

Early Weaning and Hospitalization With Alcohol-Related Diagnoses in Adult Life

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Objective: This study attempted to determine whether lack of breast-feeding or a short duration of breast-feeding during infancy is associated with an elevated risk of hospitalization with alcohol-related diagnoses in adult life.

Method: The study was a prospective longitudinal birth cohort design conducted in a sample of 6,562 men and women, all of whom were born in Copenhagen, Denmark, between October 1959 and December 1961. The sample was divided into two categories based on duration of breast-feeding, as assessed by a physician interview with mothers at a 1-year examination. Psychiatric hospitalizations with alcohol-related diagnoses according to ICD-8 or ICD-10 were identified in the Danish Psychiatric Central Register in 1999. Nine potential confounders were included as covariates: gender of the cohort member, maternal age, parental social status, maternal prenatal smoking, unwanted pregnancy, maternal and pa-

ternal psychiatric hospitalization with alcohol-related diagnosis, and maternal and paternal psychiatric hospitalization with other diagnosis.

Results: Alcohol-related diagnoses were more frequent in men, but the results were comparable for men and women. The adjusted predictive effect of early weaning was 1.47. Elevated relative risks were also associated with maternal smoking during pregnancy (1.52) and unwanted pregnancy status (1.59). Other independent predictors were male gender, maternal psychiatric hospitalization with alcohol-related diagnosis, and low parental social status.

Conclusions: Independent of a number of other risk factors for alcoholism, a significant association between early weaning and elevated risk of hospitalization with alcohol-related diagnoses was observed.

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Considerable evidence from family, twin, and adoption studies supports a heritable component of alcoholism (1–3). A role of early environmental factors has also been suggested. Two hundred years ago, Thomas Trotter (4) suggested that early weaning is causally linked with the later development of alcoholism. In 1999, Goodwin et al. (5) published results from a 30-year psychiatric follow-up of 200 Danish men at high risk for alcoholism. Their data indicated that early weaning significantly contributed to the prediction of severity in alcoholism and that the relationship between early weaning and later alcoholism was independent of family history of alcoholism. Fergusson et al. (6) studied the relationship between duration of breast-feeding and psychosocial outcomes measured between the ages of 15 and 18 years in a birth cohort of 999 New Zealand children. They did not find a significant relationship between the duration of breast-feeding and alcohol abuse or dependence among cohort members who had reached the age of 18 years.

Thus, further research was needed to illuminate the possible role of early weaning as a predictor of later alcoholism. First, it is not clear whether early weaning predicts later alcoholism in both genders. Second, an association

between early weaning and elevated risk of alcoholism may partly be explained by differences in maternal smoking habits during pregnancy because mothers who smoke during pregnancy tend to wean their infants earlier than mothers who do not smoke (7). Studies suggest that maternal prenatal smoking is associated with an elevated risk of offspring substance abuse, including alcohol abuse (8, 9).

In this study, we used data from the Copenhagen Perinatal Cohort to study the effects of early weaning on the risk of hospitalization with an alcohol-related diagnosis.

Method

The Copenhagen Perinatal Cohort consists of 9,125 individuals delivered by 8,949 pregnant women from October 1959 to December 1961 at the Maternity Department of Copenhagen University Hospital, Rigshospitalet. The mothers were mainly residents in Copenhagen, but some were admitted with obstetrical indications or due to their status as single mothers (10).

A total of 8,400 infants survived their first month after birth. Data on breast-feeding was available for 6,762 who were registered as citizens of Denmark by April 1, 1969, and identifiable in the Danish Psychiatric Central Register through a unique personal identification number. Of those, we excluded 200 men with data on breast-feeding who were interviewed at age 30 years as part of an all-male study of individuals at high risk for alcoholism

(5). The remaining 6,562 (3,245 men and 3,317 women) constituted the current study sample.

Hospitalization With Alcohol Dependence/Abuse

Written approval to conduct a registry-based psychiatric follow-up was obtained from the regional scientific and ethics committee. The Danish Psychiatric Central Register has been computerized since April 1, 1969. (11). It contains data on all admissions to Danish psychiatric inpatient facilities. The diagnostic system in use when the Danish Psychiatric Central Register was computerized was ICD-8. The register provided diagnoses according to the ICD system with ICD-8 categories used through 1993 and ICD-10 categories used thereafter.

