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► To cite this version:

Mathilde Fekom, Tri-Long Nguyen, Johanna Lepeule, Aurélie Nakamura, Katherine Keyes, et al.. Intergenerational transmission of tobacco smoking: The role of the child's behavioral difficulties. Data from the Danish National Birth cohort (DNBC). *Drug and Alcohol Dependence*, 2024, 255, pp.111056. 10.1016/j.drugalcdep.2023.111056 . hal-04423627

HAL Id: hal-04423627

<https://hal.science/hal-04423627>

Submitted on 29 Jan 2024

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Title: Intergenerational transmission of tobacco smoking: the role of the child's behavioral difficulties. Data from the Danish National Birth cohort (DNBC)

Short running title: Transmission of tobacco smoking

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Word count : 3412

Abstract

Aims

This study explores the role of offspring behavioral difficulties in the intergeneration transmission of tobacco smoking.

Methods

This longitudinal cohort study is based on children born in Denmark in 1996-2003 participating in the Danish National Birth Cohort (DNBC), followed-up until 18 years of age. We included mother-child pairs with complete data regarding the exposure (4 trajectories of maternal daily smoking quantity during pregnancy: low, intermediate/stable, intermediate/decreasing and high), outcome (offspring daily smoking status at 18 years) and mediator (offspring symptoms of hyperactivity-inattention at 11 years), that is 24,588 mother-child pairs.

Results

In our study population, during pregnancy respectively 86.2%, 6.80%, 4.08% and 2.97% mothers belonged to the low, intermediate/stable, intermediate/decreasing and high smoking trajectory groups. After controlling for covariates using propensity scores, the direct effect of maternal smoking in pregnancy on offspring smoking in adolescence was statistically significant, especially when the mother belonged to the intermediate/stable smoking trajectory group ($OR_{IPW} = 2.09$, 95% CI : 1.70 – 2.61) or to the high smoking trajectory group ($OR_{IPW} = 2.08$, 95% CI : 1.52 – 3.11) compared to the low smoking trajectory group. None of the indirect effects of maternal smoking in pregnancy were statistically significant, and neither were the proportions mediated.

Conclusion

Maternal pregnancy smoking seems to have an influence on offspring smoking in early adulthood, which does not appear to be mediated by offspring behavioral difficulties. Women

should be strongly encouraged to quit smoking in pregnancy to reduce both short and long-term health risks among their offspring.

Key words: Maternal tobacco smoking, child development, offspring tobacco smoking, mediation analysis.

1. INTRODUCTION

Tobacco smoking remains one of the strongest risk factors of diseases leading to preventable death [1] and a variety of respiratory complications [2]. In particular, the prevalence of cigarette smoking persists among adults with low socio-economic status [3] and adolescents from unprivileged backgrounds [4].

As the majority of people who smoke daily begin tobacco use in adolescence or young adulthood [5], public health interventions are most effective when they focus on adolescent tobacco initiation. This requires precise knowledge of the determinants of smoking initiation early in life.

Parental smoking [6], and particularly the mother's smoking during pregnancy, is an established risk factor of adolescent smoking [7], [8], as well as nicotine dependence in adolescence [9],[10] and young adulthood [11], [12], [13]. Yet, the causal nature of this association is still a subject of debate due to possible confounding by genetic and socioeconomic characteristics. For example, results from exposure-discordant sibling analyses failed to find an association between prenatal tobacco exposure and the child's tobacco dependence, although a potential effect of heavy prenatal nicotine exposure could not be excluded [14], [15]. Similar results were reported by another study [16], where maternal pregnancy smoking was no longer associated with offspring nicotine dependence after adjustment for social, family and parental covariates. A British study comparing the effect of maternal and paternal smoking during pregnancy further concluded that the risk of offspring smoking initiation did not seem to operate through intrauterine mechanisms [17]. This is consistent with studies involving children conceived through Assisted Reproduction Techniques (ART) or exposure-discordant siblings, which revealed that the previously observed associations between maternal prenatal smoking and offspring behavior vanish when genetic influences [18], [19] or familial elements, such as low

socio-economic status and maternal psychopathology are taken into consideration [20]. However, other studies were more nuanced: maternal withdrawal symptoms, craving for tobacco and heavy tobacco use were associated with offspring smoking after adjustment for covariates but only among girls [21].

