LITERATURE REVIEW ON EPIDEMIOLOGICAL STUDIES LINKING EXPOSURE TO PESTICIDES AND HEALTH EFFECTS

Dr Ioanna Tzoulaki
Assistant Professor in Epidemiology

MRC-PHE Centre for Environment and Health, Imperial College London
&
University of Ioannina Medical School

Background & Aims

- Abundance of epidemiological studies investigating possible associations of pesticide exposure with adverse health effects
- Systematic and comprehensive literature review (2006-2012) to:
  - collect and compile scientific publications in which possible links between pesticide exposure and adverse human health effects have been investigated
  - review and evaluate each collected study in regard to its qualitative aspects

Methodology - I

- Search algorithm for Medline and Embase (and other sources)
- Observational studies assessing the association between pesticide exposure and health-related outcomes
  - Any outcome
  - Any exposure type
  - Any study design (except ecological studies)
  - Any population
  - Any pesticide (*excluded: arsenic, α, β, hexachlorocyclohexane (HCH), lead, dioxin (and dioxin-like compounds), polychlorinated biphenyls (PCBs), and polychlorinated dibenzofurans*)

Methodology II

- Data extraction database around 7 domains: Reference, Time period, Study characteristics, Exposure assessment, Outcomes, Statistical analysis and Quality assessment

Question	High risk	Low risk
Study design (prospective, retrospective, mixed, cross-sectional)	Retrospective, mixed, NA	Prospective
Inclusion/exclusion criteria clearly stated (yes, partially, no)	No	Yes
Authors mention power calculations (yes, no)		Yes
Level of detail in describing exposure (high, medium, low)	Low	High
Robust measurement of exposure. (biomarker (yes); small area ecological measures, job titles, questionnaire (partial); was based on large area ecological measures (no)	No	Yes
Were measures of exposure specific? yes; based on broader, chemically-related groups (partial); based on broad groupings of diverse chemical and toxicological properties (no)	No	Yes
Attempt to balance the allocation between the groups (e.g., through stratification, matching)	No	Yes
Adjustment performed for potential confounders (yes, some, no)	No	Yes
Assessors blinded to exposure status (for cohort studies)	No	Yes
Outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	No	Yes
Sample size	Low	Top
Rough quality assessment	>6 answers high risk	>6 asnwers low risk

Methodology II

- Data extraction database around 7 domains: Reference, Time period, Study characteristics, Exposure assessment, Outcomes, Statistical analysis and Quality assessment
  - Different rows for different pesticides, populations, outcomes
  - Aim to exclude each time main analyses (not always easy to define)

Overall results

- 43,259 citations
- 602 eligible
- 6,479 different analyses

- Great variety of assessed outcomes covering a very wide range of pathophysiologies

- Grouped results by outcomes

Major outcome	N studies
Cancer outcomes	164
Child health	84
Reproductive diseases	64
Neurological diseases	61
Endocrine diseases	35
Mental and psychomotor development	32
Respiratory diseases	25
Neuropsychiatric diseases	15
Diabetes (type I and II)	22
Cardiovascular diseases	31
Hematological diseases	15
Mortality	11
Immune/Autoimmune diseases	10
Allergic diseases	8
Gastrointestinal diseases	7
Symptoms and general health	5
Gynecological diseases	4
Skin diseases	4
Bone diseases	3
Kidney diseases	3
Benign tumors	1
Dental diseases	1
Men health	1
Metabolic diseases	1

Existing systematic reviews

Outcome	N studies	Authors claim association	Author, Journal, Publication year
Amyotrophic lateral sclerosis	3	No	Sutedja NA et al, 2009 Kamel F et al, 2012 Malek et al, 2012
Cancers	11		
Breast cancer	*1*	No	Khanjani N et al, 2007
Childhood cancer	*2*	Yes	Infante-Rivard C et al, 2007 Vinson F et al, 2011
Childhood Leukaemia	*6*	Yes	Wingle DT et al, 2009 Turner et al, 2010 Van Maele-Fabry G et al, 2010 Van Maele-Fabry G et al, 2011 Bailey HD et al, 2011 Turner MC et al, 2011
Multiple cancers	*1*	Yes	Cooper et al, 2008
Prostate cancer	*1*	Yes	Budnik LT et al, 2012
Multiple health outcomes	1	Yes	Koureas M et al, 2012
Neurobehavioral	2	No	Ismail AA et al, 2012 Li AA et al, 2012
Parkinson disease	2	Yes	Van der Mark M et al, 2012 Van Maele Fabry G et al, 2012
Reproductive	1	No	Shirangi A, 2011
Time to pregnancy	1	Yes	Snijder CA et al, 2012

