TC Online First, published on February 26, 2014 as 10.1136/tobaccocontrol-2013-051458

Associations of lifetime active and passive smoking with spontaneous abortion, stillbirth and tubal ectopic pregnancy: a cross-sectional analysis of historical data from the Women's Health Initiative

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Received 3 December 2013
Accepted 7 January 2014

To cite: Hyland A, Piazza KM, Hovey KM, *et al*. *Tob Control* Published Online First: [*please include* Day Month Year] doi:10.1136/tobaccocontrol-2013-051458

ABSTRACT

Objective To examine the associations between tobacco exposure and adverse pregnancy outcomes using quantitative measures of lifetime active smoking and secondhand smoke (SHS) exposure.

Methods Historical reproductive data on 80 762 women who participated in the Women's Health Initiative Observational Study were examined with a cross-sectional analysis. We assessed self-reported lifetime active and passive tobacco smoke exposure, self-reported spontaneous abortions, stillbirths and ectopic pregnancies.

Results When compared with never-smoking women, participants who were ever active smokers during their reproductive years had ORs (OR) of 1.16 (95% CI 1.08 to 1.26) for 1 or more spontaneous abortions, 1.44 (95% CI 1.20 to 1.73) for 1 or more stillbirths, and 1.43 (95% CI 1.10 to 1.86) for 1 or more ectopic pregnancies. Never-smoking women participants with the highest levels of lifetime SHS exposure, including childhood >10 years, adult home >20 years and adult work exposure >10 years, when compared with never-smoking women with no SHS exposure had adjusted ORs of 1.17 (95% CI 1.05 to 1.30) for spontaneous abortion, 1.55 (95% CI 1.21 to 1.97) for stillbirth, and 1.61 (95% CI 1.16 to 2.24) for ectopic pregnancy.

Conclusions Women who were ever-smokers during their reproductive years had significantly greater estimates of risk for spontaneous abortion, stillbirth and tubal ectopic pregnancy. Never-smoking women with the highest levels of lifetime exposure to SHS had significantly increased estimates of risk for spontaneous abortion, stillbirth and tubal ectopic pregnancy.

INTRODUCTION

Numerous epidemiological and experimental studies have shown associations between tobacco smoke exposure and reproductive outcomes.[1–4] Experimental studies using cell culture and animal models have clearly demonstrated the deleterious effects of tobacco smoke on reproduction.[5] Studies of secondhand smoke (SHS) exposure in animals have shown increases in congenital anomalies, poor fetal growth of multiple organ systems and fetal death.[6] Studies using hamsters have demonstrated Fallopian tube dysfunction when exposed to unfiltered tobacco smoke—a model that suggests a mechanism for ectopic pregnancies.[7] In addition to reducing Fallopian tube mobility, polycyclic aromatic hydrocarbons and heavy metals in SHS have endocrine-disrupting and immunomodulating effects that adversely affect organogenesis in weeks 3 to 8 of gestation, and downwardly modulate the fetal-protective milieu provided by progesterone and immunosuppressive peptides from the placenta.[8]

Active smoking by pregnant women has been studied extensively for the past several decades, and is known to be associated with infertility, preterm birth, fetal loss by spontaneous abortion and stillbirth, low birth weight, slowed fetal growth, ectopic pregnancies, some congenital malformations, perinatal death and SIDS.[2 3 8 9] Maternal smoking during gestation is strongly associated with many of these adverse pregnancy outcomes, and in a few outcomes, considered to be causal.[10] While active smoking by the mother has shown significant associations with the three outcomes of fetal loss studied here—spontaneous abortion (loss <20 weeks gestation), stillbirth (loss ≥20 weeks to birth) and tubal ectopic pregnancy—such evidence for SHS exposure is less complete. For spontaneous abortion (miscarriage), five studies showed no association with SHS exposure measured only during gestation by self-report[11–14] or by cotinine levels.[15] None of these studies measured SHS using quantified, lifetime exposure levels. Two studies showed significant associations: one used quantified paternal smoking during gestation, and found significance at the highest level of exposure,[16] and the other used exposure quantified by zero, one or both parents smoking during the mother's own childhood. This study also showed trend significance for dose-response.[17] For stillbirth, a few studies have shown significant associations between SHS exposure during gestation, mainly by paternal smoking, and fetal loss >20 weeks.[11 18 19] Others have shown no effect of SHS.[20 21] Like the studies on spontaneous abortion, however, none used quantified, lifetime SHS exposure measures. One study did show significance for any fetal loss using quantified, lifetime SHS exposure including childhood. This study also showed significance in dose-response trend.[22] For tubal ectopic pregnancy, three studies showed strong associations for active maternal smoking during pregnancy, but no effect from SHS. The SHS was only measured by paternal smoking during gestation.[10 23 24] The 2006 Surgeon General's Report on SHS and reproductive outcomes states the evidence to date is inadequate to infer the presence or absence of a causal

relationship between SHS exposure during pregnancy and fetal loss and/or fecundability.[25] Again, lifetime exposure is not considered in this conclusion.

A Canadian review of SHS and breast cancer suggests inconsistent results seen in many studies on the independent effects of SHS are due largely to inadequate and incorrect exposure measurements. Studies showing reduced or insignificant risk estimates do not include adequate measurement of all lifetime periods of SHS exposure, such as childhood, adult home and adult work exposures. Additionally, the reference group for many of these studies was not strictly limited to never-smokers not exposed to any SHS throughout life. The resulting non-differential exposure misclassification dilutes the risk estimates and moves any true association toward the null.[26] In the present study, detailed information on lifetime tobacco exposure—active and passive–was collected from historical data from the large Women's Health Initiative Observational Study (WHI OS), including quantified current and former smoking status and quantified SHS exposure data from childhood and adult home and work venues. The cohort was large enough to allow for a true reference group of never-smokers not exposed to any SHS of sufficient size for analysis. We investigate potential associations between active and passive lifetime tobacco exposures and the three adverse pregnancy outcomes of fetal loss: spontaneous abortion, stillbirth and tubal ectopic pregnancy.

