

# Secondhand Smoking, 4-Aminobiphenyl, and Bladder Cancer: Two Meta-analyses

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## Abstract

**Objective:** To quantify the relation between secondhand smoking (SHS) and levels of 4-aminobiphenyl (4-ABP; in urine or blood) and SHS and bladder cancer risk in nonsmokers.

**Methods:** PubMed and Embase were searched (search terms to represent SHS, bladder cancer, and 4-ABP) to conduct two meta-analyses. Information about gender and age of participants, mean 4-ABP level for each SHS category, number of subjects, relative risk or odds ratio and 95% confidence intervals (95% CI) in each SHS category, and covariates for which adjustment was made was extracted based on predefined inclusion and exclusion criteria. Random-effects analyses were done using STATA (version 9).

**Results:** A 118 studies were reviewed for information on SHS and 4-ABP (31 studies) and SHS and bladder cancer risk (87 studies). Of those, seven case-control studies were included for analysis of SHS and 4-ABP

and eight articles (three cohort and five case-control studies) for SHS and bladder cancer risk. A random-effects model found a pooled standardized mean difference of 1.47 (95% CI, 0.23-2.71), indicating higher levels of 4-ABP among nonsmokers exposed to SHS. A random-effects model showed no evidence for an association between SHS and bladder cancer risk (relative risk, 0.99; 95% CI, 0.86-1.14), comparing nonsmokers with and without SHS exposure.

**Conclusion:** Higher levels of 4-ABP were significantly associated with SHS exposure, which is consistent with earlier findings for 4-ABP levels in sidestream smoke. The current evidence indicates that there is no association between SHS and bladder cancer, but future studies that address methodologic limitations are needed to further clarify this important question. (Cancer Epidemiol Biomarkers Prev 2009;18(4):1312-20)

## Introduction

In 2004, bladder cancer was estimated to be the 4th most common cancer among men and the 14th among women in the European Union (cumulative risk of 2.82% and 0.52%, respectively; ref. 1). Apart from age, gender, and a few occupational groups (dye workers, rubber works, leather workers, painters, truck drivers, and aluminum workers), smoking is the only risk factor of bladder cancer for which clear epidemiologic evidence has been found (2). Active cigarette smoking has been proposed to account for >50% of bladder cancers in men and ~30% in women (3-5). This association between active (cigarette) smoking and bladder cancer has been confirmed by more than 35 case-control studies and 10 cohort studies (2, 6-8). The European Prospective Investigation into Cancer and Nutrition, for instance, found an increased risk of bladder cancer for both current smokers [incidence rate ratio, 3.96; 95% confidence interval (95% CI), 3.07-5.09] and ex-smokers (incidence rate ratio, 2.25; 95% CI, 1.74-2.91; ref. 6). Moreover, the tobacco smoke constitu-

ent 4-aminobiphenyl (4-ABP) is a well-established risk factor for bladder cancer (5, 9-12). Saletta et al. (11) showed that 50% to 60% of human cells treated with 4-ABP develop chromosomal instability. Data also suggest that smokers of blond tobacco are at lower risk for bladder cancer than smokers of black tobacco (9, 13). The latter type is richer in arylamines such as 4-ABP, which is thus known as the most potent human bladder carcinogen (5, 14, 15). In addition, the concentration of 4-ABP in sidestream smoke is over 10 times greater than in mainstream smoke (16).

Despite the established association between 4-ABP and bladder cancer and known levels of 4-ABP in sidestream smoke (12, 16), the evidence for increased levels of 4-ABP (adducts) and an increased risk of bladder cancer in nonsmokers due to secondhand smoking (SHS) remains unclear (2). In this study, we set out to summarize and to quantify the associations of SHS on the levels of 4-ABP and the associations of SHS on the risk for bladder cancer in nonsmokers by conducting two meta-analyses.