Overall results – synthesis with caution

- Pesticide category
  - Studies very often concentrate on a broadly defined pesticide category
  - Often examine pesticides that have already been banned in western populations and the European Union
  - Different levels of exposure (difficult to harmonise across studies)
- Exposure assessment
  - Self assessment questionnaires (ever/ never)
  - Unvalidated questionnaires
  - Recall bias
  - Biomarkers infrequent
  - Co-exposure

Overall results – synthesis with caution

- Clinical outcomes
  - Variability in definitions
  - Surrogate outcomes
- Multiple testing
  - 602 publications resulted in >6000 analyses
- Different study designs (case-control and cohorts)
  - For many outcomes the majority of evidence comes from single study populations and the AHS in particular

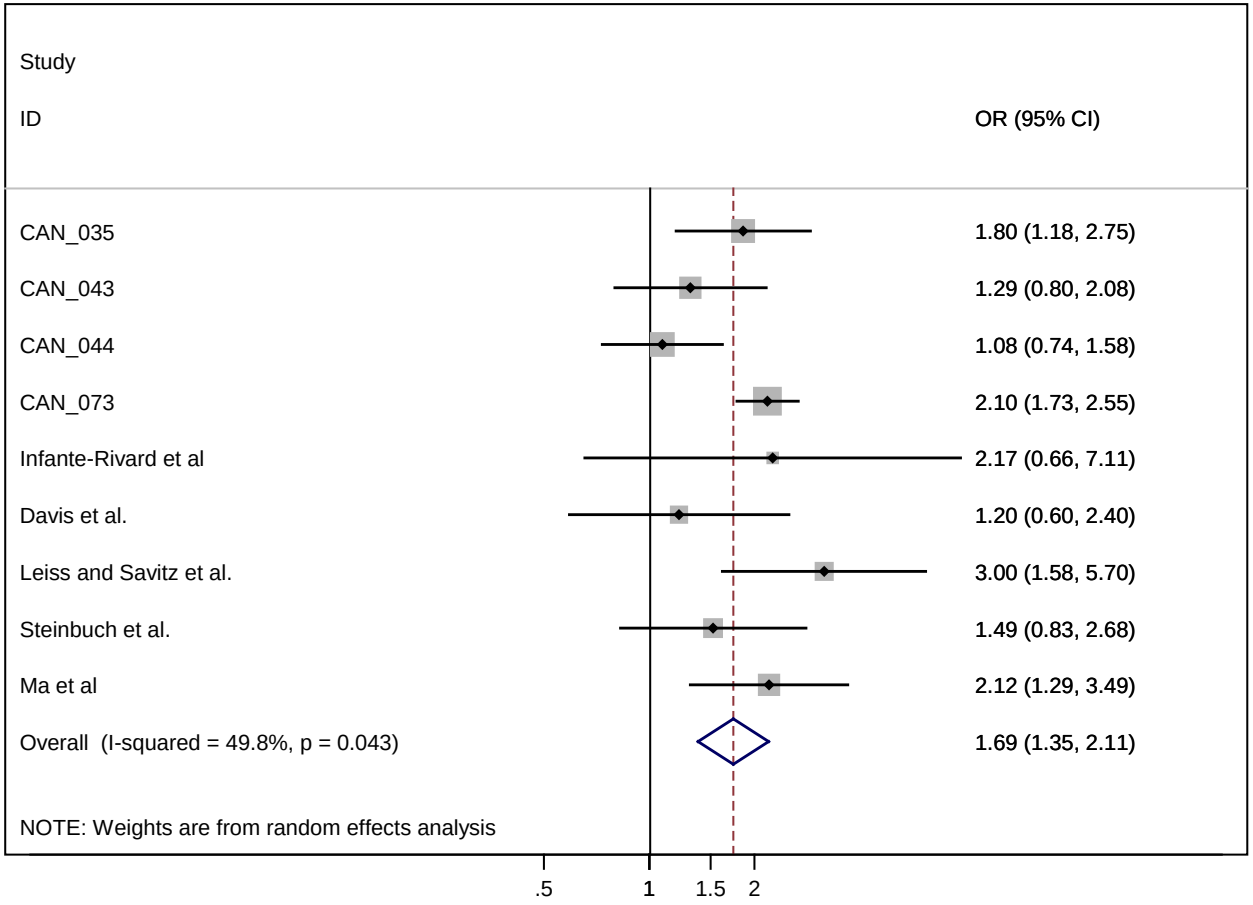
- Results are from 2006 onwards, meta-analysis cautious interpretation

