# The Norwegian Mother and Child Cohort Study (MoBa) – past, present and future

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## INTRODUCTION

The Norwegian Mother and Child Cohort Study (MoBa) is a pregnancy cohort with the ambitious aim of discovering new causes of serious diseases. Pregnant women were recruited around week 17 of gestation in the years 1999 through 2008. More than 114 000 pregnancies are included. Exposures, background variables and outcomes have been collected from questionnaires, biological materials and linkages to registries. In depth studies in the form of sub-cohorts are being performed for several childhood outcomes. International collaborations have been important for the development and maintenance of MoBa. Future research into the etiology of complex diseases will require better resolution of environmental and genetic heterogeneity. Personalized prevention and treatment of such diseases may be achievable in the future. MoBa and similar population-based cohorts with a lifetime perspective will be essential for understanding socio-economic health inequities as well as gene-environment interplay. The aim of this paper is to reflect on the past, describe the present state of affairs and discuss challenges and opportunities for the future of MoBa.

## THE PAST

The twentieth century witnessed a series of advances in the study of the etiology of diseases. Many infectious diseases were explored through microbiological research. Eventually new vaccines and antibiotics provided prevention and treatment. Genetic research explained the etiology of single gene and chromosomal disorders. However, despite intensive efforts to find infectious agents or single genes, the etiology of many of the common and disabling chronic disorders remained a puzzle. After the Second World War, a few longitudinal, observational studies were established to study such diseases. One of them, the Framingham study (1), identified risk factors for cardiovascular disease, and another, the cohort of British physicians (2), documented consequences of tobacco smoking. The field of epidemiology expanded, and population-based cohorts became instruments for etiological research, despite the drawbacks of this design; the long and tedious data collection, the large economic investment, and the problem of interpreting associations between exposures and outcomes.

Perinatal epidemiology is occupied with understanding causes behind adverse pregnancy outcomes, such as congenital malformations, preterm birth, maternal diseases of pregnancy as well as fetal growth restriction and death. Case-control studies have only limited power to detect causes since many exposures are hard to unveil retrospectively, and studies of birth registries, although they harbor a large number of subjects, mainly provide descriptive information and associations to background factors that are commonly available such as maternal age, parity and socioeconomic background. The Medical Birth Registry of Norway was established in 1967 and includes information on all births in Norway since then (3). Although the Medical Birth registry covers a complete population and can serve as a cohort, it had limited information on exposures. Thus, one of the main driving forces for establishing MoBa came from perinatal epidemiologists, as described elsewhere in this issue (4,5). Another was the debate in the 1990s on the so-called fetal origins of disease hypothesis, now more commonly referred to as the theory of developmental plasticity (6). The theory suggests that environmental influences during pregnancy or in early childhood may lead to more or less permanent changes in organs and physiological regulation that will predispose for adult disease. The empirical background for this hypothesis came from ecological studies, linking infant mortality and rates of cardiovascular disease geographically (7,8). A realistic test of the hypothesis requires prospective information, which can best be gathered from cohorts that start early in pregnancy.

These deliberations were the background for setting up MoBa. Initially, recruitment as early in pregnancy as possible was planned for. Pregnant women should be recruited at their first encounter with the health services, usually around the 8$^{th}$ week of pregnancy. A grant proposal to the National Institutes of Health in the United States was submitted, but without success. As described in more detail by others in this issue (9-11), a series of events followed that ended with a change in recruitment. When the data collection commenced in 1999, women were recruited in the second trimester of pregnancy, at the time of the routine ultrasound examination, which is offered to all women around the 17$^{th}$/18$^{th}$ week of pregnancy.

After the Parliament decision in 1998, which gave official backing as well as seed money, the scene was set for a careful start of the recruitment, first at Haukeland hospital in Bergen. The understanding of the need for this type of research was not widespread

within Norway, and promotional meetings with professional and government bodies were undertaken (10). The Research Council of Norway (RCN) made an early decision that they would not support the data collection and the basic infrastructure that was needed to establish MoBa. The Norwegian Institute of Public Health (NIPH) hosted the study, and was able to supply funding for a gradual expansion of the recruitment to additional hospitals in the years 2000-2001. A contract with the NIEHS was set up, first for a five year period, and from 2007, a ten year contract was established with the aim of supporting the data collection and the maintenance of the database and the biobank. Specifically, the contract supported the collection of extra blood and urine samples for the purpose of measuring concentrations of potential environmental toxicants from pregnant women in the second trimester.

