Path analysis reveals the direct effect of PCB28 on cognitive dysfunction in older Chinese females

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Research

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Abstract

Background

Current findings support the hypothesis that the exposure of dioxin-like polychlorinated biphenyls (dl-PCBs) has adverse cognitive effects even at levels that are generally considered to pose low or no risk. However, the effect of non-dioxin-like PCBs (ndl-PCBs) on neurobehavior of aging people is largely unknown. Therefore, this study aimed toinvestigate the association of ndl-PCBs burden with the cognition functions among elderly adults.

Methods

Using samples and data from Weitang Geriatric Diseases study (2014–2015), 6 indicator-PCBs were detected in plasma by GC-MS and cognitive dysfunction (CoD) were measured by the Abbreviated Mental Test in 266 participants (age: 61–90). Sequential logistic regression was used to analyze the effects of PCBs on cognition functions. Then the female aged less than and equal to 80 years was selected, and path analysis was used to determine the direct or indirect impacts of co-exposure PCBs on COD by Structural Equation Modeling.

Results

After sequential adjusting for potential confounder, no association of PCBs 52, 101, 138, 153, 180, LPCBs, HPCBs, and ∑PCBs with the risk of COD was observed; however, the exposure of PCB28 was significantly associated with COD ((Model 3: OR = 3.12, 95% CI = 1.19–8.11, $p = 0.020$). The final path model also fits that only exposure to PCB28 had a direct effect on COD ($\beta = 0.696$, SE = 1.14; $p = 0.036$).

Conclusions

After controlling the co-exposures and confounders, the exposure to PCB28 can directly increase the risk of cognitive impairment in older Chinese females.

Introduction

The cognitive impairment has been well-identified as a critical health risk factor for older adults. Mild Cognitive Impairment (MCI), which is the intermediate stage between the normal aging cognitive changes and dementia, is currently considered as a key risk factor to dementia [1]. Dementia, the most serious outcome of MCI, affects nearly 35.6 million people worldwide and this number will increase to 115.4 million by 2050 [2]. In China, the prevalence of dementia, cognitive dysfunction (CoD) without dementia and MCI in the older population are 2.8%, 12.7% and 14.71%, respectively [3–5]. Therefore, it is greatly important to identify the risk factors of MCI in the elderly population.

In addition to genetics and aging, environment pollutants have recently been considered as a risk factor that affects elder adults' cognition functions [6]. Toxicological studies have found that the exposure of persistent organic pollutants (POPs) can result in severe issues in the central nervous system, including the MCI [7]. As the typical POPs, polychlorinated biphenyls (PCBs) are a group of organochlorine compounds synthesized by biphenyl chlorination, with a total of 209 homologs [8]. PCBs have been banned from production and use worldwide in1970s because of their carcinogenicity, immunotoxicity and neurotoxicity [8]. However, they are still widely present in the environment due to their extensive use, unintentional leakage, and poor degradation [8].

According to the differential physical-chemical characteristics, the 209 homologs of PCBs can be categorized into 12 dioxin-like PCBs (dl-PCBs) and 197 non-dioxin-like PCBs (ndl-PCBs) [8]. They can also be divided into the lower chlorinated PCBs (LPCBs, with 5 chlorine atoms or less) and higher chlorinated congeners (HPCBs) based on the number of chlorine atoms [9].Since it is impractical to test all 197 ndl-PCBs, Beck et al (1985) suggested that research studies can primarily focus on 6 indicator PCB congeners, including PCB28, 52, 101, 138, 153, and 180 [8].

The neurotoxicities of PCBs have been a public health concern for decades.Results from epidemiological studies or animal experiments mainly focus on the neurobehavioral impairments of PCBs in neonates upon intrauterine exposure [10, 11]. However, no association has been observed between PCBs and Alzheimer's disease or Parkinson's [12, 13]. Indeed, neurodevelopment is a dynamic process from

intrauterine period to adulthood [14]. With age, the physiological changes, such as the increased permeability of the blood-brain barrier (BBB), may alter the absorption, distribution and metabolism of exogenous substances, leading to toxic accumulation that can heighten the risk of neurodegenerative diseases [14]. Current findings support the hypothesis that the exposure of dl-PCBs has adverse cognitive effects even at levels that are generally considered to pose low or no risk [15]. However, the effect of ndl-PCBs on neurobehavior of aging people is largely unknown.

