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Toxic risks and nutritional benefits of traditional diet on near visual contrast sensitivity and color vision in the Brazilian Amazon

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ABSTRACT

Background: Visual functions are known to be sensitive to toxins such as mercury (Hg) and lead (Pb), while omega-3 fatty acids (FA) and selenium (Se) may be protective. In the Tapajós region of the Brazilian Amazon, all of these elements are present in the local diet.
Objective: Examine how near visual contrast sensitivity and acquired color vision loss vary with biomarkers of toxic exposures (Hg and Pb) and the nutrients Se and omega-3 FA in riverside communities of the Tapajós.
Methods: Complete visuo-ocular examinations were performed. Near visual contrast sensitivity and color vision were assessed in 228 participants (≥15 years) without diagnosed age-related cataracts or ocular pathologies and with near visual acuity refracted to at least 20/40. Biomarkers of Hg (hair), Pb (blood), Se (plasma), and the omega-3 FAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in plasma phospholipids were measured. Multiple linear regressions were used to examine the relations between visual outcomes and biomarkers, taking into account age, sex, drinking and smoking.
Results: Reduced contrast sensitivity at all spatial frequencies was associated with hair Hg, while %EPA, and to a lesser extent %EPA + DHA, were associated with better visual function. The intermediate spatial frequency of contrast sensitivity (12 cycles/degree) was negatively related to blood Pb and positively associated with plasma Se. Acquired color vision loss increased with hair Hg and decreased with plasma Se and %EPA.
Conclusions: These findings suggest that the local diet of riverside communities of the Amazon contain toxic substances that can have deleterious effects on vision as well as nutrients that are beneficial for visual function. Since remediation at the source is a long process, a better knowledge of the nutrient content and health effects of traditional foods would be useful to minimize harmful effects of Hg and Pb exposure.

1. Introduction

Methylmercury (MeHg) neurotoxicity has been recognized for a long time and alterations of visual functions are well known signs of MeHg exposure. Minamata disease, a severe neurological disorder caused by MeHg intoxication, was largely documented following the contamination episodes in Japan and Iraq, where populations were exposed to high doses of MeHg (Watanabe and Satoh, 1996). In both incidents, visual deficits were reported and

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constriction of the visual field was a predominant sign among mercury-poisoned individuals (Iwata, 1980; WHO, 1990). Visual contrast sensitivity in Japanese patients with Minamata disease was significantly lower compared to controls in the upper spatial frequencies on the Arden grating tests (Mukuno et al., 1981). However the authors did not establish a direct association with biomarkers of mercury (Hg) exposure in this study.

In the Amazon Basin, fish is a dietary mainstay for many communities and biomarkers of Hg exposure are elevated (Barbieri and Gardon, 2009; Passos and Mergler, 2008). Studies in the Tapajós River Basin of the Brazilian Amazon have consistently shown strong correlations between fish consumption and elevated Hg in hair and blood (Passos and Mergler, 2008). On the other hand, beneficial nutrients, such as omega-3 fatty acids (FA) likewise increase with fish consumption (unpublished data), as does selenium (Se) (Lemire et al., 2006), although the major source for Se is Brazil nuts (Lemire et al., 2010b). In this region, blood Se concentrations are in the normal to elevated range (Lemire et al., 2006, 2009; Pinheiro et al., 2005). Recently, elevated blood lead levels (B-Pb) were reported in communities of the Tapajós, with median levels of more than 10 μg/dL in this population unexposed to any known occupational Pb source (Barbosa et al., 2009). The authors suggest that the artisanal metal plate used for the transformation of manioc into flour (known as *farinha*) could be transferring Pb to the flour during the roasting process (Barbosa et al., 2009).

While Hg (Bridges et al., 2007; Chang, 2007) and Pb (Kohler et al., 1997) have been shown to be ophthalmo-toxic, omega-3 FA and Se may be ophthalmo-protector. Omega-3 FAs are recognized as crucial for visual and ocular system development and maintenance (Forsyth and Carlson, 2001, Horrocks and Yeo, 1999). They play a role in the retina (Uauy et al., 2001), especially in ganglion cells (Nguyen et al., 2008) and at the ocular level in the prevention of cataract formation (Townend et al., 2007). Se is a well-known anti-oxidant and has been shown to be protective for glaucoma, age-related cataracts and macular degeneration (Bartlett and Eperjesi, 2004, Brown et al., 1998, Flohe, 2005, Lemire et al., 2010a). Several animal studies suggest that Se may protect against the toxic effects of Hg (Watanabe, 2002), although epidemiologic evidence on the effects of Se in human populations exposed to Hg is inconsistent. Some studies have observed beneficial effects of Se on neurologic and ocular outcomes negatively affected by Hg (Boucher et al., 2010; Lemire et al., 2010a, 2011), while others did not (Choi et al., 2008; Despres et al., 2005; Saint-Amour et al., 2006; Steuerwald et al., 2000).

Past studies have examined near visual contrast sensitivity loss and acquired dyschromatopsia in relation to hair Hg (H-Hg) in persons living in villages on the Tapajós River. Lebel et al. (1998) reported an inverse association between H-Hg levels and near visual contrast sensitivity at intermediate and high frequencies (6, 12 and 18 cycles/degree – cpd). In a pilot study with 29 participants, these authors likewise observed an association between H-Hg and color vision loss (Lebel et al., 1996), but they did not obtain the same results when they repeated the study in a larger group from the same region the following year (Lebel et al., 1998). Recently, a repeated measure follow-up of 31 participants from a village in this region showed that color vision deterioration observed between 1995 and 2006 was associated with 1995 H-Hg levels, despite a decrease in Hg exposure over this period, suggesting that Hg exposure could have long term non reversible effects on the visual system (Fillion et al., 2011).

