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Maternal smoking during pregnancy, offspring smoking, adverse childhood events, and risk of major depression: a sibling design study

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Abstract

Background. Evidence of a biologically plausible association between maternal smoking during pregnancy (MSP) and the risk of depression is discounted by null findings from two sibling studies. However, valid causal inference from sibling studies is subject to challenges inherent to human studies of MSP and biases particular to this design. We addressed these challenges in the first sibling study of MSP and depression conducted among adults past the peak age for the onset of depression, utilizing a prospectively collected and biologically validated measure of MSP and accounting for non-shared as well as mediating factors.

Methods. We fit GEE binomial regression models to correct for dependence in the risk of depression across pregnancies of the same mother. We also fit marginal structural models (MSM) to estimate the controlled direct effect of MSP on depression that is not mediated by the offspring's smoking status. Both models allow the estimation of within- and between-sibling risk ratios.

Results. The adjusted within-sibling risk ratios (RR_W) from both models (GEE: $RR_W = 1.97$, CI 1.16–3.32; MSM: $RR_W = 2.08$, CI 1.04–4.17) evinced an independent association between MSP and risk of depression. The overall effects from a standard model evinced lower associations (GEE: $RR_T = 1.12$, CI 0.98–1.28; MSM: $RR_T = 1.18$, CI 1.01–1.37).

Conclusions. Based on within-sibling information free of unmeasured shared confounders and accounting for a range of unshared factors, we found an effect of MSP on the offspring's risk of depression. Our findings, should they be replicated in future studies, highlight the importance of considering challenges inherent to human studies of MSP and affective disorders.

Introduction

Laboratory animals exposed to cigarette smoke *in utero* experience structural changes to their serotonin system that are associated with reduced serotonin levels and last through adulthood (Slotkin, Pinkerton, Tate, & Seidler, 2006, 2015). The strength and ubiquity of the inhibitory effect of cigarette smoke on serotonin activity among animals suggest that this effect is likely to also operate among humans exposed to maternal smoking during pregnancy (MSP) with similarly long-lasting consequences. Low serotonin level is a prominent precursor of behaviors that are consistent with depression among animals and with depression among humans (Balfour & Ridley, 2000). Thus, suggesting a biologically plausible link between MSP and offspring's elevated risk of depression (Baler, Volkow, Fowler, & Benveniste, 2008).

Epidemiologic studies among children (Ashford, Van Lier, Timmermans, Cuijpers, & Koot, 2008; Batstra, Hadders-Algra, & Neeleman, 2003; Brion et al., 2010; Hook, Cederblad, & Berg, 2006; Knopik, 2009; Lavigne et al., 2011; Moylan et al., 2015; Tiesler & Heinrich, 2014) and adolescents (Albers & Biener, 2002; Ashford et al., 2008; Indredavik, Brubakk, Romundstad, & Vik, 2007; Monshouwer et al., 2011) have yielded mixed results. However, because the median age for the onset of depressive disorders is 32 (Kessler et al., 2005), studies of adults less than age 32 are likely to under-report lifetime risk of depression. To date, seven epidemiologic studies have examined the association between MSP and risk of depression among adult offspring aged 18+, none included participants over the age of 32 (Table 1). Five studies used standard multivariate methods to control for confounding and two used a sibling design. Among a New Zealand birth cohort, MSP predicted a modest increase in the number of depressive symptoms but this trend did not reach statistical significance (Fergusson, Woodward, & Horwood, 1998). Among a Finish birth cohort, a dose–response association was evident between MSP and lifetime risk of any mood disorders (Ekblad, Gissler, Lehtonen, & Korkeila, 2010). Evidence from a Brazilian birth cohort is suggestive of a linear

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Table 1. Review of epidemiologic studies of maternal smoking during pregnancy (MSP) and risk of depression among adult offspring (1998–2020)

