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Prospective study of cigarette smoking and fecundability

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STUDY QUESTION: To what extent is cigarette smoking associated with reduced fecundability?

SUMMARY ANSWER: Current female smokers, particularly those who had smoked ≥10 cigarettes/day for ≥10 years, had lower fecundability than never smokers, but current male smoking and passive smoking in either partner showed little association with reduced fecundability.

WHAT IS KNOWN ALREADY: Female smoking has been identified as a cause of infertility, yet there has been limited characterization of the dose and duration at which an effect is observed. Results for male active smoking and passive smoking in both partners are less consistent.

STUDY DESIGN, SIZE, DURATION: We analyzed data from a North American internet-based preconception cohort study of 5473 female and 1411 male pregnancy planners, enrolled from 2013 to 2018. Participants had been attempting conception for ≤6 menstrual cycles at study entry.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We collected information on active and passive smoking history on baseline questionnaires. Pregnancy was reported on female bi-monthly follow-up questionnaires. We calculated fecundability ratios (FR) and 95% CI using proportional probabilities regression models, adjusted for demographic, behavioral, medical, reproductive and dietary variables.

MAIN RESULTS AND THE ROLE OF CHANCE: Female current regular smoking (FR = 0.90, 95% CI: 0.77, 1.07), current occasional smoking (FR = 0.88, 95% CI: 0.73, 1.06), and former smoking (FR = 0.89, 95% CI: 0.81, 0.98) were associated with small reductions in fecundability. Results were stronger among women who smoked ≥10 cigarettes/day for ≥10 years (FR = 0.77, 95% CI: 0.53, 1.10). Male current regular and former smoking, and current passive smoking in either partner were not meaningfully associated with reduced fecundability. *In utero* exposure to ≥10 cigarettes/day among females was associated with reduced fecundability (FR = 0.75, 95% CI: 0.52, 1.06).

LIMITATIONS, REASONS FOR CAUTION: Numbers of cigarette smokers, particularly within categories of intensity and duration, were small. Under-reporting of smoking may have resulted in non-differential misclassification, and smokers were more likely to be lost to follow-up.

WIDER IMPLICATIONS OF THE FINDINGS: Given the consistency of our findings with results from previous studies and our observation of a dose–response relation in intensity of smoking, this study supports an association between female cigarette smoking and lower fecundability.

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Key words: cigarettes / fecundability / fertility / preconception cohort / smoking

Introduction

Despite evidence implicating tobacco exposure in adverse pregnancy outcomes (U.S. Department of Health and Human Services, 2004, 2014), cigarette smoking remains common during the preconception period. In the 2010 US Pregnancy Risk Assessment Monitoring System survey, 23.2% of women smoked during the 3 months before pregnancy (Tong *et al.*, 2013). Smoking is a modifiable target for preconception guidance (American College of Obstetrics & Gynecology, 2005), and a goal of the Healthy People 2020 initiative is to decrease

the prevalence of smoking before pregnancy (Office of Disease Prevention and Health Promotion, 2017).

Female active cigarette smoking was identified as a cause of infertility in the 2004 Surgeon General's Report on the Health Consequences of Smoking (U.S. Department of Health and Human Services, 2004), citing evidence primarily from studies of infertile couples. Preconception cohort studies generally support this conclusion (Howe *et al.*, 1985; de Mouzon *et al.*, 1988; Weinberg *et al.*, 1989; Florack *et al.*, 1994; Jensen *et al.*, 1998; Radin *et al.*, 2014; Sapra *et al.*, 2016), although there are inconsistencies in the dose, duration, and recency of smoking at which reduced fecundability is observed. When examining intensity of smoking, studies have found adverse associations at amounts >5 (Radin *et al.*, 2014), 10 (Florack *et al.*, 1994) or 15 cigarettes/day (Howe *et al.*, 1985), whereas others have found associations at all intensities (de Mouzon *et al.*, 1988; Jensen *et al.*, 1998). Smoking may also affect fertility only after longer durations (Radin *et al.*, 2014). Some studies of former smoking and fecundability have found little association (Jensen *et al.*, 1998; Howe *et al.*, 2016), or an association only among former smokers with the highest cumulative exposure (Radin *et al.*, 2014).

Male active cigarette smoking has not been identified as a cause of infertility (U.S. Department of Health and Human Services, 2004, 2014). Although smoking has been associated with reduced sperm quality (Sharma *et al.*, 2016), and two preconception cohort studies have found strong associations between male smoking and reduced fecundability (Jensen *et al.*, 1998; Sapra *et al.*, 2016), others have found little association (de Mouzon *et al.*, 1988; Florack *et al.*, 1994; Radin *et al.*, 2014). Most studies examined male partner current smoking only and some relied on female report of male smoking.

The literature on passive smoke exposure is also mixed. The 2006 Surgeon General's Report on the Health Consequences of Involuntary Exposure to Tobacco Smoke reported inadequate evidence to infer causality in females, and no data on males (U.S. Department of Health and Human Services, 2006). Passive smoke exposure was associated with reduced semen quality and transport in rodents and rhesus monkeys (Hung *et al.*, 2007; La Maestra *et al.*, 2014). Current female passive smoke exposure has been associated with poorer IVF outcomes (Neal *et al.*, 2005; Meeker et al., 2007a; Benedict *et al.*, 2011). Some studies of female early life exposure to cigarette smoking have found decrements in fertility (Weinberg *et al.*, 1989; Jensen *et al.*, 1998, 2006), while others have found little association (Baird *and* Wilcox, 1986; Joffe and Barnes, 2000; Ye *et al.*, 2010; Radin *et al.*, 2014).

We used data from a preconception cohort study of North American pregnancy planners to examine the influence of female and male active and passive smoking on fecundability.

Materials and Methods

Study design and population

Pregnancy Study Online (PRESTO) is an internet-based preconception cohort study of North American pregnancy planners (Wise *et al.*, 2015). Eligible females are 21–45 years old, residing in the USA or Canada, and not using contraception or fertility treatments. Eligible males are ≥21 years old with an enrolled female partner. Participants complete a baseline questionnaire on demographic, behavioral, medical, and reproductive characteristics, and a food frequency questionnaire (FFQ) (Subar *et al.*, 2001). Females additionally complete follow-up questionnaires every 8 weeks for up to 12 months to ascertain pregnancy and update exposure information.

Ethical approval

All participants provided informed consent via an online form. The institutional review board at Boston Medical Center approved the study protocol.

Exclusions

From June 2013 through February 2018, 6945 women completed the baseline questionnaire. We excluded women with implausible last menstrual period (LMP) dates (n = 101) and no prospective LMP dates over follow-up (n = 27). We also excluded 1344 women who had been trying to conceive for more than six menstrual cycles at enrollment. Of the 5473 females remaining, 54.1% invited their male partners to participate, and 1411 (47.7%) males enrolled.

