Original Article

The Association between Exposure to Second-Hand Smoke and Disease in the Chinese Population: A Systematic Review and Meta-Analysis*

WANG Yu Tong, HU Kui Ru, ZHAO Jian, AI Fei Ling, SHI Yu Lin, WANG Xue Wei, YANG Wen Yi, WANG Jing Xin, AI Li Mei, and WAN Xia#

Department of Epidemiology and Biostatistics, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences / School of Basic Medicine, Peking Union Medical College, Beijing 100005, China

Abstract

Objective To analyze the association between exposure to second-hand smoke (SHS) and 23 diseases, categorized into four classifications, among the Chinese population.

Methods We searched the literature up to June 30, 2021, and eligible studies were identified according to the PECOS format: Participants and Competitors (Chinese population), Exposure (SHS), Outcomes (Disease or Death), and Study design (Case-control or Cohort).

Results In total, 53 studies were selected. The odds ratio (*OR*) for all types of cancer was 1.79 (1.56–2.05), and for individual cancers was 1.92 (1.42–2.59) for lung cancer, 1.57 (1.40–1.76) for breast cancer, 1.52 (1.12–2.05) for bladder cancer, and 1.37 (1.08–1.73) for liver cancer. The *OR* for circulatory system diseases was 1.92 (1.29–2.85), with a value of 2.29 (1.26–4.159) for stroke. The *OR* of respiratory system diseases was 1.76 (1.13–2.74), with a value of 1.82 (1.07–3.11) for childhood asthma. The original *OR*s were also shown for other diseases. Subgroup analyses were performed for lung and breast cancer. The *OR*s varied according to time period and were significant during exposure in the household; For lung cancer, the *OR* was significant in women.

Conclusion The effect of SHS exposure in China was similar to that in Western countries, but its definition and characterization require further clarification. Studies on the association between SHS exposure and certain diseases with high incidence rates are insufficient.

Key words: Second-hand smoke; Chinese population; Cancer; Diseases of the respiratory system; Diseases of the circulatory system; Systematic review; Meta-analysis

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INTRODUCTION

Second-hand smoke (SHS), also known as passive smoking or environmental tobacco smoke, is composed of side stream smoke released from the combustion of tobacco products (such as cigarettes, cigars, or pipes) and mainstream smoke exhaled by smokers[1]. It contains more than 7,000 chemicals, of which hundreds are toxic and approximately 70 are reportedly linked with cancer[2,3]. In 2014, the Surgeon General reported that SHS is associated with various diseases in both

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#Correspondence should be addressed to WAN Xia, PhD, Tel: 86-10-65233870, E-mail: xiawan@ibms.pumc.edu.cn

Biographical note of the first author: WANG Yu Tong, female, born in 1996, Master Candidate, majoring in burden of disease methodology and tobacco control.

adults and children[4], and many more recent studies have shown similar results, especially those relating to cancer[5,6], diseases of the respiratory system (DRS)[7,8], and diseases of the circulatory system (DCS)[9,10]. The World Health Organization Framework Convention on Tobacco Control (FCTC) article 8 proposed restrictive provisions on SHS exposure[11].

Studies have reported the health problems caused by SHS exposure in China. In 2010, the exposure rate reached 72.4%. Although the exposure rate decreased slightly in 2018 (44.9% in the household and 50.9% in the workplace)[12], it still attributed a significant disease burden. In 2010, the number of the disability adjusted life years (*DALYs*) caused by SHS exposure in China was 9,308 million person years, resulting in 381,547 reported deaths. In 2019, the *DALYs* increased to 9,683 million person years, resulting in 416,054 deaths[13]. Studies have shown that the development of the tobacco epidemic in China is different from that in Western countries. For active smoking, several studies have shown substantial differences in the level of risk between countries. Using lung cancer as an example, the relative risks (*RR*s) ranged from 2.4 to 6.5 in China, which were much lower than in Western countries (range, 9.4 to 23.2)[14]. The risk values reported for many studies in Western countries are generally greater than 10[15-17]. The unique cooking style involved in preparing Chinese cuisine has an impact on the levels of indoor air pollution in Chinese households. Therefore, it is of significance to explore the risks associated with SHS exposure and different diseases among the Chinese population.

A literature search identified 30 meta-analyses on the association between SHS exposure and diseases among the Chinese population, three of which were written in English and the other 27 in Chinese. In these meta-analyses, the number of included studies ranged from 6 to 51, covering the following 11 diseases: lung cancer (n = 9)[18-26], low birth weight (n = 5)[27-31], breast cancer (n = 3)[32-34], congenital heart disease (n = 3)[35-37], stroke (n = 2)[38,39], asthma in children (n = 2)[40,41], adverse pregnancy outcomes (n = 2)[42,43], COPD (n = 1)[44], birth defects (n = 1)[45], childhood autism (n = 1)[46], and gestational diabetes mellitus (n = 1)[47]. All of these studies were completed before 2017, with the exception of the latest study of lung cancer, which was published in 2020. Of the studies, 25 were not completed within the last five years and only one disease was analyzed in each paper. Therefore, there is a lack of comprehensive data and up-to-date evidence on the risk of various diseases associated with SHS exposure among the Chinese population.

The aim of this study was to systematically review the risk of all diseases related to SHS exposure in the Chinese population based on an exhaustive search of observational studies published up until June 31, 2021. Our findings provide a basis for future studies, and the data may be used for burden of disease estimations.

METHODS

Search Strategy and Selection Criteria

This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies published up until June 30, 2021, were identified through a search of Chinese databases (including CNKI, Wanfang, and VIP) and English databases (including PubMed, EMBASE, and Cochrane Library), with the keywords: “tobacco” “smoking” “cigarette” “smoker” “smokers” “smoke” “nicotine” “China” “Chinese”. The complete search used for PubMed was: (((((((tobacco[Title/Abstract]) OR (smoking[Title/Abstract])) OR (cigarette[Title/Abstract])) OR (smoker[Title/Abstract])) OR (smoke[Title/Abstract])) OR (smokers[Title/Abstract])) OR (nicotine[Title/Abstract])) AND (((case-control[Title/Abstract]) OR (case control[Title/Abstract])) OR (cohort[Title/Abstract]))) AND ((China[Title/Abstract]) OR (Chinese[Title/Abstract])).

Additional records were manually identified by searching the references of published articles, reviews, and previous meta-analyses. Based on the above search method, all articles on passive smoking and SHS exposure were included in this study.

Inclusion and Exclusion Criteria

Inclusion Criteria This was structured according to the PECOS format. 1) Participants (P): Studies were carried out among the Chinese population, and the participants were representative; 2) Exposure (E): SHS exposure; 3) Comparison (C): To actively compare with individuals unexposed to SHS; 4) Outcomes (O): Effect values for SHS exposure and corresponding outcome events [Odds Ratios (*OR*s), Relative Risks (*RR*s), or Hazard Ratios (*HR*s)]; 5) Types of study (S): Case-control and cohort studies without restriction to language or time period; 6) Studies with a score of 6 or above using the Newcastle Ottawa Scale (NOS) assessment[48].

Exclusion Criteria 1) Duplicate studies or abstracts

without the full text being available; 2) Gene or cell research, and animal experiments; 3) Special groups, such as coal miners, pregnant women, and drug users. 4) The outcomes of the study were symptoms rather than diseases, such as elevated blood sugar.

Study Selection and Data Extraction

Study screening and data extraction were carried out independently by two researchers, with verification by a third reviewer. The title, first author, year of publication, time of investigation, sampling method, location, definition of SHS, number of cases and controls, basic information about participants, and other relevant parameters were extracted. The risk of bias according to the PRISMA recommendations was assessed independently by the two researchers mentioned above.

Evaluation of Study Quality

We evaluated the quality of the included studies from two aspects. First, the mean value of the NOS scores for each group. Second, a description of whether each study clearly defined the definition and source of SHS exposure.

Statistical Analyses

In this study, *HRs* were the effect values for three studies on the risk of death, and the *RRs* for the five cohort studies. Because of the limited number of the above two types of studies, the *OR* was used as the uniform effect value. In addition, two types of analysis strategies were used in this study. 1) For those diseases for which only one or two studies had been conducted, a simple statistical description was used. 2) For those diseases for which three or more studies had been conducted, meta-analysis was conducted using the Stata 15.1 software (Computer Resource Center, U.S.A).

Therefore, meta-analysis was performed for the studies on cancer (including lung cancer, breast cancer, bladder cancer, and liver cancer), DRS (including asthma in children), and DCS (including stroke). The heterogeneity of the effects across studies was evaluated using I^2 and Q tests. The fixed effect model was used when $I^2 < 50\%$ or $P > 0.1$. The random effect model was otherwise used. The time of investigation was divided into three periods (1983–1995, 1996–2009, and after 2010) based on the changes in the definition of SHS exposure. The participants were divided into four groups: Men, Women, Men and Women, and Children. The exposure sites were divided into Household, Workplace, and Non-specified Sites. Subgroup analysis was performed for the groups mentioned above. Funnel plots, with Egger's tests, were used to evaluate publication bias, and the "leave-one-out" method was used for sensitivity analysis.

RESULTS

Basic Characteristics of the Included Studies

A total of 53 studies were identified (Figure 1), with the sample size ranging from 126 to 73,363. Most studies were published in Chinese (n = 35) and a few were published in English (n = 18), with average NOS scores of 6.34 and 7.45, respectively. There were 48 case-control studies and 5 cohort studies, with average NOS scores of 6.52 and 8.60, respectively. The year in which each study began ranged from 1983 to 2019, with the majority being initiated from 1996 to 2009. In total, 31 of the studies were conducted on women, 4 studies were conducted on men, and 9 studies were conducted on children. The exposure sites were reported in only 16 studies (household or workplace). Among the 53 studies, two included four types of diseases each. Therefore, a total of 23 diseases (n = 59) were analyzed including: 15 types of cancer (n = 42)[49-86], 2 DRS (n = 7)[87-93], 2 DCS (n = 4)[55,94-95], and 4 other diseases (n = 6)[96-101] (Table 1). More details are shown in Supplementary Table S1, available in www.besjournal.com.

Definition and Source of SHS Exposure

Among the 59 disease-specific studies, the definition of SHS exposure was clarified in 47.17% (n = 25) of cases. Of the studies, 22.64% (n = 12) were based on the time and frequency of exposure to SHS (Definition 1), and 24.53% (n = 13) were based on the family members who smoke (Definition 2).

The sources of SHS, according to three types of characteristics, were reported by 49.6% (n = 27) of studies. The first classification was "location", such as household and workplace (Type 1); the second classification was "stage of life", such as adulthood or childhood (< 18 or > 18 years), pregnant or post-pregnancy, or menopausal (Type 2); the third classification was based on specific family members (such as husband, parents), partners, or colleagues (Type 3). Because there was more than one type of SHS source in some articles, 20.75%, 24.53%, and 30.19% of the studies were classified according to the above three characteristics, respectively (Table 2). More details are shown in Supplementary Table S2, available in www.besjournal.com.

