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Childhood mercury exposure and early death in Grassy Narrows First Nation, Canada: a retrospective study

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Abstract

Background In 1962, a chloralkali plant began discharging mercury (Hg) into the Wabigoon-English River system, contaminating the territorial waters of Grassy Narrows First Nation, whose traditions, livelihood and diet centered on fish. Data from 1970 to 1997 government Hg biomonitoring programs were repatriated by Grassy Narrows. Our researcher-community partnership carried out secondary analyses to examine the association between childhood Hg exposure (between 5 and 15y) and survival to July 1, 2024.

Methods Information from the governmental biomonitoring programs and from Grassy Narrows Registry of Band members were used to create a retrospective year-based equivalent hair Hg (HHg) database, with dates of birth, sampling and death ($N=317$). Apparent cause of death was reported by community members. Different approaches were used to minimize potential unmeasured confounders in examining the relation between Hg exposure and early death: (i) matched pairs (deceased/alive; same sex, year of birth (± 1) ($n=81$) pairs for dissymmetry analysis, Kaplan-Meier survival analysis and Cox proportional hazards regression models (ii) Longitudinal Mixed Effects Models (LMEM) with individuals who had at least 7 year-based HHg measurements ($n=35$), and (iii) trajectory techniques modelling exposure.

Results HHg measurements ($n=1031$) were available for 167 boys and 150 girls. Mean age at sampling was 10.5 y (SD: 2.9); 44.2% had HHg ≥ 4 µg/g at least once. By July 1, 2024, 97 individuals (30.6%) had died (median age: 39 years (IQR: 24–49)). The Cox Hazard Ratio for HHg ≥ 4 µg/g at least once was 1.96 [1.18–3.28]. LMEM showed that HHg was 1.46 µg/g higher over the sampling period for the deceased compared to the living. Significant associations ($p \leq 0.001$) were also observed for early death with respect to HHg trajectory summary scores (OR: 1.14 to 1.24; SE ≤ 0.78). Reported suicide, liver disease and cardiovascular/metabolic conditions made up 60% of all deaths.

Conclusions Early mortality in Grassy Narrows First Nation is higher than other First Nations and the non-Indigenous populations in Canada. Convergent findings from different approaches and statistical techniques support an association between childhood Hg exposure and early death. Morbidity and mortality in this community require follow-up.

Keywords Mercury, Childhood exposure, Early death, Indigenous health, Mortality

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Background

Asubpeeschoseewagong First Nation (also known as Grassy Narrows First Nation) resides in Northern Ontario (Canada). The reserve occupies 22.5 km^2 with the traditional land use area covering over 7000 km^2 [1]. Between 1960 and 1975, a chlor-alkali plant in Dryden Ontario, Canada, discharged wastewater containing approximately 9000 kg of mercury into the Wabigoon River which flows into the rivers and lakes located in their traditional territory [2, 3]. Figure 1 contains three maps which depict: (a) Wabigoon-English River system location within Canada; b) the Wabigoon-English River

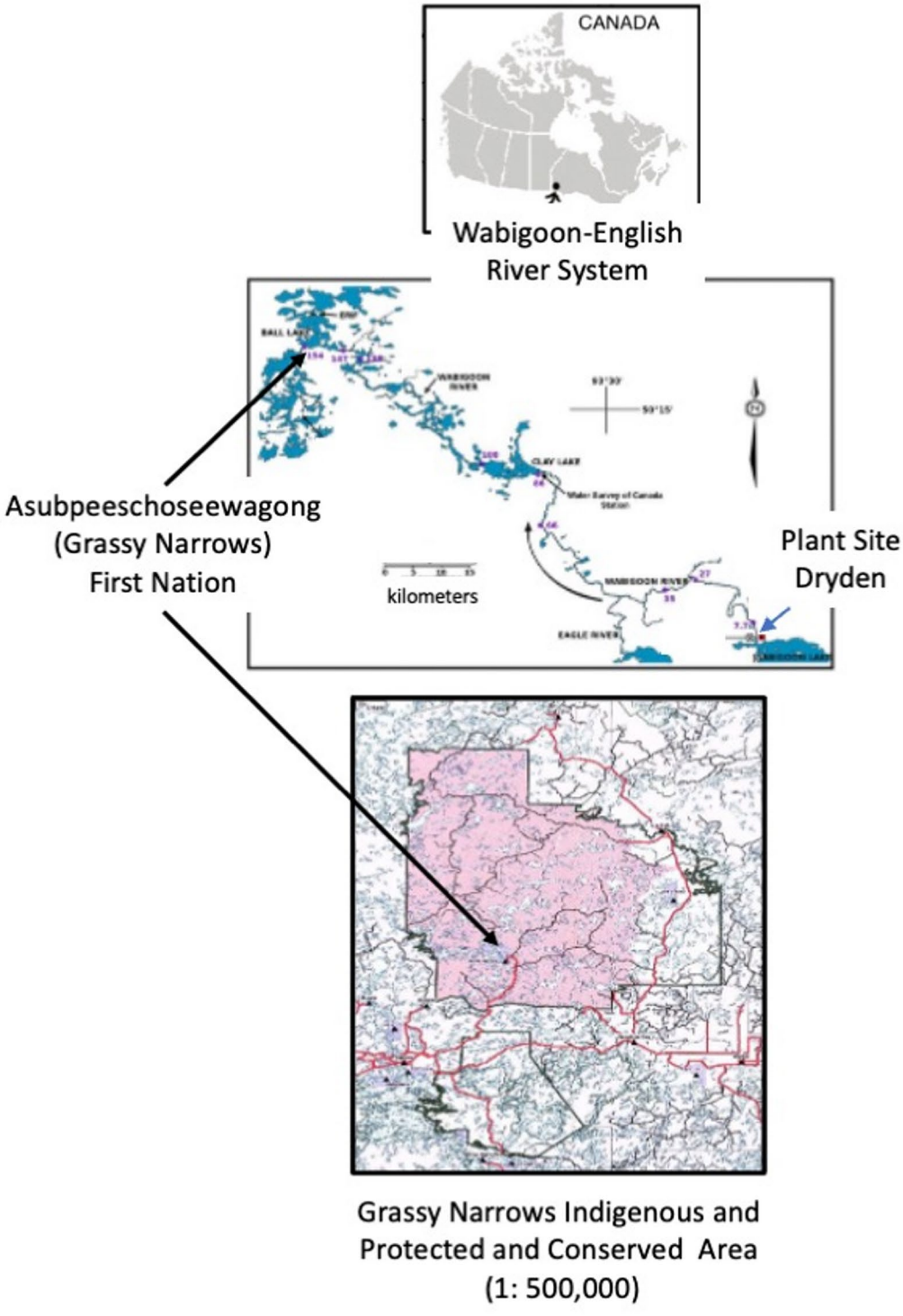

Fig. 1 Maps illustrating the location of Grassy Narrows First Nation location. Permission was obtained from the authors for use of the maps [1, 4]

System that links the Dryden plant to the Grassy Narrows reserve; c) Grassy Narrows Indigenous and Protected and Conserved Area.

