Published in final edited form as:

Tob Control. 2009 April; 18(2): 115–120. doi:10.1136/tc.2008.027961.

Associations Between Adult and Childhood Secondhand Smoke Exposures with Fecundity and Fetal Loss Among Women who Visited a Cancer Hospital

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Abstract

BACKGROUND—A large percentage of the population continues to be exposed to secondhand smoke (SHS). Although studies have consistently linked active smoking to various pregnancy outcomes, results from the few studies examining SHS exposure and pregnancy difficulties have been inconsistent.

METHODS—Approximately 4,800 women who presented to Roswell Park Cancer Institute between 1982 and 1998 and reported being pregnant at least once were queried about their childhood and adult exposures to SHS using a standardized questionnaire. Women were asked to report on selected prenatal pregnancy outcomes (fetal loss and difficulty becoming pregnant).

RESULTS—Approximately 11.3% of women reported difficulty becoming pregnant, while 32% reported a fetal loss or 12.4% reported multiple fetal losses. Forty percent reported any prenatal pregnancy difficulty (fetal loss and/or difficulty becoming pregnant). SHS exposures from their parents were associated with difficulty becoming pregnant (OR=1.26, 95%CI 1.07–1.48) and lasting > 1 year (OR=1.34, 95%CI 1.12–1.60). Exposure to SHS in both at home during childhood and at the time of survey completion was also associated with fetal loss (OR=1.39, 95%CI 1.17–1.66) and multiple fetal losses (OR=1.62, 95%CI 1.25–2.11). Increasing current daily hours of

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SHS exposure as an adult was related to the occurrence of both multiple fetal loss and reduced fecundity ($p_{\text{trend}} < 0.05$).

CONCLUSIONS—Reports of exposures to SHS during childhood and as an adult were associated with increased odds for prenatal pregnancy difficulties. These findings underscore the public health perspective that all persons, especially women in their reproductive years, should be fully protected from tobacco smoke.

Keywords

Spontaneous abortion; fertility; tobacco smoke pollution; second hand smoke; fecundity

Introduction

Active smoking has long been considered deleterious to health and a risk factor for a number of diseases [1]. Cigarette smoke contains more than 4,000 chemicals and at least 60 known carcinogens [2]. Nonsmoking individuals subjected to secondhand smoke (SHS) are exposed to these same toxins, but in varying amounts [3]. Research has found that sidestream smoke, the smoke from the tip of cigarette, contains greater amounts of tar, nicotine, and other chemicals, than mainstream smoke [4,5]. SHS also contains a number of substances that are believed to be reproductive toxins, including carbon monoxide, nicotine, anabasine, cadmium, benzene, toluene, formaldehyde, and others [3]. In recent years, the number of people exposed to SHS has declined principally due to the decrease in smoking prevalence and because of restrictions placed on smoking [6]. Despite these advances, 65% of nonsmokers are still exposed to SHS as detected by serum cotinine [7]. However, exposure to SHS as an adult may be lower due to clean indoor air laws [8].

The effects of tobacco usage and exposure on pregnancy outcomes remain a public health priority because 15% of mothers continue to smoke throughout pregnancy, and an estimated 43 million women in the United States are exposed to cigarette smoke from others [9,10]. Several articles have linked smoking during pregnancy to increased risk of spontaneous abortions [11,12]. Other research has shown that maternal smoking during pregnancy is linked to a higher rate of Sudden Infant Death Syndrome (SIDS) [11,13] in addition to decreased fecundity [14,15].

Although an abundance of studies links maternal smoking to various pregnancy difficulties (PD), fewer studies have examined SHS exposure and pregnancy difficulties. Two studies published in the early 1990s showed that exposure to SHS was associated with an increase in spontaneous abortions [16,17]. More recent research found that SHS exposure during pregnancy was associated with an increased occurrence of spontaneous abortion [3,18]. Other studies found that exposure to SHS early in life (*in utero* or in childhood) were linked with miscarriage [19,20] and reduced fecundity in adulthood [21,22].

Because evidence linking exposure to SHS and adverse pregnancy outcomes was limited, we conducted a study investigating these associations. The aim of this study was to assess the relationship between both childhood and adult secondhand smoke exposure with a variety of pregnancy difficulties. This study population was selected because of the detailed information on pregnancy difficulties in addition to data on secondhand smoke exposure that existed from women who presented for care at the Roswell Park Cancer Institute.