Health outcome	*N* studies	Meta-analysis result	I^2
Leukemia	6	1.26 (0.93,1.71)	59.4%
Hodgkin's Lymphoma	7	1.29 (0.81, 2.06)	81.6%
Childhood Leukemia (exposure to pesticides during pregnancy)	6	1.67 (1.25, 2.23)	81.2%
Childhood Leukemia (exposure to insecticides during pregnancy)	5	1.55 (1.14, 2.11)	65%
Childhood Leukemia (exposure to insecticides during pregnancy-update Turner 2010)	9	1.69 (1.35, 2.11)	49.8%
Childhood Leukemia (exposure to unspecified pesticides during pregnancy)	5	2.00 (1.73, 2.30)	39.6%
Childhood Leukemia (exposure to unspecified pesticides during pregnancy-update Turner 2010)	11	1.30 (1.09, 1.56)	26.5%
Childhood Leukemia (exposure to pesticides during childhood)	7	1.27 (0.96, 1.69)	61.1%
Childhood Leukemia (exposure to insecticides during childhood-update Turner 2010)	8	1.51 (1.28, 1.78)	0%
Childhood Leukemia (exposure to unspecified pesticides during childhood-update Turner 2010)	11	1.36 (1.19, 1.55)	0%
Breast Cancer (DDE exposure)	5	1.13 (0.81, 1.57)	0%
Breast Cancer	11	1.24 (1.08, 1.43)	0%
Testicular Cancer (DDE exposure)	5	1.40 (0.82, 2.39)	59.5%
Stomach Cancer	6	1.79 (1.30, 2.47)	0%
Liver Cancer	5	2.50 (1.57, 3.98)	25.4%
Cryptorchidism	8	1.19 (0.96, 1.49)	23.9%
Cryptorchidism (DDT exposure)	4	1.47 (0.98, 2.20)	51%
Hypospadias (general pesticide exposure)	6	1.01 (0.74, 1.39)	71.5%
Hypospadias (exposure to specific pesticides)	9	1 (0.84, 1.18)	65.9%
Abortion	6	1.52 (1.09, 2.13)	63.1%
Parkinson's disease	26	1.49 (1.28, 1.73)	54.6%
Parkinson's disease (DDT exposure)	5	1.01 (0.78, 1.30)	0%
Parkinson's disease (paraquat exposure)	9	1.32 (1.09, 1.60)	34.1%
Amyotrophic Lateral Sclerosis	6	1.58 (1.31, 1.90)	10%
Asthma (DDT exposure)	5	1.29 (1.14, 1.45)	0%
Asthma (paraquat exposure)	6	1.40 (0.95, 2.06)	53.3%
Asthma (chlorpyrifos exposure)	5	1.03 (0.82, 1.28)	0%
Type 1 Diabetes (DDE exposure)	8	1.89 (1.25, 2.86)	49%
Type 1 Diabetes (DDT exposure)	6	1.76 (1.20, 2.59)	76.3%
Type 2 Diabetes (DDE exposure)	4	1.29 (1.13, 1.48)	0%

