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ORIGINAL PAPER

Risk factors shared by COPD and lung cancer and mediation effect of COPD: two center case–control studies

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Abstract
Purpose To reveal the shared risk factors for chronic obstructive pulmonary disease (COPD) and lung cancer, and to analyze the mediation effect of COPD during lung carcinogenesis.
Methods We conducted four independent case–control studies included 1,511 COPD patients and 1,677 normal lung function controls and 1,559 lung cancer cases and 1,679 cancer-free controls during 2002–2011 in southern and eastern Chinese.
Results Eight factors were observed to be consistently associated with both diseases risk, including pre-existing tuberculosis, smoking, passive smoking, occupational exposure to metallic toxicant, poor housing ventilation, biomass burning, cured meat consumption, and seldom vegetables/fruits consumption. Furthermore, smoking and biomass burning conferred significantly higher risk effects on lung cancer in individuals with pre-existing COPD than those without. COPD also had significant mediation effects during lung carcinogenesis caused by smoking, passive smoking, and biomass burning, which explained about 12.0 % of effect, 3.8 % of effect, and 6.1 % of effect of these factors on lung tumorigenesis in turn.
Conclusion Our study mapped a shared spectrum of etiological factors for both COPD and lung cancer in Chinese, and COPD acts as a mediator during lung cancer development. These observations should be in consideration for the prevention of both diseases.

Keywords COPD · Lung cancer · Case–control study · Risk factor · Mediation effect

Introduction

Chronic obstructive pulmonary disease (COPD) and lung cancer are the most striking lung diseases with high and increasing morbidity and mortality worldwide [1, 2]. In China, COPD has achieved a prevalence of 8.2 % in adults

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over 40 years old and accounts for more than one million deaths and over five million disabilities each year, while lung cancer has been the leading cause of cancer incidence and mortality for years [1, 2]. COPD and lung cancer are closely related as that COPD patients suffer an lung cancer incidence of 16.7 cases per 1,000 person-years, which was four times the incidence in general smoking population [3]. Moreover, 40–70 % of lung cancer patients have concomitant COPD [4].

Recently, great attention has been paid on the inherent relation between COPD and lung cancer [5, 6]. It is well recognized that these two diseases share some pivotal pathologic mechanisms such as chronic inflammation in response to extracellular stimuli [6], suggesting a commonality of etiological factors that involve both diseases. Indeed, a number of epidemiologic studies have documented several environmental and genetic factors that are associated with both diseases, among them some are overlapping [2, 7–9]. Tobacco smoking is the most important risk factor for them, and we are glad to see a modest reduction in both COPD and lung cancer incidences and deaths due to a general decline in smoking rate in the USA population [10]. However, other factors such as prior chronic lung diseases (i.e., emphysema, chronic bronchitis) [11, 12], environmental factors like occupational exposure to dust at work [13, 14], house environment, and lifestyle [2, 15] are also reported to be more or less related to COPD or lung cancer risk. This reflects considerable room for prevention of the two diseases.

Revealing the shared factors of COPD and lung cancer would not only help both diseases prevention but also deepen our knowledge about their etiological link. However, current assumptions about these shared factors can only been presumed by independent studies about COPD or lung cancer that were conducted in different areas or different populations. There was no study simultaneously investigating on risk factors for COPD and lung cancer to show shared factors of both diseases. Moreover, a recent study reported a mediation effect of COPD on association between smoking and lung cancer [16], revealing a novel role of COPD on the formation of lung cancer that COPD may act as an intermediate phenotype ahead of lung malignant transformation. We have previously identified that COPD and lung cancer shared some genetically susceptible factors [9, 17]. In the current study, in order to reveal the shared risk factors for COPD and lung cancer in Chinese, we conducted four independent case–control studies in southern and eastern Chinese to test and validate associations between twenty-three environmental factors and two diseases risk in a total of 1,511 COPD patients and 1,677 normal lung function controls and 1,559 lung cancer cases and 1,679 cancer-free controls during 2002–2011. We then used the lung cancer case–control studies to analyze the mediation effect of COPD on associations between these shared factors and lung cancer risk.

Methods

Study subjects

Four independent case–control studies were conducted in southern and eastern Chinese during 2002–2011 for COPD and lung cancer. The studies were approved by the institutional review boards of Guangzhou Medical University and Soochow University. Subjects without complete or with confused information on exposure variables were excluded. Briefly, lung function of all COPD patients and controls were measured by the Spirometry test (EasyOne Spirometer, ndd Medizintechnik AG, Switzerland). Subjects with forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) <70 % after inhalation of 400 μg salbutamol, and with at least one of followed chronic airway symptoms over 2 weeks in life including chronic cough, dyspnea, sputum production, or wheezing were diagnosed to be COPD cases. A total of 1,025 COPD patients and 1,061 normal lung function controls were recruited from Guangzhou city; 486 COPD patients and 616 normal controls were enrolled form Suzhou city as described previously [9, 17]. According to the global initiative for chronic obstructive lung disease [18], there were 359 (35.0 %) cases of stage I, 356 (34.7 %) stage II, 217 (21.2 %) stage III, and 93 (9.1 %) stage IV in southern Chinese, and 213 (43.8 %) cases of stage I, 206 (43.4 %) stage II, 54 (11.1 %) stage III, and 13 (2.7 %) stage IV in eastern Chinese. A total of 1,056 histopathologically confirmed cases with primary lung cancer and 1,056 cancer-free controls were recruited from Guangzhou city; 503 lung cancer cases and 623 cancer-free controls were enrolled from Suzhou city as described previously [19–22]. All controls were age-(±5 years) and sex-frequency-matched with cases. Furthermore, there were 217 lung cancer patients with pre-existing COPD who were physician-diagnosed COPD with Spirometry testing at least 1 year before lung cancer diagnosis. Because information on pre-existing COPD of lung cancer cases was obtained by interviewing with a scheduled questionnaire, we did not have any data on the GOLD stage. The detailed information on subjects' recruitment was presented in Appendix as a supplementary material.