## Materials and Methods

**Literature Search Strategy.** We used computerized literature search databases (PubMed search followed by an Embase search) to identify full text and abstracts

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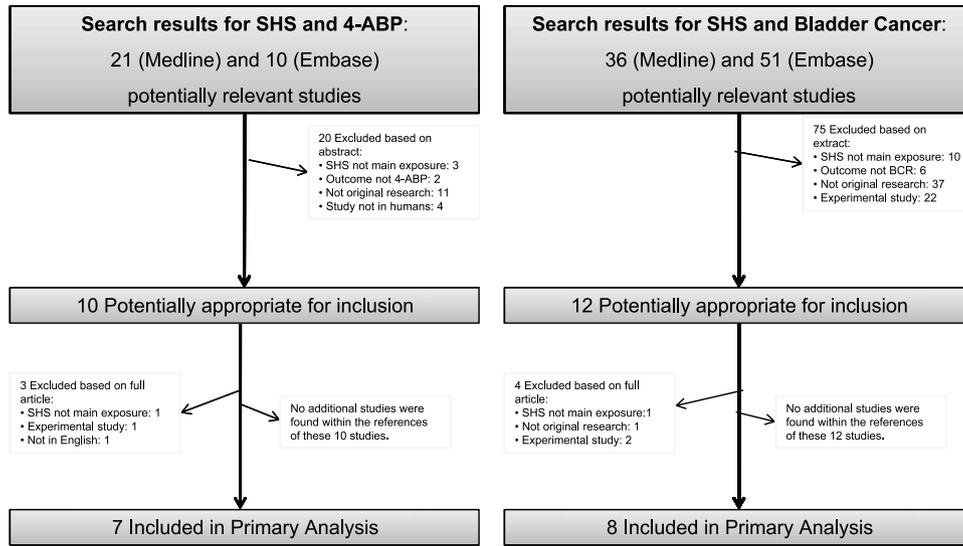


Figure 1. Flow chart of study selection.

published to date. Our searches included “secondhand smoking,” “ETS,” “passive smoking,” and “tobacco smoke pollution” as search terms for the exposure variable of interest. In addition, “4-aminobiphenyl,” “bladder cancer,” “urinary tract cancers,” and “urinary bladder neoplasm” were used as search terms for the outcome variables of interest. Except for English language, no further restrictions were added to the search strategy because few epidemiologic studies have examined the effect of SHS on 4-ABP levels or bladder cancer risk. By not restricting the search to research articles, we made it possible to include gray literature, such as letters and abstracts, presented in relevant conference meetings to address the effects of SHS on 4-ABP and bladder cancer risk. In addition, all references of selected articles were checked, including hand searches, which are effective practical ways to cross-check the completeness of the electronic searches.

**Inclusion Criteria.** The final collection of selected articles was chosen based on the following set of inclusion criteria: the publication pertained to an epidemiologic study that measured exposure to SHS among nonsmokers; the reference level of SHS exposure was clearly defined; 4-ABP levels (in blood or urine) or bladder cancer risk was assessed as an outcome; and predominantly nondiseased, nonsmoking study populations were used. Although bladder cancer only occurs among adults, exposure to SHS was not limited to adulthood as childhood SHS exposure might also influence the risk of bladder cancer or the levels of 4-ABP (1). Initially, titles of articles were reviewed to ascertain whether they might potentially fit the inclusion criteria. If, after assessing the abstract, there was any doubt about whether it met the relevant criteria, it was kept for more thorough subsequent assessment. The list of potential articles was further shortened by doing detailed evaluations of the methods and results of each remaining article. Figure 1 provides more detailed information about the progressive “flow” of the study exclusion process.

**Data Extraction.** The following details were recorded for each study: author, year of publication, SHS exposure

(binary), study type (case-control or cohort), gender of participants, time period of SHS exposure (childhood or adulthood), mean levels and units of 4-ABP, and number of cases and total subjects for each level of SHS. If SHS exposure was reported for several settings (e.g., domestic and occupational), results for the domestic setting were preferred. For qualitative purposes, extraction of covariates measured in multivariate analyses was also done (Tables 1 and 2).

**Meta-analysis Statistical Techniques.** A random-effects model was used to analyze the effect of SHS on 4-ABP levels based on differences in 4-ABP levels between nonsmokers with and without SHS exposure. Changes in these levels (effect size =  $t/\text{pooled SD}$ ) and 95% CIs were measured in units of SD [standardized mean difference (SMD)] and illustrated graphically using a forest plot. If several levels of “exposure to SHS” were reported, the weighted average was used. Use of SMDs in 4-ABP levels allows to pool and compare measures of 4-ABP in different scales, as this biomarker can be measured in both blood and urine, resulting in different units [pg/g hemoglobin (Hb) and ng/24 h, respectively]. For the further course of this article, we will use “levels of 4-ABP” for both Hb adducts and 4-ABP levels in urine. Potential heterogeneity of this study association was statistically evaluated using the Q-statistic as well as the  $I^2$  statistic.