Author	Sample	Measures of MSP and depression	Results RR (95% CI)[a]
Fergusson et al. (1998)	All births in Christ Church, New Zealand (1977) *N* = 1022 Ages 16–18	MSP self-report at birth. Composite International Diagnostic Interview (DSM-IV)	Major depression – no association. No further information provided Average number of depressive symptoms (N) Non-smoker (691) 2.05 1–9 cigs/day (158) 2.18 10–19 cigs/day (98) 2.30 ⩾20 cigs/day (75) 2.42 Regression coefficient (s.d.): 0.125 (0.12); $p > 0.25$ Covariates: maternal age, education, planned pregnancy, parental use of physical punishment, criminal behavior; offspring childhood sexual abuse
Ekblad et al. (2010)	All births in Finland (1987–89) *N* = 170 382 Ages Inpatient 0–20 Outpatients 9–20	MSP self-report during antenatal care. ICD-10 Hospital discharge data of any mood disorders	Non-smoker Ref. <10 cigs/day 1.65 (1.54–1.76) ⩾10 cigs/day 1.93 (1.78–2.10) Covariates: maternal age, parity, psychiatric diagnosis prior to offspring's birth,Offspring sex, gestational age, birth weight, 5 min Apgar
Menezes et al. (2013)	All births in urban areas of Pelotas, Brazil (1993) *N* = 4126 Age 18	MSP self-report within 24 h after delivery. Mini-International Neuropsychiatric Interview (DSM-IV)	Non-smoker Ref. <20 cigs/day 1.27 (0.95–1.71) ⩾20 cigs/day 1.89 (1.16–3.08) Covariates: maternal family income at birth, planned pregnancy, alcohol use during pregnancy, type of delivery, anxiety and depression (at offspring age 11), paternal smoking during pregnancy, support of pregnancy, offspring sex, developmental well-being at age 15
Study	Sample	Measures	Results
Meier et al. (2017)	All births in Denmark [National registers (1991–2007)] *N* = 957 635 Discordant siblings *N* = 82 041 Ages 5–21	Medical records; self-reported at first antenatal visit. Any lifetime depressive disorder (ICD-10)	Full cohort Never smoked Ref. Any MSP 1.29 (1.22–1.36) Discordant siblings Never smoked Ref. Any MSP 1.11 (0.94–1.30) Covariates: maternal age birth, income, education, psychiatric history. Offspring age, gender, birth order
Taylor et al. (2017)	Meta-analysis		
	Norway–Nord-Trøndelag study *N* = 15 493 Age 32	Inferred from offspring data and survey dates. Anxiety and Depression Scale. Depression defined as ⩾8 symptoms	No MSP Any MSP 1.20 (1.08–1.34) Covariates: offspring age, gender. Maternal age at birth, parity, maternal social class (% non-manual labor), maternal education (% >12 years education), household crowding
	UK – Avon cohort *N* = 2869 Age 18	MSP self-report during pregnancy and 8 wks postpartum. MDD: Clinical Interview Schedule – R (ICD-10)	
	Brazil – Pelotas Birth cohort *N* = 2626 Age 30	MSP self-reported within 24 h after delivery. Mini-International Psychiatric Interview V.5.0	
	Sibling study		
	Swedish birth registry. Same-sex full siblings (1983–1991) *N* = 226 Ages 0–30	MSP self-reported during first antenatal visit. Response to: 'Has a physician any time in your life told you that you had depression?'	No MSP Any MSP (Y/N) 1.03 (0.77–1.36) Covariates: maternal age, calendar period at birth, parity, birth order

[a]Results reported as risk ratios except by Fergusson et al. (1998).

pattern between MSP and offspring's lifetime risk of depressive disorder at age 18 (Menezes et al., 2013). However, this association was statistically significant only for MSP⩾20 cigarettes/day (Menezes et al., 2013). The two studies with positive results found similar effect sizes for MSP⩾20 cigarettes/day (although with a wider confidence interval for the smaller Brazilian study). The strong and relatively stable effect for MSP⩾20 cigarettes/day is consistent with other studies which have found a linear effect of MSP that reaches statistical significance only at higher doses of MSP (e.g. Buka, Shenassa, & Niaura, 2003; Stroud *et al.* 2009; Wen, Shenassa, & Paradis, 2013).

To better control for confounding by the many familial (D'Onofrio, Lahey, Turkheimer, & Lichtenstein, 2013) and genetic (Knopik, 2009) differences that distinguish pregnant women who smoke from their non-smoking counterparts, two studies capitalized on variation in smoking between pregnancies by utilizing a sibling comparison design. Taylor et al. (2017) conducted a meta-analysis among three birth cohorts, utilized the smoking history of mother's partner as a negative control and conducted a discordant sibling-pair analysis of data from a fourth cohort. The meta-analysis found an independent association between any MSP and offspring's risk of depression that was stronger than the association among negative controls. However, among sibling pairs in the fourth cohort, MSP was not associated with the risk of depression. It is noteworthy that in this study, the sibling pairs were from a birth cohort with a considerably lower prevalence of depression and differing method of assessing depression than the birth cohorts used in the meta-analyses. Among a Danish birth cohort (Meier et al., 2017), any MSP predicted offspring's lifetime risk of depression. In contrast, among sibling-pairs, all of whom were exposed to MSP, differences in the amount of maternal smoking between the two pregnancies did not predict offspring's risk of depression. In sum, evidence of a positive association between MSP and risk of depression from conventional studies is countered by evidence from sibling-pair studies that the observed association between MSP and offspring's risk of depression may be due to confounding by unmeasured familial and genetic factors. Thus, establishing the sibling-pair design as the gold standard for studies of intergenerational effects of MSP. However, valid inference regarding the causal effect of MSP is subject to threats inherent to human studies of MSP that are not addressed by the sibling-pair design and biases that are particular to this design (Frisell, Öberg, Kuja-Halkola, & Sjölander, 2012; Shenassa, 2017).