Assessment of smoking

We collected smoking information for females and males on the baseline questionnaires, and for females on the follow-up questionnaires. Participants reported whether they currently smoked cigarettes. Response choices were 'yes, on a regular basis (at least one cigarette per day)', 'yes, occasionally (not every day)' and 'no'. Current regular smokers reported how many cigarettes/day they smoked (1–4, 5–9, 10–14, 15–19, 20–29, ≥30), the age they began smoking, and the duration of any periods of cessation. Non-smokers and current occasional smokers reported whether they had ever smoked regularly and how many cigarettes/day they smoked, for how many years they smoked, and their age when they stopped smoking. We asked females if their male partner currently smoked and, if so, how many cigarettes/day he smoked. On the follow-up questionnaires, females reported whether they had smoked cigarettes during the previous 4 weeks and how many cigarettes/day they smoked.

On the baseline questionnaires, participants reported whether they were in the same room as someone who was smoking for ≥1 h/day for ≥12 consecutive months at ages: 0–10, 11–20, 21–30, 31–40 years and currently. Females reported whether their mothers smoked while pregnant with them and the number of cigarettes/day their mothers smoked (<10 or ≥10). On follow-up questionnaires, women reported their current passive smoke exposure.

Assessment of fecundability

On the follow-up questionnaires, females reported whether they were currently pregnant and whether they had any intervening pregnancy losses since their last questionnaire. We sought pregnancy information on participants lost to follow-up by contacting them via telephone, searching for baby announcements and registries online, and linking with birth registries in selected states.

On the baseline questionnaire, females reported the number of cycles they had been attempting pregnancy, their LMP date, whether their menstrual cycles were regular, and, if so, their usual cycle length. For women who reported irregular cycles, we estimated usual cycle length using follow-up LMP data. We calculated study time as follows: (menstrual cycles of attempt time at baseline)+[(LMP date from most recent follow-up questionnaire—date of baseline questionnaire)/cycle length]+1.

Assessment of covariates

On female and male baseline questionnaires, we ascertained information on demographics, behaviors and medical history. On the female baseline questionnaire, we collected information on annual household income, intercourse frequency, doing something to improve chances of conception (e.g. timing intercourse) and contraceptive history. We calculated the Healthy Eating Index (HEI) score from the FFQ (Guenther *et al.*, 2014).

Statistical analysis

Women contributed observed menstrual cycles of attempt time from study entry until pregnancy, initiation of fertility treatment, cessation of pregnancy attempt, loss to follow-up, or 12 cycles, whichever came first. We used the Anderson-Gill data structure with one observation per cycle to account for left truncation (Howards *et al.*, 2007; Schisterman *et al.*, 2013) and to update exposure and covariates over time (Therneau and Grambsch, 2000). We fitted proportional probabilities regression models (Weinberg *et al.*, 1989) to estimate the fecundability ratio (FR), the average per-cycle probability of conception in exposed compared with unexposed participants, and 95% CI.

We compared fecundability among current regular, current occasional, and former smokers with that of never smokers. Among current smokers, we examined fecundability within categories of intensity (<5, 5–9, ≥10 cigarettes/day) and duration (<10, ≥10 years). Rather than examining pack-years of smoking, a variable that combines information on intensity and duration, we examined joint categories of intensity and duration. Among former smokers, we examined fecundability within categories of intensity (<5, 5–9, ≥10 cigarettes/day) and duration (<10, ≥10 years), as well as time since cessation (<1, 1, 2–4, ≥5 years). Because of the strong association between smoking duration and age, we restricted analyses of duration and fecundability to individuals aged 25–34 years.

Among never smokers, we examined the relation of childhood, adolescent, adulthood and current passive smoke exposure, as well as *in utero* smoke exposure (among female participants). We examined current passive smoke exposure and current partner smoking jointly, to determine whether observed associations were due to passive smoke exposure or partner active smoking.

We identified confounders *a priori* based on a literature review and construction of a directed acyclic graph (Supplementary Fig. S1). Final models were adjusted for age (<25, 25–29, 30–34, ≥35 years), race/ethnicity (white non-Hispanic versus Hispanic or non-white), education (<college degree, college degree, graduate school), annual household income (<US $50 000, $50 000–$99 999, ≥$100 000), BMI (<25, 25–29, 30–34, ≥35 kg/m^2), sugar-sweetened beverage intake (0, 1, 2–6, ≥7 drinks/week), alcohol intake (0, 1–6, 7–13, ≥14 drinks/week; males only), HEI score (<60, 60–69, 70–79, ≥80; females only), daily multivitamin or folic acid intake (yes, no), sleep duration (<7, 7–8, ≥9 h/night), perceived stress scale (PSS) score (<15, 15–19, 20–24, ≥25), major depression inventory (MDI) score (<20, 20–24, 25–29, ≥30), parity (0, ≥1), intercourse frequency (<1, 1–3, ≥4 times/week), and doing something to improve chances of conception (yes, no). To evaluate reverse causation bias, we stratified models by attempt time at study entry (<3 versus 3–6 cycles). We examined the extent to which our associations varied by age (female age ≥30 versus <30 years).

We conducted a probabilistic bias analysis to quantify the effect of under-reporting of smoking on our results (Lash *et al.*, 2009). Because smoking history was ascertained before subfertility, we assumed that exposure misclassification was non-differential. We defined bias parameters across six baseline smoking categories: never, former, current occasional, and current regular 1–4, 5–9 and ≥10 cigarettes/day. We assumed that women would under-report smoking by one category. We defined trapezoidal probability distributions for this under-reporting, with a range of 0–10% and lower and upper modes of 2.5 and 7.5%. We assumed 100% specificity, as women are unlikely to over-report smoking. We sampled from this distribution 1000 times, separately by pregnancy (assuming a correlation between values for pregnant and non-pregnant women of 0.8), to calculate a corrected data set and estimate adjusted FRs for each iteration.

Female smoking history was strongly related to attrition (proportions among current regular, current occasional, former, and never smokers were 46.4, 34.2, 26.6 and 23.0%, respectively). We used inverse probability of continuation weights to account for differential attrition (Hernan *et al.*, 2000; Howe *et al.*, 2016), as has been described previously in this cohort (Wesselink *et al.*, 2018). Briefly, we calculated stabilized weights, which are inversely proportional to the probability of remaining in the study at each cycle, to reweight the population so that it is balanced for factors related to attrition.

We used a Markov chain Monte Carlo method to impute missing outcome, exposure, and covariate data. We generated five imputation data sets and combined point estimates and SEs from each data set. For the 652 women without follow-up data, we assigned them one cycle of follow-up and imputed their pregnancy status. Each of the variables on smoking history were missing for <1% of participants, with the exception of passive smoke exposure *in utero* (10.7%), from age 0 to 10 years (6.9%), and from age 11 to 20 years (5.5%). Covariate missing-ness ranged from 0 (age) to 34.8% (male PSS score).

