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Occupational Exposures and Risk of Dementia-Related Mortality in the Prospective Netherlands Cohort Study

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Background *Occupational exposures may be associated with non-vascular dementia.*
Methods *We analyzed the effects of occupational exposures to solvents, pesticides, metals, extremely low frequency magnetic fields (ELF-MF), electrical shocks, and diesel motor exhaust on non-vascular dementia related mortality in the Netherlands Cohort Study (NLCS). Exposures were assigned using job-exposure matrices. After 17.3 years of follow-up, 682 male and 870 female cases were available. Analyses were performed using Cox regression.*
Results *Occupational exposure to metals, chlorinated solvents and ELF-MF showed positive associations with non-vascular dementia among men, which seemed driven by metals (hazard ratio ever high vs. background exposure: 1.35 [0.98–1.86]). Pesticide exposure showed statistically significant, inverse associations with non-vascular dementia among men. We found no associations for shocks, aromatic solvents, and diesel motor exhaust.*
Conclusions *Consistent positive associations were found between occupational exposure to metals and non-vascular dementia. The finding on pesticides is not supported in the overall literature.* Am. J. Ind. Med. 58:625–635, 2015. © 2015 Wiley Periodicals, Inc.

KEY WORDS: cohort; dementia; Alzheimer's disease; occupation; extremely low frequency magnetic fields; pesticides; metals; solvents; diesel motor exhaust

INTRODUCTION

The increasing prevalence of dementia with age [Lobo et al., 2000; Knapp et al., 2007], combined with an aging population world-wide [United Nations: Population Division, 2002], means that dementia places an increasing health burden on society [Knapp et al., 2007]. Dementia can be classified in several subtypes, of which Alzheimer's disease is the most common with between 60 and 80% of all dementia cases [Lobo et al., 2000; Sosa-Ortiz et al., 2012].

Several occupational and environmental exposures have been proposed as risk factors for dementia, including Alzheimer's disease. Metals, such as lead [Rosin, 2009] and aluminum [Bondy, 2010], and pesticides [Hayden et al., 2010; Zaganas et al., 2013] have been under consideration due to their neurotoxic potential as well as evidence from

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epidemiological studies. Furthermore, extremely low frequency magnetic fields (ELF-MF) [Garcia et al., 2008; Huss et al., 2009], traffic related air pollution [Calderón-Garcidueñas et al., 2002], and diesel motor exhaust fumes [Ithnin et al., 2011] have been indicated as risk factors in occupational and environmental epidemiological studies.

Although some studies have indicated associations between these (occupational) exposures and dementia, not all studies have reported positive associations [Santibanez et al., 2007]. This may, in part, be due to methodological limitations in these studies such as the use of the case-control design, which is vulnerable to recall bias [Daniell et al., 1999; Bosma et al., 2000]; use of a single occupation to estimate exposure (e.g. the longest or last held job) instead of full occupational histories [Savitz et al., 1998b; Park et al., 2005]; incomplete data on confounders [Schulte et al., 1996]; and exploration of a single exposure instead of combined exposures [Bosma et al., 2000; Feychting et al., 2003; Hayden et al., 2010].

Therefore, we aim to investigate previously suggested associations between non-vascular dementia and occupational exposure to metals, solvents, pesticides and diesel motor exhaust based on full job histories in a large prospective general population cohort study with detailed information on possible confounders. We furthermore aim to study the effects of combined exposure to these occupational agents.

MATERIALS AND METHODS

The Netherlands Cohort Study on diet and cancer (NLCS) consists of 120,852 subjects (58,279 males and 62,573 females) who were enrolled in 1986 [van den Brandt et al., 1990]. Subjects were between 55 and 69 years of age and living in the Netherlands at time of enrollment. At enrollment, participants completed a questionnaire on occupational history, dietary habits, and other potential risk factors for cancer. Following a case-cohort approach, person-years were estimated using a randomly drawn subcohort (2,411 men and 2,589 women). For the subcohort as well as emerging cases, the full questionnaires were entered manually. Data entry was blinded to case/subcohort status by drawing extra questionnaires at random purely for blinding purposes and entering these simultaneously with the cases.

The NLCS was approved by the institutional review boards of the Netherlands Organization for Applied Scientific Research TNO (Zeist) and Maastricht University (Maastricht).