Methods

Study Population

The population for this study included female patients who were seen at Roswell Park Cancer Institute, Buffalo, NY, between 1982 and 1998. At their first visit, each patient was invited to complete an epidemiological questionnaire (called the Patient Epidemiology Data System or PEDS). Approximately 50% of new patients completed and returned the questionnaire. Eligible participants were females who reported at least one previous pregnancy attempt, and were lifelong never smokers. Of the 4,804 women who were determined to be eligible, 2,926 were diagnosed with a malignant disease. The remaining 1,878 patients were determined to be cancer-free. The women included in this study were predominately Caucasian (99%) and ranged in age from 18 to 96 years, with a median age of 58 years.

Dependent Variables

All the participants in this study completed the Patient Epidemiological Data System questionnaire. This 16-page instrument gathered information on reproductive and medical histories, family history of cancer, occupational and environmental exposures, tobacco and alcohol usage, and diet [23]. Eligibility for this study was restricted to those who answered “yes” to the question, “Have you ever been pregnant?”

Fetal Loss—Fetal losses included affirmative responses to any of the following survey items: “Did you ever have a stillbirth (carried for 5 months or more)?” and, if so, how many; “Have you ever had a miscarriage (carried for less than 5 months)?” and, if so, how many. Multiple fetal losses were defined as any combination of 2 or more fetal losses.

Fecundity—Difficulty becoming pregnant was based on affirmative responses to survey items which assessed for difficulty in becoming pregnant persisting for more than one year which is consistent with the accepted medical definition [24].

Fetal Loss or Difficulty Becoming Pregnant—Respondents who reported either at least one fetal loss (eg, miscarriage or stillbirth) or who reported difficulty becoming pregnant lasting more than 12 months were classified as having a history of fetal loss or difficulty become pregnant.

Although while previous manuscripts had linked secondhand smoke exposure to other pregnancy outcomes, such as SIDS and low infant birth weight, these variables were not assessed in the PEDS questionnaire.

Independent Variables

Both SHS exposure during childhood and as an adult was captured by the PEDS questionnaire, and the study was restricted to lifelong never smokers in order to assess the sole effect of SHS. For adult SHS exposure, the questionnaire asked the number of hours each day a woman is exposed to the smoke from others' cigarettes in (a) her home, (b) at work, and (c) other locations. For past SHS exposure, participants were asked “When you were a child living at home, did either of your parents smoke on a regular basis?” Based on these questions, several exposure variables were created: parental SHS exposure (no, yes), adult SHS exposure (no, yes), adult and childhood dichotomous exposure (childhood exposure but no adult exposure, adult exposure but no childhood exposure, both adult and childhood exposure, and neither childhood nor adult exposure), and total adult SHS hours (divided into 4 categories: no exposure and tertiles based on hours exposed).

Control Variables

The PEDS questionnaire included items on diet, alcohol consumption, and other lifestyle factors, allowing multiple items to be considered as potential confounders [10,20]. The inclusions of control variables was based on biological and statistical rationales [25], and included age at most recent pregnancy, marital status, education, income, birth control pill use (dichotomous), alcohol consumption (categorical), caffeine consumption (categorical), year of visit (continuous), previous miscarriage (dichotomous), problems getting pregnant (dichotomous), number of children (categorical), body mass index (categorical), menstrual irregularity (dichotomous), race (categorical), and age at admission (continuous).

Statistical Analyses

For descriptive statistics, χ^2 statistics were calculated to test the difference between those who had any adverse pregnancy outcome and those who had no adverse pregnancy outcomes for categorical variables, and Students t-tests were used to calculate the difference for continuous variables. Given the exploratory nature of this research, the results were considered statistically significant at the $p < 0.05$ level. Potential confounders considered for these analyses are listed above. All analyses were performed using SPSS version 15.0.

Unconditional multivariate logistic regression was used to calculate odds ratios (OR) and corresponding 95% confidence intervals (CI). None of the covariates met the classical definition of a confounder, where the covariate was associated with both the outcome and the exposure. Model selection was performed in a step-wise forward manner. Covariates were added to the model and included if the covariate changed the odds of the main parameter by $> 10\%$ [20]. Variables that were evaluated but not included in the final multivariate model included marital status, education, income, oral contraceptive use, alcohol and caffeine consumption, year of visit, number of children, body mass index, menstrual irregularity, race, and age at admission.

