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Association between background exposure to organochlorine pesticides and the risk of cognitive impairment: A prospective study that accounts for weight change

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ABSTRACT

Background: Background exposure to organochlorine (OC) pesticides was recently linked to cognitive impairment and dementia in cross-sectional and case–control studies. This prospective study was performed to evaluate if OC pesticides at baseline are associated with the future risk of cognitive impairment in elderly, with particular focus on weight change.

Methods: Plasma concentrations of 3 OC pesticides (p,p′-DDE, trans-nonachlor, and hexachlorobenzene) were measured among 989 men and women aged 70 years in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS). Cognitive impairment was validated by reviewing medical records. During the ten year follow-up, cognitive impairment was developed in 75 subjects. When weight change from age 70 to 75 was considered in analyses, elderly with incident cases before age 75 were excluded to keep the prospective perspective, leaving 795 study subjects and 44 incident cases.

Results: The summary measure of 3 OC pesticides predicted the development of cognitive impairment after adjusting for covariates, including weight change. Compared to subjects with OC pesticides <25th percentile, adjusted hazard ratios (HRs) in those with 25th–<75th and ≥75th percentiles were 3.5 (95% confidence interval: 1.5–8.5) and 3.2 (1.1–7.6), respectively ($P_{trend} = 0.04$). Among 506 subjects who maintained or gained body weight, adjusted HRs were 6.9 and 11.6 (1.4–92.6) among the elderly in the 25th–<75th and ≥75th percentiles compared to <25th percentile ($P_{trend} < 0.01$).

Conclusions: This prospective study demonstrates that background exposure to OC pesticides are linked to the risk of developing cognitive impairment in elderly. The role of the chronic exposure to low dose OC pesticides in the development of dementia should be further evaluated in other populations.

1. Introduction

Background exposure to organochlorine (OC) pesticides was recently linked to cognitive impairment and dementia in some (K.S. Kim et al., 2015; Richardson et al., 2014; Singh et al., 2013), but not all (Medehouenou et al., 2014) cross-sectional or case–control studies. Even though high dose OC pesticides are well-known to be neurotoxic (Colosio et al., 2003), the strong relations of OC pesticides with cognitive impairment and dementia observed in current general populations might be surprising because the background exposure levels in these populations have been very low since the banning of these chemicals in 1970s and 1980s.

Although two case–control studies have reported higher serum concentrations of some OC pesticides among patients with Alzheimer's disease compared to controls, these findings might be explainable by reverse causality, because weight loss is common among patients with dementia due to decreased food intake (Shatenstein et al., 2007; Smith and Greenwood, 2008) and serum concentrations of OC pesticides increase with weight loss (Lim et al., 2011). A cross-sectional study which reported a positive association with OC pesticides considered weight loss, but measured only one aspect of cognitive function (K.S. Kim et al., 2015).

On the other hand, weight loss is observed even before the onset of the clinical cognitive loss syndrome as well as after the development of overt dementia (Barrett-Connor et al., 1996; Stewart et al., 2005). At

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present, weight loss preceding incident dementia is considered as a result of dementia, not a contributing factor, because some subclinical neurodegenerative processes before clinical diagnosis may lead to weight loss (Buchman et al., 2005; Grundman et al., 1996; Vanhanen et al., 2001). However, weight loss can be a contributing factor of dementia if OC pesticides play a role in the development of dementia because weight loss leads to release into the blood of these neurotoxic chemicals (Lim et al., 2011), increasing their likelihood of reaching the brain. Therefore, adipose tissue dynamics raise an important methodological issue. Although one-time measurement of OC pesticides generally reflects long-term exposure levels well due to very long half-lives, this may not be the case during weight change. Thus, weight change needs to be considered in human studies which evaluate associations between OC pesticides and dementia.

This prospective study was performed to evaluate if OC pesticides at baseline were associated with the future risk of cognitive impairment among subjects initially aged 70 years, with particular focus on weight change.

2. Materials and methods

2.1. Study population

All subjects aged 70 years living in the community of Uppsala, Sweden, were eligible for the study. The subjects were chosen from the register of community living and were invited in a randomized order from April 2001 to June 2004. The subjects received an invitation letter within 2 months of their 70th birthday. Of the 2025 subjects invited, 1016 subjects were investigated at baseline (participation rate: 50.1%). When the subjects became 75 and 80, reinvestigation of the cohort was performed with follow-up rate of 81.4% and 59.7%, respectively. Among all participants, a total of 153 (15.6%) of the individuals had died during the follow-up period. Thus, the clinic follow-up rate among survivors at age 80 was 70.2%. Nevertheless, all participants were followed for medical events, including cognitive impairment/dementia through medical records and death certificates. Among participants at baseline, 992 subjects had valid measurement of OC pesticides. After excluding 3 subjects with physician-diagnosed cognitive impairment (ICD 10 F06.7) at baseline, we analyzed 989 people. The study was approved by the Ethics Committee of the University of Uppsala and the participants gave written informed consent.

