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Long-term mercury exposure and cognitive functions in a First Nation community in Northern Ontario, Canada

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ABSTRACT

Prenatal, childhood, and current mercury (Hg) exposure through fish consumption have each been associated with cognitive deficits, but little information exists on the consequences of long-term exposure among adults. Since 1962, Grassy Narrows First Nation has been exposed to Hg from an industrial discharge. Average Hair Hg (HHg) concentrations, initially very high, decreased over time and stabilized in the 1990's. Montreal Cognitive Assessment (MoCA) test outcomes were analyzed in 85 persons aged 32–75 y (median: 53 y) with respect to retrospective year-based HHg measurements between 1970 and 1997 and current blood Hg. Since the MoCA has not been clinically validated for Indigenous populations, residuals of age- and education-adjusted scores were used (MoCA-r scores). Lower MoCA-r scores were observed among persons in the higher quartile of maximum HHg compared to those in the lower quartile ($p = 0.007$). Clustering of the test items yielded 3 clusters representing verbal fluency and abstraction, cognitive flexibility and working memory, and visuospatial functioning. To model the evolution of HHg over time, longitudinal mixed effect models (LMEM) were performed with persons with ≥ 10 repeated year-based HHg measurements. Higher long-term past HHg was associated with lower MoCA-r and all cluster scores. No association was observed between MoCA-r or cluster scores and blood Hg, which reflects recent exposure. The findings suggest that legacy exposure can affect cognitive functioning decades later, even when average current concentrations have decreased to below recommended guidelines. Prospective studies could provide information on the rate of decline and the possible future impact of current exposure.

1. Introduction

Methyl mercury (Hg) is a well-known neurodevelopmental toxic. Many studies have shown that prenatal Hg, even at very low concentrations, is associated with cognitive deficits in children (Karagas et al., 2012; Ha et al., 2017). In the 22-year follow-up of the Faroe Islands birth cohort, a negative association was observed between prenatal Hg exposure and outcomes on domain-specific and general intelligence neuropsychological tests (Debes et al., 2016). Although studies of the birth cohort from the Seychelles Island have shown little or no association with prenatal exposure (Davidson et al., 2011; Huang et al., 2018), a follow-up study of young adults, up to 24 years of age, showed negative associations for several tests of neurocognitive functions with respect to a construct of post-natal Hg exposure (Thurston et al., 2022a).

Studies of adults exposed to methyl Hg through fish consumption have reported dose-related poorer performance on some neurobehavioral tests (Mergler et al., 1998; Yokoo et al., 2003; Silman et al., 2022; Oliveira et al., 2021a; Rebouças et al., 2024; Carta et al., 2003), but most used current indicators of exposure (hair, blood or reported fish consumption), which may or may not reflect long-term, prenatal and/or childhood exposure. Sixty years after the Minamata Disaster, residents from the area who had had moderate prenatal exposure and possible postnatal Hg exposure, scored significantly lower on the Montreal Cognitive Assessment (MoCA) Test (Japanese version) compared to a non-exposed reference group; the authors suggest that neurodevelopmental cognitive deficits persist throughout life (Yorifuji et al., 2023).

The Anishinaabe community of Grassy Narrows First Nation has

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been exposed to Hg since 1962, when a chlor-alkali plant began discharging Hg-containing waste into the river system that flows into their territorial waters. In the late sixties and early seventies, fish Hg concentrations were among the highest in Canada (Rudd et al., 2021). Fish have always been central to their culture, traditions, well-being, diet, and livelihood. Government biomonitoring programs of Grassy Narrows Band members, initiated in 1970, showed that hair, blood and umbilical cord blood Hg concentrations, paralleled fish Hg concentrations, with very high concentrations in the early seventies, decreasing over time and stabilizing in the nineties (Wheatley et al., 1997; Philibert et al., 2020a; Neff et al., 2012; Rudd et al., 2017). Biomonitoring continued until 1997, when average Hg concentrations in the people of Grassy Narrows were below Canadian guidelines (Wheatley et al., 1997). Although fish Hg likewise decreased, studies carried out since 2000, report that length standardized Hg concentrations were still among the highest in Ontario (Neff et al., 2012) and Canada (Rudd et al., 2017). The possible consequences of long-term Hg exposure on cognitive functions have not been addressed.

The present study sought to examine cognitive performance among adults in Grassy Narrows with respect to current blood Hg and past long-term Hg exposure, taking into account relevant co-variables.

2. Methods

2.1. Study design

This research is part of the on-going Niibin study, carried out in partnership with the Grassy Narrows First Nation, according to OCAP (Ownership, Control, Access, and Possession) principles for research with First Nation communities (FNIGC. The First Nations Principles of OCAP®, 2022). The protocols and results were presented to and discussed at community meetings. Grassy Narrows First Nation Chief and Council initiated the research partnership, approved the study and the final manuscript. Grassy Narrows Mercury Justice Team was involved in all aspects of the study.

Recruitment strategy for the Niibin study was based on a historic Hg biomarker database (1970 – 1997), constituted from governmental surveillance programs, carried out in Grassy Narrows First Nation (Philibert et al., 2022). For historic exposure, the highest measure of equivalent hair Hg (HHg) concentration for each year sampled was used; a full description the creation of the biomarker database is published elsewhere (Philibert et al., 2020b).

2.2. Material

The Montreal Cognitive Assessment test (MoCA) was developed as a screening test for mild/moderate cognitive loss in geriatric patients (Nasreddine et al., 2005). It has been since been used in many countries and in different situations around the world (O'Driscoll and Shaikh, 2017). To ensure cultural sensitivity, the choice of test, administration procedures and scoring were discussed in detail with the Grassy Narrows Mercury Justice Team. Of common accord, we chose the Vancouver Island Coastal First Nations version of the MoCA (Cress et al., 2024) (heretofore referred to as the MoCA), as the most appropriate short cognitive test for the Niibin study. This version of the MoCA uses more culturally relevant images and words for the items in the Naming Test and the Delayed Recall Test.