Follow-Up and Case Definition

At the time of this analysis, data were available for 17.3 years of follow-up (from September 1986 to December 2003). Vital status for this period was obtained from the Dutch Bureau of Genealogy and the Municipal Personal Records Database. Causes of death were obtained from Statistics Netherlands, coded according to the 9th and 10th (since 1 January 1996) version of the International Classification of Diseases (ICD-10). Non-vascular dementia was defined as mortality due to dementia, but excluding vascular dementia (ICD-9: 331.0, 290.0 and 290.1; ICD-10: G30, F00 and F03), following Huss et al. [2009]. 798 male and 1,171 female cases of non-vascular dementia were traced in the follow-up. Of these cases, information on occupational history and possible confounders was available for 682 men (85%) and 870 (74%) women.

Exposure Assessment

The baseline questionnaire contained questions on lifetime occupational history up to baseline. Subjects reported whether they had ever had a paid job and if so, supplied the name of the company or institution they worked at, the type of company or institution, what was produced at their department, their job title, and period of employment for up to five jobs.

The 2,304 men (96%) and 1,968 women (76%) in the subcohort who had ever had a paid job reported, respectively, 2.1 and 1.7 jobs on average. Jobs were coded by one designated coder according to the Dutch occupational classification system developed in 1984 by Statistics Netherlands. These job codes were subsequently translated to the International Standard Classification of Occupations 1968 [International Labour Office, 1968] (ISCO-68) and 1988 [International Labour Office, 1990] (ISCO-88) using a crosswalk described previously [Koeman et al., 2012]. Occupational exposure to selected agents were assigned by linking the job histories to various Job Exposure Matrices (JEMs) by ISCO job codes. The following JEMs were applied:

- Metals, total, aromatic and chlorinated solvents, pesticides, insecticides, herbicides, and fungicides: using the expert-based Aloha+ JEM [de Vocht et al., 2005; Matheson et al., 2005; Koeman et al., 2012].
- ELF-MF: using a recently refined ELF-JEM. This JEM was based on an earlier pure intensity-based JEM developed by Bowman et al. [2007], but modified by experts to reflect probability of exposure [Koeman et al., 2013].
- Electrical shocks: using an Electrical Shock-JEM based on registries of occupational electrical injuries [Huss et al., 2013].
- Diesel motor exhaust: using the expert-based Dom-JEM on (suspected) lung carcinogens [Peters et al., 2011].

All these JEMs assign three ordinal exposure levels: no (or background), low and high exposure.

The following metrics of occupational exposure were used in the analysis:

1) Ever/never exposed: Ever had a job with a high or only low exposure level versus only jobs with background exposure levels.
2) Cumulative exposure: Calculated by first assigning weights to the exposure ratings reflecting the known multiplicative nature of these occupational exposure distributions (i.e., no exposure: 0, low: 1, high: 4) [Stewart et al., 1991], then summing the products of the exposure weights and duration of each job over the entire job history.

Subjects who had never had a paid job (housewives or other) were assigned background exposure.

Statistical Analyses

Cox proportional hazards models were used to investigate the relationship between occupational exposures and non-vascular dementia related mortality. Risk analyses used age as the time scale and were stratified by sex. Person-years were estimated through the follow-up of the members of the subcohort. Ninety-five percent confidence intervals (CI) were calculated using the robust estimator of variance to account for the additional variance introduced by the case-cohort design of the study. Censoring occurred at the date of death, date of loss to follow-up, or end of follow-up, whichever occurred first. Models were analyzed using STATA version 12.1 (Statacorp LP, College Station, TX).

Covariates considered for a possible association with non-vascular dementia related mortality and inclusion in the risk models were based on the literature [Chen et al., 2009] and availability of data: smoking (current vs. former and non-smokers, average number of cigarettes smoked daily, number of years smoking cigarettes), attained level of education (primary vocational versus lower vocational, secondary and medium vocational and higher vocational), Body Mass Index (BMI, in kg/m^2), alcohol consumption (in g/day), and non-occupational physical activity (in min/day). Covariates with a $P < 0.10$ in univariate models were entered in a multivariate model, after which a backward, stepwise regression was performed retaining covariates with $P < 0.05$. Smoking status, physical activity and BMI were associated with non-vascular dementia and entered as potential confounding variables in the risk analyses of all selected exposures.

