Special Article

Effect of alcohol consumption in prenatal life, childhood, and adolescence on child development

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The effects of alcohol consumption in adults are well described in the literature, while knowledge about the effects of alcohol consumption in children is more limited and less systematic. The present review shows how alcohol consumption may negatively influence the neurobiological and neurobehavioral development of humans. Three different periods of life have been considered: the prenatal term, childhood, and adolescence. For each period, evidence of the short-term and long-term effects of alcohol consumption, including neurodevelopmental effects and associations with subsequent alcohol abuse or dependence, is presented.

INTRODUCTION

Alcohol consumption is recognized worldwide as a leading risk factor for disease, disability, and death. Drinking too much and too fast (i.e., binge drinking, defined by the US National Advisory Institute on Alcohol Abuse and Alcoholism [http://www.niaaa.nih.gov] as the consumption of 5 or more US standard drinks [males] or 4 or more drinks [females] in approximately 2 hours) or drinking too much and too often (i.e., heavy drinking, defined as frequent drinking of 5 or more US standard drinks by men and 4 or more US standard drinks by women per day) both constitute high-risk drinking patterns that can result in harm from a number of acute and chronic consequences. Cellular and molecular biology studies have identified the major pathways of alcohol metabolism and explored the mechanisms by which both short-term (e.g., binge) and long-term drinking can produce organ damage.[1] To date, a number of theories have been postulated for the pathogenesis of alcohol-induced complications, including direct toxicity of ethanol and its metabolites (particularly acetaldehyde), oxidative stress, accumulation of fatty acid ethyl esters, and modification of lipoprotein and apolipoprotein particles.[2] Moreover, studies in human subjects have shown chronic diseases such as heart disease, Alzheimer's disease, stroke, liver disease, cancer, chronic respiratory disease, diabetes mellitus, and bone disease may develop following chronic alcohol ingestion and contribute to alcoholism-related morbidity and mortality.[2]

Although the effects of alcohol consumption in adults are widely known, knowledge about drinking habits and drinking consequences in children is limited and less systematic. In particular, the definitions of drinking have been devised with reference to adults and have not been evaluated in younger populations. It was only in 2009 that Donovan[3] derived the first age- and gender-specific definition of binge drinking appropriate for boys and girls up to 17 years of age. Moreover, even if the quantity and the frequency of alcohol use in children were to be studied jointly,[4] there is little consistency in the definition of drinking patterns in studies published to date.[5] This variability makes it difficult to quantify the effects of alcohol use and, in particular, to compare the results of studies by means of meta-analytic techniques, which have rarely been employed in this field.[6]

This report reviews existing evidence on the adverse effects of alcohol consumption in children and adolescents. Three different periods of exposure have been considered: prenatal life, childhood, and adolescence. For

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each period, evidence of short-term and long-term effects, including neurodevelopmental effects and associations with subsequent alcohol abuse or dependence, is presented.

PRENATAL ALCOHOL EXPOSURE

The connection between alcohol and developmental defects had become clear in 1957, when a French medical student, Jacqueline Rouquette, studied a sample of 100 children with developmental abnormalities who had been born to alcoholic parents, concluding that drinking during pregnancy constitutes a relevant risk to the child. Subsequently, in 1968, Lemoine et al.[7] described a pattern of anomalies occurring in the offspring of alcohol-abusing mothers. Later dubbed "fetal alcohol syndrome" (FAS) by Jones and Smith,[8] the syndrome includes growth deficiency, facial anomalies, and neurological abnormalities.[9–11]

While FAS represents the most severe manifestation of heavy maternal alcohol consumption during pregnancy, the term "fetal alcohol spectrum disorders" (FASDs) has more recently been applied to characterize a broad range of deficits present in individuals with or without facial dysmorphology who were exposed to alcohol prenatally.[9,12,13]

The use of animal models, which increase the precision with which the nature and severity of the damage can be determined under controlled conditions,[14] has enhanced the understanding of the precise neurobiological and neurobehavioral consequences of fetal alcohol exposure.[15–19] Most of the animal studies in this field have been conducted in mice and rats. The stages of brain development are similar in both humans and rodents, except for the timing with respect to birth.[1] In fact, the full gestation period (prenatal life) in rodents is equivalent to the first and second trimesters in humans, while postnatal day one (P1) to P10 corresponds roughly to the third trimester in humans.[20–22] Thus, the exposure of rodents to alcohol during pre- and postnatal periods is expected to produce deficits similar to those seen in the offspring of human mothers who abuse alcohol during pregnancy. Experimental animal models of prenatal alcohol exposure have indicated that numerous areas of the brain are affected by alcohol, including the cerebral cortex (frontal and parietal cortex),[9,23,24] the cerebellum,[21,25–28] and the hippocampus.[29,30] Neuronal loss and structural changes occurring in these areas result in disorders such as movement, balance, and gait disturbances[31,32] and impairment of learning and memory,[33] especially spatial learning.[34,35]

In humans, various imaging modalities have been used to study individuals with FASD.[36] Morphological studies have reported volume reduction in the cerebral cortex (mainly involving the parietal and frontal lobes), the cerebellum, and basal ganglia and abnormalities in the corpus callosum, including agenesia, hypoplasia, displacement, and shape variability.[37–45]

FASD has been associated with a host of cognitive and behavioral impairments, including deficits in attention, memory, verbal fluency, executive functioning, reaction time, and motor learning.[9,10,46–49]

