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ORIGINAL ARTICLE

Familial confounding of the association between maternal smoking during pregnancy and internalizing disorders in offspring

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Background. Maternal smoking has consistently been associated with multiple adverse childhood outcomes including externalizing disorders. In contrast the association between maternal smoking during pregnancy (MSDP) and internalizing (anxiety and depressive) disorders in offspring has received less investigation.

Method. We conducted a nationwide cohort study including 957635 individuals born in Denmark between 1991 and 2007. Data on MSDP and diagnoses of depression or anxiety disorders were derived from national registers and patients were followed up from the age of 5 years to the end of 2012. Hazard rate ratios (HRRs) were estimated using stratified Cox regression models. Sibling data were used to disentangle individual- and familial-level effects of MSDP and to control for unmeasured familial confounding.

Results. At the population level, offspring exposed to MSDP were at increased risk for both severe depression [HRR 1.29, 95% confidence interval (CI) 1.22–1.36] and severe anxiety disorders (HRR 1.26, 95% CI 1.20–1.32) even when controlling for maternal and paternal traits. However, there was no association between MSDP and internalizing disorders when controlling for the mother's propensity for MSDP (depression: HRR 1.11, 95% CI 0.94–1.30; anxiety disorders: HRR 0.94, 95% CI 0.80–1.11) or comparing differentially exposed siblings (depression: HRR 1.18, 95% CI 0.75–1.89; anxiety disorders: HRR 0.87, 95% CI 0.55–1.36).

Conclusions. The results suggest that familial background factors account for the association between MSDP and severe internalizing disorders not the specific exposure to MSDP.

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Key words: Anxiety disorders, depression, familial confounding, maternal smoking, sibling.

Introduction

It is widely accepted that exposure to maternal smoking during pregnancy (MSDP) may have deleterious effects on health outcomes in children including stillbirth (Flenady *et al.* 2011), lowered birth weight (Jaddoe *et al.* 2008), obesity (Gorog *et al.* 2011), and externalizing disorders (Thapar *et al.* 2003; Obel *et al.* 2009). Animal and human studies have suggested that MSDP can disrupt neurodevelopment via effects on maturing neurotransmitter systems and brain architecture in regions associated with stress and mood regulation. Despite these findings the debate continues with regard to whether these associations represent causal relationships (Langley *et al.* 2012; D'Onofrio *et al.* 2013; Skoglund *et al.* 2014). MSDP is known to be associated with numerous social and environmental factors (e.g. teenage motherhood, lower maternal education, increased single motherhood) that influence childhood outcomes (Gilman *et al.* 2008; Ellingson *et al.* 2012). In addition genes associated with the likelihood of MSDP may also affect childhood outcomes through maternal–child genetic inheritance (Agrawal *et al.* 2008; Chang *et al.* 2012). For this reason studies utilizing sibling-control and quasi-experimental designs (such as children from *in vitro* fertilization) (Agerbo *et al.* 2013) have been undertaken in an attempt to control for unmeasured genetic and environmental confounding (Knopik, 2009; D'Onofrio *et al.*

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2013). These studies have generally demonstrated attenuation of previously observed associations (Obel *et al.* 2011; Skoglund *et al.* 2014).

In contrast to the effort expended in exploring the MSDP-externalizing behaviour association, relatively few studies have explored the association between MSDP and internalizing disorders. Studies that have investigated this association report both positive and null results (Ashford *et al.* 2008; Carter *et al.* 2008; Robinson *et al.* 2010; Moylan *et al.* 2015). Limitations of these studies such as small sample size, limited controls for potential confounders, and differential reporting of smoking, among other issues, may have contributed to these inconsistencies. Internalizing disorders such as depression and anxiety contribute significantly to the global burden of disease (Murray *et al.* 2012). MSDP is potentially preventable in contrast to many potential risk factors associated with childhood outcomes. Based on this background a greater understanding of the MSDP-internalizing behavior association is highly relevant for public health.

Utilizing the rich Danish population-based registers, we aim to examine the putative effect of MSDP on the risk of severe depression and anxiety disorders at the population level and within and between families. Specifically, we investigate, whether offspring exposed to MSDP have a higher risk of developing depression or anxiety disorders than offspring not exposed to MSDP, and whether familial factors account for this potential link. In pursuing this, we established a nationwide population-based cohort of prospectively collected data on prenatal maternal smoking within and between families and individual onset of depression and anxiety disorders.