The effect of SHS on bladder cancer risk among nonsmokers was evaluated by calculating the random-effects summary relative risk (RR). Use of the random-effects method allows for (and takes into account) heterogeneity between study results. Potential heterogeneity of the study results was assessed with a forest plot, which displays the RR estimates of bladder cancer risk comparing both levels of SHS, for each study. Potential heterogeneity of the study results was also statistically evaluated using the Q-statistic as well as the  $I^2$  statistic. Effect modification by gender and timing of SHS exposure was assessed by conducting a meta-regression. When appropriate, separate analyses were conducted for effect modifiers. Potential publication bias

**Table 1. Case-control studies selected for analysis comparing 4-ABP levels between nonsmokers with and without SHS exposure**

Author (y)	Country	n	Mean baseline age (SE) or age range	Timing of SHS exposure	Units of 4-ABP	Measurement technique and CV	SHS measure	Results: mean (SE)	Adjusted for:
Bartsch (1990; ref. 17)	Italy	35 unexposed	45-64	Adulthood	pg/g Hb adducts (blood)	Drabkin assay	Exposed vs not exposed	Slow acetylation phenotype unexposed: 30.4 (4.7)	None listed; only men included in the study
		15 exposed						Fast acetylation phenotype unexposed: 12.3 (2.4)	
Grimmer (1999; ref. 22)	Germany	14 unexposed	N/A	Adulthood	ng/24h (urine)	Drabkin assay	Exposed vs not exposed	Slow acetylation phenotype exposed: 34.8 (6.4)	None listed; both genders combined
		22 exposed						Fast acetylation phenotype exposed: 33.6 (8.6)	
Hammond (1993; ref. 16)	United States	7 unexposed	N/A	Adulthood	pg/g Hb adducts (blood)	Drabkin assay	Exposed vs not exposed	Unexposed: 68.1 (91.5)	Only women included in the study
		29 exposed						Exposed: 49.6 (6.07)	
Jiang (2007; ref. 18)	United States	203 unexposed	25-64	Adulthood	pg/g Hb adducts (blood)	Drabkin assay	Exposed vs not exposed	<0.5 µg/m <sup>3</sup> weekly average nicotine concentration: 17.6 (2.4)	Age, gender, race/ethnicity, and level of education
		27 exposed						0.5-1.9 µg/m <sup>3</sup> weekly average nicotine concentration: 20.8 (2.0)	
Maclure (1989; ref. 19)	United States	29 unexposed	N/A	Adulthood	pg/g Hb adducts (blood)	Drabkin assay	Exposed vs not exposed	≥2.0 µg/m <sup>3</sup> weekly average nicotine concentration: 27.8 (1.4)	None listed
		28 exposed						Unexposed: 19.3 (2.14)	
Richter (2001; ref. 20)	Munich (D)	15 unexposed	9.3 (2.3)	Childhood	pg/g Hb adducts (blood)	Drabkin assay	Exposed vs not exposed	Unexposed: 22.87 (1.6)	None listed
	Augsburg (D)	18 exposed	6.3 (0.3)	Childhood	pg/g Hb adducts (blood)	GC MS	Exposed vs not exposed	Unexposed: 45.86 (19.34)	None listed
	Eichstatt (D)	65 unexposed	8.2 (3.6)	Childhood	pg/g Hb adducts (blood)	CV = 9%	Exposed vs not exposed	Exposed: 47.46 (24.61)	None listed
Tang (1999; ref. 21)	United States	39 unexposed	1-6	Childhood	pg/g Hb adducts (blood)	Drabkin assay	Exposed vs not exposed	Unexposed: 25.0 (14.8)	Ethnicity
		25 exposed						Exposed: 28.5 (20.0)	
		10 unexposed						Unexposed: 19.0 (7.9)	
		41 exposed				GC MS	Exposed vs not exposed	Exposed: 23.4 (15.9)	
						CV = 4%		Unexposed: 23.8 (9.22)	
								Exposed: 34.3 (16.99)	

Abbreviations: CV, coefficient of variation; GC MS, capillary gas chromatography with detection by negative ion chemical ionization mass spectrometry.