A challenge inherent to human studies of MSP is that MSP is an imprecise proxy for the biologically relevant exposure: fetal bioavailability of nicotine metabolites (Balfour & Ridley, 2000; Slotkin et al., 2006). Another challenge pertains to errors in self-reports of MSP, particularly retrospective self-reports (Jaspers, de Meer, Verhulst, Ormel, & Reijneveld, 2010; Simard, Rosner, & Michels, 2008). All extant studies utilized self-reported MSP. In prospective studies, these two measurement errors typically occur at random, leading to underestimation of the true effect of MSP on subsequent outcomes. In sibling-pair studies, this random error causes a more severe underestimation in the within-pair estimate than would be the case in the corresponding unpaired associations, even in the absence of confounding (Frisell et al., 2012). Another issue regards the amount of MSP under consideration. The literature on intergenerational effects of MSP includes several examples of linear effects that reach statistical significance only at higher levels of MSP (e.g. ⩾20 cigarettes/day) (Buka et al., 2003; Stroud et al., 2009; Wen et al., 2013). Given that the relevant exposure is fetal bioavailability of nicotine metabolites and not the act of smoking *per se*, it is informative to assess the linear effect of MSP. The two extant sibling-pair studies, by utilizing a dichotomous measure of MSP (i.e. none *v.* any), emphasize the act of smoking over the amount of smoking. Furthermore, as noted above, it is best to study populations that are past the median age for the first onset of depression in order to avoid a large proportion of false-negative assessments. Due to these remaining challenges, we submit that the extant sibling studies have underestimated the true effect of MSP. Finally, a threat to valid inference from any sibling study is confounding by factors that are not shared between siblings (e.g. birth order; loss of a partner). Bias introduced to within-pair estimates by non-shared unmeasured confounders is more severe compared with an analysis of unrelated persons (Frisell et al., 2012).

The effect of non-shared confounders can be controlled by accounting for variables that mediate the association between that confounder and the outcome. For example, the confounding effect of family stressors can be blocked by controlling for offspring-level variables in the regression models, insofar as the confounding effect of the initial family stressors on depression is mediated by the offspring-level variables included in the regression models. Two such offspring-level variables are smoking and experiences of adversity during childhood. Family stressors elevate offspring's risk of becoming a smoker; and regular smoking, through the diminution of serotonin levels (Balfour & Ridley, 2000), can trigger the onset of depression among previously asymptomatic individuals (Bakhshaie, Zvolensky, & Goodwin, 2015; Klungsoyr, Nygard, Sorensen, & Sandanger, 2006; Mojtabai & Crum, 2013). Family stressors (during pregnancy) predict a range of later adversity (e.g. Nurius, Logan-Greene, & Green, 2012) and childhood adversity predicts later onset of depression (Merrick et al., 2019; Zhou, Yin, Wu, & Li, 2020). Therefore, the confounding effect of family-level stressors experienced during one but not the other pregnancy can be partially blocked by controlling for offspring's smoking and experiences of childhood adversity.

Finally, we consider the possibility that the effect of MSP on depression may be *mediated* by offspring smoking. Animal studies indicate that MSP up-regulates offspring's nicotinic receptors, an effect that can last through adulthood (Slotkin et al., 2006, 2015). Among the offspring who experiment with smoking, those who were exposed to MSP are more likely than others to become regular smokers (Shenassa, Papandonatos, Rogers, & Buka, 2015). In turn, regular smoking can trigger the onset of a first episode of depression (Bakhshaie et al., 2015; Klungsoyr et al., 2006; Mojtabai & Crum, 2013).

We report findings from a 40-year longitudinal study of MSP and offspring's risk of depression among adults past the peak period for the onset of depression, utilizing a sibling design and prospectively collected and biologically validated measure of MSP. We control for both offspring's regular smoking and childhood adversities and also examine the potential mediating effect of offspring smoking.

Methods

Data sources

Study participants were offspring of mothers enrolled in the Providence and Boston sites of the Collaborative Perinatal

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Project (1959–1966). Mothers were interviewed at the time of enrollment and throughout pregnancy (Shenassa, Paradis, Dolan, Wilhelm, & Buka, 2012). Additional offspring assessments were completed between birth and age 7. We refer to the mothers as 'Generation 1' (G1s) and to their offspring as 'Generation 2' (G2s).

Surviving G2 were enrolled in the New England Family Study between 2001 and 2010, a follow-up study in which participants were selected using a multistage sampling procedure (see the online Supplementary Appendix for details). Of the G2s enrolled in the New England Family Study, 85 respondents were excluded due to missing values for depression or smoking (maternal or offspring), one sibling of each of 12 twin pairs was randomly selected for exclusion, 45 participants who had begun smoking regularly after diagnosis of depression were excluded to reduce the risk of collider bias and 49 were excluded due to interview issues. The final analytic sample included 1692 G2 participants (Table 1) distributed across 1253 families, composed of 860 singletons, 350 sibling pairs, 40 trios (120 dyads), and three quartets (18 dyads). Among these 488 sibling dyads, 184 dyads were discordant for MSP, 174 for MDE, and 79 for both MSP and MDE.

Measures

At each prenatal visit throughout pregnancy, G1 mothers reported whether they were currently smoking and, if so, the number of cigarettes smoked daily. The number of visits varied by pregnancy. From these reports, we determined the maximum number of cigarettes smoked per day at any time during each pregnancy. As in our prior research (Shenassa et al., 2015), MSP was re-expressed in terms of maximum cigarette *packs* per day, leading to more meaningful effect size measures. A prior analysis of these data demonstrated agreement ($\kappa = 0.83$) between serum cotinine and maternal reports providing biochemical validation (Klebanoff, Levine, Clemens, DerSimonian, & Wilkins, 1998). At study enrollment, mothers provided information on age, gravida, race/ethnicity, and socioeconomic indicators. For socioeconomic status (SES), participants were assigned percentile ranks derived from 1960 US Census data for education and occupation of the head of household and household income (Myrianthopoulos & French, 1968). The mean percentile was used as a composite SES index (range = 0–100).

