Prenatal Smoking Exposure and the Risk of Behavioral Problems and Substance Use in Adolescence: the TRAILS Study

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Key Words

Internalizing and externalizing behavioral problems • Prenatal smoking • Substance use in adolescence • TRAILS study

Abstract

Aims: To study the prospective relationship between maternal smoking during pregnancy (MSP) and behavioral problems, heavy alcohol use, daily smoking, and ever use of cannabis in the offspring, and to assess the role of confounding and mediating factors in a systematic way. **Methods:** Population-based cohort study of 2,230 respondents, starting in 2001 when respondents were around the age of 11 years, and two follow-up measurements at intervals of about 2.5 years (response rates of 96.0 and 81.4%). **Results:** Almost one third of the respondents' mothers had smoked tobacco during pregnancy. These respondents were at an increased risk for all outcomes except internalizing problems (significant odds ratios ranged from 1.40 to 2.97). The successive models showed that the potential confounding factors reduced the strength of all relationships. In the full model, the strongest

relationship was found for mothers who smoked more than 10 cigarettes a day during pregnancy and daily smoking in early adolescence (odds ratio: 1.56), but none of the relationships were statistically significant. **Conclusions:** MSP is a marker for future behavioral outcomes in the offspring, but reducing the prevalence of MSP is unlikely to make a meaningful contribution to the prevention of these problems in adolescents.

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Introduction

It is well established that maternal smoking during pregnancy (MSP) can have detrimental effects on the fetus, in particular a low birth weight and preterm birth [1, 2]. In recent years a growing number of studies have focused on the effects of MSP during pregnancy on developmental and behavioral outcomes, reporting associations with a variety of symptoms and disorders in childhood and adolescence, including increased levels of attention deficit hyperactivity disorder (ADHD), exter-

nalizing behavioral problems [3, 4], an increased risk of psychiatric and substance use disorders and even mortality in late adolescence and early adulthood [5]. The biological plausibility of the relationship is supported by animal studies which have indicated that in utero exposure to nicotine interferes with neuronal differentiation during fetal brain development [6].

If MSP is indeed found to be causally related to developmental or behavioral problems in the offspring, this would be an important public health issue. The potential for preventive activity would be large, as smoking during pregnancy is still common, with rates of 24% in Scotland, 17% in England [7], 13% in Sweden, and 12% in the United States [1]. However, there is still uncertainty with respect to causality of the observed relationship. Firstly, although the results of animal studies appear to be convincing, generalization from animal studies to humans is hampered by several factors, particularly differences between rats and humans in timing of brain maturation [6]. Secondly, as indicated by review studies, the research literature on observational studies in humans is not conclusive [6–8]. Methodological issues, in particular on how studies deal with confounding, are likely to explain part of these inconsistencies [6, 9]. For example, low socioeconomic status, a maternal and paternal history of behavioral problems, smoking by the father, maternal smoking after pregnancy and maternal alcohol use during pregnancy are correlated with both MSP and developmental and behavioral problems in offspring [1, 6, 7, 10]. Studies which do not adequately take these variables into account may overestimate the role of MSP in offspring developmental and behavioral outcomes.

In studying the effects of prenatal smoking, also mediating variables are of interest. Controlling the analyses for both type of variables may reduce the strength of the relationship between MSP and offspring outcomes. However, in the case of mediating variables, MSP still could have an effect on offspring outcomes through the indirect pathway, and may remain of relevance for prevention. For example, MSP is shown to be a risk factor for lower birth weight and complications during pregnancy and childbirth [1]. In turn, these variables have been linked to behavioral and developmental outcomes in offspring [11–14]. However, the topic of mediation is scarcely addressed in the current research literature and studies have generally treated potential mediating variables as confounding variables [e.g. 5].

The aim of the present study is to assess the prospective relationship between MSP and behavioral outcomes in the offspring during early and middle adolescence and to as-

sess the role of potential confounding and mediating factors in a systematic way. These factors include family socioeconomic status, parental (history of) internalizing and externalizing behavioral problems, maternal alcohol use during pregnancy, paternal and maternal smoking after childbirth, birth weight and complications during pregnancy and childbirth. Finally, while most other studies focused on externalizing behavioral problems and tobacco use, the present study additionally investigates the prospective association between MSP and alcohol and cannabis use, as well as internalizing behavioral problems.