2.2. Baseline measurement

The participants were asked about their health behaviors, medical history, and regular medication. Serum cholesterol, triglycerides, and blood glucose were measured after fasting overnight. OC pesticides were measured in stored plasma samples collected at baseline. Analyses of POPs were performed using a Micromass Autospec Ultima (Waters, Mildford, MA, USA) high resolution chromatography coupled to high resolution mass spectrometry (HRGC/HRMS) system based on the method by Sandau et al. (2003). In this cohort, 5 OC pesticides compounds or their metabolites were measured. Among them, 3 OC pesticides (p,p′-DDE, trans-nonachlor, and hexachlorobenzene) were included in the final analyses (trans-chlordane and cis-chlordane, detected among <10% of participants, were omitted). Information on 16 congeners of polychlorinated biphenyl (PCBs) was also included to compare to OC pesticides. We used both wet-weight concentrations adjusted for serum cholesterol and triglyceride and lipid-standardized concentrations by dividing wet-weight concentrations by total lipids. Total lipids were calculated using the short formula: total lipids (mg/dL) = 2.27 × total cholesterol + triglycerides + 62.3 (Phillips et al., 1989). Information on detection rate, detection limits, and distribution of 5 OC pesticides and 16 PCBs were provided in supplementary Table 1.

2.3. End point determination

Diagnosis for dementia disorders were almost exclusively made by a team at the Department of Geriatrics specializing in dementia care. Medical records were scrutinized for all 1016 PIVUS participants for several diseases, including diagnoses related to cognitive impairment. Since the number of different diagnoses related to cognitive impairment were rather small, we combined these diagnoses, ranging from mild cognitive impairment (MCI) to overt Alzheimer's disease (corresponding to ICD 10 F00–F03 and F06.7), as “cognitive impairment”. Follow-up periods for incident cognitive impairment cases were calculated as the time difference from the baseline examination date at age 70 to the date they were diagnosed with cognitive impairment. Persons who were not diagnosed with cognitive impairment were censored on the date when they became age 80 or they died.

2.4. Statistical analyses

Humans are exposed to a mixture of various OC pesticides, not only the 3 compounds which were included in the current study, and their serum concentrations are highly correlated in general populations (Porta et al., 2010). In the current study subjects, correlation coefficients among serum concentrations of 3 OC pesticides were 0.17–0.45. Thus, we primarily presented results based on a summary measure of 3 OC pesticides which reflects the mixture of various OC pesticides. The summary measure was estimated using the individual ranks for the 3 OC pesticides (0 rank was assigned to the non-detectable values) and divided into 3 groups (<25th, 25th–<75th, and ≥75th percentiles). The rationale of the rank-based summary measure was that we do not know exact biological mechanisms linking the life-time exposure to very low dose mixture of various OC pesticides and cognitive impairment even though high dose individual OC pesticides are well-known neurotoxins. Rank-based summary measures are preferred to absolute concentration-based summary measures because they allow equal contributions from all constituent OC pesticides (Lee et al., 2014). Absolute concentration-based summary measures would mainly reflect only p,p′-DDE (concentrations about 10 times higher than the other two OC pesticides). We presented results for individual OC pesticides as supplementary results (Supplementary Tables 4 and 5).

Hazard ratios (HRs) and 95% confidence intervals (95% CI) for dementia risk were estimated using Cox proportional hazard models. The covariates were gender, education (<6 years, 6–9 years, and 9+ years) body mass index (BMI), cigarette smoking (current, former, and never), exercise (none, mild, moderate, and vigorous), alcohol consumption (g/week), diabetes, and hypertension which were all measured at baseline. When wet-weight concentrations were used, serum cholesterol (continuous) and triglycerides (continuous) were added to the model.

The information on weight change during 5 years between examinations at ages 70 and 75 was first considered as a covariate. Here, 795 study subjects who were examined at age 75 and had not developed dementia before then were analyzed to keep the prospective perspective. Next, we performed stratified analyses by extent of weight change during 5 years (weight loss group: <−2 kg; weight maintenance group: −2–+2 kg; weight gain group: >+2 kg). As weight loss itself is known to strongly predict the risk of dementia (Barrett-Connor et al., 1996; Stewart et al., 2005) and weight change is related to plasma concentrations of OC pesticides (Lim et al., 2011), it is reasonable to evaluate the relation between OC pesticides and dementia in different weight change groups. We used SAS statistical software (version 9; SAS Institute, Cary, NC).

3. Results

During the 10 year follow-up, 75 subjects (43 men and 32 women) developed MCI or dementia (cumulative incidence 7.6%). After age 75,