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ABSTRACT. Objective: The aim of this study was to evaluate the association between maternal smoking during pregnancy (MSP) and lifetime risk for alcohol use disorder (AUD) and to explore possible mechanisms through which MSP may be related to neurobehavioral conditions during infancy and childhood, which could, in turn, lead to increased risk for AUD. **Method:** A sample of 1,625 individuals was followed from pregnancy for more than 40 years. Capitalizing on the long follow-up time, we used survival analysis to examine lifetime risks of AUD (diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) in relation to levels of MSP (none, <20 cigarettes/day, and ≥20 cigarettes/day). We then used structural equation modeling to test hypotheses regarding potential mechanisms, including lower birth weight, neurological abnormalities, poorer academic functioning, and behavioral dysregulation. **Results:** Relative to unexposed offspring, offspring of mothers who smoked 20 cigarettes per day or more exhibited greater risks for AUD (hazard ratio = 1.31, 95% CI [1.08, 1.59]). However, no differences were observed among offspring exposed to fewer than 20 cigarettes per day. In structural equation models, MSP was associated with neurobehavioral problems during infancy and childhood, which, in turn, were associated with an increased risk for adult AUD. **Conclusions:** MSP was associated with an increased lifetime risk for AUD. Adverse consequences were evident from birth to adulthood. A two-pronged remedial intervention targeted at both the mother (to reduce smoking during pregnancy) and child (to improve academic functioning) may reduce the risk for subsequent AUD. (*J. Stud. Alcohol Drugs, 72,* 199-209, 2011)

ACCORDING TO THE Centers for Disease Control and Prevention, alcohol is the third highest lifestyle-related cause of death in the United States, with approximately 79,000 deaths annually attributable to excessive alcohol use (Centers for Disease Control and Prevention, 2004). Chronic drinking causes a variety of functional impairments and has many harmful health consequences. These include liver disease (Heron, 2007; Schiff, 1997); cancer (Baan et al., 2007); cardiovascular disease (Rehm et al., 2003); neurological damage (Corrao et al., 2002, 2004); HIV infection (Rosenbloom et al., 2007; Windle, 1997); and psychiatric problems such as depression, anxiety, and antisocial personality disorder (Castaneda et al., 1996; Kessler et al., 1997; Rosenthal and Westreich, 1999). Chronic drinking is also associated with an elevated risk for unintended accidents such as falls (Goodman et al., 1991), drowning (Cummings and Quan, 1999), burns (Hingson and Howland, 1993; McGill et al.,

1995), fatal motor vehicle crashes (National Highway Traffic Safety Administration, 2008), and interpersonal violence (Bushman, 1997; Caetano et al., 2000).

Various biological and psychological risk factors for alcohol use disorder (AUD) have been identified, including alcohol metabolism, genetic risks, and psychosocial risks (i.e., lack of parental monitoring, severe and recurrent family conflict, and poor parent–child relationships) (Quetemont, 2004; Wall et al., 2007). However, to the best of our knowledge, maternal smoking during pregnancy (MSP) has never been found to be a potential distal risk factor for alcohol use problems and AUD despite its association with a variety of adverse outcomes, including substance use disorders, in later life. For instance, the adverse effect of MSP on birth outcomes is well established, including an approximately 150-250 g decrement in birth weight (Substance Abuse and Mental Health Services Administration, 2005; Visscher et al., 2003) and a higher neonatal mortality rate (Duncan et al., 2008; Fleming and Blair, 2007). Infants exposed to MSP also displayed an elevated risk for sudden infant death syndrome (Edner et al., 2007; Markowitz, 2007; Weese-Mayer et al., 2007), neurological and language problems (Fried, 1993; Fried et al., 1992a, 1992b), difficult temperaments (Brook et al., 1998), aggression (Tremblay et al., 2004), behavioral problems (Maughan et al., 2004; Monuteaux et al., 2006; Orlebeke et al., 1997), cognitive function deficits (Keeping et al., 1989; Naeye and Peters, 1984; Nomura et al., 2008), attention deficits and hyperactivity (Button et al., 2005; Linnet et al., 2005; Wakschlag et al., 1997), early onset of delinquency and antisocial behavioral problems (Nomura et al., 2009; Piquero et

al., 2002; Wakschlag et al., 2003; Weitzman et al., 1992), cigarette smoking in adolescence and adulthood (Buka et al., 2003; Cornelius et al., 2000, 2005; Griesler et al., 1998), and drug use (Ekblad et al., 2010) Fergusson et al., 1998; Weissman et al., 1999). These findings all indicate that MSP may indeed impair the development of the fetal central nervous system in a fashion that may predispose the offspring to a wide array of neurobehavioral problems.

To date, few studies have tried to systematically elucidate potential mechanisms by which MSP may impair the child's central nervous system early in life and the subsequent increased risk for AUD. Furthermore, we are unaware of prior studies that have examined whether there is a direct link between MSP and AUD in adulthood or if their association can, at least in part, be explained by problems in the preceding stages of life. Approximately 10-20% of women smokers who become pregnant continue to smoke during pregnancy (DiFranza and Lew, 1995; Maughan et al., 2004), and MSP is one of the early modifiable risk factors that could potentially reduce the incidence of adverse outcomes throughout the life course (Ringel and Evans, 2001; Shiono and Behrman, 1995).