Recent evidence suggests that maternal smoking in pregnancy has direct effects on offspring brain development, which could lead to neurodevelopmental difficulties [22]. Hence, it has been hypothesized that maternal smoking in pregnancy is related to adolescent tobacco consumption through behavioral pathways, including impulsivity and stress reactivity, which are characteristic of children experiencing symptoms of hyperactivity and inattention and could be directly related to prenatal nicotine exposure [23] [24], [25].

In turn, evidence of an association between stress reactivity and tobacco consumption in adolescents was reported in different studies [26], [27]. For example, a 2019 study based on a Swedish cohort suggested that low stress resilience conferred an increased risk of adult regular smoking, nicotine dependence and other forms of addictive behaviors even after adjusting for childhood socioeconomic factors and additional covariates [28].

However, it's important to acknowledge the selective characteristics of both children born through ART and sibling pairs. Indeed, couples who undergo ART generally belong to higher socio-economic groups and also maintain low rates of smoking during pregnancy [29]. Concerning sibling pairs with discordant exposures, the percentage of discordance in prenatal tobacco exposure is usually relatively low (less than 8% [30]) and mothers who managed to stop smoking during at least one pregnancy tend to have globally lower smoking levels [31]. Establishing causality presents a real challenge in this field of study. Given that randomizing maternal smoking is not a possible option, we have to rely on observational data and use rigorous

designs such as mediation models or propensity scores in order to generate findings that are both robust and replicable [32].

To gain better understanding of the intergenerational transmission of smoking and the potential role of behavioral mechanisms, we used data from the Danish National Birth Cohort (DNBC). Specifically, we tested the association between the trajectory of maternal smoking during pregnancy and offspring daily smoking at age 18 years, and the extent to which offspring symptoms of hyperactivity and inattention at age 11 years are one of the underlying mechanisms.

2. MATERIALS AND METHODS

2.1. Population

The DNBC is a longitudinal cohort study of children born in Denmark in 1996-2003. More than 100,000 pregnant women were recruited by their general practitioners, and interviewed by telephone. Data collection spread over seven waves, the first two interviews during pregnancy, the third, fourth, fifth, sixth and seventh at child age 6 and 18 months, 7, 11 and 18 years. By the time of the first study wave, 96,822 women were still pregnant. Women with multiple pregnancies were unrepresented, and therefore we excluded twins and triplets ($n = 4,165$). Finally, we analyzed exclusively mother-child pairs with complete data regarding the exposure (trajectory of maternal daily smoking during pregnancy), the mediator (offspring symptoms of hyperactivity-inattention at 11 years) and the outcome (offspring daily smoking status at 18 years), that is 24,588 mother-child pairs, see **Fig. 1**. We compared the initial population and the final sample and found little significant difference, see the **Appendix**.

2.2. Variables

Exposure – Maternal pregnancy smoking trajectory

Trajectories of maternal tobacco smoking during pregnancy were derived from maternal reports of smoking obtained in the three first waves of the data collection, i.e. at approximately 12 and 30 weeks of gestation, and six months postpartum. The question was based on the reported average number of cigarettes smoked daily/weekly between i) the beginning of pregnancy and the first DNBC interview, ii) the first and the second DNBC interviews and iii) the second DNBC interview and the end of pregnancy. In addition, the number of cigars, cheroots and pipes smoked was converted into the number of cigarettes and added to the number of cigarettes.

Trajectories of maternal smoking in pregnancy were estimated using longitudinal k-means ('kml' package in R statistical software [33]) and identified based on the Calinski-Harabatz criterion [34]. Trajectories of daily smoking's best partition according to this criterion identified 4 groups: low (A), intermediate/stable (B), intermediate/decreasing (C) and high (D), see **Fig. 2**.

