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Gender Specific Effects of Perinatal Influences on the Risk for Alcoholism in a 45-Year Danish Birth Cohort

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Abstract

Objective: A large Danish birth cohort was used to test the independent and joint effects of perinatal measures on the development of lifetime alcohol dependence (N=448) in male and female subjects at age 45.

Method: Subjects were born at the State University Hospital in Copenhagen, Denmark between 1959 and 1961 (N=9,125). A comprehensive series of measures were obtained for each of the 8,109 surviving infants before, during, and shortly after birth as well as at 1 year of age. The adult alcoholism outcome was defined as any ICD 10 F10 (*Mental and Behavioral Disorders Due to Alcohol Use*) or equivalent ICD 8 diagnosis extracted from the Danish Central Psychiatric Register or the Municipal Alcohol Clinics of Copenhagen by 2007.

Results: Social class, maternal smoking and multiple perinatal markers of premature birth independently predicted ($p \leq 0.05$) the development of alcoholism. Separate logistic regression modeling for male and female subjects that included maternal smoking, social status and a global prematurity score found that the global prematurity score significantly increased the odds ratio for alcoholism in male subjects (OR=1.16, 95% CI 1.03-1.31) but not in female subjects (OR=1.04, 95% CI 0.86-1.26). When the effects of prematurity were controlled, maternal smoking in pregnancy was associated with a significant odds ratio for alcoholism in female (OR=2.06, 95% CI 1.32-3.22) but not male subjects (OR=1.29, 95% CI 0.97-1.71).

Discussion: The results suggest that the neurodevelopmental sequelae of premature birth has gender-specific effects on the risk for alcoholism. Small, premature or growth- delayed male babies appear to be selectively vulnerable to alcoholic drinking years later.

Background

Neonatal Vulnerability

Babies are at an increased risk of sustaining a neuronal injury at the time of birth due in part to the fact that natural anti-oxidant vitamins and enzymes as well as important blood clotting factors are low. Consequently, newborns have a diminished ability to respond to injury associated with premature birth, birth trauma or perinatal hemorrhage.

Male babies appear to be more vulnerable to perinatal insult than female babies for reasons that are not well-defined. Perinatal white matter appears to be selectively sensitive to damage.

Neurodevelopmental Model

Limbic structures, including dopamine reward circuitry, are highly myelinated and actively developing within the perinatal timeframe.

Direct disruption of the development of reward circuits in childhood could result in an increased vulnerability to alcoholism as an adult.

Methodology

Subjects

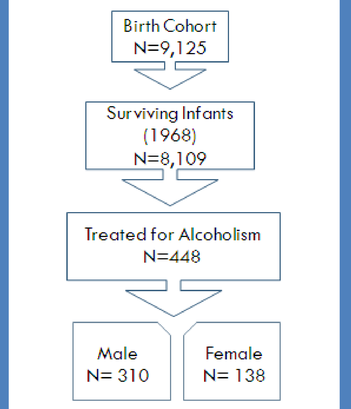
Danish Birth Cohort consisted of all babies over 20 weeks of gestational age born in the maternity ward of the State University Hospital (Rigshospitalet) between September, 1959 to December, 1961.

Perinatal Variables

The database consisted of > 1500 variables describing the social and medical status of the mother at the time of birth, details of the pregnancy as well as the condition of the infant at birth and one year of age.

Adult Psychiatric Outcomes

Danish Central Psychiatric Register and the Municipal Alcoholism Clinics were searched for all surviving offspring. Any record of an ICD10 F10 (*Mental and Behavioral Disorder due to Alcohol Use*) diagnosis or any record of treatment at a municipal alcoholism clinic.



Results

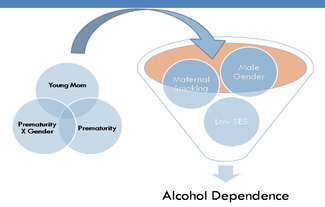
Independent Effects of Perinatal Markers of Premature Birth by Gender on the Risk of Alcohol Dependence