Clinical and animal studies have demonstrated that many risk factors influence the extent of brain damage and the corresponding cognitive and behavioral deficits. These factors include, but are not limited to, maternal patterns of alcohol consumption and the timing of exposure relative to critical fetal developmental windows (temporal vulnerability). The dosage of alcohol influences the nature and occurrence of the offspring's deficits[15,20,33,50,51] and also interacts with various maternal and genetic factors.[9] Despite the large amount of literature on the effects of alcohol consumption during pregnancy, the characteristics of the dose-response relationship between alcohol exposure and infant outcomes is not clear. In particular, while it is generally accepted that both abusive and heavy drinking are associated with FAS and fetal alcohol effects such as growth restriction, birth defects, and neurodevelopmental problems,[52] the effects of binge drinking and low-to-moderate drinking have been explored less extensively.

Animal studies have shown that binge-like drinking patterns, in which the fetus is exposed to high blood alcohol concentrations over relatively short periods of time, are in fact particularly harmful, even if the overall amount of alcohol consumed is less than that consumed with more continuous drinking patterns.[53,54] A recent review[55] of the evidence available from human observational studies evaluated the effect of a binge-drinking pattern on a spectrum of adverse outcomes, including miscarriage, stillbirth, intrauterine growth restriction, prematurity, low birth weight (small for gestational age at birth), and birth defects (including FAS and neurodevelopmental effects). Of 3,630 papers on fetal alcohol exposure, only 14 studies were related to binge drinking and were included in the analysis.[56–69] The authors did not find significant effects of alcohol on any of the outcomes considered and speculated on factors that could have led to this result, including publication bias, under-reporting of the mother's drinking habits, a definition of binge drinking that changed over the years, and a lack of information regarding the weeks of pregnancy in which the binge drinking occurred.

Even greater uncertainty is evident when low and moderate exposures to alcohol during pregnancy are investigated. In 1995, Abel and Hannigan[70] found a significant pattern of increased birth weights associated with low levels of alcohol consumption, suggesting an inverted "J-shaped" function relating drinking during pregnancy

Table 1 **Summary of studies included in the systematic reviews performed by Makarechian et al. (1998)[72] and Polygenis et al. (1998)[71] on the effects of moderate prenatal drinking.**

Meta-analytic studies: Reference	Analyzed studies: Author (year), country, design, reference	Outcome(s)
Makarechian et al. (1998)[72]	Berkowitz et al. (1982), United States, case-control study[211]	Premature birth
	Parry and Ogston (1992), Denmark, Germany, Scotland, prospective cohort study[79]	Premature birth
	Kline et al. (1980), United States, case-control study[212]	Spontaneous abortion
	Little and Weinberg (1993), United States, case-control study[213]	Stillbirth
	Marbury et al. (1983), United States, prospective cohort study[214]	Premature birth
	Verkerk et al. (1993), Netherlands, prospective cohort study[215]	Premature birth
	Windham et al. (1992), United States, case-control study[216]	Spontaneous abortion
	Walpole et al. (1989), Australia, prospective cohort study[217]	Spontaneous abortion, stillbirth
Polygenis et al. (1998)[71]	Davis et al. (1982), United States, prospective cohort study[218]	Birth defects
	Lumley et al. (1985), Australia, prospective cohort study[219]	Birth defects
	McDonald et al. (1992), Canada, case-control study[220]	Birth defects
	Mills and Graubard (1987), United States, prospective cohort study[221]	Birth defects
	Ouellette et al. (1977), United States, prospective cohort study[222]	Birth defects
	Rosett et al. (1983), United States, prospective cohort study[223]	Birth defects
	Silva et al. (1981), Brazil, prospective cohort study[224]	Birth defects

Modified from Makarechian et al. (1998)[72] and Polygenis et al. (1998).[71]

and birth weight. One possible explanation for this result may be the "healthy drinker effect," in which women with a poor obstetric history were more likely to abstain from drinking alcohol. Subsequently, the effects of moderate alcohol consumption were examined in two meta-analytic studies (Table 1). Polygenis et al.[71] conducted a meta-analysis of moderate alcohol consumption during pregnancy and the incidence of fetal malformations. Moderate consumption was defined as a range of 24 g to 168 g per week. The meta-analysis reported a relative risk for fetal malformation of 1.01 (95% confidence interval [CI], 0.94–1.08). Makarechian et al.[72] examined the association between moderate alcohol consumption and miscarriage, stillbirth, and premature birth. The definition of moderate consumption was the same as that used by Polygenis et al.[71] The odds ratios were 1.35 (95% CI, 1.09–1.67) for miscarriage, 0.65 (95% CI, 0.46–0.91) for stillbirth, and 0.95 (95% CI, 0.79–1.15) for premature birth. However, the result for stillbirth was considered unreliable and inconclusive because of the small number of studies, and significant heterogeneity existed among the individual odds ratios for miscarriage.

More recently, in 2007, Henderson et al.[73] examined in a meta-analytic study the effect of alcohol exposure on miscarriage, stillbirth, impaired growth, prematurity, birth weight, and birth defects, including FAS. The search resulted in 3,630 titles and abstracts, which were narrowed to 46 relevant articles (see Table 2). At low-to-moderate levels of alcohol consumption (up to 83 g/week), there were no consistently significant effects of alcohol on any of the outcomes considered.