Results

Over 53 months of follow-up, 5473 female participants contributed 22 330 menstrual cycles. After accounting for censoring, 69.8% of women conceived over follow-up. Out of 3131 pregnancies, 2515 were self-reported on a questionnaire, 161 were imputed among women with no follow-up, and 455 were identified via other methods. Overall, 6.9% of women initiated fertility treatment, 0.6% stopped trying to conceive, 15.8% were censored at 12 cycles, 4.5% were still participating in the study and 14.9% were lost to follow-up.

At baseline, 26.0% of women and 29.7% of men were ever smokers. Current smoking (regular or occasional) was more common among men (12.1%) than women (10.7%). 28% of female smokers and 35.9% of male smokers consumed ≥10 cigarettes/day, and the average duration among current regular smokers was 11.4 years for females and 14.3 years for males. Almost 9% of females and 11.4% of males reported current passive smoke exposure. Passive smoke exposure was more common in childhood (31.5% for females and 31.7% for males) than in adolescence (26.2 and 27.1%, respectively) or adulthood (21.9 and 26.7%, respectively); 13.5% of females reported *in utero* smoke exposure.

Only 1.9% of women reported a change in smoking over follow-up. Among 4053 never smokers, 0.2% initiated smoking. Among 834 former smokers, 3.0% became occasional smokers and 0.5% became regular smokers. 14.2% of occasional smokers quit smoking, whereas 7.3% became regular smokers. Only 4.1% of current regular smokers decreased their cigarette consumption and 2.4% of regular smokers increased their cigarette consumption.

Current regular smoking was strongly associated with partner smoking and current passive smoke exposure (Table I). Female current regular smokers had longer attempt times at study entry; higher BMI; higher caffeine, alcohol and sugar-sweetened beverage intakes; higher MDI scores; and were more likely to smoke marijuana and have short sleep durations; have a history of unplanned pregnancy, sexually transmitted infection (STI) or infertility; be gravid and parous; have irregular cycles; have frequent intercourse; and reside in Canada or the Midwestern or Southern USA. Smokers reported lower education levels and income, lower HEI scores, less physical activity, and were less likely to use multivitamin/folate supplements or do something to improve chances of

Table I Baseline characteristics of female and male pregnancy planners by active smoking status.

Characteristic[a]	Female smoking history ($n = 5473$)				Male smoking history ($n = 1411$)			
	Never, $n = 4053$	Former, $n = 834$	Current occasional, $n = 218$	Current regular, $n = 368$	Never, $n = 992$	Former, $n = 249$	Current occasional, $n = 81$	Current regular, $n = 89$
Age (years), mean	29.8	31.2	29.9	29.0	31.3	33.0	32.2	32.5
Cycles of attempt time at study entry, mean	2.0	2.2	2.4	2.9	1.8	2.1	2.1	2.5
Partner is current smoker, %	5.7	10.5	31.0	63.6	1.9	1.1	4.3	31.6
Current passive smoke exposure, %	4.9	7.2	15.5	48.1	8.3	11.0	12.8	46.1
Smoking duration (years), mean	0.0	6.0	5.3	12.2	0.0	7.2	4.7	14.0
White, non-Hispanic, %	83.4	85.2	79.3	82.8	85.5	86.0	87.9	87.7
<College degree, %	19.4	38.7	47.4	63.2	24.5	38.8	34.0	79.2
Annual household income <US$50 000, %	16.7	21.4	25.4	50.0	14.4	20.7	21.0	41.7
BMI (kg/m^2), mean	27.1	29.2	29.0	29.5	27.4	28.8	30.5	27.8
Physical activity (MET-h/wk), mean	35.5	33.1	36.2	28.8	34.4	32.3	28.2	23.5
Current alcohol consumption (drinks/wk), mean	3.0	4.1	5.9	3.7	4.9	7.6	10.2	11.7
Current caffeine intake (mg/day), mean	104.8	143.6	153.8	218.1	154.6	202.9	227.3	274.0
Current marijuana use, %	8.2	22.8	24.5	27.1	10.3	24.0	26.4	44.8
Sugar-sweetened beverage intake (drinks/wk), mean	2.4	2.7	4.6	7.6	4.0	4.3	4.9	14.1
Healthy Eating Index score, mean[b]	66.8	65.0	64.5	55.5	62.7	62.6	61.5	49.9
Daily multivitamin or folic acid intake, %	81.8	79.8	78.4	53.4	35.2	35.6	32.7	22.0
Sleep duration <7 h/night, %	21.1	26.9	28.0	38.8	31.8	37.4	44.5	48.2
Unemployed, %	2.9	6.2	7.0	10.3	3.0	4.5	3.2	5.8
Work ≥50 h/wk, %[c]	12.6	9.4	12.4	10.7	30.5	27.2	18.5	29.3
PSS-10 score, mean	15.7	16.8	16.7	17.6	13.9	16.1	15.7	16.9
MDI score, mean	9.7	11.9	13.3	14.9	8.8	9.9	10.5	12.1
Gravid, %	44.0	57.8	58.7	72.7	41.4	45.0	38.3	60.6
Parous, %	26.9	35.1	27.8	49.9	–	–	–	–
History of unplanned pregnancy, %	24.0	42.7	48.4	63.5	–	–	–	–
History of sexually transmitted infections, %	11.0	19.1	20.4	20.7	5.0	4.7	6.2	1.5
History of infertility, %	6.7	9.9	10.7	22.6	7.3	10.7	6.3	20.4
Irregular cycles, %	15.9	18.3	19.0	25.1	–	–	–	–
Menstrual cycle length (days), mean	30.0	29.7	29.8	29.9	–	–	–	–
Intercourse frequency <1 time/week, %	21.3	20.5	19.5	16.8	21.3	18.7	16.1	16.9
Intercourse frequency ≥4 times/week, %	14.8	18.6	23.1	26.3	15.4	17.3	14.5	26.9
Doing something to improve chances, %	75.5	76.4	74.8	68.3	76.6	78.2	77.2	75.2
Hormonal last method of contraception, %	39.3	38.1	40.6	38.2	34.9	34.7	47.4	37.6
Geographic region of residence, %								
US Northeast	27.2	24.2	20.1	17.2	31.4	25.0	26.0	18.5
US South	23.7	24.4	30.6	29.5	22.1	21.9	32.8	19.8
US Midwest	17.8	17.7	19.4	24.8	17.3	22.4	16.1	23.9
US West	15.7	17.4	13.2	9.7	17.0	16.4	12.8	13.3
Canada	15.6	16.2	16.6	18.9	12.3	14.0	12.3	24.6
Occupational chemical exposures, %	19.4	22.4	26.9	32.4	24.8	33.0	28.4	49.8

MDI=major depressive inventory; MET=metabolic equivalent; PSS=perceived stress scale.
[a]All characteristics except for age are standardized to the cohort age at baseline.
[b]Restricted to couples who completed the dietary questionnaire.
[c]Among employed individuals.

conception. Associations between smoking and covariates were similar among males, although male smokers were more likely than non-smokers to be non-Hispanic white.

