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# Analysis of the associations of indoor air pollution and tobacco use with morbidity of lung cancer in Xuanwei, China

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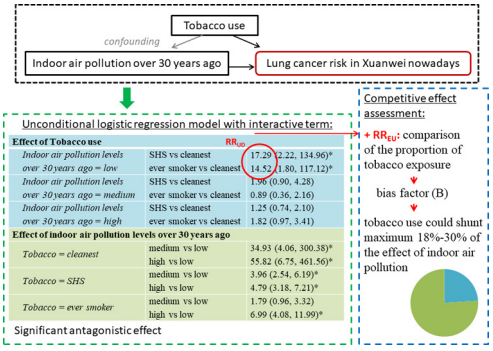
## HIGHLIGHTS

- Lung cancer (LC) mortality is still high in Xuanwei at present.
- Delayed effect of indoor air pollution is still the major risk factor for LC.
- The effect of tobacco use on LC gradually becomes more apparent.
- In areas never used smoky coal, tobacco use was the main cause of LC.

## GRAPHICAL ABSTRACT

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## ABSTRACT

*Background:* Indoor air pollution emitted by smoky coal combustion in unventilated fire pits used to cause high lung cancer mortality in Xuanwei. Stove improvements were implemented from the 1970s to the 1980s. However, the present lung cancer mortality rate in Xuanwei shows almost no significant declining trend. Tobacco use is another established risk factor for lung cancer. Smoking prevalence and secondhand smoke (SHS) exposure rate are both high in Xuanwei. Therefore, in this study we evaluated the relationship among indoor air pollution over 30 years ago, tobacco use, and lung cancer risk, to further explore the competitive effects of these two risk factors.

*Methods:* A case-control study design was used. We constructed an unconditional logistic regression model to evaluate the relationship among indoor air pollution, tobacco use, and lung cancer risk, adjusting the covariates and with an interactive term between the two key variables. We further quantitatively assessed the maximum decrease in the indoor air pollution effect when facing competition from tobacco use via a sensitivity analysis. First, the effect of indoor air pollution on lung cancer without considering tobacco use was estimated. Then, we calculated a "bias factor" and divided the effect estimation by this factor.

*Results:* We found a strong delayed effect of indoor air pollution over 30 years ago in each subgroup with different tobacco use history. The effects of tobacco use were relatively small, but in areas without smoky coal combustion and indoor air pollution over 30 years prior, the lung cancer risk caused by tobacco use became much stronger and statistically significant. Moreover, we assessed that the effects of tobacco use on lung cancer could reduce a maximum of 18%-30% of the effects of indoor air pollution, but did not influence their statistical significance; the competitive effect from ever smoking was stronger than that from SHS exposure.

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*Conclusions:* At present in Xuanwei, delayed effect of the indoor air pollution over 30 years ago remains the major risk factor for lung cancer. Concomitantly, the adverse effect of tobacco use on lung cancer is becoming more apparent; local governments should start considering public health activities for smoking cessation promotion and SHS exposure prevention.



## 1. Background

Indoor air pollution has been evaluated and reported to be a first degree carcinogen by the International Agency for Research on Cancer (IARC) (IARC, 2012). Indoor air pollution is associated with an increasing risk of lung cancer. Tobacco use, including active smoking and secondhand smoke (SHS) exposure, is another established risk factor for lung cancer (O'Keeffe et al., 2018; Kim et al., 2018; Sheng et al., 2018).

Xuanwei, in Yunnan province, China, is a county-level city with significantly high lung cancer mortality since the 1970s (Office of Research for cancer prevention in Ministry of Health: Study on Cancer Mortality in China. Beijing: People's Medical Publishing House;, 1980; Mumford et al., 1987), especially in several towns in its center. Previous studies (Mumford et al., 1987; Chapman et al., 1988; He et al., 1991; Lan et al., 1993; Tian et al., 2008; Lan et al., 2008; Large et al., 2009; Vermeulen et al., 2011; Barone-Adesi et al., 2012; Downward et al., 2014) demonstrated that exposure to extremely high levels of indoor carcinogenic substances (such as polycyclic aromatic hydrocarbons and nano-quartz) was the main cause. These indoor air pollutants were emitted by smoky coal (bituminous coal) combustion in unventilated fire pits for cooking and heating. From the 1970s to the end of the 1980s, the government-sponsored Improved Stove Program was conducted in Xuanwei city, and more than 70% of unventilated fire pits were replaced by stoves with chimneys (Barone-Adesi et al., 2012; Li et al., 2011).