In the present study, we selected the community-dwelling older adults as the research subjects to investigate the association of PCBs burden with the cognition functions among adults aged 60 years or older. The plasma concentrations of 6 indicator-PCBs were measured to determine the PCBs burden. In addition, a questionnaire survey was performed to test subjects' cognition functions. We used the logistic regression method to analyze whether the exposure of PCBs was a risk factor of cognitive impairment, and then the Structural Equation Modeling (SEM) was used for path analyses, which allowed us to determine the co-exposure effect of 6 indicator-PCBs and whether the impacts were direct or indirect. This can also help us to identify the contribution of individual PCB from the co-exposure of all indicator-PCBs.

Materials And Methods

Study population

This study was conducted based on the Weitang Geriatric Diseases study, a community-based survey that aimed to investigate the patterns, predictors, and burdens of health among elderly residents aged 60 years or older in the east China Region [16]. Weitang town is located in Suzhou city, Jiangsu Province. This study recruited 6,030 elder adults over 60 years of age from August 2014 to February 2015. Participants are excluded if they were: 1) younger than 60 years of age; 2) moved from Weitang town to another place; 3) living in Weitang town for less than 6 months; or 4) death. In summary, 5,613 subjects were included in the current study, with 4,579 of them completed a questionnaire containing Abbreviated Mental Test and provided blood samples. The blood samples of 266 people were randomly selected for measuring the plasma indicator-PCBs.

The Weitang Geriatric Diseases study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of Soochow University. At the recruitment stage of this study, all participants gave written informed consent.

Cognitive functions outcomes

The Abbreviated Mental Test(AMT) was used to assess the CoD in this study [17]. As previously described [18], according to its 10-item scale combined with the cultural background of our country, the final included items were: age, current time, year, place, features identification, date of birth, National Day, president, countdown from 20. The correct answer of each item was given 1 score and the maximum total score was 10. The total score was then grouped into normal cognitive functions (> 7) or CoD (<= 7).

PCBs concentrations in the plasma samples

Blood samples were stored at -80 ℃ for 3 years until measurements in the Shanghai Municipal Center for Disease Control and Prevention. The preparation of plasma sample was as follows: an aliquot of 0.2 mL plasma was removed and placed into 15 mL PVC centrifuge tubes, and then mixed with 3 mL ethyl acetate/n-hexane (V/V,1:1) solvent, vibrated and centrifuged. Repeated the extraction step once. The supernatant was transferred to another tube and dried with mild nitrogen blowing in 40 ℃ water bath. Then, 0.4 mL N-hexane and 0.4 mL H_2SO_4 were added in order, vibrated and centrifuged again. After the 0.2 mL supernatant was desiccated using anhydrous sodium sulfate, it was put into the internal cannula and placed in the injection bottle for subsequent analyses.The identification and quantification of plasma PCBs levels in participants were performed by gas chromatogram-tandem mass spectrometry (GC-MS/MS) on a Thermo ScientificTRACE 1300 Series gas chromatograph coupled with a Thermo Scientific TSQ 8000 EVO Triple Quadrupole mass spectrometer (Thermo Fisher Scientific, San José, CA, USA). Standards of 6 indicator-PCBs (PCB28, 52, 101, 138, 153, 180) were purchased from Dr. Ehrenstorfer (Germany) with a purity of > 98.0%. The limit of detection (LOD) was 0.03 ng/mL. "Total lipid" concentrations were calculated from short formula [19] to adjust PCBs measurements in plasma.

Statistical analysis

We performed the statistical analyses using R (version 4.0.2). In descriptive analyses, continuous variables were expressed as median (interquartile range, IQR) and compared with Mann-Whitney U test; categorical variables were expressed as number (%) and compared by chi-square test. The $p < 0.05$ was considered as statistically significant. The concentrations of PCBs in plasma were reported as lipid-adjusted concentrations. The concentrations below LOD were reported as not detected (ND).

Sequential logistic regression analysis: Since our research subjects were non-occupational exposure population, over 50% of the samples had an exposure level for the 6 indicator-PCBs that was below LOD. We split up the exposure of each PCBs, LPCBs, HPCBs, or ∑PCBs in dichotomous variable (>LOD vs. <LOD) and included as dummy variables in the models. Sequential logistic regression models were used to preliminarily explore the association between the exposure of PCBs and CoD.

(1) Model 0 were univariate logistic regression.

(2) Model 1 adjusted for baseline covariates, including: Age, Sex, Education level (formal education vs. without formal education), Monthly income (≤1 k, 1.01 – 3 k, ⩾3k), Marriage (living with a spouse vs. living without a spouse), Children (Yes vs. No).