Method

Study Design and Population

The present study is based on the data of the first, second and third waves of the TRacking Adolescents' Individual Lives Survey (TRAILS). Data collection at the first assessment started in 2001. The second and third assessment waves took place at intervals of about 2.5 years. Informed consent was obtained from all participants at each assessment wave. The Central Dutch Medical Ethics Committee has approved the study.

The target sample comprised young adolescents from five municipalities in the north of the Netherlands, including both urban and rural areas. The sample selection involved two steps. First, the municipalities were requested to provide names and addresses of all inhabitants born between 10 January 1989 and 30 September 1990 (first two municipalities) or between 1 October 1990 and 30 September 1991 (last three municipalities), which yielded 3,483 names. Simultaneously, primary schools within these municipalities were approached with a request to participate. Of the 135 schools, 122 (90.4%) agreed to participate, accounting for 90.3% of the adolescents. Of all subjects approached ($n = 3,145$), 6.7% were excluded because of severe mental or physical handicap or language problems. Of the remaining 2,935 children, 2,230 (76.0%) children and their parents agreed to participate, and all were included in the study (mean age 11.1 years, standard deviation (SD) = 0.6, 50.8% female). Responders and non-responders did not differ with respect to the prevalence of teacher-rated problem behavior or the associations between sociodemographic variables and mental health indicators. A high response rate (96%) was yielded at the second assessment ($n = 2,149$, mean age 13.6 years, SD = 0.5, 51.2% female). On the third assessment ($n = 1,816$, mean age 16.3 years, SD = 0.7, 52.3% female), the response rate was somewhat lower (81.4%). More details about the procedure have been published elsewhere [15].

Procedure

At the first assessment, well-trained interviewers visited one of the parents or guardians in their homes to administer an interview. In addition, the parent completed a written questionnaire. At the second and third assessment, parents were asked to fill out a questionnaire which they received by mail. At each of the three assessments, the self-report questionnaires were completed by the adolescent at school, in groups, supervised by a TRAILS assistant. Confidentiality of the study was emphasized.

Measures

Outcome Variables. Externalizing and internalizing behavioral problems were assessed by the Youth Self Report (YSR) [16]. Good reliability and validity of this instrument were confirmed for the Dutch translation [17]. The YSR contains 101 problem items (3 categories: not true, somewhat true, very true or often true, on the basis of the preceding 6 months), of which 32 items measure externalizing and 31 items measure internalizing behavioral problems. Behavioral problems were defined as a score above the 90th percentile on the YSR, calculated for boys and girls separately and for both internalizing and externalizing problems [18]. Those scoring above the 90th percentile were coded as 1; all others were coded as 0 (no behavioral problems). Heavy alcohol use was based on questions concerning the average number of drinking days and average number of drinks on a drinking day, asked separately for weekdays (Monday to Thursday) and weekend days (Friday to Sunday). By multiplying the days and drinks for both the weekdays and the weekend days and adding these two figures, a total number of glasses per week was calculated. In order to determine a cut-off score for heavy alcohol use at T2 and T3, the authors assessed the group representing the 10% highest scores in our sample at T2 and T3, which showed a correlation with drinking 5 or more glasses of alcohol a week at T2 and 15 glasses or more at T3. This variable was coded as 1 (heavy alcohol use) and 0 (no heavy alcohol use). Daily tobacco use was measured by the question 'How many cigarettes did you smoke on average in the last 4 weeks (7 categories: never smoked, did not smoke in the last 4 weeks, <1 cigarette a day, 1–5, 6–10, 11–20, >20 cigarettes a day). Those who reported smoking at least 1 cigarette a day (9% at T2 and 29% at T3) were classified as daily smokers (coded as 1) and all other respondents were coded as 0 (not daily smokers). Lifetime cannabis use was assessed by the question 'How often in your life have you used weed or hashish? (14 categories, ranging from 0 to 40 times or more) [19]. Those who reported having used cannabis at least once (10% at T2 and 40% at T3) were categorized as lifetime cannabis users (coded as 1) and all others were coded as 0 (never used cannabis).