Occupational exposure metrics were analyzed as categorical variables, using background exposure as the reference category.

We first analyzed occupational exposures based on the ever/never classification (ever low and ever high analyzed as separate categories as well as combined). Depending on indications of a possible association in these analyses, we further explored exposure-response associations using cumulative exposure. For cumulative exposure, sex-specific tertiles in the subcohort were used to categorize the exposed individuals. A test for trend was performed based on the medians of the exposure categories. If cumulative exposure to an agent showed a possible exposure-response association with non-vascular dementia we analyzed this exposure while mutually adjusting for other exposures one at a time. Pearson correlations were calculated to assess correlations between co-exposures.

Sensitivity Analyses

Three types of sensitivity analyses were performed. Firstly, cumulative exposure was calculated using an alternative weighting scheme of background = 0, low = 1 and high = 10, based on earlier efforts by Brophy et al. [2012]. Secondly, all subjects with missing exposure levels due to a job history containing too little information to be coded (82 male (10%) and 238 female (20%) non-vascular dementia cases and 211 men (9%) and 410 women (16%) in the subcohort) were assigned to the background or no exposure group instead of being omitted from the analyses. Thirdly, an analysis was performed where subjects who never had a paid job at baseline, i.e., housewives and unemployed (6 male (1%) and 145 female (12%) non-vascular dementia cases and 13 men (1%) and 331 women (13%) in the subcohort) were omitted from the analyses.

RESULTS

Exposure Distribution

Table I shows the exposure distribution of the selected occupational exposures for men and women in the subcohort and among the cases. Correlation analyses between the different occupational exposures among men revealed two main exposure clusters (see Fig. 1). One cluster contained metal, solvent, ELF-MF, and electrical shock exposures. This cluster could be attributed to high exposure levels for subjects working in the metal industry. The other cluster, containing exposure to pesticides, insecticides, herbicides, fungicides, and diesel motor exhaust, could be attributed to high exposure levels among farmers. Correlations between occupational exposures among women were low (see Fig. S1).

TABLE I. Distribution of Selected Occupational Exposures by Subcohort and Case Status

		Subcohort		Non-vascular dementia	
Exposure	**Level**	**Men N (%)**	**Women N (%)**	**Men N (%)**	**Women N (%)**
Metals	Background	1,642 (78)	2,072 (99)	543 (80)	860 (99)
	Only ever low[a]	190 (9)	9 (0)	60 (9)	7 (1)
	Ever high	266 (13)	2 (0)	79 (12)	3 (0)
Total solvents	Background	1,330 (63)	1,705 (82)	443 (65)	736 (85)
	Only ever low	426 (20)	344 (17)	127 (19)	119 (14)
	Ever high	342 (16)	34 (1)	112 (16)	15 (2)
Aromatic solvents	Background	1,425 (68)	2,000 (96)	485 (71)	833 (96)
	Only ever low	601 (29)	80 (4)	167 (24)	35 (4)
	Ever high	72 (3)	3 (0)	30 (4)	2 (0)
Chlorinated solvents	Background	1,589 (76)	2,000 (96)	515 (76)	834 (96)
	Only ever low	244 (12)	73 (4)	83 (12)	30 (3)
	Ever high	265 (13)	10 (1)	84 (12)	6 (1)
ELF-MF	Background	1,011 (48)	1,041 (50)	295 (43)	421 (48)
	Only ever low	922 (44)	1,027 (49)	333 (49)	443 (51)
	Ever high	165 (8)	15 (1)	54 (8)	6 (1)
Electric shocks	Background	1,256 (60)	1,957 (94)	413 (61)	796 (91)
	Only ever low	322 (15)	119 (6)	121 (18)	65 (7)
	Ever high	520 (25)	7 (0)	148 (22)	9 (1)
Total pesticides	Background	1,845 (88)	2,038 (98)	615 (90)	857 (99)
	Only ever low	87 (4)	13 (1)	28 (4)	1 (0)
	Ever high	166 (8)	32 (2)	39 (6)	12 (1)
Insecticides	Background	1,858 (89)	2,041 (98)	616 (90)	858 (99)
	Only ever low	76 (4)	10 (0)	27 (4)	0 (0)
	Ever high	164 (8)	32 (2)	39 (6)	12 (1)
Herbicides	Background	1,927 (92)	2,049 (98)	643 (94)	858 (99)
	Only ever low	78 (4)	29 (1)	18 (3)	7 (1)
	Ever high	93 (4)	5 (0)	21 (3)	5 (1)
Fungicides	Background	1,890 (90)	2,043 (94)	630 (92)	857 (99)
	Only ever low	81 (4)	29 (1)	20 (3)	5 (0)
	Ever high	127 (6)	11 (0)	32 (5)	8 (1)
Diesel motor exhaust	Background	1,449 (69)	2,041 (98)	509 (75)	856 (98)
	Only ever low	572 (27)	34 (1)	145 (21)	13 (1)
	Ever high	77 (4)	8 (0)	28 (4)	1 (0)