The MoCA assesses functioning in 7 cognitive domains: visuospatial/executive function skills (Trail Making test (TMT), visuo-constructional skills (Cube Drawing and Clock drawing (CDT)) (0–5 points), Picture naming (0–3 points), and Attention (digit span (0–2 points), Letter A tapping test (0–1 point), Serial 7 subtractions(0–3 points)), language (Sentence Repetition (0–5 points), and Verbal Fluency (0–1 point)), Abstraction (0–2 points), memory (Delayed Word Recall, (0–5 points)), and Orientation (0–6 points) (Nasreddine et al., 2005). The total score is obtained from summing of sub-scores.

2.3. Test administration

Examinations for the Niibin study took place in the summers of 2021 and 2022. In each year, a graduate student, certified in the application of the MoCA, administered the test in a quiet room in the local school. Since some of the components of the MoCA require adequate fine motor movement and vision, results of the Grooved Pegboard Test™ (Lafayette Instruments Model 32025) for the dominant hand (GPT-d), administered as part of the motor test battery, and visual acuity assessed during the eye and vision examination (Tousignant et al., 2023), were included in the present analyses. An interview-administered questionnaire, described in detail elsewhere (Philibert et al., 2022) provided information on socio-demographics, lifestyle and social support. Current blood Hg concentrations were measured as described in Philibert et al., 2024 (Philibert et al., 2024).

2.4. Study population

A total of 102 persons matched the initial inclusion criteria: (i) at least 1 year-based equivalent HHg measurement in the historic database, and (ii) lived currently in Grassy Narrows or nearby. Of these, 99 persons (97.1 %) completed the MoCA test. To ensure data homogeneity, eligibility criteria for the present analyses were (i) MoCA test raw score ≥ 12; (ii) having completed the Grooved Pegboard test with a GPT-d score < 200 sec.; (iii) having undergone the visual examination (Philibert et al., 2024) with adequate near visual acuity (logmar < 1). A total of 85 persons fulfilled these criteria and were used for the present analyses. Complementary sensitivity analyses were conducted with all persons who had completed the MoCA test ($n = 99$), including those who did not meet the eligibility criteria.

2.5. Scoring

While the MoCA provides a reliable measure of cognitive functions (Bruijnen et al., 2020), validation and cut-off thresholds were determined with older patients with mild and moderate cognitive deficits (Nasreddine et al., 2005; Carson et al., 2018; Julayanont and Nasreddine, 2017). A study of healthy persons whose age range was between 18 and 70 years of age confirmed its psychometric properties, but showed strong correlations with age and education (Bruijnen et al., 2020). Education has likewise been identified as a significant determinant of MoCA scores in Indigenous communities (Ryman et al., 2025). Studies of cut-off thresholds have shown important cross-cultural misclassifications, which can lead to false positives (O'Driscoll and Shaikh, 2017; Ratcliffe et al., 2023; Jacklin et al., 2020; Wong et al., 2015; Walker et al., 2021).

Prior to statistical analyses, we confirmed that the MoCA raw scores of the selected study group ($n = 85$) were normally distributed (median and mean difference $= 0.2$; 2nd quartile $=$ 3rd quartile; Shapiro-Wilk test for normality: $W = 0.98$; $p = 0.110$). The contributions of age and education to the MoCA raw score were then examined, using a multivariate regression model. For the total MoCA score, age and years of education entered very significantly into the model (beta estimate $= -0.11$ [95 % CI: -0.117 – -0.04] $p = 0.002$ and education: beta estimate $= 0.35$ [95 % CI: 0.156 – 0.56] $p < 0.001$ respectively). Since the variables age and education are true confounders due to their associations with both MoCA scores, and long-term HHg levels, we used the residuals of the MoCA scores adjusted on age and education (MoCA-r) to more accurately assess the associations with Hg exposure variables.

The MoCA-r scores were analyzed either as a continuous variable or categorized as ≥ 0 (above the expected MoCA-r score for the person's age and education) or < 0 (below the expected MoCA-r score for the person's age and education).

2.6. Statistical analyses

Descriptive statistics were used to characterize participants' socio-demographic status and current and past Hg exposure. Comparisons were performed with parametric (Student *t*-test) or non-parametric (Wilcoxon Kruskal-Wallis) tests depending upon the variable's distribution. Multivariate linear regressions were performed with MoCA-r as the dependent variable and current blood Hg and other relevant covariates as independent variables.

2.6.1. Clustering

To better understand how participants' MoCA test results grouped together, an unsupervised machine learning technique for hierarchical clustering (Chiu et al., 2009) was conducted. Scores of the individual MoCA items were used as clustering features. Hierarchical clustering uses a simultaneous two-step multivariate segmentation approach (Chavent et al., 2011, 2013; Kuentz Simonet et al., 2015). One is agglomerative and aims at maximizing a homogeneity criterion by aggregating the variables into clusters using a hierarchical ascendant clustering algorithm and the other uses a mixed factorial approach (PCAMIX method in ClustOfVar R package) that imposes orthogonality of principal components (Chavent et al., 2011; Kuentz Simonet et al., 2015; Kuentz-Simonet et al., 2017). A bootstrap approach was used for maximizing the homogeneity criterion within clusters and ensuring the suitable number of clusters. The mean-adjusted Rand Index was based on the generation of 60 bootstrap samples. The number of clusters (K) was determined using aggregation levels, stability of the partitions via bootstrapped mean-adjusted Rand Index, and the distribution of box-plots. The cohesion of the partition obtained with the hierarchical approach was tested against k-means type partitioning algorithm with 2–10 random initializations (Chavent et al., 2012). A total of 3 clusters were retained.