Study outcome – Offspring daily smoking at 18 years

Offspring frequency of cigarette smoking at 18 years of age was self-reported, and divided in two groups: 'Yes' if the offspring reported smoking daily and 'No' otherwise.

Mediating variable – Offspring symptoms of hyperactivity-inattention at 11 years of age

Children's socio-emotional development was assessed using the Danish version of the Strengths and Difficulties Questionnaire (SDQ) at 11 years of age [35]. The questionnaire was completed by the parents. Reliability of this measure across different respondent types was assessed in the DNBC cohort [36]. This validated tool includes 5 sub-scales measuring children's behavior:

emotional symptoms, conduct problems, symptoms of hyperactivity/inattention, peer relationship problems and pro-social behaviors. Each sub-scale is computed by summing 5 items each scored 0 (never), 1 (sometimes true) or 2 (certainly true). We specifically focused on children's symptoms of hyperactivity-inattention, which range from 0 to 10. Children's scores were dichotomized based on the 10th highest percentile of the sample for boys and girls separately, which corresponds to a cut-off value of 6 for boys and 5 for girls.

Covariates

Covariates were chosen using prior scientific literature and grouped in two categories: prenatal and post-birth. Prenatal covariates are potential confounders for the exposure-outcome and the exposure-mediator relationships. Post-birth variables are potential confounders of the mediator-outcome relationship which should also be controlled for. For this analysis, we used propensity score models which enabled us to use a larger number of covariates than in standard multivariate adjustment [37]. Unless otherwise indicated, covariates were reported by the parent, most frequently the mother. See **Table 1**, **Fig. 3** and the **Appendix** for more details on the variables.

- a) *Prenatal covariates* included *family socio-demographic characteristics before the birth*: maternal and paternal age at birth, maternal and paternal psychiatric disorder (yes vs. no), maternal childhood symptoms of hyperactivity-inattention (yes vs. no), maternal level of education (primary, secondary, higher), partner smoking status (daily, less than daily, does not smoke, no partner) and family income one year before birth (in quartiles).

- b) *Post-birth covariates* included *family socio-demographic characteristics during/after the birth*: the child's sex (girl vs. boy), maternal self-rated mental well-being (really well, well, fair/bad), parents living together (yes vs. no), child going to school at age 7 (yes vs.

no), maternal and paternal employment status (employed, unemployed, other), whether the child was living with the mother at age 11 (yes vs. no), whether the child had a severe disability/handicap (yes vs. no), gender dysphoria (not true vs. true), difficulty making friends (yes vs. no), experienced a negative life event during the past year at age 11 (yes once, yes more than once).

3. Statistical analyses

To test associations between maternal smoking in pregnancy and offspring tobacco use, and the role of early symptoms of hyperactivity and inattention, we proceeded as follows.

Descriptive analyses

First, associations between exposure and outcome, as well as the main mediating factor and covariates were tested in bivariate analyses. Statistical significance was evaluated using Pearson chi-square tests for categorical variables and Wilcoxon-Mann-Whitney tests for continuous variables. Due to a large sample size, p-values should be examined critically [38].

Mediation analyses

Second, we performed a mediation analysis following the recent Guideline for Reporting Mediation Analyses [39]. To control for confounding and estimate the direct and indirect effects of the exposure on the outcome, we built statistical models given all potential exposure-mediator-outcome confounders. First, we derived an exposure model, which estimated the probability of each level of the exposure (i.e. maternal smoking trajectory), given the confounders. This model (so-called propensity score) was incorporated by inverse probability weighting (IPW). Second, we derived a mediator model, which estimated the probability of each mediator value given the exposure (i.e. maternal smoking trajectory) and the confounders. We used this mediator model to

compute specifically the direct and indirect effects of the exposure on the outcome using a weighting-based approach [40] which consisted of weighting each observation by the ratio-of-mediator-probability weight (RMPW) [41].