METHODS

Data source

Women's health initiative

The Observational Study Arm of the WHI is part of a large cohort of postmenopausal women that can be used to study health issues using data at baseline, and prospectively for two decades or more. Initial enrolment was for 93 676 women aged 50–79 years at 40 clinical centres in the USA from 1993 to 1998.[27 28] Human subjects committees and a central data monitoring board oversee ethical conduct of the study. Data used in this study is from a comprehensive questionnaire completed by participants enrolled at all centres. For this study, 80 762 women who reported being pregnant at least once were included in the data analysis. Women with missing values for smoking status, SHS exposure, the outcomes of interest, or any of the multiple covariates were excluded from the final analysis. After exclusions, 77 805 (96.3%) women were used in the final adjusted analysis.

Measurement of tobacco exposure and confounders

All data used in this study were collected at enrolment about exposures, potential confounders and reproductive events occurring in the participants' past. Question lines were structured to minimise recall bias and error, and a reliability subsample demonstrated acceptable limits.[28] Women were initially classified by active smoking status into current, former or never-smokers (participants who had not smoked 100 cigarettes in life). Out of 80 762 women with data on pregnancy outcomes, 5082 (6.3%) were current smokers and 34 830 (43.1%) were former smokers: these ever-smokers were defined as answering 'yes' to 'have you smoked 100 cigarettes in your life?'; 40 850 (50.6%) were never-smokers, defined as answering 'no' to the same question. For quantification of active smoking, current and former smokers at baseline were combined into one exposure variable, 'ever-smoker' since age at quitting for former smokers could not be correlated with individual pregnancies. Active, ever-smoking, was quantified with variables of age at which subjects started smoking, the number of years smoked before menopause, and the average number of cigarettes smoked per day. Pack-years smoked during reproductive years calculated by the number of years smoked before menopause times the average number of cigarettes per day divided by 20.

Both classes of ever-smoker (current and former) and never-smoker were further classified by SHS exposure: initially this was a dichotomous measure—yes or no for childhood (exposed <18 years of age), yes or no for adult home and work venues (exposed >18 years of age at home, >18 years of age at a workplace). Because active smoking confounds the effects of SHS, analysis of SHS exposure was limited to never-smoking women (n=40 850). Quantification of SHS exposure was related to the number of years women were exposed in childhood, adult at home and adult at work venues. Considering a priori estimates and classifications of SHS in other WHI studies,[29] exposure to SHS was quantified as '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 ears;' 'childhood ≥10 years+adult home ≥20 years+adult work <10 years;' and 'childhood ≥ 10 years+adult home ≥20 years+adult work ≥10 years.'

Potential confounders used in the multivariate analyses included age cohort at baseline (<60, 60–69 and 70+ years), mean Body Mass Index (BMI) from age 18 to 50 (<20, 20–<26, 26–<30 and 30+ years) years, ethnicity (non-Hispanic Caucasian, African–American, Hispanic, and other), education (<HS grad, HS or some college and college degree or higher), parity (never had term pregnancy, 12 345+), alcohol use (12 drinks ever in lifetime, yes/no), and oral contraceptive use (ever/no). See table 1 for baseline characteristics. Potential confounders not in the final adjustment models were ages at first and last term birth, induced abortions, income at baseline and insecticide exposure in the past, and number of pregnancies. The excluded covariates had large amounts of missing data, and early models including them were not different from the final model.

Pregnancy outcomes

Self-reported data on none or one or more adverse pregnancy outcomes of spontaneous abortion (gestation <20 weeks), stillbirth (gestation 20 weeks to term), and tubal ectopic pregnancy were taken from historical reproductive datasets on current, former and never-smoking women who were pregnant at least once (n=80 762). Among these women, 26 307 (32.6%) reported having at least one spontaneous abortion, 3552 (4.4%) reported at least one stillbirth and 2033 (2.5%) reported at least one tubal ectopic pregnancy. Sample sizes for two or more events were too small for analysis.

Statistical analysis

In the dataset, active smoking was defined as 'current,' 'former,' or 'never' smokers. Because it could not be established precisely when active smoking or quitting smoking occurred in relation to reproductive events, current and former smokers were included in a new variable, 'ever-smoker.' The two categories used in the analysis were then 'ever-smokers' and 'never-smokers'. As described above, never-smokers were further categorised by exposure to SHS; the reference group was never-smokers not exposed to any SHS. The variable for ever-smokers was quantified by using the following measures: age started smoking with the categories <15 years, 15–19 years, 20–24 years, 25–29 years and 30+ years of age. For smoking before first term birth, categories were 'yes'/'no'/ 'not sure', and participants without at least one term pregnancy were excluded from this analysis. Average number of

Table 1 Baseline characteristics of 80 762 women from the Women's Health Initiative Observational Study