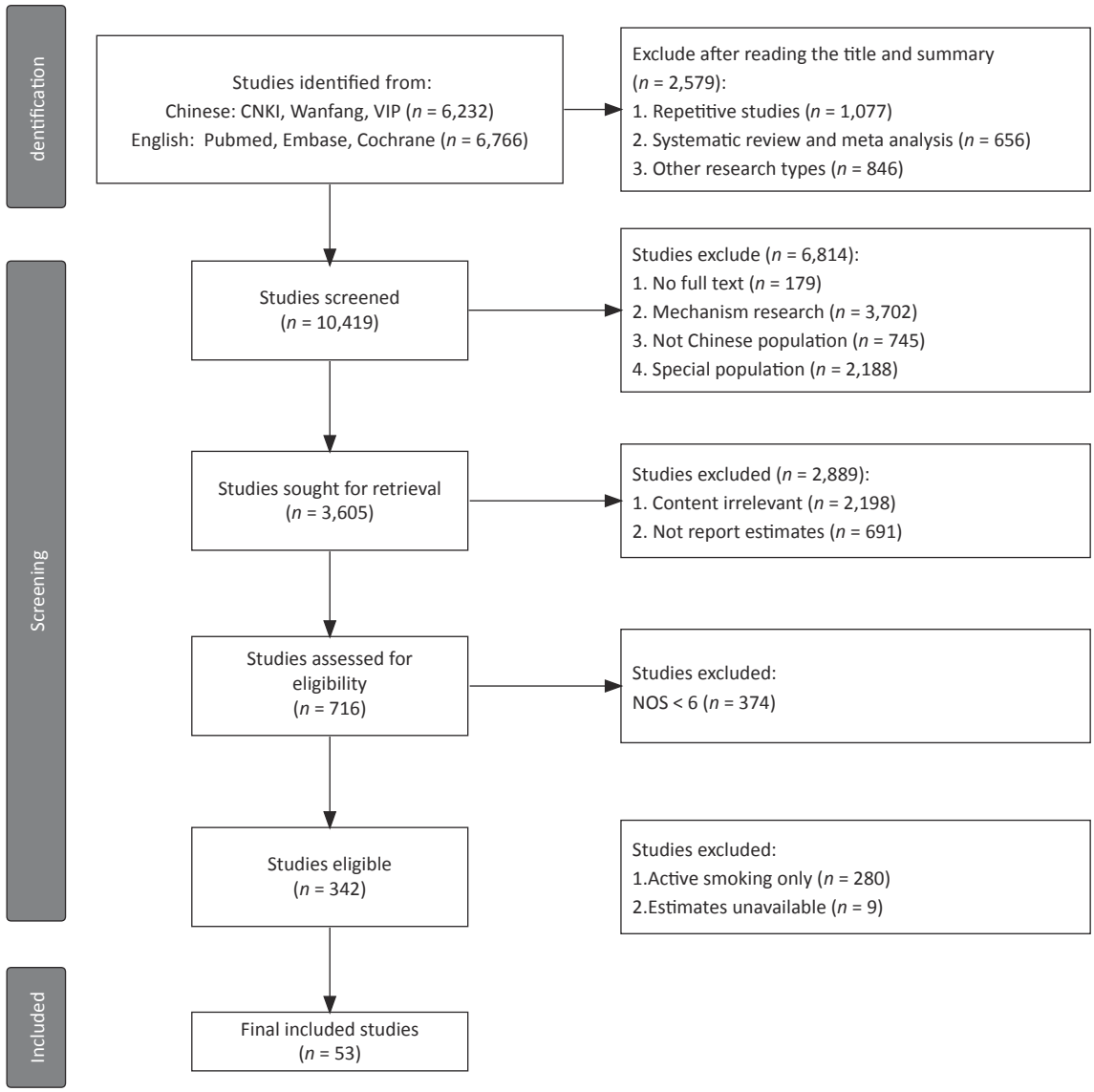

Figure 1. The study selection process.

Table 1. Basic information regarding the selection of studies

Basic information		Chinese (*n*, %)		English (*n*, %)		Total (*n*, %)		Number of participants		NOS (mean score)
								Min	Max	
Total		35	100.0	18	100.0	53	100.0	126	73,363	6.72
Language	Chinese	35	100.0	–	–	35	66.0	126	73,363	6.34
	English	–	–	18	100.0	18	34.0	204	72,829	7.45
Study design	Case-control	35	100.0	13	72.2	48	90.6	126	2,082	6.52
	Cohort	0	0	5	27.8	5	9.4	15,486	73,363	8.60
Start year of investigation	1983–1995	8	22.9	1	5.6	9	17.0	126	1,776	6.56
	1996–2009	17	48.6	16	88.9	33	62.3	210	73,363	6.91
	2010–2021	9	25.7	1	5.6	10	18.9	218	1,284	6.30
	None	1	2.9	0	0	1	1.9	552	552	6.00

Continued

Basic information		Chinese (*n*, %)		English (*n*, %)		Total (*n*, %)		Number of participants		NOS (mean score)
								Min	Max	
Sex	Women	15	39.5	16	61.5	31	48.4	244	73,363	7.19
	Men	2	5.3	2	7.7	4	6.3	456	1,776	7.75
	Both	13	34.2	7	26.9	20	31.3	210	23,415	7.05
	Children	8	21.1	1	3.8	9	14.1	126	1,209	6.00
Exposure site	Household	7	15.6	9	23.7	16	19.3	244	72,829	7.08
	Workplace	9	20.0	7	18.4	16	19.3	244	72,829	7.08
	Total	29	64.4	22	57.9	51	61.4	126	73,363	6.91
Cancer type	Total	25	100.0	17	100.0	42	100.0	214	72,829	6.95
	Lung Cancer[49-63]	9	36.0	6	35.3	15	35.7	244	72,829	6.73
	Breast Cancer[64-71]	4	16.0	4	23.5	8	19.0	372	1,767	6.63
	Bladder Cancer[72-74]	2	8.0	1	5.9	3	7.1	456	1,215	8.00
	Liver Cancer[61,75,76]	2	8.0	1	5.9	3	7.1	794	23,415	7.00
	Cervical Cancer[77,78]	2	8.0	0	0	2	4.8	312	413	6.00
	Acute Lymphoblastic Leukemia[79]	1	4.0	0	0	1	2.4	613	613	6.00
	Colon Cancer[80]	1	4.0	0	0	1	2.4	396	396	8.00
	Colorectal Cancer[61]	0	0	1	5.9	1	2.4	23,415	23,415	9.00
	Endometrial Cancer[81]	1	4.0	0	0	1	2.4	2,082	2,082	8.00
	Esophageal Squamous Cell Carcinoma[82]	0	0	1	5.9	1	2.4	214	214	7.00
	Intracranial Tumors[83]	1	4.0	0	0	1	2.4	537	537	6.00
	Oral Cancer[84]	0	0	1	5.9	1	2.4	708	708	7.00
	Papillary Thyroid Cancer[85]	1	4.0	0	0	1	2.4	369	369	6.00
	Stomach Cancer[61]	0	0	1	5.9	1	2.4	23,415	23,415	9.00
	Tongue Cancer[86]	1	4.0	0	0	1	2.4	876	876	7.00
	Cancer[55]	0	0	1	5.90	1	2.4	72,829	72,829	9.00
DRS*	Total	5	100.0	2	100.0	7	100.0	212	1,209	6.14
	Asthma in Children[87-92]	5	100.0	1	50.0	6	85.7	212	1,209	6.00
	Small Airway Obstruction[93]	0	0	1	50.0	1	14.3	648	648	7.00
DCS*	Total	2	100.0	2	100.0	4	100.0	210	72,829	7.75
	Stroke[55,94,95]	2	100.0	1	50.0	3	75.0	210	72,829	7.33
	Cardiovascular Disease[55]	0	0	1	50.0	1	25.0	72,829	72,829	9.00
Other Diseases	Total	3	100.0	3	100.0	6	100.0	126	28,177	7.17
	Tuberculosis[96,97]	1	33.3	1	33.3	2	33.3	348	15,486	7.00
	Legionnaires' Disease (Children)[98]	1	33.3	0	0	1	16.7	126	126	6.00
	Otitis Media (Children)[99]	1	33.3	0	0	1	16.7	534	534	6.00
	Type 2 Diabetes Mellitus[100]	0	0	1	33.3	1	16.7	28,177	28,177	9.00
	All Causes of Mortality[101]	0	0	1	33.3	1	16.7	73,363	73,363	8.00

Note. For the basic information on sex, exposure site, and disease type, some studies contained more than one result, so the total number for each group could be more than that of the study design and the start year of investigation, respectively. *DRS: Diseases of the Respiratory System; DCS: Diseases of the Circulatory System; NOS: Newcastle Ottawa Scale.

Diseases Associated with SHS Exposure

Following meta-analysis, we observed an *OR* of 1.79 (95% *CI*: 1.56–2.05) for all cancers, and *OR*s of 1.92 (95% *CI*: 1.42–2.59) for lung cancer, 1.57 (95% *CI*: 1.40–1.76) for breast cancer, 1.52 (95% *CI*: 1.12–2.05) for bladder cancer, and 1.37 (95% *CI*: 1.08–1.73) for liver cancer. The *OR* for DCS was 1.92 (95% *CI*: 1.29–2.85), and further 2.29 (95% *CI*: 1.26–4.16) for stroke. The *OR* for DRS was 1.76 (95% *CI*: 1.13–2.74), and further 1.82 (95% *CI*: 1.07–3.11) for asthma in children (Figures 2 and 3).

For the other 17 diseases for which meta-analysis was not performed, the *OR*s for colorectal cancer, endometrial cancer, cardiovascular disease, and tuberculosis were not statistically significant. Whereas the *OR*s for the other diseases ranged from 1.17 to 4.87, which did show a statistically significant difference. More details are provided in Table 3.

Subgroup Analysis

Because of the limited number of studies, subgroup analysis for different time periods, sexes, and exposure sites, were only performed for studies on lung cancer and breast cancer. Regarding the different time periods, the *OR* for lung cancer peaked in 2010–2019 (7.85, 95% *CI*: 5.11–12.07), and this value was significantly different from the values derived from the other two time periods, 1.64 (95% *CI*: 1.33–2.03) for 1983–1995 and 1.34 (95% *CI*: 1.03–1.74) for 1996–2009. For breast cancer, all of the studies were published before 2009, and the *OR* decreased from 2.60 (95% *CI:* 1.84–3.68) in 1983–1995 to 1.47 (95% *CI*: 1.30–1.66) in 1996–2009, which showed a significant difference. Regarding sex, exposure to SHS increased the risk of lung cancer in women (*OR* = 1.65, 95% *CI*: 1.22–2.24) and in both sexes (*OR* = 2.76, 95% *CI*: 1.28–5.96), but not in men (*OR* = 1.12, 95% *CI*: 0.77–1.63). Regarding exposure site, the *OR*s (1.38–2.20) showed a statistically significant difference for non-specified sites or households for the two diseases analyzed. While the *OR*s for the workplace were 1.38 (95% *CI*: 0.94–2.04) for lung cancer and 1.16 (95% *CI*: 0.89–1.51) for breast cancer. Further details are provided in Table 3 and the forest plots are shown in Supplementary Figure S1, available in www.besjournal.com.

Bias Test

Publication bias was unlikely to be found in the studies of bladder cancer, liver cancer, DCS (including stroke), and DRS (including asthma in children), but may exist in the studies of all cancers (including lung cancer and breast cancer). The results of the Egger's test are shown in Table 3 and the funnel plots are shown in Supplementary Material Figure 2.

