The Norwegian Mother and Child Cohort Study (MoBa) (1) is a valuable resource for studying the effects of maternal alcohol consumption. MoBa’s strengths include a large, population-based sample of over 107,000 pregnancies, concurrent and retrospective assessment of maternal prenatal and postnatal alcohol consumption, and prospective follow-up for pregnancy and child outcomes. Direct questions were asked on the frequency, dose and timing of maternal alcohol consumption. Screening tools including the T-ACE and partial Rutgers Alcohol Problem Index were used to identify women at risk for drinking during pregnancy. Comprehensive information on potential confounders was collected including maternal medical history, reproductive history, smoking, and other substance use. The detailed alcohol data allow the differentiation between non-binge and binge-level drinking, important for studying different thresholds of exposure. The availability of maternal and infant DNA enables the study of genetic differences in alcohol metabolism. Besides conventional analyses, sibship studies of differentially exposed siblings can be conducted among the offspring of over 15,000 women who participated in the study for more than one pregnancy. Although there are low levels of social disadvantage in Norway (poverty increases the risk of harms from prenatal drinking), binge drinking is a common pattern of consumption and previous studies found that drinking alcohol during pregnancy is not uncommon. Here, I provide a brief review of prenatal alcohol literature and measurement issues, describe MoBa alcohol variables, and discuss how MoBa can contribute to maternal alcohol research within the context of Norway.

ACKNOWLEDGMENTS

This is an open access article distributed under the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
exacerbate the effects of alcohol but may also act as independent risk factors for negative outcomes (8).

Whereas there is strong scientific evidence that heavy maternal alcohol consumption is associated with fetal harm (10), there is considerable debate on the risks of lower-level prenatal alcohol consumption (11,12). The evidence for “low to moderate” prenatal alcohol exposure is mixed and overall unconvincing (13-17). The outcomes studied, including child behavioral problems and learning disorders, are non-specific to alcohol and often subjectively evaluated through parent or teacher reports. It may be problematic to disentangle the effects of prenatal alcohol exposure from those of a negative early caregiving environment or other exposures (such as lead) that are also associated with cognitive deficits or behavioral problems (18). In some populations, moderate drinkers have higher education, higher income, better mental health, and stronger social networks than alcohol abstainers or heavy drinkers (19,20), factors that may also be associated with good parenting and positive child outcomes. Some of these attributes are not easily captured by available socio-demographic variables, and it has been suggested that residual confounding could obscure the detrimental effects of lower-level prenatal alcohol exposure or bias results in the opposite direction (17,21). Besides the possibility of biases and confounding, methodological weaknesses of these studies include small sample size and inadequate statistical power, lack of an unexposed referent group, and inadequate alcohol measures (lacking timing or pattern) (17).

The classification of maternal alcohol consumption has varied considerably across studies, and the definition of low and moderate drinking has been inconsistent. The peak blood alcohol concentration (BAC) is thought to be the most important determinant of alcohol-related fetal harm (22,23) and is a critical factor in fetal brain injury (24). Peak BAC is a function of the amount of alcohol consumed, time spent drinking, blood volume, and the rate of alcohol metabolism. In pregnancy, alcohol diffuses across the placenta, reaching concentrations in the fetal circulation similar to that in the mother’s (25). Binge drinking, usually defined as drinking 5 or more drinks per sitting (26) (sometimes 4 or more for women) (27), results in higher peak BACs than drinking fewer drinks over more occasions. Due to the relatively constant rate of alcohol metabolism, the body takes longer to clear the alcohol with binge drinking, resulting in prolonged fetal alcohol exposure (24). Many studies have assessed maternal drinking using the average number of drinks consumed per week but this measure obscures the amount consumed per occasion, which is the best proxy for peak BAC (23). For example, “moderate” consumption of 7-14 drinks per week pools together women drinking as low as one drink per day with those having up to three binge drinking episodes per week. Studies that do not distinguish between non-binge and binge drinking are difficult to interpret in terms of low to moderate exposure because any increased risks may be due to the inclusion of heavy, binge-level drinking.