Baseline characteristics	Spontaneous abortions			Stillbirths			Tubal ectopic		
	1 or more n (%)	None n (%)	p Value	1 or more n (%)	None n (%)	p Value	1 or more n (%)	None n (%)	p Value
Age (years)									
<60	7723 (29.4)	17 852 (32.8)	<0.0001	954 (26.9)	24 621 (31.9)	<0.0001	709 (34.9)	24 866 (31.6)	0.0053
60–<70	12 071 (45.9)	23 914 (43.9)		1647 (46.4)	34 338 (44.5)		850 (41.8)	35 135 (44.6)	
≥70	6513 (24.8)	12 689 (23.3)		951 (26.8)	18 251 (23.6)		474 (23.3)	18 728 (23.8)	
Body Mass Index 18–50 (kg/m^2)									
<20	4211 (16.4)	9012 (16.9)	<0.0001	504 (14.7)	12 719 (16.8)	<0.0001	297 (15.1)	12 926 (16.8)	<0.0001
20–<26	18 634 (72.4)	38 967 (73.1)		2411 (70.4)	55 190 (73.0)		1401 (71.2)	56 200 (72.9)	
26–<30	20 303 (7.9)	3915 (7.3)		344 (10.0)	5601 (7.4)		185 (9.4)	5760 (7.5)	
≥30	857 (3.3)	1446 (2.7)		165 (4.8)	2138 (2.8)		85 (4.3)	2218 (2.9)	
Ethnicity									
Caucasian (NH)	21 626 (82.5)	45 866 (84.5)	<0.0001	2540 (71.8)	64 952 (84.4)	<0.0001	1376 (67.9)	66 116 (84.2)	<0.0001
African–American	2498 (9.5)	4036 (7.4)		548 (15.5)	5986 (7.8)		433 (21.4)	6101 (7.8)	
Hispanic	1065 (4.1)	1935 (3.6)		287 (8.1)	2713 (3.5)		139 (6.9)	2861 (3.6)	
Other	1037 (4.0)	2473 (4.6)		165 (4.7)	3345 (4.3)		78 (3.8)	3432 (4.4)	
Education									
<HS	1500 (5.7)	2735 (5.1)	<0.0001	379 (10.8)	3856 (5.0)	<0.0001	190 (9.5)	4045 (5.2)	<0.0001
HS grad/college	14 413 (55.2)	29 170 (54.0)		2000 (56.9)	41 583 (54.3)		1137 (56.6)	42 446 (54.3)	
College degree+	10 175 (39.0)	22 139 (41.0)		1139 (32.4)	31 175 (40.7)		683 (34.0)	31 631 (40.5)	
Alcohol use*									
No	2913 (11.1)	6703 (12.3)	<0.0001	583 (16.5)	9033 (11.7)	<0.0001	258 (12.7)	9358 (11.9)	0.2621
Yes	23 349 (88.9)	47 672 (87.7)		2958 (83.5)	68 063 (88.3)		1770 (87.3)	69 251 (88.1)	
OC use ever									
No	15 308 (58.2)	31 753 (58.3)	0.7490	2238 (63.0)	44 823 (58.1)	<0.0001	1289 (63.4)	45 772 (58.1)	<0.0001
Yes	10 998 (41.8)	22 702 (41.7)		1313 (37.0)	32 387 (41.9)		744 (36.6)	32 956 (41.9)	
Parity									
Never	1166 (4.4)	1273 (2.4)	<0.0001	0 (0.0)	2439 (3.2)	<0.0001	234 (11.5)	2205 (2.8)	<0.0001
1	2243 (8.5)	5901 (10.9)		123 (3.5)	8021 (10.4)		309 (15.2)	7835 (10.0)	
2	6390 (24.3)	17 121 (31.6)		346 (9.8)	23 165 (30.1)		484 (23.8)	23 027 (29.4)	
3	6665 (25.4)	14 911 (27.5)		753 (21.2)	20.823 (27.1)		468 (23.0)	21 108 (26.9)	
4	4601 (17.5)	8359 (15.4)		843 (23.8)	12 117 (15.8)		238 (11.7)	12 722 (16.2)	
5+	5224 (19.9)	6565 (12.1)		1481 (41.8)	10 308 (13.4)		298 (14.7)	11 491 (14.7)	
Smoking status									
Never smoked	12 789 (48.6)	28 061 (51.5)	<0.0001	1768 (49.8)	39 082 (50.6)	0.0002	936 (46.0)	39 914 (50.7)	<0.0001
Past smoker	11 627 (44.2)	23 203 (42.6)		1502 (42.3))	33 328 (43.2)		874 (43.0)	33 956 (43.1)	
Current smoker	1891 (7.2)	3191 (5.9)		282 (7.9)	4800 (6.2)		223 (11.0)	4859 (6.2)	
Never smoked†									
None	1134 (8.9)	2655 (9.5)	0.0006	158 (8.9)	3631 (9.3)	0.2060	69 (7.4)	3720 (9.3)	0.1764
Child only	730 (5.7)	1669 (5.9)		90 (5.1)	2.309 (5.9)		41 (4.4)	2358 (5.9)	
Adult home	861 (6.7)	1874 (6.7)		102 (5.8)	2633 (6.7)		61 (6.5)	2674 (6.7)	
Adult work	1481 (11.6)	3365 (12.0)		211 (11.9)	4635 (11.9)		108 (11.5)	4738 (11.9)	
Child+ adult home	1457 (11.4)	3084 (11.0)		190 (10.7)	4351 (11.1)		111 (11.9)	4430 (11.1)	
Child+adult work	1165 (9.1)	2877 (10.3)		164 (9.3)	3878 (9.9)		98 (10.5)	3944 (9.9)	
Adult home+work	1818 (14.2)	3826 (13.6)		250 (14.1)	5394 (13.8)		130 (13.9)	5514 (13.8)	
Child+adult home+work	4143 (32.4)	8711 (31.0)		603 (34.1)	12 251 (31.3)		318 (34.0)	12 536 (31.4)	

*Drank 12 alcoholic beverages ever.
†Second hand smoke exposure in never-smokers only.

cigarettes per day were categorised into <5, 5–14, 15–24 and 25 +. The category of total years smoking before menopause was broken down into <5, 5–9, 10–19, 20–29 and 30+ years. Pack-years before menopause were calculated by the formula mentioned previously and were categorised into <10, 10–<20, 20–<30, 30–<40 and 40+ pack-years. ORs for ever-smokers were estimated using never-smoking women with no exposure to SHS as a reference group; in the historical dataset this category had 3789 women in it.