In this study, we used data from a population-based sample of children who have been followed more than 40 years to address two aims: (a) to evaluate the lifetime risk for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994), AUD associated with exposure to MSP and (b) to elucidate possible mechanisms through which MSP affects neurobehavioral conditions during early infancy and childhood (i.e., birth weight, neurological abnormalities, academic functioning, and behavioral regulation), which may lead to an increased risk for AUD. We hypothesized that there will be a greater risk for AUD among offspring exposed to MSP than those unexposed. We also hypothesized that MSP is associated with increased risk for AUD, and that this association will be mediated in part through problems in infancy and childhood.

Method

Procedures

Data were derived from the Collaborative Perinatal Project (CPP), consisting of prospective data collected from a representative sample of pregnant women who received prenatal care and delivered their babies during 1960-1966 (Niswander and Gordon, 1972). The CPP used a single study design across all 12 sites. The sites participated in a systematic data collection from pregnancy to the first 7 years to identify perinatal and early childhood factors that adversely affect subsequent child development (Buka et al., 1993). Reports from the CPP have been summarized elsewhere (Nicholas and Chan, 1981).

Between 2001 and 2004, the New England Family Study was established to locate and interview a sample of the adult CPP offspring at the Providence, RI, and Boston, MA, sites. Participants were selected through a multistage sampling procedure, which involved a core assessment interview and three component studies. Screening questionnaires were mailed to 4,579 of the 15,721 Providence and Boston CPP offspring who lived beyond 7 years of age. Of the 3,121 questionnaires that were returned (68.2%), 2,271 were eligible for participation based on the combined inclusion criteria of the three component studies. Those who enrolled had a somewhat higher level of education (e.g., 64.1% with at least some college education) than participants who were eligible but not enrolled (e.g., 51.8% with at least some college education). Data from 49 of the individuals were excluded from the final sample either because of their participation in a pilot version of the survey ($n = 4$) or because of problems with the interview administration ($n = 45$). This resulted in 1,625 completed adult assessments (Gilman et al., 2008a, 2008b). As part of the study design, siblings were oversampled. The final sample included these 1,625 offspring of 1,254 mothers; analyses were conducted to account for these sibling sets.

Measures

Maternal smoking during pregnancy. At the first prenatal visit, women reported whether they were currently smoking and, if so, the number of cigarettes they smoked per day. These questions were repeated at each subsequent prenatal visit up until the time of delivery. From these repeated measurements, we determined the maximum number of cigarettes smoked per day at any point during pregnancy. Women were then classified into three levels of smoking: never smoked during any pregnancy day (coded 0), smoked fewer than 20 cigarettes during any pregnancy day (coded 1), and smoked 20 cigarettes or more during any pregnancy day (coded 2). This categorical smoking variable was used in this article.

Birth weight. Birth weight was recorded in grams by a nurse observer at the time of delivery.

Neurological abnormality at age 1. A trained pediatrician or pediatric neurologist performed a neurological evaluation of the child and screened for a variety of potential developmental abnormalities when the child was approximately 1 year old (50-56 weeks). There were 116 items that were used to characterize the child's neurological status. Neurological abnormality at age 1 was defined as the number of abnormalities coded either abnormal or suspect.

Academic functioning at age 7. The Wide Range Achievement Test measured learning (dis)abilities (i.e., reading, arithmetic, and spelling; Jastak and Jastak, 1965). We used the standardized scores for this analysis. The mean (*SD*) scores for the three areas were the following: reading, 104.75

(16.39); arithmetic, 99.44 (9.80); and spelling, 100.87 (13.51). The ranges were 70-165, 50-165, and 63-165, respectively. The three separate Wide Range Achievement Test scores formed a single factor (eigenvalue = 2.43), namely "academic functioning."

Behavioral regulation. Trained child psychologists evaluated the child's behavioral functioning in 15 domains using a 5-point Likert scale. Those 15 areas include shyness, fearfulness, dysinhibition, self-confidence, emotional reactivity, degree of cooperation, frustration tolerance, degree of dependency, attention span, goal orientation, activity level, nature of communication, impulsivity, assertiveness, and hostility. Because MSP has been more closely linked to self-regulatory control deficits (Huijbregts et al., 2008; Vuijk et al., 2006), we chose dysinhibition, emotional reactivity, activity level, and impulsivity as our behavioral measures. These four observed scores formed a single factor (eigenvalue = 2.17), namely "behavioral regulation."

Clinical diagnosis of alcohol use. The lifetime occurrence of three distinctive DSM-IV symptoms clusters—namely alcohol abuse, alcohol dependence, and alcohol withdrawal—were assessed with an expanded version of the AUD module of the Composite International Diagnostic Interview (World Health Organization, 1993, 1997). There were four symptoms of alcohol abuse, seven symptoms of alcohol dependence, and eight symptoms of alcohol withdrawal. Diagnosis of AUD was generated based on DSM-IV criteria. Age at onset for AUD (abuse or dependence) was defined as the age reported for the first symptom of AUD (for details, see Dierker et al., 2007). AUD is our primary outcome in both survival analysis and structural equation modeling (SEM). In survival analysis, additionally, risks for alcohol abuse and alcohol dependence were examined.

