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Demographic, lifestyle, and reproductive risk factors for ectopic pregnancy

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Abstract

Objective: To evaluate the relationship between demographic, lifestyle, and reproductive factors and risk of ectopic pregnancy (EP).

Design: Prospective cohort.

Setting: United States.

Patient(s): 41,440 pregnancies from 22,356 women in the Nurses' Health Study II.

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Capsule: Smoking, alcohol intake, diethylstilbestrol exposure in utero, oral contraceptive use at young age, history of infertility, intrauterine device use, and tubal ligation are associated with higher risk of EP.

Intervention(s): Demographic, lifestyle, and reproductive factors were self-reported in 1989 and updated every 2 years. Multivariable log-binomial regression models with generalized estimating equations were used to estimate the adjusted risk ratios (aRRs).

Main Outcome Measures: Ectopic pregnancy.

Results: Incident EP was reported in 411 (1.0%) pregnancies. Former and current smokers had 1.22 (95% CI 0.97, 1.55) and 1.73 (95% CI 1.28, 2.32) times the risk of EP than never smokers. The risk of EP 10 years after quitting was similar to never smokers (aRR=0.90 95% CI 0.60, 1.33). Women consuming 10g/day of alcohol had 1.50 (95% CI 1.08, 2.09) times the risk of EP than never consumers. In utero exposure to diethylstilbestrol (aRR= 3.55 95% CI 2.51, 5.01), earlier initiation of oral contraceptives (aRR=2.64 95% CI 1.70, 4.09 for <16 yrs vs. never), intrauterine device use (aRR=3.99 95% CI 2.06, 7.72) and history of infertility (aRR=3.03 95% CI 2.48, 3.71) or tubal ligation (aRR=16.27 95% CI 11.76, 22.53) were associated with higher risk of EP.

Conclusions: Women who were current or former smokers, consumed 10 g/day of alcohol, were exposed to diethylstilbestrol in utero, initiated oral contraceptives at <16yrs (which may be a marker of riskier sexual behaviors), and had a history of infertility, intrauterine device use, or tubal ligation had higher risk of EP.

Keywords

alcohol; body mass index; ectopic pregnancy; smoking; tubal pregnancy

Introduction

Ectopic pregnancy (EP) occurs when the developing blastocyst becomes implanted at a site other than the endometrium of the uterine cavity. In the US and Europe, while only 1–2% of pregnancies are ectopic, EP accounts for 75% of maternal deaths in the first trimester and 9–13% of all pregnancy-related deaths (1, 2). In the developing world, the situation is even more dire, with EP fatality rates that are up to 10 times higher than in industrialized countries (3). The costs of treating ectopic pregnancy are also considerable, with direct costs estimated at \$1 billion in the US alone (4).

Several risk factors for EP have been recognized including pelvic inflammatory disease (PID), chlamydia infection, certain forms of contraception, and smoking (5). While other factors such as age, sociodemographic characteristics, and reproductive history are thought to be involved, the role played by these factors remains mostly unclear because of limited sample sizes or problems with the design of previous studies. Most of the information on risk factors for EP has come from case-control studies which are susceptible to recall bias due to the retrospective assessment of exposure (6-13). Furthermore, many case-control studies have used women who gave birth at the same center (8, 11, 13) or non-pregnant women from the same geographic area as controls (6, 10) rather than on-going pregnancies matched on gestational age, which could have led to selection bias.

Using a hypothesis generating approach, we sought to examine prospectively the demographic, lifestyle, and reproductive risk factors for EP in a large cohort from the general population.

Materials and Methods.

Study Population.

The Nurses' Health Study II is an ongoing prospective cohort of 116,430 female nurses, ages 24 to 44 years at baseline in 1989 (14). Questionnaires are distributed every two years to update lifestyle and medical characteristics and capture incident health outcomes. Follow-up for each questionnaire cycle is greater than 90%. Women were eligible for this analysis if they reported at least one pregnancy during 1990-2009. Pregnancies prior to 1990 were excluded as we lacked prospective exposure assessment on them. Eligible women could contribute pregnancies until the end of follow-up in 2009. Of the eligible pregnancies (n=41,724), we excluded from the analysis those with missing (n=247) or implausible (n=37) gestational length leading to a final sample size of 41,440 pregnancies from 22,356 women (Supplemental Figure 1). This study was approved by the institutional review board of Partners Health Care, Boston, Massachusetts, with the participants' consent implied by the return of the questionnaires.

Outcome Assessment.