In this organically rich aquatic ecosystem, mercury is methylated, biomagnified and bioaccumulated in the aquatic food chain [5–7]. In 1970, mercury concentrations in the fish, walleye (*Sander vitreus),* captured in Grassy Narrows traditional fishing grounds, varied from 1.2 µg/g to 24 µg/g [5]; between 1970 and 1974, all of the walleye captured by a government monitoring program were above the commercial limit of 0.5 µg/g [8] Emission controls were ordered in 1970 and the chlor-alkali process was replaced with a non-mercury process in 1975 [3]. Hg concentrations in walleye decreased initially until the mid-1980s to early 1990s, and then plateaued, with average concentrations around 2 µg/g in the Wabigoon River near Grassy Narrows [5, 9, 10]. Hg has penetrated this extensive river and lake system and is still present today at elevated levels [4] recent sampling of walleye in lakes and rivers upstream of Grassy Narrows (see Fig. 1 for sampling sites) showed 45 cm standardized walleye Hg concentrations over 1 µg/g in the Wabigoon Rive, including the highest concentrations in Ontario [11].

Prior to the Hg disaster, Grassy Narrows First Nation was a thriving community, with a cash economy based on commercial and sports fisheries and trapping [2]. Employment levels were high, with many working as fishing guides in fly-in fishing camps and in commercial fisheries, while women worked at cleaning and cooking in the camps [2, 3] About 80% of households had one or more members fish guiding throughout the season [2]; primarily at the Barney's Ball Lake Lodge, the most prestigious fly-in fishing lodge in Northwestern Ontario [12]. Families spent winters on trap lines and sold furs to the Hudson Bay Company [3]. Fish, particularly walleye, was a dietary staple for the community. In 1970, the Medical Research Branch of Health Canada initiated a Hg biomonitoring program in Indigenous communities across Canada [13, 14]. The highest blood Hg concentration observed in Canada occurred in Grassy Narrows and was 660 µg/L, recorded in 1971 [13]. In 1976, mean blood Hg was 23.8 µg/L (range:1.5–322.9 µg/L) and by 1995, it had decreased to an average of 7.5 µg/L (range: 1.7–46.7 µg/L) [13], paralleling the decrease in Hg levels in fish [5, 9].

By the mid to late 70's, Ball Lake lodge and commercial fisheries were closed down, however some fishing lodges remained open and fishing guides were obliged by their employers to partake in shore lunches with the guests [3]. The people of Grassy Narrows began decades-long suffering from the loss of health, income, culture, traditions and a highly nutritious food source [2, 3, 15–19]. In 1975, Dr. Masazumi Harada and colleagues reported mild symptoms of Minamata Disease among people from this community [20]. In the early 2000's, 23 persons received a diagnosis of Minamata Disease or Minamata Disease with complications, using the Japanese criteria for Minamata Disease [20, 21]. Recent studies have shown that long-term past Hg exposure in this community was associated with a higher prevalence of symptoms of nervous system dysfunction [22] which increased over time [23], visual field constriction [24], and intergenerational Hg exposure was associated with increased risk of attempted suicide among children and youth [25].

Since our initial collaboration with Grassy Narrows, we have heard people at community meetings and at individual encounters, say *"Our people are dying"* [9]. Indeed, between 1957 and 1963, 32% of deaths in Grassy Narrows were due to old age ($n=12$), between 1964 and 1970, this figure dropped to 14% ($n=6$) and between 1971 and 1977, it was down to 5% ($n=3$) [26]. A recent study showed that, in this community, premature death (< 60 years old) was associated with long-term Hg exposure [9]. While that study focused on persons, who were born prior to 1959 and could have reached 60 years of age by the time of the analyses, rates of early mortality in persons born after 1959 have not previously been reported. Hg exposure *in utero* and during childhood is considered highly toxic [27–30].

Prior to 1970, the Grassy Narrows population on reserve was approximately 500 persons [2]. Postl and co-authors [26] reported a similar number for 1986 and indicated that 43% were between 0 and 14 years of age. Grassy Narrows currently has approximately 1,000 registered Band members living on reserve and a further 600 living elsewhere [31]. According to the 2016 and 2021 census 30% of registered Band members on reserve were between 0 and 14 years of age [32].

The present study sought to examine the possible contribution of childhood Hg exposure to early mortality. The aims of the study were twofold: (i) to characterize survival rates in the cohort of children, who had provided blood and/or hair samples between the ages of 5 and 15 years for the government biomonitoring program (1970–1997); (ii) to examine the possible contribution of childhood Hg exposure to early death.

Methods

This study is part of an on-going community-researcher collaboration with Grassy Narrows First Nation, initiated in 2016. The research is carried out in accordance with the First Nations Principles of Ownership, Control, Access and Possession of data (OCAP), a registered trademark of the First Nations Information Governance Centre [33] and guidelines of the Canadian Institutes of Health Research for studies with Indigenous communities [34]. The Mercury Justice Team of Grassy Narrows First Nation, led by JdS, is actively involved in all aspects

of the research. Grant applications and each proposed specific research objective and accompanying methods are presented to Chief and Council for discussion and approval. Results are presented at community meetings for feedback and discussion. The first draft of manuscripts is presented and discussed with Chief and Council and the final draft requires approval of Chief and Council. Findings of the present study were presented and discussed at a community meeting held on April 25, 2024, and final approval was obtained from Chief Rudy Turtle and Council members on September 19, 2024.

Study design

The present study is based on secondary analyses of data derived from two sources (i) a biomarker database, created from the 1970–1997 government biomonitoring programs for Hg exposure; (ii) Grassy Narrows Band Registry, which includes date of birth and date of death of all Registered Band members; this information is provided by and continually updated by Indigenous Services Canada.

Mercury exposure

The government archived files included Hg concentrations from hair and blood samples for 662 persons taken in Grassy Narrows between 1970 and 1997. Sampling was not carried out regularly. In the early seventies, the biomonitoring programs, organized by the provincial and federal governments, focused primarily on families of fishing guides, who made up approximately 80% of households at that time [13]. The Medical Research Branch of Health Canada (MRB-HC) continued taking samples from fishing guides and volunteers throughout the monitoring period [14]. In 1995, Dr. Tom Clarkson, in collaboration with the MRB-HC, carried out a house-to house survey and collected 248 hair and 80 blood samples from adults and children [35] and in 1995-96, the MRB-HC took hair samples from 208 children (average age 10 years) enrolled in the Grassy Narrows school [13]. When possible, hair was cut into centimeters to obtain monthly changes in exposure. Details of recruitment and hair and blood sampling techniques were reported by those who collected the original data [13, 35] and carried out Hg sample analyses [36–38].