Data collection

After a signed informed consent was given from each subject, a scheduled questionnaire was used to collect data on individuals' demographic characters and surrounding

variables by two trained technicians. The same questionnaire and scale were used for collecting all data in the two populations. The demographic characters covered four elements such as age, sex, body mass index (BMI: <18.0, 18.0–25.0, >25.0), and educational experience (i.e., never, primary school, secondary school, and college or university). The surrounding variables included twenty-three possible risk factors, namely pre-existing tuberculosis, pre-existing chronic bronchitis, pre-existing emphysema, pre-existing silicosis, smoking status and pack-years smoked, passive smoking and its source, drinking status, occupational exposure (to dust, arsenic, asbestos, paint, or metallic toxicants), house ventilation, kitchen ventilator, coal burning, liquefied gas burning, biomass burning, cooking times in 1 week, vegetables/fruits consumption, cured meat consumption, Chinese sauerkraut/pickles consumption, and salted fish/meat consumption. These variables are more or less reported to be risk factors for COPD or lung cancer or both in abundant studies. The detailed definitions of selected variables were presented in Appendix as a supplementary material. As a supplement, subjects who had pre-existing pulmonary diseases at least 1 year before case diagnosis or control enrollment were defined as "Yes" if they provided reliable medical records. Individuals who had at least 10 years occupational exposure history were defined as "Yes", while the reminders were defined as "No". All individuals were Chinese Han, and subjects with confused or defective information on above factors were excluded.

Statistical analysis

The differences in distribution of demographics between cases and controls were analyzed using the chi-square test. The odds ratio (OR) and 95 % confidence interval (95 % CI) were estimated by the unconditional logistic regression model. The Breslow–Day test was used to test the homogeneity of the variables' contributions to the risk of COPD and lung cancer. The multinomial logistic regression analysis was performed to compare the ORs of these shared factors between individuals with and without pre-existing COPD in the lung cancer studies [23]. A mediation model with the Sobel test tool (http://quantpsy.org/sobel/sobel.htm) was used to test the indirect effects that these shared factors had on lung cancer via COPD [24–28]. Furthermore, we applied a multiplicative interaction model to evaluate possible interactions between the shared factors and COPD on affecting lung cancer risk [29]. Detailed statistical protocol for the mediation test was presented in Appendix as a supplementary material. A sensitivity analysis was performed to analyze the mediation effect of COPD on smoking/lung cancer association with an assumed 3 % measurement error rate in smoking. All tests were two-sided and evaluated by the SAS software (version 9.3; SAS Institute, Cary, NC). $p < 0.05$ was considered to be statistically significant.

Results

As shown in Table 1, concordant results were observed for all case–control studies, age and sex matched well between cases and controls ($p > 0.05$ for all). Otherwise, there were more individuals with lower BMI (<18.0) and less education experience in cases than controls ($p < 0.05$ for all). These variables were further adjusted for in the multivariate logistic regression model to control possible confounding on the main effects of selected factors.

The frequency distributions of selected factors in the southern Chinese and their associations with risk of COPD and lung cancer are presented in Table 2. Up to sixteen factors were significantly associated with COPD risk. They were pre-existing tuberculosis, pre-existing chronic bronchitis, pre-existing emphysema, smoking (or high pack-years smoked), passive smoking (especially passive smoking from parents), occupational exposure to dust or arsenic or metallic toxicants, house ventilation, kitchen ventilator, coal burning, liquefied gas burning, biomass burning, vegetables/fruits consumption, cured meat consumption, and Chinese sauerkraut/pickles consumption ($p < 0.05$ for all). Among them, pre-existing lung diseases such as chronic bronchitis (OR = 3.02, $p = 5.28 \times 10^{-15}$) and emphysema (OR = 4.24, $p = 2.06 \times 10^{-13}$) contributed to extremely high risk of COPD, which are due to the fact that the two diseases mostly pertain to COPD if the patients have irreversible limitation in lung airflow [30]. In addition to the prior lung diseases, occupational exposure to arsenic accounted for the second highest risk (OR = 2.98, $p = 1.00 \times 10^{-4}$), while high pack-years smoked achieved the greatest statistically significance (OR = 1.88, $p = 8.63 \times 10^{-9}$). Likewise, thirteen factors conferred significantly increased risks of lung cancer ($p < 0.05$ for all), including pre-existing tuberculosis, pre-existing chronic bronchitis, pre-existing emphysema, smoking (or high pack-years smoked), passive smoking (from parents or children), occupational exposure to dust or asbestos or metallic toxicants, poor house ventilation, no kitchen ventilator, biomass burning, cured meat consumption, and seldom vegetables/fruits consumption. Among these factors, occupational exposure to metallic toxicants held the highest risk (OR = 2.85, $p = 9.00 \times 10^{-4}$), and high pack-years smoked harbored the most statistically significance (OR = 2.02, $p = 8.63 \times 10^{-9}$).