Women were asked to report their pregnancies every two years; on the 2001 and 2009 questionnaires, women also reported information on the year, length, complications, and outcomes of all previous pregnancies. Options for pregnancy outcomes were a singleton live birth, multiple birth, miscarriage or stillbirth, tubal or ectopic pregnancy, or induced abortion. Options for gestational lengths were <8, 8-11, 12-19, 20-27, 28-31, 32-36, 37-39, 40-42, and 43+ weeks. Self-reported pregnancy outcome and gestation length have been previously found to be validly reported (15). Because some pregnancy outcomes (e.g. induced abortions) were not recorded prospectively, the prospectively recorded pregnancy data was combined with the 2001 and 2009 data to obtain a complete assessment of lifetime pregnancy history. The main outcome in this study was tubal or ectopic pregnancy. All pregnancies not ending in a tubal or ectopic pregnancies were considered as non-cases.

Lifestyle Exposure Assessment.

On the 1989 questionnaire women self-reported their height and past smoking habits including time since quitting, and the average number of cigarettes smoked per day before age 15 years to present. Current weight, smoking status (cigarettes smoked/day), and multivitamin use over the previous 2 years was self-reported in 1989 and updated every two years thereafter. BMI was calculated as weight (kg) divided by height squared (m^2). If a woman reported being pregnant at the time of body weight assessment, the most recent non-pregnant body weight measure was used. In a validation study, self-reported height and weight were highly correlated with measured height ($r=0.94$) and weight ($r=0.97$) (16). Every two years, women were also asked to report their average intake of beer, wine, and liquor over the past year in 9 categories ranging from "none or less than one per month" to "6 per day" (17). We calculated the total intake of alcohol by summing the alcohol content for specific items multiplied by weights proportional to the frequency of use of each item. High correlations were previously found between total alcohol intake assessed with this questionnaire and four 1-week diet records ($r=0.90$) (17, 18).

Reproductive Risk Factors Assessment.

Biennially from 1989 through 2001, and every 4 years thereafter, women were asked whether they had tried to become pregnant for more than 1 year without success and if so, the reasons for infertility: tubal factor, ovulatory factor, endometriosis, cervical mucous factor, male factor, or unexplained. In 100 randomly selected women, 95% of self-reports of ovulatory infertility were confirmed through medical record review (19). On the 1989 questionnaire, women reported past oral contraceptive (OC) use at each age from 13 years to present. On each biennial follow-up questionnaire women also reported their contraceptive use in the past 2 years: condom, OC, diaphragm or cervical cap, foam or sponge, rhythm method, vasectomy, tubal ligation, intrauterine device (IUD). Using information on OC history and OC use during follow-up, we derived the variable of age at first OC use. In 1993 women self-reported their mothers' use of diethylstilbestrol (DES) or other hormones during pregnancies with the participants. In 2001, a validation study among participants' mothers showed high agreement between DES exposure as reported by daughters and mothers ($\kappa = 0.74$) (20). History of EP, spontaneous abortion, and induced abortion prior to the index pregnancy was derived from the 2001 and 2009 pregnancy grids.

Statistical Analysis.

To maintain a prospective analysis, information from the 1989 questionnaire was related to pregnancies in 1990 and 1991; the 1991 questionnaire information was used for pregnancies in 1992 and 1993; and so forth. Differences in baseline characteristics from the 1989 questionnaire were compared among women who had an EP during follow-up versus those who did not using a chi-squared tests for categorical variables and Kruskal-Wallis non-parametric tests for continuous variables.

The risk ratio (RR) of EP in relation to pre-pregnancy characteristics was estimated using log-binomial regression. Generalized estimating equations with an exchangeable working correlation structure were used to account for the within-person correlation between pregnancies. Where appropriate, tests for linear trend across categories were conducted by using the median values in each category as a continuous variable. To maximize our power, we only excluded women from a given model who were missing the main exposure of interest. Categorical covariables were included using indicators for missing covariates when necessary. Ongoing work from the NHSII cohort suggest that the missing indicator method produces materially the same results as those obtained by the multiple imputation method unless a covariate is missing in an extreme proportion or acts as a strong confounder (21). In our analysis, the proportion of missing covariate data was low (BMI, 7.4%; smoking, 0.3%; multivitamin use, 7.5%; alcohol intake, 9.6%; age at first OC use, 3.2%) suggesting minimal risk of bias.

