Environmental Health

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Characterizing visual field loss from past mercury exposure in an Indigenous riverine community (Grassy Narrows First Nation, Canada): a cluster-based approach

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Abstract

Background Between 1962 and 1975, a chlor-alkali plant in Canada discharged approximately 9 metric tons of mercury (Hg) into the Wabigoon River. Over the following decades, biomarkers of Hg exposure of persons from Grassy Narrows First Nation (Asubpeeschoseewagong Anishinabek), located downriver from the discharge, reflected Hg concentrations in fish. Hg exposure is known to target the calcarine fissure, resulting in visual field (VF) loss. Most studies and clinical reports focus solely on peripheral VF loss; little is known about the impact of Hg on the central and paracentral portions. The present study sought to characterize the patterns of VF loss with respect to past and current Hg.

Methods A 28-year hair-Hg (HHg) database, created from a 1970–97 government biomonitoring program, served to select study participants with ≥ 4 year-based HHg measurements ($n = 81$). Blood-Hg was assessed for current exposure. Light sensitivity thresholds across the VF were analyzed monocularly, using a Humphrey Field Analyzer (HFA). Following post-hoc exclusions, based on HFA interpretation indices, 65 participants were retained. Both eyes were combined for analyses ($n = 130$ eyes). Unsupervised hierarchical clustering of HFA plot data was used to identify patterns of VF loss. A series of mixed effects models (MEM) were performed to test the associations for current Hg exposure with respect to HFA interpretation indices and clusters, as well as for longitudinal past Hg exposure.

Results The clustering approach decomposed the light sensitivity deficits into 5 concentric clusters, with greatest loss in the peripheral clusters. No relation was observed between any of the cluster scores and current blood-Hg. VF deficits increased with past Hg exposure. Longitudinal MEM showed that HHg was significantly ($p < 0.05$) associated with all peripheral, paracentral, and central cluster scores, as well as with HFA interpretation indices.

Conclusions Past Hg exposure in Grassy Narrows First Nation was associated with present day VF loss. The cluster-based location-specific approach identified patterns of VF loss associated with long-term Hg exposure, in both the peripheral and the central areas. The functional implications of this type of visual loss should be investigated.

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Background

Worldwide mercury (Hg) and production use peaked between 1960 and 1980, increasing the Hg load in the aquatic food chain [1]. In Canada, a 1969 report indicated that chlor-alkali plants accounted for more than 47% of the total Hg used and constituted the most important point source of Hg to the aquatic environment [2]. The First Nation community of Asubpeeschoseewagong Anishinabek (also known as Grassy Narrows First Nation) territorial waters are situated downstream of a former chlor-alkali plant, which, between 1962 and 1975, discharged approximately 9 metric tons of Hg into the watershed [3]. Very high concentrations of Hg were reported in fish from lakes directly on Grassy Narrows traditional territory. Fish Hg concentrations generally exceeded 2 µg/g and reached levels as high as 17 µg/g [3]. In the years following the control of the discharge, fish Hg declined; the trend transitioned in the mid 1980s and since the early nineties, concentrations have remained relatively stable [4, 5]. They are still among the highest in Canada [6]. For the Grassy Narrows community, fish was the dietary mainstay and biomonitoring programs, initiated in 1970, showed that biomarkers of Hg exposure (hair and blood) followed a similar pattern to the fish [7]. The programs ceased in 1997 when average biomarkers of Hg exposure were below Canadian guidelines.

Methylmercury (MeHg), a highly toxic substance [8–10], makes up most of the Hg content found in fish tissue [11–13]. In fish, sampled in the rivers downstream of the chlor-alkali plant, MeHg constituted 85–100% of total Hg [14]. MeHg in hair samples, from the government biomonitoring program in this region, constituted 88% of total Hg [15].

Peripheral visual field (VF) loss, resulting from damage to the primary visual cortex in the calcarine region, is a characteristic of MeHg poisoning [16–23]. Since 1975, there have been several reports of VF loss in the Grassy Narrows First Nation community. In the early studies, peripheral field constriction was reported for 10—15% of examinees, using the Foster Perimeter or confrontation test [24–27]. A more extensive examination of VF loss was recently performed as part of the Grassy Narrows' Niibin study, using a Humphrey Field Analyzer (HFA); 36% of 70 adults (median age: 57 years) presented VF loss (Visual Field Index ≤ 81%) [28]. The authors indicated that the clinical picture presented differently from common eye and vision disorders [28].

The objectives of the present study were to conduct cluster analyses to identify patterns of light sensitivity threshold reduction across the entire VF and to examine the associations between HFA interpretation indices and VF clusters with respect to past long-term and current Hg exposure.

Methods

Study design

This research project is part of the Niibin study, developed in partnership with the Grassy Narrows First Nation (Northwestern Ontario) via their Mercury Justice Team, according to the OCAP® principles of ownership, control, access, and possession of information collected within First Nation communities [29]. OCAP® is a registered trademark of the First Nations Information Governance Centre (FNIGC) [29].

Two approaches were used: (i) longitudinal retrospective, based on historic biomarkers of Hg exposure, collected between 1970 and 1997, as part of government monitoring programs [30] and (ii) cross-sectional, based on current blood-Hg concentrations. Eye and vision examinations, carried out by three optometrists in summer 2021, were performed in a room set up in the Sakatcheway Anishinaabe School in Grassy Narrows [28].

