Occupational exposure to metals and impact on dementia incidence

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Abstract

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Objective: Determine the association between occupational exposure to copper or aluminum and incidence of all-cause dementia and Alzheimer's disease (AD).

Method: Leveraging data from the Adult Changes in Thought (ACT) study, we analyzed the association of occupational exposures to copper or aluminum with exposure quantification through a JEM (CANJEM) and incidence of dementia and AD for 4,354 participants. Exposure groups were divided into three categories: low, medium, and high, and compared to an unexposed reference group. Data collection occurred between February 1994 through June 2015.

Results: During a median follow up time of 6.4 years, the adjusted hazard ratio (HR) for low, medium, and high copper exposure groups was 1.02 (95% CI: 0.88-1.19), 0.96 (95% CI: 0.79-1.16), and 1.05 (95% CI: 0.86-1.28) for all-cause dementia, and 1.08 (95% CI: 0.91-1.28), 1.06 (95% CI: 0.86-1.30), 1.05 (95% CI: 0.84-1.31) for AD, respectively. The adjusted HR for low, medium, and high aluminum groups was 1.07 (95% CI: 0.92-1.24), 1.15 (95% CI: 0.95-1.38), 1.12 (95% CI: 0.93-1.35) for all-cause dementia, and 1.05 (95% CI: 0.88-1.24), 1.17 (95% CI: 0.95-1.43), 1.15 (95% CI:0.93-1.42) for AD, respectively.

Conclusion: Our results found little evidence that copper or aluminum increase the risk of dementia. However, the results did have wide confidence intervals with more weight above one. This study suffered from the use of a population base cohort that was older at time of entry, which could have resulted in elimination of dementia cases with an onset at younger ages This could have resulted in cases associated to early occupational exposures being excluded in this study.

INTRODUCTION

As one of the top ten leading causes of death, dementia is becoming an important health concern, especially as the United States' aging population increases (Centers for Disease Control and Prevention, 2016). In fact, the World Health Organization predicts individuals with dementia will triple by 2050 with a reported 115.4 million cases. Alzheimer's disease (AD), which is one of the leading causes of dementia, is also projected to increase in the future. A study using 2010 census data estimated an increase in Alzheimer's disease from 4.7 million in 2010 to 13.8 million by 2050 (Herbert, 2013). Furthermore, according to UCSF, the cost of care for Alzheimer's disease will exceed $1.1 trillion by 2050 if the current rate of Alzheimer's disease does not slow down (University of California San Francisco , 2013). There have been several studies focusing on environmental influences of dementia and Alzheimer's disease (Wang, 2017). However, there are limited studies on how occupational exposures influence Alzheimer's disease (Wang, 2017).

BACKGROUND AND SIGNIFICANCE

Dementia describes a series of symptoms that involve a deficit in cognition to include memory, ability to think, perform activities of daily living (ADL), as well as effectively communicate (Oxford Medical Education, 2013-2017). There are many types of dementia with a variety of mechanistic actions to include Alzheimer's, vascular, Parkinson's, Lewy body, frontotemporal, infectious, as well as Creutzfeldt-Jakob disease. Vitamin deficiencies, medications, autoimmune diseases, and drug abuse can also have manifestations of dementia. Alzheimer's disease accounts for about 60% of dementia diagnoses with vascular dementia following as the second most common representing about 25% of dementia cases (Oxford Medical Education, 2013-2017).

Alzheimer's disease (AD) is characterized by the accumulation of neuritic plaques, extracellular amyloid beta deposition, and neurofibrillary tangles, which is essentially intracellular accumulation of hyperphosphorylated tau protein (Oxford Medicine online, 2011). The exact pathogenesis of AD is unclear; however, it is believed that there is either an overproduction or decreased clearance of amyloid beta peptides. Tau protein is important for the spread of AD in the brain. It is believed that tau becomes hyperphosphorylated and aggregates forming paired helical filament (PHF) tau, which is an important element in neurofibrillary tangles in the neuronal cytoplasm (Oxford Medicine online, 2011). Neurofibrillary tangles (NFT) are toxic to neurons, and it is the transmission of this type of tau interaction between neurons that accounts for the spread of AD in brain (Oxford Medicine online, 2011). Both aluminum and copper have been implicated in both amyloid beta peptide accumulation and tau protein disruption.

Copper can bind to amyloid beta accelerating amyloid beta cross-linking thus increasing amyloid beta aggregation. The formation of oligomeric amyloid beta, which is induced by copper, supports copper as a powerful neurotoxin (Wang, 2017). Certain amyloid beta chains have proven to be more toxic after binding with copper possibly associated with increased copper affinity from the oligomeric amyloid beta formation. Copper also blocks secretion of amyloid beta due to histidine bridging between copper and amyloid beta resulting in a member-penetrating structure (Wang, 2017). Additionally, copper can induce tau phosphorylation and aggregation. This disruptive mechanism of copper has the potential to lead to Alzheimer's disease. Aluminum also plays a role as a cross-linker in amyloid-beta oligomerization, which can result in proliferation of neuro-inflammation (Wang, 2017). Studies injecting rabbit brains with aluminum have resulted in formation of NFTs, which closely resembled NFTs seen in AD individuals (Wang, 2017).

There have been multiple studies demonstrating an association between copper and aluminum and the development of Alzheimer's disease (Wang, 2017) (Tahmasebinia, 2017) (Mirza, 2017). Many of these studies have examined environmental exposures. However, there very few studies researching occupational exposures to aluminum or copper and the association with dementia. This study will specifically assess occupational exposure to aluminum and copper and the risk of developing dementia. Furthermore, through studying occupational exposures a better understanding of environmental exposures can be determined as occupational exposures are higher than those experienced by the general population. With higher levels of exposure, this study will extend the knowledge of the potential health implications of aluminum and copper. Through expansion of knowledge on the risk of Alzheimer's disease development associated with exposure to these two metals, higher jeopardy occupations can be better monitored for exposure levels. Additionally, improved regulation can be developed to better protect individuals employed in these industries.

METHODS

Study Sample

Adult Changes in Thought (ACT) study utilizes a population-based free-living cohort for its prospective longitudinal study, which was initiated in 1994. ACT is comprised of individuals from the surrounding urban and suburban areas of the Puget Sound region in Washington state who were randomly selected from the membership of a Health Maintenance Organization, Group

Health Cooperative now Kaiser Permanente. At the time of enrollment, all subjects were older than 65 years of age and determined to be dementia free through an evaluation. Currently, ACT has continuous enrollment with the goal to maintain 2,000 active at-risk person years annually. Every two years, all subjects in this study were evaluated in person and assessed for signs of cognitive decline. Additional measurements were also obtained including blood pressure data, NSAID use, smoking history, as well as employment history. From the total number of individual data initially received from ACT, our study excluded 14 individuals due to missing data that was important for this study to include absence of job title or pertinent demographic data. In total, this study considered analysis on 4,354 participants. The data collected for this study occurred between February 1994 and June 2015.

Exposure Assessment

Occupation Reporting:

The ACT study obtained the two longest held positions at baseline for all subjects as well as the years worked in those positions expressed as initial date at position and end date at that position. Essentially from the initiation of the study, every subject was given the opportunity to report this exclusive occupational history. In addition to reporting the two longest held jobs at baseline, initial participants of the ACT study were given the opportunity to complete a more detailed occupational questionnaire that reported on relevant exposure history information to include job titles of the two longest-held jobs as well as duties and tasks performed, company and department of employment, dates of employment, and specific exposures experienced during employment. An excerpt of the questionnaire is provided in the supplementary appendix Table A1 and A2. However, as this data was limited to just initial participants of the ACT study and is subject to recall and reporting bias of the self-identified exposures, the questionnaire was not utilized in this study. Instead, we used a job-exposure matrix (JEM), more specifically Canadian job-exposure matrix (CANJEM), to better quantify exposures.

In order to effectively use CANJEM, occupational codes needed to be converted into a code CANJEM used for their matrix . In the ACT study, occupations were coded according to the Integrated Public Use Microdata Series (IPUMS) occupational coding system for the year 1970. IPUMS is a large database that is supported through federal censuses and American Community Surveys form the year 2000-2012 (IPUMS USA, 2017). An occupational coding crosswalk was used in this study to covert the IPUMS occupational coding system to the Standard Occupational Classification (SOC) 2010 system, which is a more universally accepted coding system utilized by federal agencies to collect and analyze data, and it is a coding system that CANJEM equated assessments for exposures. The SOC 2010 system has four different levels of categorization detailed through a numerical coding system with the broadest level consisting of a two-digit classification system and a six-digit description of each occupation as the most specific classification category (see Table 1) (Bureau of Labor Statistics, 2011). In this study, we successfully converted a majority of occupations from the IPUMS 1970 code to a six-digit SOC 2010 code. There were about 12 IPUMS codes that need additional research to effectively convert the value to a meaningful SOC 2010 code, which is detailed in the supplementary appendix Table A3.

Table 1: SOC digit coding

Digit	Occupational Level
1st two	Major occupational group
3rd	Minor occupational group
4-5th	Broad occupational area
6th	Detailed occupation

CANJEM:

In this study, CANJEM was used to quantifying occupational exposures for aluminum and copper. CANJEM is a database that has analyzed over 31,000 jobs through detailed interviews of 8,912 subjects in the Montreal area, which has a variety of occupations to include industrial workers (Siemiatycki, 2018). CANJEM is based off of four case-control studies that looked at different types of cancers and association with a variety of occupational exposures. Exposures were assessed through detailed interviews conducted under the guidance of expert teams that included industrial hygienists, engineers, and chemists for 290 agents initially that were filtered down to 258 agents after agents with low prevalence were eliminated (Siemiatycki, 2018). Interviews for the case-control studies were carried out as early as 1979 and up until 2004. Determination of all factors that related to the JEM creation was established through a consensus among the experts involved in the analysis. To minimize weaknesses in the JEM, the creators of CANJEM utilized three dimensions in the matrix depicted in Figure 1, which included *occupation and industry, time, and an agent dimension* (Siemiatycki, 2018).