Sensitivity Analysis

None of the studies were found to have a strong influence on the results for the six diseases analyzed (lung cancer, breast cancer, bladder cancer, liver cancer, stroke, and asthma in children) or the three overall disease types (overall cancers, DCS, and DRS) in the "leave-one-out" sensitivity analysis. The results are summarized in Supplementary Material Table 3.

DISCUSSION

Our findings suggested that exposure to SHS increases the risk of various systemic diseases, especially for all cancers (*OR* = 1.77, 95% *CI*: 1.54–2.05), DCS (*OR* = 1.92, 95% *CI*: 1.29–2.85), and DRS (*OR* = 1.76, 95% *CI*: 1.13–2.74). The *OR*s fluctuated over time for lung cancer and breast cancer.

The Quality of the Included Studies

Overall, although the studies included had NOS scores of 6 or more, the overall mean score was only 6.72, so the quality was low overall. The quality of

Table 2. Definition and characteristics of second-hand smoke exposure

Variables	Definition of SHS (*n*, %)						Characteristic of SHS (*n*, %)							
	Undefined		Definition 1		Definition 2		None		Type 1		Type 2		Type 3	
DCS	2	7.14	0	0	0	0	2	7.69	0	0	0	0	1	6.25
DRS	6	21.43	0	0	1	7.69	3	11.54	1	9.09	1	7.69	4	25.00
Cancers	17	60.71	10	83.33	11	84.62	15	57.69	10	90.91	12	92.31	11	68.75
Other diseases	3	10.71	2	16.67	1	7.69	6	23.08	0	0	0	0	0	0
Total	28	52.83	12	22.64	13	24.53	26	49.06	11	20.75	13	24.53	16	30.19

Note. Specific descriptions for the definitions and characteristics are provided in Supplementary Table S2. SHS, second-hand smoke; DRS, Diseases of the Respiratory System; DCS, Diseases of the Circulatory System.

Chinese studies was relatively poor, with a lower average NOS score of 6.34, compared with English studies (mean = 7.45). In addition, the quality of cohort studies (mean = 8.60) was generally higher than that of case-control studies (mean = 6.52). As for the definition and characteristics of SHS, in National Tobacco Surveys and the National Behavior Risk Factors Surveillance System of China, the prevalence of SHS exposure was taken as one of the key indicators for supervision, which means it is important to clarify the definition of SHS exposure. In 1984, it was defined as "more than 15 minutes per day"[102], while in 1996, it was changed to "at least one day per week for more than 15 minutes"[103]. In 2010, the limit of 15 minutes was removed[104]. However, only 47.17% of the included literature in our study was reported with a clear definition. This may be an area for further development in the future. If the definition of SHS

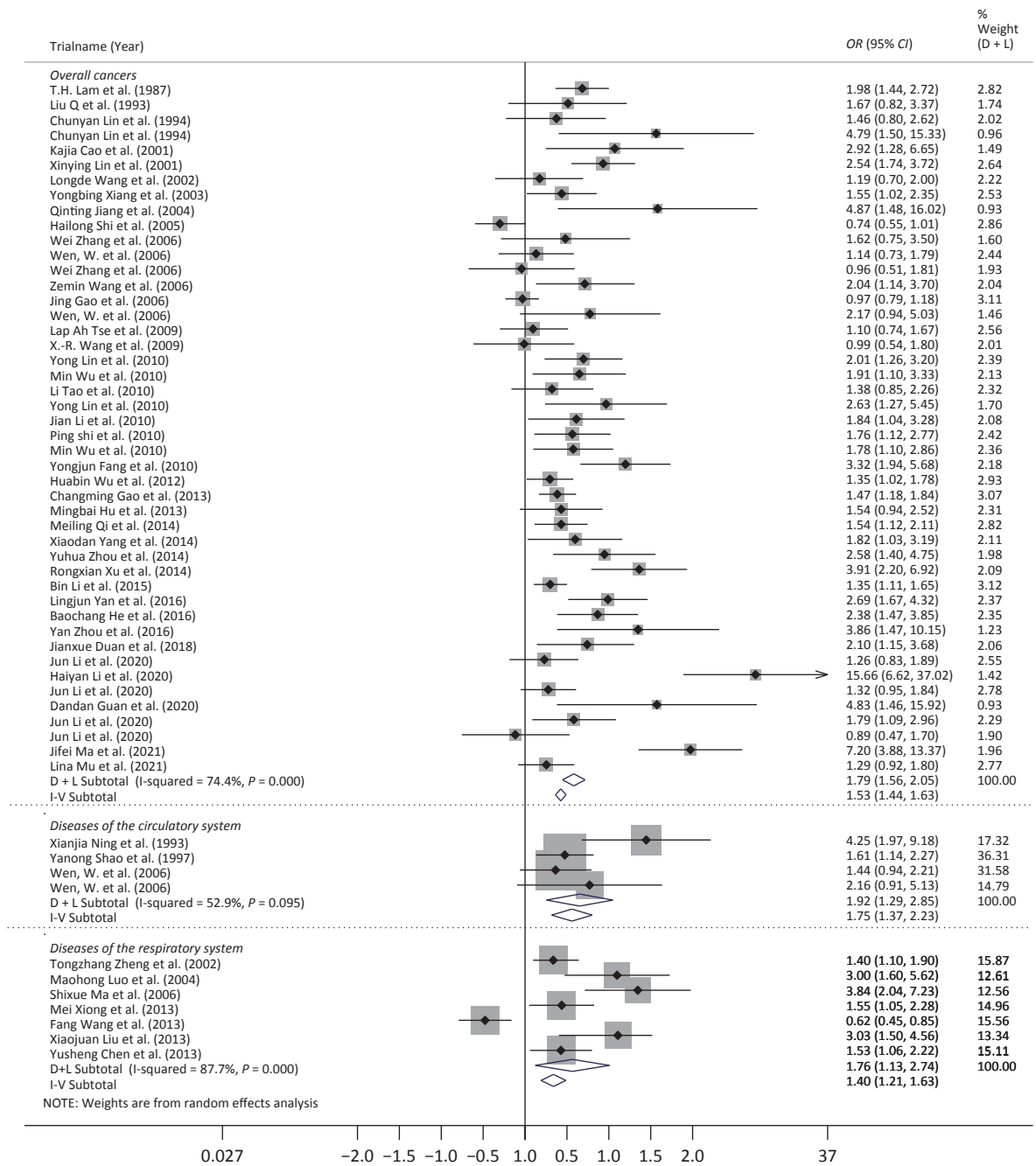

Figure 2. The odds ratios for second-hand smoke exposure.

exposure was more accurate, the *OR* may increase, which may be one explanation for the fluctuation in the *OR* for lung cancer after 2010.

The Risks Associated with SHS

"*Cancer incidence and mortality in China, 2016*", a publication released by the National Cancer Center in 2022, showed that the cancer with the highest incidence in men was lung cancer, while it was breast cancer in women[105]. The current study focused on lung cancer and breast cancer, with a specific focus on changes in *OR*s according to sex, time period, and exposure site. Data on other diseases were limited by the available literature, thereby not allowing for in-depth subgroup analyses. Our study provides a basis for subsequent studies by comparing the results with those of previous domestic and international literature.

Lung Cancer We observed an *OR* of 1.92 (95% *CI*: 1.42–2.59) for lung cancer, which did not differ

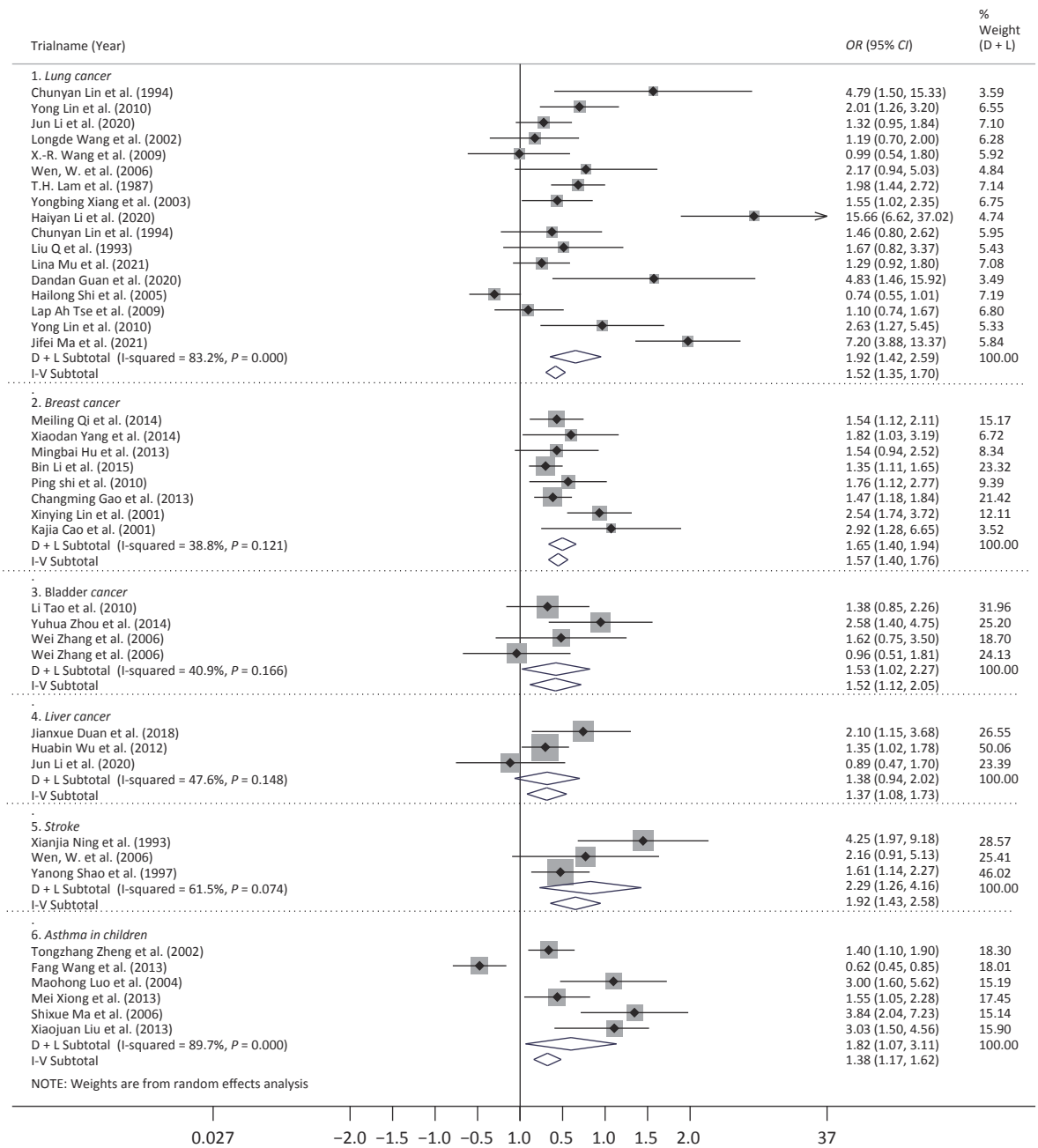

Figure 3. The disease-specific odds ratios for second-hand smoke exposure.