(3) Additionally adjusted for Sleep quality (poor vs. general vs. well) and Sleep duration based on covariates in model 2.

(4) Additionally adjusted for Headache (Yes vs. No) based on covariates in model 3.

Path analysis: Previous studies have shown the effects of PCBs on cognition function may be sex specific [20]. Therefore, we conducted a subgroup analysis of all female participants. We then excluded the age above 80 years in the predefined subgroup because the magnitude of the relationship between neuropsychological function and age remained stable from ages 65 to 80, but stronger above the age of 80 [21].

To simulate the exposure of mixtures environmental toxics, all 6 indicator-PCBs were included in the research hypothetical system and analyses framework (Fig 1.A). SEMs were conducted for path analysis using R package “lavaan”. Models were adjusted for Education level, Monthly income, Marriage and Children. Final model was fit by removing PCBs that were not significantly (p-value ≥ 0.05) associated with CoD. Good model fit was assessed with a chi-square p value above 0.05, root mean square error of approximation (RMSEA) below 0.05, comparative fit index (CFI) above 0.95 [22].

Results

Basic characteristics of the participants

The characteristics, lifestyle, and health conditions of participants are shown in Table 1. A total of 266 community elderly adults were included, with the age of participants ranged from 61 to 90, the median (IQR) age at 67 (IQR 63-74), sleep duration at 9 h (IQR 8-9), and AMT score at 9 (IQR 8-9, scale ranged from 0-10). Of all the participants, 53.8% of them were female, 50.8% had formal education, 62.9% had low monthly income (<1k CNY), 83.8% lived with a spouse, 51.9% had children, 76.3% had a good sleep quality, 78.2% had no headache, 90.6% had diabetes, and 53% with hypertension. Current or former smokers and drinkers occupied 35.7% and 23.7%, respectively.

Overall, the 266 recruited participants were divided into the Normal group (N = 211) and CoD group (N = 55) by the AMT scores. The median age of the Normal group was 66 (IQR 63-71), and median age of the CoD group was 75 (IQR 65-81), with the age difference statistically significant (p< 0.001). Compared with the Normal group, participants in the CoD group tended to be female (p< 0.001), and have lower education (p< 0.001, 76.4% without formal education) and monthly income (p= 0.004). There were more non-smokers and non-drinkers (p< 0.001; p = 0.020) in COD group. The worse sleep quality (p = 0.009), longer sleep duration (p< 0.001), and more people with headache (p = 0.043) were observed in COD group. However, there was no statistical difference in the prevalence of diabetes and hypertension between the two groups.

Plasma concentration of PCBs

We detected the plasma concentrations of 6 indicator-PCBs, which are shown in Table 2. PCB101 had the highest detection rate of 41.35%, while the PCB52 had the lowest detection rate of 0.38%. The median concentration of 6 indicator-PCBs was 12.69 ng/g lipid. The plasma concentrations of HPCBs were generally higher than LPCBs, with PCB180 showing the highest plasma concentration at 18.25 ng/g lipid (IQR 5.68-96.63), followed by the PCB138 at 15.45 ng/g lipid (IQR 8.60-30.67) and PCB28 at 8.95 ng/g lipid (IQR 8.27-10.10).

Association between PCBs burden and CoD

The results of the association analyses between 6 indicator-PCBs and CoD are shown in Table 3. The results of univariate logistic regression indicated that only the exposure of HPCBs was a protective factor for the cognitive functions (Model 0: OR = 0.28, 95% CI = 0.07-0.82, p = 0.041). In a further study, multiple risk factors were progressively corrected. As the model1 showed, the detection of LPCBs 52,101, HPCBs 138,153,180, LPCBs, HPCBs, and 6 indicator-PCBs had no significant impact on CoD, while the detection of PCB28

possessed a statistically significant association with CoD (Model 1: OR = 3.11, 95% CI = 1.26-7.60, p = 0.013). The exposure of PCB28 also had a strong impact on CoD after adjusted by the factors of sleep quality and duration (Model 2: OR = 2.70, 95% CI = 1.04-6.84, p = 0.037). The final model was additionally adjusted for disease related to cognitive dysfunction, use of Headache.The result consistently showed that the exposure of PCB28 significantly increased the risk of cognitive impairment in the elderly population (Model 3: OR = 3.12, 95% CI = 1.19-8.11, p = 0.020).

Path analyses of PCBs burden and CoD association

The research hypothetical system and analyses framework are shown in Fig 1.A. We included 6 indicator-PCBs in the basal model. PCB52 and PCB180 were not significantly associated with CoD and subsequently dropped from the model.