Results

Approximately 32% of lifelong never-smoking women experienced at least one episode of a fetal loss, with 12% of women experienced multiple episodes of fetal loss. More than 11% reported trouble becoming pregnant. Overall, more than 40% of women reported having some form of prenatal pregnancy difficulties. The prevalence of prenatal pregnancy difficulties in this study was consistent with results from other research using populations of women without cancer [26,27]. Exposure to secondhand smoke declined as date of admission became more recent.

Descriptive characteristics of those women who did and did not experience pregnancy difficulties are displayed in Table 1. Those who reported having experienced pregnancy difficulties were significantly ($p < 0.05$) younger at admission and older at the time of their most recent pregnancy. Pregnancy difficulties did not differ by marital status, but those with a higher family income and those who attained a higher educational level were more likely to have experienced pregnancy difficulties. While caffeine consumption was not associated with pregnancy difficulties ($p = 0.78$), women who consumed a greater amount of alcohol reported a higher proportion of pregnancy difficulties ($p < 0.01$). Women who reported pregnancy difficulties had fewer children and a greater proportion of menstrual irregularity ($p < 0.01$).

Table 2 displays the results examining the association between childhood SHS exposure and the various study outcomes based upon unadjusted and adjusted models. Women exposed as children to SHS from their parents reported trouble becoming pregnant (childhood SHS; OR

= 1.27; 95%CI = 1.03–1.56) more often than those not exposed to SHS during childhood. Childhood SHS exposure was not associated with the other study outcomes.

Table 3 displays the results examining the association between SHS exposure as an adult and the various pregnancy difficulties. Women exposed to SHS as an adult reported trouble becoming pregnant (adult SHS; OR = 1.24; 95%CI = 1.03–1.51) more often than those not exposed to SHS. SHS exposure as an adult was associated with fetal loss (adult SHS; OR = 1.23; 95%CI = 1.08–1.40). Lastly, adult SHS exposure increased the odds of either pregnancy difficulties or fetal loss (adult SHS; OR = 1.30; 95%CI = 1.15–1.47).

Table 4 displays the association between combined childhood and adult SHS exposure with pregnancy difficulties. Combined adult and childhood SHS exposure was associated with difficulty becoming pregnant (OR = 1.68; 95%CI = 1.28–2.20). Women exposed to SHS both as an adult and during childhood had significantly increased odds of fetal loss (OR = 1.39; 95%CI = 1.17–1.66). Multiple fetal losses were examined in relation to adult and childhood SHS, where the odds ratios found were similar to that of fetal loss (OR = 1.62; 95%CI = 1.25–2.11).

Table 5 displays the results for pregnancy difficulty odds by tertiles of adult SHS exposure. Those reporting exposure for 6 or more hours a day to SHS had a significantly higher likelihood of fetal loss (OR = 1.30; 95%CI = 1.11–1.53). There was a positive trend ($p < 0.05$) for increasing SHS hours for odds of multiple fetal loss. Women exposed to 6 or more hours of SHS were also at increased odds of difficulty becoming pregnant (OR = 1.36; 95%CI = 1.08–1.72), along with a positive trend ($p = 0.03$). Women in the highest exposure tertile had a significant 40% increase in odds ratio of any pregnancy difficulties (OR = 1.39; 95%CI = 1.19–1.62; p for trend = 0.01).

Discussion

This study found evidence that self-reported exposure to secondhand smoke (both as an adult and during childhood), was associated with an increase in the odds of various prenatal pregnancy difficulties (PD). Various SHS exposure measures were consistently associated with fetal loss, difficulty becoming pregnant (fecundity), and either of these outcomes. Statistically significant increases in the odds for these outcomes ranged between 25% and 70%, and the strongest associations were observed for those with the greatest SHS exposures. In addition, statistically significant positive trends were noted for adult SHS exposure hours and pregnancy difficulties, indicating a dose-response relationship. While significant associations were noted for adult SHS exposures and both fetal losses and difficulty becoming pregnant, childhood SHS exposures were associated with only difficulty in becoming pregnant. No indication of interaction was noted between childhood and adult SHS when included in the same logistic model. No signs of interaction were apparent when the results were stratified by those diagnosed with cancer and non-malignant conditions. The addition of multiple potential confounding variables to the regression models did not dramatically alter crude associations between SHS exposure and pregnancy difficulties. Furthermore, women with a considerable active smoking history were found to have significantly increased odds of experiencing pregnancy loss and difficulty becoming pregnant. However, due to the prevalent nature of this data, the results must be interpreted with caution, and causality cannot be concluded.

