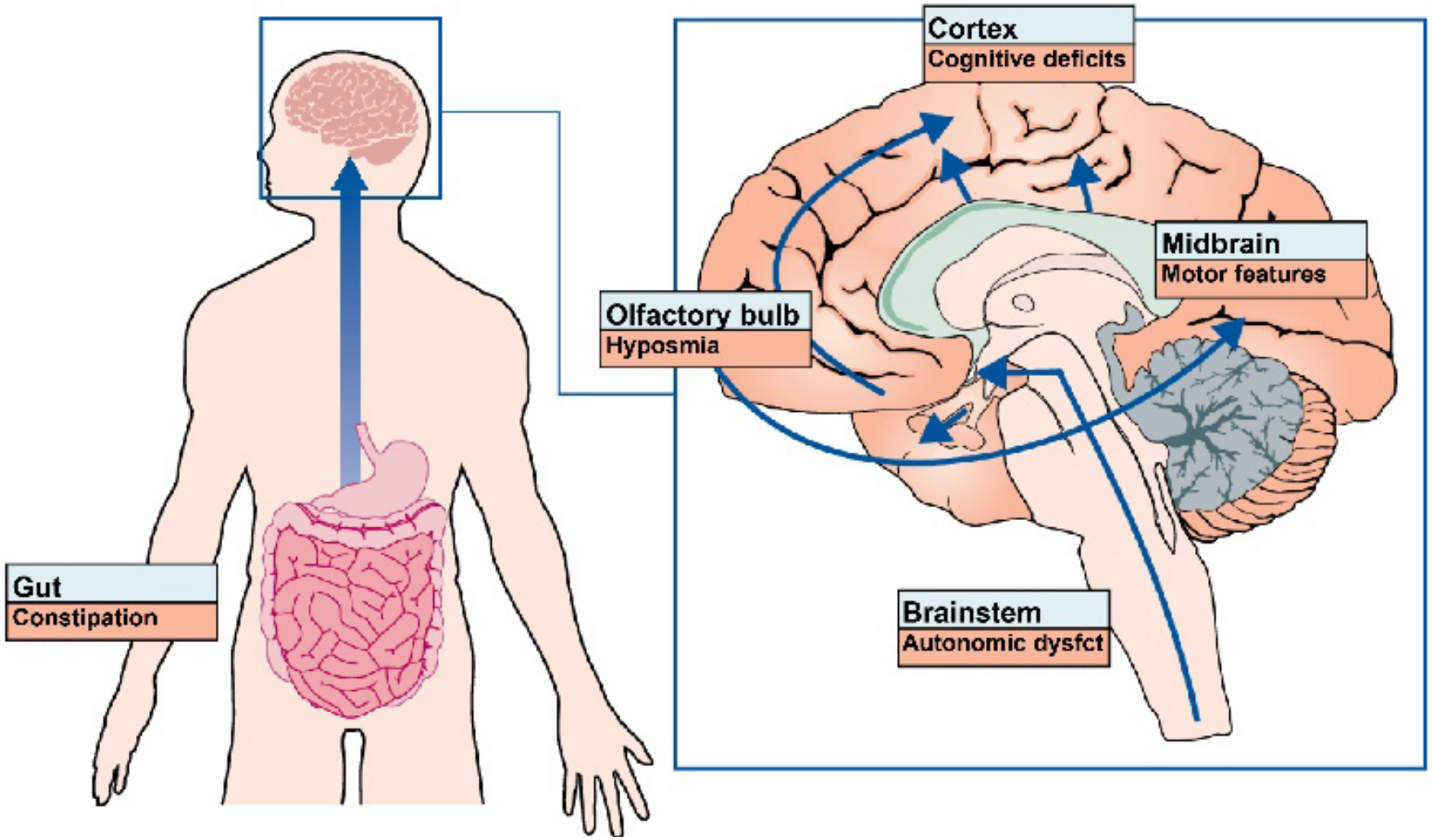
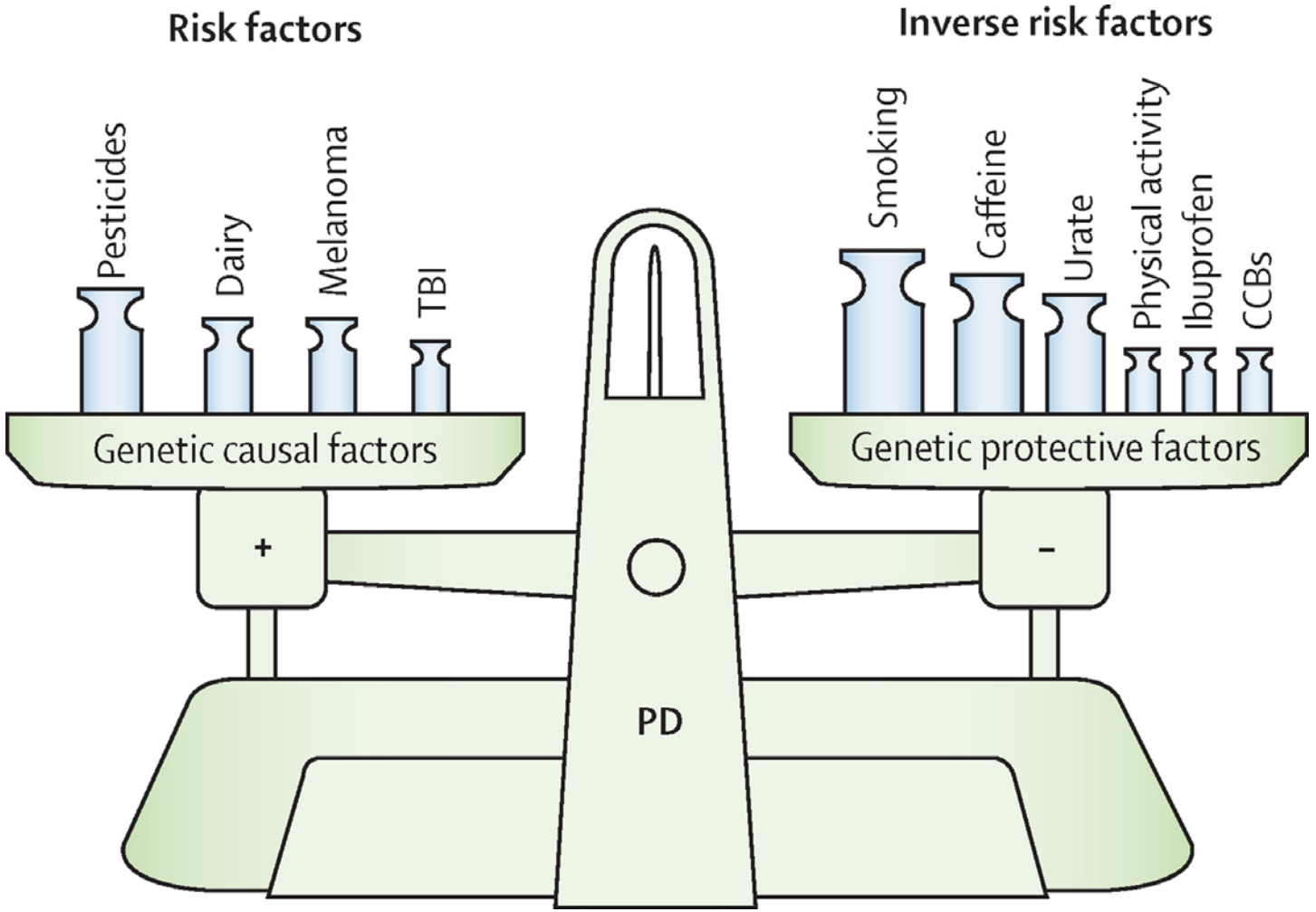


Darweesh et al. Brain 2017

Waar ontstaat Parkinson?

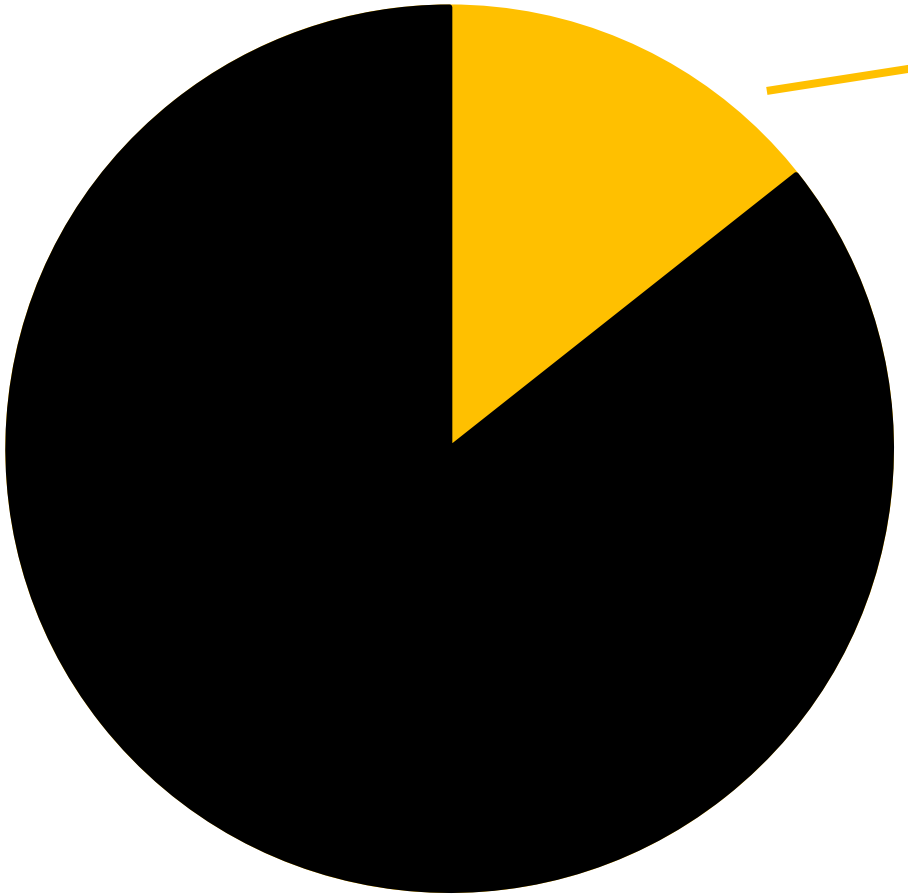


Wat veroorzaakt Parkinson?



