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COHORT PROFILE

Cohort profile: The Norwegian Mother and Child Cohort Study (MoBa)

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How did the study come about?

The Norwegian Mother and Child Cohort Study (MoBa) was planned in the 1990s partly by researchers at the Medical Birth Registry of Norway (MBRN)[1] and partly by researchers at the National Institute of Public Health (from 2002 comprising MBRN as well as other institutions and renamed the Norwegian Institute of Public Health (NIPH). The study had a long planning phase involving many scientists who contributed ideas that helped to design questionnaires and to structure the biobank, which is described in detail elsewhere.[2] Collaboration was established with the Danish Birth Cohort Study,[3] which was planned in parallel with MoBa. In 1997, a pilot study was undertaken, recruiting pregnant women at their first visit to their general practitioner. However, the main study did not implement this data collection method owing to protests made by a group of general practitioners who argued against the scientific value of the study and suggested that women would be unduly worried by its focus on risks of disease. As a consequence of the protests, the Parliament Social Committee ordered the Ministry of Health to abandon further planning until these issues had been reviewed. After the review by the Committee in 1998, Parliament voted in favour of the study. The government provided seed money. The NIPH decided to commence the study on a small scale and expand as funds became available. The total cost during the recruitment period (1999–2008) has been estimated at ~45 million dollars. Roughly two-thirds of the funding comes directly from the Ministry of Health and the NIPH. The Research Council of Norway decided early on that it would not support basic data collection but has supported DNA extraction through a programme on functional genomics. The remaining funds have been derived from national and international (National Institutes of Health, USA and integrated projects within the Frameworks for Research in the European Union) funding based on research collaboration. However, the data collection has yet to be completely funded. Sub-projects requiring additional data collection must have separate funding.

What does it cover?

The objective of MoBa is to test specific aetiological hypotheses by estimating the association between exposures (including genetic factors) and diseases, aiming at prevention. The planning has not been made on the basis of any single hypothesis or even any set of hypotheses, as one cannot foresee the specific research questions that will emerge 10–50 years ahead. Furthermore, many of the current questions may have been resolved long before the data collection is complete. The strategy is, therefore, to collect data on as many relevant exposures and health outcomes as feasible.

Who is in the sample?

Norway has ~4.5 million inhabitants, and ~55 000 births a year. The target population of the study is all women who give birth in Norway. There are no exclusion criteria. All hospitals and maternity units with more than 100 births annually, altogether 52 units, are to be included, and by January 2006, 50 units participate in the study. For practical reasons, the sampling frame comprises pregnant women who attend routine ultrasound examination. Together with appointments for ultrasound scanning in week 17–18 of pregnancy, the pregnant women receive a postal invitation that includes an informed consent form, the first questionnaire, an information brochure as well as consent form and questionnaire for the father.

The pregnancy is the unit of observation, and a woman can participate in the study with more than one pregnancy. Each pregnancy is given an identification number, and all other data, be it from the mother, father, or the child, are linked to this number. A participant is a pregnant woman who has sent in a written informed consent to participate. The consent states that biological material is only to be used for the study of causes of disease and that analyses can also be performed in other countries. No laboratory results will be provided to the participants. They agree that MoBa can access health registries as long as it is within the general aim of the study. The participants can choose to withdraw at any time (will not receive more questionnaires) or to be deleted from the study

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Table 1 Participation percentages and numbers of included pregnancies by year of recruitment and pregnancy number in the MoBa study, 1999–2005

Year of recruitment	Pregnancy 1[a]		Pregnancy 2		Pregnancy 3		Pregnancy 4		Total	
	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*
1999	47.0	862							47.0	862
2000	50.6	2643	37.5	9					50.6	2652
2001	47.8	5603	30.4	102					47.3	5705
2002	44.0	10 521	34.7	457					43.5	10 978
2003	42.8	11 617	34.1	1105	23.8	20			41.8	12 742
2004	44.2	11 819	36.0	2107	35.6	90	11.1	1	42.6	14 017
2005	41.5	13 820	36.8	3154	32.2	202	20.0	4	40.4	17 180
Total	43.8	56 885	35.8	6934	31.8	312	17.2	5	42.7	64 136

[a] Pregnancy number 1 is the first pregnancy in which the woman was invited (not the same as birth order 1).