The governmental biomonitoring programs' archived files were repatriated by Grassy Narrows leadership 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 in 2019 and shared with the academic researchers. The files included information on date of birth, sex, month and year of sampling, and blood and/or hair Hg concentrations. From these files, we derived a 28-year retrospective longitudinal year-based equivalent hair Hg (HHg) database, using the maximum value for each year [9]. Most Hg measurements (91%) were derived from hair samples; when there was only a blood sample, it was transformed to an equivalent hair sample, using a hair/blood ratio of 250:1 [39]. For each person, the final equivalent HHg database included name, date of birth and sex, the sample date (year/month/day) for each year-based HHg measurement. A detailed description of the database is published elsewhere [9].

Prior to undertaking the analyses presented here, all persons still alive, for whom Hg exposure results were available, were informed individually in written documents and were invited to a one-on one meeting with DM, AL or MF if they wished to discuss their historic exposure concentrations in all confidentiality.

Selection of the study population

The 1970–1997 HHg database was used as the point of departure for the present study population. Since few children were sampled in the first years of the program, for the present analyses, we extracted all individuals, who were born in 1961 or later, and had provided samples when they were children (5–15 years of age), over the period 1972 to 1996, inclusively. HHg data were available for 324 children in this age range. The children were then matched to the Grassy Narrows Band Registry, which contains name, dates of birth and death of all Status Grassy Narrows First Nation members, whether on or off reserve. Using the registry, we verified date of birth and sex and identified those who had died. Year of birth and year of death (where it applied) were available for 317 persons (97.8%); seven were untraceable. For each child, at least 1 HHg sample was available for a total of 1031 HHg measurements, of which 33 (3.2%) were derived from blood samples. Where possible, unofficial cause of death was obtained from the Band Office, who contacted family members of the deceased.

Statistical analyses

The study was "closed" on July 1, 2024, thus the follow-up period of survival ended at a maximum of 63 years of age, with the oldest surviving individuals born in 1961. Given the small sample size and the complexity of the database, with children entering the cohort over a long-time span, decreasing Hg exposure and uneven Hg sampling over the time period (1972–1996), several statistical techniques were used to minimize potential confounding and ensure consistency of findings. Figure 2 contains a flow chart of cohort selection and the number of individuals retained for the different statistical approaches.

Survival analyses

Kaplan-Meier (K-M) analysis [40] and Cox Proportional Hazards Model (CPHM) [41] were used for survival

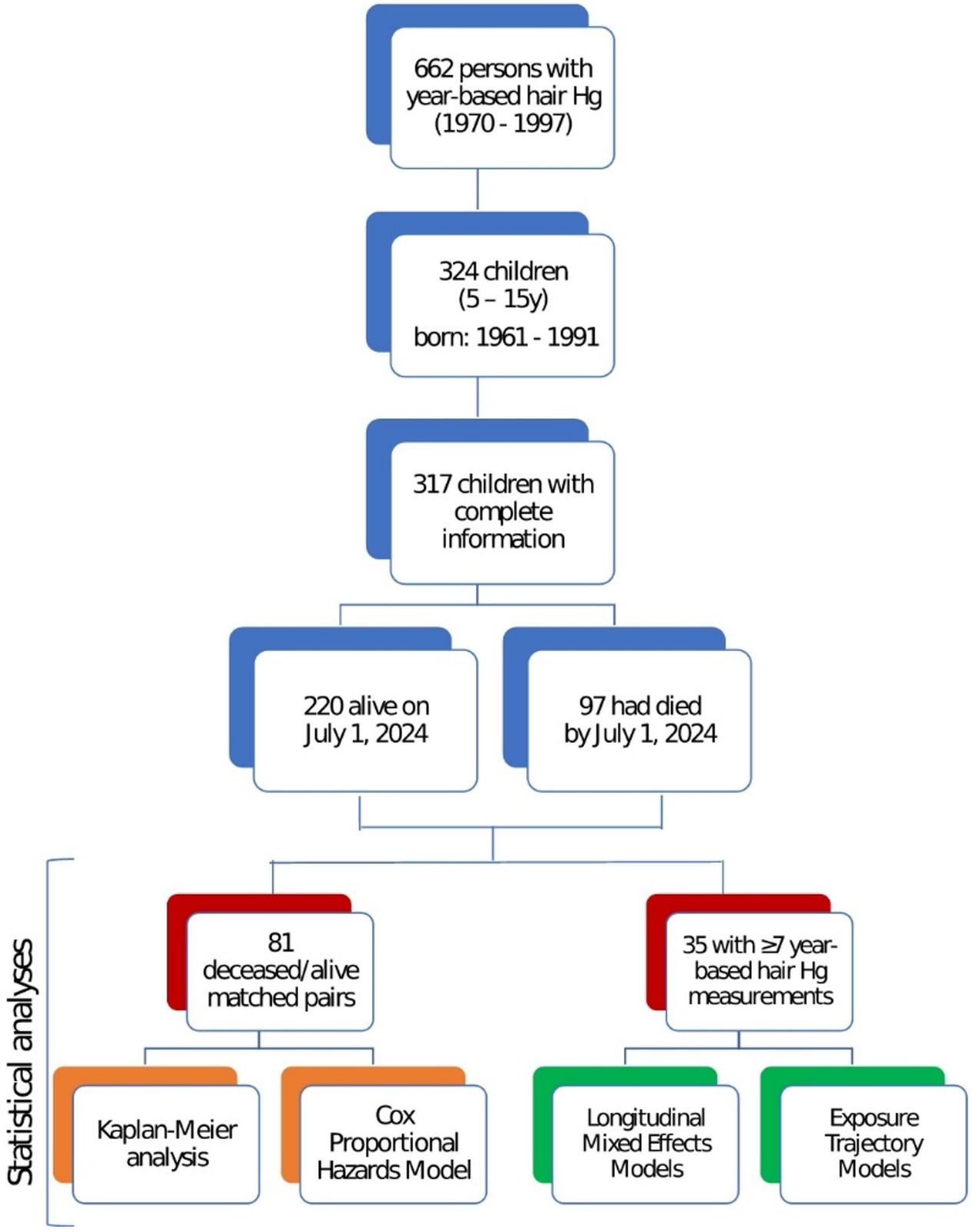

Fig. 2 Flow chart of cohort and analyses selection process

analyses. Both provide a cumulative incidence curve function illustrated by a summary curve, showing the cumulative failure rates over time [42], and use semi-parametric statistics to estimate the survival function from lifetime data. Unlike K-M, a univariate survival analysis, CPHM uses a multivariate approach, providing hazard rate functions and modelling a covariate-adjusted cumulative incidence curve as a function of all cause-specific hazards for a given set of covariates [43]. The follow-up period was right censored until July 1, 2024. For example, if a person was alive and 40 years of age on July 1, 2024, the model censored the person out at 40 years of age.

Matched pairs

Based on the underlying assumption that persons in this community of the same age and sex, would have experienced similar social and economic conditions when growing up and in adulthood, we generated matched pairs [44]. Persons who were deceased and those who were still alive as of July 1, 2024, were matched on their year of birth (± 1y) and sex, for a total of 81 pairs (162 children) (Fig. 2). Paired comparisons served to examine prevalence differences in HHg ≥ 4 µg/g between pairs, using McNemar Bowker Chi square. Persons included in the paired analyses were likewise used for the K-M and CPHM to ensure homogeneity.