Maternal Smoking during Pregnancy. MSP was assessed by asking the mother how many cigarettes she smoked during pregnancy (7 categories, ranging from none to more than 2 packs a day). In line with previous studies [4], this variable was recoded into 3 categories: no smoking (0), 1–10 cigarettes a day (1), and 11 cigarettes a day or more (2). A previous study on the same dataset, comparing these self-report data with data on MSP registered shortly after birth by Preventive Child Healthcare (data were available for a subset (32%, $n = 708$) of the sample), indicated a high level of agreement between these reports ($\kappa = 0.77$) [20].

Covariates. All covariates were measured at wave 1 and were based on reports of one of the parents (96% mothers) and included maternal age at childbirth, maternal alcohol use during pregnancy, family socioeconomic status (calculated as the average of income, educational, and occupational level of each parent at wave 1 [21]), daily smoking by the mother, daily smoking by the father and maternal/paternal (history) of internalizing and/or externalizing behavioral problems, birth weight, problems during pregnancy, problems during childbirth.

Analyses

Missing data were imputed by multiple imputation of missing data using bayesian analysis [22, 23] as implemented in Mplus

[24]. Ten imputed datasets were generated and parameter estimates were averaged over the set of analyses; standard errors were computed using the average of the standard errors over the set of analyses and the between-analysis parameter estimate variation [22, 23]. All outcome variables were included in the model as dichotomous variables and analyzed using multiple logistic regression, resulting in odds ratios [25]. To assess whether the association between MSP and child outcomes holds up when confounding factors are taken into account, successive models were tested, each adding new potentially confounding variables to the previous model. In a final model, including all putative confounding factors, variables were added to the model in order to test mediation of the relationship between MSP and outcomes.

Studies have demonstrated that propensity scores are a better alternative to logistic regression analysis when there are seven or fewer outcome events per confounder [26, 27]. Once there are eight or more outcome events per confounder, logistic regression analysis produces less bias, and performs similarly in terms of precision and slightly less, but sufficient, in terms of power [26–28]. For the present study we estimated the number of outcome events per confounder in the most elaborate model (i.e. including 10 covariates) with the smallest number of outcome events (i.e. 9% for daily smoking at T2) and found that the number of events per variable was around 20, indicating that logistic regression analysis is our preferred technique.

For reasons of comparability with previous studies, we dichotomized our outcome variables. The categorization of continuous outcomes leads to a loss of information and the choice of cut-off score will influence the information and conclusions. However, additional analyses showed that identical conclusions resulted when linear regression models were fitted to test the relationship between prenatal smoking and externalizing and internalizing behavioral problems and zero-inflated Poisson regression models were fitted for alcohol use (number of glasses per week), cannabis use (frequency of lifetime use) and smoking (number of cigarettes a day).

All regression analyses were performed using PASW Statistics – SPSS 18.0 [29], except for the zero-inflated Poisson regression analyses which were performed using Mplus [24].

Results

The prevalence of MSP was substantial. Of all respondents, almost one third of their mothers had smoked cigarettes during pregnancy (table 1). Table 1 further shows that a low birth weight (<2.5 kg), was more prevalent among children of mothers who smoked more than 10 cigarettes a day (18.3%). Mothers who smoked during pregnancy further appeared to more often come from low socioeconomic status families, to have frequently used alcohol during pregnancy (4 or more glasses of alcohol per week), to be daily smokers and to have husbands who were daily smokers in the year previous to T1. Finally, mothers who smoked cigarettes during pregnancy had higher scores on parental externalizing behavioral problems and, to a lesser extent, internalizing problems.