The objective of this study was to examine how near visual contrast sensitivity and color vision loss vary with biomarkers of toxic exposures (Hg and Pb) and the protective nutrients Se and omega-3 FA in an adult riverside population of the Tapajós River in the Brazilian Amazon.

2. Materials and methods

2.1. Study population

Since the mid-nineties, our research group has been involved in an interdisciplinary project on Hg exposure and its potential effects on human health in the Lower Tapajós River Basin (State of Pará, Brazil) (CARUSO, 2011). In this region, there are approximately 50 communities of diverse size and origin, with varying access to health care, education and goods. The results presented here are part of a cross-sectional study whose objective was to examine factors that may influence Hg toxicity. For this study, we selected 12 communities to reflect the diversity of regional populations, social conditions and ecosystems (Fig. 1). Recruitment was based on a convenience sampling procedure since it is difficult to apply a random sampling strategy in this setting (Passos et al., 2007).

Several weeks before the present study, each village was visited and persons 15 years and older were invited to participate on a voluntary basis. The study was explained at a village meeting and at home visits. A total of 448 participants, representing 25% of the adult population, volunteered to participate in the present study. Individuals in the younger range (15–40 years) were underrepresented and those in the middle-age range (40–65 years) were overrepresented, while the distribution of the oldest participants (>65 years) was similar to the underlying population (Lemire et al., 2010a).

For each day of testing, a maximum of 12 participants were brought by boat to a technical school in the nearby city, Itaituba, where there was access to electricity and freezers for storing biological material. Each village was scheduled for a specific number of days. The boats arrived in the villages the previous day and made the trip during the night. The study was carried out from May to July 2006.

The study was approved by the Ethics Review Boards of the University of Quebec at Montreal, of the Federal University of Rio de Janeiro and of the Faculty of Pharmaceutical Sciences of the University of São Paulo-Ribeirão Preto. All participants signed an informed consent form, which was read to them in Portuguese. There was no remuneration for study participation.

2.2. Socio-demographics and medical history

An interview-administered questionnaire was used to collect information on socio-demographics, occupational and residential history. A food frequency questionnaire (Passos et al., 2007) was used to collect dietary information on fish species consumed over the 7 days preceding the interview. A trained nurse administered the questionnaire on medical history. When the boats arrived in the villages, research assistants visited each participant in their homes and noted the names of all currently used medications. None of the interviewers were aware of the participants' exposure levels.

2.3. Assessment of biomarkers of Hg, Pb and Se

2.3.1. Hair

Hair has often been used as a biomarker for current and retrospective exposure to Hg (Bastos et al., 1998), and a large number of studies have shown that this biomarker reflects Hg intake from fish consumption (for a review see (Mergler et al., 2007)). This non-invasive method provides samples that can be stored for a long time without deterioration before being analyzed. Hair strands from the occipital region were cut at the root and stored in plastic bags, with the end root stapled. The first 2 cm from the root were used to determine hair total Hg concentration (H-Hg) by cold vapour atomic absorption spectrometry (CVAAS), according