Offspring smoking histories were obtained by the Life Interview of Smoking Trajectories Questionnaire, an instrument with excellent reliability ($\kappa = 0.78$–0.92) (Colby et al., 2012). This instrument obtains detailed information on participants' smoking history. Participants were asked, 'Did you ever become a weekly smoker (that is, smoke at least once per week for two months or longer)?' and for those who had, 'How many days per week (on average) do you CURRENTLY smoke cigarettes?' Respondents were categorized as never regular smokers (i.e. never became a weekly smoker), current smokers (i.e. currently smoke one or more days per week), or former regular smokers (i.e. currently smoke zero days per week).

The full depression module of the Composite International Diagnostic Interview (CIDI) was used to diagnose lifetime episode of depression according to the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) criteria (American Psychiatric Association, 2000). The CIDI is a validated structured interview (Haro et al., 2006) and it was administered by trained interviewers. A DSM-IV diagnosis of major depressive episode (MDE) requires the endorsement of five or more of the following symptoms concurrently for at least 2 weeks: depressed mood, loss of interest or pleasure, weight or appetite changes, sleep disturbance, psychomotor changes, guilt, fatigue, trouble thinking or concentrating, and suicidality. One of the endorsed symptoms must be either depressed mood or loss of interest or pleasure.

Childhood adversity was based upon an index derived by summing the following 10 measures of adverse events (Gilman, Kawachi, Fitzmaurice, & Buka, 2003): parental marital changes (0 = 0, 1 = 0.5, 2 + = 1), major shift in environment (0 = 0, 1 + = 1), moves (0 = 0, 1 = 0.5, 2 + = 1), parental unemployment at age 7, sibling death (0 = 0, 1 + = 1), household crowding (<1 = 0, 1–1.5 = 0.5, >1.5 = 1), living with a single mother at age 7, living in poverty at age 7 (1.5 × FPL = 0, <1.5 × FPL = 0.5, <1 × FPL = 1), parental occupation at age 7 (non-manual = 0, manual = 0.5, unemployed = 1), and decline in the family's financial situation between birth and age 7. Fifty-five G2s had missing data for all 10 components of the index.

For each G2, the following demographic information was collected at the mean age of 40 (range: 34–49): age, gender, current legal marital status (never married, previously married, currently married), education (no high school diploma/GED, high school diploma, technical/trade/certificate, 1–3 years college, 4 years college, graduate/professional school), and annual household income (<$38 400, $38 400–$47 000, ⩾$48 000).

We distinguish between (1) factors that potentially confound MSP and MDE and (2) factors that potentially confound offspring smoking and MDE (Fig. 1). The measured confounder between MSP, offspring smoking, and MDE is gravida. Measured factors that potentially confound offspring smoking and MDE include age, gender, marital status, education, and household income.

Statistical analysis

We estimated risk ratios (RR) and associated confidence intervals (CI) by fitting log-binomial regression models using PROC GENMOD (link = log) (Robbins, Chao, & Fonseca, 2002). Robust standard errors based on a working exchangeable correlation matrix were used to correct for dependence in the risk of depression across multiple pregnancies of the same mother using GEE methodology. Capitalizing on the study's sibling design, we fit decomposition models – for a detailed application, see Shenassa et al. (2015). Briefly, we present four coefficients: the between-pair (RR_B) and the within-pair effects (RR_W) from the decomposition model, the heterogeneity test statistic for the ratio of these two coefficients ($RR_R = RR_B/RR_W$) and the total effect (RR_T) from a model without decomposition. The RR_B is considered the contextual effect and is independent of RR_W, which is considered the individual effect, the latter representing the effect of a unit change in MSP from one pregnancy to another. The effect of mother-level factors correlated with MSP is absorbed by RR_B, and does not bias the RR_W estimates. The RR_T is the same estimate that would be obtained from a model without decomposition, it implicitly assumes the three effects to be equal (i.e. $RR_B = RR_W = RR_T$). However, in practice, when this assumption of equality does not hold, $\widehat{RR}_T$ is proportional to a weighted average of $\widehat{RR}_B$ and $\widehat{RR}_W$.

This implicit assumption of equality can be determined by the heterogeneity test statistic (RR_R). When RR_R is not meaningfully different from the null value of 1, RR_T is an unbiased estimate of the association between exposure and outcome. In contrast, when RR_R indicates that RR_B and RR_W are heterogeneous, then the interpretation of the model must focus on the two separate effects.

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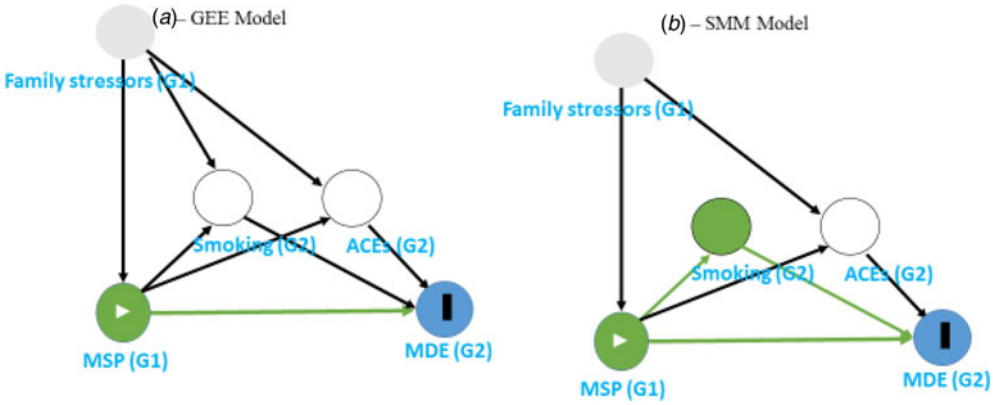

Fig. 1. Directed acyclic graphs for maternal smoking during pregnancy (MSP G1) causing offspring major depressive disorder (MDE G2). (a) GEE model, offspring regular smoking treated as a confounder. (b) SMM model, offspring regular smoking treated as a mediator.

