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A Longitudinal Study of Polychlorinated biphenyls and Neuropsychological Function Among Older Adults from New York State

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Abstract

Background: Cross-sectional studies have linked greater polychlorinated biphenyl (PCB) exposure to adverse neuropsychological effects in older adults, including learning, memory, and depressive symptoms. However, no studies among older adults have evaluated the association over time.

Objectives: To assess the effect of serum PCB levels on neuropsychological function over a 14-year period in a cohort of older men and women from a PCB-contaminated area of New York State.

Methods: In 2000–2002, we assessed serum PCB levels and neuropsychological function (including the California Verbal Learning Test Trial 1 (CVLTT1) for verbal memory and learning, and the Beck Depression Index (BDI) for depressive symptoms) in 253 men and women, ages 55–74 years. A total of 116 (46%) persons repeated the PCB and neuropsychological assessment 14 years later. To assess the association over time, we used generalized estimating equations with clustering variables time, total PCB (PCB), and PCB×time, and adjusted for baseline age, sex, smoking, and total serum-lipids. For statistically significant PCB×time interactions, we evaluated the association between PCBs and either verbal memory and learning or depressive symptoms while holding PCB constant at the 10th and 90th percentiles to clarify the direction of the interaction.

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Results: Over the study period, serum PCB levels (wet-weight) declined by 22%, and were associated with different patterns of change over time for memory (PCB×Time $\beta=0.08$ $p=0.009$) and depressive symptoms (PCB×Time $\beta=-0.16$ $p=0.013$). Specifically, verbal memory and learning decreased ($\beta=-0.08$ $p=0.008$) and depressive symptoms increased ($\beta=0.17$ $p=0.008$) among persons with low exposure (PCB levels at the 10th percentile), while persons with high exposure (90th percentile) showed non-significant improvements.

Discussion: In this cohort, declining PCB levels were likely due at least in part to low rates of local fish consumption in recent decades, given the ban since 1976. The decreased verbal memory and learning and increased depressive symptoms over time among persons with low serum PCB levels is consistent with studies of normative aging. However, the small improvements in those outcomes among those with high serum PCB levels was unexpected. Healthy survivor selection bias or uncontrolled confounding may explain this result. It may also indicate that the neurotoxic impacts of PCBs in older adults are not permanent, but future studies are needed to confirm this possibility.

Introduction

Polychlorinated biphenyls (PCBs) are a class of persistent organic pollutants, consisting of 209 synthetic congeners (ATSDR 2000). They were widely used in electrical capacitor and transformer manufacturing due to their high heat stability until banned in the U.S. in 1977 (ATSDR 2000). As legacy pollutants, PCBs remain environmental concerns decades after their manufacturing ended. They are highly persistent in both the environment and humans, bioaccumulating and biomagnifying through food chains (ATSDR 2000). In the general population, consumption of contaminated lipid-rich food, such as fish and meats (Gunderson, 1995), and inhalation of contaminated dust are the primary exposure routes (ATSDR 2000).

PCBs are a known neurotoxicant from animal experiments (Tilson and Kodavanti, 1998). Their neurotoxicity in humans has primarily been studied in children (Berghuis et al., 2015); less research focuses on adults 55 years and older. Compared to younger adults, metabolism of PCBs may be slower in older adults. With age, P450 isoenzymes necessary for PCB biotransformation have reduced activities (Kinirons and O'Mahony, 2004). High past exposure, ongoing lifetime cumulative exposure, and bio-persistence has led to older generations experiencing the highest PCB burden (Sjodin et al., 2014). Older adults also experience a decline in nervous system function, including neuronal loss and decreased protective capability of the blood-brain barrier; this aging process compromises the nervous system and leaves it vulnerable to xenobiotics (Risher et al., 2010). Therefore, like children, older adults also may be particularly vulnerable to PCB-induced neurotoxicity.

In our earlier work, we found that PCBs were associated with lower verbal memory and learning and more symptoms of depression among adults 55 to 74 years of age, even at levels of exposure that were only 25% greater than that of the general US population (Fitzgerald et al., 2008). This finding confirmed one prior study (Schantz et al., 2001), and subsequent studies also have reported neuropsychological effects (Bouchard et al., 2014; Fimm et al., 2017; Haase et al., 2009). Results from all previous studies appeared to be sex-

specific and findings for specific neuropsychological domains were not always consistent across studies. Most importantly, all prior studies were limited by cross-sectional designs (Bouchard et al., 2014; Fitzgerald et al., 2008; Haase et al., 2009; Schantz et al., 2001).

To address this research gap we conducted a longitudinal study by following-up the men and women in our earlier work (Fitzgerald et al., 2008) and re-assessing the association between serum PCB levels and neuropsychological function over a 14-year period. Based on our cross-sectional findings, we focused on verbal memory and learning and on symptoms of depression. Specifically, we hypothesized that higher serum PCB levels would be associated with lower scores on tests of verbal memory and learning, and more symptoms of depression over time. Specifically, we predicted that persons with higher serum PCB levels would exhibit a greater decline in verbal memory and learning and a greater increase in symptoms of depression than those with lower serum levels.

