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Childhood exposure to multiple persistent organic pollutants and midlife cognitive function

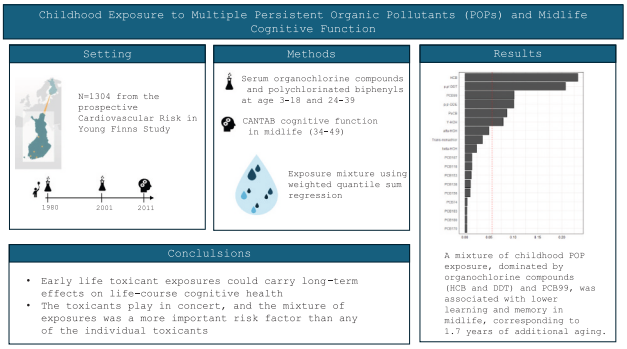
Feitong Wu [a], Noora Kartiosuo [b,c,d,*], Jari Kaikkonen [b,c,e], Costan G. Magnussen [b,c,f,g], Panu Rantakokko [h], Hannu Kiviranta [h], Katja Pahkala [b,c,i], Nina Hutri [j], Markus Juonala [k,l], Jorma S.A. Viikari [k,l], Olli T. Raitakari [b,c,m], Suvi P. Rovio [b,c,n]

[a] Department of Cardiology, the First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China
[b] Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland
[c] Centre for Population Health Research, University of Turku and Turku University Hospital, Finland
[d] Department of Mathematics and Statistics, University of Turku, Turku, Finland
[e] Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland
[f] Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia
[g] Alliance for Research in Exercise, Nutrition and Activity (ARENA), Allied Health and Human Performance, University of South Australia, Adelaide, Australia
[h] Department of Health Security, Finnish Institute for Health and Welfare (THL), Kuopio, Finland
[i] Paavo Nurmi Centre and Unit for Health and Physical Activity, University of Turku, Finland
[j] Tampere Centre for Skills Training and Simulation, Tampere University, Finland
[k] Department of Medicine, University of Turku, Turku, Finland
[l] Division of Medicine, Turku University Hospital, Turku, Finland
[m] Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland
[n] Department of Public Health, University of Turku and Turku University Hospital, Turku, Finland

HIGHLIGHTS

- Childhood persistent organic pollutant (POP) exposure is associated with adult cognition.
- Especially memory and learning are lower for those with high levels of toxicants.
- The most important POPs included organochlorine pesticides and PCB-99.

GRAPHICAL ABSTRACT



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ABSTRACT

Introduction: Whether early-life exposure to persistent organic pollutants (POPs) associates with adult cognitive function is unknown. We examined the association of childhood serum POPs levels with cognitive function in midlife.

* Corresponding author at: University of Turku, FI-20014, Turku, Finland.
E-mail address: noora.kartiosuo@utu.fi (N. Kartiosuo).

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Early-life exposures
Cohort studies

Methods: This was a prospective cohort study of 1304 children aged 3–18 years. Childhood serum levels of 18 POPs including p,p′-dichlorodiphenyltrichloroethane (p,p′-DDT), p,p′-dichlorodiphenyldichloroethylene (pp′-DDE), pentachlorobenzene (PeCB), hexachlorobenzene (HCB), hexachlorocyclohexanes (HCHs), polychlorinated biphenyls (PCBs), *trans*-nonachlor were measured in childhood and early adulthoood. In mid-adulthood, cognitive function was measured using a computerized test battery (CANTAB) including tests for 1) memory and learning, 2) working memory, 3) reaction time, and 4) information processing. We assessed the overall association of the 18 POPs with cognitive function (normalized with mean 0 and standard deviation 1) by deriving a POP mixture index using weighted quantile sum (WQS) regression.
Results: For every unit-increase in the derived POP index (range 0–3, SD = 0.7), 0.129 (95% CI: −0.244, −0.014) SD-units lower memory and learning in midlife was observed when adjusting for covariates and adult POP index. This association was stable as shown by repeated holdout validation (β = −0.086, 95% confidence interval: −0.160 to −0.011), corresponding to 1.7 years additional aging on memory and learning. The POP mixture index was predominated by HCB (23%), p,p′-DDT (21%), PCB99 (10%), and p,p′-DDE (10%).
Conclusions: Childhood exposure to a high level of multiple POPs, such as HCB, p,p′-DDT and PCB99, was associated with poorer memory and learning in midlife, independent of adult exposure to those POPs.

