Exposure to formaldehyde or diesel exhaust and risk of amyotrophic lateral sclerosis (ALS)

- use of JEMs

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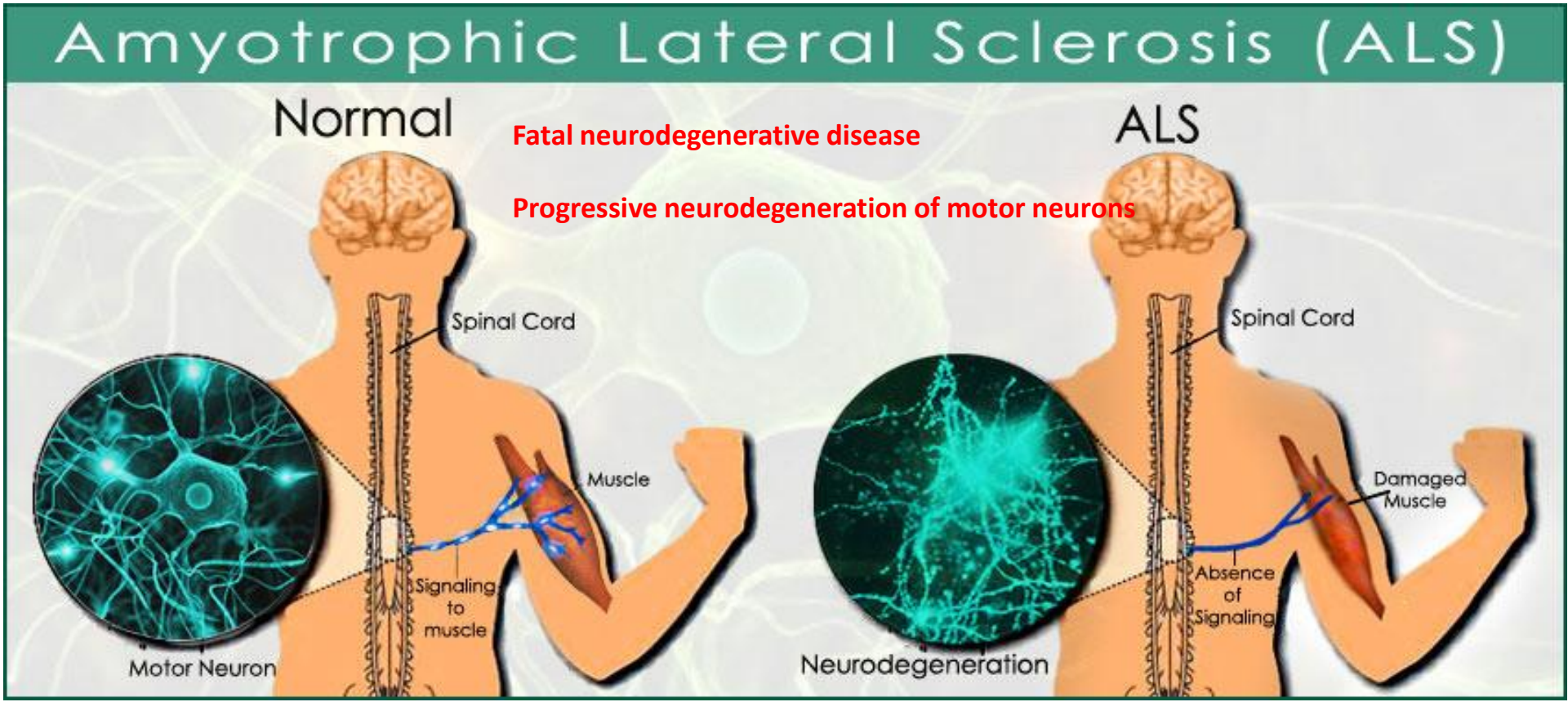
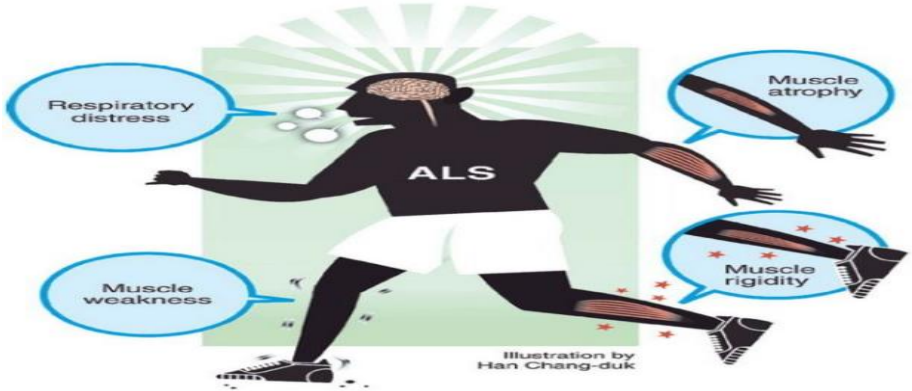
Amyotrophic Lateral Sclerosis (ALS)