Finally, to the extent that variation in family size is uninformative about outcome, inclusion of singletons is desirable, in that it improves the precision of the between-sibling estimates without biasing the model intercept.

When inference is based upon within-pair comparisons, there is no need to explicitly control for shared mother-level confounders (e.g. history of psychiatric problems). Given that this is not the case for non-shared confounders that vary across pregnancies, we adjusted models for offspring (i.e. gender, birth order, age) and maternal (i.e. marital status, education, household income) confounders. We further controlled for non-shared confounders by including offspring-level variables for smoking experiences of childhood adversity.

We tested the linearity of MSP effects across the range of observed MSP levels by fitting separate quadratic models for MSP levels across pregnancies of the same mother and the between-pair deviations. Finally, we refitted models with an analytic sample that included the 45 respondents who were excluded from the main analysis because they reported to have begun regular smoking after the onset of depression.

To consider the possibility that offspring smoking mediates the effect of MSP on MDE (Fig. 1), we fit a marginal structural model to estimate controlled direct effect of MSP (measured in packs/day) on MDE that was not mediated by offspring smoking behavior after accounting for potential measured confounder of MSP and MDE (i.e. gravida) and measured potential confounders of offspring smoking and MDE (i.e. age, gender, marital status, education, and household income). We fit a weighted logistic regression and accounted for potential confounding by measured covariates with two stabilized inverse-probability weights, one for measured confounding of the relation between MSP and depression and the other accounting for measured confounding of the relation between offspring smoking and depression. The RR from the adjusted weighted model is an estimate of the direct effect of MSP not mediated by offspring smoking provided that the two sets of measured confounders are sufficient enough to control for (1) confounding between MSP and depression and (2) confounding between offspring smoking and depression (Nandi, Glymour, Kawachi, & VanderWeele, 2012). The mediation model was also fit as a decomposition model yielding the four RR described above. Analyses were conducted using SAS/STAT V9.4.

We also calculated *E* values to evaluate the likelihood that our findings could be explained away by unmeasured confounding. An *E* value is the minimum magnitude of an unmeasured confounder that would render an observed association null (VanderWeele & Ding, 2017).

Ethical statement

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation.

Results

There were few differences between the 1692 G2 included in the current analyses, and the 1270 considered for inclusion in the New England Family Study that were ultimately determined to be ineligible (Table 2). Most notably, female G2s were over-represented in the analytic sample (57.1%) compared with those not interviewed (45.8%). Included G2s were of slightly higher SES than those excluded (mean = 55.0 *v.* 50.6). However, there were no meaningful differences in the levels of MSP. Prevalence of MDE among G2s was 22.6% among those unexposed to MSP and 24.1% among the exposed (Table 3).

The first three panels of Table 4 present the results of three GEE binomial regression models predicting the risk of lifetime MDE in relation to a single pack increase in MSP. The elevated risk of depression associated with MSP in the unadjusted model ($RR_T = 1.15$, CI 1.01–1.31) is reduced only slightly after controlling for gravida, age, gender, marital status, education, and household income ($RR_T = 1.12$, CI 0.98–1.28) and further addition of offspring smoking in the fully adjusted model had no practical influence on the estimated effect of MSP ($RR_T = 1.12$, CI 0.98–1.28). However, in each of the three GEE models, the range of values of the CI for RR_R suggest that RR_B and RR_W are sufficiently heterogeneous that the interpretation of the models is best focused on the two separate effects. The within-pair (RR_W) effect of a single pack increase in maternal smoking from one pregnancy, in the unadjusted ($RR_B = 2.04$, CI 1.20–3.47), partially adjusted ($RR_W = 1.94$, CI 1.14–3.30), and fully adjusted models ($RR_W = 1.97$, CI 1.16–3.32) are similarly consistent with similarly wide and overlapping CI. The between-pair effect for the

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Table 2. Demographic and smoking characteristics of offspring in the Boston and Providence cohorts of the Collaborative Perinatal Project ($N = 3153$ screened)

	Interviewed (1692)[a]		Not interviewed (1270)	
Characteristic	*N*	%	*N*	%
Race/ethnicity				
Non-white	225	13.3	172	13.5
White	1467	86.7	1098	86.5
Gender				
Male	726	42.9	689	54.2
Female	966	57.1	581	45.8
Maximum number of cigarettes mother smoked on any pregnancy day				
0	700	41.4	496	39.4
1–9	196	11.6	178	14.1
10–19	222	13.1	156	12.4
20–29	372	22.0	271	21.5
30+	202	11.9	158	12.6
	Mean	Range	Mean	Range
Offspring's age at interview (years)	39.7	34–49		
Mother's age at pregnancy (years)	24.8	14–43	24.3	14–43
Family socioeconomic index at birth[b]	55.0	3–93	50.6	5–93
Gravida	2.2	0–11	2.4	0–16
Maximum number of cigarettes mother smoked on any pregnancy day	10.8	0–61	10.9	0–61

