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Cohort profile: The Caribbean Consortium for Research in Environmental and Occupational Health (CCREOH) MeKiTamara Cohort Study: Influences of complex environmental exposures on maternal and child health in Suriname

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Title: Cohort profile: The Caribbean Consortium for Research in Environmental and Occupational Health (CCREOH) MeKiTamara 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 (CCREOH) MeKiTamara population-based prospective longitudinal cohort study addresses the potential adverse impact of complex chemical and non-chemical environmental exposures in mother/child dyads in Suriname. Associations between levels of environmental elements and toxicants in pregnant women and birth outcomes are determined and longitudinal neurodevelopmental outcomes in infants 0-4 years are measured. Also, levels of environmental elements and toxicants in fish, produce, and rice are assessed.

Participants: From December 2016 to date, 1067 pregnant women and 827 babies are enrolled. Exposures to mixtures of toxicants including mercury, lead, and selected pesticides are monitored and dietary, non-chemical stressors and environmental source characterization assessments take place during seven study time points: twice during pregnancy, birth, 12, 24, 36, and 48 months.

Findings to date: One out of four women, and predominantly those living in Suriname's interior, have hair mercury levels exceeding values considered safe by international standards. Almost 25% of women may suffer from depression, and 3 out of 10 have high stress levels. There was no statistically significant association found between hair mercury levels and adverse birth outcomes.

Future plans: Total mercury concentrations in blood are elevated in women from the interior of Suriname where the primary source of exposure to mercury is through consumption of fish. Fish consumption advisories may reduce exposure to these harmful substances. New research has recently been funded to examine effects of potentially beneficial neuroprotective factors in fish that may counter the neurotoxic effects of mercury. Long term effects of exposures to toxicant mixtures in infants are being evaluated through pediatric neurodevelopmental assessments up to four years of age.

Keywords environmental exposures, mercury, metal mixtures, pregnant women, pediatric neurodevelopment, Suriname

Wordcount 3995 (excl. references, acknowledgements, tables & figures)

Strengths and limitations of this study

- The study addresses two high priority public health threats in Suriname as well as for neighboring countries in the Guiana shield with similar practices: the impact of mercury exposure from artisanal gold mining and pesticide exposure associated with agricultural practices in two vulnerable subpopulations: pregnant women and children aged <5 years of age.

- The longitudinal follow up of children up to 48 months provides several timepoints to assess neurodevelopmental outcomes.
- The study has a biospecimen bank of approximately 12,000 samples, providing the opportunity for future analyses within the cohort.
- 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.
- In terms of initial challenges, the interior subcohort (N=200) is logistically difficult to reach, resulting in delayed recruitment, data collection and transport of cord blood specimens, this was corrected with additional team support onsite that facilitated recruitment of the full subcohort, and additional heelprick sampling at birth.

Introduction

The Caribbean Consortium for Research in Environmental and Occupational Health (CCREOH) addresses the goal of high-priority environmental and occupational health risks in Suriname and those common to the vulnerable Caribbean region, while preserving the unique assets pertaining to the health and cultural traditions of indigenous and other health disparate populations [1]. Environmental contaminants may affect pregnancy, and pre- and postnatal health in multiple ways: miscarriage, preterm delivery, intra-uterine growth retardation, and congenital malformations as well as other behavioral and physical health problems that may not manifest until later in development [2, 3, 4]. Prenatal exposure to multiple heavy metals is associated with adverse pediatric health outcomes [5]. Pesticide exposure has been linked to fetal growth decrements and preterm birth, and there is mounting evidence that exposure to pesticides during pre- and postnatal development is associated with neurodevelopmental deficits in young children [6-10]. The physiological effects of contaminants may differ in combination compared to individually; for instance, lead, arsenic, and mercury can potentiate each other's toxicity, even at individual levels below concentration expected to result in adverse effects [11]. Despite this knowledge, no cumulative risk assessments have been conducted to date addressing exposures to contaminant mixtures in Caribbean Low- and Middle-Income Countries [12]. Beyond this, there remains a paucity of studies that have examined the interactive impact of psychosocial exposures with environmental exposures.

The CCREOH-MeKiTamara (MeKiTamara which means "making a mother and child's tomorrow'' in Suriname's local language) environmental epidemiology cohort study fills this gap by exploring the impact of exposures to organic and inorganic neurotoxicants, including mercury, lead and multiple organophosphate pesticides, on Surinamese pregnant women and their offspring (up to 48 months of age) using a cumulative risk approach. Specifically, the study assesses the impact of exposures to chemical and non-chemical psychosocial stressors by examining the interaction between exposure to environmental chemicals and social and psychological determinants of early neurodevelopment. Few prospective studies have measured prenatal exposure through 48 months, and those that have showed contrasting results when evaluating executive function, a key neurodevelopmental outcome [13-16]. Our hypothesis is that environmental exposures to mixed 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 mercury, lead, cadmium, aluminum, iron, manganese, tin, and selenium and selected pesticides through comprehensive dietary, environmental, and occupational risk assessments, and biomarker monitoring in Surinamese pregnant women and their offspring;
- Assess the levels of environmental elements and toxicants in fish, produce, rice, and nutraceutical compounds;
- Determine the association between birth outcomes and levels of environmental elements and toxicants in pregnant women;
- Assess the impact of mobile health technology-enabled community health workers on birth outcomes and their associations with environmental contaminants;
- Determine the association between prenatal, dietary, and environmental levels of elements and toxicants and possible 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. 90% of the population of 590,549 people live in the capital Paramaribo and the coastal area. The remainder live in the tropical rainforest interior (90% of the landmass). Suriname's multi-ethnic population consists of five main groups: Hindustanis (27%), Tribal (22%), Creoles (16%), Javanese (14%), and Indigenous (4%) [17].

Recruitment

The MeKiTamara study enrolled mother/child dyads potentially exposed to complex environmental chemical- and non-chemical stressors. Main maternal and infant/child determinants included biological determinants: maternal anthropometrics, blood pressure, hemoglobin, liver and kidney function, fetal and postnatal growth characteristics and health status, heavy metals (blood and hair), pesticides (urine), telomere length (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, 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; behavior 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 Community Health Workers, quality of life and health care system utilization and comparison.

Pregnant women 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 mercury is used in artisanal gold mining and the population is highly dependent on consumption of contaminated fish (Figure 1) [18]. 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. Women who met the inclusion criteria were identified by their treating physician, midwife, 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 16 and 17 years of age.

Children were excluded for follow-up if they had: gestational age <33 weeks and/or birthweight <2000 grams, significant medical or neurological condition, Down syndrome, hydrocephalus, cerebral palsy, or significant visual or hearing impairment inconsistent with neurocognitive testing.

Follow up

This study was IRB approved by both the Government of Suriname and the Tulane University to consent 1200 pregnant women and their singleton birth children. Data were collected from the women at two timepoints (trimester 1 or 2, and 3) and 24, 36, and 48 months, while the children are followed at birth, 12, 24, 36 and 48 months (Table 1).

From December 2016 until December 2018, 1067 pregnant women were enrolled; 76 (7.1%) were ineligible (Figure 2). In comparison to participants, non-participants were more often of Creole and tribal ethnicity, lived in Paramaribo, and had lower household income. Of the 898 babies born, 827 were enrolled (92%). Initial neurodevelopmental assessments at 12 months in 491 infants are being analyzed.

Data collection during pregnancy

Questionnaires

The main categories of data collected from the women are health status, demographics, reproductive health history, social support, trauma history, exposure history, depression, perceived stress, prenatal life events, health behavior, access to prenatal care, social status and diet (Table 1). Questions on health behavior were adapted from the Pregnancy Risk Assessment Monitoring System (PRAMS), a surveillance project by state health departments and the Centers for Disease Control and Prevention (CDC). Information on maternal diet was obtained by a CDC's National Health and Nutrition Examination Survey (NHANES) based culturally tailored dietary survey focusing on fish and produce consumption, including frequency of intake and portion sizes. Table 2 presents baseline maternal characteristics.

Measurements of heavy metals in blood and hair

In 400 maternal whole blood samples (200 Paramaribo, 100 Nickerie, and 100 interior communities), we analyzed lead, mercury, cadmium, aluminum, manganese, tin, selenium, and iron using inductively coupled plasma-mass spectrometry (ICP-MS) or cold vapor atomic fluorescence spectrometry (CVAFS). Total mercury and methylmercury using CVAFS was assessed in a small subset of women (20-Paramaribo, 20-Nickerie, and 35-interior) to specify exposure sources.

Samples collected from participants in remote areas were stored at 4°C for no more than 48 hours prior to delivery and processing at the Academic Hospital Paramaribo clinical laboratory. Blood, serum, plasma, and cord blood samples were aliquoted into 2 ml plastic freezer tubes and stored at -80°C. Frozen samples were shipped for analysis to the Wisconsin State Laboratory of Hygiene Trace Element Research Laboratory conform formal chain-of-custody. All internal and external QA/QC were acceptable. Maternal hair samples were taken according to protocol, 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 (NZCS/CMO) for total mercury analysis using Cold Vapour Atomic Absorption Spectrometry (CVAAS).

To date, the total number of biospecimens collected from 1067 pregnant women include whole blood for trace elements (N=1994), whole blood collected in K_2EDTA 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); cord blood (N=441), blood from heelpricks (N=269), and buccal swabs (N=363) are collected from 710 infants. All remaining samples not (yet) analyzed are archived for future targeted and untargeted analyses.

Measurements of pesticides in urine

Urine samples were analyzed (subcohort N=220) from all three study sites. Urine samples were aliquoted into 10 ml plastic tubes, stored at -20°C and shipped for analysis by the U.S. Centers for Disease Control and Prevention's environmental health laboratory. The analysis panel consisted of dialkylphosphate metabolites of organophosphate pesticides (DAP's) including dimethylphosphate, diethylphosphate, dimethylthiophosphate, dimethyldithiophosphate, diethylthiophosphate, and diethyldithiophosphate, and a universal panel (UP) including 1 herbicide (2,4D) and its metabolite, 2,4-dichlorophenoxyacetic acid; 4 OP insecticide metabolites

(3,5,6-trichloro-2-pyridinol, 2-isopropyl-4-methyl-6-hydroxypyrimidine, para-nitrophenol, malathion dicarboxylic acid) and 3 pyrethroid metabolites (4-fluoro-3-phenoxybenzoic acid, 3-phenoxybenzoic acid, trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid).

Data collection from birth through 48 months

At birth, a cord blood or heelprick sample is taken from infants for measurements of heavy metals. Baseline characteristics of all live births on e.g. gender, weight, gestational age, and Apgar score are collected (Table 2). At each subsequent data collection timepoint (Table 1), the child's growth is measured and a blood sample is taken for heavy metal measurement. In addition, the child's health status is obtained through questionnaires on diet and history of infectious diseases, and respiratory and neurological disorders.

Telomere measurements

Consistent evidence demonstrates that telomere length (TL) is a marker of cellular aging and links TL to negative health outcomes including diabetes, cardiovascular disease and cognitive decline with aging. Oxidative stress and DNA methylation, among other factors, influence TL. Arsenic and pesticide exposure have both been linked to altered DNA methylation, while evidence also suggests a link between mercury and elevated oxidative stress [19-23]. TL may reflect multiple biological pathways through which environmental toxins influence child health and development and potentially may be an earlier indicator of exposure. DNA in infants is collected at 12, 24, 36, and 48 months of age using buccal swabs. The average relative TL, as represented by the telomere repeat copy number to single gene (albumin) copy number (T/S) ratio, will be determined with monochrome multiplex quantitative real-time PCR using a BioRad CFX96 [24].

Behavior and cognitive development

Neurodevelopmental assessments include infant mental and motor development and behavior at 12 months using the BAYLEY scale of infant development as well as assessment of cognitive and social-emotional development at 36 months, and measurement of executive function at 48 months (Table 1).

Data management & statistical plan

Informed consent was required for successful recruitment and where indicated assent was obtained. The CCREOH field team was trained in administering all questionnaires. Data from administered questionnaires are recorded on secure, encrypted iPads, uploaded and managed using REDCap electronic data management system [25]. As outlined earlier, biospecimens (blood, cord blood, urine, buccal swabs) are collected at all study areas and then subsequently transported to the study's laboratory at the Academic Hospital in Paramaribo. Hair samples were analyzed for the presence of mercury at the NZCS/CMO Environmental laboratory. Fish samples were collected in areas downstream and upstream of selected villages, including gold mining areas, and analyzed for mercury. Biomarker assessments not possible in Suriname are conducted at US specialty laboratories.

REDCap serves as the study's integrated data management system. Data collected through iPads by the field team are uploaded in the training site of REDCap for data cleaning prior to integrating questionnaire and biospecimen data. Data records are maintained to see trends on source of errors; duplicate records are scrubbed, and accuracy is validated through cross-checks with original data files and medical records. A comprehensive biospecimen tracking system is nearing completion to track analyzed samples and the overall study biospecimen repository. The data management team develops de-identified data files upon request of CCREOH investigators as specified by a standardized data request form. Statistical analyses are tailored to the specific research question. CCREOH data have been presented at multiple local, regional, and international conferences, including the Caribbean Public Health Agency, the International Society of Environmental Epidemiology, the Consortium for Universities in Global Health, the American Public Health Association and at scientific meetings convened by the US NIH.