**Table 2. Studies selected for analysis comparing bladder cancer risk between nonsmokers with and without SHS exposure**

Author (y)	Country study type	<i>n</i>	Total number cases for cohorts	Mean baseline age (SE) or age range
Alberg (2006; ref. 24)	United States	Cohort 1: 218,362 py	Cohort 1: 34	25+
	Prospective cohort study	Cohort 2: 296,246 py	Cohort 2: 48	
Bjerregaard (EPIC; 2006; ref. 6)	Europe	220,790	Adulthood: 47	59 (45-73)
	Prospective cohort study		Childhood: 47	
Chen (2005; ref. 25)	Taiwan	41 cases		50+
	Case-control study	202 controls		
Jiang (2007; ref. 18)	United States	147 cases		25-64
	Case-control study	292 controls		
Samanic (2006; ref. 8)	Spain	1,219 cases		21-80
	Case-control study	1,271 controls		
Kabat (1986; ref. 26)	United States	40 cases		Adults (not specified)
	Case-control study	72 controls		
Zeegers (2002; ref. 27)	the Netherlands	7,276 py	Adulthood: 48	55-69
	Prospective cohort study		Childhood: 52	
Burch (1989; ref. 28)	Canada	61 cases		35-79
	Case-control study	112 controls		

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; OR, odds ratio; py, person-years; BMI, body mass index.

was assessed using Begg's test and a funnel plot. All analyses were done using STATA (version 9).

## Results

The initial search for SHS and 4-ABP produced a total of 31 articles. Ten studies were selected for further evaluation based on information from abstracts. Finally, seven case-control studies were selected for primary data analysis from which four studies were conducted in the United States and three studies in Europe (Fig. 1; Table 1). Six studies reported 4-ABP Hb adduct levels (pg/ng Hb; refs. 16-21), whereas one

study reported 4-ABP levels in 24-hour urine samples (ng/24 hours; ref. 22). All studies quantifying 4-ABP adducts used the same techniques: Drabkin assays quantified with capillary gas chromatography with detection by negative ion chemical ionization mass spectrometry. The coefficients of variation varied from 1% to 10% (Table 1).

The initial search for SHS and bladder cancer risk resulted in 87 articles. After extracting information from the abstracts, 12 articles were selected for further investigation. Finally, three prospective cohort studies and five case-control studies were selected for primary data analysis from which four studies were conducted in northern America, three in Europe, and one study in

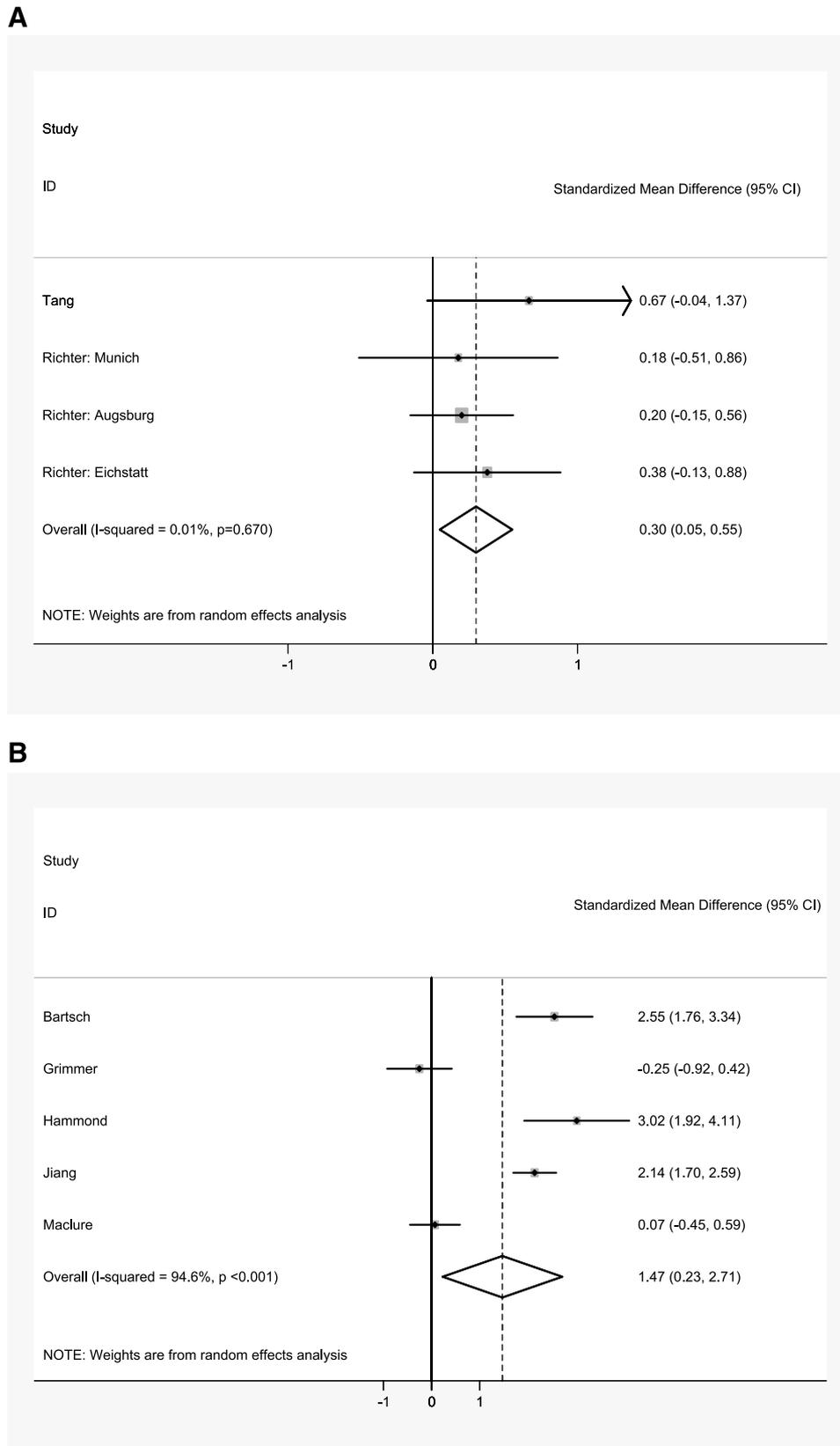
**Table 2. Studies selected for analysis comparing bladder cancer risk between nonsmokers with and without SHS exposure (Cont'd)**

