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Prenatal exposure to paternal smoking and likelihood for autism spectrum disorder

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Abstract

Genetics, environment, and their interactions impact autism spectrum disorder etiology. Smoking is a suspected autism spectrum disorder risk factor due to biological plausibility and high prevalence. Using two large epidemiological samples, we examined whether autism spectrum disorder was associated with prenatal paternal smoking in a Discovery sample (N = 10,245) and an independent Replication sample (N = 29,773). Paternal smoking was retrospectively assessed with questionnaires. Likelihood of having autism spectrum disorder was estimated with the Autism Spectrum Screening Questionnaire at three levels: low (<10), intermediate (10–14), and high (⩾15). Ordinal regression was used to examine the relationship between prenatal paternal smoking and likelihood of having autism spectrum disorder, adjusting for confounders. A total of 36.5% of Discovery sample fathers and 63.3% of Replication sample fathers smoked during the pregnancy period; 7% of the Replication sample smoker fathers smoked during the pre-conception period but quit during pregnancy period. Discovery sample prenatal paternal smoking significantly increased the likelihood of having autism spectrum disorder in their offspring (adjusted odds ratio=1.27). This was confirmed in the Replication sample with adjusted odds ratio of 1.15 among smoking pre-conception period + pregnancy period fathers; 14.4% and 11.1% increased high likelihood of autism spectrum disorder was attributable to prenatal paternal smoking in Discovery sample and Replication sample, respectively. Smoking prevention, especially in pregnancy planning, may decrease autism spectrum disorder risk in offspring.

Lay abstract

What is Already Known about This Subject: Genetics, (including *de novo* mutations), environmental factors (including toxic exposures), and their interactions impact autism spectrum disorder etiology. Paternal smoking is a candidate risk for autism spectrum disorder due to biological plausibility, high prevalence, and potential intervention.
What This Study Adds: This original study and its replication confirms that paternal factors can substantially contribute to autism spectrum disorder risk for their offspring. It specifically indicates that paternal smoking both before and during pregnancy contributes significantly to autism spectrum disorder risk.

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Implications for practice, research, or policy: Smoking prevention, especially in pregnancy planning, may decrease autism spectrum disorder risk in offspring.

Keywords
autism spectrum disorders, environmental factors, risk factor epidemiology

Introduction

Autism spectrum disorder (ASD), an early-onset neurodevelopmental disorder (NDD) with prevalence of 1.6%–3.0% worldwide, is characterized by pervasive impairment in social communication and the presence of restricted and repetitive behaviors/interests (Christensen, 2018; Fombonne, 2009; Kim et al., 2011; Maenner et al., 2014; Zablotsky et al., 2015). Epidemiological and genomic analyses demonstrate substantial etiologic contributions from additive genetic factors (Gaugler et al., 2014; Tick et al., 2016), with the remainder likely explained by a combination of non-additive genetic factors, environmental factors, and interactions, including gene–environment interactions (GxE) (Gaugler et al., 2014).

The pre- and perinatal period appears to be a critical nexus of risk for the genesis of ASD (Lyall et al., 2014; Willsey et al., 2013). Studies have reported associations between ASD and maternal prenatal exposure to some medications, toxins, and intrapartum rubella infection, suggesting that exposure to exogenous agents during critical developmental periods contribute to ASD susceptibility (Bescoby-Chambers et al., 2001; Chess, 1971; Ingram et al., 2000; L. C. Lee et al., 2008; Moore et al., 2000; Rodier et al., 1996, 1997; Stromland et al., 1994; G. Williams et al., 2001; K. Williams et al., 2008).

Prior studies examining relationships between perinatal risks and ASD have reported inconsistent findings between increased ASD risks and prenatal maternal factors, including complicated birth histories (Bilder et al., 2009; Burstyn et al., 2010; Cheslack-Postava et al., 2011; Dodds et al., 2011; Glasson et al., 2004; Hultman et al., 2002, 2010; H. J. Larsson et al., 2005; L. C. Lee et al., 2008; Mann et al., 2010; Schendel & Bhasin, 2008, K. Williams et al., 2008) as well as maternal smoking and alcohol exposure (Eliasen et al., 2010; B. K. Lee et al., 2012; Singer et al., 2017; Tran et al., 2013). Inconsistent findings are likely the result of methodological shortcomings, including small, clinical samples with phenotype heterogeneity, and confounding by comorbidity, including intellectual disability (ID). A recent meta-analysis, examining over 60 perinatal and neonatal risk factors, suggested that the following increased ASD risk: abnormal presentation, umbilical-cord complications, fetal distress, birth injury or trauma, multiple birth, maternal hemorrhage, summer birth, low birth weight, small for gestational age, congenital malformation, low 5-min Apgar score, feeding difficulties, meconium aspiration, neonatal anemia, ABO or Rh incompatibility, and hyperbilirubinemia (Gardener et al., 2011); another meta-analysis with 15 studies suggested no association between maternal smoking exposure and ASD (Rosen et al., 2015).

In prior studies, the majority of perinatal risks were limited to maternal exposures. With increased paternal age as an identified risk for ASD (Hultman et al., 2011), paternal perinatal exposures may increase ASD risk. ASD risk attributable to prenatal paternal smoking is of particular interest due to (1) biological plausibility through cumulative toxicity to the male germline (Linschooten et al., 2013) and secondary exposure to toxins (Clifford et al., 2012); (2) high smoking prevalence (43% in Korea and 15.1% in the United States) (Jamal et al., 2016; Korean Statistical Information Service [KOSIS], 2010); (3) highest prevalence of male smoking, 20–39 years, overlaps with peak age for reproduction (Li et al., 2011); (4) availability of animal models (Esakky & Moley, 2016; Nixon et al., 2015); (5) relatively accurate retrospective recall of exposure (Krall et al., 1989); and (6) availability of interventions for smoking cessation yielding other health benefits (Hopkins et al., 2001; Public Health Service Guideline Update Panel Liaisons and Staff, 2008).