However, the present lung cancer mortality rates for males and females in Xuanwei remain respectively 3 and 6 times higher than China's rural average levels (Xiao et al., 2012; Chen, 2015) and to date show no significant declining trend (Liu et al., 2019). Even the locations of towns with high, medium, and low lung cancer rates have not changed significantly (Chen, 2015; Liu et al., 2019). As no tobacco control policies have been implemented in Xuanwei, several previous studies assessed the association between tobacco use and lung cancer in the context of smoky coal use and indoor air pollution. Kim et al. (Kim et al., 2014) published a report based on data collected in Xuanwei between 1985 and 1990 (right at the end of the Improved Stove Program) demonstrating that when the association was assessed by coal use, the cigarette-lung cancer risk association was null in hazardous coal users and elevated in less hazardous smoky coal users and non-smoky coal users. However, a cohort study conducted by (Lee et al., 2010) using data from 1976 to 1996 reported that the effect of smoking on lung cancer risk was considerably higher after chimney installation and the consequent reduction in indoor coal smoke exposure.

To date, it has been more than 30 years since the Improved Stove Program. In 2014, our group conducted a survey in Xuanwei (Liu et al., 2017), discovering that smoky coal consumption had dropped, while male smoking prevalence and the level of SHS exposure among females and non-smokers were both higher than the national level in China (Chinese Center For Disease Control And Prevention, 2011; Liu et al., 2017; Yang et al., 2016). Hence, in this study, we evaluated the relationship among indoor air pollution over 30 years ago, tobacco use, and lung cancer risk to further explore the competitive effects of these two risk factors for lung cancer risk.

## 2. Methods

### 2.1. Study design

A case-control study design was used in six selected towns in Xuanwei. Detailed information on the selection of the towns was previously described elsewhere (Liu et al., 2017). In brief, based on the 2010–2012 average lung cancer mortality rates, 26 towns in Xuanwei were divided into high-, medium-, and low-level lung cancer areas. Taking into account the orientation and topography, we chose Laibin and Wanshui in the high-level lung cancer area, Tangtang and Geyi in the medium-level lung cancer area, and Reshui and Wenxing in the low-level lung cancer area as our study sites (see Fig. 1).

Face-to-face household surveys were conducted for cases in 2017 and for controls in 2014, respectively, using tablets/cell phones with electronic versions of the questionnaire. The cases were selected based on the following procedure. In the aforementioned six towns, information on living lung cancer patients was collected through the local cancer registry system, all hospital inpatient and outpatient records, and village doctors in February 2017. After excluding non-lung cancer patients, those declared dead, and the duplicates, we compiled a list of 2538 cases. All had been diagnosed in a grade II or higher hospital. Only 686 cases consented to the interview. The controls were selected based on a stratified cluster sampling survey in August 2014. The detailed implementation process was described elsewhere (Liu et al., 2017). Briefly, we chose 4 administrative villages in each town and visited 100 households along prescribed routes in each village. One adult ($\geq$30 years old, 2400 in total) in each household was randomly selected using an app pre-installed on the tablets or cell phones. A total of 2346 residents consented to the interview.

Both the cases and controls were interviewed using the same questionnaire, which consisted of informed consent, general information, development of living conditions, history of fuel and stove use, occupational history, history of lung diseases other than cancer, family history of malignant tumors, history of smoking and SHS exposure, and other behavioral risk factors (such as a history of alcohol consumption, diet, and physical exercise).

### 2.2. Quality control

Before the field work, we conducted two days of training for all of the site staff. Training included interviewers and additionally recruited quality-control staff, who participated and supervised the survey randomly. The interview was conducted using tablets/cell phones for data collection; all of the required content and logistics were established. The tablets also recorded the routes of the interviewers via GPS. In addition, we instructed the interviewers to submit their finished questionnaires every day, the quality-control staff to assess them the same day or the next day and