Another important international collaboration was established in 2002 with the Department of Epidemiology at Columbia University in New York. The aim was to screen for early signs of autism spectrum disorders and to use MoBa to explore etiology, early markers and trajectories (12). Later, the MoBa biobank was supported from an RCN infrastructure program (FUGE) that supported functional genomics (13). This made it possible to extract and aliquot DNA from fresh full-blood samples. In total, MoBa has been financed roughly one third from NIPH, one third from the Norwegian Ministry of Health and Care Services and one third from external research funding. Altogether, about 300 million NOK (approximately 50 million USD, 30 million GBP, 40 million Euro) were spent from 1999 to 2008, covering mainly recruitment and development of IT, biobank and administrative functions. The external competitive funding has been essential since the initiation of Moba and represents a large array of interests and research questions, influencing the governance of MoBa.

By 2005, MoBa recruited from 50 of the 52 birth clinics in Norway. Recruitment was completed in 2008, after nearly 10 years, and the first paper describing MoBa was published in 2006 (14). The first MoBa period was characterized by strong scientific ideas, complicated politics, competition for funding, development of infrastructures for an industrial size research enterprise, and virtually no scientific output.

## PRESENT

Today, MoBa is an active resource with a large number of scientific subprojects. Since 2006, more than 300 papers have been published in international scientific journals (www.fhi.no/moba-en). Presently, 221 subprojects are active. A subproject may be very simple: a specific research question answered by a few variables from one or more of the questionnaires, but can also be very large and complex involving clinical examinations, analyses of biological specimens and the inclusion of data from linkages to health registries.

There are several subprojects that perform clinical examinations on groups of children. Examples are: autism spectrum disorders (12,15), ADHD (16), asthma (17) and language delay. Other subprojects have examined subjects for validation purposes, as was done for the food frequency questionnaire (18), or validation is done based on scrutiny of clinical records or registry data, which has been done for pre-eclampsia (19) and is presently performed for children with epilepsy and children with cerebral palsy. Some investigators have followed subcohorts with repeated blood sampling and another has selected a random subgroup of children for magnetic resonance imaging of the brain to study normal brain development. Several subprojects have sent new questionnaires to selected groups of patients, for instance parents with epilepsy (20), coeliac disease (21) and inflammatory bowel disease.

All the MoBa children have now passed their 5-year birthday. Presently, questionnaires are sent out for children at the ages of 7 (mainly with questions on astma and allergies) and 8 (mainly developmental issues). Response rates to these as well as to the 5-year questionnaire are around 50%, while it was 60% for the 3-year, 77% for the 18 month, 87% for the 6 month and above 90% for the three pregnancy questionnaires and for the questionnaire filled in by the participating father. The data collection is managed by a tracking system (22). Data and biological materials are stored in a database (22) and a biobank (23). Both are developing to offer the best service to researchers. Linkage to registries has been performed in many subprojects. One example is the linkage to the Cancer Registry to find families where childhood cancer has occurred. Cancer is a rare outcome and collaboration with other cohorts is important for precise estimates, as discussed by Dwyer and coworkers (24). Other registries that have been used by many researchers are the National Patient Registry and the Norwegian Prescription Database. The existence of these registries implies that many outcomes can be studied for the whole cohort, compensating for the lower response rates on follow-up questionnaires.

One advantage of the relatively long recruitment period is that the exogenous exposures have changed over time. There have been significant changes in dietary patterns and other life style habits from 1999 to 2009. Infectious diseases, such as influenza, are not due to the same agents in every season. Vaccination against pneumococcal disease was introduced for infants in 2006, and we could demonstrate a reduction in the occurrence of lower respiratory tract infections using MoBa data (25).

Researchers are beginning to exploit the inbuilt family design in MoBa. Presently, grants from the RCN and the European Research Council allow us to perform whole-genome SNP genotyping for 11,000 randomly selected trios (mother, father, child). This resource will be important for both discovery and replication studies for gene-disease associations, but

also opens the field for gene-gene and gene-environment interactions in relation to disease development on a larger scale. In this issue, an example of feto-maternal gene interaction on variability in birth weight is demonstrated (26). We have also performed exome sequencing for a smaller number of trios with the aims of detecting de novo mutations and the presence of rare disease-promoting alleles and chromosomal changes associated with autism spectrum disorders. The discordant co-sibling design is increasingly used among the large number of sibships in MoBa, one example being the finding that prolonged intake of paracetamol in pregnancy was associated with adverse child developmental outcomes at three years (27).

