

Heijermanslezing 2025

Auto-immuunziekten in de dagelijkse praktijk

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Disclosure belangen spreker	
(potentiële) Belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven ¹	Bedrijfsnamen
▫ Sponsoring of onderzoeksgeld² ▫ Honorarium of andere (financiële) vergoeding³ ▫ Aandeelhouder⁴ ▫ Andere relatie, namelijk ...⁵	Niet van toepassing



Inhoud

- Hoe vaak komt het voor?
- Wat zijn de belangrijkste blootstellingen?
- Hoe gaan we om met causaliteit en preventieve acties?



Auto-immuunziekten - Definitie

“Het immuunsysteem ziet lichaamseigen cellen en stoffen als lichaamsvreemd en probeert dit met een immuunrespons op te ruimen”

Meer dan 80 verschillende ziektebeelden, voorbeelden:

Gegeneraliseerd	Orgaanspecifiek
Reumatoïde artritis	Coeliakie
Sarcoïdose	Diabetes mellitus type-1
Systemische lupus erythematoses	M. Graves
Vasculitis	Auto-immuun-hepatitis



Over hoeveel mensen hebben we het?

Conrad et al, United Kingdom;

Incidentie en prevalentie van 19 auto-immuunziekten in ruim 22 miljoen mensen;

- Incidentie

In periode 2000-2019: 1.123.789 nieuwe diagnoses bij 978.872 personen

- Prevalentie

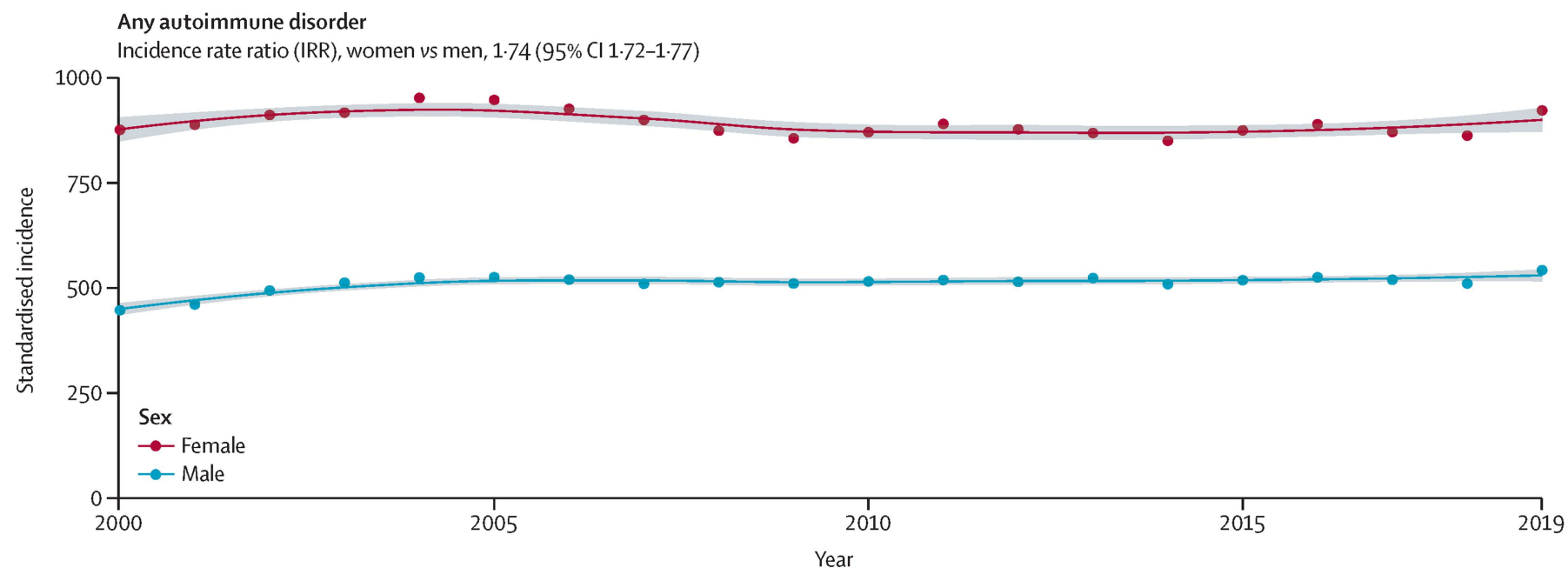
2000-2002: 7.7%

2017-2019: 11.0%

Bron: Conrad et al. Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. The Lancet, Volume 401, Issue 10391, 1878 - 1890, 2023.