Mercury exposure

Historic Hg biomarker data

In 1970, eight years after the beginning of the Hg discharge from the chlor-alkali plant upstream of Grassy Narrows, the Medical Service Branch of Health Canada and the Ontario Ministry of Health initiated Hg biomarker (blood and hair) testing programs, which continued until 1997 [30, 31]. Hair-Hg sample analyses were performed according to the methods published by Farant [15] and Giovanoli-Jakubczak [32]. Among the people of Grassy Narrows, hair-Hg was highly correlated to reported fish consumption [33, 34].

Grassy Narrows First Nation Chief and Council obtained the community's archived Hg biomarker data from the First Nations and Inuit Health Branch of the Ministry of Indigenous Services Canada, and the Ontario Ministry of Health and Long-term Care. The data, which included monthly-based hair-Hg measurements and blood-Hg, were shared with the research team. Using these data, a retrospective longitudinal year-based database for the years 1970 – 1997 was created with the highest measurement of equivalent hair total-Hg (HHg) for each year [35]. The year-based database included 662 persons with 3621 data points: (3416 (94.3%)) hair-Hg and 205 (5.7%) blood-Hg measurements). The latter were converted into HHg, using the Canadian and JEFCA guideline for Hg hair/blood ratio of 250 [36, 37]. Since, Hg exposure varied throughout the year [30, 38], the corresponding month was noted and then merged into low and high peak seasons for fish-eating practices.

The government programs' sampling schedules were not regular; persons sampled one year were not necessarily included in the following year(s). The highest number of persons sampled/year (> 250) were from

1975 to 1978. Of the 662 persons included in the 1970 – 1997 database, 296 (44.7%) have since died.

Current Hg exposure

Blood samples were collected by a single venipuncture using 21-gauge blood collection sets (BD Vacutainer™ Safety-Lok™ Blood Collection Sets, BD 367281) in BD Vacutainer™ tubes. For total-Hg analysis in whole blood, samples were collected in Sodium Heparin Vacutainer™ tubes, mixed thoroughly by gentle inversion, and kept refrigerated in upright position after mixing and during transportation. Samples were transported to LifeLabs' office in Kenora the same day. Total-Hg in whole blood was analyzed at LifeLabs Medical Laboratory Services, Victoria Reference Laboratory (Victoria, BC, Canada) by inductively coupled plasma mass spectrometry (ICP-MS), with an Agilent 8800 Triple Quadrupole ICP-MS (Agilent Technologies). Three levels of whole blood Quality Control samples were run at the beginning of each session, after every 20 samples, and following the last sample. Results were released only for samples that met the internal acceptance criteria. Samples with Hg concentrations below the detection limit of 0.2 µg/L were assigned a concentration of 0.10 µg/L.

Eye and vision examination

Eye and vision examinations included visual acuity, autorefraction, slit lamp examination, color vision testing, contrast sensitivity testing, optical coherence tomography and automated VF testing. The full testing protocol is described elsewhere[28]. Here, the VF and visual acuity assessments are presented.

Visual acuity

Distance and near visual acuity (DVA and NVA) were performed. DVA was assessed monocularly using the distance Early Treatment Diabetic Retinopathy Study (ETDRS) computerized letter chart, with participants wearing habitual distance spectacle correction, if any. Pinhole acuity was determined when the monocular measure was poorer than 6/12 Snellen equivalent. NVA was measured with the near ETDRS logarithmic chart, with habitual near spectacle correction, when available. All acuity measurements were transformed to logarithm of the Minimum Angle of Resolution (LogMAR).

Visual Field (VF)

A comprehensive assessment of VF was conducted using the Humphrey Field Analyzer 3 Model 840 (HFA) (Carl Zeiss Meditec Inc, Dublin, CA, USA), with the 30–2 Swedish Interactive Threshold Algorithm Standard-Fast (SITA-Fast) algorithm. This test uses a size III white stimulus, across a 30 degrees field globe, testing 76 grid points. The participants were asked to fixate an illuminated cross in the center of the globe and indicate when they see sporadic lights at different intensities and locations. The test was performed monocularly and as needed, lenses were used to compensate for testing distance and autorefraction results. The HFA provides reliability measures for fixation loss (% time not fixating) and false negatives (% false responses). HFA interpretation indices include the following:

- Total Deviation Plot (TDP)—a numeric map of the difference between the measured VF sensitivity and the expected normal age-corrected sensitivity at each test point.
- Total Deviation Probability Plot (TDPP)—a numeric map of the probability that visual loss is outside the confidence interval of a normal age-corrected value ($p < 5\%$, 2%, 1%, and 0.5%) [39]; for each test point; the probability level of < 0.5% is considered abnormal.
- Pattern Deviation Plot (PDP)—a numeric map of focal VF loss, obtained by adjustment to the height of the hill of vision.
- Pattern Deviation Probability Plot (PDPP)—a numeric map, representing the likelihood that each point is within the normal range (abnormal points $P < 0.5\%$).
- Mean Deviation (MD)—a uniform loss index, derived from the weighted average of the TDP values, based on the differences between age-matched normative data and measured thresholds of retinal sensitivity.
- Pattern standard deviation (PSD) is a non-uniform sensitivity loss index, derived from the weighted standard deviation of the differences from the age-corrected normal threshold values, after adjustment for any overall elevation or depression of the field at each test point.
- Visual Field Index (VFI) is an index of the total amount of VF loss, expressed as a percentage of normal vision ranging from perimetrically blind (0%) to normal (100%).
- Glaucoma Hemifield Test Index (GHT) provides an indicator of asymmetry between superior and inferior hemifield, reflecting potential VF loss resulting from glaucoma. Its results are expressed as either "Within normal limits", "Borderline", "Outside normal limits", "General Depression" or "Abnormally High Sensitivity". These were grouped into Normal ("Within normal limits" and "Borderline") and Abnormal ("Outside normal limits", "General Depression" or "Abnormally High Sensitivity").