ALS-characteristics



- Incidence & mortality ~2-4 per 100,000
- About 150 cases/year in DK
- Median survival: <3 years
- Some recent evidence of an increase

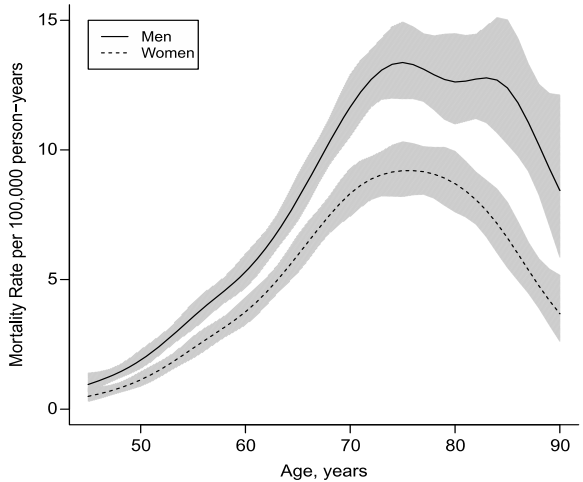
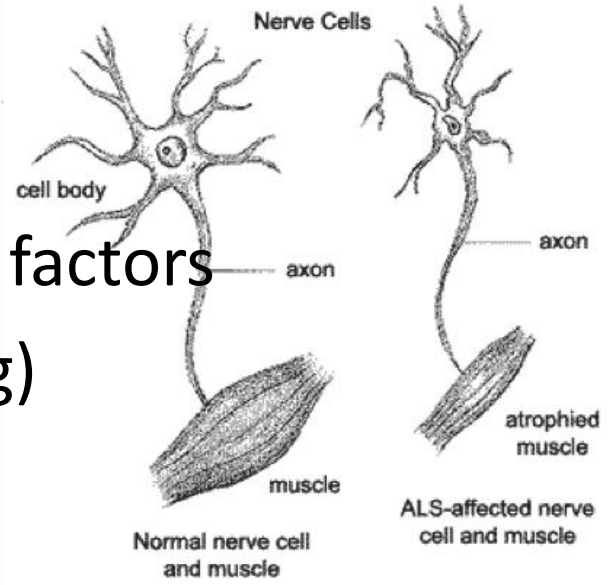


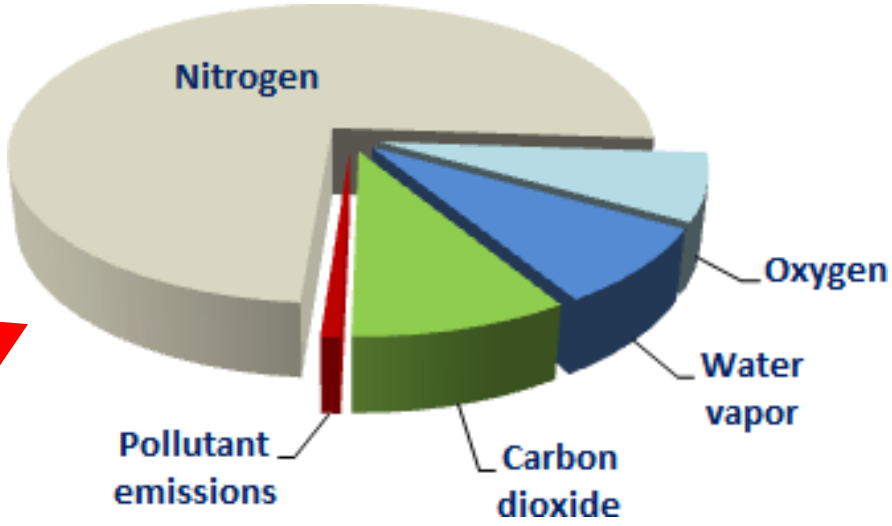
Figure 1. Age-specific amyotrophic lateral sclerosis mortality rate in Denmark, 1970–2009.

