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Associations between lifetime tobacco exposure with infertility and age at natural menopause: the Women's Health Initiative Observational Study

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ABSTRACT

Background Several studies have investigated the association of tobacco use with infertility and age at natural menopause, yet few have explored secondhand smoke (SHS) exposure with these outcomes. This study offers a comprehensive, quantified secondary data analysis of these issues using the Women's Health Initiative Observational Study (WHI OS).

Purpose This study examines associations between lifetime tobacco exposure—active smoking and SHS—and infertility and natural menopause (before age 50).

Methods Information on smoking, lifetime fertility status, and age at natural menopause was collected and available from 93 676 postmenopausal women aged 50–79 enrolled in the WHI OS from 1993 to 1998 at 40 centres in the USA. Multivariate-adjusted regression models were used to estimate ORs and 95% CI according to levels of active smoking and SHS exposure, and trends were tested across categories.

Results Overall, 15.4% of the 88 732 women included in the analysis on infertility met criteria for the condition. 45% of the 79 690 women included in the analysis on natural menopause (before age 50) met criteria for the condition. Active-ever smokers had overall OR's of 1.14 (95% CI 1.03 to 1.26) for infertility, and 1.26 (95% CI 1.16 to 1.35) for earlier menopause than never-smoking women. Never-smoking women with the highest levels of lifetime SHS exposure had adjusted OR's of 1.18 (95% CI 1.02 to 1.35) for infertility, and 1.18 (95% CI 1.06 to 1.31) for earlier menopause. Active-ever smokers reached menopause 21.7 months earlier than the mean of 49.4 years for never-smokers not exposed to SHS, and women exposed to the highest level of SHS reached menopause 13.0 months earlier.

Conclusions Active smoking and SHS exposure are associated with increased risk of infertility and natural menopause occurring before the age of 50 years.

INTRODUCTION

It is well accepted that dozens of the approximate 4000 compounds found in mainstream smoke (from active smoking) and sidestream smoke (from secondhand smoke, (SHS)) negatively affect women's reproductive health. For example, tobacco toxins affect fertility by impacting folliculogenesis, oogenesis, steroidogenesis, embryonic transport and implantation, endometrial angiogenesis, uterine blood flow and myometrial growth.[1] Tobacco toxins also seem to lower the age of natural menopause by reducing circulating estrogen—from both synthesis inhibition and endocrine disruption.[1] To date, epidemiological research has demonstrated consistent and significant associations with two women's reproductive health issues and active smoking—infertility[2–6] and experiencing earlier age at menopause.[7–15] However, the relationship between infertility and SHS, along with the relationship between earlier age at menopause and SHS, is less well-defined.

In the case of infertility, earlier studies looking at its relationship with SHS yielded mixed findings,[16–18] but later evidence began to demonstrate and quantify the potential damaging effects of SHS on fertility, even suggesting SHS exposure was equally deleterious as maternal active smoking.[19–21] Recent studies (although limited in power and/or employing non-comprehensive measurements to assess lifetime SHS exposure), began to show significant associations between the inability to conceive and exposure to SHS.[6 16 19 22–24] The 2006 Surgeon General's Report on SHS stated that the evidence for SHS and infertility is 'inadequate to infer causality' and "as exposure of women of reproductive age to SHS continues, this topic needs further rigorous investigation" with studies of greater statistical power having more precise exposure measurements.[25] The recent 2014 Surgeon General's report echoes these concerns regarding current gaps in the literature on this topic.[26]

In the case of age at natural menopause, about half of studies examining the associated biological factors with the outcome show significant associations with active and passive smoking.[7 9 11 12 14] Yet, many of the studies are small and do not address the challenges of studying SHS exposure, of which there are two main issues. First, many studies lack measurements that can be quantified in four major potential periods of exposure: *in utero*, childhood, adult at home, and adult at work. Second, the reference group must be strictly limited to never-smokers who have not been exposed to SHS during any portion of their life. Previous studies have noted that failing to address these issues could result in an increased probability of non-differential exposure misclassification, biasing any true association toward the null.[11 27] Several studies investigated SHS and menopause-related outcomes using the aforementioned 'pure' reference group,[9–11 13] but the results were mixed, largely because the studies were small ($n<550$) and complete, quantified lifetime exposures of SHS were not used.

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In light of the limitations in the existing literature on active and passive smoke exposure with infertility and menopause occurring before the age of 50 years, our team sought to add to the evidence base by thoroughly examining these associations using data from a prospective cohort. We sought to address two main hypotheses: (1) lifetime exposure to tobacco smoke (from active smoking and SHS) is associated with a history of infertility and (2) women who were exposed to active smoking or SHS throughout their reproductive lives will have a greater likelihood of natural menopause occurring before the age of 50 years.

METHODS

Data source

Women's health initiative

The Observational Study (OS) of the Women's Health Initiative (WHI) is a prospective cohort of postmenopausal women from 40 centres across the USA. The WHI OS enrolled 93 676 women aged 50–79 from 1993 to 1998. Participants were consented and Human Subjects Committees at participating centres approved the study.[28] Data used in this analysis comes from comprehensive questionnaires completed by study participants at baseline. Questions throughout the data set were structured to minimise recall bias and error, and a reliability subsample demonstrated acceptable limits.[29] Of the 93 676 women, those who did not respond to questions related to the analysis or who had missing values for SHS exposure, the outcomes of interest, or any of the multiple covariates were excluded from the final multivariate models. After exclusions, 88 732 women had complete data on tobacco exposure, key covariates and lifetime fertility status—including reports of a fertile partner and the seeking of medical attention for the inability to conceive. Among the same 93 676 women, 79 690 had a natural menopause defined as amenorrhoea for 12 consecutive months and not having had a bilateral oophorectomy, had complete data on exposures and covariates, and reported the age at which natural menopause occurred.