In the area of neurobehavioral consequences, Testa et al.[6] in 2003 examined by means of a meta-analytic study the effects of prenatal alcohol exposure on infant mental development, assessed using the Mental Development Index (MDI) from the Bayley Scales of Infant Development. The effects of three levels of average daily exposure during pregnancy (less than 1 drink per day, between 1 and 1.99 drinks per day, and 2 or more drinks per day) were analyzed in 10 studies. Moderate consumption was reported in five studies, while only four described low consumption.[74–81] The authors of the meta-analysis found that all three levels of consumption were associated with significantly lower MDI scores among 12–13-month-old children. Greater deficits were associated with greater exposure, and significant negative effects were apparent even at the lowest level of exposure. However, the effect is not consistent across all age classes: in fact, despite the significant effects observed among 12–13-month-old children, fetal alcohol exposure was not associated with lower MDI scores among 6–8- or 18–24-month-old children. Moreover, the effect was eliminated for dosages less than 2 drinks per day when the effect sizes used were adjusted for the relevant covariates.

Some authors suggest that low levels of prenatal ethanol exposure, even if they do not generate evident morphological or neurobehavioral alterations in the offspring, still have negative effects that might not be noticed for many years, possibly exerting a significant impact upon later ethanol-seeking and -intake behaviors.[82,83]

Many studies in animals have shown that prenatal exposure to ethanol increases the offspring's postnatal responsiveness to ethanol.[84–86] Several studies in rats have found that maternal administration of low or moderate doses of ethanol enhances the palatability of ethanol's flavor and increases ethanol consumption during infancy

Table 2 **Summary of studies included in the systematic review performed by Henderson et al. (2007)[73] on the effects of low-to-moderate prenatal drinking.**

Outcome	References	Results	Comments
Miscarriage	Armstrong et al. (1992)[225]; Davis et al. (1982)[218]; Harlap and Shiono (1980)[226]; Henriksen et al. (2004)[227]; Kesmodel et al. (1987)[228]; Long et al. (1994)[229]; Windham et al. (1997)[230]; Windham et al. (1992)[216]	Five studies found significant increase, RR ranged from 2.0 to 3.79, OR 1.1	Some of these studies did not adjust for confounding factors or did so only for smokers
Stillbirth	Davis et al. (1982)[218]; Faden et al. (1997)[231]; Kesmodel et al. (2002)[232]; Little and Weinberg (1993)[213]; Marbury et al. (1983)[214]	One study found a significant increase (OR 7.6) at 25–60 g/week	The high OR was based on a small sample
Impaired growth	Lundsberg et al. (1997)[233]; McDonald et al. (1992)[220]; Mills and Graubard (1987)[221]; Verkerk et al. (1994)[234]; Windham et al. (1995)[235]; Whitehead and Lipscomb (2003)[69]; Yang et al. (2001)[236]	One study found a significant increase in impaired growth	This analysis was not adjusted for confounders
Birth weight	Bell and Lumley (1989)[57]; Brooke et al. (1989)[237]; Day et al. (1990)[238]; Jacobson et al. (1994)[239]; Lazzaroni et al. (1993)[240]; Lumley et al. (1985)[219]; Lundsberg et al. (1997)[233]; McDonald et al. (1992)[220]; Marbury et al. (1983)[214]; Mills et al. (1984)[241]; O'Callaghan et al. (2003)[59]; Ogston and Parry (1992)[242]; Orskou et al. (2003)[243]; Passaro et al. (1996)[62]; Primatesta et al. (1994)[244]; Shu et al. (1995)[245]; Sulaiman et al. (1988)[246]; Verkerk et al. (1993)[215]; Virji (1991)[247]; Virji and Talbott (1990)[248]	One study found a significant increase in low birth weight	This analysis was not adjusted for confounders
Preterm birth	Albertsen et al. (2004)[249]; Bell and Lumley (1989)[57]; Berkowitz et al. (1982)[211]; Day et al. (1990)[238]; Kesmodel et al. (2000)[250]; Lazzaroni et al. (1993)[240]; Lundsberg et al. (1997)[233]; McDonald et al. (1992)[220]; Marbury et al. (1983)[214]; Ogston and Parry (1992)[242]; Passaro et al. (1996)[62]; Peacock et al. (1995)[251]; Primatesta et al. (1994)[244]; Shiono and Klebanoff (1986)[252]; Shu et al. (1995)[245]; Sulaiman et al. (1988)[246]; Verkerk et al. (1994)[234]; Verkerk et al. (1993)[215]; Wisborg et al. (1996)[253]	One study found a significant increase in preterm birth	Did not control for socioeconomic status
Birth defects	Davis et al. (1982)[218]; Ernhart et al. (1989)[254]; Lumley et al. (1985)[219]; Marbury et al. (1983)[214]; Mills and Graubard (1987)[221]; Olsen and Tuntiseranee (1995)[60]	One study found a significant increase in major malformations	Included white women only and did not adjusted for confounders

Modified from Henderson et al. (2007).[73]
Abbreviations: OR, odds ratio; RR, relative risk.

and adolescence.[84,87–89] The acquired preference for ethanol seems to be a conditioned response established prenatally by the association between ethanol's sensory and reinforcing aspects, the latter of which is mediated by the opioid system.[90–92] In general, the outcome of this animal research is congruent with data from human studies investigating whether newborns exhibit differential responsiveness to ethanol odor as a function of maternal ethanol consumption during pregnancy[93] and showing infantile recognition of, and preference for, substances experienced previously.[94,95] Recent experiments suggest more severe effects when alcohol is administered all at once rather than gradually, even when small quantities of ethanol are injected.[96,97]