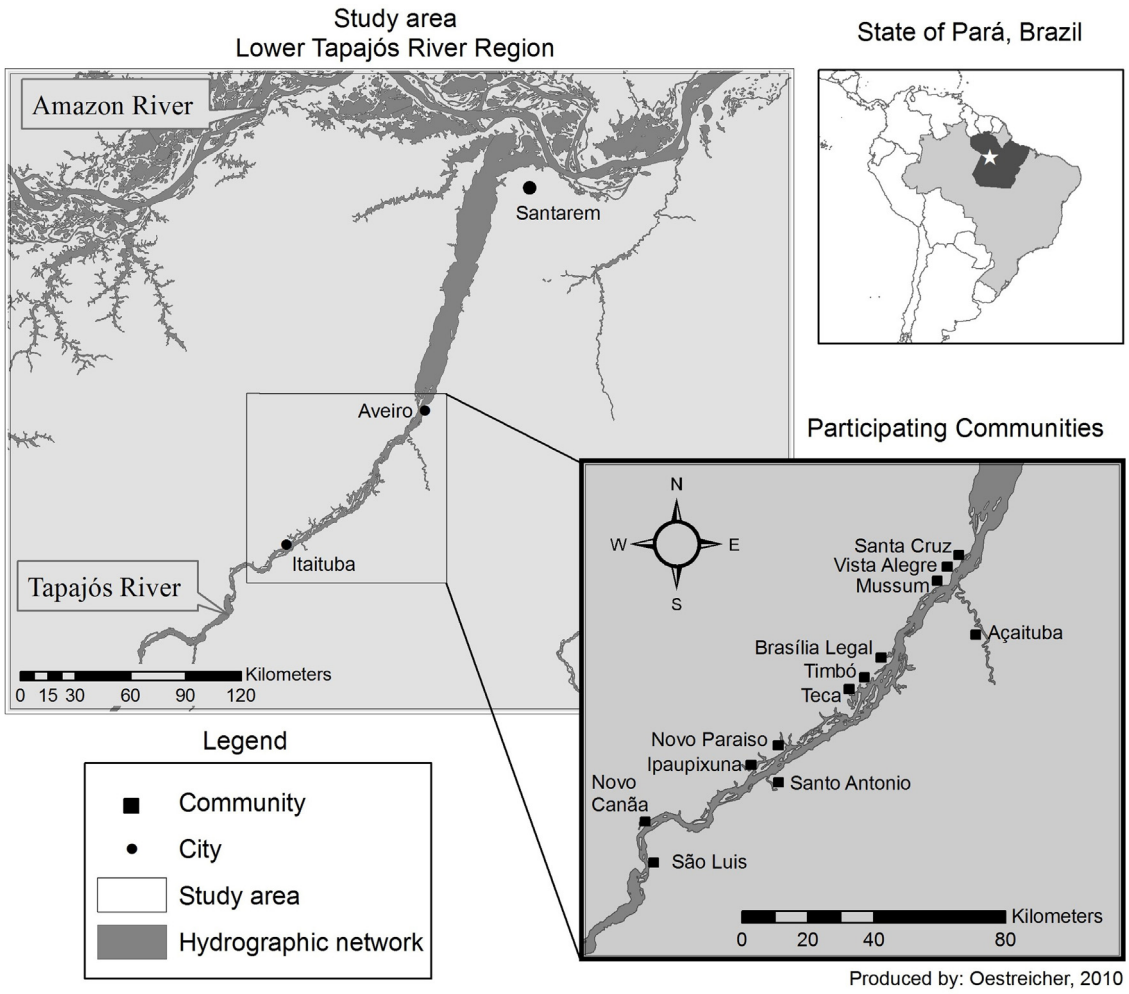

Fig. 1. Map of the study region.

to the method described (Farant et al., 1981). Analyses were carried out at the laboratories of the First Nations and Inuit Health Laboratory of Health Canada (Ottawa, Canada). Analytical quality control was ensured with certified reference hair samples, provided by the Hair Mercury Inter-laboratory Comparison Program of Health Canada, Ottawa, Canada. Using a paired *t*-test, no statistical differences at 95% confidence level were observed between measured and target values. The coefficient of variation for Hg measurements in hair was always lower than 6%.

2.3.2. Blood

For each participant, an experienced Brazilian phlebotomist collected a 6 mL blood sample in "trace metals free" evacuated tubes (BD Vacutainer®), containing heparin as anticoagulant. For plasma separation, blood samples were centrifuged ($800 \times g$ for 6 min). Plasma fractions were then pipetted into previously cleaned Eppendorf tubes (2 mL) previously cleaned in a class 100 clean room, and immediately frozen at −20 °C. Blood total Hg (B-Hg), blood Se (B-Se) and blood lead (B-Pb), as well as plasma total Hg (P-Hg) and plasma Se (P-Se) were determined by inductively coupled plasma mass spectrometry (ICP-MS, Perkin Elmer DRC II) according to the method proposed by Batista et al. (2009), at the Laboratório de Toxicologia e Essencialidade de Metais, Universidade de São Paulo, Ribeirão Preto, SP, Brazil. Quality control was guaranteed by analyzing two secondary reference materials, provided by the external quality assessment scheme (EQAS) for trace elements operated by the *Institut National de Santé Publique du Québec*, Canada. Reference materials were analyzed before and after ten ordinary samples. Measured values for reference samples were in good agreement with target values (95% confidence/paired *t*-test). Moreover, the coefficient of variation for Hg, Pb and Se measurements in blood were always lower than 5, 3 and 4%, respectively, while for Hg and Se in plasma were lower than 6 and 4%, respectively.

2.4. Plasma phospholipid fatty acid analysis

Plasma phospholipid FA were assessed for a subgroup of 349 people. Total plasma phospholipid FA were measured using a modified method of Bondia-Pons and colleagues (Bondia-Pons et al., 2006). Analyses were carried out at the School of Dietetics and Human Nutrition of McGill University, Ste-Anne-de-Bellevue, Canada. Percent eicosapentaenoic acid (%EPA), percent docosahexaenoic acid (%DHA) and the sum of the two (%EPA + DHA) were considered in the present study. Omega-3 FA in plasma phospholipid was expressed as an absolute concentration (mg/mL) and as percentage of total plasma phospholipid FA.

2.5. Visual functions assessment

Visual and ocular health examinations were carried out by four optometrists from the School of Optometry of the University of Montreal, who were trained prior to the field study, to minimize inter-observer differences. They were not involved in assessment of toxins or nutrients.

The anterior segment of the eye was examined using slit-lamp biomicroscopy. The posterior segment of the retina and its periphery were examined during pupillary dilation using two mydriatic agents (tropicamide 1%, w/v, and phenylephrine 2.5%, w/v). This procedure provided information on ocular pathologies that were used for post hoc exclusions. The presence of pterygia, a corneal eye disease attributed to chronic ultraviolet-B exposure (Bradley et al., 2010; West and Munoz, 2009) common in this region, was noted by the examiners.

Near visual acuity was assessed by the optometrists with the Allen Charts. Participants' were provided with corrective lenses to perform the visual tests when necessary, and refracted near visual acuity was noted. All examinations were made in the same room and under the same conditions of luminance.