Potential confounders and missing values. We chose socioeconomic status, child gender and race, and mother's self-reported mental health status during pregnancy as the most pertinent potential demographic and maternal characteristic confounders, because they are known to be associated with birth weight, neurological abnormality, and childhood problems with behavior and learning (Gilman et al., 2008a). They were included in all analyses for statistical adjustment.

Information on parental race/ethnicity and socioeconomic status was collected during the first prenatal visit. A composite index was calculated on the basis of methods developed by the U.S. Census Bureau. The index reflects the education and occupation of the head of household, along with household income (Myrianthopoulos and French, 1968). Mother's self-reported mental health status was recoded as none, hospitalized, receiving outpatient treatment, or alcohol/drug addiction.

Rates of missing data were 6.6% for AUD diagnostic outcome, 2.0% for age at first alcohol-abuse symptom, and 0.2% for age at first alcohol-dependence symptom. Missing data for predictors were approximately 3.0% for Wide Range Achievement Test, Wechsler Intelligence Scale for Children, and behavioral observation scores at age 7. Missing data for other covariates were 4.2% for family socioeconomic status and 6.4% for mother's self-reported mental health status during pregnancy. There were no missing data for gender, race, birth weight, MSP, or age at the time of interview.

Statistical analysis

After an initial descriptive univariate analysis, we tested our hypothesized models using survival analysis and SEM techniques. First, using survival analysis techniques, the Wilcoxon test showed the overall differences for proportion of subjects free from AUD, alcohol abuse, and dependence over time, for the three MSP groups. Cumulative lifetime rates of AUD, as well as alcohol abuse and dependence separately, were then evaluated by the Kaplan-Meier method (Williams, 1995). To estimate the risk of AUD, and alcohol abuse and dependence separately, among offspring exposed to MSP (<20 cigarettes/day and ≥20 cigarettes/day), compared with that among offspring unexposed to MSP, Cox proportional hazards regression models (Binder, 1992; Cox, 1972) were fitted using SUDAAN (Shah et al., 1997) to account for potential nonindependence of outcomes for offspring from the same family.

Second, using SEM we attempted to explain our findings regarding the association between MSP (none, <20 cigarettes/day, and ≥20 cigarettes/day) and the risk for AUD through childhood neurological, cognitive, and behavioral problems, as well as the direct effect of MSP on the increased risk for AUD. SEM allows simultaneous testing of all of the associations among the different risk factors studied and hence the assessment of direct and indirect associations of all predictors, while taking into account a variety of control variables (Linver et al., 2002). We used the software Mplus (van Horn et al., 2009; Muthén and Muthén, 1998-2007) to adjust for potential nonindependence of outcomes for offspring from the same family and to normalize our nonlinear (i.e., dichotomous) outcome. The transformation used in Mplus is the logit function, which is the natural log of the odds. As we have done in the survival analysis, potential nonindependence of outcomes for offspring from the same family has been adjusted, using Mplus (van Horn et al., 2009). We assessed two childhood risk constructs (i.e., academic functioning and behavior regulation) as forms of latent variables, which are hypothetical underlying constructs that cannot be measured directly (MacCallum and Austin, 2000). Behavioral regulation was measured by four observed variables, and academic functioning was measured by three. Our final outcome measure of AUD in adulthood was a dichotomous diagnostic outcome. SEM with latent variable modeling has been shown to be useful in situations in which (a) measurement error is an issue, (b) the phenomena under study are not directly observed, and (c) multiple indicators

are needed to describe various aspects of a phenomenon (Muthen, 1992). Our two hypothesized latent constructs fit all of the previously described circumstances, thus warranting the use of SEM with latent variables. Because the constructs to be examined are based on latent variables, to maintain the validity of the two latent variables, we ran exploratory factor analysis to determine if the number of factors (i.e., single factor) and the loadings of observed variables on the factor conformed to what is expected. If the factor analysis suggested a single latent construct, we mapped these observed variables onto a single latent variable. Cronbach's alpha was obtained as an index of reliability associated with the variation accounted for by the true score of the underlying latent construct (Hatcher, 1994).

We used the full information maximum-likelihood method for estimation. This method uses all available observed data without deleting records from participants with missing values on covariates and, therefore, provides a more efficient and less biased analysis than complete case methods (Arbuckle, 1996; Enders and Bandalos, 2001; McArdle and Hamagami, 1996). Before the analysis, the data were evaluated for normality by examining the univariate indices of skewness. If normal assumption was found to be violated, normalization through log transformation was applied. Path coefficients (standardized beta weights) can be interpreted both in terms of their significance and magnitude. The overall fit of the hypothesized model was evaluated by various indices: A nonsignificant chi-square, Tucker-Lewis index (TLI) greater than .95, a normed fit index (NFI) greater than .95, and root mean square error of approximation (RMSEA) less than .06 were used to indicate a good fit (Joreskog and Sorbom, 1986; Tucker and Lewis, 1973). Potential confounders, including race, gender, socioeconomic status, and mother's self-reported mental health status during pregnancy, were included in the SEM for statistical adjustment. Specifically, the model included paths from race, socioeconomic status, and mother's self-reported mental health status during pregnancy to MSP; paths from race, gender, socioeconomic status, and mother's self-reported mental health status during pregnancy to birth weight, neurological abnormality, behavioral regulation, and academic achievement; and paths from gender and socioeconomic status to AUD.