Methods

Study Population

In 2000–2002, we studied community-dwelling men and women from communities along the upper Hudson River in New York State (NYS). These communities were chosen because they were historically exposed to high levels of PCBs arising from two local capacitor plants that used PCBs and subsequently contaminated that portion of the Hudson River. Full sampling and recruitment procedures were previously described in detail (Fitzgerald et al., 2008). Briefly, we identified 2,704 persons, ages 55–74, living in the study region through multiple databases. A random sample was contacted, screened and invited to participate. A total of 253 persons (40% of those eligible and invited) participated. In 2014–2016, we traced the original 253 persons and invited them to participate in this follow-up study. Exclusion criteria included stroke, severe head injury, or diagnosis of any neurodegenerative disease since these conditions may preclude completion of the full neuropsychological assessment. Data collection occurred at a local urgent care facility. All protocols were approved for human subject protection by the University at Albany, State University of New York Institutional Review Board.

Interview and Neuropsychological Assessment

We conducted in-person structured interviews to obtain personal medical history, family history of neurological disorders, medication and supplement use, diet, tobacco, alcohol and caffeine use, and physical activity. All survey data was entered in real time into REDCap, a secure, online questionnaire and database with built in quality control features (Harris et al., 2009). Licensed neuropsychologists administered a battery of neuropsychological tests (NPTs). The California Verbal Learning Test (CVLT) and Wechsler Memory Scale (WMS) evaluated verbal memory and learning (Delis et al., 2000; Russell, 1975). The Trail Making, Stroop, and Wisconsin Card Sorting Tests assessed executive function (Reitan and Wolfson, 1993; Trenerry et al., 1993). The Block Design Test assessed visuospatial ability, the Digit Symbol Coding Test assessed visuomotor speed and attention (Wechsler, 1981), and the Grooved Pegboard Test assessed visuomotor coordination and visual-spatial orientation (Klove, 1963). Reaction time, Static Motor Steadiness (SMS), and Finger Tapping Tests

were used to assess motor function (Lezak et al., 2012). Finally, the Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI) assessed affective state (Beck et al., 1961; Spielberger et al., 1970). A full list of individual tests assessed is in Supplemental Table 2.

Based on our prior cross-sectional findings for verbal learning and memory and symptoms of depression, the primary outcomes of interest were the CVLT Trial 1 score and the BDI, respectively. The CVLT Trial 1 score is the raw number of words recalled during a first attempt, from a verbally given list. The BDI score is the raw number of depressive symptoms reported on the self-administered BDI instrument. All other NPTs were considered secondary outcomes.

PCB and Lipid Analysis

Serum analysis for baseline PCB and lipid levels (2000–2002) were previously described (Fitzgerald et al., 2008). Briefly, 30 serum PCB congeners (PCB - 28, 52, 60, 66, 74, 99, 101, 105, 110, 118, 130, 138, 146, 153, 156, 167, 170, 172, 177, 178, 180, 183, 187, 193, 194, 199, 201, 203, 206, and 209), accounting for 95% of total serum PCBs in humans (Humphrey et al., 2000), were measured using dual capillary gas chromatography with microelectron capture, and cholesterol and triglycerides were measured enzymatically. The limit of detection (LOD) was 0.02 ng/mL; all congeners had 50% detection rates. Values < LOD were set to LOD/ 2).

At follow-up (2014–2016), twenty-five mL of venous blood was drawn by licensed nurses using Teflon-free, EDTA-free evacuated glass tubes, and centrifuged immediately. The resulting serum was transported on ice to the New York State Department of Health Wadsworth Center in Albany, NY, where they were frozen at -80°C within 48 hours. Serum was analyzed for the same 30 PCB congeners measured at baseline using gas chromatography isotope dilution high resolution mass-spectrometry (GC-HRMS) (Fitzgerald et al., 2012). One-gram serum samples were randomly assigned to 30-sample batches that included 3 blanks and 2 quality-control standards (standard reference material (SRM) 1958). Internal standards were spiked for all target PCBs, negating matrix matched calibration. The LODs ranged from 0.001 to 0.0025 ng/mL. For quantitation of PCBs, 10–11-point calibrations curves, ranging 0.01–50 ng/mL were used. Triglycerides and cholesterol were measured enzymatically using the Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN USA).

Follow-up PCB values < LOD also were substituted with LOD/ 2. We recognize that current methods suggest that imputing values < LOD with a constant may introduce bias (Schisterman et al. 2006). This procedure was necessary, however, to ensure the comparability of the follow-up PCB data with those of the baseline study. The average detection rate over all congeners at baseline was 74%, and ranged from 22%–99%. In contrast, the average detection rate at follow-up was 89%, ranging from 33% to 100% due to use of newer methods with lower LODs. Therefore, comparisons between time points may be limited at the lowest PCB levels. We used the Philips' formula to calculate both total lipids for use as a covariate, and for lipid-standardized PCB levels (Phillips et al., 1989).