Figure 1: Dimensions of CANJEM

Occupation/Industry Dimension	Time Dimension	Agent Dimension
• OCDO 1971 • National Occupational Classification (Canada, 2011) • ISCO 1968 • SOC 2010 • Standard Industrial Classification (Canada, 1980) • North American Industry Classification System (2012) • International Standard Industrial Classification of all Economic Activities (UN, 1968)	• 1920-2005 • 1920-1969, 1970-2005 • 1920-1949, 1950-1969, 1970-1984, 1985-2005	

OCDO: Canadian Classification and Dictionary of Occupations
ISCO: International Standard Classification of Occupations
SOC: Standard Occupational Classification

The *occupation and industry dimension* allows for a wider aspect of interpretability internationally. The creators incorporated four occupational classification systems based on job and three systems on industry that are represented in a variety of other countries. The four occupation based systems included Canadian Classification and Dictionary of Occupations (OCDO 1971), National Occupational Classification (Canada, 2011), International Standard Classification of Occupations (ISCO 1968), and the Standard Occupational Classification (SOC) (USA, 2010), and the three industry-based systems included Standard Industrial Classification (Canada, 1980), North American Industry Classification System (2012), and International Standard Industrial Classification of all Economic Activities (UN, 1968) (CANJEM, 2017). This dimension was further categorized by the resolution of each classification system. For example, when incorporating the SOC 2010 data, there were assessments performed at the various numerical coding systems. CANJEM data can be retrieved for two-digit, three-digit, five-digit, or six-digit SOC 2010 codes. This retrieval process is the same for other relevant classification systems (Siemiatycki, 2018).

CANJEM created a *time dimension* to account for changing exposures perhaps through legislation, safety measures, or evolving occupational agents. The JEM covers a time period of 1920 through 2005. Data for this time period can be obtained through three different methods corresponding to different levels of data resolution. The first method is through a compilation of the entire time period, 1920 through 2005, and is considered the lowest resolution. Another method is through ascertainment of data divided broadly into two time periods, 1920-1969 and 1970-2005. The last method with the highest resolution divides the entire time period into four categories: 1920-1949, 1950-1969, 1970-1984, 1985-2005 (Siemiatycki, 2018). Depending on the population, a specific method can be chosen to correspond most closely to the experienced exposures.

For the *agent dimension* the creators quantified occupational agents. There were four main factors considered in this dimension, which included probability of exposure, confidence or reliability of exposure, concentration or intensity of exposure, and frequency of exposure (Siemiatycki, 2018). Probability of exposure was determined by taking the number of individuals assessed as exposed to a certain agent in a specific occupation and dividing by the number of individual jobs in that occupation. For example, looking at the occupation of farmers, ranchers, and other agricultural managers, which has a SOC 2010 code of 11-9013, if there are 5 individual exposed jobs and a total of 100 jobs for this occupation, then the probability of exposure would be 5. An individual in the study was only considered to have been exposed to a specific agent if it was determined to be present in the work environment at higher levels than would be represented in a non-occupational setting (Siemiatycki, 2018). The CANJEM creators recommended using data that correlated with a probability that had at the minimum ten individual jobs for a specific occupation, which was used as the denominator for probability calculations for exposed jobs. Once a probability of an exposure was established, the confidence or reliability of exposure occurrence was assessed as possible, probable, or definite, which summed to 100% (CANJEM, 2017). The confidence of exposure was subjective but aligned with CANJEM experts' opinions (Siemiatycki, 2018). Next, a concentration or intensity of exposure was determined as low, medium, or high, again summed to 100%. Background levels to an exposure were considered to be low with the highest concentrations deemed as such based off what the highest levels of that agent was experienced in the Montreal workforce. Lastly, the frequency denoted the percentage of time the exposure occurred in a typical working week

(Siemiatycki, 2018). This was divided into four proportions: 0-2 hours, 2-12 hours, 12-39 hours, and more than 40 hours per week (CANJEM, 2017).

To better analyze and externalize exposures, the creators of CANJEM developed an index, frequency-weight intensity (FWI), that incorporated intensity of exposure averaged over a 40-hour work-week (CANJEM, 2017). FWI was calculated as the intensity multiplied by exposure frequency (hours/week worked) averaged over a 40-hour work-week (CANJEM, 2017). Intensity was converted to a numerical value for the three exposure levels of low, medium, and high. CANJEM provided the calculated FWI using a continuous frequency variable as exposure hours a week and the attributed numerical representation for intensity; both the mean and the median were represented for these values, which in turn resulted in either the mean FWI or median FWI with appropriate calculations. Given the manner in which FWI was calculated, the value was unitless. Figure 2 provides an example of median FWI calculation. Experts at CANJEM further determined that the relationship of medium and high levels of exposure closely resembled absolute values of 5 and 25 times the value of a low level of exposure (1-5-25 pattern), respectively (CANJEM, 2017). For example, if an individual had a FWI of 10, this would correspond to 250 hours at low intensity exposure, 50 hours at medium intensity exposure, or 10 hours at high intensity exposures (CANJEM, 2017).

Figure 2: Median frequency-weighted intensity (FWI) calculation

Equation:

$$\text{FWI: } \frac{\text{(median intensity)x(median frequency)}}{40\ hour\ workweek}$$

Example: Farmer, rancher, other agricultural managers and median FWI for copper exposure

Median intensity: 5
Median frequency: 5 hours/week

$$\text{FWI: } \frac{(5)x(5\frac{hours}{week})}{40\ hour\ workweek} = 0.625$$

Through these different dimensions, CANJEM provided many different approaches in extracting data. Data can be ascertained through utilization of occupation, exposure agent, or time period of interest depending on a study's available initial data. Furthermore, depending on the approach taken different scientific questions can be addressed. For example, if a study is attempting to determine what occupations have copper exposure, the appropriate method for this study would be to approach CANJEM through the agent dimension. However, if a study wanted to know what exposures a specific occupation may be at risk, utilization of the occupational dimension would assist with this question. Lastly, the time dimension could be used to help assess possible legislative changes in certain time periods as it pertains to exposure levels. In the *Exposure Measures* the dimension used in this study will be further elaborated.

Exposure Measures:

We used the *agent dimension* as the approach method to quantify exposures through CANJEM with data expressed in the six-digit SOC 2010 occupation coding system and the single time period representing 1920 through 2005. The CANJEM agent label that was used in the study was specifically labeled Copper and Aluminum. The Copper and Aluminum agents included all forms of exposure and was chosen in attempts to encompass all potential exposure assessments for these metals. The broad coverage of time was used in consideration of the time period the ACT cohort would have predominantly been employed and to maximize quantification of occupations. The six-digit SOC 2010 coding system was used to help minimize misclassification of exposures. We did not discriminate by excluding CANJEM exposure assessments that had lower than ten individual jobs for a specific occupation as recommended by the JEM developers. This was decided to maximize exposure assessments for all occupations in the ACT study dataset.

We determined median FWI, 1-5-25 pattern, was the best measure for exposure for this study given previously stated CANJEM expert opinion of reliability as detailed in the *CANJEM* section for the 1-5-25 pattern. The median FWI measure was used over the mean FWI to prevent suasion of potential outlier data points. Probability of exposure as determined by CANJEM experts was not factored into the exposure variable for this study. However, in order to create a meaningful exposure measure for ACT study participants and to better valuate their exposure, we incorporated years in occupation into the exposure measurement. To accomplish this, median FWI for an occupation was multiplied by a participant's duration of years in that occupation, which created a new variable of median FWI-years. If a participant had more than one occupation, then his or her duration in the second occupation was multiplied by the represented median FWI. Then these two values were added together to determine the total median FWI-years of exposure. Figure 3 details this calculation with an example. This calculation allows for better interpretation of the exposure variable so that total occupational exposures to copper or aluminum were represented. Additionally, this measurement helps to impartially address exposures for an individual who may have a low intensity for the metal but over a prolonged period of time versus someone who had a high intensity for a short period of time. Consider two individuals one who was a mechanical engineer, which has a median FWI of 0.2 for copper, for ten years and another individual who was a mining and geological engineer, which has a median FWI of 0.1, for 20 years. Both individuals have the same median FWI-years of 2, which is a fair weighted measure for both individuals given the differences in median FWI and duration experienced with that median FWI. Therefore, the larger the median FWI-years an individual has will correspond to an overall higher occupational exposure to that metal.

Figure 3: Median FWI-years calculation

Equation:

$$\text{median FWI-years: } [(\text{median FWI}_{\text{occupation1}})\text{x}(\text{duration}_{\text{occupation1}})] + [(\text{median FWI}_{\text{occupation2}})\text{x}(\text{duration}_{\text{occupation2}})]$$

Example:

median $\text{FWI}_{\text{occupation1}}$: 0.625
$\text{duration}_{\text{occupation1}}$: 10 years
median $\text{FWI}_{\text{occupation2}}$: 0.15
$\text{duration}_{\text{occupation2}}$: 5 years

$$\text{median FWI-years: } [(0.625)\text{x}(10 \text{ years})] + [(0.15)\text{x}(5 \text{ years})] = 7 \text{ median FWI-years}$$

Outcome Assessment

Cognition was assessed using Cognitive Abilities Screening Instrument (CASI). CASI is a 40-item global cognitive test assessing attention, concentration, orientation, short and long-term memory, language, visual construction, list-generating fluency, abstraction, and judgment (Teng, 1994). CASI scores range from 0 to 100 with higher scores indicating better cognition (Teng, 1994). Individuals who had CASI scores below 86, in this study, underwent further medical and psychometric evaluation that included detailed medical histories, neurocognitive testing, and appropriate laboratory and imagining studies. After all data was obtained, a diagnosis of dementia was made as per Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria and through a multidisciplinary study team in a consensus conference (Kukull, 2002). The diagnosis of possible and probable AD was determined utilizing criteria from National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann G, 1984). CASI was tested through an in-person interview at time of initial enrollment and each biennial follow up visit. If at time of enrollment, a participant was found to have a low score, they were excluded from the study. At each biennial visit, individuals were again assessed with a CASI score with additional medical evaluation and diagnostic work-up for low CASI scores. If they were found to have a form of dementia, then they were considered to have an event, and the date of event was typically determined to be midway between the date of study follow up at which time they were diagnosed and the previous biennial visit (Kukull, 2002). Individuals who were not found to have dementia continued with scheduled biennial follow up visits, and they were considered censored after date of last ACT follow up date or June 2015, which was the end date for this study.

