Trinity College Dublin

The University of Dublin

Euro-MOTOR: A multi-centre case-control study of metals and solvents exposure as risk factors for Amyotrophic Lateral Sclerosis

Presented by: Dr James Rooney
HRB Research Fellow (Epidemiology), Trinity College Dublin
Presented on behalf of the Euro-MOTOR Consortium

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euroMOTOR

Introduction

- Exposure to metals and solvents have been proposed as a risk factor for Amyotrophic Lateral Sclerosis (ALS)

- Mixed results in the literature
  - Complicated by heterogenous study designs
    - Difficult to compare results across studies
  - Difficult to assess historical exposures

Introduction

- **Euro-Motor consortium:**
  - **large case control study of environmental exposures across five European populations: Italy x 3, Ireland & The Netherlands**
  - **explore the pathobiology of ALS using a system biology approach**
  - **Here we report results from assessment of occupational exposure to metals and solvents and ALS risk**

Methods

Case Ascertainment

- Between 2011 to 2015
  - Incident cases recruited in Ireland, Italy and The Netherlands
  - Inclusion: Possible, Probable and Definite revised El-Escorial criteria
  - Controls recruited matched by age, gender and location

Methods

Data Collection

- Demographic details:
  - Age, gender, education, residential history
- Clinical details:
  - Age & site of onset, diagnostic delay, EEC, ALSFRS-r
  - Medical history – cardiovascular, DM, cancer, trauma
- Other lifestyle factors:
  - Sports, hobbies, cigarettes, alcohol, drugs etc.
- Occupational exposure assessment

Methods

Data Collection

- Occupational exposure assessment:
  - Full occupational history obtained
    - Job title, tasks performed, years worked, hrs/week
  - ISCO* coding applied to each job
    - ISCO ‘68 & ’88
  - Job-exposure matrices applied using ISCO codes:
    - ALOHA-JEM: biodust, gasfumes, mineral dust, pesticides, metals, solvents (aromatic, chlorinated & other solvents)
    - DOM-JEM: asbestos, diesel exhaust, chromium, nickel, silica, biodust, endotoxin, PAH
    - BEN-JEM: benzene

* ISCO = International Standard Classification of Occupations

Methods

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Methods

Statistical Analysis

- Multivariate Logistic regression
  - Ever exposure for each variable
  - Corrected for age, education, study site
  - Including & excluding known C9orf72 patients
  - Built additional models adjusting for lifestyle factors after imputation of missing values:
    - Alcohol, smoking, physical activity
  - As sensitivity stratified by gender, education & site of onset
  - Bayesian mixed effects model to allow for heterogeneity by study site

Results

Demographics: Patients = 1,557 ; Controls = 2922

Variable	Apulia N=353		Lombardy N = 376		Piedmont and Valle d'Aosta N = 552		Ireland N = 526		The Netherlands N = 2671		
	Patients (n = 141)	Controls (n = 213)	Patients (n = 186)	Controls (n = 190)	Patients (n = 262)	Controls (n = 290)	Patients (n = 177)	Controls (n = 349)	Patients (n = 791)	Controls (n = 1880)	Overall missing rate, n (%)
Male, n (%)	81 (57.4)	113 (53.1)	100 (53.8)	101 (53.2)	138 (52.7)	153 (52.8)	106 (59.9)	211 (60.5)	478 (60.4)	1127 (59.9)	0 (0)
Age at survey (median IQR)	64.7 (58.4, 71.2)	64.8 (56.9, 71.4)	66.5 (58.8, 72.5)	67.1 (58.9, 73.7)	67.6 (59.7, 73.9)	65.4 (57.3, 72.8)	66.4 (57.7, 73.3)	67.5 (59.1, 73.0)	65.5 (58.4, 71.2)	64.8 (58.5, 70.4)	0 (0)
Age at onset (median IQR)	62.5 (56.5, 69.1)		64.9 (57.4, 70.8)		66.2 (57.5, 72.5)		64.4 (56.6, 71.2)		64.0 (57.2, 69.9)		
Bulbar onset, n (%)	36 (26.5)		55 (29.6)		97 (37.0)		42 (23.7)		275 (35.3)		
Education											30 (0.6)
ISCED '97: 0-4	122 (92.4)	192 (90.1)	165 (90.7)	117 (63.6)	239 (93.7)	243 (84.1)	148 (83.6)	273 (78.2)	583 (74.0)	1348 (71.7)	
ISCED '97: 5-6 [L, P]	10 (7.6)	21 (9.9)	17 (9.3)	67 (36.4)	16 (6.3)	46 (15.9)	29 (16.4)	76 21.8)	205 (26.0)	532 (28.3)	