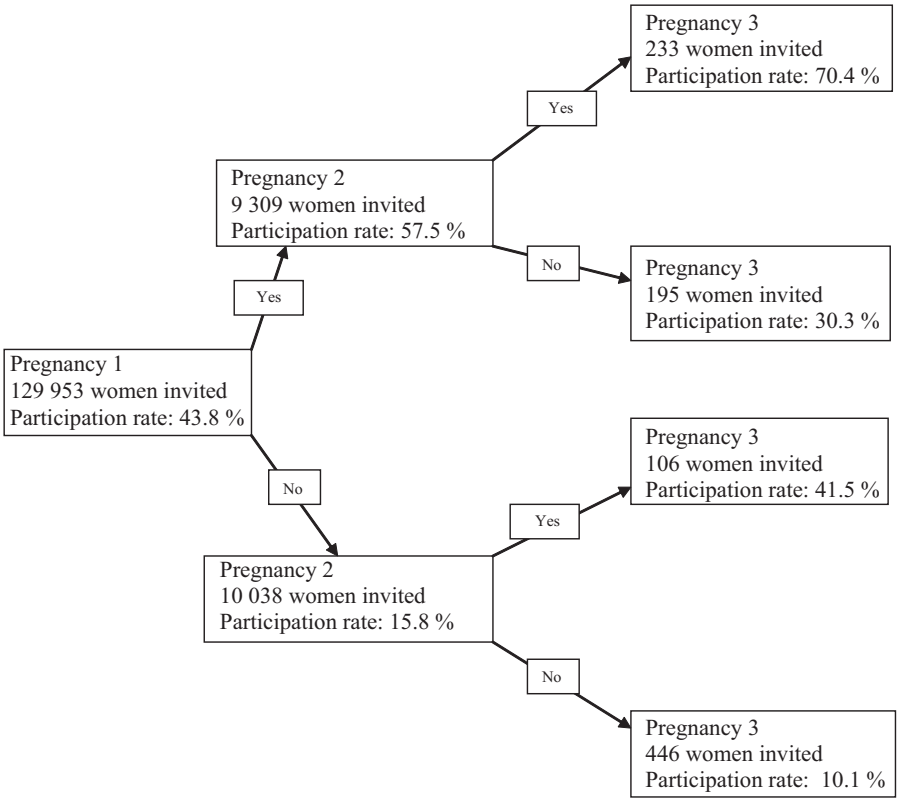

Figure 1 Participation rates by participation in previous pregnancies. Pregnancy 1 means the first pregnancy in which the woman was invited to participate in MoBa, and it does not correspond to birth order

(so that all data are deleted). New sub-projects require a new written consent if they imply direct contact with the participants. A detailed protocol of the study including the consent can be found elsewhere (http://www.fhi.no/morogbarn).

From mid-year 1999 to the end of 2005, 150 309 pregnant women have been invited to participate. Since many women have been invited more than once during this time period, the number of different women that have been invited is lower: $n = 129\,953$. We define the first pregnancy for which a woman is invited pregnancy 1; this does not necessarily correspond to birth order. Table 1 shows the participation rates by pregnancy number and year of ultrasound appointment. The total participation rate for all invited pregnancies is 42.7% (64 136/150 309), whereas the participation rate for women is 45.0% (58 515/129 953). Among participating women, 53 060 (90.7%) participate with one pregnancy, 5290 (9.0%) with two pregnancies, 164 (0.3%) with three, and one woman with four.

This participation rate has decreased from 1999 to 2005 but is more stable within pregnancy number (Table 1). As shown in Figure 1, the rate of recruitment in pregnancies 2 and 3 depended on the response to the invitation in earlier pregnancies. The participation rate when invited for a second time was 57.5% if the woman participated in MoBa in the preceding pregnancy and 15.8% if she did not. The participation rate was

70.4% if she participated in both two preceding pregnancies. In 55 991 of the pregnancies (87.3% of all participating pregnancies), the father was invited to participate and in 46 438 (82.9%) of these he consented to participate.

How often have they been followed-up?

The hospitals provide lists of pregnant women, which include the national identification number, name, address, and date of ultrasound appointment. These lists are the basis for the postal invitation. When she attends the ultrasound examination, the woman is asked whether she has consented to participate. If yes, the woman is referred to the laboratory for blood and urine samples and, if he consents, also a blood sample from the father. If a woman or a couple decides to participate in the study while attending the ultrasound examination, a consent form can be filled out there and then.