Confounding was addressed by reviewing the prior literature and creating casual diagrams. Covariables included in the final multivariable models included pre-pregnancy age, BMI, smoking status, race, alcohol intake, history of infertility, age at first OC use, and multivitamin use. As we lacked information on sexually transmitted infections (STIs) or risky sexual behaviors which have been linked to EP (10, 11, 13) and certain lifestyle

behaviors such as drinking and smoking (22), we adjusted all of our analyses for age at first OC use, as the best proxy.

Several sensitivity analyses were conducted to test the robustness of our findings. We performed sub-analyses including only women with complete information on the variables of interest (e.g. a complete case analysis), only women without a history of EP, only the first pregnancy per woman, and only pregnancies without any infertility diagnosis prior to pregnancy. Since the number of cases was reduced in these sensitivity analyses, we used a modified Poisson regression model as the log-binomial model would not always converge. To quantify the impact of unmeasured confounding due to history of STIs or PID, we assumed a risk ratio between 2 to 4 for the relationship between history of STIs or PID and EP (based on previous case-control studies) and calculated the bias adjusted risk ratio for a variety of different values for the association between the exposure and history of STIs or PID (23). We also plotted the value of the joint minimum strength of association that a history of STIs/PID must have with the exposure (RR_{EU}) and the outcome (RR_{UD}) to fully explain away the observed associations. All analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC).

Results.

During 20 years of follow-up 22,356 women contributed 41,440 pregnancies to this analysis. Incident EP was reported in 411 (1.0%) pregnancies from 359 women. The majority of these women contributed 1 EP (87.2%) while very few contributed multiple EPs (2: 11.7%, 3: 0.6%, 4: 0.6%). On average, women who had an EP during follow-up were more likely to be a former or current smoker, consume more alcohol, have started OCs at a younger age, used an IUD in the past 2 years, undergone tubal ligation, experienced all types of infertility, have a history of ectopic pregnancy, and had mothers who took DES during their pregnancy (Table 1).

Demographic and Lifestyle Factors.

Age at index pregnancy and race were not associated with risk of EP in unadjusted or multivariable adjusted analyses. After multivariable adjustment, women who were former or current smokers prior to pregnancy had 22% (95% CI -3, 55%) and 73% (95% CI 28, 132%) higher risk of EP compared to never smokers (Table 2). There was not a linear relationship between frequency or duration of past or current smoking and risk of EP. Even among light current smokers (1-4 cigarettes/day) and those who had smoked for 15 years there was still an elevated risk of EP (aRR=1.65 and 1.60, respectively). Among former smokers, the risk of EP 10 or more years after quitting smoking was similar to never smokers (aRR=0.90). Among former or current smokers, the risk of EP was similar across the categories of age at first smoke. Women who consumed 10 g/day of alcohol prior to pregnancy had 50% (95% CI 8, 109%) higher risk of EP compared to non-consumers; however the association across categories of intake was not entirely linear (p-trend=0.07). There were no associations between pre-pregnancy BMI and multivitamin use and EP in the univariate or multivariate analyses

Reproductive Risk Factors.

Women who began OCs at 13-16 years had 2.64 (95% CI 1.70, 4.09) times the risk of EP compared to women who never used OCs prior to pregnancy (Table 3). Type of contraceptive use in the 2 years prior to pregnancy was also associated with risk of EP. Women using condoms, reporting tubal ligation, or using an IUD had 0.72 (95% CI 0.53, 0.97), 16.27 (95% CI 11.76, 22.53), and 3.99 (95% CI 2.06, 7.72) times the risk of EP compared to women using no contraception. History of infertility was associated with 3.03 (95% CI 2.48, 3.71) times the risk of EP. This association was largely driven by tubal factor infertility (aRR=7.28) followed by ovulatory disorders (aRR=2.31), an uninvestigated or unreported diagnosis (aRR=2.19), unexplained (aRR=2.15), and cervical mucous factors (aRR=1.76). History of EP prior to the index pregnancy (aRR=8.45 95% CI 6.57, 10.86) and *in utero* exposure to DES (aRR=3.55 95% CI 2.51, 5.01) were also associated with increased risk of EP. The association between DES exposure and risk of EP remained even after restricting the incident period to 1993-2009 (e.g. after the exposure was assessed via questionnaire) (aRR=3.38 95% CI 1.98, 5.77).

Sensitivity Analyses.