As explained above, analysis of SHS exposure was limited to 40 850 women who had never smoked. Since the outcomes of interest were spontaneous abortions, stillbirths and tubal ectopic pregnancies, all the 40 850 women were pregnant at least once. In order to analyse all possible combinations of SHS exposures from all venues (childhood, adult home and adult work), we started with a bivariate analysis using combinations of the three exposure periods with a dichotomous outcome—yes or no. A variable of mutually exclusive categories was constructed covering these combinations: childhood only, adult home only, adult work only, childhood + adult home, childhood+adult work, and a complete lifetime exposure category of childhood+adult home+adult work. Based on frequency of responses and

Table 2 Adverse pregnancy outcomes and OR's associated with smoking status among 77 805 women in the Women's Health Initiative Observational Study

	Spontaneous abortions		Stillbirths		Ectopic pregnancy	
	n	OR (95% CI)*	n	OR (95% CI)*	n	OR (95% CI)*
Smoking status						
Never smoker						
Never, SHS none	1083	1.0 (Ref)	138	1.0 (Ref)	64	1.0 (Ref)
Never, SHS	11 224	1.05 (0.97 to 1.13)	1526	1.22 (1.02 to 1.47)	826	1.25 (0.96 to 1.62)
Ever smokers	13 079	**1.16 (1.08 to 1.26)**	1700	**1.44 (1.20 to 1.73)**	1043	**1.43 (1.10 to 1.86)**
Age started smoking						
Never, SHS None	1083	1.0 (ref)	138	1.0 (ref)	64	1.0 (ref)
Never, SHS	11 224	1.05 (0.98 to 1.14)	1526	1.22 (1.02 to 1.47)	826	1.25 (0.96 to 1.62)
<15	964	**1.37 (1.23 to 1.53)**	129	**1.55 (1.20 to 2.01)**	90	**1.79 (1.28 to 2.49)**
15–19	6598	**1.18 (1.09 to 1.28)**	801	**1.39 (1.14 to 1.68)**	473	**1.34 (1.02 to 1.75)**
20–24	3873	**1.10 (1.02 to 1.20)**	511	**1.45 (1.19 to 1.77)**	315	**1.39 (1.06 to 1.84)**
25–29	868	**1.18 (1.05 to 1.31)**	125	**1.47 (1.14 to 1.90)**	90	**1.66 (1.19 to 2.32)**
≥30	730	**1.15 (1.02 to 1.29)**	129	**1.62 (1.25 to 2.09)**	71	**1.67 (1.18 to 2.37)**
p Value for trend		<0.001		<0.001		<0.001
Started smoking before 1st term birth†						
Never, SHS None	1083	1.0 (Ref)	138	1.0 (Ref)	64	1.0 (Ref)
Never, SHS	11 224	1.05 (0.97 to 1.13)	1526	**1.22 (1.02 to 1.47)**	826	1.25 (0.97 to 1.62)
Yes	7575	**1.29 (1.19 to 1.39)**	938	**1.56 (1.29 to 1.88)**	475	**1.38 (1.05 to 1.80)**
No	1530	**1.27 (1.15 to 1.40)**	268	**1.56 (1.25 to 1.94)**	159	**1.97 (1.46 to 2.66)**
Not Sure	2636	**1.19 (1.09 to 1.30)**	406	**1.46 (1.19 to 1.79)**	207	**1.56 (1.17 to 2.09)**
Average cig/day						
Never, SHS None	1083	1.0 (Ref)	138	1.0 (Ref)	64	1.0 (Ref)
Never, SHS	11 224	1.05 (0.98 to 1.14)	1526	**1.23 (1.02 to 1.47)**	826	1.25 (0.96 to 1.62)
<5	2878	**1.13 (1.04 to 1.23)**	352	**1.23 (1.00 to 1.52)**	235	**1.38 (1.04 to 1.83)**
5–14	4015	**1.16 (1.07 to 1.26)**	524	**1.40 (1.14 to 1.70)**	361	**1.57 (1.20 to 2.07)**
15–24	3442	**1.18 (1.08 to 1.29)**	434	**1.49 (1.22 to 1.83)**	259	**1.40 (1.06 to 1.86)**
≥25	2215	**1.22 (1.12 to 1.34)**	323	**1.88 (1.52 to 2.32)**	159	**1.40 (1.03 to 1.89)**
p Value for trend		<0.001		<0.001		0.003
Number of years smoked before menopause						
Never, SHS None	1083	1.0 (Ref)	138	1.0 (Ref)	64	1.0 (Ref)
Never, SHS	11 224	1.05 (0.98 to 1.14)	1526	**1.22 (1.02 to 1.46)**	826	1.25 (0.96 to 1.62)
<5	688	**1.25 (1.11 to 1.41)**	85	**1.38 (1.04 to 1.84)**	49	1.34 (0.92 to 1.96)
5–9	1318	1.10 (0.99 to 1.22)	143	1.14 (0.89 to 1.46)	89	1.18 (0.85 to 1.64)
10–19	3272	1.16 (1.06 to 1.26)	436	1.49 (1.22 to 0.83)	280	1.52 (1.15 to 2.01)
20–29	3935	**1.16 (1.06 to 1.26)**	508	**1.45 (1.19 to 1.77)**	336	**1.50 (1.14 to 1.98)**
30+	2492	**1.18 (1.08 to 1.29)**	320	**1.41 (1.14 to 1.74)**	158	1.18 (0.87 to 1.59)
p Value for trend		<0.001		<0.001		0.023
Pack-years before menopause						
Never, SHS None	1083	1.0 (Ref)	138	1.0 (Ref)	64	1.0 (Ref)
Never, SHS	11 224	1.05 (0.98 to 1.14)	1526	**1.22 (1.02 to 1.47)**	826	1.25 (0.96 to 1.62)
<10	4537	**1.14 (1.05 to 1.24)**	568	**1.32 (1.08 to 1.61)**	366	**1.40 (1.07 to 1.84)**
10–<20	2777	**1.16 (1.06 to 1.27)**	375	**1.48 (1.20 to 1.82)**	240	**1.51 (1.13 to 2.00)**
20–<30	1491	**1.18 (1.07 to 1.30)**	179	**1.43 (1.13 to 1.81)**	123	**1.51 (1.11 to 2.07)**
30–<40	1246	**1.17 (1.06 to 1.29)**	152	**1.44 (1.12 to 1.83)**	72	1.08 (0.77 to 1.53)
40+	1239	**1.26 (1.14 to 1.39)**	173	**1.78 (1.40 to 2.26)**	90	**1.46 (1.05 to 2.04)**
p Value for trend		<0.001		<0.001		0.051