[a]At maximum a low exposure over the entire work history of the subject.

Single Exposure Analyses

In women, non-vascular dementia showed a significant, positive association with selected categories of exposure, i.e., ever low exposure to metals, and ever high exposure to electrical shocks and herbicides (see Table II). Due to the low number of cases per category in the ever/never analysis, a cumulative exposure analysis could not be performed.

In the ever/never analyses non-vascular dementia showed a statistically significant positive association with exposure to ELF-MF, chlorinated solvents, and metals among men (see Table II). Of these exposures, cumulative exposure to chlorinated solvents and metals were also positively associated with non-vascular dementia (see Table III). In contrast, exposure to pesticides, insecticides, herbicides, and fungicides showed an inverse association with non-vascular dementia among men, both in the ever/never analyses and in the cumulative exposure analysis (see Tables II and III).

Combined Exposure Analyses (Men Only)

When analyzing exposure to ELF-MF, chlorinated solvents, and metals in combination with one other

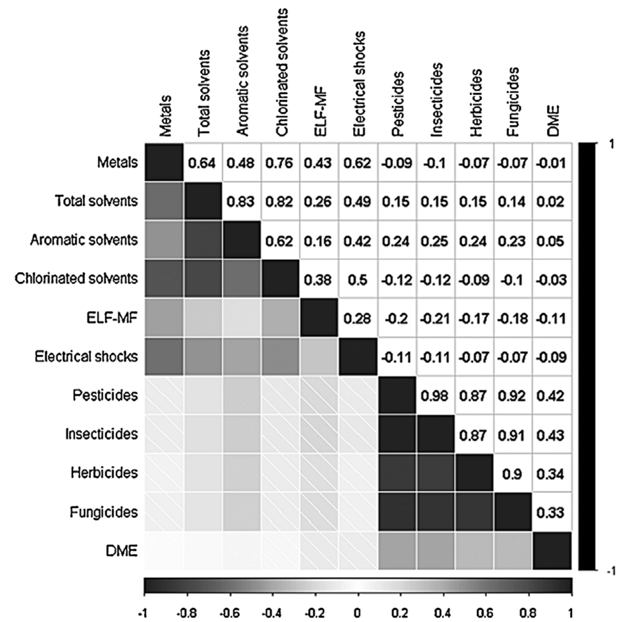

FIGURE 1. Correlogram displaying the Pearson correlations between cumulative occupational exposures among men in the subcohort. ELF-MF, extremely low frequency magnetic fields; DME, diesel motor exhaust; Striped, negative correlation; Smooth, positive correlation; **lighter coloring** = lower correlation.

occupational exposure at a time in men, most combinations of exposures showed only marginal changes in the HRs. However, combining chlorinated solvents and metals attenuated the HRs for both, with the strongest attenuation for chlorinated solvents. The HR for the 3rd tertile of exposed versus background changed from 1.58 to 1.14 for chlorinated solvents, and from 1.68 to 1.46 for metals.

The negative associations shown for pesticides overall, insecticides, herbicides, and fungicides, showed only marginal changes when adjusted for other non-pesticides occupational exposures.

Sensitivity Analysis

In the three sensitivity analyses, i.e., using an alternative weighting scheme to calculate cumulative occupational exposure, assigning background/no exposure to all subjects without exposure information and excluding subjects who never had a paid job, marginal effects were seen on the risk estimates and the analyses did not lead to other conclusions (results not shown).