Thus, the combination of IPW and RMPW allowed us to estimate the direct and indirect effects of maternal smoking in pregnancy, while adjusting for confounding factors. The same set of confounders was used to model the exposure and the mediator due to implementation constraints. Finally, to take into account the uncertainty generated by weights estimation, we computed standard errors associated with the direct and indirect effects by bootstrapping. This mediation analysis was performed using the medflex package in R [42]. In the supplementary file are provided results for the two-by-two analyses, i.e. exposure-outcome, exposure-mediator and mediator-outcome.

Missing data

Data on covariates were mostly complete (less than 1% missing), except for the following variables: difficulty making friends, negative life events (both approximately 6% missing), maternal symptoms of hyperactivity-inattention, parents living together at child age 7 years, child going to school at age 7 years, maternal self-report of mental well-being after pregnancy (all at most 22% missing and collected at child age 7 years which did not need to be complete for the analyses) and child gender dysphoria (25% missing because the question was asked only in the second version of the questionnaire).

To impute missing data under the assumption that this information could be recovered by the observed variables (so-called missing-at-random assumption), we used random forest models (missForest package in R [43]). See the list of missing variables in the **Appendix**.

Supplementary sensitivity analyses

Several supplementary sensitivity analyses were implemented to test the robustness of the results of our mediation analysis. First, we included interaction terms between the exposure and the mediator in our statistical analyses. Second, we stratified the statistical analyses by gender. Third, to evaluate uncontrolled confounding bias, the partner's smoking during pregnancy was tested as a negative control exposure [44]. Fourth, we used the Stress in Children (SiC) scale as a proxy for stress reactivity instead of the hyperactivity-inattention SDQ subscale. Finally, to account for attrition from the 1st interview to when the child was 11 and 18 years of age, we weighted all analyses with participants' inverse probability of belonging to the final sample.

All statistical analyses were conducted using R 4.0.4.

4. RESULTS

4.1. Descriptive analyses

Table 1 displays the characteristics of the DNBC mother-child pairs included in our study after stratifying on maternal smoking trajectory in pregnancy.

Prenatal characteristics

Maternal and paternal average age at birth were similar across exposure groups, except for the intermediate/decreasing smoking trajectory in which parental age was slightly lower than the average (-1.2 years for fathers and -1.1 years for mothers).

1.4% of participating mothers had no partner during pregnancy, and this proportion was higher in the high smoking trajectory group (6.7%). Among mothers who had a partner, 72.6% reported

that their partner did not smoke, but this proportion was 36.2% and 32.0% respectively in the intermediate/stable and high smoking trajectory groups. Family income was lower in the high smoking trajectory group than among other groups, with a larger proportion of participants in the 1st quartile (24.2%) and a smaller proportion in the 4th quartile (15.2%).

Post-birth characteristics

57.8% of participating children were female, somewhat more in the intermediate/stable smoking trajectory group than the average (61.6%). Both maternal mental health after pregnancy and family income were worse in the high smoking trajectory group (respectively 18.5% reported a fair/bad mental health and 23.5% were in the 1st income quartile). Similarly, there was a higher proportion of children with a severe disability (5.2%), with gender dysphoria (9.4%), having difficulties making friends (16.8%) and with a high hyperactivity SDQ score (16.9%) in the high trajectory group than in all other exposure groups. However, the proportion of children not living with their mother at 11 years of age was higher in the intermediate/decreasing smoking group (18.4%) and lower in the high smoking trajectory group (11.6%).

4.2. Associations between prenatal trajectories of maternal smoking and offspring daily smoking at age 18 years

Table 2 displays results of the mediation analysis before (left-hand side) and after (right-hand side) controlling for potential confounders.

After adjusting for confounding factors included using inverse probability weights, all effects (direct and indirect) were weaker than in unadjusted analyses. Yet the direct effects of maternal

smoking in pregnancy on offspring smoking in adolescence remained statistically significant, especially when the mother was in the intermediate/stable smoking trajectory group (B) ($OR_{IPW} = 2.10$ 95% CI : 1.83 – 2.71) or in the high smoking trajectory group (D) ($OR_{IPW} = 2.08$ 95% CI : 1.57 – 3.36) compared to the low smoking trajectory group (A). On the other hand, none of the indirect effects of maternal smoking in pregnancy were statistically significant, and neither were the proportions mediated even in the high smoking trajectory group (D) (2.7%).