The results presented in this study are consistent with a number of previous publications examining the association between secondhand smoke exposure and various pregnancy difficulties [3,16–20]. The odds ratio estimates obtained in this study are similar in magnitude to the risk estimates in the studies that reported an association between SHS and

PD [17,28]. Although a small number of studies have found an association between SHS and PD, not all studies have reported a positive association [29].

Overall, the exact etiologies of prenatal pregnancy difficulties remain uncertain. Some mechanism which may explain these occurrences include chromosomal and uterine abnormalities, endocrine abnormalities, stress, exposure to environmental factors (e.g. tobacco smoke), and unidentified factors [30]. Compared to mainstream smoke (inhaled by the smoker), diluted side-stream smoke (the major component of SHS), especially after it has aged, can be more toxic [31]. DNA comet assays demonstrate more cells with DNA damage in never smokers exposed to secondhand smoke than in active smokers [32]. Likewise, toxins that create more reactive oxygen species (ROS) with resulting oxidative stress are also found in higher concentrations in side-stream smoke [33].

It is possible that secondhand smoke exposure involves the inhibition of reproductive hormone synthesis (estrogens and progesterones) at various sites including the ovary, the fat stores and the placenta if the woman is pregnant. Aromatase converts androgens to estradiol in the granulosa cells of ovarian follicles and in placental trophoblasts. Nicotine, cotinine and anabasine from tobacco smoke are endocrine disruptors that inhibit aromatase activity in granulosa cells and in trophoblasts, which reduce fertility [34]. In addition, secondhand smoke constituents produce changes in cervical mucus, which can impair fertility [15,35].

Although estrogens are associated with fertility and fecundity, progesterone is strongly linked to ovarian cyclicity and maintenance of pregnancy [36]. Cadmium, at levels found in secondhand smoke, inhibits the synthesis of progesterone in trophoblasts and interferes with multiple intrafollicular processes including meiotic maturation and oocyte cumulus expansion [36]. Nicotine, cotinine, and anabasine also inhibit progesterone synthesis in granulosa cells [37]. Oxidative stress, generated by hypoxia and detoxification of xenobiotics via phase I enzymes and more so, phase II enzymes (the glutathione S transferase family), is implicated in pregnancy difficulties, especially spontaneous abortion, mainly as a result of endothelial cell damage to placental vessels [26]. All of the mechanisms are induced via exposure to second-hand smoke and may account for the findings of this study.

The present study had a number of advantages and disadvantages. The data used in this study is prevalence data. Because the participants were reporting on past behaviors, it is unknown whether their reported exposure levels were those that prevailed at the time of the prenatal pregnancy difficulty. Research shows that SHS exposure steadily decreases over a woman's lifetime [38]. If misclassification was present, it was most likely in the conservative direction, underestimating SHS exposure, which would bias the odds estimates towards the null [39]. While recall bias may be a limitation of this study, it is unclear if this would be differential between cases and controls, especially for an exposure that was generally considered commonplace and socially acceptable. Because of the prevalent nature of the data, it is impossible to establish temporality. Another limitation of this study is the potential of misclassification of the exposure and the various outcomes, since the data used in this study were self-reported. For example, the questionnaire only asked about parental smoking in the home during childhood, but there could have been other relatives living in the house who smoked. Much of this misclassification was an underestimation of their true SHS exposure and there is no evidence to suggest the bias was differential in any direction [40]. Data presented in table 5 shows a U-shaped relationship between hours of daily exposure and study outcomes. While the point estimate for those in 2–5 hours/day category is slightly less than those in the 0.5–1.5 hours/day category, their confidence intervals overlap considerably. Due to this, we have relied on the overall test for trend across the categories as noted on the table. Lastly, only 50% of eligible women who came to RPCI

completed the PEDS questionnaire. There is no way to determine whether those individuals who did not complete the questionnaire differed from participants in this study with respect to SHS exposure and the occurrence of PD, which could affect the generalizability of the results. Other authors have used the PEDS database for case-control studies examining cancer odds and successfully replicated those associations [23,41]. Furthermore, both the descriptive characteristics and odds found in this study are consistent with previous literature examining the association between SHS and PD [10,17,28].