The Fig 1.B and Table 4 showed the standardization regression coefficients (factor loads) among variables in the final model. The results indicated that the exposure of PCB28 had a direct effect on CoD in females age 80 and below, with the factor load at 0.696. This effect size indicated that the exposure of PCB28 was associated with an increase in the risk of CoD by 0.696 points after controlling for the other PCBs, age, education level, monthly income, marriage and children. Meanwhile, none of the PCBs were indirectly associated with the CoD through the mediation of headache, sleep quality and sleep duration. But these three factors worked in the model framework. We observed that PCB138 and PCB101 had effects on sleep duration. PCB138 was revealed a negative association with sleep duration with a factor load of -1.044, and PCB101 was revealed a positive association with sleep duration with a factor load of 0.479. The headache and sleep quality were associated with CoD in females age 80 and below, with the factor load at 0.306 and -0.331, respectively.

We also analyzed the association of female participants and all the participants with the exposure of PCBs based on the final model [see Additional file 1]. Although the models were not good fitted in these participants assessed by X^2 p value, CFI and RMSEA, the direction of associations were similar with the final model (Table 4).

Discussion

The results of our studies suggested that exposure to PCBs was associated with CoD in elderly people over 60 years of age. More specifically, after controlling the co-exposures and confounders, exposure to PCB28 can directly increase the risk of cognitive impairment in elderly females. Significant effects were found in participants aged 80 or younger, indicating the real effect of PCBs exposure rather than the age-related cognitive decline.

The level of PCBs in plasma was not related to long-term exposure, but related to the dietary intake pattern of local residents [23–25].Compared with other studies in China, the exposure level of PCBs in our study population was at a low level (the plasma median in our study: 12.69 ng/g lipid; the venous serum median in the study of pregnant woman in Taiwan: 28.3 ng/g lipid [26]). This low exposure of PCBs may be caused by the different dietary pattern between the elderly people and pregnant woman. Compared with other countries studies, the exposure level of PCBs in our study population was at an average level (the range of PCB28, 52, 101, 138, 153, 180 in our study: ND -127.07,ND -162.74, ND -247.46,ND -247.46, ND -309.88, ND -283.12,ND -294.27 ng/g lipid; from the National Health and Nutrition Examination Survey (NHANES), the range of PCB138, 153, 180 in American elderly adults: 2.1–310, 2.1–433, 4.4–397 ng/g lipid [27]; the range of PCB28, 52, 90 + 101, 138, 153, 180 in United Kingdom dwellers: < 1.0–14, < 0.25–4.7, < 1.3–9, < 7.1–110, < 9.3–200, < 4.7–200 ng/g lipid [28]).

Previous studies focus on the effects of ndl-PCBs on the cognition performances have provided inconsistent results. The report from Canada [29] showed that exposure to PCB153 was associated with reduced mean cognitive performances. Using data from NHANES, Przybyla observed a opposite trend of cognitive functioning, when PCB153 was simultaneously exposed with PCB74, 118, 146 (β = 0.200, 95% CI: 0.05, 0.35; p = 0.010) [27]. Besides, both the two epidemiological studies have some shortages. For instance, Medehouenou et al. did not consider about the co-exposures, and Przybyla et al. did not detect all of the 6 indicator-PCBs. The present study was designed to evaluate such associations among Chinese aged 60 and above, after controlling for the co-exposure and confounders. In our study, we found that PCB153 was not directly or indirectly associated with cognitive dysfunction, when PCB153 was simultaneously exposed with PCB28, 101, 138 (β = − 0.309, SE = 1.14; p = 0.786). In this co-exposure system, after controlling co-exposures and confounders, only exposure to PCB28 was directly associated with cognitive dysfunction (β = 0.696, SE = 1.14; p = 0.036). Furthermore, the 'Headache, Sleep quality, Sleep duration' produced no mediated effect to explain the exposure of PCBs increased prevalence of CoD.