In supplementary analyses, the interaction between maternal smoking in pregnancy and offspring symptoms of hyperactivity-inattention was not statistically significant. Moreover, we found no differences in indirect effects between boys and girls, however the direct effect was higher in girls than in boys for the intermediate/stable trajectory, and the opposite for the intermediate/decreasing trajectory, see **Appendix 4.a) Table 4**. In addition, the partner's smoking during pregnancy had a significant direct effect on offspring smoking at age 18 years ($OR_{IPW} = 2.09$ 95% CI 1.89 – 2.37), although the association was weaker than that related to maternal smoking during pregnancy, and the indirect effect was not statistically significant, see **Appendix 4.b) Table 5**. When using the self-reported Stress in Children (SiC) scale as a mediator we found very similar results to the the main analysis, see **Appendix 4.c) Table 6**. Finally, there was no major difference between the participants who were excluded and included, see **Appendix 4.d)**. Therefore, for simplicity, we present unweighted results.

5. DISCUSSION

5.1. Main findings

Testing the association between maternal tobacco smoking in pregnancy and offspring tobacco use in a large study of Danish adolescents, we found that those whose mother smoked on average

more than 5 cigarettes per day throughout pregnancy were more likely to smoke daily at age 18 years than those whose mother did not smoke (intermediate/stable trajectory (C) $OR_{IPW} = 2.09$ 95% CI 1.70 – 2.61 and high smoking trajectory (D) $OR_{IPW} = 2.08$ 95% CI 1.52 – 3.11). Our results are consistent with studies showing an association between parental and adolescent smoking patterns even when adjusting for multiple confounding variables [6]–[8]. We also showed that this association was not mediated by offspring childhood symptoms of inattention and hyperactivity, which exerted independent effects on smoking.

5.2. Limitations and strengths

Our study presents several limitations which need to be acknowledged prior to interpreting the data. First, maternal smoking during pregnancy was self-reported, which probably induced reporting bias due to social desirability, particularly regarding the number of cigarettes smoked. Nevertheless, self-reports are generally valid and the repeated measures we used in this study strengthened data validity [45]. Second, offspring symptoms of hyperactivity-inattention were reported by the mother, and could also suffer from bias due to mental/emotional difficulties or maternal expectations [46]. Nevertheless, maternal reports of children's behavioral difficulties, particularly externalizing symptoms, are generally valid [47]. Third, women included in the DNBC were more likely to be white and had a higher average socioeconomic position than the overall Danish population, implying lack of generalizability [48]. Fourth, there is a significant rate of loss to follow-up. Consequently, the findings could be biased, potentially leading to underestimating the connections between parental and adolescent smoking habits, as well as the influence of hyperactivity. However, we investigated this phenomenon in sensitivity analyses and found no major difference between the participants included and those excluded. Finally, there is a possibility of residual confounding due to genetic, environmental, behavioral or socio-

demographic confounders that were unmeasured. In particular, a Swedish cohort study using a cousin and sibling design showed that unmeasured familial confounding could play a role in the association between maternal pregnancy smoking and ADHD in offspring [49].

Despite limitations, our study also has strengths, which should be highlighted. First, we used longitudinal data from before pregnancy until the offspring were 18 years, which allowed us to study the association between maternal smoking and offspring outcomes prospectively, thereby limiting information bias. Second, the mediation analysis we performed accounted for a large set of confounders and followed recent causal methods that allow one to disentangle direct and indirect effects under a clear (assumed) causal structure. Third, missing information relative to maternal or paternal characteristics were retrieved directly from Danish national registries, making it possible to ascertain characteristics which were not collected in study questionnaires. Fourth, we conducted several sets of sensitivity analyses, to verify the robustness of our findings.