1. Introduction

Poor cognitive function in midlife is a major risk factor for dementia in later life (Singh-Manoux et al., 2012). Thus, optimising cognitive reserve in midlife is important in any preventive strategies of dementia (Livingston et al., 2017). Potential causes of poor cognitive function could be genetic, lifestyle and environmental factors (Livingston et al., 2017). Although studies have suggested that environmental pollutants may play a role in cognitive function across life stages (Bible, 2014; Davis et al., 2019; Gaspar et al., 2015; Gonzalez-Alzaga et al., 2015; Kim et al., 2015; Medehouenou et al., 2019; Richardson et al., 2014; van Wendel de Joode et al., 2016), data on the long-term influence of early life exposure to environmental pollutants on cognitive function later in life is limited. Furthermore, the existing findings based on follow-up periods from pregnancy or early childhood until childhood or adolescence are inconclusive (Berghuis et al., 2018; Davis et al., 2019; Kokroko et al., 2020; Simeone et al., 2022), positive or negative associations (Davis et al., 2019; Gaspar et al., 2015; Gonzalez-Alzaga et al., 2015).

Persistent organic pollutants (POPs) are considered priority pollutants because of their bio-accumulative and long persistent nature (Alharbi et al., 2018). These chemicals were mainly used in pesticides and industry, and while they were banned in Europe in 1970s and globall (Secretariat, 2001), and while they were banned in Europe in 1970s (Füll, 2001) and globally by Stockholm Convention in 2001 (Secretariat, 2001), due to their bioaccumulation and persistence, they can still be found in the environment as well as human samples (Tang et al., 2025; Vorkamp and Rigét, 2014). After these policies took place, the main source of exposure to these chemicals has been food, especially fish (Kiviranta et al., 2004; Kiviranta IV et al., 2001), although the levels of e.g. PCBs in Baltic herring have significantly decreased (Airaksinen et al., 2014; Suomi et al., 2024). Among various POPs, Dichlorodiphenyltrichloroethane (DDT) is the first synthetic organochlorine pesticide, most widely used around the world from the 1940s to the 1980s. Despite being prohibited in the 1970s by many countries, and in particular, banned in Finland in 1976, (Füll, 2001), it was reintroduced by the World Health Organization in 2006 to prevent malaria in high-risk areas (Rehwagen, 2006; WHO, 2023). Nonetheless, debate continues about its use and its influence on cognitive health is not well known. Previous studies have suggested a detrimental association of DDT and dichlorodiphenyldichloroethylene (DDE, breakdown product of DDT) with cognitive function in children and dementia in older adults (Bible, 2014; Davis et al., 2019; Kim et al., 2015; Medehouenou et al., 2019; Richardson et al., 2014). However, the long-term association of early life exposure to DDT/DDE on cognitive function in adulthood is unknown. Likewise, many other POPs have been associated with cognitive function (e.g., polychlorinated biphenyls (PCBs)) (Alharbi et al., 2018; Berghuis et al., 2018; Bible, 2014; Cowell et al., 2018; Davis et al., 2019; Gibson et al., 2018; Gonzalez-Alzaga et al., 2015; Kokroko et al., 2020; Richardson et al., 2014; Simeone et al., 2022; van Wendel de Joode et al., 2016), but few studies have investigated early life exposures, with conflicting results (Berghuis et al., 2018; Gonzalez-Alzaga et al., 2015; Kokroko et al., 2020; Simeone et al., 2022). Importantly, none of these studies considered how the multiple POPs may function in concert, and whether they have a long-term influence on cognitive health. Therefore, this study examined the association of childhood exposure to multiple POPs (e.g., p,p′-DDT, p,p′-DDE and penta- and hexachlorobenzene (PeCB, HCB) and PCBs) with adulthood cognitive function, independent of corresponding adulthood POPs exposure.

2. Methods

2.1. Participants

Participants were from the Cardiovascular Risk in Young Finns Study, which is an ongoing nationwide population-based cohort study to assess childhood risk factors underlying cardiovascular diseases (Raitakari et al., 2008). In 1980, 4320 individuals aged 3, 6, 9, 12, 15 and 18 years of age were randomly selected from the population register of all five university cities with medical schools and their rural surroundings in Finland and invited to the study. Of these, 3596 children participated in the baseline survey. Due to resource reasons, the POPs levels in serum samples collected in 1980 and 2001 were assessed at two stages, first in 2016/2017 (with overrepresentation of participants with type 2 diabetes) and second in 2022/2023. Cognitive function was assessed in the 2011 follow-up visit. In the final dataset, we included 1304 participants who had data on adulthood cognitive function, childhood and adulthood POPs and who did not have missing data on covariates (Fig. S1). All participants provided written informed consent, and the study was approved by local ethics committees.

2.2. Cognitive function

In 2011, cognitive function was measured using a computerized cognitive testing battery (CANTAB®, Cambridge Cognition, Cambridge, United Kingdom) (Rovio et al., 2016; Rovio et al., 2017). The test battery in our study included: 1) Motor Screening (MOT) test used as a training/screening tool to indicate difficulties in test execution; 2) Paired Associates Learning (PAL) test measuring visual and episodic memory and visuospatial associative learning (hereafter memory and learning); 3) Spatial Working Memory (SWM) test measuring short-term and spatial working memory and problem solving (working memory); 4) Reaction Time (RTI) test measuring reaction and movement speed and attention (reaction time); and 5) Rapid Visual Information test (RVP) measuring visual processing, recognition, and sustained attention (information processing).