Genetic variation may also influence fetal exposure. Variants in the genes encoding alcohol dehydrogenase and aldehyde dehydrogenase, the main alcohol metabolism enzymes, produce enzymes with differing rates of metabolism that affect the time required for alcohol clearance (28). These genes are expressed in the placenta and fetal liver (29), suggesting that both fetal and maternal genes may play a role.

**The MoBa Study Alcohol Variables**

MoBa’s data collection methods, maternal alcohol questions, and longterm follow up make it a valuable resource for studying the effects of prenatal alcohol exposure on birth and child outcomes. Alcohol consumption during pregnancy is uncommon in most populations, but MoBa’s large sample size of over 107,000 pregnancies allows the study of a range of alcohol exposures and includes a large group of alcohol abstainers that can serve as the referent group. Data on prenatal exposures were collected prospectively, before the pregnancy ended, which avoids the potential for recall bias. Two complementary approaches were used for the collection of alcohol information: direct questions on alcohol consumption and the use of screening tools. The T-ACE (Tolerance, Annoyed, Cut-Down, Eye-opener) screening tool was used to identify women with alcohol-related problems who were at risk for drinking during pregnancy (30) and five questions from the Rutgers Alcohol Problems Index (31) were used to estimate alcohol problems in the last year. Direct questions on alcohol intake are critical for establishing the amount, frequency, timing, and type of alcohol consumed and the pattern of drinking. Not all risk drinking occurs among people with alcohol problems, so direct questions can identify risk drinkers who would be missed by screening tools. However, direct questions on alcohol use can trigger denial and underreporting, particularly among problem drinkers. Proponents of screening tools suggest that indirect questions on drinking consequences can avoid these problems (32). The availability of data from both direct and indirect questions allows the examination of self-reported prenatal alcohol consumption while taking into account whether the woman had a history of problem drinking.

Information on the frequency of drinking alcohol, the usual number of units consumed per occasion, and the frequency of drinking 5 or more units per occasion was collected across several self-administered questionnaires for different time periods before, during and after the pregnancy (Table 1). Questions on alcohol were asked retrospectively for the three months prior to the pregnancy and concurrently for each of the three pregnancy trimesters. One unit of alcohol was defined
Table 1. Collection of maternal alcohol information by questionnaire number and referent period, MoBa Cohort Study.

| Lifetime/ | Month pre-pregnancy | Month during pregnancy | Month post-pregnancy |
| no time, | Past year | 1-3 | 4-6 | 6-9 | 0-3 | 4-6 | 18 | 36 | 60 | 96 |
| reference |            | Q1 | Q1 | Q3 | Q4 | Q4 | Q4 | Q5 | Q6 | Q-Y5 | Q-Y8 |
| Ever consumed alcohol | Q1 | Q1 | Q1 | Q3 | Q4 | Q4 | Q4 | Q5 | Q6 | Q-Y5 | Q-Y8 |
| Usual type(s) consumed | Q1 | Q1 | Q1 | Q3 | Q4 | Q4 | Q4 | Q5 | Q6 | Q-Y5 | Q-Y8 |
| Frequency of consuming alcohol | Q1 | Q1 | Q3 | Q4 | Q4 | Q4 | Q4 | Q5 | Q6 | Q-Y5 | Q-Y8 |
| Usual number of units consumed per time | Q1 | Q1 | Q3 | Q4 | Q4 | Q4 | Q4 | Q5 | Q6 | Q-Y5 | Q-Y8 |
| T-ACE Screening Tool | Q1 | Q1 | Q3 | Q4 | Q4 | Q4 | Q4 | Q5 | Q6 | Q-Y5 | Q-Y8 |
| Rutgers Alcohol Problem Index | Q1 | Q1 | Q3 | Q4 | Q4 | Q4 | Q4 | Q5 | Q6 | Q-Y5 | Q-Y8 |
| Changes in drinking habits | Q1 | Q1 | Q3 | Q4 | Q4 | Q4 | Q4 | Q5 | Q6 | Q-Y5 | Q-Y8 |
| AUDIT* Screening Tool | Q1 | Q1 | Q3 | Q4 | Q4 | Q4 | Q4 | Q5 | Q6 | Q-Y5 | Q-Y8 |