The associations between modifiable lifestyle and traditional risk factors for EP were consistent in magnitude and significance in the complete case analysis, when analyses were restricted to women without a history of EP, those without a history of infertility, and to the first eligible pregnancy per women (Supplemental Table 1). The unmeasured confounding analyses showed that if we assume the risk ratio between 2 to 4 for the association between prior STIs/confirmed PID and EP, only very strong associations between current smoking and history of STIs/PID and moderate associations between alcohol intake 10 g/day and history of STIs/PID would completely explain away the observed associations (Supplemental Figure 2 & 3). For example, if the risk ratio for the association between prior STIs/confirmed PID and EP is 3.4 as suggested by the largest case-control study (11), current smokers would have to have 2.5 times the risk of STIs/PID to completely explain the association and women with alcohol intakes 10 g/day would have to have 1.9 times the risk of STIs/PID to completely explain away the observed association.

Discussion.

In this exploratory analysis of the demographic, lifestyle, and reproductive exposures associated with EP in a large prospective cohort, we identified smoking, alcohol intake, history of tubal ligation, history of infertility, and IUD use prior to pregnancy, OC use before 16 years, and *in utero* exposure to DES as risk factors for EP.

Our results which found a higher risk of EP among former and current smokers is consistent with several other studies (11, 24-26) and suggests that the effects of cigarette smoke on the etiology of EP may be both short- and long-term. Further supporting this notion is our finding that the risk of EP only returns to that of never smokers after >10 years of quitting. Cigarette smoke alters oviductal motility in both humans (27) and rabbits (28) and delays preimplantation embryo transport through the oviduct in hamsters (29). *In vivo* muscle contractions of the ampulla were inhibited during smoke exposure and while contraction

rates increased after smoke exposure stopped, they did not return to control levels (29). More recent work on smoking and Fallopian tube gene expression suggests that smoking may also alter tubal epithelial cell turnover resulting structural alteration (30). Alternate mechanisms of action linking smoking and EP include lower estrogen levels among smokers (31) which could affect tubal contractions which are under estrogenic control (32) and reduced immunity among smokers (33) which might affect the incidence of tubal infection and PID, both strong risk factors for EP (34).

To our knowledge, we are the first epidemiologic study to find a positive association between pre-pregnancy alcohol intake and EP. Recent results from an experimental study provide evidence supporting an interpretation of this relation as causal. *In vivo*, ethanol triggered a concentration-dependent suppression of spontaneous contraction in isolated human fallopian tubes which appeared to be mediated through the nitric oxide pathway (35). In mice, acute and chronic alcohol intake impeded embryo transport through the Fallopian tubes by altering the spontaneous motility of the oviduct and/or impairing the oviduct epithelium (35). Of note, pre-conception alcohol intake was not associated with infertility (36) or spontaneous abortion (37) in our cohort of women, which further supports the notion that alcohol could be impairing oviduct motility as opposed to early embryo development.

The link between previous use of an IUD and EP was established in 1995 by a meta-analysis of 16 case-control studies (38). More recent studies have further confirmed this association (39, 40). While the risk of EP appears to be much higher in women experiencing contraceptive failure while using an IUD (39), there still appears to be a slightly elevated risk of EP in former users– which has been suggested to be related to the tubal inflammation caused by IUDs (40). The higher risk of EP in women with tubal ligation has also been established previously (41-43) and is not unexpected given the nature of this surgery which impairs the normal structure and functioning of the oviduct. It is important to note that the occurrence of pregnancy with IUD use or after tubal ligation was very low (<1%) in our cohort, suggesting that both are highly effective at preventing pregnancy; however, when pregnancy occurs, the risk of EP is elevated.

History of infertility, specifically due to tubal, ovulatory, unexplained, and cervical cause, was associated with increased risk of EP in our cohort, similar to other studies (6, 8, 11, 44). While it is likely that some of the increased risk was due to the use of infertility treatments (45), endometriosis and spousal infertility were not associated with risk of EP suggesting that these former associations are not solely due to medical intervention. Other studies have demonstrated a link between infertility and EP even among women conceiving without medical assistance (11). In utero exposure to DES has been linked to several adverse reproductive outcomes (46), including increased risk of EP (44, 47). This association is likely driven by the gross anatomical changes of the reproductive tract that result from in utero DES exposure (48). The increased risk of EP we found among women who used OCs before 16 years is likely not causal but rather due to the correlation between this variable and other sexually risky behaviors such as age at first intercourse, number of sexual partners, and history of sexually transmitted diseases that have been associated with increased risk of EP (9, 10, 13). Finally, consistent with previous studies we found a strong elevated risk of EP among women with a history of EP, however, in contrast to some studies, women with a

history of induced or spontaneous abortion did not have an increased risk. While the previous positive findings between induced abortion and EP are likely due to a combination of recall (49) and selection bias (50) there are thought to be many common risk factors for EP and spontaneous abortion such as chromosomal abnormalities (51) and hormonal factors that could be explaining the association seen elsewhere (52).