Mean years of follow-up time	SHS measure	Timing of SHS measure	Results: RR or OR (95% CI)	Adjusted for:
15	Never vs current	Adulthood	RR for cohort 1 (both genders): 1.5 (0.8-3.00)	Age
		Adulthood	RR for cohort 2 (both genders): 0.8 (0.4-1.8)	
		Adulthood	RR for cohort 1 (females): 2.2 (0.9-5.2)	
		Adulthood	RR for cohort 2 (females): 1.0 (0.4-2.7)	
N/A	Exposed vs not exposed	Adulthood	RR (both genders): 0.82 (0.46-1.48)	Intake of fruit and vegetables, exposure to SHS in childhood or adulthood
		Childhood	RR (both genders): 2.02 (0.94-4.35)	
	Exposed vs not exposed	Adulthood	OR males: 7.16 (1.87-27.40)	Age, BMI, cumulative arsenic, hair dye usage, and education
		Adulthood	OR females: 1.09 (0.42-2.80)	
	Exposed vs not exposed	Childhood	OR males: 0.75 ( $P > 0.05$ )	Age, gender, race/ethnicity, and level of education
		Childhood	OR females: 1.64 ( $P > 0.05$ )	
		Adulthood	OR males: 0.73 ( $P > 0.05$ )	
	Exposed vs not exposed	Adulthood	OR females: 1.33 ( $P > 0.05$ )	
		Childhood	OR males <18 y exposure: 1.2 (0.6-2.3)	Age, hospital region, fruit/vegetable consumption, and high-risk occupation
		Childhood	OR males 18 y exposure: 0.9 (0.3-2.6)	
		Childhood	OR females <18 y exposure: 0.7 (0.3-1.4)	
		Childhood	OR females 18 y exposure: 0.6 (0.2-1.7)	
		Adulthood	OR males 0-26 y exposure: 1.1 (0.5-2.4)	
		Adulthood	OR males 17-54 y exposure: 0.8 (0.3-2.2)	
		Adulthood	OR males >54 y exposure: 1.3 (0.5-3.2)	
		Adulthood	OR females 0-26 y exposure: 2.2 (0.8-6.2)	
		Adulthood	OR females 17-54 y exposure: 1.9 (0.7-4.8)	
		Adulthood	OR females >54 y exposure: 0.8 (0.3-1.9)	
	Exposed vs not exposed	Adulthood	No OR reported	NA
7	Exposed vs not exposed	Adulthood	RR partner ex-smoker (both genders): 0.95 (0.46-2.0)	Age and sex
		Adulthood	RR partner current smoker (both genders): 0.74 (0.29-1.9)	
		Childhood	RR parents smoking (both genders): 1.2 (0.56-2.4)	
	Exposed vs not exposed	Adulthood	OR males: 0.94 (0.45-1.95)	Age and study location
		Adulthood	OR females: 0.75 (0.33-1.71)	

Asia. Four studies reported SHS exposure during both childhood and adulthood, whereas the other studies were restricted to adulthood. Gender-specific results were reported in six studies (Fig. 1; Table 2).