Findings in the eastern Chinese were generally consistent with the above results as listed in Table 2. The aforementioned sixteen factors that are found to be

Table 1 Frequency distribution of demographics in COPD/lung cancer cases and controls

Variables	COPD discovery set (southern Chinese)			COPD validation set (eastern Chinese)			Lung cancer discovery set (southern Chinese)			Lung cancer validation set (eastern Chinese)		
	Cases *n* (%)	Controls *n* (%)	p^a	Cases *n* (%)	Controls *n* (%)	p^a	Cases *n* (%)	Controls *n* (%)	p^a	Cases *n* (%)	Controls *n* (%)	p^a
Total no. of subjects	1,025	1,061		486	616		1,056	1,056		503	623	
Age (years)												
≤60	463 (45.2)	507 (47.8)	0.231	241 (49.6)	292 (47.4)	0.471	536 (50.8)	534 (50.6)	0.931	273 (54.3)	343 (55.1)	0.793
>60	562 (54.8)	554 (52.2)		245 (50.4)	324 (52.6)		520 (49.2)	522 (49.4)		230 (45.7)	280 (44.9)	
Sex												
Male	610 (59.5)	638 (60.1)	0.773	273 (56.2)	345 (56.0)	0.956	746 (70.6)	746 (70.6)	1.000	345 (68.6)	439 (70.5)	0.500
Female	415 (40.5)	423 (39.9)		213 (43.8)	271 (44.0)		310 (29.4)	310 (29.4)		158 (31.4)	184 (29.5)	
Body mass index												
<18.0	148 (14.4)	38 (3.6)	<0.001	42 (8.6)	14 (2.3)	<0.001	144 (13.6)	44 (4.1)	<0.001	63 (12.5)	42 (6.7)	<0.001
18.0–25.0	645 (62.9)	702 (66.2)		333 (68.5)	407 (66.1)		809 (76.6)	704 (66.7)		382 (75.9)	413 (66.3)	
>25.0	232 (22.6)	321 (30.2)		111 (22.8)	195 (31.7)		103 (9.8)	308 (29.2)		58 (11.5)	168 (27.0)	
Educational experience												
Never	123 (12.0)	115 (10.9)	0.051	66 (13.6)	66 (10.7)	0.526	62 (5.9)	36 (3.4)	0.037	33 (6.6)	43 (6.9)	0.013
Primary school	315 (30.7)	276 (26.0)		148 (30.4)	187 (30.4)		342 (32.4)	372 (35.2)		141 (28.0)	127 (20.4)	
Secondary school	526 (51.3)	603 (56.8)		240 (49.4)	321 (52.1)		555 (52.5)	559 (53.0)		284 (56.5)	405 (65.0)	
College or university	61 (6.0)	67 (6.3)		32 (6.6)	42 (6.8)		97 (9.2)	89 (8.4)		45 (8.9)	48 (7.7)	
Histological types												
Adenocarcinoma								384 (36.4)			231 (45.9)	
Squamous cell cancer								369 (34.9)			158 (31.4)	
Large cell carcinoma								43 (4.1)			23 (4.6)	
Small cell lung cancer								128 (12.1)			65 (12.9)	
Other carcinomas[b]								132 (12.5)			26 (5.2)	

[a] p values for a two-sided χ^2 test between cases and controls

[b] Mixed-cell or undifferentiated carcinoma

Table 2 Frequency distributions and ORs of physical and environmental factors on risk of COPD and lung cancer in southern and eastern Chinese