Table 1. Maternal smoking during pregnancy by background factors

Background characteristics	Maternal smoking during pregnancy							
	total sample		0 cigarettes		1–10 cig./day		>10 cig./day	
	n	%	n	%	n	%	n	%
Total sample	2,230	100	1,549	69.5	528	23.7	153	6.9
Maternal age at childbirth, years								
<20	49	2.2	32	2.1	9	1.7	8	5.2
20–34	1,937	86.9	1,333	86.1	469	88.8	135	88.2
≥35	244	10.9	184	11.9	50	9.5	10	6.5
Gender								
Male	1,132	50.8	777	50.2	281	53.2	74	48.4
Female	1,098	49.2	772	49.8	247	46.8	79	51.6
Birth weight, kg								
<1.5	23	1.0	15	1.0	7	1.3	1	0.7
1.5–2.5	242	10.9	132	8.5	83	15.7	27	17.6
2.5–4.0	1,820	81.6	1,285	83.0	415	78.6	120	78.4
≥4.0	145	6.5	117	7.6	23	4.4	5	3.3
Problems during pregnancy								
No	1,657	74.3	1,141	73.7	404	76.5	112	73.2
Minor	571	25.6	406	26.2	124	23.5	41	26.8
Severe	2	0.1	2	0.1	0	0.0	0	0.0
Problems during childbirth								
No	1,332	59.7	913	58.9	314	59.5	105	68.6
Minor	896	40.2	634	40.9	214	40.5	48	31.4
Severe	2	0.1	2	0.1	0	0.0	0	0.0
Alcohol use during pregnancy								
No use	1,813	81.3	1,276	82.4	415	78.6	122	79.7
<1 glass/week	311	13.9	217	14.0	80	15.2	14	9.2
1–3 glasses/week	80	3.6	50	3.2	22	4.2	8	5.2
4–10 glasses/week	24	1.1	6	0.4	11	2.1	7	4.6
>10 glasses/week	2	0.1	0	0.0	0	0.0	2	1.3
Socioeconomic status of family								
Low	563	25.2	298	19.2	174	33.0	91	59.5
Medium	1,105	49.6	787	50.8	266	50.4	52	34.0
High	562	25.2	464	30.0	88	16.7	10	6.5
Daily smoking by mother at T1								
No	1,305	58.5	1,198	77.3	87	16.5	19	12.4
Yes	925	41.5	351	22.7	441	83.5	134	87.6
Daily smoking by father at T1								
No	1,267	57.2	1,002	64.7	212	40.2	53	34.6
Yes	963	43.2	547	35.3	316	59.8	100	65.4
<i>Mean score</i>								
Parental internalizing problems	0.558		0.515		0.634		0.726	
Parental externalizing problems	0.147		0.102		0.189		0.456	

Table 2 shows that in the unadjusted analyses (model 1) MSP is significantly associated with externalizing but not internalizing behavioral problems. The strongest association (odds ratio (OR) = 1.79, 95% confidence interval (CI) = 1.32–2.43) is found for prenatal smoking of 1–10 cigarettes a day and externalizing behavioral problems at

T2. Adding confounding factors in each of the successive models results in a decrease of the size of the ORs to 1.42 (1–10 cigarettes a day) and 1.18 (>10 cigarettes a day) for externalizing behavioral problems in the final model (both non-significant, i.e. $p > 0.05$).

Table 2. Longitudinal associations between smoking behavior during pregnancy and externalizing and internalizing problems among adolescent offspring, in successive models, each adjusting for a different set of confounders^a

Number of cigarettes/day ^b	Externalizing behavioral problems				Internalizing behavioral problems			
	T2		T3		T2		T3	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Model 1								
None	1		1		1		1	
1–10 cigarettes	1.79***	1.32–2.43	1.53*	1.03–2.26	0.92	0.67–1.28	1.14	0.78–1.68
>10 cigarettes	1.70*	1.05–2.77	1.50	0.86–2.61	1.43	0.88–2.33	1.40	0.75–2.63
Model 2								
None	1		1		1		1	
1–10 cigarettes	1.71*	1.25–2.34	1.47	0.98–2.19	0.89	0.64–1.24	1.12	0.76–1.66
>10 cigarettes	1.59	0.95–2.67	1.35	0.76–2.37	1.36	0.81–2.29	1.34	0.71–2.54
Model 3								
None	1		1		1		1	
1–10 cigarettes	1.67***	1.22–2.29	1.43	0.95–2.14	0.87	0.63–1.21	1.11	0.75–1.64
>10 cigarettes	1.41	0.83–2.39	1.19	0.66–2.15	1.32	0.77–2.24	1.33	0.70–2.55
Model 4								
None	1		1		1		1	
1–10 cigarettes	1.56**	1.12–2.16	1.43	0.93–2.18	0.87	0.62–1.23	1.10	0.73–1.67
>10 cigarettes	1.30	0.75–2.25	1.19	0.65–2.18	1.32	0.77–2.28	1.33	0.68–2.58
Model 5								
None	1		1		1		1	
1–10 cigarettes	1.42	0.96–2.08	1.39	0.83–2.33	1.02	0.69–1.50	1.28	0.81–2.03
>10 cigarettes	1.18	0.66–2.11	1.16	0.59–2.56	1.55	0.87–2.78	1.55	0.74–3.25