We identified cohort members with a history of hospitalization with an alcohol-related diagnosis and those without on the basis of lifetime psychiatric hospitalization records obtained in 1999. Hospitalization with an alcohol-related diagnosis was defined as the presence of any recorded hospitalization with ICD-8 code 303 or ICD-10 code F10. None of the cohort members had received an ICD-10 diagnosis of F10.5 ("psychosis due to alcohol"). In the following, we use the term "alcoholism" and "alcohol-related diagnosis" interchangeably to refer to ICD-8 or ICD-10 discharge diagnoses.

Breast-Feeding

As used in this article, "weaning" refers to the termination of breast-feeding as assessed by a physician interview with mothers at a 1-year examination. Duration of breast-feeding was originally recorded on a 1–11-point scale (from 1–2 weeks to >12 months). On the basis of this scale, the subjects were classified into two categories according to duration of breast-feeding: 1) 1 month or less (early-weaning subsample comprising 2,233 individuals or 34%) and 2) more than 1 month (later-weaning subsample comprising 4,329 or 66%). It was not possible to include a separate category for children who were never breast-fed because they had been coded as 1–2 weeks or less. Duration of breast-feeding was divided into two categories to facilitate comparability with the previous study (5). To analyze linear and quadratic trends, the subjects were classified into five categories according to duration of breast-feeding: 1 month or less, 2–3 months, 4–6 months, 7–9 months, and more than 9 months (12).

Potential Confounders

Maternal prenatal smoking. In prenatal and postnatal interviews, the mothers reported the number of cigarettes smoked daily in their third trimester of pregnancy. The reported rates were typical of the general population of Denmark at the time. For this study, the subjects were divided into two groups: the offspring of mothers who smoked (N=3,389) and the offspring of nonsmokers (N=3,024). Data on maternal smoking during pregnancy were missing for 149 individuals (2.3%).

Parental psychiatric hospitalization. The parents were added to the Danish Psychiatric Central Register. Maternal and paternal psychiatric hospitalization histories with alcohol-related diagnosis were defined as the presence of maternal or paternal lifetime psychiatric hospitalization based on records obtained in 1999 with any of the following ICD-8 or ICD-10 discharge diagnoses: alcohol intoxication, withdrawal, abuse or dependence (ICD-8 code 303 or ICD-10 code F10) versus no maternal or paternal psychiatric hospitalization.

Another binary variable was created to control for parental psychiatric hospitalization history with other (not alcohol-related) diagnoses. This variable was coded positive in the presence of any maternal or paternal lifetime psychiatric hospitalization records, obtained in 1999, except ICD-8 code 303 and ICD-10 code F10.

Unwanted pregnancy. At the establishment of the cohort, data were recorded for the mother's attitude toward the pregnancy. The term "unwanted" refers to situations in which pregnancy was not desired at the time of conception (10, 13). The sample was divided into offspring of wanted pregnancy (N=2,738) and offspring of unwanted pregnancy (N=3,580). Data were missing for 244 (3.7%).

Parental social status. Parental social status was recorded when the child was 1 year old according to an 8-point scale (13). Data on social status were missing for 788 (12.0%). To avoid dilution of the data set, missing values were replaced with the mean social status score, and a dummy variable was included to indicate missing data on social status in the logistic regression analysis.

Other variables. Maternal age at the time of delivery was registered for the Copenhagen Perinatal Cohort. Data from the cohort also included previously described weighted indices of pregnancy and delivery complications (13) and information on prescribed medication during pregnancy (13, 14). However, preliminary analyses showed that these variables were not associated with the offsprings' alcohol-related diagnoses and thus were not included in the statistical analysis.

Statistical Analysis

Tests of differences between the early- and later-weaned subsamples were conducted with chi-square tests and analyses of variance for qualitative and continuous variables, respectively. We estimated the relative risks with logistic modeling with SPSS version 12.0 (SPSS, Chicago), a binary indicator variable coded early (1 month or less), and later weaning. The analysis also included binary variables for maternal prenatal smoking in the third trimester, offspring gender, unwanted pregnancy, maternal psychiatric hospitalization with alcohol-related diagnosis, maternal psychiatric hospitalization with another diagnosis, paternal psychiatric hospitalization with alcohol-related diagnosis, and paternal psychiatric hospitalization with another diagnosis. Maternal age and parental social status (on an 8-point scale) were treated as continuous variables. First, the unadjusted associations between each of these factors and the outcome were calculated. Second, we calculated the predictive effects of each of the following variables: early weaning, maternal prenatal smoking, unwanted pregnancy, maternal psychiatric hospitalization, and paternal psychiatric hospitalization with adjustment for parental social status and maternal age. Third, we estimated the joint influences of the binary variables with adjustment also for parental social status and maternal age.