Total (Σ) PCB levels (ng/g wet-weight and ng/g lipid-weight) were calculated by summing all 30 congeners.

Statistical Analysis

Univariate and Bivariate Analysis—PCB levels natural-log-transformed to approximate a normal distribution and reduce the influence of extreme observations (Kutner et al., 2005). Univariate analyses were conducted to examine the distribution and summary statistics of PCBs, NPTs, and potential covariates. To estimate change in PCBs, we calculated both the absolute difference ($x_1 - x_0$) and relative difference ($=(x_1 - x_0)/x_0$) in values between baseline (x_0) and follow-up (x_1). To estimate physical activity level, total weekly hours spent doing moderate and harder activities was summed and dichotomized on the median to limit measurement error since our internal reliability testing suggested reported intensities may have low reproducibility. Changes in demographic variables and PCBs over time were evaluated using paired t-tests. In bivariate analyses, we assessed associations between all exposures, outcomes, and potential covariates using frequency tables, t-tests, correlations, and analysis of variance. All statistical analyses were conducted in SAS v9.4 (SAS Institute Inc., 2018). We assessed statistical significance as 2-tailed p-values ≤ 0.05 .

Loss to Follow-up—We assessed differences between those who participated in 2014–2016 interviews (“completers”) and those lost to follow-up (“dropouts”) to evaluate potential selection bias. Differences in demographic characteristics by dropout status (yes/no) were assessed using t-tests and the chi-squared test for independence. Since crude comparisons of PCB levels and NPTs by dropout status may be misleading, we calculated confounder-adjusted least squared means using linear regression. Mean PCB levels were adjusted for age and total lipids (Phillips et al., 1989; Xue et al., 2014), and mean NPTs were adjusted for age, sex, and education (Lezak et al., 2012).

Multivariable Analysis—To assess the associations between PCB levels and NPTs over time, we used marginal models fitted using generalized estimating equations (GEE) with robust standard errors (Zeger et al., 1988). Regression terms included baseline age, continuous time, PCB levels at each time point, and $\text{PCB} \times \text{time}$ (Morrell et al., 2009), where time, PCB, and $\text{PCB} \times \text{time}$ are clustering variables. Confounders were identified via literature and construction of directed acyclic graphs (Greenland et al., 1999); they included sex, smoking, and total serum lipids (Bouchard et al., 2014; Morrell et al., 2009; Schantz et al., 1999). For regressions assessing affective state, antidepressant use was also included as a confounder since it may impact anxiety and depression levels. The tests of our primary hypotheses were the $\text{PCB} \times \text{time}$ interactions for the CVLT Trial 1 and the BDI, since we predicted that changes over time in verbal memory and learning and in depressive symptoms would differ according to serum PCB levels. For statistically significant $\text{PCB} \times \text{time}$ interactions, we also calculated simple slopes (e.g. holding PCB levels constant) to aid interpretation. Specifically, we calculated the change over time holding PCB levels constant at the 10th and 90th percentiles to compare those with high versus low exposure, setting the covariates at their means. Since prior literature indicates there are differences in PCB-induced neuropsychological changes between relatively younger versus older persons,

and men versus women (Bouchard et al. 2014), we assessed also stratified results by age and sex.

First we conducted a complete-case only analysis, then adjusted for loss to follow-up using stabilized inverse probability-of-attrition weighting (SIPW) (Cole and Hernán, 2008). SIPWs are a form of propensity score adjustment where each subject in the current sample is assigned a weight to approximate the original sample (Cole and Hernán, 2008). To derive SIPWs, a logistic regression model with “dropout” as the dependent variable was assessed in relation to age, sex, smoking, diabetes, physical activity, PCB levels, total lipids, and the corresponding baseline NPT score as the independent variables (Baumgart et al., 2015; Weuve et al., 2012). To derive SIPWs for the affective state outcomes (e.g. depression and anxiety), independent variables included age, sex, education, comorbidity polypharmacy score, antidepressant use, PCB levels, total lipids, and the respective baseline affective state test score (Djernes, 2006; Stawicki et al., 2014). Predicted values from these logistic models then were used to estimate the probabilities of dropout for each subject, the inverse of which were incorporated as weights in the GEE analysis. The results of this procedure are statistical estimates of what the findings may have been without any loss to follow-up.

Sensitivity Analysis—To evaluate the robustness of regression results, we assessed the impact of additional potential confounders based on prior literature including income, education, BMI, Mediterranean diet adherence, dietary animal fat, dietary fish, omega-3 supplementation, and age at each time point (vs. age at entry and follow-up time) (Fernández-González et al., 2015; Gil and Gil, 2015; Knutsen et al., 2011; Weuve et al., 2015). Since debate exists over how best to adjust for total lipids (O’Brien et al., 2016), we also assessed associations using lipid-standardized PCB levels to compare with our primary analysis which adjusted for total lipids as a covariate (Schisterman et al., 2005). Prior research also suggests PCB effects may vary by structure-activity relationships, therefore we also evaluated natural-log transformed PCB exposure using summed total dioxin-like (PCB-105, 118, 156, 167) and non-dioxin-like congeners (PCB 28, 52, 60, 66, 74, 95, 99, 101, 110, 130, 138, 146, 153, 170, 172, 177, 178, 180, 183, 187, 193, 194, 199, 201, 203, 206, 209) (Van den Berg et al., 2006).