Incidentie auto-immuunziekten algemeen

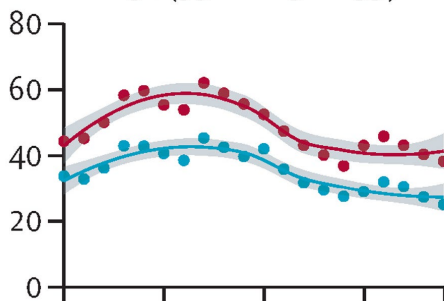


Bron: Conrad et al. Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. The Lancet, Volume 401, Issue 10391, 1878 - 1890, 2023.

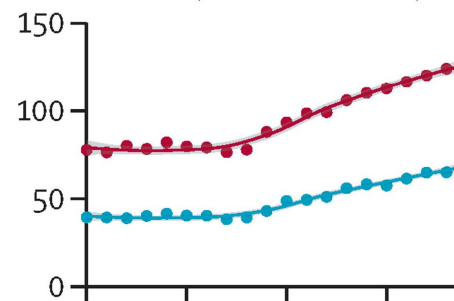


Verloop incidentie enkele ziektebeelden

Pernicious anaemia
IRR 1.38 (95% CI 1.36–1.39)

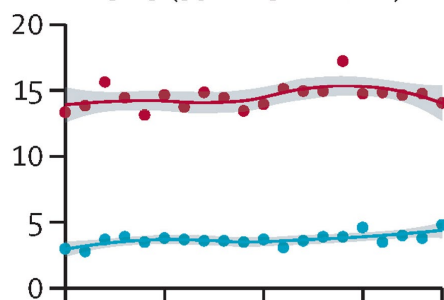


Rheumatoid arthritis
IRR 1.94 (95% CI 1.88–1.99)

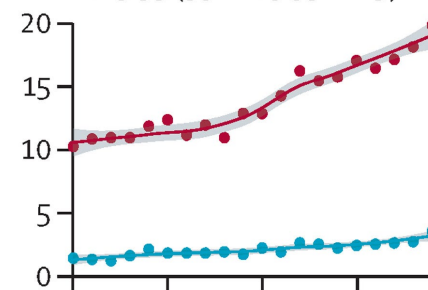


versus

Systemic lupus erythematosus
IRR 3.83 (95% CI 3.64–4.02)



Sjögren's syndrome
IRR 5.93 (95% CI 5.59–6.29)



Bron: Conrad et al. Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. The Lancet, Volume 401, Issue 10391, 1878 - 1890, 2023.