Changes in 4-ABP levels between the different SHS exposure levels are graphically illustrated in a forest plot (Fig. 2A and B). The random-effects model yielded a pooled SMD of 0.95 (95% CI, 0.26-1.64). The  $I^2$  statistic indicated evidence for heterogeneity (92.2%; 95% CI, 90-97), which warranted the use of a random-effects model. When looking at those studies measuring SHS exposure during childhood, the SMD equals 0.30 (95% CI, 0.05-0.55), whereas restricting to SHS exposure during adulthood results in a SMD of 1.47 (95% CI, 0.23-2.71).

The random-effects analysis, comparing bladder cancer risk and SHS exposure status, indicated a pooled effects RR of 0.99 (95% CI, 0.86-1.14). The Q-statistic and  $I^2$  statistic suggested heterogeneity ( $Q = 32.61$ ; degree of freedom = 21;  $P = 0.05$ ;  $I^2 = 35.6\%$ ), which can also be observed in the corresponding forest plot (Fig. 3A and B). Meta-regression analysis did not show any effect modification by gender or time of exposure. However, when conducting the analysis for men and women separately, the pooled RRs differed slightly but neither was significant [women: RR, 1.06 (95% CI, 0.87-1.28) and men: RR, 0.96 (95% CI, 0.79-1.17)]. Conducting the analysis for childhood and adulthood SHS exposure separately also showed slightly different but not statistically significant results [childhood SHS exposure: RR,