Contrast sensitivity is a physical dimension referring to the light–dark transition of a border or an edge in an image and refers to a measure of how much contrast a person requires to see a target (Owsley, 2003). It is assessed on a range of sinusoidal spatial frequencies, representing different neuro-optic pathways. In this study, near visual contrast sensitivity was assessed at 5 spatial frequencies between 1.5 and 18 cycles per degree (cpd) with the Vistech VCTS 6000 charts (Vistech Consultants, Inc., Dayton, Ohio) applied monocularly and under standard lighting. The test is composed of three charts, each containing 45 circles (diameter of 1.3 cm) distributed in five rows of nine circles of increasing sinusoidal grating frequency (1.5, 3, 6, 12, and 18 cpd); in each row, the contrast diminishes from left to right along the 9 circles. For each circle, participants were required to indicate whether the gratings' orientation was upright, to the left, or to the right. Participants indicated the direction of the gratings with their hand. The lowest contrast grating correctly identified constitutes the sensitivity score for that spatial frequency. The criterion for contrast threshold determination, at every frequency, was the same correct response on at least two of the three charts. The test was administered to all participants under the same conditions and by the same Brazilian research assistant, who was unaware of the participants' exposure. For every participant, the score of both eyes was averaged for each spatial frequency tested. When only one eye could be tested, the value for that eye was used.

Acquired color vision loss has been reported in persons exposed to several neurotoxic substances. Contrary to congenital color vision loss, it can be monocular and is most often initiated in the blue-yellow range (Gobba, 2000; Hart, 1992; Iregren et al., 2002). Acquired color vision loss was evaluated using the Lanthony D-15 desaturated test (Lanthony, 1978). This test has since been extensively used in studies of neurotoxic chemicals (Gobba, 2000; Iregren et al., 2002). The Lanthony D-15 desaturated test requires the participants to arrange 15 color caps into a natural color order (Lanthony, 1978). Since acquired color vision loss can be monocular (Verriest, 1964), the test was carried out separately in each eyes. The Bowman's color confusion index (CCI) was calculated for each eye (Bowman, 1982). A CCI of 1.0 represents a perfect score, and as CCI increases, acquired color vision loss increases. The test was performed under standard conditions of illumination, in the same room, by the same research assistant who was not aware of the participants' past and current Hg levels. The CCI of both eyes was averaged. When only one eye could be tested, the value for that eye was used.

Exclusion criteria. From the sub-group of 349 participants for whom there are data for FA, women who were pregnant ($n = 5$) or breastfeeding ($n = 5$), persons reporting diagnosed diabetes ($n = 5$), use of psychotropic drugs ($n = 4$), a cerebro-vascular accident ($n = 10$) and those who reported having worked in gold mining in the past year ($n = 2$) were excluded from the present analyses. Persons with diagnosed cataracts ($n = 56$) and ocular pathologies ($n = 14$) were excluded from the present analyses, as were persons for whom we were not able to refract to at least 20/40 ($n = 19$). The final group for the present analyses included 228 persons (115 women and 113 men).

2.6. Statistical analyses

Descriptive statistics were used to illustrate the participants' general characteristics, the distribution of the biomarkers, as well as near visual contrast sensitivity and CCI. Values of Hg, Pb and Se were log transformed, in order to obtain a normal distribution of the residuals in the multiple regressions. Non-parametric analyses were performed (Wilcoxon/Kruskall–Wallis Rank Sums test and Spearman's ρ), to compare medians and assess the strength of the relation between two variables. Two-tailed Fisher's exact tests were used for the analyses of contingency tables.

A series of multiple linear regressions were carried out to examine the factors associated with each frequency of near visual contrast sensitivity and color vision loss. H-Hg, B-Pb, P-Se were simultaneously included in the multiple regression models. The different biomarkers of omega-3 FA status (%EPA, %DHA or %EPA + DHA) were separately and successively tested in these models to determine which biomarker of FA best predicted visual outcomes, based on higher standardized estimates and model R^2. All the models were adjusted for the following variables: age, sex, current smoking (yes vs. no), current drinking (yes vs. no). Homoskedasticity was verified using Studentized residuals and

Table 1
Socio-demographic characteristics, fish consumption and biomarkers of exposure and nutrients.

	n	%	Mean ± SD	Median	Range
Women	115	50.4			
Men	113	49.6			
Age, years		228	35.3 ± 12.5	33.0	15–66
Alcohol drinkers	139	61.0			
Current smokers	50	22.0			
Fish consumption					
Total meals/week	228		5.5 ± 3.9	5	0–15
Piscivore meals/week	227		2.2 ± 2.4	2	0–11
Non-piscivore meals/week	227		3.3 ± 3.4	2	0–13
H-Hg, μg/g	228		14.4 ± 10.6	11.5	1.0–57.9
P-Se, μg/L	226		182.3 ± 124.9	144.5	53.6–913.2
B-Pb, μg/dL	226		12.8 ± 8.4	10.5	0.6–48.3
EPA, mg/mL	228		0.006 ± 0.004	0.005	0.0–0.022
DHA, mg/mL	228		0.025 ± 0.014	0.021	0.003–0.085
EPA + DHA, mg/mL	228		0.030 ± 0.017	0.027	0.003–0.100
% EPA	228		0.44 ± 0.23	0.44	0–1.19
% DHA	228		1.97 ± 0.73	1.89	0.33–4.39
%(EPA + DHA)	228		2.41 ± 0.88	2.40	0.43–5.23

Table 2
Spearman's r correlation between the biomarkers of exposure and nutrients.