Patient and public involvement

The CCREOH/ MeKiTamara cohort study was preceded by a pilot fish assessment study as well as initial hair mercury assessment among communities in the interior which required approval from the village Chiefs or Tribal captain. This community engagement component provided us a rich foundation to build on as we developed the research questions. The initial study design was revised based on guidance from an External Scientific Advisory Board (EAB) and multi-stakeholder Community Advisory Board (CAB; consisting of respected persons in society representing organizations such as from the interior tribal and indigenous peoples, midwives, general practitioners and green wildlife), all participating hospitals and clinicians, and representatives from the Ministry of Health, the US Embassy, the Pan American Health

Organization and the Caribbean Public Health Agency (CARPHA). For example, the CAB was instrumental in urging the study team to lower the inclusion age to 16 years since many women in the interior conceive at an earlier age. All stakeholders are convened annually to inform and give updates about the study progress and results, and to seek advice on future directions and dissemination of results. The study team is actively working with the EAB and the CAB on a collaborative translation and dissemination strategy. However, a participant with neurotoxicant levels of imminent public health concern is contacted by the study coordinator and asked to repeat the test for confirmation. If the level remains of concern the participant is referred to her attending physician according to the study's formal health care provider referral protocol. Children that are found to have a neurodevelopmental delay are referred to the child psychologist for further evaluation. Participants and the general public were invited to multiple health fairs, meetings and conferences, where the researchers discussed the study in a broader context, provided updates on the latest results and answered questions. Additionally, a Facebook account was created for study participants and others interested in this study, with general information on exposure to heavy metals and pesticides as well as the opportunity to ask questions of the research team and provide feedback about the study.

Findings to date

Available results include total mercury concentrations in hair from pregnant women and urinary pesticide metabolites that were measured in a subset of 220 women. Results on heavy metals in blood, telomeres and neurodevelopmental assessments are pending.

Biological specimens

Results for median total mercury concentrations in hair from pregnant women from Paramaribo (N=522) were 0.64 μg/g hair (interquartile ranges (IQR) 0.36-1.09; minimum 0.00 – maximum 7.12), from Nickerie (N=176) 0.73 μg/g (IQR 0.45-1.05; 0.00-5.79) and the interior (N=178) 1.92 μg/g (IQR 1.92-7.39; 0.38-18.20). Pregnant women from the interior are exposed to high levels of mercury compared to women in the coastal area and thus fetal exposures are expected to be high. Median concentrations are well above health action levels of 1.1 μg/g hair for mercury [26]. Most of these women are primarily exposed to methylmercury from consuming fish that are contaminated by the artisanal gold-mining activities in those areas [18,27]. Other possible sources of exposure to mercury may include active participation in or living very close to gold mining activities.

Urinary pesticide metabolites measured in a subset of 220 women are presented in Table 3. Concentrations varied geographically among participants: in Nickerie, participants' pyrethroid and herbicide metabolite concentrations were higher compared to Paramaribo and the interior, probably because of widespread agricultural use. Organophosphate metabolite concentrations were higher in Paramaribo compared to Nickerie and the interior, which could be attributed to residential use and more intense mosquito control.

Prenatal depression and perceived stress

Depression and prenatal stress in 722 participants were assessed using the standardized Edinburgh Postnatal Depression Scale (EPDS) (cut off ≥12 for probable depression) and Cohen Perceived Stress Scale (cut off ≥20 for high stress) respectively. One in 4 (24.9%) pregnant study participants potentially exposed to mercury had EPDS scores indicative of probable depression. Three in ten participants had high stress levels and nearly half of these women had probable depression.

Dietary exposure to pesticides

An assessment of Surinamese agricultural produce done by our group found pesticide residues exceeding European Union maximum residue limits, including prohibited- worldwide endosulfan and lindane in the leafy vegetable tannia, *Xanthosoma brasiliense* [27]. Tannia is commonly used in baby food preparation in Suriname.

Dietary exposures to mercury

One in four pregnant women in our cohort, and predominantly those living in the interior who rely heavily on local freshwater fish, have hair mercury levels exceeding those considered safe by the US and the WHO. The dietary questionnaire (n=990) showed overall fish consumption of 96.1%. Previous environmental assessments of most frequently consumed carnivorous fish by interior participants, *Hoplias aimara*, *Serrasalmus rhombeus*, and *Cichla ocellaris*, showed high levels of mercury [28]. Respective consumption of these three carnivorous species was 44.4%, 19.3%, and 26.3%. Carnivorous fish consumption was greater among the subcohort (N=123) living in the interior: 89.4%, 67.5%, and 74.8%, respectively.

Polyunsaturated omega-3 fatty acids (PUFA-3) docosahexaenoic acid and eicosapentaenoic acid from fish consumption offer neuroprotective benefits during prenatal and pediatric development which could potentially counteract mercury neurotoxicity. 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: 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 eicosapentaenoic acid (0.8 vs. 1.9 mg/g) compared to marine species. Frequent consumption of *Hoplias aimara*, a freshwater fish with high mercury and low PUFA-3 content, is likely to increase mercury exposure whereas consumption of *Plagioscion squamosissimus*, a freshwater fish with high mercury and high PUFA-3, may have nutritional benefits that outweigh mercury neurotoxicity. While freshwater species are a good source of these nutrients, corresponding mercury content must be assessed and considered as well.

Mercury exposure and birth outcomes

Data from 763 pregnant women were analyzed for total hair mercury and associated with birth outcomes. Adverse birth outcomes included preterm birth (PTB<37 weeks), low birthweight (LBW<2500g) and low Apgar score (AS<7 at 5 minutes). 27.3% of the women had elevated total mercury hair levels that exceeded the USEPA action level, 23.8% had adverse birth outcomes, 18.4% PTB, 14.7% LBW and 5.1% had low AS. There was no statistically significant association between hair mercury level and adverse birth outcomes. Neurodevelopmental assessment of the children is ongoing.

Strengths and limitations

The CCREOH-MeKiTamara environmental epidemiologic study is the first to examine the potential impact of complex environmental exposures on maternal and child health in Suriname by a multi-disciplinary team of scientists The study’s strengths include: 1) addressing two high priority public health threats: the impact of mercury 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 aged <5 years; 3) the longitudinal follow up with children up to 48 months with several built-in timepoints to assess neurodevelopmental outcomes; and 4) a biospecimen bank of approximately 12,000 samples, providing the opportunity for future analyses within the cohort. 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. Research dissemination throughout the Caribbean region is completed in collaboration with the Caribbean Public Health Agency.

In terms of initial challenges, the interior subcohort is logistically difficult to reach, resulting in delayed recruitment and data collection. Additional team support onsite facilitated recruitment of the full subcohort (N=200). Initial delays in transporting interior biospecimens rendered some early cord blood specimens not analyzable. This has been corrected by collecting an additional heelprick sample at birth.

Future plans

Since the most likely source of exposure to mercury in pregnant women in Suriname is through consumption of locally harvested fish, fish consumption advisories may aid in reducing exposure to environmental contaminants. Recent additional funding allows us to examine potentially beneficial neuroprotective factors such as selenium and dietary polyunsaturated fatty acids in fish that may counter the neurotoxic effects of mercury. To address the large scale and poorly regulated use of pesticides, we are developing a pesticide literacy scale through a recently funded fellowship. Cohort-wide, we will undertake a comprehensive assessment of the neurodevelopmental outcomes of the children, and create a robust, sharable data management system of biospecimen and non-biospecimen data building on the current REDCap database.

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Collaborators

We welcome collaboration with fellow researchers working on similar projects. Specific research proposals can be sent directly to the Principal Investigators Drs Wilco Zijlmans

(cwrzijlmans@researchcentersuriname.org) 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.

Author Contributions

MYL, JKW, HHC, EWH, AS, SSD and WCWRZ designed and established the cohort. MSMO, ADHM, EWH and AG participated in the design of the questionnaires. WCWRZ, MSMO, ED, WBH, GKB, RR and MYL are responsible for the continued management of the cohort. AG, GKB, RR, AG and FAW are actively involved with recruitment of participants and collection of non-biospecimen data and biospecimens. JC, JR, PEO and GAL store, archive and analyze the biomarker samples. ADHM, AS, MSMO, AG, MYL and WCWRZ are responsible for data management. SSD, AWEG, RR and EB manage neurodevelopmental testing of babies. JKW, LFS, CSA, SSD interpret all results. WCWRZ, JKW, HHC and MYL 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

Obtained

Ethical approval

This study was 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.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

MekiTamara cohort data will be made publicly available upon publication of the results in scientific articles. Questionnaire, registry and biospecimen data could be made accessible in de-identified form after an application process that includes submission of a research plan that will undergo evaluation by the CCREOH scientific board and relevant research ethics committees. Currently, only part of the data is available since data collection is ongoing.

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Table 1. Assessments completed by the CCREOH-MeKiTamara Cohort with timeline

Assessments	Trimester 1st/2nd	Trimester 3rd	Birth	12 mos	24 mos	36 mos	48 mos
Mother							
Obstetric history	●	●					
Demographics	●						
Residency	●	●					
Anthropometrics	●	●					
Marital status	●						
Ethnicity	●						
Occupation	●						
Education	●						
Income	●						
Household composition	●						
Maternity care	●	●					
Questionnaires							
SF 36 Health Survey	●	●					
Social Support List	●						
Brief Trauma Interview	●	●			●	●	●
Cohen 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					●	●	●
Biological samples							
Hair	●						
Blood	●	●					
Urine	●	●					
Buccal swab	●						
Infant at birth							
Mode of delivery			●				
Cord blood sample			●				
Birth outcomes			●				
Child							
Physical examination				●	●	●	●
Questionnaires							
General Health Questionnaire				●	●	●	●
M-CHAT						●	
Child Behavior Checklist						●	●
Neurodevelopmental tests							
Bayley				●			

WIPPSI			●	
CANTAB				●
Biological samples				
Buccal swab	●	●	●	●
Blood		●	●	●

Notes: ASSIST V3.0 = Alcohol, Smoking and Substance Involvement Screening Test Version 3, Subjective Social Status = MacArthur Scale of Subjective Social Status, M-CHAT = Modified Checklist for Autism in Toddlers, Bayley = Bayley Scales of Infant Development, WIPPSI = Wechsler Preschool and Primary Scale of Intelligence, CANTAB = Cambridge Neuropsychological Test Automated Battery.

Table 2. Maternal and infant characteristics

Maternal characteristics (N=1067)	N	%	Infant characteristics (N=898)	N	%
Age at intake			Gender		
16-19 years	133	12.4	Male	461	52.3
20-24 years	239	22.4	Female	421	47.7
25-29 years	280	26.2	Missing	16	1.8
30-34 years	252	23.6			
35-39 years	129	12.1	Birth status		
40+ years	34	3.2	Live birth	863	96.1
Missing	0	0.0	Stillbirth	35	3.9
			Missing	0	0.0
Parity					
0 previous live births	344	33.0	Birthweight		
1 previous live birth	298	28.6	Low birthweight (<2500 g)	113	12.9
2 previous live births	174	16.7	Normal birthweight (≥2500g)	760	87.1
3 previous live births	102	9.8	Missing	25	2.8
4+ previous live births	124	11.9			
Missing	25	2.3	Gestational age		
			Miscarriages	10	1.1
Ethnicity			Very preterm births (22+0-32+6 weeks)	36	4.1
Creole	245	23.0	Moderately preterm births (33+0-36+6 weeks)	93	10.7
Hindustani	222	20.8	Term births (≥37+0 weeks)	733	84.1
Indigenous	149	14.0	Missing	26	2.9
Javanese	94	8.8			
Tribal	223	20.9	Apgar score at 5 minutes		
Mixed	128	12.0	0 - 6	46	5.2
Other	5	0.5	7 - 10	832	94.8
Missing	1	0.1	Missing	20	2.2
Educational level					
No or primary	223	20.9			
Lower vocational/secondary	375	35.2			
Upper vocational/secondary	302	28.3			

Tertiary	166	15.6
Missing	1	0.1
Household income SRD*		
<1500	321	33.2
1500-2999	330	34.1
3000-4999	210	21.7
5000+	106	11.0
Missing	100	9.4
Marital status		
Married or living with partner	922	86.8
Not married/not living with partner	140	13.2
Missing	5	0.5

* SRD = Surinamese dollar, equivalent to 0.13 USD.