Each test describing different domain of cognition produced several variables. To reduce the dimension of the data and build variables that better describe the multifaceted nature of each cognitive domain

measured by the tests, principal component analyses (PCA) were conducted separately for all individual tests to identify linear combinations accounting for most of the variation within the dataset (Rovio et al., 2016). For each test, the first principal components were used to represent cognitive function in the specific cognitive domains. Table S1 presents the loadings of the variables within each test pattern on the first principal component and Fig. S2 presents the scree plots of each PCA. The MOT test component was excluded because all participants had the maximum score. Other components were normalized into z-scores using a rank order normalization procedure by subtracting the average from each observation and scaling this difference by the standard deviation of the variable. This resulted in four variables describing cognitive function, each with mean 0 and standard deviation (SD) 1.

2.3. Persistent organic pollutants

Serum samples were collected in childhood (1980) and adulthood (2001) and stored at −20 °C until they were analyzed in 2016/2017 and 2022/2023. From the samples (200 μl) 10 polychlorinated biphenyl (PCB) congeners (74, 99, 118, 138, 153, 156, 170, 180, 183 and 187), 9 oganochlorine (OC) compounds (PeCB, HCB, α-HCH, β-HCH, γ-HCH, oxy-chlordane, trans-nonachlor, p,p′-DDT and p,p′-DDE), and 3 polybrominated biphenyl ethers (BDEs; 47, 99 and 153) were analyzed (for details of analytical method and quality control see Method S1). Values below the quantitation limits (LOQ) were assigned a value equal to one half of the detection limit in statistical analysis. Oxychlordane, BDE47, BDE99, and BDE153 were removed from analysis as almost all participants (>98%) had undetectable childhood levels. All POP results are presented on volume basis (pg/ml). When comparing levels with other studies in the discussion, we crudely converted results to lipid-based values (ng/g lipid) by scaling the measurements with 0.5 g/100 ml, assuming an average serum lipid level of 0.5%.

2.4. Covariates

Potential confounders of the toxicant exposure – cognition association were adjusted for in the analyses (Fig. S3, Method S2). Children's height and weight were measured and BMI was calculated as weight/(height)^2 (kg/m^2). Childhood blood pressure and serum total cholesterol were measured using standard methods (Porkka et al., 1997). Participant's own smoking in childhood was defined as smoking daily prior to age 18 years using available data from baseline and the subsequent 3- and 6-year follow-ups. At each follow-up, participants below the age of 12 were considered non-smokers. Childhood school performance, which is here considered as a proxy of cognitive function childhood, was measured as the mean of grades in all individual school subjects. The grades here refer to the teacher's evaluaion of the child's performance in each of the school subject, ranging from 4 to 10. Data for those who were not of school age at baseline (≤6 years) were obtained from the subsequent 3- and 6-year follow-ups. Childhood socioeconomic status (SES) was constructed as the mean of three indicators (Laitinen et al., 2020): the number of study years of the parent with the highest education (standardized into z-scores, mean = 0, SD = 1), mean household income (standardized into z-scores, mean = 0, SD = 1), and a dichotomised indicator of parental unemployment (0 for a history of unemployment and 1 otherwise). Adulthood SES was defined as the self-reported number of years studied based on the follow-up questionnaires in years 2011, 2007, or 2001, using the most recent available information.

2.5. Statistical analysis

The concentration distributions of all POPs were skewed and were transformed by means of the natural logarithm and then standardized into z-scores (mean = 0, SD = 1) for analyses. Linear regressions were used to estimate the association between individual childhood POPs and adult cognitive function, adjusting for sex, childhood age, BMI, SES, smoking, systolic blood pressure, serum total cholesterol, school performance, adulthood education, year of POPs analysis, and the corresponding adulthood POP level.