## Future

The opportunities and advantages of MoBa increase over time. MoBa is a family and population based cohort currently with participants that are related as mothers, fathers, children, siblings, twins and even triplets. There may also be sisters and brothers among the parents. Additional recruitment among grandparents and other siblings could be considered. The cohort is embedded in the Norwegian Medical Birth Registry and other registries can be used to follow up the complete cohort and to assess selection biases in MoBa and subcohorts within MoBa. This is an advantage of running a cohort in Norway that only a few other countries can match. While we will see similar cohorts develop in many other countries, such as England (The Life Study), China and South Korea, MoBa and the Danish National Birth Cohort (DNBC) will continue to be of great value due to the length of follow-up and linkage to national registries. Similar cohorts are future collaborators and replicators of findings in MoBa, rather than competitors. We expect the quest for more reliable and valid scientific knowledge to increase rapidly, and infrastructures for research such as MoBa and national registries to develop as a response to the need for knowledge. Thus, the challenge is to use and develop MoBa further to be able to maintain our competitive advantages.

Our first priority and obligation is to analyze existing data and samples. Scientifically, we want more highly ambitious applications, projects and publications. MoBa represents an excellent opportunity for high quality research, and we believe that we have only seen the beginning of MoBa's scientific opportunities. Samples should preferably be analyzed in large scale MoBa-driven projects to ensure that they become part of the shared MoBa resource which is accessible for the broad research community, rather than restricted to specific research projects. The oldest children in MoBa are already adolescents. We need to address issues regarding puberty immediately, and prepare for issues of relevance for young adults.

Although science based on the existing MoBa resource is our priority number one, we also aim to expand MoBa through additional recruitment and further data and sample collections. We should consider inviting family members to participate, and to fund new cycles of collection of biological samples.

In addition, we want to develop new ways of communicating with and involving MoBa participants, streamline the governance and administration of MoBa, develop communication of ongoing projects and results to the society at large nationally and internationally, and establish a broad collaboration with the Danish cohort.

MoBas scientific challenges (28) are increasing. The complex diseases have not become less complex while MoBa has been under development. The idea behind the study was to assemble as many different exposures as possible along the way from fetal life to adulthood. The biological material has proven to be useful for measuring exogenous exposures, genes, proteins and metabolites as well as biomarkers of early disease. A disadvantage is that we have not had financial opportunities to include repeated blood sampling for all participants.

We are now preparing new questionnaires to be sent to mothers and fathers. One intention is to understand parental influences on child health, but we are increasingly interested in the health of the parents themselves. Chronic, non-communicable diseases dominate the burdens of disease in all countries. Better prevention of these diseases will have enormous impact on the health of our aging populations. The findings from genome-wide association studies tell us that most of these diseases are genetically heterogeneous. In a few years we hope to be able to sort out these complexities as well as to better understand the environmental impact.

## References

1. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health* 1951; **41**: 279-86.
2. Doll R, Hill AB. The mortality of doctors in relation to their smoking habits. A preliminary report. *BMJ* 1954; **228**: 1451-55.
3. Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand* 2000; **79**: 435-9.
4. Irgens LM. The background of the Norwegian Mother and Child Cohort Study. *Norsk Epidemiologi* 2014; **24** (1-2): 7-8.