DISCUSSION

We used a prospective study design to analyze the effects of selected occupational exposures on non-vascular dementia risk. We observed a consistent positive association in the ever/never and the cumulative exposure analyses between chlorinated solvents and metals and non-vascular dementia related mortality. The association with metal exposure was corroborated by the observation of an increased risk of non-vascular dementia among women with ever high exposure to metals. The robustness of the metal effect in the bivariate combined exposure models in men further indicates that the positive associations with ELF-MF and chlorinated solvents in the single occupational exposure analysis might be attributable to metals. Unexpectedly, exposure to pesticides showed a significant, negative association with non-vascular dementia related mortality in men, both in the ever/never analyses and in the cumulative exposure analyses, which were retained when combined exposures were considered.

Strengths and Limitations

Our study has a number of strengths compared to earlier studies. Firstly, the prospective cohort design of our study avoids selection bias, a problem with some earlier studies on chemical exposures and dementia or Alzheimer's disease [Daniell et al., 1999; Bosma et al., 2000]. Secondly, the use of JEMs applied to individual job histories rather than self-reported occupational exposures provides a potentially less biased manner of exposure assessment. Self-reporting of exposure tends to lead to differential bias in case-control studies [Daniell et al., 1999; Bosma et al., 2000; de Vocht et al., 2005]. Thirdly, we assessed multiple occupational exposures and investigated their combined effects. Fourthly, our analyses are based on a large number of (exposed) cases, owing to the large size of the NLCS cohort and the fact that the age of the cohort at baseline is high (55–69 years) while the incidence of and mortality due to dementia increases sharply after 65 years of age [de Lange et al., 2003]. Lastly, the comprehensive covariate data gave us the opportunity to consider a number of (non-occupational) covariates like smoking and non-occupational physical activity for their possible confounding effects.

A major limitation of this study was the reliance on mortality data to assess the health outcome of interest. Even though we included both primary and secondary causes of death, international studies have indicated that dementia is often not listed as a cause of death or complication on death certificates [Ganguli and Rodriguez, 1999; Zilkens et al., 2009]. There is no reason to assume that the under-reporting of non-vascular dementia would be differential by occupational exposure, but it does influence our ability to detect possible effects of occupational exposures.

In our study population we identified a total of 2,236 cases of dementia (ICD-10: F00–F03, G30), of which 284 (13%) were coded as vascular dementia (ICD-10: F01) and

TABLE II. Number of Cases, Person-Years in the Subcohort and Hazard Ratios for Associations Between Ever/Never Exposure and Mortality Related to Non-Vascular Dementia*

		Men				Women			
		Cases	Person-years in subcohort	Hazard ratio	95% Confidence interval	Cases	Person-years in subcohort	Hazard ratio	95% Confidence interval
Metals	No exposure	543	22,984		Reference	860	31,527		Reference
	Only ever low[a]	60	2,555	1.21	(0.84–1.74)	7	141	4.55	(1.35–15.32)
	Ever high	79	3,689	1.35	(0.98–1.86)	3	34	1.78	(0.23–13.84)
Total solvents	No exposure	443	18,596		Reference	736	25,884		Reference
	Only ever low	127	5,884	0.95	(0.72–1.25)	119	5,312	0.80	(0.61–1.05)
	Ever high	112	4,747	1.20	(0.90–1.61)	15	505	0.73	(0.33–1.61)
Aromatic solvents	No exposure	485	19,951		Reference	833	30,424		Reference
	Only ever low	167	8,269	0.94	(0.74–1.19)	35	1,237	0.96	(0.58–1.57)
	Ever high	30	1,008	1.08	(0.64–1.85)	2	41	3.46	(0.59–20.48)
Chlorinated solvents	No exposure	515	22,276		Reference	834	30,440		Reference
	Only ever low	83	3,300	1.25	(0.89–1.76)	30	1,093	0.82	(0.48–1.40)
	Ever high	84	3,652	1.33	(0.96–1.83)	6	168	2.08	(0.60–7.14)
ELF–MF	Background	295	13,999		Reference	421	15,724		Reference
	Only ever low	387	15,228	1.26	(1.01–1.57)	443	15,748	1.17	(0.96–1.40)
	Ever high	333	13,043	1.40	(0.92–2.14)	6	229	1.03	(0.34–2.89)
Electrical shocks	No exposure	413	17,627		Reference	796	29,778		Reference
	Only ever low	121	4,424	1.08	(0.81–1.45)	65	1,816	1.25	(0.85–1.84)
	Ever high	148	7,177	1.10	(0.85–1.42)	9	107	11.11	(3.84–32.16)
All pesticides	No exposure	615	25,696		Reference	857	31,022		Reference
	Only ever low	28	1,204	0.93	(0.55–1.59)	1	199	0.40	(0.05–3.41)
	Ever high	39	2,328	0.61	(0.40–0.93)	12	480	0.86	(0.39–1.88)
Insecticides	No exposure	616	25,840		Reference	858	31,073		Reference
	Only ever low	27	1,078	1.06	(0.60–1.86)	0	148	NC	NC
	Ever high	39	2,310	0.61	(0.40–0.94)	12	480	0.86	(0.39–1.87)
Herbicides	No exposure	643	26,833		Reference	858	31,187		Reference
	Only ever low	18	1,097	0.60	(0.33–1.09)	7	445	0.53	(0.21–1.35)
	Ever high	21	1,299	0.57	(0.32–1.01)	5	69	5.27	(1.30–21.42)
Fungicides	No exposure	630	26,338		Reference	857	31,090		Reference
	Only ever low	20	1,114	0.64	(0.38–1.17)	5	447	0.38	(0.13–1.08)
	Ever high	32	1,777	0.68	(0.42–1.09)	8	164	2.83	(0.87–9.16)
DME	No exposure	509	20,313		Reference	856	31,084		Reference
	Only ever low	145	7,870	0.77	(0.60–0.99)	13	498	0.78	(0.37–1.63)
	Ever high	28	1,045	1.09	(0.61–1.93)	1	119	0.58	(0.06–5.30)