While our study expands on previous research, it had limitations. First, we lacked information on history of PID and STIs which have been implicated in the etiology of EP (11). While we controlled for age at first OC use as our best proxy, there is likely residual confounding. As evidenced by our sensitivity analyses though, in the absence of very strong associations between current smoking and history of PID/STIs and moderate associations between alcohol intake ≥ 10 g/day and history of PID/STIs, our observed associations could not be completely explained by this unmeasured confounder. Second, we were unable to differentiate women who were using contraception at the time of conception versus previous users which, in previous studies, has been related to differing risks of EP (12, 39). Similarly, regarding the effects of infertility on risk of EP, we could not differentiate women who experienced infertility and became pregnant after medical assistance versus those who experienced infertility and eventually conceived unassisted, which has been shown to be important in determining risk of EP (12, 39). The validity of maternal self-report of EP has not been assessed but recall of other early pregnancy outcomes has shown to be accurate (53). Due to the prospective nature of our study in which reporting of the exposures predated reporting of the outcome, measurement error of our exposure variables would not be expected to differ between women experiencing ectopic pregnancies versus those who did not. This type of non-differential measurement error would likely result in observed risk ratios that are an underestimate of the true associations. This suggests that many of the associations may be stronger than reported here. The use of self-reported EP could also be seen as an advantage over hospital discharge surveys as increasingly $>50\%$ of EPs in the US are being managed non-surgically and/or on an outpatient basis (54). The incidence of EP in our cohort was almost identical to that from a large administrative claims database of more than 200 US commercial health plans (2002-2007) which lends further support to the validity of our outcome assessment (55). Despite these limitations, our study had many strengths including the prospective design, the large number of pregnancies, the detailed assessment of lifestyle factors, and the nearly-complete follow-up over 20 years.

In our exploratory analysis among women in our study who became pregnant during follow-up, those who were current or former smokers, consumed ≥ 10 g/day of alcohol, were exposed to diethylstilbestrol in utero, initiated oral contraceptives at a young age, and had a history of infertility, intrauterine device use, or tubal ligation had higher risk of EP. Given the high prevalence of past (19%) and current smoking (16%) (56) and consuming ≥ 1 alcohol drink/day (20%) (57) among women of reproductive age, clinical and public health interventions aimed at preventing smoking, smoking cessation and reducing pre-conception alcohol intake may have a positive impact on the incidence of ectopic pregnancies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline characteristics from the 1989 questionnaire comparing women who had a tubal/ectopic pregnancy to those who had a non-tubal/ectopic pregnancy during follow-up (1990-2009) among 22,356 women in the Nurses' Health Study II.

Demographic Characteristics ^a	Tubal/Ectopic Pregnancy During Follow-up?		p-value ^b
	No (n=21,997)	Yes (n=359)	
Age, years	30 (28, 33)	31 (28, 34)	0.34
BMI, kg/m ²	21.8 (20.2, 24.2)	21.7 (20.5, 23.8)	0.87
Married, n (%)	17388 (79.1)	269 (74.9)	0.06
White, n (%)	20508 (93.2)	336 (93.6)	0.79
Smoking Status, n (%)			<0.001
Never Smoked	15496 (70.5)	217 (60.5)	
Former Smoker	4381 (19.9)	86 (24.0)	
Current Smoker	2090 (9.5)	56 (15.6)	
Frequency of Smoking, n (%)			<0.001
Never Smoked	15496 (70.5)	217 (60.5)	
Former, 1-4 cigarettes/day	1209 (5.5)	20 (5.6)	
Former, 5-14 cigarettes/day	1379 (6.3)	25 (7.0)	
Former, 15+ cigarettes/day	1793 (8.2)	41 (11.4)	
Current, 1-4 cigarettes/day	382 (1.7)	12 (3.3)	
Current, 5-14 cigarettes/day	597 (2.7)	17 (4.7)	
Current, 15+ cigarettes/day	1111 (5.1)	27 (7.5)	
Multivitamin Use, n (%)			0.06
None	9940 (45.5)	177 (49.4)	
2 tablets/week	1915 (8.8)	39 (10.9)	
3-5 tablets/week	3134 (14.4)	54 (15.1)	
6 tablets/week	6784 (31.1)	88 (24.6)	
Alcohol Intake, g/day	1.0 (0.0, 3.5)	1.7 (0.0, 5.7)	0.02
Age at first OC Use, n (%)			<0.001
Never	3854 (17.5)	40 (11.1)	
13-16 yrs	1350 (6.1)	39 (10.9)	
17-20 yrs	8180 (37.2)	150 (41.8)	
21-24 yrs	5796 (26.4)	87 (24.2)	
25+ yrs	2461 (11.2)	38 (10.6)	
Contraceptive Use in Past 2 years, n (%)			
None	7068 (32.1)	146 (40.7)	<0.001
Condom	6041 (27.5)	71 (19.8)	0.001
OC	4808 (21.9)	62 (17.3)	0.04
Diaphragm/Cervical cap	4046 (18.4)	52 (14.5)	0.06
Foam or Sponge	3274 (14.9)	46 (12.8)	0.27
Rhythm Method	2370 (10.8)	27 (7.5)	0.05