The clustering results, constructed in R software, were validated using the VARCLUS function of the SAS computer application (JMP Professional 18.0 software), which uses a similar approach, and with Hopach package in R software, a hybrid approach to clustering.

Confirmatory factor analysis (CFA) was conducted to ensure construct validity of clustering, using a series of fit parameters (Chavent et al., 2017; Hu and Bentler, 1999): Chi-square divided by the degrees of freedom($\chi 2$/df), Standardized Root Mean Square Residual (SRMR), Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI) and Tucker Lewis Index (TLI). Internal consistency (scale reliability) for each cluster was validated using the Cronbach alpha (Cronbach, 1951).

2.6.2. Longitudinal analyses

For the Longitudinal Mixed Effect Models (LMEM), we used year-based repeated HHg measurements as the outcome (y variable) in an inverse regression to properly account for the longitudinal structure of the model. The cognitive scores, represented by a single value, and relevant covariates, constituted the independent variables (x). The approach is methodologically appropriate when the exposure is measured repeatedly over time, while the outcome of interest is fixed, as it provides an estimate of the association between long-term exposure patterns and current performance. This regression technique is flexible, suitable for small sample size, and is robust with missing data (Wiley and Rapp, 2019; Brauer and Curtin, 2018). Moreover, LMEM can accommodate complex data structures and is well-suited for hierarchical and nested data structures. The models allow for controlling of both fixed and random-effects (Gelman, 2007).

A series of LMEM were conducted for analyses with respect to long-term past Hg exposure over the sampling period. Since the profile of Hg exposure changed over the 28-year sampling period (Wheatley et al., 1997; Philibert et al., 2020a), LMEM analyses were limited to persons with ≥ 10 repeated past year-based equivalent HHg measurements (n = 28; 32.94 % of participants, representing 10–19 measurement-years (median: 11 years) and 344 year-based HHg measurements. The criterion of at least 10 year-based HHg measurements was selected to capture temporal trends, sequential variation, and to ensure measurement consistency over time. Complementary LMEM analyses were performed for persons with 5 HHg measurements or more (n = 52; 5–19 HHg measurement-years (median: 10 years; 508 HHg measurements).

To guarantee that there were sufficient observations for the LMEM, we estimated the minimal required sample size, based on formulas from Hedeker and co-authors (Hedeker et al., 1999) and direct calculations using the G*power 3.1 software (Faul et al., 2009, 2013; Kyonka, 2018). We ran *a priori* power analyses to calculate the minimum sample size. Required sample size was computed as a function of the required power level, the prespecified significance level (alpha error prob: 5 %), power (1-beta error prob: 95 %), and the population effect size (Faul et al., 2009, 2013, 2007; Kang, 2021). As there is no evidence-based measures of effect 0.2 was deemed reasonable and conservative (Cohen, 1988; Schäfer and Schwarz, 2019). The minimum number of participants required was 22 for ≥ 10 HHg and 32 for $\geq$ for 5 HHg.

The robustness of findings to potential selection bias was tested using sensitivity analyses with all persons (n = 99), who had completed the MoCA test, including those who did not fulfill all eligibility criteria. Verification of the normality of the distribution of MoCA scores for the entire group showed that they were left-skewed (median and mean difference = 0.3; 2nd quartile = 3rd quartile; Shapiro-Wilk test for normality: W = 0.97; p = 0.021).

Threshold of statistical significance in all statistical analyses was set at $p \leq 0.05$.

Database management and descriptive statistical analyses were performed using JMP Professional 18.0 (Statistical Analysis Hardware, SAS Institute). All clustering analyses were computed using the following packages of R statistical software version 3.6.1. (R Core Team, 2016), ClustOfVar and HOPACH). CFA was performed using lavaan and semPlot and Cronbach alpha analyses with psych R packages. LMEM were conducted with Stata 18 software. (Stata Statistical Software: Release 18.0 College Station, TX: Stata Corporation). LMEM analyses were verified with R packages (lme4, lmerTest, robustlmm and ggplot2).

3. Results

Table 1 presents the characteristics of the entire group (n = 85) and the sub-group with ≥ 10 repeated equivalent HHg measurements over the sampling period (n = 28). The average age of the entire group at the time of testing was 52.7 y, with a median of 53 y, ranging from 32 y – 75 y. The average number of years of education was 10 y (median 10 y, ranging from 0 – 19 y). Younger participants (< 50 y) had more formal education compared to older participants, while the range of years of education among the older persons was greater (median: 11 y; IQR: 10 –

Table 1
Characteristics of the entire group and the subgroup with ≥ 10 repeated equivalent HHg measurements over the sampling years.

	Equivalent hair mercury years			
			≥ 10 sample years	
	N	n (%)	N	n (%)
Age ≥ 50 y	85	50 (58.8)	28	23 (82.1)
Gender (Women)	85	51 (60.0)	28	18 (64.3)
Education (high school diploma +)[a]	85	18 (22.7)	28	8 (30.8)
Residential school (yes/no)	79	23 (29.1)	25	8 (32.0)
Current smoker	79	35 (44.3)	26	10 (38.5)
Current drinker	80	31 (38.8)	26	< 6
Working or looking for work	79	58 (73.5)	26	17 (65.4)
Retired or disabled	79	14 (17.7)	26	7 (26.9)

[a]. Includes persons with a high school diploma and persons with post-secondary training (certificates, degrees).