ELF-MF, extremely low frequency magnetic fields; DME, diesel motor exhaust; NC, not calculated.
*Cox regression models with age as the time axis, adjusted for smoking status, physical activity and body mass index.
[a]At maximum a low exposure over the entire work history of the subject.

287 (14%) as Alzheimer's disease (ICD-10: F00, G30). Unclassified dementia (ICD-10: F03) made up 75% of all cases. In the Netherlands it is estimated that approximately 15% of incident cases had vascular dementia and 73% had Alzheimer's disease [de Lange et al., 2003]. From this perspective, it seems that especially Alzheimer's disease mortality is under-reported on death certificates. It is therefore likely that the ICD-10 category of unspecified dementia consists predominantly of Alzheimer's disease. It is also unclear exactly when a doctor decides to list Alzheimer's disease as a cause of death, rather than dementia. This is why we decided to analyze non-vascular dementia rather than Alzheimer's disease specifically. The associations found between occupational exposures and non-vascular dementia therefore may reflect associations between occupational exposures and Alzheimer's disease.

TABLE III. Number of Cases, Person-Years in Subcohort and Hazard Ratios for the Associations Between Cumulative Occupational Exposures and Non-Vascular Dementia Related Mortality, Men Only*

Exposure	Cumulative exposure level	Cases	Person-year in subcohort	Hazard ratio	95% Confidence interval
Metals	No exposure	509	20,313		Reference
	1st tertile	57	2,963	0.92	(0.59–1.45)
	2nd tertile	60	2,857	1.47	(0.99–2.18)
	3rd tertile	56	3,096	1.68	(1.12–2.51)
	Test for trend	682	29,2258		$P = 0.01$
Chlorinated solvents	No exposure	485	19,951		Reference
	1st tertile	47	3,079	0.99	(0.65–1.51)
	2nd tertile	77	3,169	1.36	(0.94–1.99)
	3rd tertile	73	3,029	1.58	(1.08–2.31)
	Test for trend	682	29,228		$P = 0.01$
ELF	Background	295	13,999		Reference
	1st tertile	123	5,047	1.18	(0.87–1.58)
	2nd tertile	131	4,987	1.74	(1.29–2.36)
	3rd tertile	133	5,195	1.08	(0.82–1.44)
	Test for trend	682	29,228		$P = 0.09$
All pesticides	No exposure	483	20,700		Reference
	1st tertile	55	2,911	1.31	(0.74–2.31)
	2nd tertile	78	2,777	0.60	(0.35–1.05)
	3rd tertile	66	2,840	0.49	(0.27–0.89)
	Test for trend	682	29,228		$P = 0.01$
Insecticides	No exposure	615	25,696		Reference
	1st tertile	27	1,115	1.39	(0.77–2.51)
	2nd tertile	22	1,273	0.63	(0.36–1.11)
	3rd tertile	18	1,144	0.50	(0.27–0.92)
	Test for trend	682	29,228		$P = 0.01$
Herbicides	No exposure	616	25,840		Reference
	1st tertile	26	1,022	1.07	(0.52–2.18)
	2nd tertile	22	1,276	0.52	(0.24–1.11)
	3rd tertile	18	1,090	0.41	(0.21–0.81)
	Test for trend	682	29,228		$P = 0.01$
Fungicides	No exposure	643	26,833		Reference
	1st tertile	15	754	1.10	(0.58–2.10)
	2nd tertile	10	833	0.73	(0.39–1.38)
	3rd tertile	14	809	0.45	(0.24–0.81)
	Test for trend	682	29,228		$P = 0.01$

