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Active and Passive Smoking and Fecundability in Danish Pregnancy Planners

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Abstract

Objective—To investigate the extent to which fecundability is associated with active smoking, time since smoking cessation, and passive smoking.

Design—Prospective cohort study.

Setting—Denmark, 2007–2011.

Patients—3,773 female pregnancy planners aged 18–40 years.

Intervention—None.

Main Outcome Measures—Self-reported pregnancy. Fecundability ratios (FR) and 95% confidence intervals (CI) were estimated using a proportional probabilities model that adjusted for menstrual cycle at risk and potential confounders.

Results—Among current smokers, smoking duration ≥10 years was associated with reduced fecundability compared with never smokers (FR=0.85, 95% CI: 0.72–1.00). Former smokers who had smoked ≥10 pack-years had reduced fecundability regardless of when they quit smoking (1–1.9 years FR=0.83, 95% CI: 0.54–1.27; ≥2 years FR=0.73, 95% CI: 0.53–1.02). Among never smokers, the FRs were 1.04 (95% CI: 0.89–1.21) for passive smoking in early life and 0.92 (95% CI: 0.82–1.03) for passive smoking in adulthood.

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Conclusions—Among Danish pregnancy planners, cumulative exposure to active cigarette smoking was associated with delayed conception among current and former smokers. Time since smoking cessation and passive smoking were not appreciably associated with fecundability.

Keywords

Fecundability; Fertility; Cigarette Smoking; Tobacco Smoke Pollution; Cohort Study

INTRODUCTION

Tobacco smoke constituents demonstrate acute effects on female reproductive physiology, including damaging the oocyte (1, 2) and altering concentrations of endogenous hormones (3–9). In addition, smoking may have persistent effects (10–13) by depleting the ovarian reserve (14, 15) and increasing susceptibility to sexually transmitted infection (16–18).

Epidemiologic studies have consistently shown an inverse association between intensity of current smoking and fecundability (19), defined as the cycle-specific probability of conception among non-contracepting couples. Studies of former smokers have not found reduced fecundability (20–22) or an increased risk of infertility (16, 23) relative to never smokers, implying that the effect of smoking on fecundability does not persist. However, these studies did not use information on the amount or duration of smoking among the former smokers, which may have obscured possible tobacco effects with high cumulative levels of exposure (19, 24). With regard to prenatal exposure to tobacco smoke, studies of fecundability in relation to *in utero* exposure to maternal smoking are mixed, with some showing an inverse association (22, 25, 26) and others showing little association (27–29).

We examined the association of cumulative exposure to active smoking with fecundability among both current and former smokers in a prospective cohort study of pregnancy planners in Denmark. In addition, we assessed the association between cumulative exposure to smoking and fecundability among former smokers in sub-groups of time since cessation. Among never smokers, we assessed the extent to which exposure to passive smoking during various life stages (*in utero* or in childhood; adolescence; and adulthood) was associated with reduced fecundability.

MATERIALS AND METHODS

Study Population

The Snart Gravid study enrolled women in Denmark aged 18–40 years who were planning a pregnancy during 2007–2011. Eligible participants were in a stable relationship with a male partner, not using fertility treatments, and willing to provide their identification number from the Danish Civil Registration System and email address (30). The study used Internet-based questionnaires to obtain informed consent and self-reported exposure and outcome data (31). The study protocol was approved by the ethical review boards of Boston University Medical Center and the Danish Data Protection Board (J. no. 2010-41-4345).

Assessment of Exposure

Participants reported their current smoking habits and history of active and passive smoking exposure on the baseline questionnaire. Current smokers were categorized as regular smokers if they smoked at least one cigarette per day and occasional smokers if they smoked less. Regular smokers reported the current intensity in categories of cigarettes smoked per day (1–4, 5–9, 10–19, 20–29, and ≥30), the age they started, and the number of years they had abstained from smoking. Former smokers reported the average number of cigarettes smoked per day in the same categories, the ages when they started and stopped, and the duration of smoking in years. Participants reported their history of passive smoking exposure as the average number of hours per day during the following ages: 0–10, 11–20, 21–30, and 31–40 years. The questionnaire also asked participants about their exposure *in utero*: “Did your mother smoke cigarettes while she was pregnant with you?”