Method

Data sources

We utilized data from a record linkage of six Danish population-based registries: the Danish Civil Registration System (Pedersen, 2011), the Danish Psychiatric Central Register (Mors *et al.* 2011), the Danish National Hospital Registry (Lynge *et al.* 2011), the Danish Medical Birth Register (Knudsen & Olsen, 1998), the Danish Education Registers (Jensen & Rasmussen, 2011), and the Registers on Personal Income and Transfer Payments (Baadsgaard & Quitzau, 2011).

All residents of Denmark including immigrants have a unique personal identification number that is used in all national registers, which enables data to be linked across registers at an individual level. The Danish Civil Registration System was computerized in 1968 and gathers information on gender, date of birth, and vital status (continuously updated) of all persons, who have lived in Denmark since 1968 (Pedersen, 2011). The Danish Psychiatric Central Register includes data on all people admitted to a psychiatric hospital for assessment, treatment, or both in Denmark from 1969 onwards, or people who had appointments with psychiatric outpatient services from 1995 onwards (Mors *et al.* 2011). In the Danish National Hospital Registry all inpatient treatments at non-psychiatric facilities have been recorded from 1977 onwards, whereas outpatient and emergency-room contacts have been recorded from 1995 onwards (Andersen *et al.* 1999). Diagnoses are based on the International Classification of Diseases – eighth (ICD-8) and tenth (ICD-10) revisions. The Danish Medical Birth Registry was established in 1968 and was computerized in 1973, it provides data on antenatal and delivery care services and health of newborns (Knudsen & Olsen, 1998). Common to Danish Education Registers is individual-level information, which links education and educational institutions of students enrolled in Denmark, but the oldest information goes back to a full population census in 1970. For each year individual-level information on enrolment status, and completed levels of education and examinations is available (Jensen & Rasmussen, 2011). From 1980 onwards the Income Statistics Register includes information on salaries, entrepreneurial income, taxes, public transfer payments, capital income, private pension contributions, and pay-outs (Baadsgaard & Quitzau, 2011).

Study population

We identified all persons born in Denmark between 1991 and 2007 ($N = 1\,185\,152$) with complete linkage available for both parents. After the exclusion of persons with missing values on MSDP ($N = 118\,023$), multiple births ($N = 40\,223$), death, emigration, or diagnosis of depression or an anxiety disorder before 5 years of age or before 1996 ($N = 18\,625$), and those with serious congenital malformations ($N = 50\,646$) the study population included 957 635 persons, covering 770 315 siblings nested within 331 396 families (see Fig. 1). In this study all the individuals were followed up from their 5th birthday until the diagnosis of interest (depression or anxiety disorders), or until censoring due to death, emigration or end of study (31 December 2012), whichever occurred first. The study was approved by the Danish Data Protection Agency. The investigators were blind to the identity of study members. According to Danish legislation informed consent was not required.

Measures

Outcomes

Using the Danish Psychiatric Central Register and the Danish National Patient Register, we identified all