The adverse impact of perinatal paternal smoking on fetal and newborn health has been reported (e.g. low birth weight, prematurity, heart defects, and childhood cancer), but little is known about its impact on ASD risk (Ahluwalia et al., 1997; Budi et al., 2015; Duan et al., 2014; Forest & Priest, 2016; Ion et al., 2015; Kaur, 2014; M. Larsson et al., 2009; K. M. Lee et al., 2009; Newman et al., 2010, Thacher et al., 2014, Windham et al., 2000; Zhang et al., 2010). Four studies have examined paternal smoking effects, including secondhand smoking on offspring ASD risk (Table 1). The small number of subjects and lack of control for known confounders (e.g. maternal smoking and parental age) make it difficult to arrive at conclusions.

We attempted to overcome these shortcomings by using an internal replication design, with two large, community cohorts to (1) test the hypothesis that paternal prenatal smoking increases likelihood for offspring with having ASD, in a "Discovery sample (DS)" and (2) use a "Replication sample (RS)" to confirm the initial findings while determining whether the timing of paternal smoking timing modifies the risk.

Method

Participants

DS and RS were two independent, epidemiologically ascertained cohorts of school-aged children. DS participants are from a Simons Foundation Autism Research

Table 1. Summary of prior studies that examined the relationship between prenatal paternal smoking and offspring autism risks.

Reference	Country	Time period	Definition of smoking	Diagnostic assessment	Odds of smoking in ASD (%)	Odds of smoking in control (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Study design
M. Larsson et al. (2009)	Sweden	2000/2005[a]	Father's smoking during pregnancy	Diagnosis history	1/49 (2.0)	50/3846 (1.28)	1.73 (0.93–3.20)	NA	Case/control
Zhang et al. (2010)	China	2007	Secondhand smoking during pregnancy	CARS (childhood autism rating scale)	18/77 (18.9)	6/89 (6.32)	No information	3.53 (1.30–9.56)[b]	Case/control
Duan et al. (2014)	China	2011–2013	Passive smoking on perinatal period	CARS	60/226 (21.0)	17/269 (5.94)	3.07 (0.51–3.62)	1.58 (1.02–2.63)[c]	Case/control
Budi et al. (2015)	Indonesia	2013	Father smoking during pregnancy	DSM-IV-TR	28/22 (56.0)	33/67 (33.0)	2.6 (1.3–5.2)	3.2 (1.5–6.9)[d]	Case/control

ASD: autism spectrum disorder; OR: odds ratio; CI: confidence interval; CARS: Childhood Autism Rating Scale; DSM-IV TR: *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.).
[a]Initial assessment in 2000 and follow-up in 2005.
[b]Adjusted for paternal age at delivery, gender, and birth year.
[c]Adjusted for father and mother's education level, father and mother's age, father and mother's character, family history of psychiatric disorder, mental stress, anxiety and nervousness, pregnancy complications, edema, threatened abortion, infection with fever during pregnancy, premature rupture of fetal membranes, premature delivery, cesarean, umbilical cord around the neck, birth asphyxia, and severe jaundice.
[d]Adjusted for paternal age at pregnancy and history of asphyxia.

Initiative (SFARI) project; the RS subjects are from the Korean Environmental Risk and Children's Health Project.

The 15,981 target subjects in the DS were drawn from the 7- to 13-year-old children participating in the SFARI project in 13 cities representative of South Korea in 2009–2011 (Figure 1). Of 12,447 questionnaires distributed to children with up-to-date contact information, 10,503 parents agreed to participate in the survey (84.4% response); 10,245 questionnaires were used for the final analyses, after deleting those with missing data (Autism Spectrum Screening Questionnaire (ASSQ) > 5 missing items ($N = 141$), gender ($N = 108$), and age ($N = 9$). RS subjects were ascertained between 2007 and 2008 from Cheonan City, a mixed urban and rural area in the center of South Korea (population = ~629,000) (Statistics Korea, 2015). The target population was 49,570 children attending in 65 elementary schools. Of 42,746 questionnaires distributed, 30,552 were retrieved from the parents via the school system (71.5% response). After excluding subjects with missing data (ASSQ ($N = 510$) gender and/or age ($N = 269$) 29,773 questionnaires were used in the final analyses. Missing values for parental smoking and maternal drinking were treated as "no response" and included in the final analyses. Questionnaires were completed by principal caregivers, (usually mothers) in both the DS and RS samples.

The Yale and Dankook University Institutional Review Boards approved the study; informed consent was obtained from the parents.

Measurement

Predictor: parental smoking. Parental smoking data were retrospectively collected, using a questionnaire: "Did the father smoke during pregnancy with an index child (response: Yes/No)?" in the DS, and "Has father ever smoked (responses: never, ex-smoker, current smoker)?" and "Did father smoke during pregnancy?" in the RS. The same questions were asked about the mother. Using a method of an indicator variable for missingness of categorical predictor (Gelman & Hill, 2006), missing DS and RS data were coded as "no response" and were included in the analyses.

Use of two items in the RS allowed refinement of timing for parental smoking into four groups: "never smoker," "smoking before (pre-conceptual period (PCP)) and throughout the entire pregnancy period (PP)," "Smoked but quit during pregnancy (PCP only)," and "smoking of unknown exposure timing" (Supplementary Figure 1).

In the RS, three additional questions were asked about the amount and duration of smoking: "How many cigarettes did father/mother smoke?" "When did father/mother start to smoke?" and "When did father/mother quit smoking?"

Outcome: autism spectrum phenotyping. The ASSQ, a 27-item questionnaire for ASD, measures social interaction, communication problems, RRBs, and associated

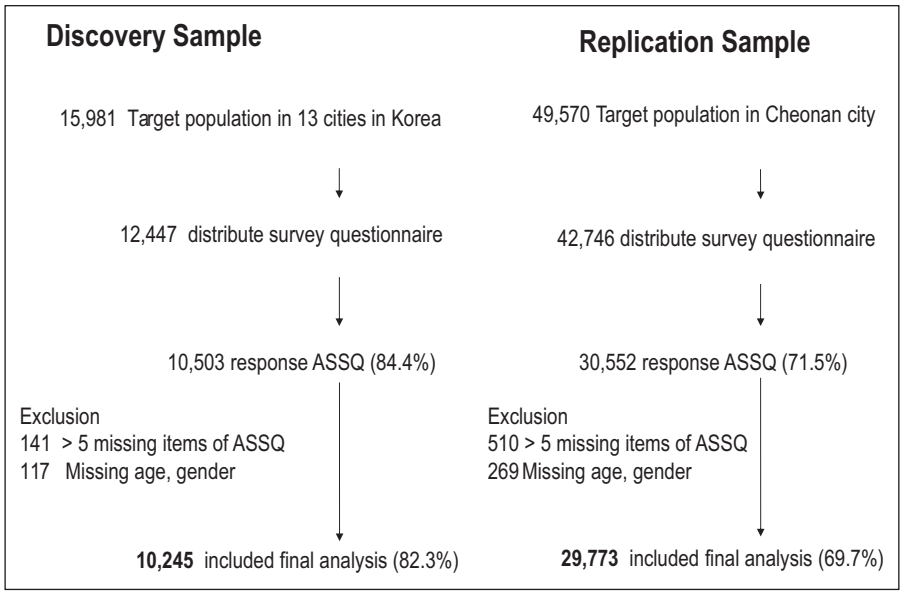

Figure 1. Sample ascertainment in discovery and replication samples.