Former smokers had slightly lower fecundability than never smokers (adjusted FR = 0.89, 95% CI: 0.81, 0.98; Table II). The association was strongest among women who had smoked with the greatest intensity

Table II Association between female active smoking history at baseline and fecundability.

	No. of cycles	No. of Pregnancies	Unadjusted FR (95% CI)	Adjusted[a,c] FR (95% CI)	Adjusted[b,c] FR (95% CI)
Never smokers	16 431	2431	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Former smokers	3575	447	0.87 (0.79, 0.96)	0.89 (0.81, 0.98)	0.89 (0.81, 0.98)
Current occasional smokers	921	100	0.78 (0.64, 0.94)	0.84 (0.70, 1.02)	0.88 (0.73, 1.06)
Current regular smokers	1403	153	0.81 (0.68, 0.95)	0.87 (0.74, 1.02)	0.90 (0.77, 1.07)
Former smokers					
Time since regular smoking (years)					
<1	274	36	0.89 (0.65, 1.22)	0.96 (0.72, 1.28)	0.99 (0.74, 1.32)
1	372	51	0.96 (0.73, 1.25)	0.93 (0.72, 1.21)	0.86 (0.67, 1.12)
2–4	1094	135	0.84 (0.72, 0.99)	0.86 (0.73, 1.00)	0.90 (0.77, 1.05)
≥5	1835	225	0.86 (0.76, 0.98)	0.90 (0.79, 1.03)	0.88 (0.77, 1.01)
Intensity (cigarettes/day)					
<5	1275	168	0.92 (0.79, 1.06)	0.93 (0.81, 1.08)	0.92 (0.79, 1.06)
5–9	963	123	0.90 (0.75, 1.06)	0.89 (0.75, 1.06)	0.89 (0.75, 1.06)
≥10	1337	156	0.81 (0.69, 0.94)	0.86 (0.74, 1.00)	0.87 (0.75, 1.01)
Duration (years)[d]					
<10	1726	236	0.91 (0.80, 1.03)	0.92 (0.81, 1.04)	0.91 (0.80, 1.03)
≥10	577	78	0.82 (0.65, 1.02)	0.83 (0.66, 1.04)	0.86 (0.69, 1.08)
Intensity and duration[d]					
<10 cigarettes/day, <10 years	1270	175	0.92 (0.80, 1.07)	0.93 (0.80, 1.07)	0.90 (0.78, 1.04)
≥10 cigarettes/day, <10 years	456	61	0.87 (0.68, 1.11)	0.89 (0.70, 1.12)	0.95 (0.75, 1.19)
<10 cigarettes/day, ≥10 years	241	40	0.98 (0.72, 1.34)	1.02 (0.75, 1.39)	1.06 (0.78, 1.44)
≥10 cigarettes/day, ≥10 years	336	38	0.70 (0.51, 0.95)	0.69 (0.51, 0.94)	0.72 (0.53, 0.98)
Current regular smokers					
Intensity (cigarettes/day)					
<5	261	35	0.93 (0.68, 1.27)	1.04 (0.78, 1.40)	1.10 (0.82, 1.47)
5–9	488	53	0.75 (0.57, 1.00)	0.85 (0.64, 1.12)	0.84 (0.63, 1.10)
≥10	654	65	0.79 (0.62, 1.01)	0.81 (0.63, 1.04)	0.87 (0.68, 1.12)
Duration (years)[d]					
<10	230	30	0.93 (0.65, 1.32)	1.08 (0.77, 1.52)	1.04 (0.74, 1.45)
≥10	674	69	0.74 (0.58, 0.94)	0.76 (0.60, 0.97)	0.81 (0.64, 1.03)
Intensity and duration[d]					
<10 cigarettes/day, <10 years	157	23	0.98 (0.59, 0.92)	1.11 (0.74, 1.64)	1.12 (0.78, 1.61)
≥10 cigarettes/day, <10 years	73	7	0.77 (0.35, 1.73)	0.96 (0.45, 2.06)	0.79 (0.38, 1.66)
<10 cigarettes/day, ≥10 years	295	38	0.82 (0.58, 1.17)	0.91 (0.65, 1.28)	0.91 (0.65, 1.26)
≥10 cigarettes/day, ≥10 years	379	31	0.66 (0.47, 0.94)	0.64 (0.45, 0.92)	0.77 (0.53, 1.10)

[a]Adjusted for age, race/ethnicity, education and annual household income.
[b]Additionally adjusted for BMI, sugar-sweetened beverage intake, Healthy Eating Index score, multivitamin or folic acid supplement use, sleep duration, PSS-10 score, MDI score, parity, intercourse frequency and doing something to improve chances of conception.
[c]Adjusted models are also weighted for censoring.
[d]Restricted to women age 25–34 years.
FR = fecundability ratio.

(FR for ≥10 cigarettes/day versus never smokers was 0.87, 95% CI: 0.75, 1.01). The association was similar regardless of smoking duration or time since quitting.

In unadjusted analyses, female current regular smoking was associated with a 19% reduction in fecundability, compared with never smokers (Table II). After adjusting for age, race/ethnicity, education, and income, the association was attenuated to 13%; after adjustment for other covariates associated with a healthy lifestyle (Supplementary Fig. S1), the association was attenuated to 10%. The adjusted FR for women smoking ≥10 cigarettes/day compared with never smokers was 0.87 (95% CI: 0.68, 1.12). Results were slightly stronger among women who smoked for ≥10 years (adjusted FR = 0.81, 95% CI: 0.64, 1.03). Women who smoked ≥10 cigarettes/day for ≥10 years had the lowest fecundability (adjusted FR compared with never

Table III Exposure to passive smoking and fecundability among female never smokers.