Other Risk Factors

Risk factors that could possibly impact the relationship between occupational exposures and incidence of dementia were addressed in this study. Two important potential confounders that were considered in this study included chronic NSAID use of more than two years at baseline and smoking history at baseline. NSAIDs are thought to reduce amyloid beta peptide accumulation and hyperphosphorylated tau proteins thereby decreasing cognitive decline and thus the outcome variable of AD and in turn all-cause dementia (McKee, 2008). Additionally, NSAIDs could very well be associated with the predictor variable of occupational exposure of metal as individuals in occupations exposed to copper or aluminum may have resulted in a greater incidence of NSAID use possibly through musculoskeletal injuries. In this study, NSAID use was assessed as a binary variable (coded 0=less than two years of chronic use, 1=greater than two years at baseline). Smoking history has also been implicated as a risk factor for AD. Various pathways have been suggested such as oxidative damage and stress that stimulates an AD pathophysiological response leading to an increased risk for AD (Durazzo, 2014). Additionally, studies without an affiliation with a tobacco company have reported that current and former smokers are at an increased risk for developing AD (Cataldo JK, 2010). Tobacco use can be associated with the predictor variable as well. Tobacco use at baseline was also assessed as a binary variable (0=never smoked, 1=former or current smoker). Other risk factors and potential precision variables that were controlled in this study included some demographic data such as gender (coded 0=male, 1=female), race (coded 0=White, 1=Black, 2=Asian, 3=Other), education (coded 0=high school or less, 1=some college or more), and living situation (coded 0=lives with another individual or at a nursing home, 1=alone).

Effect Modifiers

APOE gene, located on chromosome 19, is known to be associated with Alzheimer's disease development more specifically late onset Alzheimer's disease (LOAD) (Tang, 1998). The ε4 variant is a risk factor for LOAD. The ACT study has tested more than 80% of its subjects for the APOE ε4 allele. Individuals who had one or more APOE ε4 allele were considered positive for the gene. This study leveraged APOE data (coded 0=no APOE gene, 1=APOE positive) obtained through ACT in order to determine if the presence of the gene modified the relationship between copper or aluminum and AD or all-cause dementia.

Statistical Analysis

Descriptive Analyses:

Demographic, occupational, and outcome data were analyzed for the entire cohort. To better assess the exposure measure, the distribution of median FWI-years was evaluated through histogram plots for both metals (see supplementary appendix Figure A1). Boxplots were also created to better gauge the distribution and potential outliers (see supplementary appendix Figure A2). The histogram figures for both metals were left-skewed predominantly due to individuals without an exposure measure for either metal with median FWI-years of 0. The boxplots demonstrated a few outliers with extremely high exposure measures for both metals. Categorizing the exposure measure was considered over log transformation of the data due to relatability and transparency of results. A descriptive analysis was performed for median FWI-years of the exposed individuals to copper and aluminum, which is represented in Table 2. Based off these values the median FWI-years were categorized into three groups, low, medium, and high. To ascertain the groups, the cutoff was established at the median and 3rd quartile values. For copper exposure, the low group consisted of individuals with a median FWI-years greater than 0 to 3.3, the medium group had a value between 3.4 and 9.9, and the high group consisted of individuals with median FWI-years of 10 or above. For aluminum exposure, the same technique was applied with median FWI-years greater than 0 to 6.5 in the low group, 6.6 to 16.7 for the medium group, and 16.8 and above for the high group. Another group for each metal was also established labeled unexposed and consisted of individuals that had zero median FWI-years for corresponding metals. Mean was not used to determine categories due to the potential inflated values given the high valued outlier. Three levels of categorization was decided for exposed individuals in order to help better interpret the higher valued median FWI-years. By dividing the medium and high groups by the 3rd quartile, misclassification of exposure measure can be combated to some degree.

Table 2: Distribution of median FWI-years for exposed individuals

Exposure	Number exposed	Minimum	1st Quartile	Median	Mean	3rd Quartile	Maximum
Copper	1,925	0.0938	1.219	3.281	11.24	9.9	1025
Aluminum	1,996	0.0731	2.75	6.5	15.18	16.7	1128

Once the four categories of unexposed, low, medium, and high for both copper and aluminum were established, demographic data for each group was analyzed. Descriptive analysis of the diagnoses: no dementia, all-cause dementia, and AD, were also examined for the four groups separately. However, occupational breakdown was determined for all copper and aluminum exposed occupations (groups low, medium, and high), which would provide more meaning and understanding of copper or aluminum exposed occupations as a whole.

Kaplan Meier Curves:

To compare survivability among the groups created for both metals, Kaplan Meier (KM) curves were created. We created a plot for each metal (copper and aluminum) and outcome (all-cause dementia dementia and AD), and each plot compared survivability of unexposed, low, medium, and high exposed individuals. Events were classified as a diagnosis meeting the criteria for all-cause dementia or AD as stated in the *Outcome Assessment* section. Individuals were censored if they were lost to follow up or did not experience the event by the end of the data collection date for this study (June 2015) for all-cause dementia analysis, and for AD analysis additional participants were censored if another type of dementia developed. Survival probability was plotted against age with a range between 60-110 years.

Cox Proportional Hazards Regression:

Our study used Cox proportional hazards (PH) regression to analyze the hazard ratio (HR) through hazard rates corresponding to the four groups of exposure measure (unexposed, low, medium, high) with unexposed being the reference group for each metal and the association to the outcome; all-cause dementia and AD were analyzed separately. Using the four groups of unexposed, low, medium, and high exposure, as specified above in *Descriptive Analyses*, three different models were prepared representing varying levels of adjustment. The subject's age was used as the time axis, controlling for the impact aging has with dementia, with left truncation to account for time since birth not under observation in the study (Canchola, 2003). Similar to the KM curve analysis, individuals were censored if they were lost to follow up or did not experience the event by the end of the data collection date for this study (June 2015) for all-cause dementia analysis, and for AD analysis, participants were additionally censored if another type of dementia developed. Three different models were fit for each different exposure-outcome combination, detailed in Table 3. Model 1 was a crude representation without any adjustments. Model 2 was considered level 1 of adjustment, adjusting for gender, race, chronic NASID use, and smoking history. Model 3, level 2 adjustment, further adjusted for living situation and years of education. Our study used Model 3, level 2 adjustment for analysis and interpretation of data.

Table 3: Cox PH model equations
Model 1: crude $\log(\lambda(t, x, \beta))=\log(\lambda_0(t)) + \text{exposure}\beta_1$
Model 2: level one adjustment $\log(\lambda(t, x, \beta))=\log(\lambda_0(t)) + \text{exposure}\beta_1 + \text{gender}\beta_2 + \text{race}\beta_3 + \text{NSAID}\beta_4 + \text{smoke}\beta_5$
Model 3: level two adjustment $\log(\lambda(t, x, \beta))=\log(\lambda_0(t)) + \text{exposure}\beta_1 + \text{gender}\beta_2 + \text{race}\beta_3 + \text{NSAID}\beta_4 + \text{smoke}\beta_5 + \text{living}\beta_6 + \text{education}\beta_7$
$\lambda_0(t)$: baseline hazard function λ: hazard for event and exposure $\boldsymbol{\beta}_1$: vector of exposure measures (low, medium, high) β_2: gender at baseline (male, female) $\boldsymbol{\beta}_3$: vector of race at baseline (Caucasian, Black, Asian, other) β_4: chronic NSAID use of 2 or more years at baseline β_5: smoking history at baseline (past or current smoker) β_6: living situation at baseline (alone, with another individual) β_7: education at baseline (high school or less, some or more college)

In order to determine if an interaction term for the APOE gene and exposure measure should be included in the study analysis, a likelihood ratio test was assessed. To accomplish this, a new data frame was established to exclude individuals who did not have APOE gene testing. The new cohort comprised of 3,790 participants, and Model 3, level 2 adjustment, was used for comparison, see Table 4 for equations. The full Interaction Model was compared to the reduced Interaction Model for both metals (copper and aluminum) and outcomes (all-cause dementia and AD) separately. The likelihood ratio test was non-significant for all the calculated comparison groups (supplementary Table A4). Therefore, it was not necessary to add this interaction term to the analysis.

Table 4: Cox PH interaction model equations
Interaction Model 1: Full model $\log(\lambda(t, x, \beta))=\log(\lambda_0(t)) + \text{exposure}\beta_1 + \text{gender}\beta_2 + \text{race}\beta_3 + \text{NSAID}\beta_4 + \text{smoke}\beta_5 + \text{living}\beta_6 + \text{education}\beta_7 + \text{APOE}\beta_8 + \text{APOE*exposure}\beta_9$
Interaction Model 2: Reduced model $\log(\lambda(t, x, \beta))=\log(\lambda_0(t)) + \text{exposure}\beta_1 + \text{gender}\beta_2 + \text{race}\beta_3 + \text{NSAID}\beta_4 + \text{smoke}\beta_5 + \text{living}\beta_6 + \text{education}\beta_7 + \text{APOE}\beta_8$
$\lambda_0(t)$: baseline hazard function λ: hazard for event and exposure (is occupational exposure to aluminum $\boldsymbol{\beta}_1$: vector of exposure measures (low, medium, high) β_2: gender at baseline (male, female) $\boldsymbol{\beta}_3$: vector of race at baseline (Caucasian, Black, Asian, other) β_4: chronic NSAID use of 2 or more years at baseline β_5: smoking history at baseline (past or current smoker) β_6: living situation at baseline (alone, with another individual) β_7: education at baseline (high school or less, some or more college) β_8: APOE gene at baseline (gene absent, gene present) $\boldsymbol{\beta}_9$: vector of interaction term of APOE and exposure measure

We assessed robustness of the results with sensitivity analyses with models that included marriage history (0=never married, 1=previously of currently married) and baseline cohort data (0=original cohort, 1=expansion of replacement in cohort) as covariates. The proportional hazards assumption was tested by examining potential interactions between covariates and age through Schoenfeld residuals.