Table 3: Urinary pesticide metabolites presented as arithmetic mean (± standard deviations) and median concentrations. Ranges from minimum (LOD*-corrected) to maximum are presented as well as the LODs and the percentage of samples below the LOD. Total sample size is 218

Analyte	Mean (Standard Deviation) (ug/L)	Median (ug/L)	Range (ug/L)	LOD (ug/L)	% Below LOD
Chemical Class: Phenoxy Acetic Acid Herbicide					
2, 4- Dichlorophenoxyacetic acid	0.61 (0.92)	0.28	0.11-7.50	0.15	35.32
Chemical Class: Organophosphate Insecticide					
Malathion dicarboxylic acid	0.82 (3.55)	0.35	0.35-51.68	0.50	76.61
3,5,6-Trichloro-2-pyridinol	1.45 (3.73)	0.56	0.07-46.70	0.10	22.02
2-isopropyl-4-methyl-6-hydroxypyrimidine	1.28 (4.32)	0.31	0.07-52.00	0.10	16.51
para-Nitrophenol	1.28 (5.10)	0.59	0.07-73.30	0.10	40.92
Diethyldithiophosphate	0.07 (0.01)	0.07	0.07-0.14	0.10	98.62
Diethylphosphate	2.07 (5.12)	0.77	0.07-52.50	0.10	11.93
Dimethyldithiophosphate	0.36 (1.20)	0.07	0.07-11.70	0.10	72.48
Dimethylphosphate	1.90 (3.42)	1.06	0.07-42.50	0.10	3.67
Dimethylthiophosphate	2.64 (3.74)	1.22	0.07-25.00	0.10	5.05
Diethylthiophosphate	1.16 (4.54)	0.33	0.07-58.20	0.10	18.35
Chemical Class: Pyrethroid Insecticide					
4-fluoro-3-phenoxybenzoic acid	0.07 (0.02)	0.07	0.07-0.29	0.10	98.17
3-phenoxybenzoic acid	1.47 (3.88)	0.71	0.07-50.70	0.10	15.14
trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid	1.63 (3.32)	0.42	0.42-27.20	0.60	60.55

*LOD = Limit of Detection.

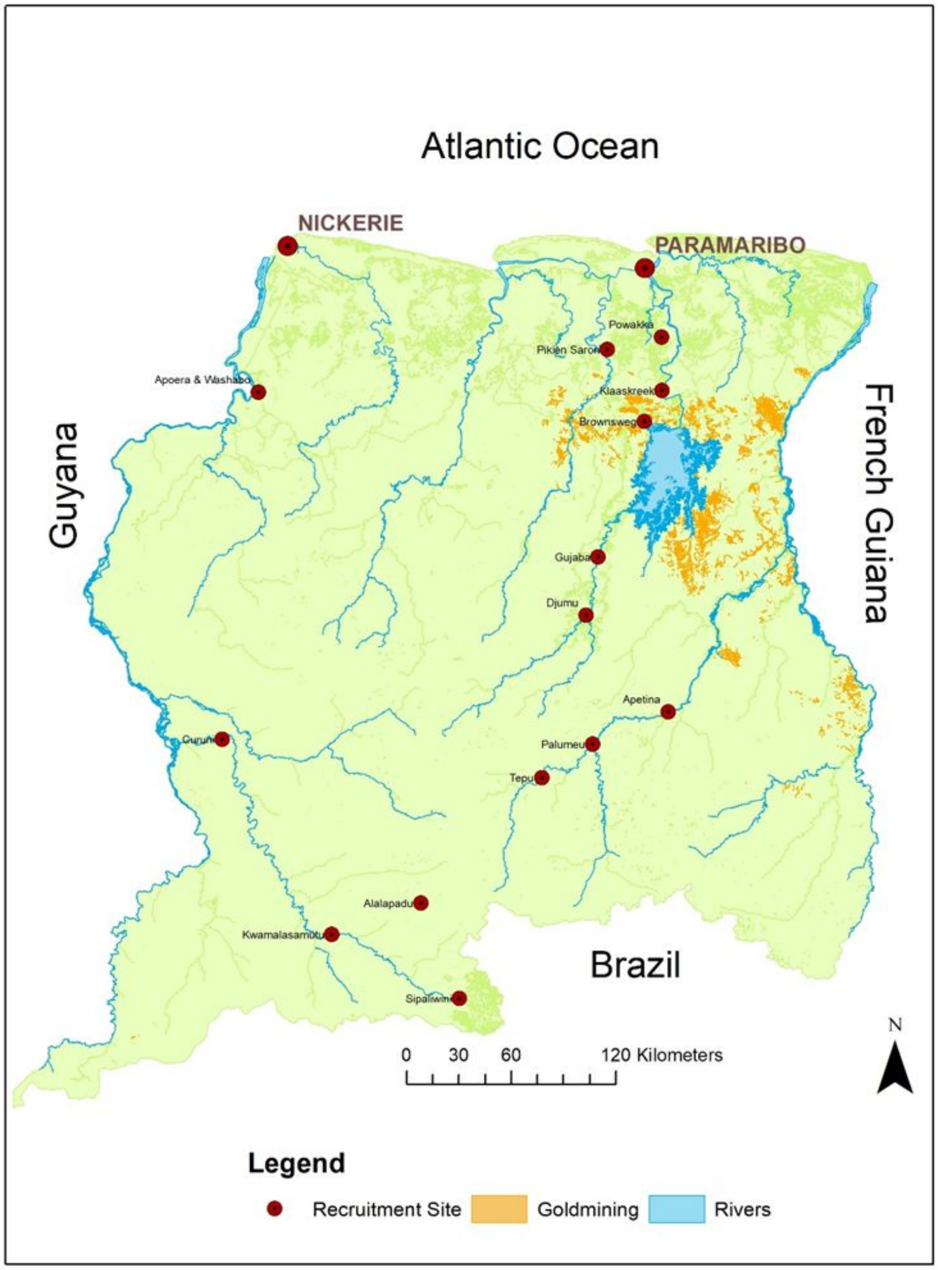

Figure 1. CCREOH-MeKiTamara study area with recruitment sites from three regions of Suriname: 1) the capital Paramaribo 2) Nickerie, the major rice-producing region in western Suriname and 3) the tropical rainforest interior where mercury is used in artisanal gold mining.

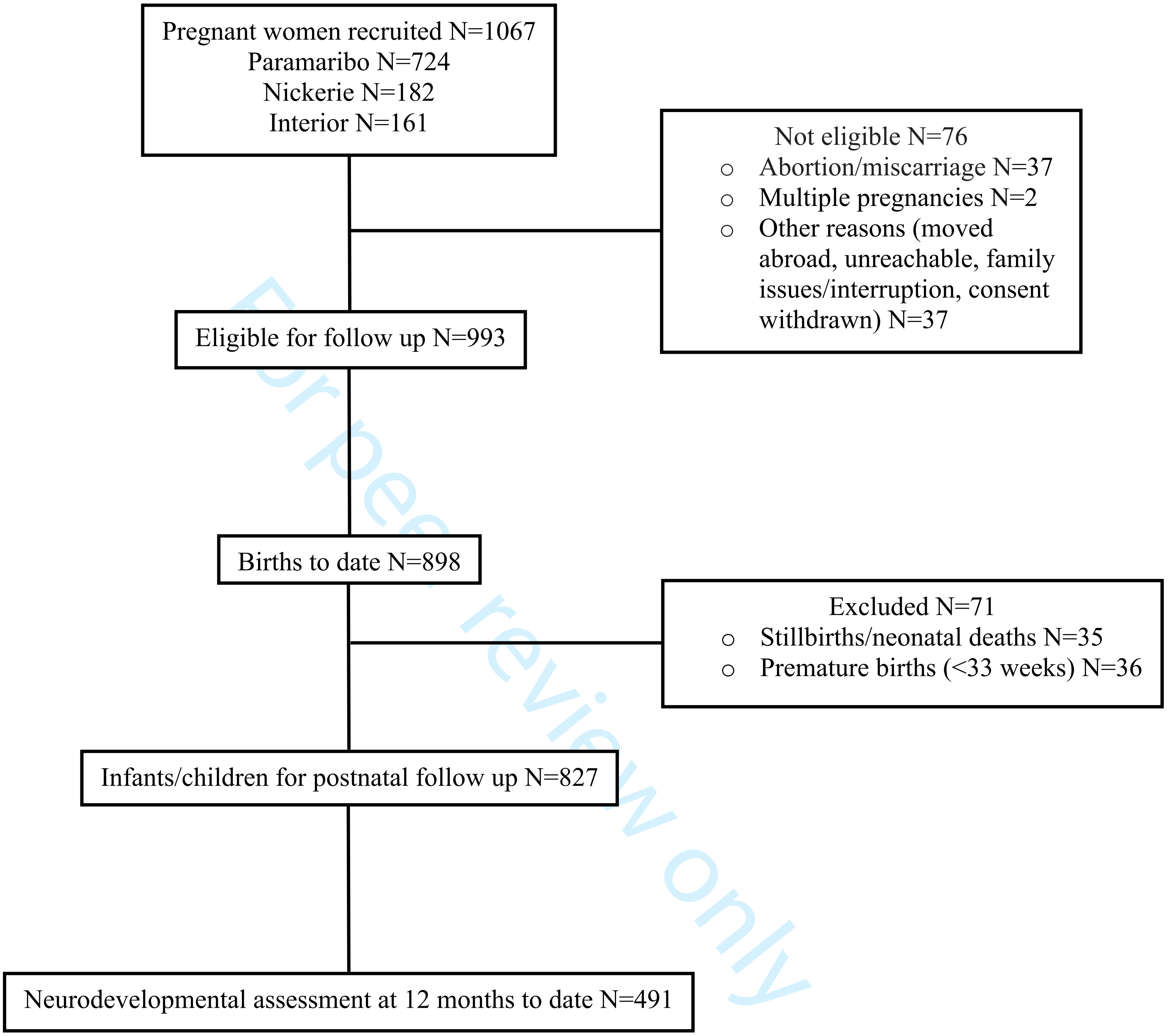
Pregnant women recruited N=1067
Paramaribo N=724
Nickerie N=182
Interior N=161
Not eligible N=76
Abortion/miscarriage N=37
Multiple pregnancies N=2
Other reasons (moved abroad, unreachable, family issues/interruption, consent withdrawn) N=37
Eligible for follow up N=993
Births to date N=898
Excluded N=71
Stillbirths/neonatal deaths N=35
Premature births (<33 weeks) N=36
Infants/children for postnatal follow up N=827
Neurodevelopmental assessment at 12 months to date N=491

Figure 2. Flowchart with participant enrolment.

BMJ Open

Cohort profile: The Caribbean Consortium for Research in Environmental and Occupational Health (CCREOH) MeKiTamara 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 (CCREOH) MeKiTamara prospective environmental epidemiologic cohort study addresses the potential adverse impact of complex chemical and non-chemical environmental exposures in 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 the child cohort. Environmental assessments include fish, produce, and rice.

Participants: From December 2016 to date, 1067 pregnant women and 827 babies were enrolled. Data collection occurs at seven study time points: twice during pregnancy and at birth, 12, 24, 36, and 48 months.

Findings to date: Four out of ten women, and predominantly those living in Suriname's interior, had hair mercury (Hg) levels exceeding values considered safe by international standards. Findings from a dietary survey indicated that 96.1% of women ate fish potentially contaminated with mercury 3-5 times per week, while 89% frequently consumed a vegetable called tannia, samples of which showed the presence of worldwide banned pesticides. One in four pregnant study participants had high Edinburgh Postnatal Depression Scale scores indicative of probable depression.

Future plans: Total blood mercury concentrations were elevated in interior women for whom fish consumption is the primary source of mercury exposure. Culturally tailored fish consumption advisories are in development. Research is ongoing to examine effects of potentially beneficial neuroprotective factors in fish that may counter neurotoxic effects of mercury. A pesticide literacy assessment in pregnant Surinamese women is in progress. Long-term effects of exposures to toxicant mixtures in infants/toddlers are being evaluated through pediatric neurodevelopmental assessments up to four years of age. Telomere length measurements of the mothers and children as an indicator of prenatal exposure to environmental toxins are ongoing, as are the analyses of biospecimen samples.

Keywords environmental exposures, mercury, metal mixtures, pregnant women, pediatric neurodevelopment, Suriname

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Strengths and limitations of this study

- The study addresses two high priority public health threats in Suriname and neighboring 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 12,000 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=200) was logistically difficult to reach, resulting in delayed recruitment, data collection and transport of cord blood specimens. Additional team support onsite resulted in 100% recruitment of the subcohort, and heel prick sampling replaced cord blood collection at birth.

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 [1]. Exposure to environmental contaminants at levels of public health concern may adversely affect pregnancy, and pre- and postnatal health in multiple ways: miscarriage, preterm delivery, intra-uterine growth retardation, congenital anomalies, and behavioral and physical consequences in later developmental stages [2, 3, 4]. Prenatal exposure to multiple heavy metals is associated with adverse pediatric health outcomes [5]. Pesticide exposure has been linked to fetal growth decrements and preterm birth, and there is mounting evidence that exposure to pesticides during pre- and postnatal development is associated with neurodevelopmental deficits in young children [6-10]. Exposure to contaminant mixtures can exacerbate adverse health effects: e.g. lead (Pb), arsenic (As), and mercury (Hg) can potentiate each other's toxicity, even at individual levels below concentration expected to result in adverse effects [11]. Despite this knowledge, no cumulative risk assessments have been conducted to date addressing exposures to contaminant mixtures in Caribbean Low- and Middle-Income Countries [12]. Furthermore, a paucity of studies examined the interactive impact of exposures to chemical and non-chemical (psychosocial) stressors.