We tested two structural equation models: (a) a model with a direct path only from MSP to AUD and (b) a model with a direct path and an indirect association between MSP and AUD through lower birth weight, neurological abnormality, and lower academic functioning.

Results

Participants' characteristics

The sample was 59.2% female, 61.1% were married, and the mean age was 39.1 years (*SD* = 1.9; range: 34-44). The racial/ethnic composition was 83.5% non-Hispanic White, 9.6% Black/African American, 1.1% Hispanic/Latino, and 5.9% other. Six percent of the participants had not completed high school, 19.1% had received a high school diploma or general educational development credential only, 46.4% had had some postsecondary education, 18.9% had college degrees, and 9.6% had graduate degrees. The mean for the maximum number of cigarettes smoked among mothers, birth weight, and number of neurological abnormalities were 11.04 (*SD* = 0.16), 3,257 g (*SD* = 538), and 1.32 (*SD* = 1.92), respectively. The mean for spelling, reading and arithmetic scores were 100.9 (*SD* = 13.5), 104.7 (*SD* = 16.4), and 99.4 (*SD* = 9.8), respectively.

Cumulative risk for AUD among offspring as affected by the amount of maternal smoking during pregnancy

Initial univariate analysis shows that 40.3% of the offspring had lifetime AUD (39.6% offspring had lifetime abuse, and 11.6% had lifetime alcohol dependence). The amount of MSP (none, <20 cigarettes/day, and ≥20 cigarettes/day) was linearly associated with an increased rate of AUD 37.0% for the offspring of nonsmoker mothers; 39.7% for the offspring of mothers who smoked fewer than 20 cigarettes per day at any time during pregnancy, and 44.2% for the offspring of mothers who smoked 20 cigarettes or more per day at any time during pregnancy (p = .01). This pattern is the same for alcohol abuse (35.9% for none; 39.2% for <20 cigarettes/day; and 44.0% for ≥20 cigarettes/day, p = .005) and for dependence (9.8% for none; 11.1% for <20 cigarettes/day; and 13.8% for ≥20 cigarettes/day, p = .04).

The results of survival analyses of AUD by MSP are presented in Figure 1. The test of equality of strata (Wilcoxon test) shows that there was a significant difference in the onset of AUD among the three groups by MSP, $\chi^2(1)$ = 5.78, p = .016. Table 1 further shows the cumulative risks for lifetime AUD (alcohol abuse or alcohol dependence), as measured by the hazard ratio (HR) in offspring exposed to MSP (<20 cigarettes/day and ≥20 cigarettes/day), relative to offspring unexposed to MSP, the reference group. Offspring exposed to 20 cigarettes or more per day had a greater cumulative lifetime risk for AUD (HR = 1.24, 95% CI [1.03, 1.49], p = .02) relative to the reference group. The increased risk remained significant after adjustment for potential confounders (adjusted HR = 1.31, 95% CI [1.08, 1.59], p = .009), but offspring exposed to fewer than 20 cigarettes per day had no significant increase in the risk of AUD (adjusted HR = 1.13, 95% CI [0.91, 1.41], p = .26) relative to the reference group. Similarly, offspring exposed to 20 cigarettes or more per day had a greater cumulative lifetime risk for alcohol abuse (adjusted HR = 1.34, 95% CI [1.10, 1.62], p = .004), but offspring exposed to fewer than 20 cigarettes per day had no significant increase in the risk of AUD (adjusted HR = 1.12, 95% CI [0.94, 1.46], p = .16) relative to the reference

TABLE 1. Cumulative risk and 95% confidence interval (CI) for lifetime alcohol use disorder among offspring exposed to varying degrees of smoking in utero

Variable	n	Unadjusted HR [95% CI]	p	Adjusted HR [95% CI]	p
Alcohol use disorder					
None	658	reference		reference	
<20 cigarettes/day	401	1.10 [0.89, 1.35]	.39	1.13 [0.91, 1.41]	.26
≥20 cigarettes/day	558	1.24 [1.03, 1.49]	.02	1.31 [1.08, 1.59]	.009
Alcohol abuse					
None	658	reference		reference	
<20 cigarettes/day	401	1.12 [0.91, 1.38]	.29	1.12 [0.94, 1.46]	.16
≥20 cigarettes/day	558	1.28 [1.06, 1.54]	.009	1.34 [1.10, 1.62]	.004
Alcohol dependence					
None	658	reference		reference	
<20 cigarettes/day	401	1.15 [0.77, 1.71]	.49	1.10 [0.73, 1.65]	.65
≥20 cigarettes/day	558	1.44 [1.02, 2.04]	.04	1.38 [0.97, 1.95]	.07

Notes: Adjusted for gender, family socioeconomic status at birth, mother's self-reported mental health status during pregnancy, and child's race. Potential cluster effect due to multiple children from the same family has been adjusted. There are eight missing cases. HR = hazard ratio.

group. However, there was only a marginal difference in the increased risk for alcohol dependence among offspring exposed to 20 cigarettes or more per day relative to the reference group.

Descriptives for latent measures used in the SEM

Academic functioning. The mean (*SD*) scores for the three areas were as follows: reading = 104.75 (16.39), arithmetic = 99.44 (9.80), and spelling = 100.87 (13.51). The ranges were 70-165, 50-165, and 63-165, respectively. The three separate Wide Range Achievement Test scores had excellent internal consistency (Cronbach's α = .87).