However, neurodevelopmental outcomes resulting from animal studies are not easily generalized to humans,[98] and at present, evidence regarding the contribution of fetal alcohol exposure to the development of alcohol disorders in clinical studies is lacking. In Table 3, the evidence available to date is summarized. Two[98,99] of seven retrieved articles report results coming from the Mater-University of Queensland Study of Pregnancy and its Outcomes, in which 7,223 women and their babies were enrolled between 1981 and 1984 and followed up at birth, 6 months, and at 5, 14, and 21 years. Three other works[100–102] collected data from the Seattle Longitudinal Study on Alcohol and Pregnancy, in which 1,529 consecutive women presenting between 1974 and 1975 at one

Table 3 **Summary of studies exploring the relationship between prenatal maternal drinking and alcohol use in adolescence.**

Author (year), country, design, reference	Sample	Measures of maternal alcohol consumption	Outcome measure and age at outcome evaluation	Covariates	Results
Alati et al. (2008), Australia, prospective cohort study[98]	Subsample of 4,363 participants in the Mater-University of Queensland Study of Pregnancy	Quantity of alcohol per drinking occasion: up to 2 glasses, 3 glasses or more before pregnancy, 3 glasses or more before and during pregnancy, 3 glasses or more before and after pregnancy, 3 glasses or more during pregnancy, 3 glasses or more after pregnancy, 3 glasses or more during and after pregnancy	Child's drinking pattern at age 14: never used alcohol, 1 or 2 glasses per drinking occasion, 3 or more glasses per drinking occasion	Three logistic regression models were used. Model 1: adjusted for child's sex. Model 2: variables in model 1 plus smoking over time. Model 3: variables in model 2 plus birth weight, gestational age, family income, maternal age and marital status at the antenatal visit, and maternal anxiety, depression, and child's behavior at age 5	Alcohol consumption before and during pregnancy is positively associated with the child's consumption of 3 or more drinks on a single occasion (OR 2.28 [1.11–4.68] in Model 1). Alcohol consumption before, during, and after pregnancy is positively associated with a child's consumption of up to 2 drinks (OR 2.07 [1.34–3.20] in Model 1, OR 1.85 [1.18–2.91] in Model 2, OR 1.91 [1.21–3.02] in Model 3) and with a child's consumption of 3 or more drinks on a single occasion (OR 3.56 [2.26–5.61] in Model 1, OR 3.03 [1.89–4.85] in Model 2, OR 2.97 [1.84–4.77] in Model 3). Alcohol consumption during and after pregnancy is positively associated with a child's consumption of 3 or more drinks on a single occasion (OR 12.20 [5.36–27.76] in Model 1, OR 12.27 [5.42–27.78] in Model 2, OR 11.87 [5.22–26.98] in Model 3)
Alati et al. (2006), Australia, prospective cohort study[99]	Subsample of 2,555 participants in the Mater-University of Queensland Study of Pregnancy	Quantity of alcohol per drinking occasion: up to 2 glasses, 3 glasses or more in early pregnancy, 3 glasses or more in late pregnancy, 3 glasses or more during both periods, 3 glasses or more but not during pregnancy	Onset of alcohol disorder from adolescence to 21 years, according to DSM-IV criteria: no criteria for a disorder, early onset (13–17 years), late onset (18–21 years)	Three logistic regression models were used. Model 1: adjusted for child's sex. Model 2: variables in model 1 plus smoking over time, birth weight, gestational age, maternal education, and maternal age and marital status at the antenatal visit. Model 3: variables in model 2 plus maternal anxiety at the 5-year follow-up and maternal depression and child's behavior at 14 years	Three glasses or more in early pregnancy are positively associated with early onset (OR 3.93 [2.21–6.97] in Model 1, OR 3.04 [1.68–5.50] in Model 2, OR 2.95 [1.62–5.36] in Model 3) and with late onset (OR 3.37 [1.80–6.28] in Model 1, OR 3.37 [1.78–6.37] in Model 2, OR 3.29 [1.74–6.24] in Model 3). Three glasses or more during both periods are positively associated with early onset (OR 3.45 [1.50–7.95] in Model 1, OR 2.49 [1.06–5.85] in Model 3)
Baer et al. (2003), United States, prospective cohort study[100]	Subsample of 433 participants in the Seattle Longitudinal Study on Alcohol and Pregnancy	Alcohol Dependence Scale latent variable score at 21 years of age: composite score of 2 outcome blocks: drinking rates at 21 years and items in the Alcohol Dependence Scale	Prenatal alcohol exposure latent variable: composite score of 13 exposure measures referring to quantity, frequency, and timing	Four separate regression analyses were used. Model 1: family history of alcohol problems and child's sex. Model 2: model 1 plus other prenatal exposures. Model 3: model 2 plus postnatal alcohol and other drug use in the offspring's environment. Model 4: model 3 plus other postnatal environmental factors	Evidence of significant association between prenatal alcohol exposure, latent variable, and the outcome (t = 4.97) in a simple model, attenuated but not removed in the complete model (t = 2.38). Family history contributed to the model less than prenatal exposure