Table 3. The pooled odds ratios or odds ratios for SHS exposure

Diseases		Subgroup	Number of observations	I^2 (%)	*P*-value	Model	*POR/OR* and 95% *CI*			Egger's test	
							POR/OR	*LL*	*UL*	*t*	*P*-value
Cancers*			46	74.4	< 0.001	Random	1.79	1.56	2.05	2.74	0.000
	Lung cancer*		17	83.2	< 0.001	Random	1.92	1.42	2.59	3.87	0.009
		1983–1995*	4	0.3	0.390	Fixed	1.64	1.33	2.03	−3.17	0.125
		1996–2009*	9	64.7	0.004	Random	1.34	1.03	1.74	3.02	0.072
		2010–2019*	4	22.7	0.275	Fixed	7.85	5.11	12.07	−1.14	0.687
		Women*	12	71.1	< 0.001	Random	1.65	1.22	2.24	2.41	0.076
		Men*	2	0	0.843	Fixed	1.12	0.77	1.63	0.38	–
		Both*	5	92.5	< 0.001	Random	2.76	1.28	5.96	8.51	0.062
		Household*	6	65.6	0.012	Random	1.59	1.08	2.35	0.03	0.991
		Workplace*	6	72.1	0.003	Random	1.38	0.94	2.04	4.54	0.023
		Total*	9	87.4	< 0.001	Random	2.20	1.33	3.62	4.60	0.061
	Breast cancer*		8	38.8	0.121	Fixed	1.57	1.40	1.76	2.11	0.044
		1983–1995*	2	0	0.763	Fixed	2.60	1.84	3.68	0.62	–
		1996–2009*	6	0	0.853	Fixed	1.47	1.30	1.66	1.35	0.021
		Household*	2	0	0.338	Fixed	1.38	1.15	1.65	3.42	–
		Workplace*	2	0	0.519	Fixed	1.16	0.89	1.51	−8.86	–
		Total*	8	38.8	0.121	Fixed	1.57	1.40	1.76	2.11	0.044
	Bladder cancer*		4	40.9	0.166	Fixed	1.52	1.12	2.05	0.76	0.891
	Liver cancer*		3	47.6	0.148	Fixed	1.37	1.08	1.73	0.02	0.997
	Cervical cancer		2				1.84	1.04	3.28		
							3.91	2.21	6.92		
	Acute Lymphoblastic Leukemia		1				3.32	1.94	5.68		
	Intracranial Tumors		2				1.78	1.10	2.86		
							1.91	1.10	3.33		
	Colon cancer		1				4.87	1.48	16.02		
	Colorectal cancer		1				1.26	0.83	1.89		
	Endometrial cancer		1				0.97	0.28	2.42		
	Stomach cancer		1				1.79	1.09	2.96		
	Esophageal Squamous Cell carcinoma		1				2.04	1.14	3.70		
	Oral cancer		1				2.38	1.47	3.85		
	Papillary thyroid Cancer		1				3.86	1.47	10.15		
	Tongue cancer		1				2.69	1.67	4.32		
	Cancer		1				1.14	0.73	1.79		
DCS*			4	52.9	0.095	Random	1.92	1.29	2.85	2.72	0.236
	Stroke*		3	61.5	0.074	Random	2.29	1.26	4.16	2.59	0.410
	Cardiovascular Disease		1				1.44	0.94	2.21		

Continued

Diseases		Subgroup	Number of observations	I^2 (%)	*P*-value	Model	*POR/OR* and 95% *CI*			Egger's test	
							POR/OR	*LL*	*UL*	*t*	*P*-value
DRS*			7	87.7	< 0.001	Random	1.76	1.13	2.74	6.70	0.053
	Asthma in Children*		6	89.7	< 0.001	Random	1.82	1.07	3.11	6.71	0.085
	Small airway Obstruction		1				1.54	1.06	2.22		
Other diseases			6								
	Tuberculosis		2				1.62	0.92	2.85		
							1.70	1.04	2.80		
	Legionnaires' Disease (Children)		1				2.10	1.22	3.63		
	Otitis media (Children)		1				2.24	1.52	3.16		
	Type 2 diabetes mellitus		1				1.17	1.00	1.37		
	All causes of mortality		1				1.08	1.00	1.17		

Note. For the subgroups of sex and exposure site, some studies contained more than one result, so the number of results included in the subgroup analysis may be more than that of the disease-specific results. DRS: Diseases of the Respiratory System; DCS: Diseases of the Circulatory System. *POR*: pooled odds ratio; *OR*: odds ratio; *LL*: 95% lower limit; *UL*: 95% upper limit. *The results of meta-analysis.

significantly from the six previously-published meta-analyses among the Chinese population (*OR* range, 1.13 to 2.11). In 2018, a review reported that the *OR* among the global population was 1.245 (95% *CI*: 1.026–1.511)[106], and the association among the Chinese population was slightly higher. The *OR* for Chinese women was 1.65 (95% *CI*: 1.22–2.24) in our study, which was supported by three previous studies (*OR* range, 1.50–1.58)[18-20], but two other data sets showed that there was no correlation among Chinese women[21,22]. This may be due to the increase in research on women after 2000. A study published in 2018 observed an *OR* of 1.33 (95% *CI*: 1.17–1.51) among women globally[107], and the results among Chinese women were slightly higher. The *OR* for Chinese men was not statistically significant in this study (*OR* = 1.12, 95% *CI*: 0.77–1.63), which was supported by a previous study (*OR* = 1.00, 95% *CI*: 0.68–1.48, for hospital-based studies)[23]. Since the other two previous results were significant [*OR* = 1.34, 95% *CI*: 1.08–1.65[19] and *OR* = 1.85, 95% *CI*: 1.10–3.10 (population-based studies)[23]], the association among Chinese men requires further study. It is noteworthy that the *OR* values have rapidly increased since 2010. The tobacco industry in the West has been promoting low-tar cigarettes as a healthier alternative to regular cigarettes since the 1950s. In China, the sale of cigarettes with a tar content of more than 15 mg per cigarette was banned by the State Tobacco Monopoly Administration in 2004. From this study, we see that the health risk associated with SHS did not reduce with low-tar cigarettes.

Breast Cancer We observed an *OR* of 1.57 (95% *CI*: 1.40–1.76) for breast cancer, which was similar to three previous meta-analyses (*OR* range, 1.62–1.94) of the Chinese population[32-34], but was more reliable because of lower heterogeneity. Globally, there were a few pooled *OR*s from meta-analyses, including 1.07 (95% *CI*: 1.02–1.13) for 11 prospective studies and 1.30 (95% *CI*: 1.10–1.54) for 20 retrospective studies in 2015[108], 1.235 (95% *CI*: 1.102–1.385) in 2018[106], and 1.07 in the results of the Global Burden of Disease (GBD) 2017[3]. Therefore, the risk in Chinese women may be slightly higher than the global level. The *OR*s decreased in 1996–2009, compared with those in 1983–1995, and this difference was statistically significant. However, we could not draw any conclusions regarding the secular trend of *OR*s in breast cancer because there were no studies published after 2010. Future studies on breast cancer are therefore needed.

Subgroup Analysis of the Exposure Sites in Lung and Breast Cancer Our results revealed that exposure in households or in non-specific places increased the risk of lung cancer and breast cancer, which was supported by five previous meta-analyses of the Chinese population[18-20,23,32]. However, the risk was not significant in the workplace, which may indicate that the smoke-free policy or law was well implemented in the workplace. It also suggests that smoke-free policies in public places or homes need

to be reinforced. Another factor is that in most studies, SHS exposure was defined as exposure to family members only, workplace was not included in this definition (Supplementary Table S2, definition 2), but the impact of the workplace should not be ignored.

Other Diseases Currently, no meta-analyses have been conducted for bladder cancer or liver cancer among the Chinese population. Globally, a meta-analysis in 2009 showed no statistically significant association between bladder cancer and SHS exposure (*OR* = 0.99, 95% *CI*: 0.86–1.14)[109]. However, because only three studies were included, the reliability of these results is under question. In our study, the *OR* for the association between SHS and stroke was 2.29 (95% *CI*: 1.26–4.16), which is similar to previous meta-analyses results for the Chinese population in 2005 (*OR* = 3.22, 95% *CI*: 2.04–5.07)[38]. Globally, the pooled estimates were 1.64 (95% *CI*: 1.12–2.40) in 2012[110] and 1.35 (95% *CI*: 1.22–1.50) in 2015[111]. Because of the limited number of articles available, subgroup analysis based on sex could not be performed. From literature published in 2016, the *OR* for Chinese women was 2.11 (95% *CI*: 1.19–3.74)[39]. However, the NOS scores of the included studies were not specified in the literature, meaning that the quality of the included studies was unconfirmed. There is sufficient evidence to prove that parental smoking, especially by the direct care-giver, decreases pulmonary function[112] and increases asthma prevalence[113] in children. The results of our study (*OR* = 1.82, 95% *CI*: 1.07–3.11) were lower than those of a previous study (*OR* = 3.13, 95% *CI*: 2.23–4.03)[40], but did not show statistical significance. Furthermore, there was no significant difference between our data and the global data reported in 2013 (*OR* = 1.32, 95% *CI*: 1.23–1.42)[114] and 2020 (*OR* = 1.24, 95% *CI*: 1.20–1.28)[115].

Limitations

The limitations of the current study include the limited number of eligible studies in the literature and the resulting bias. A large number of studies are currently being undertaken regarding the association between exposure to SHS and certain diseases. Cancer has become one of the major health problems that seriously threatens the health of the Chinese population. However, our study revealed that research into diseases affected by SHS has mainly focused on lung cancer and breast cancer. For other highly-prevalent cancers associated with SHS, such as gastric cancer, colon cancer, and liver cancer, only one to three studies were included in our analysis because of the low quality of the literature or the lack of relevant research. Only original results were included for such studies, and meta-analyses were not performed. The number of cohort studies was also low, with only five such studies out of the 53 extracted from the database. There was heterogeneity among the studies in the meta-analysis of diseases, with the exception of breast cancer, bladder cancer, and liver cancer, which may have led to bias. Publication bias exists in the results for lung cancer and breast cancer; therefore, a minimum sample size should be ensured in future studies. In addition, the definition of SHS exposure varied widely between the included studies, with some not even reporting a definition, which may also have conferred some bias.

CONCLUSIONS

SHS exposure is a known cause of various diseases. After meta-analysis, exposure to SHS was found to be positively associated with cancer (including lung cancer, breast cancer, and liver cancer), DCS (including stroke), and DRS (including asthma in children) among the Chinese population. Our findings did not show a significant difference from global findings. The same is not the case for active smoking. The definition and characteristics of SHS exposure need to be further clarified. The variations in risk during different time periods may reflect changes to this definition. Further studies are required to confirm the correlation between SHS exposure in the workplace and the risk of disease among men. There remains a lack of research on some other diseases caused by SHS. Our results provide a reference for public health professionals, researchers, and policymakers in the development of effective SHS exposure prevention strategies.