Population

Participant selection and recruitment was based on the 1970 – 1997 Grassy Narrows historic equivalent year-based HHg biomarker database, which included 277 persons still living in 2021. Inclusion criteria were: (i) at least four year-based HHg biomarker measurements, and (ii) currently living in or nearby Grassy Narrows. A total of 131 community members (69 men and 62 women) were eligible and 81 (61.8%) persons (36 men and 45 women) underwent eye and vision examinations. There was no age difference between participants and non-participants (median: 57 years; interquartile range: 52 – 63; and median: 55 years; interquartile range: 51 – 60, respectively). All participants provided informed consent.

Post hoc exclusion criteria were based on the visual examination: (i) persons that did not meet criteria for reliable test results on the HFA [40]: fixation loss for > 20% of stimuli points (excessive ocular movements during testing) and false positive responses exceeding 15% (participant responses in absence of stimuli) for one or the other eye; (ii) participants with cataracts with grade 3 or higher on the WHO cataract grading scale [41] upon slit lamp examination. Both eyes were eligible for a total of 65 persons.

A total of 554 retrospective equivalent hair-Hg samples were available for the 65 participants, of which 25 (4.5%) were derived from blood-Hg concentrations. Hg analyses for all current blood samples met the Quality Control criteria; two participants did not provide blood samples.

Statistical analyses

There are several approaches to examining data involving both eyes. Some authors present the left and right eyes separately, others use random selection of the right and left eye, and still others use both-eye data, accounting for the inter-eye correlation [42–44]. We opted for analyzing both eyes together since Hg is known to affect many components of the visual system, including the visual cortex [17, 18], optic nerve pathways [45, 46], and the retina [47–50]. Based on the VFI, the intra-class correlation between the two eyes was 0.73 [95% Confidence Interval (CI) 0.6 – 0.83]. Because many statistical methods assume independence of observations and two eyes are not independent since they belong to the same individual, participant ID code was included as a random factor in all mixed effects models to account for the intra-participant correlation between eyes [44, 51, 52]. The data points from the pattern deviation plot were combined by transposing the data points of the left eye to the right eye (mirror transposition).

Since diabetes can contribute to eye disease [53, 54], the possible contribution of diabetes to visual functions was examined. Binary and multivariate associations (with age and sex) were tested using data collected in other aspects of the Niibin study: physician-diagnosed diabetes, medication for diabetes and the current concentration of glycolate hemoglobin (HbA1c). No associations were observed ($p > 0.20$) and diabetes was not retained for the present analyses. Other potential covariates (smoking, drinking, blood pressure, socio-economic status (struggle to pay for food)) were likewise tested and did not reach significance threshold.

Clustering approach

Clustering can serve as a dimension-reduction tool to optimize our understanding of the distribution of sensitivity loss across VF by mapping. We used a mixed factorial approach (PCAMIX method in R software) on the 74 test points (two points corresponding to the blind spot) on PDP and then divided into clusters [55]. When there was no PDP due to exceeded deviation threshold, the deviation test points from the TDP were used.

The appropriate number of clusters was determined using a bootstrap approach for maximizing the homogeneity criterion within clusters, analysis of aggregation levels and stability of the partitions via bootstrapped mean-adjusted Rand Index and boxplots.

We validated the clustering results constructed in R software, using the VARCLUS function of the SAS computer application (JMP Professional 16.0 software), which uses a similar approach, and with Hopach package in R software, which is a hybrid approach to clustering.

For each cluster, a composite variable was calculated from the weighted linear combination of the visual test points. Along each composite variable, defect severity increased with higher deviation from age-adjusted standard values. The sum of the cluster scores (Cluster Sum) was tested with respect to the VFI. A series of heatmaps illustrated the distribution of light sensitivity thresholds across the VF.

Descriptive statistics

Simple and multiple comparisons were conducted with non-parametric Wilcoxon/Kruskal–Wallis Tests (Rank Sums). Matched-pairs analyses of light sensitivity loss between clustered compartments were conducted using participant ID code as a nested variable. The visual field concentric square model, proposed by Sayo et al. [56], was used to compare peripheral and central VF loss with respect to a year-based HHg maximum value at least once over the sampling period.

Mixed effects models

Mixed effects models (MEM) are powerful tools for analyzing complex datasets with nested and/or repeated observations. The possible contribution of current

blood-Hg to vision outcomes was examined using MEM, with age and sex as fixed effects and participant ID code as random effect to account for the correlation between paired eyes [52]. Longitudinal MEM (LMEM) were performed using direct measurements of past longitudinal HHg with respect to vision outputs.

LMEM analyses were limited to persons with 10 or more HHg data to ensure measurement consistency over the years. These analyses included 56 eyes from 28 persons (10 men and 18 women), for a total of 352 HHg measurements, sampled over a period of 10 to 21 years (median: 11 years). To ensure that there were sufficient observations for the analyses, we estimated the minimal required sample size, using the G*power software [57]. Since one centimeter of a hair sample represents an accumulation of Hg during approximately one month, we used a correlation of repeated measures between yearly-based samples (rho of 0.2/0.5). Because the effect size was unknown, 0.25 was chosen [58]. Power analyses were set at 80%, with a two-tailed 5% hypothesis test, 10 time points, within and between factors were used to calculate sample size adequacy. The minimum number of participants required was between 23 and 30. LMEM were adjusted with age and sex as fixed effects, while age of sampling was nested in time of sampling; participant ID code was included as random effect.