The CCREOH-MeKiTamara (MeKiTamara means "making a mother and child's tomorrow'' in Suriname's local language) environmental epidemiology cohort study fills this gap by exploring the impact of exposures to organic and inorganic neurotoxicants, including Hg, Pb 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 [13-16]. 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, Pb, cadmium (Cd), aluminum (Al), iron (Fe), manganese (Mn), tin (Tn), selenium (Se) and selected pesticides through comprehensive dietary and environmental risk assessments, and biomarker monitoring in Surinamese pregnant women and their offspring;
- Assess the 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 on birth outcomes and their associations with environmental contaminants;
- Determine the association between prenatal, dietary, and environmental levels of elements and toxicants and possible 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. 90% of the population of 590,549 people live in the capital Paramaribo and the coastal area. The remainder live in the tropical rainforest interior (90% of the landmass). Suriname's multi-ethnic population consists of five main groups: Hindustani (27%), Tribal (22%), Creole (16%), Javanese (14%), and Indigenous (4%) [17].

Recruitment

The MeKiTamara study enrolled mother/child dyads potentially exposed to complex environmental chemical- and non-chemical stressors. This study was approved by the Institutional Review Boards of both the Government of Suriname and Tulane University to consent 1200 pregnant women and their singleton birth children. Pregnant women 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 (Figure 1) [18].

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 community health workers (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 time point 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 16 and 17 years of age.

Infants were not eligible for follow-up if they were born <33 completed weeks of gestation and/or had a birthweight <2000 grams, 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, hemoglobin, liver and kidney function, fetal and postnatal growth characteristics and health status, heavy metals (blood and hair), pesticides (urine), telomere length (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, 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; behavior 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 health care system utilization on prenatal health and birth outcomes.

Data management & 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 REDCap, which serves as the study electronic, integrated data management system [19]. Data collected through iPads by the field team 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 cross-checks with original data files and medical records. A comprehensive biospecimen tracking system tracks analyzed samples and the study's overall biospecimen repository. Communication of data updates and changes in the process are delivered through emails as well as during bimonthly meetings of the data management team. The data management platform allows for the interrogation of environmental, non-biospecimen and biospecimen data in an integrated fashion to facilitate scientific inquiries associated with the impact of exposures to complex mixtures of chemical and non-chemical stressors on pregnancy, birth outcomes and neurodevelopment.

The data management team develops de-identifies data files upon request of CCREOH investigators as specified by a standardized data request form. Statistical analyses are tailored to the specific research question. Frequency analyses are used for descriptive statistics and presented as means with standard deviations or median with interquartile range for continuous variables and proportions for categorical variables. Associations between categorical variables are studied using crosstabs; bivariate linear and logistic regression models are computed to study crude and independent associations, respectively. Comparison between study sites will primarily be analyzed by comparing participants, but can also be clustered depending on the research question.

Data Collection

Maternal data were collected during pregnancy at two timepoints (trimester 1 or 2, and 3). Post-partum assessments are ongoing and target both mothers and children: biomarker and questionnaire data are collected from mothers during the child's neurodevelopmental testing at 12, 24, 36, and 48 months. (Table 1).

Data collection during pregnancy

Questionnaires

Table 1 provides a list of standardized validated questionnaires to assess both physiological and psychosocial prenatal health. 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 behavior, access to prenatal care, social status and diet. Questions on health behavior were adapted from the Alcohol, Smoking and Substance Involvement Screening Test version 3 (ASSIST V3.0) that was developed for the World Health Organization (WHO). Information on maternal diet was obtained by adapting the 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.

Biospecimen collection

The study's biospecimen repository, housed at the Academic Hospital Paramaribo's (AZP) clinical laboratory, contains 12,000 samples. 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 were stored at 4°C for no more than 48 hours prior to delivery and processing at the Academic Hospital Paramaribo clinical laboratory. Blood, serum, plasma, and cord blood samples were aliquoted into 2 ml plastic freezer tubes and stored at -80°C.

400 frozen 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 (%RPD) limits.

In these 400 maternal whole blood samples (200 Paramaribo, 100 Nickerie, and 100 interior communities), we analyzed Pb, Hg, Cd, Al, Mn, Tn, Se, and Fe using inductively coupled plasma-mass spectrometry (ICP-MS) or cold vapor atomic fluorescence spectrometry (CVAFS). Total Hg and methylmercury using CVAFS was assessed in a small subset of women (20-Paramaribo, 20-Nickerie, and 35-interior) to specify exposure sources.

Maternal hair samples were taken according to the following protocol: 1.5 gram 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 (NZCS/CMO) for total mercury analysis using Cold Vapour Atomic Absorption Spectrometry (CVAAS).

Urine collection for pesticides analyses

Urine samples from pregnant women were analyzed (subcohort N=218) from all three study sites. Urine samples were aliquoted into 10 ml plastic tubes, stored at -20°C and shipped for analysis by CDC's environmental health laboratory using well-established protocols. The six dialkylphosphate metabolites were measured using a modified method of Jayatilaka et al. [20] by solid phase extraction high performance liquid chromatography-tandem mass spectrometry1. The eight specific urinary metabolites were analyzed using a semi-automated solid phase extraction mass spectrometry method and reversed-phase high performance liquid chromatography [21]. The analysis panel consisted of dialkylphosphate metabolites of organophosphate pesticides (DAP's) including dimethylphosphate, diethylphosphate, dimethylthiophosphate, dimethyldithiophosphate, diethylthiophosphate, and diethyldithiophosphate, and a universal panel (UP) including 1 herbicide (2,4D) and its metabolite, 2,4-dichlorophenoxyacetic acid; 4 OP insecticide metabolites (3,5,6-trichloro-2-pyridinol,2-isopropyl-4-methyl-6-hydroxypyrimidine,para-nitrophenol, malathion dicarboxylic acid) and 3 pyrethroid metabolites (4-fluoro-3-phenoxybenzoic acid, 3-phenoxybenzoic acid, 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. In case a cord blood sample was not available, a blood sample was taken by heel prick shortly after birth. Baseline characteristics of all live births (e.g. 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 blood sample is taken for heavy metal measurement. In addition, the child's health status is obtained through questionnaires on diet and history of infectious diseases, and respiratory and neurological disorders.

Buccal swab collection for telomere assessments

Evidence exists that telomere length (TL) is a marker of cellular aging and links TL to negative health outcomes including diabetes, cardiovascular disease and cognitive decline with aging. Oxidative stress and DNA methylation, among other factors, influence TL. As and pesticide exposure have both been linked to altered DNA methylation, while evidence also suggests a link between Hg and elevated oxidative stress [22-26]. TL may reflect multiple biological pathways through which environmental toxins influence child health and development and potentially may be an earlier indicator of exposure. Buccal swabs are collected to extract DNA and analyze TL prenatally in mothers and in children at 12, 24, 36, and 48 months of age. 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 CFX96 [27].

Behavior and cognitive development

Neurodevelopmental assessments include infant cognitive and motor development and behavior at 12- 27 months using the Bayley Scales of Infant Development as well as an assessment of cognitive and social-emotional development at 36 months, and measurement of executive function at 48 months (Table 1). The Bayley assessment was administered by a team of trained psychologists, psychiatrists, and members of the study team specifically trained to administer the test. Data checking following data entry of each Bayley sub-scale is being conducted by other team members. Administration of Bayley assessments will be completed by May 2020. Assessments at 36 and 48 months will take place as the cohort ages.

Patient and public involvement

The CCREOH/ MeKiTamara cohort study was preceded by a planning grant which included a pilot fish assessment study as well as an initial hair mercury assessment among communities in the interior which required approval from the village Chiefs or Tribal captains. This community engagement component provided us a rich foundation to build on as we developed the research questions. The initial study design was revised based on guidance from an External Scientific Advisory Board (EAB) and a multi-stakeholder Community Advisory Board (CAB). For example, the CAB was instrumental in urging the study team to lower the inclusion age to 16 years since many women in the interior conceive at an earlier age. The CAB consists of respected leaders representing organizations 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 the study progress and results, and to seek advice on future directions and dissemination of results.

Dissemination of study results

The study team is actively working with the EAB and the CAB on a collaborative translation and dissemination strategy of overall study results. However, every participant with neurotoxicant levels of imminent public health concern is contacted by the study coordinator and asked to repeat the test for confirmation. If the level remains of concern, the participant is referred to her attending physician according to the study's formal health care provider referral protocol. Children that are found to have a neurodevelopmental delay are referred to a child psychologist for further evaluation. Participants and the general public were invited to multiple health fairs, meetings and conferences, where the researchers discussed the study in a broader context, provided updates on the latest results and answered questions. Additionally, a Facebook page was created for study participants and others interested in this study, with general information on exposure to heavy metals and pesticides as well as the opportunity to ask questions of the research team and provide feedback about the study. Periodic briefings were also provided to officials of the Suriname's Ministry of Health. CCREOH data have been presented at multiple local, 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 convened by the US NIH.

Findings to date

From December 2016 until December 2018, 1067 pregnant women were enrolled; 76 (7.1%) were ineligible (Figure 2). In comparison to 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 of age, ethnic distribution was representative of the Surinamese population, and more than half had no or lower vocational/secondary education level.

Of the 898 babies born, 827 were enrolled (92%). Initial neurodevelopmental assessments using the Bayley instrument at 12-27 months in 824 infants are being analyzed. To date, the total number of biospecimens collected from 1067 pregnant women include whole blood for trace elements (N=1994), whole blood collected in K2EDTA 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). Cord blood (N=441), blood from heel prick (N=269), and buccal swabs (N=363) have been collected from 710 infants. All samples not yet analyzed are archived for future targeted and untargeted analyses. Available results include total mercury concentrations in hair from pregnant women, prenatal maternal depression and perceived stress, level of pesticides in produce, and dietary exposure to Hg in fish. Results of heavy metals in blood, urinary pecticide metabolites, telomere analysis, and neurodevelopmental assessments are pending.

Biological specimens

Total hair Hg was measured in 876 pregnant women from all three study sites. Overall, 39.1% of the women had elevated total mercury hair levels that exceeded the U.S. Environmental Protection Agency's (US EPA) action level [28]. For women from the interior, Nickerie and Paramaribo these percentages were 95.8%, 26.3%, and 25.5% respectively. Results for median total Hg concentrations in hair from pregnant women from Paramaribo (N=522) were 0.64 µg/g hair (interquartile ranges (IQR) 0.36-1.09; range 0.00-7.12), from Nickerie (N=176) 0.73 µg/g (IQR 0.45-1.05; 0.00-5.79) and the interior (N=178) 1.92 µg/g (IQR 1.92-7.39; 0.38-18.20). Pregnant women from the interior were exposed to high levels of Hg compared to 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 [18,29]. Other possible sources of exposure may include active participation in or living very close to gold mining areas.

Prenatal depression and perceived stress

Depression and prenatal stress in 722 participants were assessed using the standardized Edinburgh Postnatal Depression Scale (EPDS) (cut off ≥12 for probable depression) and Cohen Perceived Stress Scale (cut off ≥20 for high stress) respectively. One in four (24.9%) pregnant study participants had EPDS scores indicative of probable depression. Three in ten participants had high stress levels and nearly half of these women had probable depression.

Dietary exposure to pesticides

An assessment of Surinamese agricultural produce conducted by members of our study team found pesticide residues exceeding European Union maximum residue limits, including prohibited-worldwide endosulfan and lindane in the leafy vegetable tannia, *Xanthosoma brasiliense* [30]. An interviewer-assisted NHANES-based dietary survey of 522 participants showed that 98.2% of women reported consumption of leafy vegetables. Tannia was the most frequently consumed (89.3%); 36.5% of surveyed women had high intake rates of tannia (≥36 gram/day) [31]. Tannia is also a commonly used vegetable in baby food preparation in Suriname.

Dietary exposure to Hg in fish

One in four pregnant women in our cohort, and predominantly those living in the interior who rely heavily on local freshwater fish, have hair mercury levels exceeding those considered safe by the US EPA and the World Health Organization (WHO). The dietary questionnaire (n=990) showed overall fish consumption of 96.1%. Previous environmental assessments of most frequently consumed carnivorous fish by interior participants, specifically *Hoplias aimara*, *Serrasalmus rhombeus*, and *Cichla ocellaris*, showed high levels of Hg [29]. Respective consumption of these three carnivorous species was 44.4%, 19.3%, and 26.3%. Carnivorous fish consumption was greater among the subcohort (N=123) living in the interior: 89.4%, 67.5%, and 74.8%, respectively.

Polyunsaturated omega-3 fatty acids (PUFA-3) docosahexaenoic acid and eicosapentaenoic acid from fish consumption offer neuroprotective benefits during prenatal and pediatric development which could potentially counteract mercury neurotoxicity. 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: 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 eicosapentaenoic acid (0.8 vs. 1.9 mg/g) compared to marine species. Frequent consumption of *Hoplias aimara*, a freshwater fish with high Hg and low PUFA-3 content, is likely to increase mercury exposure whereas consumption of *Plagioscion* *squamosissimus*, a freshwater fish with high mercury and high PUFA-3, may have nutritional benefits that outweigh mercury neurotoxicity. While freshwater species are a good source of these nutrients, corresponding mercury content must be assessed and considered as well.