AUTHOR CONTRIBUTIONS

WANG Yu Tong: Identified the studies; checked and analyzed the data; wrote the initial draft of the manuscript. HU Kui Ru, ZHAO Jian, AI Fei Ling, SHI Yu Lin, WANG Xue Wei, AI Li Mei, YANG Wen Yi, WANG Jing Xin: Identified the studies; extracted and checked the data. WAN Xia: Conceived and designed the study; checked and verified the data; contributed to the revision and finalization of the paper; was responsible for submitting the article for publication.

DECLARATION OF COMPETING INTERESTS

The authors have no possible conflicts of interest.

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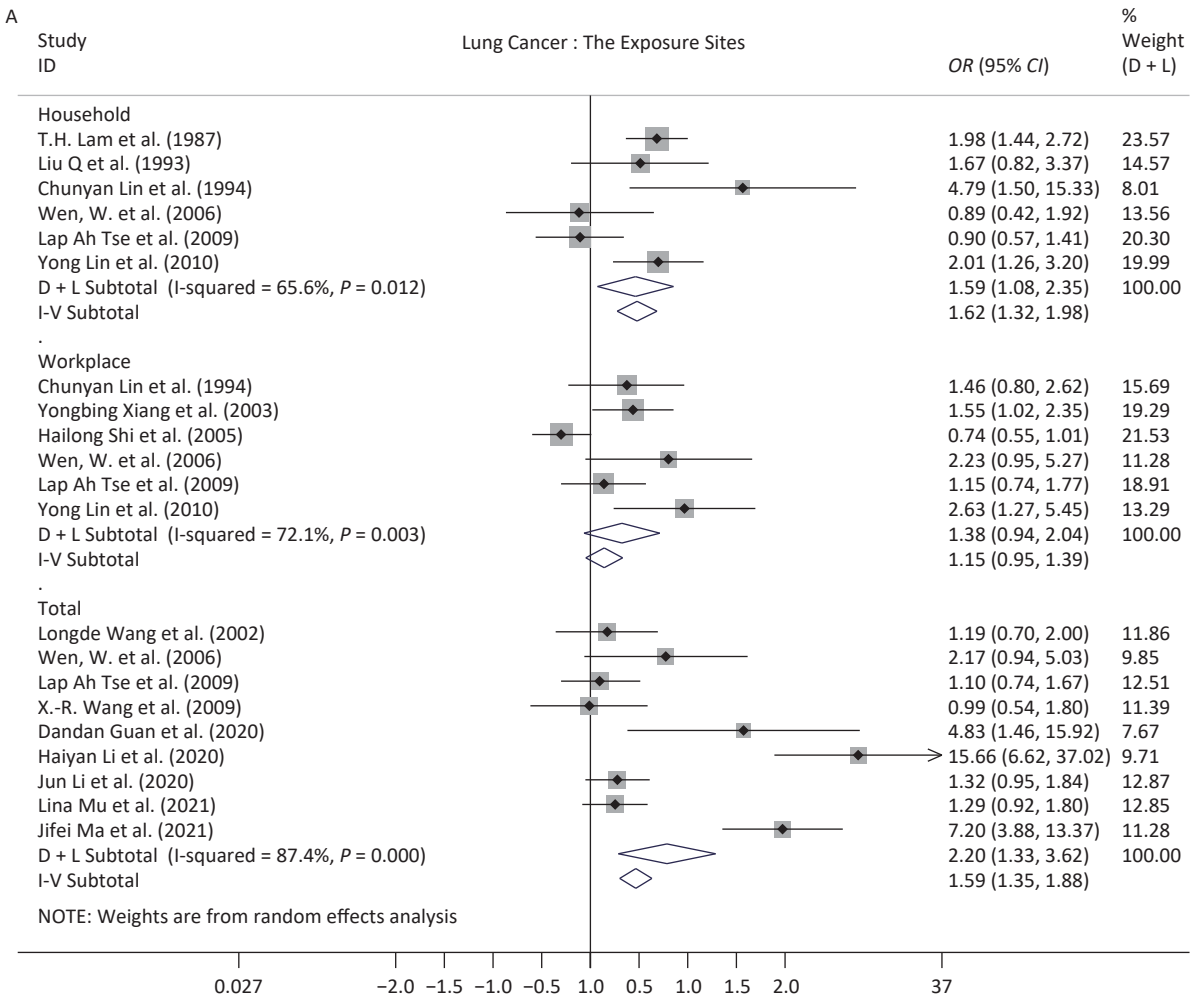
A
Study ID
Lung Cancer : The Exposure Sites
OR (95% CI)
% Weight (D + L)
Household
T.H. Lam et al. (1987) 1.98 (1.44, 2.72) 23.57
Liu Q et al. (1993) 1.67 (0.82, 3.37) 14.57
Chunyan Lin et al. (1994) 4.79 (1.50, 15.33) 8.01
Wen, W. et al. (2006) 0.89 (0.42, 1.92) 13.56
Lap Ah Tse et al. (2009) 0.90 (0.57, 1.41) 20.30
Yong Lin et al. (2010) 2.01 (1.26, 3.20) 19.99
D + L Subtotal (I-squared = 65.6%, P = 0.012) 1.59 (1.08, 2.35) 100.00
I-V Subtotal 1.62 (1.32, 1.98)
.
Workplace
Chunyan Lin et al. (1994) 1.46 (0.80, 2.62) 15.69