5.3. Interpretations of the results

Offspring of mothers in the intermediate/decreasing trajectory group, who smoked approximately 13 cigarettes per day on average at the beginning of pregnancy before quitting, had a probability of smoking lower than that of the intermediate/stable smoking trajectory group, who smoked 7 cigarettes per day on average throughout pregnancy. Thus, (i) the end of pregnancy seems to be a key period for predicting the offspring's later addictive behavior and (ii) stable smoking during pregnancy is a proxy of postnatal smoking which could also influence the offspring [50], [51] as women who did not quit smoking during pregnancy are more likely to continue smoking as the child is growing up [52]. This finding also indicates that there are benefits to quitting smoking in pregnancy, even after the first few weeks which are deemed especially important in terms of

neurogenesis and child development [53]. Among the smoking cessation interventions available to individuals who wish to stop smoking during pregnancy, counselling, feedback and incentives have shown to be particularly effective [54]. In adolescents, behavioral interventions such as education or brief counselling appear to effectively prevent the initiation of tobacco smoking. Conversely, the efficacy of pharmacotherapy-based interventions remains to be fully comprehended [55]. There are also actions to take at the family, school, and broader levels, in particular by prohibiting tobacco and reducing adolescents access to cigarettes [56].

5.4. Mechanisms contributing to intergeneration transmission of smoking

Besides offspring behavioral problems, which we specifically tested as a possible mediating mechanism, other pathways could explain this association. First, genetic factors passed on from parents to children could favor nicotine dependence [57]. Unfortunately, we were not able to test this hypothesis as genetic data are not available in the DNBC, but our analyses were controlled for maternal and paternal addictive behaviors, and the remaining association we observed could suggest that heritability is not the sole explanation. Second, the association between maternal smoking in pregnancy and offspring tobacco smoking might partly reflect epigenetic mechanisms, a reversible transmissible and adaptive process that affects gene expression and could be triggered by tobacco smoking during pregnancy [58]. We used negative control exposure and compared paternal smoking to maternal smoking in supplementary analyses, under the assumption that only maternal smoking potentially reflects intrauterine effects. Our findings show that partner smoking during pregnancy has a similar impact as maternal smoking during pregnancy, suggesting that epigenetic mechanisms might not be involved in the association and that we should support both parents to try to quit smoking whenever possible. Finally, other

mediating variables such as socioeconomic position changes during childhood or educational-related factors could explain this association.

6. CONCLUSION

Maternal pregnancy smoking seems to have an influence on offspring smoking in early adulthood which does not appear to be mediated by children's behavioral difficulties. There is much to explore regarding the effects of in utero exposure to tobacco use on brain development, however women should be strongly encouraged to quit smoking in pregnancy and given assistance in this area, to reduce short as well as long-term health risks among their offspring.

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Figure Legends

Figure 1 : Flowchart of the DNBC study sample data used to test association with maternal smoking in pregnancy (1996-2003, follow-up of 18 years).

Figure 2: Trajectories of maternal number of daily cigarettes in pregnancy in the DNBC (1996-2003). The best model has 4 trajectories: low (A), intermediate/stable (B), intermediate/decreasing (C) and high (D), N = 24,588.

Figure 3: Mediation model of the study. See the complete list of covariates in **Table 1**.

Tables

Table 1: Characteristics of mother-child pairs stratified according to the prenatal maternal tobacco trajectory (% , p-value): Danish National Birth Cohort (1996 - 2022).