Baer et al. (1998), United States, prospective cohort study[101]	Subsample of 464 participants in the Seattle Longitudinal Study on Alcohol and Pregnancy	Adolescent alcohol latent variable score at 14 years of age: composite score of 6 measures from 2 questionnaires (Lifestyle Choice Survey and Rutgers Alcohol Problems Index – short version)	Prenatal alcohol exposure latent variable: composite score of 13 exposure measures referring to quantity, frequency, and timing	Three separate regression analyses were used. Model 1: family history. Model 2: model 1 plus prenatal smoking and adolescent age. Model 3: model 2 plus measures of parenting style and adolescent self-esteem	Evidence of significant association between prenatal alcohol exposure, latent variable, and the outcome (t = 5.30) in a simple model, attenuated but not removed in the complete model (t = 3.34). Model 1 shows that prenatal alcohol exposure retains a greater effect after adjustment for family history than vice versa; thus, it seems to account for the effect otherwise attributed to family history
Barr and Goldman (2006), United States, prospective cohort study[102]	Subsample of 400 participants in the Seattle Longitudinal Study on Alcohol and Pregnancy	Binge-drinking pattern (5 or more drinks on at least 1 occasion): no binge episode during mid-pregnancy; 1 or more episodes of binge drinking	Administration of the Structured Clinical Interviews for DSM-IV at an average age of 25.7 years. Axis I includes the substance abuse or dependence item	Prenatal cigarette and marijuana exposure, prenatal nutrition, breast-feeding, socioeconomic status, the Mother/Infant Interaction Scale, surrogate parenting of the subject, biological family history of mental health problems, family history of alcohol problems, sex, subject's smoking history	Unadjusted OR for substance dependence or abuse disorders = 2.56 (1.54–4.32); the OR is stable against confounding
Griesler and Kandel (1998), United States, prospective cohort study[255]	Sample of 185 mother-firstborn child dyads (members of the New York State Cohort)	Average ounces of absolute alcohol per day: Abstainer Light (<0.14 oz) Moderate to heavy (≥0.14 oz)	Two outcome measures: 1) Alcohol consumption over lifetime in children aged 9–17: Ever drank. Currently drinking. 2) Alcohol consumption 12 months before the interview in children aged 9–17: Ever drank. Drank in the last year	Three hierarchical logistic regression models were used. Model 1: child's sex, child's age, maternal education, interaction term between sex and prenatal drinking. Model 2: model 1 plus demographic covariates. Model 3: model 1 plus maternal smoking, maternal current drinking, maternal delinquent behavior, child's problems, maternal monitoring, maternal role against drinking	Moderate to heavy consumption had a significant positive effect on adolescent daughters' current drinking (OR 21.6, $P < 0.01$ in Model 1 and OR 15.7, $P < 0.05$ in Model 3), but a slight negative effect on sons' lifetime drinking (OR 0.3, $P < 0.1$ in Model 1 and OR 0.2, $P < 0.1$ in Model 3)
Yates et al. (1998), United States, case-control study[256]	95 adoptees with biological parents having a diagnosis of alcohol/drug abuse/dependence or antisocial personality. Control sample of 102 adoptees without biological parents having a diagnosis of alcohol/drug abuse/dependence or antisocial personality	Data from adoption agency, hospital, and prison records: no fetal alcohol exposure, possible fetal alcohol exposure, definite fetal alcohol exposure	Alcohol abuse or dependency diagnosis according to DSM-III-R criteria	Four regression analyses were performed. Model 1: gestational age, birth weight, sex. Model 2: model 1 plus biological mother alcoholism, biological father alcoholism. Model 3: model 2 plus biological mother abuse/dependency, biological father abuse/dependency. Model 4: model 3 plus biological mother antisocial personality, biological father antisocial personality	In all models, alcohol symptoms show significant differences between levels of fetal alcohol exposure

Abbreviations: DSM-III, *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; OR, odds ratio.

of two Seattle, Washington, prenatal clinics by the fifth month of pregnancy underwent screening via personal interview regarding their health habits. In Table 2, the publication of Barr and Goldman (2006)[102] is also included for completeness, even though it was not possible to discriminate between alcohol consumption and consumption of other drugs in that report. Moreover, studies frequently have only limited capacity to assess the frequency of alcohol consumption,[99,100] and in general, self-reported measures may be inaccurate.

Despite these common limitations, the findings of the few human studies performed to date seem to provide support for a biological origin of some cases of early drinking through a "programming" effect on the brain's natural reward circuitry. They confirm emerging evidence pointing to in utero alcohol exposure, at least at high doses, in the development of addictions.[99,100,102] However, it is possible that the effect seen is not completely explained by intrauterine mechanisms but may be due to shared familial, environmental, and modeling factors, which existing studies have not been able to quantify appropriately.

ALCOHOL EXPOSURE IN CHILDHOOD

Recently, some authors have commented on the paucity of interest and scientific attention directed toward the effects of alcohol exposure in childhood.[103] Until now, in fact, little attention had been paid to alcohol use by children aged 12 years and younger, with longitudinal research focused mainly on the outcomes of adolescent, young adult, or adult rather than childhood alcohol use.[103–105] The incidence of diagnosed alcohol use disorders at age 12 years and under seems to be close to zero in the general population,[106–108] and subclinical levels of alcohol problems are only slightly more prevalent in childhood.[103,109–111]

Moreover, while the onset of alcohol use in adolescence and periadolescence has been investigated as a predictor of subsequent alcohol disorders, when childhood initiation has been studied, the focus has been on substance use in more general terms (alcohol, tobacco, or marijuana use) rather than on alcohol exclusively, due to the generally low rates of use in children.[112–114]

In the existing literature, only Fergusson et al.[115] appear to have focused attention on the relationship between childhood alcohol consumption and adolescent drinking patterns at 15 years of age. This research utilized a birth cohort of 739 children and also extensively investigated the effect of early exposure to alcohol. Age at first alcohol consumption was classified into four categories: 0–5 years, 6–10 years, 11–12 years, and after 13 years. The authors note that children who had been introduced to alcohol before the age of 6 years were 1.9–2.4 times more likely to report frequent, heavy, or problem drinking at age 15 years than children who did not drink alcohol before the age of 13 (Table 4).