The most appropriate model for MEM and LMEM was selected using the Wald test, the Akaike Information Criterion (AIC), the Bayesian Information Criteria (BIC) and the likelihood ratio (LR) test at $p <= 0.05$. In all models, we tested whether age and/or sex moderated the relation between past or current Hg exposure and vision outcomes. All model assumptions were verified by residual homogeneity.

To support the LMEM results, a series of sensitivity analyses were conducted with each eye separately and with all participants. The latter provides higher power, but a lower minimum number for repeated HHg measurements (at least 4 year-based HHg).

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

Database management and descriptive statistical analyses were performed using JMP Professional 16.0 (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): PCAmixdata, cluster and ClustOfVar and HOPACH. Cronbach alpha data analyses were performed with SPSS software (IBM SPSS statistics version 28.0.1.0 (142)). MEM and LMEM were conducted with Stata 18 software. (Stata Statistical Software: Release 18.0 College Station, TX: Stata Corporation). The MEM and LMEM analyses, including the assumptions, conducted on Stata were verified using the lme4, lmerTest, robustlmm and ggplot2 R packages. Matched paired analyses on nested data used the lme4 R package. Heatmap representations were performed using the akima and ggplot2 R packages.

Results

Among the 65 participants with eligible VF test results for both eyes, there were 36 women and 29 men (mean age: 57 years (median: 56 years; IQR: 50.5 – 64.5 years)). Figure 1 shows their year-based HHg concentrations, between 1970 and 1997. Mean current blood-Hg was 6.19 µg/L (median 4.21 µg/L (IQR: 1.20 – 9.63 µg/L)).

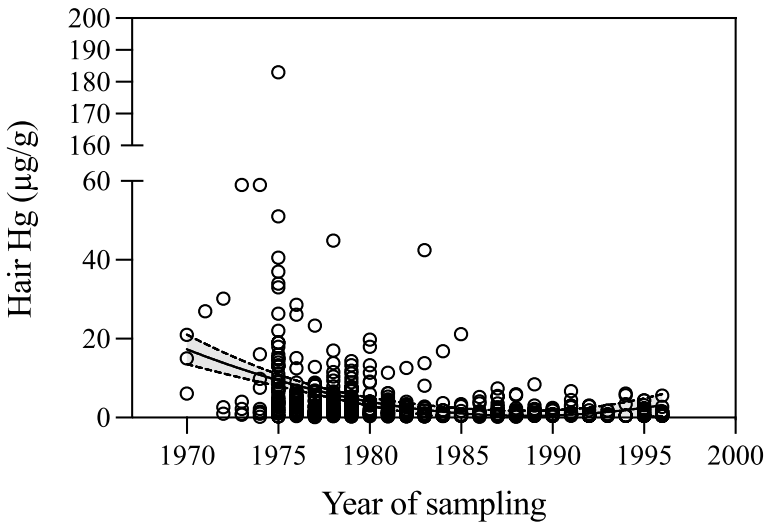

Fig. 1 Distribution of equivalent hair-Hg (µg/g) from samples collected between 1970 and 1997 (554 data points for 65 participants)

Table 1 Characteristics of visual acuity measurements and Humphrey Visual Field Analyzer (HFA) interpretation indices ($n = 130$ eyes)

	Mean [95% CI]	Median	IQR
DVA (logMAR)	0.16 [0.12 – 0.21]	0.10	0 – 0.2
NVA (logMAR)	0.46 [0.42 – 0.50]	0.40	0.3 – 0.6
HFA interpretation indices			
VFI (%)	79.5 [74.6 – 84.4]	93.5	71.3 – 98
MD (dB)	-9.20 [-10.7 – -7.36]	-5.23	-12.8 – -2.0
PSD (dB)	5.29 [4.72 – 5.86]	3.86	2.23 – 7.88
	%		
GHT (outside normal limits)	66.9		
MD (*p*-value < 0.5%)	43.1		
PSD (*p*-value < 0.5%)	52.3		

DVA was optimized with pinhole when necessary

Abbreviations: *CI* Confidence Interval, *IQR* Interquartile range, *DVA* Distance Visual Acuity, *LogMAR* Logarithm of the Minimum Angle of Resolution, *NVA* Near Visual Acuity, *VFI* Visual Field Index, *MD* Mean Deviation, *PSD* Pattern Standard Deviation, *GHT* Glaucoma Hemifield Test

Visual acuity and HFA interpretation indices for the combined eyes are presented in Table 1.

DVA decreased with age and was similar for men and women. The VFI for 20% of eyes was below 62%, the cut-off for abnormal VF score, representing 17 persons (26.1%) with at least one abnormal VFI. A total of 70.8% of eyes were classified as normal, with a VFI ≥ 81%. At least 43% of eyes had abnormal MD (< 0.5%) and more than 53% for PSD (< 0.5%). The GHT was outside of the normal range for more than two-thirds of participants. HFA interpretation indices are age-corrected, and indeed no relations were observed with age; no differences were observed between men and women.

The heatmap of mean sensitivity thresholds from the PDP matrices showed a series of concentric losses, increasing towards the periphery (Fig. 2).

The clustering approach revealed five clusters that were concentrically distributed, with the greatest loss in the periphery (Fig. 3).

Non-parametric matched-pair analyses of mean PDP in clusters showed that sensitivity loss in the peripheral superior and latero-peripheral clusters were similar, but significantly higher than the more central clusters (Wilcoxon Signed Rank one-way test; $p \leq 0.05$) (Table 2).