Several evidences showed that PCBs, as a neurotoxicants, could deficit on cognitive flexibility, working memory, and inhibitory control by influencing intracellular signaling, disruption of Ca^{2+} homeostasis and neurotransmitters [30, 31]. PCB28 belongs to LPCBs and has a lower potential for bioaccumulation in the body [9]. PCB28 also belongs to ortho-substituted PCBs and the NEQ is 0.298 [32]. Previously

animal experiment findings have demonstrated that the exposure of PCB28 could result in long-lasting deficits in learning and the effects may be female specific [20]. When exploring the relationship between PCBs exposure and cognitive dysfunction, we conducted Gender-stratification analysis in final SEM. The relationship only found in female, indicating that females were more sensitive to PCBs exposure in terms of cognitive dysfunction in our study. Another animal experiment indicated that Lower-Chlorinated Non-Dioxin-Like PCBs can act as the $GABA_A$ receptor agonist that disrupt brain development, motor coordination, learning, and memory [33], which may be a possible mechanism for the PCB28 exposure on cognitive dysfunction, and more specific mechanisms need to be studied in the future.

There are several limitations of this study should to be noted. One of the limitations of this study is that the variables in the questionnaire, such as the sleep quality and sleep duration, were self-reported, which may lead to recall biases. Besides, a gender stratified analysis should be further applied in larger sample size, to compare the differences between females and males. Thirdly, the detection rates of the 6 indicator-PCBs in the study population were relatively low. For PCB52, the NEQ was higher than that of other five PCBs [32], but plasma concentration appeared too low in our study participants to observe the effect of PCB52 on cognitive impairment effectively. The low detection rates may be due to the insufficient sample size or the PCBs low exposure to the study population. In addition, all the sample were selected from a town of China, the extrapolation of the results was limited. Therefore, studies with a larger sample size and more representative samples should be carried out in future to further validate the results and conclusions of this study.

In conclusion, this study, for the first time, reveals that after controlling the co-exposures of indicator-PCBs and confounders, the exposure to PCB28 can directly increase the risk of cognitive impairment in Chinese elderly females. The identified effect of PCB28 showed that more mechanism research on neurotoxicity and control strategy should be focused on PCB28. Our study established the analysis framework for determine the co-exposure effects of mixture chemicals and identifying contribution of individual chemical from co-exposure of mixtures. These results provide a scientific basis and case for the identification and prevention of environmental pollutants on CoD among the community elderly people, so as to reduce the potential risk of CoD.

Abbreviations

CoD	Cognitive dysfunction
MCI	Mild Cognitive Impairment
PCBs	Polychlorinated Biphenyls
dl-PCBs	dioxin-like polychlorinated biphenyls
ndl-PCBs	non-dioxin-like polychlorinated biphenyls
LPCBs	lower chlorinated polychlorinated biphenyls
HPCBs	higher chlorinated polychlorinated biphenyls
SEM	Structural Equation Modeling
AMT	Abbreviated Mental Test
NEQ	Neurotoxic Equivalent

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Soochow University.

Consent for publication

Not applicable.

Availability of data and materials

The data are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no competing financial interests.

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Authors' contributions

CP: Resources, Data curation, Conceptualization. HZ: Formal analysis, Software, Writing - original draft. YX: Data curation. DT: Formal analysis, Software. SX: Validation. HW: Validation. XW: Methodology. YR: Writing - review &editing. GT: Methodology, Resources, Conceptualization. WZ: Resources, Supervision, Conceptualization, Writing - review &editing.

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Tables

Table 1. Participants characteristics (N = 266)				
	Total	Normal (N = 211)	CoD [a] (N = 55)	*p* [b]
Age (yrs) [d]	67 [63, 74]	66 [63, 71]	75 [65, 81]	< 0.001
Sex (%)				< 0.001
Male	123 (46.2)	111 (52.6)	12 (21.8)	
Female	143 (53.8)	100 (47.4)	43 (78.2)	
Education level (%)				< 0.001
Without formal education	131 (49.2)	89 (42.2)	42 (76.4)	
Primary school	106 (39.8)	94 (44.5)	12 (21.8)	
Middle school	25 (9.4)	24 (11.4)	1 (1.8)	
High school	4 (1.5)	4 (1.9)	0 (0.0)	
College	0 (0.0)	0 (0.0)	0 (0.0)	
Monthlyincome CNY (%)				0.004
≤1 k	166 (62.9)	121 (57.9)	45 (81.8)	
1.01–3 k	83 (31.4)	74 (35.4)	9 (16.4)	
⩾3k	15 (5.7)	14 (6.7)	1 (1.8)	
Livingwithaspouse (%)				0.058
Without	43 (16.2)	29 (13.7)	14 (25.5)	
With	223 (83.8)	182 (86.3)	41 (74.5)	
Children (%)				0.222
No	128 (48.1)	97 (46.0)	31 (56.4)	
Yes	138 (51.9)	114 (54.0)	24 (43.6)	
Smoking status (%)				< 0.001