Bloem et al. Lancet. 2022

Wat veroorzaakt Parkinson?



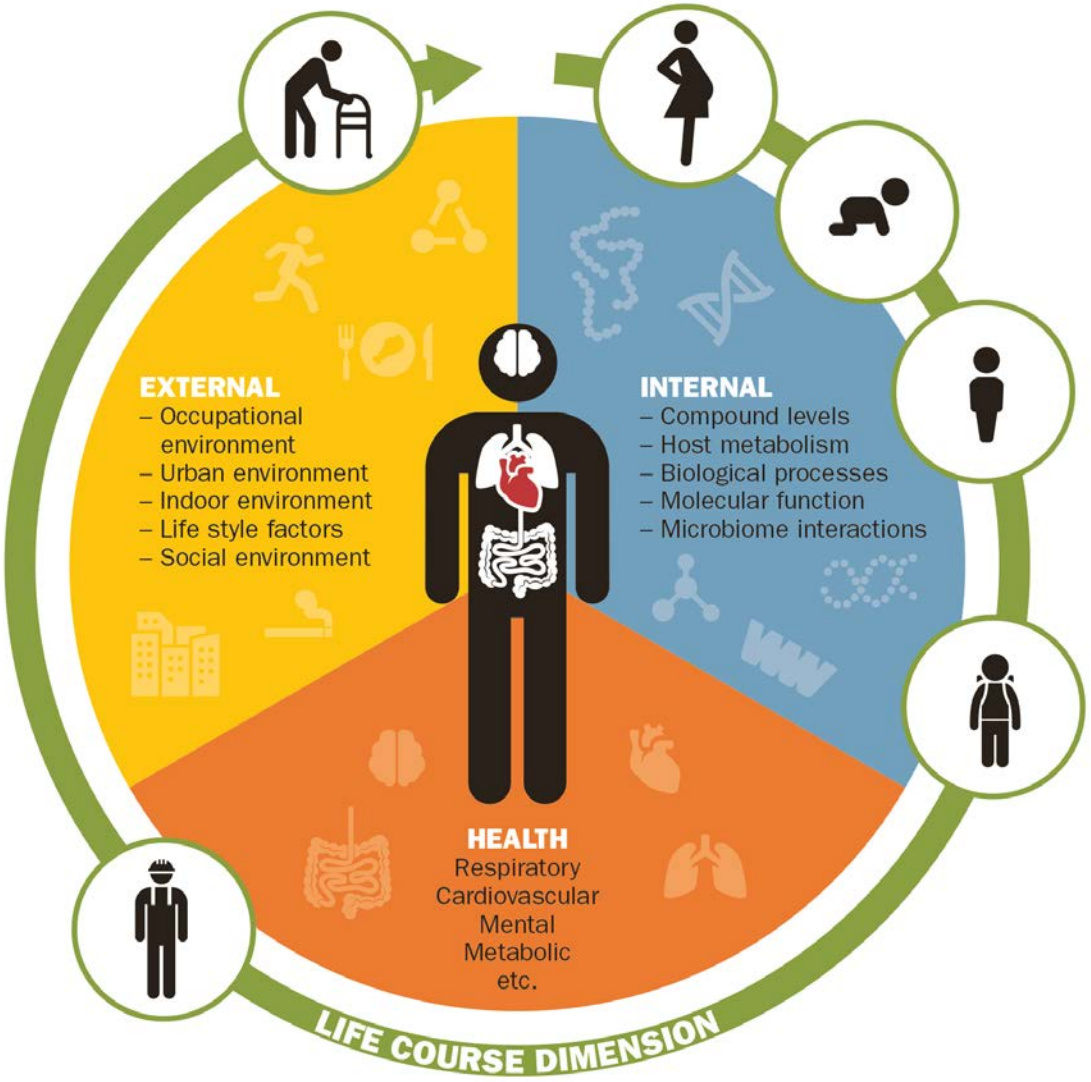
Adapted from Ben-Shlomo, Darweesh et al. Lancet. In print

Exposoom

Alles wat gezondheid en ziekte bepaalt, maar niet is vastgelegd in de genen

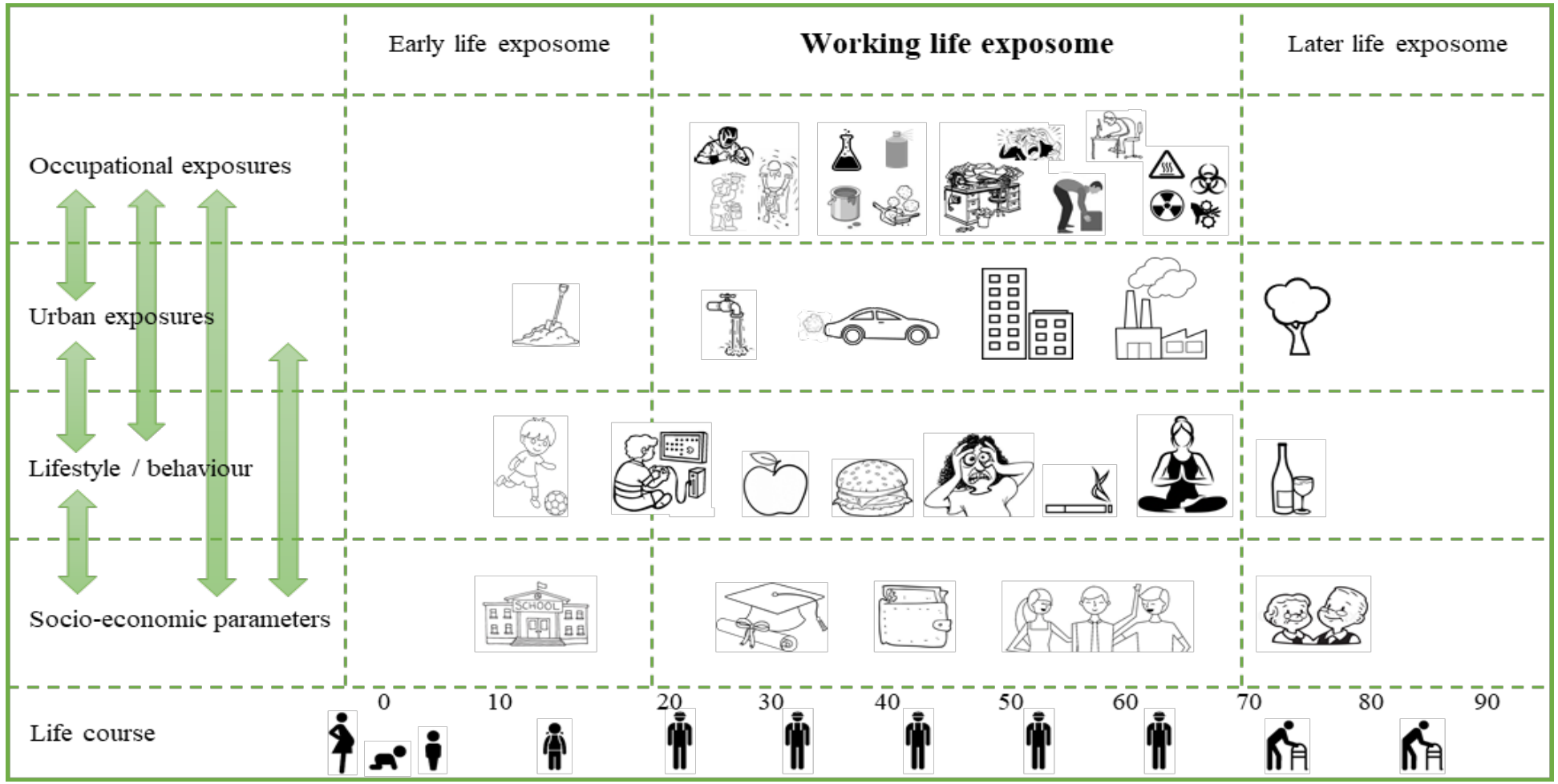
Omvat alle externe blootstellingen en interne biologische effecten gedurende iemands gehele leven

Verklaart waarschijnlijk 70-80% van de ziektelast



Source: White paper Exposome TNO 2018

Exposoom



Source: White paper Exposome TNO 2018

Risicofactoren op werkplek neurodegeneratie

Aandoening	Sterke aanwijzingen	Mogelijke associatie, beperkt bewijs
ALS	ELF-MF Militaire dienst	Luchtvervuiling; Dieseluitstoot; Electrische schokken; Metalen (incl. Pb, Cd); Fysieke activiteit; Pesticiden; Silica; Oplosmiddelen; Virale infectie
PD	Pesticiden	ELF-MF; Oplosmiddelen (incl. TCE); Metalen (incl. Pb); Luchtvervuiling
Parkinsonisme	Mangaan	
Dementie	Luchtvervuiling	ELF-MF; Job complexiteit; Job controle; Metalen; Nachtwerk; Geluid; Pesticiden; Oplosmiddelen
MS		Nachtwerk; Organische oplosmiddelen

Onderzoek risicofactoren neurodegeneratieve aandoeningen

Uitdagingen bij het onderzoeken van mogelijke oorzaken van neurodegeneratieve aandoeningen:

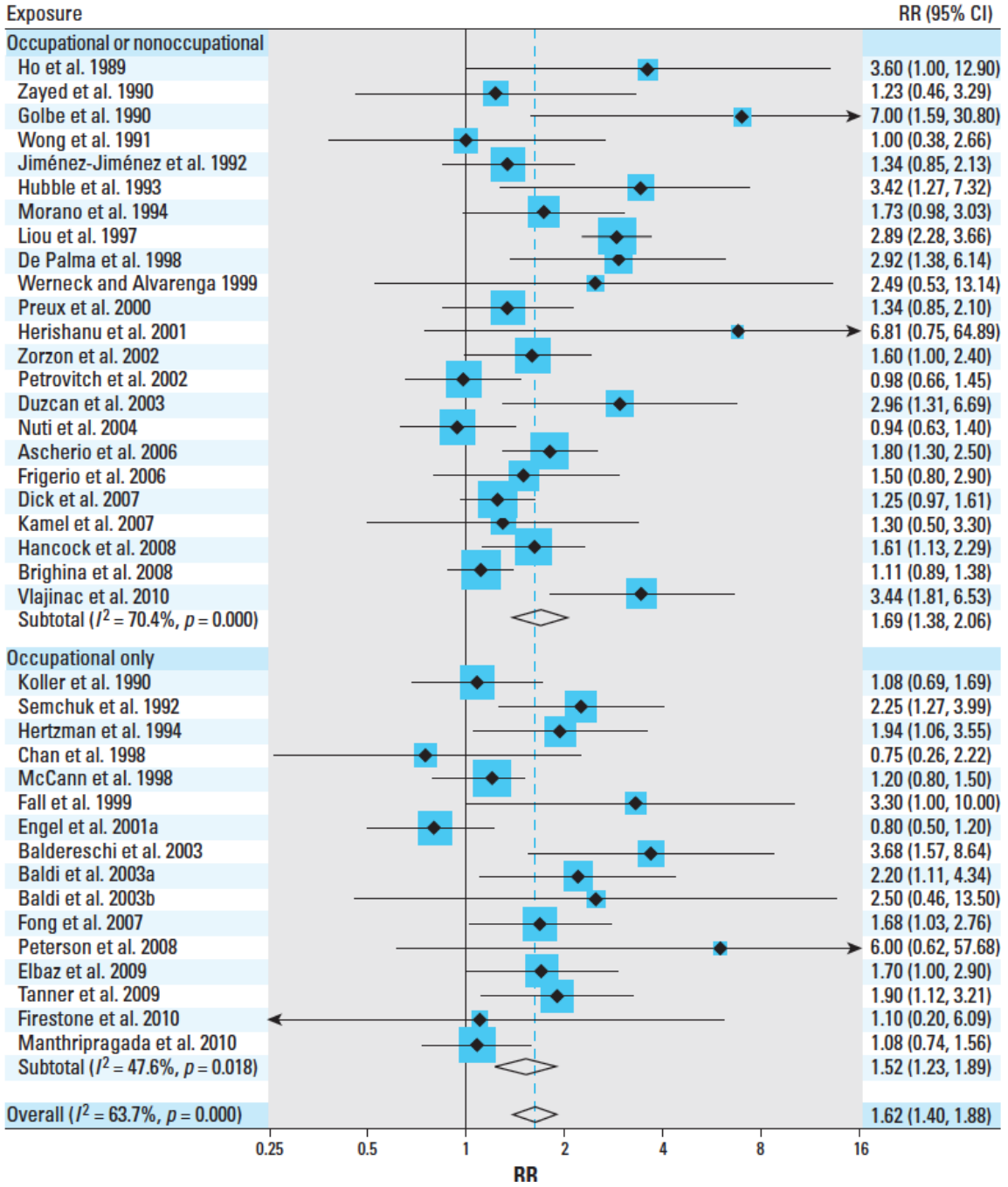
- Ziekte op latere leeftijd, ontstaat niet direct na blootstelling
- Multicausale aandoeningen
- Relatief zeldzaam (vooral ALS)
- Complexe diagnose
- Geheugenproblemen (vooral bij dementie, maar ook bij ALS en PD)

Parkinson

Beroepsmatige blootstelling aan pesticiden en het risico op Parkinson

35 +

4 Null



Van der Mark et al. (2012). EHP

Nederlandse studies sinds meta-analyse 2012

Patient-controle onderzoek (PAGES)

352 incidente PD patiënten en 607 ziekenhuis controles

Algemene populatie-cohort (NLCS)

609 PD patiënten en 5000 sub-cohort (mortaliteit)

Patient-controle onderzoek (PAGES)

Table 3 Cumulative exposure to pesticides, specific subclasses and endotoxin and Parkinson disease risk: job-exposure matrix (JEM) approach

	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Model 1* OR (95% CI)	Model 2† OR (95% CI)
Pesticides‡					
Never	358 (80.6)	709 (80.9)	1	1	1
1–19	26 (5.9)	56 (6.4)	0.92 (0.57 to 1.48)	0.91 (0.55 to 1.52)	0.90 (0.52 to 1.56)
20–32	22 (5.0)	56 (6.4)	0.77 (0.46 to 1.30)	0.74 (0.43 to 1.27)	0.75 (0.42 to 1.36)
33–216	38 (8.6)	55 (6.3)	1.36 (0.89 to 2.09)	1.28 (0.79 to 2.10)	1.56 (0.86 to 2.83)

Based on crop exposure matrix:

Benomyl‡					
Never	420 (94.6)	841 (96.0)	1	1	1
>0–0.27	7 (1.6)	20 (2.3)	0.69 (0.29 to 1.66)	0.80 (0.31 to 2.05)	0.88 (0.34 to 2.27)
>0.27	17 (3.8)	15 (1.7)	2.46 (1.16 to 5.22)	2.23 (1.01 to 4.82)	2.47 (1.05 to 5.78)

Van der Mark et al. (2014). Occ Env Med *71*

Prospectieve cohort studie (NLCS)

Conclusie:

"… we found suggestions for an association between PD mortality and occupational exposure to pesticides…"

"However, … absence of a monotonic trend with either duration of exposure or cumulative exposure."

Brouwer et al. (2015) Occ Env Med *72:448–455*

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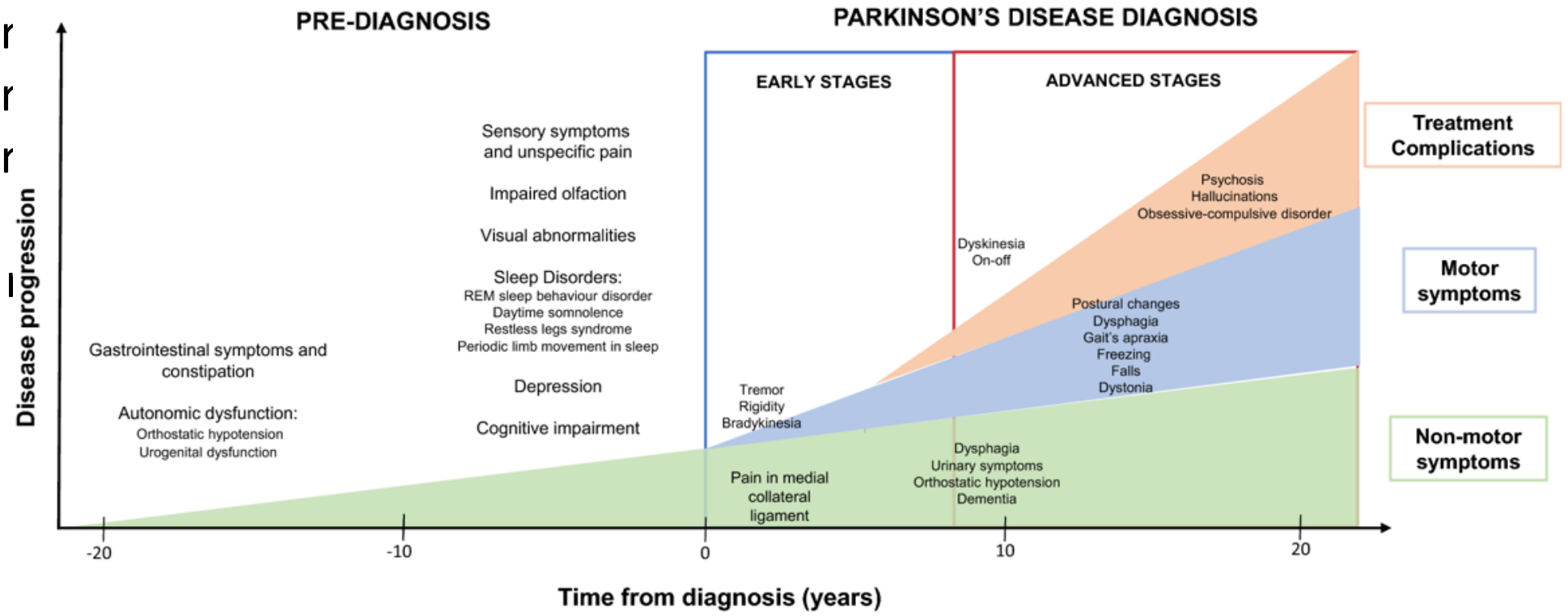
Is er een link tussen beroepsmatige pesticiden blootstelling en Parkinson?