To account for the multicollinearity among POPs, weighted quantile sum (WQS) regression was used to derive POP indices associated with cognitive function (Carrico et al., 2015). This method estimates relative weights for each of the POPs, treated here as quartiles, and uses these weights in building a weighted sum of the POP quartiles. The final POP index, i.e., the weighted sum of POP quartiles for each participant was the mean of the estimated scores across the bootstrap samples ($n = 100$), indicating the relative importance of each POPs in the mixture-outcome association. Bootstrapping approach was used to improve the sensitivity to identify the important predictors in the mixture (Carrico et al., 2015). In each bootstrap sample, data were randomly divided in 40% of the dataset for training, which was used for estimating the weights, and 60% for validation, which was used to test the statistical significance of the obtained index (Carrico et al., 2015). As the WQS regression tests for mixture effects in one direction with the outcome (positive or negative), positively and negatively constrained POP indices were separately used to assess the association with each cognitive domain. To improve the stability of the estimates when a significant association was found, we performed repeated holdout validation where data were randomly partitioned 100 times (a 40–60 training validation split); the median of the estimates and 95% confidence intervals from the 100 repeated holdout sampling distribution were calculated as the final effect estimates (Tanner et al., 2019). Prior to our main analysis concerning childhood POP levels, we constructed an adult POP index for each cognitive domain using the same approach in order to adjust the models for adulthood POP index to gain insights on the effects of childhood POPs on adult cognition that are 'independent' of tracking of POP exposure levels and the effect of adulthood POPs on cognitive function. The analyses for the childhood POP index (the index with stronger association from either negatively or positively constrained WQS regressions) obtained for each cognitive domain were adjusted for sex, childhood age, BMI, SES, smoking, systolic blood pressure, serum total cholesterol, school performance, adulthood education, year of POPs analysis, and the corresponding adult POP index. Similarly, the analyses for the adult POP index obtained for each cognitive function domain were adjusted for the same covariates mentioned above and the corresponding child POP index.

The threshold of weight for potentially concerning childhood POPs was calculated based on the number of POP included in the WQS analysis (5.6% = 100%/18).

To demonstrate the clinical relevance of the data, we estimated POP-related years of cognitive aging for all significant associations between POP indices and cognitive function according to the effect estimate of age reported in the same cohort (Rovio et al., 2016).

To account for missing data, we performed a sensitivity analysis by repetaingrepeating above-mentioned WQS regression for associations of childhood POPs with cognitive function using inverse probability weighting. The inverse of the probability of being observed was obtained by logistic regression with age, sex, childhood SES, total cholesterol, school performance, smoking, and adult education and type 2 diabetes as predictors. Before inverse probability weighting, missing data for the predictors were imputed by multiple imputation using chained equations (20 imputed datasets). Interactions between childhood POP index for each cognitive function domain with age and sex were tested by including a product term between age/sex and each POP index. Because individuals born in the 60s were exposed to much higher levels of POPs than those born in the 70s, we also performed separate analyses stratified by age groups: aged 3–9 (n range: 521 to 564) vs. 12–18 (n range: 660 to 731) years at baseline (Table S2). All analyses were conducted in Stata 14.0 (Stata Corporation, Texas, USA) and R (version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p value<0.05 was considered statistically significant.

3. Results

Over the 31-year follow-up, 2292 participants were excluded because child POPs were not measured, covariates were missing, participants were lost to follow-up in adulthood, adult POPs were not measured, or cognitive function data was not available (Fig. S1). The analysis included 1304 participants. Mean age was 11.2 years at baseline (43% females). Those who were lost to follow-up or excluded from analysis were younger, more likely to be females, and had lower childhood SES, lower childhood school performance and adulthood education level (Table 1). Childhood serum levels of all POPs had right skewed distributions (Fig. 1). Also, due to POP restrictions during 21 years between baseline and follow-up POP measurements, serum concentrations of most POPs had decreased substantially and detection rates of p,p′-DDT, PeCB, α-HCH and γ-HCH had decreased from >80% in 1980 (childhood) to <20% in 2001 (adulthood) (Table S3). The multicollinearity of the POPs measured in childhood and adulthood are presented in Fig. S4.

In single-pollutant analysis, children exposed to high serum p,p′-DDT levels had poorer memory and learning in midlife (β = −0.077 SD per SD increase in the level, 95% confidence interval (CI): −0.136 to −0.017), adjusting for childhood covariates, adulthood education, year of POPs analysis, and the corresponding adult POP (Fig. 2). Serum trans-nonachlor level was negatively associated with working memory (β = −0.065, 95% CI: −0.131 to −0.0002). Serum p,p′-DDE levels were negatively associated with reaction time (β = −0.074, 95% CI: −0.146 to −0.002) and visual processing (β = −0.073, 95% CI: −0.140 to −0.007), while serum levels of α-HCH were positively associated with reaction time (β = 0.058, 95% CI: 0.002 to 0.114) and PeCB level was positively associated with visual processing (β = 0.080, 95% CI: 0.027 to 0.133).

WQS regression models showed a 0.129 standard deviation lower memory and learning in midlife (95% CI: −0.244 to −0.014) for every unit increase in the negative POP index (Table 2). This association was stable in repeated holdout validation (β = −0.086, 95% CI: −0.160 to −0.011) (Fig. 3). The weights of HCB (23%), p,p′-DDT (21%), PCB99 (10%), p,p′-DDE (10%), PeCB (9%) and γ-HCH (8%) predominated in this POP index (Fig. 3), indicating their relative contribution in driving the observed association. When scaled with respect to the effect of age on memory and learning, this estimate corresponds, in our population, to an additional 1.5–2 years aging on the cognitive domain of memory and learning (Rovio et al., 2016). WQS regressions did not demonstrate any associations of childhood POPs with other cognitive domains (Table 2), or adulthood POPs with any cognitive domains (Table S4).