	Overall	Low	Inter. stable	Inter. decreasing	High	p-value ^a
N	24,588	21,193	1,665	998	732	
Prenatal variables						
Maternal age at birth (mean (SD))	30.7 (4.14)	30.8 (4.06)	30.4 (4.61)	29.6 (4.30)	30.9 (4.77)	<0.001
Paternal age at birth (mean (SD))	32.4 (5.04)	32.4 (4.96)	32.3 (5.54)	31.4 (5.14)	32.7 (5.80)	<0.001
Maternal psychiatric disorder before preg. ^b = Yes (%)	167 (0.7)	119 (0.6)	19 (1.1)	16 (1.6)	13 (1.8)	<0.001
Paternal psychiatric disorder before preg. ^b = Yes (%)	204 (0.8)	149 (0.7)	31 (1.9)	8 (0.8)	16 (2.2)	<0.001
Maternal hyperactivity disorder in childhood = Partly/Very true (%)	1812 (9.4)	1395 (8.3)	199 (16.2)	100 (13.0)	118 (21.3)	<0.001
Maternal level of education ^b (%)						<0.001
Low	1980 (8.1)	1288 (6.1)	340 (20.5)	138 (13.9)	214 (29.4)	
Medium	10839 (44.2)	9077 (43.0)	902 (54.4)	465 (46.7)	395 (54.2)	
High	11682 (47.7)	10755 (50.9)	415 (25.0)	392 (39.4)	120 (16.5)	
Partner smoking status ^c (%)						<0.001
Don't smoke	17836 (72.6)	16440 (77.6)	603 (36.2)	559 (56.1)	234 (32.0)	
Less than daily	724 (2.9)	649 (3.1)	30 (1.8)	32 (3.2)	13 (1.8)	
Daily	5674 (23.1)	3896 (18.4)	958 (57.5)	384 (38.5)	436 (59.6)	
No partner	340 (1.4)	195 (0.9)	74 (4.4)	22 (2.2)	49 (6.7)	
Family income ^{b,d} (%)						<0.001
1 st quartile	3332 (13.6)	2676 (12.7)	295 (17.7)	184 (18.4)	177 (24.2)	
2 nd quartile	5718 (23.4)	4736 (22.5)	476 (28.6)	254 (25.5)	252 (34.5)	
3 rd quartile	7101 (29.0)	6102 (29.0)	513 (30.8)	295 (29.6)	191 (26.1)	
4 th quartile	8309 (34.0)	7554 (35.9)	379 (22.8)	265 (26.6)	111 (15.2)	
Post-birth variables						
Child sex ^b = Girl (%)	14216 (57.8)	12160 (57.4)	1025 (61.6)	596 (59.7)	435 (59.4)	0.004
Maternal mental self-evaluation after pregnancy ^{e,f} (%)						<0.001
Really well	7208 (35.5)	6248 (35.6)	482 (35.4)	278 (34.2)	200 (33.1)	
Well	11019 (54.2)	9577 (54.6)	716 (52.6)	434 (53.3)	292 (48.3)	
Fair/bad	2097 (10.3)	1719 (9.8)	164 (12.0)	102 (12.5)	112 (18.5)	
<i>At child age 7 years</i>						
Parents living together = No (%)	2439 (12.5)	1813 (10.7)	299 (23.7)	154 (19.8)	173 (31.2)	<0.001