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	Total	Normal (N = 211)	CoD [a] (N = 55)	*p* [b]
Never smoker	171 (64.3)	124 (58.8)	47 (85.5)	
Current/former smoker	95 (35.7)	87 (41.2)	8 (14.5)	
Habitual alcohol drinker (%)				0.020
No	203 (76.3)	154 (73.0)	49 (89.1)	
Yes	63 (23.7)	57 (27.0)	6 (10.9)	
Sleep quality (%)				0.009
poor	28 (10.5)	16 (7.6)	12 (21.8)	
general	35 (13.2)	28 (13.3)	7 (12.7)	
well	203 (76.3)	167 (79.1)	36 (65.5)	
Sleep duration(hrs) [d]	264[c]	210[c]	54[c]	
	9.0 [8.0, 9.0]	8.0 [8.0, 9.0]	9.0 [8.0, 10.0]	< 0.001
Headache (%)				0.043
No	208 (78.2)	171 (81.0)	37 (67.3)	
Yes	58 (21.8)	40 (19.0)	18 (32.7)	
Diabetes (%)				0.057
No	241 (90.6)	187 (88.6)	54 (98.2)	
Yes	25 (9.4)	24 (11.4)	1 (1.8)	
Hypertension (%)				0.916
No	241 (90.6)	187 (88.6)	54 (98.2)	
Yes	141 (53.0)	111 (52.6)	30 (54.5)	
AMT score [d]	9.0 [8.0, 10.0]	10.0 [8.0, 10.0]	6.0 [5.0, 7.0]	< 0.001

a: CoD = Cognitive dysfunction.

b: *p* values were obtained from Mann-Whitney U test or chi-square test.

c: 2 participants were missing in 'Sleep duration'.

d: median [IQR].

Table 2. Plasma PCBs levels (ng/g lipid) of the participant sample (N =266)				
PCBs	**Median [IQR]**	**Range**	**> MDL [a] (n)**	**> MDL (%)**
PCB28[b]	8.95 [8.27, 10.10]	ND-127.07	37	13.91%
PCB52[b]	162.74	ND-162.74	1	0.38%
PCB101[b]	11.30 [8.50, 16.10]	ND-247.46	110	41.35%
PCB138 [c]	15.45 [8.60, 30.67]	ND-309.88	25	9.40%
PCB153 [c]	10.96 [6.95, 15.92]	ND-283.12	22	8.27%
PCB180 [c]	18.25 [5.68, 96.63]	ND-294.27	4	1.50%
[d]	12.69 [8.91, 21.89]	ND-1424.54	140	52.63%

a: MDL= method detection limit. The range is 4.02-9.72ng/g lipid, which is reported for lipid-adjusted values.

b: Lower chlorinated PCB congeners (LPCBs).

c: Higher chlorinated congeners (HPCBs)

d: means the sum of 6 indicator-PCBs (PCB28, 52, 101, 138, 153 and 180).

Table 3. Association of Plasma PCB burden with cognitive impairment (N = 266).

	Number of		Model 0[a]			Model 1[b]			Model 2[c, e]			Model 3[d,e]		
Variable	**Normal**	**CoD**	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
PCB28														
Not detected	186	43	1.00	-	ref [g]	1.00	-	ref	1.00	-	ref	1.00	-	ref
Detected	25	12	2.08	(0.94-4.39)	0.061	3.11	(1.26-7.60)	0.013	2.70	(1.04-6.84)	0.037	3.12	(1.19-8.11)	0.020
PCB52														
Not detected	210	55	1.00	-	ref	1.00	-	ref	1.00	-	ref	1.00	-	ref
Detected	1	0	< 0.01	(< 0.01, > 99.99)	> 0.99	< 0.01	(< 0.01, > 99.99)	> 0.99	< 0.01	(< 0.01, > 99.99)	>0.99	< 0.01	(< 0.01, > 99.99)	> 0.99
PCB101														
Not detected	121	35	1.00	-	ref	1.00	-	ref	1.00	-	ref	1.00	-	ref
Detected	90	20	0.77	(0.41-1.41)	0.400	0.98	(0.48-1.97)	0.959	0.95	(0.46-1.97)	0.899	0.97	(0.46-2.03)	0.951
PCB138														
Not detected	189	52	1.00	-	ref	1.00	-	ref	1.00	-	ref	1.00	-	ref
Detected	22	3	0.50	(0.11-1.50)	0.269	0.47	(0.09-1.59)	0.265	0.52	(0.10-1.91)	0.366	0.53	(0.10-2.00)	0.391
PCB153														
Not detected	191	53	1.00	-	ref	1.00	-	ref	1.00	-	ref	1.00	-	ref
Detected	20	2	0.36	(0.06-1.29)	0.178	0.45	(0.06-1.90)	0.338	0.40	(0.05-1.82)	0.295	0.41	(0.06-1.84)	0.301