	No. of cycles	No. of pregnancies	Unadjusted FR (95% CI)	Adjusted[a] FR (95% CI)	Adjusted[b] FR (95% CI)
Current passive smoke exposure					
None	15660	2349	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Any	771	82	0.80 (0.61, 1.05)	0.85 (0.65, 1.12)	0.93 (0.70, 1.25)
Current passive smoke exposure, partner smoking					
None, partner not regular smoker	15035	2271	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Any, partner not regular smoker	415	58	1.01 (0.75, 1.36)	1.05 (0.77, 1.42)	1.12 (0.81, 1.55)
None, partner is regular smoker	625	78	0.88 (0.71, 1.09)	0.96 (0.78, 1.19)	0.98 (0.79, 1.21)
Any, partner is regular smoker	356	24	0.54 (0.35, 0.83)	0.59 (0.38, 0.91)	0.66 (0.42, 1.04)
Lifetime passive smoke exposure					
Age 0–10 years	4608	629	0.99 (0.87, 1.13)	1.02 (0.89, 1.15)	1.03 (0.91, 1.16)
Age 11–20 years	3459	457	0.94 (0.81, 1.08)	0.96 (0.84, 1.11)	0.99 (0.87, 1.14)
Age >20	2143	263	0.94 (0.82, 1.08)	0.99 (0.86, 1.13)	1.00 (0.87, 1.14)
Current	771	82	0.85 (0.64, 1.13)	0.86 (0.65, 1.14)	0.93 (0.69, 1.26)
In utero smoke exposure					
None	13951	2069	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<10 cigs/day	2148	331	1.03 (0.93, 1.15)	1.06 (0.95, 1.19)	1.11 (0.98, 1.25)
≥10 cigs/day	332	31	0.64 (0.45, 0.91)	0.65 (0.46, 0.93)	0.75 (0.52, 1.06)

[a]Adjusted for age, race/ethnicity, education and annual household income. *In utero* smoke exposure models adjusted for age, race/ethnicity, and mother and father's education.
[b]Additionally adjusted for BMI, sugar-sweetened beverage intake, Healthy Eating Index score, multivitamin or folic acid supplement use, sleep duration, PSS-10 score, MDI score, parity, intercourse frequency and doing something to improve chances of conception.

smokers=0.77, 95% CI: 0.53, 1.10). Results for time-varying female active smoking were similar to baseline results.

Inverse associations between female current and former smoking and fecundability were generally stronger among couples attempting to conceive for <3 cycles at study entry (Supplementary Table SI). We found a stronger association between female active smoking and fecundability among women <30 years old (Supplementary Table SII).

The exposure misclassification simulation resulted in 1000 corrected FRs for each category of current smoking (<1, 1–4, 5–9 and ≥10 cigarettes/day) relative to never smokers. The median and 95% simulation intervals were 0.88 (0.82–0.93), 1.12 (0.98–1.30), 0.85 (0.74–1.04) and 0.94 (0.86–1.01), respectively.

The fully adjusted FR for current exposure to passive smoke was 0.93 (95% CI: 0.70, 1.25; Table III). Results for time-varying current passive smoking were similar to baseline results. When jointly examining categories of female passive smoking and partner current active smoking, only those reporting passive smoke exposure whose partners were current smokers had reduced fecundability (FR = 0.66, 95% CI: 0.42, 1.04).

Passive smoking throughout the life course was not meaningfully associated with fecundability. However, never smoking women reporting *in utero* exposure to ≥10 cigarettes/day had lower fecundability than unexposed women (FR = 0.75, 95% CI: 0.52, 1.06).

Male former smoking was associated with improved fecundability compared with never smoking (FR = 1.14, 95% CI: 0.97, 1.35; Table IV). This relation was strongest for men who had quit smoking within 1 year, who had smoked ≥10 cigarettes/day, and who had smoked for ≥10 years (Table IV). The association was weaker among couples who had been attempting conception for <3 cycles (FR = 1.06, 95% CI: 0.87, 1.28). Male current regular smoking showed little association with fecundability (FR = 0.96, 95% CI: 0.70, 1.34; Table IV), but current occasional smoking was associated with slightly reduced fecundability (FR = 0.83, 95% CI: 0.61, 1.13).

There was good agreement between male and female reports of male smoking (94.3% of couples reported identically). Agreement remained high for report of smoking intensity (92.8%), but when restricted to current smokers, agreement was lower (51.2% of couples reported identically; 89.4% reported within one category). We found higher agreement between female and male report when the male partners reported being non-smokers (98.6%) or high intensity smokers (72.1%).

Male current passive smoke exposure was associated with slightly reduced fecundability (FR = 0.87, 95% CI: 0.62, 1.22), particularly among men whose female partners smoked (FR = 0.35, 95% CI: 0.05, 2.63). Passive smoking throughout the life course was not substantially associated with fecundability (Table V).

Discussion

In this preconception cohort study, we found small reductions in fecundability for current female smokers who had smoked with high intensity and duration. Former female smokers had slightly lower fecundability, but neither intensity nor duration of former smoking were clearly related to fecundability. Among men, current smoking was not substantially associated with reduced fecundability. Passive smoking was not meaningfully associated with fecundability in either partner, but women exposed *in utero* to high intensity smoking had lower fecundability than unexposed women.

Table IV Association between male active smoking history at baseline and fecundability.

	No. of cycles	No. of pregnancies	Unadjusted FR (95% CI)	Adjusted[a] FR (95% CI)	Adjusted[b] FR (95% CI)
Never smokers	4180	639	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Former smokers	982	171	1.09 (0.94, 1.28)	1.15 (0.98, 1.34)	1.14 (0.97, 1.35)
Current occasional smokers	413	43	0.74 (0.56, 0.99)	0.77 (0.58, 1.03)	0.83 (0.61, 1.13)
Current regular smokers	396	46	0.85 (0.64, 1.12)	0.96 (0.72, 1.29)	0.96 (0.70, 1.34)
Former smokers					
Time since regular smoking (years)					
<1	64	14	1.26 (0.78, 2.01)	1.50 (0.92, 2.43)	1.41 (0.80, 2.48)
1	103	17	1.01 (0.66, 1.56)	1.02 (0.66, 1.57)	0.99 (0.62, 1.56)
2–4	320	51	1.03 (0.79, 1.35)	1.11 (0.85, 1.45)	1.05 (0.79, 1.38)
≥5	495	89	1.12 (0.92, 1.37)	1.16 (0.95, 1.42)	1.21 (0.98, 1.50)
Intensity (cigarettes/day)					
<5	285	48	1.07 (0.82, 1.39)	1.06 (0.81, 1.38)	1.04 (0.79, 1.36)
5–9	255	40	1.01 (0.75, 1.36)	1.06 (0.79, 1.43)	1.08 (0.79, 1.47)
≥10	442	83	1.14 (0.93, 1.40)	1.25 (1.01, 1.54)	1.23 (0.98, 1.53)
Duration (years)[c]					
<10	429	76	1.05 (0.85, 1.31)	1.07 (0.86, 1.33)	1.11 (0.88, 1.39)
≥10	169	35	1.22 (0.90, 1.65)	1.34 (0.99, 1.82)	1.35 (0.94, 1.92)
Current regular smokers					
Intensity (cigarettes/day)					
<5	34	6	1.21 (0.58, 2.55)	1.34 (0.63, 2.84)	1.12 (0.63, 1.99)
5–9	80	9	0.77 (0.43, 1.39)	0.89 (0.49, 1.62)	0.96 (0.55, 1.67)
≥10	282	31	0.82 (0.58, 1.16)	0.93 (0.65, 1.32)	0.95 (0.69, 1.32)
Duration (years)[c]					
<10	29	2	0.76 (0.22, 2.56)	0.92 (0.27, 3.16)	0.76 (0.21, 2.72)
≥10	204	23	0.73 (0.48, 1.10)	0.83 (0.55, 1.27)	0.82 (0.51, 1.33)

[a]Adjusted for age, race/ethnicity, education and annual household income.
[b]Additionally adjusted for BMI, sugar-sweetened beverage intake, multivitamin or folic acid supplement use, sleep duration, PSS-10 score, MDI score, ever impregnated female partner, intercourse frequency, doing something to improve chances of conception, and female partner age, BMI, and education.
[c]Restricted to men age 25–34 years.