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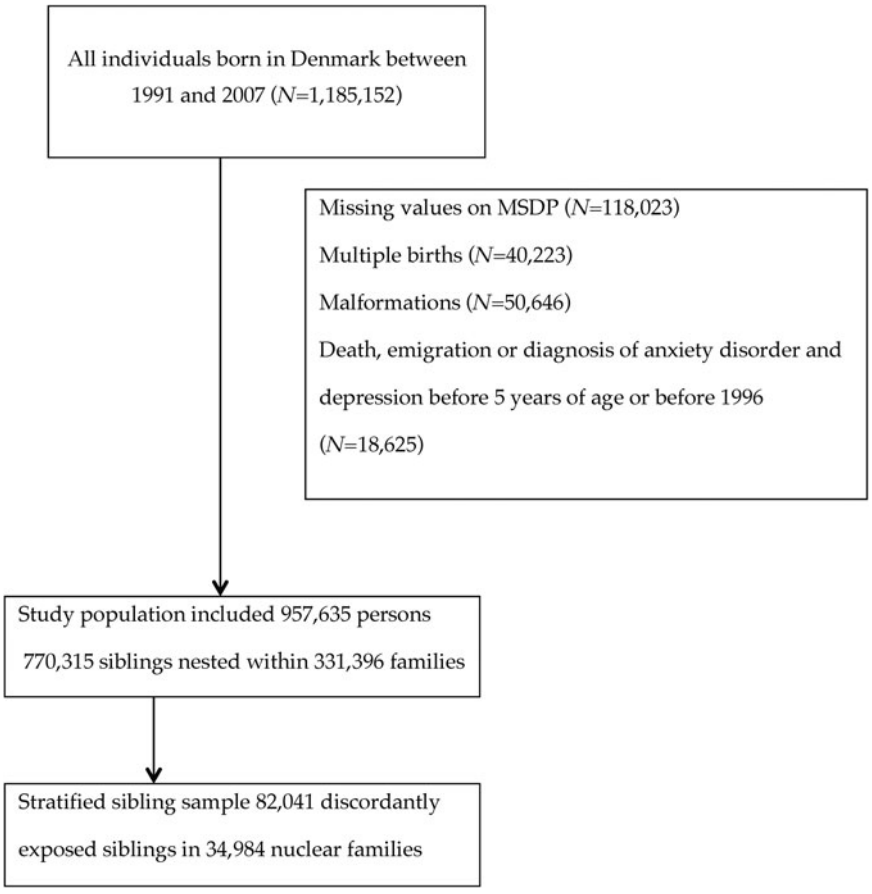

Fig. 1. Sample selection.

persons diagnosed with depression (ICD-10 codes: F32.00-F33.99 F34.10-F34.90 F38.00-F39.99), or anxiety disorders (ICD-10 codes: F40.00-F40.20 F41.00-F41.10 F42.00-F43.10); including acute stress reaction, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, specific phobia, and social phobia. For each individual the date of first psychiatric contact leading to the diagnosis of interest was designated as the date of onset.

Exposures

MSDP reported at the first antenatal visit was derived from the Danish Medical Birth Register from 1991 onwards (more detailed from 1997 onwards). All women were asked by the midwife at their first antenatal visit (13–15 weeks of gestation), whether they had ever smoked during the present pregnancy. For analyses the following variables for maternal smoking were constructed: (i) never smoker (women who at the visit to the midwife stated that they had never smoked during the present pregnancy) and (ii) ever smoker (women who at the first visit to the midwife stated that they had stopped smoking during the first trimester, stopped smoking at the beginning of the second trimester, or were current smokers at the first visit to the midwife) (Knudsen & Olsen, 1998).

Confounding and mediating factors

Based on previous research measured covariates included sex, calendar year, mother's parity (1st, 2nd, 3rd, 4th or $\geqslant$5th), parental age at childbirth ($\leqslant$20, 21–25, 26–30, 31–35, >35 years), parental psychiatric history (yes/no), substance abuse (ICD-8 codes: 291.xx, 303.xx, 304.xx, 571.09, 571.1x; ICD-10 codes: F10-F16, F18, F19, I85, K70), divorce, abuse (ICD-8 codes: E960-E969; ICD-10 codes: T74.xx, X85.00-Y09.99), parental highest education at time of birth (categorized as unknown, elementary school, above elementary school), and parental income at time of birth (annual gross income in tertiles). Maternal somatic illness was assessed using the Charlson Comorbidity Index (Charlson *et al*. 1987). The Charlson Index is an indicator of the somatic disease burden based on 19 severe chronic diseases, each assigned a weight from 1 to 6 corresponding to the severity of the disease.

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As low birth weight, early gestational age, and a low Apgar score 5 min after birth might mediate the association of MSDP with depression or anxiety disorders, we chose to not adjust for these measures. However, we conducted a sensitivity analysis with the cohort restricted to individuals with gestational age 37–44 weeks, birth weight >2500 g, and Apgar score of 10 at 5 min.