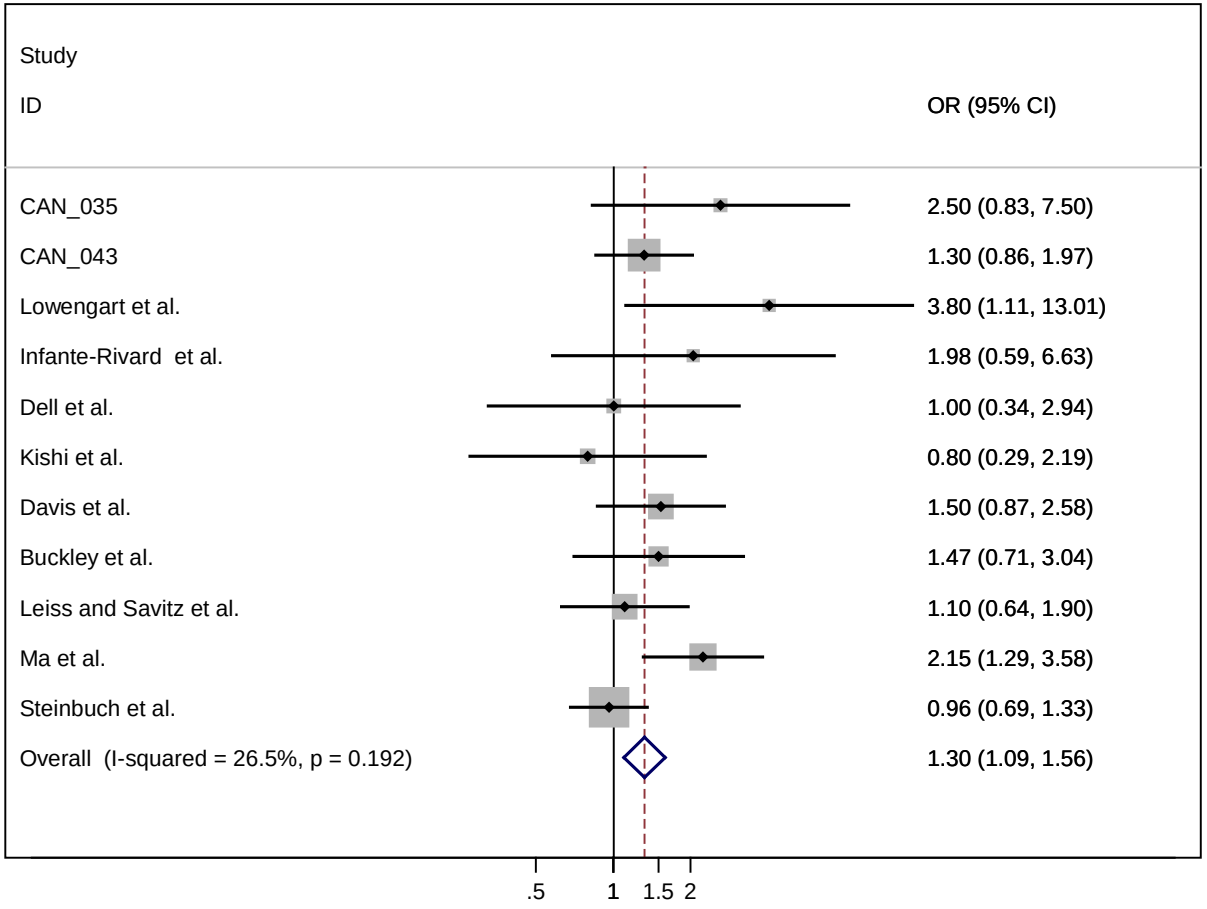
Childhood leukemia

- 17 studies examined childhood leukemia
- Two large studies: Northern Region Young Persons' Malignant Disease Registry and national registry-based case–control study ESCALE (Etude sur les cancers de l'enfant):
  - 42 and 64 separate analysis
- Most examined residential exposure
- Exposure to pesticides, pesticide subgroups, specific pesticides
- Previous meta-analysis: Turner et al. 2010 'Residential Pesticides and Childhood Leukemia'