Studies of infertile couples show a consistent adverse effect of female active smoking on fertility treatment outcomes (U.S. Department of Health and Human Services, 2004). Preconception cohort studies (Howe *et al.*, 1985; de Mouzon *et al.*, 1988; Weinberg *et al.*, 1989; Florack *et al.*, 1994; Jensen *et al.*, 1998; Radin *et al.*, 2014; Sapra *et al.*, 2016) support this observation, although effect sizes and intensities at which an association is observed vary across studies. Our findings were weaker than those from prior studies, most of which were conducted between 1968 (Howe *et al.*, 1985) and 2011 (Radin *et al.*, 2014), compared with our more contemporary cohort. Given the secular decline in smoking in the USA (American Lung Association, 2011), and the observation that active smoking may be associated with fecundability only at high intensities (Howe *et al.*, 1985; Florack *et al.*, 1994; Radin *et al.*, 2014), our comparatively weak findings may reflect lower intensity smoking in our cohort. For example, in a UK study conducted from 1968 to 1974, 13.0% of women smoked ≥10 cigarettes/day, and FRs for 1–5, 6–10, 11–15, 16–20 and >20 cigarettes/day were 1.00, 0.97, 0.93, 0.79 and 0.78, respectively (Howe *et al.*, 1985). Only 3.0% of PRESTO women smoked ≥10 cigarettes/day, and we were unable to separate the highest intensity category into finer levels due to small numbers.

Female active smoking history was strongly related to attrition. If women smokers who do not conceive are disproportionately underrepresented in our analysis, their under-representation would result in an upward bias. We corrected for this bias using inverse probability weights, and observed stronger inverse associations between female active smoking and fecundability, consistent with the hypothesized direction of bias. Nevertheless, this bias does not explain the difference between our results and those of earlier studies, because failing to correct for differential attrition is expected to result in weaker associations.

We quantified bias due to under-reporting of smoking intensity using a probabilistic bias analysis. We expected that non-differential misclassification of a multi-level exposure variable would attenuate results in the extreme exposure categories. However, simulated and observed FRs were similar, and the simulation intervals varied only slightly around the median, indicating that non-differential exposure misclassification was unlikely to have been strong enough to dilute a strong association to the level that we observed.

Table V Exposure to passive smoking and fecundability among male never smokers.

	No. of cycles	No. of pregnancies	Unadjusted FR (95% CI)	Adjusted[a] FR (95% CI)	Adjusted[b] FR (95% CI)
Current passive smoke exposure					
None	3804	591	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Any	376	48	0.89 (0.65, 1.22)	0.92 (0.67, 1.26)	0.87 (0.62, 1.22)
Current passive smoke exposure, partner smoking					
None, partner not regular smoker	3755	584	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Any, partner not regular smoker	339	46	0.92 (0.67, 1.26)	0.95 (0.70, 1.29)	0.91 (0.65, 1.27)
None, partner is regular smoker	49	7	0.93 (0.45, 1.91)	1.04 (0.50, 2.16)	1.08 (0.48, 2.42)
Any, partner is regular smoker	37	2	0.37 (0.05, 2.56)	0.44 (0.06, 3.10)	0.35 (0.05, 2.63)
Lifetime passive smoke exposure					
Age 0–10 years	1213	176	0.99 (0.77, 1.27)	1.00 (0.77, 1.29)	0.96 (0.73, 1.28)
Age 11–20 years	1003	144	0.97 (0.74, 1.26)	1.00 (0.76, 1.31)	1.09 (0.80, 1.47)
Age > 20	759	106	0.95 (0.72, 1.26)	0.98 (0.72, 1.32)	0.96 (0.73, 1.28)
Current	376	48	0.93 (0.64, 1.34)	0.93 (0.64, 1.35)	0.87 (0.60, 1.27)

[a]Adjusted for age, race/ethnicity, education and annual household income.
[b]Additionally adjusted for BMI, sugar-sweetened beverage intake, multivitamin or folic acid supplement use, sleep duration, PSS-10 score, MDI score, ever impregnated female partner, intercourse frequency, doing something to improve chances of conception, and female partner age, BMI, and education.

We found that controlling for a range of potential confounders substantially attenuated our findings. In addition to socioeconomic variables, BMI and dietary factors explained most of the attenuation. While these variables are not causes of smoking, they do help control for 'healthy lifestyle': women who smoke are more likely to make other unhealthy choices. No previous studies controlled for dietary factors, and some have not controlled for socioeconomic factors, BMI or parity. Thus, residual confounding by incomplete control for healthy lifestyle may explain the stronger results observed in previous studies.

We found little association between current female passive smoking and fecundability. Studies of couples undergoing fertility treatment report mixed results, with some showing no association between passive smoking and fertility (Sterzik *et al.*, 1996; Meeker *et al.*, 2007b) and others showing inverse associations with IVF outcomes (Neal *et al.*, 2005; Meeker *et al.*, 2007b; Benedict *et al.*, 2011). However, a preconception cohort study of Danish pregnancy planners reported only an 8% reduction in fecundability among never smokers exposed to passive smoking in adulthood (Radin *et al.*, 2014). Our findings may have been attenuated by exposure misclassification, if the biologic window of susceptibility is narrower than we were able to measure (e.g. if exposure during ovulation or implantation is more relevant than exposure over the past year). Moreover, we did not collect information on the intensity of passive smoking, which may have attenuated our results if only high intensity passive smoking adversely affects fertility. Passive smoke exposure may be more intense when it comes from a male partner or other member of the household, which could explain our finding of an association between passive smoke exposure and lower fecundability only among female never smokers whose partner currently smoked.

We observed an inverse association between *in utero* smoke exposure and fecundability among women whose mothers smoked ≥10 cigarettes/day during pregnancy. Preconception cohort studies have not examined intensity of maternal smoking during pregnancy, but rather have classified exposure as any versus none. Studies published before 1990 have found inverse associations between *in utero* smoke exposure and fecundability (Weinberg *et al.*, 1989; Jensen *et al.*, 1998), whereas a more recent study found no association (Radin *et al.*, 2014). These discrepancies may reflect decreased smoking intensity over time, with the 'any' category in earlier studies including more mothers with high intensity smoking than later studies. *In utero* smoke exposure, and in particular intensity of exposure, is prone to misclassification; while we expect that results in the high intensity category are biased towards the null, bias in the low intensity category may be towards or away from the null.