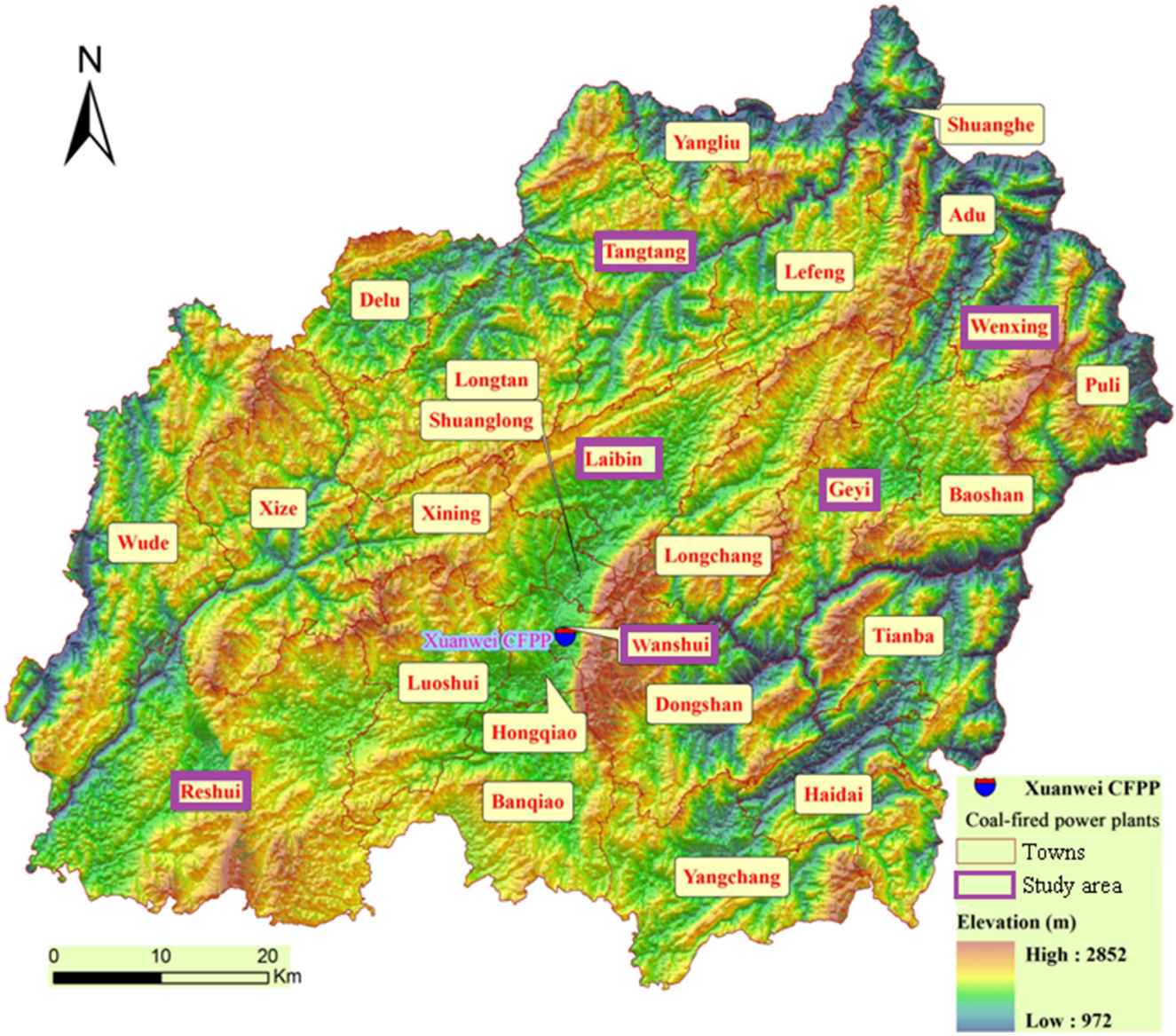


**Fig. 1.** Locations and topography of towns in Xuanwei.

report dubious answers, and the interviewers to provide feedback in three days.

### 2.3. Statistical analysis

There were two key variables in our models. We used the ternary variable "high-, medium-, and low-level lung cancer areas" as a surrogate for indoor air pollution levels over 30 years ago, since it is impossible for us to actually measure them. We believe this surrogate was suitable to use, as the locations of towns with high, medium, and low lung cancer rates at present are not different from that defined before the 1980s (Chen, 2015; Liu et al., 2019). At that time, the associations of smoky coal combustion, fire pits, and lung cancer were first discovered; indoor air pollution was the decisive factor for the high-, medium-, and low-level lung cancer towns then (He et al., 1995). The low-level lung cancer area was reference category 0, while the medium-level and high-level lung cancer areas were 1 and 2, respectively. We constructed a ternary variable for tobacco exposure. We set never smokers without SHS exposure (referred to as "the cleanest") as reference category 0, never smokers with SHS exposure as 1 and ever smokers as 2.