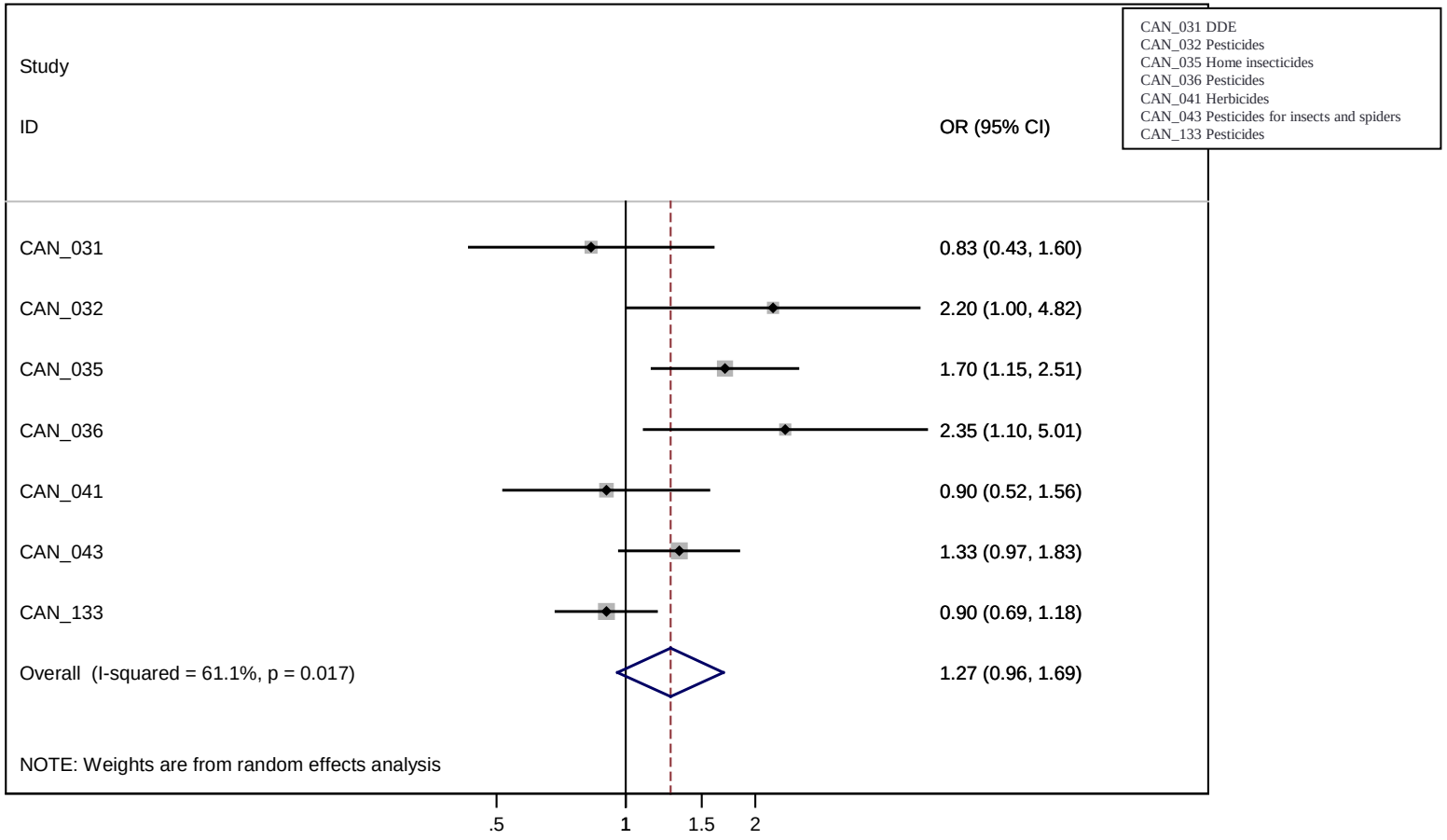
Childhood leukemia – exposure during pregnancy