features. Each item is rated from 0 to 2, (total score = 0–54). The ability of the ASSQ to distinguish ASD from other diagnoses is well-established for European and Korean children (Ehlers et al., 1999; Mattila et al., 2007; Yim, 2012) and assessing the environmental effects on ASD (Lyall et al., 2014). ASSQ scores in the upper 5th percentile (⩾15) defined children as "screen positive"; this definition demonstrated optimal agreement with the best estimate diagnoses of ASD in Korean children (Kim et al., 2011). We categorized ASSQ scores into three groups for an ASD diagnosis: (1) "High likelihood" score ⩾ 15 (⩾5th percentile); (2) "Intermediate likelihood" score 10–14 (10th–6th percentile); and (3) "Low likelihood" score < 10 (<10th percentile).

Potential confounders. Based on a review of the literature, potential confounders were selected to include parental age at pregnancy, maternal smoking and drinking during pregnancy, and family history of psychiatric disorders (Durkin et al., 2008; Modabbernia et al., 2017; Ornoy et al., 2015; Singer et al., 2017). These potential confounders were included in our final analyses.

Demographic covariates. Childrens' age, gender, and parental demographic characteristics (education and marital status) were included in our final analyses.

Statistical analysis. The Pearson's chi square test was used for comparing categorical demographic variables between the ASD likelihood groups. While the ASSQ's skewed distribution does not meet the assumption for linear regression, it met the proportional odds assumptions for ordinal logistic regression, which was used to examine the relationship between paternal smoking and the incremental increase in likelihood of having ASD in their offspring ("low," "intermediate," and "high" likelihood). Potential confounders and demographic covariates were controlled in a multivariable model. In order to avoid the use of inaccurate assumptions for missing data imputations, we used "no response" as data points for missing responses in predictor variables in multivariable regression.

In a subsample from the RS (N = 4660: PCP only = 439, PCP + PP = 3675, unknown timing = 546) which completed additional items about the duration and number of cigarettes smoked, one-way analysis of variance (ANOVA) was performed to determine whether the pack-years of smoking by the time of pregnancy (a proxy for smoking exposure dose) was associated with smoking cessation during pregnancy.

In addition, the attributional risk fraction (ARF) was computed to examine the proportion of offspring at high likelihood of having ASD attributable to paternal smoking in the study population.

All analyses were conducted using STATA (version 13.0); there is no community involvement in this study.

Results

Study subjects

In the DS and RS, males accounted for 51.5% and 49.2% of participants, respectively, while the mean ages were 9.61 (±1.69) and 9.19 (±1.74) years, respectively. In the DS, 6.9% were at intermediate and 4.3% at high likelihood of having ASD. In the RS, 7.2% were at intermediate and 5.3% at high likelihood of having ASD (Supplementary Table 2).

Parental smoking

Of the 35.0% of DS fathers who smoked during pregnancy, 88% had children at low likelihood for ASD, 7% had children at intermediate likelihood, and 5% had children at high likelihood for ASD (Supplementary Table 2). Among RS fathers, 56.3% smoked before and during pregnancy (PCP + PP). Of these, 87% of their children were at low likelihood for ASD, 8% of their children were at intermediate likelihood, and 5% had children at high ASD likelihood. It was also noted that 7.0% of RS fathers smoked only during the pre-conceptual period (PCP only); for this group, 90% of offspring were at low likelihood of having ASD while 6% of the children were at intermediate likelihood and 4% were at high ASD likelihood.

A total of 53.1% of RS fathers were current smokers, and 75.7% had a smoking history. In comparison, prevalence of current smoking and smoking history in the general population of Korean males are 43% and 69%, respectively. In the RS, age-specific prevalence of current smokers was 62% and 80.4% had past smoking histories <29 years old. In 30- to 39-year-old males, the current smoking rate was 50.5% and 74.5% smoked in the past. For those over 40 years old, 47.2% were current smokers and 73.0% smoked in the past. Similar smoking patterns have been reported for males in the general Korean population: for 20- to 29-year-olds, 53.5% currently smoke, 63% previously smoked; for 30- to 39-year-olds 54% currently smoke and 73% previously smoke; and, for those over 40 years of age, 48% currently smoke and 75% smoked previously. In the RS, when compared with fathers who smoked but stopped smoking during pregnancy (PCP only), those who continued smoking during the pregnancy period (PCP + PP) had significantly higher levels of exposure to smoking, as measured in pack-years in the subgroup analysis (Supplementary Table 1). By the time of conception, the average pack-years were 7.71 ± 6.04 in the PCP + PP group, 6.65 ± 6.02 in the PCP group, and 5.03 ± 5.17 in the unknown timing group (p = 1.04e-22).

In DS, compared to 4.49% of non-smoking fathers, 7.08% of smoking fathers had family psychiatric histories ($p < 0.001$). Similarly, more smoking fathers (0.59%) had paternal psychiatric histories than non-smoking fathers (0.30%, $p < 0.001$) in DS (Table 2). In the RS, 5.24% of PCP + PP smokers, 4.77% of PCP-only smoker fathers, and 4.80% of non-smoking fathers had family psychiatric histories ($p = 0.127$). In addition, 1.84% of PCP + PP smoker fathers, 1.53% of PCP-only smoker fathers, and 1.19% of non-smoking fathers had previous psychiatric diagnoses histories in RS ($p = 0.011$).

Frequencies of maternal smoking during pregnancy were low in both the DS and RS groups: in the DS, 0.25% overall and in the RS 0.3% for PCP only and 0.2% for PP + P.