All statistical analyses were performed with the use of RStudio version 1.1.447.

RESULTS

Demographics:

The cohort in this study consisted of 4,354 subjects with a median age of 73.7 years at baseline and a median follow up time of 6.4 years. Table 5 depicts demographic information in more detail. Essentially there was a predominance of Caucasians (89.5%), females (58.9%), and some college or more educated (69.4%). Among the cohort population, 51.5% were either past or current smokers and 38.5% were considered chronic NSAID users with at least two years of use at baseline. A majority of the population lived with another individual, which included a spouse, relative, care taker, or at an assisted living facility, and 35.8% of the subjects lived alone. APOE testing was accomplished on 3,788 individuals (87%) of all subjects represented in this data frame with 22.6% positive for the gene. About 44.2% were exposed to copper, and 45.8% were exposed to aluminum.

Table 5: Baseline Characteristics of the Study Participants stratified by exposure groups

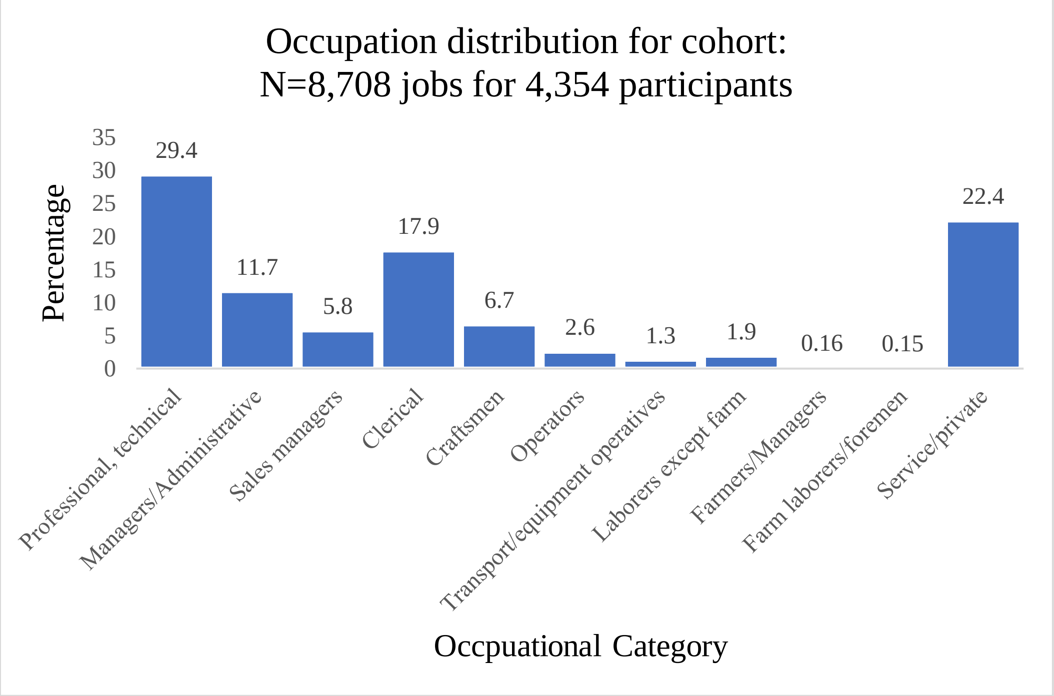
Characteristics	Cohort N= 4,354	Copper Exposure				Aluminum Exposure			
		Unexposed N=2,429	Low N= 966	Medium N=478	High N= 481	Unexposed N=2,358	Low N= 1,003	Medium N=494	High N= 499
Age Median - years (25%, 75%)	73.7 (69.7, 79.1)	73.1 (69.5, 78.2	74.0 (69.7, 79.6)	74.7 (70.2, 80.1)	74.8 (70.4, 80.2)	73.2 (69.4, 78.3)	74.2 (69.8, 79,6)	73.3 (69.6, 78.9)	75.6 (71.1, 80.5)
Original cohort, %	53.5	48.8	56.1	64.0	61.5	48.3	59.0	57.7	62.9
Female, %	58.9	61.1	73.8	46	31	63.4	56.7	54.3	46.7
Race, %									
White	89.5	89	91.6	91.8	85.9	89.1	89.7	91.7	88.2
Black	3.9	4	2.5	2.9	6.4	3.7	4.3	2.2	5
Asian	3.5	3.6	3.1	2.5	4.9	3.9	2.3	3.4	4.4
Other	3.2	3.5	2.8	2.7	2.9	3.3	3.7	2.4	2.4
Never married, %	3.9	4.8	2.6	3.3	2.5	4.5	3.0	4.0	2.8
Some college or more, %	69.4	77.8	65.3	56.9	47.4	77.3	59.7	65	55.7
Past or current smoker, %	51.5	48.4	52.6	55.4	61.1	49.2	54.1	53.8	55.1
Chronic NSAID Use of 2 years or more, %	38.5	38	40.4	38.9	36.4	38	39.8	36.6	39.9
Living alone, %	35.8	36.6	38.9	31.8	29.5	37.4	33	34.8	34.7
APOE, %									
No	64.4	64.2	63	66.7	65.9	63.8	63.9	64.2	68.3
Yes	22.6	22.5	23.2	23	21.8	22.8	22.6	22.7	21.8
Missing	13	13.3	13.8	10.3	12.3	13.4	13.5	13.2	9.8

Among individuals exposed to copper, 50.2% were considered low exposure, 24.8% medium exposure, and 25% high exposure. For participants exposed to aluminum, 50.3% reflected low exposure, 24.7% medium exposure, and 25% high exposure. A majority of the population resembled the cohort demographics as detail in Table 4 for both metals. The median ages for all groups were within a few years of one another and did not represent a large difference. There were also no hard discerptions of individuals tested for the APOE gene in all groups. However, there were a few notable distinctions. For the medium and high exposed copper groups, the population consisted of 46% and 31% female, respectively. Additionally, the high exposed aluminum group consisted of 46.7% female. Another interesting finding was that the unexposed groups for both metals had a lower smoking history than compared to their exposed counterparts. The last interesting aspect of the demographic data among the groups was education. Participants in the unexposed groups presented with a larger percentage of some or more college education at baseline within their subgroup as compared to the exposed groups for both metals.

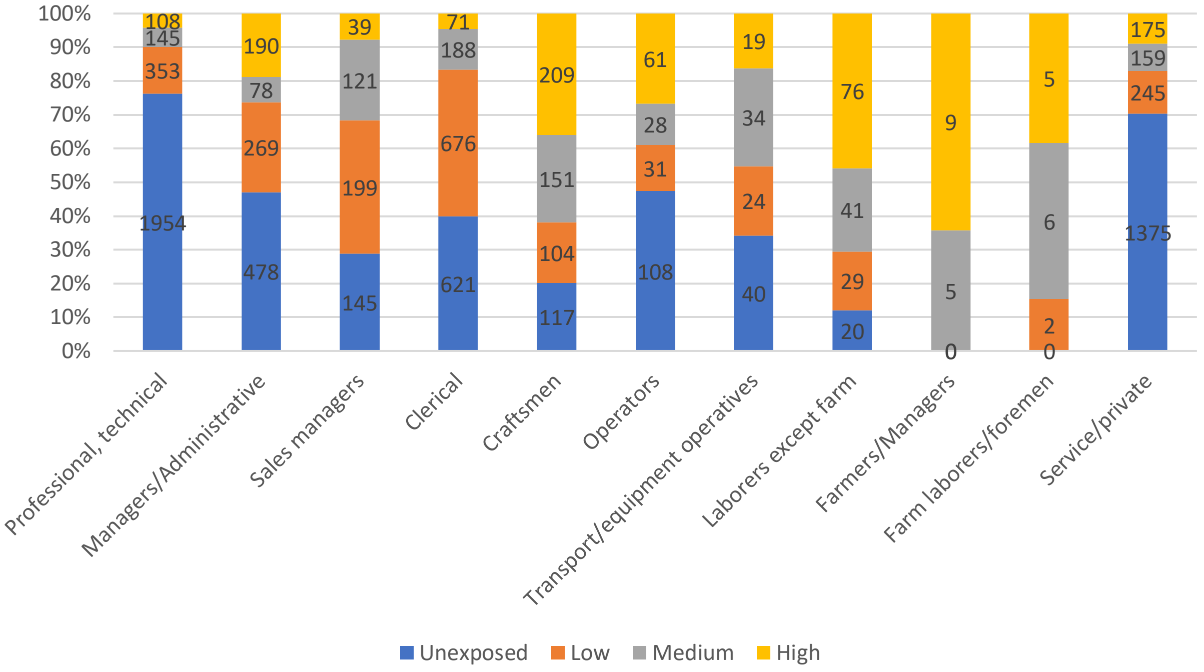
Occupations:

There were a total of 8,708 occupations for 4,354 participants. This was essentially two job titles per participant, which reflected ACT data collection feature of obtaining two longest held jobs participants have held at baseline. Figure 4 illustrates the distribution of occupations for the cohort as well as copper and aluminum exposed positions. A majority of occupations held in the cohort consisted of profession, technical work (29%), which included engineers, scientists, computer technicians, and teachers. The second largest category of jobs was for service and private household workers (22%); homemakers, health aides, custodians, and protective services fell under this category. Individuals exposed to copper and aluminum followed a similar occupational trends as the cohort except that clerical workers represented the largest occupational group, 24% and 22% respectively. Clerical workers comprised of messengers, office machine operators, and administrative workers. Professional, technical workers were the second largest group for both metals.