Childhood leukemia – exposure in childhood I



Childhood leukemia – exposure in childhood II

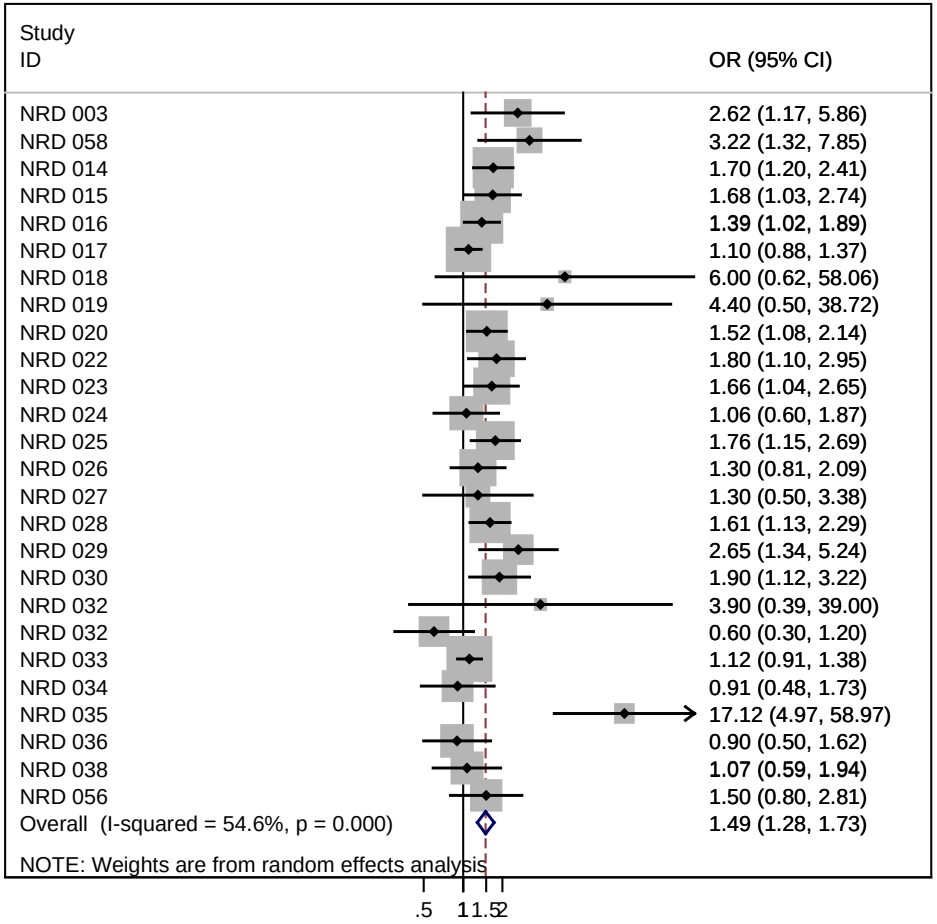


Neurological diseases

- 30 related outcomes, largest proportion on Parkinson's disease (32 studies)
  - general pesticide (28 studies), DDT (5 studies), paraquat (9 studies)
- Small studies (largest study in the domain smaller than largest in cancer outcomes)

Health outcome		
Abnormal alternating hand movements	Alzheimer's disease	Narcolepsy with cataplexy
Abnormal ankle reflex	Amyotrophic lateral sclerosis	Neurological symptoms
Abnormal distal motor amplitude	Cryptogenic polyneuropathy	Parkinson's disease
Abnormal distal motor latency	Decline in hand-grip strength	Parkinsonism
Abnormal facial expression	Delayed memory impairment	Peripheral neuropathy
Abnormal nerve conduction velocity	Dementia	Progressive supranuclear palsy
Abnormal postural tremor	Essential tremor	Restless legs syndrome
Abnormal posture	Gait disorder	Romberg sign
Abnormal short F-wave latency	Hearing loss	Sporadic Motor Neuron Disease
Abnormal toe proprioception	Multiple System Atrophy	Subclinical neuropathy
Abnormal toe vibration perception	Narcolepsy (with and without cataplexy)	Tandem gait abnormality

Parkinson disease – any pesticide



Parkinson disease- Pezzoli et al. 2013

Table 1 Risks for strata of study quality (by the Newcastle-Ottawa Scale) in case-control studies investigating the association between PD and exposures to pesticides or solvents or proxies of exposure

Exposure	Strata (NOS score)	Studies included, n	sOR (95% CI)	I^2, %	*p* Value[a]
Pesticides	Overall	51	1.76 (1.56–2.04)	67.3	0.433
	<7	33	1.88 (1.52–2.32)	72.2	
	≥7	18	1.58 (1.34–1.86)	45.1	
Herbicides	Overall	19	1.33 (1.09–1.65)	55.0	0.806
	<7	9	1.44 (0.90–2.30)	68.0	
	≥7	10	1.36 (1.11–1.66)	33.3	
Insecticides	Overall	18	1.53 (1.12–2.08)	78.8	0.245
	<7	8	2.03 (1.06–3.89)	79.7	
	≥7	10	1.31 (0.92–1.86)	79.2	
Fungicides	Overall	12	0.97 (0.69–1.38)	35.4	0.597
	<7		1.12 (0.56–1.26)	0.0	
	≥7	75	0.94 (0.61–1.43)	54.2	
Rodenticides	Overall[b]	4	0.99 (0.53–1.66)	0.0	