Alcohol exposure in childhood seems to be a multilevel phenomenon that includes a wide spectrum of behaviors other than drinking, such as sipping or tasting alcoholic beverages, the prevalence of which could be expected to be high among children aged 12 years and under.[104]

Developmental studies have shown that postnatal exposure to ethanol has some relatively immediate consequences. In fact, children as young as 3–5 years old can recognize alcoholic beverages by smell,[95,116] and children as young as 3 years have a developed alcohol schema[117]; if parents consume ethanol, children become more effective at detecting and identifying ethanol odor and recognizing alcoholic beverages.[94] Moreover, the emotional context that accompanies parental use of ethanol has a profound effect on how young children (3–6 years of age) judge the pleasantness of the smell of an ethanol beverage, similar to what occurs with tobacco smoke.[118] Children whose parents use ethanol primarily as a means of obtaining relief from their problems are more likely to consider the odor of beer unpleasant than those whose parents drink for other reasons.[94]

Table 4 **Estimates of the relationships between the risks of alcohol-related outcomes and age at first drink, adjusted for covariates (family social position, family size, parental history of alcohol/drug problems, parental drinking, parental approval of drinking, parental conflict, gender, conduct disorder).**

Age at first exposure to alcohol (years)	Consumes alcohol monthly (%)	Usually drinks the equivalent of at least 30 ml of alcohol (%)	Consumes the equivalent of at least 90 mL of alcohol on one occasion (%)	Experiences alcohol-related problems (%)
1–5	29.4	29.4	21.2	25.4
6–10	24.0	24.0	17.3	19.5
11–12	19.3	19.3	14.0	14.7
13+	15.2	15.2	11.2	10.8
N	734	733	733	733
P value	<0.05	<0.05	<0.05	<0.01

Reproduced with permission from Fergusson et al.[115]

Table 5 **Summary of sipping/tasting contexts by age cohort, with the percentage of respondents who checked the option as a single response shown in parentheses.**

Context of sipping/tasting	Total sample ($n = 177$)	8-year-olds ($n = 71$)	10-year-olds ($n = 106$)
As part of a religious observance	25% (15%)	24% (16%)	26% (14%)
With family at dinner	33% (24%)	41% (32%)	28% (18%)
As part of a family celebration	36% (27%)	23% (18%)	45% (32%)
With friends	2% (!%)	0% (0%)	4% (2%)
By myself	2% (!%)	0% (0%)	4% (1%)
Somewhere else	23% (16%)	27% (23%)	21% (11%)

Modified from Donovan and Molina (2008).[104]

The developmental process through which children's attitudes toward alcohol are transformed from sipping to drinking has been largely unexplored, and relatively little is known about this transition.[105]

In particular, a recent study[104] demonstrated that alcohol sipping or tasting by young children occurs most often in a family context and that it may reflect explicit family socialization into alcohol use (Table 5). Having some alcohol as a regular part of mealtimes in a family context has long been viewed as a forerunner of moderation in alcohol use,[119] despite the absence of empirical verification. The location of child sipping and tasting in a family context is in distinct contrast to what is known of adolescent drinking. Alcohol use among adolescents occurs more often in peer contexts, such as outside the home, at unsupervised parties, outdoors, and in cars, than at home or with parents.[120,121]

In addition, Donovan and Molina[104] found that sipping/testing do not relate to variables reflecting psychosocial propensity to problem behavior. Instead, the variables more predictive of sipping were perceived parental drinking status, perceived parental approval of children sipping, mother's drinking frequency, and children's attitudes toward sipping/testing alcohol (Table 6).

Therefore, even if some studies show that early childhood represents a "sensitive period" for the development of expectancies and cognitions about alcohol and, in particular, that associative learning in the context of emotionally salient conditions is a powerful mechanism by which odors acquire personal significance, it is possible to argue that not enough evidence exists to determine whether such emotional contexts promote or discourage alcohol use during adolescence and adulthood.[104]

Table 6 **Results of stepwise (forward selection) multivariate logistic regression analyses predicting sipping/tasting status by age cohort.**

Sipping/tasting status	OR (95% CI)
8-year-olds ($n = 71$)	
Perceived parents' approval of sipping	1.78 (1.05–3.03)
Perceived parents' drinking status	8.89 (2.92–27.65)
Child's attitude toward sipping	2.26 (1.66–3.08)
Constant	0.001
10-year-olds ($n = 106$)	
Perceived mother's drinking status	2.31 (1.06–5.05)
Mother's frequency of drinking	1.29 (1.03–1.62)
Child's attitude toward sipping	1.47 (1.22–1.77)
Constant	0.042

Modified from Donovan and Molina (2008).[104]
Abbreviations: CI, confidence interval; OR, odds ratio.