H-Hg	P-Se	B-Pb	EPA	DHA	EPA + DHA	%EPA	%DHA
H-Hg							
P-Se	0.360***						
B-Pb	0.398***	0.180**					
EPA	0.067	0.033	0.033				
DHA	0.101	0.093	−0.079	0.768***			
EPA + DHA	0.092	0.081	−0.061	0.854***	0.987***		
%EPA	0.125†	−0.035	0.133*	0.912***	0.588***	0.687***	
%DHA	0.241**	0.086	0.024	0.555***	0.866***	0.827***	0.528***
%EPA + DHA	0.242**	0.074	0.059	0.693***	0.877***	0.871***	0.689***	0.975***

† $p < 0.10$.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.0001$.

outliers were excluded at >|3| (Pardoe, 2012). Collinearity between variables of the final models was avoided by excluding from a same model two variables highly correlated.

Results were defined as statistically significant at $p < 0.05$. Analyses were performed using JMP 8.0.1 (SAS Institute Inc.) and SPSS 16.0 software.

3. Results

Socio-demographic characteristics of the study group and biomarkers of toxics and nutrients are presented in Table 1. Because of the exclusions for cataracts and ocular pathologies, the group was relatively young, with a maximum age of 66 years. Men were older than women (median: 35 years vs. 31 years, Wilcoxon/Kruskal–Wallis $p = 0.05$). More men reported drinking (median: 70.3 vs. 51.8%, $p = 0.004$) and smoking (median: 31.5 vs. 13.2%, $p = 0.001$) compared to women. Alcohol, mostly beer, was consumed mainly during the weekend and on special occasions. Among smokers, cigarette consumption was relatively low (median: 8 cigarettes/day). Tobacco and alcohol consumption were not related to age. A total of 91.7% of the participants had eaten at least one fish meal in the week preceding the interview.

The concentration of H-Hg was higher in men compared to women (median: 14.3 vs. 9.7 μg/g, $p = 0.001$) and increased with age ($\rho = 0.157$, $p = 0.02$). For P-Se, concentrations were similar in men and women and were not related to age and any of the biomarkers. B-Pb was higher in men than in women (median: 14.0 vs. 7.4 μg/dL, $p < 0.0001$) and B-Pb increased with age ($\rho = 0.173$, $p = 0.009$). All biomarkers of omega-3 FA in plasma phospholipids were positively associated with age (%EPA: $\rho = 0.306$, $p < 0.0001$; %DHA $\rho = 0.250$, $p < 0.0001$; %EPA + DHA: $\rho = 0.292$, $p < 0.0001$) and similar for men and women.

Correlations between the biomarkers of exposure and nutrients are presented in Table 2. Hair Hg was positively correlated to P-Se, B-Pb and %DHA and %EPA + DHA, and B-Pb was correlated to P-Se. The measures of omega-3 FA were highly correlated, with the lowest correlation between %DHA and %EPA.

Results of the visual tests are presented in Table 3. Men performed better than women on all visual contrast spatial frequencies, while no difference was observed between men and women for color confusion index. Alcohol drinkers performed better on all visual contrast spatial frequencies ($p < 0.05$) with the exception of 3 cpd. No differences were observed between smokers and non-smokers for near visual contrast sensitivity or for acquired color vision loss.

In bivariate analyses, near visual contrast sensitivity was negatively associated with H-Hg at 6 cpd ($p = 0.02$), 12 cpd ($p = 0.06$) and 18 cpd ($p = 0.05$). H-Hg was not associated with color vision loss. No associations were observed for near visual contrast sensitivity for B-Pb and P-Se. For the FA, positive associations were observed at 3 cpd with %EPA ($p = 0.07$), and at 8 cpd with %DHA ($p = 0.02$) and %EPA + DHA ($p = 0.03$). Mean color confusion index (CCI) tended to be negatively associated with P-Se ($p = 0.08$), color vision was not associated with %EPA, %DHA or %EPA + DHA.

Multiple regression analyses were performed for all of the near visual contrast spatial frequencies and color confusion index with the socio demographic variables (age, sex, smoking and drinking), the bioindicators of toxic exposures (H-Hg and B-Pb) and %EPA %DHA or %EPA + DHA. Table 4 presents the results of these models (results for age, sex, smoking and drinking were similar to the above and not shown). In the models with %EPA, negative associations were observed for H-Hg for all frequencies (Table 4a), except for 12 cpd; the strongest associations were at 3 and 6 cpd. B-Pb was associated with poorer performance at 12 cpd. A positive association was observed between P-Se and near visual contrast at 12 cpd, while %EPA was associated with better contrast sensitivity at the lower and intermediate frequencies (1.5–12 cpd). %DHA was associated with better visual function at 3 cpd (Table 4b). %EPA + DHA was associated with near visual contrast sensitivity at 1.5 cpd, 3 cpd and 6 cpd (Table 4c). Similar

Table 3
Results of the visual tests for each eye.