“Causes” of ALS

- ~10% “familial”
- ~90% “sporadic”
  - No family history
  - No strong genetic factors
  - Sex, age, (smoking)



Aim 1:
Diesel Exhaust



+ particles

Diesel-ALS Hypothesis

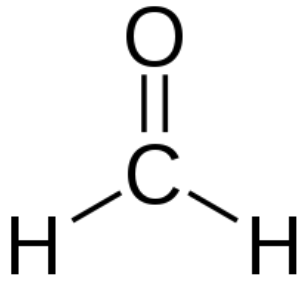
- Diesel exhaust involves genotoxicity and oxidative stress

- Previous diesel studies showing higher risk of ALS:
  - Truck drivers (Kurtzke and Beebe 1980; Pamphlett and Rikard-Bell 2013)
  - Construction workers (Andrew et al. 2017; Fang et al. 2009)
  - Machine operators (Park et al. 2005; Sutedja et al. 2009)
  - Bus drivers (Park et al. 2005)
  - Military employee (Logroscino et al. 2008; Park et al. 2005; Peters et al. 2017; Seals et al. 2016)

Aim 2: Formaldehyde

- Used in carpentry, plastics, glues, lacquers, disinfection, embalming
- Top 5 occupational exposures in the EU

- Acute effects
  - Upper respiratory irritant
  - Transient neurobehavioral effects
- Chronic effects
  - Bronchitis, chronic irritation
  - Nasopharyngeal cancer + leukemia



Formaldehyde-ALS Hypothesis

- Oxidative stress
  - Reduced SuperOxideDissmutaceMaturation1 activity
- Mitochondrial dysfunction
- Blood-brain barrier permeability

Formaldehyde and ALS: Epidemiologic Evidence

- Weisskopf et al. 2009
  - CPS-II prospective study; self-report
  - RR = 1.34 (0.93-1.92); p trend = 0.0004 in 21 cases
- Fang et al. 2009
  - Case-control in New England; self-report
  - OR = 0.8 (0.5-1.5) in 20 cases
    - OR = 1.3 (0.5-3.2) in 9 cases with high probability of exposure
- Pinkerton et al. 2013
  - Cohort of garment workers
  - SMR = 0.89 (0.38-1.75) in 8 cases
- Roberts 2015
  - NLMS cohort; job exposure matrix
  - HR = 2.98 (0.78-11.30) in 2 cases with high probability of exposure

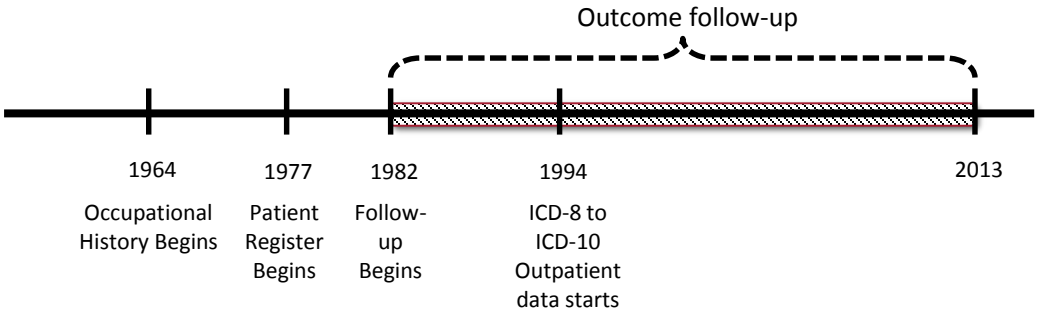
DK Study Population

- Nested case-control study

- **1826 ALS Cases:** ascertained from the *Danish National Patient Registry* diagnosed between 1982 and 2013.
    - Validatation study
- **182,600 Controls:** obtained from the *Central Person Registry* and 1:100 matched based on birth year, sex, and vital status at the diagnosis date of the matched case.