Based on the date of the ultrasound scan and, subsequently, the estimated date of birth (taken from the ultrasound registration form, which is routinely sent to the study) or, if this is missing, the recorded date of last menstrual period (information from hospital lists), the timing of contacts with the participants is determined.

All filled-in questionnaires are sent by mail to a central facility where they are registered, scanned, and verified. Furthermore, a series of identity checks is made, and the answers to specific questions are checked for logical content and consistency. The first questionnaire (Q1: 16 pages), received in pregnancy weeks 13–17, asks for data on outcomes of previous pregnancies, medical history before and during pregnancy, medication, occupation, exposures in workplace and at home, lifestyle habits, and mental health. A food frequency questionnaire (14 pages) is sent to participants at about week 22 of pregnancy. A third questionnaire is sent at 30 weeks (16 pages) and covers the woman's health status during pregnancy as well as changes in work situation and habits. A questionnaire when the child is 6 months (16 pages) has a focus on child health and nutrition as well as maternal disorders, well-being, and mental health. Questionnaires at 18 months and 3 years have a main focus on the child's developmental status. A questionnaire is planned when the children are 7 years old. The paternal questionnaire (16 pages) covers exposures at work, lifestyle, and medical history. After quality control, all data are entered into an Oracle database organized in many sub-components. The MBRN-record is added as well as all new variables generated by linkage or analyses of biological specimens. All biological samples are sent to a central biobank for registration, processing, and storage.[2] Further follow-up after 7 years has not yet been determined.

What has been measured?

In addition to the questionnaire variables (http://www.fhi.no/morogbarn), variables are added as a result of laboratory analyses or record linkage. Norway has several mandatory national health registries. For every birth that takes place in Norway after gestational week 16 (from 2002 week 12), a medical record is sent to the MBRN.[1] All records from this registry for MoBa participants are included in the study database. In addition to the MBRN, a cancer registry, a prescription database, a cause of death registry, and a vaccination registry exist. The Ministry of Health has also recently proposed that a Norwegian patient registry (hospital and outpatient clinic discharge registry) shall be established. Thus, even if no questionnaires or biological samples are returned from the participating woman, her partner, or the child, her pregnancy will provide information.

What is attrition like?

During pregnancy, all three questionnaires (Q1–Q3) were well received with response rates between 92 and 95% (Table 2). After birth, the response rates dropped to 87% for the 6 month (Q4) and 77% for the 18 month questionnaires (Q5). There was no large variability in response by year of recruitment. Of those fathers who provided consent, the response rate to the questionnaire on paternal health and exposures was 94.6%.

Since sending in their written consent, women contributing 917 pregnancies (1.4%) to MoBa have decided that they no longer want to participate in the sense that they do not want to receive more questionnaires. In addition, 19 women have demanded that all data supplied by them should be deleted. Also, 438 women (0.7%) have been lost to follow-up.

The main selection is related to the low rate of recruitment (42.7%). Table 3 shows that there are minor differences between the MoBa births and the total number of births in the same period.

Table 2 Response rates (%) and number of returned questionnaires (Q1–Q5) in MoBa according to year of recruitment into the study

	Q1		Q2		Q3		Q4		Q5	
	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*
1999	96.4	831	93.3	795	94.0	373	90.6	763	79.7	662
2000	89.7	2364	88.5	2325	88.7	2037	85.7	2169	76.8	1926
2001	92.6	5282	92.1	5253	91.5	5112	87.8	4831	77.6	4256
2002	94.7	10 393	94.3	10 356	92.7	9991	87.7	9406	76.9	8180
2003	95.7	12 191	95.5	12 164	93.1	11 672	88.1	11 001	75.8	9412
2004	95.6	13 393	93.6	12 742	92.1	12 632	85.3	11 692		
2005	95.5	16 401	91.0	13 471	90.0	11 213				
Total	94.9	60 855	93.1	57 106	91.8	53 030	87.0	39 862	76.7	24 436

Questionnaires 1–3 are sent during pregnancy, Q4 6 months after birth and Q5 18 months after birth.

