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Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa)

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Abstract

This is an update of the Norwegian Mother and Child Cohort Study (MoBa) cohort profile which was published in 2006. Pregnant women attending a routine ultrasound examination were initially invited. The first child was born in October 1999 and the last in July 2009. The participation rate was 41%. The cohort includes more than 114 000 children, 95 000 mothers and 75 000 fathers. 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 and from mothers and children (umbilical cord) after birth. Samples of DNA, RNA, whole blood, plasma and urine are stored in a biobank. During pregnancy, the mother responded to three questionnaires and the father to one. After birth, questionnaires were sent out when the child was 6 months, 18 months and 3 years old. Several sub-projects have selected participants for in-depth clinical assessment and exposure measures. The purpose of this update is to explain and describe new additions to the data collection, including questionnaires at 5, 7, 8 and 13 years as well as linkages to health registries, and to point to some findings and new areas of research. Further information can be found at [www.fhi.no/moba-en]. Researchers interested in collaboration and access to the data can complete an electronic application available on the MoBa website above.

Key Messages

- MoBa is a pregnancy cohort with a family design. The oldest children are now teenagers. The cohort is open for international collaboration. The main aim is to understand the etiology of complex diseases.

What is the rationale for the new data collection beyond age 3 years?

The Norwegian Mother and Child Cohort Study (MoBa) was planned in the early 1990s by a group of perinatal epidemiologists who had been using data from the Medical Birth Registry of Norway (MBRN) for a long time and mainly studied pregnancy outcomes such as birthweight, pre-eclampsia, preterm birth, stillbirth and congenital malformations.[1] There was a clear need for better exposure data if new aetiological factors, such as infections, genes, medications, pollutants, nutritional factors and lifestyles, were to be detected. Another impetus at the time was the fetal origins of adult disease hypothesis.[2,3]

The main aim of MoBa is therefore to detect causes of serious diseases through estimation of specific exposure-outcome associations especially among the children but also among parents. It has, however, become clearer that MoBa contributes to the description of disease trajectories and comorbidities, as well as to the analyses of factors that are associated with progression of disease. MoBa also serves as a source of research on the social determinants of health and on health as a determinant of educational, social and economic achievement. This is accomplished by assembling as many data as possible on exposures, mediators, effect-modifying variables and outcomes, so that data are in place to answer as many research questions as possible.[4] This consideration remains the rationale for the new data collections.

New data collections extend the observation period for children, and plans are presently being made for further follow-up through adolescence. The intention is to collect data on lifestyle habits and other exposures, as well as to capture the occurrence of diseases in this period of life. The data on parental exposures and outcomes are relevant for understanding their offspring's health, but are equally important for aetiological analyses of the diseases that occur among themselves.

What will be the new areas of research?

The scientific landscape has changed. In the early 1990s, one did not envisage the wealth of research possibilities that would emerge from genotyping, sequencing, epigenetics, transcriptomics, proteomics, metabolomics or the study of the exposome. The prospect of personalized prevention and treatment of disease through genetic specificity is new. MoBa is a large cohort with rich exposure and endpoint information, and can respond to the challenge of estimating joint effects of genes and environment. The individual genetic and environmental exposure information, linked to the Norwegian Prescription Database[5] and disease registries in longitudinal studies, will be a rich source for studies of precision medicine.

Recent studies of single-gene disorders have taught us that many different mutations may give nearly identical phenotypes. The mutations may be in the same gene, as for cystic fibrosis, but also in different genes. A large number of genes show associations to complex diseases and traits in genome-wide studies. Understanding the genetic heterogeneity of complex diseases is a challenge for the coming years. MoBa has a trio (mother, father and child) design, which resolves the problem of population admixture as a confounder in gene-disease associations. In addition, in about 16 400 families, two or more pregnancies were included in the cohort. The discordant (either for exposure or disease) sibling design also removes family-constant confounding factors. Associations between diseases and high-dimensional data (genes, proteins, metabolites) within and between families will be essential for dissecting the heterogeneity of complex disorders, in the same way that genetic analyses in families have clarified the molecular heterogeneity in single gene disorders.

In a new project called HARVEST that also includes other Norwegian cohorts, funded partly by the Norwegian Research Council and partly by the European Research Council, we have performed single nucleotide polymorphism (SNP) genotyping in 11 000 randomly selected trios in MoBa, using the Illumina Human Core Exome Bead Chip [http://www.illumina.com/products/humancore_exome_beadchip_kits.html]. HARVEST is important for Norwegian population genetics and will be a powerful tool for in-depth understanding of the myriad of diseases and other phenotypes that can be studied in MoBa. Genome-wide association studies have been performed for preterm birth, hyperemesis and pre-eclampsia in nested case-control studies, and whole-genome methylation in cord blood has been performed in a random sample of 1000 children plus 400 children who developed asthma. Exome sequencing has been performed in autism trios.