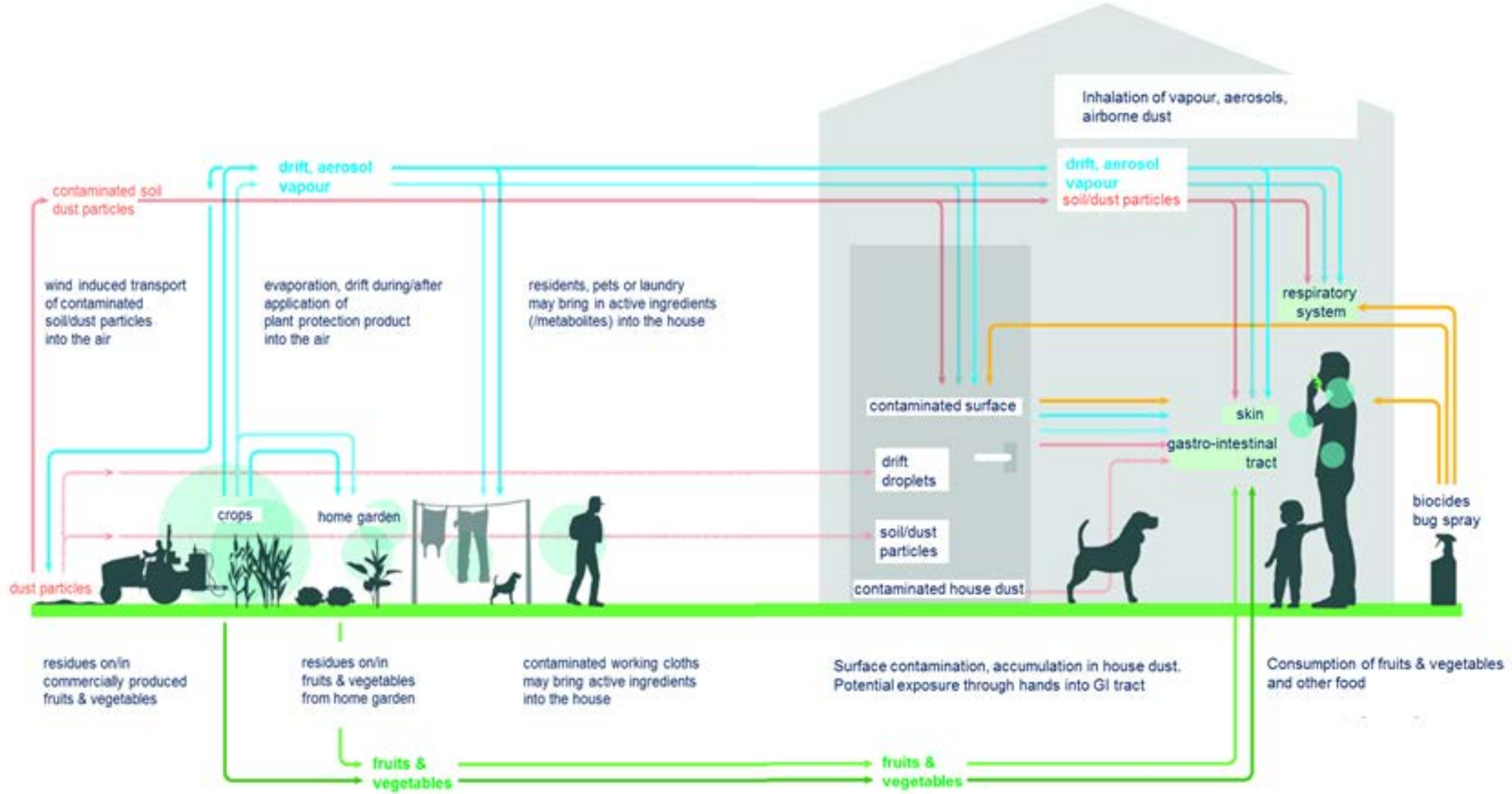
Pesticiden met een mogelijke relatie met PD

Rotenon – Verbod 2008
Lindaan – Verbod 2007
Paraquat – Ver
Maneb – Ver
Benomyl – Ver

Mancozeb (zineb + r



Milieublootstelling en het risico op Parkinson?



Milieublootstelling en het risico op Parkinson?

Eur J Epidemiol (2017) 32:203–216
DOI 10.1007/s10654-017-0229-z

NEURO-EPIDEMIOLOGY

Agricultural activities and the incidence of Parkinson's disease in the general French population

Sofiane Kab[1,2] · Johan Spinosi[2,3] · Laura Chaperon[2,3] · Aline Dugravot[1] · Archana Singh-Manoux[1,4] · Frédéric Moisan[2] · Alexis Elbaz[1,2]

Received: 8 September 2016 / Accepted: 27 January 2017 / Published online: 9 February 2017

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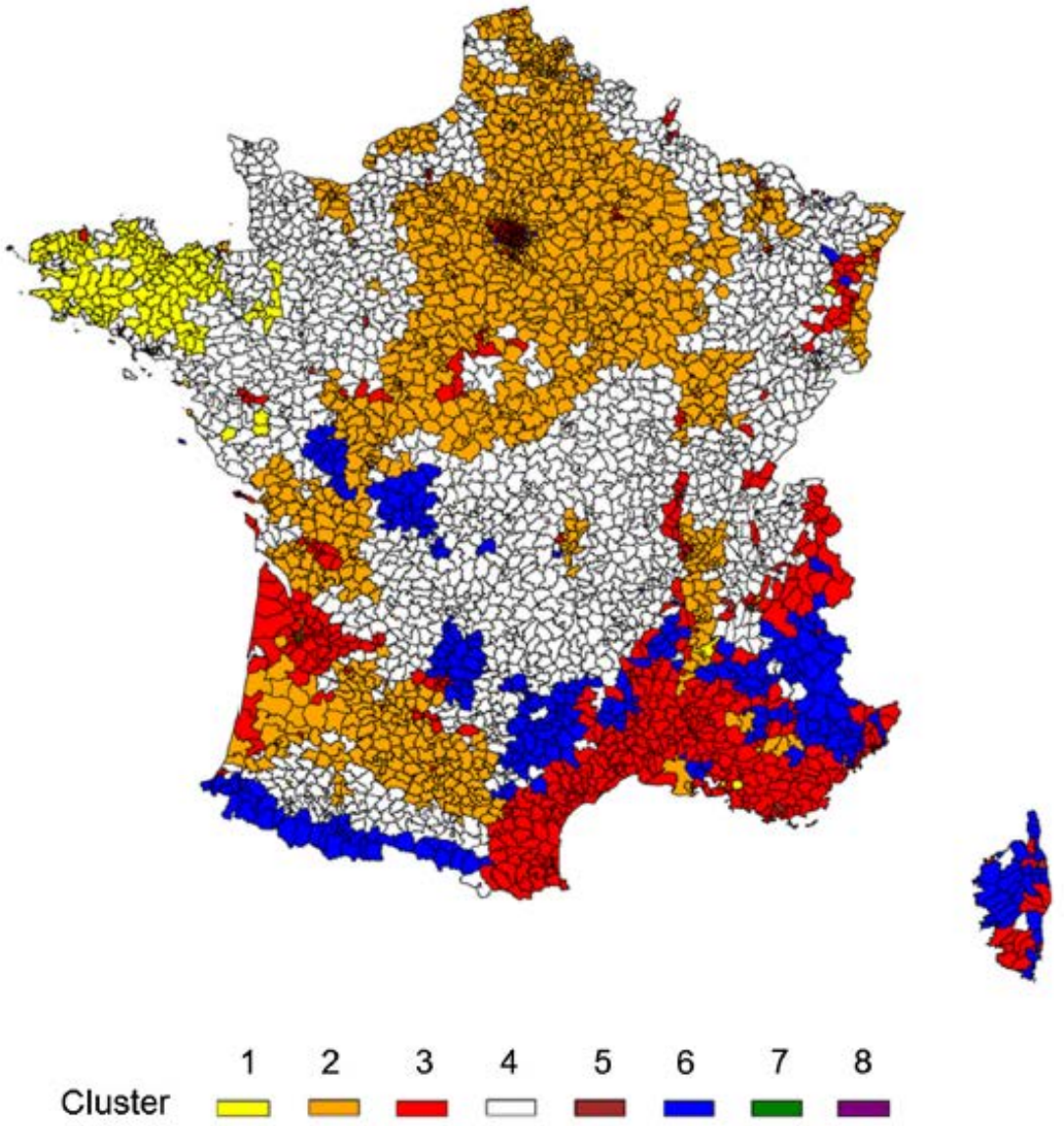
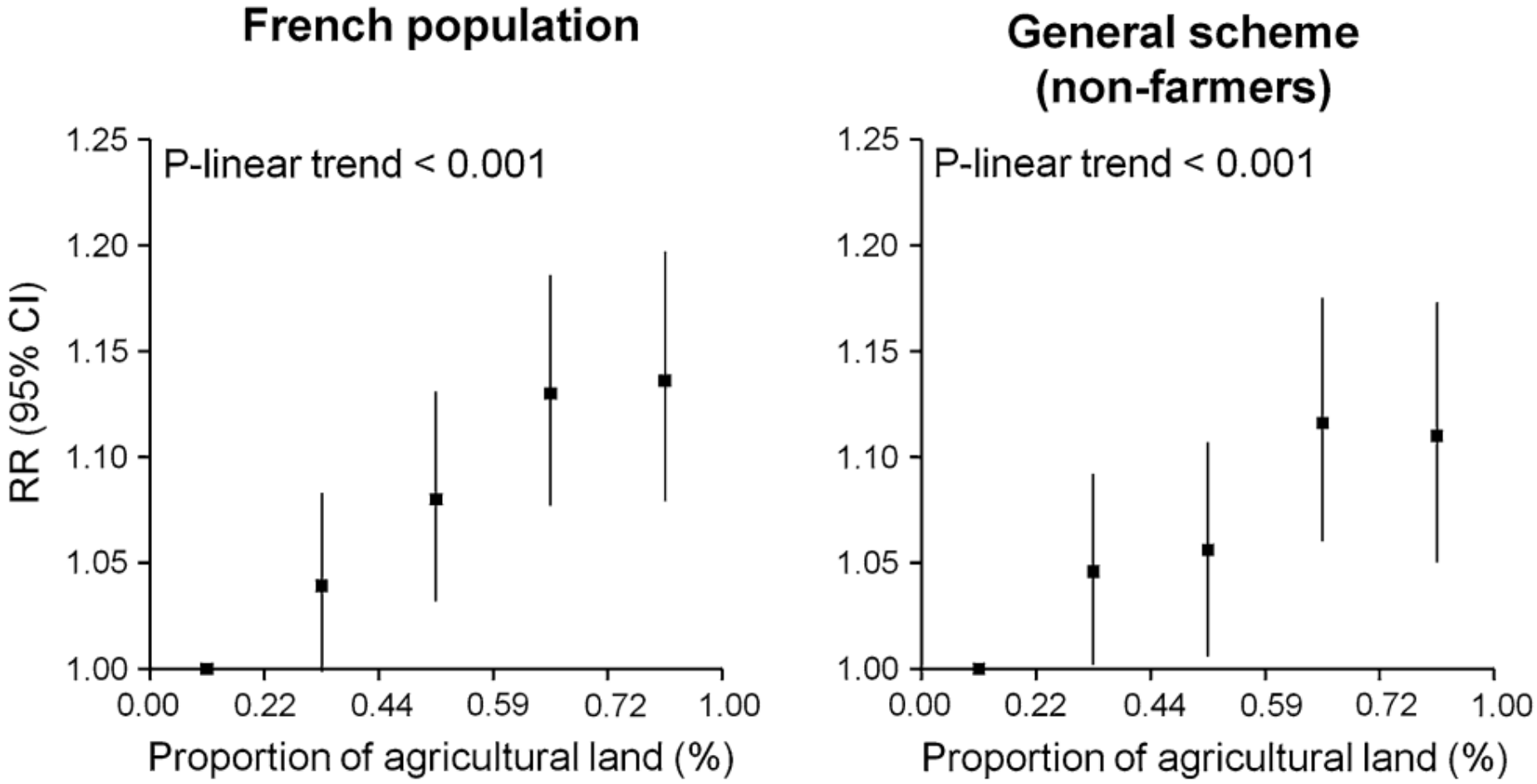
Milieublootstelling en het risico op Parkinson?