Cluster scores were summed to provide a Cluster Sum (median: -7.14, IQR: -11.20 – 3.09), which was highly inversely correlated to the VFI (Spearman rank-order correlation: ρ: -0.70, $p < 0.0001$) (Fig. 4). The good correspondence between higher Cluster Sum scores and lower values of VFI, indicated that the clusters, taken together, reflected the VFI. Participants with abnormal GHT had significantly higher Cluster Sum scores compared to those with normal GHT scores (Wilcoxon / Kruskal–Wallis Tests (Rank Sums): Chi2 = 60.5; $p < 0.0001$).

No relation was observed between visual acuity and Cluster Sum score or any of the HFA interpretation indices.

Using PDP matrices, heatmaps were produced, using three categories of point HHg values over the sampling period (a) all HHg values < 3 µg/g ($n = 24$), (b) at least one HHg value ≥ 3 µg/g and < 10 µg/g ($n = 50$), and (c) at least one HHg ≥ 10 µg/g ($n = 56$) (Fig. 5).

To support the heatmap illustrations, the concentric VF diagram proposed by Sayo et al. in 2017 [56], was used and mean light sensitivity threshold loss for the 16 data points of the periphery and the 8 data points at the

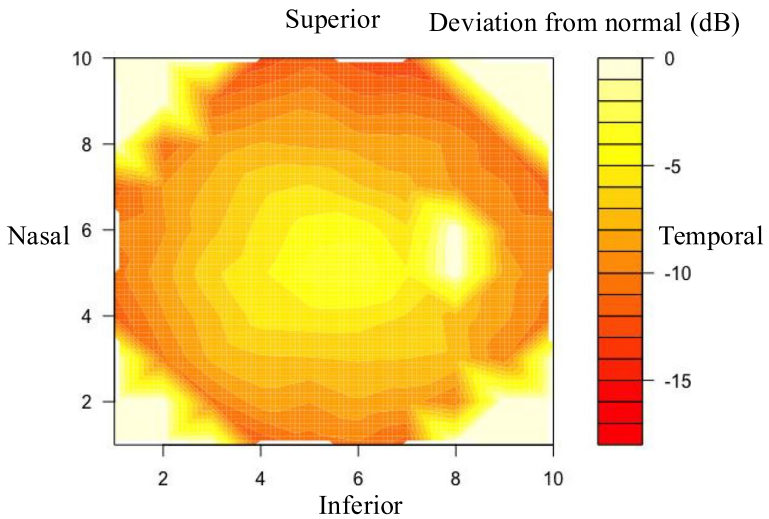

Fig. 2 Heatmap of mean sensitivity threshold in the Pattern Deviation matrix for two-eye analysis ($n = 130$ eyes), imposed on the equivalent right eye

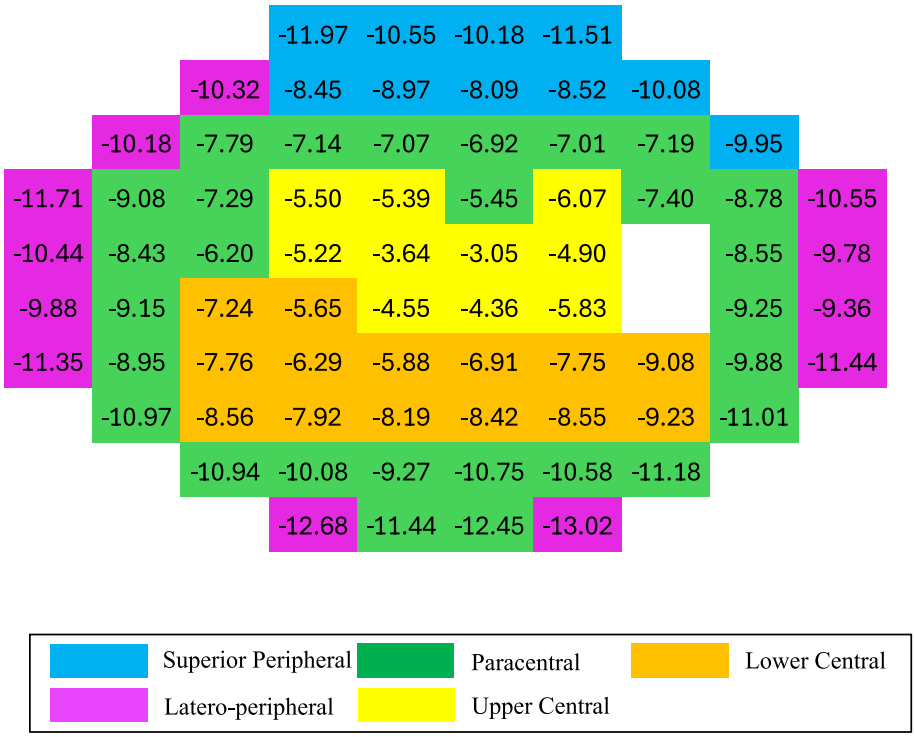

Fig. 3 Distribution of clusters from the Pattern Deviation matrix (5 clusters, $n = 130$ eyes)

Table 2 Results of matched pair analyses for the mean difference (Cluster a – Cluster b) of Pattern Deviation matrix

Cluster a	Cluster b	S	*P*-value
Superior peripheral	Latero-peripheral	-0.89	0.374
	Paracentral	-4.17	< 0·001
	Upper central	-6.02	< 0·001
	Lower central	-7.56	< 0·001
Latero-peripheral	Paracentral	-4.39	< 0·001
	Upper central	-5.90	< 0·001
	Lower central	-5.64	< 0·001
Paracentral	Upper central	-5.02	< 0·001
	Lower central	-6.45	< 0·001
Upper central	Lower central	-3.14	< 0·001

Analyses were nested on individuals

Abbreviation: S Wilcoxon Signed rank coefficient

center were compared (Table 3). The light sensitivity loss threshold increased with increasing past Hg exposure.