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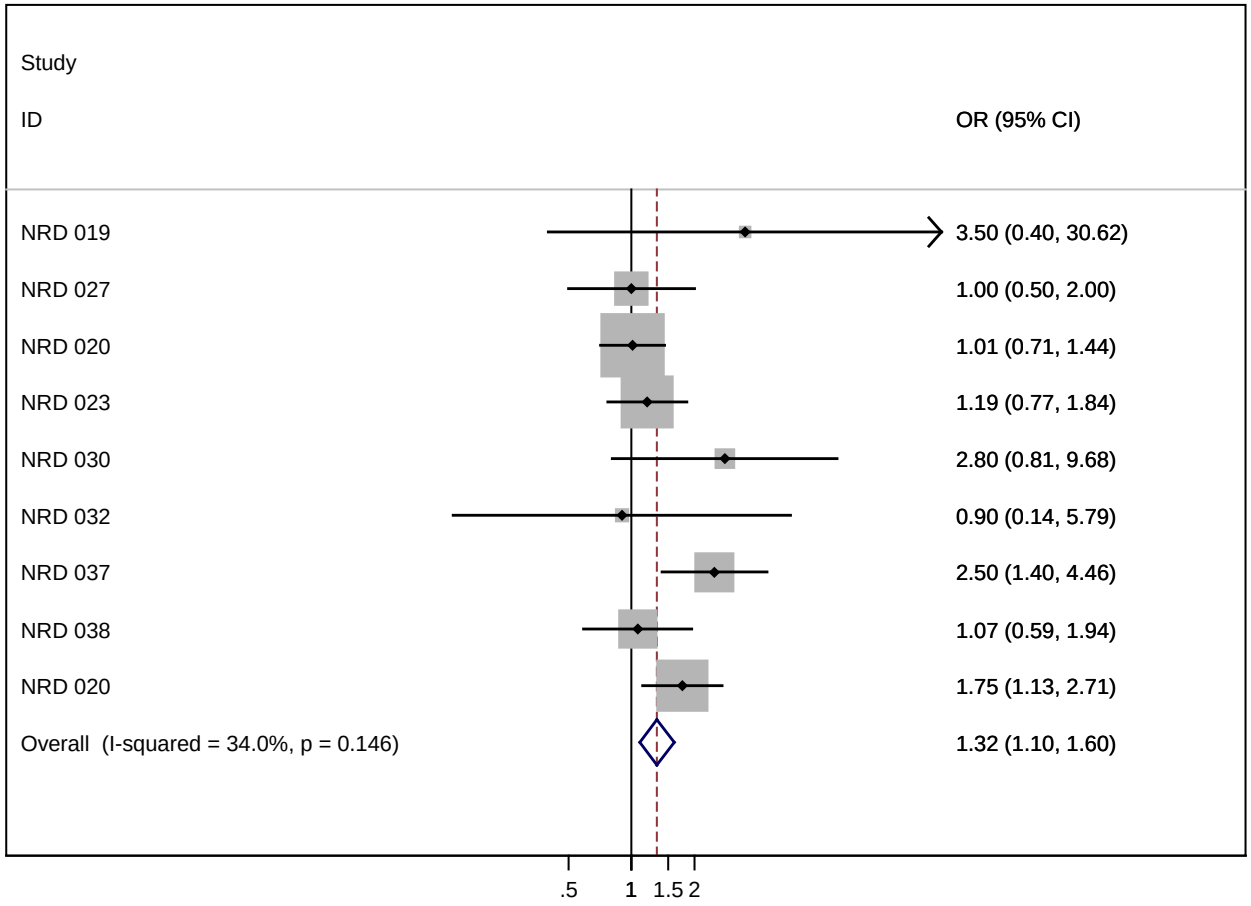
Parkinson disease – paraquat



Conclusions

- Vast amount of epidemiological studies including wide range of outcomes and pesticides studied
- Wealth of data has limited impact:
  - Detailed information on the nature of exposure needed
    - which pesticides, at what dose, and for how long?
    - chronic, low-dose exposure
  - Heterogeneity of study quality
- Good quality studies, large sample sizes with detailed definition of exposure and transparent reporting
  - Consider novel technologies - Omics
- Neurological conditions and childhood leukaemia relatively consistent evidence
- Endocrine disorders, asthma and allergies, diabetes and obesity, are showing increased risk and should be explored further

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