* ISCED = International Standard Classification of Education

Results

Descriptive statistics – lifestyle factors

Variable	Apulia N=353		Lombardy N = 376		Piedmont and Valle d'Aosta N = 552		Ireland N = 526		The Netherlands N = 2671		
	Patients (n = 141)	Controls (n = 213)	Patients (n = 186)	Controls (n = 190)	Patients (n = 262)	Controls (n = 290)	Patients (n = 177)	Controls (n = 349)	Patients (n = 791)	Controls (n = 1880)	Overall missing rate, n (%)
Ever smoked (%) [N]	100 (47.4)	106 (55.7)	102 (56.2)	99 (52.4)	121 (47.6)	145 (50.2)	98 (56.0)	179 (51.4)	530 (67.4)	1248 (66.4)	36 (0.7)
Ever drank alcohol (%) [A N]	93 (43.7)	84 (63.6)	126 (69.2)	133 (70.0)	165 (64.7)	197 (68.2)	148 (83.6)	286 (81.9)	691 (87.4)	1728 (92.0)	22 (0.4)
Leisure time METs Median (IQR) [N]	0.0 (0.0, 0.3)	0.0 (0.0, 0.3)	0.3 (0.0, 1.0)	0.2 (0.0, 0.9)	0.59 (0.19, 1.46)	0.45 (0.12, 1.35)	1.07 (0.36, 2.18)	0.80 (0.26, 1.84)	0.76 (0.23, 1.71)	0.96 (0.38, 1.84)	1199 (27)

Results

Exposure models

	Complete cases results†		Excluding 118 C9orf72 cases †		Adj. for lifestyle factors††	
Exposure	**Odds ratio (95% CI)**	**P value**	**Odds ratio (95% CI)**	**P value**	**Odds ratio (95% CI)**	**P value**
DOM-JEM						
Chromium	1.24 (0.98 – 1.58)	0.075	1.31 (1.03 – 1.67)	0.029	1.33 (1.04 – 1.79)	0.024
Nickel	1.12 (0.84 – 1.48)	0.436	1.18 (0.89 – 1.57)	0.245	1.21 (0.91 – 1.61)	0.192
ALOHA-JEM						
Metals	1.23 (1.03 – 1.48)	0.021	1.28 (1.06 – 1.54)	0.008	1.26 (1.05 – 1.51)	0.014
Aromatic solvents	1.20 (1.03 – 1.40)	0.020	1.22 (1.04 – 1.43)	0.014	1.21 (1.04 – 1.42)	0.017
Chlorinated solvents	1.13 (0.96 – 1.34)	0.148	1.15 (0.97 – 1.37)	0.103	1.16 (0.98 – 1.38	0.088
Other solvents	1.02 (0.89 – 1.17)	0.766	1.02 (0.88 – 1.17)	0.816	1.02 (0.88 – 1.18)	0.793
BEN-JEM						
Benzene	1.26 (1.08 – 1.47)	0.003	1.29 (1.11 – 1.51)	0.001	1.29 (1.10 – 1.50)	0.002

† Adjusted for age, gender, education and cohort

†† Adjusted for age, gender, education, cohort, physical activity, smoking and alcohol status