[a]Data from 191 interviewed G2s were not included in these analyses: 49 were excluded due to interview administration issues, 73 were excluded due to missing data on maternal or offspring smoking or MDE diagnosis, 12 were excluded due to missing on other covariates, and 45 were excluded due to reporting age of regular smoking onset occurring after a diagnosis of depression. Finally, one sibling of 12 twin pairs was randomly selected for inclusion, resulting in a final analytic sample of $N = 1692$.
[b]A composite index of socioeconomic status was calculated on the basis of methods developed by the US Census Bureau (possible range = 0–100).

unadjusted model ($RR_B = 1.12$, CI 0.98–1.29) is not meaningfully different from the estimates from partially adjusted ($RR_B = 1.09$, CI 0.95–1.25) and fully adjusted ($RR_B = 1.09$, CI 0.95–1.25) models, with stable estimate and CI that included the null value but suggest a modest elevation in risk. The *E* value for this effect (*E* value RR_W 3.35, CI 1.59–6.10) shows the minimum strength of an unmeasured confounder that would have rendered this effect null.

We tested the linearity of MSP effects across the range of observed MSP levels by fitting separate quadratic models for the between- and within-pair mean MSP levels and deviations across pregnancies. Neither quadratic effect attained significance at the 5% level. Furthermore, we refit the models with the 45 respondents who were excluded from the main analysis because they had begun regular smoking after the onset of depression. Inclusion of these respondents did not alter the results by more than hundredths of a decimal place.

Results of the mediation analysis based on MSM models appear in the fourth and fifth panels of Table 4. The RR_R from these models indicates that the between- and within-pair effects are homogenous; and therefore, RR_T is an unbiased estimate of the association between MSP and offspring's risk of depression. The unadjusted estimate indicates the existence of a modest controlled direct effect of MSP on MDE ($RR_T = 1.21$, CI 1.03–1.42). Once the mediating effect of offspring's smoking status is accounted for, the controlled direct effect of MSP on offspring's risk of depression remains practically the same ($RR_T = 1.18$, CI 1.01–1.37). The *E* value for this effect is 1.64 (CI 1.01–2.08). Controlling for the confounding effect of adverse childhood experiences (Table 5) yields results that are qualitatively similar and support the existence of a modest controlled direct effect of MSP on offspring's risk of depression ($RR_T = 1.15$, CI 0.98–1.34).

Discussion

A biologically plausible association between MSP and offspring's risk of depression (Balfour & Ridley, 2000; Slotkin et al., 2006, 2015) has been observed among several birth cohorts (Ekblad et al., 2010; Fergusson et al., 1998; Menezes et al., 2013). However, null findings from two sibling studies suggested that the observed association between MSP and depression may be due to confounding by unmeasured family-level factors (Meier et al., 2017; Taylor et al., 2017). While these two studies further establish the importance of controlling for familial and genetic factors and the importance of sibling design for achieving this goal, challenges to valid inference regarding the health effects of MSP remain even when utilizing a sibling study. We addressed some of these challenges by conducting a sibling study of MSP and the risk of depression among adults past the peak age for onset of depression, utilizing prospectively collected and biologically validated measure of MSP. We blocked the confounding effect of unmeasured and unshared family-level stressors by controlling for offspring's smoking and experiences of adversity during childhood. We also examined the potential mediating effects of offspring's smoking on the association between MSP and depression.

Unlike the previous two family studies, we found a modest elevation in the risk of depression among offspring exposed to MSP. Controlling for offspring's smoking history (and experiences of childhood adversity among a smaller sample) yielded similar results, implicating an independent effect of MSP on the risk of depression. We found this effect of MSP to be linear and hold across the entire observed range of MSP in the study sample. In addition, the mediation models revealed a direct effect of MSP on the risk of depression. The contrast between our positive findings and the earlier sibling studies' null findings may be due to several features of the current study. The prospectively collected and biologically validated measure of MSP rendered a more accurate proxy measure of fetal bioavailability of nicotine metabolites than preceding studies. Our parameterization of MSP as a continuous variable better reflected the amount of smoking rather than the act of smoking as was the case in the previous two sibling studies which dichotomized MSP (yes/no). The current study also benefitted from a diagnostic assessment of depression among cohort members who have all passed the peak age for onset of depression. Finally, the *E* values associated with the effect estimates among this sample suggest it is unlikely that our findings can be entirely due to confounding by unmeasured factors. On the balance, evidence from this study is consistent with the existence of an independent but modest positive association between MSP and elevated risk of depression, an association that is biologically plausible (Balfour & Ridley, 2000; Slotkin et al., 2006, 2015).