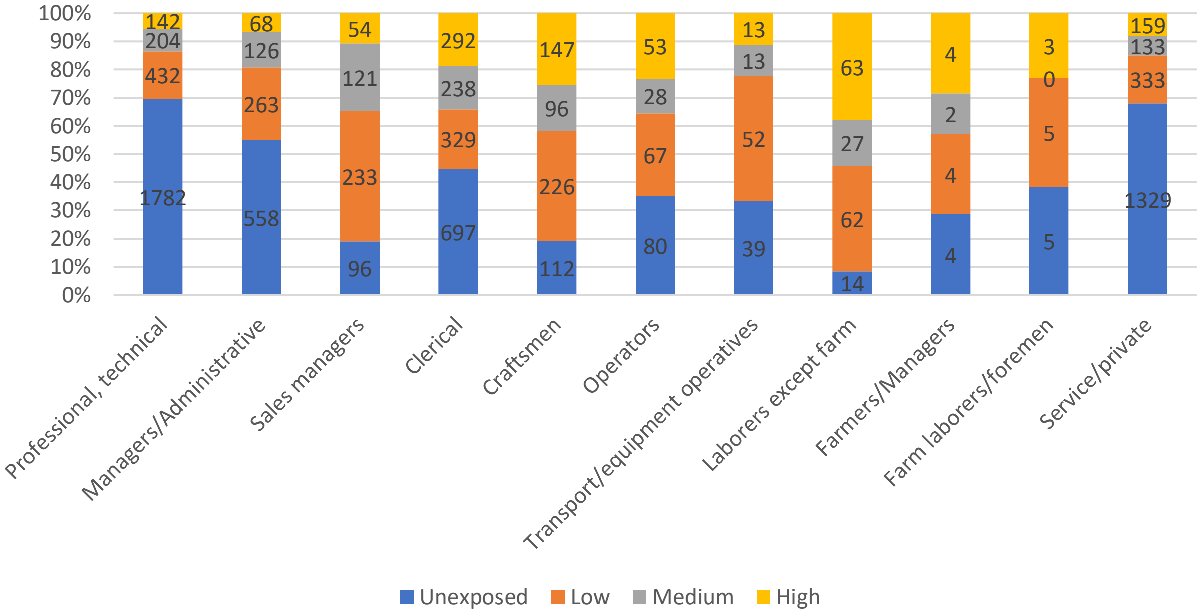
Figure 4: Distribution of occupations



Copper Exposure: Distribution of Occuaptions
N=8,708 jobs for 4,354 participants



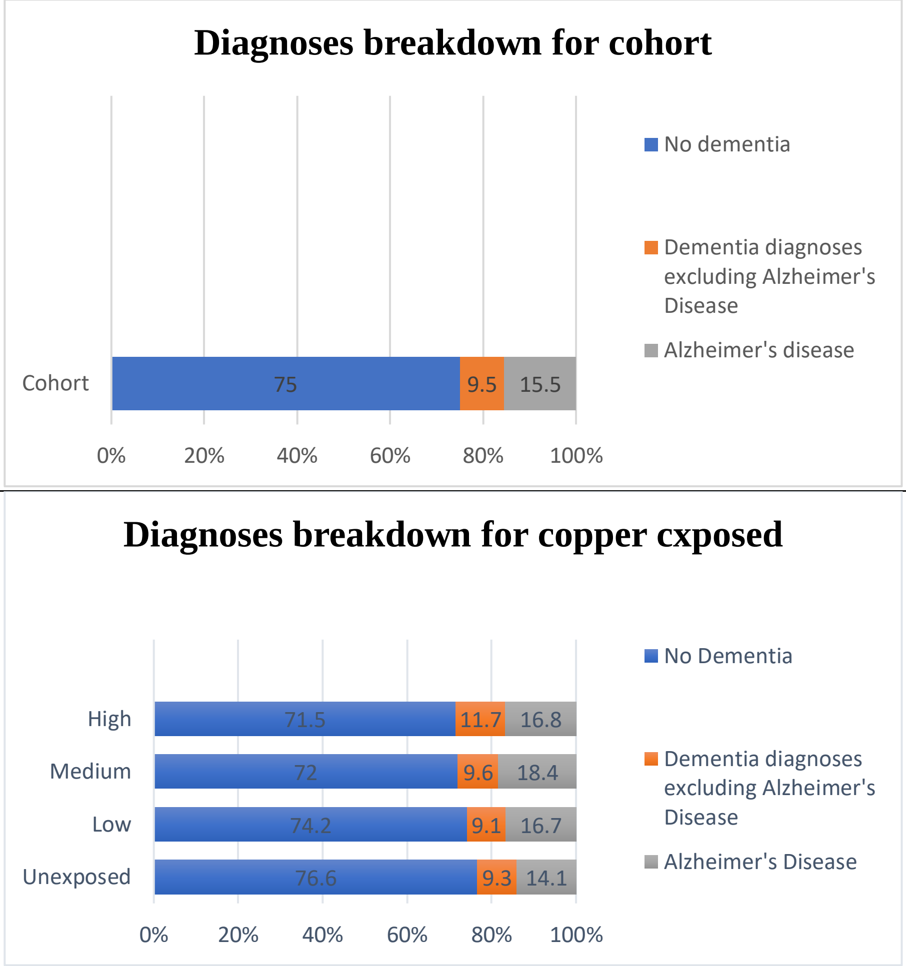
Aluminum Exposure: Distribution of Occuaptions
N=8,708 jobs for 4,354 participants

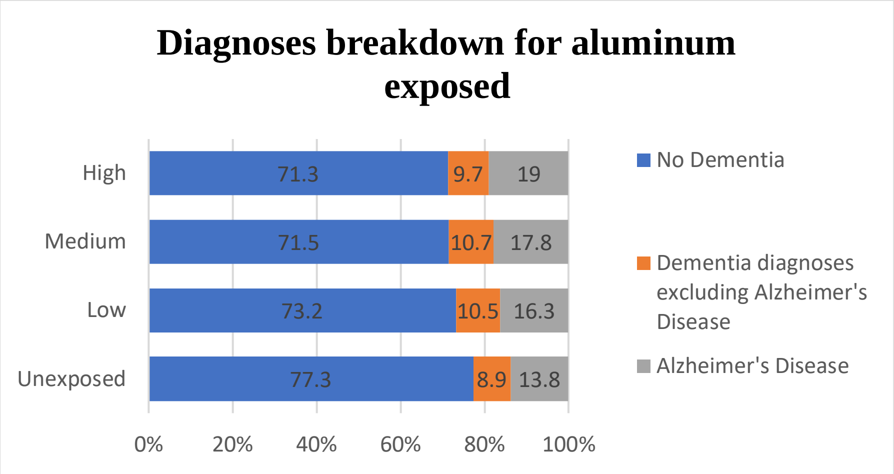


Outcome:

We looked at two different outcomes in this study: all cause dementia versus no dementia and AD versus no AD. All-cause dementia included AD, vascular dementia, substance induced dementia, and any other form of disease inhibiting cognition. At the end of June 2015, 75% of participants did not develop any form of dementia in the cohort, and 15.5% of all-causes dementia were diagnosed with AD as depicted in Figure 5. Among participants with copper or aluminum exposure, the outcome was similar to the cohort's percentages. However, it should be noted that compared to the unexposed groups the corresponding exposed groups had a higher proportion of all-cause dementia.

Figure 5: Diagnoses data stratified by exposure group, %



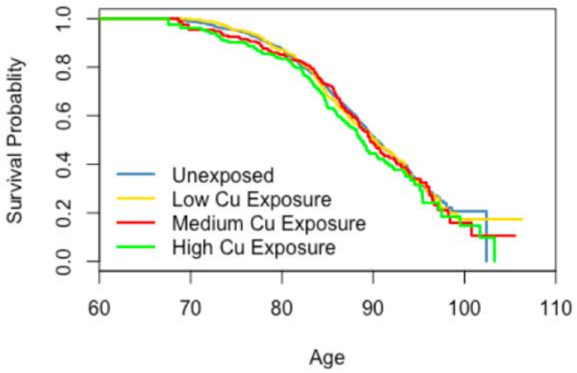


Kaplan Meier Curves:

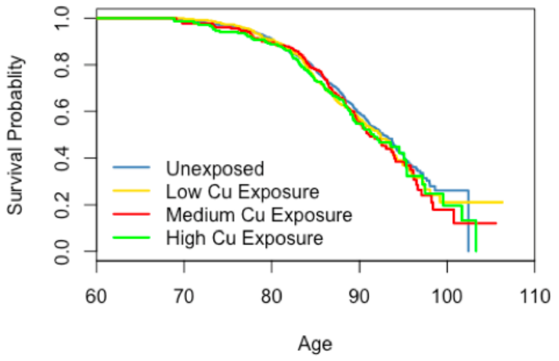
Four different Kaplan Meier (KM) Curves were generated, shown in Figure 6, with a tabular breakdown (supplementary appendix Table A5). As depicted in Figure 5, there were minimal observable variations in the survival probability curves. However, the two curves assessing aluminum exposure demonstrated a visible difference in the survival curve for high exposed groups. The median survival age was 89.6 (95% CI: 88.4-91.3) and 91.3 (95% CI: 89.7-93.9) for high aluminum exposed with an outcome of all-cause dementia and AD, respectively. This does not vary by much when compared with unexposed groups for these categories, 90.9 years (95% CI: 89.2-92.2) and 93.2 (95% CI: 92.1-94.2) respectively. In general, the KM curves allow for visualization of the impact of metal exposure and time until event, all-cause dementia and AD.