Results

Stratified models

	Gender†		Education††		Site of onset†††	
Exposure	**Males (N = 2542)**	**Females (N = 1819)**	**ISED 0 – 4 (N = 3331)**	**ISED 5 – 6 (N = 1001)**	**Spinal (N = 956*)**	**Bulbar (N = 467*)**
DOM-JEM						
Chromium	1.28 (0.99, 1.65)	0.90 (0.36, 2.19)	1.21 (0.96, 1.54)	2.77 (0.76, 10.1)	1.27 (0.97, 1.66)	1.25 (0.85, 1.81)
Nickel	1.17 (0.87, 1.57)	0.74 (0.26, 1.93)	1.09 (0.82, 1.45)	2.80 (0.65, 12.0)	1.17 (0.85, 1.59)	1.03 (0.64, 1.60)
ALOHA-JEM						
Metals	1.23 (1.01, 1.49)	1.33 (0.76, 2.29)	1.20 (1.00, 1.43)	1.40 (0.85, 2.25)	1.23 (1.01, 1.51)	1.27 (0.95, 1.69)
Aromatic solvents	1.26 (1.05, 1.50)	1.10 (0.79, 1.52)	1.26 (1.08, 1.47)	0.80 (0.54, 1.19)	1.22 (1.02, 1.45)	1.26 (0.99, 1.61)
Chlorinated solvents	1.16 (0.96, 1.41)	1.06 (0.75, 1.50)	1.22 (1.02, 1.45)	0.75 (0.48, 1.15)	1.10 (0.91, 1.33)	1.26 (0.97, 1.63)
Other solvents	1.08 (0.90, 1.29)	0.95 (0.75, 1.20)	1.07 (0.91, 1.24)	0.87 (0.63, 1.20)	1.06 (0.90, 1.25)	0.99 (0.80, 1.23)
BEN-JEM						
Benzene	1.28 (1.07, 1.54)	1.24 (0.92, 1.66)	1.36 (1.16, 1.60)	0.72 (0.47, 1.10)	1.25 (1.05, 1.49)	1.35 (1.07, 1.71)

† Adjusted for age, education and cohort.
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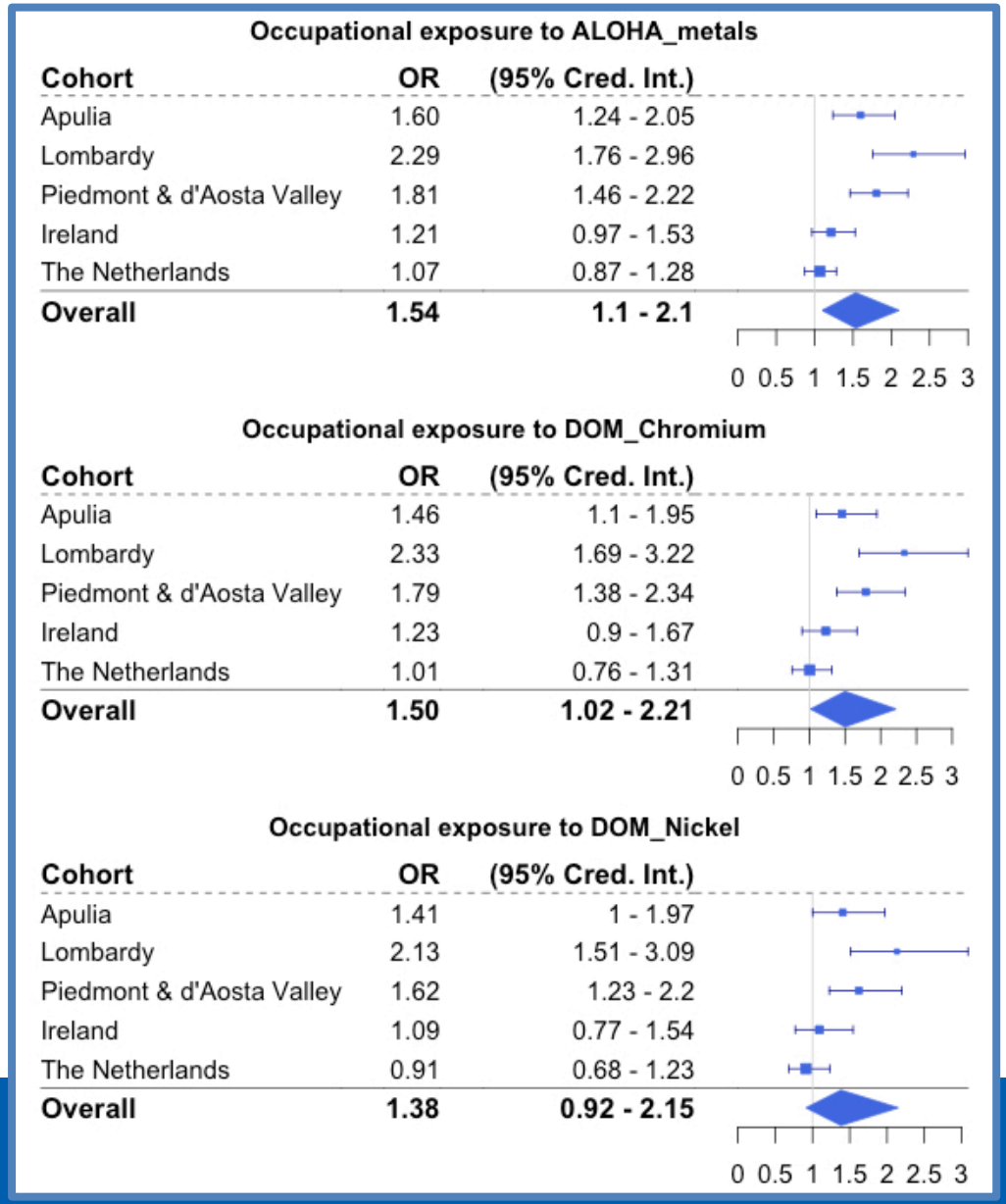
††† Adjusted for age, gender, education and cohort.
* N reflects count of spinal/bulbar patients. Control N for both was 2908