In Table 1 and Table 2, the results are presented for the current study sample, but all analyses were replicated on a sample that included the 200 men who were the basis for the previous report on early weaning and alcoholism (5). All statistical tests were two-tailed.

Results

In the study sample, 138 individuals had been hospitalized with an alcohol-related diagnosis (cumulative incidence: 2.1%). Sixty-three cases (2.8%) were from the early-weaning category, whereas 75 cases (1.7%) were registered in the later-weaned category ($\chi^2=8.48$, $df=1$, $p=0.004$). Ninety-eight cases were identified in men (3.0%) and 40 in women (1.2%). The mean parental social status was significantly lower in the group that was hospitalized with alcohol-related diagnoses than in the rest of the cohort ($F=15.77$, $df=1$, $p<0.0001$).

Table 1 compares the covariates for the early- and the later-weaned subsamples. Univariate analyses indicated

TABLE 1. Demographic and Clinical Characteristics of 6,562 Members of the Copenhagen Perinatal Cohort by Their History of Breast-Feeding

Variable	Weaned Early (by 1 month) (N=2,233)		Weaned Later (>1 month) (N=4,329)		Analysis	
	Mean	SD	Mean	SD	F (df=1, 6560)	p
Parental social status (8-point scale)	3.7	1.5	4.1	1.8	71.70	<0.0001
Mother's age (years)	25.8	6.5	25.9	6.5	0.38	0.54
	N	%	N	%	χ^2 (df=1)	p
Male sex	1,130	50.6	2,115	48.9	1.80	0.18
Maternal prenatal smoking ^a	1,265	57.3	2,159	50.4	28.00	<0.0001
Unwanted pregnancy ^b	1,403	65.2	2,177	52.2	97.36	<0.0001
Psychiatric hospitalization of parents ^c						
Mother						
Any alcohol-related diagnosis	92	4.1	148	3.4	2.06	0.15
Lifetime, other diagnosis ^d	265	11.9	531	12.3	0.22	0.64
Father						
Any alcohol-related diagnosis	132	5.9	227	5.2	1.27	0.26
Other diagnosis	113	5.1	200	4.6	0.63	0.43

^a Percents are based on N=2,207 for the early-weaned group and N=4,284 for the later-weaned group.

^b Percents are based on N=2,151 for the early-weaned group and N=4,167 for the later-weaned group.

^c The psychiatric hospitalization rates may seem high for both parents. However, data from the Danish Psychiatric Central Register for a sample of 12,900 fathers and 14,292 mothers to children born in Copenhagen in 1960 show that 8.8% of the fathers and 12.7% of the mothers had a history of psychiatric hospitalization (Preben Bo Mortensen, personal communication).

^d Percents are based on N=4,606 for the later-weaned group.

that maternal prenatal smoking ($p<0.0001$) and unwanted pregnancy ($p<0.0001$) were significantly more common in the early-weaned group. Mean parental social status was also significantly lower in the early-weaned group ($p<0.0001$).

In logistic regression analysis with the binary breast-feeding variable as a single predictor, early weaning was associated with an odds ratio of 1.65 (95% confidence interval [CI]=1.17–2.31). The odds ratio associated with early weaning was 1.48 in men (95% CI=0.99–2.22) odds ratio and was 2.03 in women (95% CI=1.09–3.78).

Table 2 presents the results of multivariate analyses. With adjustment for parental social status and maternal age, the odds ratio associated with early weaning was 1.56 (95% CI=1.11–2.19). With inclusion of all covariates, the adjusted estimate was 1.47 (95% CI=1.03–2.10).

Other significant predictors in the multivariate model were male gender, maternal prenatal smoking, unwanted pregnancy, maternal psychiatric hospitalization with alcohol-related diagnosis, maternal psychiatric hospitalization with other diagnoses, and low parental social status when the child was 1 year old. Paternal psychiatric hospitalization with an alcohol-related diagnosis was not a significant predictor in this sample.

To examine the possibility of a dose-response relationship between duration of breast-feeding and the outcome, breast-feeding was analyzed as a five-category semicontinuous variable, as described in Methods. The linear relation between duration of breast-feeding and outcome was significant ($p=0.003$), with an odds ratio of 0.77 (95% CI=0.64–0.92), whereas a test of nonlinear (quadratic) association was insignificant ($p=0.39$). With the inclusion of all the covariates, the semicontinuous variable indicating duration of breast-feeding remained significantly associated

with the outcome, with a significance level of 0.046 and an odds ratio of 0.82 (95% CI=0.68–1.00).