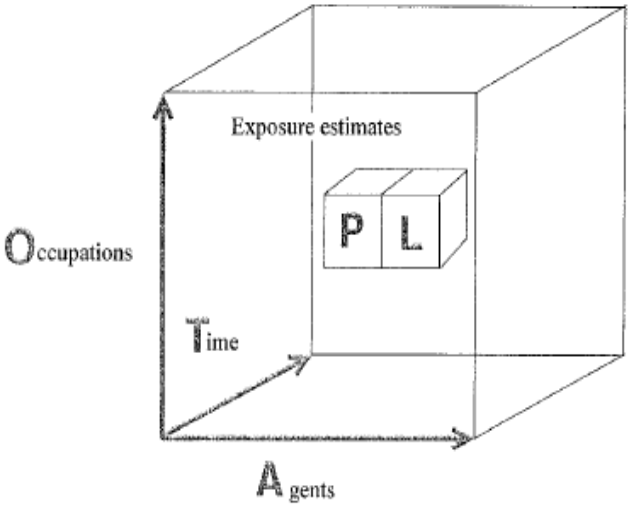
Exposure Assessment

- **Occupation:** obtained from the *Danish Pension Fund*.
  - Data for the employment history of all Danish employees **16 to 66** years of age since **1964.**



Job Exposure Matrices: DANJEM/DOC*X

- Derived from the Nordic Occupational Cancer study (NOCCA)
  - Levels of specific work related exposure (L)
  - Prevalence of exposure (P)



DANJEMs

Chemicals:

- SILICA
- ASBESTOS
- NICKEL
- LEAD
- BENZO(A)PYRENE (PAH)
- FORMALDEHYDE
- CHROMIUM(6+)
- IRON
- SULPHUR DIOXIDE

Organic solvents

- GASOLINE
- ALIPHATIC
- AROMATIC
- CHLORINATED
- OTHER SOLVENTS
- Benzene
- Toluene
- Methylene chloride
- Perchloroethylene
- Trichloroethylene
- 1,1,1-trichloroethane

Other exposures:

- DIESEL EXHAUST
- BITUMEN FUMES
- WELDING FUMES

- WOOD DUST
- ANIMAL DUST

*new agents, not originally in FINJEM

Use of Job Exposure Matrices

1. **Exposure**: ∑([(Probability X Level of exposure)/100] X Days employed)

2. **Intensity**: ∑(Level of exposure X Days employed) for occupations with at least **50% probability** of exposure.

