

# BMJ Open Caribbean Consortium for Research in Environmental and Occupational Health (CCREOH) Cohort Study: influences of complex environmental exposures on maternal and child health in Suriname

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## ABSTRACT

**Purpose** The Caribbean Consortium for Research in Environmental and Occupational Health prospective environmental epidemiologic cohort study addresses the impact of chemical and non-chemical environmental exposures on mother/child dyads in Suriname. The study determines associations between levels of environmental elements and toxicants in pregnant women, and birth outcomes and neurodevelopment in their children.

**Participants** Pregnant women (N=1143) were enrolled from December 2016 to July 2019 from three regions of Suriname: Paramaribo (N=738), Nickerie (N=204) and the tropical rainforest interior (N=201). Infants (N=992) were enrolled at birth. Follow-up will take place until children are 48 months old.

**Findings to date** Biospecimens and questionnaire data on physiological and psychosocial health in pregnant women have been analysed. 39.1% had hair mercury (Hg) levels exceeding values considered safe by international standards. Median hair Hg concentrations in women from Paramaribo (N=522) were 0.64 µg/g hair (IQRs 0.36–1.09; range 0.00–7.12), from Nickerie (N=176) 0.73 µg/g (IQR 0.45–1.05; range 0.00–5.79) and the interior (N=178) 3.48 µg/g (IQR 1.92–7.39; range 0.38–18.20). 96.1% of women ate fish, respective consumption of the three most consumed carnivorous species, *Hoplias aimara*, *Serrasalmus rhombeus* and *Cichla ocellaris*, known to have high Hg levels, was 44.4%, 19.3% and 26.3%, respectively, and was greater among the interior subcohort. 89% frequently consumed the vegetable tannia, samples of which showed presence of worldwide banned pesticides. 24.9% of pregnant women had Edinburgh Depression Scale scores indicative of probable depression.

**Future plans** Fish consumption advisories are in development, especially relevant to interior women for whom fish consumption is likely to be the primary source of Hg exposure. Effects of potentially beneficial neuroprotective factors in fish that may counter neurotoxic effects of Hg are being examined. A pesticide

## Strengths and limitations of this study

- The study addresses two high-priority public health threats in Suriname and neighbouring countries in the Guiana Shield: the impact of mercury exposure from artisanal gold mining and pesticide exposure associated with agricultural practices in two vulnerable subpopulations: pregnant women and children younger than 5 years of age.
- The longitudinal follow-up of children to 48 months provides several timepoints to assess neurodevelopmental outcomes.
- The study has a biospecimen bank of approximately 13 000 samples, providing the opportunity for future biomarker analyses.
- A linked research training grant facilitates the training of nine Surinamese PhD candidates with dissertation research embedded in the study, thereby building critical in-country environmental health research capacity.
- The interior subcohort (N=201) was logistically difficult to reach, resulting in delayed recruitment of some participants until the second or early third trimester. This may limit our ability to understand differential effects of exposure across gestation. Transportation challenges resulted in heel prick sampling replacing cord blood collection.

literacy assessment in pregnant women is in progress. Neurodevelopmental assessments and telomere length measurements of the children to evaluate long-term effects of prenatal exposures to toxicant mixtures are ongoing.

## INTRODUCTION

The Caribbean Consortium for Research in Environmental and Occupational Health



(CCREOH) addresses high-priority environmental and occupational health risks in Suriname and those common to the vulnerable Caribbean region, while preserving unique cultural traditions of indigenous people and other health disparate populations.<sup>1</sup> Exposure to environmental contaminants at levels of public health concern may adversely affect pregnancy, and prenatal and postnatal health in multiple ways: miscarriage, preterm delivery, intrauterine growth retardation, congenital anomalies and behavioural and physical consequences in later developmental stages.<sup>2–4</sup> Prenatal exposure to multiple heavy metals is associated with adverse paediatric health outcomes.<sup>5</sup> Pesticide exposure has been linked to fetal growth decrements and preterm birth, and there is mounting evidence that exposure to pesticides during prenatal and postnatal development is associated with neurodevelopmental deficits in young children.<sup>6–10</sup> Exposure to contaminant mixtures can exacerbate adverse health effects: for example, lead, arsenic and mercury (Hg) can potentiate each other's toxicity, even at individual levels below concentration expected to result in adverse effects.<sup>11</sup> Despite this knowledge, no cumulative risk assessments have been conducted to date addressing exposures to contaminant mixtures in Caribbean low-income and middle-income countries.<sup>12</sup>