Demographic Characteristics ^a	Tubal/Ectopic Pregnancy During Follow-up?		
	No (n=21,997)	Yes (n=359)	p-value ^b
Tubal Ligation	97 (0.4)	30 (8.4)	<0.001
Vasectomy	305 (1.4)	5 (1.4)	0.99
Intrauterine Device	201 (0.9)	8 (2.2)	0.01
History of Infertility, n (%)	3364 (15.3)	109 (30.4)	<0.001
Tubal blockage	248 (1.1)	28 (7.8)	<0.001
Ovulatory disorder	1045 (4.8)	45 (12.5)	<0.001
Endometriosis	497 (2.3)	11 (3.1)	0.31
Cervical factors	198 (0.9)	10 (2.8)	<0.001
Spousal	547 (2.5)	9 (2.5)	0.98
Unexplained	665 (3.0)	20 (5.6)	0.006
History of Ectopic Pregnancy, n (%)	247 (1.1)	26 (7.2)	<0.001
History of Spontaneous Abortion, n (%)	3705 (16.8)	64 (17.8)	0.62
History of Induced Abortion, n (%)	3613 (16.4)	70 (19.5)	0.12
In Utero Exposure to DES, n (%)	450 (2.1)	30 (8.4)	<0.001

Abbreviations: BMI, body mass index; DES, diethylstilbestrol; OC, oral contraceptive.

^aData are presented as median (25th, 75th percentile) or n (%).

^bP-values are presented from chi-squared tests for categorical variables and Kruskal-Wallis non-parametric tests for continuous variables.

Table 2.

Association of demographic and lifestyle factors prior to pregnancy and risk of ectopic pregnancy among women in the Nurses' Health Study II (1990-2009).