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	Number of		Model 0[a]			Model 1[b]			Model 2[c, e]			Model 3[d,e]		
Variable	**Normal**	**CoD**	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
PCB180														
Not detected	207	55	1.00	-	ref	1.00	-	ref	1.00	-	ref	1.00	-	ref
Detected	4	0	< 0.01	(< 0.01, > 99.99)	> 0.99	< 0.01	(< 0.01, > 99.99)	> 0.99	< 0.01	(< 0.01, > 99.99)	>0.99	< 0.01	(< 0.01, > 99.99)	> 0.99
LPCBs[f]														
Not detected	101	25	1.00	-	ref	1.00	-	ref	1.00	-	ref	1.00	-	ref
Detected	110	30	1.10	(0.61-2.01)	0.75	1.59	(0.80-3.26)	0.188	1.45	(0.71-3.03)	0.315	1.55	(0.75-3.30)	0.241
HPCBs [f]														
Not detected	175	52	1.00	-	ref	1.00	-	ref	1.00	-	ref	1.00	-	ref

Detected	36	3	0.28	(0.07-0.82)	0.041	0.32	(0.07-1.05)	0.091	0.33	(0.07-1.15)	0.115	0.33	(0.07-1.16)	0.117
∑PCBs [f]														
Not detected	101	25	1.00	-	ref	1.00	-	ref	1.00	-	ref	1.00	-	ref
Detected	110	30	1.10	(0.61-2.01)	0.75	1.60	(0.80-3.26)	0.241	1.44	(0.71-3.03)	0.315	1.55	(0.75-3.30)	0.241

a: Model 0 was univariate logisticregressionanalyses.

b: Model 1 was adjusted for age, sex, education level (formal education vs. without formal education), Monthly income (≤1 k, 1.01 – 3 k, ⩾3k), Marriage (living with a spouse vs. living without a spouse), Children (Yes vs. NO).

c: Model 2 was adjusted for covariates in model 1 and Sleep quality (poor vs. general vs. well), Sleep duration.

d: Model 3 was adjusted for covariates in model 2 and Headache (Yes vs. NO).

e: N = 264, 2 participants were missing in 'Sleep duration'.

f: LPCBs meanslowerchlorinated PCB congeners (PCB 28, 52, 101). HPCBsmeans higher chlorinated congeners (PCB 138, 153, 180). ∑PCBsmeans the 6 indicator PCBs (LPCBs: PCB 28, 52, 101; HPCBs: PCB 138, 153, 180).

g: ref = reference.

Table 4. Final SEM path coefficients showed the association among 4 indicator-PCBs, cognitivedysfunction and covariates for female participants.			
Path	**Path coefficient**		***p*[b]**
	Estimate	**Standard Error (SE)**	
Females & Age ≤80 (N=125) [a]			
Age → CoD	0.058	0.030	0.053
Education level → CoD	-0.618	0.322	0.055
Monthly income → CoD	-0.074	0.305	0.809
Marriage → CoD	-0.154	0.429	0.719
Children → CoD	-0.304	0.278	0.274
Sleep duration → CoD	0.148	0.114	0.193
Sleep quality → CoD	-0.331	0.133	0.013*
Headache → CoD	0.306	0.131	0.020*
PCB 28 → CoD	0.696	0.332	0.036*
PCB 101 → CoD	0.093	0.288	0.746
PCB 138 → CoD	-0.394	1.203	0.743
PCB 153 → CoD	-0.309	1.140	0.786
PCB 28 → Headache	-0.513	0.405	0.206
PCB 138 → Headache	-0.334	0.465	0.473
PCB 153 → Headache	0.143	0.540	0.792
Age → Sleep duration	0.074	0.021	<0.001***
PCB 101→ Sleep duration	0.479	0.234	0.040*
PCB 138→ Sleep duration	-1.044	0.485	0.031*
Age → Sleep quality	0.037	0.027	0.174
PCB 153 → Sleep quality	-0.028	0.679	0.968
a: model fit index (X^2 *p* value= 0.443, CFI = 967, RMSEA =0.010).			
Criterion for good fit: X^2 *p* value > 0.05, CFI > 0.95, RMSEA < 0.05.			
b: * *p*<0.05, ** *p*<0.01, ****p*<0.001.			