Measures

Tobacco exposure

Data on lifetime active and passive smoking were collected on baseline enrolment questionnaires. Women were initially classified by active smoking status into current smokers, former smokers or never-smokers (participants who had not smoked 100 cigarettes in their lifetime). Ever-smokers were defined as answering 'yes' to the question, 'Have you smoked 100 cigarettes in your life?'. Other variables considered included 'age started smoking' with the categories <15, 15–19, 20–24, 25–29 and 30+ years of age; 'average number of cigarettes per day throughout smoking years' was categorised into <5, 5–14, 15–24, and 25+.

A series of questions related to SHS exposure were asked "As a child (<18 years old), did you ever live with someone who smoked cigarettes inside your home?", "Since age 18, have you ever lived with someone (including a parent, husband, or other adult person) who smoked cigarettes inside your home?" and "Have you ever worked in a space where people smoked cigarettes?", from these questions women were categorised as: no exposure to SHS ever, exposure during childhood (<18 years of age), adult exposure (>18 years of age) at home and work. Participants who reported any SHS exposure were further asked the number of years exposed in each of these three categories, initially predefined as <1, 1–4, 5–9 and 10–18 years for childhood exposure; and <1, 1–4, 5–9, 10–19 and 20+ years for adult home and work exposure. From these survey items, we created a variable to quantify SHS exposure in never-smokers into the following categories: none; no childhood + any adult; childhood <10 years + any adult; childhood ≥10 years + adult home <20 years + adult work <10 years; childhood ≥10 years + adult home <20 years + adult work ≥10 years; childhood ≥10 years + adult home ≥20 years + adult work <10 years; and childhood ≥10 years + adult home ≥20 years + adult work ≥10 years.[30] Passive smoking variables were defined among never-smokers only because active smoking confounds the effects of SHS and because our interest is the independent effects of SHS on women's health.

Covariates

Potential confounders used in the multivariate analyses included age at baseline (<60, 60–69 and 70+ years), body mass index (BMI) at 18 years (<20, 20–<26, 26–<30 and >30 kg/m^2)—calculated from reported bodyweight at 18 years and adult height, self-reported ethnicity (non-Hispanic Caucasian, African-American, Hispanic, and other), education (less than a high school (HS) graduate, HS or some college, and college degree or higher), alcohol use (12 drinks ever in lifetime, yes/no), alcohol intake (non-drinker, ex-drinker, <1 drink/month, <1 drink/week, >1 to <7 drinks/week, and 7 or more drinks/week), oral contraceptive use (ever/never), very hard exercise 3 or more times per week at 18 years, and any insecticide exposure in the past (yes/no). Age at menarche was included in models examining age at natural menopause. Potential confounders were primarily chosen based on a review of the literature discussed above, and we included potential confounders commonly used in analyses related to these outcomes.[31] Potential confounders considered but not in the final adjustment models were age at first and last term birth, any induced abortions, parity, number of term births, income at baseline, BMI at 35 years and very hard exercise 3 or more times per week at 35 years. Some of the excluded covariates had large amounts of missing data, and early models including them were not different from the final model.

Outcome measures

Self-reported questionnaires administered at baseline included questions on reproductive health and were used to define history of infertility and age at menopause. Infertility was defined as the inability to conceive after 12 months of actively trying, seeking medical advice, and the male partner not being a cause, was reported by 13 621 women (15.4%). Natural menopause was defined as amenorrhoea for >1 year and no surgical or chemotherapeutic cause. Age at natural menopause was categorised as <50 years (earlier age at menopause) and ≥50 years, with 35 834 (45%) reported reaching natural menopause earlier than 50 years. This cut-off was chosen based on the median age of natural menopause within the cohort of never-smoking women not exposed to any SHS throughout life.

STATISTICAL ANALYSIS

Baseline characteristics are presented as N (%) by infertility or status of natural menopause occurring before the age of 50 years, χ^2 tests were performed to assess statistical differences. Using logistic regression, ORs and 95% CIs were calculated for all categories of smoking exposure with the reference group being never-smokers not exposed to any SHS. The results were adjusted for the potential confounders described previously and footnoted in all tables. Only participants with complete data on exposure, potential confounders and outcomes were included in multivariate regression models. Of the women who answered