Variables	COPD case–control[a]			COPD case–control[b]		
	Cases *n*	Controls *n*	Adjusted OR[c]	Cases *n*	Controls *n*	Adjusted OR[c]
Tuberculosis						
No	920	1,014	1.00 (ref.)	457	598	1.00 (ref.)
Yes	105	47	**2.30 (1.59–3.31)**	29	18	**2.11 (1.14–3.92)**
Chronic bronchitis						
No	808	975	1.00 (ref.)	421	555	1.00 (ref.)
Yes	217	86	**3.02 (2.29–3.98)**	65	61	**1.51 (1.03–2.22)**
Emphysema						
No	880	1,023	1.00 (ref.)	455	599	1.00 (ref.)
Yes	145	38	**4.24 (2.89–6.24)**	31	17	**2.54 (1.35–4.77)**
Silicosis						
No	1,016	1,056	1.00 (ref.)	482	613	1.00 (ref.)
Yes	9	5	1.43 (0.50–4.07)	4	3	1.65 (0.36–7.50)
Smoking status						
Never	526	637	1.00 (ref.)	271	389	1.00 (ref.)
Ever	499	424	**1.72 (1.38–2.15)**	215	227	**1.54 (1.12–2.12)**
Pack-years smoked						
Low (0–5)	584	685	1.00 (ref.)	289	398	1.00 (ref.)
Moderate (6–20)	138	162	1.18 (0.89–1.57)	71	89	1.16 (0.78–1.73)
High (>20)	303	214	**1.88 (1.47–2.41)**	126	129	**1.42 (1.01–2.02)**
Male smoking						
Never	151	240	1.00 (ref.)	83	138	1.00 (ref.)
Ever	459	398	**1.76 (1.37–2.27)**	190	207	**1.48 (1.05–2.09)**
Female smoking						
Never	375	397	1.00 (ref.)	188	251	1.00 (ref.)
Ever	40	26	**2.08 (1.22–3.55)**	25	20	1.84 (0.96–3.53)
Passive smoking						
No	281	384	1.00 (ref.)	120	203	1.00 (ref.)
Yes	245	253	**1.29 (1.01–1.63)**	151	186	**1.37 (1.01–1.88)**
Passive smoking from parents						
No	469	591	1.00 (ref.)	235	360	1.00 (ref.)
Yes	57	46	**1.52 (1.01–2.31)**	36	29	1.68 (0.98–2.89)
Passive smoking from companion						
No	382	491	1.00 (ref.)	176	297	1.00 (ref.)
Yes	144	146	1.01 (0.75–1.35)	95	92	1.38 (0.94–2.03)
Passive smoking from children						
No	437	540	1.00 (ref.)	213	308	1.00 (ref.)
Yes	89	97	1.27 (0.91–1.76)	58	81	1.19 (0.79–1.80)
Drinking status						
Never	839	852	1.00 (ref.)	389	489	1.00 (ref.)
Ever	186	209	0.90 (0.72–1.14)	97	127	0.97 (0.71–1.32)
Occupational exposure						
Dust						
No	824	922	1.00 (ref.)	390	525	1.00 (ref.)
Yes	201	139	**1.57 (1.24–2.00)**	96	91	**1.43 (1.04–1.97)**
As						
No	974	1,043	1.00 (ref.)	465	600	1.00 (ref.)
Yes	51	18	**2.98 (1.72–5.17)**	21	16	1.65 (0.85–3.23)

Table 2 continued

Variables	COPD case–control[a]			COPD case–control[b]		
	Cases *n*	Controls *n*	Adjusted OR[c]	Cases *n*	Controls *n*	Adjusted OR[c]
ASB						
No	971	1,018	1.00 (ref.)	452	591	1.00 (ref.)
Yes	54	43	1.30 (0.85–1.97)	34	25	**1.79 (1.05–3.08)**
Paint						
No	935	985	1.00 (ref.)	442	565	1.00 (ref.)
Yes	90	76	1.26 (0.91–1.74)	44	51	1.10 (0.71–1.69)
Metallic toxicant						
No	951	1,017	1.00 (ref.)	454	593	1.00 (ref.)
Yes	74	44	**1.93 (1.31–2.85)**	32	23	**1.82 (1.04–3.19)**
Housing ventilation						
Well	598	673	1.00 (ref.)	270	376	1.00 (ref.)
General	369	356	1.15 (0.95–1.38)	178	217	1.15 (0.89–1.34)
Poor	58	32	**2.03 (1.30–3.19)**	38	23	**2.19 (1.27–3.80)**
Kitchen ventilator						
Yes	851	941	1.00 (ref.)	425	557	1.00 (ref.)
No	174	120	**1.53 (1.18–1.99)**	61	59	1.22 (0.83–1.80)
Coal burning						
No	861	935	1.00 (ref.)	412	546	1.00 (ref.)
Yes	164	126	**1.30 (1.01–1.68)**	74	70	1.25 (0.87–1.81)
Liquefied gas burning						
No	52	27	1.00 (ref.)	27	8	1.00 (ref.)
Yes	973	1,034	**0.56 (0.35–0.92)**	459	608	**0.26 (0.12–0.60)**
Biomass burning						
No	851	970	1.00 (ref.)	453	597	1.00 (ref.)
Yes	174	91	**1.97 (1.49–2.60)**	33	19	**2.02 (1.11–3.67)**
Cooking times						
Never	96	104	1.00 (ref.)	50	68	1.00 (ref.)
Seldom	274	282	1.07 (0.76–1.50)	130	155	1.09 (0.68–1.73)
Often	655	675	1.06 (0.78–1.45)	306	393	0.92 (0.60–1.41)
Cured meat consumption						
Never	54	90	1.00 (ref.)	26	63	1.00 (ref.)
Seldom	852	862	**1.67 (1.17–2.38)**	423	512	**1.88 (1.16–3.05)**
Often	119	109	**1.93 (1.23–3.03)**	37	41	**2.16 (1.10–4.22)**
Vegetables/fruits eating						
Every day	726	832	1.00 (ref.)	338	471	1.00 (ref.)
Often	203	186	1.23 (0.98–1.54)	118	119	**1.41 (1.05–1.90)**
Seldom	96	43	**2.40 (1.63–3.53)**	30	26	1.63 (0.94–2.85)
Chinese sauerkraut/pickles consumption						
Never	106	117	1.00 (ref.)	38	54	1.00 (ref.)
Seldom	821	866	1.12 (0.84–1.49)	403	499	1.07 (0.68–1.66)
Often	98	78	**1.82 (1.19–2.80)**	45	63	1.21 (0.66–2.22)
Salted fish/meat consumption						
Never	109	100	1.00 (ref.)	45	66	1.00 (ref.)
Seldom	814	868	0.91 (0.68–1.23)	402	487	1.19 (0.79–1.80)
Often	102	84	1.35 (0.89–2.06)	39	63	0.96 (0.53–1.74)