Strengths of this study include the diversity of information collected on a number of variables. The exposure variables used in this study included both past exposure to SHS from parents and adult exposure at home, at work, and in other locations. This study is also one of the few with the ability to examine the association between SHS exposure and a number of prenatal pregnancy difficulties (PD). A large number of potential confounders that were used in previous publications were used in this study, which reduced the likelihood that the results seen in this study were due to confounding [10,20]. Other strengths of this study include the number of women included in the statistical analyses. This study used approximately 4,800 lifelong never-smoking women to examine the association between SHS exposure and PD. The large sample permitted this study to stratify exposures by multiple levels, which allowed for the observation of dose-response relationships while maintaining adequate statistical power. Lastly, another strength of this study is the consistency of the association observed across the various SHS exposure measures for each of the various PD.

The results from this study are consistent with results from a number of other studies that linked SHS exposure to various adverse pregnancy outcomes [3,16–22]. Although one cannot infer from this study that exposure to SHS causes various adverse pregnancy outcomes, this study adds valuable evidence to the current scientific knowledge and demonstrates the imperative need for further research into this area. The significance of the associations between SHS exposure and adverse pregnancy outcomes underscores the public health doctrine that all persons, especially women in their reproductive years, should be fully protected from tobacco smoke. Based on the current state of knowledge, clinicians are encouraged to strongly recommend smoking cessation and the reduction SHS exposure to women of child bearing age, and to their household contacts, in an attempt to minimize prenatal pregnancy difficulties.

Key Points

- ▶ Exposure to secondhand smoke was associated with pregnancy difficulties in a dose-response manner.
- ▶ Exposure to secondhand smoke during childhood was related to difficulty becoming pregnant later in life.
- ▶ Secondhand smoke during adulthood was associated with both increased fetal losses and difficulty in becoming pregnant.

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Table 1

Characteristics of 4,794 Never Smoking Women by Prenatal Pregnancy Difficulty, Roswell Park Cancer Institute, 1982–1998

Characteristic	No Pregnancy Difficulty %	At Least One Episode of Pregnancy Difficulty* %	p-value
Total	59.8%	40.2%	
Age at Most Recent Pregnancy			
<= 20	4.7%	3.5%	
21–25	18.9%	14.3%	
26–30	33.1%	27.6%	
31–35	26.0%	27.9%	
> 35	17.1%	26.6%	<0.01
Marital Status			
Married	69.4%	71.5%	
Widowed	19.9%	17.6%	
Divorced or Separated	8.5%	9.3%	
Never Married	2.2%	1.6%	0.08
Education			
Did Not Graduate High School	22.0%	17.4%	
High School Graduate	38.8%	36.8%	
At Least Some College	39.2%	45.8%	<0.01
Family Income			
Under \$16,000	46.5%	42.8%	
\$16,000–\$30,000	29.1%	29.9%	
\$30,000 or More	24.5%	27.3%	0.03
Ever Use Oral Contraception			
No	69.7%	67.2%	
Yes	30.3%	32.8%	0.07
Alcohol Consumption (1 bottle beer, 4 ounces of wine, or 1 ounce of liquor)			
Abstainer	47.4%	43.1%	
1 or Less/Week	20.4%	21.9%	
2–3/Week	15.4%	16.1%	
3 or More/Week	16.8%	18.9%	0.03
Caffeine Consumption (1 cup of non-decaffeinated coffee, tea, or cola)			
Less Than 1/Day	11.3%	10.8%	
1–2/Day	17.3%	16.5%	
2–3/Day	29.0%	28.8%	

Characteristic	No Pregnancy Difficulty	At Least One Episode of Pregnancy* Difficulty	p-value
	%	%	
3–5/Day	19.2%	19.2%	0.78
5 or More/Day	23.2%	24.7%	
Number of Children			
No Children	1.2%	5.7%	<0.01
1 Child	13.1%	14.9%	
2 Children	31.3%	28.4%	
3 Children	26.2%	22.9%	
4 or more Children	28.1%	28.1%	
Menstrual Regularity			
Normal Periods	88.4%	81.9%	<0.01
Irregular Periods	11.6%	18.1%	
BMI (Kg/m²)			
Underweight (<18.5)	1.9%	1.8%	0.94
Normal (18.5–25)	48.7%	49.4%	
Overweight (25–30)	29.1%	28.6%	
Obese (>30)	20.2%	20.2%	

* Defined as reporting one of the following: (a) fetal loss or (b) difficulty becoming pregnant.