Table 4 presents the results of the LMEM linking repeated past HHg concentrations and visual acuity and HFA interpretation indices for participants who had at least 10 year-based HHg measurements (704 hair measurements; $n = 56$ eyes). Past long-term Hg exposure over the biomonitoring period was significantly associated with lower VFI, abnormal GHT and lower MD.

Participants with higher longitudinal past HHg presented higher scores on all five clusters and Cluster Sum (Table 5). The position within the VF indicated in the Table, refers to the clusters displayed in Fig. 3. Similar results were found when using the average light sensitivity loss for each test point within each cluster rather than cluster scores.

Sensitivity analyses with each eye separately (≥ 10 HHg measurements) are presented in Supplementary Material for visual acuity and HFA interpretation indices (Supplementary Tables 1a and 1b), as well for clusters (Supplementary Tables 2a and 2b). Further sensitivity analyses with all participants are presented in Supplementary Tables 3 and 4. Results were similar, with lower coefficients and probability values.

No relations were observed between current blood-Hg and any of the vision parameters or clusters. The results are presented in Supplementary Tables 5 and 6.

Discussion

This study provides evidence of the magnitude of VF loss among persons from Grassy Narrows First Nation, with a history of Hg exposure through fish consumption between 1970 and 1997. While the commonly-used VF indices confirmed an association between global loss

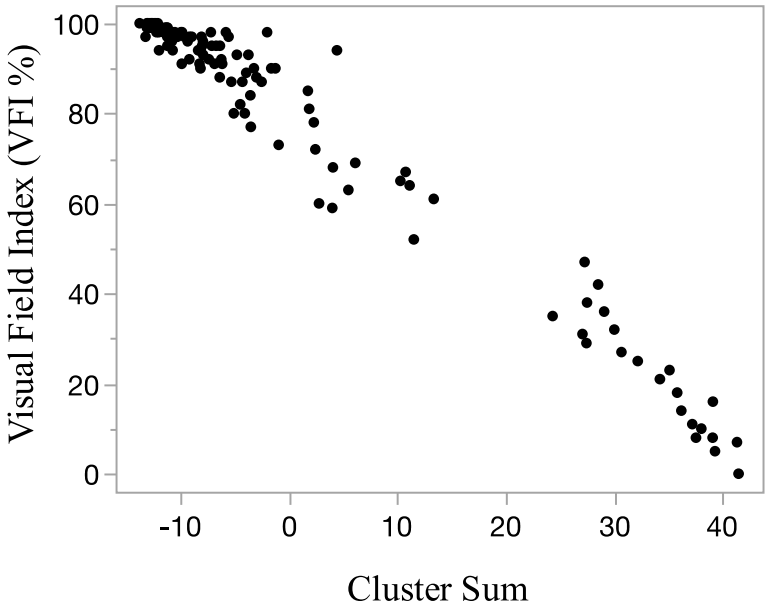

Fig. 4 Association between Global Cluster Indices and Visual Field Index using two eyes analyses ($n=130$)

and long-term past Hg exposure, the clustering approach provided the means of identifying localized patterns. In this community, Hg-related VF loss was concentric, with the greatest reduction in the periphery. With increasing exposure, the central areas became more and more affected, as illustrated in the heatmap portraits of the entire study group and quantified in the longitudinal mixed model analyses.

Peripheral VF constriction was first noted among workers with MeHg poisoning [59]. It has since been identified as a common feature of Minamata Disease, resulting from the consumption of Hg-contaminated fish [16]. Several clinical reports and studies carried out in Grassy Narrows and in other First Nation communities in Canada likewise observed VF loss [26, 27, 38]. The present study demonstrates the severity of the VF loss among adults in Grassy Narrows First Nation and confirms the contribution of long-term Hg exposure. These findings are consistent with those from Minamata patients 40 years after their initial diagnosis [17, 60].

VF loss is not a common disorder, and is known to increase with aging [61–64]. In a two-eye populational study of older persons, the prevalence of VF loss among persons between 55 – 64 years of age was 3%, and it progressively increased to 17% for those 85 years and older [61]. In contrast, in the present study, 30.4% of participants in the 55 – 64 year-old age range ($n=46$) presented at least one abnormal VFI, representing 28.3% of total eyes ($n=92$).

It is noteworthy that although almost two-thirds of participants in the present study scored in the abnormal range of the GHT, and its association with past Hg exposure was significant with 10 repeated HHg measurements, no relation was observed for PSD, which is also used in the diagnosis of early glaucoma [65, 66]. Sensitivity analyses for these three indicators did not show

Table 3 Mean light sensitivity loss threshold with respect to HHg measurements at least once over the sampling period

	At least 1 HHg measurement				
	< 3 µg/g (*n* = 24)	**> = 3 and < 10 µg/g (*n* = 50)**	**≥ 10 µg/g (*n* = 56)**	**Chi2[a]**	***p*-value**
Periphery (16 data points)	-9.73 [-10.50 – -9.00]	-11.36 [-12.08 – -10.63]	-11.84 [-12.57 – -11.12]	12.03	0.002
Center (8 data points)	-2.96 [-4.01 – -1.91]	-4.72 [-5.77 –—3.66]	-5.97 [-7.03 – -4.92]	10.06	0.005