13 vs median: 8 y IQR: 6.25 – 11, respectively; Wilcoxon/Kruskal-Wallis Chi Square= 14.9; $p < 0.0001$). In Canada, Indigenous children were taken from their homes and placed in residential schools (Wilk et al., 2017; The Truth and Reconciliation Commission of Canada, 2015). In the present study, among the older persons (≥ 50 y), 47.8 % had spent time in a residential school, for an average of 5 y (median: 4.5 y, ranging from 1 – 12).

The sub-group (≥10 HHg measurements) were older (median age 58 y, ranging from 41 to 74 y); 82.0 % were over 50 years of age (Table 1), and proportionally more were retired or disabled. With respect to the entire group, proportionally fewer persons smoked and there were fewer heavy drinkers (<6 persons); a lower proportion were currently working or looking for a job and more were retired or disabled.

Fig. 1a shows the distribution of the residual MoCA scores, adjusted on age and education (MoCA-r). No differences were observed in the MoCA-r scores between men and women, having been sent to a residential school, or current smoking and heavy drinking ($p > 0.7$). Participants, who were currently in the workforce had higher MoCA-r scores compared to those who were retired or disabled (mean: 0.53; SD: 2.87 vs mean: −1.34; SD: 3.56; one-tailed *t*-test = 2.39; $p > |t| = 0.010$).

Fig. 1b provides the distribution of MoCA-r for the subgroup with ≥ 10 HHg repeated measurements. No differences were observed with respect to having been sent to a residential school, current drinking, or smoking ($p > 0.2$). In this subgroup, there was no difference in the MoCA-r mean score between those who worked and those who were retired or were disabled.

No difference was observed in the MoCA-r mean score between those who were included in the sub-group with ≥ 10 year-based HHg measurements (n = 28) and those who had fewer repeated HHg measures (n = 57) (mean: 0.08 (SD: 2.77); median: −0.034; IQR: −1.56 – 1.52; < 10 HHg measures: mean: −0.04 (SD: 3.31); median −0.23; IQR: −2.11 – 2.57; Kruskal-Wallis Chi Square = 0.04; p = 0.844)

Current blood Hg samples were available for 82 participants. Mean blood Hg concentration was 5.46 μg/L; SD: 5.56 (median 4.01 μg/L (IQR: 1.00– 7.82 μg/L). Men had higher blood Hg compared to women (median: 5.52 μg/L (IQR: 1.00– 11.63 μg/L) vs 3.41 μg/L (IQR: 0.85 – 5.72 μg/L), respectively), but the difference did not reach significance threshold (Wilcoxon Kruskal-Wallis Chi square = 2.76; p = 0.097). No significant relations between MoCA-r and current blood Hg were observed in linear multivariate regression analyses, with sex, as a covariate, included the model.

For the 1970 – 1997 sampling period, Figs. 2a and 2b illustrate the mean year-based equivalent HHg on a base 10 log scale, for (a) the entire group and for (b) those with ≥ 10 repeated measurements, respectively. Overall, HHg decreased over time.

Fig. 3a and b illustrate the HHg evolution over time for those with MoCA-r scores higher than their age and educational level (≥ 0) and those with lower values (<0) for the entire group and the subgroup with ≥ 10 HHg measurements over the 28 years.

For the entire group, maximum HHg varied between 0.5 μg/g and 183 μg/g (mean: 11.43 μg/g; median: 5.2 μg/g; IQR: 1.9 – 12.45 μg/g). MoCA-r scores were significantly higher (one-tailed *t*-test = 2.57; p = 0.007) among those with maximum HHg in the lower 25th percentile (≤ 1.9 μg/g) compared to those with maximum HHg in the upper 75th percentile (≥ 12.45 μg/g). Fig. 4 shows the density plot of MoCA-r scores for persons in the lower and upper quartiles.

Cluster analyses for the MoCA items identified 3 distinct clusters, confirmed through CFA.: Cluster 1: Trail making and Digit Span; Cluster 2: Cube drawing and Clock drawing; Cluster 3: Language Fluency and Abstraction (Similarities). The memory (Delayed Word Recall), Sentence Repetition, Serial 7 subtractions, Letter A tapping test, and Orientation items did not enter into the clusters. In the orientation test, all participants responded accurately for where they were (school), the community (Grassy Narrows), and the year; very few (<6) did not know the month or the day of the week and 15 % did not know the exact date.

Taking age and education into account, women had higher scores compared to men for Cluster 1 (one-tailed *t*-test: 2.03; p = 0.022); the other cluster scores were similar for men and women. No difference was observed for any of the clusters with respect to drinking practices over the past year or current smoking. No association was observed for any of the cluster scores with current blood Hg.

Table 2 presents the results of the LMEM for retrospective repeated HHg measurements (y-variable) with the MoCA-r score and the 3 clusters (adjusted for age and education) for persons with at least 10 samples of year-based HHg (n = 28). Since some items that were included in Clusters 1 and 2 depend on fine motor dexterity, the models were re-run with GPT-d as a covariate. GPT-d did not enter significantly into the models, nor did it modify the outcomes (Supplementary Material Table 1).

Sensitivity analyses, performed with persons who had ≥ 5 HHg measurements (Table 3), showed similar associations between MoCA-r and long-term repeated hair measurements. Including GPT-d as a covariate did not modify the associations (Supplementary Material Table 2).