Figure 6: Kaplan Meier Curves

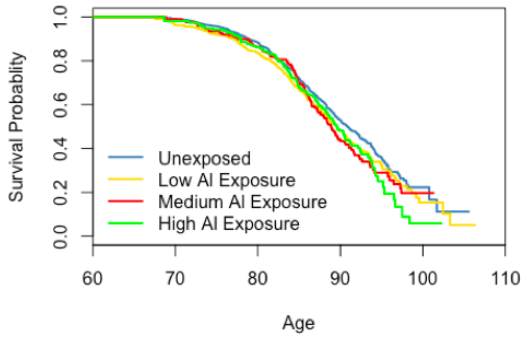
All-cause dementia stratified by copper exposure



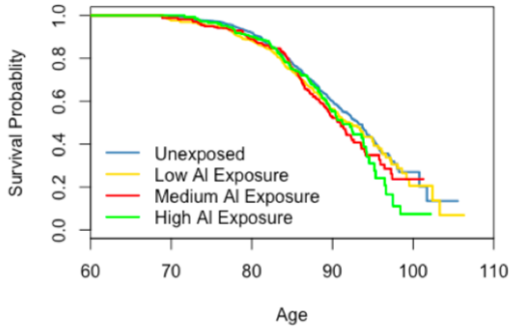
Alzheimer’s disease stratified by copper exposure



All-cause dementia stratified by aluminum exposure



Alzheimer’s disease stratified by aluminum exposure

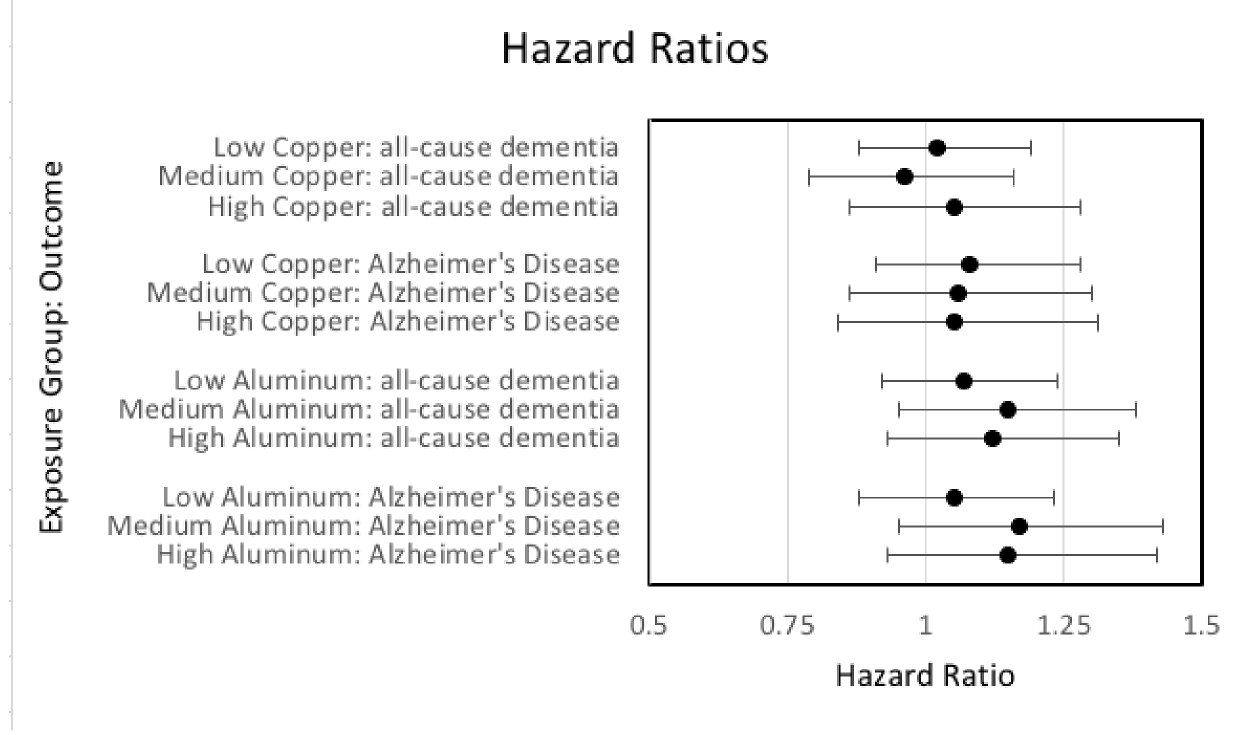


Cox Proportional Hazards Regression:

Associations between exposure for copper and aluminum and the development of all-cause dementia with Model 3, level 2 adjustments, are exhibited in Figure 7. In general, the HR for dementia exceeded 1.0 among the copper exposed groups with the exception of the medium exposed group, which had a HR of 0.96 (95% CI: 0.79-1.16) for all-cause dementia. This was not reflected in the HR for the medium copper group and Alzheimer’s disease, which had a HR of 1.06 (95% CI: 0.86-1.30). Among the aluminum exposed groups, the HR exceeded 1.0 for dementia with both medium and high groups having the a higher HR compared to the low groups. When looking at AD as the event, the medium exposed aluminum group had a HR of 1.17 (95% CI: 0.95-1.43), which was higher than the low group, which had a HR of 1.05 (95% CI: 0.88-1.24). The complete results of analyses to include models 1, 2, and 3 are reported in the supplementary appendix under Table A6.

Schoenfeld residuals plotted to test the proportional hazards assumption are represented in the supplementary appendix, Figure A3. The residuals for exposure groups, low, medium, and high, displayed a relatively horizontal line suggesting the proportional hazard assumption was upheld, and the risk for associated metal exposure and dementia remains proportion through time, which in this case is age. Sensitivity testing with two additional covariates, marital status and ACT cohort type, was used to test the robustness of the results. These covariates did not meaningfully influence the results. Table A6 in the supplementary appendix displays these results.

Figure 7: Hazard Ratios



	All-Cause Dementia			Alzheimer’s Disease		
	Hazard Ratios (95% CI)			Hazard Ratios (95%CI)		
Exposure	Low exposure	Medium exposure	High exposure	Low exposure	Medium exposure	High exposure
Copper	1.02 (0.88-1.19)	0.96 (0.79-1.16)	1.05 (0.86-1.28)	1.08 (0.91-1.28)	1.06 (0.86-1.30)	1.05 (0.84-1.31)
Aluminum	1.07 (0.92-1.24)	1..15 (0.95-1.38)	1.12 (0.93-1.35)	1.05 (0.88-1.24)	1.17 (0.95-1.43)	1.15 (0.93-1.42)

Adjusted for baseline gender, race, smoking status, NSAID use for at least 2 years, living situation, and education, n=4,354

DISCUSSION

In this elderly population-based cohort, this study found occupational exposures to copper or aluminum was associated with a wide range of evidence suggestive for both protective and adverse outcomes. These findings were stable through sensitivity analysis. Previous environmental studies have implicated these metals as a risk factor for dementia (Bondy, 2017) (Vaz, 2017). Unfortunately, this study was unable to find consistent evidence of an association between copper or aluminum and dementia incidence. This study is one of the first to assess occupational exposure to copper or aluminum through a JEM and association to dementia. Furthermore, this is the first study to leverage the ACT study data for an occupational exposure assessment to copper or aluminum and relationship with dementia.

ACT study has a large cohort with 4,354 participants analyzed in the study. For each individual, two of the longest held job positions along with duration in occupation as well as start and end date in that job were consistently reported for most participants totaling 8,708 jobs. ACT study participants were excluded if they had signs of dementia or were younger than 65 years of age at baseline. These exclusion criteria can prove difficult when determining the impact of occupational exposures. Individuals who may have had higher exposures to copper or aluminum earlier in life, may have developed AD prior to the age of 65 years, in which case those individuals would have been excluded in this study. Future research could focus on a cohort that captures dementia cases at younger ages or perhaps utilizes an occupation-based cohort. In addition, studies could consider initial dates of exposures to both metals in order to better assess latency of dementia diagnosis or to better capture individuals with earlier exposures in life.

This study found occupational exposure to copper or aluminum resulted in varying HR for dementia. However, when comparing the confidence intervals (Figure 7), there is more weight on values above one. For example, when looking at the HR for high aluminum and AD development, the confidence interval is 0.93-1.43. This indicates the risk for dementia for these exposed individuals can reach as high as 43% increase. In contrast, the lower limit drops to about 7% less risk. This range may not be significant, but it can be meaningful for potential opportunities to minimize all risk factors for dementia development.

The trend across exposure levels did not suggest a monatomic dose-response. When comparing low to medium to high exposure groups the HR fluctuated favoring a trend of increased HR from low to high exposure; however, this was not representative of the medium exposure group, which would at times have lower HR than low exposure and higher HR than high exposure groups. This discrepancy is apparent in Figure 7. There are a few explanations for this inconsistency. The first being in which the groups were created. Categorizing the exposures into three groups caused the distinction across individuals in the same group to be lost. All values in the low exposure group are treated equally regardless if there was an extremely low or high value. This holds true for the other two groups, medium and high, as well. The wide range of values may have impacted the medium group when compared to that of the low exposed groups. However, in general, the HR for the medium exposed group is higher than the high group. For both metals, there appears to be a few significantly higher values that may have lost their importance once categorized. Given the inconsistent progression of HR from the low to medium to high groups, a trend based on exposure levels cannot reliably be generalized from this study. A solution to potentially combat this discrepancy could have included treating the exposure variable as continuous versus categorical.

