The Mab016 data product

Original number of samples	1,154
Number of samples (per 26.02.2024)	1,150
Number of unique participants	1,145
Biological sample type	Urine
Participant type(s)	MoBa mothers
Collection timepoint	Gestational week ~17
Case-control selection criteria	Attention deficit hyperactivity disorder (ADHD)
Biomarker type(s)	Organophosphorous pesticides (OPs)
Original reference article	Engel *et al*. 2018
Analytical method(s)	UPLC
Related MoBaBIO product(s)	Gtp002, Mab015, Mab017, Pro006
FHI Project number(s)	PDB1040

The project that generated these data

Prenatal Phthalate, Phenol and organophosphate (OPs) exposure and symptoms of ADHD in Norway

Project lead: Heidi Aase

The main purpose of this project was to investigate the link between exposures to pesticides and endocrine disruptors in pregnancy, and the development of ADHD during childhood. The specific aims of this project were to study organophosphate and phthalate exposure during pregnancy and the effect this has on risk for developing ADHD in childhood, to investigate thyroid hormone exposure during pregnancy and the effect this has on the risk for developing ADHD in childhood, as well as the effect of phthalate exposure during pregnancy and how this affects maternal and neonatal thyroid biomarkers. Genetic modification of the association between ADHD in childhood and organophosphate exposure was a further investigative aim, using genotype data on important loci involved in xenobiotic metabolism and specific mutations that are known to be linked.

Study population

The original Mab016 biomarker data source is based on urine samples from **1,149 mothers** and the study population comprises a case-cohort study design. Cases were defined as mothers of children diagnosed with attention deficit hyperactivity disorder (ADHD) in the National Patient Registry (NPR), or who were evaluated as having ADHD symptoms in the clinical or subclinical range in the MoBa-based ADHD-study during a clinical evaluation of children at around child 3.5 years of age. The ADHD-study (PDB299) aimed to study risk factors 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 resulting ADHD classifications consisted of those with ADHD symptoms in the clinical and subclinical ranges or no ADHD symptoms. 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, mothers (and their children) were eligible for inclusion as a case or MoBa control if they had been pregnant in 2003 or after, had completed the questionnaire

administered when the child was 36 months of age, the child did not have a diagnosis of Down's syndrome or cerebral palsy, urine and blood samples from mid-pregnancy were available, and they lived in a geographic area that made them eligible for inclusion in the ADHD-study. Children born in 2003 or after were identified as cases based on a clinical diagnosis of ADHD from the Norwegian Patient Registry (NPR). NPR cases were included based on a minimum of two registrations of "Hyperkinetic disorder" (ICD-10 codes F90, F90.0, F90.1, F90.8 or F90.9). Two registrations were a prerequisite for inclusion to avoid false diagnoses or registrations. In addition, children demonstrating clinical/subclinical symptoms of ADHD in based on the PAPA interview with one parent in the ADHD-study clinical assessment, were included. Subcohort members (~MoBa controls) were selected by a birth-year stratified random sample (frequency matched to preschool ADHD cases by birth-year) from the population of eligible mothers that had been defined for this study. From the ADHD-study population, we also included children who screened negative (i.e. below the 90th pct) for ADHD at the 3-year MoBa questionnaire and tested negative (i.e. no ADHD symptoms based on the PAPA interview) for ADHD symptoms in the clinical assessment.

For more information on sample selection, refer to the original article describing the sampling and data collection by Engel *et al.* 2018, and for the preschool population sampling and data collection by Manley *et al.* 2022.

Available biomarker measures (variable names in bold)

Diethyldithiophosphate (**DEDTP**)
Diethylphosphate (**DEP**)
Diethylthiophosphate (**DETP**)
Dimethyldithiophosphate (**DMDTP**)
Dimethylphosphate (**DMP**)
Dimethylthiophosphate (**DMTP**)

The above are dialkylphosphate metabolites of organophosphorous insecticides, which are non-specific biomarkers of exposure. See Odetokun *et al.* 2010 for a discussion of these exposure biomarkers.

Other metadata variables

- Batch
- Rack
- Position
- Specific gravity

Definition of cases and controls in the dataset

There are two case/control variables that are provided with the Mab016 dataset, **CaseControlGrpAlt1** and **CaseControlGrpAlt2**. Each of these 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 and associated description is provided below.

CaseControlGrpAlt1

- Case_ADHDClinic : *Subclinical/clinical symptoms of preschool ADHD*
- Case_ADHDClinic + Case_ADHDNPR : *Subclinical or clinically significant symptoms of preschool ADHD and an ADHD diagnosis registered in National Patient Registry*
- Case_ADHDNPR: *ADHD diagnosis registered in National Patient Registry*
- Case_ADHDNPR + Control_MoBa: *ADHD diagnosis registered in National Patient Registry and randomly sampled as a MoBa control*
- Control_ADHDClinic: *Screened negative for ADHD symptoms in 3-year MoBA Questionnaire, and no ADHD symptoms from in the ADHD-study clinical assessment.*
- Control_MoBa: *Randomly sampled as a MoBa subcohort member (~MoBa control)*

CaseControlGrpAlt2

- Control_MoBa: *Randomly sampled as a MoBa subcohort member (~MoBa control)*
- Other: *ADHD cases base on diagnoses in NPR as well as participants from the ADHD-study (Case_ADHDClinic and Control_ADHDClinic)*

Biological sampling and processing

Urine samples were collected in urine cups at volumes of 8 ml from pregnant mothers and transferred to urine transport tubes (Becton-Dickinson (BD), Franklin Lakes, NJ, USA). Samples collected prior to 2003 were shipped in tubes without any bacteriostatic additive (BD, Plymouth, UK), while samples collected in 2003 and after were shipped in urine tubes containing chlorhexidine (UAP Vacutainers, BD, Franklin Lakes, NJ, USA).