Assessment of Covariates

The baseline questionnaire included information on female age, height and weight, education, household income, occupation, reproductive and medical histories, and lifestyle habits such as frequency of intercourse, consumption of alcoholic and caffeinated beverages, physical activity. Participants reported whether they had daily or near-daily exposure to the following environmental hazards at home or at work: agricultural pesticides; metal particulates or fumes; solvents, oil-based paints, or cleaning compounds; environments with temperatures >25° C; chemotherapeutic drugs; engine exhaust; chemicals for hair dyeing, straightening, or curling; chemicals for manicure and pedicure. Females also reported information on their male partner’s age, height and weight, smoking habits and history, and exposure to environmental hazards.

Assessment of Pregnancy and Cycles at Risk

On bi-monthly follow-up questionnaires, participants reported whether they had conceived and, if so, whether the pregnancy was confirmed by a home pregnancy test and/or clinician. Total menstrual cycles at risk were calculated from participants’ reported number of months spent trying to conceive at the time of enrollment, date of last menstrual period (LMP) before enrollment, usual menstrual cycle length, and LMP date on each follow-up questionnaire (32). A participant contributed menstrual cycles from the time she enrolled until she reported a confirmed pregnancy or was censored. Censoring occurred if the woman initiated fertility treatment, was no longer attempting pregnancy, withdrew from the study, was lost to follow up, or completed 12 cycles from the beginning of her attempt to conceive, whichever came first.

Exclusions

From June 2007 through December 2011, 5,921 eligible women enrolled. We excluded 297 women (5%) with incomplete or implausible information about their LMP date or the start date of their pregnancy attempt; 580 women (10%) who did not fill out a follow-up questionnaire; 1,153 women (20%) who had attempted pregnancy for >6 cycles at baseline; and 118 women (2%) who reported smoking cessation <1 year ago (because of uncertainty of the timing of smoking cessation with respect to the start of the pregnancy attempt). After

these exclusions, 3,773 women were included in the present analysis. The 475 women (13%) subsequently lost to follow-up (mean follow-up time = 3.3 months) were on average younger (27.9 *vs.* 28.4 years), heavier (BMI: 25.1 *vs.* 24.0 kg/m^2), less educated (≥4 years of vocational training: 50% *vs.* 59%), and more likely to be parous (33% *vs.* 28%), regular smokers (18% *vs.* 11%) and exposed to passive smoking in adulthood (42% *vs.* 34%) than those not lost to follow-up. Similar proportions used oral contraceptives as their last form of birth control (61% *vs.* 61%).

Data Analysis

We analyzed exposure to smoking among current smokers in terms of duration and intensity, and among former smokers, in terms of duration, intensity, pack-years, and time since cessation. We also assessed joint categories of these variables where appropriate. Never-smokers were the reference category for these analyses. Pack-years among current smokers depended greatly on the current intensity category; because of the ambiguity of whether it captured current intensity of exposure or cumulative exposure, we did not analyze exposure among current smokers in terms of pack-years. We defined exposure to passive smoking as spending ≥1 hour per day in the same room with someone who was smoking. We categorized this exposure according to life stage: early life (*in utero* or in childhood), adolescence, adulthood, no exposure at any life stage (reference category).

We estimated fecundability ratios (FR) and 95% confidence intervals (CI) for each category of exposure relative to the reference category. An FR < 1.0 corresponds to reduced fecundability among exposed relative to unexposed women. To model probabilities of conception in a given cycle at risk of pregnancy, we used PROC GENMOD in SAS version 9.2 (33) to fit a proportional probabilities model (25). The proportional probabilities model differs from the Cox proportional hazards model mainly in that it uses discrete time to event, and it incorporates the decline of baseline fecundability over time with a binary indicator variable for cycle number at risk (34). Potential confounders were selected *a priori* based on a literature review and causal graphs. The primary analysis also modeled different types of exposure with mutual adjustment (e.g., active *vs.* passive smoking) to assess their independent effects. Results presented in the text were adjusted for age (18–24, 25–29, 30–34, 35–40 years), passive smoking in adulthood (0, 1–2, and ≥3 hours/day), and whether the male partner was a current, regular smoker (yes, no). Selected models were further adjusted for education (no vocational training, basic vocational training, 1–2 years of higher education, >2 years of higher education) because it changed the crude FR by ≥5% in models for regular smoker, occasional smoker, intensity in current smokers, and passive smoking. No other potential confounder changed the crude FR by ≥5%. Adjusting for parity strengthened the associations by about 5%; we did not present these results because they could be biased if parity is affected by both the exposure and underlying fecundity (35). We also computed the FR and 95% CI for smoking intensity with additional adjustment for duration and vice versa. The assumption of proportional probabilities was evaluated by examining the FRs stratified by number of cycles, in two categories: 1–5 and 6–12. Analyses of certain exposures in former smokers were restricted by age in order to avoid sparse data problems: duration (25–40 years), duration and intensity (25–34 years), pack-years and time since cessation (25–34 years).