	n	Mean	SD	25th quantile	Median	75th quantile	Range
Near visual contrasts sensitivity							
Spatial frequency (cycles/degree)							
Right eye							
1.5 cpd	228	49.4	7.8	40.0	53.0	53.0	11.0–71.0
3 cpd	228	75.6	12.4	73.0	73.0	73.0	17.0–130.0
6 cpd	228	76.4	16.7	72.0	72.0	96.0	20.0–128.0
12 cpd	228	60.7	26.8	39.0	70.0	93.0	0–168.0
18 cpd	227	21.3	10.9	12.0	22.0	30.0	0–53.0
Left eye							
1.5 cpd	228	47.5	8.8	40.0	53.0	53.0	11.0–71.0
3 cpd	228	73.6	15.4	73.0	73.0	73.0	17.0–174.0
6 cpd	228	73.8	17.6	72.0	72.0	72.0	20.0–128.0
12 cpd	228	58.4	25.3	39.0	52.0	70.0	0–125.0
18 cpd	227	20.9	10.9	12.0	22.0	30.0	0–53.0
Acquired color vision loss							
Color confusion index (CCI)							
Right eye	225	1.54	0.48	1.17	1.45	1.77	1.00–4.24
Left eye	225	1.58	0.50	1.20	1.49	1.81	1.00–4.16

Table 4
Results of multiple linear regression models for near visual contrast sensitivity and color vision, adjusted for age, sex, smoking, drinking, showing β estimates and level of significance.

	n	Adjusted r^2	β estimates log H-Hg	log B-Pb	log P-Se	%EPA
(a) With %EPA						
Spatial frequency						
1.5 cpd	221	0.07	−1.96 (−4.56; 0.64)†	−1.32 (−4.30; 1.65)	2.53 (−1.57; 6.62)	3.52(0; 7.04)*
3 cpd	220	0.10	−6.80(−11.10; −2.49)**	2.06(−2.87; 6.99)	2.03(−4.72; 8.79)	7.77(1.96; 13.57)**
6 cpd	222	0.15	−8.48(−14.29;−2.66)**	0.60(−6.04; 7.25)	0.60(−8.56; 9.77)	10.01(2.15; 17.87)*
12 cpd	224	0.27	−6.71(−15.24; 2.02)	−13.33(−23.28; −3.49)**	14.99(1.41; 28.56)*	12.36(0.69; 24.03)*
18 cpd	222	0.28	−4.44(−8.13;−0.74)*	−2.43(−6.64; 1.79)	3.43(−2.39; 9.25)	2.95(−2.06; 7.96)
CCI	215	0.09	0.17(0.01; 0.33)*	0.16(−0.03; 0.33)	−0.38(−0.63;−0.13)**	−0.24(−0.46;−0.02)*
	n	Adjusted r^2	β estimates log H-Hg	log B-Pb	log P-Se	%DHA
(b) With %DHA						
Spatial frequency						
1.5 cpd	221	0.06	−2.22(−4.92; 0.48)†	−1.03(−4.02; 1.95)	2.28(−1.83; 6.40)	0.81(−0.37; 1.98)
3 cpd	220	0.08	−7.35(−11.82;−2.88)**	2.75(−2.22; 7.71)	1.47(−5.34; 8.28)	1.79(−0.15; 3.74)†
6 cpd	222	0.14	−9.11(−15.17;−3.07)**	1.45(−5.24; 8.14)	−0.10(−9.35; 9.15)	2.10(−0.53; 4.74)
12 cpd	224	0.26	−7.15(−16.11; 1.82)	−12.35(−22.24;−2.45)*	14.21(0.53; 27.88)*	2.18(−1.71; 6.07)
18 cpd	222	0.28	−4.59(−8.41;−0.77)*	−2.18(−6.40; 2.03)	3.22(−2.61; 9.06)	0.56(−1.11; 2.24)
CCI	215	0.08	0.18(0.01; 0.35)*	0.14(−0.05; 0.32)	−0.37(−0.62;− 0.11)**	−0.04(−0.11; 0.03)
	n	Adjusted r^2	β estimates log H-Hg	log B-Pb	log P-Se	%EPA + DHA
(c) With %EPA + DHA						
Spatial frequency						
1.5 cpd	221	0.06	−2.27(−4.94; 0.41)†	−1.08(−4.05; 1.90)	2.31(−1.79; 6.42)	0.80(−0.16; 1.76)†
3 cpd	220	0.09	−7.45(−11.88;−3.02)**	2.63(−2.31; 7.57)	1.54(−5.24; 8.32)	1.77(0.19; 3.36)*
6 cpd	222	0.14	−9.28(−15.28;−3.28)**	1.33(−5.34; 7.99)	−0.03(−9.24; 9.19)	2.15(−0.001; 4.30)†
12 cpd	224	0.26	−7.41(−16.30; 1.48)	−12.46(−2.33;−2.60)*	14.27(0.63; 27.91)*	2.37(−0.81; 5.55)
18 cpd	222	0.28	−4.65(−8.44;−0.85)*	−2.21(−6.42; 1.99)	3.24(−2.59; 9.07)	0.60(−0.77; 1.97)
CCI	215	0.08	0.19(0.02; 0.36)*	0.14(−0.04; 0.32)	−0.37(−0.62;−0.12)**	−0.04(−0.10; 0.02)

† $p < 0.10$.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.0001$.

results were observed when including both eyes in a MANOVA for repeated measures. Fig. 2 shows how contrast sensitivity at 3 cpd, adjusted for the co-variates, varies with log H-Hg and %EPA.

Acquired color vision loss was positively associated with H-Hg and negatively with P-Se and %EPA, Models with %DHA or %EPA + DHA did not show beneficial effects of the FA on visual function.

The same models were run for the entire group without any exclusions, as well as with untransformed data, and similar results were obtained although the associations were weaker. The contribution of pterygia was tested in all the models and showed no association nor did it alter the multiple regression estimates.

4. Discussion

The findings of this study suggest that the toxic substances in the Amazonian diet, such as Hg and Pb, negatively affect visual functions, while nutrients, such as Se and omega-3 FA, particularly %EPA, are associated with better visual function.