Pre-pregnancy Characteristics	Ectopic/Total (%)	Unadjusted RR (95% CI)	Adjusted RR ^a (95% CI)
Age (per 5 years) (n=41,440)	411/41440 (1.0)	1.18 (1.06, 1.32)	1.06 (0.95, 1.19)
Race (n=41,440)			
Other	26/2762 (0.9)	1.00 (REF)	1.00 (REF)
White	385/38678 (1.0)	1.06 (0.71, 1.57)	0.99 (0.66, 1.47)
Body Mass Index (n=38,355)			
<18.5 kg/m ²	18/1482 (1.2)	1.28 (0.80, 2.05)	1.19 (0.74, 1.91)
18.5-24.9 kg/m ²	274/26925 (1.0)	1.0 (REF)	1.0 (REF)
25-29.9 kg/m ²	71/6667 (1.1)	1.12 (0.87, 1.45)	0.99 (0.76, 1.28)
30-34.9 kg/m ²	21/2140 (1.0)	1.03 (0.66, 1.61)	0.89 (0.57, 1.38)
35 kg/m ²	16/1141 (1.4)	1.48 (0.90, 2.43)	1.22 (0.74, 2.02)
P-trend		0.58	0.91
Smoking Status (n=41,327)			
Never Smoked	249/29445 (0.9)	1.0 (REF)	1.0 (REF)
Former Smoker	104/8774 (1.2)	1.40 (1.12, 1.76)	1.22 (0.97, 1.55)
Current Smoker	57/3108 (1.8)	2.17 (1.63, 2.89)	1.73 (1.28, 2.32)
Frequency of Smoking (n=41,327)			
Never Smoked	249/29445 (0.9)	1.0 (REF)	1.0 (REF)
Former, 1-4 cigarettes/day	34/2601 (1.3)	1.55 (1.08, 2.21)	1.33 (0.93, 1.91)
Former, 5-14 cigarettes/day	30/2809 (1.1)	1.26 (0.87, 1.84)	1.08 (0.74, 1.59)
Former, 15+ cigarettes/day	40/3364 (1.2)	1.41 (1.01, 1.96)	1.22 (0.87, 1.71)
Current, 1-4 cigarettes/day	12/701 (1.7)	2.02 (1.14, 3.60)	1.65 (0.92, 2.93)
Current, 5-14 cigarettes/day	16/994 (1.6)	1.90 (1.15, 3.14)	1.61 (0.97, 2.68)
Current, 15+ cigarettes/day	29/1413 (2.1)	2.43 (1.66, 3.55)	1.85 (1.25, 2.74)
Duration of Smoking (n=41,327)			
Never Smoked	249/29445 (0.9)	1.0 (REF)	1.0 (REF)
Past, 8 years	25/2160 (1.2)	1.37 (0.91, 2.06)	1.22 (0.81, 1.84)
Past, 9-14 years	42/4008 (1.1)	1.24 (0.90, 1.72)	1.11 (0.80, 1.54)
Past, 15 years	37/2606 (1.4)	1.68 (1.19, 2.37)	1.34 (0.94, 1.90)
Current, 15 years	17/1146 (1.5)	1.75 (1.08, 2.86)	1.60 (0.98, 2.63)
Current, 16-20 years	25/1205 (2.1)	2.45 (1.63, 3.69)	1.93 (1.28, 2.93)
Current, 21 years	15/757 (2.0)	2.34 (1.40, 3.93)	1.61 (0.95, 2.73)
Years since Quitting Smoking (n=38,184)			
Never Smoked	249/29445 (0.9)	1.0 (REF)	1.0 (REF)
5 years ago	40/2988 (1.3)	1.58 (1.14, 2.21)	1.37 (0.98, 1.92)
6-10 years ago	35/2707 (1.3)	1.53 (1.08, 2.17)	1.35 (0.95, 1.93)
>10 years ago	29/3044 (1.0)	1.13 (0.77, 1.65)	0.90 (0.60, 1.33)
Age started Smoking (n=41,195)			

Pre-pregnancy Characteristics	Ectopic/Total (%)	Unadjusted RR (95% CI)	Adjusted RR ^a (95% CI)
Never Smoker	249/29445 (0.9)	1.0 (REF)	1.0 (REF)
<15 yrs	34/2295 (1.5)	1.75 (1.23, 2.50)	1.43 (0.99, 2.06)
15-19 yrs	88/6633 (1.3)	1.57 (1.23, 2.00)	1.33 (1.04, 1.71)
20 yrs	37/2822 (1.3)	1.55 (1.10, 2.19)	1.33 (0.94, 1.88)
Multivitamin Use (n=38,328)			
None	164/15593 (1.1)	1.0 (REF)	1.0 (REF)
2 tablets/week	32/2879 (1.1)	1.06 (0.73, 1.53)	1.06 (0.73, 1.54)
3-5 tablets/week	62/5618 (1.1)	1.05 (0.79, 1.39)	1.06 (0.79, 1.42)
6 tablets/week	120/14238 (0.9)	0.80 (0.64, 1.00)	0.86 (0.68, 1.09)
P-trend		0.09	0.28
Alcohol Intake, g/day (n=37,444)			
0	123/14329 (0.9)	1.0 (REF)	1.0 (REF)
0.1-1.9	96/9445 (1.0)	1.18 (0.91, 1.54)	1.12 (0.85, 1.46)
2.0-4.9	53/6212 (0.9)	0.99 (0.72, 1.37)	0.90 (0.65, 1.25)
5-9.9	46/4306 (1.1)	1.24 (0.89, 1.74)	1.08 (0.76, 1.52)
10	53/3152 (1.7)	1.96 (1.42, 2.70)	1.50 (1.08, 2.09)
P-trend		<0.001	0.07

Abbreviations: BMI, body mass index; RR, risk ratio.

^aAdjusted for age, race, smoking status, alcohol intake, BMI, history of infertility, age at first oral contraceptive use, and multivitamin use.

Table 3.

Association of reproductive factors prior to pregnancy and risk of ectopic pregnancy the Nurses' Health Study II (1990-2009).