Table 1 Baseline characteristics of studied women from the WHI OS study

	Infertility, n (%) (N=88 732)			Age at menopause, n (%) (N=79 690)		
	Yes	No	p Value	<50	≥50	p Value
N (%)	13 621 (15.4)	75 111 (84.6)		35 834 (45.0)	43 856 (55.0)	
Age (years)						
<60	4433 (32.5)	23 951 (31.9)	<0.001	13 112 (36.6)	12 550 (28.6)	<0.001
60 to <70	5793 (42.5)	33 216 (44.2)		14 468 (40.4)	20 516 (46.8)	
≥70	3395 (24.9)	17 944 (23.9)		8254 (23.0)	10 790 (24.6)	
BMI at age 18 (kg/m²)						
<20	6486 (48.5)	32 493 (44.3)	<0.001	16 252 (46.4)	18 965 (44.2)	<0.001
20 to <26	6418 (48.0)	37 870 (51.7)		17 392 (49.6)	22 357 (52.1)	
26 to <30	333 (2.5)	2006 (2.7)		946 (2.7)	1104 (2.6)	
≥30	137 (1.0)	941 (1.3)		458 (1.3)	462 (1.1)	
Ethnicity						
Caucasian (non-Hispanic)	11 681 (86.0)	62 555 (83.5)	<0.001	29 618 (82.9)	37 670 (86.1)	<0.001
African-American	861 (6.3)	6232 (8.3)		3180 (8.9)	2754 (6.3)	
Hispanic	388 (2.9)	2898 (3.9)		1452 (4.1)	1348 (3.1)	
Other	648 (4.8)	3229 (4.3)		1489 (4.2)	1964 (4.5)	
Education						
<HS	526 (3.9)	3921 (5.3)	<0.001	1975 (5.6)	1738 (4.0)	<0.001
HS graduate/some college	7134 (52.8)	39 354 (52.8)		19 749 (55.6)	21 513 (49.4)	
College degree or more	5843 (43.3)	31 259 (41.9)		13 819 (38.9)	20 281 (46.6)	
Alcohol use*						
Never	1448 (10.7)	8943 (11.9)	<0.001	4257 (11.9)	4794 (11.0)	<0.001
Ever	12 128 (89.3)	65 905 (88.1)		31 420 (88.1)	38 876 (89.0)	
Alcohol use						
Non-drinker	1386 (10.2)	8456 (11.3)	<0.001	4041 (11.3)	4540 (10.4)	<0.001
Ex-drinker	2445 (18.0)	14 156 (19.0)		7132 (20.0)	7311 (16.8)	
<1 drink/month	1588 (11.7)	8650 (11.6)		4101 (11.5)	5040 (11.6)	
<1 drink/week	2819 (20.8)	14 884 (19.9)		7158 (20.1)	8804 (20.2)	
1 to <7 drinks/week	3443 (25.4)	19 287 (25.8)		8804 (24.7)	12 004 (27.5)	
7 or more drinks/week	1881 (13.9)	9256 (12.4)		4396 (12.3)	5895 (13.5)	
Age at menarche						
Mean (SD)	12.6 (1.5)	12.6 (1.5)	<0.001	12.6 (1.5)	12.6 (1.5)	<0.001
OC use ever						
No	8201 (60.2)	44 604 (59.4)	0.072	20 789 (58.0)	26 298 (60.0)	<0.001
Yes	5420 (39.8)	30 506 (40.6)		15 044 (42.0)	17 558 (40.0)	
Insecticide exposure ever						
No	4610 (36.1)	27 966 (39.9)	<0.001	12 710 (38.1)	16 346 (39.6)	<0.001
Yes	8157 (63.9)	42 146 (60.1)		20 616 (61.9)	24 907 (60.4)	
Very hard exercise 3 times/week at age 18						
No	7134 (54.3)	39 844 (55.1)	0.085	18 703 (54.3)	23 830 (56.3)	<0.001
Yes	6000 (45.7)	32 429 (44.9)		15 759 (45.7)	18 477 (43.7)	
Smoking status						
Never-smoker	6615 (49.2)	37 945 (51.1)	<0.001	17 157 (48.5)	22 648 (52.3)	<0.001
Past smoker	5951 (44.3)	31 641 (42.6)		15 461 (43.7)	18 556 (42.8)	
Current smoker	879 (6.5)	4637 (6.2)		2764 (7.8)	2113 (4.9)	
SHS in never-smoker†						
None	573 (8.7)	3577 (9.4)	<0.001	1499 (8.7)	2211 (9.8)	<0.001
Childhood only	357 (5.4)	2240 (5.9)		1029 (6.0)	1317 (5.8)	
Adult home only	398 (6.0)	2439 (6.4)		1043 (6.1)	1464 (6.5)	
Adult work only	798 (12.1)	4806 (12.7)		2079 (12.1)	2960 (13.1)	
Childhood + adult home	660 (10.0)	4120 (10.9)		1837 (10.7)	2449 (10.8)	
Childhood + adult work	713 (10.8)	3914 (10.3)		1838 (10.7)	2300 (10.2)	
Adult home + work	895 (13.5)	5124 (13.5)		2364 (13.8)	3032 (13.4)	
Childhood + adult home + work	2221 (33.6)	11 725 (30.9)		5468 (31.9)	6915 (30.5)	

Continued

Table 1 Continued

	Infertility, n (%) (N=88 732)			Age at menopause, n (%) (N=79 690)		
	Yes	No	p Value	<50	≥50	p Value
SHS exposure quantified†						
None	573 (8.7)	3577 (9.5)	0.014	1499 (8.8)	2211 (9.8)	<0.001
No childhood + any adult	2074 (31.6)	12 271 (32.6)		5440 (32.0)	7406 (32.9)	
Childhood <10 years + any adult	583 (8.9)	3429 (9.1)		1567 (9.2)	2022 (9.0)	
Childhood ≥10 years + adult home <20 years + adult work <10 years	1592 (24.2)	8695 (23.1)		4012 (23.6)	5290 (23.5)	
Childhood ≥10 years + adult home <20 years + adult work ≥10 years	687 (10.5)	3727 (9.9)		1741 (10.2)	2159 (9.6)	
Childhood ≥10 years + adult home ≥20 years + adult work <10 years	515 (7.8)	3106 (8.3)		1419 (8.3)	1799 (8.0)	
Childhood ≥10 years + adult home ≥20 years + adult work ≥10 years	544 (8.3)	2833 (7.5)		1337 (7.9)	1600 (7.1)	
Age started smoking (years)						
Never-smoker, SHS none	573 (4.2)	3577 (4.8)	<0.001	1499 (4.2)	2211 (5.1)	<0.001
Never-smoker, SHS	6042 (44.8)	34 368 (46.1)		15 658 (44.1)	20 437 (47.0)	
<15	452 (3.3)	2376 (3.2)		1304 (3.7)	1217 (2.8)	
15–19	3437 (25.5)	18 183 (24.4)		9189 (25.9)	10 402 (23.9)	
20–24	2235 (16.6)	11 336 (15.2)		5590 (15.7)	6678 (15.4)	
25–29	451 (3.3)	2492 (3.3)		1229 (3.5)	1367 (3.1)	
≥30	306 (2.3)	2147 (2.9)		1030 (2.9)	1134 (2.6)	
Average cigarette/day						
Never-smoker, SHS none	573 (4.3)	3577 (4.9)	<0.001	1499 (4.3)	2211 (5.2)	<0.001
Never-smoker, SHS	6042 (45.7)	34 368 (47.1)		15 658 (45.0)	20 437 (48.0)	
<5	1445 (10.9)	8311 (11.4)		3825 (11.0)	4939 (11.6)	
5–14	2079 (15.7)	11 150 (15.3)		5454 (15.7)	6451 (15.1)	
15–24	1876 (14.2)	9490 (13.0)		4987 (14.3)	5309 (12.5)	
≥25	1197 (9.1)	6095 (8.4)		3361 (9.7)	3237 (7.6)	