Results

Bayesian Mixed models by study site

Logistic regression	Odds ratio (95% CI)
Metals	1.28 (1.06 – 1.54)
Chromium	1.31 (1.03 – 1.67)
Nickel	1.18 (0.89 – 1.57)

=> Allowing for heterogeneity leads to increased estimates



Results

Bayesian Mixed models by study site

Logistic regression	Odds ratio (95% CI)
Aromatic solvents	1.22 (1.04 – 1.43)
Chlorinated solvents	1.15 (0.97 – 1.37)

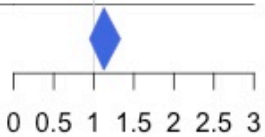
=> Allowing for heterogeneity – little change in estimates

Occupational exposure to ALOHA_sol_aromatic

Cohort	OR	(95% Cred. Int.)
Apulia	1.19	1 - 1.4
Lombardy	1.19	1.01 - 1.41
Piedmont & d'Aosta Valley	1.19	1.01 - 1.43
Ireland	1.19	1 - 1.39
The Netherlands	1.18	1 - 1.38
Overall	**1.19**	**1.01 - 1.4**

Occupational exposure to ALOHA_sol_chlorinated

Cohort	OR	(95% Cred. Int.)
Apulia	1.13	0.95 - 1.35
Lombardy	1.12	0.95 - 1.35
Piedmont & d'Aosta Valley	1.13	0.95 - 1.38
Ireland	1.12	0.94 - 1.34
The Netherlands	1.12	0.94 - 1.32
Overall	**1.13**	**0.95 - 1.33**