Table 2 continued

Variables	Lung cancer case–control[a]			Lung cancer case–control[b]		
	Cases *n*	Controls *n*	Adjusted OR[c]	Cases *n*	Controls *n*	Adjusted OR[c]
Tuberculosis						
No	969	1,004	1.00 (ref.)	459	591	1.00 (ref.)
Yes	87	52	**1.46 (1.01–2.11)**	44	32	**1.76 (1.08–2.87)**
Chronic bronchitis						
No	913	964	1.00 (ref.)	439	564	1.00 (ref.)
Yes	143	92	**1.65 (1.23–2.21)**	64	59	1.20 (0.81–1.78)
Emphysema						
No	957	1,000	1.00 (ref.)	451	581	1.00 (ref.)
Yes	99	56	**1.94 (1.37–2.74)**	52	42	**1.66 (1.07–2.57)**
Silicosis						
No	1,044	1,052	1.00 (ref.)	497	619	1.00 (ref.)
Yes	12	4	2.54 (0.77–8.31)	6	4	1.40 (0.38–5.13)
Smoking status						
Never	455	514	1.00 (ref.)	280	400	1.00 (ref.)
Ever	601	542	**1.41 (1.12–1.76)**	223	223	**1.51 (1.16–1.96)**
Pack-years smoked						
Low (0–5)	511	601	1.00 (ref.)	298	402	1.00 (ref.)
Moderate (6–20)	137	177	1.09 (0.82–1.46)	56	74	1.10 (0.89–1.64)
High (>20)	408	278	**2.02 (1.59–2.56)**	149	147	**1.38 (1.03–1.85)**
Male smoking						
Never	186	236	1.00 (ref.)	137	224	1.00 (ref.)
Ever	560	510	**1.37 (1.08–1.74)**	208	215	**1.56 (1.17–2.09)**
Female smoking						
Never	269	278	1.00 (ref.)	143	176	1.00 (ref.)
Ever	41	32	1.32 (0.81–2.17)	15	8	1.97 (0.79–4.91)
Passive smoking						
No	228	295	1.00 (ref.)	153	255	1.00 (ref.)
Yes	227	219	**1.35 (1.04–1.77)**	127	145	**1.41 (1.02–1.93)**
Passive smoking from parents						
No	396	475	1.00 (ref.)	247	356	1.00 (ref.)
Yes	59	39	**1.74 (1.10–2.73)**	33	44	1.08 (0.67–1.75)
Passive smoking from companion						
No	322	374	1.00 (ref.)	221	333	1.00 (ref.)
Yes	133	140	0.88 (0.64–1.23)	59	67	1.49 (0.97–2.28)
Passive smoking from children						
No	357	435	1.00 (ref.)	245	361	1.00 (ref.)
Yes	98	79	**1.66 (1.18–2.36)**	35	39	1.41 (0.85–2.35)
Drinking status						
Never	827	829	1.00 (ref.)	439	508	1.00 (ref.)
Ever	229	227	1.05 (0.84–1.31)	64	115	**0.65 (0.46–0.91)**
Occupational exposure						
Dust						
No	933	961	1.00 (ref.)	443	563	1.00 (ref.)
Yes	123	95	**1.38 (1.03–1.85)**	60	60	1.30 (0.88–1.92)
As						
No	1,026	1,034	1.00 (ref.)	481	616	1.00 (ref.)
Yes	30	22	1.35 (0.76–2.41)	22	7	**3.92 (1.64–9.39)**

