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Cognitive decline, mortality, and organophosphorus exposure in aging Mexican Americans

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ARTICLE INFO

ABSTRACT

Background: Cognitive impairment is a major health concern among older Mexican Americans, associated with significant morbidity and mortality, and may be influenced by environmental exposures.

Objectives: To investigate whether agricultural based ambient organophosphorus (OP) exposure influences 1) the rate of cognitive decline and mortality and 2) whether these associations are mediated through metabolic or inflammatory biomarkers.

Methods: In a subset of older Mexican Americans from the Sacramento Area Latino Study on Aging (n = 430), who completed modified mini-mental state exams (3MSE) up to 7 times (1998–2007), we examined the relationship between estimated ambient OP exposures and cognitive decline (linear repeated measures model) and time to dementia or being cognitively impaired but not demented (CIND) and time to mortality (cox proportional hazards model). We then explored metabolic and inflammatory biomarkers as potential mediators of these relationships (additive hazards mediation). OP exposures at residential addresses were estimated with a geographic information system (GIS) based exposure assessment tool.

Results: Participants with high OP exposure in the five years prior to baseline experienced faster cognitive decline (β = 0.038, p = 0.02) and higher mortality over follow-up (HR = 1.91, 95% CI = 1.12, 3.26). The direct effect of OP exposure was estimated at 241 (95% CI = 27–455) additional deaths per 100,000 person-years, and the proportion mediated through the metabolic hormone adiponectin was estimated to be 4% 1.5–19.2). No other biomarkers were associated with OP exposure.

Conclusions: Our study provides support for the involvement of OP pesticides in cognitive decline and mortality among older Mexican Americans, possibly through biologic pathways involving adiponectin.

1. Introduction

Cognitive impairment is a major health concern for older adults, which threatens to become even more prominent with increasing life expectancy and the aging of populations (Hebert et al., 2013; Weuve et al., 2015). Due to the current limitations of treatments for impairment, primary prevention is imperative for reducing this burden. Few risk factors for cognitive impairment or dementia have been established. These include age, apolipoprotein E allele ε4 (APOE4), cerebrovascular diseases, and type 2 diabetes (Ishii and Iadecola, 2016; Kalaria, 2010; Rizzi et al., 2014; Tilvis et al., 2004).

Unlike other chemicals, pesticides are designed to impact living

systems (http://www.cdc.gov/niosh/docs/81-123/). Many target the nervous system, with potential health consequences among exposed populations (Blair et al., 2015). More than a billion pounds of pesticides are used annually in the United States (Grube et al., 2011), the majority in agricultural applications. Organophosphorus pesticides (OPs) are among the most acutely toxic and commonly used insecticides (Grube et al., 2011; Terry, 2012). Acute OP exposure is widely associated with significant increases in morbidity, including neurocognitive impairment and mortality (Terry, 2012). The potential toxic effects of long-term low-level OP exposure are less clear. Though, there is increasing evidence linking low-level exposure to OPs with impaired cognitive and neurobehavioral function, among other health outcomes (Ross et al.,

2013; Zaganas et al., 2013; Abdollahi et al., 2004). OPs may influence cognitive function both via the targeted neurotoxic cholinergic stimulation as well as their ability to induce inflammation, oxidative stress, and mitochondrial dysfunction in the nervous system or other less well understood neuropathologic mechanisms (Terry, 2012; Banks and Lein, 2012). Furthermore, multiple studies have associated OP exposure with type 2 diabetes, a well-recognized risk factor for cognitive decline (Montgomery et al., 2008; Starling et al., 2014).

Certain populations are known to disproportionately experience OP exposure. According to the Centers for Disease Control and Prevention, Hispanics of Mexican descent living in the United States have 1.3–5 times the amount of OP pesticide metabolites in urine than non-Hispanic whites (CDC, 2005; Quintero-Somaini, 2004), suggesting higher levels of exposure. In California, as many as 91% of agricultural workers are of Mexican descent (Quintero-Somaini, 2004; Villarejo, et al., 2000). Communities and family members of agricultural workers may also be exposed from drift of ambient pesticides following aerial crop spraying or from pesticides in dust and from volatilization after applications to fields (Baker et al., 1996). Furthermore, individuals of Hispanic ancestry are nearly 1.5 times more likely to develop dementia or Alzheimer's disease than non-Hispanic whites (Gurland et al., 1999; Post et al., 2007). Much of this has been attributed to high rates of diabetes among other risk factors.

Here we aim to examine the impact of residential proximity to agricultural OP application on cognitive functional decline and mortality during 10 years of follow-up among older Mexican Americans living in the Sacramento region of California. Further, to help understand potential biologic pathways, in secondary, exploratory analysis we will examine metabolic, inflammatory, and neurodegenerative biomarkers as possible mediators of OP exposure and morbidity/mortality associations.