For K-M stratified by HHg categories (< 4 µg/g over the sampling period and ≥ 4 µg/g at least once), the log-rank test (non-parametric) was used to evaluate differences between groups across their survival curves [45]. Univariate analyses were used to screen potential predictors before constructing a multivariate CPHM. For the continuous predictors, univariate CPHM were used, while for categoric ones, the log-rank test of equality across categories was employed. All predictors with a *p*-value of less than 0.2 were considered for covariates in the final CPHM [46]. In the final CPHM, the response is the 'hazard', which provides the probability of dying at a given point in time [42]. Covariates considered in the analyses were HHg, categorized as < and ≥ 4 µg/g, year of birth and sex.

CPHM must have hazard functions that are proportional over time (i.e., constant relative hazard) [47]. The proportional hazard (PH) assumption [49] was verified using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. We also compared the Kaplan–Meier observed survival curves with the CPHM predicted curves variables of interest. Close predicted and observed curves indicate that proportional-hazards assumption has not been violated.

Longitudinal analyses

Longitudinal analyses were performed with a sub-group with at least 7 HHg measurements between 5 and 15 years of age (Fig. 2). To ensure that there were sufficient data for the analyses (number of children and hair samples), we estimated the minimal required sample size, based on formulas from Hedeker and co-authors [48] and direct calculations using the G*power software [49–52].

Linear mixed-effects models (LMEM) were used to account for both fixed effects of covariates and random individual-level variability, allowing for the analysis of repeated measures and the modeling of within-subject correlations over time. For LMEM, age, sex, year of sampling, sampling season were tested for fixed effects, while age at sampling nested in year of sampling was tested for random effects. Covariates were kept in the LMEM if they showed a p-value < = 0.10 or if they substantively altered the estimate (≥ 20% change), with the exception of age and sex, which were always maintained in the models with a p-value < = 0.20. The most appropriate LMEM was identified by the Akaike information criterion, the Bayesian information criteria, and the likelihood ratio test at p < = 0·05. The normality of residuals was tested with a q-q plot.

Finally, different techniques to model individual Hg exposure trajectories across childhood were used to derive summary scores. (i) Locally Estimated Scatterplot Smoothing (LOESS): a non-parametric smoothing approach which provides a curve for each individual; the summary score is calculated by taking the mean of all deviations [53, 54]. The Random Effect Extraction method: linear mixed-effects models extract subject-specific random effects, reflecting individual deviation from baseline average Hg levels; summary scores represent individual variability [55, 56]. The spline within mixed effect models: natural cubic splines extract subject-specific trajectories by capturing non-linear exposure trends over time [57, 58]. The empirical Bayes estimates of the random spline coefficients were used as individual summary scores to capture the shape and trend of Hg exposure over time. The summary scores were then used in logistic regressions, with deceased (yes/no) as an outcome.

Database management, descriptive analyses, paired analyses, and Bowker-McNemar statistical tests were performed using JMP Professional 17·0 Statistical Analysis Hardware (SAS Institute). The survival analyses, LMEM and Hg trajectory techniques were conducted with Stata Stata/SE 18.0 Software (StataCorp. 2019. Stata Statistical Software: Release 16·0 College Station, TX: Stata Corporation). The survival analyses and LMEM results in Stata were compared with those found in the R package (survival, survminer, ggplot2, dplyr, lattice and nlme, lme4, lmerTest, robutslmm, sjPlot, respectively).

Results

Characteristics of the study population

The 317 children included 167 boys and 150 girls, born between 1961 and 1991, (median: 1970; IQR: 1965–1984). Among the 97 individuals (30.59%) who had died, 55 were listed as men (32.93%) and 42 as women (28.00%). The average age at death was 37.02 years, ranging from 12 to 61 years (median: 39.00 years; IQR: 24.00–49.00 years). The average age of those who were living ($n = 220$) was 48.25 years, ranging from 33 to 63 years (median: 48.00 years; IQR: 39.00–58.00 years). Of the 190 persons, born between 1961 and 1974, who could have reached 50 years of age at the time of analyses, 83 (43.68%) had died.

Figure 3 shows the K-M survival curve, illustrating the right-censored cumulative survival probability as a function of survival age ($n = 317$). For each time interval, survival probability is the number of surviving persons divided by the number of persons at risk.

Calculations for the K-M estimates of the survival function with respect to age categories and sex are provided in Supplementary Material (Table 1). No differences were observed between boys/men and girls/women at any age category. The log-rank test for equality of survivor function shows no gender difference (Chi square = 1.27, $p = 0.27$).

Mercury exposure over the sampling period (1970–1997)

The year-based HHg concentrations for samples collected from the children are presented in Fig. 4, with the number of HHg samples analyzed in each year.

There was a total of 1031 HHg measurements, unevenly sampled over the period. The median number of year-based HHg measurements for each child was 2; [IQR: 2–7]; range 1–11. There was no difference in the number of HHg measurements for boys and girls ($n = 563$ and 468 measurements, respectively). Since Hg exposure decreased over time (Fig. 4), a negative relation was observed between year-based HHg concentrations and year of birth (Spearman's rho = -0.390; $p < 0.0001$), as well as year of sampling (Spearman's rho = -0.507; $p < 0.0001$). Over the sampling period, boys had higher year based HHg concentrations ($n = 563$ measurements; median 1.90 µg/g; IQR: 0.7–4.90) compared to girls ($n = 468$ measurements; median: 1.40 µg/g; IQR: 8.50–3.88) (Wilcoxon Kruskal-Wallis Chi square = 10.47; $p = 0.0012$).

HHg concentrations were equal to or surpassed 4 µg/g at least once over the sampling period for 140 children (44.16%). There was no difference in the relative frequency of boys and girls with at least one HHg ≥ 4 µg/g (47.90% ($n = 80$) vs. 40.00% ($n = 60$). A total of 117 (36.91%) had one or more HHg concentrations ≥ 6 µg/g, which, at that time, was the Canadian guideline for "above the normal acceptable range" [59]. Eleven children (3.47%) had surpassed the Canadian guideline