Child going to school ^g = No (%)	208 (1.1)	171 (1.0)	16 (1.3)	8 (1.0)	13 (2.3)	0.022
Maternal work status ^{b,h} (%)						<0.001
Employed	22442 (91.4)	19537 (92.3)	1436 (86.4)	877 (88.0)	592 (81.0)	
Unemployed	1044 (4.2)	777 (3.7)	127 (7.6)	55 (5.5)	85 (11.6)	
Other	1079 (4.4)	861 (4.1)	99 (6.0)	65 (6.5)	54 (7.4)	
Paternal work status ^{b,h} (%)	702 (2.9)	504 (2.4)	83 (5.0)	58 (5.8)	57 (7.8)	<0.001
Employed	22989 (94.6)	19969 (95.2)	1483 (91.2)	896 (91.4)	641 (90.4)	
Unemployed	452 (1.9)	318 (1.5)	64 (3.9)	37 (3.8)	33 (4.7)	
Other	854 (3.5)	693 (3.3)	79 (4.9)	47 (4.8)	35 (4.9)	
<i>At child age 11 years</i>						
Family income ^{b,d} (%)						<0.001
1 st quartile	2466 (10.1)	1890 (8.9)	285 (17.2)	120 (12.0)	171 (23.5)	
2 nd quartile	5407 (22.1)	4395 (20.8)	483 (29.2)	277 (27.8)	252 (34.7)	
3 rd quartile	7734 (31.6)	6742 (31.9)	510 (30.8)	303 (30.4)	179 (24.6)	
4 th quartile	8898 (36.3)	8099 (38.3)	377 (22.8)	297 (29.8)	125 (17.2)	
Child living with mother = No (%)	3056 (12.4)	2529 (11.9)	258 (15.5)	184 (18.4)	85 (11.6)	<0.001
Child severe disability = Yes (%)	801 (3.3)	658 (3.1)	78 (4.7)	27 (2.7)	38 (5.2)	<0.001
Child gender dysphoria ^f = True (%)	926 (5.6)	769 (5.3)	74 (7.0)	41 (6.2)	42 (9.4)	<0.001
Child difficulty making friends ^f = Yes (%)	2746 (11.9)	2305 (11.5)	225 (14.6)	104 (11.1)	112 (16.8)	<0.001
Child negative life event (%)						<0.001
No	8630 (36.8)	7667 (37.9)	458 (29.3)	314 (33.3)	191 (28.1)	
Yes	6855 (29.3)	5983 (29.6)	414 (26.5)	287 (30.4)	171 (25.2)	
Yes, more than once	7938 (33.9)	6589 (32.6)	690 (44.2)	342 (36.3)	317 (46.7)	
Mediator variable						
Child hyperactivity SDQ score = High (%)	2198 (8.9)	1763 (8.3)	220 (13.2)	91 (9.1)	124 (16.9)	<0.001
Outcome variable						
Child daily smoking at 18 y-o ^f = Yes (%)	1640 (6.7)	1136 (5.4)	244 (14.7)	121 (12.1)	139 (19.0)	<0.001

^aPearson chi-square tests for categorical variables and Wilcoxon-Mann-Whitney tests for continuous variables.

^bVariables taken from the Danish registry data.

^cCollected at the time of the 1st DNBC interview

^dThe quartiles are based on the general population.

^eCollected at the time of the 3rd DNBC interview

^fSelf-reported

^gAccording to the Danish law, children enter school the calendar year they turn 6.

^hThe 'other' category includes retired, student, disabled, children and those not registered in the Employment Classification Module (AKM) from Statistics Denmark.

Table 2: Maternal pregnancy smoking trajectory (exposure), child SDQ hyperactivity group at 11 (mediator) and offspring daily smoking at 18 years of age (outcome). Data come from the Danish National Birth Cohort (1996 - 2022). Logistic regressions were used for both the mediator and the outcome models. N = 24,588.

	Analysis not controlled for covariates	Analysis controlled for propensity scores via IPW
	OR (95% CI)	OR (95% CI)
Direct effect		
Inter. stable (B)	2.91 (2.46 - 3.48)	2.09 (1.70 - 2.61)
Inter. decreasing (C)	2.41 (1.89 - 3.06)	1.80 (1.42 - 2.38)
High (D)	3.96 (3.29 - 4.68)	2.08 (1.52 - 3.11)
Indirect effect		
Inter. stable (B)	1.04 (1.02 - 1.06)	1.00 (1.00 - 1.01)
Inter. decreasing (C)	1.01 (0.99 - 1.02)	1.00 (0.99 - 1.00)
High (D)	1.07 (1.04 - 1.10)	1.01 (1.00 - 1.01)
Total effect		
Inter. stable (B)	3.03 (2.56 - 3.61)	2.10 (1.71 - 2.61)
Inter. decreasing (C)	2.43 (1.91 - 3.07)	1.80 (1.42 - 2.37)
High (D)	4.25 (3.53 - 5.01)	2.09 (1.53 - 3.12)
Proportion mediated		
Inter. stable (B)	3.54%	0.00%
Inter. decreasing (C)	1.12%	0.00%
High (D)	4.68%	1.35%

^aAll variables from Table 1 were included in the propensity scores model.