Association between paternal smoking and offspring likelihood of having ASD

In the DS, paternal smoking during pregnancy was associated with a higher likelihood to have offspring with ASD: crude odds ratio (OR)= 1.21 (95% CI: 1.06–1.39). The significant association was held in the subsequent model adjusting other confounders and demographic covariates, with adjusted OR (aOR)= 1.27 (95% CI: 1.10–1.47, p = 0.001) (Table 3). This finding was replicated in the RS: crude OR of offspring having higher likelihood for ASD = 1.26 (95% CI: 1.16–1.38, $p < 0.001$) and the aOR = 1.15 (95% CI: 1.05–1.25, p = 0.003) among fathers who smoked during the PCP + PP. ARFs of paternal smoking during pregnancy for likelihoods of having offspring with ASD in DS and RS were 14.4% and 11.1%, respectively (Supplementary Method 1).

Analyses were repeated with two additional missing data methods (complete-case analyses and chained multiple imputation analyses), and the results remained identical (Supplementary Method 2).

Discussion

Male smoking is associated with many adverse health consequences, including adverse reproductive outcomes. However, the impact of paternal smoking on the risk for having offspring with ASD has not been systematically studied. Compared to earlier research examining small numbers of children in case–control study designs (Budi et al., 2015; Duan et al., 2014; Zhang et al., 2010), our study included 40,000 community-ascertained children, using a two-step, internal replication design. Our results demonstrate that prenatal paternal smoking is associated with a modestly increased risk (OR = 1.15, CI: 1.05–1.26, p = 0.003) for having offspring at high likelihood for ASD. When combined with the high prevalence of paternal smoking, modest increases in risk may contribute meaningfully to increased ASD prevalence. Based on our findings, we estimate that, in our DS, 14.4% of children at high likelihood of having ASD are attributable to prenatal paternal smoking; similarly, in the RS, 11.1% of high likelihood of having ASD is due to prenatal paternal smoking.

Initial associations between prenatal paternal smoking and offspring likelihood of having ASD in the DS were confirmed in the RS. These findings have public health implications because smoking is a common and modifiable risk factor.

The observed association between prenatal paternal smoking and offspring likelihood to have ASD may shed light on potential biological mechanisms underlying the genesis of ASD, if, indeed, the observed association reflects a causal effect, even though it has not been established in the current study. While there are many possibilities, our

Table 2. Demographic and risk characteristics of subjects by paternal smoking status.

Characteristics	Discovery sample				Replication sample					
	Total (N = 10,245)	No smoking (n = 4944)	Smoking (n = 3587)	NR[d] (n = 1714)	Total (N = 29773)	Never Smoker (n = 6896)	PCP only[a] (n = 2096)	PCP + PP[b] (n = 16768)	UK[c] (n = 3103)	NR[d] (n = 910)
Children characteristics										
Age, *M* (*SD*), year	9.61 (1.69)	9.83 (1.66)	9.30 (1.64)	9.63 (1.76)	9.19 (1.74)	9.16 (1.74)	9.11 (1.79)	9.18 (1.73)	9.38 (1.78)	9.23 (1.76)
Male sex, *N* (%)	5277 (51.46)	2493 (50.42)	1876 (52.30)	903 (52.68)	14,871 (49.95)	3385 (49.09)	1076 (51.34)	8395 (50.07)	1541 (49.66)	474 (52.09)
Prematurity										
Yes	463 (4.52)	205 (4.15)	183 (5.10)	75 (4.38)***	1489 (5.00)	315 (4.57)	89 (4.25)	872 (5.20)	167 (5.38)	46 (5.05)***
No	8659 (84.52)	4353 (88.05)	3177 (88.57)	1129 (65.87)	27,502 (92.37)	6402 (92.84)	1972 (94.08)	15,550 (92.74)	2842 (91.59)	736 (80.88)
Unknown	1123 (10.96)	386 (7.81)	227 (6.33)	510 (29.75)	782 (2.63)	179 (2.60)	35 (1.67)	346 (2.06)	94 (3.03)	128 (14.07)
Birth order										
First	4633 (45.22)	2303 (46.58)	1627 (45.36)	703 (41.02)***	14,781 (49.65)	3387 (48.12)	993 (47.38)	8454 (50.42)	1463 (50.37)	384 (42.20)***
Second	4113 (40.15)	2039 (41.24)	1505 (41.96)	569 (33.20)	12,414 (41.70)	2852 (41.36)	920 (43.89)	7004 (41.77)	1287 (41.48)	351 (38.57)
Third	1006 (9.82)	513 (10.38)	401 (11.18)	92 (5.37)	2253 (7.57)	586 (8.50)	157 (7.49)	1191 (7.10)	230 (7.41)	89 (9.78)
⩾Fourth	131 (1.28)	64 (1.29)	47 (1.31)	20 (1.17)	214 (0.72)	60 (0.87)	26 (1.24)	96 (0.57)	16 (0.52)	16 (1.76)
Unknown	362 (3.53)	25 (0.51)	7 (0.20)	330 (19.25)	111 (0.37)	11 (0.16)	0	23 (0.14)	7 (0.23)	70 (7.69)
Parents' characteristics										
Parental marriage status										
Unmarried	366 (3.57)	178 (3.60)	133 (3.71)	55 (3.21)***	2164 (7.27)	539 (7.82)	183 (8.73)	1178 (7.03)	221 (7.12)	43 (4.73)***
Married/cohabitation	8667 (84.60)	4288 (86.73)	3104 (86.53)	1275 (74.39)	24,560 (82.49)	5796 (84.05)	1792 (85.50)	14,186 (84.60)	2425 (78.15)	361 (39.67)
Separation/divorce/widowed	639 (6.24)	296 (5.99)	207 (5.77)	136 (7.93)	1443 (4.85)	249 (3.61)	35 (1.67)	724 (4.32)	201 (6.48)	234 (25.71)
Unknown	573 (5.59)	182 (3.68)	143 (3.99)	248 (14.47)	1606 (5.39)	312 (4.52)	86 (4.10)	680 (4.06)	256 (8.25)	272 (29.89)
Fa[e] age at pregnancy, year										
M, years (*SD*)	30.91 (4.46)	30.62 (4.52)	31.13 (4.54)	31.31 (3.88)***	32.11 (3.97)	32.61 (3.89)	32.81 (3.94)	31.87 (3.92)	31.75 (4.14)	32.47 (4.73)***
<20	40 (0.39)	21 (0.42)	17 (0.47)	2 (0.12)***	17 (0.06)	1 (0.01)	0	11 (0.07)	4 (0.13)	1 (0.11)***
20–29	3706 (36.17)	1983 (40.11)	1337 (37.27)	386 (22.52)	7231 (24.29)	1375 (19.94)	401 (19.13)	4490 (26.78)	855 (27.55)	110 (12.09)
30–34	4054 (39.57)	1905 (38.53)	1536 (42.82)	613 (35.76)	14,639 (49.17)	3530 (51.19)	1080 (51.53)	8341 (49.74)	1477 (47.60)	211 (23.19)
35–39	1286 (12.55)	616 (12.46)	506 (14.11)	164 (9.57)	5625 (18.89)	1487 (21.56)	462 (22.04)	3063 (19.27)	529 (17.05)	84 (9.23)
>40	295 (2.88)	135 (2.73)	126 (3.51)	34 (1.98)	1183 (3.97)	302 (4.38)	116 (5.53)	604 (3.60)	122 (3.93)	39 (4.29)
Unknown	864 (8.43)	284 (5.74)	65 (1.81)	515 (30.05)	1078 (3.62)	201 (2.91)	37 (1.77)	259 (1.54)	116 (3.74)	465 (51.10)
Mo[f] age at pregnancy, year										
M, years (*SD*)	27.96 (4.21)	27.58 (4.31)	28.22 (4.21)	28.68 (3.59)***	29.27 (3.71)	29.72 (3.68)	29.77 (3.56)	29.06 (3.66)	29.00 (3.82)	29.53 (4.46)***
<20	179 (1.75)	107 (2.16)	68 (1.90)	4 (0.23)***	67 (0.23)	8 (0.12)	2 (0.10)	44 (0.26)	10 (0.32)	3 (0.33)***
20–29	6250 (1.01)	3193 (64.58)	2283 (63.65)	774 (45.16)	16,194 (54.39)	3454 (50.09)	1045 (49.86)	9637 (57.47)	1734 (55.88)	324 (35.60)
30–34	2411 (23.53)	1098 (22.21)	939 (26.18)	374 (21.82)	10,063 (33.80)	2595 (37.63)	810 (38.65)	5497 (32.78)	956 (30.81)	205 (22.53)
35–39	453 (4.42)	207 (4.19)	192 (5.35)	54 (3.15)	2017 (6.77)	539 (7.82)	171 (8.16)	1043 (6.22)	192 (6.19)	72 (7.91)
>40	60 (0.59)	26 (0.53)	24 (0.67)	10 (0.58)	341 (1.15)	96 (1.39)	22 (1.05)	172 (1.03)	38 (1.22)	13 (1.43)
Unknown	892 (8.71)	313 (6.33)	81 (2.26)	498 (29.05)	1091 (3.66)	204 (2.96)	46 (2.19)	375 (2.24)	173 (5.58)	293 (32.20)