Strengths and limitations

The CCREOH-MeKiTamara environmental epidemiologic study is the first to examine the potential impact of complex environmental exposures on maternal and child health in Suriname by a multi-disciplinary team of research scientists. The 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 with children until 48 months with built-in timepoints to assess neurodevelopmental outcomes; and 4) a biospecimen bank of approximately 12,000 samples, providing the opportunity for future analyses within the cohort. 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. Research dissemination throughout the Caribbean region is implemented in collaboration with CARPHA.

The study team overcame two initial logistical challenges: 1) delayed recruitment and data collection of the logistically difficult to reach subcohort in the interior region (N=200) was ameliorated by additional team support onsite; and 2) delays in transporting interior biospecimens rendered some early cord blood specimens not analyzable was corrected by collecting an additional heelprick sample at birth.

Future plans

Culturally tailored fish consumption advisories are in development to reduce Hg exposure. Recent additional funding allows us to examine potentially beneficial neuroprotective factors such as selenium and dietary polyunsaturated fatty acids in fish that may counter the neurotoxic effects of mercury. To address the large scale and poorly regulated use of pesticides, we are also developing a pesticide literacy scale. Cohort-wide, we will undertake a comprehensive assessment of the neurodevelopmental outcomes of the children, and create a robust, sharable data management system of biospecimen and non-biospecimen data building on the current REDCap database.

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Collaborators

We welcome collaboration with fellow researchers working on similar projects. Specific research proposals can be sent directly to the Principal Investigators Drs. Wilco Zijlmans (cwrzijlmans@researchcentersuriname.org) 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.

Author Contributions

MYL, JKW, HHC, EWH, AS, SSD and WCWRZ designed and established the cohort. MSMO, ADHM, EWH and AG participated in the design of the questionnaires. WCWRZ, MSMO, EB, WBH, GKB, RR and MYL are responsible for the continued management of the cohort. AG, GKB, RR, AG and FAW are actively involved with recruitment of participants and collection of non-biospecimen data and biospecimens. JC, JR, PEO and GAL store, archive and analyze the biomarker samples. ADHM, AS, MSMO, AG, MYL and WCWRZ are responsible for data management. SSD, AWEG, RR and EB manage neurodevelopmental testing of babies. JKW, LFS, CSA, SSD interpret all results. WCWRZ, JKW, HHC and MYL 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

Obtained

Ethical approval

This study was 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.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

MeKiTamara cohort data will be made publicly available upon publication of the results in scientific articles. Questionnaire, registry and biospecimen data could be made accessible in de-identified form after an application process that includes submission of a research plan that will undergo evaluation by the CCREOH scientific board and relevant research ethics committees. Currently, data is partially available since data collection is ongoing.

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Table 1. Assessments completed by the CCREOH-MeKiTamara Cohort with timeline

Assessments	Trimester		Birth	12 mos	24 mos	36 mos	48 mos
	1st/2nd	3rd					
Mother							
Obstetric history	●	●					
Demographics	●						
Residency	●	●					
Anthropometrics	●	●					
Marital status	●						
Ethnicity	●						
Occupation	●						
Education	●						
Income	●						
Household composition	●						
Maternity care	●	●					
Questionnaires							
SF 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					●	●	●
Biological samples							
Hair	●						
Blood	●	●					
Urine	●	●					
Buccal swab	●						
At birth							
Mode of delivery			●				
Cord or heelprick blood sample			●				
Birth outcomes			●				
Child development							
Physical examination				●	●	●	●
Questionnaires							
General Health Questionnaire				●	●	●	●
M-CHAT						●	
Child Behavior Checklist						●	●
Bayley SEQ						●	
Ages and Stages Questionnaire						●	

Neurodevelopmental tests				
BSID-III	●			
CANTAB				●
Biological samples				
Buccal swab	●	●	●	●
Blood		●	●	●

Notes: ASSIST V3.0 = Alcohol, Smoking and Substance Involvement Screening Test Version 3, Subjective Social Status = MacArthur Scale of Subjective Social Status, M-CHAT = Modified Checklist for Autism in Toddlers, Bayley SEQ = Bayley Social Emotional Questionnaire, BSID-III = Bayley Scales of Infant Development Third Edition, CANTAB = Cambridge Neuropsychological Test Automated Battery.

Table 2. Distribution of maternal and infant characteristics

Maternal characteristics (N=1067)	N	%	Infant characteristics (N=898)	N	%
Age at intake			Gender		
16-19 years	133	12.4	Male	461	52.3
20-24 years	239	22.4	Female	421	47.7
25-29 years	280	26.2	Missing	16	1.8
30-34 years	252	23.6			
35-39 years	129	12.1	Birth status		
40+ years	34	3.2	Live birth	863	96.1
Missing	0	0.0	Stillbirth	35	3.9
			Missing	0	0.0
Parity					
0 previous live births	344	33.0	Birthweight		
1 previous live birth	298	28.6	Low birthweight (<2500 g)	113	12.9
2 previous live births	174	16.7	Normal birthweight (≥2500g)	760	87.1
3 previous live births	102	9.8	Missing	25	2.8
4+ previous live births	124	11.9			
Missing	25	2.3	Gestational age		
			Miscarriages	10	1.1
Ethnicity			Very preterm births (22+0-32+6 weeks)	36	4.1
Creole	245	23.0	Moderately preterm births (33+0-36+6 weeks)	93	10.7
Hindustani	222	20.8	Term births (≥37+0 weeks)	733	84.1
Indigenous	149	14.0	Missing	26	2.9
Javanese	94	8.8			
Tribal	223	20.9	Apgar score at 5 minutes		
Mixed	128	12.0	0 - 6	46	5.2
Other	5	0.5	7 - 10	832	94.8
Missing	1	0.1	Missing	20	2.2
Educational level					
No or primary	223	20.9			
Lower vocational/secondary	375	35.2			
Upper vocational/secondary	302	28.3			

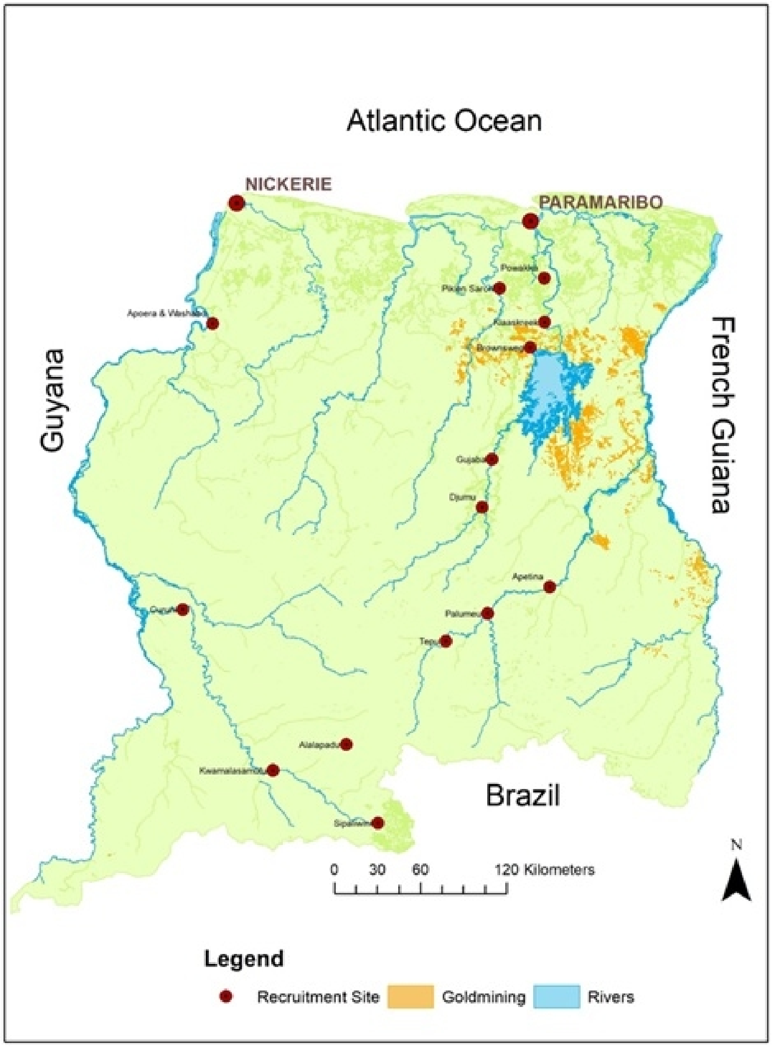
Tertiary	166	15.6
Missing	1	0.1
Household income SRD*		
<1500	321	33.2
1500-2999	330	34.1
3000-4999	210	21.7
5000+	106	11.0
Missing	100	9.4
Marital status		
Married or living with partner	922	86.8
Not married/not living with partner	140	13.2
Missing	5	0.5

* SRD = Surinamese dollar, equivalent to 0.13 USD.

Figure legends

Figure 1. CCREOH-MeKiTamara study area with recruitment sites from three regions of Suriname: 1) the capital Paramaribo 2) Nickerie, the major rice-producing region in western Suriname and 3) the tropical rainforest interior where mercury is used in artisanal gold mining.

Figure 2. Flowchart with participant enrolment.



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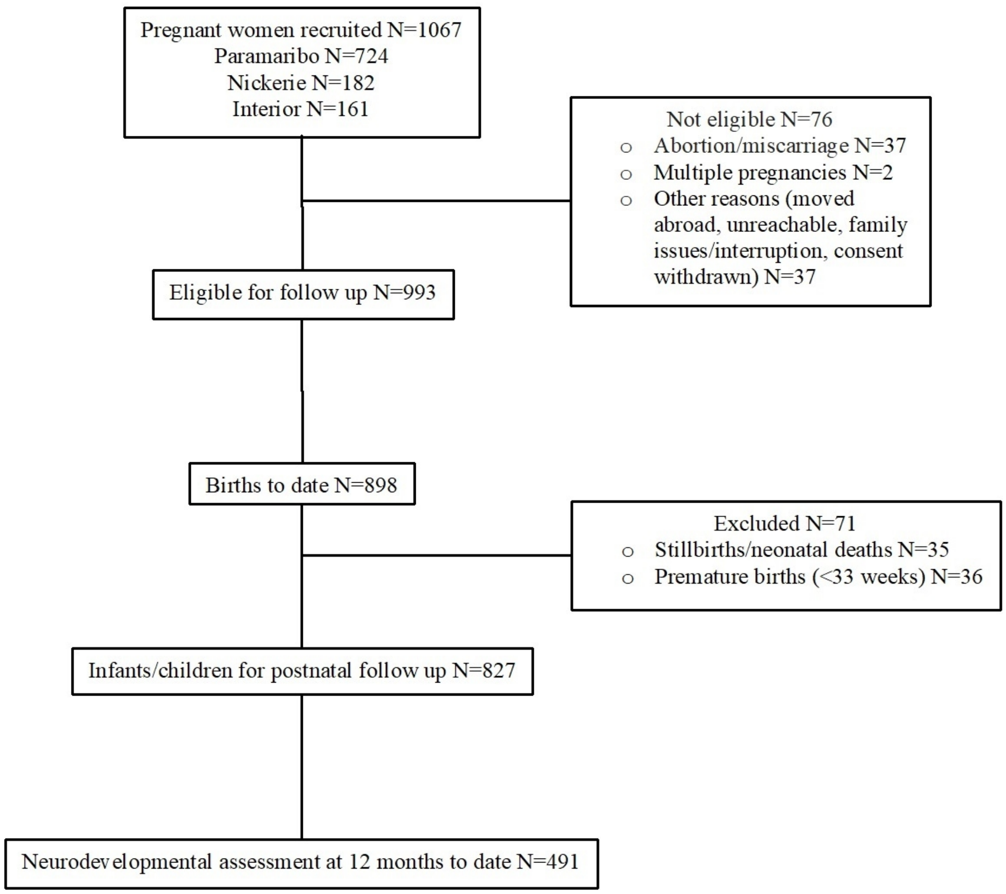

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Cohort profile: The Caribbean Consortium for Research in Environmental and Occupational Health (CCREOH) Cohort Study: Influences of complex environmental exposures on maternal and child health in Suriname

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Title: Cohort profile: The 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 (CCREOH) prospective environmental epidemiologic cohort study addresses the impact of complex chemical and non-chemical environmental exposures in 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 the child cohort.

Participants: From December 2016 until July 2019, biomarker data on hair, blood, urine, buccal swab and questionnaire data on physiological and psychosocial prenatal health were collected from 1143 enrolled pregnant women, neurodevelopmental assessments were completed in 832 of 992 eligible infants.