[a] Wilcoxon-Kruskal Wallis Chi square

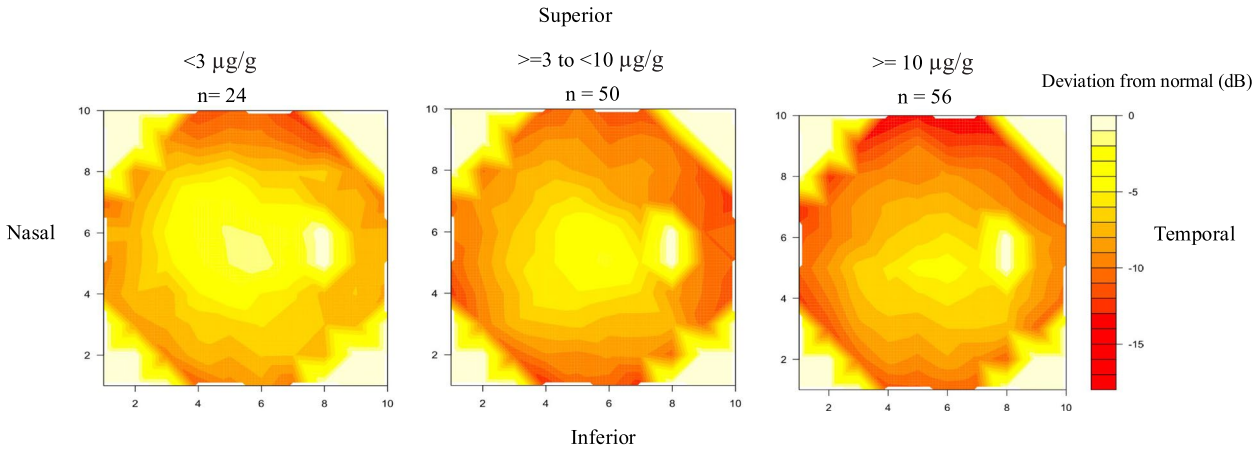

Fig. 5 Heatmaps of mean sensitivity thresholds in the Pattern Deviation Matrix based on two-eye analysis with respect to three levels of HHg, at least once between 1970 and 1997 ($n=56$)

consistent associations with long-term Hg exposure, as was the case for VFI, MD and the clusters. In situations where health care providers are unaware of past Hg exposure and the possible consequences of Hg poisoning, this might further complicate clinical diagnosis in cases of patients with suspected glaucoma, based on the presence of other risk factors[67]. Distance and near visual acuity were likewise not associated with long-term Hg exposure.

In the present study, past Hg exposure, but not current blood-Hg concentration, was associated with VF loss, suggesting that the process leading to Hg-related VF constriction occurs over time or is a delayed reaction to long-term exposure. Delayed Hg visuo-toxicity has been put forward by several authors [22, 68]. In a study of 6 macaques with low MeHg exposure, Merigan and co-authors noted reversible early VF loss, especially in the inferior-nasal field; more severe poisoning resulted in persistent VF constriction [69]. A case study of children, who had eaten MeHg-contaminated pork for a period of 3 months, reported neurologic signs and symptoms, and constricted VF, 22 years following the poisoning [70]. Although in the present study, we did not have VF measurements prior to exposure, the absence of a relation with current Hg exposure suggests that the effect may be cumulative over time, or that this is a manifestation of delayed neurotoxicity. Permanent adverse effects on spatial vision in adult monkeys ($n=21$) were observed in relation to in utero MeHg exposure [71]. Weiss and

Table 4 Longitudinal mixed effect model estimates for repeated past HHg concentrations (µg/g) for persons with ≥ 10 HHg measurements with respect to visual acuity and Humphrey Field Analyzer interpretation indices (704 hair measurements; $n=56$ eyes)

	Coefficient (µg/g)	95% Confidence Interval	*P*-value
DVA	0.10	-0.71 – 0.91	0.809
NVA	-0.54	-2.15 – 1.06	0.509
VFI (%)	-0.07	-0.11 – -0.03	0.001
MD (dB)	-0.14	-0.20 – -0.07	0.000
PSD (dB)	0.11	-0.06 – 0.28	0.210
GHT (outside normal limits)	-0.45	-0.77 – -0.14	0.004
MD (*p*-value < 0.5%)	1.17	-0.19 – 2.53	0.092
PSD (*p*-value < 0.5%)	0.08	-0.53 – 0.69	0.797

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

Abbreviations: *DVA* Distance Visual Acuity, *NVA* Near Visual Acuity, *VFI* Visual Field Index, *MD* Mean Deviation, *PSD* Pattern Standard Deviation, *GHT* Glaucoma Hemifield Test

Table 5 Longitudinal mixed effect model estimates for past HHg concentration (µg/g) for persons with ≥ 10 HHg measurements with respect to clusters scores (704 hair measurements; $n=56$ eyes)

Cluster location	Coefficient (µg/g)	[95% Confidence Interval]	*P*-value
Superior peripheral	0.59	[0.06 – 1.13]	0.029
Latero-peripheral	0.54	[0.21 – 0.87]	0.001
Paracentral	0.40	[0.16 – 0.60]	0.001
Upper Central	0.69	[0.27 – 1.10]	0.001
Lower Central	0.31	[0.07 – 0.46]	0.000
Cluster Sum	0.12	[0.05 – 0.19]	0.001

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

The position within the visual field indicated in the table refers to the clusters displayed in Fig. 3

co-authors [68] have proposed mechanisms for delayed Hg neurotoxicity.