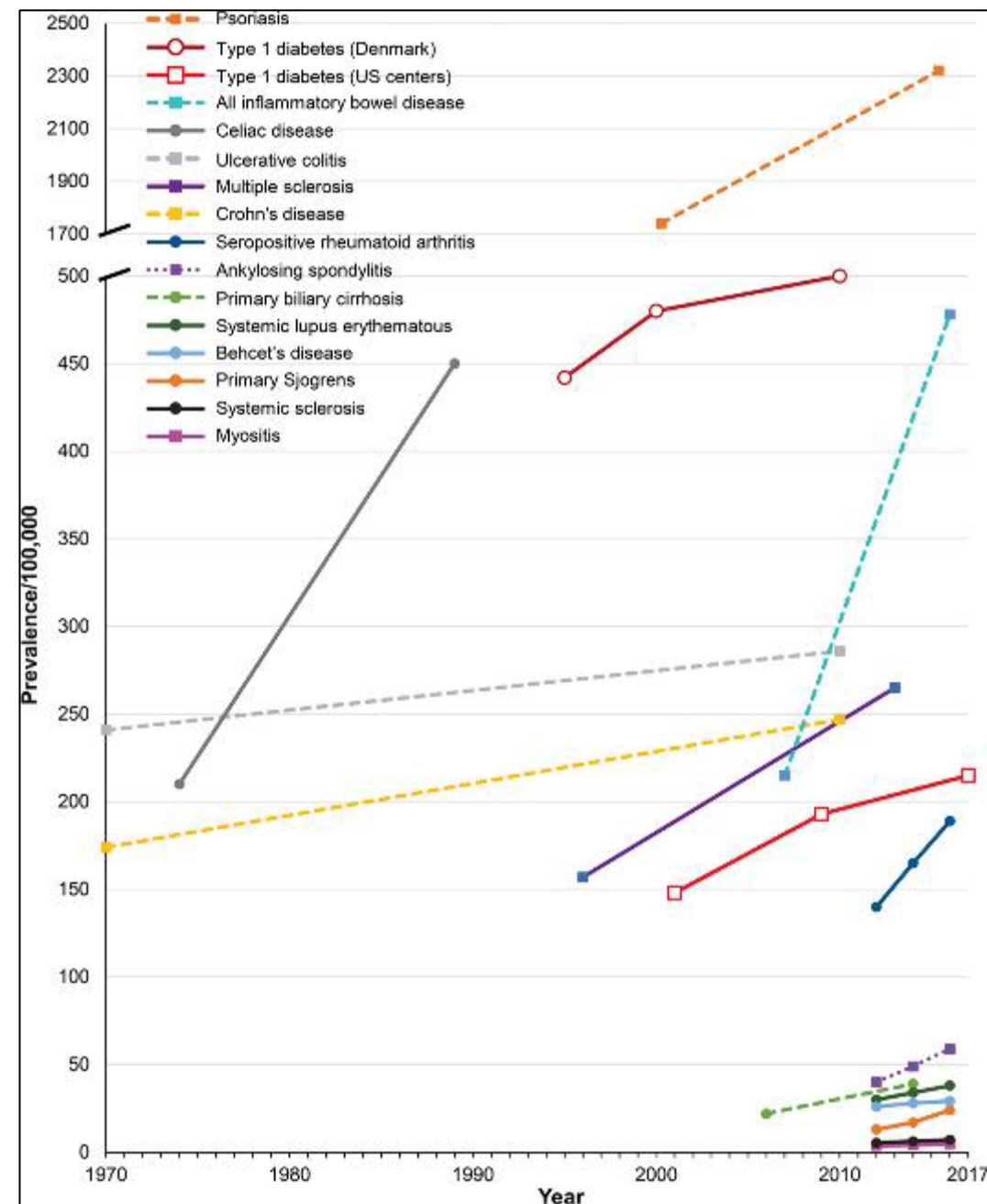


Stijging aantallen

Incidentie en prevalentie lijken jaarlijks toe te nemen

- Stijging incidentie 19,1%
- Stijging prevalentie 12,5%

Bron: Miller FW. The increasing prevalence of autoimmunity and autoimmune diseases: an urgent call to action for improved understanding, diagnosis, treatment, and prevention. Curr Opin Immunol. 2023 Feb;80:102266. doi: 10.1016/j.coi.2022.102266. Epub 2022 Nov 26. PMID: 36446151; PMCID: PMC9918670.c





Hoe zit het in Nederland?

- Geen duidelijke cijfers over auto-immuunziekten in het algemeen
- Schatting prevalentie algemeen; 10% van de bevolking
- Vaak wel gegevens per ziektebeeld



Wat weten we over werkgerelateerde blootstellingen?

- Weinig overzichtspublicaties
- Wel publicaties over specifiek ziektebeeld in relatie tot specifieke blootstelling

Table 2

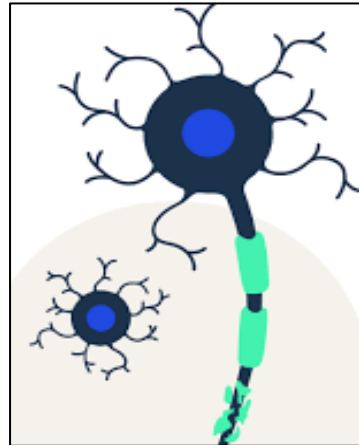
Epidemiologic cohort and case-control studies of occupational exposures and autoimmune diseases

	Reference(s)	Disease	Results
Silica	[14–17,24–28]	scleroderma	threefold increased risk in four occupational cohort studies; mixed results in five population-based case-control studies
	[16,18–21,23]	rheumatoid arthritis	threefold (or higher) increased risk in five occupational cohort studies
	[15,16,22]	lupus	> 10-fold increased risk in three occupational cohort studies
	[33–35]	ANCA-vasculitis	fourfold increased risk in three case-control studies
Solvents	[24,28,49,50]	scleroderma	mixed results, but some evidence of two- to threefold increased risk with specific solvents (e.g., paint thinners and removers, trichloroethylene) and with “any” solvent
	[51]	undifferentiated connective tissue disease	twofold increased risk with paint thinners and removers, mineral spirits, threefold increased risk with specific solvent-related occupations
	[52]	rheumatoid arthritis	weak or no association with specific solvents, but twofold increased risk among spray painters and lacquer workers
	[53,54]	multiple sclerosis	two- to threefold increased risk with solvent exposures in most studies
Pesticides	[52,63,64]	rheumatoid arthritis	weak associations (relative risks <2.0 seen with pesticide exposure and in farmers and horticultural workers)
Ultraviolet radiation	[86]	multiple sclerosis	reduced risk (OR 0.74) of multiple sclerosis (mortality) with increased occupational exposure to sunlight

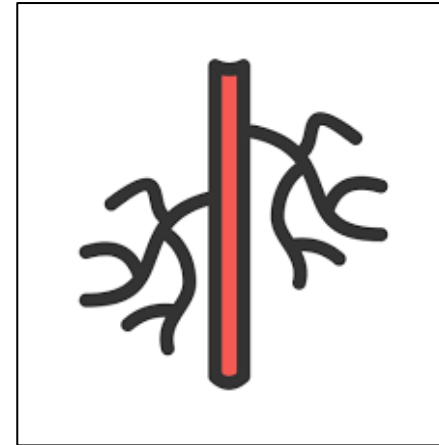
Bron: Cooper GS, Miller FW, Germolec DR. Occupational exposures and autoimmune diseases. Int Immunopharmacol. 2002 Feb;2(2-3):303-13. doi: 10.1016/s1567-5769(01)00181-3. PMID: 11811933.