Table 1
Baseline characteristics of study participants in young Finns study.

Characteristics[a]	Participants	
	Included	Excluded
	n = 1304	n = 2292
Age, years	11.2 (4.6)	10.0 (5.2)
Sex (females), %	43	53
Body mass index, kg/m^2	18.0 (3.1)	17.7 (3.1)
Socioeconomic status[b]	0.003 (0.59)	−0.06 (0.59)
School performance, GPA	7.8 (0.7)	7.7 (0.7)
Systolic blood pressure, mmHg	113 (11)	112 (13)
Serum total cholesterol, mmol/L	5.3 (0.9)	5.3 (0.9)
Daily smoking, %	16	15
Adulthood education, years[c]	15.5 (3.6)	14.6 (3.5)

Abbreviations: GPA, grade point average, mean of all school grades.
Values are mean (SD) unless otherwise stated.
[a] Variables are childhood data unless otherwise stated.
[b] SES was defined as the mean of the length of the parent with the highest education, mean household income and parental unemployment (coded as 0 for a history of unemployment and 1 otherwise).
[c] Including basic and vocational schooling.

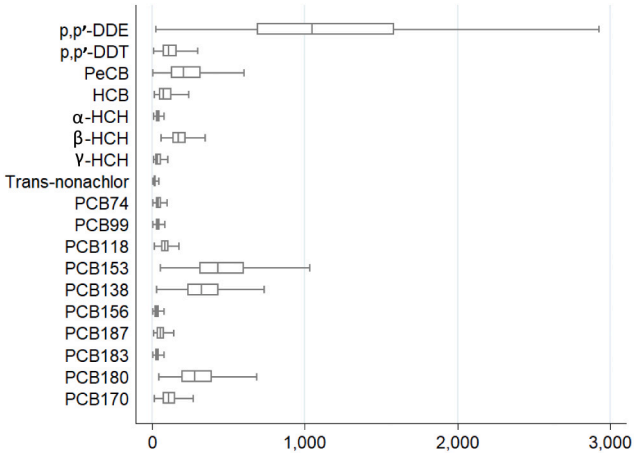

Fig. 1. Boxplot distributions of childhood serum levels (pg/ml) of the 18 persistent organic pollutants (POPs).

In the sensitivity analyses with inverse probability weighting applied to the above-mentioned WQS analyses, the results of the analyses remained nearly identical (Fig. S5 and Table S5). There were no significant interactions between age or sex with any of the POP WQS indices for any cognitive function domain (p > 0.05 for all). However, analysis stratified by baseline age showed that the association between childhood POPs and adult memory and learning was primarily seen in those older at baseline (aged 12–18 years, β = −0.156, 95% CI: −0.303 to −0.008 vs. aged 3–9 years, β = −0.020, 95% CI: −0.168 to 0.128) (Table S6).

4. Discussion

This 31-year prospective cohort study showed that high childhood serum levels of multiple POPs, predominated by HCB, p,p′-DDT, PCB99, p,p′-DDE, PeCB and γ-HCH were associated with poorer memory and learning in midlife, even after accounting for adulthood POPs, corresponding to the effect of around 1.7 years additional aging on memory and learning in this population (Rovio et al., 2016). The potential long-term harms of these chemicals highlight the importance of public health efforts to reduce environmental exposures in early life, especially in areas where these chemicals are widely used. It is worth noting, that for 3 (p,p′-DDT, PeCB and γ-HCH) of the 6 chemicals that exceeded the threshold of weight for potentially concerning POPs (Fig. 3), childhood detection rates of 84–100% had dropped to detection rates of 0–20% in adulthood (Table S3). This highlights the importance of life-course monitoring of exposures that may change drastically over time. Interestingly, in the analyses stratified by childhood age, an association between POPs exposure and cognitive function was only seen in the older participants. Due to the study setting, where a single measurement was taken in early life in year 1980, we were unable to distinguish whether this effect is due to adolescence being more sensitive period than childhood, or due to e.g. secular trends in the exposure levels, as the different age groups in our data have likely had different levels of exposure in their early life. Importantly, in our sample, the older participants were born before the bans on POPs took place and thus have potentially had also “direct” exposure to these chemicals. Previous studies have been primarily focussed on associations between prenatal exposure to POPs and neurodevelopmental outcomes, whereas studies encompassing childhood or adulthood exposure levels or follow-up periods until adulthood are sparser (Gao et al., 2025).