Yongbing Xiang et al. (2003) 1.55 (1.02, 2.35) 19.29
Hailong Shi et al. (2005) 0.74 (0.55, 1.01) 21.53
Wen, W. et al. (2006) 2.23 (0.95, 5.27) 11.28
Lap Ah Tse et al. (2009) 1.15 (0.74, 1.77) 18.91
Yong Lin et al. (2010) 2.63 (1.27, 5.45) 13.29
D + L Subtotal (I-squared = 72.1%, P = 0.003) 1.38 (0.94, 2.04) 100.00
I-V Subtotal 1.15 (0.95, 1.39)
.
Total
Longde Wang et al. (2002) 1.19 (0.70, 2.00) 11.86
Wen, W. et al. (2006) 2.17 (0.94, 5.03) 9.85
Lap Ah Tse et al. (2009) 1.10 (0.74, 1.67) 12.51
X.-R. Wang et al. (2009) 0.99 (0.54, 1.80) 11.39
Dandan Guan et al. (2020) 4.83 (1.46, 15.92) 7.67
Haiyan Li et al. (2020) 15.66 (6.62, 37.02) 9.71
Jun Li et al. (2020) 1.32 (0.95, 1.84) 12.87
Lina Mu et al. (2021) 1.29 (0.92, 1.80) 12.85
Jifei Ma et al. (2021) 7.20 (3.88, 13.37) 11.28
D + L Subtotal (I-squared = 87.4%, P = 0.000) 2.20 (1.33, 3.62) 100.00
I-V Subtotal 1.59 (1.35, 1.88)
NOTE: Weights are from random effects analysis
0.027
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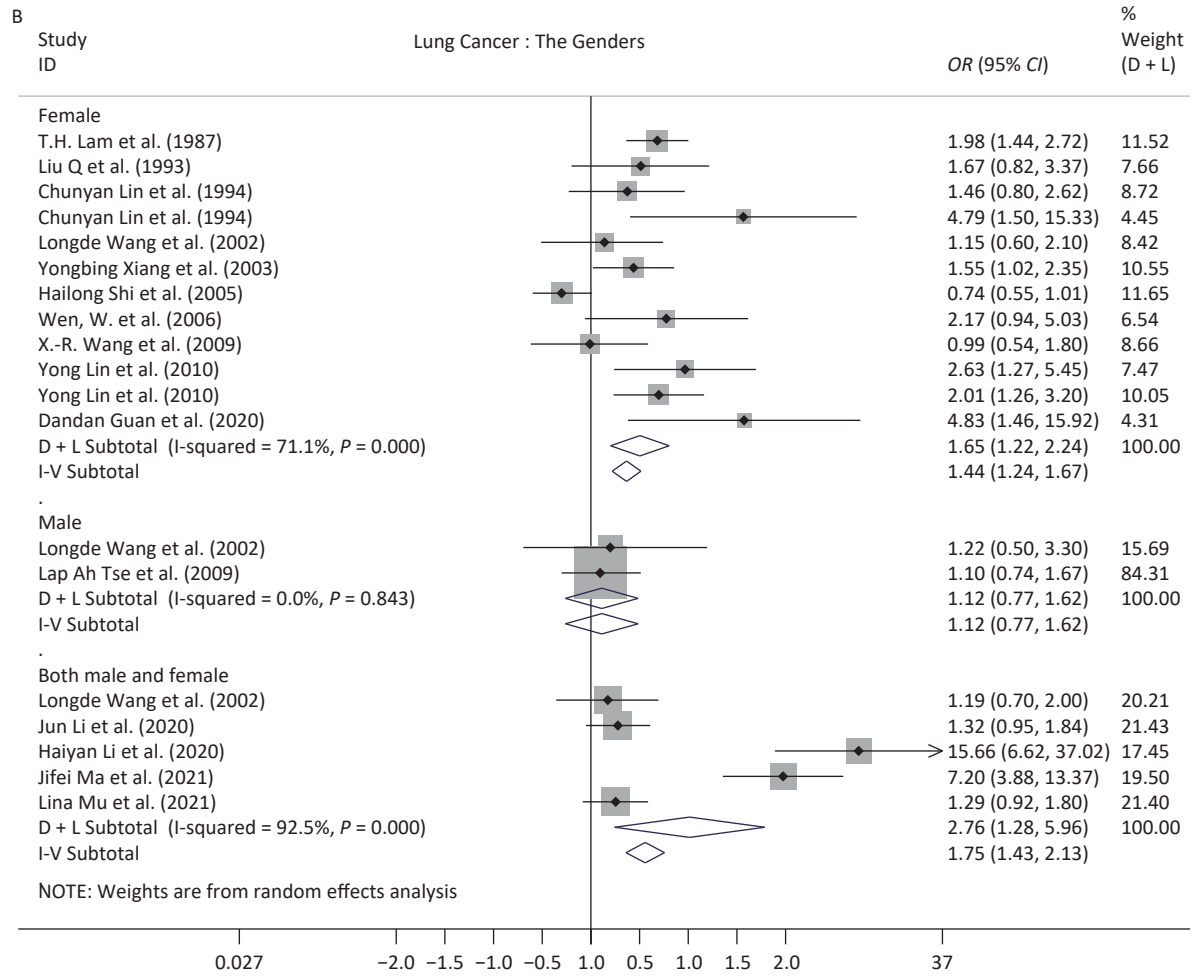
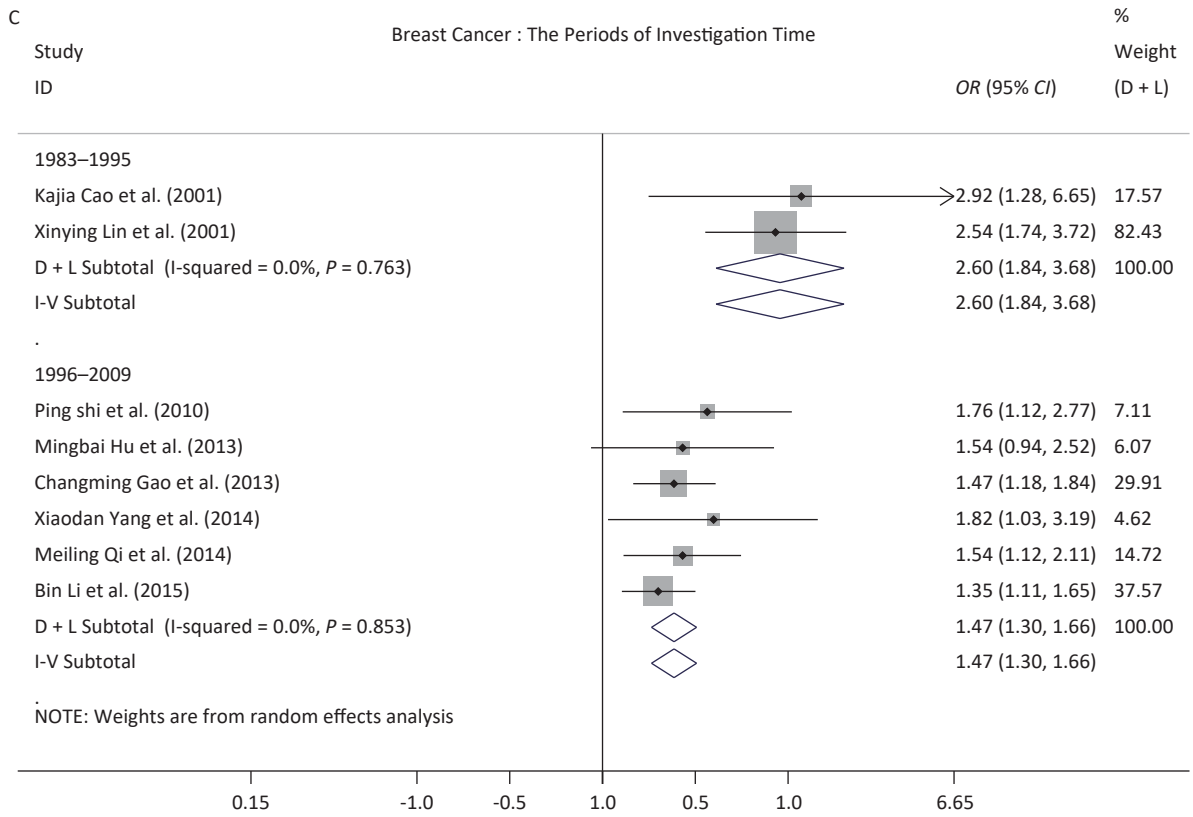
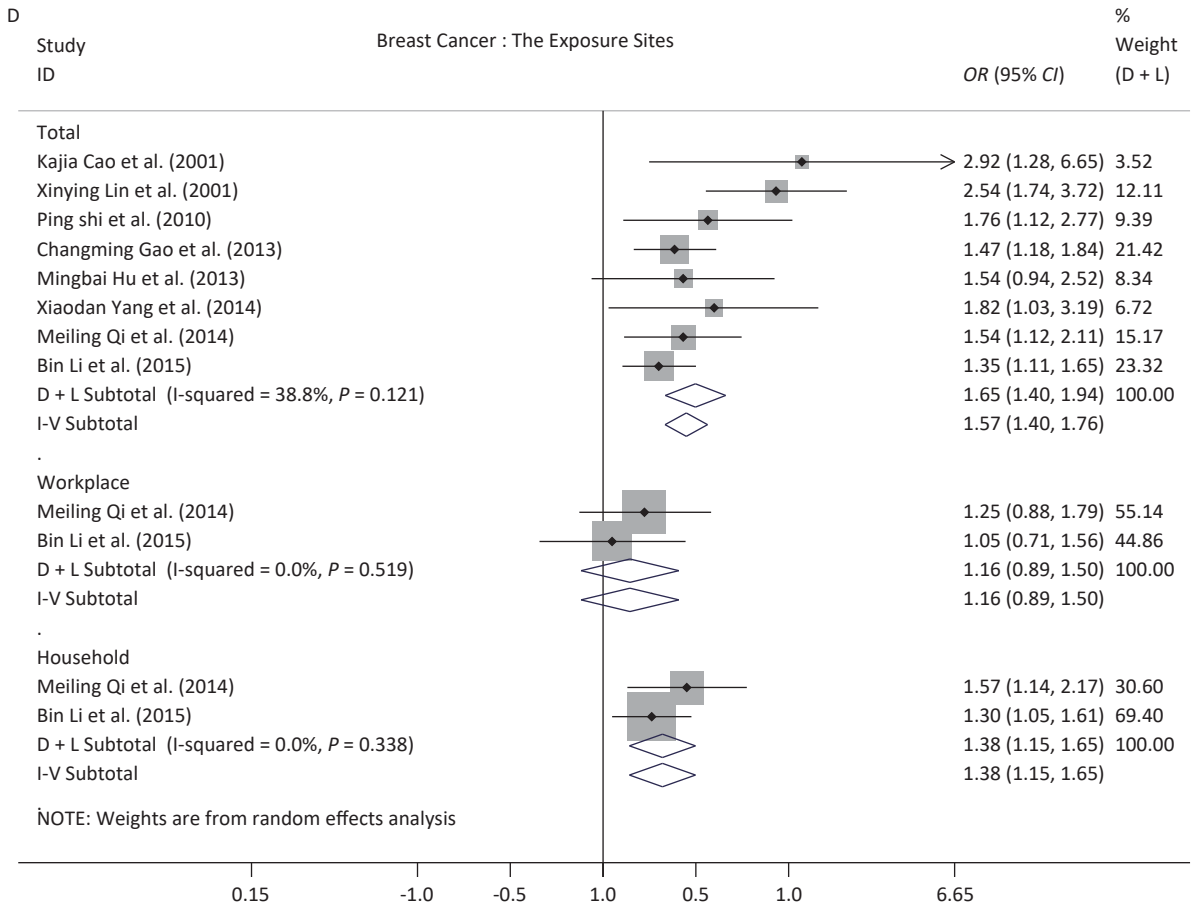
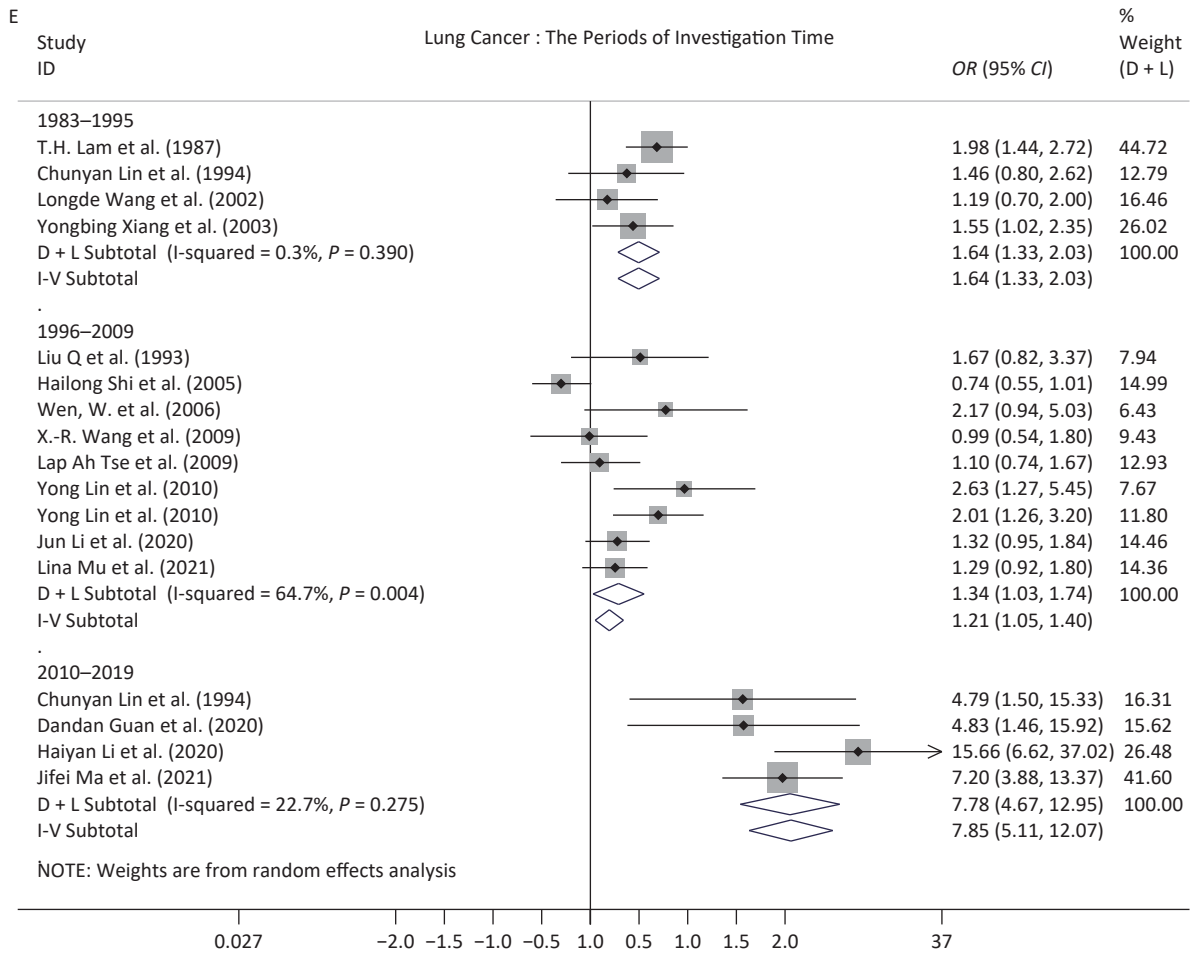
37