Sarcoïdose



MS

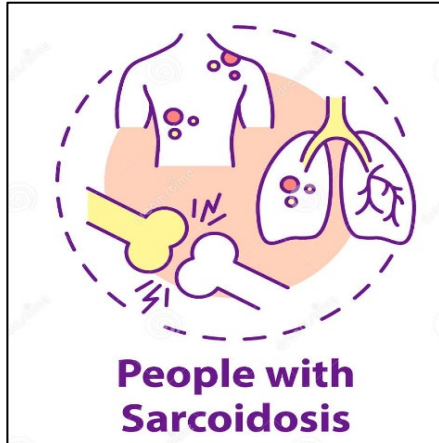


Vasculitis

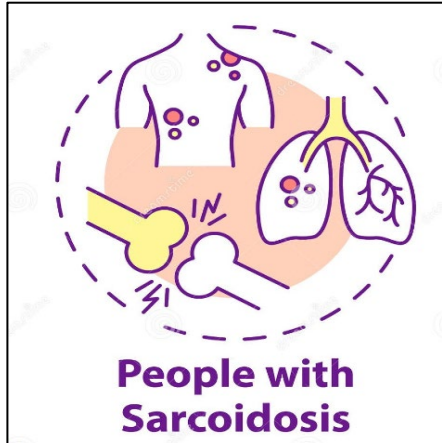


Epidemiologie

- Systemische ziekte waarbij ontstekingen (granulomen) ophopen in verschillende organen
- Incidentie NL 20 per 100.000 mensen per jaar
 (±3.600 per jaar)
- Prevalentie NL 50 per 100.000 inwoners (±9000)
 450 per 100.000 inwoners (±81.000)
- Alle leeftijden, piek 30-50 jaar, tweede piek bij ♀ na menopauze
- Bij jongvolwassenen: na astma de meest voorkomende longaandoening



Sarcoïdose



Sarcoïdose

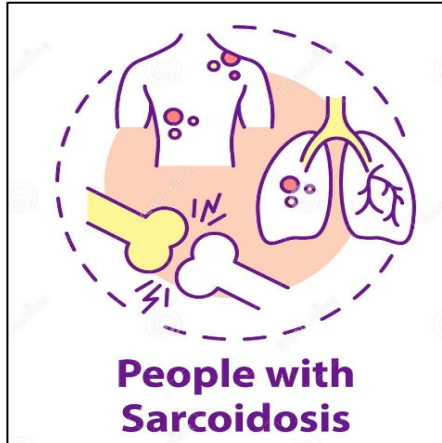
Relatie met werk



- Interactie genetica, immuunsysteem en omgeving
- Aandeel werk gerelateerde blootstelling geschat op **30%**¹
- Huntley et al - beschreven associaties;
 - Silica - OR 1.26 (95%BI 1.02 tot 1.56)
 - Pesticiden - OR 1.42 (95%BI 1.09 tot 1.85)
 - Schimmels - OR 1.52 (95%BI 1.21 tot 1.91)

Bronnen:

1. Blanc PD, Annesi-Maesano I, Balmes JR, Cummings KJ, Fishwick D, Miedinger D, Murgia N, Naidoo RN, Reynolds CJ, Sigsgaard T, Torén K, Vinnikov D, Redlich CA. The Occupational Burden of Nonmalignant Respiratory Diseases. An Official American Thoracic Society and European Respiratory Society Statement. Am J Respir Crit Care Med. 2019 Jun 1;199(11):1312-1334. doi: 10.1164/rccm.201904-0717ST. PMID: 31149852; PMCID: PMC6543721.
2. Huntley CC, Patel K, Mughal AZ, Coelho S, Burge PS, Turner AM, Walters GI. Airborne occupational exposures associated with pulmonary sarcoidosis: a systematic review and meta-analysis. Occup Environ Med. 2023 Oct;80(10):580-589. doi: 10.1136/oemed-2022-108632. Epub 2023 Aug 28. PMID: 37640537.