^a Model 1: unadjusted. Model 2: adjusted for maternal alcohol use during pregnancy, age mother at childbirth and socioeconomic status. Model 3: adds to model 2 parental history of internalizing problems, parental history of externalizing problems. Model 4: adds to model 3 paternal smoking at T1. Model 5: adds to model 4 maternal smoking at T1.

^b None (n = 1,549), 1–10 cigarettes a day (n = 528), >10 cigarettes a day (n = 153).

* p < 0.05; ** p < 0.01; *** p < 0.001.

Table 3 shows that in the unadjusted model (model 1), all substance use outcomes are significantly associated with MSP, except for heavy alcohol use at T3. The strongest association is found for mothers who smoked more than 10 cigarettes a day during pregnancy and daily smoking by the child at T2 (OR = 2.97, 95% CI = 1.84–4.80). For the substance use outcomes, there appears to be a dose-effect relationship, i.e. the ORs are generally highest among those mothers who have smoked more than 10 cigarettes a day. Adding more potential confounding factors in each of the successive models, results in a strong decrease of the ORs. In the fifth model, when all confounding factors are included, the strength of the ORs varies between 1.56 and 0.85, which are all statistically non-significant (p > 0.05).

The tests for mediation are not performed, since mediation requires a significant association between the

predictor and outcome variable, which appeared not to be the case for any of the outcome variables tested in the present study.

Discussion

This study has investigated the prospective relationship between smoking by the mother during pregnancy and outcomes of her offspring during early and middle adolescence and has systematically investigated the role of potentially confounding and mediating factors. Our findings suggest that children of mothers who smoke one or more cigarettes a day during pregnancy are at a higher risk for developing externalizing problems, becoming daily smokers, using cannabis and drinking heavily in adolescence. However, the inclusion of potentially con-

Table 3. Longitudinal associations between smoking behavior during pregnancy and substance use among adolescent offspring, in successive models, each adjusting for a different set of confounders^a

Number of cigarettes/day ^b	Daily smoking				Ever use of cannabis				Heavy alcohol use			
	T2		T3		T2		T3		T2		T3	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Model 1												
None	1		1		1		1		1		1	
1–10 cigarettes	2.14***	1.49–3.07	1.71***	1.34–2.20	1.45*	1.02–2.05	1.40*	1.12–1.76	1.58**	1.13–2.20	1.43	0.91–2.24
>10 cigarettes	2.97***	1.84–4.80	1.71***	1.16–2.52	1.76*	1.03–3.01	1.54*	1.06–2.23	1.90*	1.14–3.16	1.71	0.99–2.97
Model 2												
None	1		1		1		1		1		1	
1–10 cigarettes	1.98***	1.43–2.76	1.54***	1.18–2.00	1.39	0.97–1.99	1.36*	1.07–1.71	1.46*	1.04–2.06	1.32	0.84–2.08
>10 cigarettes	2.60	1.62–4.17	1.29	0.87–1.91	1.64	0.94–2.87	1.45	0.99–2.12	1.58	0.93–2.68	1.40	0.80–2.48
Model 3												
None	1		1		1		1		1		1	
1–10 cigarettes	1.85***	1.27–2.69	1.50***	1.15–1.96	1.33	0.92–1.92	1.34*	1.05–1.70	1.43*	1.01–2.01	1.32	0.84–2.10
>10 cigarettes	2.01**	1.19–3.41	1.18	0.78–1.77	1.34	0.75–2.41	1.37	0.93–2.01	1.43	0.83–2.46	1.44	0.80–2.58
Model 4												
None	1		1		1		1		1		1	
1–10 cigarettes	1.70**	1.15–2.52	1.33*	1.01–1.75	1.29	0.88–1.88	1.25	0.97–1.61	1.34	0.94–1.89	1.24	0.78–1.97
>10 cigarettes	1.83*	1.06–3.15	1.02	0.67–1.55	1.30	0.71–2.38	1.26	0.85–1.89	1.32	0.77–2.28	1.34	0.75–2.39
Model 5												
None	1		1		1		1		1		1	
1–10 cigarettes	1.46	0.95–2.25	1.12	0.83–1.50	1.17	0.76–1.80	1.07	0.79–1.45	1.18	0.79–1.77	1.17	0.68–2.00
>10 cigarettes	1.56	0.88–2.78	0.85	0.54–1.35	1.18	0.63–2.21	1.08	0.71–1.65	1.17	0.66–2.07	1.26	0.68–2.32