ALCOHOL EXPOSURE IN ADOLESCENCE

Alcohol use usually begins in the second decade of life, typically in early adolescence. The rate of alcohol use increases sharply between the ages of 12 and 21 years, and adolescents frequently adopt a binge-like drinking pattern.[122,123]

Results based on animal models have revealed how adolescents are considerably less sensitive than adults to most consequences of ethanol consumption, including ethanol-induced motor impairment, dysphoria, social impairment, sedation, and certain post-intoxication "hangover" effects.[124–126] By contrast, they are more sensitive than adults to a few effects of ethanol, including the social facilitation seen at low doses of ethanol[127]; this attenuated sensitivity to the negative consequences of ethanol and the social facilitation induced by ethanol[128,129] may encourage ethanol consumption and allow the consumption of large quantities of alcohol in a short period. This elevated intake increases the adverse effect of alcohol; adolescents seem to be notably more vulnerable than adults to the brain damage induced with a binge model of alcohol exposure in rats, with adolescent but not adult rats showing frontal cortex degeneration.[130,131]

Moreover, animal studies have shown adolescents to be more sensitive than adults to ethanol-related impairments in brain plasticity and memory, with the latter effect being reported for human adolescents as well.[132–136] Finally, adolescent rats were found to be less sensitive to the sedative effects of ethanol compared with older animals.[137,138]

Although these studies have revealed that adolescent alcohol exposure can have lasting effects on neural and behavioral function, the comparability of these

Table 7 **Age at first alcohol use and prevalence of lifetime alcohol dependence/abuse.**

Age at first alcohol use (years)	Prevalence (standard error) of lifetime dependence ($n = 27,616$)	Prevalence (standard error) of lifetime abuse ($n = 27,616$)
12 or younger	40.6 (2.1)	8.3 (1.1)
13	47.3 (2.7)	11.5 (1.8)
14	40.8 (1.9)	13.8 (1.5)
15	38.7 (1.4)	11.9 (0.9)
16	30.6 (0.9)	10.6 (0.7)
17	24.5 (1.0)	9.5 (0.6)
18	16.6 (0.6)	7.8 (0.4)
19	16.5 (1.0)	6.3 (0.6)
20	11.4 (0.8)	4.8 (0.5)
21	10.0 (0.6)	4.8 (0.4)
22	9.5 (1.1)	4.9 (1.0)
23	14.7 (1.9)	3.6 (0.9)
24	13.6 (2.1)	3.1 (1.0)
25 or older	7.9 (0.6)	2.5 (0.4)

Modified from Grant and Dawson.[175]

exposures to those seen in human adolescents has yet to be determined.

When the potential long-term consequences of adolescent alcohol use are being considered, an important question is whether alcohol exposure in adolescence increases the probability of later use and the development of alcohol use disorders. Studies using animal models have begun to explore whether there is a causal relationship between early exposure and later alcohol consumption. It is also possible that early exposure to alcohol alters developmental processes during adolescence, with long-term effects on neurobehavioral functions that increase the propensity for later abuse. Although findings are mixed,[139,140] voluntary drinking of alcohol during adolescence has been reported to facilitate acquisition of alcohol self-administration in adulthood, to increase "craving" behavior and probability of relapse, and to exacerbate stressor-specific increases in alcohol intake.[141,142] Chronic exposure to alcohol during adolescence also has been reported to induce long-lasting tolerance that serves to "stamp in" the adolescent-associated insensitivity to the sedative[143] and motor-impairing effects of ethanol,[131,134] such that these insensitivities persist into adulthood and perhaps contribute to a greater propensity for high levels of alcohol use in adulthood.

In human studies, the early onset of alcohol use, operationalized as the age at first drink or age at onset of drinking, has been explored extensively.[144–199]

Pape and Hammer[162] in 1996 explored how age at first intoxication with alcohol relates to mental health, social integration, and adjustment to the adult role. A U-shaped association between intoxication debut and psychological problems was revealed among males, implying that not only early but also late beginners had more such problems than those who had followed the mainstream. In particular, male late beginners were psychologically healthy, but they showed indications of a delayed entry into the adult role. Thus, the authors concluded that getting drunk for the first time in mid-adolescence seems to be an ingredient in the normal developmental process in young males. All other authors who have focused their attention on early onset in adolescence have recognized it as a reliable predictor of later problematic use and dependence on alcohol and other drugs.

Several cross-sectional studies have found that the age at which a first, single alcoholic drink was consumed is associated with subsequent drinking behavior. Among high school senior drinkers, those who recalled drinking at the earliest ages reported greater alcohol abuse, alcohol misuse, alcohol consumption (frequency and quantity), and self-reported drinking/driving during their senior year.[183] Adult drinkers who recalled having their first alcoholic drink before age 14 were more likely to have been diagnosed with alcohol abuse or dependence at some time during their lives. In 1997, Grant and Dawson[175] published an influential analysis of the Alcohol Epidemiologic Survey, in which they reported a strong association between age at first drink and rate of alcoholism (Table 7). In a sample of more than 27,000 ever-drinking adults, the rate of lifetime alcohol dependence was four times higher among those who started to drink by age 14 compared with those who had not started to drink until age 20 years or older. Grant and Dawson's findings have been replicated in subsequent research.