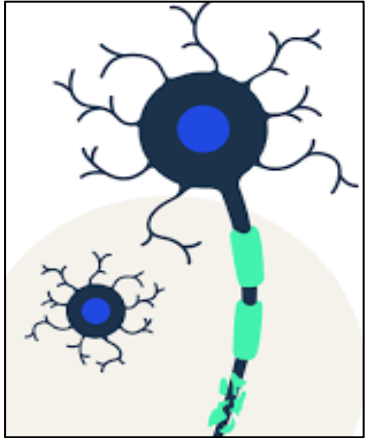
Sarcoïdose

In 26 studies werd met o.a. elektronenmicroscopie elementenanalyse toegepast op de longbiopten:
In alle monsters paste resultaat analyse bij blootstelling op werkplek!

→ Silica, metalen zoals aluminium, titanium, ijzer, chroom en nikkel en diverse legeringen

Bron: Huntley CC, Patel K, Mughal AZ, Coelho S, Burge PS, Turner AM, Walters GI. Airborne occupational exposures associated with pulmonary sarcoidosis: a systematic review and meta-analysis. *Occup Environ Med.* 2023 Oct;80(10):580-589. doi: 10.1136/oemed-2022-108632. Epub 2023 Aug 28. PMID: 37640537

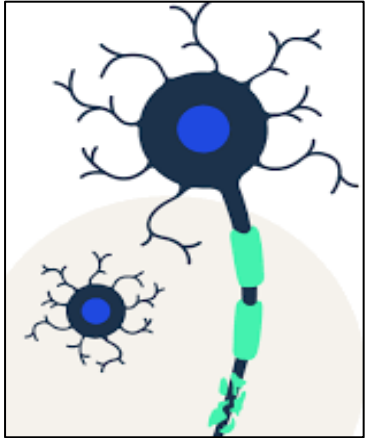




MS

Epidemiologie

- Systemische auto-immuun ontsteking van CZS
→ demyelinisatie en neurodegeneratie
- Presentatie tussen 20e en 40e jaar
- Incidentie NL 7 per 100.000 mensen per jaar
 (± 1260 per jaar)
- Prevalentie NL 210 per 100.000 inwoners
 (± 36.000)
- Vrouwen > mannen, 2:1



MS

Relatie met werk

Vitturi et al

- Meta-analyse - inclusie 24 studies
19.004 MS patiënten en 4.164.162 controles
- Studies onderzochten verschillende stoffen en beroepen
- Resultaat:
 - Dampen uit oliebronnen (OR = 16,80, 95% BI 8,33-33,90)
 - Kappers (OR = 8,25, 95% BI 1,02-66,52)
 - Offshore werknemers (OR = 3,56, 95% BI 2,74-4,61)
 - Pesticiden (OR = 3,17, 95% BI = 2,53-3,99)
 - Agrarische sector (OR = 1,44, 95% BI 1,13-1,83)

Bron: Vitturi BK, Montecucco A, Rahmani A, Dini G, Durando P. Occupational risk factors for multiple sclerosis: a systematic review with meta-analysis. Front Public Health. 2023 Nov 16;11:1285103. doi: 10.3389/fpubh.2023.1285103. PMID: 38054069; PMCID: PMC10694508.

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Occupational risk factors for multiple sclerosis: a systematic review with meta-analysis

Bruno Kuznir Vitturi^{1*}, Alfredo Montecucco^{1,2},
Albazzor Rahmani¹, Guglielmo Dini^{1,2} and Paolo Durando^{1,2}

¹Department of Health Sciences, University of Leoben, Leoben, Austria, ²Occupational Medicine Unit, IRCCS
Gigante Foundation San Martino, Genova, Italy

Objective: We decided to conduct the first systematic review with meta-analysis
to provide the highest level of up-to-date evidence on the occupational risk
factors for Multiple Sclerosis.

Methods: A systematic, comprehensive literature search was performed in four
electronic academic databases. We included any case-control study that enrolled
working-age subjects and compared the proportion of MS cases with controls
who were not exposed to an occupational risk factor. The primary outcome was
the occurrence of MS. The quality assessment was performed with the Critical
Appraisal Checklist for Case-Control Studies, developed and validated by the
Joanna Briggs Institute. All the selection process was also carried out by two
independent and previously trained researchers.

Results: Overall, the total sample included 19,004 people with MS and 4,164,162
controls. Agricultural workers (OR = 1.44, 95% CI 1.13–1.83), offshore workers
(OR = 3.56, 95% CI 2.74–4.61), and hairdressers (OR = 8.25, 95% CI 1.02–66.52)
were associated with a higher probability of being diagnosed with MS. In parallel,
workers exposed to toxic fumes from oil wells (OR = 16.80, 95% CI 8.33–33.90),
low-frequency magnetic fields (OR = 1.71, 95% CI 1.03–2.72), and pesticides
(OR = 3.17, 95% CI = 2.53–3.99) also had an increased likelihood of having MS.