(Continued)

Table 2. (Continued)

Characteristics	Discovery sample					Replication sample					
	Total (N = 10,245)	No smoking (n = 4944)	Smoking (n = 3587)	NR (n = 1714)		Total (N = 29,773)	Never Smoker (n = 6896)	PCP only (n = 2096)	PCP + PP (n = 16,768)	UK (n = 3103)	NR (n = 910)
Fa education level, year											
<12	233 (2.27)	115 (2.33)	94 (2.62)	24 (1.40)***		601 (2.02)	99 (1.44)	33 (1.57)	370 (2.21)	76 (2.45)	23 (2.53)***
12	3421 (33.39)	1632 (33.01)	1401 (39.06)	388 (22.64)		11,074 (37.19)	2074 (30.08)	649 (30.96)	6871 (40.98)	1244 (40.09)	236 (25.93)
>12	5747 (56.10)	2947 (59.61)	2003 (55.84)	797 (46.50)		17,126 (57.52)	4573 (66.31)	1371 (65.41)	9260 (55.22)	1668 (53.75)	254 (27.91)
Unknown	844 (8.24)	250 (5.06)	89 (2.48)	505 (29.46)		972 (3.26)	150 (2.18)	43 (2.05)	267 (1.59)	115 (3.71)	397 (43.63)
Mo education level, year											
<12	225 (2.20)	130 (2.63)	73 (2.04)	22 (1.28)***		609 (2.05)	105 (1.52)	31 (1.48)	359 (2.14)	68 (2.19)	46 (5.05)***
12	4314 (42.11)	2083 (42.13)	1706 (47.56)	525 (30.63)		15,599 (52.39)	3198 (46.37)	945 (45.09)	9366 (55.86)	1655 (53.34)	435 (47.80)
>12	4815 (47.00)	2441 (49.37)	1701 (47.42)	673 (39.26)		12,526 (42.07)	3432 (49.77)	1069 (51.00)	6637 (39.58)	1190 (38.35)	198 (21.76)
Unknown	891 (8.70)	290 (5.87)	107 (2.98)	494 (28.82)		1039 (3.49)	16,192 (33)	51 (2.43)	406 (2.42)	190 (6.12)	231 (25.38)
Mo drinking pregnancy											
Yes	289 (2.82)	170 (3.44)	106 (2.96)	13 (0.76)***		2942 (9.88)	492 (7.13)	161 (7.68)	1789 (10.67)	382 (12.31)	118 (12.97)***
No	3238 (31.61)	2252 (45.55)	885 (24.67)	101 (5.89)		22,047 (74.05)	5100 (73.96)	1524 (72.71)	12,720 (75.86)	2208 (71.16)	495 (54.40)
No response	6718 (65.57)	2522 (51.01)	2596 (72.37)	1600 (93.39)		4784 (16.07)	1304 (18.91)	411 (19.61)	2259 (13.47)	513 (16.53)	297 (32.64)
Fhx of psychiatric dis[g]											
Yes	598 (5.84)	222 (4.49)	254 (7.08)	122 (7.12)***		1513 (5.08)	331 (4.80)	100 (4.77)	878 (5.24)	145 (4.67)	59 (6.48)
Fa Psychiatric hx											
Yes	56 (0.55)	15 (0.30)	21 (0.59)	20 (1.17)***		485 (1.63)	82 (1.19)	32 (1.53)	308 (1.84)	49 (1.58)	14 (1.54)*
Mo smoking pregnancy											
Yes	26 (0.25)	10 (0.20)	12 (0.33)	4 (0.23)***	PCP + PP	47 (0.16)	1 (0.01)	1 (0.05)	38 (0.23)	1 (0.03)	6 (0.66)***
No	3627 (35.40)	2530 (51.17)	1004 (27.99)	93 (5.43)	PCP only	78 (0.26)	3 (0.04)	11 (0.52)	50 (0.30)	11(0.35)	3 (0.33)
No response	6592 (64.34)	2404 (48.62)	2571 (71.68)	1617 (94.34)	UK	114 (0.38)	11 (0.16)	3 (0.14)	65 (0.39)	23(0.74)	12 (1.32)
					NR	2003 (6.73)	148 (2.15)	80 (3.82)	1072 (6.39)	305 (9.83)	398 (43.73)
					Never	27,531 (92.47)	6733 (97.64)	2001 (95.47)	15,543 (92.69)	2763 (89.04)	491 (53.96)