The CCREOH environmental epidemiology cohort study fills this gap by exploring the impact of exposures to organic and inorganic neurotoxicants, including Hg, lead and multiple organophosphate pesticides, on Surinamese pregnant women and their offspring using a cumulative risk approach. Specifically, the study assesses the impact of exposures to chemical and non-chemical stressors by examining the interaction between exposure to environmental chemicals and social and psychological determinants of early neurodevelopment. Few prospective studies have measured exposure prenatally through 48 months in mother/child dyads, and those that have showed contrasting results when evaluating executive function, a key neurodevelopmental outcome.<sup>13–16</sup> Our hypothesis is that environmental exposures to mixtures of neurodevelopmental toxicants and non-chemical stressors will result in increased adverse birth outcomes and poorer child neurodevelopmental trajectories. Our research aims are to:

- ▶ Identify exposures to a complex mixture of environmental elements and toxicants, including Hg, lead, cadmium, aluminium, iron, manganese, tin, selenium and selected pesticides through comprehensive dietary and environmental risk assessments, and biomarker monitoring in Surinamese pregnant women and their offspring.
- ▶ Assess levels of environmental elements and toxicants in fish, produce, rice and nutraceutical compounds.
- ▶ Determine the association between levels of environmental elements and toxicants in pregnant women and birth outcomes.
- ▶ Assess the impact of mobile health technology-enabled community health workers (CHWs) on birth

outcomes and their associations with environmental contaminants.

- ▶ Determine associations between prenatal, dietary and environmental levels of elements and toxicants and potential neuroprotective nutraceuticals on neurodevelopment.

CCREOH is funded by the Fogarty International Center at the US National Institutes of Health (NIH).

## COHORT DESCRIPTION

### Study area

The Republic of Suriname is located on the northeastern coast of South America, bordered by Brazil, Guyana, French Guiana and the Atlantic Ocean. Overall, 90% of the 590 549 population lives in the capital Paramaribo and the coastal area. The remainder lives in the tropical rainforest interior (90% of the landmass). Suriname's multiethnic population consists of five main groups: Hindustani (27%), Tribal (22%), Creole (16%), Javanese (14%) and Indigenous (4%).<sup>17</sup>

### Recruitment

Pregnant women potentially exposed to complex environmental chemical and non-chemical stressors were recruited from three regions of Suriname: (1) Paramaribo, where pesticides are primarily used for residential purposes; (2) Nickerie, the major rice producing region in western Suriname where pesticide use is abundant and (3) the tropical rainforest interior, where Hg is used in artisanal gold mining and the population is highly dependent on consumption of contaminated fish.<sup>18</sup> Taking into account, a potential 20% lost to follow-up, we requested and were approved to consent 1200 pregnant women and their singleton birth children by the Institutional Review Boards of both the Government of Suriname and Tulane University.

Eighty-five per cent of all deliveries in Suriname are hospital based, with the remainder (14%) taking place in primary healthcare clinics under the supervision of a general practitioner or midwife at the Regional Health Department or a skilled healthcare worker at the Medical Mission Primary Health Care Suriname; a small proportion (1%) occurs at home. Recruitment sites included all hospitals and clinics of the Regional Health Department in Paramaribo and Nickerie and the Medical Mission Primary Health Care Suriname in the interior. In Nickerie, trained CHWs were integrated in the research team and played a key role in every aspect of the study, from recruitment to assessments at every study timepoint prenatally and during the neurodevelopmental assessments of the child cohort. Women who met the inclusion criteria were identified by their physician, midwife, CHW or health assistant during regular prenatal appointments and invited to participate. Inclusion criteria were: pregnant women 16 years or older; speaking Dutch, Sranan Tongo, Sarnami, Saramaccan or Trio; singleton gestation; planning to deliver at one of the study hospitals,

prenatal clinics or midwife facilities associated with those hospitals or clinics; and signed informed consent. Assent was obtained from participants aged 16 and 17 years. Informed consent forms and questionnaires were translated into the local languages Sranan Tongo, Sarnami, Saramaccan or Trio. If a participant was unable to read, the recruiter read the questions in the local language.

Infants were not eligible for follow-up if they were born before 33 completed weeks of gestation and/or had a birth weight less than 2000 g, significant medical or neurological condition, down syndrome, hydrocephalus, cerebral palsy or significant visual or hearing impairment inconsistent with neurocognitive testing.