First, an unconditional logistic regression model with an interactive term was used to evaluate the relationships among indoor air pollution, tobacco use, and lung cancer risk. The covariate variables included age, sex, heating method during winter 10 years prior, occupational history, frequency of eating white meat, eggs or milk, history of alcohol consumption, history of non-malignant lung diseases, history of cancer in relatives, and education. These covariate variables were used based on previous reports and the model fit. Odd ratios (ORs) and 95% confidence intervals (CIs) for all of the variables were calculated. Together with the estimation coefficient and standard error of the interactive term, the ORs (95% CIs) of the indoor air pollution levels were calculated within each category of tobacco use and vice versa.

Second, we were also interested in assessing how much the effect size of indoor air pollution would decrease when facing competition from tobacco exposure using a sensitivity analysis technique introduced by VanderWeele TJ and Ding P (Ding and VanderWeele, 2016; VanderWeele and Ding, 2017). The core of this

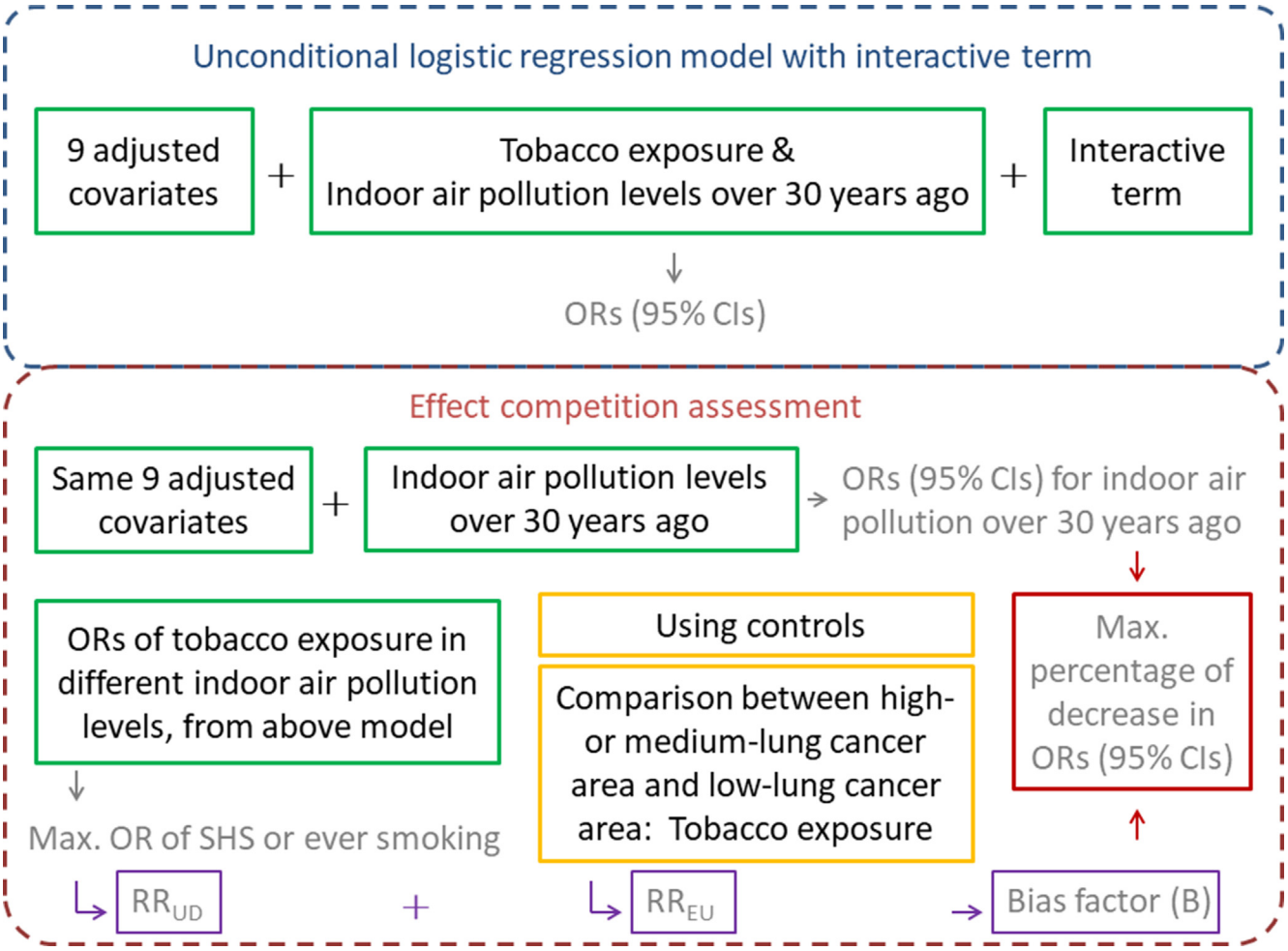


**Fig. 2.** Flowchart of statistical analysis process.

technique is to estimate how much unmeasured confounders may explain an observed association between an exposure (or treatment) and an outcome. Briefly, researchers calculated a "bias factor (B)" and adjusted the observed relative risk (RR) and corresponding 95% CIs according to this factor. We borrowed the technique structure (see Fig. 1 in VanderWeele TJ and Ding P (VanderWeele and Ding, 2017) and the following formula for calculating the B value. U refers to "unmeasured confounder," D refers to "outcome," and E refers to "exposure." VanderWeele TJ and Ding P clearly described the definitions of $RR_{UD}$ and $RR_{EU}$.

$$B = RR_{UD} * RR_{EU}/(RR_{UD} + RR_{EU} - 1)$$

Regarding our analysis, indoor air pollution, tobacco use, and lung cancer cases could be regarded as an exposure, a confounder, and the outcome, respectively. Thus, $RR_{UD}$ means the maximum strength of the association between tobacco use and lung cancer within different indoor air pollution levels. In our analysis, that meant the maximum estimated OR point value for SHS or ever smoking in high-level, medium-level, and low-level indoor air pollution exposure