PCP: pre-conception period; NDD: neurodevelopmental disorder; DSM-5: *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.).
Chi-square between no smoking, smoking, and smoking unknown timing groups.
[a]PCP only: pre-conception period only.
[b]PCP + PP: PCP + pregnancy period.
[c]UK: smoking unknown timing.
[d]NR: no response.
[e]Fa: father.
[f]Mo: Mother.
[g]Family history of psychiatric disorder, included father, mother and siblings with NDD, schizophrenia, depressive disorder, bipolar disorder, anxiety disorder, substance use and addictive disorder, neurocognitive disorders, trauma-related disorder, and other neuropsychiatric disorder by DSM-5.
*$p < 0.05$.
***$p < 0.001$.

Table 3. Ordinal logistic regression analysis[a] to examine the relationship between prenatal paternal smoking exposure and offspring likelihood of having ASD.

	Discovery sample (N = 10,245)					Replication sample (N = 29,773)			
	Unadjusted		Adjusted[b]			Unadjusted		Adjusted[b]	
	OR (95% CI)	p value	aOR[a] (95% CI)	p value		OR (95% CI)	p value	aOR[a] (95% CI)	p value
Main predictors									
Fa[c] smoking pregnancy									
No	1 (reference)	NA	1 (reference)	NA	Never	1 (reference)	NA	1 (reference)	NA
Yes	1.21 (1.06–1.39)	0.005	1.27 (1.10–1.47)	0.001	PCP + PP	1.26 (1.16–1.38)	<0.001	1.15 (1.05–1.25)	0.003
No response	1.31 (1.11–1.56)	0.001	1.07 (0.87–1.30)	0.520	PCP only	0.96 (0.82–1.13)	0.635	0.95 (0.81–1.11)	0.507
					UK timing	1.22 (1.07–1.39)	0.002	1.03 (0.90–1.18)	0.657
					No response	1.61 (1.33–1.96)	<0.001	0.86 (0.68–1.08)	0.199
Covariates									
Characteristics of children									
Age	1.04 (1.00–1.08)	0.033	0.98 (0.93–1.02)	0.284		1.05 (1.03–1.08)	<0.001	1.05 (1.03–1.07)	<0.001
Sex									
Female	1 (reference)	NA	1 (reference)	NA		1 (reference)	NA	1 (reference)	<0.001
Male	1.59 (1.40–1.80)	<0.001	1.63 (1.43–1.85)	<0.001		1.42 (1.32–1.52)	<0.001	1.43 (1.33–1.53)	
Characteristics of parents									
Fa age at pregnancy, year									
20–29	1 (reference)	NA	1 (reference)	NA		1 (reference)	NA	1 (reference)	NA
<20	1.86 (0.82–4.22)	0.135	0.75 (0.30–1.86)	0.534		2.88 (1.02–8.13)	0.045	1.52 (0.50–4.64)	0.459
30–34	1.00 (0.86–1.16)	0.979	1.11 (0.93–1.30)	0.252		0.83 (0.77–0.91)	<0.001	0.93 (0.84–1.02)	0.107
35–39	1.05 (0.85–1.30)	0.629	1.04 (0.80–1.34)	0.769		0.90 (0.81–1.00)	0.044	0.91 (0.80–1.03)	0.136
>40	2.03 (1.48–2.77)	<0.001	1.88 (1.26–2.79)	0.002		1.51 (1.29–1.78)	<0.001	1.16 (0.93–1.43)	0.180
Unknown	2.33 (1.92–2.84)	<0.001	1.79 (1.10–2.91)	0.019		1.67 (1.42–1.97)	<0.001	0.99 (0.75–1.30)	0.929
Mo[d] age at pregnancy, year									
20–29	1 (reference)	NA	1 (reference)	NA		1 (reference)	NA	1 (reference)	NA
<20	2.20 (1.51–3.20)	<0.001	1.80 (1.19–2.74)	0.006		2.35 (1.32–4.19)	0.004	1.61 (0.88–2.97)	0.125
30–34	1.02 (0.87–1.19)	0.839	0.97 (0.81–1.16)	0.719		0.94 (0.87–1.01)	0.095	1.04 (0.95–1.14)	0.409
35–39	1.69 (1.29–2.21)	<0.001	1.23 (0.88–1.73)	0.222		1.29 (1.13–1.47)	<0.001	1.20 (1.02–1.42)	0.029
>40	0.77 (0.31–1.92)	0.571	0.37 (0.14–0.99)	0.049		1.80 (1.38–2.36)	<0.001	1.19 (0.87–1.67)	0.254
Unknown	2.41 (2.01–2.89)	<0.001	1.07 (0.67–1.73)	0.767		2.33 (2.01–2.70)	<0.001	1.74 (1.35–2.24)	<0.001

(Continued)

Table 3. (Continued)