An additional observation noted in this study regarding the exposure variable is the values to which copper and aluminum were categorized. As evident in Table 2, the median FWI-years for aluminum were almost double than that of copper. For example, the median for copper’s median FWI-years was 3.3 and for aluminum it was 6.5. This trend is similar for the 3rd quartile as well with the median FWI-years being 9.9 and 16.7 for copper and aluminum, respectively. This suggests the that HR for the categorized exposures should be interpreted differently. Essentially to achieve the HR as seen in Figure 7, the exposure variable for aluminum had to be almost twice as much as for copper. This could be carried out as either higher exposures or longer duration periods of exposure to aluminum. This is important when assessing the actual level of exposures and the effects.

Another important observation is the impact certain variables had on the HR. The HR markedly decreased when adjustment for living situation and education were considered as seen in the supplementary appendix Table A6. This decrease occurred across all of the exposure groups, which suggests the additional adjustment of covariates was an important factor to consider. Both of these covariates could have acted as confounders in this study. From Table 5, years of education appears to be indirectly related to increasing exposure group for both metals with some or more college decreasing in higher exposed groups as compared to the unexposed groups. Additionally, there have been some studies that have demonstrated an association between lower educated individuals with dementia (Schoenhofen Sharp, 2012). Living situation may have also played a role as a confounder given the trend for living alone generally decreased as exposure level increased as compared to the unexposed group as seen in Table 5. Living situation could have also impacted when the diagnosis of dementia was made. These factors could explain the notable decrease in HR once these covariates were adjusted.

This study did not control for environmental exposures to these metals. This decision was based predominantly on the lack of appropriate data to analyze this variable. However, the exposure determination in this study is based off a JEM that concluded occupational exposures only occurred if it was above the ambient environment (Siemiatycki, 2018). It can also be safely assumed that occupational exposures would be much higher than environmental exposures resulting in negligible values (Roels, 1999). For these reasons environmental exposures were not addressed in this study.

Utilization of CANJEM to quantify exposures was an important aspect of this study. CANJEM in itself goes beyond simply assigning an exposure based on job code. In contrast, it used expert opinion to assess validity of exposure and to what intensity occupations were exposed. This approach allowed for richer exposure information and provided better exposure quantification. Comparatively to a binary self-reported exposure variable, this study helped to minimize reporting and response biases of self-identified exposures. The ability to convert all ACT study participant data from the IPUMS codes to a six-digit SOC code for CANJEM use was also helpful for lowering potential misclassification bias through a more accurate ascertainment of job titles. However, the exposure CANJEM agent used in this study incorporated all forms of exposure to copper or aluminum to include dermal and inhalation. It is expected that the exposure experienced through dermal contact would result in negligible systemic exposures as compared to inhalatory exposures, which could resulted in systemic absorption and directly impact the central nervous system through entrance from the olfactory neuron tract (Sunderman Jr, 2001). Future studies will benefit from data that exclusively considers inhalatory exposures.

An important limitation for this study predominantly relate to the assessment of the exposure variable. An important factor is the lack of probability consideration in terms of the exposure variable. CANJEM provided a probability of exposure for each job title, which was not considered in the overall calculation of the exposure variable, median FWI-years. Moreover , CANJEM recommendations to include exposure assessments only if there was a minimum of 10 individual jobs for each occupation, which was ignored in this analysis. Instead CANJEM data was used for all occupations regardless if there was only one job or ten jobs in a specific occupation; this factor lowered the resolution of the JEM data. Another aspect of the JEM in which resolution was lost was the time period used for accessing CANJEM data; this study utilized CANJEM's single time period of 1920-2005 versus the divided time periods with varying exposures depicting more accurately the exposure experienced for certain time periods. The single time period does not interpret evolving exposure levels that the two time periods (1920-1969 and 1970-2005) or four time periods (1920-1949, 1950-1969, 1970-1984, 1985-2005) would otherwise consider. Furthermore, the exposure variable in this study was categorized in comparison to being treated as a continuous variable. This decision possibly resulted in less information that would have been evident if the variable was treated as continuous. For example, the potential trend of lower exposure values to higher exposure values may have been more evident if the exposure variable was treated as continuous. Lastly, using a JEM, can subject the analysis to some degree of Berkson error. This error is most likely minimal when compare to the alternative of using self-reported exposures to copper and aluminum. The supplementary appendix, Tables A7 and A8, demonstrates that about 25% of participants who self-reported an occupational exposure to copper or aluminum were found to not have an exposure according to their job title as evident in CANJEM quantification of exposures. Utilizing of CANJEM combated this potential misclassification that may have occurred if self-reported data was exclusively used.

Our results found little evidence that copper or aluminum increased the risk of dementia. Future research for this cohort could consider additional occupational exposures, positions, or even stressors and association to dementia given that most participants reported the two longest held positions in their careers at baseline. Additional studies could better quantify exposures by determining exact levels of copper and aluminum presence in high exposure jobs and relation to dementia incidence or utilizing the probability assessment from CANJEM into exposure calculations.

CONCLUSION

This study is one of the first to use a JEM to quantify occupational exposures to metals and dementia. CANJEM provided exposure estimates expressed in median FWI-years, which was used to determine the association between copper or aluminum and dementia diagnosis. This study evaluated both metals independently to determine the HR for development of all-cause dementia and AD. It was found that there is an increased HR for exposed participants compared to unexposed though the results were not significant. Future research will benefit from furthering exposure quantification and validity. However, given the findings in this study, preventive measures could be considered to address high occupational exposures to these metal.

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SUPPLEMENTARY APPENDIX

Table A1: Occupational History Questionnaire excerpt

1.0 What was your employment status during most of this year?

- Employed
- Homemaker
- Retired
- Disabled
- Unemployed, seeking work
- Unemployed, not seeking work
- Don't know

1.1 What was or is your usual occupation or job title (the one you've worked at for the longest)?
1.2 What were your duties?
1.3 Type of company/department:
1.4 Years in this job:
1.5 Dates in this job:
1.6 The second longest job or occupation:
1.7 What were your duties?
1.8 Type of company/department:
1.9 Years in this job:
1.10 Dates in this job:

Table A2: Occupational Substances Questionnaire excerpt

2.0 I am going to give you a list of substances. Did you work with any of them on a regular basis (e.g., at least once per week) in any job lasting one year or more?

Substance	Yes (1)	No (0)	? (9)	Beginning Year	Duration, Years
Ammonia					
Etc.					

Table A3: IPUMS codes converted to SOC 2010 with additional research				
IPUMS Code: Job title	SOC 2010 code: job title	Number of jobs converted from IPUMS to SOC	Copper median FWI	Aluminum median FWI
77: health technologists/technicians/ assistants	39-9099: personal care and service workers, all other	2	0	0
200: managers/ Administrative except farms workers	11-3011: administrative service managers	2	0.075	0.25
206: managers/ Administrative except farms workers	11-3011: administrative service managers	1	0.075	0.25
241: managers/ Administrative except farms workers	11-3011: administrative service managers	2	0.075	0.25
247: sales workers	11-3011: administrative service managers	1	0.075	0.25
256: Sales workers	11-3011: administrative service managers	1	0.075	0.25
300: clerical workers	43-4151: order clerks	5	0	0
500: mechanics and repair workers	49-9071: maintenance and repair workers, general	1	0	0.125
600: operative except transport	51-4190: miscellaneous metal and plastic workers	2	0	0
757: Laborers except farm	37-3011: landscaping and grounds keeping workers	1	0	0
888: retired/homemaker/ unknown	39-9099: personal care and service workers, all other	1,113	0	0
999: Homemaker/ unknown	39-9099: personal care and service workers, all other	11	0	0

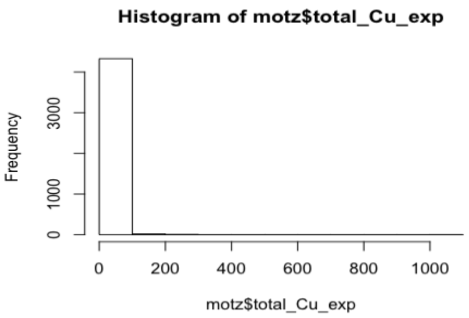
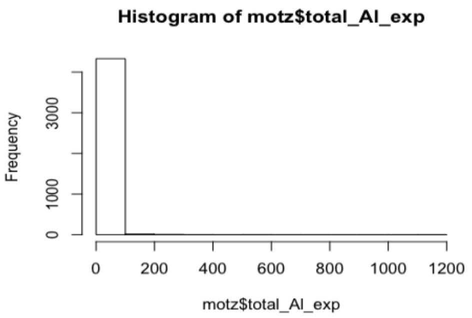
Figure A1: Histogram plot	
Copper median FWI-years	Aluminum median FWI-years
	

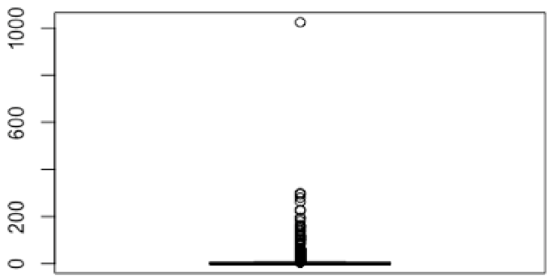
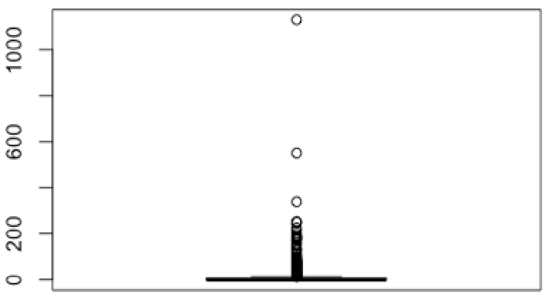
Figure A2: Boxplot	
Copper median FWI-years	**Aluminum median FWI-years**
	

Table A4: Likelihood ratio: testing interaction	
Exposure: Outcome group	Test statistic
Copper: all-cause dementia	0.30
Copper: Alzheimer’s disease	0.45
Aluminum: all-cause dementia	0.54
Aluminum: Alzheimer’s disease	0.52