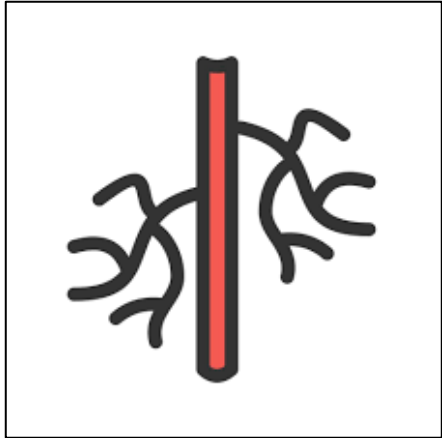
Conclusion: Our study has the potential to influence more accurate public
policies. Nevertheless, future studies on how the occupational setting may
contribute to the incidence of MS are highly recommended.

Systematic review registration: The protocol was registered in the international
prospective register of systematic reviews (PROSPERO – CRD42023443215).

KEYWORDS:
multiple sclerosis, occupational, risk factors, environmental, demyelination,
epidemiology, etiology

Introduction

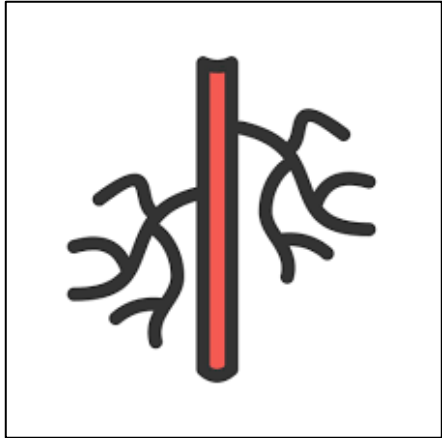
Multiple Sclerosis (MS) is a chronic autoimmune disease that affects the central nervous
system, causing demyelination and neurodegeneration (1, 2). Most individuals manifest the first
symptoms between 20 and 40 years old. The disease affects women more than men, with a ratio
of approximately 3:1 (3). The global prevalence is approximately 50 per 100,000 people and an
estimated 2.8 million people worldwide are living with MS. Its incidence has been increasing
globally every year since 2013, making it a subject of great public concern (3). MS is one
of the main causes of disability among young workers and it is associated with devastating socio-



ANCA - vasculitis

Algemeen - epidemiologie

- Zeldzame auto-immuunziekte met ontsteking van de bloedvaten
→ schade aan verschillende organen zoals de nieren, longen, huid en het centrale zenuwstelsel
- ANCA-antilichamen tegen antigenen van neutrofiele granulocyten
→ Leukocytenproteïnase 3 (PR3) en myeloperoxidase (MPO)
- Incidentie 1.3-2.0 per 100.000
- Prevalentie: 20-40 per 100.000
- Drie klinische varianten renale ANCA vasculitis
 - Granulomatose met polyangiitis (GPA)/ziekte van Wegener
 - Microscopische polyangiitis (MPA)
 - Eosinofiele GPA (EGPA)/ziekte van Churg-Strauss



ANCA - vasculitis

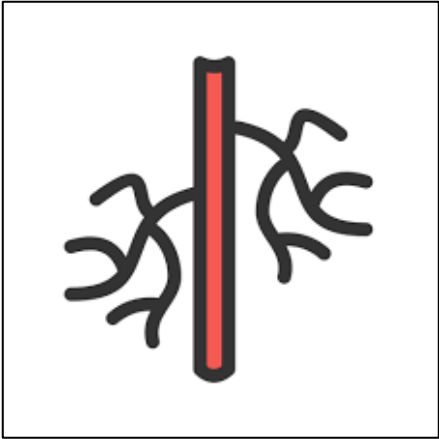
Relatie met werk

- Werkgerelateerde silicablootstelling in patiënten met GPA en MPA¹
 - Overall risico OR 3,12 (95%BI 1.67-5,83)
 - Gemiddelde blootstellingsduur: 21 ± 7.1 jaar
- Studie werkgerelateerde factoren in EGPA²
 - Silica - OR 2.79 (95% CI 1.55-5.01)
 - Oplosmiddelen - OR 3.19 (95% CI 1.91-5.34)
 - Agrarische sector - OR 2.71 (95% CI 1.71-4.29)

Bronnen:

1. Gómez-Puerta JA, Gedmintas L, Costenbader KH. The association between silica exposure and development of ANCA-associated vasculitis: systematic review and meta-analysis. Autoimmun Rev. 2013 Oct;12(12):1129-35. doi: 10.1016/j.autrev.2013.06.016. Epub 2013 Jun 29. PMID: 23820041; PMCID: PMC4086751.