Table 2

Odds ratios and 95% confidence intervals for various pregnancy difficulties by childhood SHS status, Roswell Park Cancer Institute, 1982–1998

Childhood SHS Exposure from Parents	Total N	Crude Odds Ratio	95% Confidence Interval	Total N	Partially Adjusted Odds Ratio [†]	95% Confidence Interval	Total N	Fully Adjusted Odds Ratio [‡]	95% Confidence Interval
Fetal Loss	4,794	1.04	0.92 – 1.17	4,747	1.01	0.89 – 1.13	4,379	1.02	0.89 – 1.18
Difficulty Becoming Pregnant	4,794	1.34	1.12 – 1.60	4,747	1.31	1.10 – 1.55	4,349	1.27	1.03 – 1.56
Fetal Loss or Difficulty Becoming Pregnant	4,782	1.07	0.96 – 1.20	4,741	1.09	0.97 – 1.24	4,389	0.99	0.82 – 1.16

[†] Adjusted for: age at most recent pregnancy, marital status, adult SHS exposure (yes/no), and education.

[‡] Adjusted for: age at most recent pregnancy, marital status, education, income, oral contraceptive use, alcohol consumption, caffeine consumption, year of visit, problems getting pregnant, number of children, body mass index, period irregularity, age at admission, and adult SHS exposure.

Table 3

Odds ratios and 95% confidence intervals for various pregnancy difficulties by Adult SHS status, Roswell Park Cancer Institute, 1982–1998

SHS Exposure as an Adult	No. of Exposed Cases	Adjusted [†] Odds Ratio	95% Confidence Interval
Fetal Loss	932	1.23	1.08 – 1.40
Difficulty Becoming Pregnant	369	1.24	1.03 – 1.51
Fetal Loss or Difficulty Becoming Pregnant	1,291	1.30	1.15 – 1.47

[†] Adjusted for age at most recent pregnancy and childhood SHS exposure

Adjusted odds ratios and 95% confidence intervals for various pregnancy difficulties by adult and childhood SHS status, PEDS Data Series, 1982–1997

Table 4

Dichotomous Adult and Childhood SHS Exposure	Fetal Loss		Difficulty Becoming Pregnant		Fetal Loss or Difficulty Becoming Pregnant	
	Adjusted OR n= 4,790	- Referent	Adjusted OR [†] n= 4,794	- Referent	Adjusted OR [†] n= 4,782	- Referent
None	1.00		1.00		1.00	
Childhood SHS but No Adult SHS	1.07	0.87 – 1.32	1.57	1.15 – 2.15	1.08	0.89 – 1.36
Adult SHS but No Childhood SHS	1.28	1.07 – 1.53	1.41	1.06 – 1.87	1.32	1.12 – 1.62
Both Adult and Childhood SHS	1.39	1.17 – 1.66	1.68	1.28 – 2.20	1.37	1.16 – 1.76

[†] Adjusted for age at most recent pregnancy.

Adjusted odds ratios and 95% confidence intervals for various pregnancy difficulties by adult SHS hours/day, Roswell Park Cancer Institute, 1982–1998

Table 5

Adult SHS Hours per Day	Fetal Loss	Difficulty Becoming Pregnant	Fetal Loss or Difficulty Becoming Pregnant
	Adjusted OR n= 4,800	Adjusted OR [†] n= 4,728	Adjusted OR [†] n= 4,794
None	1.00 - Referent	1.00 - Referent	1.00 - Referent
0.5–1.5 Hrs/Day	1.24 1.06 – 1.46	1.24 0.97 – 1.58	1.31 1.12 – 1.53
2–5 Hrs/Day	1.13 0.95 – 1.35	1.11 0.86 – 1.45	1.18 1.00 – 1.40
6 or More Hrs/Day	1.30 1.11 – 1.53	1.36 1.08 – 1.72	1.39 1.19 – 1.62
	p for trend = 0.10	p for trend = 0.03	p for trend = 0.01

[†] Adjusted for age at most recent pregnancy.