Categories for some variables do not add up to the total n because of missing value.
*Twelve drinks ever in lifetime.
†In never-smokers.
BMI, body mass index; HS, high school; OC, oral contraceptive; OS, Observational Study; SHS, secondhand smoke; WHI, Women's Health Initiative.

the initial questions on infertility and age at menopause, less than 5% and 15% of participants were excluded from analyses of all models due to missing data, respectively. P values were calculated for trends across categories. Using analysis of variance (ANOVA) analysis of means, age at menopause was quantified with year fractions for each exposure level. Statistical analyses were carried out using SAS (V.9.2 SAS Institute, Cary, North Carolina, USA).

RESULTS

Baseline characteristics according to infertility and age at natural menopause are shown in table 1. Characteristics associated with infertility were a BMI<20 kg/m^2 at 18 years, Caucasian (non-Hispanic) ethnicity, college or higher education, ever use of alcohol, ever exposure to insecticide, ever smoking, and higher levels of quantified SHS exposure.

Participants who were in a younger age cohort at enrolment, had a BMI<20 kg/m^2 at 18 years, reported Caucasian (non-Hispanic) as their ethnicity, reported less than a HS education, reported never having used alcohol, ever use of oral contraceptives, ever exposure to insecticide, and reported very hard exercise 3 times per week at 18 years, tended to reach natural menopause earlier than the cohort median of 50 years. Women who were (active) ever-smokers were more likely to report menopause before the age of 50 years than never-smokers. The highest levels of quantified SHS exposure produced the same results (table 1).

In the primary analysis using never-smokers with no lifetime exposure to SHS as the reference group, we compared total tobacco exposure of ever-smokers (active) and found a statistically significant, positive association with infertility and menopause occurring before the age of 50 years with adjusted ORs of 1.14 (95% CI 1.03 to 1.26) and 1.27 (95% CI 1.18 to 1.37), respectively (table 2). Earlier age at smoking initiation was associated with earlier age at menopause (p value for trend <0.001), but not infertility (p value for trend=0.124) (table 2). Positive trends for cigarettes smoked per day were significant for infertility (p value for trend <0.001) and menopause occurring before the age of 50 years (p value for trend <0.001).

Table 3 shows the mean age at menopause by smoking status, age started smoking, and average cigarettes smoked per day. The mean age at menopause was found to be significantly earlier than never-smokers not exposed to SHS (49.4) for the highest levels of active tobacco usage: 1.8 years earlier (or 21.6 months) for those who reported starting smoking at <15 years old, and 1.5 years earlier (or 18.0 months) for those who reported the highest level of cigarettes smoked per day (25+). There are significant positive trends for heavier active tobacco use, suggesting a dose–response (p value for trend <0.001).

The analysis of the independent relationship of SHS with the outcomes of infertility and menopause occurring before the age of 50 years was limited to women who were never-smokers, with never-smokers with no lifetime exposure to SHS serving as

Table 2 Adjusted OR's—infertility and earlier age at menopause (<50 years) by smoking status