The calcarine fissure (also known as striate or visual cortex) of the occipital lobe is a major target for MeHg toxicity, resulting in VF loss [48, 72, 73]. Korogi and co-authors [17] reported on magnetic resonance imaging (MRI) of 8 patients with MeHg poisoning (Minamata Disease) with moderate to severe concentric VF loss. The MRI showed significant dilation of the ventral portion of the calcarine fissure and T2-weighted images showed hyperintense lesions sparing the most posterior portion of the calcarine cortex [17]. There was a logarithmic correlation between VF loss and the extent of dilation of the calcarine fissure [17]. On autopsy, microscopic examination of Minamata patients have revealed neuropathological lesions including disintegration and loss of neurons in the calcarine cortex [17, 18].

The central portion of the VF (macula) has a considerably higher representation in the calcarine fissure compared to the periphery [74]. The anterior portion of the calcarine fissure receives input from the peripheral field, while the posterior portion is linked to the central VF [48]. In the present study, there appears to be progressive involvement not only of the peripheral portion of the VF, but also of the paracentral and central portions, with increasing Hg exposure. Autopsy data from 21 persons from Grassy Narrows, who died between 1976 and 1986, show a significant correlation between Hg content of the calcarine cortex and hair Hg, but no difference in Hg concentration between the anterior and posterior calcarine cortex (submitted manuscript).

This study has several strengths. The unique 28-year HHg database provided the means of examining longitudinal effects of Hg exposure on today's VF loss. The mean values of HFA plots were used to derive heatmaps which illustrated increasing severity of concentric VF constriction. Clustering HFA outputs provided a segmental map of regions of sensitivity loss in the VF that could be individually related to long-term Hg exposure. The strong correlation between the Cluster Sum and VFI provided credibility to the segmentation of deficits into clusters and the underlying methodology.

Since VF loss can be monocular [61, 62], most analyses were performed with the two eyes. Data collected from both eyes from each individual cannot be jointly analyzed without taking into account their intra-correlation. Such a procedure, however, is likely to underestimate standard errors, result in lower probability values, and the calculation of the confidence intervals may be imprecise [51]. These problems become more profound as the degree of correlation between eyes increases [51]. Among the statistical procedures that are available for two-eye analyses, incorporating eyes as a 'within subjects' factor in paired analyses and in longitudinal mixed effect model analyses constituted the best alternative [52].

Although the HHg database, used in the present study, is unique in providing a portrait of long-term exposure, the information was derived from government monitoring programs that did not rely on rigorous sampling strategies. Although HHg measurements constituted the large majority of points in the database, approximately 4.8% of equivalent HHg values were derived from blood-Hg, using the conversion ratio of 250:1, as recommended in the Canadian guidelines [36, 37]. This ratio has been questioned by several studies that suggest that it is underestimated and highly variable [75–77]. Removal of the derived data points did not change the outcome of the analyses.

For this community, as illustrated in Fig. 1, Hg exposure decreased over the sampling period [30, 31, 38]. No information was available regarding previous VF status. It would have been useful to have longitudinal VF measures to better understand the progression of the disorder. Further studies should follow-up VF constriction in this population.

The findings of this study demonstrate the importance of long-term follow-up, even after biomarkers of Hg exposure are below official guidelines. Eye care professionals such as ophthalmologists and optometrists, especially in the context of suspected glaucoma, would benefit from knowledge of participants' past Hg exposure. Coastal and riparian Indigenous communities, where fish consumption is historically much higher than in non-Indigenous communities [78], may be at increased risk for VF loss.

Conclusion

This study of adults from Grassy Narrows First Nation demonstrates the relationship between long-term Hg exposure and VF constriction, involving not only the periphery, but also the more central areas. To date, there are no programs available for visual rehabilitation in this community. The people of Grassy Narrows have fought for the past 50 years for recognition of the impact of Hg poisoning on their health and their lives. The Canadian government has recently committed to their long-stated demand for a Mercury Care Home and Wellness Centre, which should include eye and vision examinations and a visual rehabilitation program.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-024-01119-6.

Supplementary Material 1.

Acknowledgements
The study was carried out in partnership with the Mercury Justice Team of Grassy Narrows. We thank the people of Grassy Narrows who contributed their time as participants and as discussants to the understanding and interpretation of the findings. Without the hard work and support of the many people from Grassy Narrows First Nation for recruitment, community organization and data collection, this study would not have been possible. We thank Drs. Annie Chatillon and Mathieu Khoury, optometrists, who performed the eye and visual examinations. We greatly appreciate the work of Florence Fiola-Racine and Rosa Nalini, who entered the HFA pattern deviation data by hand. We are particularly grateful to Vanessa Tremblay-Carter who provided the backbone administrative support throughout the project.

Authors' contributions
A.P. first author, D.M. principal investigator and M.F. and J.D., co-principal investigators, ensured the community collaboration, grant proposal and data collection. B.T. designed the eye and vision examination protocol and supervised the optometrists who performed the examinations. A.P. conceived the innovative statistical approach and carried out the analyses. A.P., D.M and B.T. wrote the main manuscript. A.P. prepared all of the figures. All authors reviewed the manuscript.

Availability of data and materials
The datasets generated and analysed in the present study are the property of Grassy Narrows First Nation. Permission for use of the data lies with Grassy Narrows Chief and Council.

Declarations

Ethics approval and consent to participate
Ethics approval for the Niibin Study was obtained from the Université du Québec à Montréal (UQAM) Research Ethics Board (certificate #3763_e_2020) and Manitoulin Anishinaabek Research Review Committee (certificate #2022-06). This manuscript has been reviewed and approved for publication by Grassy Narrows Chief and Council.

Competing interests
The authors declare no competing interests.

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Received: 12 August 2024 Accepted: 23 September 2024
Published online: 07 October 2024

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