Results

Study Sample

Of the 253 participants at baseline, 56 were deceased at follow-up, 8 relocated out of NYS, 11 were excluded due to disqualifying neurological diagnoses (stroke or neurodegenerative disease), 5 were medically unable to participate (for example, undergoing chemotherapy), and we were unable to locate 10 individuals. Of the 173 (68% of total) who were alive and eligible, 116 agreed to participate in the follow-up study (67%), and 114 provided blood samples for analysis of PCBs.

Completers were statistically significantly younger, had higher income, education, and physical activity levels, lower BMI, and were less likely to be diabetic than were the dropouts (Table 1). Both unadjusted, and age- and total lipid- adjusted PCB levels were statistically similar between completers and dropouts. After adjusting for age, sex, and

education, completers scored better than dropouts on many NPTs, although there was no statistically significant difference in baseline scores on the CVLT Trial 1 or BDI (Supplemental Table 1).

Population Characteristics, PCB Levels, and NPT Scores—Among completers, 53.5% were male and mean years of education was 14.5 years (Table 2). Over the study period, physical activity levels decreased, and more were diagnosed with diabetes. On average, 14 years elapsed since baseline and mean age at follow-up was 76.3 years. BMI increased 7.9% over that time ($p < 0.001$). Based on World Health Organization BMI classifications (1995), at follow-up 18% of participants were considered normal weight (BMI 18.5–24.9), 38% were overweight (BMI 25–29.9), and 44% were obese (BMI 30+). Between baseline and follow-up, 71% showed an increase in BMI. In comparison, total lipids declined by 10.6% over the study period ($p < 0.001$). This finding was likely due to the increased use of cholesterol lowering medications which rose from 26% at baseline to 57% at follow-up ($p < 0.001$). At baseline and follow-up, geometric mean (GM) serum Σ PCB levels were 3.1 and 2.1 ng/g wet-weight, respectively. Mean absolute change was -1.0 ng/g wet-weight ($p < 0.001$), and mean relative change was -22% ($p < 0.001$). Results were similar for lipid-adjusted PCB levels. Over time, the CVLT Trial 1 scores did not significantly decline, but there was a 37% relative increase in BDI scores ($p < 0.001$) (Supplemental Table 2).

Association between PCBs and Neuropsychological Function—Confounder-adjusted GEE results using complete case analysis are shown in Table 3, with NPT scores denoted by (+) indicating that a higher score indicates impairment, whereas scores denoted by (–) indicate that lower scores indicate impairment. Higher baseline age was related to significantly lower NPT scores across all neuropsychological domains. The PCB $\times$ time interaction term for CVLT Trial 1 score was statistically significant ($\beta = 0.08$ $p = 0.009$). However, the direction of the association was opposite to that hypothesized, with higher serum PCB levels being associated with higher CVLT Trial 1 scores over time (Figure 1). When PCB levels are held constant at the 10th percentile, CVLT Trial 1 scores significantly decreased over the 14-year study period ($\beta = -0.08$ $p = 0.008$), corresponding to a 16% decline. In contrast, when overall PCB levels are held constant at the 90th percentile, CVLT Trial 1 scores non-significantly increased ($\beta = 0.04$ $p = 0.128$), corresponding to an 8% increase.

The PCB $\times$ time interaction term for the BDI was also statistically significant ($\beta = -0.16$ $p = 0.013$), but again the interaction was in the opposite direction as predicted. That is, higher overall serum PCB levels were associated with lower BDI scores over time (Figure 2). When overall PCB levels are held constant at the 10th percentile, BDI scores significantly rose over time ($\beta = 0.17$ $p = 0.008$), corresponding to a 45% increase in depressive symptoms over the 14-year study period. When overall PCB levels are held at the 90th percentile, BDI scores non-significantly declined ($\beta = -0.07$ $p = 0.186$), corresponding to an 18% decline in depressive symptoms over the study period.

The PCB $\times$ time interaction term was not statistically significant for any secondary outcome (Table 3). After adjusting for loss to follow-up using SIPW, results were similar to

the complete case analysis (Supplemental Table 3). Regarding the sensitivity analyses, adjustment for income, education, BMI, Mediterranean diet adherence, dietary animal fat, dietary fish, omega-3 supplementation, or age at each time point produced similar results (data not shown). Regression results for lipid-standardized PCB levels were similar to those using total lipids covariate adjustment (Supplemental Table 4). We also observed similar results when we assessed PCB exposure using dioxin-like and non-dioxin-like PCBs (data not shown).