Explored 3-, 5- and 10-year lag exposures

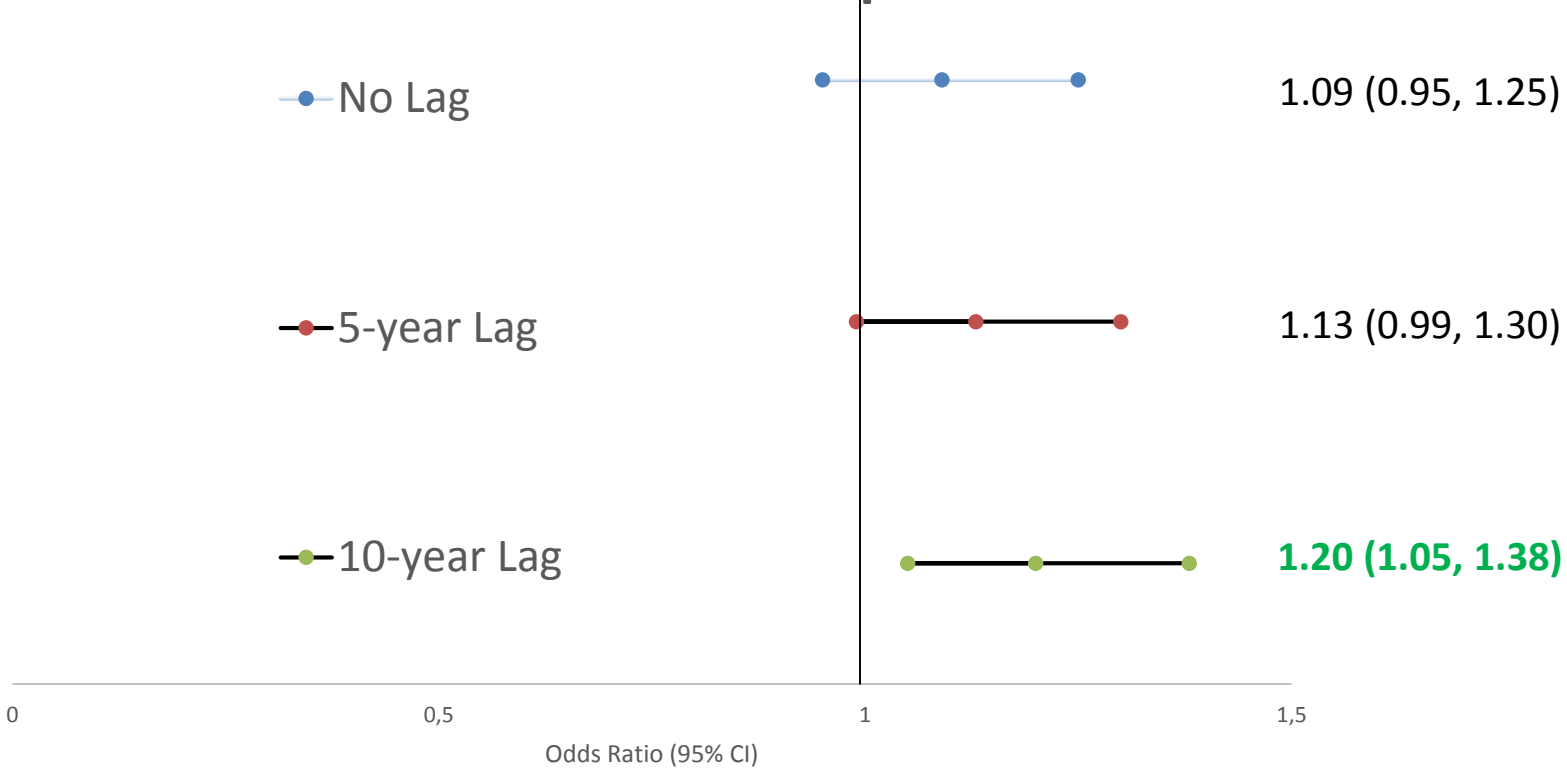



Statistical Analysis

- Conditional logistic regression
- ALS cases and controls were classified as “ever” or “never” exposed
  - Formaldehyde
  - Diesel exhaust (DE)
- Measures categorized into quartiles based on the distribution in controls
- Adjusted for socioeconomic status, marital status, and residential location at the index date

