The Mab007 data product

Original number of samples	1,886
Number of samples (per 26.02.2024)	1,873
Number of unique participants	1,869
Biological sample type	Whole blood
Participant type(s)	MoBa mothers
Collection timepoint	Gestational week ~17-18
Case-control selection criteria	Attention deficit hyperactivity disorder (ADHD)
Biomarker type(s)	Toxic/non-essential metals and essential elements
Original reference article	Skogheim *et al*. 2021
Analytical method(s)	ICP-SFMS
Related MoBaBIO product(s)	Mab008
FHI Project number(s)	PDB1606

The project that generated these data

Prenatal exposure to organic and inorganic neurotoxic compounds and relationship with ADHD symptoms and diagnosis in Norwegian children

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The purpose of this study was to assess the relationship between prenatal exposure to organic (perfluoroalkyl substances, PFAS) and inorganic (toxic/non-essential metals and essential elements) contaminants and clinically assessed Attention Deficit/Hyperactivity Disorder (ADHD) symptoms and cognitive functions in preschool children (3.5 years), and in children diagnosed with ADHD identified through the Norwegian patient registry (NPR).

The present study/data is a part of **phase 1 of the NeuroTox study** (PDB1606/2322), aiming to investigate prenatal exposure to PFAS and inorganic contaminants and a wider range of neurologic and neurodevelopmental conditions in children. Data attainment was done in 2 phases. **Phase I** consisted of PDB 1606 with attainment of maternal toxicant data for NPR-ADHD cases and MoBa controls, as well as participants from the ADHD-study. **Phase II** consisted of PDB 2322, in which maternal toxicant data for ASD, Epilepsy and CP case groups and additional MoBa controls were attained. See Table 1 for a data overview.

Table 1: Overview of toxicant data and populations in the NeuroTox project (PDB1606/2322)

				Complete NeuroTox dataset	
NeuroTox	**PDB**	**Biomarker results, N**	**Mab**	**Diagnostic case groups**	**ADHD-study**
Phase I	1606	PFAS (plasma) N=2334	Mab008	Sub-population 1: ~ 700 ADHD cases ~700 controls	Sub-population 2: ~900 ADHD-study participants
		Metals/elements (whole blood), N=1872[a]	Mab007		
Phase II	2322	PFAS (plasma), N=1099	Mab010	~400 ASD cases ~300 Epilepsy cases ~170 CP cases ~300 additional controls[b] ~100 ADHD cases[c]	
		Metals/elements (whole blood), N=1045[a]	Mab009		

[a] For metals/element, NeuroTox utilized available data from the Norwegian Environmental Biobank (PDB1440) for participants that overlapped with NeuroTox participants. Thus, N with measured metals/elements are fewer than for PFAS data.
[b] To be added to controls from phase 1 (PDB1606).
[c] These ADHD cases are additional to those available from PDB1606, as they overlapped with ASD, Epilepsy and/or CP cases in the present dataset. These extra cases can be added to ADHD cases from PDB1606.

Study population

The original Mab007 biomarker data source is based on whole blood samples from **1,878 mothers** and the study population comprises a case-cohort study design. The dataset is comprised of two sub-populations from MoBa:

Sub-population 1 ("Utvalg 1"): ADHD-study population (N≈800):
This sub-population uses data from a nested case-cohort study within MoBa called the ADHD-study (PDB299) with the aim to study causes and trajectories of early (preschool) symptoms of ADHD. The child (with parents) was eligible to participate if the index child was born at one of the larger hospitals in Norway between April 2004 and January 2008 and had completed the 3-year MoBa questionnaire. This questionnaire included 11 items about ADHD, including six items from the Child Behavior Checklist/1.5-5 and five items from the DSM-IV-TR criteria for ADHD. Children with scores higher than 90th percentile on these 11 items (N=2798) were invited to participate, along with randomly selected children (N=654). In total, about 35% agreed to participate in the present sub-study, and from 2007 to 2011, 1195 children (mean age: 3.5 years, age range: 3.1 – 3.8 years) took part in a 1-day clinical assessment covering various cognitive functions and behavioral difficulties and more, including diagnostic interviews with parents (with few exceptions, mothers) assessing among others ADHD symptom levels using the Preschool Age Psychiatric Assessment (PAPA) interviews with one the parents. The ADHD classification/diagnosis defined by PAPA is not equivalent to clinical ADHD diagnoses that would require a broader assessment. For more details about the ADHD-study, see Overgaard *et al*. 2018.

In the present study's sub-population 1, mother-child pairs from the ADHD-study were selected based on the following criteria:

- Non-withdrawals from MoBa or the ADHD-study
- Singleton pregnancies
- No child congenital malformation or affected by Down's syndrome
- Available maternal plasma or whole blood sampled during the routine ultrasound assessment (K1) approximately 17-18th week of pregnancy.

In sub-population 1, the ADHD classifications included those with ADHD symptoms in the clinical and subclinical ranges or no ADHD symptoms based on the PAPA interview with the parent (see "Definition of cases and controls").