In separate analyses, we divided the sample into offspring of mothers who smoked during the third trimester (N=3,389) and offspring of nonsmokers (N=3,024). Among the offspring of mothers who smoked, the unadjusted odds ratio associated with early weaning was 1.32 (95% CI=0.86–2.02). Among the offspring of mothers who did not smoke during pregnancy, the unadjusted odds ratio associated with early weaning was 2.19 (95% CI=1.22–3.95).

In analyses including the 200 men from the previous study (5), the total sample was 6,762, and the number of cases was 147 (cumulative incidence: 2.2%). The unadjusted odds ratio for early weaning was 1.65 (95% CI=1.19–2.30). Adjustment for parental social status and maternal age resulted in an odds ratio of 1.56 (95% CI=1.12–2.17), and inclusion of the remaining covariates resulted in an odds ratio of 1.46 (95% CI=1.03–2.06). Paternal psychiatric hospitalization with alcohol-related diagnosis did not emerge as a significant predictor in this larger sample (unadjusted odds ratio=1.38 [95% CI=0.75–2.51]).

Discussion

Our results suggest an association between early weaning and an increased risk of alcoholism in offspring in adult life. We found a 1.47-fold elevated risk of being hospitalized in a psychiatric department with an alcohol-related diagnosis among offspring who had been weaned early compared to offspring who had been breast-fed longer. The predictive effect of early weaning remained significant when adjusted for a number of potential confounders. Alcohol-related diagnoses were more frequent in men, but the results were comparable for men and women.

TABLE 2. Multiple Logistic Regression Analysis of Factors Predicting Hospitalization With Alcohol-Related Diagnoses in 6,562 Members of the Copenhagen Perinatal Cohort

Variable	Model 1		Model 2 ^a		Model 3 ^b	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Duration of breast-feeding up to 1 month	1.65	1.17–2.31	1.56	1.11–2.19	1.47	1.03–2.10
Potential confounding variables						
Male gender	2.55	1.76–3.70	2.60	1.79–3.77	2.81	1.89–4.17
Parental social status	0.80	0.72–0.89			0.87	0.77–0.99
Mother's age	0.98	0.95–1.00			0.99	0.97–1.02
Maternal smoking	1.77	1.23–2.54	1.63	1.13–2.35	1.52	1.04–2.22
Unwanted pregnancy	1.95	1.33–2.86	1.63	1.09–2.44	1.59	1.05–2.41
Maternal lifetime psychiatric hospitalization						
Alcohol-related diagnosis ^c	3.64	2.08–6.36	3.47	1.98–6.09	3.03	1.65–5.59
Other diagnoses ^c	1.69	1.07–2.68	1.58	0.99–2.50	1.50	0.92–2.44
Paternal lifetime psychiatric hospitalization						
Alcohol-related diagnosis ^d	1.11	0.54–2.28	0.95	0.46–1.96	0.78	0.33–1.81
Other diagnoses ^d	1.77	0.94–3.31	1.66	0.88–3.12	1.58	0.81–3.08

^a Model outputs were adjusted for parental social status and maternal age.

^b Model outputs were adjusted for social status of the breadwinner, mother's age, and all other variables listed.

^c The reference category was mothers who were not registered with any psychiatric diagnosis during the follow-up.

^d The reference category was fathers who were not registered with any psychiatric diagnosis during the follow-up.

Our findings confirm the results of the previous study based on the Copenhagen Perinatal Cohort (5). This study was based on face-to-face psychiatric interviews with men at high risk for alcoholism, and early weaning was found to predict the severity of alcoholism. It is likely that our hospitalization-based study predominantly identified individuals with more severe alcohol problems or individuals who were admitted with other psychiatric problems and obtained an alcohol-related codiagnosis.

It is a methodological advantage of our study that we were able to address the effect of early weaning in both men and women. Additionally, we were able to control for a relatively large number of potential confounding factors, including parental social status and maternal prenatal smoking during the third trimester of pregnancy. Although both parental social status and parental psychiatric hospitalization with alcohol-related and other diagnoses were included as covariates, some parents with psychiatric problems or severe alcohol or substance abuse problems do not appear in the psychiatric registry.

A potential confounder that could not be controlled in this study was the teratogenic effect of maternal alcohol use during pregnancy because data on maternal alcohol consumption during pregnancy were not available. However, alcohol consumption among women was quite rare in Denmark when the cohort was established and was therefore not registered systematically (13).