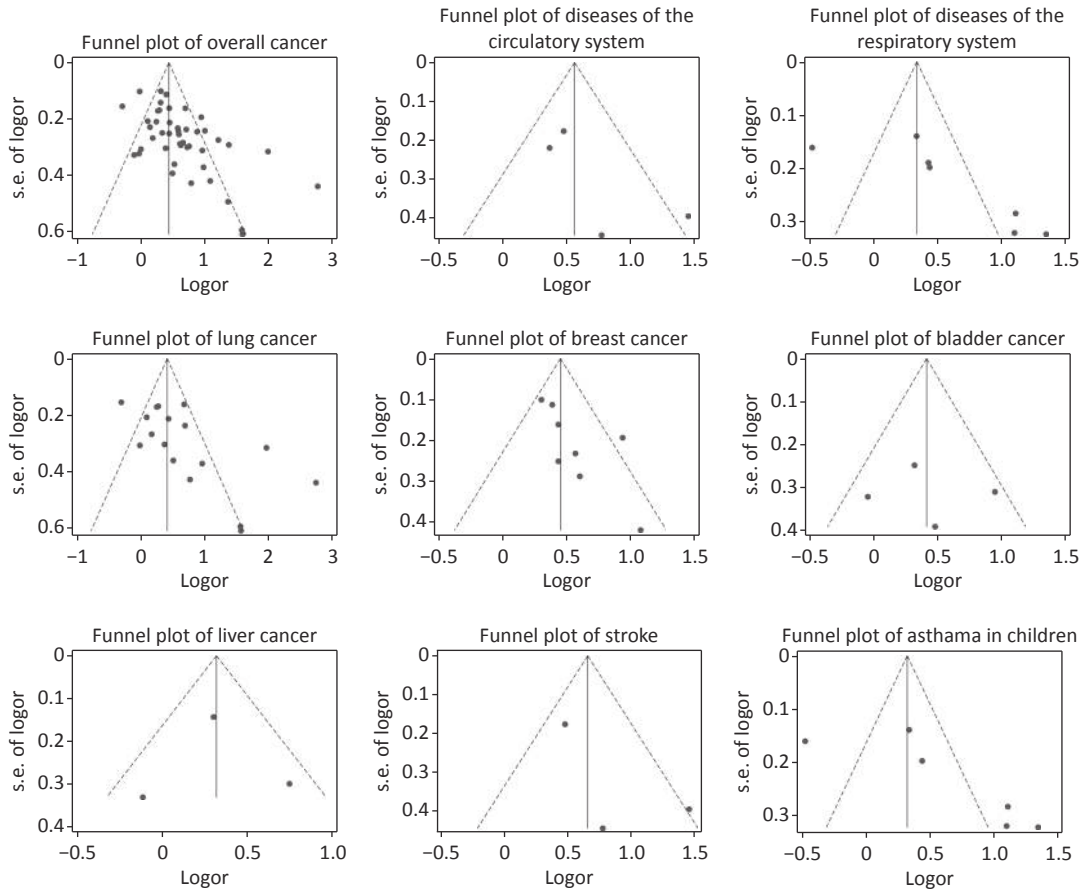

B
Study ID
Lung Cancer : The Genders
OR (95% CI)
% Weight (D + L)
Female
T.H. Lam et al. (1987) 1.98 (1.44, 2.72) 11.52
Liu Q et al. (1993) 1.67 (0.82, 3.37) 7.66
Chunyan Lin et al. (1994) 1.46 (0.80, 2.62) 8.72
Chunyan Lin et al. (1994) 4.79 (1.50, 15.33) 4.45
Longde Wang et al. (2002) 1.15 (0.60, 2.10) 8.42
Yongbing Xiang et al. (2003) 1.55 (1.02, 2.35) 10.55
Hailong Shi et al. (2005) 0.74 (0.55, 1.01) 11.65
Wen, W. et al. (2006) 2.17 (0.94, 5.03) 6.54
X.-R. Wang et al. (2009) 0.99 (0.54, 1.80) 8.66
Yong Lin et al. (2010) 2.63 (1.27, 5.45) 7.47
Yong Lin et al. (2010) 2.01 (1.26, 3.20) 10.05
Dandan Guan et al. (2020) 4.83 (1.46, 15.92) 4.31
D + L Subtotal (I-squared = 71.1%, P = 0.000) 1.65 (1.22, 2.24) 100.00
I-V Subtotal 1.44 (1.24, 1.67)
.
Male
Longde Wang et al. (2002) 1.22 (0.50, 3.30) 15.69
Lap Ah Tse et al. (2009) 1.10 (0.74, 1.67) 84.31
D + L Subtotal (I-squared = 0.0%, P = 0.843) 1.12 (0.77, 1.62) 100.00
I-V Subtotal 1.12 (0.77, 1.62)
.
Both male and female
Longde Wang et al. (2002) 1.19 (0.70, 2.00) 20.21
Jun Li et al. (2020) 1.32 (0.95, 1.84) 21.43
Haiyan Li et al. (2020) 15.66 (6.62, 37.02) 17.45
Jifei Ma et al. (2021) 7.20 (3.88, 13.37) 19.50
Lina Mu et al. (2021) 1.29 (0.92, 1.80) 21.40
D + L Subtotal (I-squared = 92.5%, P = 0.000) 2.76 (1.28, 5.96) 100.00
I-V Subtotal 1.75 (1.43, 2.13)
NOTE: Weights are from random effects analysis
0.027
−2.0 −1.5 −1.0 −0.5 1.0 0.5 1.0 1.5 2.0
37


C
Breast Cancer : The Periods of Investigation Time
Study
ID
OR (95% CI)
% Weight (D + L)
1983–1995
Kajia Cao et al. (2001) 2.92 (1.28, 6.65) 17.57
Xinying Lin et al. (2001) 2.54 (1.74, 3.72) 82.43
D + L Subtotal (I-squared = 0.0%, P = 0.763) 2.60 (1.84, 3.68) 100.00
I-V Subtotal 2.60 (1.84, 3.68)
1996–2009
Ping shi et al. (2010) 1.76 (1.12, 2.77) 7.11
Mingbai Hu et al. (2013) 1.54 (0.94, 2.52) 6.07
Changming Gao et al. (2013) 1.47 (1.18, 1.84) 29.91
Xiaodan Yang et al. (2014) 1.82 (1.03, 3.19) 4.62
Meiling Qi et al. (2014) 1.54 (1.12, 2.11) 14.72
Bin Li et al. (2015) 1.35 (1.11, 1.65) 37.57
D + L Subtotal (I-squared = 0.0%, P = 0.853) 1.47 (1.30, 1.66) 100.00
I-V Subtotal 1.47 (1.30, 1.66)
NOTE: Weights are from random effects analysis
0.15
-1.0
-0.5
1.0
0.5
1.0
6.65


D
Study ID
Breast Cancer : The Exposure Sites
OR (95% CI)
% Weight (D + L)
Total
Kajia Cao et al. (2001) 2.92 (1.28, 6.65) 3.52
Xinying Lin et al. (2001) 2.54 (1.74, 3.72) 12.11
Ping shi et al. (2010) 1.76 (1.12, 2.77) 9.39
Changming Gao et al. (2013) 1.47 (1.18, 1.84) 21.42
Mingbai Hu et al. (2013) 1.54 (0.94, 2.52) 8.34
Xiaodan Yang et al. (2014) 1.82 (1.03, 3.19) 6.72
Meiling Qi et al. (2014) 1.54 (1.12, 2.11) 15.17
Bin Li et al. (2015) 1.35 (1.11, 1.65) 23.32
D + L Subtotal (I-squared = 38.8%, P = 0.121) 1.65 (1.40, 1.94) 100.00
I-V Subtotal 1.57 (1.40, 1.76)
.
Workplace
Meiling Qi et al. (2014) 1.25 (0.88, 1.79) 55.14
Bin Li et al. (2015) 1.05 (0.71, 1.56) 44.86
D + L Subtotal (I-squared = 0.0%, P = 0.519) 1.16 (0.89, 1.50) 100.00
I-V Subtotal 1.16 (0.89, 1.50)
.
Household
Meiling Qi et al. (2014) 1.57 (1.14, 2.17) 30.60
Bin Li et al. (2015) 1.30 (1.05, 1.61) 69.40
D + L Subtotal (I-squared = 0.0%, P = 0.338) 1.38 (1.15, 1.65) 100.00
I-V Subtotal 1.38 (1.15, 1.65)
ÌNOTE: Weights are from random effects analysis
0.15
-1.0
-0.5
1.0
0.5
1.0
6.65



Supplementary Figure S1. The subgroup odds ratios for second-hand smoke exposure.



Supplementary Figure S2. The disease-specific funnel plots.

Supplementary Table S1. Basic characteristics of the included studies

Diseases		Trialname	Year	Study design	Participants (*n*)	Date of Investigation	Gender	Exposure sites	Language	NOS
Cancers	Lung cancer	Yong Lin et al.	2010	Case-control	416	2006.12–2010.1	Female	Workplace, Household	Chinese	6
		Hailong Shi et al.	2005	Case-control	1,490	2000.6–2002.12	Female	Workplace	Chinese	6
		Lina Mu et al.	2021	Case-control	861	2005.3–2007.9	Both	Total	Chinese	6
		Longde Wang et al.	2002	Case-control	1,776	1994.1–1998.4	Both, Male, Female	Total	Chinese	7
		X.-R. Wang et al.	2009	Case-control	363	2002.7.1–2004.6.30	Female	Total	English	7
		T.H. Lam et al.	1987	Case-control	741	1983–1986	Female	Household	English	7
		Lap Ah Tse et al.	2009	Case-control	668	2004–2006	Male	Total, Household, Workplace	English	7
		Liu Q et al.	1993	Case-control	632	1983.6–1984.6	Female	Household	English	6
		Wen, W. et al.	2006	Cohort	72,829	1997.3–2000.5	Female	Total, Household, Workplace	English	9
		Yongbing Xiang et al.	2003	Case-control	828	1992.2–1993.12	Female	Workplace	Chinese	6
		Chunyan Lin et al.	1994	Case-control	244	1985–1990	Female	Household, Workplace	Chinese	6
		Dandan Guan et al.	2020	Case-control	1,284	2015.6–2018.12	Female	Total	Chinese	7
		Jifei Ma et al.	2021	Case-control	750	2015.1–2016.6	Both	Total	Chinese	6
		Haiyan Li et al.	2020	Case-control	296	2011.1–2019.6	Both	Total	Chinese	6
		Jun Li et al.	2020	Cohort	23,415	2008–2011	Both	Total	English	9
	Breast cancer	Ping shi et al.	2010	Case-control	446	2005.1–2006.12	Female	Total	Chinese	6
		Xiaodan Yang et al.	2014	Case-control	604	2009.7.1–2012.10.11	Female	Total	Chinese	6
		Kajia Cao et al.	2001	Case-control	696	1992–1996	Female	Total	Chinese	6
		Meiling Qi et al.	2014	Case-control	849	2008.10–2010.2	Female	Total, Household, Workplace	English	7
		Mingbai Hu et al.	2013	Case-control	407	2009.1–2011.2	Female	Total	English	6
		Bin Li et al.	2015	Case-control	1,767	2007–2013	Female	Total, Household, Workplace	English	7
		Changming Gao et al.	2013	Case-control	1,351	2004.6–2007.12	Female	Total	English	9
		Xinying Lin et al.	2001	Case-control	372	None	Female	Total	Chinese	6

Continued

Diseases		Trialname	Year	Study design	Participants (*n*)	Date of Investigation	Gender	Exposure sites	Language	NOS
Cancers	Bladder cancer	Wei Zhang et al.	2006	Case-control	1,215	1996–1999	Male, Female	Total, ousehold, Workplace	Chinese	9
	Liver cancer	Yuhua Zhou et al.	2014	Case-control	824	2005.9–2008.6	Both	Household	Chinese	7
		Li Tao et al.	2010	Case-control	231	1996.7–1999.6	Both, Male, Female	Total	English	8
		Jianxue Duan et al.	2018	Case-control	794	2010.1.1–2016.12.31	Both	Total	Chinese	6
		Huabin Wu et al.	2012	Case-control	1,254	2003.1.1–2010.10.31	Both	Total	Chinese	6
		Jun Li et al.	2020	Cohort	23,415	2008–2011	Both	Total	English	9
	Acute lymphoblastic leukemia	Yongjun Fang et al.	2010	Case-control	613	2006.6.1–	Children	Total	Chinese	6
	Cancer	Wen, W. et al.	2006	Cohort	72,829	1997.3–2000.5	Female	Total, ousehold, Workplace	English	9
	Cervical cancer	Jian Li et al.	2010	Case-control	312	2007.9–2010.6	Female	Total	Chinese	6
		Rongxian Xu et al.	2014	Case-control	413	2007.11–2008.12	Female	Total	Chinese	6
	Colon cancer	Qinting Jiang et al.	2004	Case-control	396	1990.5–2002.5 1989–1990	Both	Workplace	Chinese	8
	Colorectal cancer	Jun Li et al.	2020	Cohort	23,415	2008–2011	Both	Total	English	9
	Endometrial cancer	Jing Gao et al.	2006	Case-control	2,082	1997.1–2002.12	Female	Total, Household, Workplace	Chinese	8
	Esophageal squamous cell carcinoma	Zemin Wang et al.	2006	Case-control	214	2002–2003	Both	Total	English	7
	Intracranial tumors	Min Wu et al.	2010	Case-control	537	2007.1–2008.7	Both	Household, Workplace	Chinese	6
	Oral cancer	Baochang He et al.	2016	Case-control	708	2010.9–2015.1	Female	Total	English	7
	Papillary thyroid ancer	Yan Zhou et al.	2016	Case-control	369	2103.4–2014.6	Both	Total	Chinese	6
	Stomach cancer	Jun Li et al.	2020	Cohort	23,415	2008–2011	Both	Total	English	9
	Tongue cancer	Lingjun Yan et al.	2016	Case-control	876	2010.9–2015.1	Both	Total	Chinese	7
	Asthma in Children	Xiaojuan Liu et al.	2013	Case-control	218	2011.1–2012.12	Children	Total	Chinese	6
		Fang Wang et al.	2013	Case-control	726	2010	Children	Total	Chinese	6
		Mei Xiong et al.	2013	Case-control	552	None	Children	Total	Chinese	6