Sub-Population 2 ("Utvalg 2"):
Case-cohort population (N≈1100): *Cases* are in this context defined as MoBa mother-child pairs where the child had received a medical diagnosis of ADHD from the Norwegian Patient Registry (NPR; ICD-10 codes F90, F90.0, F90.1, F90.8, or F90.9) identified via the MoBa-substudy "Risk factors and biomarkers for Attention-deficit/hyperactivity disorder (ADHD) in a population based birth cohort" (PDB1223). Eligible cases for the current study required ≥2 registrations of ICD-10 F90 in the NPR (linkage from January 2014; diagnoses 2008-2013). From the eligible ADHD-cases, the cases were selected using **criteria** below, and the final N≈700 cases were then randomly selected with a slight oversampling on girls when possible (i.e included all available girl ADHD-cases; oversampling of n=18 girls).

Controls comprised of a randomly selected MoBa sample from the same eligible group as cases, frequency-matched to the case group by child sex and birth year, as well as geographical area; Norway divided into four geographical areas by county of birthplace (hospital). The detailed matching information can be made available on upon request to MorBarnData.

Selection criteria *for cases* and *control* mother-child pairs:

- Non-withdrawals from MoBa
- Singleton pregnancies
- Child born in 2000 or later
- Available records from the Medical Birth Registry of Norway (MBRN)
- Mother's questionnaire 1 available (week 17)
- No child serious malformation or affected by Down's syndrome
- Available maternal plasma and/or whole blood sampled during the routine ultrasound assessment (K1) approximately 17-18th week of pregnancy.

Selection of sub-populations 1 and 2 are based on version 8 of MoBa's self-report questionnaire data.

Available biomarker measures (variable names in bold)

Essential elements:

Cobalt (**Co**)
Copper (**Cu**)
Magnesium (**Mg**)
Manganese (**Mn**)
Molybdenum (**Mo**)
Potassium (**K**)
Selenium (**Se**)
Sodium (**Na**)
Zinc (**Zn**)

Toxic/non-essential metals:

Arsenic (**As**)
Cadmium (**Cd**)
Cesium (**Cs**)
Lead (**Pb**)
Mercury (**Hg**)
Thallium (**Tl**)

Other metadata variables

- Rack
- Position

Definition of cases and controls in the dataset

There are two alternative case/control variables that can be provided with the Mab008 dataset, **CaseControlGrpAlt1** or **CaseControlGrpAlt2**, as well as **MatchingInfo** for the controls in the case-cohort population (population 2). Each of the two alternatives subcategorizes cases and controls into the specific selection groups to which they belong and from which they were derived for inclusion in this study. A variable key with associated descriptions is provided below.

CaseControlGrpAlt1

Sub-Population 1 (Retrieval ID: 730)

- Case_ADHDClinic: *Mother-child pairs participating in the ADHD-study, and where child had ADHD symptoms in the clinical range.*
- Subthreshold_ADHDClinic: *Mother-child pairs participating in the ADHD-study, and where child had ADHD symptoms in the sub-clinical range.*
- NoADHD_ADHDClinic: *Mother child-pairs that were included in the ADHD-study, and where child had no symptoms of ADHD.*

Sub-Population 2 (Retrieval ID: 762)

- Case_ADHDNPR: *Mother-child pairs where the child was diagnosed with ADHD.*
- Control: MoBa m*other-child control pairs frequency-matched to ADHD cases.*
- Case_ADHDNPR + Control: *Mother-child pairs that where child was both NPR-ADHD case and control*

CaseControlGrpAlt2

- Control: *Mother-child controls from sub-population 2.*
- Other: *All other mother-child pairs in sub-population 2 as well as sub-population 1*.

Biological sampling and processing

Whole blood samples were collected from mothers at 17-18 weeks' gestation into 3 mL trace-free sampling tubes, and shipped from the collecting hospital overnight to MoBa's biobank at the Norwegian Institute of Public Health (NIPH). The samples most often arrived at the biobank within 1–2 days of blood donation, and were placed in long-term storage at a temperature of −80 °C.

For more information on biological sampling, processing and storage, please refer to the original reference articles for NIPH's biobank by Rønningen *et al*. 2006 and Paltiel *et al*. 2014.

Analytical methodology

Data on heavy metals and essential elements were measured using **inductively coupled plasma–sector field mass spectrometry (ICP-SFMS)** after microwave-assisted sample decomposition by ALS Laboratory group, at the ALS laboratory in Luleå, Sweden. The analyses of blood samples for sub-populations 1 and 2 were performed in two separate analytical rounds. For each round, five reference samples consisting of standard reference material (Seronorm Trace Elements whole blood L-1, SERO AS, Billingstad, Norway) were randomly placed within the sample batches, blinded to the analyst. The results of the reference material can be used to adjust for analytical variation across analytical rounds.

For more information on the analytical method used in this study, refer to the original reference articles by Rodushkin *et al*. 2000 and Rodushkin *et al*. 2004.