Our examination of active and passive smoking from the prenatal through preconception periods allows for detailed hypotheses as to potential biologic mechanisms through which cigarette constituents affect fertility. Our finding of similar declines in fecundability for current and former smokers and the strongest associations among those who smoked ≥10 cigarettes/day for ≥10 years indicates that cumulative exposure may be more important than acute exposure around the time of the conception attempt. Cigarette smoke contains ~4000 compounds, some of which are ovotoxic (Budani and Tiboni, 2017). Exposure can cause apoptosis in primordial oocytes (Mattison *et al.*, 1983), alter folliculogenesis (Sadeu and Foster, 2011), impair follicle growth (Neal *et al.*, 2007), and affect oocyte growth and development (Zenzes *et al.*, 1995). In humans, smoking has been associated with premature ovarian failure (Chang *et al.*, 2007), early menopause (Sun *et al.*, 2012), and lower anti-Müllerian hormone levels (Freour *et al.*, 2008; Plante *et al.*, 2010). Smoking may also increase susceptibility to STIs and harm tubal function (Marchbanks *et al.*, 1990; Scholes *et al.*, 1992).

We did not observe substantially reduced fecundability among male current smokers, even at high intensities and long durations. Our findings were weaker than, but in the same direction as, findings from two preconception cohort studies (Jensen *et al.*, 1998; Sapra *et al.*, 2016),

but inconsistent with others reporting no association (de Mouzon *et al.*, 1988; Radin *et al.*, 2014) or a positive association (Florack *et al.*, 1994). We observed that male former smoking was associated with improved fecundability, although results were attenuated among couples trying to conceive for <3 cycles.

We found high agreement between male and female report of male current smoking status, but lower agreement for smoking intensity, consistent with results from two validation studies (Hatch *et al.*, 1991; Passaro *et al.*, 1997). Most of this error is likely due to differences in reporting (either because the female does not know how much her partner smokes, or either the female or male under-report smoking intensity). Because the female and male baseline questionnaires were not completed at the same time (range: 0–1505 days, 76.3% within 1 week), some disagreement could result from true change in smoking intensity over time.

Our study was restricted to couples planning a pregnancy. If smokers are more likely to have unintended pregnancies relative to non-smokers because of differences in contraceptive use, as hypothesized by some researchers (Baird *and* Wilcox, 1985), our cohort would enroll fewer fertile smokers, resulting in an exaggerated inverse association between smoking and fecundability. In analyses restricted to couples attempting pregnancy for <3 cycles at study entry, we observed slightly stronger associations for current active smoking. Moreover, we did not observe large differences in last method of contraception by smoking history, although smoking history was associated with history of unplanned pregnancy.

Home pregnancy testing was not standardized in PRESTO. Current cigarette smoking may be associated with delayed pregnancy recognition: we observed a slightly longer median gestational weeks at first positive pregnancy test in current compared with never smokers (4.3 versus 4.0 weeks). Given the high incidence of pregnancy losses early in gestation (Wilcox *et al.*, 1988), non-smokers may have identified more early losses than non-smokers, which could have resulted in bias away from the null.

This study adds to the extensive literature on smoking and fertility. Female current active smoking at high intensity and for long duration was associated with lower fecundability. However, the low prevalence and intensity of smoking in this contemporary cohort limited our ability to estimate associations at high intensity or duration. We also observed that *in utero* smoke exposure among females was associated with reduced fecundability, but that passive smoking throughout the life course was not associated with fecundability in either partner.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

A.K.W. analyzed and interpreted the data and drafted the article. E.E.H., K.J.R. and E.M.M. contributed to the conception and design of the study and assisted with interpretation of the data. A.A. assisted with interpretation of the data. L.A.W. contributed to the conception and design of the study, in collecting the data, and assisted with interpretation of the data. All authors critically revised the article.

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Conflict of interest

The authors declare no competing interests.

References

American College of Obstetrics & Gynecology. ACOG Committee Opinion number 313, September 2005. The importance of preconception care in the continuum of women's health care. *Obstet Gynecol* 2005; **106**:665–666.

American Lung Association. *Trends in Tobacco Use*. Washington, DC: American Lung Association Research and Program Services Epidemiology and Statistics Unit, 2011.

Baird DD, Wilcox AJ. Cigarette smoking associated with delayed conception. *J Am Med Assoc* 1985;**253**:2979–2983.

Baird DD, Wilcox AJ. Future fertility after prenatal exposure to cigarette smoke. *Fertil Steril* 1986;**46**:368–372.

Benedict MD, Missmer SA, Vahratian A, Berry KF, Vitonis AF, Cramer DW, Meeker JD. Secondhand tobacco smoke exposure is associated with increased risk of failed implantation and reduced IVF success. *Hum Reprod* 2011;**26**:2525–2531.

Budani MC, Tiboni GM. Ovotoxicity of cigarette smoke: a systematic review of the literature. *Reprod Toxicol* 2017;**72**:164–181.

Chang SH, Kim CS, Lee KS, Kim H, Yim SV, Lim YJ, Park SK. Premenopausal factors influencing premature ovarian failure and early menopause. *Maturitas* 2007;**58**:19–30.

de Mouzon J, Spira A, Schwartz D. A prospective study of the relation between smoking and fertility. *Int J Epidemiol* 1988;**17**:378–384.

Florack EI, Zielhuis GA, Rolland R. Cigarette smoking, alcohol consumption, and caffeine intake and fecundability. *Prev Med* 1994;**23**:175–180.

Freour T, Masson D, Mirallie S, Jean M, Bach K, Dejoie T, Barriere P. Active smoking compromises IVF outcome and affects ovarian reserve. *Reprod Biomed Online* 2008;**16**:96–102.

Guenther PM, Kirkpatrick SI, Reedy J, Krebs-Smith SM, Buckman DW, Dodd KW, Casavale KO, Carroll RJ. The Healthy Eating Index-2010 is a valid and reliable measure of diet quality according to the 2010 Dietary Guidelines for Americans. *J Nutr* 2014;**144**:399–407.

Hatch MC, Misra D, Kabat GC, Kartzmer S. Proxy respondents in reproductive research: a comparison of self- and partner-reported data. *Am J Epidemiol* 1991;**133**:826–831.

Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology* 2000;**11**:561–570.

Howards PP, Hertz-Picciotto I, Poole C. Conditions for bias from differential left truncation. *Am J Epidemiol* 2007;**165**:444–452.

Howe CJ, Cole SR, Lau B, Napravnik S, Eron JJ Jr. Selection bias due to loss to follow up in cohort studies. *Epidemiology* 2016;**27**:91–97.

Howe G, Westhoff C, Vessey M, Yeates D. Effects of age, cigarette smoking, and other factors on fertility: findings in a large prospective study. *Br Med J (Clin Res Ed)* 1985;**290**:1697–1700.