Differences by Age and Sex—When stratified by median age at follow-up, the PCB $\times$ time interaction term for CVLT Trial 1 score was only statistically significant among those ages 76 years and older ($\beta=0.10$ $p=0.008$). Among these older adults, when overall PCB levels are held constant at the 10th percentile, CVLT Trial 1 scores significantly declined over the 14-year study period ($\beta=-0.10$ $p=0.016$). When overall PCB levels are held constant at the 90th percentile, CVLT Trial 1 scores non-significantly increased ($\beta=0.05$ $p=0.105$). In contrast, when stratified by median age at follow-up the PCB $\times$ time interaction term for the BDI was only statistically significant among those younger than 76 years ($\beta=-0.30$ $p=0.005$). Among these younger individuals, when overall PCB levels are held constant at the 10th percentile, BDI scores significantly increased ($\beta=0.27$ $p=0.003$). When overall PCB levels are held constant at the 90th percentile, BDI scores non-significantly decreased ($\beta=-0.15$ $p=0.094$).

When stratified by sex, the PCB $\times$ time interaction term for CVLT Trial 1 score was only statistically significant among men ($\beta=0.13$ $p<0.001$). Among men, when overall PCB levels are held constant at the 10th percentile, CVLT Trial 1 scores significantly declined over the 14-year study period ($\beta=-0.10$ $p<0.001$). Among men, when overall PCB levels are held constant at the 90th percentile, CVLT Trial 1 scores non-significantly increased ($\beta=0.07$ $p=0.065$). In contrast, when stratified by sex the PCB $\times$ time interaction term for the BDI was only statistically significant among women ($\beta=-0.17$ $p=0.032$). Among women, when overall PCB levels are held constant at the 10th percentile, BDI scores significantly increased ($\beta=0.23$ $p=0.009$). Among women, when PCB levels are held constant at the 90th percentile, BDI scores non-significantly decreased ($\beta=-0.11$ $p=0.113$).

Discussion

This study examined the association between PCB exposure and neuropsychological function among older adults from NYS over an average 14-year time period. During that time, serum PCB levels (wet-weight) declined by 22%, and most NPTs showed declining levels of cognitive performance. We observed that the interaction terms between overall serum PCB and time were statistically significant for the CVLT Trial 1 and BDI scores, indicating that the pattern of change over time differed according serum PCB concentrations. However, contrary to our primary hypothesis we found that serum PCB levels were not associated with greater declines in neuropsychological function over time. Specifically, verbal memory and learning significantly decreased (CVLT Trial 1), and depressive symptoms (BDI) increased among persons with low exposure (overall PCB levels at the 10th percentile), while persons with high exposure (the 90th percentile) showed non-significant improvements. We did not detect changes over time for any other NPT.

Serum PCB levels declined significantly over the study period from a geometric mean of 3.1 ng/g (wet-weight) to 2.1 ng/g and from a geometric mean of 466 ng/g lipid to 368 ng/g lipid. In the baseline study, serum PCB levels were approximately 20–30% higher than the US general population (Bloom et al., 2014; Fitzgerald et al., 2012). At follow-up, however, levels were similar to those in the general population; the 2007–2008 National Health and Nutrition Examination Survey (NHANES) indicates that serum total PCB concentrations among non-Hispanic whites, ages 60 and over, were approximately 347 ng/g lipid-weight (CDC and NCHS 2008). However, the NHANES data were collected in 8–9 years earlier and based on pooled, not individual serum samples. Consequently, comparison of our findings at follow-up to those of NHANES may not be valid.

An important source of PCB exposure in the baseline study was the lifetime consumption of PCB-contaminated fish from the Hudson River, with most consumption occurring in the 1970s or earlier (Fitzgerald et al., 2007). In the baseline study, 98% were aware of a ban and advisories against Hudson River fish consumption in place since 1976 (NYS DEC 2003), and no one in the follow-up study reported consuming fish from the Hudson River any time after 2000–2002. Consequently, it is likely that the decline over time in serum PCB in this population was due at least in part to their cessation of Hudson River fish consumption. It is also consistent with national time trends showing declines in PCB body burden since PCBs were banned in the U.S. (Hopf et al., 2009; Sjödin et al., 2014, 2004).

In our analysis, when overall PCB levels were held constant at lower concentrations, CVLT Trial 1 scores declined significantly by 16% over the 14-year study period, while scores for the BDI increased significantly by 45%. Although an increase of this magnitude in BDI score may be clinically relevant (Button et al., 2015), it is important to note that on average the scores were relatively low, suggesting only minimal or mild depression. In general, these findings are consistent with research indicating that verbal memory and learning decreases over time (Harrington et al., 2017; Hoogendam et al., 2014), while depressive symptoms increase (Brailean et al., 2017; Sutin et al., 2013), among older populations with no unusual exposures. In contrast, when overall PCB levels were held constant at higher concentrations, CVLT-Trial 1 scores increased and BDI scores decreased non-significantly. As a result, the differences in verbal learning and memory and depressive symptoms according to serum PCB levels in our cross-sectional baseline study were no longer apparent at follow-up.