Table 2 continued

Variables	Lung cancer case–control[a]			Lung cancer case–control[b]		
	Cases *n*	Controls *n*	Adjusted OR[c]	Cases *n*	Controls *n*	Adjusted OR[c]
ASB						
No	1,007	1,027	1.00 (ref.)	469	602	1.00 (ref.)
Yes	49	29	**1.82 (1.11–2.96)**	34	21	**2.10 (1.19–3.73)**
Paint						
No	920	939	1.00 (ref.)	459	580	1.00 (ref.)
Yes	136	117	1.23 (0.93–1.62)	44	43	1.28 (0.82–1.99)
Metallic toxicant						
No	1,016	1,041	1.00 (ref.)	464	591	1.00 (ref.)
Yes	40	15	**2.85 (1.53–5.31)**	39	32	**1.73 (1.05–2.84)**
Housing ventilation						
Well	611	644	1.00 (ref.)	310	408	1.00 (ref.)
General	362	359	1.05 (0.87–1.28)	171	203	1.12 (0.86–1.44)
Poor	83	53	**1.82 (1.25–2.64)**	22	12	**2.50 (1.20–5.23)**
Kitchen ventilator						
Yes	828	925	1.00 (ref.)	448	561	1.00 (ref.)
No	228	131	**2.02 (1.59–2.59)**	55	62	1.02 (0.69–1.51)
Coal burning						
No	959	962	1.00 (ref.)	474	602	1.00 (ref.)
Yes	97	94	1.05 (0.77–1.43)	29	21	1.62 (0.90–2.93)
Liquefied gas burning						
No	83	62	1.00 (ref.)	16	17	1.00 (ref.)
Yes	973	994	0.83 (0.58–1.19)	487	606	0.88 (0.43–1.80)
Biomass burning						
No	918	960	1.00 (ref.)	470	605	1.00 (ref.)
Yes	138	96	**1.42 (1.06–1.90)**	33	18	**2.02 (1.12–3.72)**
Cooking times						
Never	168	174	1.00 (ref.)	64	96	1.00 (ref.)
Seldom	489	479	1.12 (0.86–1.46)	296	365	1.22 (0.85–1.76)
Often	399	403	1.04 (0.80–1.36)	143	162	1.30 (0.87–1.95)
Cured meat consumption						
Never	109	153	1.00 (ref.)	23	25	1.00 (ref.)
Seldom	811	750	**1.53 (1.15–2.02)**	415	562	0.86 (0.47–1.55)
Often	136	153	1.25 (0.87–1.79)	65	36	**2.15 (1.03–4.45)**
Vegetables/fruits eating						
Every day	854	909	1.00 (ref.)	360	479	1.00 (ref.)
Often	118	113	1.09 (0.81–1.45)	87	107	1.12 (0.81–1.54)
Seldom	84	34	**2.40 (1.58–3.66)**	56	37	**1.82 (1.16–2.85)**
Chinese sauerkraut/pickles consumption						
Never	137	131	1.00 (ref.)	35	52	1.00 (ref.)
Seldom	802	792	1.01 (0.77–1.33)	427	540	1.19 (0.75–1.88)
Often	117	133	0.96 (0.67–1.39)	51	31	**2.26 (1.14–4.51)**
Salted fish/meat consumption						
Never	97	124	1.00 (ref.)	38	46	1.00 (ref.)
Seldom	847	767	1.05 (0.80–1.38)	442	543	0.98 (0.62–1.54)
Often	112	165	0.80 (0.55–1.13)	23	34	0.74 (0.35–1.53)

Bold values indicate the statistically significant $P < 0.05$

As arsenic, *Asb* asbestos

[a] Data from the southern Chinese

[b] Data from the eastern Chinese

[c] ORs were adjusted for age, sex, BMI, and educational experience in the logistic regression model

associated with COPD risk were confirmed to be risk factors for COPD except for occupational exposure to arsenic, kitchen ventilator, coal burning, and Chinese sauerkraut/pickles consumption. Besides, the risk factors for lung cancer in the southern Chinese were also confirmed except for pre-existing chronic bronchitis, occupational exposure to dust, and kitchen ventilator.

Factors that were significantly associated with both COPD and lung cancer risk in the southern and eastern Chinese were recognized to be shared risk factors for COPD and lung cancer as shown in Table 3. Risk of COPD and lung cancer was increased in individuals with pre-existing tuberculosis, pre-existing emphysema, smoking or high pack-years smoked, passive smoking, occupational exposure to metallic toxicants, poor house ventilation, biomass burning, cured meat consumption, and seldom vegetables/fruits consumption ($p < 0.05$ for all). The homogeneity test further indicated that the differences in frequency distributions of these shared factors between cases and controls were consistent in COPD groups and lung cancer groups (Breslow–Day test: $p > 0.05$ for all) except for pre-existing emphysema ($p = 6.48 \times 10^{-5}$). In addition, given the dramatic sex differences of exposures to active tobacco smoking throughout China, we specially tested the effect of smoking on COPD and lung cancer risk stratified by sex. Although significant associations were observed between smoking and either COPD or lung cancer risk in males but not in females, the differences between stratum ORs by sex were not significant in each case–control study (Breslow–Day test: $p > 0.05$ for all).

On account of the fact that almost all these shared factors conferring consistent risks of COPD and lung cancer, we further performed the multinomial logistic regression analysis using the cancer-free controls as a reference group to infer the effect differences of these factors with regard to COPD status on lung cancer development (Table 4). The comparison between the ORs for the eight shared factors revealed that smoking ($p = 4.53 \times 10^{-6}$), high pack-years smoked ($p = 0.001$ for <20; $p = 2.00 \times 10^{-4}$ for ≥20), and biomass burning ($p = 8.42 \times 10^{-5}$) harbored significantly higher risk of lung cancer in individuals with pre-existing COPD than those without pre-existing COPD, while the others did not ($p > 0.05$ for all).

