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Looking for effects of environmental contaminants in a large birth cohort: Summarizing results of the Norwegian Mother and Child Cohort Study (MoBa)

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ABSTRACT

The Norwegian Mother and Child Cohort Study (MoBa) includes about 113 000 pregnancies, recruited during the years 1999–2008. Using information from questionnaires and biological samples, a major purpose has been to estimate the association between exposures to environmental contaminants and disease occurrence in parents and children. The intention of this article is to describe the available data in MoBa together with a short synopsis of some recent MoBa-publications that relate to exposure assessment and associations between toxicants and health outcomes. The majority of these papers display negative results, in the sense that no strong associations between contaminants and health outcomes have been found, whereas others suggest adverse effects. The positive associations between fetal exposure to contaminants and child growth and development will need replication in other cohorts and further risk assessment. Large prospective pregnancy cohorts remain an important resource for surveillance and detection of effects of environmental hazards on human health.

1. Introduction

The etiology of congenital malformations, preterm birth, stillbirth and diseases in childhood such as autism, allergies and type 1 diabetes, to mention only some disorders, is largely unknown. For all these conditions, it is conceivable that exposure to environmental contaminants during pregnancy may be causal. Prospective cohorts are needed since retrospective assessment of exposure is difficult and often impossible. Even with prospective data, being able to measure the cumulative exposure to the relevant tissue in the correct time-window is not feasible. Ambitious and costly efforts to set up large scale prospective pregnancy cohorts with detailed measures have been made. In some instances, such as the National Children's Study in the USA, the effort has failed (Kaiser, 2014). In Scandinavia, building on the infrastructure of national health services, the Danish National Birth Cohort (DNBC) (Olsen et al., 2001) and The Norwegian Mother and Child Cohort Study (MoBa) (Magnus et al., 2016), were planned and started in the 1990s. A major aim was to collect biological material as well as questionnaire information on life style habits during pregnancy for later analysis of environmental exposures in relation to specific outcomes. The studies were not designed for human biomonitoring as such, although the cohorts have also contributed to population-based exposure assessments.

The aim of this paper is to give a short summary of what has been found in subprojects in MoBa where environmental contaminants, some of which have been assessed through the diet, have been addressed.

2. The Norwegian Mother and Child Cohort Study (MoBa)

MoBa was initiated in 1999 and completed the recruitment in 2008. The unit of data collection was the pregnancy. During the recruitment period, invitations were sent to women in 277 702 pregnancies, with a participation rate of 41%. The cohort includes more than 114 000 children, 95 000 mothers and 75 000 fathers (Magnus et al., 2016). About 1900 pairs of twins have been born. There are approximately 16 400 women who participate with more than one pregnancy. Blood samples were obtained from both parents during pregnancy (around week 16–18) and from mothers and children (umbilical cord) after birth. Samples of DNA, RNA, whole blood, plasma and urine are stored in a biobank (Paltiel et al., 2014). Through a contract with the National Institute of Environmental Health Sciences (NIEHS) in the USA, extra resources were used to collect bloods and urine during pregnancy (week 16–18) for the purpose of assessment of environmental toxicants. Primary teeth were collected when the child was between 6 and 7 years. No rou-

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tine measurements have been performed on the samples, the idea being to perform nested case-control studies at a later time.

During pregnancy, the mother responded to three questionnaires and the father to one. The birth record from the Medical Birth Registry of Norway, that includes maternal health during pregnancy as well as procedures around birth and pregnancy outcomes, is integrated in the MoBa database. The development of the child, the health of the mother and the child, as well as lifestyle exposures are major parts of questionnaires sent out when the child is 6 months, 18 months and 3 years. At the ages of 5 and 8 years, new questionnaires focusing on children's learning, language and neurocognitive development have been mailed to the participating mothers. A questionnaire at child age 7 is devoted to somatic diseases with specific attention to allergies and asthma. These questionnaires also interrogate maternal health. Presently, a new questionnaire has been developed for participating fathers, and is being distributed in 2016. Also, a new questionnaire to the mother and the child will be sent out at the time the child becomes 14 years (Magnus et al., 2016).

One sub-cohort in MoBa has been set up to understand causes and trajectories of autism spectrum disorders (Stoltenberg et al., 2010). In another sub-cohort on language development, detailed questionnaire responses have been received from the employees in pre-school child care institutions for more than 7000 children, making MoBa one of the largest studies to follow children with this type of exposure information. Presently, questionnaires are sent to school teachers as part of the follow-up. We have performed single nucleotide polymorphism (SNP) genotyping in 11 000 randomly selected trios in MoBa, using the Illumina Human Core Exome Bead Chip. In a subset of 1000 trios, we are collecting new biological materials from the mother, father and child at age 8 for bio-monitoring of environmental chemicals and comparisons with levels measured earlier. About 400 papers, covering a large range of exposures and outcomes, have been published using data from the MoBa study (www.fhi.no/moba).