Although infectious diseases are still important and emerging threats present new challenges, non-communicable diseases are responsible for the major part of the global burden of disease.[6] New aetiological insights are needed if these diseases are to be prevented and better managed. We will gather new data on exposures and health outcomes in mothers and fathers. Table 1 shows the age distribution of participants as of September 2015. The mean age of the mothers is 40.8 years. Almost 53% of the mothers are between 40 and 50 years old, and 3.6% are 50 years old or more. For fathers, the mean age is 43.0 years, with 59.0% between 40 and 50 years and 10.9% above 50. In the years to come, we can predict that MoBa data

Table 1. Age distribution of participants in the Norwegian Mother and Child Cohort Study (MoBa) as of September 2015

	Mothers		Fathers	
Mean age (SD) years	40.8 (5.2)		43.0 (5.8)	
	n	(%)	*n*	(%)
< 30 years	1796	1.9	523	0.7
30–34	11113	11.7	4754	6.3
35–39	28406	29.8	17444	23.1
40–44	33924	35.6	27324	36.2
45–49	16552	17.4	17247	22.8
50+	3448	3.6	8190	10.9
	Children			
Mean age (SD) years	10.2 (2.2)			
	n	(%)		
6–7 years	21639	18.9		
8–9	36376	31.8		
10–11	29842	26.1		
12–13	21130	18.5		
14+	5492	4.8		

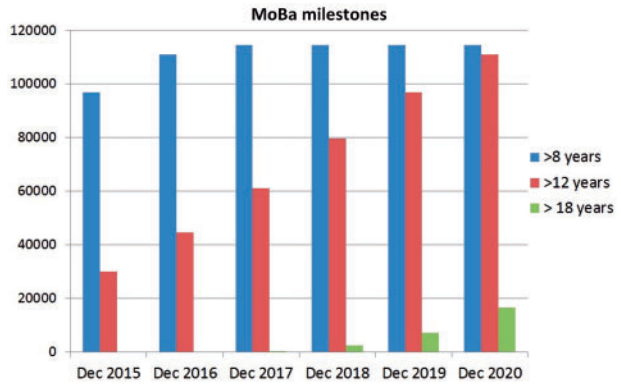

Figure 1 The figure shows the number of children in MoBa who have reached the ages of 8, 12 and 18 years according to calendar time.

will be used in a multitude of studies of the aetiology, pathogenesis, natural history and consequences of non-communicable diseases. One specific example of interest is the follow-up of women with diseases in pregnancy, for instance pre-eclampsia which has been linked to increased risk of later cardiovascular disease.[7]

The mean age of the children is now 10.2 years (Table 1), and the proportion aged above 10 years is 49.3%. Figure 1 shows that all children will be above 7 years of age by December 2016. The first signs of neurological (e.g. multiple sclerosis), psychiatric (e.g. schizophrenia), autoimmune (e.g. type 1 diabetes) and many other chronic disorders will be recognized in adolescence and early adulthood. A decision has not yet been made to what extent MoBa shall be expanded to include children of the children.

Table 2. Numbers of pregnancies, mothers, fathers and children participating in the Norwegian Mother and Child Cohort Study (MoBa) as of September 2015. Note that many mothers and fathers have participated in more than one pregnancy

	Recruited[a]	All participants[b]	Active participants[c]
Pregnancies	112908	112762	101545
Pregnancies, fathers included	87436	87302	78726
Mothers	95369	95244	86169
Fathers	75618	75500	68314
Children	114622	114479	103219
Pairs of twins	1950	1946	1705
Sets of triplets	21	21	17

[a]All recruited participants from 1999 through 2008.
[b]Participants who can be followed through linkage with health registries.
[c]Participants who are sent questionnaires and can be invited to sub-studies.

Who is in the cohort?

In principle, as described earlier,[4] all pregnant women in Norway were eligible for participation. A major restriction was, however, the ability to read Norwegian, as all information material and questionnaires were only in Norwegian. The sampling was opportunistic, due to limited initial funding. The recruitment commenced in a large hospital in the city of Bergen in the summer of 1999 and gradually expanded to include 50 of Norway's 52 hospitals with maternity units.[8]

During the recruitment period, invitations were sent to women in 277 702 pregnancies, with a participation rate of 41%. After the initial phase of recruitment, it was decided to also invite the fathers-to-be. The left column in Table 2 ('recruited') shows the numbers of women and men who were recruited to the cohort from July 1999 to December 2008, together with the number of pregnancies they contributed as well as the number of children that were born. Over the years, more than 100 families have decided to leave the cohort and have their data deleted. The remaining participants are shown in the second column ('all participants'), and they include all subjects who can be followed up through linkage to health registries. Some of these remaining participants have asked not to be sent further questionnaires, but stay in the cohort. Thus, the third column represents subjects who are active participants in the sense that they are sent questionnaires and invitations to sub-studies.