subgroups over 30 years ago, which was the OR of the SHS or ever smoking in the low-level indoor air pollution exposure subgroup estimated using the previously described unconditional logistic regression model. $RR_{EU}$ should be the ratio of the tobacco exposure rate in the indoor air pollution exposure category to that of the indoor air pollution reference category. In other words, $RR_{EU}$ was the comparison between the proportion of subjects with SHS exposure or ever smokers calculated as "SHS exposure/never smokers" or "ever smokers/the sum of ever smokers and the cleanest," respectively, in the high- or medium-level lung cancer areas and that in low-level lung cancer area. Note that $RR_{EU}$ was calculated based on the data from the control group, as it was a random sample of the population in our study area.

By running the same unconditional logistic regression model, but without tobacco use and consequently the interactive term, we obtained OR (95% CIs) estimations for the indoor air pollution levels over 30 years ago (see Supplemental table 1). These corresponded to the "observed association between an exposure (or treatment) and an outcome before considering unmeasured confounders" according to VanderWeele TJ and Ding P. We then divided the ORs (95% CIs) by the corresponding B values for SHS exposure or ever smoking to obtain their maximum percentages of decrease when facing competition from tobacco exposure. Fig. 2 shows a flowchart of the statistical analysis methods.

All of the analyses were performed using R software (version 3.2.3). This study was approved by the Ethics Committee of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences (Project No. 2017008). All of the respondents provided oral informed consent before the questionnaire survey started.

## 3. Results

Two cases and 30 controls were deleted from the dataset due to the lack of smoking or SHS exposure status (key information). A total of 684 cases and 2316 controls were used for the analysis.

The results of the descriptive statistics and univariate analysis are shown in Table 1. The distribution of most of the risk factors differed significantly in the cases and controls.

Therefore, in addition to the two key variables, 9 other risk factors were included in the final model. Table 2 shows the results of the unconditional logistic regression model with the interactive