Findings to date: 39.1% of participants had hair mercury (Hg) levels exceeding values considered safe by international standards. Median Hg concentrations in women from Paramaribo (N=522) were 0.64µg/g hair (interquartile ranges (IQR) 0.36-1.09; range 0.00-7.12), from Nickerie (N=176) 0.73µg/g (IQR 0.45-1.05;0.00-5.79) and the interior (N=178) 3.48µg/g (IQR 1.92-7.39;0.38-18.20). 96.1% participants ate fish, respective consumption of the three most consumed carnivorous species *Hoplias aimara*, *Serrasalmus rhombeus*, and *Cichla ocellaris* was 44.4%, 19.3%, and 26.3%, and was greater among the interior subcohort: 89.4%, 67.5%, and 74.8% respectively; 89% frequently consumed the vegetable tannia, samples of which showed presence

of worldwide banned pesticides; 24.9% had high Edinburgh Postnatal Depression Scale scores indicative of probable depression.

Future plans: Culturally tailored fish consumption advisories are in development, especially relevant to interior women for whom fish consumption is the primary source of mercury exposure. Research is ongoing to examine effects of potentially beneficial neuroprotective factors in fish that may counter neurotoxic effects of mercury. A pesticide literacy assessment in pregnant Surinamese women is in progress. Long-term effects of exposures to toxicant mixtures in infants/toddlers are being evaluated through neurodevelopmental assessments. Telomere length measurements of the mothers and children as an indicator of prenatal exposure to environmental toxins are ongoing.

Keywords environmental exposures, mercury, metal mixtures, pregnant women, pediatric neurodevelopment, Suriname

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Strengths and limitations of this study

- The study addresses two high priority public health threats in Suriname and neighboring 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 sub-cohort (N=200) was logistically difficult to reach, resulting in delayed recruitment of some women in the second or early third trimester of pregnancy, data collection and transport of cord blood specimens. This may limit our ability to understand differential effects of exposure across gestation for the interior cohort; heel prick sampling replaced cord blood collection at birth.

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 [1]. Exposure to environmental contaminants at levels of public health concern may adversely affect pregnancy, and pre- and postnatal health in multiple ways: miscarriage, preterm delivery, intra-uterine growth retardation, congenital anomalies, and behavioral and physical consequences in later developmental stages [2, 3, 4]. Prenatal exposure to multiple heavy metals is associated with adverse pediatric health outcomes [5]. Pesticide exposure has been linked to fetal growth decrements and preterm birth, and there is mounting evidence that exposure to pesticides during pre- and postnatal development is associated with neurodevelopmental deficits in young children [6-10]. Exposure to contaminant mixtures can exacerbate adverse health effects: e.g. lead, arsenic, and mercury (Hg) can potentiate each other's toxicity, even at individual levels below concentration expected to result in adverse effects [11]. Despite this knowledge, no cumulative risk assessments have been conducted to date addressing exposures to contaminant mixtures in Caribbean Low- and Middle-Income Countries [12].

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 [13-16]. 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, aluminum, 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. 90% of the population of 590,549 people live in the capital Paramaribo and the coastal area. The remainder live in the tropical rainforest interior (90% of the landmass). Suriname's multi-ethnic population consists of five main groups: Hindustani (27%), Tribal (22%), Creole (16%), Javanese (14%), and Indigenous (4%) [17].

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 [18]. 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.

85% of all deliveries in Suriname are hospital-based, with the remainder (14%) taking place in primary health care 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 time point 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 birthweight less than 2000 grams, 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, hemoglobin, liver and kidney function, fetal and postnatal growth characteristics and health status, heavy metals (blood and hair), pesticides (urine), telomere length (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; behavior 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 health care system utilization on prenatal health and birth outcomes.

Data management & 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 REDCap, which serves as the study electronic, integrated data management system [19]. 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 cross-checks with original data files and medical records obtained through the general practitioner, midwife, health assistant or hospital administration. A comprehensive biospecimen tracking system tracks analyzed 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 to facilitate scientific inquiries associated with the impact of exposures to complex mixtures of chemical and non-chemical stressors on pregnancy, birth outcomes and neurodevelopment.

De-identified data files are developed upon request of CCREOH investigators through standardized data request forms; statistical analyses are tailored to the specific research question. Frequency analyses are used for descriptive statistics and presented as means with standard deviations or median with interquartile range for continuous variables and proportions for categorical variables. Associations between categorical variables are studied using crosstabs; bivariate linear and logistic regression models are computed to study crude and independent associations, respectively. Comparison between study sites will be analyzed by comparing participants, or clustered depending the research question.

Multiple logistic regression analysis will be used to develop predictive models for binomial and multinomial variables, multiple linear regression to develop predictive models for continuous outcome variables, and nonparametric methods if assumptions are not met. Sample size was calculated based on a multiple linear regression model using a coefficient of determination of 0.10 and a R-square differential of 0.02. Using these parameters, a number of 495 was needed to have an 80% power at a 0.05 level of significance. Multiple approaches to develop and compare models for multiple exposures to toxic metals will be used. In the first approach, we will use a Bayesian kernel machine regression, a nonparametric Bayesian variable selection framework that will allow us to explore joint (or combined) effects of the multiple chemicals. In the second approach, principal component analysis will be used to group correlated exposure variables using the principal component scores as the main exposure measures. Finally, we will use structural equation models to create latent constructs of similar exposure variables and then finding associations between these latent constructs and the outcome variable.

Data Collection

Maternal data were collected during pregnancy at two timepoints (first/second and third trimester). Post- partum assessments are ongoing and target both mothers and children: biomarker and questionnaire data are collected from mothers during the child's neurodevelopmental testing at 12, 36, and 48 months. (Table 1).

Data collection during pregnancy

Questionnaires

Table 1 provides a list of standardized validated questionnaires to assess both physiological and psychosocial prenatal health. All questionnaires were translated into Dutch and other local languages to address the multiple language needs of our interior sub-cohort. 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 behavior, access to prenatal care, social status and diet. Questions on health behavior were adapted from the Alcohol, Smoking and Substance Involvement Screening Test version 3 (ASSIST V3.0) that was developed for the World Health Organization (WHO). Information on maternal diet was obtained by adapting the 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.

Biospecimen collection

The study's biospecimen repository, housed at the Academic Hospital Paramaribo's (AZP) clinical laboratory, contains 13,000 samples. 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 were stored at 4°C for no more than 48 hours prior to delivery and processing at the Academic Hospital Paramaribo clinical laboratory. Blood, serum, plasma, and cord blood samples were aliquoted into 2 ml plastic freezer tubes and stored at -80°C.

400 frozen 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 (%RPD) limits.

In these 400 maternal whole blood samples (200 Paramaribo, 100 Nickerie, and 100 interior communities), we analyzed Hg, lead, cadmium, aluminum, manganese, tin, selenium and iron using inductively coupled plasma-mass spectrometry (ICP-MS) or cold vapor 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.

Maternal hair samples were taken according to the following protocol: 1.5 gram 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 (NZCS/CMO) for total mercury analysis using Cold Vapour Atomic Absorption Spectrometry (CVAAS).

Urine collection for pesticides analyses

Urine samples from pregnant women were analyzed (sub-cohort N=218) from all three study sites. Urine samples were aliquoted into 10 ml plastic tubes, stored at -20°C and shipped for analysis by CDC's environmental health laboratory using well-established protocols. The six dialkylphosphate metabolites were measured using a modified method of Jayatilaka et al. [20] by solid phase extraction high performance liquid chromatography-tandem mass spectrometry1. The eight specific urinary metabolites were analyzed using a semi-automated solid phase extraction mass spectrometry method and reversed-phase high performance liquid chromatography [21]. The analysis panel consisted of dialkylphosphate metabolites of organophosphate pesticides (DAP's) including dimethylphosphate, diethylphosphate, dimethylthiophosphate, dimethyldithiophosphate, diethylthiophosphate, and diethyldithiophosphate, and a universal panel (UP) including 1 herbicide (2,4D) and its metabolite, 2,4-dichlorophenoxyacetic acid; 4 OP insecticide metabolites (3,5,6-trichloro-2-pyridinol,2-isopropyl-4-methyl-6-hydroxypyrimidine, para-nitrophenol, malathion dicarboxylic acid) and 3 pyrethroid metabolites (4-fluoro-3-phenoxybenzoic acid, 3-phenoxybenzoic acid, 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. In case a cord blood sample was not available, a blood sample was taken by heel prick shortly after birth. Baseline characteristics of all births (e.g. 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 blood sample is taken for heavy metal measurement. In addition, the child's health status is obtained through questionnaires on diet and history of infectious diseases, and respiratory and neurological disorders.

Buccal swab collection for telomere assessments

Isohelix SK1 buccal swabs (Cell Projects, Kent, United Kingdom) were used for the collection of maternal and infant DNA for telomere length (TL) analyses. Swabs were air dried and then stored with a dessicator pellet at 4 degrees until DNA is extracted. DNA is extracted using the QIAamp DNA mini kit protocol (Qiagen, Valencia, CA) and stored at −80°C until assayed. Concentration of dsDNA is quantified with a Qubit dsDNA BR assay kit (Invitrogen, Carlsbad, CA), purity of the DNA is determined by using a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA), and DNA integrity is confirmed by gel electrophoresis to ensure high molecular weight DNA [22]. 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 CFX96 [23]. All samples are run in triplicate on duplicate plates with a standard curve and known controls.

Behavior and cognitive development

Neurodevelopmental assessments include infant cognitive and motor development and behavior at 12-27 months using the Bayley Scales of Infant Development as well as an assessment of cognitive and social-emotional development at 36 months, and measurement of executive function at 48 months (Table 1). The Bayley assessment was administered by a team of trained psychologists, psychiatrists, and members of the study team specifically trained to administer the test. Data checking following data entry of each Bayley sub-scale is being conducted by other team members. Administration of Bayley assessments will be completed by July 2020. Assessments at 36 and 48 months will take place as the cohort ages.

Data collection from fish

Previous assessments of carnivorous fish from different regions in the interior of Suriname showed high levels of Hg, specifically the frequently consumed species *Hoplias aimara* (0.43-0.66ug/g) and *Serrasalmus rhombeus* (0.23-1.38ug/g). These levels are well above international accepted standards and in certain regions, up to 7 times the norm for human consumption [24]. Polyunsaturated omega-3 fatty acids (PUFA-3) docosahexaenoic acid and eicosapentaenoic acid from fish consumption offer neuroprotective benefits during prenatal and pediatric development which could potentially counteract mercury neurotoxicity [25-27]. 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.

Patient and public involvement

The CCREOH cohort study was preceded by a planning grant which included a pilot fish assessment study as well as an initial hair mercury assessment among communities in the interior which required approval from the village Chiefs or Tribal captains. This community engagement component provided us a rich foundation to build on as we developed the research questions. The initial study design was revised based on guidance from an External Scientific Advisory Board (EAB) and a multi-stakeholder Community Advisory Board (CAB). The CAB consists of respected leaders representing organizations 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 the study progress and results, and to seek advice on future directions and dissemination of results.

Dissemination of study results

The study team is actively working with the EAB and CAB on a collaborative translation and dissemination strategy of overall 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, where 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 convened by the US NIH.

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 to 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 of age, ethnic distribution was representative of the Surinamese population, and more than half had no or lower vocational/secondary education level.

Of the 1069 babies born, 992 were enrolled (93%) (Figure 1). Initial neurodevelopmental assessments using the Bayley instrument at 12-27 months in 832 infants are being analyzed. To date, the total number of biospecimens (N=13,379) collected from 1143 pregnant women include whole blood for trace elements (N=1994), whole blood collected in K2EDTA 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 cord blood (N=441), blood from heel prick (N=323), and buccal swabs (N=842). All samples not yet analyzed are archived for future targeted and untargeted analyses. Available results include total mercury concentrations in hair from pregnant women, prenatal maternal depression and perceived stress, level of pesticides in produce, and dietary exposure to Hg in fish. 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 three study sites. Overall, 39.1% had elevated total mercury hair levels that exceeded the U.S. Environmental Protection Agency's (USEPA) action level (1.1µg/g hair) [28]. For women from the interior, Nickerie and Paramaribo these percentages were 95.8%, 26.3%, and 25.5% respectively. Results for median total Hg concentrations in hair from pregnant women from Paramaribo (N=522) were 0.64µg/g hair (interquartile ranges (IQR) 0.36-1.09;range 0.00-7.12), from Nickerie (N=176) 0.73µg/g (IQR 0.45-1.05;0.00-5.79) and the interior (N=178) 3.48µg/g (IQR 1.92-7.39;0.38-18.20). Pregnant women from the interior were exposed to high levels of Hg compared to 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 [18,24]. Other possible sources of exposure may include active participation in or living very close to gold mining areas. Mercury concentrations from women residing in Paramaribo and Nickerie are similar to those found in other studies [29,30].

Prenatal depression and perceived stress

Depression and prenatal stress in 722 participants were assessed using the standardized Edinburgh Postnatal Depression Scale (EPDS) (cut-off ≥12 for probable depression) and Cohen Perceived Stress Scale (cut-off ≥20 for high perceived stress) respectively. One in four (24.9%) participants had EPDS 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 conducted by members of our study team found pesticide residues exceeding European Union maximum residue limits, including prohibited-worldwide endosulfan and lindane in the leafy vegetable tannia, *Xanthosoma brasiliense* [31]. 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 gram/day) [32]. 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%. Respective consumption in the total cohort of the three most consumed carnivorous species *Hoplias aimara*, *Serrasalmus rhombeus* and *Cichla ocellaris*, that are 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. These dietary assessments support our hypothesis that fish consumption is consistent with the Hg exposures. In addition, we have speciated Hg in blood and hair and found that the majority of Hg in these human samples is methylmercury which is consistent with fish consumption being the primary source of Hg exposure in our participants.