^a Model 1: unadjusted. Model 2: adjusted for maternal alcohol use during pregnancy, age mother at childbirth and socioeconomic status. Model 3: adds to model 2 parental history of internalizing problems, parental history of externalizing problems. Model 4: adds to model 3 paternal smoking at T1. Model 5: adds to model 4 maternal smoking at T1.

^b None (n = 1,549), 1–10 cigarettes a day (n = 528), >10 cigarettes a day (n = 153).

* p < 0.05; ** p < 0.01; *** p < 0.001.

founding variables lowered the strength of the relationship to ORs varying between 0.85 and 1.56 in the full model, which were all statistically non-significant (p > 0.05).

These results are based on a large (n = 2,230) population-based cohort study, comprising multiple informants (adolescent and parent reporting), including data on a wide range of background characteristics and using a validated instrument to assess child psychopathology (i.e. the YSR) [16] which has been widely used and shown to be highly predictive of disorders at later ages (based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)). Furthermore, by using self-report and not parent reported data for the outcome measures, there was no risk of information bias induced by awareness among the parents that smoking during pregnancy could have had adverse effects on their child. Finally, the findings appeared to be robust as including the outcome variables as continues/count variables in the analyses led to similar

conclusions as the analyses on the dichotomized outcome variables.

The findings of our study demonstrate the important role of confounding factors in the relationship between MSP and offspring's risk for behavioral problems, i.e. the strength of all relationships decreased substantially when potentially confounding factors were included in the model. These findings are in line with a number of recent quasi-experimental studies, comparing siblings differentially exposed to MSP, concluding that familial background factors and not the specific exposure to MSP account for the associations between MSP and offspring behavioral outcomes [30–33]. The fact that a substantial number of studies [3, 34–37], including a recent, well-designed and powered birth cohort study in Finland [5], concluded that MSP increases the risk for offspring behavioral problems, is most likely explained by the fact that these studies did not adequately address the issue of confounding. For example, almost none of the studies

concluding that MSP increases the risk for externalizing behavioral problems [3, 5, 35–37] controlled for mothers' and fathers' smoking patterns after the birth of their child. Additionally, studies did not take into account family socioeconomic status and paternal psychiatric morbidity [5] or parental psychiatric morbidity [37], while Fergusson et al. [3] accounted for parental criminal behavior but not for other types of parental psychiatric morbidity. A Dutch birth cohort study appeared to account for all relevant confounding factors, but did not use a standardized and validated instrument to assess externalizing behavioral problems [34]. In line with the results of the present study, a population-based study in Sweden, comparing siblings differentially exposed to prenatal smoking, demonstrated that the association between maternal smoking in pregnancy and offspring criminality was fully accounted for by familial background factors [38]. Boutwell and Beaver [39], using a propensity score-matching analysis, concluded that the relationship between smoking during pregnancy and externalizing behavioral problems was spurious. Roza et al. [40] demonstrated that the relationship between MSP and child behavior problems was fully accounted for by family socioeconomic status and parental psychopathology. Convincing evidence for the role of inheritable pathways was reported by Rice et al. [41], comparing the association between MSP and antisocial behavior in the offspring of mothers who were either biologically related or unrelated to their child as a result of *in vitro* fertilization. The authors concluded that the relationship was entirely explained by inherited pathways, as the offspring of mothers who smoked during pregnancy and were biologically related to their child were at higher risk for conduct problems, while such an effect was not found in the offspring of mothers who smoked during pregnancy but were biologically unrelated to their child [41]. Based on a longitudinal twin study, it was concluded that around half of the observed association between MSP and young children's conduct problems was attributable to correlated genetic effects [42]. Additional control for environmental risks reduced the initial effect of MSP by 75–100% [32]. D'Onofrio et al. [38], comparing siblings differentially exposed to MSP, concluded that familial background factors and not the specific exposure to MSP account for the associations between MSP and offspring disruptive behaviors.