Fig. 2 Spatial distribution of the clusters of cantons. Please see Table S6 for the description of the clusters. Clusters 7 and 8 were excluded from the analyses as they included one and two cantons respectively and represent outliers



Milieublootstelling en het risico op Parkinson?



Nederlandse studies milieublootstelling

Landgebruik als indicator voor blootstelling

Bestand Landelijk Grondgebruik Nederland (LGN) en Basis Registratie Percelen (BRP)

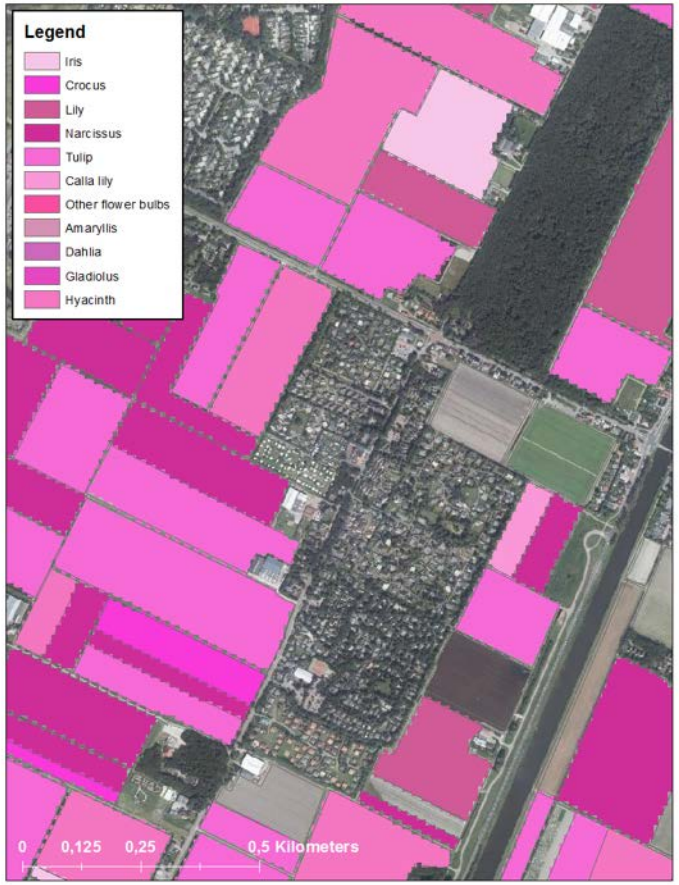
Oppervlakte aan landbouwpercelen berekend in ‘’buffers’’ (vierkanten rond het woonadres)

- 50 meter
- 100 meter

→ Direct spray drift

- 250 meter
- 500 meter

→ Secondaire emissie



Milieublootstelling: PD risico

Pesticide (crops)	0–100 m		
	PD cases (n = 352) n (%)	Controls (n = 607) n (%)	Adj. OR (95% CI)[a]
Paraquat (POT, BUL, ORC)			
Not exposed	171 (48.6)	285 (47.0)	Reference
Ever exposed	181 (51.4)	322 (53.0)	1.00 (0.73–1.36)
Cumulative, T1	44 (12.5)	106 (17.5)	0.74 (0.47–1.16)
Cumulative, T2	58 (16.5)	110 (18.1)	0.93 (0.61–1.40)
Cumulative, T3	79 (22.4)	106 (17.5)	1.46 (0.95–2.23)
p-Value for trend[b]			0.19
Lindane (POT, BEE)			
Not exposed	146 (41.5)	241 (39.7)	Reference
Ever exposed	206 (58.5)	366 (60.3)	0.96 (0.70–1.30)
Cumulative, T1	56 (15.9)	121 (19.9)	0.82 (0.54–1.25)
Cumulative, T2	75 (21.3)	125 (20.6)	0.96 (0.65–1.40)
Cumulative, T3	75 (21.3)	120 (19.8)	1.11 (0.73–1.68)
p-Value for trend[b]			0.66
Maneb (POT, CER, BUL, ORC)			
Not exposed	91 (25.9)	136 (22.4)	Reference
Ever exposed	261 (74.1)	471 (77.6)	0.86 (0.61–1.22)
Cumulative, T1	82 (23.3)	155 (25.5)	0.83 (0.54–1.27)
Cumulative, T2	71 (20.2)	161 (26.5)	0.69 (0.45–1.04)
Cumulative, T3	108 (30.7)	155 (25.5)	1.23 (0.80–1.90)
p-Value for trend[b]			0.62
Benomyl (BEE, CER, BUL)			
Not exposed	328 (93.2)	574 (94.6)	Reference
Ever exposed	24 (6.8)	33 (5.4)	1.48 (0.77–2.84)
Cumulative, T1	5 (1.4)	11 (1.8)	1.28 (0.39–4.15)
Cumulative, T2	13 (3.7)	13 (2.1)	1.58 (0.65–3.88)
Cumulative, T3	6 (1.7)	9 (1.5)	1.54 (0.47–5.04)
p-Value for trend[b]			0.24

In exploratieve analyse werd een verhoogd PD risico gevonden voor 21 pesticiden, die vooral op granen en aardappelen worden gebruikt

Verder waren de resultaten suggestief voor een associatie tussen bollenteelt en PD

Hoge correlatie tussen pesticiden: blootstelling aan combinaties

Brouwer, et al. Env Int. 2017

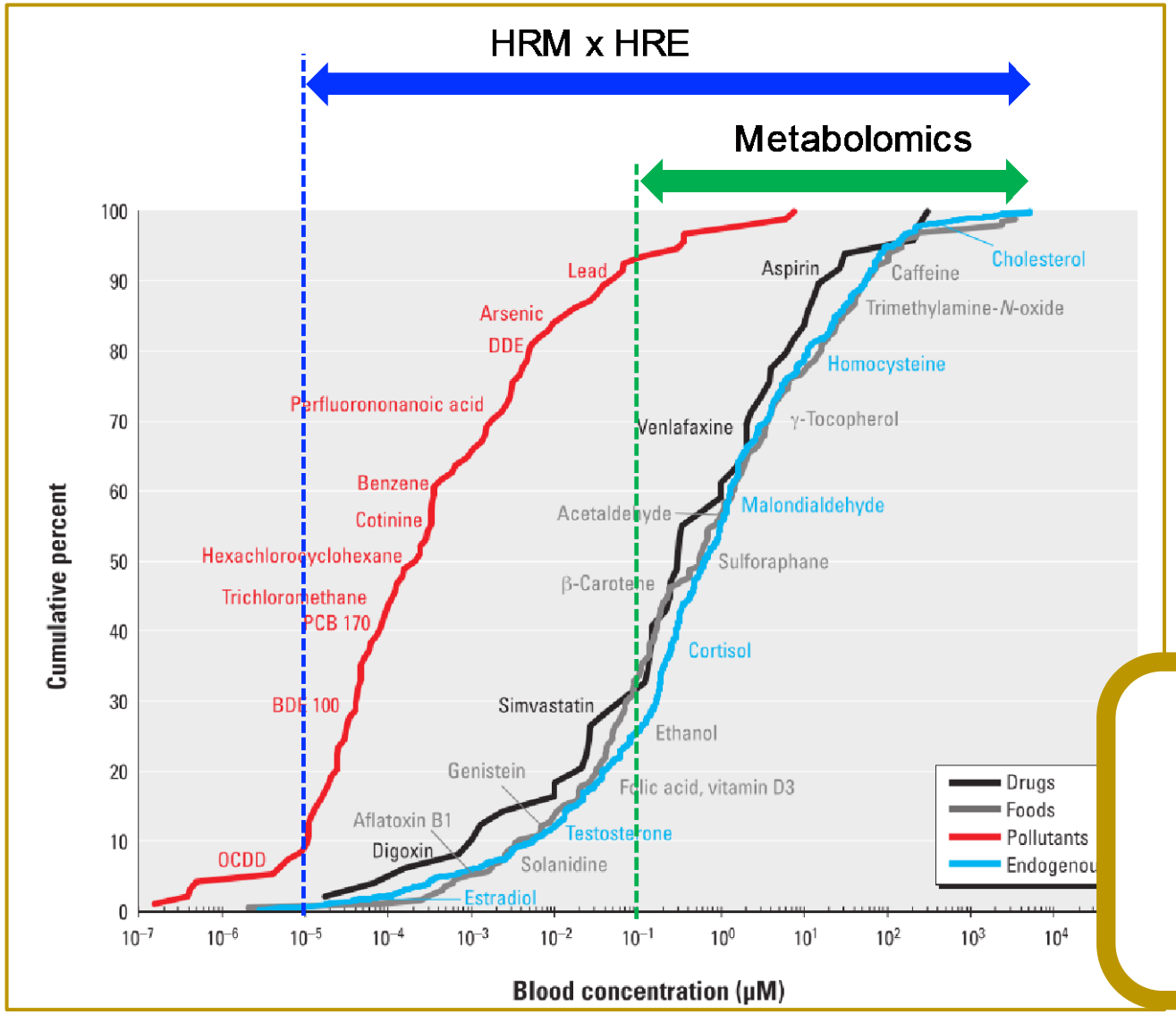
Is er een link tussen milieublootstelling en Parkinson?