Toxicological evidence (Tilson and Kodavanti, 1998) and the results from cross-sectional epidemiological studies (Bouchard et al., 2014; Fimm et al., 2017; Fitzgerald et al., 2008; Haase et al., 2009; Schantz et al., 2001) clearly demonstrate that PCBs are neurotoxic. Therefore, we considered several possible explanations for the unexpected results. One possible explanation is healthy survivor bias. Observing null or even protective effects from known harmful exposures in older adults over time is not unexceptional. Smoking, hypertension, obesity, and elevated cholesterol levels during mid-life increase dementia risk, but paradoxically appear to either have no effect or reduce risk in later life (Anstey et al., 2017; Hernán et al., 2008; Pedditizi et al., 2016; Power et al., 2011). Rather than these risk factors eliciting real protective effects in the oldest old, this phenomena is believed to largely result from bias in the selective enrollment and retention of healthier, less susceptible

individuals (Hernán et al., 2008; Power et al., 2011; Weuve et al., 2015). This aging effect is consistent with our finding that high PCB levels were associated with improved memory and learning over time among the study completers. Our stratified results also indicated improvement was stronger among older participants.

Described as the ‘*healthier, wealthier, and wiser*’ selection process (Zajacova and Burgard, 2013), attrition in longitudinal studies of older adults is related to lower socioeconomic status, poorer health, and cognitive impairment, leading to compositional changes in a cohort over time (Chatfield et al., 2005; Zajacova and Burgard, 2013). Participants in our study were enrolled at ages 55–74, and 54% dropped out 14 years later, largely due to death or illness. Those lost to follow-up had lower educational attainment and incomes, poorer health, and performed worse on baseline neuropsychological tests.

Secondly, an unmeasured confounder may be obscuring the true associations. For example, dietary fish is a recognized source of both PCBs and healthy polyunsaturated fatty acids, and the benefits of fish consumption may negate the harms (Gil and Gil, 2015). Current fish consumption from all sources was not related to PCB levels in this study group, but we do not have information on consumption from contaminated water bodies other than the Hudson River. In sensitivity analyses, we also observed no differences in results when adjusting for several other factors including dietary fat and omega-3 supplementation. Although PCB levels did not differ between completers and dropouts, it also is possible that the dropouts were more susceptible to the cognitive effects of PCBs. This contention is supported by the fact that the baseline impact on the CVLT Trial 1 score was weaker among current study participants compared to the original study population. The lack of information on this susceptibility factor, an unmeasured confounder, may also explain why results after adjusting for loss to follow-up with SIPW were similar to the complete case analysis. Family history of neurological disease did not differ between completers and dropouts, but this information was based on small numbers and self-report, which may be biased (Elbaz et al., 2003).

It is also possible that the neurotoxic effects of PCBs were not permanent among older adults. In other words, the adverse effects we detected in our baseline study for memory and depressive symptoms among those with higher PCB levels did not persist once PCB levels declined. This differs from studies of children that demonstrate persistent harmful effects on neuropsychological endpoints through the teenage years, even at relatively low PCB concentrations (Berghuis et al., 2018, 2015). However, the developing and aging brains may differ in susceptibility to neurotoxicants.

We did not adjust for multiple comparisons because our primary goal was to test two a priori hypotheses regarding the interactions between PCB levels and time for the CVLT-Trial 1 and BDI scores, based on the findings of our earlier study (Rothman, 1990). We analyzed the remaining neuropsychological test outcomes for completeness and no results were statistically significant. Consequently, although the possibility of chance cannot be completely ruled out, we believe that it is an unlikely explanation for the observed findings.

Consistent with our prior cross-sectional findings (Fitzgerald et al., 2008), we observed stronger associations for the CVLT-Trial 1 among men and for the BDI among women. We believe these results reflect known sex-differences for these tests (Beck et al., 1988; Delis et al., 2000). Given the small sample size, however, our power to detect effect modification was limited.

This study demonstrates the difficulties of conducting longitudinal studies among elderly participants. Half of the study population was lost to follow-up, mostly from death or illness, resulting in selection for healthier participants. Another limitation of our study is that we only conducted one follow-up assessment 14 years after the cross-sectional study. More frequent follow-up may have limited loss over time by allowing for assessments at shorter intervals, provided more complete and sensitive longitudinal assessments of PCB exposure and cognitive functioning, and allowed for a more robust dropout adjustment. As a result of attrition, our sample size was relatively small, limiting statistical power. Our study is strengthened by the fact that we were able to establish temporality and used sensitive and specific methods of assessing both exposure and outcome, controlled for multiple confounders, used SIPW to adjust for loss to follow-up, and conducted sensitivity analyses.

Conclusion

In this older adult population from NYS, we found that lower serum PCB levels were associated with normative declines in verbal learning and memory and an increase in depressive symptoms over a 14-year period. Higher serum PCB levels, however, were associated with relatively small and statistically non-significant improvements in these outcomes. Uncontrolled confounding and healthy survivor bias may explain this finding. It is also possible that the adverse effects of higher PCB exposure on verbal memory and learning and on symptoms of depressive in older adults diminish as body burdens decline. More longitudinal studies with larger sample sizes, younger age of entry, and more frequent follow-ups are needed to definitively conclude how PCBs influence cognitive decline and other central nervous system functions in older adults over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Predicted CVLT Trial 1 Scores and 95% Confidence Bands Over Time by High vs. Low PCB Levels

Figure 2.
Predicted Beck Depression Inventory Scores and 95% Confidence Bands Over Time by
High vs. Low PCB Levels

Table 1.