Behavioral regulation. The mean (SD) scores for the four measures were as follows: dysinhibition = 2.91 (0.65), emotional reactivity = 2.89 (0.42), activity level = 2.96 (0.48), and impulsivity = 2.98 (0.28). All ranges were from 1 to 5. The four behavioral characteristics scores had good internal consistency (Cronbach's α = .72).

Model fit for structural equation model

The use of SEM allowed for a simultaneous test of the associations between MSP, birth weight, neurological abnormality within a year after birth, academic functioning (reading, spelling, and arithmetic scores), and behavioral regulation (inhibition, emotional regulation, activity level, and impulsivity). The correlation matrix of the variables used for testing the model is presented in Table 2. We found that correlations between the hypothesized relationships were significant but modest.

We tested two models: one (simple model) with only one path from MSP to AUD and another (expanded model) based on the hypothesis that the effect of MSP is both directly and indirectly associated with increased risk for AUD through elevated problems in infancy and childhood. The simple

model demonstrated good fit, including an NFI of .98, a TLI of .97, and a RMSEA of .043. The expanded model (see Figure 2) also demonstrated good fit, including an NFI of .98, a TLI of .96, and a RMSEA of .035. We reached this conclusion despite the significant chi-square test of model fit, $\chi^2(89) = 229.31$, $p < .01$, because this statistic is known to be especially sensitive to large sample sizes and captures even small deviations from the causal model (Byrne, 2001).

The magnitude of associations in the hypothesized models between MSP and AUD

Our initial model with only MSP and AUD showed good fit (figure not shown). There was a strong association between MSP and AUD (β = .07, *p* = .01). The unstandardized path coefficient for this standardized path coefficient of .07 in a logit scale was .18, which represents the odds ratio of 1.2. This estimation is very similar to what we estimated in our survival analysis. The expanded model, which includes childhood outcomes as possible preceding conditions, is presented in Figure 2 with the standardized path coefficients. MSP was inversely associated with birth weight (β = -.20, *p* < .0001), which in turn was inversely associated with a greater number of neurological abnormalities at age 1 year (β = -.16, *p* < .0001). Although MSP was not directly associated with neurological abnormality, it was associated with subsequent lower academic functioning at age 7 (β = -.23, *p* < .0001). However, there was no notable association between neurological abnormality and behavioral regulation at age 7. MSP was also associated with academic functioning (β = -.10, *p* = .02) but not behavioral regulation (β = -.02, *p* = .60) at age 7. Greater academic functioning was associated with a decreased risk of AUD (β = -.13, *p* = .002). In addition, although only marginally significant, MSP was found to be directly associated with a greater risk for AUD (β = .04, *p* = .07). Of note, there was a reduction in the stan-
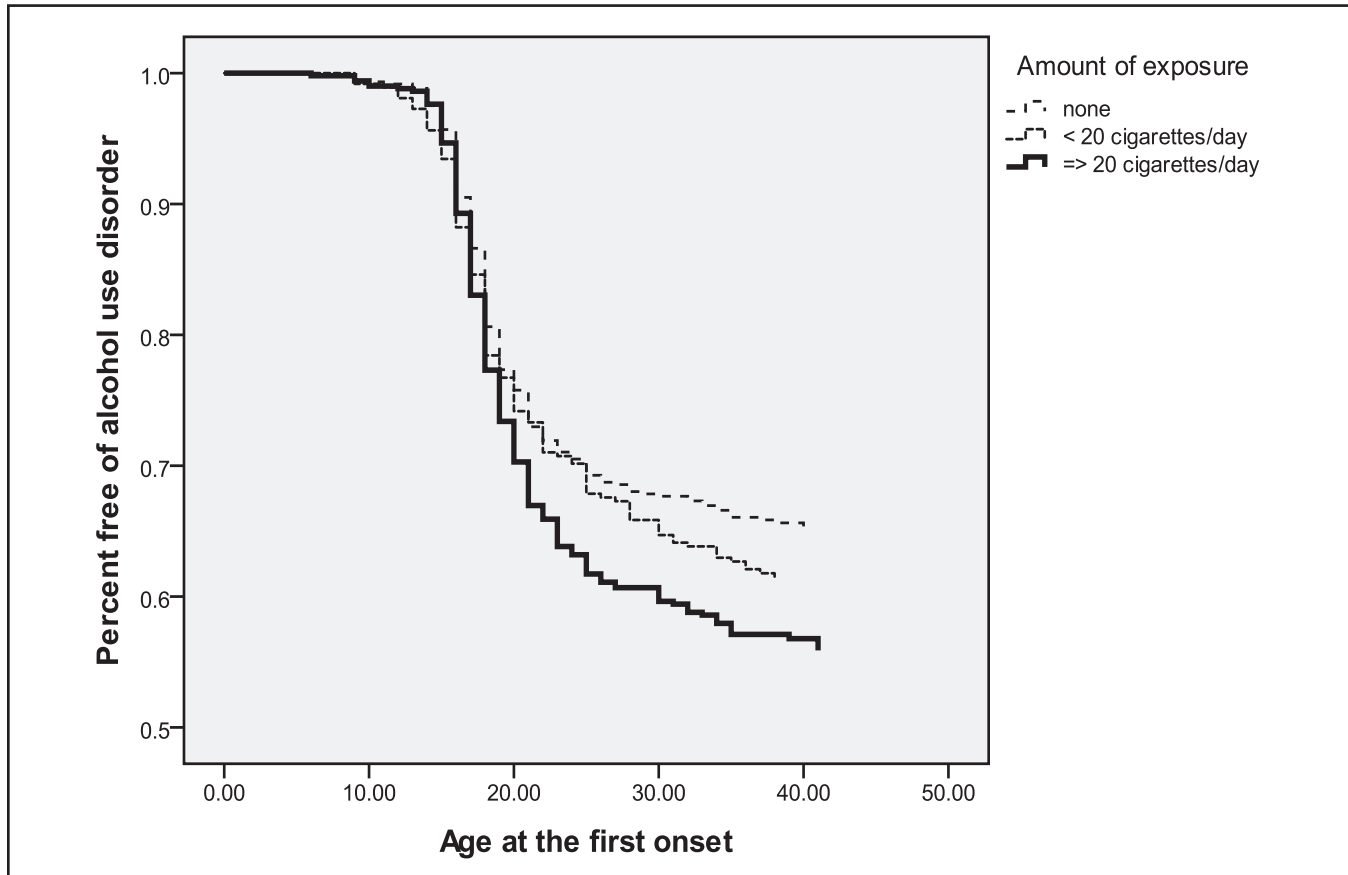
FIGURE 1.   Survival curves for alcohol use disorders among offspring exposed to maternal smoking during pregnancy in varying degrees (none, <20 cigarettes/day, and ≥20 cigarettes/day during any pregnancy day). Bold solid line = offspring of mothers who smoked ≥20 cigarettes/day during pregnancy; dashed line = offspring of mothers who smoked <20 cigarettes//day during pregnancy; dotted line = offspring of mothers who did not smoke during pregnancy. Significant difference among groups by amount of maternal smoking (none; <20 cigarettes/day; and ≥20 cigarettes/day) was found in the test of equality of strata (Wilcoxon test), $\chi^2(1) = 5.78$, $p = .016$. The cumulative risks of lifetime alcohol use disorder in offspring exposed to smoking (<20 cigarettes/day and ≥20 cigarettes/day), relative to those unexposed, were estimated after adjusting for gender, race, social economic status, and mother's self-reported mental health status during pregnancy.