**Table 1**
Descriptive statistics and univariate analysis of the risk factors for lung cancer in the questionnaire.

| Risk factors for lung cancer | Levels or categories | Cases (684) | | Controls (2316) | | Chi-Squared test | |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | Chi-Squared | p |
| Sex | male | 370 | 54.1% | 1017 | 43.9% | 22.021 | <0.001 |
| | female | 314 | 45.9% | 1299 | 56.1% | | |
| Age group[a] | <40 | 12 | 1.8% | 659 | 28.9% | 548.29 | <0.001 |
| | 40–49 | 109 | 15.9% | 745 | 32.6% | | |
| | 50–59 | 198 | 28.9% | 533 | 23.3% | | |
| | ≥60 | 365 | 53.4% | 347 | 15.2% | | |
| Method of warming in winter 10 years ago with indoor air pollution emission | no | 33 | 4.8% | 237 | 10.2% | 18.861 | <0.001 |
| | yes | 651 | 95.2% | 2079 | 89.8% | | |
| Smog during cooking | none or slight | 253 | 37.0% | 951 | 41.1% | 3.648 | 0.056 |
| | moderate or heavy | 431 | 63.0% | 1365 | 58.9% | | |
| Work experience in coal mine or other jobs with PM exposure [b] | no | 445 | 65.1% | 1784 | 77.1% | 39.87 | <0.001 |
| | yes | 239 | 34.9% | 531 | 22.9% | | |
| Frequency of eating vegetables, fruits or beans | 0–2 days per week | 170 | 24.9% | 879 | 38.0% | 39.847 | <0.001 |
| | 3–7 days per week | 514 | 75.1% | 1437 | 62.0% | | |
| Frequency of eating white meat, eggs or milk | 0–2 days per week | 471 | 68.9% | 942 | 40.7% | 168.37 | <0.001 |
| | 3–7 days per week | 213 | 31.1% | 1374 | 59.3% | | |
| Frequency of eating pickled, smoked, fatty food or sweets | 0–2 days per week | 282 | 41.2% | 910 | 39.3% | 0.827 | 0.363 |
| | 3–7 days per week | 402 | 58.8% | 1406 | 60.7% | | |
| History of alcohol consumption | no | 506 | 74.0% | 2011 | 86.8% | 64.591 | <0.001 |
| | yes | 178 | 26.0% | 305 | 13.2% | | |
| History of non-malignantlung diseases | no | 551 | 80.6% | 2266 | 97.8% | 275.451 | <0.001 |
| | yes | 133 | 19.4% | 50 | 2.2% | | |
| History of cancer in relatives | no | 494 | 72.2% | 2031 | 87.7% | 94.855 | <0.001 |
| | yes | 190 | 27.8% | 285 | 12.3% | | |
| Ethnic | Han | 658 | 96.2% | 2195 | 94.8% | 2.296 | 0.130 |
| | minority | 26 | 3.8% | 121 | 5.2% | | |
| Education [c] | primary or illiteracy | 529 | 77.3% | 1620 | 70.0% | 14.086 | <0.001 |
| | junior high or above | 155 | 22.7% | 695 | 30.0% | | |
| Tobacco use | the cleanest | 40 | 5.8% | 264 | 11.4% | 38.42 | <0.001 |
| | never smoker with SHS exposure | 348 | 50.9% | 1310 | 56.6% | | |
| | ever smoker | 296 | 43.3% | 742 | 32.0% | | |
| Indoor air pollution levelover 30 years ago | low | 71 | 10.4% | 800 | 34.5% | 242.378 | <0.001 |
| | medium | 187 | 27.3% | 785 | 33.9% | | |
| | high | 426 | 62.3% | 731 | 31.6% | | |

b. and c. 1 missing value in the controls.
Note: not all risk factors were included in the final logistic regression models.
[a] 32 missing values in the controls

**Table 2**
ORs (95%CIs) estimations from the unconditional logistic regression model with the interactive term.

| Risk factors for lung cancer | Exposure *vs* reference | ORs (95%CIs) |
|---|---|---|
| Sex | *female vs male* | 1.02 (0.69, 1.49) |
| Age | *per 1 year older* | 1.13 (1.12, 1.15)* |
| Method of warming in winter 10 years ago with indoor air pollution emission | *yes vs no* | 2.37 (1.49, 3.80)* |
| Work experience in coal mine or other jobs with PM exposure | *yes vs no* | 1.58 (1.17, 2.14)* |
| Frequency of eating white meat, eggs or milk | *3–7 days vs* | 0.42 (0.33, 0.54)* |
| History of alcohol consumption | *yes vs no* | 1.54 (1.11, 2.15)* |
| History of non-malignant lung diseases | *yes vs no* | 4.57 (2.96, 7.04)* |
| History of cancer in relatives | *yes vs no* | 2.10 (1.57, 2.81)* |
| Education | *junior high or above vs primary or illiteracy* | 1.48(1.11, 1.97)* |
| Tobacco | | |
| Indoor air pollution levels over 30 years ago = low | *SHS vs cleanest* | 17.29 (2.22, 134.96)*,# |
| | *ever smoker vs cleanest* | 14.52 (1.80, 117.12)*,# |
| Indoor air pollution levels over 30 years ago = medium | *SHS vs cleanest* | 1.96 (0.90, 4.28) |
| | *ever smoker vs cleanest* | 0.89 (0.36, 2.16) |
| Indoor air pollution levels over 30 years ago = high | *SHS vs cleanest* | 1.25 (0.74, 2.10) |
| | *ever smoker vs cleanest* | 1.82 (0.97, 3.41) |
| Indoor air pollution levels over 30 years ago | | |
| Tobacco = cleanest | *medium vs low* | 34.93 (4.06, 300.38)* |
| | *high vs low* | 55.82 (6.75, 461.56)* |
| Tobacco = SHS | *medium vs low* | 3.96 (2.54, 6.19)* |
| | *high vs low* | 4.79 (3.18, 7.21)* |
| Tobacco = ever smoker | *medium vs low* | 1.79 (0.96, 3.32) |
| | *high vs low* | 6.99 (4.08, 11.99)* |