Baseline Characteristics by Follow-up Study Completion Status

Baseline Characteristic	Completers (N=116)			Dropouts (N=137)		
	N	%		N	%	p
Male	62	53.5		65	47.5	0.341
Income						
<\$30,000	25	22.5		51	37.8	0.013
\$30,000 – <\$60,000	48	43.2		56	41.5	
\$60,000+	38	34.2		28	20.7	
Physical Activity (median level)	58	50.0		41	29.9	0.001
Diabetic	11	9.5		27	19.7	0.023
	Mean	SD		Mean	SD	p
Age (years)	62.1	5.6		65.5	6.0	<0.001
Education (years)	14.5	2.4		13.3	2.6	<0.001
BMI	27.9	4.7		29.6	7.4	0.027
Total Lipids (mg/dL)	685.0	129.8		677.5	131.5	0.654
PCB (ng/g wet-weight) ^a	3.1	1.7		3.2	1.6	0.610
Adjusted PCB (ng/g wet-weight) ^{a,b}	3.2	-		3.1	-	0.682
PCB (ng/g lipid) ^a	466.4	1.6		492.2	1.6	0.367
Adjusted PCB (ng/g lipid) ^{a,b}	485.9	-		475.2	-	0.712

^aGeometric mean/SD;^bAdjusted for age and total lipids

Abbreviations: BMI, body mass index; N, number; p, p-value; SD, standard deviation; PCB, total polychlorinated biphenyls; p, p-value

Notes: Income has 7 missing values and lipid-adjusted PCB has 8 missing values

Table 2.

Baseline, Follow-up, and Change in Health Characteristics and PCB Levels

Characteristic	Baseline			Follow-up			Absolute Change		Relative Change	
	Characteristic			Characteristic						
	N	N	%	N	N	%				
Male	116	62	53.5	-	-	-	-	-	-	-
Income	111	25	22.5	110	28	25.5	-	-	-	-
		48	43.2	38	34.2					
		38	34.2	44	39.6					
Physical Activity (median level)	116	58	50.0	116	39	33.6	-	-	-	-
Diabetic	116	11	9.5	116	20	17.2	-	-	-	-
Categorized BMI	116	2	1.7	116	0	0.0	-	-	-	-
		25	21.6		21	18.1				
Normal (18.5–24.9)		54	46.6		44	37.9				
Overweight (25–29.9)		35	30.2		51	44.0				
Obese (30+)										
	N	Mean	SD	N	Mean	SD	N	Mean	p	Mean%
Age (years)	116	62.1	5.6	116	76.3	5.8	116	14.1	-	22.9
Education (years)	116	14.5	2.4	-	-	-	-	-	-	-
BMI (continuous)	116	27.9	4.7	116	29.9	5.5	116	2.0	<0.001	7.9
Total Lipids (mg/dL)	113	685.0	129.8	114	600.0	136.0	111	-82.5	<0.001	-10.6
PCB (ng/g wet-weight) ^a	116	3.1	1.7	114	2.1	1.9	114	-1.0	<0.001	-22.2
PCB (ng/g lipid) ^a	113	466.4	1.6	114	368.1	1.9	111	-80.9	0.007	-10.9

^aGeometric mean/SD presented

Abbreviations: BMI, body mass index; N, number observations; p, p-value; PCB, total polychlorinated biphenyls; SD, standard deviation

Notes: p-value for t-test that the change=0; N for absolute change applies to relative change

Table 3.
GEE Estimates for *ln*PCB Levels (ng/g wet-weight) in Association with NPTs – Complete Case Analysis