Main maternal and infant/child determinants included biological determinants: maternal anthropometrics, blood pressure, haemoglobin, liver and kidney function, fetal and postnatal growth characteristics and health status, heavy metals (blood and hair), pesticides (urine), telomere length (TL) (buccal swab) and medication use; environmental determinants: maternal and child diet and exposure history; social determinants: ethnicity, social support, trauma, prenatal life events, maternal education, household income, household size, employment status and marital status. Main maternal and infant/child outcomes were growth and physical development: pregnancy complications, fetal and postnatal growth patterns, risk factors for maternal liver and renal impairment; behaviour and cognitive development: infant neuromotor development, autism spectrum disorder and neuropsychological development; childhood diseases: infectious diseases, respiratory and neurological disorders; health and healthcare: impact of mobile health technology-enabled CHWs on prenatal health and birth outcomes, quality-of-life assessments and the impact of healthcare system utilisation on prenatal health and birth outcomes.

### Data management and statistical plan

The CCREOH field team was trained in administering all questionnaires. Data from administered questionnaires are recorded on secure, encrypted iPads, uploaded and managed using Research Electronic Data capture (REDCap), which serves as the study electronic, integrated data management system.<sup>19</sup> Data are uploaded in REDCap's training site for data cleaning prior to integrating questionnaire and biospecimen data. Data records are maintained to examine trends on source of errors, duplicate records are scrubbed, and accuracy is validated through crosschecks with original data files and medical records obtained through the general practitioner, midwife, health assistant or hospital administration. A comprehensive biospecimen tracking system tracks analysed samples and the study's overall biospecimen repository. Communication of data updates and changes in the process are delivered through emails and during bimonthly data management team meetings. The data management platform allows for the interrogation of environmental, non-biospecimen and biospecimen data in an integrated fashion.

Deidentified data files are developed on request of CCREOH investigators through standardised data request forms. Statistical analysis plans are tailored to specific research questions and include descriptive statistics, bivariate linear and logistic regression models, multiple logistic regression analysis to develop predictive models, and non-parametric methods if assumptions are not met. Comparison between study sites will be analysed by comparing participants, or clustered depending the research question.

Multiple approaches to develop and compare models for multiple exposures to toxic metals will be used including a Bayesian kernel machine regression and a non-parametric Bayesian variable selection framework to explore joint (or combined) effects of the multiple chemicals. Structural equation models will be employed to create latent constructs of similar exposure variables and then finding associations between these latent constructs and the outcome variable. Sample size was calculated based on a multiple linear regression model using a coefficient of determination of 0.10 and an  $R^2$  differential ranging between 0.01 and 0.02. Using these parameters, a number between 495 and 986 was needed to have an 80% power at a 0.05 level of significance. Using the more conservative  $R^2$  differential of 0.02 and to account for attrition we planned on recruiting around 1200 participants.

### Data collection

Maternal data were collected during pregnancy at two timepoints (first/second and third trimester). Postpartum assessments are ongoing and target both mothers and children: questionnaire data from mothers and biospecimens and neurodevelopmental assessments data from children are collected at 12, 36 and 48 months (table 1).

### Data collection during pregnancy

#### Questionnaires

Table 1 lists standardised validated questionnaires used to assess both physiological and psychosocial prenatal healths. All questionnaires were translated into Dutch and other local languages to address the multiple language needs of our interior subcohort. The main categories of data collected from maternal participants were health status, demographics, reproductive health history, social support, trauma history, exposure history, depression, perceived stress, prenatal life events, health behaviour, access to prenatal care, social status and diet. Questions on health behaviour were adapted from the Alcohol, Smoking and Substance Involvement Screening Test version V.3 that was developed for WHO. Information on maternal diet was obtained by adapting the Centers for Disease Control and Prevention (CDC)'s National Health and Nutrition Examination Survey (NHANES) into a culturally tailored dietary survey focusing on fish and produce consumption, including frequency of intake and portion sizes.