Our study examined childhood exposure and extended the influence on cognitive function into adulthood, with consideration of various correlated POPs. In line with our findings, an adverse association has been reported in most studies (Casadó et al., 2019; Kyriklaki et al.,

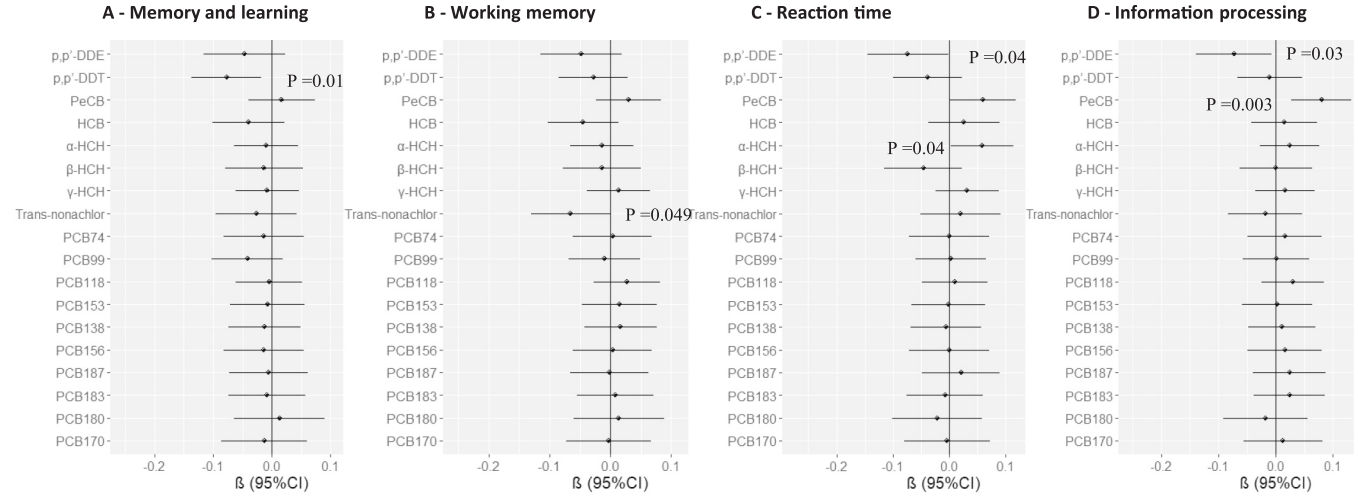

Fig. 2. Beta coefficients and 95% confidence intervals for each cognitive function domain (standardized) per standard deviation increase in log-transformed serum level of each persistent organic pollutant (single-exposure analysis).

Table 2
Weighted quantile sum (WQS) regression for association of childhood POP index with cognitive function in midlife.

	Positive POP index	Negative POP index
	β (95% CI)	β (95% CI)
Memory and learning (PAL)	−0.057 (−0.160 to 0.046)	**−0.129 (−0.244 to −0.014)**
Working memory (SWM)	−0.046 (−0.158 to 0.066)	−0.032 (−0.132 to 0.068)
Reaction time (RTI)	0.063 (−0.046 to 0.172)	0.014 (−0.092 to 0.120)
Information processing (RVP)	−0.047 (−0.152 to 0.059)	−0.051 (−0.153 to 0.052)

Abbreviations: CI, confidence interval. POP, persistent organic pollutants. PAL, paired associated learning. SWM, spatial working memory. RTI, reaction time. RVP, rapid visual information test.
The WQS regression is inherently one-directional and tests only for mixture effects positively or negatively associated with the outcome. Thus, we presented results for analyses constrained to mixture effects of POPs both positively and negatively associated with the outcome. The beta coefficient indicates a standard deviation increase in the cognitive function domain per unit increase in the POP WQS index.
Bold denotes statistical significance, $p < 0.05$.
All analyses were adjusted for sex, childhood age, body mass index, social economic status, systolic blood pressure, total cholesterol, school performance, adulthood education, year of POPs analysis (2016/2017 vs. 2022/2023), and adulthood POP WQS index.

2016), though some studies did not show an association (Forns et al., 2012; Gascon et al., 2013). For example, a Greek mother-child cohort showed that children with high maternal HCB concentrations had poorer perceptual performance, general cognitive, executive function and working memory at age 4 years (Kyriklaki et al., 2016). In contrast, a Spanish birth cohort did not show an association between postnatal exposure to HCB and mental scores (e.g., cognitive and language scale) at age 14 months (Gascon et al., 2013). The reasons of the discrepancy might be explained by the different measures of cognitive outcomes and the level, sources, and timing (historical and life-course) of exposure measurement.