	Infertility, n (%)			Age at menopause, n (%)		
Tobacco exposure	**No**	**Yes**	**OR (95% CI)**	**<50**	**≥50**	**OR (95% CI)**
Smoking status						
Never-smoker, SHS none	3076 (4.7)	506 (4.3)	1.0 (Ref)	1301 (4.2)	1935 (5.1)	1.0 (Ref)
Never-smoker, SHS	29 838 (46.0)	5347 (45.0)	1.08 (0.98 to 1.19)	13 573 (44.0)	18 003 (47.0)	1.07 (0.99 to 1.15)
Ever smokers	31 980 (49.3)	6019 (50.7)	1.14 (1.03 to 1.26)	15 977 (51.8)	18 394 (48.0)	1.27 (1.18 to 1.37)
Age started smoking (years)						
Never-smoker, SHS none	3076 (4.7)	506 (4.3)	1.0 (Ref)	1301 (4.2)	1935 (5.0)	1.0 (Ref)
Never-smoker, SHS	29 838 (45.8)	5347 (44.9)	1.08 (0.98 to 1.20)	13 573 (43.9)	18 003 (46.9)	1.07 (0.99 to 1.15)
<15	2035 (3.1)	391 (3.3)	1.18 (1.02 to 1.36)	1138 (3.7)	1037 (2.7)	1.42 (1.27 to 1.59)
15–19	16 153 (24.8)	3049 (25.6)	1.14 (1.03 to 1.27)	8100 (26.2)	9309 (24.2)	1.27 (1.17 to 1.37)
20–24	10 040 (15.4)	1975 (16.6)	1.19 (1.07 to 1.32)	4914 (15.9)	5981 (15.6)	1.24 (1.14 to 1.35)
25–29	2136 (3.3)	378 (3.2)	1.10 (0.95 to 1.27)	1043 (3.4)	1192 (3.1)	1.27 (1.13 to 1.42)
≥30	1819 (2.8)	256 (2.2)	0.86 (0.73 to 1.01)	878 (2.8)	964 (2.5)	1.31 (1.16 to 1.47)
p Value for trend			0.124			<0.001
Average cigarettes/day						
Never-smoker, SHS none	3076 (4.8)	506 (4.3)	1.0 (Ref)	1301 (4.3)	1935 (5.1)	1.0 (Ref)
Never-smoker, SHS	29 838 (46.7)	5347 (45.9)	1.08 (0.98 to 1.20)	13 573 (44.7)	18 003 (47.7)	1.07 (0.99 to 1.16)
<5	7241 (11.3)	1240 (10.6)	1.04 (0.93 to 1.17)	3282 (10.8)	4357 (11.6)	1.11 (1.01 to 1.20)
5–14	9821 (15.4)	1836 (15.7)	1.14 (1.02 to 1.27)	4751 (15.7)	5780 (15.3)	1.21 (1.11 to 1.31)
15–24	8474 (13.3)	1647 (14.1)	1.17 (1.05 to 1.31)	4413 (14.5)	4770 (12.7)	1.37 (1.26 to 1.49)
≥25	5413 (8.5)	1085 (9.3)	1.21 (1.08 to 1.36)	3022 (10.0)	2865 (7.6)	1.53 (1.40 to 1.67)
p Value for trend			<0.001			<0.001
Years smoked before menopause						
Never-smoker, SHS none	3076 (5.0)	506 (4.5)	1.0 (Ref)	1301 (4.37)	1935 (5.2)	1.0 (Ref)
Never-smoker, SHS	29 838 (48.3)	5347 (47.0)	1.08 (0.98 to 1.19)	13 573 (45.6)	18 003 (48.4)	1.06 (0.99 to 1.15)
<5	1688 (2.7)	304 (2.7)	1.08 (0.93 to 1.26)	824 (2.8)	995 (2.7)	1.17 (1.04 to 1.31)
5–9	3463 (5.6)	632 (5.6)	1.09 (0.96 to 1.24)	1742 (5.9)	2046 (5.5)	1.22 (1.11 to 1.35)
10–19	8034 (13.0)	1718 (15.1)	1.29 (1.16 to 1.44)	4617 (15.5)	4348 (11.7)	1.54 (1.42 to 1.68)
20–29	9710 (15.7)	1833 (16.1)	1.15 (1.03 to 1.28)	6185 (20.8)	4593 (12.3)	1.97 (1.81 to 2.14)
30+	5976 (9.7)	1033 (9.1)	1.05 (0.94 to 1.18)	1509 (5.1)	5314 (14.3)	0.41 (0.37 to 0.45)
p Value for trend			0.007			0.220
Pack-years before menopause						
Never-smoker, SHS none	3076 (5.1)	506 (4.5)		1301 (4.5)	1935 (5.3)	1.0 (Ref)
Never-smoker, SHS	29 838 (49.2)	5347 (47.9)	1.08 (0.98 to 1.19)	13 573 (46.5)	18 003 (49.2)	1.07 (0.99 to 1.15)
<10	11 343 (18.7)	2121 (19.0)	1.13 (1.02 to 1.26)	5677 (19.4)	6796 (18.6)	1.22 (1.12 to 1.32)
10 to <20	6693 (11.0)	1324 (11.9)	1.20 (1.07 to 1.35)	3524 (12.1)	3992 (10.9)	1.29 (1.19 to 1.41)
20 to <30	3680 (6.1)	767 (6.9)	1.26 (1.12 to 1.43)	2427 (8.3)	1702 (4.7)	2.11 (1.92 to 2.32)
30 to <40	3116 (5.1)	554 (5.0)	1.08 (0.94 to 1.23)	1256 (4.3)	2232 (6.1)	0.82 (0.74 to 0.90)
40+	2958 (4.9)	549 (4.9)	1.12 (0.98 to 1.28)	1453 (5.0)	1912 (5.2)	1.10 (0.99 to 1.21)
p Value for trend			0.005			<0.001

Adjusted for age decades, race, education, alcohol use, insecticide exposure, OC use, BMI at 18 years, and hard exercise at 18 years.
Models for age at menopause are also adjusted for age at menarche.
BMI, body mass index; OC, oral contraceptive; SHS, secondhand smoke.

the reference group for each outcome. In the primary analysis among never-smokers who had any exposure to SHS (table 2), associations were not significant for either of the outcomes: OR's 1.08 (95% CI 0.98 to 1.19) and 1.07 (95% CI 0.99 to 1.15) respectively. In the quantified analysis of SHS and infertility (table 4), we observed positive, statistically significant associations at the highest level of lifetime exposure: childhood ≥10 years, adult home ≥20 years, adult work ≥10 years (OR 1.18; 95% CI 1.02 to 1.35). There was a significant dose–response trend with a p value of 0.013.

Adjusted OR's between quantified exposures to SHS in never-smokers and age at menopause earlier than 50 years were significant for the three highest levels of exposure (table 5), with the OR for the highest level (childhood ≥10 years, adult home ≥20 years and adult work ≥10 years) being 1.17 (95% CI 1.05 to 1.30). The observed positive trend for the adjusted values was significant (p≤0.001).

Table 6 shows a reduction in year fractions from the cohort mean age at menopause of never-smoking women not exposed to SHS (49.4±5.8 years) with each increasing level of exposure to SHS. At the highest level of exposure to SHS, the mean age at natural menopause is 48.3±6.8 years, a difference of 13.2 months; the trend in age reduction is significant with a p value of <0.001.