**Table 1** Assessments completed by the CCREOH-MeKi Tamara Cohort with timeline

Assessments	Trimester		Birth	12 months	36 months	48 months
	1st/2nd	3rd				
<b>Mother</b>						
Obstetric history	●	●				
Demographics	●					
Residency	●	●				
Anthropometrics	●	●				
Marital status	●					
Ethnicity	●					
Occupation	●					
Education	●					
Household income	●					
Household composition	●					
Maternity care	●	●				
Medication		●				
<b>Questionnaires</b>						
Short Form 36 Health Survey	●	●				
Social Support List	●					
Brief Trauma Interview	●	●			●	●
Cohen's Perceived Stress Scale	●	●			●	●
Edinburgh Depression Scale	●	●			●	●
ASSIST V3.0	●	●			●	●
Exposure history	●					
Prenatal Life Events Scale	●	●				
Subjective Social Status	●	●				
Dietary Assessment	●	●				
Family Environment Scale					●	●
Parenting Stress Index					●	●
<b>Biological samples</b>						
Hair	●					
Blood	●	●				
Urine	●	●				
Buccal swab	●					
<b>At birth</b>						
Mode of delivery			●			
Cord or heelprick blood sample			●			
Birth outcomes			●			
<b>Child development</b>						
Physical examination				●	●	●
<b>Questionnaires</b>						
Generation R				●	●	●
M-CHAT					●	
Child Behavior Checklist					●	●
Bayley SEQ					●	
Ages and Stages Questionnaire					●	
Neurodevelopmental tests						

Continued

Table 1 Continued

Assessments	Trimester		Birth	12 months	36 months	48 months
	1st/2nd	3rd				
BSID-III				●		
CANTAB						●
Biological samples						
Buccal swab				●	●	●
Blood					●	●
Urine					●	●

ASSIST V3.0, Alcohol, Smoking and Substance Involvement Screening Test Version 3; Bayley SEQ, Bayley Social Emotional Questionnaire; BSID-III, Bayley Scales of Infant Development third edition; CANTAB, Cambridge Neuropsychological Test Automated Battery; Generation R, questionnaires on paediatric health and diet history (with permission from The Generation R Study Group); M-CHAT, Modified Checklist for Autism in Toddlers; Subjective Social Status, MacArthur Scale of Subjective Social Status.

### Biospecimen collection

The study's biospecimen repository, housed at the Academic Hospital Paramaribo's (AZP's) clinical laboratory, contains 13000 samples. Table 1 lists timepoints at which biospecimens are collected. All biospecimens are collected at study site hospitals and shipped to the AZP laboratory using established chain-of-custody procedures. Samples collected from participants in remote areas are stored at 4°C for not more than 48 hours prior to delivery and processing at the AZP clinical laboratory. Blood, serum, plasma and cord blood samples are aliquoted into 2 mL plastic freezer tubes and stored at -80°C. Urine samples (60 mL) are collected in sterile bar-coded urine collection cups, aliquoted into 10 mL plastic tubes, stored in ziplock bags at -20°C and shipped for analysis by CDC's environmental health laboratory using well-established protocols.

Maternal hair samples, collected once during pregnancy, were taken according to the following protocol: 1.5 g of hair was cut as close as possible to the hair roots with disinfected scissors and placed in patient-coded ziplock bags, stored at room temperature in a climate-controlled room and sent to the National Zoological Collection of Suriname/Center for Environmental Research lab at the Anton de Kom University of Suriname for total Hg analysis using Cold Vapour Atomic Absorption Spectrometry.

### Buccal swab collection for telomere assessments

Isohelix SK1 buccal swabs (Cell Projects, Kent, United Kingdom) are used for the collection of maternal DNA for TL analyses. Swabs are air dried, and then stored with a dessicator pellet at 4°C until DNA is extracted. DNA is extracted using the QIAamp DNA mini kit protocol (Qiagen, Valencia, CA, USA) and stored at -80°C until assayed. Concentration of dsDNA is quantified with a Qubit dsDNA Broad Range (BR) assay kit (Invitrogen, Carlsbad, CA, USA), purity of the DNA is determined by using a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) and DNA integrity is confirmed by gel electrophoresis to ensure high molecular weight DNA.<sup>20</sup> The average relative TL, represented

by the telomere repeat copy number to single gene (albumin) copy number (T/S) ratio, is determined with monochrome multiplex quantitative real-time PCR using a BioRad CFX V.96.<sup>21</sup> All samples are run in triplicate on duplicate plates with a standard curve and known controls.

### Trace element analyses in blood

Four hundred frozen maternal whole blood samples were shipped for analysis to the Wisconsin State Laboratory of Hygiene Trace Element Research Laboratory. A chain-of-custody approach was used to ensure samples were collected, maintained, processed, stored, shipped and received according to acceptable standards. Quality assurance/quality control (QA/QC) procedures for elemental analyses and methylmercury analyses included reagent blanks, blank spikes (lab fortified blanks), sample matrix spikes, ongoing precision and recovery spikes, second source spikes, sample matrix duplicates and external standard reference materials. All sample and QA/QC results were within the acceptable recovery limits. Duplicates for all runs were within the acceptable relative percent difference limits. In these 400 blood samples (200 Paramaribo, 100 Nickerie and 100 interior communities), we analysed Hg, lead, cadmium, aluminium, manganese, tin, selenium and iron using inductively coupled plasma-mass spectrometry or cold vapour atomic fluorescence spectrometry (CVAFS). Total Hg and methylmercury using CVAFS were assessed in a small subset of women (20—Paramaribo, 20—Nickerie and 35—interior) to specify exposure sources.