Hung PH, Baumber J, Meyers SA, VandeVoort CA. Effects of environmental tobacco smoke in vitro on rhesus monkey sperm function. *Reprod Toxicol* 2007;**23**:499–506.

Jensen TK, Henriksen TB, Hjollund NH, Scheike T, Kolstad H, Giwercman A, Ernst E, Bonde JP, Skakkebaek NE, Olsen J. Adult and prenatal exposures to tobacco smoke as risk indicators of fertility among 430 Danish couples. *Am J Epidemiol* 1998;**148**:992–997.

Jensen TK, Joffe M, Scheike T, Skytthe A, Gaist D, Petersen I, Christensen K. Early exposure to smoking and future fecundity among Danish twins. *Int J Androl* 2006;**29**:603–613.

Joffe M, Barnes I. Do parental factors affect male and female fertility? *Epidemiology* 2000;**11**:700–705.

La Maestra S, De Flora S, Micale RT. Does second-hand smoke affect semen quality? *Arch Toxicol* 2014;**88**:1187–1188.

Lash TL, Fox MP, Fink AK. *Applying Quantitative Bias Analysis to Epidemiologic Data*. New York: Springer-Verlag, 2009.

Marchbanks PA, Lee NC, Peterson HB. Cigarette smoking as a risk factor for pelvic inflammatory disease. *Am J Obstet Gynecol* 1990;**162**:639–644.

Mattison DR, Shiromizu K, Nightingale MS. Oocyte destruction by polycyclic aromatic hydrocarbons. *Am J Ind Med* 1983;**4**:191–202.

Meeker JD, Missmer SA, Cramer DW, Hauser R. Maternal exposure to second-hand tobacco smoke and pregnancy outcome among couples undergoing assisted reproduction. *Hum Reprod* 2007a;**22**:337–345.

Meeker JD, Missmer SA, Vitonis AF, Cramer DW, Hauser R. Risk of spontaneous abortion in women with childhood exposure to parental cigarette smoke. *Am J Epidemiol* 2007b;**166**:571–575.

Neal MS, Hughes EG, Holloway AC, Foster WG. Sidestream smoking is equally as damaging as mainstream smoking on IVF outcomes. *Hum Reprod* 2005;**20**:2531–2535.

Neal MS, Zhu J, Holloway AC, Foster WG. Follicle growth is inhibited by benzo-[a]-pyrene, at concentrations representative of human exposure, in an isolated rat follicle culture assay. *Hum Reprod* 2007;**22**:961–967.

Office of Disease Prevention and Health Promotion. *Healthy People 2020*. Washington, DC: United States Department of Health and Human Services, 2017.

Passaro KT, Noss J, Savitz DA, Little RE. Agreement between self and partner reports of paternal drinking and smoking. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *Int J Epidemiol* 1997;**26**:315–320.

Plante BJ, Cooper GS, Baird DD, Steiner AZ. The impact of smoking on antimullerian hormone levels in women aged 38 to 50 years. *Menopause* 2010;**17**:571–576.

Radin RG, Hatch EE, Rothman KJ, Mikkelsen EM, Sorensen HT, Riis AH, Wise LA. Active and passive smoking and fecundability in Danish pregnancy planners. *Fertil Steril* 2014;**102**:183–191 e182.

Sadeu JC, Foster WG. Cigarette smoke condensate exposure delays follicular development and function in a stage-dependent manner. *Fertil Steril* 2011;**95**:2410–2417.

Sapra KJ, Barr DB, Maisog JM, Sundaram R, Buck Louis GM. Time-to-pregnancy associated with couples' use of tobacco products. *Nicotine Tob Res* 2016;**18**:2154–2161.

Schisterman EF, Cole SR, Ye A, Platt RW. Accuracy loss due to selection bias in cohort studies with left truncation. *Paediatr Perinat Epidemiol* 2013;**27**:491–502.

Scholes D, Daling JR, Stergachis AS. Current cigarette smoking and risk of acute pelvic inflammatory disease. *Am J Public Health* 1992;**82**:1352–1355.

Sharma R, Harlev A, Agarwal A, Esteves SC. Cigarette smoking and semen quality: a new meta-analysis examining the effect of the 2010 World Health Organization Laboratory Methods for the Examination of Human Semen. *Eur Urol* 2016;**70**:635–645.

Sterzik K, Strehler E, De Santo M, Trumpp N, Abt M, Rosenbusch B, Schneider A. Influence of smoking on fertility in women attending an in vitro fertilization program. *Fertil Steril* 1996;**65**:810–814.

Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, McIntosh A, Rosenfeld S. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires: the Eating at America's Table Study. *Am J Epidemiol* 2001;**154**:1089–1099.

Sun L, Tan L, Yang F, Luo Y, Li X, Deng HW, Dvornyk V. Meta-analysis suggests that smoking is associated with an increased risk of early natural menopause. *Menopause* 2012;**19**:126–132.

Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York: Springer-Verlag, 2000.

Tong VT, Dietz PM, Morrow B, D'Angelo DV, Farr SL, Rockhill KM, England LJ. Trends in smoking before, during, and after pregnancy—Pregnancy Risk Assessment Monitoring System, United States, 40 sites, 2000–2010. *MMWR Surveill Summ* 2013;**62**:1–19.

U.S. Department of Health and Human Services. The Health Consequences of Smoking. 2004. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta, GA.

U.S. Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. 2006. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta, GA.

U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: a Report of the Surgeon General. 2014. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta, GA.

Weinberg CR, Wilcox AJ, Baird DD. Reduced fecundability in women with prenatal exposure to cigarette smoking. *Am J Epidemiol* 1989;**129**:1072–1078.

Wesselink AK, Hatch EE, Rothman KJ, Weuve JL, Aschengrau A, Song RJ, Wise LA. Perceived stress and fecundability: a preconception cohort study of North American couples. *Am J Epidemiol* 2018;**187**:2662–2671.

Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early loss of pregnancy. *N Engl J Med* 1988;**319**:189–194.

Wise LA, Rothman KJ, Mikkelsen EM, Stanford JB, Wesselink AK, McKinnon C, Gruschow SM, Horgan CE, Wiley AS, Hahn KA *et al*. Design and conduct of an internet-based preconception cohort study in North America: pregnancy study online. *Paediatr Perinat Epidemiol* 2015;**29**:360–371.

Ye X, Skjaerven R, Basso O, Baird DD, Eggesbo M, Cupul Uicab LA, Haug K, Longnecker MP. In utero exposure to tobacco smoke and subsequent reduced fertility in females. *Hum Reprod* 2010;**25**:2901–2906.

Zenzes MT, Wang P, Casper RF. Cigarette smoking may affect meiotic maturation of human oocytes. *Hum Reprod* 1995;**10**:3213–3217.