2. Maritati F et al. Occupational Exposures and Smoking in Eosinophilic Granulomatosis With Polyangiitis: A Case-Control Study. Arthritis Rheumatol. 2021 Sep;73(9):1694-1702. doi: 10.1002/art.41722. Epub 2021 Aug 9. PMID: 33750006.



ANCA - vasculitis

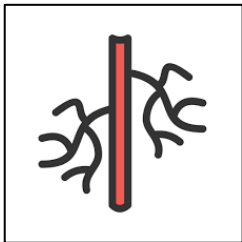
Er komt een helpdeskvraag binnen van een nefroloog..

In afgelopen 4 jaar, vier gevallen van renale ANCA-vasculitis.

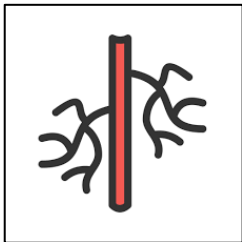
Beroepen: drie loodgieters/bouwvakkers en één tegelzetter.

Vraag; Is er een verband tussen hun ziekte en hun beroep?

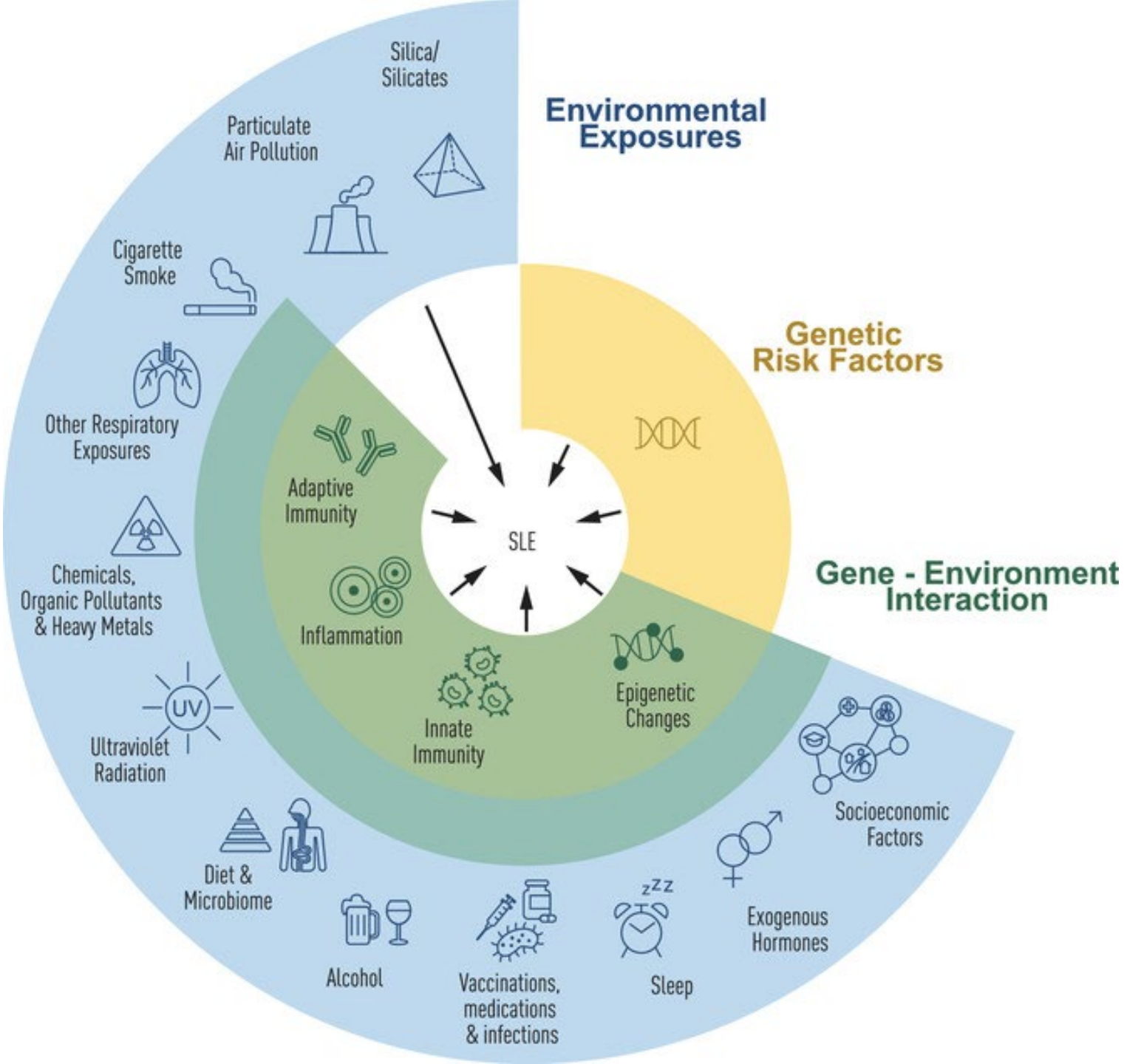
→ Bij nagaan patiëntenpopulatie komt ze uiteindelijk tot 10 vermoedelijke gevallen