We used multiple imputation to impute missing values for exposure and covariates (36), producing five imputed data sets with PROC MI. For smoking variables, the proportions missing were as follows: duration 0.4%, intensity 1.1%, passive smoke exposure in early life 1.8%, adolescence 11%, and adulthood 14%. We used PROC MIANALYZE to account for the use of five imputed data sets.

RESULTS

The analysis included 3,773 women (474 regular smokers, 212 occasional smokers, 741 former smokers, and 2,346 never smokers) contributing 15,774 menstrual cycles and 2,578 confirmed pregnancies.

Current Smokers

At baseline, smoking intensity (cigarettes/day) was positively associated with passive smoking, BMI, use of hormonal last method of contraception, parity, gravidity, history of infertility, consumption of alcohol and caffeine, partner smoking, and partner age (Table 1). Participant and partner exposure to certain environmental hazards were also positively associated with smoking: solvents, oil-based paints, and detergents; high temperature environments; and, for the partner only, metal particulates and fumes. Intensity was inversely associated with female age, education, and household income.

Compared with never smokers, the FR for regular smokers was 0.89 (95% CI: 0.77–1.03) and the FR for occasional smokers was 1.11 (95% CI: 0.95–1.25) (Table 2). The FRs for the four levels of smoking intensity, 1–4, 5–9, 10–19, and ≥20 cigarettes/day, were 1.01 (95% CI: 0.78–1.32), 0.86 (95% CI: 0.70–1.07), 0.86 (95% CI: 0.71–1.05) and 0.84 (95% CI: 0.55–1.29). Further adjustment for duration of smoking attenuated the association between smoking intensity and fecundability (Model 3 FR and 95% CI).

The association of smoking duration with fecundability appeared to depend on intensity. Duration of smoking among regular smokers was inversely associated with fecundability (<10 years FR=0.92, 95% CI: 0.74–1.14; ≥10 years FR=0.85; 95% CI: 0.72–1.00). Smoking ≥10 cigarettes/day was associated with reduced fecundability among those with both short and long durations of smoking (<10 years: FR=0.81, 95% CI: 0.60–1.10; ≥10 years: FR=0.82, 95% CI: 0.66–1.01). However, among participants who smoked <10 cigarettes/day, we observed adverse effects on fecundability only with greater duration of smoking (1–4 cigarettes/day and <10 years, FR=0.99, 95% CI: 0.66–1.49; 1–4 cigarettes/day and ≥10 years duration, FR=0.91, 95% CI: 0.65–1.27; 5–9 cigarettes/day and <10 years duration FR=0.95, 95% CI: 0.69–1.31; 5–9 cigarettes/day and ≥10 years duration FR=0.76, 95% CI: 0.58–0.99).

Former Smokers

Among former smokers, time since cessation was positively associated with age at baseline (Table 1). Former smokers who had quit 1–1.9 years ago were less likely to be parous, more likely to be passive smokers in adulthood and exposed to partner smoking, and more likely to report exposure to environmental hazards than never smokers.

Fecundability among former smokers was similar to that of never smokers (FR=0.99, 95% CI: 0.90–1.08) (Table 3). The FRs for the four levels of smoking intensity, 1–4, 5–9, 10–19, and ≥20 cigarettes/day, were 0.88 (95% CI: 0.75–1.05), 1.13 (95% CI: 0.97–1.32), 1.04 (95% CI: 0.90–1.19) and 0.92 (95% CI: 0.71–1.19). No trend in fecundability was found when former smokers were grouped by both intensity and time since cessation (Supplemental Table 1).

Relative to never smokers, the FR for having smoked <10 years was 1.10 (95% CI: 0.99–1.23) and the FR for having smoked ≥10 years was 0.89 (95% CI: 0.75–1.04) in women age 25–40. The FRs for smoking duration ≥10 years in women age 25–34 who had smoked 1–4, 5–9, 10–19 and ≥20 cigarettes/day were: 0.85 (95% CI: 0.59–1.23), 0.96 (95% CI: 0.71–1.31), 0.84 (95% CI: 0.65–1.08) and 0.80 (95% CI: 0.54–1.18). High cumulative exposure to smoking (≥10 pack-years) was associated with reduced fecundability, regardless of time since smoking cessation in women age 25–34 (1–1.9 years FR=0.83, 95% CI: 0.54–1.27; ≥2 years FR=0.73, 95% CI: 0.53–1.02).