Numbers in bold are significant at the p<0.05 level.
*Adjusted for mean BMI (age 18–50), age cohort at baseline, ethnicity, education, alcohol intake, parity and oral contraceptive use (ever).
†Excluding those with no term pregnancy.
SHS, secondhand smoke

working from a previous WHI analysis of SHS,[29] we quantified the categories into 10-year exposure segments for all venues. The 10-year quantified categories of never-smokers' SHS exposure are described above and listed in table 3–5. Using logistic regression, ORs and 95% CIs were calculated for all categories of never-smokers and ever-smokers with the reference group being never-smokers not exposed to any SHS. A second reference group of never-smokers with SHS exposure for analysis of the effects of ever-smoking alone on outcomes was not created for two reasons. First, SHS exposure is a confounder of active (ever) smoking, and precise adjustment for this is difficult; second, our goal was to investigate the effects of total lifetime tobacco exposure and the independent effect of SHS but not the independent effect of active smoking alone. It is well

Table 3 Spontaneous abortions (miscarriages) and odds ratios (95% confidence limits) of associations with lifetime SHS exposure among 40 850 never-smoking women* who were pregnant at least once

Never-smokers exposed to secondhand smoke	Spontaneous abortions n (%) of total	Crude OR (95% CI)	Adjusted OR† (95% CI)
No SHS exposure	1134 (29.9) of 3789	1.0 (Reference)	1.0 (Reference)
Any:			
Childhood only	730 (30.4) of 2399	1.02 (0.92 to 1.14)	1.04 (0.93 to 1.17)
Adult home only	861 (31.5) of 2735	1.08 (0.97 to 1.20)	1.03 (0.92 to 1.15)
Adult work only	1481 (30.6) of 4846	1.03 (0.94 to 1.13)	1.04 (0.94 to 1.14)
Childhood+adult home	1457 (32.1) of 4541	**1.11 (1.01 to 1.21)**	1.08 (0.98 to 1.19)
Childhood+adult work	1165 (28.8) of 4042	0.95 (0.86 to 1.04)	0.97 (0.87 to 1.07)
Adult home+adult work	1818 (32.2) of 5644	**1.11 (1.02 to 1.22)**	1.08 (0.98 to 1.18)
Childhood+adult home+work	4143 (32.2) of 12 854	**1.11 (1.03 to 1.20)**	**1.10 (1.02 to 1.20)**
Quantified SHS exposure:			
No childhood+any adult	4133 (31.5) of 13 125	1.08 (0.99 to 1.16)	1.05 (0.97 to 1.14)
Childhood <10 years+any adult	1120 (30.7) of 3653	1.04 (0.94 to 1.14)	1.01 (0.91 to 1.11)
Childhood ≥10 years+adult home<20 years+adult work <10 years	2927 (30.8) of 9506	1.04 (0.96 to 1.13)	1.06 (0.97 to 1.15)
Childhood ≥10 years+adult home <20 years+adult work ≥10 years	1123 (29.6) of 3789	0.99 (0.89 to 1.09)	1.00 (0.90 to 1.10)
Childhood ≥10 years+adult home ≥20 years+adult work <10 years	1197 (33.8) of 3538	**1.20 (1.08 to 1.32)**	**1.14 (1.03 to 1.26)**
Childhood ≥ 10 years+adult home ≥ 20 years+adult work ≥ 10 years	1046 (33.5) of 3125	**1.18 (1.06 to 1.30)**	**1.17 (1.05 to 1.30)**
p Value for trend		0.007	0.008

Numbers in bold are significant at the p<0.05 level.
*39 206 after adjustment of categorical exposure; 38 910 after adjustment of quantified exposure.
†Adjusted for mean Body Mass Index (age 18–50 years), age cohort at baseline, ethnicity, education, alcohol intake, parity and oral contraceptive use (ever).
SHS, secondhand smoke

accepted that active smoking is strongly associated with the three outcomes of this study, and further analysis would add little. The results were adjusted for the potential confounders described previously and footnoted in tables 2–5. All variables considered for the models were chosen based on a review of the literature.[14 15 22] Only participants with complete data on exposure, potential confounders and outcomes were included in multivariate regression models. Less than 10% of subjects were excluded from analyses of all models due to missing data. p Values were calculated for trends across categories. Statistical analyses were carried out using SAS (V.9.2 SAS Institute, Cary, North Carolina, USA).