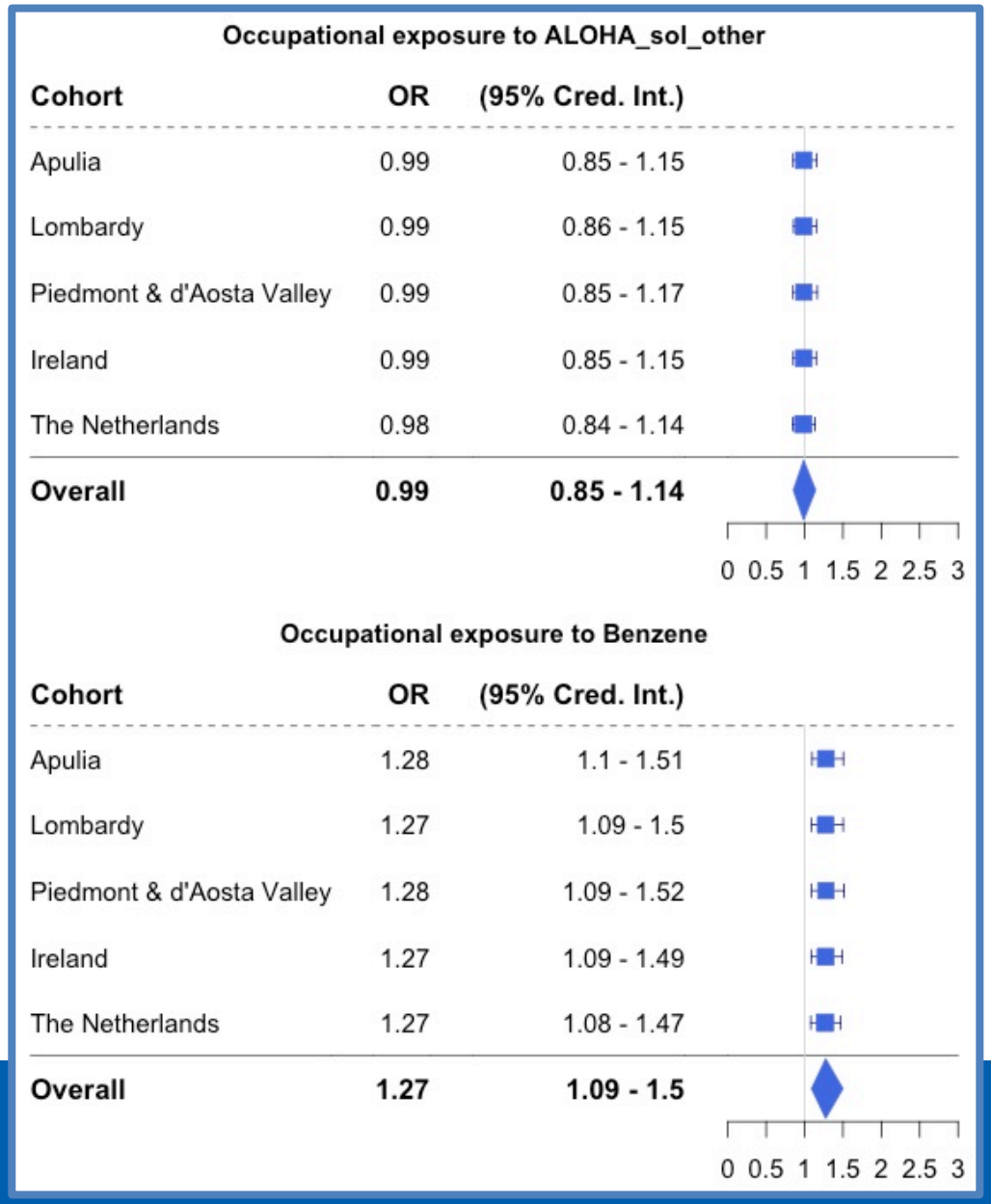


Results

Bayesian Mixed models by study site

Logistic regression	Odds ratio (95% CI)
Other solvents	1.02 (0.88 – 1.17)
Benzene	1.29 (1.11 – 1.51)

=> Allowing for heterogeneity – little change in estimates



Results

Bayesian Mixed models by study site

- Why heterogeneity for metals but not solvents ?
  - Higher prevalence of exposure to metals in Northern Italy compared to other sites determined by occupations
  - Overall prevalence of exposures – statistical noise?
    - From entire cohort (N = 4479)
      - » 26% exposed to aromatic solvents (ALOHA)
      - » 25% exposed to benzene (BEN)
      - » 16% exposed to metals (ALOHA)
      - » 8% exposed to chromium (DOM)

Conclusions

Bayesian Mixed models by study site

1. Metals, chromium and aromatic solvent exposures associated with increase odds of ALS
   - Robust to adjustment for lifestyle factors

2. Removing *C9orf72* patients increases odds ratios.
   - Consistent with multi-step theory of ALS and multiple pathways to ALS
   - Implicates exposures in sporadic ALS
   - ? Exposure studies in ALS may need to stratify by or exclude *C9orf72* expanded patients ?

3. Heterogeneity by study site for metals but not solvents

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Thank You