Paracelsus (1493-1541)

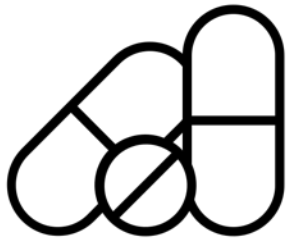
"All things are poison
and nothing is without
poison;
only the dose makes a thing
not a poison."
Often paraphrased as …
The dose makes the poison

?

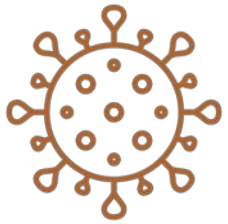
Biologische monitoring en Parkinson – EPIC4PD



Endogenous



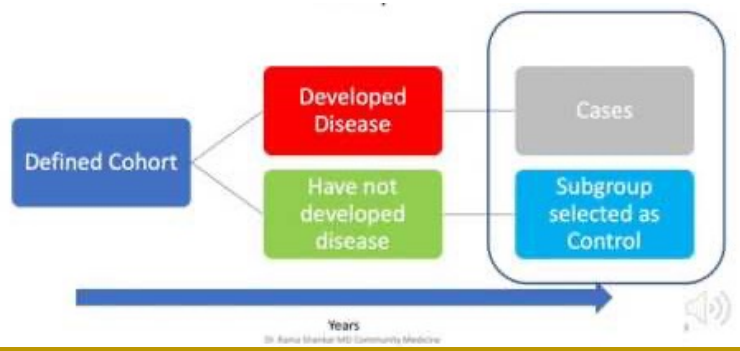
Pharmaceuticals



Bacteria
Virus

Food

Chemicals



352 PD cases

352 controls

Relatie pesticiden en Parkinson

Beroepsmatig
Specifieke pesticiden

→ Hoe blootstelling te schatten aan specifieke middelen?

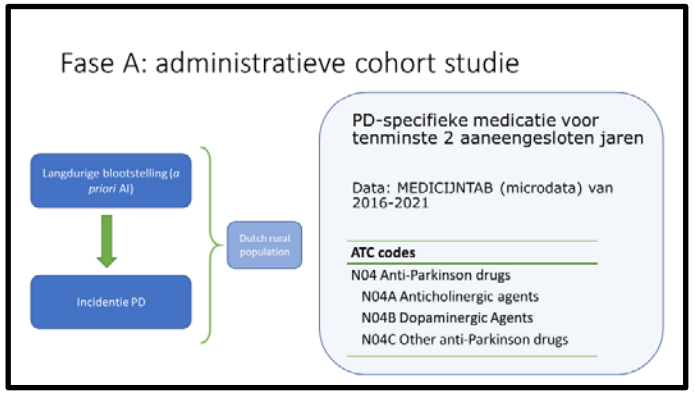
Omwonenden
Risico?
Specifieke pesticiden

→ Hoe beter de blootstelling te karakteriseren?
→ Hoe specifieke middelen te schatten?

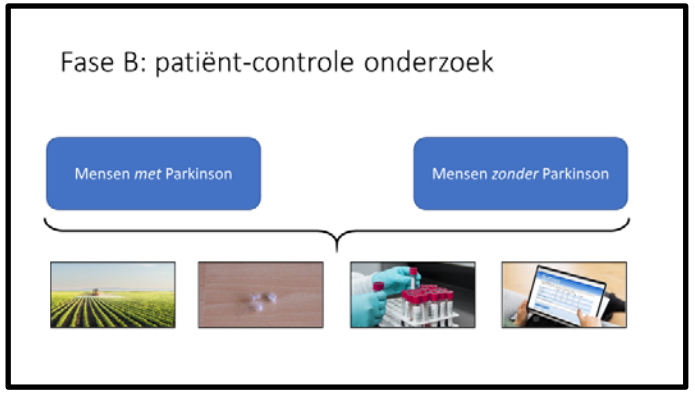
Dieet?

→ Blootstelling via voeding – realistische schattingen

Parkinson-PEST



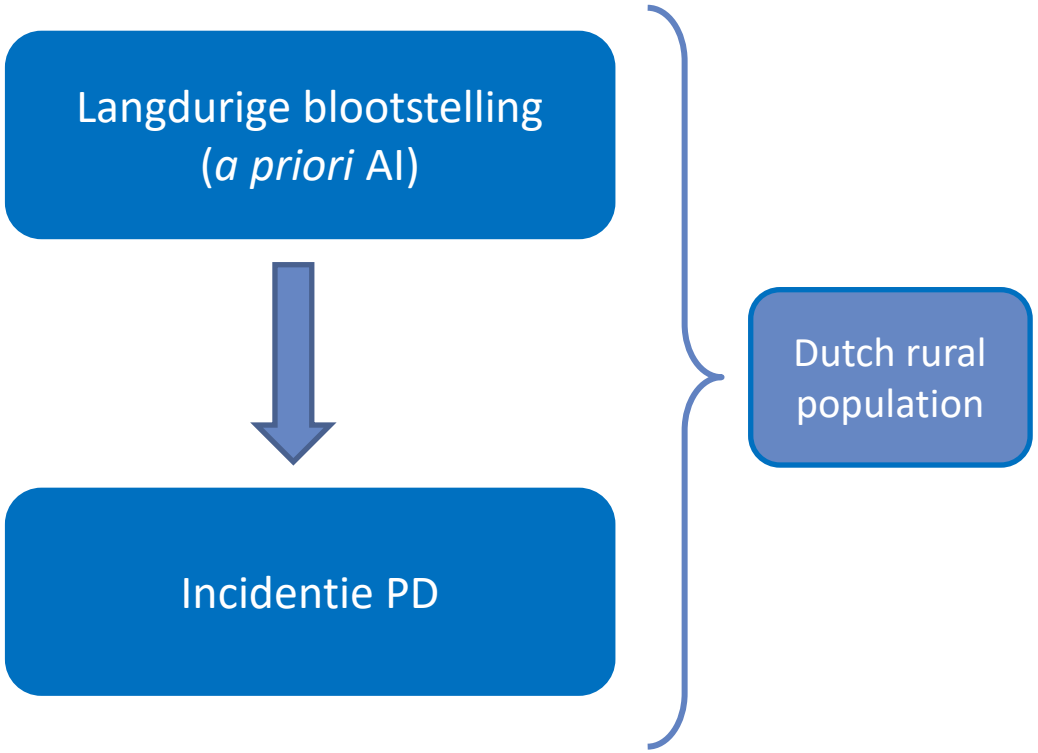
Bestaande gegevens optimaal benutten



Innovatieve multimodale dataverzameling

Parkinson-PEST

Fase A: administratieve cohort studie



PD-specifieke medicatie voor tenminste 2 aaneengesloten jaren

Data: MEDICIJNTAB (microdata) van 2016-2021

ATC codes
N04 Anti-Parkinson drugs
N04A Anticholinergic agents
N04B Dopaminergic Agents
N04C Other anti-Parkinson drugs

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Parkinson-PEST

Fase A: administratieve cohort studie

Geselecteerde actieve ingrediënten (AI)

Selectie op basis van:
- Gebruik in NL (uitvraag bij boeren in 2008, 2012, 2016, 2020)
- Bestaande kennis over associatie met PD

Evidence of association with PD	AI	Type
Individuele AIs	maneb	Fungicide
	glyphosate	Herbicide
	paraquat	Herbicide
Groepen van AIs	ethoprophos	Insecticide
	dimethoate	Insecticide
	malathion	Insecticide
	pirimiphos-methyl	Insecticide
	asulam	Herbicide
	chlorpropham	Herbicide
	carbofuran	Insecticide
	methomyl	Insecticide
	oxamyl	Insecticide
	pirimicarb	Insecticide
	propamocarb	Fungicide
	methiocarb	Insecticide
	thiram	Insecticide
	deltamethrin	Insecticide
	esfenvalerate	Insecticide
	lambda-cyhalothrin	Insecticide
	pyrethrins	Insecticide
AIs geïdentificeerd in Brouwer et al.	carbendazim	Fungicide
	pencycuron	Fungicide
	chlormequat	Plant growth regulator
	cymoxanil	Fungicide
	fenpropimorph	Fungicide
	fluroxypyr	Herbicide
	isoproturon	Herbicide
	mcpa	Herbicide
	metribuzin	Herbicide
	prochloraz	Fungicide
	triadimenol	Fungicide