Table 3 Distribution of parity, maternal age, preeclampsia, gestational age, preterm birth (below 37 weeks), birth weight, and low birth weight (<2500 g) for 26 777 participants in MoBa and for the total 226 057 births in Norway 2000–2003

	MoBa participants	Total population
Parity (%)		
0	40.3	40.7
1	36.9	35.7
2+	22.8	23.6
Maternal age (%)		
<20	1.2	2.4
20–24	11.1	14.9
25–29	34.7	34.2
30–34	37.5	33.2
35+	15.5	15.3
Preeclampsia (%)		
Yes	3.8	3.9
Gestational age (days)		
Mean (SD)	277.3 (14.7)	276.8 (15.0)
Median	280	279
Preterm birth (%)		
Yes	7.2	7.7
Birth weight (g)		
Mean (SD)	3587 (626)	3538 (632)
Median	3630	3575
Low birth weight (%)		
Yes	4.6	5.1

The births have gestational age >22 weeks and birth weights >400 g.

What are the main strengths and weaknesses?

A weakness that must be discussed in relation to each specific research question is the possible selection bias related to low recruitment or loss to follow-up. It is likely that there is a socioeconomic gradient that influences prevalence estimates, as reflected in the lower rates of preterm birth and low birth weight (Table 3). However, the aim of MoBa is to provide valid estimates of associations between putative causal factors and disease, and both the prevalence of exposures and diseases may be different from what is found in the total population, but the estimate of association can still be valid. Several validity studies will be performed in MoBa to address this question.

In 1999, at the first collaborating hospital, the study started to recruit pregnant women based on their appointments for ultrasound scans. The slow start had the advantage that procedures in the laboratory and data collection instruments could be evaluated and adjusted. Also, new elements could be added to the data collection. In 2000, it was decided that fathers should also be invited to join the study. From 2002, a maternal urine sample and an extra blood sample have been collected and, from 2005, RNA from the umbilical cord has been included.

MoBa has several valuable sub-designs. One is the case–parent design, which opens the possibility of detecting effects of maternal genes, fetal genes, and their interaction. Case–parent triads can be stratified by environmental exposure to detect gene–environment interactions. Another sub-design is the repeated pregnancy design, in which the maternal genome is unchanged, the fetal genotype is in each pregnancy a random sample from the parental genotypes and the environment may change. By modelling this design, the interaction between the maternal genotype and the environment can be partitioned out as can also the interaction between the fetal genotype and the environmental exposure. Other designs are the nested case–control study and the establishment of specific sub-cohorts that can be followed with more close clinical assessments.

Large variability in exposures strengthens a cohort study. MoBa has a long recruitment period and covers many geographically different areas. We decided not to collect cells but to include urine, plasma, extracted DNA and RNA in many aliquots. This will serve many researchers, but can be criticized by researchers with more specific interest in cell metabolism. A strength of MoBa is that measures of both genes and the environment are available in the same study. Among cohort studies, pregnancy cohorts are particularly valuable since environmental exposure in pregnancy are included, whether these measures are obtained through biomarkers or questionnaires. In addition, biomarkers can detect early, sub-clinical signs of disease development.

The prenatal period has been highlighted as a sensitive period for exposures that may have lasting effect on the risk of many complex diseases. One example of a hypothesis that is possible to test is the fetal programming hypothesis,[4] suggesting that adverse environmental conditions, acting through fetal growth restriction, are determinants for diseases in later life. Owing to the amount of data assembled by MoBa, one can also test the alternatives; that the associations between fetal growth restriction and adult disease may be due to pleiotropic genes or to more permanent environmental influences that are related to socioeconomic status.

Pregnancy cohorts, such as the Danish National Birth Cohort[3] and ALSPAC[5] are richer sources for aetiological studies than cohorts starting at birth. A large series of hypotheses can be addressed in MoBa alone. To enhance scientific quality, international collaboration is essential. Also, for the study of rare diseases and gene–environment interactions, MoBa will join forces with other pregnancy cohorts.

Can I get hold of the data? Where can I find out more?

A set of guidelines for researchers applying for data has been set up (http://www.fhi.no/morogbarn). The main criterion for access to data is scientific quality. A short protocol with specific research question, choice of variables, and plan for analysis and publication must be provided. A contract is signed for each data delivery.

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