Statistical analyses

We used Cox proportional survival analysis to estimate the effect of MSDP on the risk of depression or anxiety disorders at the population level. The models calculated hazard rate ratios (HRRs) for time to depression or anxiety diagnosis using age as underlying timescale. Robust standard errors adjusted the 95% confidence intervals (CIs) for the presence of familial clustering in the analyses at the population level. We further adjusted the crude model for the above-mentioned measured covariates. Analyses were conducted at the population level and the cohort restricted to at least one maternal sibling. In the sibling cohort, we followed the suggestions of Begg & Parides (2003) in order to disentangle familial- and individual-level effects of MSDP. We assessed the effect of the mother smoking during one specific pregnancy (individual-level effect of MSDP) and adjusted for how often the same mother was smoking during all her pregnancies (familial mean exposure to MSDP). We therefore added to the model the familial mean exposure to MSDP and a 'centred' form of individual MSDP ($MSDP_{ij} - \overline{MSDP}_i$), where the i and j indexes represent the families and the individuals, respectively, and where $\overline{MSDP}_i$ is the average over individuals in the ith family. Since the individual measurement is replaced by its deviation from the familial level mean, this new version of the individual score represents, how much larger or smaller the individual measurement is compared to other individuals in its family. We also tested the deviation of individual MSDP from familial mean exposure as the sole predictor of depression and anxiety disorders.

We supplemented the analyses exploring the effect of unmeasured familial confounding. We hereby applied stratified Cox regression models with a separate stratum for each set of maternal siblings. In the sibling sample, there were 82 041 siblings discordantly exposed to MSDP, nested in 34 984 nuclear families. Sibling comparisons adjust for all unmeasured factors that are shared and constant within the nuclear family. The stratified Cox regression models using sibling data were adjusted for the same covariates as in the models on the population level. All statistical analyses were conducted in SAS software v. 9.4 (SAS Institute Inc., USA).

Ethical statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Results

A total of 957 635 persons born between 1991 and 2007 were followed from their 5th year birthday for the development of severe depression and anxiety disorders. During the 49 148 258 person-years at risk, 6525 persons were diagnosed with depression and 6739 with anxiety disorders. In 13 484 (1.4%) cohort members follow-up was ended before the end of the study, 927 died, 12 354 emigrated from Denmark, and 203 were lost to follow-up. Table 1 shows the distribution of offspring and maternal covariates. In families with MSDP, parents were more likely to be mentally ill ($p < 0.0001$), of younger age ($p < 0.0001$), lower education ($p < 0.0001$), and lower income ($p < 0.0001$).

MSDP and offspring's risk for internalizing disorders

The crude association showed that offspring exposed to MSDP were at increased risk for both severe depression (HRR 1.39) and anxiety disorders (HRR 1.36). This association was marginally attenuated after adjustment for measured covariates (depression: HRR 1.29; anxiety disorders: HRR 1.26; see Table 2). Of the covariates included parental psychopathology particularly had an effect on risk estimates. Mental illness of the mother increased the risk for depression (HRR 1.66, 95% CI 1.55–1.77) and anxiety disorders (HRR 1.52, 95% CI 1.39–1.66) in offspring more than paternal mental illness (depression: HRR 1.29, 95% CI 1.20–1.39; anxiety disorders: HRR 1.18, 95% CI 1.07–1.30). In the cohort restricted to individuals having maternal siblings, the association of MSDP and risk for depression (HRR 1.34) and anxiety disorders (HRR 1.28) were comparable to the entire cohort. Sensitivity analyses restricting the cohort to individuals with gestational age 37–44 weeks, birth weight >2500 g, and Apgar score of 10 at 5 min resulted in very similar associations (depression: HRR 1.34, 95% CI 1.25–1.44; anxiety disorders: HRR 1.27, 95% CI 1.18–1.36).

Familial- and individual-level effects of MSDP and offspring's risk for internalizing disorders

After adjustment for the familial mean exposure to MSDP in the sibling cohort no differences in the risk of severe depression (HRR 1.11) or anxiety disorders (HRR 0.94) were observed for individual MSDP,

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Table 1. *Baseline characteristics of individuals exposed to maternal smoking during pregnancy*