ELF-MF, extremely low frequency magnetic fields; DME, diesel motor exhaust.
*Cox regression models with age as the time axis, adjusted for smoking status, physical activity and body mass index.

When we restricted our analyses to the ICD-codes for Alzheimer's disease (ICD = F00, G30, 14% of all dementia), the associations found for non-vascular dementia were not reproduced (see Table SI).

Metals

Metals such as aluminum [Bondy, 2010] and lead [Rosin, 2009] are known for their acute neurotoxicity at high levels of exposure. Other metals such as iron and copper are also suspected neurotoxins [Caban-Holt et al., 2005]. However, whether these metals are also related to long-term health effects such as dementia or Alzheimer's disease is still under debate. Aluminum has been extensively researched and epidemiological studies have shown weak, positive associations between environmental exposure to aluminum through drinking water and Alzheimer's disease [Shcherbatykh and Carpenter, 2007; Bondy, 2010], although results have been inconsistent [Flaten, 2001]. Similar associations have been shown for dietary consumption of aluminum, although the evidence for this association is less consistent [Shcherbatykh and Carpenter, 2007]. In contrast, studies on occupational exposure to aluminum have not shown significant associations with Alzheimer's disease [Santibanez et al., 2007]. Due to these negative findings, aluminum is not considered a possible risk factor for dementia by many researchers [Lidsky, 2014], although some disagree with this assessment [Walton, 2014]. The effects of other metals on Alzheimer's disease have not been studied as extensively as aluminum, and less is known of their effects [Caban-Holt et al., 2005; Shcherbatykh and Carpenter, 2007; Santibanez et al., 2007; Brewer, 2012].

Copper, zinc, and iron ions have been under investigation for their role in the etiology of Alzheimer's disease. These metals have been posited to increase the formation of Aβ-plaques and determine the structure and charge of Aβ-plaques [Faller et al., 2013]. Metals may also cause direct neuronal damage through metal-mediated inflammatory responses [Savelieff et al., 2013]. However, it is still unclear if and to what extent environmental exposures have an impact on these mechanisms.

The results of our study offer some further support for the relationship between exposure to metals and non-vascular dementia. Occupational exposure to metals showed the strongest, most consistent, positive associations with dementia-related mortality in our analyses. However, the Aloha+ JEM does not assign exposure to specific metals, and includes metals not under suspicion for their neurotoxic effects, preventing insight into which (type of) metal might be responsible for the association. Furthermore, the occupational coding system ISCO-88 classifies workers on the basis of occupation, and on its own offers little insight in the specific metals workers are exposed to.

Solvents

Solvents have been suspected as a risk factor for Alzheimer's disease, but the evidence is inconsistent. Subjects in occupations with possible solvent exposure have shown decreased performance in cognition tests [Daniell et al., 1999; Park et al., 2005] and increased risks of neurodegenerative diseases, including dementia and Alzheimer's disease in some studies [Schulte et al., 1996]. However, the epidemiological evidence for an association between solvent exposure and Alzheimer's disease has largely been negative [Santibanez et al., 2007].

In our study, we also did not find associations between occupational exposure to total solvents or aromatic solvents and non-vascular dementia. However, we did find indications of an association between occupational exposure to chlorinated solvents and mortality related to non-vascular dementia. Based on bivariate exposure models, this risk seemed to be associated more with metals than with chlorinated solvents. Our results therefore provide marginal support for an association between occupational exposure to chlorinated solvents and dementia.