Parkinson-PEST

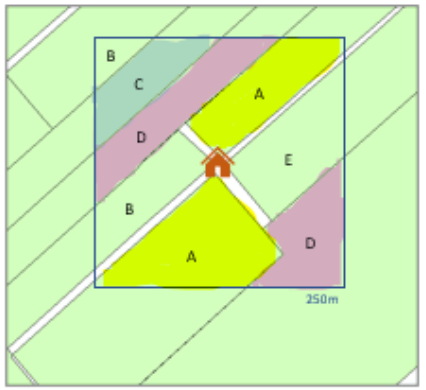
Fase A: administratieve cohort studie

Blootstellingskarakterisering

Kaarten van landgebruik gebaseerd op Basisregistratie percelen (BRP)

Hoeveelheid, in kg (*a priori* AI)

Buffers van 50, 100, 250, 500m rondom huisadressen



Year	Area (ha) in 250m [from BRP maps]				
	Crop A	Crop B	Crop C	Crop D	Crop E
2009	0.05	0.04	0.1	0.1	0.2
...	...	...	...	...	...
2012	0.5	0.3	0.1	0.1	0.3
2013	0.5	0	0.3	0.3	0.3
2014	0.4	0	0	0.5	0.3

Year	Dosage glyphosate (kg/ha) [from farmers' surveys]		
	Crop A	Crop C	Crop D
2008	0.1	0.2	0.3
2009 avg(2008, 2012)	0.055	0.105	0.16
...			
2012	0.01	0.01	0.02
2013 avg(2012, 2016)	0.055	0.055	0.001
2014 avg(2008, 2012)	0.055	0.055	0.001

Year	Amount glyphosate (kg) in 250m
2009	$area_{CropA} * dosage_{CropA} + area_{CropC} * dosage_{CropC} + area_{CropD} * dosage_{CropD}$
...	...
2012	$area_{CropA} * dosage_{CropA} + area_{CropC} * dosage_{CropC} + area_{CropD} * dosage_{CropD}$
2013	$area_{CropA} * dosage_{CropA} + area_{CropC} * dosage_{CropC} + area_{CropD} * dosage_{CropD}$
2014	$area_{CropA} * dosage_{CropA} + area_{CropC} * dosage_{CropC} + area_{CropD} * dosage_{CropD}$

Exposure proxy:

$glyphosate_{2009-2014}^{250m} = \overline{amount}$ or $\sum amount$

Parkinson-PEST

Fase B: patiënt-controle onderzoek

Mensen *met* Parkinson

Mensen *zonder* Parkinson

Parkinson-PEST

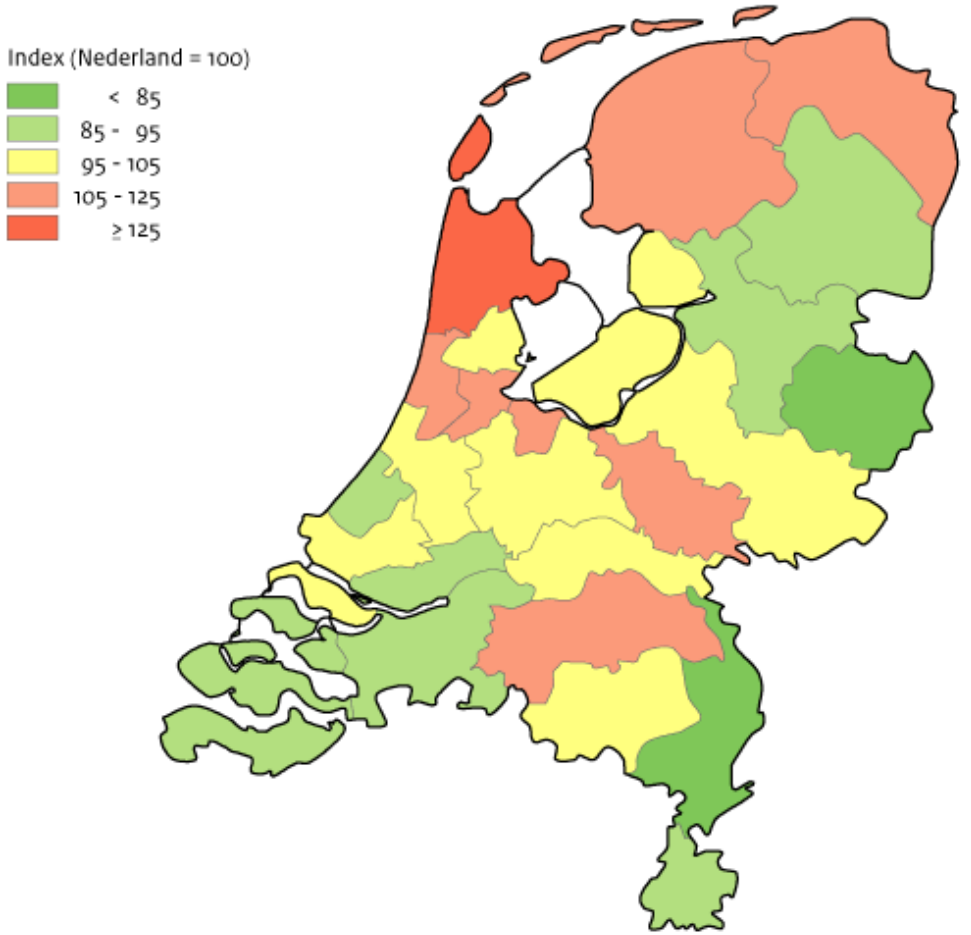
Fase B: patiënt-controle onderzoek

Mensen *met* Parkinson:

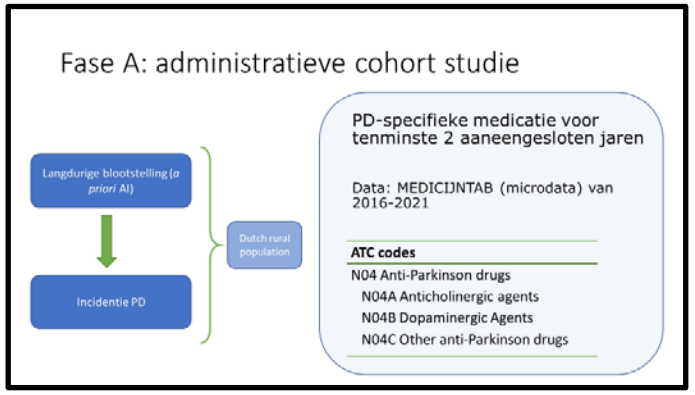
nieuw gediagnosticeerd

diagnose bevestigd door BWS-neuroloog

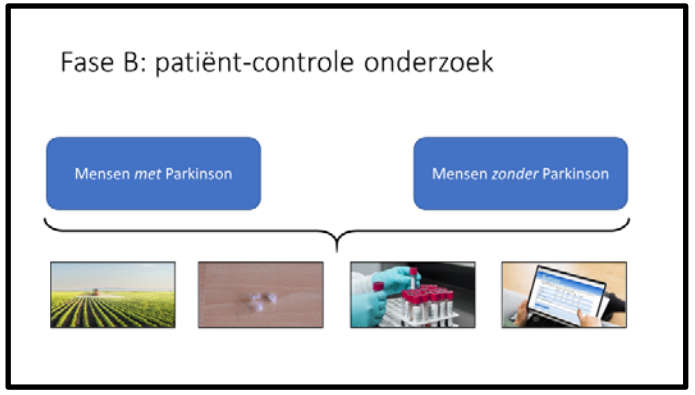
representatieve steekproef Nederland



Parkinson-PEST

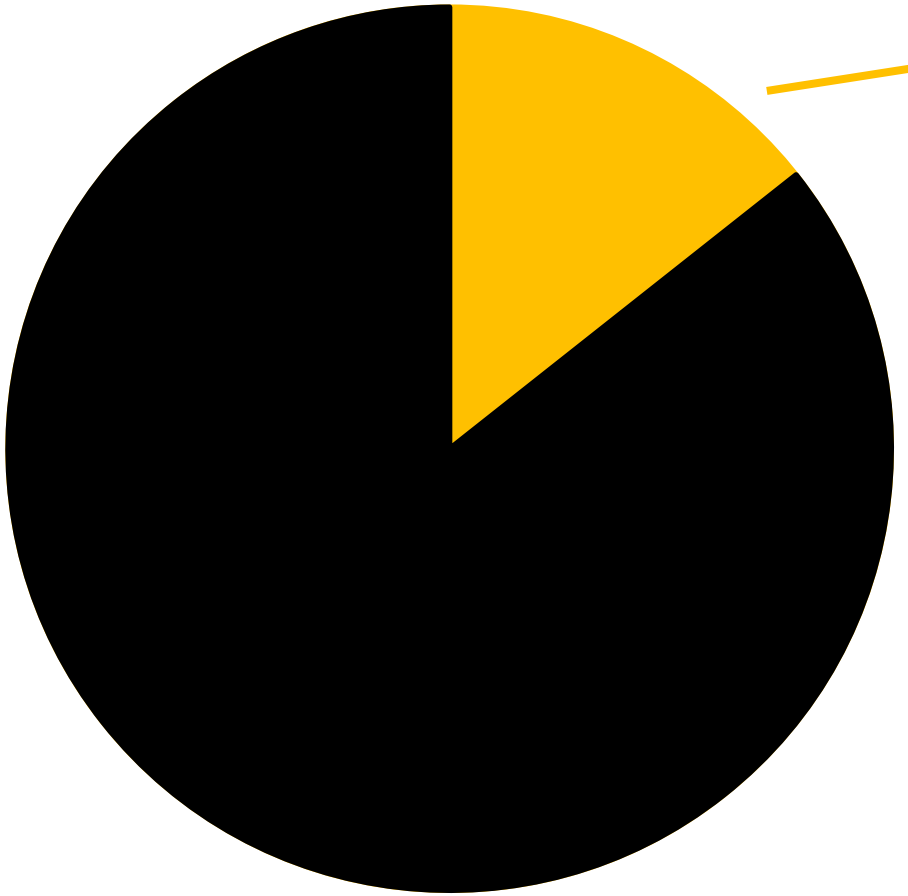


- Bestaande gegevens optimaal benutten
- Op relatief korte termijn resultaten



- Innovatieve multimodale dataverzameling
- Op lange termijn geheel nieuwe inzichten