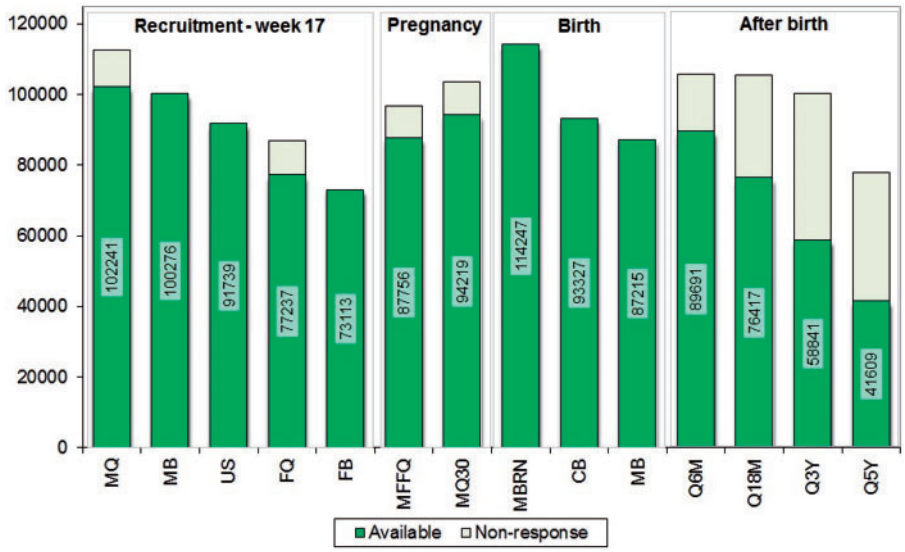

Figure 2 The figure shows the number of responses to questionnaires (MQ = mother, week 17 of pregnancy; FQ = father, week 17; MFFQ = mother, food frequency questionnaire, week 22; MQ30 = mother, week 30; Q6M = 6 months after birth; Q18M = 18 months of age; Q3Y = 3 years; Q5Y = 5 years), number of pregnancies for which external information was added (US = result of ultrasound examination at 17 weeks; MBRN = the pregnancy record in the Medical Birth Registry of Norway) and blood samples (MB = mother, week 17 and after birth; FB = father, week 17; CB = child, umbilical cord).

What has been measured?

The invitation to participate was sent to pregnant women before their appointment for the routine ultrasound scan around pregnancy week 17. The result of the ultrasound scan is kept registered in the MoBa database together with the questionnaire data. The number of responses for each questionnaire is shown in Figure 2 for questionnaires up to age 5. The questionnaires at weeks 17 and 30 include general background information as well as details on previous and present health problems and exposures. Dietary information is part of most MoBa questionnaires. In addition, a semi-quantitative food frequency questionnaire was sent out in week 22 of pregnancy.[9,10] The birth record from the Medical Birth Registry of Norway,[1] which 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 and 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 old. 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. A questionnaire has been developed for participating fathers, and was sent out in December 2015. A questionnaire to be filled in by the children themselves as well as a questionnaire to be filled in by the mother will be sent out when the child is 13 years old. The participation rate for follow-up questionnaires is falling as can be seen in Figure 2. By using the unique identification number given to all residents in Norway, all participants can be linked to a number of health registries (Box 1) to allow a more complete follow-up for many diseases.

Box 1 National health registries that have been linked to the Norwegian Mother and Child Cohort Study (MoBa)

Medical BirthRegistry
National Patient Registry
Cause of Death Registry
Prescription Database
Vaccination Registry
Cancer Registry

Biological material from fathers and mothers was collected when they came to the hospital for the ultrasound scans (Figure 2). DNA was extracted and aliquoted from fresh samples on arrival in the biobank. Plasma was separated at the hospitals and sent in separate vials, and whole blood and plasma were aliquoted and stored as described in more detail in previous publications.[11,12] Additional blood samples and a urine sample were collected in about 78 000

pregnancies at week 17 of gestation for the study of environmental contaminants, funded through a contract with the National Institute of Environmental Health Sciences in the USA. After birth, cord blood was collected and a second blood sample was taken from the mother. In addition to DNA and plasma from umbilical cord blood samples, an RNA sample was included from about 45 000 children. Primary teeth were collected when the child was between 6 and 7 years.[13] Biological materials have also been collected from participants who take part in sub-studies. One example is a study to understand causes and trajectories of autism spectrum disorders.[14] Box 2 gives a list of diseases for which sub-studies have assembled additional data and specimens. In the 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.