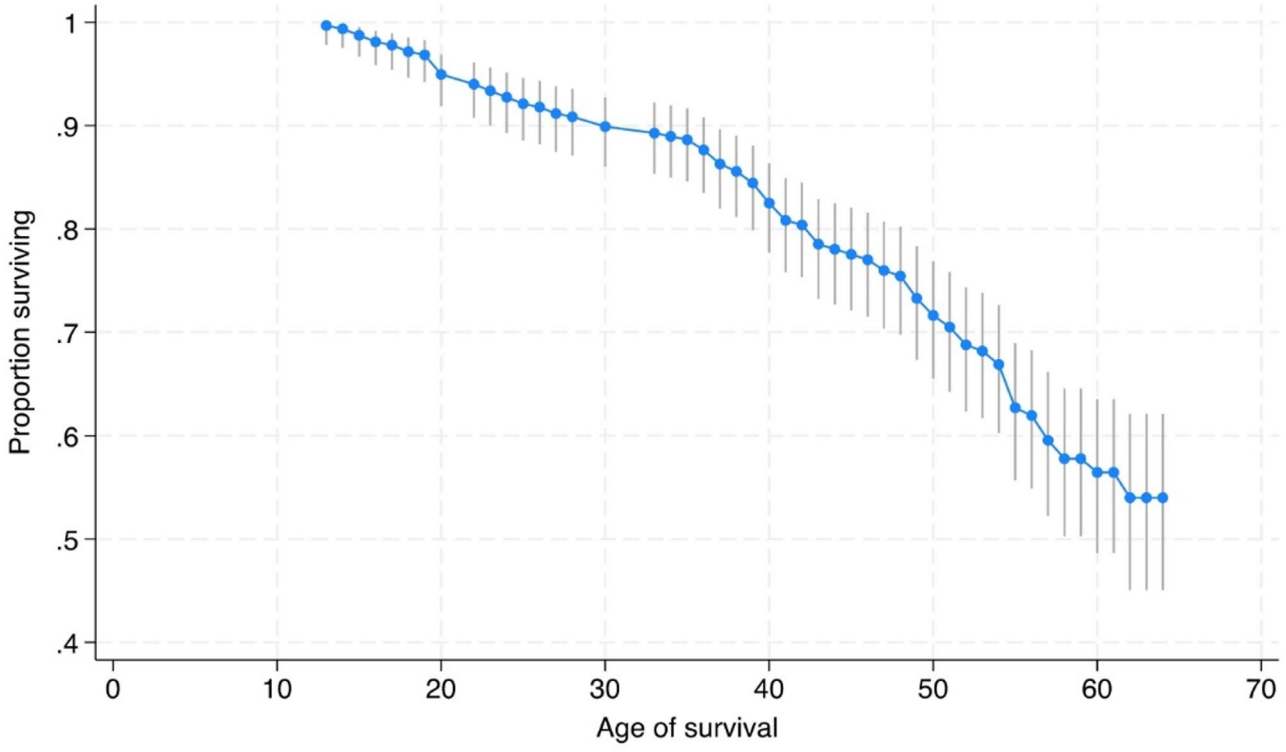

Fig. 3 Kaplan Meier cumulative probability survival curve ($n = 317$) with 95% Confidence Interval

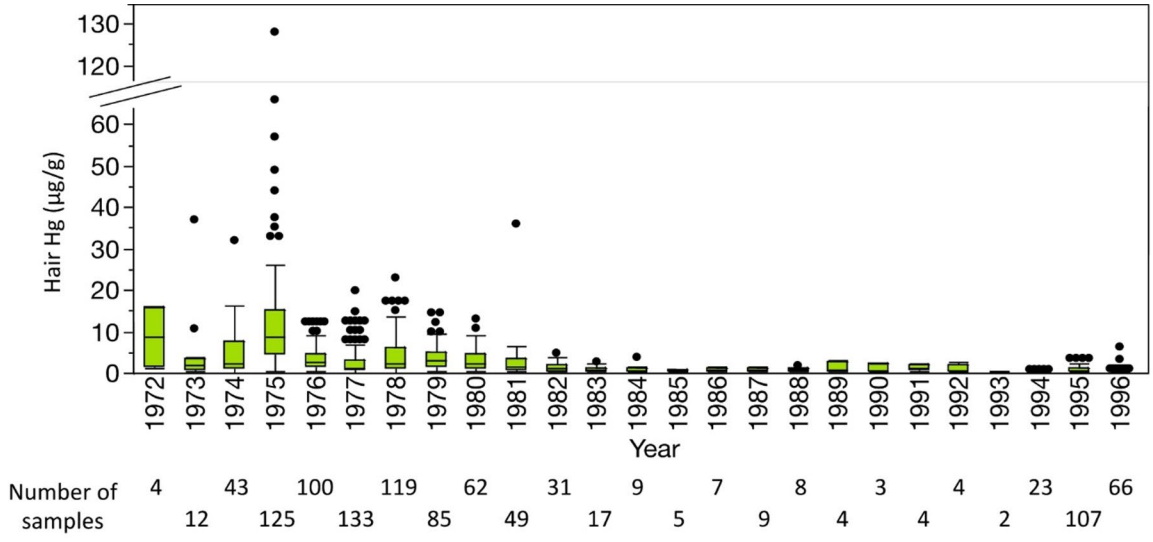

Fig. 4 Box plots of equivalent HHg concentrations for each sampling year ($n = 317$ children)

for "at risk", which was 30 µg/g [59]. Among those who had died, 67 (69.07%) had at least one HHg measurement ≥ 4µg/g. For those considered "at risk", with at least one HHg ≥ 30 µg/g, 8 of the 11 had died. The current Canadian guidelines for blood Hg for children 18 years of age and younger is 8µg/L (hair equivalent 2µg/g) [39].

Childhood Hg exposure and survival

To account for the strong correlation between HHg and year of birth, as well as the chronological entry into the cohort, analyses were performed with the 81 pairs, which included 40 and 41 pairs of men and women, respectively, born between 1961 and 1990 (median: 1966 (IQR: 1964–1970). For the deceased within the pairs, median age at death was 37.00 years, ranging from 12.00 to 59.00 (IQR: 22.75–47.25 years). For those who were still alive on July 1, 2024, the median age was 58.00 years, ranging from 34–63years (IQR: 54.00–60.00 years). Symmetry of disagreement analysis with respect to ≥ 4 g/g showed that for 20 pairs (24.69% of all pairs), the deceased person had HHg ≥ 4 µg/g at least once, while only 6 pairs (7.41% of all pairs) of those who were still alive had ≥ 4 µg/g HHg (McNemar Bowker Chi square: 7.54; $p = 0.006$).

Figure 5a contains the K-M curves for the cumulative proportion of persons surviving over time for those whose childhood with respect to < 4 µg/g ($n = 60$) and HHg ≥ 4 µg/g ($n = 102$) for the 162 persons included in the pairs. Comparison of the Kaplan–Meier observed survival curves with the Cox predicted curves for the max-HHg < and ≥ 4 µg/g, showed that the observed values were close to the predicted ones, indicating that the proportional-hazards assumption had not been violated (Fig. 5b).

The log-rank test for equality of survivor functions for HHg at 4 µg/g was inferior to 0.2 (Chi square = 2.23; $p = 0.14$), which was sufficient to test the CPHM. Table 1 presents the results of the Cox Proportional Hazards Model for the 162 persons that make up the 81 pairs with respect to 4 µg/g HHg. The Hazard Ratio for HHg ≥ 4 µg/g was 1.96 [1.18–3.28], adjusted for year of birth.