Sensitivity analyses, carried out with the MoCA raw scores for all persons who completed the MoCA test (n = 99), showed similar distributions of socio-demographic characteristics to the study group (Supplementary Table 3). Multivariate linear regression analyses showed no association between MoCA raw scores and current blood Hg, taking into account age, education and sex. A 2.70 MoCA point

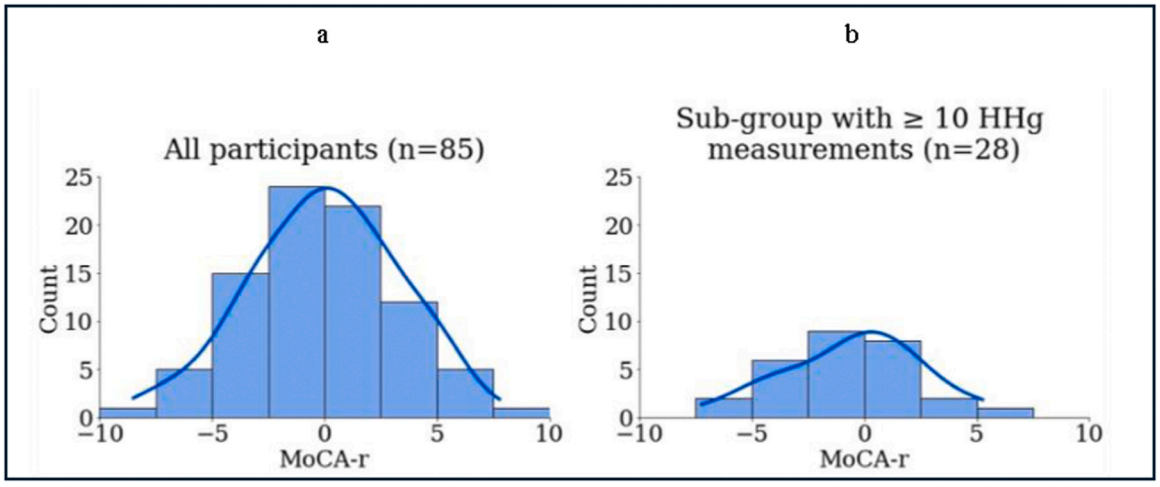

Fig. 1. Distribution of MoCA-r scores for (1a) the entire group (n = 85) and (1b) the sub-group with ≥ 10 repeated hair Hg measurements (n = 28).

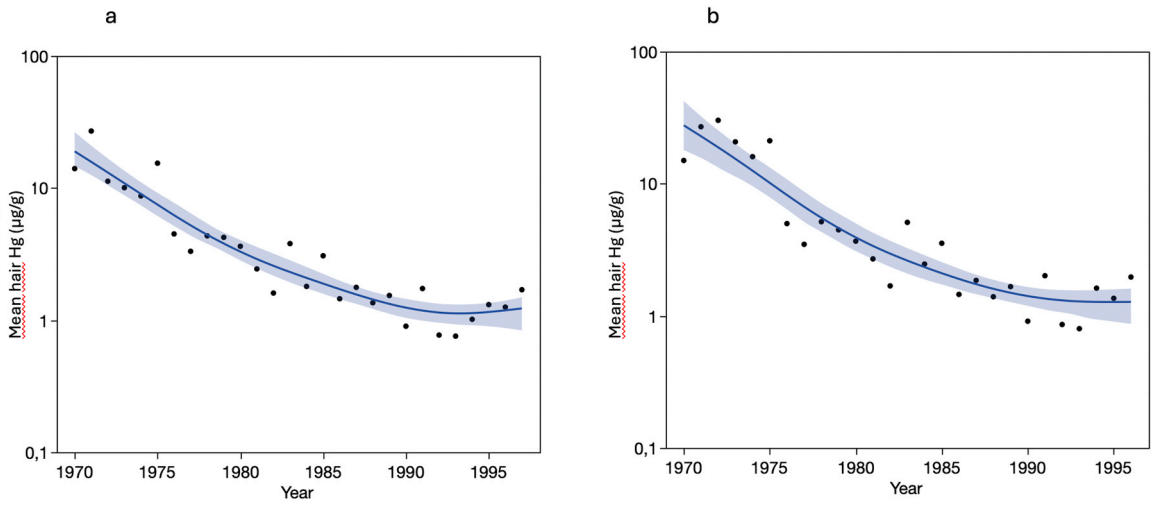

Fig. 2. Mean hair Hg concentrations over time for (1a) the entire group (n = 85; 591 HHg measurements) and (2b) the sub-group with ≥ 10 repeated hair Hg measurements (n = 28; 344 HHg measurements). The shaded area is the 95 % Confidence Interval.

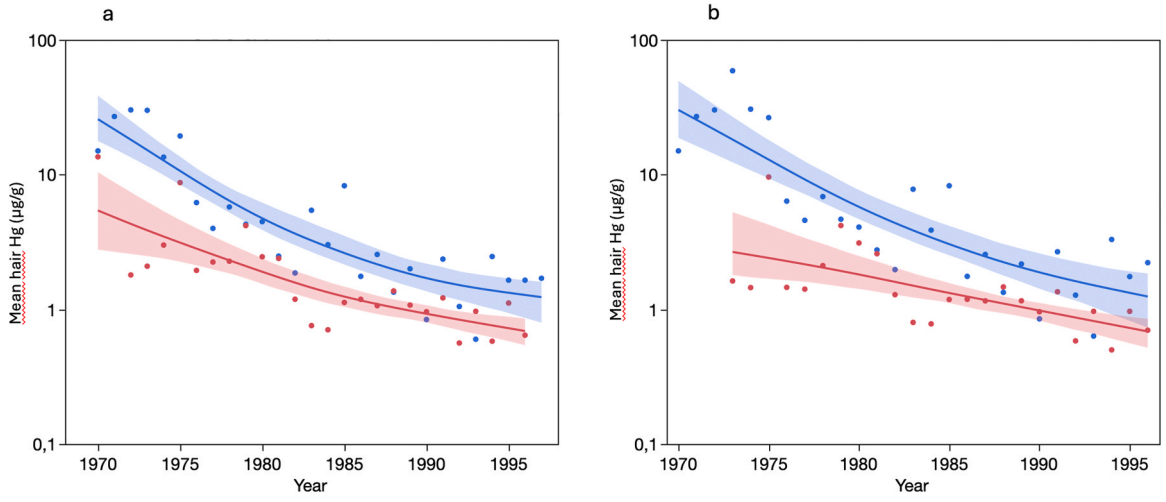

Fig. 3. Mean hair Hg concentrations for persons whose MoCA-r was ≥ 0 (higher than expected for the same age and educational level over time (red line) and < 0 (lower than expevted for their age and educational level) (3a) for the entire group (red line: n = 40; blue line: n = 45) and (3b) for the subgroup (red line: n = 14; blue line: n = 14). The shaded areas are the 95 % Confidence Intervals.