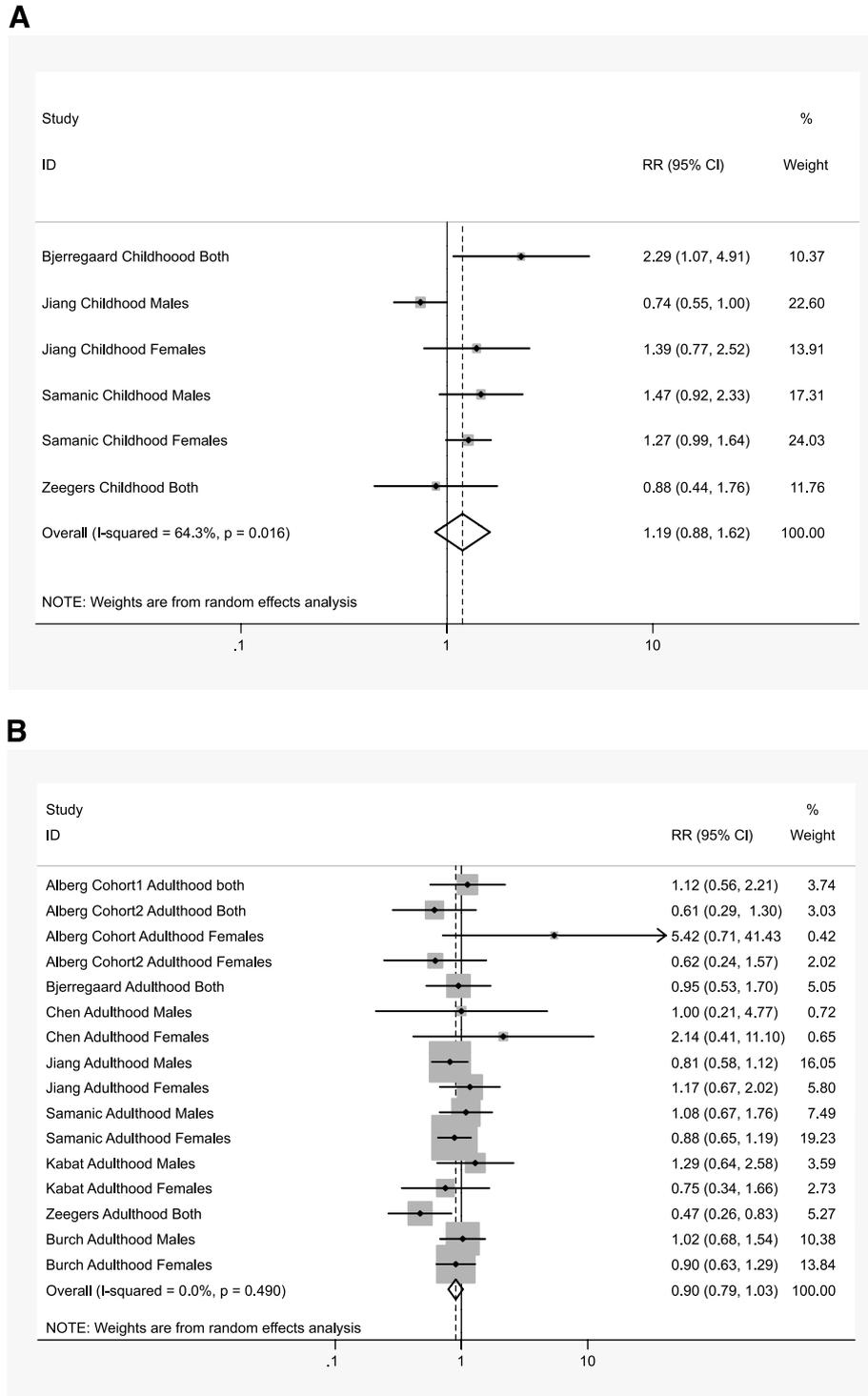


**Figure 2.** Forest plot for studies comparing the mean level of 4-ABP among nonsmokers with and without exposure to childhood SHS (A) or adulthood SHS (B).

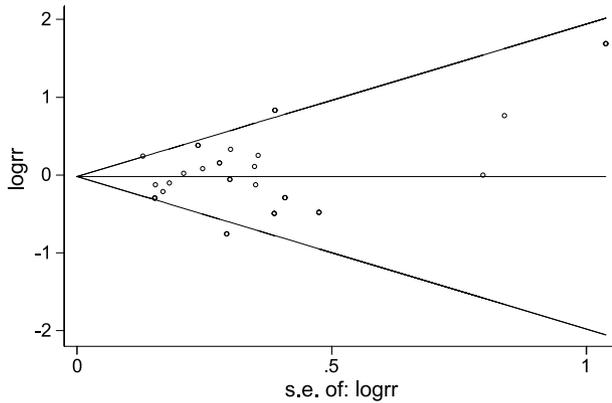
1.19 (95% CI, 0.88-1.62) and adulthood SHS exposure: RR, 0.90 (95% CI, 0.79-1.02). Begg's test did not indicate publication bias ( $P = 0.32$ ), which is also evident from the funnel plot, as there is a symmetric distribution observed among studies with small sample size (Fig. 4).

**Discussion**

This is the first meta-analysis looking at the effect of SHS on 4-ABP levels and bladder cancer risk among nonsmokers. The finding of a positive statistically



**Figure 3.** Forest plot for studies comparing the RR for bladder cancer risk among nonsmokers with and without exposure to childhood SHS (A) or adulthood SHS (B).



**Figure 4.** Begg's funnel plot for meta-analysis of SHS and bladder cancer risk: verifying publication bias.

significant SMD suggests a higher level of 4-ABP among nonsmokers exposed to SHS (16, 18) and thus suggests an association between SHS and 4-ABP. Nevertheless, we did not find an effect of SHS on bladder cancer risk, despite the robust plausibility for such an association, given the underlying biological mechanisms. However, both our findings may be diluted due to measurement error in exposure assessment of SHS and in measurement of 4-ABP levels. In addition, the number of comprehensive studies published to date that address both these associations is limited.

**Findings from Meta-analysis Looking at SHS and 4-ABP.** Our statistically significant findings for both adults and children confirm previous findings of a positive association between SHS and 4-ABP. However, given that measurement errors are likely to be present for both exposure and outcome assessment, our findings may not provide the absolute value of the difference in 4-ABP levels. The SMD for adulthood SHS exposure was about five times larger than the difference for childhood SHS exposure, however, which suggests that SHS exposure is much larger in adults than in children.

Dichotomization of SHS exposure (ever versus never), for example, could lead to substantial variations in exposure levels for "ever." Unfortunately, it was not possible in this meta-analysis to use dose-response data (23), as the number of relevant studies available to date was small and the qualitative classifications of SHS varied. Two of the included studies subdivided exposure levels of SHS and both showed increasing levels of 4-ABP adducts with increasing levels of SHS. Maclure et al., for instance, found that people with low exposure to SHS had a mean value of 45.5 pg/g Hb 4-ABP, whereas people who reported high levels of passive smoking had a mean value of 54 pg/g Hb 4-ABP (whereas those who had no exposure to SHS had a mean value of 42 pg/g Hb 4-ABP). In addition, Hammond et al. showed an increasing mean level of 4-ABP adducts with increasing amounts of nicotine measured in blood. People with levels of nicotine  $<0.5 \mu\text{g}/\text{m}^3$  reported a mean level of 13.7, whereas nicotine levels between 0.5 and  $1.9 \mu\text{g}/\text{m}^3$  were associated with 4-ABP levels of 20.8, and nicotine levels  $\geq 2.0 \mu\text{g}/\text{m}^3$  with

4-ABP levels of 28.2. This dichotomization of SHS levels also limited the comparison in SHS exposure between studies (i.e., domestic versus occupation exposure to SHS and amount of hours exposed to cigarettes). The development of a standard questionnaire to assess exposure to SHS as well as long-term prospective cohort studies can solve some of these issues.