* $p < 0.05$
# OR of SHS or ever smoking in the low indoor air pollution level subgroup was used as $RR_{UD}$ next.

**Table 3**
Quantitative assessment of the effect competition tobacco use caused on the effect of indoor air pollution on lung cancer.

| ORs (95%CIs) of indoor air pollution levels over 30 years ago without considering tobacco use | | Effect competition from tobacco exposure | $RR_{EU}$ | $RR_{UD}$ (95%CIs)[#] | B | Decreased ORs (95%CIs) of indoor air pollution levels over 30 years ago | Percentage of decrease (%) |
|---|---|---|---|---|---|---|---|
| Medium | 3.55 (2.48, 5.08)* | Ever smoking *vs* the cleanest | 1.47 | 14.52 (1.80, 117.12)* | 1.42 | 2.49 (1.74, 3.57)* | −29.77% |
| High | 6.63 (4.72, 9.31)* | | 1.45 | | 1.41 | 4.71 (3.36, 6.62)* | −28.90% |
| Medium | 3.55 (2.48, 5.08)* | Never smokers with SHS | 1.24 | 17.29 (2.22, 134.96)* | 1.22 | 2.90 (2.03, 4.15)* | −18.24% |
| High | 6.63 (4.72, 9.31)* | *vs* the cleanest | 1.25 | | 1.23 | 5.38 (3.83, 7.56)* | −18.84% |

[#] Only the point estimate value of OR was used as $RR_{UD}$ to calculate B, not the 95% CIs.
* $p < 0.05$

term. The ORs estimated for the indoor air pollution levels were much higher than those estimated for tobacco use. The interactive effect between the two key variables was antagonistic and showed statistical significance. The harmful effect of indoor air pollution on lung cancer was much smaller in the subgroups with tobacco exposure, but mostly remained significant, while the harmful effect of tobacco use on lung cancer in the subgroups under indoor air pollution exposure both decreased and lost statistical significance. The OR (95% CIs) estimations of the other covariate variables in Table 2 were almost the same as those in Supplemental table 1, indicating that the model was robust.

Table 3 shows the results of the effect competition assessment. We calculated the B values and the maximum percentages of the decrease in the effect sizes of the medium- or high-level indoor air pollution when facing competition from SHS exposure or ever smoking. Tobacco use could explain away 18%-30% of the effect of indoor air pollution on lung cancer; the competitive effect from ever smoking was stronger than that from SHS exposure. The competition from tobacco use only lowered the size but did not influence the statistical significance of the indoor air pollution effect.

## 4. Discussion

The ORs (95% CIs) estimated by our analyses indicated that at present in Xuanwei, indoor air pollution over 30 years prior remains the major risk factor for lung cancer, while the effect of tobacco use was still relatively small and could be non-significant. But in those areas without smoky coal combustion (smokeless coal and wood instead) and indoor air pollution over 30 years ago, the lung cancer risk caused by tobacco use was much stronger and statistically significant. Moreover, we assessed that the effect of smoking or SHS exposure on lung cancer could reduce a maximum of 18%-30% of the effect of indoor air pollution.

Our study indicated that the high level of indoor air pollution emitted by smoky coal combustion had a significantly strong delayed effect on lung cancer, and the period of delay could be more than 30 years. Our previous study also confirmed this point (Liu et al., 2019). In that study, by analyzing the trend in lung cancer mortality rates from 1990 to 2016, we found that the mortality rate of lung cancer in Xuanwei decreased since 2004, but the decrease was not statistically significant, except for residents aged < 40 years old in 2014–2016. This population subgroup was born at the end of the 1970s or in the early 1980s, in other words, during or after the Improved Stove Program. That is to say, this population subgroup was barely exposed to the extremely high indoor air pollution emitted by smoky coal combustion in unventilated fire pits. However, residents aged 40 years or older in 2014–2016 were likely exposed to extremely high indoor air pollution, at least a few times in their early lives; therefore, the non-significant declining trend in their lung cancer mortality rates indicated a delayed effect of indoor air pollution exposure.