DeWit et al.[161] in 2000 sought to describe the natural course of DSM-III-R (*Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised) alcohol disorders as a function of the age at first alcohol use and to investigate the influence of early use as a risk factor for progression to the development of alcohol disorders, exclusive of the effect of confounding influences. Data were obtained from a community sample of more than 5,000 lifetime drinkers participating in the 1990–1991 Mental Health Supplement of the Ontario Health Survey. Survival analyses revealed a rapid progression to alcohol-related harm among those who reported having their first drink at ages 11 to 14. After 10 years, 13.5% of the subjects who began to drink at ages 11 and 12 met the criteria for a diagnosis of alcohol abuse, and 15.9% had a diagnosis of dependence. Rates for subjects who began to drink at ages 13 and 14 were 13.7% and 9.0%, respectively. In contrast, rates for those who started drinking at ages 19 and older were 2.0% and 1.0%.

Few studies have utilized longitudinal data to determine drinking onset age and to examine subsequent alcohol-related behavior. In studies that have done so, an earlier age of drinking onset was associated with subsequent adolescent alcohol misuse,[191] alcohol consumption and problem drinking in young adulthood,[166] a diagnosis of DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition) alcohol abuse or dependence by young adulthood,[187] and alcohol and other substance use in young adulthood.[167]

The same relationship was reported for other alcohol-related behaviors among adult drinkers; earlier onset of alcohol use (before 14 years of age) was associated with self-reported adult alcohol-related injury,[200] physical fights after drinking,[201] self-reported drinking-and-driving arrests and crashes,[202] academic and employment problems, criminal and violent behavior,[167] and risky sex.[195]

It remains unclear, however, whether early use of alcohol is causal or merely serves as a marker for later problematic ethanol use.[185] Early onset of alcohol use is, in fact, correlated with a number of other risk factors, including family tendency to drink and peer association.[160,191,203]

While some authors have concluded that the association between early exposure to alcohol and later alcohol abuse is not entirely explained by genetic or shared environmental factors,[148,150,170,181] other recent prospective studies have shown that the onset of drinking in early adolescence is no longer a predictor of alcohol dependence in young adults after controlling for variables known to play a role in alcohol abuse, such as adverse family environment and poor quality of parent-child relationships, family history of alcoholism, and childhood and adolescent externalizing symptoms.[151,154]

Drinking alcohol at an early age has repeatedly been found to be preceded by aggressive/antisocial and hyperactivity symptoms.[160,182,204] This result reinforces the idea that the age at which the first alcoholic drink is consumed is not specifically associated with alcoholism but rather is correlated with a broad range of indicators of disinhibited behaviors and psychopathology. More generally, it implies that early onset of alcohol use does not, in itself, influence the risk for later dependence, it may merely be a marker of an environmentally or genetically determined vulnerability to alcoholism.[174]

CONCLUSION

The present review shows how alcohol consumption may negatively influence the neurobiological and neurobehavioral development of humans. In the earliest stages of human development, i.e., prenatal life, heavy alcohol exposure can have devastating consequences, resulting in behavioral and cognitive deficits.[15,16] Maternal alcohol consumption and the interaction between maternal and genetic factors may cause serious damage to a child's brain, with the complex syndrome of FASD representing the most severe manifestation of heavy maternal alcohol consumption.

In contrast to the many studies conducted on alcohol exposure during prenatal life, alcohol use during childhood has received relatively little attention (as Donovan[103] has noted), even though childhood represents an important period for the development of expectations and cognition about alcohol. It may be hypothesized that in this period, the child learns "drinking rules", i.e., he or she learns to associate emotional feelings and behaviors with a particular context. It has been demonstrated that alcohol sipping or tasting in this age range occurs more often in the family context.[104] For this reason, the family influence during childhood is probably fundamental for creating an emotional context that promotes or discourages alcohol use during adolescence and adulthood. Further research should explore this factor more fully to promote healthier approaches to alcohol use in families with children.

Finally, a considerable number of studies have focused on alcohol use during the adolescent period. Usually, adolescence is considered the time in which many consequential life decisions are made and, in particular, the time when risky behaviors (including experimenting with alcohol) become temporarily more normative than they are at other times in the lifespan.[205] Adolescence is usually believed to be the period of onset for drinking, particularly to facilitate social interactions between peers. Apart from this social role of alcohol, other serious factors have been linked to alcohol use at this age. Family problems (e.g., parental separation,

maltreatment, paternal substance use, and psychopathology),[206,207] school-related problems,[172] substance use,[206] and various forms of externalizing problems[170,172,205] are important factors that may lead to alcohol abuse in adolescence and later in adulthood.[147]

Although important milestones have been reached, research in the area of alcohol exposure in all periods of early life is still hampered by the absence of a unified methodological background and set of definitions.[3,5] This is reflected in the difficulty of conducting much-needed large-scale epidemiological studies, which in turn prevents researchers from conducting systematic reviews and meta-analyses. Evidence-based practice involves integrating the best available knowledge by means of a systematic, comprehensive review and synthesis of the research literature[208]; however, the small number of studies satisfying the criteria for inclusion in systematic reviews, the heterogeneity in terms of the outcomes measured and child ages submitted to meta-analysis, and the frequent lack of information regarding drinking patterns and timing of drinking necessitate prudence in interpreting the results of meta-analytic studies.[6,55,71–73,209] For this reason, in agreement with the World Health Organization,[210] a cautionary approach that emphasizes abstinence during pregnancy and the early stages of childhood is recommended, particularly since a safe limit of ethanol intake has not been yet identified.

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