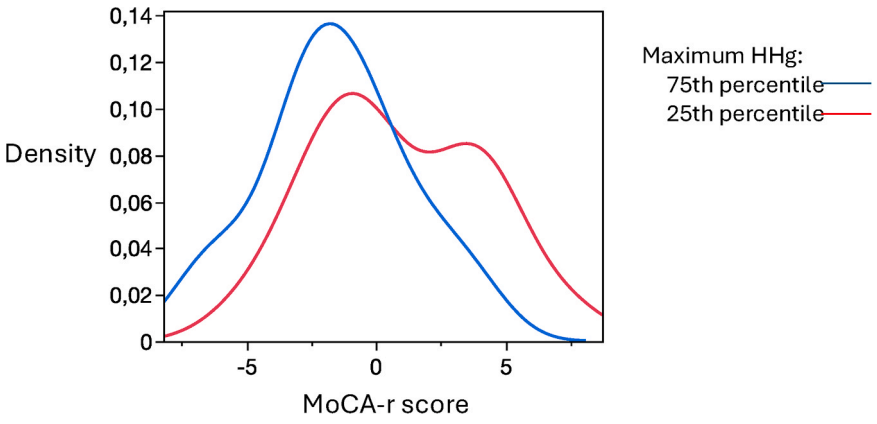

Fig. 4. MoCA-r density plot of those in the 75th percentile of maximum hair Hg (n = 21) and those in 25 the percentile (n = 21).

Table 2
Longitudinal Mixed Effects Model (LMEM) estimates for retrospective HHg with the MoCA-r score and the 3 clusters (adjusted for age and education) for persons with ≥ 10 samples of year-based past HHg (n = 28; 344 HHg measurements).

	Estimate (μg/g)	95 % Confidence Interval	p-value
MoCA-r	−0.62	−1.09 – −0.14	0.011
Cluster1 (Trail making and Digit Span)	−1.06	−1.97 – −0.15	0.023
Cluster2 (Block Drawing and Clock)	−1.88	−2.72 – −1.04	0.000
Cluster3 (Language Fluency and Abstraction)	−0.67	−1.30 – −0.04	0.037

Mixed effects models included sex, month and year of sampling as fixed effects and age of sampling nested in year of sampling as random effects.

Table 3
MoCA-r score and the 3 clusters (adjusted for age and education) for persons with ≥ 5 samples of year-based past HHg (n = 52; 508 HHg measurements).

	Estimate (μg/g)	95 % Confidence Interval	p-value
MoCA-r	−0.45	−0.71 – −0.20	0.000
Cluster1 (Trail making and Digit Span)	−0.97	−1.61 – −0.32	0.003
Cluster2 (Block drawing and Clock drawing)	−1.29	−1.89 – −0.69	0.000
Cluster3 (Language fluency and Abstraction)	−0.78	−1.39 – −0.27	0.013

Mixed effects models included sex, month and year of sampling as fixed effects and age of sampling nested in year of sampling as random effects

difference was observed between those in the lowest maximum HHg quartile (n = 25) and those in the highest HHg quartile (n = 26) (ANOVA F = 8.87; p = 0.005), with age, education and sex included in the model. LMEM analyses for those with 10 HHg measurements or more (n = 32) showed an inverse association between MoCA scores and HHg over the time period. (Supplementary Table 4).

4. Discussion

In Grassy Narrows First Nation adults, higher long-term past Hg exposure, but not current exposure, was significantly associated with present-day poorer performance on the overall education and age-adjusted score of the MoCA scale. Clustered individual scores representing verbal fluency and abstraction, cognitive flexibility and working memory, and visuospatial functioning, declined with long-term past Hg exposure.

The findings of the present study are consistent with long-term effects observed among residents from the Minamata region, Japan, where an industrial methyl Hg discharge was halted in 1968 (Yorifuji et al., 2023). In 2020, the Japanese version of the MoCA was administered to older adults, who had experienced moderate Hg exposure from local fish consumption, decades previously. Their performance was significantly lower than a reference group of non-exposed residents (Yorifuji et al., 2023). In the present study, cognitive testing was carried out over 50 years after the Hg discharge from a chlor-alkali plant was controlled, among persons with documented Hg exposure between 1970 and 1997. The authors of the study of Minamata residents suggest that the cognitive loss may be due to the long-term consequences of prenatal exposure (Yorifuji et al., 2023). Animal studies of Hg neurotoxicity suggest that adolescence may be a particularly sensitive period for methyl Hg neurotoxicity (Kendricks et al., 2022). In the present study, approximately 25 % were born prior to the beginning of the Hg discharge and all were exposed during adolescence. Given the sample size, the possible specific contribution of prenatal exposure and/or during adolescence could not be examined.