### Pesticide analyses in urine

Urine samples from pregnant women were analysed (subcohort, N=218) from all three study sites. The six dialkylphosphate metabolites were measured using a modified method of Jayatilaka *et al*<sup>22</sup> by solid-phase extraction high-performance liquid chromatography-tandem mass spectrometry. The eight specific urinary metabolites were analysed using a semiautomated solid-phase extraction mass spectrometry method and

reversed-phase high-performance liquid chromatography.<sup>23</sup> The analysis panel consisted of dialkylphosphate metabolites of organophosphate pesticides including dimethylphosphate, diethylphosphate, dimethylthiophosphate, dimethyldithiophosphate, diethylthiophosphate and diethyldithiophosphate, and a universal panel including one herbicide (2,4D) and its metabolite, 2,4-dichlorophenoxyacetic acid; four organophosphates (OP) insecticide metabolites (3,5,6-trichloro-2-pyridinol, 2-isopropyl-4-methyl-6-hydroxypyrimidine, par-nitrophenol and malathion dicarboxylic acid) and three pyrethroid metabolites (4-fluoro-3-phenoxybenzoic acid, 3-phenoxybenzoic acid and trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid).

### Data collection from birth through 48 months

At birth, a cord blood sample was taken from infants for measurements of heavy metals. When a cord blood sample was not available, a blood sample was obtained by heel prick. Baseline characteristics of all births (eg, gender, weight, gestational age and Apgar Score) were collected (table 2). At each subsequent data collection timepoint (table 1), the child's growth is measured and a buccal swab taken for TL analyses. In addition, the child's health status is obtained through questionnaires on diet, history of infectious diseases and respiratory and neurological disorders. To date, we have completed the first follow-up with 85% of children. A blood sample will be taken for heavy metal measurement at 36 and 48 months. Blood samples and buccal swabs are collected and stored in the same manner as described above for mothers.

### Behaviour and cognitive development

Neurodevelopmental assessments over the lifetime of the study include infant cognitive and motor development and behaviour at 12–27 months using the Bayley Scales of Infant Development as well as assessments of cognitive and social–emotional development at 36 months, and executive function at 48 months (table 1). The Bayley Scales are currently being administered to enrolled children by trained psychologists, psychiatrists and study team members. Data checking following data entry of each Bayley subscale is conducted by other team members. To date, 832 of 992 children have been tested; remaining assessments will be completed by September 2020. Assessments at 36 and 48 months will take place as the cohort ages.

### Data collection from fish

Carnivorous fish from different regions in the interior of Suriname have shown high levels of Hg, specifically the frequently consumed species *Hoplias aimara* (0.43–0.66 µg/g) and *Serrasalmus rhombeus* (0.23–1.38 µg/g). These levels are well above international accepted standards and in certain regions, up to seven times the norm for human consumption.<sup>24</sup> Polyunsaturated omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from fish consumption may offer

neuroprotective benefits during prenatal and paediatric development which could potentially counteract Hg neurotoxicity.<sup>25–27</sup> Some studies examining developmental trajectories of children born to women exposed to Hg in utero fail to link that exposure to adverse neurodevelopmental outcomes, suggesting that fish nutrients may ameliorate Hg toxicity and offer neuroprotective benefits.<sup>28–31</sup>

To better inform fish consumption risk, fatty acids in fish muscle tissue were measured in samples (N=5 per species) of five freshwater and three marine fish species. The levels of 27 fatty acids, including DHA and EPA, in fish muscle tissue were measured (expressed as mg fatty acid per gram dry weight) by the University of Texas Marine Science Institute. Fifty milligrams dry weight samples were homogenised in a chloroform–methanol solution (2:1 v/v) for lipid cold extraction. Lipids were then saponified in potassium hydroxide to yield fatty acid methyl esters, and then methylated in a 14% boron trifluoride solution. Individual fatty acid concentrations were determined by gas chromatography (Shimadzu GC-2014 gas chromatograph) set with a Supelcowax V.10 fused silica capillary column (Milipore Sigma). Freshwater species had higher levels of linoleic acid (2.0 vs 0.2 mg/g), alpha-linoleic acid (0.4 vs 0.1 mg/g), arachidonic acid (3.0 vs 1.5 mg/g), omega-6 fatty acids (6.5 vs 2.3 mg/g) and lower levels of EPA (0.8 vs 1.9 mg/g) compared with marine species.