As DDT was a predominant POP in the negative association of multiple POPs with memory and learning, it provides first evidence to suggest a long-term unfavourable influence of childhood exposure to this chemical, regardless of the much lower level of exposure in adulthood to DDTand other POPs. The association is biologically plausible since exposure of human neuroblastoma cells to DDT has been associated with elevated amyloid precursor protein levels (Richardson et al., 2014). Previous studies have primarily focussed on prenatal exposure to DDT or DDE and cognitive function, although two small cross-sectional studies have assessed the association between childhood exposure to other (non-DDT/DDE) pesticides and cognitive function (Gonzalez-Alzaga et al., 2015; van Wendel de Joode et al., 2016). In line with our findings, Gaspar et al. found that high prenatal DDT levels were associated with slower processing speed at age 7 years, and prenatal DDE levels were inversely associated with processing speed at age 7 years in girls, but not in boys (Gaspar et al., 2015). However, that study found no associations between prenatal DDT and DDE levels and working memory at age 10.5 years (Gaspar et al., 2015). This may be due to the lower level of DDT compared to that in our study (median = 12.1 vs. ~22.6 ng/g-lipid) and that the adverse influence diluted over time. In line with this, our data also showed that the association of childhood POPs with adult memory and learning was primarily seen in those older at baseline, who have been exposed to higher DDT levels for a longer duration. Moreover, adulthood POPs (including DDT) were not associated with any cognitive function, when DDT levels were substantially reduced (median ~ 4.5 ng/g-lipid among 20 participants with a detectable adulthood level). Together, the results regarding prenatal and early life-course exposure to DDT highlight the potential influence of early life exposure to a high level of DDT on cognitive function later in life. Our results further suggest these effects to last until mid-adulthood.

Of 10 PCBs measured, PCB99 contributed to the adverse association with cognitive function in our multiple-exposure analysis. Consistent with this, previous studies have generally shown inverse associations of prenatal PCB levels with cognitive function in infancy or childhood (Kyriklaki et al., 2016; Patandin et al., 1999; Schantz et al., 2003; Stewart et al., 2008). In contrast, two studies have shown no associations between childhood exposure to PCB with cognitive function in young children (Patandin et al., 1999; Simeone et al., 2022). For example, a Dutch study showed that prenatal but not childhood exposure to PCB was associated with poorer overall cognitive and sequential and simultaneous processing domains in children aged 42 months (Patandin et al., 1999). Of note, the findings from our study may not be directly comparable to previous studies as they generally used an approach of single-exposure analysis. This highlights the importance of applying a multiple-exposure analytic approach in environmental research, which could help describe the overall association of correlated chemicals.

We are not aware of any studies examining the association of childhood HCHs with adult cognitive function. Our WQS-analysis showed γ-HCH as the main effect driver among HCH congeners that