In the present study, no association was observed between blood Hg concentrations at time of testing and any of the measures of performances on the MoCA. In contrast positive associations between biomarkers of Hg exposure at time of testing and poor performance on neurobehavioral tests have been reported for adult fish-eating populations (Yokoo et al., 2003; Silman et al., 2022; Oliveira et al., 2021a; Rebouças et al., 2024; D'Ascoli et al., 2016; Chang et al., 2008). For these communities, exposure levels were, for the most part, relatively constant in the decades preceding the studies. For the Taiwanese adults living near a highly contaminated reservoir of a deserted chlor-alkali factory (Huang et al., 2008), persons with > 19.2 μg/L blood methyl Hg obtained significantly lower total scores on both the Cognitive Abilities Screening Instrument (CASI) and the Mini Mental State Examination (MMSE) compared to those with lower exposure (Chang et al., 2008). In the present study, where fish were likewise contaminated by a chlor-alkali plant, whose emissions were controlled in 1970 and mercury cell use was ceased in 1975 (Government of Canada, 1994), current blood Hg concentrations were much lower, with a median value of 4.01 μg/L and only one individual had blood Hg greater than 20 μg/L. Blood Hg reflects Hg content in fish consumed recently (Abdelouahab et al., 2008; Clarkson and Magos, 2006). In Grassy Narrows, not only did Hg in fish decline notably following the discharge (Neff et al., 2012), but so did fish consumption (Chan et al., 2005; Usher et al., 1979). Recent analyses of fish Hg in the Wabigoon River indicate that concentrations remain above consumption advisory levels and are among the highest in Canada (Rudd et al., 2017). Methyl Hg from fish consumption easily crosses the blood-brain barrier, thereby increasing Hg content in the brain (Nogara et al., 2019). Prospective studies are needed to determine whether current exposure contributes to further cognitive loss over time.

The MoCA items span different cognitive domains (Julayanont and Nasreddine, 2017), using simplified versions of standardized neuropsychological tests. Neuropsychological test batteries have been widely used in studies on environmental neurotoxic exposures of children and adults (Bowler and Lezak, 2015; Hartman, 2012; White et al., 2022). In the present study, individuals with higher Hg exposure between 1970 and 1997 showed poorer present-day performance on clustered subtests, including verbal fluency and abstraction, cognitive flexibility and working memory, and visuospatial functioning. In the large-scale longitudinal cohort study of the marine seafood-consuming Faroe Islands population, prenatal Hg exposure has been negatively associated with performance on tasks requiring attention, language, memory, and visuospatial skills at age 7 (Grandjean et al., 1997, 2001), attention and language at age 14 (Debes et al., 2006), and deficits in verbal performance as late as 22 years of age (Debes et al., 2016). The Seychelle Islands birth cohort study showed no significant neuropsychological associations with prenatal exposure throughout early childhood (Davidson et al., 2011; Huang et al., 2018; Myers et al., 2003). However, time-weighted constructs of post-natal Hg exposure from both childhood (6 months – 5.5 y) and adulthood (17–24 y) (Thurston et al., 2022b) were significantly associated with an array of neuropsychological tests involving verbal fluency, memory, attention, and executive functioning (Thurston et al., 2022a). Long-term Hg exposure during early adulthood was adversely associated with executive functioning and attention, as well as measures of language comprehension and fluency in this cohort (Thurston et al., 2022a). These prospective studies further underscore the importance of long-term Hg exposure as well as the possible evolution of cognitive deficits throughout adolescence and adulthood.

Hg exposure-related language deficits are well-documented in age groups spanning early childhood to late adulthood (Chang et al., 2008; Vejrup et al., 2018; Hsi et al., 2014; Freire et al., 2010). Postnatal Hg exposure was associated with poorer expressive language skills in 3 year old Taiwanese children, living near an abandoned chloralkali plant (Hsi et al., 2014). Deficits in the Boston Naming Test during early adulthood have also been associated with measures of long-term exposure during both childhood and adulthood (Debes et al., 2016; Thurston et al., 2022a). Studies carried out in Indigenous communities in the Brazilian Amazon have reported mercury-related loss in a semantic verbal fluency

test (Oliveira et al., 2021a, 2021b; Dos Santos Freitas et al., 2018) and semantic verbal fluency (Rebouças et al., 2024). Deficits in verbal fluency are one of the more consistently reported neuropsychological findings following focal or degenerative cerebellar lesions (Schweizer et al., 2010; Stoodley and Schmahmann, 2009; Molinari and Leggio, 2016). Autopsy findings from around the world, including a recent study of historic autopsies from Grassy Narrows (Lee et al., 2025), indicated the cerebellum as a particularly important site of Hg accumulation in the brain (Eto and Takeuchi, 1977; O'Donoghue et al., 2020; Pedersen et al., 1999). A selective loss of cerebellar granular cells and relatively well-preserved Purkinje cells has been observed among patients with Minamata Disease (Eto and Takeuchi, 1977; Takeuchi et al., 1962). Both imaging and lesion studies support the existence of a crossed cerebrocerebellar network subserving language function (Stoodley and Schmahmann, 2009).

In the present study, clustered visuospatial performance, on the clock-drawing and cube-copying items was associated with long-term HHg. Several studies have reported inverse relations between HHg and tasks requiring visuomotor skills in Indigenous children in fish-eating communities in the Amazon (Chevrier et al., 2009; Grandjean et al., 1999; Cordier et al., 2002; Reuben et al., 2020). The mechanisms by which methyl Hg exposure affects complex visuospatial tasks may be manifold. In the community of Grassy Narrows, visual field loss has been associated with past long-term Hg exposure (Philibert et al., 2024). While Hg-related deficits on visual-motor integration or visuospatial reasoning tasks have been documented in children and adults (Debes et al., 2016; Silman et al., 2022; Yorifuji et al., 2023; Chang et al., 2008; Peplow and Augustine, 2014), more work is needed to disentangle the contributions of higher-order cognitive processes compared to lower-level visual and motor processes in assessing Hg-related impairment on these tasks.