DISCUSSION

Summary of results

In the primary analysis, active-ever smokers (current or former) had significant associations for infertility and menopause occurring before the age of 50 years. Women who started smoking

Table 3 Smoking status and age at menopause quantified in mean-years

	Age at menopause	
	N (%)	Mean±SD Years
Smoking status		
Never-smoker		
Never-smoker, SHS none	3710 (4.7)	49.4±5.8
Never-smoker, SHS	36 095 (45.9)	48.8±6.2
Ever smokers	38 894 (49.4)	48.3±6.2
Crude model p value	<0.001	
Adjusted p value	<0.001	
Age started smoking (years)		
Never-smoker, SHS none	3710 (4.7)	49.4±5.8
Never-smoker, SHS	36 095 (45.7)	48.8±6.2
<15	2521 (3.2)	47.6±6.6
15–19	19 591 (24.8)	48.4±6.1
20–24	12 268 (15.5)	48.5±6.1
25–29	2596 (3.3)	48.1±6.6
≥30	2164 (2.7)	48.2±6.6
Crude model p value	<0.001	
Adjusted p value	<0.001	
Average cigarette/day		
Never-smoker, SHS none	3710 (4.8)	49.4±5.8
Never-smoker, SHS	36 095 (46.7)	48.8±6.2
<5	8764 (11.3)	48.7±6.2
5–14	11 905 (15.4)	48.4±6.2
15–24	10 296 (13.3)	48.2±6.1
≥25	6598 (8.5)	47.9±6.2
Crude model p value	<0.001	
Adjusted p value	<0.001	
Years smoked before menopause		
Never-smoker, SHS none	3710 (4.9)	49.4±5.8
Never-smoker, SHS	36 095 (47.5)	48.8±6.1
<5	2029 (2.7)	47.7±7.3
5–9	4227 (5.6)	47.7±7.3
10–19	10 080 (13.3)	47.0±7.1
20–29	12 177 (16.0)	47.8±4.9
30+	7709 (10.1)	51.9±3.5
Crude model p value	<0.001	
Adjusted p value	<0.001	
Pack-years before menopause		
Never-smoker, SHS none	3710 (5.0)	49.4±5.8
Never-smoker, SHS	36 095 (48.4)	48.8±6.1
<10	14 044 (18.8)	48.1±6.7
10 to <20	8485 (11.4)	48.3±6.1
20 to <30	4606 (6.2)	47.2±5.6
30 to <40	3905 (5.2)	49.9±5.0
40+	3773 (5.1)	49.7±4.8
Crude model p value	<0.001	
Adjusted p value	<0.001	

Adjusted for age decades, race, education, alcohol use, insecticide exposure, OC use, BMI at 18 years, hard exercise at 18 years, and age at menarche (n=69 183).
BMI, body mass index; OC, oral contraceptive; SHS, secondhand smoke.

before the age of 15 years had increased odds for difficulty conceiving lasting >1 year; these same women also reached natural menopause earlier than the cohort median of 50 years for never-smokers not exposed to SHS—this quantified as 21.6 months earlier. Risk estimates increased with positive trends for both outcomes with greater average number of cigarettes per day: at the highest number of 25+ cigarettes per day. Trend analyses for quantified active-ever smoking suggest dose–response effects.

For SHS exposure, associations were seen at the highest level of childhood and adult exposure for infertility. For SHS and menopause occurring before the age of 50 years, positive associations were seen for the three highest levels of exposure. The mean age at menopause was reduced by 13.2 months also at the highest level of SHS exposure.

Comparison with other studies

It has been well established that tobacco smoke exposure through active smoking adversely affects hormone-dependent women's health issues by multiple physiological mechanisms. Tobacco toxins affect multiple sites in hormonal synthesis and overall physiology to the deleterious effect on fecundity, fetal survival and age at natural menopause.[1 7 8 32] Recent studies support the hypothesis that tobacco exposure through active smoking adversely affects fertility.[1 4 6 21 32] Our large secondary data analysis of the WHI OS concurs with these established studies both in the primary analysis and in quantified levels of age starting smoking and average number of cigarettes smoked per day throughout life.

For age at natural menopause, several recent large prospective studies and meta-analyses reiterate the effects of active smoking on the timing of menopause.[31 33–36] Biologically, tobacco toxins negatively affect the hormonal milieu through differing mechanisms, and various studies have investigated levels of oestrone, oestradiol, oestriol, progesterone, follicle-stimulating hormone, luteinising hormone, and anti-Müllerian hormone (a direct measure of ovarian reserve); the results predict an early end to the reproductive life of the ovaries and uterus in women exposed to active smoke and SHS.[7–10 37–39] Similarly, genetic changes occur in exposed women that explain lower levels of reproductive hormones, retarded uterine growth from fewer bone marrow stem cells, and aneuploidy in diminishing numbers of viable oocytes.[10 37 39] Our results on active smoking concur with previous findings: for active-ever smokers, OR's for menopause occurring earlier than the cohort median of never-smokers with no SHS exposure (50 years) are significant for all levels of quantified smoking, and the mean age of menopause.[13 34] Consistent with other studies,[31 36] we observed an approximate 1–2 year earlier onset of menopause in participants exposed to passive and active smoke, the clinical importance of which is somewhat unclear. However, we should note that evidence shows that the risk of all-cause mortality increases with earlier age at menopause.[40] Given the association between tobacco smoke exposure and age at menopause, it is important for clinicians to discuss how lifestyle factors (such as exposure to tobacco smoke) may impact their patient's reproductive health.