	Discovery sample (N = 10,245)					Replication sample (N = 29,773)			
	Unadjusted		Adjusted			Unadjusted		Adjusted	
	OR (95% CI)	p value	aOR (95% CI)	p value		OR (95% CI)	p value	aOR (95% CI)	p value
Characteristics of parents									
Parental marriage status									
Married/cohabitation	1 (reference)	NA	1 (reference)	NA		1 (reference)	NA	1 (reference)	NA
Unmarried	1.26 (0.92–1.74)	0.153	1.19 (0.86–1.65)	0.295		1.18 (1.04–1.34)	0.012	1.10 (0.97–1.26)	0.151
Separation/divorce/widowed	2.59 (2.13–3.16)	<0.001	1.90 (1.53–2.34)	<0.001		2.36 (2.08–2.68)	<0.001	1.59 (1.38–1.83)	<0.001
Unknown	1.72 (1.37–2.18)	<0.001	1.12 (0.85–1.47)	0.421		1.28 (1.11–1.48)	0.001	1.04 (0.88–1.23)	0.632
Fa education level, year									
12	1 (reference)	NA	1 (reference)	NA		1 (reference)	NA	1 (reference)	NA
<12	2.37 (1.72–3.25)	<0.001	1.39 (0.96–2.04)	0.089		2.79 (2.34–3.34)	<0.001	1.77 (1.44–2.19)	<0.001
>12	0.76 (0.66–0.87)	<0.001	0.85 (0.72–1.00)	0.062		0.65 (0.61–0.70)	<0.001	0.78 (0.71–0.85)	<0.001
Unknown	1.78 (1.46–2.17)	<0.001	0.82 (0.49–1.37)	0.450		1.22 (1.02–1.45)	0.028	1.05 (0.79–1.38)	0.759
Mo education level, year									
12	1 (reference)	NA	1 (reference)	NA		1 (reference)	NA	1 (reference)	NA
<12	2.50 (1.81–3.46)	<0.001	1.67 (1.13–2.46)	0.010		2.61 (2.18–3.12)	<0.001	1.40 (1.13–1.73)	0.002
>12	0.82 (0.72–0.95)	0.006	0.98 (0.83–1.15)	0.784		0.70 (0.65–0.76)	<0.001	0.89 (0.82–0.98)	0.016
Unknown	1.98 (1.64–2.39)	<0.001	1.55 (0.94–2.55)	0.084		1.58 (1.35–1.86)	<0.001	1.03 (0.79–1.33)	0.844
Family psychiatric history[e]									
No	1 (reference)	NA	1 (reference)	NA		1 (reference)	NA	1 (reference)	NA
Yes	1.44 (1.14–1.81)	0.002	1.53 (1.20–1.94)	0.001		1.95 (1.72–2.22)	<0.001	1.69 (1.48–1.93)	<0.001
Mo drinking at pregnancy									
No	1 (reference)	NA	1 (reference)	NA		1 (reference)	NA	1 (reference)	NA
Yes	1.17 (0.82–1.67)	0.387	1.02 (0.70–1.48)	0.913		1.75 (1.58–1.94)	<0.001	1.55 (1.40–1.72)	<0.001
No response	0.93 (0.81–1.06)	0.264	0.87 (0.65–1.17)	0.370		0.90 (0.82–1.00)	0.049	0.83 (0.75–0.93)	0.001
Mo smoking pregnancy									
No	1 (reference)	NA	1 (reference)	NA	Exposure time	1 (reference)	NA	1 (reference)	NA
Yes	2.46 (0.98–6.15)	0.055	1.61 (0.62–4.14)	0.327	Never	3.80 (2.06–6.99)	<0.001	2.00 (1.07–3.76)	0.031
No response	0.93 (0.82–1.06)	0.283	0.94 (0.70–1.27)	0.694	PCP + PP[f]	3.54 (2.23–5.60)	<0.001	2.74 (1.71–4.40)	<0.001
					PCP only[g]	3.04 (2.04–4.54)	<0.001	1.92 (1.27–2.92)	0.002
					UK timing	1.77 (1.57–1.99)	<0.001	1.30 (1.14–1.49)	<0.001
					No response				

OR: odds ratio; CI: confidence interval; PCP: pre-conception period; DSM-5: *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.).

[a]Proportional odds assumption upheld.

[b]Adjusted for children's age, sex, parents' age, education level and marital status, family history of psychiatric disorder, and maternal smoking and drinking during pregnancy.

[c]Father.

[d]Mother.

[e]PCP only: pre-conception period only.

[f]PCP + PP: PCP + pregnancy period.

[g]Family history of psychiatric disorder, which included father, mother, and siblings with NDD, schizophrenia, depressive disorder, bipolar disorder, anxiety disorder, substance use and addictive disorder, neurocognitive disorders, trauma-related disorder, and other neuropsychiatric disorder by DSM-5.

findings suggest three possible mechanisms: (1) paternal smoking is a marker for unmeasured inherited genetic risk for ASD; (2) *de novo* mutations generated by prenatal paternal smoking lead to germline disruptions which contribute to development of ASD; and (3) direct toxic effects via maternal exposure to secondhand smoke during pregnancy may underlie ASD etiology.

To examine the first mechanism, family and paternal psychiatric histories (as a marker for genetic risks for ASD) (Robinson et al., 2014) were compared, based on paternal smoking status in both DS and RS (Supplementary Table 1). Family and paternal histories of psychiatric disorders were more common for DS smoker fathers: 7.08% of smoking fathers versus 4.49% of non-smoking fathers had family psychiatric histories ($p < .001$), and 0.59% of smoking fathers versus 0.30% of non-smoking fathers had paternal psychiatric histories ($p < .001$). In the RS, there were no differences in family psychiatric histories (5.24% of fathers who smoked in PCP + PP; 4.77% for PCP only smokers; and 4.80% for non-smoking fathers, $p = 0.127$). However, there were differences noted in the fathers' personal histories of psychiatric disorder: 1.84% of PCP + PP smoker fathers; 1.53% of PCP-only smoker fathers; and 1.19% of non-smoking fathers ($p = 0.011$). To adjust for unmeasured inherited genetic risk for ASD in smoking fathers, family psychiatric history that included both maternal and paternal psychiatric histories was included in our final model. Family history was a significant factor for having a child at high likelihood of having ASD (for DS: aORs = 1.52 [95% CI: 1.20–1.93], $p = 0.001$); for RS aOR = 1.68 [95% CI: 1.47–1.92], $p < .001$. Prenatal paternal smoking remained as a risk factor, independent of parental psychiatric histories.