Never Smokers

Passive smoking exposure in adulthood was positively associated with partner regular smoking (Supplemental Table 2). Passive smoking exposure at all life stages was positively associated with participant and partner BMI, use of hormonal last method of contraception, parity, and exposure to environmental hazards; it was inversely associated with education.

Among never smokers, passive smoking in adulthood was slightly associated with reduced fecundability, whether the participant was exposed for 1–2 or ≥3 hours/day (1–2 hours/day FR=0.92, 95% CI: 0.81–1.04; ≥3 hours/day FR=0.92, 95% CI: 0.73–1.14) (Table 4). Having a partner who was a current or former smoker was not associated with reduced fecundability (data not shown). Stratified by partner's smoking status, FR=1.01, 95% CI: 0.83–1.22 if the partner was a regular smoker, and FR=0.90, 95% CI: 0.79–1.02 if not.

Never smokers exposed to passive smoking in earlier life stages had similar fecundability to those with no exposure to passive smoking at any life stage (early life only FR=1.04, 95% CI: 0.89–1.21; adolescence only FR=0.97, 95% CI: 0.72–1.32; early life and adolescence FR=1.01, 95% CI: 0.90–1.13). The FR for exposure to smoking *in utero* was also similar to that for exposure in early life (FR= 1.01, 95% CI: 0.92–1.11).

DISCUSSION

In this prospective study of pregnancy planners, high cumulative exposure to active smoking was associated with reduced fecundability in both current and former regular smokers relative to never smokers. Among former smokers, more recent (<1 year ago) and more distant quitters (≥1 year ago) had similar reductions in fecundability. Current intensity of regular smoking (≥10 cigarettes/day; among smokers with duration ≥10 years, ≥5 cigarettes/day) was associated with reduced fecundability relative to never smokers. Exposure to passive smoking in early life, adolescence, and adulthood was not materially associated with fecundability among never smokers.

Studies with exposure and outcome definitions similar to ours reported a stronger inverse association between current smoking ≥20 cigarettes/day and fecundability: Baird and Wilcox (37) (FR=0.57), Howe et al. (FR=0.78) (21), and Curtis et al. (FR=0.74) (20). We found an association between smoking 5–9 cigarettes/day and reduced fecundability that was similar in magnitude to that observed in the higher exposure categories, and this association was only present among smokers with ≥10 years duration. Previous studies of the association between smoking 5–9 cigarettes/day and fecundability reported weakly inverse (38) or null (20, 21) associations. It is possible that under-reporting of smoking by heavy smokers in our study led to exaggerated effects on fecundability for light smoking, although we have no evidence for this type of misclassification. Women who were occasional smokers had an 11% increase in fecundability relative to never smokers, but there were comparatively few women who were occasional smokers. Previous studies reported little difference in fecundability among light regular smokers versus non-smokers (20, 21).

Our study found that former smokers with high cumulative exposure (≥10 pack-years) had reduced fecundability, although former smokers as a group had no appreciable difference in fecundability compared with never smokers. Prior studies show that former smokers have similar fecundability to never smokers (20–22), even within one year of cessation (20, 22), but these studies did not separate out heavy from light smokers. De Ziegler et al. advanced the theory that tobacco smoke affects growing but not dormant ovarian follicles after observing that women treated with low toxicity chemotherapy regained pretreatment levels of anti-Müllerian hormone (AMH), an indicator of ovarian reserve (39), within six months (40). However, this theory is contradicted by our data and findings from other studies among former smokers showing that greater pack-years of smoking was associated with reduced ovarian function among women undergoing assisted reproductive technology (14) and shorter cycle length (41), a correlate of reduced fecundability (42–45).