Meanwhile, we performed the mediation model to assess the mediation effect of COPD on associations between these shared factors and lung cancer risk. Only smoking was observed to have a borderline significant interaction with pre-existing COPD on increasing lung cancer risk ($p = 0.062$); therefore, the interaction was introduced into the model for mediation analysis. As shown in Fig. 1, α was the comparable regression coefficient for association between the shared risk factors and COPD; β was the comparable regression coefficient for association between COPD and lung cancer; τ' was the comparable regression coefficient for association between the shared risk factors and lung cancer; and θ was the comparable regression coefficient for interaction between the risk factors and pre-existing COPD on lung cancer risk. We found that COPD acted as a mediator in associations between smoking ($\alpha = 0.168$, $\beta = 0.068$, $\tau' = 0.111$, $\theta = 0.115$), high pack-years smoked ($\alpha = 0.099$, $\beta = 0.065$, $\tau' = 0.058$), passive smoking ($\alpha = 0.031$, $\beta = 0.065$, $\tau' = 0.051$), biomass burning ($\alpha = 0.078$, $\beta = 0.065$, $\tau' = 0.079$), and lung cancer risk. The indirect effect of COPD was statistically significant as results from the Sobel test shown (p values were 0.005 for smoking, 0.006 for pack-years smoked, 0.041 for passive smoking, and 0.039 for biomass burning), and COPD in turn explained about 12.0, 9.9, 3.8, and 6.1 % of the effects of above factors on cancer risk. COPD also harbored 13.0 % of the effect that pre-existing tuberculosis had on lung cancer risk ($p = 0.005$). In terms of the other factors, although the mediation model suggested COPD might explain about 2.6 % of house ventilation, 9.8 % of vegetables/fruits consumption, and 0.06 % of cured meat consumption on cancer risk, none of these mediation effects were statistically significant (p values in turn were 0.273, 0.392, and 0.984). In addition, we performed a sensitivity analysis for mediation effect of COPD on smoking/lung cancer association with an assumed 3 % measurement error rate in smoking. The test showed that the mediation effects of COPD on smoking-caused lung cancer were all significant (all $p < 0.05$) in the three scenarios with the minimum smoking rate, current smoking rate and maximum smoking rate, and the mediated proportions were approximately same.

Discussion

We conducted four independent case–control studies for COPD and lung cancer in southern and eastern Chinese and identified that eight factors, namely pre-existing tuberculosis, smoking status (or high pack-years smoked), passive smoking, occupation exposure to metallic toxicant, poor housing ventilation, biomass burning, cured meat consumption, and seldom vegetables/fruits consumption, contributed to consistently increased risk of both diseases. Smoking (or high pack-years smoked) and biomass burning conferred significantly higher lung cancer risk in individuals with pre-existing COPD than those without. Moreover, COPD acted as a mediator of associations between smoking, passive smoking, biomass burning, and lung cancer risk.

All the shared factors discovered in the current study were without exception proposed to be associated with COPD or lung cancer risk in previous studies. Pre-existing

Table 3 The frequency distributions and ORs of shared risk factors for COPD and lung cancer in the pooled population

Variables	COPD case–control			Lung cancer case–control			p^b
	Cases *n* (%)	Controls *n* (%)	Adjusted OR[a]	Cases *n* (%)	Controls *n* (%)	Adjusted OR[a]	
Pre-existing tuberculosis							
No	1,377 (91.1)	1,612 (96.1)	1.00 (ref.)	1,428 (91.6)	1,595 (95.0)	1.00 (ref.)	0.124
Yes	134 (8.9)	65 (3.9)	**2.26 (1.65–3.09)**	131 (8.4)	84 (5.0)	**1.52 (1.13–2.04)**	
Pre-existing emphysema							
No	1,335 (88.4)	1,623 (96.8)	1.00 (ref.)	1,408 (90.3)	1,581 (94.6)	1.00 (ref.)	**6.48×10^{-5}**
Yes	176 (11.6)	54 (3.2)	**3.73 (2.69–5.16)**	151 (9.7)	98 (5.8)	**1.82 (1.39–2.38)**	
Smoking status							
Never	797 (52.7)	1,026 (61.2)	1.00 (ref.)	735 (47.1)	914 (54.4)	1.00 (ref.)	0.601
Ever	714 (47.3)	651 (38.8)	**1.67 (1.39–2.01)**	824 (52.9)	765 (45.6)	**1.46 (1.24–1.73)**	
Pack-years smoked							
Low (0–5)	873 (57.8)	1,083 (64.6)	1.00 (ref.)	809 (51.9)	1,003 (59.7)	1.00 (ref.)	0.439
Moderate (6–20)	209 (13.8)	251 (15.0)	1.18 (0.93–1.48)	193 (12.4)	251 (15.0)	1.04 (0.79–1.28)	
High (>20)	429 (28.4)	343 (20.4)	**1.72 (1.40–2.10)**	557 (35.7)	425 (25.3)	**1.75 (1.46–2.10)**	
Passive smoking							
No	401 (50.3)	587 (57.2)	1.00 (ref.)	381 (51.8)	550 (60.2)	1.00 (ref.)	0.657
Yes	396 (49.7)	439 (42.8)	**1.26 (1.04–1.52)**	354 (48.2)	364 (39.8)	**1.37 (1.12–1.68)**	
Occupational exposure to metallic toxicant							
No	1,405 (93.0)	1,610 (96.0)	1.00 (ref.)	1,480 (94.9)	1,632 (97.2)	1.00 (ref.)	0.929
Yes	106 (7.0)	67 (4.0)	**1.91 (1.39–2.63)**	79 (5.1)	47 (2.8)	**2.09 (1.43–3.06)**	
Housing ventilation							
Well	868 (57.5)	1,049 (62.5)	1.00 (ref.)	921 (59.1)	1,052 (62.7)	1.00 (ref.)	0.753
General	547 (36.2)	573 (34.2)	1.14 (0.98–1.33)	533 (34.2)	562 (33.5)	1.08 (0.92–1.25)	
Poor	96 (6.3)	55 (3.3)	**2.10 (1.48–2.97)**	105 (6.7)	65 (3.8)	**1.95 (1.40–2.72)**	
Biomass burning							
No	1,304 (86.3)	1,567 (93.4)	1.00 (ref.)	1,388 (89.0)	1,565 (93.2)	1.00 (ref.)	0.100
Yes	207 (13.7)	110 (6.6)	**2.04 (1.59–2.63)**	171 (11.0)	114 (6.8)	**1.54 (1.19–2.00)**	
Cured meat consumption							
Never	80 (5.3)	153 (9.1)	1.00 (ref.)	132 (8.5)	178 (10.6)	1.00 (ref.)	0.187
Seldom	1,275 (84.4)	1,374 (81.9)	**1.75 (1.31–2.33)**	1,226 (78.6)	1,312 (78.1)	**1.32 (1.02–1.69)**	
Often	156 (10.3)	150 (9.0)	**2.06 (1.42–2.98)**	201 (12.9)	189 (11.3)	**1.44 (1.05–1.98)**	
Vegetables/fruits consumption							
Every day	1,064 (70.4)	1,303 (77.7)	1.00 (ref.)	1,214 (77.9)	1,388 (82.7)	1.00 (ref.)	0.379
Often	321 (21.3)	305 (18.2)	**1.28 (1.07–1.53)**	205 (13.1)	220 (13.1)	1.09 (0.88–1.35)	
Seldom	126 (8.3)	69 (4.1)	**2.13 (1.56–2.92)**	140 (9.0)	71 (4.2)	**2.07 (1.53–2.80)**	