5. Bakketeig LS. Why did we start the MoBa study? *Norsk Epidemiologi* 2014; **24** (1-2): 9.
6. Hanson M, Godfrey KM, Lillycrop KA, Burdge GC, Gluckman PD. Developmental plasticity and developmental origins of non-communicable disease: theoretical considerations and epigenetic mechanisms. *Prog Biophys Mol Biol* 2011; **106**: 272-80.
7. Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *Brit J Prev Soc Med* 1977; **31**: 91-5.
8. Barker DJ. Fetal origins of coronary heart disease. *BMJ* 1995; **311**: 171-4.
9. Nordhagen R, Lie KK. The Norwegian Mother and Child Cohort Study (MoBa) – its birth and early development. *Norsk Epidemiologi* 2014; **24** (1-2): 15-22.
10. Hareide B. How the "Newborn cohort" was established in terms of management and governance – a personal report from Bodolf Hareide, general director of NIPH from 1984 to 2001. *Norsk Epidemiologi* 2014; **24** (1-2): 11-2.
11. Haug K, Schreuder P. Choosing a model for recruiting 100,000 pregnant women to the Norwegian Mother and Child Cohort Study (MoBa). *Norsk Epidemiologi* 2014; **24** (1-2): 13-4.
12. Stoltenberg C, Schjølberg S, Bresnahan M, Hornig M, Hirtz D, Dahl C, et al. Perspective: The Autism Birth Cohort (ABC): a paradigm for gene-environment-timing research. *Molecular Psychiatry* 2010; **15**: 676-80.
13. Stoltenberg C, Budin-Ljøsne I, Harris JR, Hveem K. From Biobanks for health to Biobank Norway. *Norsk Epidemiologi* 2012; **21** (2): 135-9.
14. Magnus P, Irgens LM, Haug K, Nystad W, Skjærven R, Stoltenberg C and the MoBa study group. The Norwegian Mother and Child Cohort Study. *Int J Epidemiol* 2006; **35** (5): 1146-50.
15. Surén P, Schjølberg S, Øyen A-S, Lie KK, Hornig M, Bresnahan M, et al. The Autism Birth Cohort (ABC): a study of autism spectrum disorders in MoBa. *Norsk Epidemiologi* 2014; **24** (1-2): 39-50.
16. Biele G, Zeiner P, Aase H. Convergent and discriminant validity of psychiatric symptoms reported in The Norwegian Mother and Child Cohort Study at age 3 years with independent clinical assessment in the Longitudinal ADHD Cohort Study. *Norsk Epidemiologi* 2014; **24** (1-2): 169-76.
17. Nystad W, Magnus MC, Parr CL, Håberg SE, on behalf of the MoBa Asthma Group. Causal pathways for asthma (CASPAR) – MoBa "a happy hunting ground". *Norsk Epidemiologi* 2014; **24** (1-2): 103-6.
18. Brantsæter AL, Haugen M, Alexander J, Meltzer HM. Validity of a new food frequency questionnaire for pregnant women in the Norwegian Mother and Child Cohort Study (MoBa). *Matern Child Nutr* 2008; **4**: 28-43.
19. Klungsøyr K, Harmon QE, Skard LB, Simonsen I, Austvoll ET, Alsaker ER, et al. Validity of pre-eclampsia registration in the Medical Birth Registry of Norway for women participating in the Norwegian Mother and Child Cohort Study, 1999-2010. *Paediatr Perinatal Epidemiol* 2014; **28**: 362-71.
20. Bjørk MH, Veiby G, Spigset O, Gilhus NE. Using the Norwegian Mother and Child Cohort Study to determine risk factors for delayed development and neuropsychiatric symptoms in the offspring of parents with epilepsy. *Norsk Epidemiologi* 2014; **24** (1-2): 79-89.
21. Stene LC, Joner G, Størdal K. Prediction of autoimmune diabetes and celiac disease in childhood by genes and perinatal environment: Design and initial aims of the PAGE study. *Norsk Epidemiologi* 2014; **24** (1-2): 111-9.
22. Schreuder P, Alsaker E. The Norwegian Mother and Child Cohort Study (MoBa) – MoBa recruitment and logistics. *Norsk Epidemiologi* 2014; **24** (1-2): 23-7.
23. Paltiel L, Haugan A, Skjerden T, Harbak K, Bækken S, Stensrud NK, Knudsen GP, Magnus P. The biobank of the Norwegian Mother and Child Cohort Study – present status. *Norsk Epidemiologi* 2014; **24** (1-2): 29-35.
24. Dwyer T, Tikellis G, Ghantous A, Lemeshow S, Håberg SE, Olsen J, et al. MoBa and the International Childhood Cancer Cohort Consortium (I4C). *Norsk Epidemiologi* 2014; **24** (1-2): 129-33.
25. Magnus MC, Vestrheim DF, Nystad W, Håberg SE, Stigum H, London SJ, et al. Decline in early childhood respiratory tract infections in the Norwegian mother and child cohort study after introduction of pneumococcal conjugate vaccination. *Pediatr Infect Dis J* 2012; **31**: 951-5.
26. Farrell LE, Hiby SE, Apps R, Chazara O, Trogstad L, Gjessing HK, et al. KIR and HLA-C: Immunogenetic regulation of human birth weight. *Norsk Epidemiologi* 2014; **24** (1-2): 107-10.
27. Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. *Int J Epidemiol* 2013; **42**: 1702-13.
28. Magnus P. The Norwegian Mother and Child Cohort Study (MoBa) – new research possibilities. *Norsk Epidemiologi* 2007; **17**: 107-10.