*Q=questionnaire; Y=year
*Information collected separately for weekdays and weekends
*Partial index: 5 of 18 questions used
*Alcohol Use Disorders Identification Test

as 1.5 cl of pure alcohol and definitions of drink equivalents were provided for different types of alcoholic beverages. The data collected allows for the important differentiation between non-binge and binge alcohol consumption, the further delineation of binge drinkers into periodic bingers and those who drank at binge levels continually (each time they drank), and the estimation of the number of binge drinking episodes. The ability to make these distinctions and quantify the extent of heavy drinking is essential for studying different thresholds of exposure.

Respondents tend to reveal greater consumption of alcohol in self-administered questionnaires than interviews (33), suggesting that MoBa’s mode of data collection may have avoided underreporting of prenatal alcohol consumption. Most studies rely on maternal self-report because even when biomarkers are available, they usually provide no information on timing or dose, and are often meaningful only in conjunction with maternal report (34). A special feature of the MoBa Study is the availability of repeat measures of alcohol consumption for some of the time periods. See Table 1 for the overlap in data collection by referent time period and MoBa Study questionnaire number. For example, women were queried around the end of the first trimester about alcohol intake up to that point in the pregnancy and were later asked again retrospectively (in a subsequent questionnaire) about alcohol intake during the first trimester. Studies have shown that women tend to report greater prenatal alcohol intake retrospectively than concurrently (35-37) perhaps because it is easier to disclose socially sensitive behavior when it occurred in the past. Given that underreporting prenatal drinking is more likely than overreporting (35), one approach to using the repeated self-reports is to use the greatest amount of consumption reported for a particular period when reports differ across questionnaires.

The information on the timing of maternal alcohol consumption is important because it enables researchers to tailor the alcohol exposure to the most relevant period for the particular outcome under study. For example, the first trimester is the relevant exposure period for structural birth defects because organogenesis takes place during this time, whereas alcohol exposures throughout pregnancy could affect cognition and behavior because brain growth and development is ongoing (38). MoBa collected information on changes in drinking habits and the timing of such changes before and during pregnancy, which can be used to further refine exposure measurements. In addition to periconceptional and prenatal drinking, follow-up questionnaires collected ‘snapshots’ of women’s alcohol consumption at various times after the pregnancy. The Alcohol Use Disorders Identification Test (AUDIT) that identifies harmful patterns of alcohol consumption was administered in the 8-year questionnaire. Heavy post-pregnancy maternal drinking and alcohol problems may be indicative of the early home environment and can be taken into account in the assessment of longterm child outcomes.

The characteristics of the MoBa Study data allow for some special study designs and analyses that can facilitate the interpretation of results and strengthen...
causal inference pertaining to prenatal alcohol exposure. The availability of parental and child DNA allows for the study of gene-environment interactions between alcohol metabolism gene variants and prenatal alcohol exposure that, if found, would support causal associations. For example, one would expect the fetus to be more vulnerable to the effects of prenatal alcohol exposure when the mother and/or infant have gene variants for slower alcohol metabolism (39). Sibship studies of differentially exposed siblings are possible due to the large number of women who participated in MoBa for more than one pregnancy. The sibship design provides tight control for familial factors (genetic and social) that are difficult to adjust for in conventional analyses (40). The utility of this design is illustrated in a Swedish study (41) that initially found an association between prenatal smoking and increased risk of low intellectual performance in male offspring in a conventional analysis, but the sibship analysis revealed no association, suggesting that residual confounding accounted for the association in the conventional analysis. The sibship study design requires a sufficient number of siblings who differ on exposure status, but when feasible, it is a powerful method for enhancing causal inference (40).