Xuanwei city, located in one of China's largest tobacco producing provinces, Yunnan, has high levels of smoking and SHS prevalence (Liu et al., 2017). In 1985–1990, just at the end of the Improved Stove Program, Kim et al. (Kim et al., 2014) reported that the use of coal could attenuate the association between ever smoking and lung cancer risk, even toward null when certain hazardous types of coal were used. Our analysis inferred that as coal use declines (Liu et al., 2017) and indoor air quality improves, the adverse effects of tobacco use on lung cancer may become more apparent in Xuanwei. Therefore, it makes sense to start considering certain tobacco control policies.

Establishing a conventional logistic regression model with interactive terms is a common method to explore effect modification. The results of our conventional interaction model can improve the understanding of whether there is an interactive effect and show the OR (95% CIs) estimations of indoor air pollution on lung cancer in three different tobacco exposure subgroups. However, it could not provide a quantitative assessment of the extent of competition that tobacco use brought to the association of indoor air pollution and lung cancer. By calculating B, we attempted to quantitatively assess the effect of the competition degree between the two risk factors. Moreover, this assessment method could also be used if the interactive effect between indoor air pollution and tobacco use was not significant. As it requires selecting the maximum OR of the unmeasured confounder (tobacco use) on the outcome (lung cancer) within different exposure (indoor air pollution) levels, regardless of whether or not there is an interaction between the exposure and the unmeasured confounder. When the common method examines no interactive effect, this assessment method could provide additional information on the competition tobacco use may bring to indoor air pollution and improve the understanding of the relationship between lung cancer and the two important risk factors more comprehensively. More precise lung cancer control and prevention policies could be implemented.

When applying this quantitative assessment method, we paid attention to several points. First, this method required three elements: confounder, exposure, and outcome. In our study, smoking or SHS exposure could affect both indoor air pollution and lung cancer, while air pollution was not supposed to affect smoking or SHS. Therefore, smoking or SHS exposure, indoor air pollution, and lung cancer could be the confounder, exposure, and outcome, respectively. Second, when estimating the ORs for both of the risk factors, the other covariate variables in the models must remain the same, as stated by VanderWeele TJ and Ding P. Third, since $RR_{EU}$ is supposed to capture the imbalance of the distribution of the unmeasured confounder in the exposed and non-exposed subgroups in the study population, it

must be calculated based on the study population or a random sample. In our analysis, the data of the 2316 controls was eligible for use.

There were some limitations to our study. First, since the lung cancer mortality hasn't significantly decreased and the locations of high-, medium- and low- level lung cancer mortality areas haven't changed much in Xuanwei, perhaps we have missed some other potential risk factors, which affect lung cancer risk or influence the association between it and indoor air pollution. Therefore, in the next step, we propose that indoor air pollution concentration measurement (considering the energy structure change in Xuanwei (Liu et al., 2017) and possibly ambient air pollution) and human biological sampling should be carried out in order to investigate actual external exposure and internal exposure and their association with lung cancer risk. Second, our survey of the controls was conducted in 2014, while that of the cases was conducted in 2017; there was a 3-year gap in between. However, since all of the risk factors we surveyed were characteristics, experiences, or behavior habits that did not likely change rapidly within 3 years, this should not have caused any significant difference.

## 5. Conclusion

We found a strong delayed effect of indoor air pollution over 30 years ago on lung cancer risk in Xuanwei. In the areas without smoky coal consumption over 30 years ago, the effect of tobacco use on lung cancer was stronger. Moreover, we estimated that tobacco use could reduce a maximum of 18%-30% of the effect of indoor air pollution. Local governments should start considering public health activities for smoking cessation promotion and SHS exposure prevention.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Author contributions

Liqun Liu participated in the study field work, organized and analyzed the data, and drafted and revised the manuscript, including the tables and figures.

Xiaoyan Liu participated in the study field work and data cleaning.

Xiangyun Ma and Bofu Ning managed the local coordination of the study field work.

Xia Wan designed the study, guided its implementation, and helped with the interpretation of the results and revision of the manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2019.135232.

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