In addition, several studies have shown significant associations with SHS exposure and earlier age at menopause, both from physiological and population studies.[9 11–15 35 38 39] A very early study in 1986 found such an association and brought out the necessity of using never-smoking women who have not been exposed to any SHS throughout life as a reference group.[11] Our study concurs and quantifies significant associations between lifetime SHS and earlier menopause.

Recent studies also support the hypothesis that tobacco exposure through active smoking adversely affects fertility.[1 4 6 21 32] Findings from laboratory and epidemiological studies specify mechanisms postulated for delayed conception, including fetal ovarian germ cell loss, increases in zona pellucida thickness, and pathways in steroidogenesis that were negatively affected by

Table 4 Infertility and ORs (95% CIs) of associations with lifetime SHS exposure among 44 560 never-smoking women

	Infertility			
Never-smokers exposed to SHS	No N (%)	Yes N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*
No SHS exposure	3577 (9.4)	573 (8.7)	1.0 (Ref)	1.0 (Ref)
Any				
Childhood only	2240 (5.9)	357 (5.4)	0.99 (0.86 to 1.15)	0.99 (0.86 to 1.16)
Adult home only	2439 (6.4)	398 (6.0)	1.02 (0.89 to 1.17)	1.05 (0.91 to 1.22)
Adult work only	4806 (12.7)	798 (12.1)	1.04 (0.92 to 1.16)	1.00 (0.88 to 1.13)
Childhood + adult home	4120 (10.9)	660 (10.0)	1.00 (0.89 to 1.13)	1.04 (0.91 to 1.18)
Childhood + adult work	3914 (10.3)	713 (10.8)	1.14 (1.01 to 1.28)	1.11 (0.98 to 1.26)
Adult home + work	5124 (13.5)	895 (13.5)	1.09 (0.97 to 1.22)	1.08 (0.96 to 1.22)
Childhood + adult home + work	11 725 (30.9)	2221 (33.6)	1.18 (1.07 to 1.31)	1.17 (1.05 to 1.30)
Quantified SHS exposure				
No childhood + any adult	12 271 (32.6)	2074 (31.6)	1.06 (0.95 to 1.17)	1.04 (0.94 to 1.16)
Childhood <10 years + any adult	3429 (9.1)	583 (8.9)	1.06 (0.94 to 1.20)	1.08 (0.94 to 1.23)
Childhood ≥10 years + adult home <20 years + adult work <10 years	8695 (23.1)	1592 (24.2)	1.14 (1.03 to 1.27)	1.13 (1.01 to 1.27)
Childhood ≥10 years + adult home <20 years + adult work ≥10 years	3727 (9.9)	687 (10.5)	1.15 (1.02 to 1.30)	1.13 (0.99 to 1.29)
Childhood ≥10 years + adult home ≥20 years + adult work <10 years	3106 (8.3)	515 (7.8)	1.04 (0.91 to 1.18)	1.04 (0.90 to 1.19)
Childhood ≥10 years + adult home ≥20 years + adult work ≥10 years	2833 (7.5)	544 (8.3)	1.20 (1.06 to 1.36)	1.18 (1.02 to 1.35)
Missing		47		
p trend			0.005	0.013

*Adjusted for age decades, race, education, alcohol use, insecticide exposure, OC use, BMI at 18 years and hard exercise at 18 years (n=38 767).
BMI, body mass index; OC, oral contraceptive; SHS, secondhand smoke.

tobacco smoke exposure.[5 6 23 32–34 41 42] Our findings support the association between active smoking and infertility. The suggestive dose–response relationship between heavier smoking and infertility found in our analysis are similar to measures of association found in another large prospective cohort study.[3] Associations between SHS and infertility have been studied since the 1980's with mixed results, perhaps due to small sample sizes and/or methodological limitations.[7 16 18–24 43] Using data from a large prospective cohort, our study adds to the evidence base by demonstrating significant associations between the highest SHS exposure during reproductive life and delayed conception.

Strengths and limitations

The large sample sizes of the WHI's OS give this secondary data analysis greater statistical power than that seen in previous studies. The data for the WHI is from 40 clinical centres across the USA, producing broad demographic generality across birth

Table 5 Earlier age at menopause (<50 years) and ORs (95% CIs) of associations with lifetime SHS exposure among 39 805 never-smoking women

	Earlier age at menopause			
Never-smokers exposed to SHS	<50, n (%)	≥50, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*
No SHS exposure	1499 (8.7)	2211 (9.8)	1.0 (Ref)	1.0 (Ref)
Any				
Childhood only	1029 (6.0)	1317 (5.8)	1.15 (1.04 to 1.28)	1.13 (1.01 to 1.26)
Adult home only	1043 (6.1)	1464 (6.5)	1.05 (0.95 to 1.16)	1.02 (0.91 to 1.14)
Adult work only	2079 (12.1)	2960 (13.1)	1.04 (0.95 to 1.13)	1.03 (0.94 to 1.13)
Childhood + adult home	1837 (10.7)	2449 (10.8)	1.11 (1.01 to 1.21)	1.07 (0.97 to 1.18)
Childhood + adult work	1838 (10.7)	2300 (10.2)	1.18 (1.08 to 1.29)	1.12 (1.01 to 1.23)
Adult Home + work	2364 (13.8)	3032 (13.4)	1.15 (1.06 to 1.25)	1.09 (0.99 to 1.19)
Childhood + adult home + work	5468 (31.9)	6915 (30.5)	1.17 (1.08 to 1.26)	1.09 (1.01 to 1.19)
Quantified SHS exposure				
No childhood + any adult	5440 (32.0)	7406 (32.9)	1.08 (1.01 to 1.17)	1.05 (0.97 to 1.14)
Childhood <10 years + any adult	1567 (9.2)	2022 (9.0)	1.14 (1.04 to 1.25)	1.06 (0.96 to 1.18)
Childhood ≥10 years + adult home <20 years + adult work <10 years	4012 (23.6)	5290 (23.5)	1.12 (1.04 to 1.21)	1.07 (0.98 to 1.16)
Childhood ≥10 years + adult home <20 years + adult work ≥10 years	1741 (10.2)	2159 (9.6)	1.19 (1.09 to 1.30)	1.13 (1.03 to 1.25)
Childhood ≥10 years + adult home ≥20 years + adult work <10 years	1419 (8.3)	1799 (8.0)	1.16 (1.06 to 1.28)	1.13 (1.02 to 1.26)
Childhood ≥10 years + adult home ≥20 years + adult work ≥10 years	1337 (7.9)	1600 (7.1)	1.23 (1.12 to 1.36)	1.17 (1.05 to 1.30)
Missing	142			
p trend			<0.001	<0.001