### PATIENT AND PUBLIC INVOLVEMENT

The CCREOH Cohort Study was preceded by a planning grant which included pilot fish and hair Hg assessments among interior communities approved by the village Chiefs or Tribal captains. Building on this community partnership, the initial study design was revised based on guidance from a multistakeholder Community Advisory Board (CAB) and an External Scientific Advisory Board (EAB). The CAB consists of respected leaders representing organisations from the interior tribal and indigenous peoples, midwives, general practitioners and environmentalists. The EAB members represent medical directors and other clinicians of all participating hospitals, representatives from the Ministry of Health, the US Embassy, the Pan American Health Organization and the Caribbean Public Health Agency (CARPHA). Both advisory boards are convened annually to inform and give updates about study progress and results, and to seek advice on future directions and dissemination of results.

### Dissemination of study results

Every participant with neurotoxicant levels of imminent health concern is contacted and asked to repeat the test for confirmation. If the level remains of concern, the participant is referred to her attending physician. Children with neurodevelopmental delay are referred to a child psychologist. Participants and the general public were invited to health fairs, meetings and conferences,

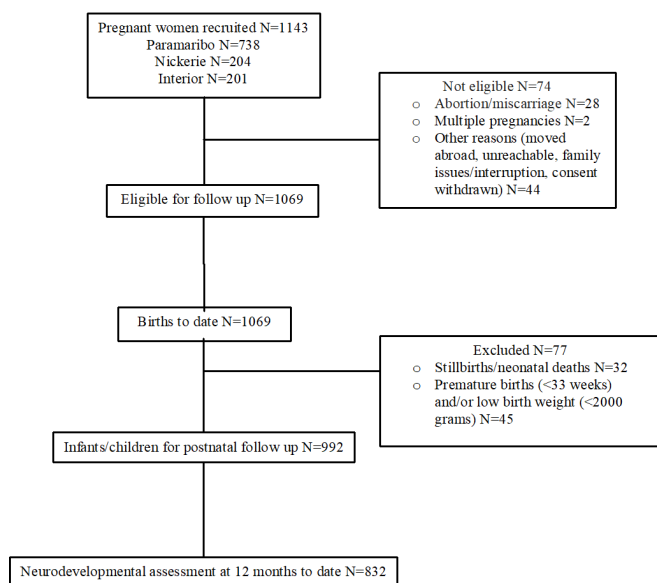
**Table 2** Distribution of maternal and infant characteristics

Maternal characteristics (n=1143)	N	%	Infant characteristics (n=971)	N	%
<b>Age at intake</b>			<b>Gender</b>		
16–19 years	142	12.6	Male	510	52.5
20–24 years	260	22.8	Female	457	47.1
25–29 years	291	25.5	Missing	4	0.4
30–34 years	268	23.5	<b>Birth status</b>		
35–39 years	140	12.3	Live birth	947	97.5
40+ years	39	3.4	Stillbirth	23	2.4
Missing	1	0.1	Missing	1	0.1
<b>Parity</b>			<b>Birth weight (in grams)</b>		
0 previous live births	384	33.7	Low birth weight (<2500)	127	13.1
One previous live birth	312	27.3	Normal birth weight (≥2500)	835	86.0
Two previous live births	187	16.4	Missing	9	0.9
Three previous live births	112	9.8	<b>Gestational age (in weeks)</b>		
4+previous live births	146	12.8	Very preterm births (22+0–32+6)	39	4.0
Missing	2	0.2	Moderately preterm births (33+0–36+6)	107	11.0
			Term births (≥37+0)	817	84.1
			Missing	8	0.8
<b>Ethnicity</b>			<b>Apgar score at 5 min</b>		
Creole	249	21.8	0–6	31	3.2
Hindustani	233	20.4	7–10	918	94.5
Indigenous	155	13.6	Missing	22	2.3
Javanese	101	8.8			
Tribal	271	23.7			
Mixed	127	11.1			
Other	7	0.6			
Missing	0	0.0			
<b>Educational level</b>					
No or primary	276	24.1			
Lower vocational/secondary	382	33.4			
Upper vocational/secondary	317	27.7			
Tertiary	168	14.7			
Missing	0	0.0			
<b>Household income SRD*</b>					
<1500	401	35.1			
1500–2999	362	33.0			
3000–4999	221	20.2			
5000+	112	9.8			
Missing	47	4.1			
<b>Marital status</b>					
Married or living with partner	1000	87.6			
Not married/not living with partner	141	12.4			
Missing	2	0.2			