Paternal exposure to chemical substances is known to affect spermatogenesis (Fabia & Thuy, 1974) in humans and increase mutations in sperm in the mouse epididymis (Nixon et al., 2015), due to the genesis of *de novo* mutations in the sperm. Tobacco contains more than 7000 chemicals, many of which have been identified as systemic mutagens in humans (DeMarini, 2004). Cigarette smoking affects the genomic components of sperm and contributes to developmental defects in offspring (Esakky & Moley, 2016). In rodent studies, cigarette smoking increases the variability in copy number at a hypermutable genetic locus, potentially through inducing mutations in sperm DNA which are passed on to offspring; these permanent, irreversible changes in the genetic composition of the offspring persist in subsequent generations (Yauk et al., 2007). From human studies, male smokers frequently demonstrate several anomalies in spermatogenesis, including increased levels of oxidative DNA damage (Fraga et al., 1996; Shen et al., 1997), sperm DNA strand breaks (Potts et al., 1999), DNA adducts (Horak et al., 2003), chromosomal abnormalities (Robbins et al., 1997; Rubes et al., 1998), and decreased viability and fertility (Kunzle et al., 2003).

For smoking-induced *de novo* mutations to occur in the sperm and increase risk for offspring with ASD, it appears most likely that paternal smoking exposure occurs prior to conception; from the present study this includes the PCP only and/or the PCP + PP groups. In the RS, this prediction was partially supported by evidence for increased risks of having offspring at high likelihood of having ASD in the PCP + PP group. The PCP only group did not have significant associations ($p = 0.537$); indeed, there seemed to be a mild protective effect (aOR = 0.95 with 95% CI: 0.81–1.12), albeit statistically not significant; this unexpected finding in the PCP only group may be an artifact due to the relatively small sample size (7% of the RS sample). Dose response in smoking exposure is also a possible explanation for increasing ASD likelihood. At the time of conception, smoking fathers who continue to smoke during pregnancy (PCP + PP) had higher exposure to smoking (7.71 pack-years), compared to 6.65 pack-years for the smoking fathers who stopped smoking during pregnancy (PCP only) (Supplementary Table 2, $p < 0.001$). This suggests that PCP + PP exposure is a marker not only for exposure timing, but also for the exposure dose. Ultimately, sequencing DNA from nuclear families will be necessary to demonstrate the presence of *de novo* mechanisms in ASD risk.

Alternatively, significant findings in the PCP + PP, but not in PCP only, may indicate that the direct toxic effect via maternal exposure to secondhand smoke during pregnancy might play a role in increasing offspring ASD risk. While the research findings are inconclusive (Rosen et al., 2015), there is evidence to suggest a role for maternal smoking during pregnancy and the development of other NDDs such as attention deficit hyperactivity disorder, conduct/antisocial disorders, alcohol abuse, depressive disorder, anxiety, aggression, and cognitive impairment in their offspring (Carter et al., 2008; Cornelius & Day, 2009; Hsieh et al., 2010; Perera et al., 2007; Wakschlag et al., 1997). Future studies designed to examine the independent impact of timing (pre-conception, pregnancy, and postnatal periods) and dose of maternal and paternal, direct and secondhand smoke exposures can help further understand the role of smoking, and possibly other toxins, in the underlying mechanisms for offspring ASD risk.

Our study has several strengths. First, our two-step, internal replication provides greater confidence in the observed associations between prenatal paternal smoking and having offspring at high likelihood of having ASD. Second, study subjects were drawn from epidemiologically ascertained, representative samples with greater than 70% response rates. Third, study subjects were assessed using a dimensional instrument, ASSQ, with three incremental likelihood categories. Such methods are likely to reduce phenotype heterogeneity (Abrahams & Geschwind, 2008; Losh et al., 2008) and sampling bias including missed ASD cases (Berkson, 2014). The observed association between prenatal paternal smoking and having

offspring at high likelihood for ASD persisted even after the adjusting for potential confounders, such as maternal smoking and drinking, and a family history of psychiatric disorders (a proxy for genetic risk for ASD).

Limitations of our study include the retrospective collection of prenatal paternal smoking data, ASD outcome measurement by questionnaire only, missing data from non-responders, and the potential impact of unmeasured genetic risks. Especially, missing rates of maternal smoking are high since mothers, the main primary caregivers, were reluctant to reply to the smoking status for themselves. In this sense, maternal smoking was at higher odds ratio for having children with likelihood of having ASD than paternal smoking. Prenatal exposure data for parental smoking were collected by questionnaire, retrospectively, and the majority of questionnaires were completed by the mothers. While the reliability and validity of the short-term and long-term recall of perinatal events, as well as recall of spouse smoking status are well-accepted in epidemiologic research (Buka et al., 2004; Mejia et al., 2017; Sou et al., 2006; Yawn et al., 1998), there is still potential for misclassification of paternal smoking. Such misclassification is likely to be random in a cohort study design, which might have attenuated observed associations (Hennekens & Mayre, 1987). ASD phenotypes were measured with a 27-item screening questionnaire, not by direct clinical examination. While our prior Korean prevalence study demonstrated that the ASSQ is an excellent screening instrument with good positive predictive values for the best estimate diagnoses of ASD (Kim et al., 2014), in our samples, the diagnoses of children at high and intermediate likelihood of having ASD were not clinically validated. Therefore, children without ASD could have been included in the high and/or intermediate ASD likelihood groups; this might diminish the magnitude of the observed associations. While participation rates in both the DS and RS are >70% at every stage, we do not have data on non-participants. It is possible that unknown characteristics in the non-respondents could have affected the observed relationships between prenatal paternal smoking and having increased offspring ASD likelihood. Finally, we attempted to account for genetic risk by controlling for family psychiatric histories. While psychiatric history is correlated with polygenetic risks of NDDs, including ASD (Robinson et al., 2016), we cannot rule out the potential impact of unmeasured genetic risks on the observed associations.

Conclusion

Using two independent, large community samples of children and their families, our study demonstrates that prenatal paternal smoking increases the risk for having a child at high likelihood for ASD. While independent replication is warranted, our findings add further support to the importance of education and intervention to reduce smoking. This is especially crucial for individuals planning to have children as the elimination of paternal smoking can reduce the risk of having a child at high likelihood for ASD by as much as 11%–14%.

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Supplemental material

Supplemental material for this article is available online.

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