Measurements of fatty acids showed that freshwater species had higher levels of linoleic acid (2.0 vs. 0.2mg/g), alpha-linoleic acid (0.4 vs. 0.1mg/g), arachidonic acid (3.0 vs. 1.5mg/g), omega-6 fatty acids (6.5 vs. 2.3mg/g) and lower levels of eicosapentaenoic acid (0.8 vs. 1.9mg/g) compared to marine species.

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 multi-disciplinary team of research 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 with 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 within the cohort. 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 sub-cohort in the interior region (N=200) was ameliorated by additional team support onsite; delays in transporting interior biospecimens rendered some early cord blood specimens not analyzable 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. Some participants from the interior sub-cohort were recruited in the second or early third trimester because of the distance to prenatal clinics. This may limit our ability to understand differential effects of exposure across gestation for this sub-cohort.

Future plans

Culturally tailored fish consumption advisories are in development to reduce Hg exposure. Recent additional funding allows us to examine potentially beneficial neuroprotective factors such as selenium and dietary polyunsaturated fatty acids in fish that may counter the neurotoxic effects of mercury. To address the large scale and poorly regulated use of pesticides, we are also developing a pesticide literacy scale. Cohort-wide, we will undertake a comprehensive assessment of the neurodevelopmental outcomes of the children, and create a robust, sharable data management system of biospecimen and non-biospecimen data building on the current REDCap database.

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Collaborators

We welcome collaboration with fellow researchers working on similar projects. Specific research proposals can be sent directly to the Principal Investigators Drs. Wilco Zijlmans (cwrzijlmans@researchcentersuriname.org) 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.

Author Contributions

MYL, JKW, HHC, EWH, AS, SSD and WCWRZ designed and established the cohort. MSMO, ADHM, EWH, FAW and AG participated in the design of the questionnaires. WCWRZ, MSMO, EB, WBH, GKB, RR and MYL are responsible for the continued management of the cohort. GKB, RR, AG and FAW are actively involved with recruitment of participants and collection of non-biospecimen data and biospecimens. JC, JR, PEO and GAL store, archive and analyze the biomarker samples. ADHM, AS, MSMO, AG, MYL and WCWRZ are responsible for data management. SSD, AWEG, RR and EB manage neurodevelopmental testing of babies. JKW, LFS, CSA, SSD interpret all results. WCWRZ, JKW, HHC, ADHM and MYL 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

Obtained

Ethical approval

This study was 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.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

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 de-identified form after an application process that includes submission of a research plan. We are currently collaborating with Research Triangle Institute International (RTI), 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 PIs. Such requests will be discussed with the full investigator Committee, the Data Management Committee, and the Administrative Oversight Committee.

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Table 1. Assessments completed by the CCREOH-MeKiTamara Cohort with timeline

Assessments	Trimester 1st/2nd	Trimester 3rd	Birth	12 mos	36 mos	48 mos
Mother						
Obstetric history	●	●				
Demographics	●					
Residency	●	●				
Anthropometrics	●	●				
Marital status	●					
Ethnicity	●					
Occupation	●					
Education	●					
Household income	●					
Household composition	●					
Maternity care	●	●				
Medication		●				
Questionnaires						
SF 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					●	●
Biological samples						
Hair	●					
Blood	●	●				
Urine	●	●				
Buccal swab	●					
At birth						
Mode of delivery			●			
Cord or heelprick blood sample			●			
Birth outcomes			●			
Child development						
Physical examination				●	●	●
Questionnaires						
Generation R				●	●	●
M-CHAT					●	
Child Behavior Checklist					●	●
Bayley SEQ					●	

Ages and Stages Questionnaire		●	
Neurodevelopmental tests			
BSID-III	●		
CANTAB			●
Biological samples			
Buccal swab	●	●	●
Blood		●	●

Notes: ASSIST V3.0 = Alcohol, Smoking and Substance Involvement Screening Test Version 3, Subjective Social Status = MacArthur Scale of Subjective Social Status, M-CHAT = Modified Checklist for Autism in Toddlers, 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 pediatric health and diet history (with permission from The Generation R Study Group)

Table 2. Distribution of maternal and infant characteristics

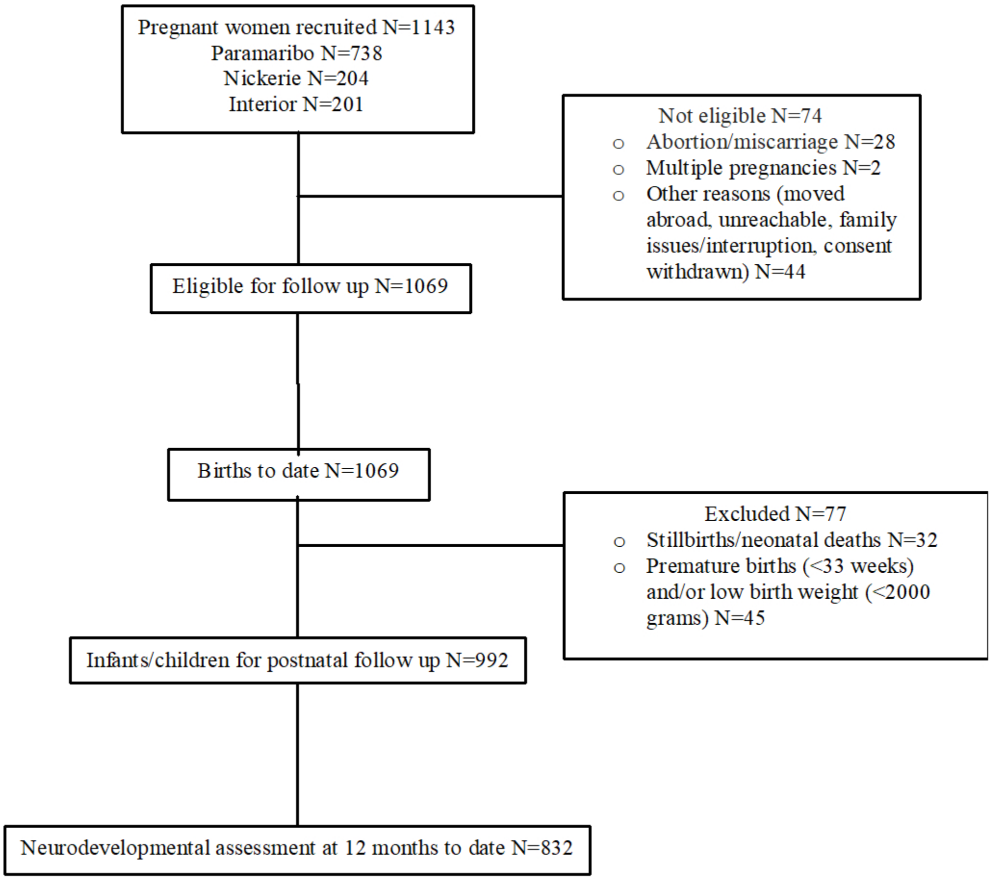
Maternal characteristics (N=1143)	N	%	Infant characteristics (N=971)	N	%
Age at intake			Gender		
16-19 years	142	12.6	Male	510	52.5
20-24 years	260	22.8	Female	457	47.1
25-29 years	291	25.5	Missing	4	0.4
30-34 years	268	23.5			
35-39 years	140	12.3	Birth status		
40+ years	39	3.4	Live birth	947	97.5
Missing	1	0.1	Stillbirth	23	2.4
			Missing	1	0.1
Parity					
0 previous live births	384	33.7	Birthweight (in grams)		
1 previous live birth	312	27.3	Low birthweight (<2500)	127	13.1
2 previous live births	187	16.4	Normal birthweight (≥2500)	835	86.0
3 previous live births	112	9.8	Missing	9	0.9
4+ previous live births	146	12.8			
Missing	2	0.2	Gestational age (in weeks)		
			Very preterm births (22+0-32+6)	39	4.0
Ethnicity			Moderately preterm births (33+0-36+6)	107	11.0
Creole	249	21.8	Term births (≥37+0)	817	84.1
Hindustani	233	20.4	Missing	8	0.8
Indigenous	155	13.6			
Javanese	101	8.8	Apgar score at 5 minutes		
Tribal	271	23.7	0 - 6	31	3.2
Mixed	127	11.1	7 - 10	918	94.5
Other	7	0.6	Missing	22	2.3
Missing	0	0.0			
Educational level					
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
Household income SRD*		
<1500	401	35.1
1500-2999	362	33.0
3000-4999	221	20.2
5000+	112	9.8
Missing	47	4.1
Marital status		
Married or living with partner	1000	87.6
Not married/not living with partner	141	12.4
Missing	2	0.2

* SRD = Surinamese dollar, equivalent to 0.13 USD.

Figure legends

Figure 1. Flowchart with participant enrolment.


Pregnant women recruited N=1143
Paramaribo N=738
Nickerie N=204
Interior N=201
Not eligible N=74
Abortion/miscarriage N=28
Multiple pregnancies N=2
Other reasons (moved abroad, unreachable, family issues/interruption, consent withdrawn) N=44
Eligible for follow up N=1069
Births to date N=1069
Excluded N=77
Stillbirths/neonatal deaths N=32
Premature births (<33 weeks) and/or low birth weight (<2000 grams) N=45
Infants/children for postnatal follow up N=992
Neurodevelopmental assessment at 12 months to date N=832

BMJ Open

Cohort profile: The 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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Title: Cohort profile: The 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 (CCREOH) prospective environmental epidemiologic cohort study addresses the impact of chemical and non-chemical environmental exposures in 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 analyzed. 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 0.64µg/g hair (interquartile ranges (IQR) 0.36-1.09; range 0.00-7.12), from Nickerie (N=176) 0.73µg/g (IQR 0.45-1.05;0.00-5.79) and the interior (N=178) 3.48µg/g (IQR 1.92-7.39;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%, 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 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.

Keywords environmental exposures, mercury, metal mixtures, pregnant women, pediatric neurodevelopment, Suriname

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Strengths and limitations of this study

- The study addresses two high priority public health threats in Suriname and neighboring 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 sub-cohort (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.

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 [1]. Exposure to environmental contaminants at levels of public health concern may adversely affect pregnancy, and pre- and postnatal health in multiple ways: miscarriage, preterm delivery, intra-uterine growth retardation, congenital anomalies, and behavioral and physical consequences in later developmental stages [2, 3, 4]. Prenatal exposure to multiple heavy metals is associated with adverse pediatric health outcomes [5]. Pesticide exposure has been linked to fetal growth decrements and preterm birth, and there is mounting evidence that exposure to pesticides during pre- and postnatal development is associated with neurodevelopmental deficits in young children [6-10]. Exposure to contaminant mixtures can exacerbate adverse health effects: e.g. lead, arsenic, and mercury (Hg) can potentiate each other's toxicity, even at individual levels below concentration expected to result in adverse effects [11]. Despite this knowledge, no cumulative risk assessments have been conducted to date addressing exposures to contaminant mixtures in Caribbean Low- and Middle-Income Countries [12].

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 [13-16]. 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, aluminum, 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. 90% of the 590,549 population lives in the capital Paramaribo and the coastal area. The remainder live in the tropical rainforest interior (90% of the landmass). Suriname's multi-ethnic population consists of five main groups: Hindustani (27%), Tribal (22%), Creole (16%), Javanese (14%), and Indigenous (4%) [17].

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 [18]. 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.

85% of all deliveries in Suriname are hospital-based, with the remainder (14%) taking place in primary health care 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 time point 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 birthweight less than 2000 grams, 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, hemoglobin, liver and kidney function, fetal and postnatal growth characteristics and health status, heavy metals (blood and hair), pesticides (urine), telomere length (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; behavior 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 health care system utilization on prenatal health and birth outcomes.

Data management & 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 REDCap, which serves as the study electronic, integrated data management system [19]. 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 cross-checks with original data files and medical records obtained through the general practitioner, midwife, health assistant or hospital administration. A comprehensive biospecimen tracking system tracks analyzed 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.

De-identified data files are developed upon request of CCREOH investigators through standardized 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 nonparametric methods if assumptions are not met. Comparison between study sites will be analyzed 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 nonparametric 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-square 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 square 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). Post-partum 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 standardized validated questionnaires used to assess both physiological and psychosocial prenatal health. All questionnaires were translated into Dutch and other local languages to address the multiple language needs of our interior sub-cohort. 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 behavior, access to prenatal care, social status and diet. Questions on health behavior were adapted from the Alcohol, Smoking and Substance Involvement Screening Test version 3

(ASSIST V3.0) that was developed for the World Health Organization (WHO). Information on maternal diet was obtained by adapting the 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.