The published studies that included data from Mab007 (and Mab009) also utilized subsets of data on blood concentrations of metals/elements in pregnant MoBa mothers from the Norwegian Environmental Biobank (PDB1440, see Mab011). These samples were analysed at the Department of Occupational and Environmental Medicine at Lund University, Sweden, using comparable analytical methods as the ALS Laboratory group, as described in Caspersen *et al*. 2019; however, these analyses did not include magnesium, caesium, potassium or sodium. For these analyses, the same standard reference material (Seronorm Trace Elements whole blood L-1, SERO AS, Billingstad, Norway) were analysed and these can be used to adjust for inter-laboratory variations in metal/element concentrations in addition to intra-laboratory variations across analytical rounds.

For more details on results from standard reference material and adjustment for inter- and intra-laboratory variations, contact Gro.Dehli.Andersen@fhi.no

Measurement units:

Cobalt, Copper, Manganese, Molybdenum, Selenium, Zinc, Arsenic, Cadmium, Cesium, Lead, Mercury, Thallium: µg/L

Magnesium, Potassium, Sodium: mg/L

Limit of quantification (LOQ):

Arsenic (As): 1 µg/L
Cadmium (Cd): 0.05 µg/L
Cesium (Cs): 0.05 µg/L
Cobalt (Co): 0.05 µg/L

Copper (Cu): 1 µg/L
Lead (Pb): 0.5 µg/L
Magnesium (Mg): 0.2 mg/L
Manganese (Mn): 0.5 µg/L
Mercury (Hg): 0.2 µg/L
Molybdenum (Mo): 0.2 µg/L
Potassium (K): 0.5 mg/L
Selenium (Se): 5 µg/L
Sodium (Na): 0.5 mg/L
Thallium (Tl): 0.05 µg/L
Zinc (Zn): 10 µg/L

Total Hg and total As were measured, which included both inorganic and organic forms.

Concentrations above LOQ were reported for most metals/elements, except for arsenic, cadmium, mercury and lead where concentrations above limit of detection (LOD) were reported. LOD was approximately one third of the LOQ.

Published articles using Mab007

Note: This section also includes publications that used Mab009, as these datasets were often combined and analyzed together

This section also includes articles related to study design, sampling, and data collection.

- Weyde KVF, Winterton A, Surén P, Andersen GL, Vik T, Biele G, Knutsen HK, Thomsen C, Meltzer HM, Skogheim TS, Engel SM, Aase H, Villanger GD. Association between gestational levels of toxic metals and essential elements and cerebral palsy in children. Front Neurol. 2023.
- Weyde KVF, Olsen AK, Duale N, Kamstra JH, Skogheim TS, Caspersen IH, Engel SM, Biele G, Xia Y, Meltzer HM, Aase H, Villanger GD. Gestational blood levels of toxic metal and essential element mixtures and associations with global DNA methylation in pregnant women and their infants. Sci Total Environ. 2021 Sep 15;787:147621.
- Skogheim TS, Weyde KVF, Engel SM, Aase H, Surén P, Øie MG, Biele G, Reichborn-Kjennerud T, Caspersen IH, Hornig M, Haug LS, Villanger GD. Metal and essential element concentrations during pregnancy and associations with autism spectrum disorder and attention-deficit/hyperactivity disorder in children. Environ Int. 2021 Jul;152:106468.

Restrictions for use

None currently known.

Acknowledgements recommended for use

We recommend that any use of these data in analyses that are presented in peer-review publications acknowledges the original articles describing sampling and data collection:

Weyde KVF, Olsen AK, Duale N, Kamstra JH, Skogheim TS, Caspersen IH, Engel SM, Biele G, Xia Y, Meltzer HM, Aase H, Villanger GD. Gestational blood levels of toxic metal and essential element mixtures and associations with global DNA methylation in pregnant women and their infants. Sci Total Environ. 2021 Sep 15;787:147621.

Skogheim TS, Weyde KVF, Engel SM, Aase H, Surén P, Øie MG, Biele G, Reichborn-Kjennerud T, Caspersen IH, Hornig M, Haug LS, Villanger GD. Metal and essential element concentrations during pregnancy and associations with autism spectrum disorder and attention-deficit/hyperactivity disorder in children. Environ Int. 2021 Jul;152:106468.

For data from sub-population 1 (ADHD-study), also cite:

Øvergaard KR, Oerbeck B, Friis S, Pripp AH, Biele G, Aase H, Zeiner P. Attention-Deficit/Hyperactivity Disorder in Preschoolers: The Accuracy of a Short Screener. J Am Acad Child Adolesc Psychiatry. 2018 Jun;57(6):428-435.

Disclaimer

The data in Mab007 that are available for use are provided by MoBa on an *as is* basis as they were received from the generating laboratory and have not been curated or quality controlled prior to release. FHI does not provide any guarantees related to data quality and assurance of the original dataset. We reserve the right to periodically remove samples from the dataset belonging to participants who have retracted their consent to participate in this cohort study, and may alter the contents of the associated documentation accordingly.