Pre-pregnancy Characteristics	Ectopic/Total (%)	Unadjusted RR (95% CI)	Adjusted RR ^a (95% CI)
Age at first OC Use (n=40,094)			
Never	36/6021 (0.6)	1.0 (REF)	1.0 (REF)
13-16 yrs	47/2488 (1.9)	3.16 (2.05, 4.86)	2.64 (1.70, 4.09)
17-20 yrs	167/14800 (1.1)	1.89 (1.32, 2.70)	1.67 (1.16, 2.41)
21-24 yrs	102/11162 (0.9)	1.53 (1.05, 2.23)	1.51 (1.03, 2.21)
25+ yrs	49/5623 (0.9)	1.46 (0.95, 2.24)	1.46 (0.95, 2.24)
Contraceptive Use (n=41,440)			
None	226/19978 (1.1)	1.0 (REF)	1.0 (REF)
Condom	55/9825 (0.6)	0.57 (0.43, 0.76)	0.72 (0.53, 0.97)
Oral Contraceptives	33/5384 (0.6)	0.55 (0.39, 0.80)	0.70 (0.48, 1.02)
Diaphragm/Cervical Cap	38/5290 (0.7)	0.82 (0.58, 1.17)	1.04 (0.72, 1.48)
Foam or Sponge	27/3850 (0.7)	0.81 (0.53, 1.22)	0.88 (0.58, 1.34)
Rhythm Method	23/4171 (0.6)	0.65 (0.43, 0.99)	0.80 (0.52, 1.22)
Vasectomy	3/371 (0.8)	0.84 (0.32, 2.24)	1.03 (0.39, 2.72)
Tubal Ligation	41/290 (14.1)	12.66 (9.34, 17.16)	16.27 (11.76, 22.53)
Intrauterine Device	9/259 (3.5)	3.13 (1.63, 6.02)	3.99 (2.06, 7.72)
History of Infertility (n= 40,296)			
No	242/33398 (0.7)	1.0 (REF)	1.0 (REF)
Yes	157/6898 (2.3)	3.14 (2.57, 3.83)	3.03 (2.48, 3.71)
History of Infertility (n= 40,296)			
No	242/33398 (0.7)	1.0 (REF)	1.0 (REF)
Yes, Tubal	43/529 (8.1)	7.67 (5.49, 10.71)	7.28 (5.24, 10.11)
Yes, Ovulatory Disorder	50/1914 (2.6)	2.23 (1.61, 3.09)	2.31 (1.67, 3.20)
Yes, Endometriosis	18/907 (2.0)	0.94 (0.57, 1.53)	0.87 (0.53, 1.42)
Yes, Cervical Mucous Factors	14/392 (3.6)	1.64 (0.96, 2.80)	1.76 (1.03, 3.01)
Yes, Spousal	13/1041 (1.3)	0.73 (0.41, 1.27)	0.73 (0.42, 1.28)
Yes, Unexplained	31/1586 (2.0)	2.21 (1.54, 3.18)	2.15 (1.50, 3.10)
Yes, No Diagnosis Reported	38/2046 (1.9)	2.34 (1.67, 3.30)	2.19 (1.55, 3.08)
History of Ectopic Pregnancy (n=41,440)			
No	339/40712 (0.8)	1.0 (REF)	1.0 (REF)
Yes	72/728 (9.9)	11.88 (9.31, 15.15)	8.45 (6.57, 10.86)
History of Induced Abortion (n=41,440)			
No	333/34368 (1.0)	1.0 (REF)	1.0 (REF)
Yes	78/7072 (1.1)	1.14 (0.89, 1.45)	0.98 (0.76, 1.26)
History of Spontaneous Abortion (n=41,440)			
No	283/29446 (1.0)	1.0 (REF)	1.0 (REF)
Yes	128/11994 (1.1)	1.11 (0.90, 1.37)	0.98 (0.79, 1.21)

Pre-pregnancy Characteristics	Ectopic/Total (%)	Unadjusted RR (95% CI)	Adjusted RR ^a (95% CI)
In Utero Exposure to DES (n=41,440)			
No	377/40580 (0.9)	1.0 (REF)	1.0 (REF)
Yes	34/860 (4.0)	4.26 (3.02, 6.01)	3.55 (2.51, 5.01)

Abbreviations: BMI, body mass index; DES, diethylstilbestrol; OC, oral contraceptive; RR, risk ratio.

^aModels were run adjusting for age, race, smoking status, alcohol intake, BMI, history of infertility, age at first oral contraceptive use, and multivitamin use.