RESULTS

Baseline characteristics of 80 762 women from the WHI Observational Study are shown in table 1 by the three adverse pregnancy outcomes. Women who were <60 years of age at enrolment were less likely to have one or more miscarriages or

Table 4 Stillbirths and ORs (95% confidence limits) of associations with lifetime secondhand smoke (SHS) exposure among 40 850 never-smoking women* who were pregnant at least once

Never-smokers exposed to SHS	Stillbirths n (%) of total	Crude OR (95% CI)	Adjusted OR† (95% CI)
No SHS exposure	158 (4.2) of 3789	1.0 (Reference)	1.0 (Reference)
Any:			
Childhood only	90 (3.8) of 2399	0.90 (0.69 to 1.17)	1.07 (0.81 to 1.42)
Adult home only	102 (3.7) of 2735	0.89 (0.69 to 1.15)	0.81 (0.62 to 1.08)
Adult work only	211 (4.4) of 4846	1.05 (0.85 to 1.29)	**1.33 (1.06 to 1.67)**
Childhood+adult home	190 (4.2) of 4541	1.00 (0.81 to 1.24)	1.08 (0.86 to 1.37)
Childhood+adult work	164 (4.1) of 4042	0.97 (0.78 to 1.21)	**1.31 (1.03 to 1.66)**
Adult home+adult work	250 (4.4) of 5644	1.07 (0.87 to 1.31)	1.22 (0.98 to 1.53)
Childhood+adult home+work	603 (4.7) of 12 854	1.13 (0.95 to 1.35)	**1.38 (1.14 to 1.69)**
Quantified SHS exposure:			
No childhood+any adult	555 (4.2) of 13 125	1.01 (0.85 to 1.22)	1.16 (0.96 to 1.42)
Childhood <10 years+any adult	152 (4.2) of 3653	1.00 (0.79 to 1.25)	1.10 (0.86 to 1.40)
Childhood ≥10 years+adult home <20 years+adult work <10 years	369 (3.9) of 9506	0.93 (0.77 to 1.12)	1.16 (0.94 to 1.43)
Childhood ≥10 years+adult home <20 years+adult work ≥10 years	178 (4.7) of 3789	1.13 (0.91 to 1.41)	**1.61 (1.27 to 2.04)**
Childhood ≥10 years+adult home ≥20 years+adult work <10 years	164 (4.6) of 3538	1.12 (0.89 to 1.40)	1.18 (0.93 to 1.50)
Childhood ≥10 years+adult home ≥20 years+adult work ≥10 years	164 (5.2) of 3125	**1.27 (1.02 to 1.59)**	**1.55 (1.21 to 1.97)**
p Value for trend		0.022	<0.001

Numbers in bold are significant at the p<0.05 level.
*39 206 after adjustment of categorical exposure; 38 910 after adjustment of quantified exposure.
†Adjusted for mean BMI (age 18–50), age cohort at baseline, ethnicity, education, alcohol intake, parity and oral contraceptive use (ever).

Table 5 Tubal ectopic pregnancy and ORs (95% confidence limits) of associations with lifetime secondhand smoke (SHS) exposure among 40 850 never-smoking women* who were pregnant at least once

Never-smokers exposed to SHS	Ectopic pregnancy n (%) of total	Crude OR (95% CI)	Adjusted OR† (95% CI)
No SHS exposure	69 (1.8) of 3789	1.0 (Reference)	1.0 (Reference)
Any:			
Childhood only	41 (1.7) of 2399	0.94 (0.64 to 1.38)	1.01 (0.67 to 1.51)
Adult home only	61 (2.2) of 2735	1.23 (0.87 to 1.74)	1.20 (0.83 to 1.72)
Adult work only	108 (2.2) of 4846	1.23 (0.91 to 1.67)	1.16 (0.85 to 1.60)
Childhood+adult home	111 (2.4) of 4541	1.35 (1.00 to 1.83)	1.36 (0.99 to 1.87)
Childhood+adult work	98 (2.4) of 4042	1.34 (0.98 to 1.83)	**1.39 (1.00 to 1.92)**
Adult home+adult work	130 (2.3) of 5644	1.27 (0.95 to to 1.71)	1.14 (0.83 to 1.55)
Childhood+adult home+work	318 (2.5) of 12 854	**1.37 (1.05 to 1.78)**	1.31 (0.99 to 1.73)
Quantified SHS exposure:			
No childhood+any adult	294 (2.2) of 13 125	1.24 (0.95 to 1.61)	1.15 (0.87 to 1.51)
Childhood <10 years+any adult	92 (2.5) of 3653	**1.39 (1.02 to 1.91)**	1.26 (0.91 to 1.76)
Childhood ≥10 years+adult home <20 years+adult work <10 years	202 (2.1) of 9506	1.17 (0.89 to 1.54)	1.23 (0.92 to 1.64)
Childhood ≥10 years+adult home <20 years+adult work ≥10 years	93 (2.5) of 3789	1.36 (0.99 to 1.86)	1.24 (0.89 to 1.72)
Childhood ≥ 10 years+adult home ≥ 20 years+adult work <10 years	80 (2.3) of 3538	1.25 (0.90 to 1.73)	1.33 (0.95 to 1.86)
Childhood ≥10 years+adult home ≥20 years+adult work ≥10 years	96 (3.1) of 3125	**1.71 (1.25 to 2.34)**	**1.61 (1.16 to 2.24)**
p Value for trend		0.011	0.004