The test of proportional-hazards assumption showed that HHg < and ≥ 4 µg/g and year of birth hazard functions were not time-dependent (Global Chi square 2.92, $p = 0.232$; Chi square for max-HHg < and ≥ 4 µg/g 0.48 $p = 0.489$; and Chi square for year of birth 1.23 $p = 0.267$). The homogeneity of the Schoenfeld residuals over time likewise ensured that both covariates satisfied the proportional hazard assumption (Supplemental Material Fig. 1).

The survival rate for the pairs ($n = 162$) with respect to age category for those with childhood HHg < and ≥ 4 µg/g are presented in Supplementary Material Table 2. The survival rate was consistently lower among those with higher HHg, reaching 0.41 at 60 years of age for those with HHg ≥ 4 µg/g ($n = 102$) and 0.53 for those with lower exposure ($n = 60$).

Longitudinal analyses with at least 7 repeated HHg measurements

To support the above findings, a series of longitudinal analyses were performed with a sub-group of persons, extracted from the total child cohort, with at least 7 year-based equivalent HHg measurements or more between 5 and 15 years of age, ($n = 35$). A total of 14 (40.0%) had since died; their median age at death was 39.50 years

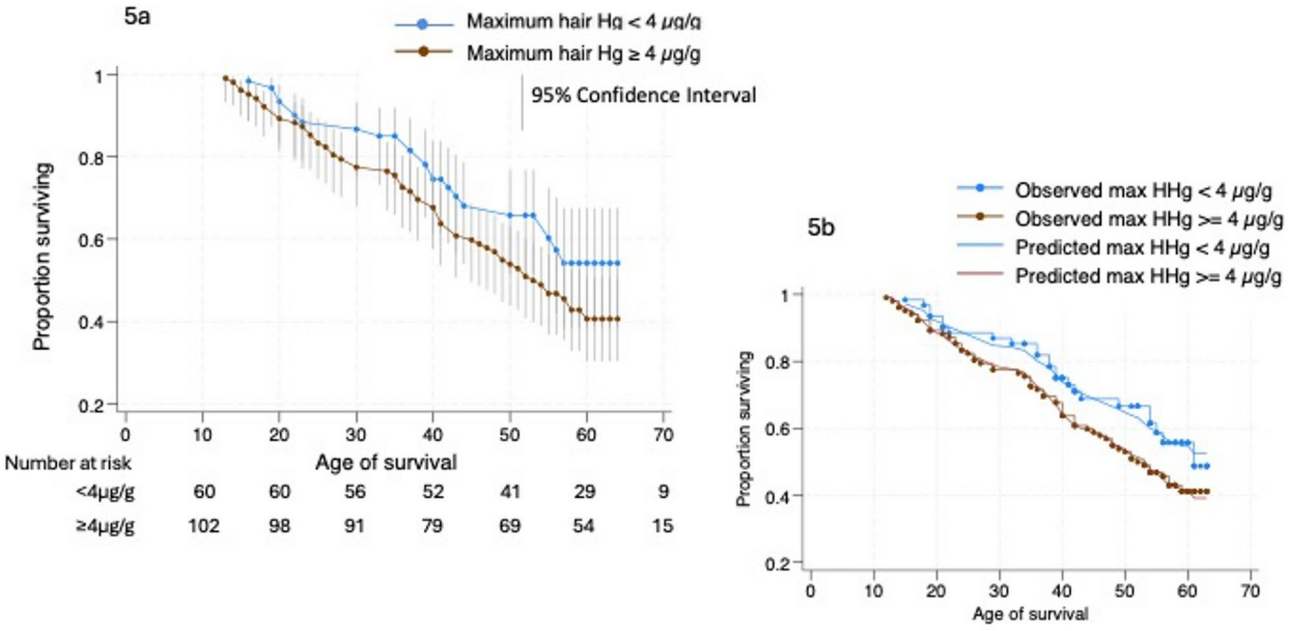

Fig. 5 5a. Kaplan Meier survival probability curves for persons included in the pairs with respect to HHg categories, 5b. Distribution of observed and predicted survival curves

Table 1 Hazard ratios of the Cox proportional hazards model

	Hazard Ratio	95% Confidence Interval	Standard Error	*p*-value
HHg ≥ 4 µg/g	1.96	1.18–3.28	0.51	0.010
Year of birth	1.06	1.02–1.10	0.02	0.004

Note: sex was tested but did not enter into the model ($p > 0.20$)

Table 2 Coefficients of longitudinal mixed effect models (LMEM) with respect to hhg (≥ 7 samples over the 10-year period between 5 and 10 years of age) for persons extracted from the entire database ($n = 35$)

	HHg (µg/g) over the sampling period			
	Coefficient	95% CI	Standard error	p - value
Deceased	1.46	0.38–2.53	0.55	0.008
Sex (women)	-1.73	-2.73–0.72	0.51	0.000
Time	-0.42	-0.61 - -0.23	0.10	0.000

Wald Chi square = 36.65; $p = 0.0000$. Age at sampling, nested in time of sampling, was included as random effect

Table 3 Results of logistic regression analyses for early death (with alive in 2024 as the reference value), with respect to trajectory summary scores of hhg over time for individuals with at least 7 hhg measurements ($n = 35$)

HHg trajectory summary score	Odds Ratio	95% confidence interval	Standard Error	*p*-value
Random Spline	1.24	1.10–1.42	0.078	0.001
Random Effect Extraction	1.23	1.10–1.38	0.073	0.000
Locally Estimated Scatterplot Smoothing (LOESS)	1.14	1.06–1.23	0.044	0.001

Covariates for all of the logistic regressions: year of birth and sex

(IQR: 22–49.30 years). Table 2 presents the results for the LMEM with HHg as the y variable. HHg, over the ≥ 7 childhood sampling years, was higher among the deceased compared to those who were alive by 1.46 µg/g. The difference was greater for men compared to women.

Table 3 presents the Odds Ratios for early death (yes/no) with respect to the summary scores for the HHg trajectories, derived using different modeling techniques for longitudinal HHg exposure and early death (yes/no). In all models, early death was significantly associated with past mercury exposure.