Animal models with non-human primates have examined the neuronal impairments associated with visual contrast sensitivity loss. Contrast sensitivity deficits at low spatial frequencies could be due to selective damage to the magnocellular pathway, whereas deficits at intermediate and high spatial frequencies could be attributed to selective damage to the parvocellular pathway (Merigan and Eskin, 1986; Merigan et al., 1991; Merigan and Maunsell, 1990). Rice and Gilbert (1990), who studied the developmental effects of dietary MeHg on non-human primate spatial and temporal visual functions, reported contrast sensitivity deficits at spatial frequencies of 3–7 cpd, suggesting a preferential damage to the parvocellular pathway and relative sparing of the magnocellular stream (Rice and Gilbert, 1990). The present results suggest that the effects of Hg exposure could also be damaging the

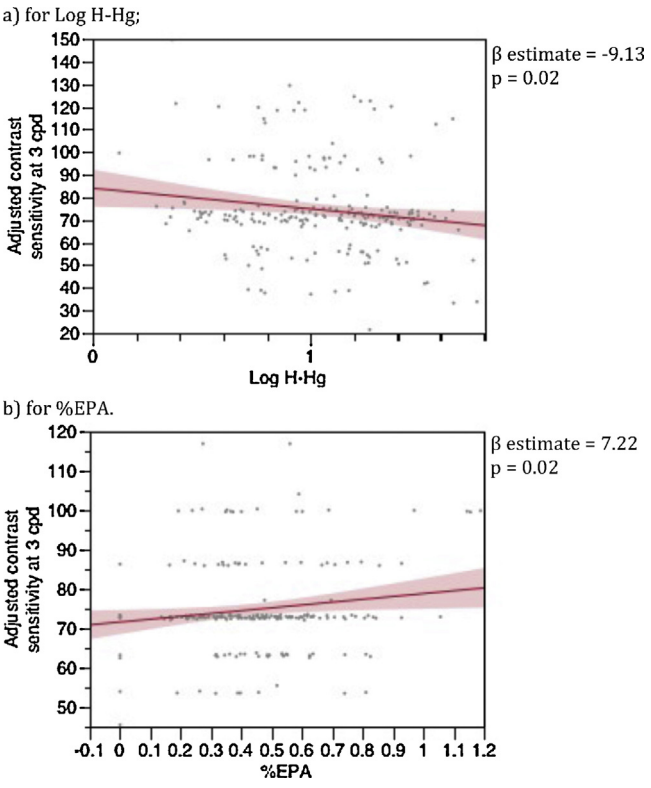

Fig. 2. Plots of adjusted near visual contrast sensitivity at 3 cpd; (a) for log H-Hg; (b) for %EPA.

magnocellular pathway, as the low and intermediate spatial frequencies are affected by Hg exposure.

Our results are consistent with the studies on people suffering from Minamata disease, exposed to MeHg during development or adult life, showing impaired near contrast sensitivity at low and intermediate spatial frequencies (0.2, 0.4, 0.8, 1.6, 3.2 and 6.4 cpd) (Mukuno et al., 1981). In a study carried out in the same region, Lebel et al. (1998) observed a negative association between H-Hg and near visual contrast sensitivity at 6, 12 and 18 cpd. In our study, near visual contrast sensitivity at 12 cps is negatively associated with B-Pb but not H-Hg. B-Pb was not measured in the study by Lebel et al. (1998), and this could explain the difference in the results. Indeed, when B-Pb is removed from the multiple regression model, H-Hg becomes significantly associated with decreasing contrast sensitivity at 12 cpd, leading to similar results. In addition, our study suggests an effect of Hg at low spatial frequencies of near visual contrast sensitivity (1.5 and 3 cpd), which were not observed in the study by Lebel et al. (1998).

Our results also show an association between H-Hg and acquired color vision loss. Previous studies in the region were inconsistent regarding the effects of Hg exposure on color vision: in a first study by Lebel et al. (1996), an association between H-Hg and color vision loss was observed among a group of 26 people, but a second study with a larger group did not lead the same results (Lebel et al., 1998). Color vision has shown to be sensitive to neurotoxic exposures, and the effects of Hg on this function have mainly been studied in workers exposed to inorganic Hg (Barboni et al., 2009; Cavalleri et al., 1995; Urban et al., 2003).

Acquired color vision deficits have been associated to a variety of lesions in different parts of the visual system. At the pre-retinal level, there is a subtle and gradual decrease in color vision with normal aging process, mainly due to the yellowing of the crystalline lens which results in a reduced sensitivity to blue light (Morgan, 1986). There is evidence to suggest that Hg could accumulate in ocular structures (El-Sherbeeny et al., 2006; Warfvinge and Bruun, 1996, 2000) and in the retina (Mela et al., 2010) and affect rods and cones (Fox and Sillman, 1979; Goto et al., 2001). MeHg exposure could also disrupt monoaminergic neurotransmission in the visual system (Beyrouty et al., 2006; Stamler et al., 2006). The evaluation of retinal function by electroretinography showed possible retinal origins of color vision losses in Hg contaminated retired workers form a fluorescent lamp industry (Ventura et al., 2004).