2.1. Synopsis of MoBa-studies

2.1.1. Methodological issues

A few papers are mainly concerned with issues of sample collection and reliability in urine and plasma samples.

2.1.1.1. Urine samples. Urine sampling is particularly important to assess exposure to non-persistent contaminants. However, bacterial growth may compromise samples. Hoppin et al. (2006) examined the influence of temperature, added preservatives and time from sampling to freezing on a series of contaminants and found that most analytes were stable. The effect of storage temperature was less important than time since collection.

In some urine samples from MoBa, unexpectedly high concentrations of bisphenol A were detected, suggesting contamination. An experiment was performed that suggested two different contamination mechanisms for free bisphenol A, one of them through the preservative used (Longnecker et al., 2013).

In MoBa, women are asked to deliver a spot urine sample at the time of the routine ultrasound examination at 17 weeks. To estimate reliability, 45 women living in 4 areas of Norway were recruited to deliver urine spot samples also at pregnancy weeks 23 and 29. Looking at the concentrations of both conjugated and free phenols, including bisphenol A, Guidry et al. (2015) found low to moderate intraclass correlation coefficients for repeated measures, and noted that analysing both total and free concentrations allows for the detection of contamination. Using the same subset of samples, Bertelsen et al. (2014) found an intraclass correlation of 0.49 for triclosan.

An automated setup for fast and sensitive determination of 12 phthalate metabolites in urine has been developed and tested in 116 MoBa participants (Sabaredzovic et al., 2015). Daily intakes of bisphenol A, phthalates and organophosphate pesticides were estimated based on urine data in MoBa, and compared with data from pregnant women in a Dutch (Generation R) and an American (NHANES) study (Ye et al., 2009). Women in MoBa had a higher estimated intake of bisphenol A, while the level of phthalates varied depending on the chemical that was assayed. Norwegian and Dutch women were exposed to higher levels of organophosphates than US women. All estimated intakes were below recommended thresholds.

To be able to estimate acrylamide intake from a food frequency questionnaire (FFQ), given to all MoBa participants during pregnancy (Meltzer et al., 2008), 24 h urine samples from a subset of 119 MoBa women were analysed with respect to mercapturic acid metabolites and correlated to responses from the FFQ as well as a four-day weighed food diary (Brantsaeter et al., 2008). Crisp bread and potato crisps along with cooking oil and onion were independent predictors, and it was demonstrated that the FFQ was able to identify most subjects with high dietary exposure to acrylamide.

2.1.1.2. Plasma samples. MoBa non-fasting EDTA-plasma samples taken at week 17 as well as after birth, were originally stored on 96-well plates. Thus, each sample on a plate undergoes a freeze-thaw cycle whenever one sample is retrieved. A quality control study was designed to assess the impact of multiple freeze-thaw cycles on sample integrity over the course of two years. The results showed relatively little change after up to 100 cycles for sodium, cholesterol, triglycerides, free fatty acids, vitamin E and aspartate aminotransferase. The largest change was seen for free fatty acids (Paltiel et al., 2008).

Perfluoroalkyl substances (PFAS) are excreted in proportion to the glomerular filtration rate (GFR). To assess to which degree GFR might be a confounder for the association between PFAS and fetal growth, Morken et al. (2014) examined the relationship between maternal GFR and offspring birth weight in 953 MoBa participants. GFR was assessed indirectly by measuring creatinine levels in plasma from week 17. The analysis showed a linear relationship between GFR and birth weight. For each ml/min increase in estimated GFR, birth weight increased by 0.73 g, implying that GFR to some extent can confound associations between the blood concentrations of some contaminants and fetal growth.

Using 123 paired samples of maternal and cord blood from a subcohort in MoBa, it was found that the median concentrations of seven PFAS were 30–80% lower in cord blood than in maternal blood drawn after birth (Gützkow et al., 2012). Relatively strong correlations (from 0.69 to 0.82) were found between maternal and offspring levels, indicating placental transfer.

Since fish consumption is relatively high in Norway, a search for good biomarkers of fish intake was made in a validation subset of 119 MoBa participants (Brantsaeter et al., 2010). Using both blood (measuring fatty acids, arsenic, Se and Hg) and 24 h urine (measuring iodine) samples, it was found that arsenic was a good measure for total fish intake, and that Hg was related to the intake of lean fish.

2.1.2. Exposure-outcome associations

2.1.2.1. Perfluoroalkyl substances (PFAS). In a subset of 100 MoBa women who had contributed two pregnancies to the cohort, ten perfluoroalkyl substances (PFAS) were measured in the plasma sample taken at week 17 in both pregnancies. The correlations between measurements of the same substance in the two pregnancies varied from 0.39 to 0.80 for the different substances (Papadopoulou et al., 2015). One half of the women had breastfed their first child for at least 6 months, while the other half had not.