Biospecimen collection

The study's biospecimen repository, housed at the Academic Hospital Paramaribo's (AZP) clinical laboratory, contains 13,000 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 no more than 48 hours prior to delivery and processing at the Academic Hospital Paramaribo clinical laboratory. Blood, serum, plasma, and cord blood samples are aliquoted into 2 ml plastic freezer tubes and stored at -80°C. Urine samples (60ml) 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 gram 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 (NZCS/CMO) for total Hg analysis using Cold Vapour Atomic Absorption Spectrometry (CVAAS).

Buccal swab collection for telomere assessments

Isohelix SK1 buccal swabs (Cell Projects, Kent, United Kingdom) are used for the collection of maternal DNA for telomere length (TL) analyses. Swabs are air dried and then stored with a dessicator pellet at 4 degrees until DNA is extracted. DNA is extracted using the QIAamp DNA mini kit protocol (Qiagen, Valencia, CA) and stored at −80°C until assayed. Concentration of dsDNA is quantified with a Qubit dsDNA BR assay kit (Invitrogen, Carlsbad, CA), purity of the DNA is determined by using a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA), and DNA integrity is confirmed by gel electrophoresis to ensure high molecular weight DNA [20]. 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 CFX96 [21]. All samples are run in triplicate on duplicate plates with a standard curve and known controls.

Trace element analyses in blood

400 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 (%RPD) limits. In these 400 blood samples (200 Paramaribo, 100 Nickerie, and 100 interior communities), we analyzed Hg, lead, cadmium, aluminum, manganese, tin, selenium and iron using inductively coupled plasma-mass spectrometry

(ICP-MS) or cold vapor 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 analyzed (sub-cohort N=218) from all three study sites. The six dialkylphosphate metabolites were measured using a modified method of Jayatilaka et al. [22] by solid phase extraction high performance liquid chromatography-tandem mass spectrometry1. The eight specific urinary metabolites were analyzed using a semi-automated solid phase extraction mass spectrometry method and reversed-phase high performance liquid chromatography [23]. The analysis panel consisted of dialkylphosphate metabolites of organophosphate pesticides (DAP's) including dimethylphosphate, diethylphosphate, dimethylthiophosphate, dimethyldithiophosphate, diethylthiophosphate, and diethyldithiophosphate, and a universal panel (UP) including 1 herbicide (2,4D) and its metabolite, 2,4-dichlorophenoxyacetic acid; 4 OP insecticide metabolites (3,5,6-trichloro-2-pyridinol,2-isopropyl-4-methyl-6-hydroxypyrimidine, para-nitrophenol, malathion dicarboxylic acid) and 3 pyrethroid metabolites (4-fluoro-3-phenoxybenzoic acid, 3-phenoxybenzoic acid, 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 (e.g. 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.

Behavior and cognitive development

Neurodevelopmental assessments over the lifetime of the study include infant cognitive and motor development and behavior 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 sub-scale 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* (0.43-0.66ug/g) and *Serrasalmus rhombeus* (0.23-1.38ug/g). These levels are well above international accepted standards and in certain regions, up to 7 times the norm for human consumption [24]. Polyunsaturated omega-3 fatty acids (PUFA-3) docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from fish consumption may offer neuroprotective benefits during prenatal and pediatric development which could potentially counteract mercury neurotoxicity [25-27]. 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 [28-31].

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. Levels of 27 fatty acids, including DHA and EPA, in fish muscle tissue were measured (expressed as mg fatty acid g^{-1} dry weight) by the University of Texas Marine Science Institute. 50mg dry weight samples were homogenized 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 Suplecowax 10 fused silica capillary column (Milipore Sigma). Freshwater species had higher levels of linoleic acid (2.0 vs. 0.2mg/g), alpha-linoleic acid (0.4 vs. 0.1mg/g), arachidonic acid (3.0 vs. 1.5mg/g), omega-6 fatty acids (6.5 vs. 2.3mg/g) and lower levels of eicosapentaenoic acid (0.8 vs. 1.9mg/g) compared to 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 multi-stakeholder Community Advisory Board (CAB) and an External Scientific Advisory Board (EAB). The CAB consists of respected leaders representing organizations 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, 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 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 to 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 include whole blood for trace elements (N=1994), whole blood collected in K2EDTA 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 analyzed 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. 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 three study sites. Overall, 39.1% had elevated total Hg hair levels that exceeded the U.S. Environmental Protection Agency's (USEPA) action level (1.1µg/g hair) [32]. Elevated Hg levels were found in 95.8%, 26.3%, and 25.5% of participants from the interior, Nickerie and Paramaribo, respectively. Results for median total Hg concentrations in hair from pregnant women from Paramaribo (N=522) were 0.64µg/g hair (interquartile ranges (IQR) 0.36-1.09; range 0.00-7.12), from Nickerie (N=176) 0.73µg/g (IQR 0.45-1.05;0.00-5.79) and the interior (N=178) 3.48µg/g (IQR 1.92-7.39;0.38-18.20). Pregnant women from the interior were exposed to high levels of Hg compared to 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 [18,24]. 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 sub-cohorts were similar to other studies [33,34].

Prenatal depression and perceived stress

Depression and prenatal stress in 722 participants were assessed using the standardized 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* [35]. 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 gram/day) [36]. 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- *Hoplias aimara*, *Serrasalmus 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 0.01-2.5 kilograms per 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 multi-disciplinary 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 sub-cohort in the interior region (N=200) was ameliorated by additional team support onsite; delays in transporting interior biospecimens rendered some early cord blood specimens not analyzable 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 sub-cohort.

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 telomere length 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 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.

Author Contributions

MYL, JKW, HHC, EWH, AS, SSD and WCWRZ designed and established the cohort. MSMO, ADHM, EWH, FAW and AG participated in the design of the questionnaires. WCWRZ, MSMO, EB, WBH, GKB, RR and MYL are responsible for the continued management of the cohort. GKB, RR, AG and FAW are actively involved with recruitment of participants and collection of non-biospecimen data and biospecimens. JC, JR, PEO and GAL store, archive and analyze the biomarker samples. ADHM, AS, MSMO, AG, MYL and WCWRZ are responsible for data management. SSD, AWEG, RR and EB manage neurodevelopmental testing of babies. JKW, LFS, CSA, SSD interpret all results. WCWRZ, JKW, HHC, ADHM and MYL 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

Obtained

Ethical approval

This study was 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.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

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 de-identified form after an application process that includes submission of a research plan. We are currently collaborating with Research Triangle Institute International (RTI), 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 PIs. Such requests will be discussed with the full investigator Committee, the Data Management Committee, and the Administrative Oversight Committee.

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Table 1. Assessments completed by the CCREOH-MeKiTamara Cohort with timeline

Assessments	Trimester 1st/2nd	Trimester 3rd	Birth	12 mos	36 mos	48 mos
Mother						
Obstetric history	●	●				
Demographics	●					
Residency	●	●				
Anthropometrics	●	●				
Marital status	●					
Ethnicity	●					
Occupation	●					
Education	●					
Household income	●					
Household composition	●					
Maternity care	●	●				
Medication		●				
Questionnaires						
SF 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					●	●
Biological samples						
Hair	●					
Blood	●	●				
Urine	●	●				
Buccal swab	●					
At birth						
Mode of delivery			●			
Cord or heelprick blood sample			●			
Birth outcomes			●			
Child development						
Physical examination				●	●	●
Questionnaires						
Generation R				●	●	●
M-CHAT					●	
Child Behavior Checklist					●	●
Bayley SEQ					●	

Ages and Stages Questionnaire		●	
Neurodevelopmental tests			
BSID-III	●		
CANTAB			●
Biological samples			
Buccal swab	●	●	●
Blood		●	●
Urine		●	●

Notes: ASSIST V3.0 = Alcohol, Smoking and Substance Involvement Screening Test Version 3, Subjective Social Status = MacArthur Scale of Subjective Social Status, M-CHAT = Modified Checklist for Autism in Toddlers, 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 pediatric health and diet history (with permission from The Generation R Study Group)

Table 2. Distribution of maternal and infant characteristics

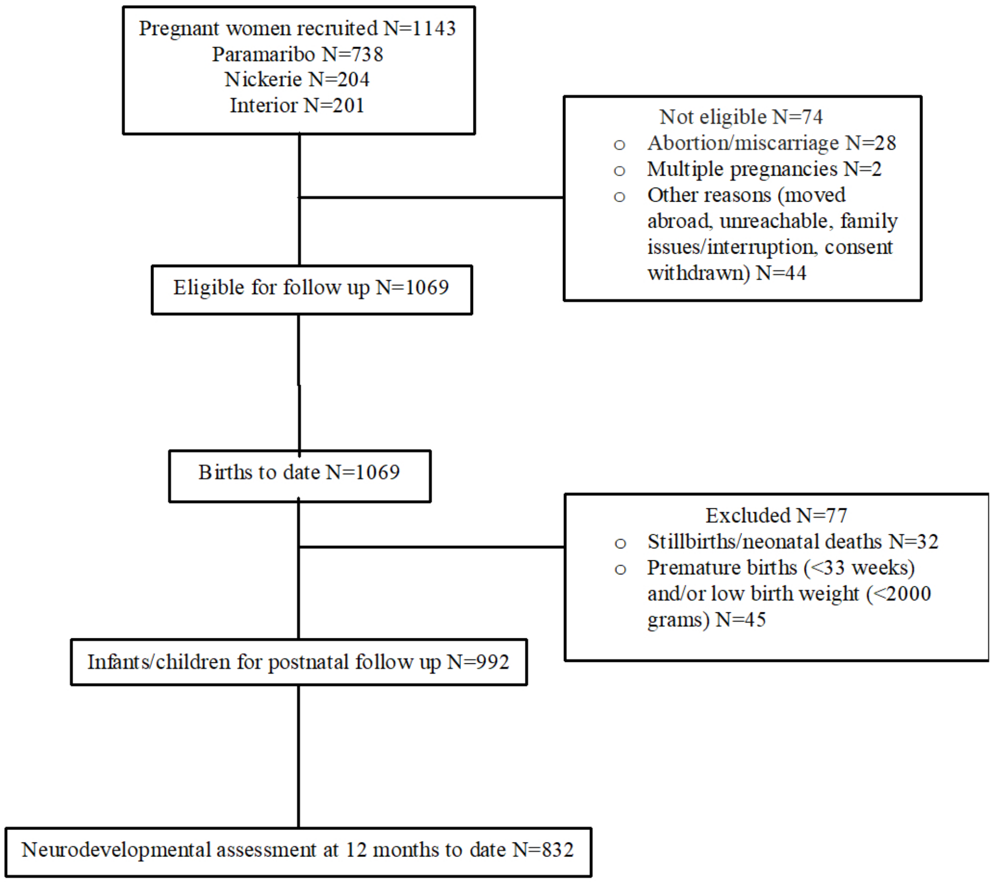
Maternal characteristics (N=1143)	N	%	Infant characteristics (N=971)	N	%
Age at intake			Gender		
16-19 years	142	12.6	Male	510	52.5
20-24 years	260	22.8	Female	457	47.1
25-29 years	291	25.5	Missing	4	0.4
30-34 years	268	23.5			
35-39 years	140	12.3	Birth status		
40+ years	39	3.4	Live birth	947	97.5
Missing	1	0.1	Stillbirth	23	2.4
			Missing	1	0.1
Parity					
0 previous live births	384	33.7	Birthweight (in grams)		
1 previous live birth	312	27.3	Low birthweight (<2500)	127	13.1
2 previous live births	187	16.4	Normal birthweight (≥2500)	835	86.0
3 previous live births	112	9.8	Missing	9	0.9
4+ previous live births	146	12.8			
Missing	2	0.2	Gestational age (in weeks)		
			Very preterm births (22+0-32+6)	39	4.0
Ethnicity			Moderately preterm births (33+0-36+6)	107	11.0
Creole	249	21.8	Term births (≥37+0)	817	84.1
Hindustani	233	20.4	Missing	8	0.8
Indigenous	155	13.6			
Javanese	101	8.8	Apgar score at 5 minutes		
Tribal	271	23.7	0 - 6	31	3.2
Mixed	127	11.1	7 - 10	918	94.5
Other	7	0.6	Missing	22	2.3
Missing	0	0.0			
Educational level					
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
Household income SRD*		
<1500	401	35.1
1500-2999	362	33.0
3000-4999	221	20.2
5000+	112	9.8
Missing	47	4.1
Marital status		
Married or living with partner	1000	87.6
Not married/not living with partner	141	12.4
Missing	2	0.2

* SRD = Surinamese dollar, equivalent to 0.13 USD.

Figure legends

Figure 1. Flowchart with participant enrolment.


Pregnant women recruited N=1143
Paramaribo N=738
Nickerie N=204
Interior N=201
Not eligible N=74
Abortion/miscarriage N=28
Multiple pregnancies N=2
Other reasons (moved abroad, unreachable, family issues/interruption, consent withdrawn) N=44
Eligible for follow up N=1069
Births to date N=1069
Excluded N=77
Stillbirths/neonatal deaths N=32
Premature births (<33 weeks) and/or low birth weight (<2000 grams) N=45
Infants/children for postnatal follow up N=992
Neurodevelopmental assessment at 12 months to date N=832