ELF-MF and Electrical Shocks

Studies on the association between occupational exposure to ELF-MF and Alzheimer's disease have shown positive associations [Savitz et al., 1998a; Feychting et al., 2003; Håkansson et al., 2003; Roosli et al., 2007]. However, these associations have not been present in all studies [Savitz et al., 1998a; Sorahan and Kheifets, 2007], or were limited to specific subgroups [Park et al., 2005]. A meta-analysis showed an increased risk of Alzheimer's disease with higher levels of ELF-MF exposure, with case-control studies providing a stronger pooled association than cohort studies [Garcia et al., 2008]. In our cohort study we found an association between ever high occupational versus background ELF-MF exposure and non-vascular dementia related mortality in men, but not with cumulative, occupational ELF-MF exposure. Therefore, our study provides only limited support for a possible association between occupational ELF-MF exposure and non-vascular dementia.

Electric shocks have been proposed as an alternative explanation for the possible association between ELF-MF exposure and amyotrophic lateral sclerosis [Håkansson et al., 2003]. No such proposal has been made for Alzheimer's disease nor has an association between electrical shocks and dementia or Alzheimer's disease been addressed in prior publications. In our study we did find indications for an association between electrical shocks and non-vascular dementia mortality in women. However, because this association was only found among women and not among men, and the number of high exposed female cases was very low (approximately 1% of all female cases), we could not explore cumulative or combined exposures. Hence this observation should be interpreted with caution.

Pesticides

Pesticide exposure has been associated with mild cognitive impairment (MCI) [Bosma et al., 2000], which is considered to be a prodromal stage of Alzheimer's disease. In their review, Zaganas et al. [2013] found that several studies have shown an association between use of occupational pesticide and a lower performance on neurocognitive tests. Of the seven studies on Alzheimer's disease reviewed by Zaganas et al. [2013], five reported a positive association between increased pesticide use and Alzheimer's disease mortality [Parron et al., 2011] and incidence [Hayden et al., 2010], while two did not report an association. In contrast, we found inverse associations between pesticide exposure and non-vascular dementia related mortality in men. This unexpected inverse association might be related to healthier living patterns among farmers, the main occupational group that was exposed to high levels of pesticides in our study. Especially as a more physically active lifestyle has been associated with an increase in cognitive function and a decreased risk of dementia [Chen et al., 2009]. Because high occupational exposure to pesticides was found mainly in farmers, these effects could not be disentangled. In women, a positive association was found between (ever vs. never) occupational exposure to herbicides and non-vascular dementia related mortality, but we could not assess consistency with cumulative exposure due to low numbers of high exposed female cases. Other than a markedly lower prevalence of exposure among women, we found no clear differences in exposure patterns to pesticides between men and women in the NLCS. Therefore, it seems the difference in associations between men and women may be an artifact caused by the low number of exposed women. These differences in association might be related to different exposure patterns among men and women, related to different tasks. However, the number of exposed subjects and the lack of detail regarding the actual work tasks in the data did not allow for a more detailed analysis. In all, our results offer no clear support for a positive association between occupational pesticides exposure and dementia or Alzheimer's disease mortality.

Diesel Motor Exhaust

Traffic-related air pollution has been postulated as a possible risk factor for Alzheimer's disease through the increase of oxidative stress [Moulton and Yang, 2012]. Living in areas with high levels of traffic-related air pollution has also been associated with decreased cognitive function [Chen and Schwartz, 2009; Wellenius et al., 2012], although other reports found no such associations [Loop et al., 2013]. In their review, Guxens and Sunyer [Guxens and Sunyer, 2012] concluded that the current evidence on this issue is not conclusive, given the low number of studies and methodological constraints of these studies. So far, there is a paucity of epidemiological studies investigating the association between air pollution and dementia or Alzheimer's disease [Moulton and Yang, 2012]. In our study, we investigated occupational exposure to diesel motor exhaust and found no significant associations with non-vascular dementia related mortality.

CONCLUSION

In conclusion, exposure to metals showed a consistent, positive association with non-vascular dementia among men and women. Occupational exposure to chlorinated solvents and to ELF-MF also showed associations with non-vascular dementia in men, but these associations seemed more likely attributable to exposure to metals with which they were highly correlated.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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