In line with most previous studies [3, 34, 37, 40] the authors did not find evidence for an association between MSP and internalizing problems in the offspring. Jaspers et al. [43], using data from the first wave of the TRAILS

study when respondents were around the age of 11, found a weak, but significant relationship between MSP and internalizing problems. A Dutch study concluded that prenatal smoking was related to increased levels of internalizing problem from ages 5 to 18 years [44]. Furthermore, Robinson et al. [36] found an association with higher scores on the internalizing scale of the Child Behavior Check List (CBCL), but not with clinically meaningful internalizing behavioral problems. None of these studies [36, 43, 44] controlled for mothers' and fathers' smoking patterns after the birth of their child.

Relatively few studies have investigated the relationship between MSP and offspring's substance use patterns, mainly with regard to smoking. Buka et al. [45] showed that the offspring of mothers who smoked one pack or more a day during pregnancy had a greater likelihood of becoming nicotine-dependent as adults, but not of ever smoking or becoming a regular smoker. Fergusson et al. [3] found no relationship between MSP and nicotine dependence in late adolescence. There is preliminary evidence that MSP may affect offspring smoking behavior through an indirect pathway [46, 47]. Children with prenatal exposure to maternal smoking had higher ADHD symptom scores and were not susceptible to the positive impact of an intervention on the course of their ADHD symptoms and on the probability of early-onset experimentation with smoking [46, 47]. A few studies tried to disentangle the effect of pregnancy smoking and non-pregnancy smoking on the smoking behavior of the children [48, 49]. The general conclusion of these studies was that both pregnancy smoking and non-pregnancy smoking were associated with an elevated risk for regular smoking in their offspring, with smoking during pregnancy constituting an additional risk. Perhaps the inability to quit smoking during and after pregnancy reflects a genetic vulnerability for nicotine addiction in these mothers, which is passed down to their children. Studies on the relationship between MSP and substance use other than tobacco are scarce and their focus is on abuse and dependency in their offspring and not on use as in the present study. The study of Ekblad et al. [5] found a relationship between MSP and ICD-10 diagnoses due to substance use, but as discussed earlier, these findings may be (partly) explained by incomplete adjustment for confounding factors. Nomura et al. [50] found that the adult offspring of mothers who smoked 20 cigarettes a day or more were at greater risk for a lifetime diagnoses for alcohol use disorders, but the magnitude of the effect was modest. Fergusson et al. [3] found no relationship with illicit substance use or dependency in late adolescence.

Similarly, Buka et al. [45] concluded that the odds of marijuana dependence were not significantly elevated among the offspring of mothers who smoked during pregnancy.

The present study has some limitations. First, the measure of smoking during pregnancy was asked retrospectively which may have resulted in recall bias. However, a previous study on the same dataset [20] and other studies [e.g. 51] have indicated that the strength of agreement between maternal report and antenatal medical records of MSP is good. Second, the measure of MSP was not very precise in measuring in utero tobacco smoke exposure, as it was not known if the reported number of cigarettes a day was stable over the entire pregnancy period. Therefore, we were unable to address the possible effects of the timing of MSP on the child outcomes. Third, although this study is among the few to take into account the smoking behavior of the mother and father after the birth of their child, the parental smoking measure only referred to smoking in the year prior to the first measurement, so information on parental smoking in the period from birth to around the age of 10 was not available.

In conclusion, MSP is a marker for future externalizing behavioral and substance use problems in the adolescent offspring, but the results of the present study do not suggest that the relationship is causal. Other, correlated parental factors (e.g. parental behavioral problems and parental smoking after the birth of the child) appear to explain an important part of the observed relationship

between MSP and offspring behavioral and substance use outcomes. Reducing the prevalence of smoking during pregnancy is therefore unlikely to make a meaningful contribution to the prevention of these problems in adolescents.

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