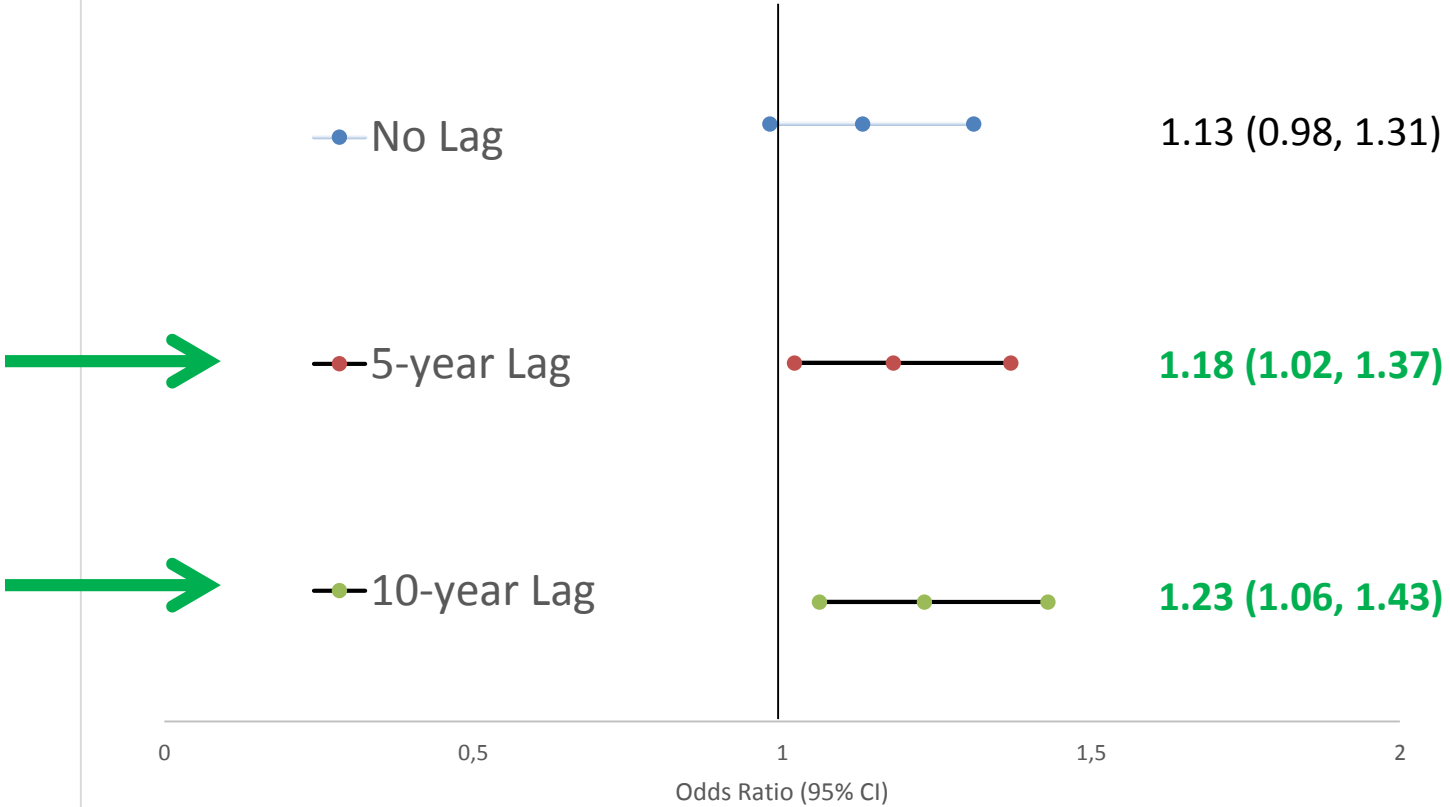
Results

Cumulative exposure to diesel exhaust in males "ever exposed"