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Table 3. Characteristics of G2 offspring included in the analytic sample according to maternal smoking during pregnancy, stratified by singletons *v.* siblings ($N = 1692$)

			Singletons				Siblings			
	Total ($N = 1692$)		No maternal smoking during pregnancy ($N = 342$)		Maternal smoking during pregnancy ($N = 518$)		No maternal smoking during pregnancy ($N = 358$)		Maternal smoking during pregnancy ($N = 474$)	
Characteristic	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Race/ethnicity										
Non-white	225	13.3	61	17.8	74	14.3	38	10.6	52	11.0
White	1467	86.7	281	82.2	444	85.7	320	89.4	422	89.0
Gender										
Male	726	42.9	147	43.0	228	44.0	155	43.3	196	41.3
Female	966	57.1	195	57.0	290	56.0	203	56.7	278	58.7
Marital status										
Married	1028	60.8	212	62.0	302	58.3	224	62.6	290	61.2
Previously married	297	17.6	65	19.0	87	16.8	58	16.2	87	18.3
Never married	367	21.7	65	19.0	129	24.9	76	21.2	97	20.5
Highest level of education										
No high school diploma or GED	174	10.3	28	8.2	73	14.1	14	3.9	59	12.4
High school diploma/GED	224	13.2	50	14.6	59	11.4	51	14.2	64	13.5
Technical/trade/certificate	308	18.2	66	19.3	102	19.7	55	15.4	85	17.9
1–3 years college	495	29.3	98	28.6	172	33.2	100	27.9	125	26.4
4 years college	331	19.6	59	17.2	78	15.1	88	24.6	106	22.4
Graduate/professional school	160	9.5	41	12.0	34	6.6	50	14.0	35	7.4
Household income										
Less than $38 400	377	22.3	85	24.8	132	25.5	61	17.0	99	20.9
$38 400–$47 999	154	9.1	33	9.7	55	10.6	31	8.7	35	7.4
$48 000 or more	1161	68.6	224	65.5	331	63.9	266	74.3	340	71.7
Maximum number of cigarettes mother smoked on any pregnancy day										
0	700	41.4	342	100.0			358	100.0		
1–9	196	11.6			110	21.2			86	18.1
10–19	222	13.1			111	21.4			111	23.4
20–29	372	22.0			175	33.8			197	41.6
30+	202	11.9			122	23.6			80	16.9

Offspring smoking history										
Never regular smoker	720	42.5	153	44.7	205	39.6	160	44.7	202	42.6
Regular smoker, not current	434	25.7	92	26.9	127	24.5	99	27.7	116	24.5
Regular smoker, current	538	31.8	97	28.4	186	35.9	99	27.7	156	32.9
Major depressive episode										
No	1295	76.5	263	76.9	400	77.2	279	77.9	353	74.5
Yes	397	23.5	79	23.1	118	22.8	79	22.1	121	25.5
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Offspring's age at interview (years)	39.7	34–49	39.5	34–48	39.4	34–48	39.7	35–48	40.1	35–49
Mother's age at pregnancy (years)	24.8	14–43	24.2	14–43	25.3	15–42	25.5	16–41	25.7	15–43
Family socioeconomic index at birth[a]	55.0	3–93	50.3	3–93	54.5	3–93	56.0	7–93	60.8	7–93
Gravida	2.2	0–11	2.1	0–11	2.2	0–11	2.2	0–11	2.2	0–11
Maximum number of cigarettes mother smoked on any pregnancy day	10.8	0–61	0.0	0	19.1	0.1–61	0.0	0	17.9	0.1–60

[a]A composite index of socioeconomic status was calculated on the basis of methods developed by the US Census Bureau (possible range = 0–100).

Table 4. Binomial regression models predicting relative risk of major depressive episode for offspring in the Boston and Providence cohorts of the Collaborative Perinatal Project ($N = 1692$)

	Unadjusted[a]		Partially-adjusted[b]		Fully-adjusted[c]		Marginal structural model: unadjusted for smoking[d]		Marginal structural model: adjusted for smoking[d]	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Maternal smoking during pregnancy										
Between (RR_B)	1.12	(0.98–1.29)	1.09	(0.95–1.25)	1.09	(0.95–1.25)	1.18	(1.00–1.39)	1.14	(0.98–1.34)
Within (RR_W)	2.04	(1.20–3.47)	1.94	(1.14–3.30)	1.97	(1.16–3.32)	2.05	(0.93–4.52)	2.08	(1.04–4.17)
Ratio (RR_R)	0.55	(0.31–0.96)	0.56	(0.32–0.98)	0.55	(0.32–0.96)	0.57	(0.25–1.29)	0.55	(0.27–1.13)
Total (RR_T)	1.15	(1.01–1.31)	1.12	(0.98–1.28)	1.12	(0.98–1.28)	1.21	(1.03–1.42)	1.18	(1.01–1.37)
Smoking history (ref: never regular smoker)										
Former smoker	1.17	(0.93–1.48)			1.03	(0.81–1.31)			1.46	(1.07–1.99)
Current smoker	1.43	(1.16–1.75)			1.15	(0.91–1.44)			2.03	(1.53–2.69)

[a]Models include only the indicated variable.
[b]Model includes gravida, age, gender, marital status, education, and household income.
[c]Model includes gravida, age, gender, marital status, education, household income, and smoking history.
[d]Potential confounding by gravida, age, gender, marital status, education, and household income accounted for by stabilized inverse probability weights.