The primary exposure, duration of breast-feeding, was based on the mothers' recollection 1 year after giving birth. We do not have data on the quality of the information on duration of breast-feeding, but when the mothers left the maternity department, they were asked to record developmental milestones and were told about the 1-year examination. In addition, misclassification with respect to early and later weaning would most likely not result in bias but only attenuate the association between early weaning and hospitalization with alcohol-related diagnosis.

A number of other significant associations with alcohol-related diagnoses were found. Male gender, parental social status, and maternal psychiatric hospitalization were not unexpected risk factors, whereas the literature contains few studies of maternal smoking and unwanted pregnancy.

Brennan et al. (14) observed a significant relationship between maternal prenatal smoking and offsprings' risk of hospitalization with substance abuse in both male and female offspring in the Copenhagen Perinatal Cohort. We found a weaker predictive effect of early weaning in the offspring of mothers who smoked than in the offspring of nonsmoking mothers. Nicotine that passes from mother to fetus stimulates nicotinic receptors, which are present from the early stages of fetal neurodevelopment (15). Nicotine levels in breast milk may be higher than in the mother's blood (16), and the levels of a nicotine derivative were found to be higher in infants of smoking mothers who were also breast-fed than in non-breast-fed infants of mothers who smoked (17). In our study, the relatively small odds ratio for the offspring of smoking mothers may be related to the fact that these infants were likely exposed to nicotine prenatally as well as during infancy through breast milk.

To our knowledge, our results are the first to indicate a link between increased risk of hospitalization with alcohol-related diagnoses and unwanted pregnancy. Because being a single mother was among the admission criteria to the university hospital, quite a large proportion of the cohort members had been characterized as "unwanted" pregnancies by their mothers. This variable refers to the mothers' attitude toward the pregnancy at the time of conception (10, 13) and does not necessarily reflect their attitude as the pregnancy progressed or during the child's upbringing. Another follow-up study observed no association between unwanted pregnancy and adult drinking, but that study

used a stricter definition of "unwanted" (application for abortion) and was based on a much smaller sample (18).

Several factors may explain the observed relationship between early weaning and increased risk of hospitalization with alcohol-related diagnoses:

1. Adverse factors while raising their children may have been more frequent among the parents in the early-weaning group, although such factors would presumably correlate with parental social status, and this factor was statistically controlled in the present study.
2. Factors associated with the feeding situation, i.e., physical and psychological contact between the mother and the child may play a role, and in addition, duration of breast-feeding may be an indicator of the time and energy that the mother is able to invest in the child during the whole upbringing period (12). Data from the New Zealand birth cohort (6) indicate significant positive associations between the duration of breast-feeding and levels of parental attachment, as well as perceived maternal care.
3. The relationship between early weaning and alcohol-related diagnoses may be mediated through low intelligence. Low intelligence has been linked with short duration of breast-feeding (12), and some patterns of drinking (high-risk drinking) appear to be associated with low intelligence (19, 20).
4. Finally, developmental disorders, such as attention deficit hyperactivity disorder (ADHD), that show continuity into adult life appear to have high comorbidity with substance abuse, and an association between early weaning and the development of ADHD may mediate the association between early weaning and hospitalization with alcohol-related diagnoses.

Breast milk contains long-chain polyunsaturated fatty acids, such as docosahexaenoic acid (DHA), that influence brain development. There is evidence that DHA is of importance in CNS development and function (21) and may play a role in the development of disorders, such as ADHD (22). Recent research in normal healthy infants showed more mature brainstem auditory-evoked potential and somatosensory-evoked potential in breast-fed infants relative to formula-fed infants (23). Of interest, certain deficits in neonatal markers related to development have been shown to predict male alcohol dependence at age 30 (24). It is attractive to speculate that early weaning (or a correlate of early weaning) might have given rise to a cascade of early events that influenced, for instance, dopamine, serotonin, or opioid neurotransmission. Some (25, 26), but not all (27), animal studies have provided support for a role of early weaning in the development of dopaminergic mechanisms that play an important role in theories of addiction. A study showed that low brain levels of DHA during development alter dopamine-related behavior in adult rats (28). The mechanisms involved in this ob-

served relationship in rats were alterations in the mesocortical and mesolimbic dopamine systems caused by low brain levels of DHA at critical stages during development.

In conclusion, this study points in the same direction as the previous high-risk study (5), suggesting that early weaning may be associated with increased risk of offspring of alcohol abuse and alcohol-related hospitalization in adult life. We were able to control a large number of potential confounding factors, and the association between breast-feeding and adult alcohol abuse seems relatively robust. However, it remains an open question whether this relationship can be explained by breast milk containing particular nutrients that influence brain development or by other factors that correlate with duration of breast-feeding.

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