TABLE 2.   Inter-correlations among study variables

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
1. Maximum no. cigarettes smoked during pregnancy[a]	—	-.21**	.004	-.10**	-.10**	-.08	-.03	-.02	.02	-.007	.05*	.03	-.03*	-.13**	.06**
2. Birth weight (g)		—	-.20**	.07**	.08**	.09**	-.04	.004	-.02	-.008	.02	-.13**	-.07**	.08**	-.07*
3. Neurological abnormality (1 year)			—	-.20**	.20**	-.23**	.007	-.08**	.08**	.002	-.02		.07**	-.16**	.09**
4. Spelling (7 year)				—	.88**	.64**	.05*	.10**	-.08**	.02	-.002	.15**	-.16**	.32**	-.03
5. Reading (7 year)					—	.62**	.08**	.14**	-.07*	.01	-.02	.12**	-.15**	.34**	-.02
6. Arithmetic (7 year)						—	.08**	.13**	-.05*	.07**	-.007	.05*	-.19**	.30**	-.03
7. Emotional reactivity (7 year)							—	.44**	.43**	.35**	-.001	-.05	.01	.02	-.01
8. Dysinhibition level (7 year)								—	.39**	.33**	-.04	-.04	.008	.08**	.01
9. Activity level (7 year)									—	.39**	-.007	-.07**	.04§	-.06*	.03
10. Impulsivity (7 year)										—	-.04	-.05*	.05*	.01	-.03
11. Alcohol use disorder											—	-.19**	-.01	-.01	-.03
12. Gender												—	-.03	.005	-.03
13. Race													—	-.16**	.02
14. Socioeconomic status														—	-.03
15. Mother's self-reported mental health status															—