Reported cause of death

Among the 91 persons for whom cause of death was known, the most reported causes were suicide ($n = 21$ (23.07%)) and liver disease ($n = 21$ (23.07%). Deaths

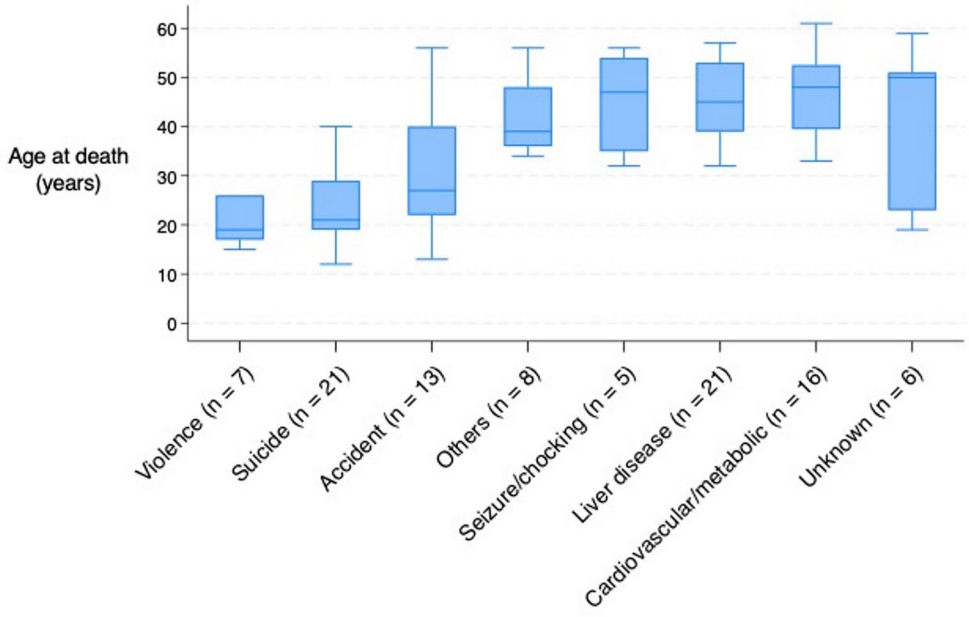

Fig. 6 Box plots of age at death with respect to cause of death

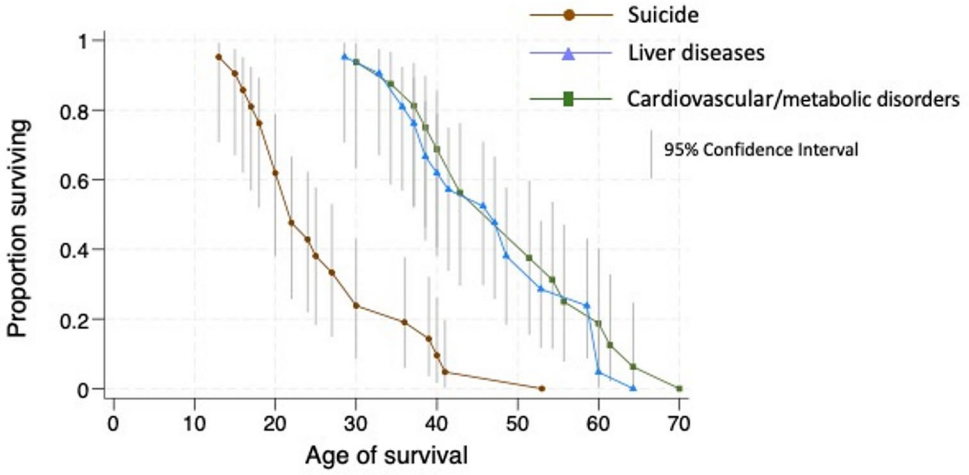

Fig. 7 Kaplan-Meier survival probablity curve for suicide, liver diseases and cardiovascular/metabolic conditions

attributed to cardiovascular/metabolic conditions (heart disease, aneurysm, diabetes, kidney disease) constituted 17.58% ($n=16$). A total of 13 deaths (14.29%) were due to accidents, which included car accidents, house fires, drowning, freezing to death and head trauma. The "Other" category ($n=8$ (8.79%)) included cancers, tumors and pneumonia. Violent deaths refer to homicides ($n=7$ (7.69%)). Choking and seizure were grouped ($n=5$ (5.49%)).

Figure 6 presents box plots for the age at death with respect to cause of death. The youngest were those who died by violence, followed closely by suicide. Median age for those who died due to accidental deaths was 28 years. For those who died of seizure/choking, liver disease or cardiovascular/metabolic conditions the medians were similar (between 44 and 48 years of age).

Figure 7 shows the survival probability curves, with 95% confidence intervals, for those who died from suicide ($n=21$), liver diseases ($n=21$) and cardiovascular/metabolic conditions ($n=16$). The risk of dying of suicide is higher prior to 40 years of age, while for liver and cardiovascular/metabolic conditions, the curve starts dropping in the mid-thirties.

No gender difference was observed for suicide (boys/men: ($n=12$) 21.82% and girls/women ($n=9$) 21.43% of all deaths of men and women, respectively). Proportionally more women died of liver diseases (men: ($n=7$) 12.73% and women ($n=14$) 33.3% of all deaths of men

and women, respectively). While more men died violent deaths, there was no gender difference in accidental deaths. Seizure/choking was reported cause of death only for men.

Discussion

The findings of this study reveal that almost a third of the 317 children/youth of Grassy Narrows First Nation, who had provided hair and/or blood samples between 1972 and 1996 for the government Hg biomonitoring programs, had died at a young age; half of the deaths occurred younger than 40 years of age. For those who might have reached 60 years of age, 50% had died. Various statistical approaches showed that higher childhood Hg exposure was associated with early death.

There is an extensive literature, based on Canadian census data, on higher mortality rates and lower life expectancy among First Nations in Canada [60–68]. Between 2006 and 2016, the Age-Standardized Mortality Rate per 100,000 person-years for First Nations on Reserve was 581 vs. 335 for the non-Indigenous population [67]. A comprehensive analysis of Canadian mortality between 1974 and 2013 showed that, over that period, there had been no improvement in relative, age-standardized mortality rates between First Nation people on-reserve and the general population [65]. Although it is difficult to compare the findings from this study, whose cohort entry covered a 28-year period, with census mortality studies carried out on First Nations in Canada, some similarities and differences merit attention.

The findings of this study suggest that for the persons in the present cohort, early mortality occurred at a higher rate and at a younger age compared to other First Nations in Canada and at a much higher rate compared to non-Indigenous people. The estimated probability of dying before the age of 75 for First Nation men and women, who were 25 years of age or older in 1991, was 49% and 38% respectively, while for non-Indigenous people in Canada, these figures were 36% and 21% respectively [60]. By contrast, in the present study, of the 113 persons, who were at least 25 years of age in 1991, 60% of men and 38% of women had already died prior to 63 years of age. The findings are consistent with a 1989 report on mortality in Grassy Narrows First Nation; the authors indicate that only 6 (21%) of deceased individuals were over 60 years old; they calculated a crude death rate for all causes of 1137 per 100,000/year - approximately two and a half times the Ontario rate per 100,000 during this time-period [26]. Data from 2021 Statistics Canada census (15 year of age or more) shows that 9% of the population of Grassy Narrows was over 65 years of age, compared to 13% and 23% for the Indigenous and non-Indigenous population of Canada [69].

Higher mortality in First Nations in Canada has been attributed to the long-term consequences of colonization, racism and intergenerational trauma, that has led to low socio-economic status, land dispossession, environmental degradation, displacement, unsuitable education, inadequate housing, poor access to health care, insufficient and ineffective public health initiatives [61–63, 65, 67, 68, 70]. For the people of Grassy Narrows, this situation was further compounded by the discharge of mercury into the Wabigoon-English River system.