Figures

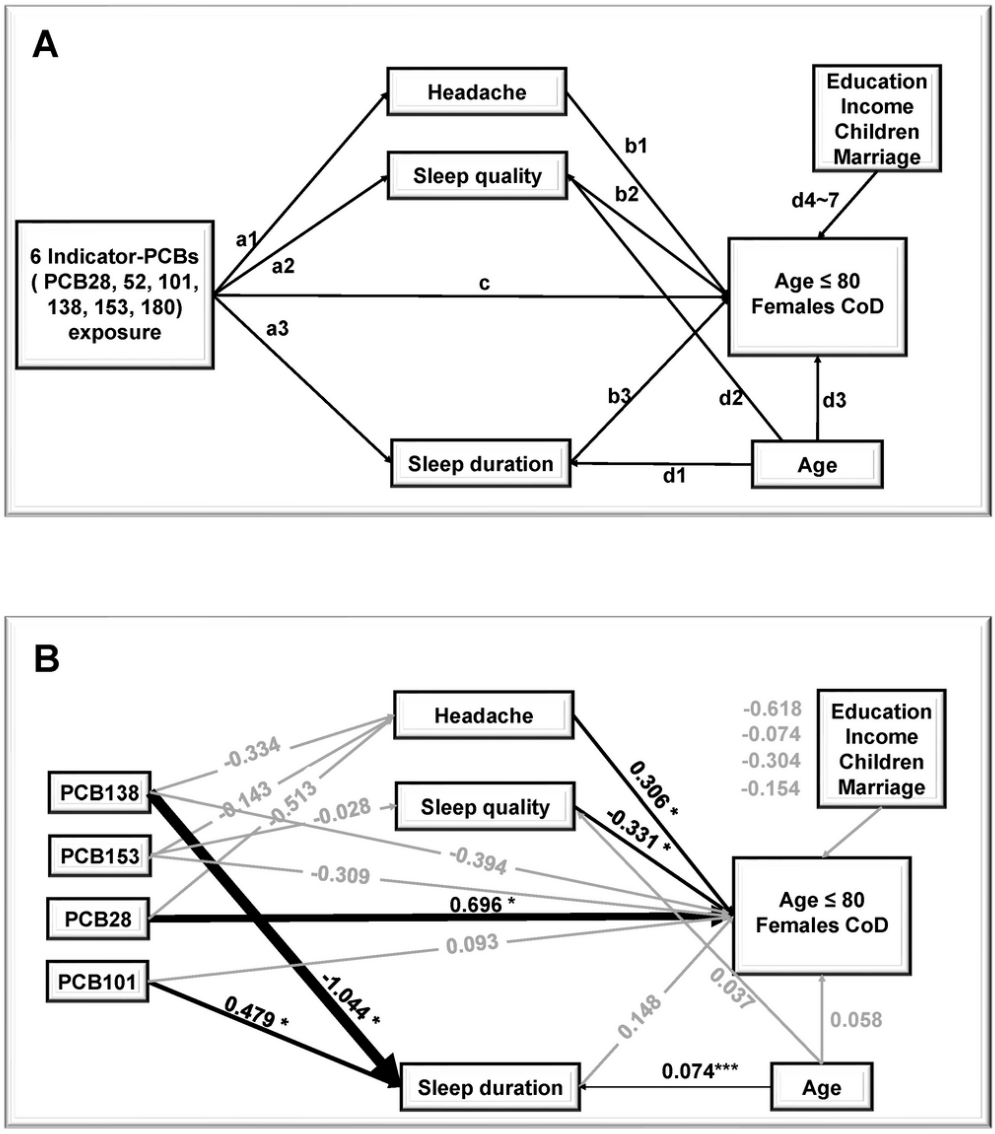

Figure 1

Process of path analysis by Structural Equation Modeling (SEM). A. The hypothesis model of 6 indictor-PCBs and female participants CoD and confounding factors; B. The final SEM for the direct effect of PCB28 exposure on COD in female participants with age below and equal to 80 years. The path coefficients were calculated using SEM in R (version 4.0.2) by the 'lavaan' package. The a1-3 and b1-3 estimated for indirect effects of each of the five variables (6 indictor-PCBs, headache, sleep duration, sleep quality and COD). The c estimated for direct effects between PCBs and COD. The d1-7 estimated for the confounding factors' effects on COD, sleep duration and sleep quality.

Supplementary Files

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- Additionalfile122122020EH.docx