Results

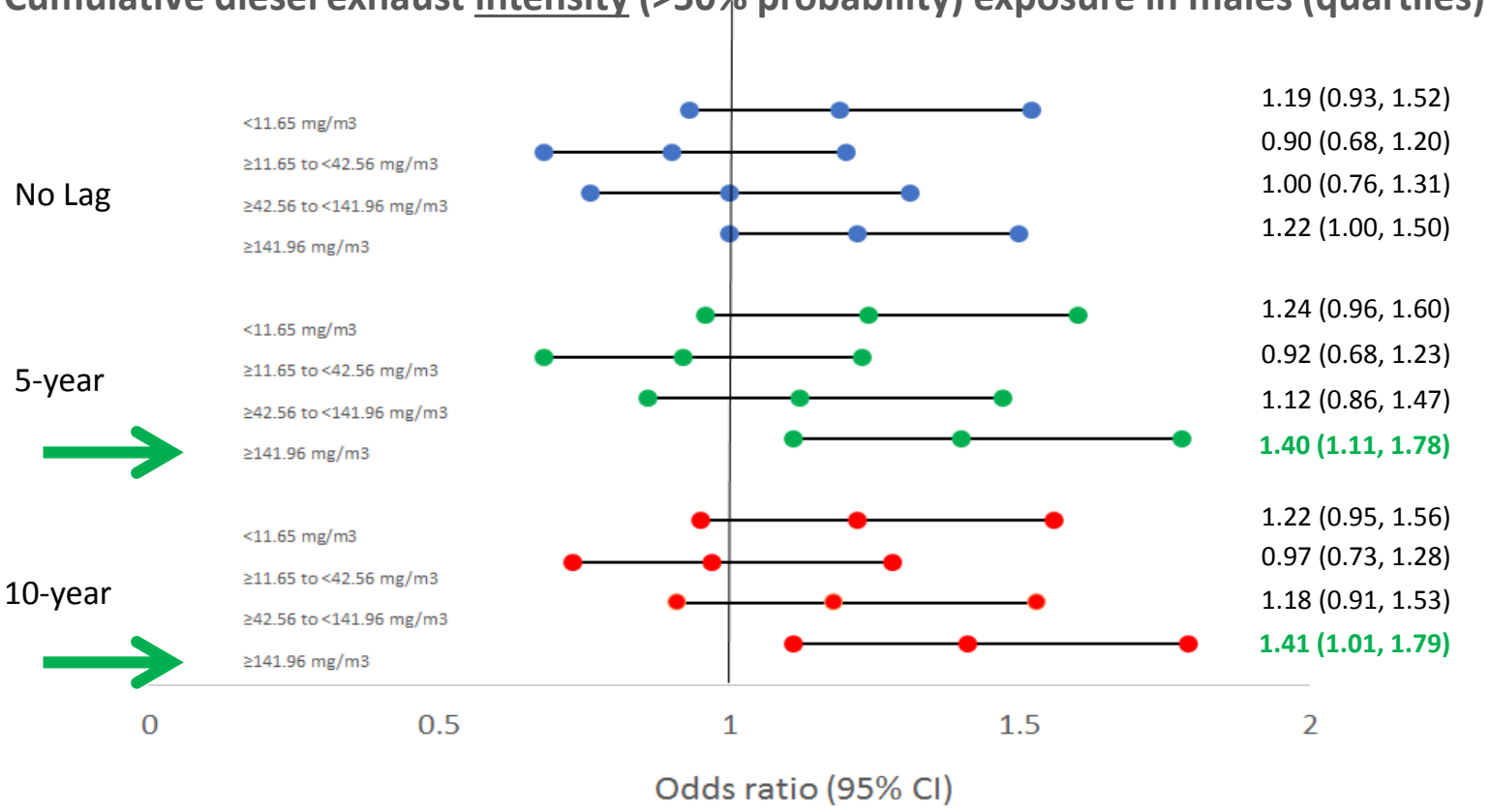
Cumulative diesel exhaust intensity* exposure in males "ever exposed"



*P>50%

Results

Cumulative diesel exhaust intensity (>50% probability) exposure in males (quartiles)



Formaldehyde Results

Formaldehyde Exposure**	Controls N (%)	Cases N (%)	OR* (95% CI)
No Exposure	**12869 (88)**	**3148 (86)**	**ref**
Any Exposure	**1731 (11.9)**	**502 (13.8)**	**1.2 (1.1-1.4)**
1st Quartile	*425 (2.9)*	*115 (3.2)*	*1.2 (0.9-1.4)*
2nd Quartile	*447 (3.1)*	*137 (3.8)*	*1.3 (1.1-1.6)*
3rd Quartile	*406 (2.8)*	*123 (3.4)*	*1.3 (1.1-1.6)*
4th Quartile	*453 (3.1)*	*127 (3.5)*	*1.2 (1.0-1.4)*

*All models adjusted for matching factors (age, sex and calendar date), residence, marital status, and SES.
**Quartiles of exposure determined from cases, with cutoffs: 1.48×10^{-3} ppm, 4.59×10^{-3} ppm, and 1.26×10^{-2} ppm.