Numbers in bold are significant at the p<0.05 level.
*39 206 after adjustment of categorical exposure; 38 910 after adjustment of quantified exposure.
†Adjusted for mean BMI (age 18–50 years), age cohort at baseline, ethnicity, education, alcohol intake, parity and oral contraceptive use (ever).

stillbirths than older women. The opposite is true for tubal ectopic pregnancy. Women who were overweight (BMI 26–<30) or obese (BMI 30+) throughout their reproductive years were more likely to have each of the three outcomes.

Women who did not have any spontaneous abortions, stillbirths or tubal ectopic pregnancies were more likely to be non-Hispanic Caucasian, but a greater percentage of African–American and Hispanic women were more likely to have any of the three outcomes than not. A greater percentage of college-educated women had no adverse outcomes compared with lesser educated women. Women who had one or more spontaneous abortions were slightly more likely to have ever consumed 12 alcoholic beverages in their lifetime. As expected, women with more term pregnancies were more likely to have any of the three adverse outcomes. Women who never smoked were less likely to have an adverse pregnancy outcome than former or current smokers, and women never-smokers exposed to any SHS throughout life were more likely to have one or more spontaneous abortions than women never-smokers who were not exposed to any SHS throughout life.

In the primary analysis, using never-smokers not exposed to any SHS throughout life as a reference group, total lifetime tobacco exposures of ever-smokers (exposed from active smoking and resulting SHS exposure) had significant associations for all three outcomes with ORs of 1.16 (95% CI 1.08 to 1.26), 1. 44 (95% CI 1.20 to 1.73), and 1.43 (95% CI 1.10 to 1.86) for spontaneous abortion, stillbirth and tubal ectopic pregnancy, respectively (table 2). Compared with never-smokers not exposed to SHS, the quantified analyses for the same ever-smokers had ORs for spontaneous abortion, stillbirth and tubal ectopic pregnancy that were positively associated with number of cigarettes per day, number of years smoked before menopause and pack years of active cigarette smoking, and inversely associated with age started smoking. Participants who started active smoking before the first term birth had the same significant associations with adverse pregnancy outcomes as those who did not. Dose-response trends for all measures were at or near significance.

The analysis of SHS was limited to women who were never-smokers (n=40 850) with never-smokers not ever exposed to SHS as the single reference group. In the primary analysis (table 2) of all women never-smokers exposed to SHS, associations were significant for stillbirth—1.22 (95% CI 1.02 to 1.47), but not for spontaneous abortion—1.05 (95% CI 0.97 to 1.13) nor tubal ectopic pregnancy—1.25 (95% CI 0.96 to 1.62). In the quantified analysis for spontaneous abortion (table 3), associations with SHS became significant at the two highest levels of lifetime exposure: childhood ≥10 years, adult home ≥20 years, adult work <10 years; and childhood ≥10 years, adult home ≥20 years, adult work >10 years. A significant dose-response trend was found—a p value of 0.008. OR for the association of spontaneous abortion and the highest level of SHS exposure was 1.17 (95% CI 1.05 to 1.30).

In the quantified analysis for stillbirth (table 4), significant associations were seen for the highest level of SHS exposure—OR 1.55 (95% CI 1.21 to 1.97), and also for the third highest level—OR 1.61 (95% CI 1.27 to 2.04). Dose-response trend for the adjusted highest category was <0.001. In the quantified exposure analysis for ectopic pregnancy (table 5), a significant association was also seen for the highest level of SHS exposure, with an OR of 1.61 (95% CI 1.27 to 2.24). A significant dose-response was suggested with a p value for trend of 0.004.

Total N for each smoking variable included in table 6

Table 6 Total number for each smoking variable

Variable	n
Smoking status	77 805
Age started smoking	77 675
Started smoking before 1st term birth*	72 744
Average cig/day	76 142
Number of years smoked before menopause	73 937
Pack-years before menopause	72 613

DISCUSSION

Using historical data from a large cohort of postmenopausal women, we observed significant associations between women who were active smokers during their reproductive years and three adverse outcomes of fetal mortality—spontaneous abortion, stillbirth and tubal ectopic pregnancy. There was a significant trend with intensity, duration and pack-years of smoking during reproductive years. Significant trends across categories were observed in never-smoking women for all three adverse pregnancy outcomes of fetal death.

Comparison with other studies

In this study, particular interest was given as to whether particular time periods or venues of SHS exposure would affect pregnancy outcomes more than other periods. An earlier study investigated quantified childhood exposure and in utero exposure of the future mother. ORs for such SHS exposures and spontaneous abortion years later in the mother's own reproductive years were significant.[30] In our study, significance for childhood-only exposure to SHS was not found for any of the three outcomes studied. Only the highest levels of exposure for the longest periods of time produced significant associations, and this suggests the necessity to consider lifetime exposure measures for all venues and for all time periods in future studies. The majority of studies on each of the three outcomes did not consider lifetime tobacco exposure.[10–21 23–25] In this study, the strongest associations between SHS and adverse pregnancy outcomes were observed with the highest exposures over lifetime. The linear trends were significant, demonstrating that incremental exposure increases risk.