The cumulative amount of active smoking may be related to the degree of persistent harm to certain processes necessary for reproduction. First, cigarette smoke may accelerate ovarian depletion. Polycyclic aromatic hydrocarbons (PAH), which are found in cigarette smoke, were detectable in the granulosa cells and follicular fluid of smokers (11). *In vitro* studies have found that toxicological concentrations of PAH induce apoptosis in primordial oocytes (1, 2). Animal studies of exposure to PAH at doses more consistent with those from active smoking have found that benzo[a]pyrene inhibits follicle growth *in vitro* (46), while cigarette smoke exposure *in vivo* significantly decreases the number of primordial follicles without increasing the rate of apoptosis (15). These observations suggest that cigarette smoke shortens the follicular phase, thereby shortening the menstrual cycle and increasing the rate of follicle recruitment (15).

However, the evidence from epidemiologic studies of ovarian aging comparing former with never smokers is uncertain. Age at natural menopause among former smokers was either slightly lower (47, 48) or similar (49, 50) to what it was in never smokers. Serum AMH concentrations were lower among current smokers (51–53) but not former smokers (51). These studies may also have missed an effect from ≥10 pack-years if that is required for accelerated ovarian depletion. We evaluated the evidence of this biological pathway

indirectly by stratifying the association of ≥10 pack-years and fecundability among former smokers by age. The association was somewhat stronger among women age≥35 years than in women age<35 years, suggesting that this biological pathway may be operating in our population (multivariable-adjusted FR=0.62, 95% CI: 0.35–1.11 among women aged≥35 years, FR=0.78, 95% CI: 0.60–1.02 among women aged<35 years).

Second, smoking may impair tubal function and increase susceptibility to ascending infection (54). These impairments include reduced muscular contraction, cilial beat frequency, and blood flow, demonstrated in animal models (10, 12, 55–57). Poorer systemic immune responses in smokers have also been observed; for example, less lymphocyte response to T-cell mitogens (58,59), less leukocyte chemotaxis and migration (60), and lower titers of influenza antibodies (58). Case-control studies found that current smokers were at an increased risk for pelvic inflammatory disease (17, 18) and tubal factor infertility (16) compared with never smokers. However, only one of these studies also found an increased risk in former smokers (17). In our data, the age-standardized prevalence of self-reported history of pelvic inflammatory disease was 14% among never smokers and 14%, 19%, and 23% among former smokers with <5, 5–9, and ≥10 pack-years of smoking, respectively.

Among women with no history of active smoking, passive smoking in adulthood appeared to have little effect on fecundability. Exposure misclassification may have attenuated the relation between current passive smoking exposure and fecundability, if exposure during the menstrual cycle at risk is the biologically relevant exposure (61, 62). The questionnaire asked about hours per day of passive smoking exposure during the current decade of age, which could easily differ from the exposure during the current menstrual cycle (63). The literature on this relation is mixed, possibly due to differences in exposure definition and measurements (61). Passive smoking was associated with time-to-pregnancy>6 months among non-smokers in one study (64). Non-smokers exposed to passive or partner smoking had a modest increased risk of implantation failure following *in vitro* fertilization (10%–17%) in some (61, 65, 66) but not all studies (67, 68). Our finding that partner smoking was not associated with reduced fecundability is in agreement with a meta-analysis of four studies (24). Other studies found that partner smoking was associated with reduced fecundability (20, 22, 69) and early pregnancy loss (70), which could manifest as reduced fecundability.

The current study is the largest prospective study of passive smoking in early life and fecundability, adding to evidence against a large adverse effect on future fertility. *In utero* exposure to maternal smoking was associated with reduced fecundability (FRs in the range from 0.53 to 0.81) in two prospective cohort studies (22, 25) and one retrospective cohort study (26), while the association was nearly null in three retrospective cohort studies (FRs in the range from 0.96 to 1.02) (27–29). These studies ascertained exposure as we did, except for one study that used the subject's mother's self-report after delivery to ascertain exposure and found no association (28).

Regular smokers were more likely to be lost to follow up than never smokers. If the smokers who were lost to follow up were more likely to get pregnant than those who remained in the

cohort, our results would have overestimated the inverse association. Another methodological consideration is the extent to which the inverse association of cumulative exposure to smoking and fecundability is overestimated as a result of the study's recruitment of pregnancy planner volunteers. This volunteer cohort could exclude smokers who are highly fertile, since smokers may be more likely to have unplanned pregnancies (37). Baird and Wilcox demonstrated via simulation that this exclusion by itself would result in smoking FR=0.91, assuming that 30% of pregnancies were accidental (37). This is less of a problem in our study because unplanned pregnancies are relatively rare in Denmark (71, 72). When we restricted the analyses to participants who had tried to conceive ≤ 2 cycles at enrollment, our results were essentially unchanged (Regular smoker FR=0.86, 95% CI: 0.72–1.02; former smoker ≥10 pack-years FR=0.83, 95% CI: 0.63–1.10).