THE CONTEXT OF NORWAY

MoBa joins other large-scale pregnancy studies and birth cohorts that have examined maternal alcohol consumption including the Avon Longitudinal Study of Parents and Children, the Danish National Birth Cohort, the Generation R Study, the Western Australian Pregnancy Cohort Study, and the UK Millennium Cohort Study, but the particular political and social characteristics of Norway make it a distinctive setting for this research. Norway has low levels of social disadvantage and poverty, which would tend to decrease the risk of harms from prenatal alcohol exposure. However, binge drinking, which produces high BACs that can cause fetal harm, is a common pattern of alcohol consumption (42,43). A wealthy, social-democratic nation, Norway has an elaborate social safety net, free education and universal health care. Relative income poverty is not absent (6.8% in 2004), but is less common than in many other countries (44). Norway has strict policies governing the sale, serving, and use of alcoholic beverages, but social norms are permissive of heavy drinking and drunkenness (45). In general, alcohol consumption tends to be reserved for weekends and special occasions, with large quantities consumed per drinking session (46). In a population-based survey of 28-year old Norwegians, 46% of women reported “usually” drinking 5-6 units or more per sitting, with 4% reporting extremely high usual intake of 10 or more units per sitting; the most important factor predicting alcohol use was parental alcohol habits, with drinking practices seemingly transmitted from one generation to the next (47). Because of the acceptance of heavy drinking in Norway and the relatively high gender equality, there may be less social stigma for women to report alcohol use than in the United States and other settings.

The Norwegian Directorate of Health recommends that women abstain from drinking alcohol during pregnancy (48), but available evidence suggests that prenatal drinking is not uncommon. In a representative sample of pregnant women receiving routine ultrasound in Oslo in 2000-2001, 25% of respondents overall and 20% of those with planned pregnancies reported at least one binge-drinking episode during early pregnancy (37). Characteristics associated with binge drinking in this sample included older maternal age and smoking but not income or education level. A survey sponsored by the Norwegian Health Directorate found that 1 in 4 pregnant women found it difficult to turn down alcohol at work parties or Friday beer gatherings, suggesting that some women feel pressure to partake in social drinking before they have announced their pregnancy publicly (48). The 1997 prevalence of FAS/FASD in Norway was estimated at 0.3 per 1,000 births based on a national survey, but an educational campaign for healthcare and social workers to identify and refer children with FAS/FASD yielded a higher estimate of 1.1 per 1000 in Hordaland County during 1999-2004 (49). For the 41 children identified with FAS or FASD as part of this campaign, prenatal alcohol exposure was likely high – 85% were in foster care, some placed immediately after birth because of the mother’s drinking problem.

Although the MoBa Study had a target enrollment population of all women who gave birth in Norway, less than half of invited women enrolled in the study (1). The women who agreed to participate differ from the population of women giving birth in Norway in 2000-2006 on several characteristics generally associated with higher socioeconomic status (SES) – they were less likely to be young (<25 years), single, or smoke cigarettes, and more likely to be married or cohabitating, have higher education, and take multivitamin and folic acid supplements than women who did not enroll in the study (50). The unrepresentative sample does not necessarily impede the calculation of valid exposure-outcome estimates (50,51), and the relatively homogeneous sample may even help avoid confounding by maternal factors to the extent that women are similar. However, MoBa mothers and their offspring may be a low-risk group for prenatal alcohol-related harms overall and therefore findings concern- ing alcohol exposures in MoBa may not generalize to disadvantaged populations.

MoBa has the capacity to contribute well-designed, longterm studies of the effects of prenatal alcohol exposure, particularly for low to moderate consumption levels. This is important given the high percentage of alcohol-exposed pregnancies in Norway reported in previous studies and the likelihood that some women will drink alcohol before pregnancy recognition. Like
many countries, Norway has adopted the precautionary principle in regard to its current alcohol policy, recommending that women completely abstain from drinking alcohol during pregnancy. While many believe this is the safest approach, others argue that policies should reflect research evidence and that believing this is the safest approach, others argue that drinking alcohol during pregnancy. While many

principle in regard to its current alcohol policy, recommending that women completely abstain from drinking alcohol during pregnancy. While many believe this is the safest approach, others argue that policies should reflect research evidence and that believing this is the safest approach, others argue that drinking alcohol during pregnancy. While many

REFFERENCES