Box 2 Diseases that are followed with additional data collections in sub-cohorts in the Norwegian Mother and Child Cohort Study (MoBa)

Autism spectrum disorders (ASD)
Attention-deficit hyperactivity disorder (ADHD)
Epilepsy
Cerebral palsy
Language development
Asthma
Inflammatory bowel disease
Coeliac disease
Type 1 diabetes

What has been found using MoBa data?

About 400 papers, covering a large range of exposures and outcomes, have been published using data from the MoBa study [www.fhi.no/moba-en]. Some of the papers have negative findings in the sense that no link has been found between a specific exposure and disease. One of the benefits of MoBa is the ability to reduce undue worry among pregnant women. Such unnecessary worry may be connected to use of medications, for instance antidepressants, anxiolytics or hypnotics, or environmental exposures, such as cellphones.[15,17] MoBa has also led to some potentially important findings relating to different exposures. Some examples are: peri-conceptional supplementation of folate apparently reduces the risks of autism and severe language delay in children;[18,19] use of antiepileptic drugs is associated with adverse child development at 18 and 36 months;[20] paracetamol use during pregnancy is associated with delayed neurodevelopment in children;[21] early infections are associated with increased risk of coeliac disease;[22] high level of relationship satisfaction predicts lower risk of maternal infections during pregnancy;[23] male obesity is related to increased risk of infertility;[24] grandmaternal smoking is associated with increased risk of asthma;[25] maternal smoking seems to lead to epigenetic changes in the child;[26] intake of probiotic dairy products is related to reduced risk of preterm birth;[27] introduction of pneumococcal vaccination in 2006 is associated with reduced risk of childhood respiratory tract infections;[28] acrylamide intake in pregnancy is associated with reduced fetal growth;[29] and maternal dietary pattern is related to the risk of preterm birth.[30] Some results extend or supplement earlier observations, but many are new and will require replication in other studies.

What are the main strengths and weaknesses?

An obvious strength is the large sample size which allows studies of relatively rare disorders as well as gene-environment interactions. The family structure supports inquiries into maternal and paternal genetic effects on offspring phenotypes. The relationships between parent-offspring, spouses, siblings, twins and half-sibs are well suited for quantitative genetic studies. Prospectively collected biomaterials can be used for hypothesis-driven research as well as hypothesis-free searches into human and microbial genetic and metabolic structures and pathways. In this respect, MoBa will partner with other cohorts using state-of-the-art methodologies. The possibility of measuring biomarkers for exposure is particularly valuable for understanding the contribution of environmental hazards in disease causation, in a setting where confounders can be controlled for. The cohort approach furthermore means that predictive biomarkers and early signs of disease can be detected

In such a large cohort, detailed clinical examination of all participants is not possible, and repeated blood sampling has not been conducted except in some sub-projects. This is a clear weakness. However, linkage to health registries is possible. Since these registries are mandatory, we avoid the loss to follow-up selection bias. This type of systematic error complicates the interpretation of studies based on questionnaire or clinical follow-up alone. The potential bias introduced by selective recruitment to the cohort is an obvious limitation regarding prevalence/incidence measures, but appears to have minimal influence on exposure-disease associations. [31]

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

The data are available for researchers with study questions that fall within the general aims of MoBa. Approval from a Norwegian regional committee for medical and health research ethics [https://helseforskning.etikkom.no] is a prerequirement. The MoBa protocol and guidelines for access to data are found at [www.fhi.no/moba-en]. Enquiries can be sent to [Datatilgang@fhi.no].

Conflict of interest: There are no conflicts of interest.