Table 5. Binomial regression models predicting relative risk of major depressive episode for offspring in the Boston and Providence cohorts of the Collaborative Perinatal Project, additionally adjusting for childhood adversity ($N = 1637$)

	Unadjusted[a]		Partially-adjusted[b]		Fully-adjusted[c]		Marginal structural model: unadjusted for smoking[d]		Marginal structural model: adjusted for smoking[d]	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Maternal smoking during pregnancy										
Between (RR_B)	1.11	(0.96–1.28)	1.08	(0.93–1.24)	1.08	(0.94–1.24)	1.14	(0.97–1.36)	1.12	(0.95–1.31)
Within (RR_W)	2.05	(1.21–3.50)	1.90	(1.09–3.33)	1.93	(1.10–3.37)	2.00	(0.88–4.55)	2.04	(0.99–4.21)
Ratio (RR_R)	0.54	(0.31–0.95)	0.56	(0.32–1.01)	0.56	(0.31–1.00)	0.57	(0.25–1.33)	0.55	(0.26–1.16)
Total (RR_T)	1.14	(1.00–1.31)	1.10	(0.96–1.27)	1.11	(0.97–1.27)	1.17	(0.99–1.39)	1.15	(0.98–1.34)
Smoking history (ref: never regular smoker)										
Former smoker	1.16	(0.92–1.47)			1.03	(0.81–1.31)			1.33	(1.04–1.71)
Current smoker	1.43	(1.16–1.76)			1.15	(0.91–1.46)			1.71	(1.37–2.14)
Childhood Adversity Index (ref: <1)										
1–2			0.95	(0.75–1.20)	0.94	(0.74–1.19)				
2.5–3			0.81	(0.58–1.12)	0.79	(0.57–1.10)				
>3			1.01	(0.76–1.35)	0.99	(0.75–1.33)				

[a]Models include only the indicated variable.
[b]Model includes gravida, age, gender, marital status, education, household income, and childhood adversity.
[c]Model includes gravida, age, gender, marital status, education, household income, childhood adversity, and smoking history.
[d]Potential confounding by gravida, age, gender, marital status, education, household income, and childhood adversity accounted for by stabilized inverse probability weights.

We also note that prior studies of unrelated individuals have yielded elevated effect estimates which were reduced after controlling for confounding. In these studies, mothers who smoked during pregnancy also had higher rates of other independent risks for offspring depression (Meier et al., 2017; Menezes et al., 2013). In the current study, the between-sibling effects were positive but did not reach conventional significance thresholds. Moreover, compared to the within-sibling effect, the between-sibling effect for MSP is smaller in magnitude. While there is a lower prevalence of depression (22.5%) among siblings concordant for MSP and singletons than among discordant siblings (26.9%), it is unlikely that reduced statistical power to estimate the between-sibling effect fully explains the discrepancy in the within- and between-sibling effects.

There are at least two likely explanations for the relatively weaker between-sibling effects. First, our study population was recruited in the early 1960s when smoking was normative across all socioeconomic and demographic groups within the USA. Second, our sample, although socioeconomically heterogeneous, reflects the ethnically homogenous demography of Boston and Providence in the early 1960s. Consequently, contextual effects, such as socioeconomic factors, do not distinguish women who

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smoked during their pregnancies from women who did not smoke as sharply as they would today and thus do not yield a strong effect over the life-course. For these reasons, our findings should not be interpreted to negate the importance of contextual factors associated with MSP in the development of depressive disorders over the life-course.

We also acknowledge the shortcomings of the current study. We had no measure of maternal exposure to secondhand smoke. However, our validity study revealed excellent agreement ($k = 0.83$) between serum cotinine and maternal reports of smoking during pregnancy (Klebanoff et al., 1998). Thus, although a number of G2 respondents classified as unexposed to MSP based on their maternal smoking history may have been in fact exposed to cigarette smoke through maternal exposure to secondhand smoke, any such unreported exposure has not resulted in significant misclassification. Furthermore, secondhand smoke and MSP activate the same biologic pathways. Consequently, confounding by unmeasured exposure to secondhand smoke is not a serious threat to the validity of our findings. Second, low within-mother variation in maternal smoking across pregnancies did not allow us to assess a dose–response association between MSP and offspring's risk of depression. The limited number of discordant pairs led to some imprecision of within-sibling effects and prevented us from examining gender differences. Third, our analytic sample includes only ~10% of the original CPP participants. However, because we found no statistically significant difference in MSP between our analytic sample and the original CPP cohort, differential loss to follow-up as a source of bias may be discounted (online Supplementary Appendix 1). Finally, it is possible that the consequences of MSP are biologically inert in regards to the risk of depression other than through interactions with other biological or social processes (McEwen & Akil, 2020; Shenassa, Wen, & Braid, 2016). Our models did not account for such interactions. A potential for bias in the within-sibling estimates remains (Zetterqvist, Vansteelandt, Pawitan, & Sjolander, 2016).

In conclusion, our study which was designed to discount the role of shared genetic and social vulnerabilities to depression supports a modest independent association between MSP and offspring's lifetime risk of depression. Our findings do not negate earlier studies of MSP and depression. Furthermore, to the extent that biological pathways between MSP and various outcomes are distinct from one another and some remain to be fully illustrated, our findings are of limited generalizability to outcomes other than depression. A final verdict on the causal effects of MSP on health during adulthood in general, and on depression in particular, awaits further evidence. Our findings suggest that a future verdict will be more compelling should it be informed by clear evidence of biologic plausibility, and consideration of issues related to the measurement and parameterization of MSP, which among humans, is only a proxy for the biologically relevant exposure.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721001392

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Conflict of interest. None.

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