We were able to adjust for numerous potential confounders. After first adjusting for age, there was little difference in the observed associations with further adjustment for lifestyle, reproductive, environmental, and medical factors. There may have been confounding from factors that we did not measure, e.g., unhealthy diet (73) or asymptomatic pelvic inflammatory disease (74). We assessed exposure to environmental hazards with self-report from a check-list of broad categories; any misclassification resulting from this method would have limited our ability to adjust for confounding by environmental hazards.

The female participants may have been motivated to participate in an Internet-based study of time-to-pregnancy, but we would not expect this to limit generalizability. The biologic relation of smoking exposure and fecundability should not be affected by Internet use and study participation.

In conclusion, we found that women with high cumulative exposure to active smoking had reduced fecundability. This was apparent in current smokers as well as in former smokers, with similar reductions in fecundability among more recent and more distant quitters. Passive smoking in early life, adolescence, and adulthood did not have a strong effect on fecundability. Our data support the theory that heavy, prolonged exposure to regular active smoking increases the risk of persistent damage to female fertility, apart from the established acute effect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline characteristics of 3,773 women age 18–40 years according to smoking status: The Snart Gravid Cohort, Denmark, 2007 – 2011.[a]

	Never Smoker	Current smoker: number of cigarettes/day					Former smoker: time since cessation, years	
		<1	1–4	5–9	10–19	≥20	1–1.9	≥2
Number of women	2,346	212	70	146	223	35	135	606
Participant's age, years (mean)	28.3	28.0	28.1	26.9	27.3	27.5	28.4	29.9
Male Partner's age, years (mean)	30.8	30.5	29.6	30.9	31.5	32.3	30.9	31.2
Smoking duration, years (mean)	0	10.1	11.8	12.0	12.5	13.7	10.5	7.1
Partner is a regular smoker (%)	11	23	58	60	71	76	16	12
Passive smoking exposure in adulthood (%)	23	49	56	72	83	80	52	36
Participant's mother smoked while pregnant (%)	34	29	30	43	55	66	35	35
Intercourse frequency ≥4/week (%)	18	16	24	26	29	21	20	17
Doing something to time intercourse (%)	46	46	45	43	46	45	49	49
Body mass index of participant, kg/m^2 (mean)	24.0	23.7	24.4	24.4	25.2	25.2	24.4	24.4
Body mass index of partner, kg/m^2 (mean)	25.3	25.0	25.8	26.3	26.0	26.0	25.3	25.6
Last contraceptive method: hormonal[b] (%)	63	64	65	60	64	81	68	57
Parous (%)	31	27	41	43	40	32	21	44
Ever pregnant (%)	41	44	56	66	57	67	39	54
History of infertility (%)	8	7	15	14	13	13	11	9
History of pelvic inflammatory disease (%)	14	15	21	20	25	40	15	17
Regular cycles (%)	76	74	80	76	84	78	74	74
No vocational training or higher education (%)	10	10	11	18	27	25	13	11
Household income <25,000 Danish Kroner/year (%)	13	18	14	17	16	33	14	11
Participant exposure to environmental hazards (%)	17	19	19	22	29	25	26	18
Partner exposure to environmental hazards (%)	22	24	31	34	39	45	30	28
Caffeine intake, mg/day (mean)	108	170	141	184	239	322	160	160
Consumes ≥7 alcoholic beverages/week (%)	8	26	26	10	18	23	16	12

[a] All characteristics except age are age-standardized to the distribution of the cohort at baseline.

[b] Includes oral contraceptive pills and other hormonal contraceptives such as patch and injection.

Table 2

Current active smoking exposure in relation to fecundability in 3,302 women: The Snart Gravid Cohort, Denmark, 2007–2011.