2. Methods

All procedures described here were approved by the Institutional Review Boards of the University of California San Francisco, Los Angeles, and Davis and the University of Michigan.

2.1. Study population

For these analyses we relied on a subset of the Sacramento Area Latino Study on Aging (SALSA). SALSA is a population-based cohort of older Mexican Americans living in the Sacramento Valley area of California designed to investigate metabolic and cardiovascular risk factors for dementia. A total of 1789 participants, aged 60 years and over and self-identified as Latino, were enrolled between 1998 and 1999. Participants were interviewed in their homes every 12–15 months for up to seven study visits, ending in 2007. A detailed description of study sampling and procedures has been published (Haan et al., 2003).

In order to assess ambient pesticide exposure, we used California state mandated pesticide use reports (see below). However, California does not require pesticide applicators to submit the coordinates of non-agricultural pesticide applications (right-of way, structural, etc.) mainly found in urban environments. Thus, it is difficult to estimate ambient pesticide exposure from these major sources for urban participants at a better than county-wide spatial scale. Therefore, we restricted our study population to a subset of the SALSA population comprised of 459 participants who were exposed to at least one agricultural use chemical – thus designating their residences as being in proximity to agricultural fields – and who had at least one follow-up cognitive evaluation. We further excluded 29 participants who had baseline dementia/CIND, leaving 430 participants for analysis. A flow chart of study participants is detailed in Fig. 1.
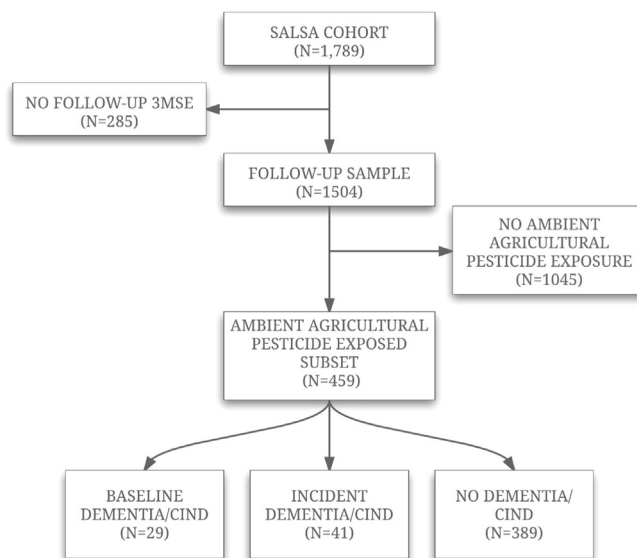

Fig. 1. Flow chart to SALSA participants used in analysis.

2.2. Pesticide exposure assessment

For our record-based, environmentally constructed exposure assessment, we estimated ambient exposure to OP pesticides from commercial agricultural pesticide applications in proximity to each participant's residential address. This exposure assessment method uses a geographic information systems (GIS) based computer model (Cockburn et al., 2011), which links California state mandated (since 1974) pesticide use reports (CA-PUR) from commercial agricultural application (CDPR, 2013a), land use surveys providing locations of specific crop (CDPR, 2013b), and geocoded residential addresses for each participant. For each pesticide reported to the CA-PUR, we estimated the pounds applied each year within a 500-m buffer of each residential address of our participants.

For each participant, we have residential addresses at baseline interview and self-reported information on how long the participant lived at the location. We limited exposure assessment to the 5 years prior to baseline, as 93.5% of the study population reported living at their baseline residential location for 5 years or more, while only 83% reported living at the address for 10 or more and 62% for 20 or more years. There are 24 different pesticides that were applied within residential proximity to our population that are considered OPs according to the pesticide action network (PAN) pesticide database, see Supplemental table S1 for a list of chemicals (Kegley et al., 2014). For each of these 24 OP pesticides, we calculated the yearly average pounds of pesticide applied within 500-m of each participants residence over the 5 years prior to baseline (i.e. total pounds applied over the 5 years/ 5). For participants who reported having moved within the 5 year exposure window, we calculated the yearly average based only on the years they reported living at the address, and also conducted sensitivity analysis excluding these participants.

Given the uncertainty in this assessment method (e.g. assuming the participant was at the recorded location during the relevant time period, wind patterns, etc.), we did not use the yearly average pounds of pesticide applied as a continuous variable. We dichotomized this average to specify those with high application near their residence and thus more likely to have ambient exposure. As the toxicity per poundage of each chemical is not necessarily similar across all OPs, we dichotomized the yearly average for each of the 24 OP pesticides according to the *chemical-specific* median of all exposed participants living in non-urban locations (all non-metropolitan areas based on Census tract 2000) (http://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes.aspx). We then counted the number of