	Smoking: yes ($N = 227\,272$)	Smoking: no ($N = 730\,363$)
Depression	2514 (38.53%)	4011 (61.47%)
Anxiety disorders	2475 (36.73%)	4264 (63.27%)
Gender		
Female	111 145 (23.75%)	356 782 (76.25%)
Male	116 127 (23.71%)	373 581 (76.29%)
Parity		
1	96 318 (23.33%)	316 449 (76.67%)
2	82 805 (22.88%)	280 241 (77.12%)
3	34 985 (25.72%)	101 031 (74.28%)
4	9727 (29.30%)	23 470 (70.70%)
⩾5	3437 (27.26%)	9172 (72.74%)
Calendar year of birth		
1991–1994	73 166 (31.57%)	158 541 (68.43%)
1995–1998	59 087 (25.81%)	169 848 (74.19%)
1999–2002	48 905 (21.84%)	174 992 (78.16%)
2003–2007	46 114 (16.89%)	226 982 (83.11%)
Paternal age, years		
⩽20	4785 (49.40%)	4873 (50.60%)
21–25	34 445 (35.91%)	61 469 (64.08%)
26–30	73 919 (23.96%)	234 618 (76.04%)
31–35	65 642 (20.57%)	253 519 (79.43%)
>35	48 481 (21.61%)	175 884 (78.39%)
Maternal age, years		
⩽20	13 458 (43.84%)	17 241 (56.16%)
21–25	55 313 (31.56%)	119 972 (68.45%)
26–30	82 640 (21.66%)	298 918 (78.34%)
31–35	47 474 (20.05%)	189 270 (79.95%)
>35	28 387 (21.29%)	104 962 (78.71)
Divorce		
No	156 560 (21.20%)	581 984 (78.80%)
Yes	70 712 (32.28%)	148 379 (67.72%)
Offspring abuse		
No	224 832 (23.61%)	680 712 (76.39%)
Yes	2440 (44.65%)	3025 (55.35%)
Maternal abuse		
No	225 981 (23.67%)	728 799 (76.33%)
Yes	1291 (45.22%)	1564 (54.78%)
Paternal psychiatric illness		
No	197 840 (22.52%)	680 712 (77.48%)
Yes	29 432 (37.22%)	49 651 (62.78%)
Maternal psychiatric illness		
No	187 604 (21.95%)	667 195 (78.05%)
Yes	39 668 (38.57%)	63 168 (61.43%)
Maternal substance abuse		
No	220 135 (23.23%)	727 499 (76.77%)
Yes	7137 (71.36%)	2864 (28.64%)
Maternal somatic illness		
No	180 719 (22.40%)	626 118 (77.60%)
Yes	46 553 (30.87%)	104 245 (69.13%)
Paternal income		
1st tertile	98 520 (30.71%)	222 272 (69.29%)
2nd tertile	80 193 (25.19%)	238 131 (74.81%)
3rd tertile	48 559 (15.25%)	269 960 (84.75%)
Maternal income		
1st tertile	97 858 (30.64%)	221 483 (69.36%)

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Table 1 (*cont.*)

	Smoking: yes ($N = 227\,272$)	Smoking: no ($N = 730\,363$)
2nd tertile	83 289 (26.10%)	235 841 (74.90%)
3rd tertile	46 125 (14.45%)	273 039 (85.55%)
Paternal education		
Unknown	7865 (24.21%)	24 626 (75.79%)
Elementary school	80 244 (38.25%)	129 524 (61.75%)
Above elementary school	139 163 (19.45%)	576 213 (80.55%)
Maternal education		
Unknown	4341 (18.61%)	18 982 (81.39%)
Elementary school	95 616 (43.02%)	126 669 (56.98%)
Above elementary school	127 315 (17.88%)	584 712 (83.12%)

Table 2. *Hazard rate ratios of internalizing disorders exposed to maternal smoking during pregnancy (MSDP)*

		Hazard rate ratio (95% CI)		
	Exposure	Entire population (crude)[a]	Entire population (adjusted)[b]	Maternal siblings (adjusted)[b]
Depression	MSDP no	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
	MSDP yes	1.39 (1.32–1.46)	1.29 (1.22–1.36)	1.34 (1.25–1.43)
Anxiety	MSDP no	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
	MSDP yes	1.36 (1.30–1.43)	1.26 (1.20–1.32)	1.28 (1.20–1.37)

[a] Hazard rate ratio adjusted for calendar year of birth and gender.