Lastly, in the present study, higher HHg was associated with lower scores on a cluster which grouped the abridged versions of the Trail Making Test B and Digit Span, reflecting deficits in aspects of cognitive flexibility and working memory (Julayanont and Nasreddine, 2017; Oosterman et al., 2010). While Hg-related working memory deficits have been reported in several studies (Silman et al., 2022; Chang et al., 2008; dos Santos-Lima et al., 2020), deficits on the Trail-making Test are not consistently observed (Thurston et al., 2022a; dos Santos-Lima et al., 2020). Performance on other tests requiring executive functioning, response inhibition, and dimensional set-shifting have been associated with methyl Hg exposure in both humans (Thurston et al., 2022a; Yokoo et al., 2003) and animal studies (Newland et al., 2008, 2013).

Frontal lobe regions are known to play an important role in both executive function and working memory (Lezak, 2004), with the prefrontal cortex and basal ganglia thought to coordinate access to working memory (McNab and Klingberg, 2008). The Trail-making test in particular evokes activity in the left dorsomedial frontal region (Godefroy et al., 2024) and lesion and imaging studies further suggest that the basal ganglia play a particularly important role in tasks requiring dimensional set-shifting (Robbins, 1996; Monchi et al., 2006). In autopsies performed in Grassy Narrows between 1976 and 1986, elevated Hg concentrations were found in all cortical areas, including the frontal cortex; particularly high concentrations were found in both the cerebellum and basal ganglia (Lee et al., 2025). The present findings are consistent with the hypothesis that long-term effects of methyl Hg exposure on executive functioning and short-term verbal memory may more readily appear in older adulthood, with subtle manifestations foreshadowing the emergence of more severe challenges later on in life (Weiss et al., 2002; Weiss, 2011; Rice, 1996).

An important strength of this study is the equivalent HHg database over a 28-year span. In a population like Grassy Narrows, where average exposure has decreased dramatically over time, measures of current or recent exposure alone are unlikely to capture possible long-lasting effects of Hg on the brain. A further strength of the present study is its strong community-university partnership design, which allowed for feedback from community members in the design, analysis, and conclusions of the study, helping to ensure that studies contribute to the well-being of community members.

The study posed several complexities. While the MoCA is a clinically relevant screening tool for detecting mild cognitive impairment among older populations (Nasreddine et al., 2005), no MoCA cut-off score is uniformly applicable to all demographic groups (Ratcliffe et al., 2023). Consistent with population-based studies (Bruijnen et al., 2020; Freitas et al., 2011; Krist et al., 2019; Kessels et al., 2022), MoCA raw scores were associated with both age and years of education. Additionally, in the Grassy Narrows population, age and education were themselves correlated and both were correlated to HHg since exposure levels significantly declined over time. Using age- and education-adjusted residual MoCA scores reduced potential confounding and minimized multicollinearity in the analyses examining its association with Hg exposure. This approach allowed us to examine whether individuals of similar age and educational level with lower cognitive scores had higher past Hg exposure. Sensitivity analyses with the entire group supported the findings.

Culturally informed cognitive assessment tests for Anishinaabe and other Indigenous communities are being developed and validated (Walker et al., 2021; Rowat et al., 2025; Dyer et al., 2017). These will be useful, not only for the detection of dementia, but also for examining the long-term consequences of legacy and current exposure to Hg and other contaminants in this and other Indigenous communities. In Canada, 23 % of the 38,571 Indigenous individuals who were tested for Hg exposure between 1970 and 1992, had equivalent blood Hg concentrations $\geq$ 20 μg/L (Wheatley and Paradis, 1995). Worldwide, coastal and riverine Indigenous communities consume more fish compared to non-Indigenous communities in the same regions (Cisneros-Montemayor et al., 2016; Marushka et al., 2021).

In the present study, the MoCA provided important information about Hg-related deficits in cognitive functioning, reflecting coordinated mechanisms by which an individual perceives, reacts, remembers, understands, solves problems, makes decisions, and produces appropriate responses according to select elements of a given environment (Arthanat et al., 2004; Morley et al., 2015). The data do not provide a measure of day-to-day abilities and challenges in this population. Far from describing a static characteristic of an individual, the terms *ability, disability,* and *impairment* describe the evolving relationship between an individual and their natural, social, and built environment (Davidson-Hunt and Berkes, 2003). For example, the discharge of Hg into the Wabigoon-English River system was a mass-disabling event, structurally limiting the ability of the community to engage in fishing, among other critical traditional activities (Usher et al., 1979; Vecsey, 1987). C*ognitive abilities* of an individual are described with respect to a particular activity and are mutually determined by both the individual and the enabling or disabling elements of their social or physical environment (Arthanat et al., 2004; Davidson-Hunt and Berkes, 2003; Ellen, 2011). Future research should actively build on these findings by incorporating ecologically and culturally relevant assessments of daily functioning, and by implementing community-led interventions designed to strengthen autonomy and improve quality of life for the community members.

5. Conclusions

The findings of this study show that persons with higher long-term past Hg exposure, performed more poorly on a cognitive screening test than those of similar age and educational level, with lower past exposure. They suggest that even in communities where average exposure has decreased to levels below current guidelines, the cognitive effects of high long-term past Hg exposure can be long-lasting. School and community-oriented programs and cognitive therapy in Grassy Narrows and other Indigenous communities that have been exposed to high concentrations of neurotoxic substances need to understand

neurotoxicity resulting from exposure to these environmental contaminants and provide adequate preventive and therapeutic interventions.

CRediT authorship contribution statement

Philibert Aline: Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mergler Donna:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Filliion Myriam:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Jennifer Lee:** Writing – review & editing, Writing – original draft, Visualization. **Da Silva Judy:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

All 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. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuro.2025.07.005.

Data availability

The authors do not have permission to share data.

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