Our results also suggest that Pb exposure reduces spatial contrast sensitivity at intermediate spatial frequency (12 cpd), but is not related to color vision. These results differ from what has been reported so far in the literature. In a study of adult monkeys' with a lifetime exposure to Pb, Rice and Hayward (1999) observed a reduction in temporal visual function, but not in spatial visual function (Rice and Hayward, 1999). The simultaneous effects of Hg and Pb on contrast sensitivity has also been studied in pre-school children from Germany, but no association between contrast sensitivity values and B-Pb was observed (Altmann et al., 1998). Immunocytochemistry analyses of the retina of monkeys chronically exposed to Pb showed a decrease in tyrosine hydroxylase in dopaminergic amacrine cells, the rate limiting enzyme for catecholamine synthesis (Kohler et al., 1997). For the population in the present study, we do not know when Pb exposure began or for how long it has been occurring.

Previous studies have shown that P-Se may be a good biomarker of Se status (Lemire et al., 2011). In the present study, P-Se was associated with better performance on visual functions, but this beneficial effect was restricted to one intermediate frequency of near visual contrast sensitivity (12 cpd) and color vision. Some authors have suggested that Se may play a protective role in age-related eye diseases such as cataracts and maculopathies (Flohe, 2005; Head, 2001). Recent findings from our team showed that P-Se was negatively associated to age-related cataract prevalence in people exposed to Hg from fish consumption (Lemire et al., 2010a). Several selenoproteins may be involved in lens protection against reactive oxygen species that causes protein cross-linking and lipid peroxidation in the lens (Flohe, 2005). Since both near visual contrast sensitivity and color vision loss have an optical component, Se may be acting directly on the lens to prevent oxidative stress caused by the toxic exposures.

Despite the relatively low levels of omega-3 FA in this study population, a positive effect was observed on near visual contrast sensitivity and color vision. In the communities on the Tapajós, plasma phospholipid omega-3 FA increased with fish consumption, but levels were low compared to populations who eat marine fish and/or marine mammals and freshwater fish (Amiano et al., 2001; Cole et al., 2002; Dewailly et al., 2003; Saadatian-Elahi et al., 2009; Welch et al., 2006). For example, Dewailly et al. (2003) reported an average of 8.0% for EPA + DHA in Inuit populations, whose diet includes marine mammals and 3.9%, in Cree, whose diet includes freshwater fish. In moderate consumers of freshwater of Quebec, EPA + DHA was 0.23% in serum (Philibert et al., 2006). The mean percent EPA + DHA (2.1%) in this Amazonian population is close to the mean of 1.8% reported for a Quebec non-indigenous general population (Dewailly et al., 2003).

Omega-3 FA are necessary for the visual system (Bazan, 1989; Calder and Yaqoob, 2009). Studies have shown that DHA has beneficial effects on the retina, where it contributes to optimizing ganglion cells function (Nguyen et al., 2008), DHA deficiency has also been associated to a delay in rod recovery throughout life and an age-dependent loss in rod phototransduction sensitivity (Jeffrey and Neuringer, 2009). In the present study, %EPA and to lesser extent %EPA + DHA, but not %DHA concentrations, were associated with improvement of visual functions. A recent study showed that oral administration of EPA in mice with endotoxin-induced uveitis inhibits the markers of inflammatory molecules in the retina (Suzuki et al., 2010). Since Hg has shown to induce inflammatory processes (Kempuraj et al., 2010), EPA could prevent Hg-induced inflammation in the retina. However, formation and bioactivity of lipid mediators in the eye are still relatively unexplored and of considerable interest (Liclican and Gronert, 2010).

This study has several strong points and limits. One of the important strengths is the use of clinical eye examinations performed by experienced optometrists to identify persons with ocular disorders of diverse origins. In these villages, located far from regional urban centers, eye care is minimal and persons are not necessarily able to adequately attend to visual difficulties. This procedure allowed us to exclude a relatively large number of persons on the basis of visual problems from other sources. Another strength is in the choice of tests that are not dependent on culture, that were applied by the same test administrators adequately trained throughout the study. The protocol, which involved bringing participants by boat to a regional urban center, allowed us to immediately freeze blood samples for later analyses for toxics and nutrients. The study is limited by its cross-sectional design and measures of toxic exposure and nutrients were taken at one point in time. Previous studies, however, indicate that in this region, H-Hg and P-Se concentrations reflect dietary habits 2001(Dolbec et al., 2001; Lebel et al., 1997; Lemire et al., 2010a,b), which are relatively constant because of the subsistence life style. A further limit is the use of a convenience sample because of the difficulty in applying a random sampling procedure (Passos et al., 2008). It is possible that the study attracted a higher percentage of persons with visual disorders; however, this was counteracted by the eye examinations, which served for exclusion. Like the examiners, participants were unaware of the concentrations of both toxics and nutrients.

5. Conclusion

In this study, we observed an association between Hg and Pb exposure and near visual contrast sensitivity and acquired color vision loss in fish-eating adults of the Brazilian Amazon; omega-3 FA and Se were associated to better visual function. These findings are particularly interesting since they show that elements in the local diet of this population have a positive effect on visual functions in the presence of toxic exposure. While the mechanisms of Hg toxicity on near visual contrast sensitivity and color vision are fairly well documented, there is a need to better understand how in the context of Hg exposure from fish consumption, visual deficits are associated to Hg. Since remediation in this region will take decades, there is also a need to better investigate how combination with other contaminants or nutrients can affect visual function in order to maximize nutritional inputs from local diet while reducing the toxic risks.

Conflict of interest statement

The authors declare that there are no conflict of interest.

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