	Pregnancies	Cycles	Model 1 FR (95% CI)[a]	Model 2 FR (95% CI)[b]	Model 3 FR (95% CI)[c]
Never smoker	1,626	9,709	1.00 (ref)	1.00 (ref)	1.00 (ref)
Current occasional smoker	153	826	1.07 (0.93–1.25)	1.11 (0.95–1.25)	
Current regular smoker[d]	288	2,174	0.82 (0.73–0.92)	0.89 (0.77–1.03)	
Intensity, cigarettes/day[d]					
1–4	49	313	0.94 (0.73–1.22)	1.01 (0.78–1.32)	1.04 (0.79–1.37)
5–9	87	675	0.80 (0.65–0.97)	0.86 (0.70–1.07)	0.88 (0.71–1.10)
10–19	132	1,026	0.81 (0.69–0.95)	0.86 (0.71–1.05)	0.89 (0.72–1.09)
≥ 20	20	160	0.76 (0.50–1.15)	0.84 (0.55–1.29)	0.88 (0.57–1.37)
Duration, years					
< 10	99	743	0.82 (0.68–0.99)	0.92 (0.74–1.14)	0.90 (0.70–1.17)
≥ 10	189	1,431	0.82 (0.72–0.95)	0.85 (0.72–1.00)	0.85 (0.69–1.04)
Intensity and Duration[e]					
1 – 4 cigarettes, < 10 years	20	116	1.00 (0.67–1.49)	0.99 (0.66–1.49)	
1 – 4 cigarettes, ≥ 10 years	29	197	0.90 (0.64–1.26)	0.91 (0.65–1.27)	
5 – 9 cigarettes, < 10 years	35	251	0.85 (0.63–1.16)	0.95 (0.69–1.31)	
5 – 9 cigarettes, ≥ 10 years	52	424	0.76 (0.59–0.99)	0.76 (0.58–0.99)	
≥ 10 cigarettes, < 10 years	44	376	0.73 (0.55–0.97)	0.81 (0.60–1.10)	
≥ 10 cigarettes, ≥ 10 years	108	810	0.83 (0.70–1.00)	0.82 (0.66–1.01)	

FR = Fecundability Ratio, CI=Confidence Interval.

[a] Model 1 FR and 95% CI are adjusted for cycle number at risk.

[b] Model 2 FR and 95% CI are adjusted for cycle number at risk, age, partner smoking, and passive smoking.

[c] In model 3, the FR and 95% CI of intensity are additionally adjusted for duration--set to the modal category, nine years—and the FR and 95% CI of duration are additionally adjusted for intensity—set to the modal category, 10–19 cigarettes per day—and education.

[d] Model 2 FR and 95% CI are also adjusted for education.

[e] The FRs and 95% CIs for the combination of intensity and duration were computed from a model that did not include terms for the main effects of intensity and duration.

Table 3

Past active smoking exposure in relation to fecundability in 3,087 women: The Snart Gravid Cohort, Denmark, 2007–2011.

	Pregnancies	Cycles	Model 1 FR (95% CI)[a]	Model 2 FR (95% CI)[b]	Model 3 FR (95% CI)[c]
Never smoker	1,626	9,709	1.00 (ref)	1.00 (ref)	1.00 (ref)
Former smoker	511	3,065	1.00 (0.92–1.10)	0.99 (0.90–1.08)	
Time since cessation, years					
1	91	591	0.94 (0.78–1.14)	0.93 (0.77–1.13)	
≥ 2	420	2,474	1.02 (0.92–1.12)	1.02 (0.93–1.13)	
Intensity, cigarettes/day					
1–4	126	864	0.89 (0.75–1.05)	0.88 (0.75–1.05)	0.84 (0.70–1.00)
5–9	157	798	1.13 (0.97–1.31)	1.13 (0.97–1.32)	1.11 (0.95–1.29)
10–19	178	1,054	1.03 (0.89–1.18)	1.04 (0.90–1.19)	1.07 (0.93–1.24)
≥ 20	50	349	0.90 (0.70–1.17)	0.92 (0.71–1.19)	1.00 (0.76–1.30)
Duration, years[d]					
< 10	280	1,506	1.07 (0.97–1.18)	1.10 (0.99–1.23)	1.10 (0.94–1.27)
≥ 10	177	1,271	0.85 (0.75–0.97)	0.89 (0.75–1.04)	0.89 (0.76–1.05)
Intensity and duration[e]					
1–4 cigarettes, <10 years	81	517	0.92 (0.77–1.11)	0.92 (0.75–1.14)	
1–4 cigarettes, ≥10 years	25	154	0.79 (0.57–1.10)	0.85 (0.59–1.23)	
5–9 cigarettes, <10 years	80	383	1.11 (0.94–1.32)	1.11 (0.90–1.38)	
5–9 cigarettes, ≥10 years	36	215	0.99 (0.77–1.26)	0.96 (0.71–1.31)	
10–19 cigarettes, <10 years	81	388	1.16 (0.98–1.37)	1.16(0.95–1.42)	
10–19 cigarettes, ≥10 years	56	401	0.85 (0.70–1.03)	0.84 (0.65–1.08)	
≥20 cigarettes, <10 years	20	70	1.18 (0.85–1.65)	1.54 (1.07–2.23)	
≥20 cigarettes, ≥10 years	23	174	0.74 (0.54–1.03)	0.80 (0.54–1.18)	
Pack-years					
< 5	331	1,880	1.01 (0.91–1.12)	1.00 (0.91–1.11)	
5–9	116	640	1.08 (0.92–1.26)	1.08 (0.92–1.27)	
≥ 10	64	545	0.75 (0.61–0.93)	0.74 (0.60–0.92)	
Time since cessation and pack-years[f]					