[b] Hazard rate ratio adjusted for calendar year of birth, gender, parity, parental age at time of birth, parental income, parental education, and parental psychiatric history.

whereas we observed strong familial-level effects of MSDP (depression: HRR 1.39; anxiety disorders: HRR 1.37; see Table 3). A total of 82 041 siblings were discordantly exposed to MSDP nested in 34 984 nuclear families (18 554 mothers smoked during the first pregnancy compared to 13 576 in the second, 8192 in the third). Stratified sibling comparisons showed similarly that associations observed at the population level were completely attenuated (depression: HRR 1.18; anxiety disorders: HRR 0.87). Exposed and unexposed siblings had nearly equivalent rates of depression and anxiety disorders, indicating that unmeasured familial factors, that are constant within nuclear families, explain the associations between MSDP and the later risk of depression and anxiety.

Discussion

This large prospective study of offspring born in Denmark explored the risk associated with MSDP for depression and anxiety disorders. Consistent with previous research offspring exposed to MSDP were more often diagnosed with depression or anxiety disorders at the population-level (Ashford *et al.* 2008; Carter *et al.* 2008; Brion *et al.* 2010). The association between MSDP and offspring internalizing disorders was generally robust to the use of measured statistical covariates such as parental education or income. However, after accounting for unknown but shared family-level factors, there remained no individual-level effect of MSDP on the offspring's risk of internalizing disorders. As such these results strongly suggest that unmeasured genetic factors or shared familial environment are likely to account for the increased risk of severe internalizing disorders among offspring exposed to MSDP, and not putative biological effects of MSDP. These conclusions are strengthened by the observation that siblings within the same family, who were differentially exposed to MSDP, did not differ in their risk of developing a severe internalizing disorder.

The results are further consistent with sibling-control studies exploring the contribution of unmeasured genetic and environmental confounds of MSDP and other offspring's outcomes such as poor academic achievement (Lambe *et al.* 2006; D'Onofrio *et al.* 2010*b*), low intellectual abilities (Lundberg *et al.* 2010), criminality (D'Onofrio *et al.* 2010*a*), and attention deficit hyperactivity disorder (Knopik *et al.* 2005; Skoglund *et al.*

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Table 3. *Individual and familial level effects of maternal smoking during pregnancy (MSDP)*

		Hazard rate ratio (95% CI)		
	Exposure	Individual and familial MSDP[a]	Individual MSDP adjusted for familial mean[b]	Individual MSDP in sibling stratum[c]
Depression	Individual-level effect of MSDP	1.11 (0.94–1.30)	1.13 (0.95–1.33)	1.18 (0.75–1.89)
	Familial-level effect of MSDP	1.39 (1.29–1.51)		
Anxiety	Individual-level effect of MSDP	0.94 (0.80–1.11)	0.96 (0.93–1.01)	0.87 (0.55–1.36)
	Familial-level effect of MSDP	1.37 (1.28–1.48)		

[a] Hazard rate ratio of familial and individual MSDP adjusted for calendar year of birth, gender, parity, parental age at time of birth, parental income, parental education, and parental psychiatric history.

[b] Hazard rate ratio of the deviation of individual MSDP from familial mean exposure adjusted for calendar year of birth, gender, parity, parental age at time of birth, parental income, parental education, and parental psychiatric history.

[c] Hazard rate ratio of MSDP derived from stratified Cox regression models with a separate stratum for each set of maternal siblings adjusted for calendar year of birth, age, gender, parity, parental age at time of birth, parental income, parental education, and parental psychiatric history.

2014; Obel *et al.* 2015). One possible mechanism is that mothers transmit liability genes to offspring that influence behaviours in both generations (Kuja-Halkola *et al.* 2014).

Our study builds significantly on previous studies based observational data that have demonstrated inconsistent results (Ashford *et al.* 2008; Carter *et al.* 2008; Brion *et al.* 2010). For example the RAINE study including 2758 mother–child pairs reported that children displayed higher internalizing behaviours between ages 2 and 14 years, if their mother failed to quit smoking, even after controlling for a range of potential confounders (Robinson *et al.* 2010). In the Norwegian Mother and Child Cohort Study, MSDP was similarly associated with increased internalizing behaviours at 18 and 36 months even after controlling for smoking in past pregnancies (Moylan *et al.* 2015). These results contrast with outcomes from two other large cohorts, in which adjustment for confounders eliminated associations with MSDP. In the Generation R study ($N = 4680$) effects of MSDP on childhood behavioural problems at 18 months were strongly confounded by parental characteristics chiefly socioeconomic status and parental psychopathology (Roza *et al.* 2009). In the Avon Longitudinal study ($N = 4394$) MSDP was not associated with increased internalizing behaviours in children aged 4 years, after controlling for a range of potential confounders including socioeconomic status, parental psychopathology and alcohol consumption (Brion *et al.* 2010).