Table A5: Kaplan Meier tabular data summary					
		All-cause Dementia		Alzheimer's Disease	
Comparison Groups	At risk-No	Events-No	Median Survival time-yrs (95%CI)	Events-No	Median Survival time-yrs (95%CI)
Copper Assessment					
Unexposed	2,429	568	90.3 (89.6-91.2)	447	92.7 (91.6-94.0)
Low Copper exposure	966	423	90.2 (88.9-92.1)	208	92.4 (90.6-93.7)
Medium Copper Exposure	478	216	89.7 (88.4-92.3)	116	91.0 (89.7-94.0)
High Copper Exposure	481	207	88.7 (87.3-90.5)	105	91.7 (89.3-95.3)
Aluminum Assessment					
Unexposed	2,358	535	90.9 (89.9-92.2)	432	93.2 (92.1-94.2)
Low Aluminum exposure	1,003	269	89.5 (88.3-90.8)	212	92.1 (90.4-93.9)
Medium Aluminum exposure	494	141	88.9 (87.5-90.6)	115	91.0 (89.3-93.5)
High Aluminum Exposure	499	143	89.6 (88.4-91.3)	117	91.3 (89.7-93.9)

Table A6: Risk of Incident dementia associated with exposures to copper and aluminum

	All-Cause Dementia			Alzheimer’s Disease		
	Hazard Ratios (95% CI)			Hazard Ratios (95%CI)		
Copper Exposure	Low exposure	Medium exposure	High exposure	Low exposure	Medium exposure	High exposure
Model 1[*]	1.05 (0.90-1.21)	1.02 (0.84-1.23)	1.15 (0.95-1.38)	1.10 (0.94-1.30)	1.11 (0.90-1.36)	1.11 (0.90-1.38)
Model 2[**]	1.05 (0.90-1.24)	0.99 (0.82-1.20)	1.12 (0.92-1.35)	1.10 (0.91-1.30)	1.09 (0.89-1.34)	1.11 (0.89-1.32
Model 3[***]	1.02 (0.88-1.19)	0.96 (0.79-1.16)	1.05 (0.86-1.28)	1.08 (0.91-1.28)	1.06 (0.86-1.30)	1.05 (0.84-1.31)
Sensitivity Analysis#	1.02 (0.89-1.19)	0.96 (0.79-1.16)	1.04 (0.86-1.27)	1.08 (0.91-1.27)	1.07 (0.87-1.32)	1.04 (0.84-1.30)
Aluminum Exposure	Low exposure	Medium exposure	High exposure	Low exposure	Medium exposure	High exposure
Model 1[*]	1.13 (0.97-1.30)	1.18 (0.98-1.42)	1.18 (0.98-1.42)	1.09 (0.92-1.29)	1.18 (0.96-1.46)	1.20 (0.97-1.47)
Model 2[**]	1.10 (0.95-1.28)	1.18 (0.98-1.42)	1.16 (0.97-1.40)	1.08 (0.92-1.28)	1.19 (0.97-1.47)	1.19 (0.97-1.47)
Model 3[***]	1.07 (0.92-1.24)	1..15 (0.95-1.38)	1.12 (0.93-1.35)	1.05 (0.88-1.24)	1.17 (0.95-1.43)	1.15 (0.93-1.42)
Sensitivity Analysis#	1.07 (0.92-1.24)	1.15 (0.95-1.38)	1.12 (0.93-1.35)	1.05 (0.89-1.24)	1.17 (0.95-1.44)	1.16 (0.94-1.42)

*Model 1: crude variable with no adjustment, n=4,354

**Model 2: adjusted for gender, race, baseline smoking status, and baseline NSAID use for at least 2 years, n=4,354

***Model 3: further adjusted for baseline living situation, and baseline education, n=4,354

#Sensitivity analysis: further adjusted for baseline cohort status and marital status, n=4,354

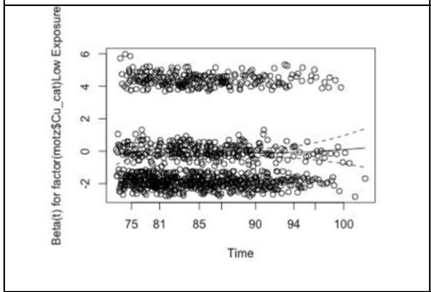
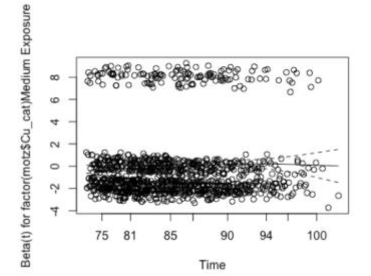
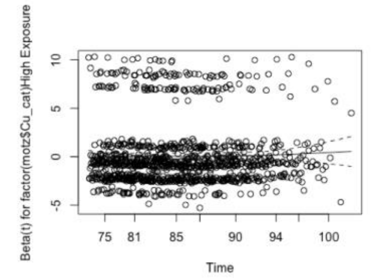
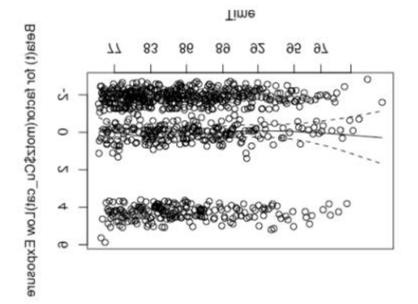
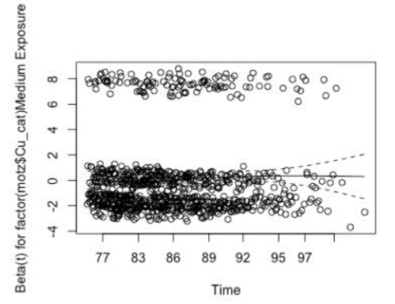
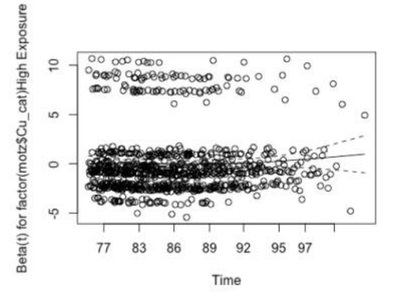
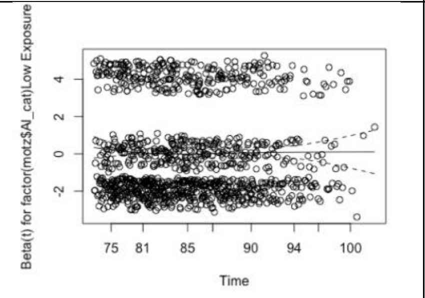
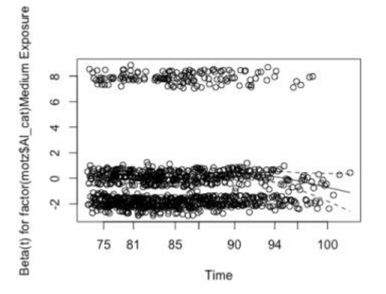
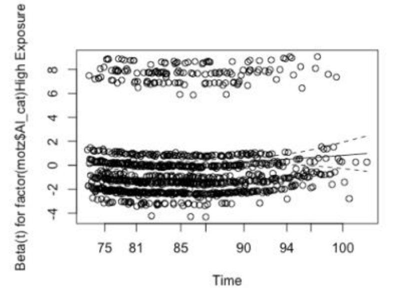
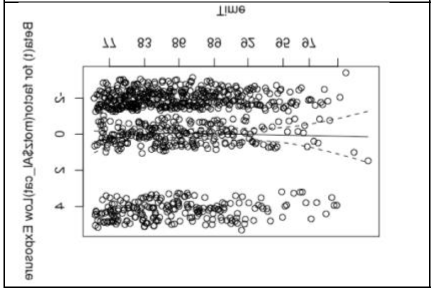
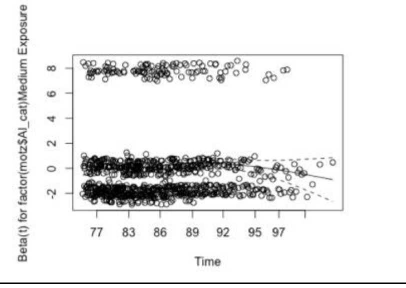
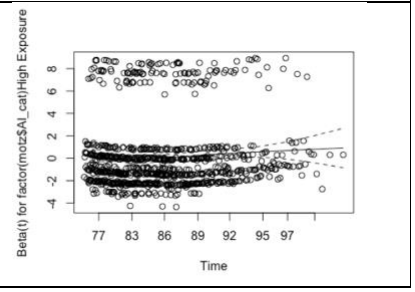
Figure A3: Schoenfeld residuals		
Model 3: Low copper and all-cause dementia	Model 3: Medium copper and all-cause dementia	Model 3: High copper and all-cause dementia
		
Perfect 3: Low copper and Alzheimer's disease	Model 3: Medium copper and Alzheimer's disease	Model 3: High copper and Alzheimer's disease
		
Model 3: Low aluminum and all-cause dementia	Model 3: Medium aluminum and all-cause dementia	Model 3: High aluminum and all-cause dementia
		
Perfect 3: Low aluminum and Alzheimer's disease	Model 3: Medium aluminum and Alzheimer's disease	Model 3: High aluminum and Alzheimer's disease
		

Table A7: Copper Self-reported exposure compared to CANJEM quantified groups

Self-reported	Unexposed	Low	Medium	High
No exposure	1633	734	367	371
Yes exposure	23	14	27	37
Exposure unknown	197	55	33	23
Not reported	576	163	51	50

Table A8: Aluminum Self-reported exposure compared to CANJEM quantified groups

Self-reported	Unexposed	Low	Medium	High
No exposure	1581	754	374	365
Yes exposure	24	43	22	43
Exposure unknown	187	63	33	25
Not reported	566	143	65	66