[a]The maximum number of cigarettes smoked per day at any point during pregnancy was classified into three levels of smoking: never smoked during any pregnancy day (coded 0), smoked fewer than 20 cigarettes during any pregnancy day (coded 1), and smoked 20 cigarettes or more during any pregnancy day (coded 2).
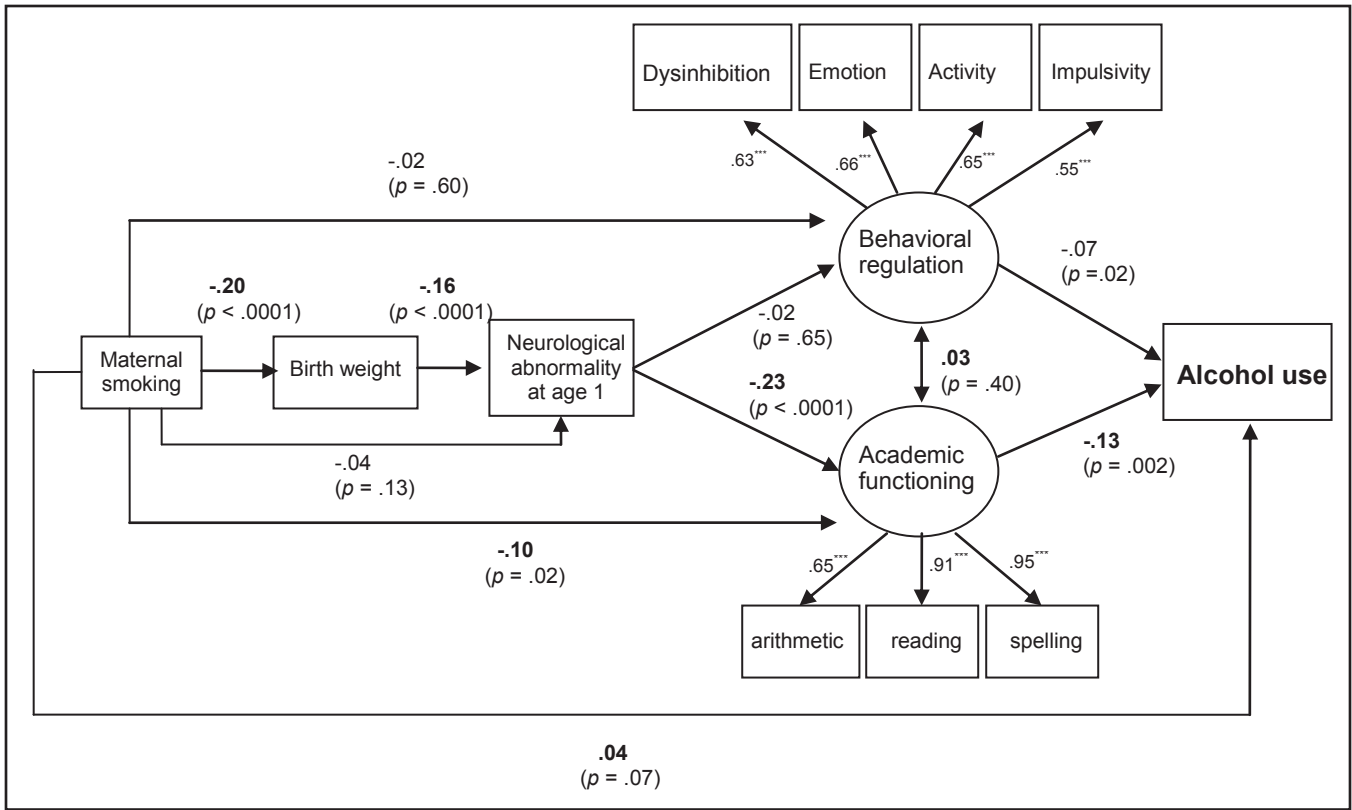§$p < .10$. *$p < .05$; **$p < .01$.

FIGURE 2. Hypothesized model of adult alcohol use disorder (abuse or dependence) directly from maternal smoking during pregnancy and indirectly through various problems in infancy and childhood Parameter estimates are standardized. Model-fit indices: $\chi^2(89) = 229.31$, $p < .001$, normed fit index = .98, Tucker-Lewis index = .96, root mean square error of approximation = .035.
***$p < .0001$.

dardized path coefficient for the path from MSP to AUD in the expanded model, compared with the one in the simple model. This indicates that some of the effect between MSP and AUD was explained by childhood factors. Furthermore, although behavioral regulation did not play a role in our hypothesized mechanism, poorer behavioral regulation was associated with an increased AUD risk ($\beta = -.07$, $p = .02$).

Discussion

Capitalizing on the extended follow-up time (more than 40 years), the study evaluated the lifetime risk of AUD among adults according to prior exposure to MSP. We further investigated whether increased risk for AUD can, at least in part, be explained by conditions at birth and in infancy and in childhood to test hypotheses regarding potential mechanisms by which MSP leads to adverse consequences. The study has three main findings and provides a foundation for future studies on the pathways through which MSP can influence risk for AUD in adulthood. First, adults whose mothers smoked 20 or more cigarettes per day during pregnancy, but not fewer than 20 cigarettes, had a significantly increased risk for AUD, compared with adults whose mothers did not

smoke during pregnancy. Second, in SEM, we also found that MSP is associated with a significant increased risk for AUD, which is equivalent to the estimate in the survival analysis (1.3 times increase). Third, this increase was partially explained by problems in infancy (e.g., lower birth weight) and in childhood (e.g., lower academic functioning).

Our study demonstrates that MSP is associated with a significant increased risk for AUD (adjusted HR = 1.31, $p = .009$) among offspring exposed to 20 cigarettes or more in utero, relative to offspring not exposed to any cigarettes in utero. Although the magnitude of the effect is modest, even a small increase in risk at one point in time could lead to a change in trajectory that would lead to significant implications at a different time.