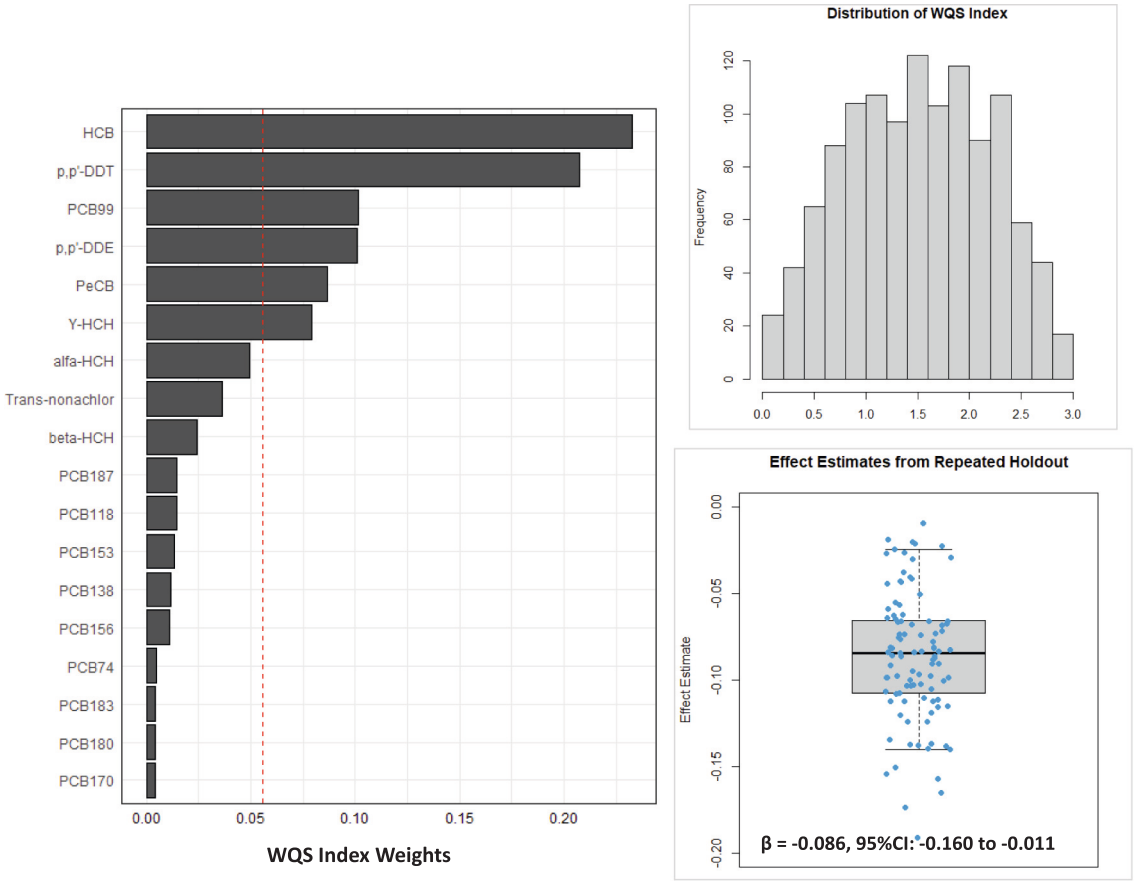

Fig. 3. Negatively Constrained Weighted Quantile Sum (WQS) Regression with 100 Repeated Holdouts for Association of Childhood POPs with Memory and Learning (PAL) in Midlife.

have very different toxicokinetic behaviour. For γ-HCH the serum half-life is approximately 20 h among children whereas β-HCH accumulates in fatty tissues and is metabolized more slowly, resulting in a half-life of approximately seven years. As γ-HCH has complex metabolism mainly to a variety of chlorophenol metabolites (Fitzloff et al., 1982), the actual effect can be due to these metabolites. In line with this, higher levels of urinary 2,4,6-trichlorophenol, an organochlorine compound, were associated with increased risk of attention deficit hyperactivity disorder among 2546 US school-aged children (Xu et al., 2011).

The main strength of this study is the longitudinal follow-up commmenced in childhood in a large population-based cohort, allowing us to examine the early-life exposures with adulthood cognitive function. Our analyses acknowledged the multifaceted nature of childhood POPs by considering their multicollinearity using the WQS approach and had the possibility to adjust the corresponding exposure in adulthood. Thus, our results present the independent associations between exposure to childhood POPs and adulthood cognitive function. Limitations of our study include, like all single country studies, that the findings may not be generalizable to other areas of the world. Moreover, we had missing data after an extensive study period of 31 years. We showed that participants who were lost to follow-up or excluded from analysis were younger and had lower social economic status and school performance and low adulthood education level than those remaining in the analytical sample. However, sensitivity analyses using inverse probability weighting did not alter the associations of POPs with cognitive function, suggesting minor influence of missing data on our findings. While treating the POPs as quartiles in the WQSR analyses limits the influence of non-normal distribution and potential outliers, especially in adulthood, some variables had majority of the values below the limit of quantification. The reduced variability in the quartiles for these variables may limit the interpretability and stability of the weights estimated in the WQSR. Finally, while we were able to recognize and adjust for various potential confounders, some potential confounders, such as nutrition, especially intake of various fish species or breast-feeding through the early life-course, have remained unobserved or uncontrolled for.

In conclusion, childhood exposure to high levels of multiple POPs, especially HCB, p,p′-DDT, PCB99, p,p′-DDE, PeCB and γ-HCH, was associated with poorer performance on memory and learning in midlife, corresponding to approximately 1.7 years additional aging with regard to this cognitive domain.

CRediT authorship contribution statement

Feitong Wu: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Conceptualization. **Noora Kartiosuo:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Jari Kaikkonen:** Writing – review & editing, Data curation. **Costan G. Magnussen:** Writing – review & editing, Supervision. **Panu Rantakokko:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Hannu Kiviranta:** Writing – review & editing, Methodology, Data curation. **Katja Pahkala:** Writing – review & editing, Funding acquisition, Data curation. **Nina Hutri:** Writing – review & editing, Data curation. **Markus Juonala:** Writing – review & editing, Data curation. **Jorma S.A. Viikari:** Writing – review & editing, Data curation. **Olli T. Raitakari:** Writing – review & editing, Supervision, Resources, Funding acquisition, Data curation. **Suvi P. Rovio:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2026.181552.

Data availability

Data collected within EU comprises health related participant data and their use is therefore restricted under the regulations on professional secrecy (Act on the Openness of Government Activities, 612/1999) and on sensitive personal data (Personal Data Act, 523/1999, implementing the EU data protection directive 95/46/EC). Due to these legal restrictions, the data from YFS study cannot be made publicly available. However, data access may be permitted on a case-by-case basis upon request only. Data sharing outside the group is done in collaboration with the YFS group and requires a data-sharing agreement. Investigators can submit an expression of interest to the coordinator of the YFS (Olli Raitakari, olli.raitakari@utu.fi).

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