\*Surinamese Dollar, equivalent to US\$0.13.  
SRD, Surinamese Dollar.

where preliminary study results were presented and discussed. CCREOH data have been presented at regional and international conferences, including CARPHA, the

International Society of Environmental Epidemiology, the Consortium for Universities in Global Health, the American Public Health Association and at scientific meetings



**Figure 1** Flowchart with participant enrolment.

convened by the US NIH. The study team is working with the EAB and CAB to develop a collaborative translation and dissemination strategy for overall, final study results when those become available.

## FINDINGS TO DATE

From December 2016 until July 2019, 1143 pregnant women were enrolled; 74 (6.5%) were ineligible (figure 1). Geographically, 738 women were enrolled in Paramaribo, 204 in Nickerie and 201 in the interior. In comparison with participants, non-participants were more often of Creole and Tribal ethnicity, lived in Paramaribo and had lower household income. Table 2 presents baseline maternal characteristics: one in eight women was 16–19 years old, ethnic distribution was representative of the Surinamese population, and >50% had no or lower vocational/secondary education level.

Of the 1069 babies born, 992 were enrolled (93%) (figure 1). To date, the total number of biospecimens (N=13 379) collected from 1143 pregnant women includes whole blood for trace elements (N=1994), whole blood collected in dipotassiummethylenediaminetetraacetic acid (K<sub>2</sub>EDTA) anticoagulant (N=1994), serum collected in serum separator tubes (N=1994), plasma (N=1994), urine (N=1980), buccal swabs (N=941) and hair (N=876). From 992 infants, either cord blood (N=441) or blood from heel prick (N=323) was collected at birth, and buccal swabs (N=842) during neurodevelopmental assessment at 12 months. All samples not yet analysed are archived for future targeted and untargeted analyses. Available results include total Hg concentrations in hair, prenatal maternal depression and perceived stress, level of pesticides in produce, and dietary exposure to Hg in fish. The results of heavy metals in blood, urinary pesticide

metabolites, telomere analysis and neurodevelopmental assessments are pending.

## Biological specimens

Total hair Hg was measured in 876 participants from all 3 study sites. Overall, 39.1% had elevated total Hg hair levels that exceeded the United States Environmental Protection Agency's action level (1.1 µg/g hair).<sup>32</sup> Elevated Hg levels were found in 95.8%, 26.3% and 25.5% of participants from the interior, Nickerie and Paramaribo, respectively. The results for median total Hg concentrations in hair from pregnant women from Paramaribo (N=522) were 0.64 µg/g hair (IQRs 0.36–1.09; range 0.00–7.12), from Nickerie (N=176) 0.73 µg/g (IQR 0.45–1.05; range 0.00–5.79) and the interior (N=178) 3.48 µg/g (IQR 1.92–7.39; range 0.38–18.20). Pregnant women from the interior were exposed to high levels of Hg compared with women from the coastal area, and thus fetal exposures are expected to be high. Most of these women are primarily exposed to methylmercury from consuming contaminated fish from local artisanal gold-mining activities.<sup>18 24</sup> Other possible sources of exposure may include active participation in or living very close to gold mining areas. Hg concentrations from the Nickerie and Paramaribo subcohorts were similar to other studies.<sup>33 34</sup>

## Prenatal depression and perceived stress

Depression and prenatal stress in 722 participants were assessed using the standardised Edinburgh Depression Scale (EDS) (cut-off ≥12 for probable depression) and the Cohen Perceived Stress Scale (cut-off ≥20 for high perceived stress). One in four (24.9%) participants had EDS scores indicative of probable depression, three in ten (30.2%) had high stress levels and nearly half (49.1%) of these women had probable depression.

## Dietary exposure to pesticides

An assessment of Surinamese agricultural produce showed pesticide residues exceeding European Union maximum residue limits, including prohibited worldwide endosulfan and lindane in the leafy vegetable tannia, *Xanthosoma brasiliense*.<sup>35</sup> An interviewer-assisted NHANES-based dietary survey of 522 participants showed that 98.2% reported consumption of leafy vegetables. Tannia was the most frequently consumed (89.3%); 36.5% participants had high intake rates of tannia (≥36 g/day).<sup>36</sup> Tannia is also a commonly used vegetable in baby food preparation in Suriname.