Results from SEM also show a direct link from MSP to AUD in adulthood in our simple model, which examined only direct links between MSP and AUD. The model has been expanded with problem factors in infancy and childhood. We found that MSP was indirectly associated with an increased risk for AUD through problems in infancy and childhood. Those results suggest that MSP may be indirectly associated with an increased risk for AUD through problems in infancy and childhood as well. These results provide

important clues regarding how MSP may increase the AUD later in life through developmental deviations as a result of neurocognitive impairment in early childhood. Specifically, the current study found that MSP was associated with decreased birth weight, which in turn led to increased frequency in neurological abnormality. Neurological abnormality was strongly associated with lower academic functioning (β = -.23, p < .0001), and lower academic functioning was associated with a subsequent AUD (β = -.13, p = .002). However, (lower) behavioral regulation was not influenced by neurological abnormality in the preceding stage. Of note, the association between the two was significant and showed that neurological abnormality was negatively associated with lower behavioral regulation before adjustments for confounder effects. This may suggest that the link between neurological abnormality and lower behavioral regulation is explained, at least in part, by psychosocial and demographic risk factors such as maternal poverty, low socioeconomic status, and race, all of which are known to correlate with MSP.

The expanded model in our SEM analysis found that, although the direct path from MSP to AUD was marginally significant, the mediating paths leading to AUD was significant. If these associations represent causal effects, they suggest that interventions directly addressing MSP reduction—as well as early identifications of problems at birth and during infancy and childhood—may contribute to the reduction of the risk for AUD in adulthood. Some evidence for a direct path from MSP to increased subsequent substance use has been found in animal studies. For example, after being exposed to nicotine in utero, nicotine receptors (Lv et al., 2008) and altered catecholamine systems (Dwyer et al., 2008) have been found in the brains of neonates. These influences on the developing brain could make offspring susceptible to substance use during adolescence and adulthood (Azam et al., 2007; Dwyer et al., 2008). However, we should also note that the effect of MSP through childhood problems is small. Specifically, the standardized path coefficient for MSP and AUD in the simple model was just a little greater (.07 vs. .04) than in the extended model with childhood outcomes such as birth weight, neurological problems, behavioral regulation, and academic functioning. The direct path may be explained, in part, by pertinent mediating conditions such as adolescent delinquency, peer influences, and family conflict, which were not measured. If we are able to identify the factors that mediate between childhood academic function impairment and AUD, it might provide additional options for potential intervention. Although our current study did not include factors in adolescence, these may be of particular significance given that adolescence has the highest risk for substance use initiation.

This study needs to be evaluated in light of its various methodological strengths. Notably, this was a population-based cohort that was systematically followed from pregnancy and studied longitudinally more than 40 years. Maternal smoking histories were ascertained at every prenatal visit prospectively. Birth weight was recorded by a nurse observer at the time of delivery, a method far superior to mothers' retrospective reports. Research pediatricians or pediatric neurologists prospectively evaluated potential neurological problems at 4, 8, and 12 months. Latent variable academic functioning was based on Wide Range Achievement Test scores, and behavioral profiles at age 7 were ascertained by child psychologists who were trained for high reliability and validity. AUD was assessed using structured interviews administered by trained interviewers blind to the mother's smoking status.

Despite these strengths, there are also several limitations. First, the sample was not designed to be representative of the broader population, which potentially limits external validity. Second, the level of obstetric care in the 1960s is different from the current standard of care. Our sample was born in the pre-neonatal intensive care unit era, and the mortality rate for those born prematurely with very low birth weight was higher than it is currently. Also, since the late 1960s, there has been considerable progress in the development of more extensive special or remedial education along with the introduction of early intervention programs. It is, therefore, likely that many of the children who had problems with academic functioning would have been offered more effective and targeted remedial assistance had they been born today. However, we know that access to health care is substantially underused or unrecognized, especially among the most vulnerable children with biological and social risk factors (Roberts et al., 2008). We can only speculate whether children with poorer academic functioning and behavioral regulation would qualify for and receive such services. It is hoped that more specific and accurate delineations of underlying risk mechanisms in future birth cohort studies will enable clarification of the extent to which the risk for AUD can be modified through early cognitive remediation and intervention for behavioral regulation. Third, although we included key confounders in our model, given that maternal smoking occurs within a broad constellation of social and behavioral factors that also may influence developmental trajectory, our findings could have been subject to bias in an unknown fashion. Gilman et al. (2008b), for example, evaluated associations with MSP and various childhood outcomes using conditional fixed-effects models that controlled for shared familial vulnerability to adverse outcomes of MSP; in these analyses, there were no detectable effects of MSP on childhood neurological and psychological outcomes. Therefore, unmeasured confounding factors may have resulted in an overestimation of the causal effects of MSP on AUDs and a similar overestimation of the strength of the mediating pathways observed.

In a similar vein, as noted above, beyond childhood strength/problems at age 7, we do not have measures of

adolescent social behavior, such as delinquent offending, in our model. If we had a measure of delinquency or familial conflicts for adolescence, we could have evaluated whether they further mediated the associations between childhood problems (i.e., lower academic functioning and behavioral dysregulation) and alcohol use in adulthood or whether those additional psychosocial burdens at the time of adolescence would only moderate the magnitude of the association between MSP and alcohol use.

Results obtained from the current study could potentially guide research into effective intervention programs that promote abstinence from drinking, especially in vulnerable populations such as those who had been exposed to MSP. Vulnerabilities as a result of MSP may be reversible if identified early (Bergh, 1990; Fisher et al., 2000) and could be targeted to limit or prevent alcohol use or to delay the time of initiation. Furthermore, enhanced awareness of the potential adverse consequences of MSP at different times in life could lead to developing and testing targeted interventions, especially for high-risk children, which would presumably modify the trajectory of subsequent alcohol use problems.

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