References

1. Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand* 2000;**79:**435–39.
2. Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease?. *Br J Prev Soc Med* 1977;**31:**91–95.
3. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1986;**327:**1077–81.
4. Magnus P, Irgens LM, Haug K *et al*. Cohort Profile: The Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol* 2006;**35:**1146–50.
5. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sørensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol* 2010;**106:**86–94.
6. Murray CLJ, Vos T, Lozano R *et al*. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380:**2197–223.
7. Brown MC, Best K, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. *Eur J Epidemiol* 2013;**28:**1–19.
8. Schreuder P, Alsaker E. The Norwegian Mother and Child Cohort Study (MoBa) – MoBa recruitment and logistics. *Norw J Epidemiol* 2014;**24:**23–27.
9. Meltzer HM, Brantsæter AL, Ydersbond T, Alexander J, Haugen M; Group TMDS. Methodological challenges when monitoring the diet of pregnant women in a large study; experiences from the Norwegian Mother and Child Cohort Study. *Matern Child Nutr* 2008;**4:**14–27.
10. 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.
11. Rønningen KS, Paltiel L, Meltzer HM *et al*. The biobank of the Norwegian Mother and Child Cohort Study: a resource for the next 100 years. *Eur J Epidemiol* 2006;**21:**619–25.
12. Paltiel L, Haugan A, Skjerden T *et al*. The biobank of the Norwegian Mother and Child cohort Study – present status. *Norw J Epidemiol* 2014;**24:**29–35.
13. Tvinnereim HM, Lygre GB, Haug K, Schreuder P, Klock K. A biobank of primary teeth within the Norwegian Mother and Child Cohort Study (MoBa) per 2014: A resource for the future. *Norw J Epidemiol* 2014;**24:**135–40.
14. Stoltenberg C, Schjølberg S, Bresnahan M *et al*. Perspective: The Autism Birth Cohort (ABC): a paradigm for gene–environment–timing research. *Mol Psychiatry* 2010;**15:**676–80.
15. Handal M, Skurtveit S, Furu K *et al*. Motor development in children prenatally exposed to selective serotonin reuptake inhibitors: a large population-based pregnancy cohort study. *BJOG* 2015, Sep 15.
16. Odsbu I, Skurtveit S, Selmer R, Roth C, Hernandez-Diaz S, Handal M. Prenatal exposure to anxiolytics and hypnotics and language competence at 3 years of age. *Eur J Clin Pharmacol* 2015;**71:**283–91.
17. Baste V, Oftedal G, Møllerløkken OJ, Mild KH, Moen BE. Prospective study of pregnancy outcomes after parental cell phone exposure: the Norwegian Mother and Child Cohort Study. *Epidemiology* 2015;**26:**613–21.
18. Surén P, Roth C, Bresnahan M *et al*. Association between maternal use of folate supplements and risk of autism spectrum disorders in children. *JAMA* 2013;**309:**570–77.
19. Roth C, Magnus P, Schjølberg S *et al*. Folic acid supplements in pregnancy and severe language delay in children. *JAMA* 2011;**306:**1566–73.
20. Veiby G, Daltveit AK, Schjølberg S *et al*. Exposure to antiepileptic drugs in utero and child development: A prospective population-based study. *Epilepsia* 2013;**54:**1462–72.
21. 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.
22. Mårild K, Kahrs CR, Tapia G, Stene LC, Størdal K. Infections and risk of celiac disease: a prospective nationwide cohort study. *Am J Gastroenterol* 2015;**110:**1475–84.
23. Henriksen RE, Torsheim T, Thuen F. Relationship satisfaction reduces the risk of maternal infectious diseases in pregnancy: The Norwegian mother and child cohort study. *PLoS One* 2015. doi:10.1371.
24. Nguyen RHN, Wilcox AJ, Skjærven R, Baird DD. Men's body mass index and infertility. *Hum Reprod* 2007;**22:**2488–93.
25. Magnus MC, Håberg SE, Karlstad Ø, Nafstad P, London SJ, Nystad W. Grandmother's smoking when pregnant with the mother and asthma in the grandchild: the Norwegian mother and child cohort study. *Thorax* 2015;**70:**237–43.
26. Joubert BR, Håberg S, Nilsen RM *et al*. 450K epigenome-wide scan identifies differential DNA methylation in newborns related to maternal smoking during pregnancy. *Environ Health Perspect* 2012;**120:**1425–31.
27. Myhre R, Brantsæter AL, Myking S *et al*. Intake of probiotic food and risk of spontaneous preterm delivery. *Am J Clin Nutr* 2011;**93:**151–57.
28. Magnus MC, Vestrheim DF, Nystad W *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:**951–55.

29. Duarte-Salles T, von Stedingk H, Granum B *et al*. Dietary acrylamide intake during pregnancy and fetal growth – results from the Norwegian Mother and Child Cohort Study (MoBa). *Environ Health Perspect* 2013;**121:**374–79.
30. Englund-Ögge L, Brantsæter AL, Sengpiel V *et al*. Maternal dietary pattern and preterm delivery: results from large prospective cohort study. *BMJ* 2014;**348:**g1446.
31. Nilsen RM, Vollset SE, Gjessing HK *et al*. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinatal Epidemiol* 2009;**23:**596–608.