Furthermore, assessment of 4-ABP levels can vary substantially between studies. The use of SMDs in 4-ABP levels allowed us to compare measures of 4-ABP in different scales (4-ABP levels in urine and 4-ABP adducts in blood), but this did not take into account between-lab variation and within-person variation. Nevertheless, we believe that between-lab variation is small, as all studies (except for Grimmer et al.) used capillary gas chromatography with detection by negative ion chemical ionization mass spectrometry to quantify 4-ABP adducts in blood. Detection limits varied from 0.5 to 10 pg/10 mL blood and coefficients of variation varied from 1% to 10%. They all ran internal control test such as analysis of samples in duplicate. It is thus likely that most imprecision is due to sample preparation rather than instrumental analysis. Within-person variation is likely to affect the results as only one measurement in time might not be representative for a person's average 4-ABP level. In addition, few studies adjusted results for important confounders such as age and gender. However, sample sizes were small and often only men or women were included. Future studies with larger sample sizes, adjustments for age and gender, and repeated measurements for 4-ABP levels could provide a more precise estimate for the difference in levels between people exposed and not exposed to SHS.

**Findings from Meta-analysis Looking at SHS and Bladder Cancer Risk.** It is possible that there is no association between SHS and bladder cancer. Assessment of SHS, however, is also subject to measurement error in this meta-analysis and may explain the null findings. Nevertheless, because the first meta-analysis (in this article) suggests that even a crude ever versus "never" categorization of SHS can detect different 4-ABP levels, SHS assessment is still a useful measure of environmental exposure to smoke.

When looking at active (cigarette) smoking and bladder cancer, a strong dose-response curve is observed: risk increases with increasing intensity of smoking, with RR estimates for moderate-to-heavy smokers, compared with nonsmokers (2). Consequently, the use of dose-response data for SHS exposure levels is recommended for future studies investigating the association between SHS and bladder cancer risk. Moreover, it is important that studies make a more distinct difference between childhood and adulthood exposure to SHS. In our findings, although not statistically significant, a suggestive increase in risk of bladder cancer was noted for childhood SHS exposure. It could be that different biological mechanisms are involved: for example, childhood SHS exposure may involve initiation of mutations in bladder cancer cells, which may later become cancerous through other promotional factors, whereas adulthood exposure to SHS may act through promotion of existing initiated cells through inflammation mechanisms.

**Strengths and Limitations of this Study.** Overall, measurement error is the main issue for both meta-analyses (assessment of SHS exposure and 4-ABP levels). There could be residual confounding stemming from confounders that were either unmeasured or insufficiently measured in the individual studies. In addition, exposure to other sources of bladder carcinogens was rarely assessed in the studies reviewed, and residual confounding from other sources of 4-ABP is probable. However, it is difficult to predict the direction of these biases and what effect they might have had on our findings.

The greatest strength of this study is that we examined the two outcomes among nonsmoking individuals. We also made all possible efforts to include all relevant publications available to date through various sources, including gray literature, and the two main online databases (PubMed and Embase). In addition, clearly defined objective criteria for exposure, outcome, and other study characteristics were specified a priori. There was also no evidence of publication bias in these analyses. As already mentioned, limited information about potential confounders in addition to measurement errors for SHS exposure and 4-ABP levels could bias our findings. Furthermore, the limited number of available studies and the rather small sample sizes (especially for those studies looking SHS and 4-ABP) restrict the power of these meta-analyses.

**Conclusion.** Higher levels of 4-ABP were significantly associated with SHS exposure, which is consistent with earlier findings about 4-ABP levels and sidestream smoke. Stratified studies (by gender and/or timing of exposure) are necessary to show whether this effect differs by gender and/or childhood versus adulthood SHS exposure. The current evidence indicates that there is no association between SHS and bladder cancer, but future studies that address methodologic limitations such as SHS exposure assessment are needed to further clarify this important question.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Acknowledgments

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