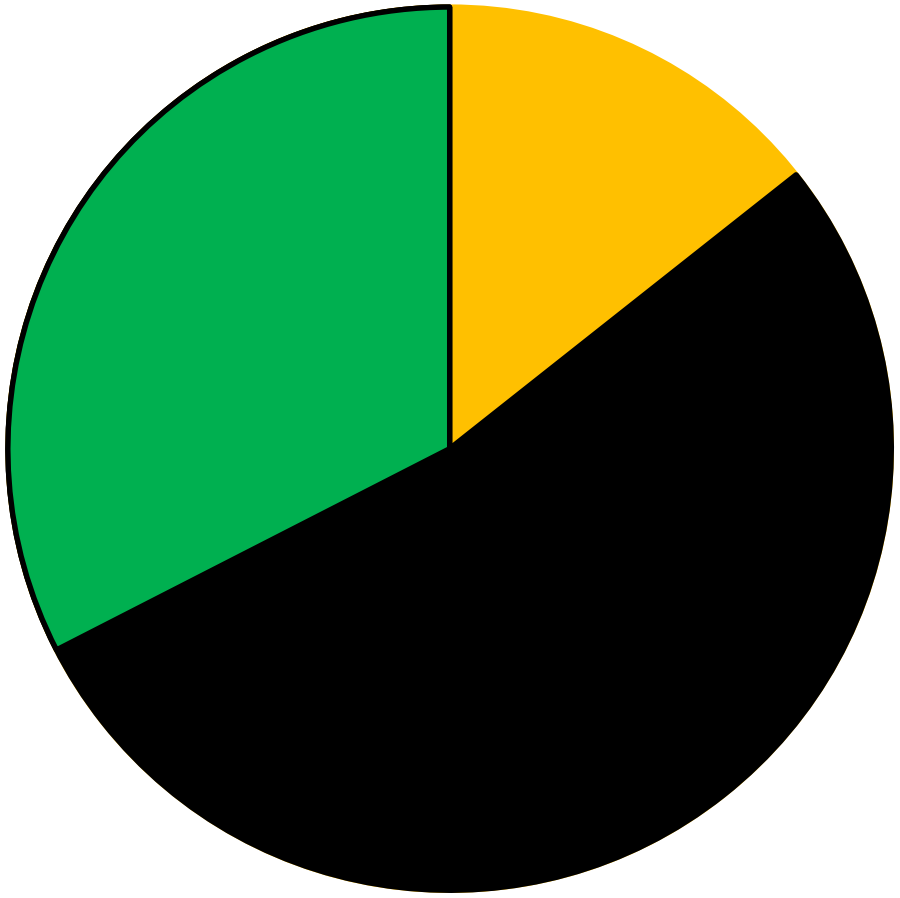
Wat veroorzaakt Parkinson?



Adapted from Ben-Shlomo, Darweesh et al. Lancet. In print

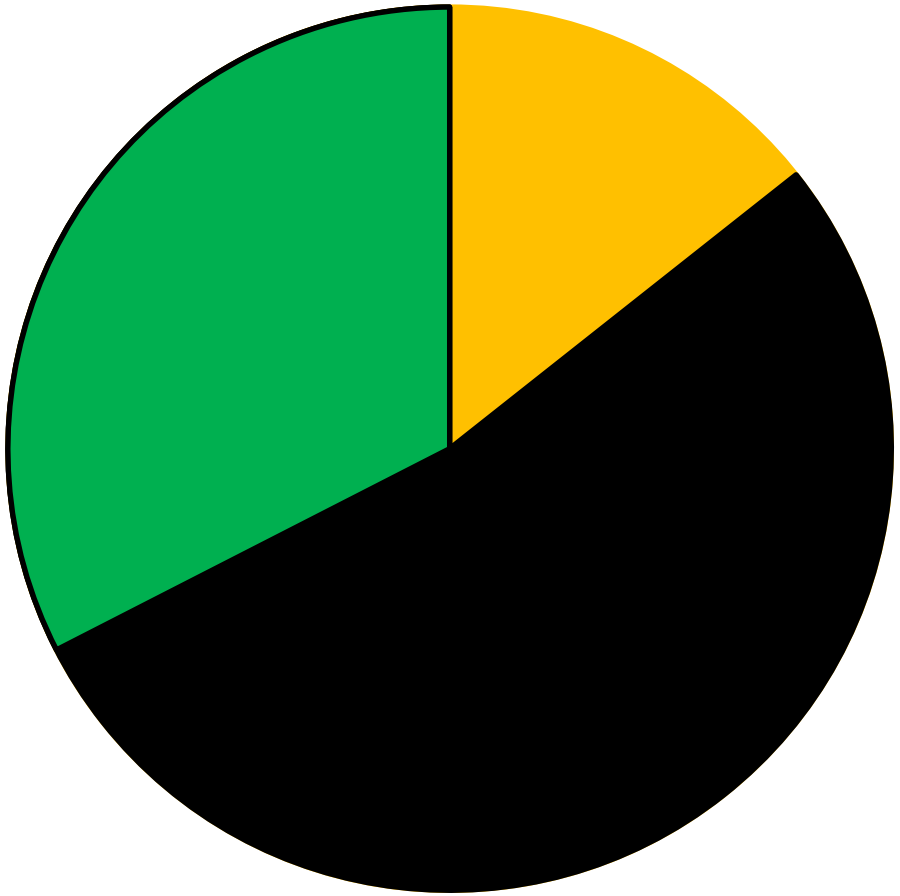
Beoogde kennisvergaring

In kaart gebrachte risico’s

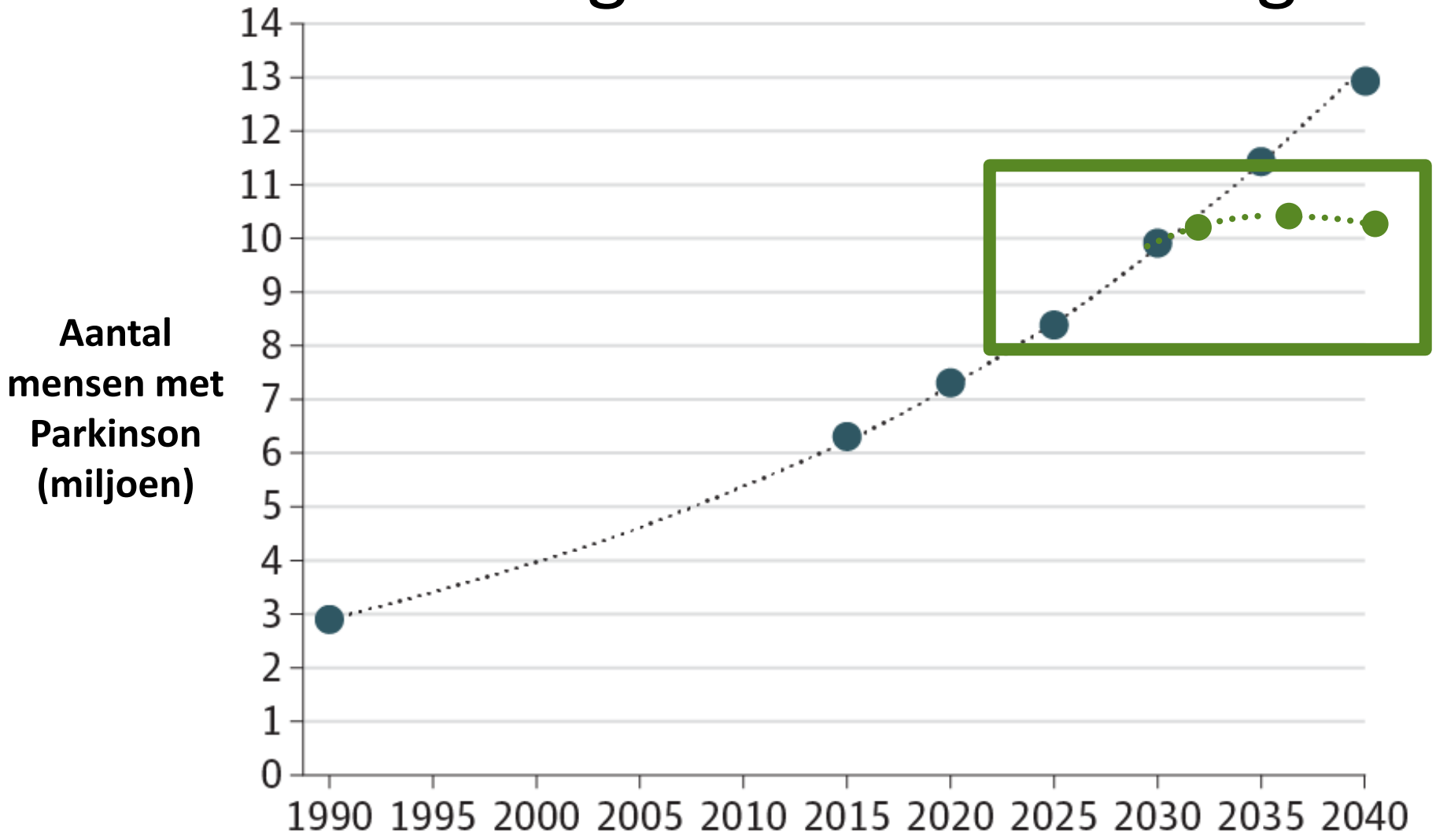


Beoogde kennisbenutting

Doelwit voor___ preventie



Beoogde kennisbenutting



Utrecht University

INSTITUTE FOR RISK ASSESSMENT SCIENCES

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EXPERTISECENTRUM PARKINSON

Veroorzaakt onze werkomgeving Parkinson?

Pesticiden en overige risico's in kaart brengen

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NVvA symposium
Zeist, 5 april 2023