In our study a robust statistical association between MSDP and internalizing behaviours was found while controlling for confounding factors. However, the results of the sibling analyses revealed strong familial confounding indicating that familial factors not frequently measured (or measured well) in research protocols are actually responsible for the increased risk in offspring whose mothers smoke during pregnancy. In our study we were unable to capture these confounding effects by adjusting for parental psychology. The inconsistencies observed across studies might be explained by differences in sensitivity of the confounders included in these studies to account for such familial factors.

In contrast to most previous research, our study covers a longer follow-up period of 21 years and internalizing disorders can be identified at any time point during this period. Internalizing disorders were defined as diagnoses made at inpatient and outpatient facilities, for which the offspring also received treatment. In contrast to the parents' reports of children's problem behaviour employed in other studies, this constitutes a more severe outcome definition. Further, we accounted for range of parental somatic and mental disorders, but we were unable to explore the effects of lifestyle, such as breastfeeding, diet, physical activity or alcohol consumption.

Our results should be interpreted in the context of some limitations. Although sibling comparison will not be confounded by factors shared by siblings, the estimates might be more sensitive to bias due to non-shared confounders than the unpaired estimates (Frisell *et al.* 2012). The strict control for shared family factors further limits the analyses to a quite small subset of the population, namely those women who managed to change smoking habits from one pregnancy to another, whose change in smoking is assumed to be independent of their offspring's traits. Despite the obvious limitation in extrapolation to all smokers and

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especially heavy smokers it may, however, from a public health point of view be the most interesting group to focus on. In addition using the method of Begg & Parides (2003), which enabled us to include the entire sibling cohort, also revealed that familial effects account for the effect of MSDP on internalizing behaviour in offspring. Finally, it should be noted that our sample is rather young, which could imply that MSDP may have an effect on late onset of internalizing disorders.

The study made use of register-based diagnoses of severe depression or anxiety. As patient registers record contacts with clinics and psychiatric outpatient services, but not contacts with general practitioners, offspring with transitional or mild symptoms of depression and anxiety may have been missed. Thus our strategies probably could not avoid producing false negatives, while we consider bias due to false positives more unlikely. Primary findings were further in line with other representative studies in terms of prevalence of depression and anxiety disorders. Moreover, the use of a nationwide cohort minimized the risk for selection bias and allowed this longitudinal follow-up with minimal attrition. As in all observational studies we were not able to rule out residual confounding due to the lack of intact information on the exposure variable and other potential confounders. As pregnant women may also conceal their smoking habits there is a possibility of misclassification of exposure (Lindqvist *et al*. 2002). However, previous studies have repeatedly shown support for a causal association between MSDP and low birth weight suggesting that the effect of exposure misclassification is small in magnitude (Cnattingius, 2004; Obel *et al*. 2015). Further information on smoking quantity and timing (in the first trimester, throughout pregnancy) was only available in the minority of our study members, which prevented us from studying these factors. Finally, information on smoking habits of fathers and other family members would have been desirable. Interestingly, we have recently shown strong consistency between the risk estimates obtained using self-reports of MSDP, as in this study, or biomarkers such as maternal cotinine levels (Meier *et al*. in press).

The conclusions drawn from this study will need to be replicated in other studies, including more precise measures of MSDP and make use of other designs (Dolan *et al*. 2016) to further rule out alternative processes. In summary our data suggest that the previously observed association between MSDP and internalizing disorder can be attributed to unmeasured familial confounding. Although MSDP is known to be harmful in many ways (e.g. low birth weight, and infant mortality) and pregnant women should still be encouraged to stop smoking, our study does not support MSDP as an independent risk factor for internalizing disorders. It is essential for clinicians, researchers, and policy makers to focus on true and amendable causal risk factors and MSDP is most probably not one of those.

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Declaration of Interest

None.

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