NPT	N ^a	Baseline Age			Time			PCB			PCB × Time		
		β	SE	p	β	SE	p	β	SE	p	β	SE	p
Primary Outcomes													
CVLT Trial 1 (–)	227	–0.07	0.02	0.001	–0.09	0.03	0.007	–0.42	0.34	0.221	0.08	0.03	0.009
Beck Depression Inventory (+)	225	–0.04	0.07	0.536	0.20	0.07	0.007	2.32	1.03	0.024	–0.16	0.06	0.013
Secondary Outcomes													
Memory & Learning													
CVLT Short Delay Free Recall (–)	227	–0.09	0.05	0.057	–0.11	0.05	0.023	0.29	0.44	0.515	0.04	0.04	0.297
CVLT Long Delay Free Recall (–)	227	–0.08	0.04	0.087	–0.01	0.04	0.831	0.90	0.45	0.045	–0.02	0.04	0.574
CVLT Semantic Cluster Ratio (–)	227	0.01	0.01	0.629	–0.01	0.01	0.461	0.08	0.12	0.528	0.00	0.01	0.790
CVLT Learning Slope (–)	227	0.00	0.01	0.641	0.01	0.01	0.307	0.10	0.10	0.361	–0.01	0.01	0.412
CVLT Perseverations (+)	227	0.06	0.06	0.371	0.00	0.08	0.955	1.03	0.98	0.293	–0.06	0.07	0.378
CVLT Discriminability (–)	227	–0.19	0.08	0.019	–0.02	0.09	0.829	1.13	0.95	0.236	–0.05	0.08	0.495
CVLT Proactive Interference (+)	227	0.35	0.59	0.556	0.62	0.59	0.299	–0.11	8.20	0.989	–0.65	0.59	0.273
CVLT Recognition vs. LDFR (–)	227	2.19	1.72	0.203	2.00	1.26	0.111	–1.15	10.84	0.915	–0.87	0.82	0.289
WMS Logical Immediate Recall (–)	227	–0.09	0.08	0.257	–0.05	0.07	0.533	–0.32	1.00	0.749	–0.01	0.07	0.849
WMS Logical Delayed Recall (–)	227	–0.08	0.08	0.260	0.02	0.07	0.805	0.46	0.85	0.586	–0.02	0.06	0.761
WMS Visual Immediate Recall (–)	226	–0.18	0.04	<0.001	–0.13	0.04	0.003	0.43	0.51	0.395	0.01	0.04	0.875
WMS Visual Delayed Recall (–)	226	–0.16	0.05	0.001	–0.08	0.04	0.050	0.50	0.58	0.387	–0.05	0.04	0.197
Affective State													
State Anxiety (+)	227	–0.15	0.11	0.192	–0.26	0.17	0.125	–0.08	1.89	0.965	0.07	0.14	0.647
Trait Anxiety (+)	227	–0.36	0.14	0.008	0.03	0.12	0.832	0.39	1.19	0.746	–0.06	0.10	0.509
Executive Function													
Trail Making Test, Part A (+)	226	0.48	0.15	0.001	0.15	0.21	0.454	–3.19	2.07	0.124	0.08	0.16	0.632
Trail Making Test, Part B (+)	225	2.62	0.59	<0.001	1.65	0.45	<0.001	–7.19	4.50	0.111	–0.14	0.35	0.699
Stroop Color-Word (–)	226	0.15	0.10	0.139	–0.39	0.12	0.002	0.75	1.53	0.624	–0.07	0.10	0.488
WCST Categories Completed (–)	222	–0.08	0.03	0.005	–0.06	0.03	0.043	0.24	0.30	0.410	0.02	0.02	0.457
WCST Failure to Maintain Set (+)	221	0.03	0.02	0.079	0.01	0.02	0.632	–0.23	0.24	0.343	0.01	0.02	0.512
WCST Perseverative Errors (+)	221	0.76	0.30	0.011	0.54	0.34	0.108	–2.00	3.21	0.533	–0.16	0.26	0.547

NPT	N ^a	Baseline Age			Time			PCB			PCB × Time			
		β	SE	p	β	SE	p	β	SE	p	β	SE	p	
WCST Perseverative Response (+)														
Spatial Ability														
	221	0.96	0.38	0.012	0.70	0.47	0.135	-2.93	4.38	0.504	-0.20	0.36	0.583	
	226	-0.69	0.16	<0.001	-0.58	0.15	<0.001	0.74	1.99	0.711	0.01	0.12	0.939	
	226	-0.32	0.14	0.018	-0.22	0.09	0.009	1.54	1.32	0.242	-0.14	0.07	0.065	
Reaction Time														
	215	4.72	1.33	<0.001	-1.68	1.76	0.338	-4.29	15.06	0.776	-1.11	1.58	0.482	
Motor Skills														
	224	0.15	0.06	0.008	0.13	0.07	0.050	-0.42	0.44	0.331	-0.02	0.05	0.715	
	224	0.23	0.06	<0.001	0.14	0.06	0.019	-0.13	0.51	0.796	0.04	0.05	0.389	
	224	2.84	0.45	<0.001	2.08	0.45	<0.001	-6.47	3.81	0.090	0.09	0.39	0.813	
	225	2.69	0.50	<0.001	2.35	0.48	<0.001	-2.51	3.25	0.441	0.30	0.40	0.460	
	224	-0.35	0.11	0.001	-0.03	0.09	0.718	-0.18	1.01	0.856	0.08	0.09	0.392	
	224	-0.36	0.10	<0.001	-0.07	0.09	0.431	-0.47	1.20	0.698	0.11	0.09	0.207	

^aN visits; (-), lower scores indicate impairment; (+), higher scores indicate impairment;

Abbreviations: CVLT, California Verbal Learning Test; GEE, generalized estimating equations; N, number assessments; NPT, neuropsychological test; SE, standard error; SIPW, stabilized inverse probability weighting; WMS, Wechsler Memory Scale

Notes: All models confounder-adjusted for sex, smoking, and total lipids; Affective state models also confounder-adjusted for antidepressant use; Significant results are bolded