- p trend = 0.013
- Adjustment for proxies of medical history (# of hospitalizations, Charlson Comorbidity Index) did not change results
- No difference by sex
- Slightly stronger effect in ALS diagnoses above the age of 65 (OR=1.4; 1.2-1.6)

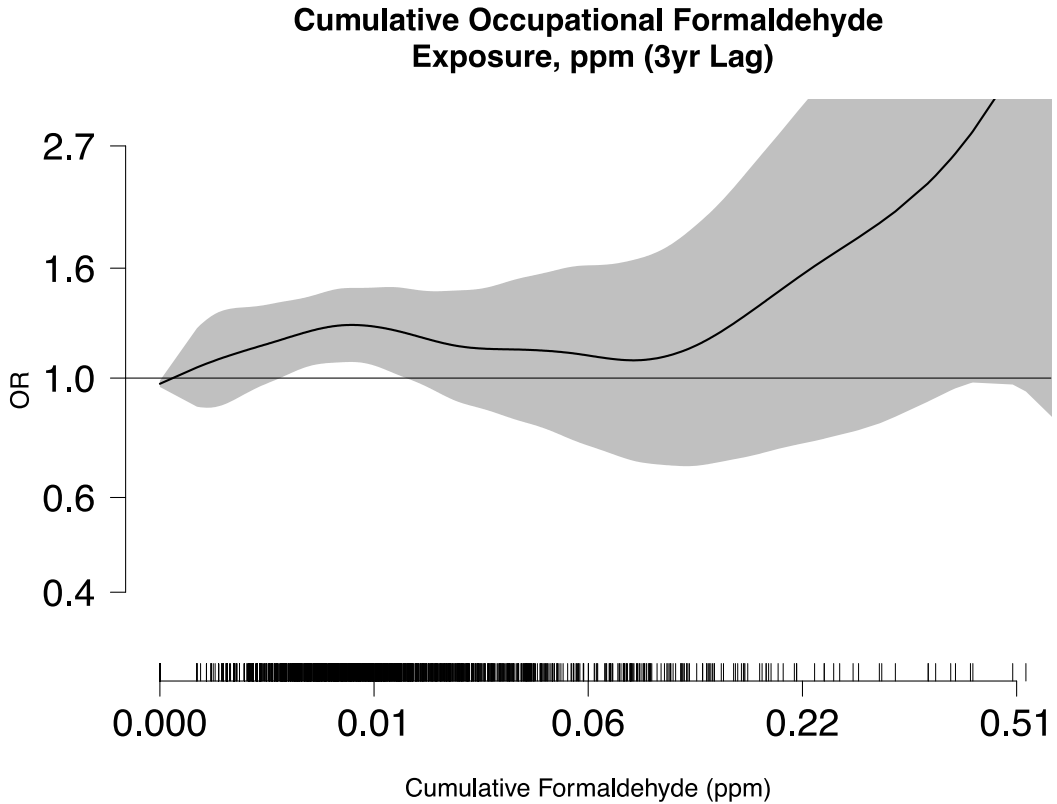
Formaldehyde: Highly Exposed

- Prior evidence of effects only at high exposure levels

Formaldehyde Exposure**	Controls N (%)	Cases N (%)	OR* (95% CI)
No Exposure	12869 (88)	3148 (86)	ref
95th Percentile	46 (0.3)	17 (0.5)	1.5 (0.9-2.7)
99th Percentile	4 (0.03)	4 (0.1)	4.5 (1.1-18.4)

*All models adjusted for matching factors (age, sex and calendar date), residence, marital status, and SES.
**95th Percentile: 0.11 ppm; 99th Percentile: 0.40 ppm

Formaldehyde Results



Conclusions

Diesel exhaust (DE)

- First study to specifically consider DE exposure in relation to ALS risk
- Evidence for association between ALS and DE exposure
  - Results were stronger with longer exposure lags
  - A reduction of healthy worker survivor bias with increasing exposure lag times?
  - A more relevant time window of exposure?

- Given the mutagenic potential of diesel exhaust and the potential role of mutations and oxidative stress in ALS, these findings suggest DE is an exposure that warrants more attention in ALS etiology

Formaldehyde

- Evidence for association between ALS and formaldehyde exposure
  - No clear dosis-response, but substantially higher at extreme levels

- Similar point estimates to some prior studies
  - OR=1.3 in high-probability-of-exposure subjects (Fang et al. 2009)
  - RR= 1.3 (Weisskopf et al. 2009)

Acknowledgements