Continued

Diseases		Trialname	Year	Study design	Participants (*n*)	Date of Investigation	Gender	Exposure sites	Language	NOS
DRS*	Small airway obstruction	Tongzhang Zheng et al.	2002	Case-control	1,209	1999.1–2001.3	Children	Total	English	6
		Shixue Ma et al.	2006	Case-control	212	2002.1–2004.6	Children	Total	Chinese	6
		Maohong Luo et al.	2004	Case-control	262	1998–1999	Children	Total	Chinese	6
		Yusheng Chen et al.	2013	Case-control	648	2011.10.17–2011.11.1	Both	Total	English	7
	Stroke	Xianjia Ning et al.	1993	Case-control	256	1990.10–1990.12	Female	Total	Chinese	7
		Yanong Shao et al.	1997	Case-control	210	1996.10–1997.3	Both	Total	Chinese	6
DCS*		Wen, W. et al.	2006	Cohort	72,829	1997.3–2000.5	Female	Total, Household, Workplace	English	9
	Cardiovascular disease	Wen, W. et al.	2006	Cohort	72,829	1997.3–2000.5	Female	Total, Household, Workplace	English	9
Other diseases	All cause mortality	Kim, C. et al.	2016	Cohort	65,226	1996–2000/2009	Female	Total	English	8
	Legionnaires' diseases (Children)	Suping Wang et al.	1994	Case-control	126	1991.4.4–1992.4.3	Children	Total	Chinese	6
	Otitis media (Children)	Ke Li et al.	2018	Case-control	534	2013.1–2016.12	Children	Total	Chinese	6
	Tuberculosis	Birong Dong et al.	2001	Case-control	348	1996.3–1997.3	Both	Total	Chinese	6
		Leung, Chi C. et al.	2010	Cohort	15,486	2000.1–2003.12	Female	Total	English	8
	Type 2 diabetes mellitus	Huang, C. et al.	2019	Cohort	28,177	2004–2008	Female	Total	English	9

Note. * DRS: Diseases of the Respiratory System; DCS: Diseases of the Circulatory System

Supplementary Table S2. The definition and types of characteristics of second-hand smoke exposure

Definition of SHS	Undefined	
	Definiton 1	Exposure to SHS at home /workplace ≥ 15 min/d, 1 d/week.
	Definition 2	Exposure to SHS ≥ 15 min/d.
		Exposure to SHS: once (5 min), twice (≥ 5 min but ≤ 1min), more than twice (≥ 1 min).
		Lived or worked with smokers ≥ 1 h/d, ≥ 1 year.
		Exposure to SHS 1 time/wk, 1–2 d/week, 3–5 d/week, daily, or almost daily.
		Exposure to family members (especially husband) had ever smoked at home and/or the smoke of others in the workplace.
		Living with smoking husband in the same household for at least one year continuously.
		Living with 1 or more smokers in the same household.
		Exposure to parents.
Types of Characteristics of SHS	None	
	Type 1	Location, such as household and workplace.
	Type 2	Adulthood and childhood (before age 18 or after age 18).
		Adulthood only.
		Before age 18 years or after age 18 years.
		Menopausal status.
		Childhood and adulthood.
		Pregnant with the child, and after the birth of the child.

Supplementary Table S3. "Leave One Out" sensitivity test

Disease	Trialname	POR	LL	UL
Cancers				
	T.H. Lam et al.	1.52	1.42	1.62
	Liu Q et al.	1.53	1.44	1.63
	Chunyan Lin et al.	1.53	1.44	1.63
	Chunyan Lin et al.	1.53	1.43	1.63
	Xinying Lin et al.	1.51	1.42	1.61
	Kajia Cao et al.	1.53	1.43	1.63
	Longde Wang et al.	1.54	1.44	1.64
	Yongbing Xiang et al.	1.53	1.44	1.63
	Qinting Jiang et al.	1.53	1.43	1.63
	Hailong Shi et al.	1.58	1.48	1.69
	Zemin Wang et al.	1.53	1.43	1.63
	Wen W. et al.	1.53	1.44	1.63
	Jing Gao et al.	1.61	1.51	1.72
	Wen W. et al.	1.54	1.45	1.64
	Wei Zhang et al.	1.54	1.44	1.64
	Wei Zhang et al.	1.53	1.44	1.63
	Lap Ah Tse et al.	1.54	1.45	1.65
	X.-R. Wang et al.	1.54	1.44	1.64

Continued

Disease	Trialname	POR	LL	UL
	Jian Li et al.	1.53	1.43	1.63
	Yong Lin et al.	1.53	1.43	1.63
	Yong Lin et al.	1.52	1.43	1.62
	Yongjun Fang et al.	1.52	1.42	1.61
	Li Tao et al.	1.53	1.44	1.64
	Min Wu et al.	1.53	1.43	1.63
	Ping shi et al.	1.53	1.43	1.63
	Min Wu et al.	1.53	1.43	1.63
	Huabin Wu et al.	1.54	1.45	1.65
	Mingbai Hu et al.	1.53	1.44	1.63
	Changming Gao et al.	1.54	1.44	1.64
	Rongxian Xu et al.	1.51	1.42	1.61
	Xiaodan Yang et al.	1.53	1.43	1.63
	Meiling Qi et al.	1.53	1.44	1.63
	Yuhua Zhou et al.	1.52	1.43	1.62
	Bin Li et al.	1.55	1.45	1.66
	Yan Zhou et al.	1.53	1.43	1.63
	Baochang He et al.	1.52	1.43	1.62
	Lingjun Yan et al.	1.52	1.42	1.62
	Jianxue Duan et al.	1.53	1.43	1.63
	Jun Li et al.	1.53	1.43	1.63
	Jun Li et al.	1.54	1.44	1.64
	Jun Li et al.	1.54	1.45	1.64
	Haiyan Li et al.	1.51	1.42	1.61
	Dandan Guan et al.	1.53	1.43	1.63
	Jun Li et al.	1.54	1.44	1.64
	Lina Mu et al.	1.54	1.45	1.64
	Jifei Ma et al.	1.51	1.41	1.61
	Combined	1.53	1.44	1.63
DCS				
	Xianjia Ning et al.	1.59	1.23	2.05
	Yanong Shao et al.	1.90	1.35	2.68
	Wen W. et al.	1.92	1.43	2.58
	Wen W. et al.	1.72	1.33	2.21
	Combined	1.75	1.37	2.23
DRS				
	Tongzhang Zheng et al.	1.40	1.18	1.68
	Maohong Luo et al.	1.34	1.15	1.56
	Shixue Ma et al.	1.32	1.14	1.54
	Fang Wang et al.	1.77	1.49	2.09
	Xiaojuan Liu et al.	1.32	1.14	1.54

Continued

Disease	Trialname	POR	LL	UL
	Mei Xiong et al.	1.38	1.18	1.62
	Yusheng Chen et al.	1.38	1.17	1.62
	Combined	1.40	1.21	1.63
Lung cancer				
	T.H. Lam et al.	1.46	1.29	1.65
	Liu Q et al.	1.51	1.35	1.70
	Chunyan Lin et al.	1.50	1.34	1.69
	Chunyan Lin et al.	1.52	1.35	1.71
	Longde Wang et al.	1.54	1.37	1.73
	Yongbing Xiang et al.	1.52	1.34	1.71
	Hailong Shi et al.	1.71	1.51	1.94
	Wen W. et al.	1.51	1.34	1.69
	X.-R. Wang et al.	1.54	1.37	1.74
	Lap Ah Tse et al. 1.56 1.38	1.56	1.38	1.76
	Yong Lin et al.	1.50	1.33	1.68
	Yong Lin et al.	1.49	1.32	1.68
	Jun Li et al.	1.55	1.37	1.75
	Haiyan Li et al.	1.45	1.30	1.63
	Dandan Guan et al.	1.50	1.34	1.69
	Lina Mu et al.	1.55	1.37	1.76
	Jifei Ma et al.	1.44	1.28	1.61
	Combined	1.52	1.35	1.70
Breast cancer				
	Kajia Cao et al.	1.55	1.38	1.74
	Xinying Lin et al.	1.49	1.32	1.68
	Ping shi et al.	1.55	1.38	1.75
	Mingbai Hu et al.	1.57	1.39	1.76
	Changming Gao et al.	1.60	1.40	1.83
	Meiling Qi et al.	1.57	1.39	1.78
	Xiaodan Yang et al.	1.56	1.38	1.75
	Bin Li et al.	1.69	1.47	1.94
	Combined	1.57	1.40	1.76
Bladder cancer				
	Wei Zhang et al.	1.73	1.23	2.44
	Wei Zhang et al.	1.50	1.08	2.08
	Li Tao et al.	1.61	1.10	2.35
	Yuhua Zhou et al.	1.28	0.91	1.81
	Combined	1.52	1.12	2.05

Continued

Disease	Trialname	POR	LL	UL
Liver cancer				
	Huabin Wu et al.	1.43	0.93	2.20
	Jianxue Duan et al.	1.26	0.98	1.63
	Jun Li et al.	1.46	1.14	1.88
	Combined	1.37	1.08	1.73
Stroke				
	Xianjia Ning et al.	1.67	1.22	2.30
	Yanong Shao et al.	3.15	1.77	5.60
	Wen, W. et al.	1.89	1.38	2.58
	Combined	1.92	1.43	2.58
Asthma in Children				
	Tongzhang Zheng et al.	1.37	1.12	1.67
	Maohong Luo et al.	1.31	1.11	1.54
	Shixue Ma et al.	1.28	1.09	1.52
	Mei Xiong et al.	1.35	1.13	1.61
	Xiaojuan Liu et al.	1.28	1.08	1.52
	Fang Wang et al.	1.83	1.52	2.21
	Combined	1.38	1.17	1.62

Note. *POR*: pooled odds ratio; *OR*: odds ratio; *LL*: 95% lower limit; *UL*: 95% upper limit.