*Adjusted for age decades, race, education, alcohol use, insecticide exposure, OC use, BMI at 18 years, hard exercise at 18 years, and age at menarche (n=34 812).
BMI, body mass index; OC, oral contraceptive; SHS, secondhand smoke.

Table 6 Age at menopause quantified years by means and SHS exposure among 39 805 never-smoking women

	Age at menopause	
Never-smokers exposed to SHS	**N (%)**	**Mean±SD**
Quantified SHS exposure		
No SHS exposure	3710 (9.4)	49.4±5.8
No childhood + any adult	12 846 (32.5)	48.9±6.1
Childhood <10 years + any adult	3589 (9.1)	48.8±6.2
Childhood ≥10 years + adult home <20 years + adult work <10 years	9302 (23.7)	48.9±5.8
Childhood ≥10 years + adult home <20 years + adult work ≥10 years	3900 (9.9)	48.5±6.4
Childhood ≥10 years + adult home ≥20 years + adult work <10 years	3218 (8.2)	48.7±6.1
Childhood ≥10 years + adult home ≥20 years + adult work ≥10 years	2937 (7.4)	48.3±6.8
Missing	303	
Crude model p value	<0.001	
Adjusted p value	<0.001	

Adjusted for age decades, race, education, alcohol use, insecticide exposure, OC use, BMI at 18 years, hard exercise at 18 years and age at menarche (n=34 580).
BMI, body mass index; OC, oral contraceptive; SHS, secondhand smoke.

cohorts, race, education, socioeconomic status, and fertility status. The detailed data on exposures, outcomes and potential confounders provided the opportunity for comprehensive and quantified analyses, including lifetime quantitative measures of active and passive smoke exposure. This detail allows quantified analyses of SHS exposure in three critical areas of life: childhood, adult at home and adult at work. The questionnaires have been designed to provide credible data and baseline measures have shown to be reliable.[29]

Limitations of this study include those associated with any cross-sectional study, especially since the data are historical and self-reported. For example, errors in recall can impact accuracy in reporting age at menopause,[44] and exposure to tobacco smoke has been shown to be under-reported in certain populations on the basis of recall issues.[45] Questions throughout the data set were structured to minimise recall bias and error, and a reliability subsample demonstrated acceptable limits.[29] Therefore, we conclude that any potential misclassification resulting from recall issues related to smoke exposure could result in more conservative estimates on the outcomes of interest. Additionally, the issue of causality called for by the Surgeon General's Report of 2006 is strengthened by our findings, but causality cannot be inferred. Historical data on these reproductive outcomes—particularly difficulty conceiving—have the potential for misclassification of exposures: tobacco exposures may have occurred after any attempt at conception. The effect of this type of error may have manifested itself for infertility in table 2—this would explain the loss of significance for associations with infertility: women who started smoking after the age of 25 years would be less likely to attempt conception, especially for the older age cohorts in the WHI. There is no such loss of significance for age at menopause.

Another source of potential error is underadjustment by covariates in analysis models. The historical data in this cohort do not specify the temporality of covariates in relation to the outcome of infertility, particularly oral contraceptive and alcohol use. To minimise such error in adjustment, broad categories were used for these covariates—'ever/never' use of oral contraceptives and 'yes/no' to 12 drinks ever in lifetime. Largely due to the age of participants at enrolment (50–79 years), there is no data on the smoking habits of the participants' own mothers, precluding a measure of *in utero* exposure to tobacco smoke. This important period of tobacco exposure has been studied for many outcomes in the female offspring of smokers, including fecundity and age at menopause, where many studies, including those with epigenetic analyses, demonstrate significant associations.[46–48]

Finally, there may be potential confounding by male factor infertility. Although we defined infertility as 'the inability to conceive after 12 months of actively trying, seeking medical advice, and the male partner not being a cause', we cannot completely rule out infertility due to the male partner. However, there is no reason to think that this would be differential between the exposure categories.

Conclusions

Our study demonstrates significant associations between lifetime tobacco exposure—by active smoking of current and former smokers and by independently studied SHS exposure—and women's health issues of infertility and menopause occurring before the age of 50 years. It is one of the first studies of this size and statistical power to investigate and quantify active and passive smoking and women's health issues. It strengthens the current evidence that all women need to be protected from active and passive tobacco smoke.

What this paper adds

- This study demonstrates significant associations between lifetime tobacco exposure—by active smoking of current and former smokers and by independently studied secondhand smoke exposure—and women's health issues of infertility and menopause occurring before the age of 50 years.
- This is one of the first studies of this size and statistical power to investigate and quantify active and passive smoking and women's health issues.
- This strengthens the current evidence that all women need to be protected from active and passive tobacco smoke.

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