## Dietary exposure to Hg in fish

Dietary questionnaire analyses (N=990) showed an overall fish consumption of 96.1%. Consumption of the three most consumed carnivorous species—*H. aimara*, *S. rhombeus* and *Cichla ocellaris*—, known to have high Hg levels, was 44.4%, 19.3% and 26.3%, and was greater among the interior subcohort (N=123): 89.4%, 67.5% and 74.8%, respectively. Intake rates (based on reported meal frequency and portion sizes) for these three carnivorous species ranged between 0.01 and 2.5 kg/week. Hg



speciation indicated that methylmercury was predominantly found in the biospecimens. This is consistent with fish consumption likely being the primary source of Hg exposure in our participants.

### Strengths and limitations

This CCREOH study is the first to examine the potential impact of complex environmental exposures on maternal and child health in Suriname by a multidisciplinary team of scientists. Study's strengths include: (1) addressing two high-priority public health threats: the impact of Hg exposure from artisanal gold mining, and pesticide exposure associated with agricultural practices; (2) inclusion in the cohort of two vulnerable subpopulations: pregnant women and children; (3) the longitudinal follow-up of children until 48 months with built-in timepoints to assess neurodevelopmental outcomes and (4) a biospecimen bank of approximately 13 000 samples, providing the opportunity for future analyses. Moreover, a linked research training grant facilitates the training of nine Surinamese PhD candidates with dissertation research embedded in the study, thereby building critical in-country environmental health research capacity.

Delayed recruitment and data collection of the logistically difficult to reach subcohort in the interior region (N=200) were ameliorated by additional team support onsite; delays in transporting interior biospecimens rendered some early cord blood specimens not analysable and was corrected by collecting an additional heelprick sample. Other limitations include differences in educational level between women from the three recruitment sites that could confound or impact literacy. Participants may have moved between regions with different sources of exposure. Delayed recruitment of some interior participants may limit our ability to examine differential effects of exposure across gestation for this subcohort.

### FUTURE PLANS

Culturally tailored fish consumption advisories are in development to reduce Hg exposure. An expanded assessment of potentially neuroprotective fish nutrients is under way. A Pesticide Literacy Scale will assist in countering pesticide exposure. Repeated TL measurements of children as an indicator of exposure to environmental toxins will be taken. Neurodevelopmental assessments will take place at 36 and 48 months. An integrated, sharable data management system is in development.

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**Collaborators** We welcome collaboration with fellow researchers working on similar projects. Specific research proposals can be sent directly to the CCREOH Principal Investigators Drs Wilco Zijlmans (wilco.zijlmans@uvs.edu) and Maureen Lichtveld (mlichtve@tulane.edu). Areas of collaboration include further environmental and biomarkers assessment of arsenic exposure, occupational health risk assessments associated with mercury and pesticide exposure, and exposomic analyses including metabolomic assessments.

**Contributors** ML, JW, HC, EH, AS, SSD and WZ designed and established the cohort. SM-O, AH-M, EH, FAW and AWG participated in the design of the questionnaires. WZ, SM-O, EB, WH, GB, RR and ML were responsible for the continued management of the cohort. GB, RR, AWG and FAW were actively involved with recruitment of participants and collection of non-biospecimen data and biospecimens. JC, JR, PO and GL store, archive and analyze the biomarker samples. AH-M, AS, SM-O, AWG, ML and WZ were responsible for data management. SSD, AWG, RR and EB managed neurodevelopmental testing of babies. JW, LFS, CA and SSD interpreted all results. WZ, JW, HC, AH-M and ML drafted and edited the manuscript. All authors critically reviewed and approved the final manuscript.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This study was Institutional Review Board (IRB) approved by both the Government of Suriname and the Tulane University, New Orleans, Louisiana, USA, to consent 1200 pregnant women and their singleton birth children.

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**Data availability statement** Data are available upon reasonable request. Our cohort study data will be made publicly available upon publication of the results in scientific articles. Questionnaire, registry and biospecimen data could be made accessible in deidentified form after an application process that includes submission of a research plan. We are currently collaborating with Research Triangle Institute International, a global data management enterprise, to develop an integrated database of biospecimen and non-biospecimen data. Once that is fully developed, data can be made available based on a reasonable request to the Principal Investigators. Such requests will be discussed with the full investigator Committee, the Data Management Committee and the Administrative Oversight Committee.

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