While this is the first study, to our knowledge, to examine hair Hg in childhood with respect to early mortality, other studies have linked past hair Hg concentrations to an increased risk of dying, A 10-year follow-up study of healthy Finnish men, reported that the risk of dying, whether adjusted on age, or on age with a series of other relevant variables, increased significantly with past hair Hg concentration [71, 72]. In Grassy Narrows, Harada and co-authors [73] noted in their 2002 follow-up of persons assessed in 1975, that all of those who had had hair Hg concentrations above 50 μg/g were deceased; unfortunately, no information was provided on their age at death. In 2020, a retrospective longitudinal study showed that long-term past hair Hg concentrations among persons from Grassy Narrows, born prior to 1959, was associated with dying younger than 60 years of age [9].

In the present study, there were few persons in each category of reported cause of death and only observational analyses could be performed. However, the information obtained on cause of death may be useful for future health care and preventive follow-up. Suicide is high on the list of avoidable deaths in First Nation communities in Canada [63, 74, 75]. In the present study, when excluding persons who died by violence, accident and unknown causes, suicide constituted 30% of all deaths; the large majority were among 12 to 24-year-olds. Prior to 1970, no suicide had ever been recorded in Grassy Narrows [15], but between 1970 and 1977, the incidence of suicide was 3.6 times higher compared with another First Nation community, selected for its pre-1970 socioeconomic similarities to Grassy Narrows [2]. In a recent study, the risk of attempted suicide in Grassy Narrows' youth was associated with prenatal Hg exposure [25]. Among Inuit adolescents, both prenatal and childhood Hg exposure has been associated with higher scores on anxiety scales, independently of other risk factors, such as bullying and food insecurity [76, 77]. Functional magnetic resonance imaging (MRI) of these adolescents showed altered functional activations of prefrontal brain areas during emotional processing of fear [77].

Among persons in the present cohort, there was a high prevalence of early death from liver diseases and conditions grouped as cardiovascular/metabolic, with rates increasing rapidly after 40 years of age. Increased

mortality from liver cancer and chronic liver disease has been reported for fishing areas where a majority of registered Minamata disease patients resided (Tamishiro et al., 1983 and 1984, cited in (Tamashiro et al., 1986) [78]. Hg exposure has likewise been associated with higher mortality from cardiovascular disease and heart disorders [71, 72, 79]. These studies, coupled with the present findings, suggest that special attention should be given to early signs of liver dysfunction, cardiovascular and metabolic conditions among persons with a history of Hg exposure.

The major strength of this study was the possibility of linking mortality information obtained from the Grassy Narrows Band Registry to almost all of the children, who between the ages of 5–15 years had provided blood and/or hair samples for government biomonitoring programs between 1972 and 1996. There were sufficient data from children with at least 7 year-based HHg measurements between the ages of 5–15 years of age to carry out longitudinal analyses.

Analysis of the relation between childhood Hg exposure with early deaths posed several challenges. First, children entered the cohort at different ages over time; those who entered in the 1960's could have attained an older age compared to those who had entered in the 1990's. However, by the end of the follow-up period, all participants had reached an age at which mortality would not typically be anticipated. Second, there was an important decrease in Hg exposure over the biomonitoring period, which was strongly correlated to year of birth. Complementary statistical approaches, including survival regression models and longitudinal analyses (linear mixed-effects models and trajectory-based methods), revealed significant associations between childhood mercury exposure and early death.

The study size constituted an important, but unavoidable constraint. The numbers reflect the size of the population in Grassy Narrows [2, 26, 31, 80]. A further limitation is possible misclassification about cause of death, which was obtained from the Grassy Narrows Band Office and the families of the individuals who had died. Despite this, very few deaths were classified as cause unknown. Using age and date of death, it was possible to cross-verify the reported cause of death for some individuals based on reports from the 1970s and 1980s [2, 26]. A further limitation to the present study is the absence of information on childhood adversities, which have been shown to contribute to adulthood mortality [81–83].

The secondary data used in the present study only included date of birth, date of death and sex; no information was available for other characteristics. To address possible confounding, matched pairs, which minimize the effects of societal and environmental time-varying unmeasured confounders [44], were used to compare dissymmetry and for the survival analyses with respect to Hg exposure. The LMEM with individual-specific random-effects can partially absorb time-stable, unmeasured confounders [84, 85]. While each method has its inherent biases, the robustness of our findings lies in the triangulation of different approaches and statistical techniques [86, 87]. Nonetheless, residual confounding cannot be entirely ruled out.

The findings of the present study are applicable not only to Grassy Narrows, but to many Indigenous communities worldwide for whom marine and/or freshwater fish have been and still are a dietary mainstay [88–90]. Mercury production and use reached a peak in the 1970's [91] and past elevated exposure may contribute to today's early and premature mortality, which is consistently higher in Indigenous communities throughout the world. Cumulative results from 514 First Nation communities from the Canadian biomonitoring program, carried out in different provinces reported that 17,601 blood samples (24.5% of all samples) had blood concentrations ≥ 20 µg/L (equivalent hair Hg of 5 µg/g, using a ratio 250:1 [39]). In the months of August and September, average concentrations were twofold higher (42–43 µg/L) [14]. Recognition of the long-term consequences of childhood Hg exposure should lead to improved preventive measures and adequate treatment throughout exposed persons' lives.

Conclusion

Early mortality in this community is higher than in First Nations and the non-Indigenous Canadian population. Among the people of Grassy Narrows, persons who died young had higher childhood hair Hg concentrations compared to those who were still alive. Although we were not able to account for all factors, the convergent findings from different statistical techniques support an association between childhood Hg exposure and early death. Follow-up of morbidity and mortality in this community should be continued. Childhood Hg exposure should be considered for adequate prevention and treatment in this and other First Nation communities.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-025-01190-7.

Supplementary Material 1

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Exposure data was provided by the First Nations and Inuit Health Branch of Indigenous Services Canada and by the Ontario Ministry of Health and Long-term Care. Sarah Jane Strong of Grassy Narrows verified dates of birth and death on the Grassy Narrows First Nation Registry for all of the persons for whom there were Hg childhood exposure measurements. She likewise contacted the families for cause of death. Grassy Narrows' Chief and Council approved the study and agreed that the manuscript be submitted. Philippe

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Author contributions
DM is principal investigator and main author of the present research and prepared Figs. 1, 2 and 5. AP created the database, determined the statistical approaches performed the analyses and prepared Figs. 3, 4 and 6. JdS provided guidance and input. DM, AP, MF and JdS were involved in the organization of community collaboration, contributed to data interpretation, critical revision and final approval.

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Data availability
The datasets generated and analyzed 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
Ethics approval was obtained from the Institutional Review Board of the *Université du Québec à Montréal* (Ethics Certificate 2016_e_1350).

Consent for publication
Grassy Narrows First Nation Chief and Band Council consented to publication.

Competing interests
The authors declare no competing interests.

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