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

The organophosphate ester metabolites in the present study were measured from maternal urine using **ultra performance liquid chromatography (UPLC)** coupled with quadrupole-

time-of-flight (QTOF), using a modified analytical method that has been published previously (for more information, see Cequier *et al*. 2014).

Measurement units:

Concentration in **ng/mL** for all included measures.

Limit of quantification (LOQ):

Diethyldithiophosphate (DEDTP): 0.594 ng/mL
Diethylphosphate (DEP): 1.089 ng/mL
Diethylthiophosphate (DETP): 0.594 ng/mL
Dimethyldithiophosphate (DMDTP): 1.32 ng/mL
Dimethylphosphate (DMP): 3.003 ng/mL
Dimethylthiophosphate (DMTP): 0.429 ng/mL

Published articles using Mab016

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

- Ramos AM, Herring AH, Villanger GD, Thomsen C, Sakhi AK, Cequier E, Aase H, Engel SM. The association of prenatal phthalates, organophosphorous pesticides, and organophosphate esters with early child language ability in Norway. Environ Res. 2023 May 15;225:115508.
- Hall AM, Thistle JE, Manley CK, Roell KR, Ramos AM, Villanger GD, Reichborn-Kjennerud T, Zeiner P, Cequier E, Sakhi AK, Thomsen C, Aase H, Engel SM. Organophosphorus Pesticide Exposure at 17 Weeks' Gestation and Odds of Offspring Attention-Deficit/Hyperactivity Disorder Diagnosis in the Norwegian Mother, Father, and Child Cohort Study. Int J Environ Res Public Health. 2022 Dec 15;19(24):16851.
- Thistle JE, Ramos A, Roell KR, Choi G, Manley CK, Hall AM, Villanger GD, Cequier E, Sakhi AK, Thomsen C, Zeiner P, Reichborn-Kjennerud T, Øvergaard KR, Herring A, Aase H, Engel SM. Prenatal organophosphorus pesticide exposure and executive function in preschool-aged children in the Norwegian Mother, Father and Child Cohort Study (MoBa). Environ Res. 2022 Sep;212(Pt D):113555.
- Manley CK, Villanger GD, Thomsen C, Cequier E, Sakhi AK, Reichborn-Kjennerud T, Herring AH, Øvergaard KR, Zeiner P, Roell KR, Engel LS, Kamai EM, Thistle J, Hall A, Aase H, Engel SM. Prenatal Exposure to Organophosphorus Pesticides and Preschool ADHD in the Norwegian Mother, Father and Child Cohort Study. Int J Environ Res Public Health. 2022 Jul 2;19(13):8148.
- Engel SM, Villanger GD, Nethery RC, Thomsen C, Sakhi AK, Drover SSM, Hoppin JA, Zeiner P, Knudsen GP, Reichborn-Kjennerud T, Herring AH, Aase H. Prenatal Phthalates, Maternal Thyroid Function, and Risk of Attention-Deficit Hyperactivity Disorder in the Norwegian Mother and Child Cohort. Environ Health Perspect. 2018 May 10;126(5):057004.

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:

Engel SM, Villanger GD, Nethery RC, Thomsen C, Sakhi AK, Drover SSM, Hoppin JA, Zeiner P, Knudsen GP, Reichborn-Kjennerud T, Herring AH, Aase H. Prenatal Phthalates, Maternal Thyroid Function, and Risk of Attention-Deficit Hyperactivity Disorder in the Norwegian Mother and Child Cohort. Environ Health Perspect. 2018 May 10;126(5):057004.

Manley CK, Villanger GD, Thomsen C, Cequier E, Sakhi AK, Reichborn-Kjennerud T, Herring AH, Øvergaard KR, Zeiner P, Roell KR, Engel LS, Kamai EM, Thistle J, Hall A, Aase H, Engel SM. Prenatal Exposure to Organophosphorus Pesticides and Preschool ADHD in the Norwegian Mother, Father and Child Cohort Study. Int J Environ Res Public Health. 2022 Jul 2;19(13):8148.

Hall AM, Thistle JE, Manley CK, Roell KR, Ramos AM, Villanger GD, Reichborn- Kjennerud T, Zeiner P, Cequier E, Sakhi AK, Thomsen C, Aase H, Engel SM. Organophosphorus Pesticide Exposure at 17 Weeks' Gestation and Odds of Offspring Attention-Deficit/Hyperactivity Disorder Diagnosis in the Norwegian Mother, Father, and Child Cohort Study. Int J Environ Res Public Health. 2022 Dec 15;19(24):16851.

For data from 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 Mab016 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.