National trends and effects on populations

National trends of SHS exposure seem to follow trends for adverse pregnancy outcomes, specifically spontaneous abortions and stillbirths. From 1988 to 2002, data from NHANES centres show a decline in SHS exposure—measured by cotinine levels—of about 75% overall.[31] Rates of spontaneous abortion have declined by about 4% over the same period, but this number is suspect: up to 35% of spontaneous abortions go undetected and unreported, and data collection varies greatly by centre. Stillbirths have declined by about 11% due to many factors, including more intense obstetrical care, such as antenatal monitoring and increased preterm deliveries when detected abnormalities suggest fetal jeopardy, and increased public health awareness of potential perils to fetal well-being, such as eclampsia and unhealthy lifestyles. Undoubtedly, improved and expanded collection of public health data will clarify the exact nature of these reduced percentages. Many states are enacting mandatory death certificates for fetal death>20 weeks. Another potential confounder to these trend correlations is the fact that pregnancy rates for women over 35 years of age are increasing dramatically, an age level above which there is higher fetal loss. Still, our findings of significant risk estimates suggest that lifetime SHS exposure contributes to a great number of adverse pregnancy outcomes each year.

Strengths and limitations

Our study's strengths include the statistical power gained from the large size of the cohort, generality from the broad geographical distribution of the cohort from which the historical data was obtained, and detailed data on exposures, outcomes and potential confounders. The detailed information in the datasets permitted comprehensive assessments, including lifetime quantitative measures of active and passive smoke exposure in all critical periods—childhood, adult home and adult work exposure.

The limitations include potential under-reporting of total, lifetime tobacco exposure (ever-smoking and SHS exposure), which would be expected since the data was collected at enrolment from postmenopausal women. The large size of the cohort and structuring of questions about tobacco use and exposure on several different questionnaire forms would ideally minimise inaccuracies. Additionally, quantitative estimates of lifetime ever-smoking alone were calculated from data on smoking at enrolment, but lifetime intensity of active smoking is also likely to be underestimated—such misclassification of active and passive smoking would move any associations toward the null. Likewise, estimates of lifetime SHS exposures alone were for years exposed only: intensity measured by the number of people smoking during the various periods would add precision to the analysis. In spite of this, our associations for active and passive smoking and fetal loss were significant with positive dose-response trends. Largely due to the age of participants at enrolment, the cohort did not have any data on in utero exposure to tobacco smoke (the participants' own mothers smoking while pregnant); as mentioned above, such data might have strengthened our associations of childhood-only SHS exposure and fetal loss.[30] During the reproductive years of the participants, home pregnancy tests were not available for most women. Thus, our analyses only include fetal loss that was recognised by the participant or in a clinical setting. Again, such underestimation would drive any association toward the null. The elevation of ORs from crude to adjusted results for stillbirth seen in Table 4 may be due to interaction of covariates in the adjusted model. These covariates were identified as 'parity' for the third highest category (childhood ≥10 years, adult home <20 years, and adult work ≥10 years. For the highest level category, 'education' was the covariate responsible.

CONCLUSIONS AND GENERALISABILITY

These data and results in this study provide new evidence that suggests that SHS can have previously unstudied effects on pregnancy outcomes, including spontaneous abortion, stillbirth and tubal ectopic pregnancy. The data have been collected from 40 data centres across the USA, giving generalisability to the results: the participants come from a broad geographic range, and have multiple ethnic, educational and socioeconomic backgrounds. This information significantly expands the scope of populations that are potentially impacted by SHS. Continuing evolution of policies to eliminate SHS would be expected to protect women and their future children.

What is already known on this topic

- Active smoking during pregnancy is associated with multiple adverse pregnancy outcomes, and in some instances, is considered to be causal, but evidence necessary to infer causality for secondhand smoke exposure and adverse pregnancy results is suggestive but incomplete.
- In some studies, fetal loss is associated with secondhand smoke exposure at or around the time of conception and throughout gestation, mainly from partner active smoking.

What this study adds

- This cohort is large enough to study multiple levels of active and passive tobacco exposure throughout lifetime during childhood, adult at home and adult at work exposures.
- In this study, active smoking was associated with spontaneous abortion, stillbirth and tubal ectopic pregnancy with a significant dose-response trend; secondhand exposure to never-smoking women at the highest levels were also associated with all three adverse pregnancy outcomes with significant dose-response trends.

Acknowledgements The Women's Health Initiative: Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Dale Burwen, Joan McGowan, Leslie Ford, and Nancy Geller. Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg. Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker.

Contributors KMP, AH, JWW and KMH participated in the study design. KMH and CAA completed the data analysis. All authors participated in data collection, data interpretation, and drafting of the manuscript. CR contributed to drafting of the manuscript. AH is guarantor for the study.

Funding The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. The funding source had no role in the collection, analysis, or interpretation of the data, in the preparation of the manuscript, or its submission for publication.

Competing interests All authors have completed the Unified Competing Interests form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: support from the National Heart, Lung, and Blood Institute for the submitted work as described above; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Patient consent Obtained.

Ethics approval The ethics committees at the Women's Health Initiative Coordinating Center, Fred Hutchinson Cancer Research Center, and at all 40 clinical centres.

Provenance and peer review Not commissioned; internally peer reviewed.

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Associations of lifetime active and passive smoking with spontaneous abortion, stillbirth and tubal ectopic pregnancy: a cross-sectional analysis of historical data from the Women's Health Initiative

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Tob Control published online February 26, 2014