	Pregnancies	Cycles	Model 1 FR (95% CI)[a]	Model 2 FR (95% CI)[b]	Model 3 FR (95% CI)[c]
1 year, <10 pack-years	53	356	0.86 (0.67–1.11)	0.87 (0.67–1.12)	
1 year, ≥ 10 pack-years	18	133	0.84 (0.55–1.29)	0.83 (0.54–1.27)	
≥ 2 years, <10 pack-years	299	1,554	1.08 (0.96–1.21)	1.08 (0.96–1.21)	
≥ 2 years, ≥ 10 pack-years	32	259	0.75 (0.54–1.05)	0.73 (0.53–1.02)	

FR= fecundability ratio; CI = confidence interval.

[a] Model 1 FR and 95% CI are adjusted for cycle number at risk.

[b] Model 2 FR and 95% CI are adjusted for cycle number at risk, age, partner smoking, and passive smoking.

[c] In model 3, the FR and 95% CI of intensity are additionally adjusted for duration--set to the modal category, eight years—and the FR and 95% CI of duration are additionally adjusted for intensity—set to the modal category, 10–19 cigarettes per day.

[d] Analyzed in participants age ≥25 years at baseline.

[e] The FRs and 95% CIs for the combination of intensity and duration were analyzed in participants age ≥25 years at baseline. The model did not include terms for the main effects of intensity and duration.

[f] Analyzed in participants age 25–34 years at baseline.

Table 4

Exposure to passive smoking in relation to fecundability in 2,346 women with no history of active smoking: The Snart Gravid Cohort, Denmark, 2007 – 2011.

	Pregnancies	Cycles	Model 1 FR (95% CI)[a]	Model 2 FR (95% CI)[b]
Passive smoking in adulthood, hours/day				
0	1,272	7,385	1.00 (reference)	1.00 (reference)
≥ 1	354	2,324	0.90 (0.81–1.00)	0.92 (0.82, 1.03)
1–2	275	1,798	0.90 (0.80–1.02)	0.92 (0.81,1.04)
≥ 3	79	526	0.89 (0.72–1.10)	0.92 (0.73,1.14)
Passive smoking in adulthood and partner's current smoking status				
None, partner is not a regular smoker	1,211	7,024	1.00 (reference)	1.00 (reference)
Some, partner is not a regular smoker	253	1,693	0.88 (0.77–0.99)	0.90 (0.79,1.02)
None, partner is a regular smoker	61	361	0.98 (0.78–1.24)	1.00 (0.79,1.26)
Some, partner is a regular smoker	101	631	0.96 (0.80–1.16)	1.01 (0.83,1.22)
Passive smoking exposure by life stage				
No exposure	414	2,399	1.00 (reference)	1.00 (reference)
Early life only	217	1,217	1.04 (0.89–1.22)	1.04 (0.89,1.21)
Adolescence only	43	278	0.96 (0.71–1.30)	0.97 (0.72,1.32)
Recent adulthood only	73	444	0.91 (0.72–1.16)	0.92 (0.72,1.17)
Early life and adolescence	598	3,491	1.00 (0.89–1.12)	1.01 (0.90,1.13)
Early life and adulthood	20	192	0.68 (0.43–1.08)	0.69 (0.43,1.10)
Adolescence and adulthood	38	256	0.91 (0.65–1.29)	0.94 (0.66,1.34)
Exposed at all stages	223	1,432	0.93 (0.80–1.07)	0.97 (0.84,1.13)

FR = fecundability ratio, CI = confidence interval.

[a] Model 1 adjusted for cycle at risk.

[b] Model 2 additionally adjusted for age, education, and partner smoking (where applicable).