Patiënt	Geslacht	Leeftijd	Diagnose	Jaar van diagnose	Relevante medische VG
1	Man	44	ANCA-vasculitis, anti-MPO	2024	-
2	Man	52		2023	-
3	Man	55		2023	2023 COPD GOLD 2A
4	Man	63		2023	-
5	Man	52		2020	1993 Sarcoïdose
6	Man	51		2021	-
7	Man	65		2015	2013 Mediastinale/ hilaire lymfadenopathie bij uitgebluste sarcoïdose
8	Man	78		2013	-
9	Man	51	ANCA-vasculitis, anti-PR3	2023	-
10	Man	51	Nefrotisch syndroom - Minimal change nephropathy	2024	2019 Sarcoïdose



Patiënt	Leeftijd	Diagnose	Jaar van diagnose	Beroep
1	44	ANCA-vasculitis, anti-MPO	2024	Hovenier (1994 - heden) Producent zwembaden (2008 • heden)
2	52		2023	Loodgieter (1995 - heden)
3	55		2023	Hoofd technische dienst (1998 - heden) Loodgieter /elektricien (1988-1998)
4	63		2023	Volledige WIA uitkering (2020 - heden) Meewerkend voorman in de bouw (1989 - 2020) Loodgieter (1978 - 1982)
5	52		2020	Loodgieter (1988 - heden)
6	51		2021	Stoffeerder (1989 - heden)
7	65		2015	Taxichauffeur, gedeeltelijke WIA uitkering (2018 - heden) Loodgieter (1980 -2018)
8	78		2013	Medewerker productie houten trappen (2000-pensioen) Medewerker/bedrijfsleider bezinepomstation (1968 - 2000)
9	51	ANCA-vasculitis, anti-PR3	2023	Tegelzetter (1991 - heden)
10	51	Nefrotisch syndroom - Minimal change nephropathy	2024	Loodgieter (tm heden)



- Associatie versus causaliteit
- Multifactorieel
- Lastig om aandeel van werk te bepalen

Bron: Woo JMP, Parks CG, Jacobsen S, Costenbader KH, Bernatsky S. The role of environmental exposures and gene-environment interactions in the etiology of systemic lupus erythematosus. J Intern Med. 2022 Jun;291(6):755-778. doi: 10.1111/joim.13448. Epub 2022 Feb 10. PMID: 35143075.



Stelling 1

“In deze case-serie is er mogelijk sprake van een causale relatie, en dus van een mogelijke beroepsziekte”

Zes stappenplan NCvB



Stap 1. Diagnose

- Renale ANCA vasculitis

Stap 2. Relatie met werk

Literatuur;

- Silica → OR 3,12 (95%BI 1.67-5,83)
- Gemiddelde blootstellingsduur 21 ± 7.1 jaar

Stap 3. Blootstellingen

- Loodgieters/tegелzetter/voorman
- Allen blootstelling aan silica
- Meer dan 20 jaar werkzaam in beroep

Zes stappenplan NCvB



Stap 4. Andere verklaringen

- Roken
- Andere blootstellingen op het werk?
- Blootstellingen vanuit de woonomgeving?
- Hebben van andere auto-immuunziekte (sarcoïdose n=3)?

Stap 5. Weging

- Vinden we dit nu een mogelijke beroepsziekte?

Zes stappenplan NCvB



Stap 5. Wegin

Afwegingskaders voor etiologie beroepsziekten



Zes stappenplan



Stap 6. Preventie

- Primair
- Secundair
- Tertiair



Stap 0. Arbovigilantie

- Bewustwording
- Alertheid



Stap 0 - Risicogroepen

- **Silica** → bouwsector
- **Oplosmiddelen** → Bouw, autoherstel, timmer- en meubelindustrie, kunststofverwerkende industrie, chemische sector
- **Pesticiden en andere landbouwchemicaliën** → Landbouw



Stelling 2

“Werk kan auto-immuniteit aanwakken —
herkennen we dat als bedrijfsarts wel op tijd in onze
eigen populatie?”



Afronding

- Werk gerelateerde blootstelling heeft een rol bij meerdere auto-immuunziekten
- Bewustwording en registratie van belang voor preventie