Perinatal Measure	N	Male: Alcohol Dep. N=310 freq(%) or x	Male: Non-Alcohol Dep. N=3804 freq(%) or x	Male: P	Female: Alcohol Dep. N=138 freq(%) or x	Female: Non-Alcohol Dep. N= 3857 freq(%) or x	Female: P
Mom's Wt Increase*	4722	3.65(1.58)	3.96(1.56)	.0123	3.82(1.68)	3.79(1.58)	.8406
Prematurity Score	8109	0.97(1.15)	0.75(1.05)	.0005	0.9(1.2)	0.82(1.04)	.3596
Gestational Age	6520	26.34%	19.28%	.0079	18.02%	18.62%	.8727
Weight (<2500 g)	8108	19.35%	11.33%	.0001	15.94%	13.84.%	.4843
Length	8096	4.99(1.32)	5.25(1.14)	.0004	4.80(1.19)	4.91(1.12)	.2940
Head Circ. (<34 cm)	5016	61.69%	53.54%	.0069	73.68%	74.99%	.7321
Unable to Walk (1yr)	1047	18.39%	12.51%	.0031	17.39	12.70%	.1061

Independent Effects of Maternal Characteristics by Gender on the Risk of Alcohol Dependence

Maternal Characteristics	N	Male: Alcohol Dep. N=310 freq(%) or x	Male: Non-Alcohol Dep. N=3804 freq(%) or x	Male: P	Female: Alcohol Dep. N=138 freq(%) or x	Female: Non-Alcohol Dep. N= 3857 freq(%) or x	Female: P
Socioeconomic*	6476	3.34(1.61)	4.04(1.84)	.0001	3.32 (1.72)	4.00(1.83)	.0002
Smoking 3rd Tri	7919	187 (61.51%)	1876 (50.59%)	.0003	96 (72.18%)	1999 (52.97%)	.0001
Mother's age	8108	24.87(6.54)	25.41(6.56)	.1583	23.78(5.92)	25.32(6.50)	.0061

Regression Analyses



Logistic Regression Model Building

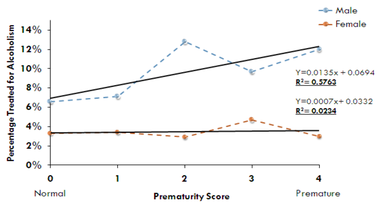
Stepwise Logistic Regression Procedure

AD = Gender + SES + Maternal Smoking + Prematurity Score*Gender

Wald = 102.7, df = 4, p-value= 0.0001

Parameter	Std Error	Wald	p-value
Male Gender	0.1363	25.7	0.0001
Maternal Smoking	0.1207	11.1	0.0009
Low SES	0.0357	33.3	0.0001
Prematurity Score*Gender	0.0609	5.44	**0.0196**

Gender Effects on the Relationship Between Prematurity and Alcoholism in Adulthood



Logistic Regression Models by Gender

Male Gender

Parameter	Std Error	Wald	p-value	OR	95% CI
Maternal Smoking	0.2537	3.07	0.0795	1.29	0.97-1.71
SES	0.0434	24.4	**0.0001**	**0.81**	**0.75-0.88**
Prematurity Score	0.0610	6.05	**0.0139**	**1.16**	**1.03-1.31**

Female Gender

Parameter	Std Error	Wald	p-value	OR	95% CI
Maternal Smoking	0.2274	10.1	**0.0015**	**2.06**	**1.32-3.22**
SES	0.0631	8.97	**0.0027**	**0.83**	**0.73-0.94**
Prematurity Score	0.0960	0.18	0.6750	1.04	0.86-1.26

Discussion

The results suggest that the neurodevelopmental sequelae of premature birth has gender-specific effects on the risk for alcoholism. Small, premature or growth- delayed male babies appear to be selectively vulnerable to alcoholic drinking years later. The previously identified association between maternal smoking and risk for alcoholism among males may be partially explained by the effects of premature birth. Female infants appear to be more directly sensitive to the influence of maternal smoking or established correlates of maternal smoking, such as maternal mental illness. However, the association between prematurity and alcoholism was not significant for female babies. The findings implicate neuro-developmental influences in the pathophysiology of alcoholism and suggest the presence of distinct, gender-specific pathways that lead to the development of alcoholism in men and women.

Conclusions

1) The sequelae of premature birth induces a specific biological change in male babies that increases their vulnerability to develop alcoholism later in life.

2) The nature of this change may be a function of direct injury to developing brain systems or possibly a genetic imprinting phenomenon.

3) Female babies are either resistant to the induction of this change or this change has no effect on their vulnerability to develop alcoholism.

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