Bold values indicate the statistically significant $P < 0.05$

[a] ORs were calculated with a multivariate regression model including age, sex, BMI, educational experience, and center, and all above factors are listed in table

[b] Homogeneity test of the frequency distributions of factors between lung cancer groups and COPD groups using the Breslow–Day test

lung diseases such as tuberculosis [31], emphysema [30], smoking and passive smoking [2], occupation exposure to metallic toxicant [32], housing ventilation [33], biomass burning [2], vegetables/fruits consumption [34], and cured meat consumption [35] have been proven to be risk factors for COPD. Likewise, these factors are also related to lung cancer [11, 36–38]. Our study was unique in that we compared the risk effects of these factors between COPD and lung cancer, which was not allowed in previous respective epidemiological studies. We found that except for pre-existing emphysema, the associations of these shared factors with COPD and lung cancer risk were consistent. Pre-existing emphysema exerted a significantly higher risk of COPD than of lung cancer, which is due to the fact that emphysema is mostly recognized to be COPD when the patients have irreversible limitation in lung airflow [30]. Moreover, we found that there was no significant difference between the risk effects of smoking on either

Table 4 Comparison of the ORs for shared factors associated with COPD and lung cancer risk in lung cancer groups with and without pre-existing COPD by the multinomial logistic regression analysis

Surrounding factors		Controls	Lung cancer cases without pre-existing COPD	Lung cancer cases with pre-existing COPD	*p* value[a]
Tuberculosis	Yes versus no	1.00 (ref.)	1.52 (1.12–2.06)	1.92 (1.18–3.15)	0.335
Smoking status	Ever versus never	1.00 (ref.)	1.31 (1.10–1.56)	3.13 (2.16–4.52)	$\mathbf{4.53 \times 10^{-6}}$
Pack-years smoked	Moderate versus low	1.00 (ref.)	0.93 (0.73–1.19)	2.07 (1.30–3.28)	**0.001**
	High versus low	1.00 (ref.)	1.61 (1.33–1.94)	3.23 (2.24–4.68)	$\mathbf{2.00 \times 10^{-4}}$
Passive smoking	Yes versus no	1.00 (ref.)	1.29 (1.04–1.61)	1.73 (1.01–2.93)	0.287
Occupation exposure to metallic toxicant	Yes versus no	1.00 (ref.)	2.15 (1.46–3.18)	1.72 (0.82–3.62)	0.538
Housing ventilation	General versus well	1.00 (ref.)	1.08 (0.92–1.27)	1.05 (0.77–1.43)	0.820
	Poor versus well	1.00 (ref.)	1.96 (1.40–2.76)	1.69 (0.88–3.26)	0.648
Biomass burning	Yes versus no	1.00 (ref.)	1.34 (1.02–1.76)	2.99 (1.99–4.50)	$\mathbf{8.42 \times 10^{-5}}$
Cured meat consumption	Seldom versus never	1.00 (ref.)	1.30 (1.00–1.68)	1.19 (0.73–1.95)	0.739
	Often versus never	1.00 (ref.)	1.55 (1.12–2.15)	1.58 (0.85–2.88)	0.978
Vegetables/fruits consumption	Often versus every day	1.00 (ref.)	1.07 (0.85–1.33)	1.23 (0.81–1.86)	0.515
	Seldom versus every day	1.00 (ref.)	2.08 (1.53–2.85)	1.97 (1.15–3.37)	0.820

Bold values indicate the statistically significant $P < 0.05$

[a] A multinomial logistic regression to test the differences between ORs of subjects with and without pre-existing COPD including age, sex, BMI, educational experience, and center, and all above factors are listed in table in regression model

COPD or lung cancer between males and females, although most of smokers were tended to be males. This was consistent with a recently published cohort study [39].

Many studies have reviewed the shared pathological mechanisms of COPD and lung cancer such as airway inflammation, DNA damage, and epithelial-to-mesenchymal transition (EMT) [6, 40]. The above shared factors are all well-established inducers of lung lesion by virtue of chronic infection, DNA damage, or functional change of various genes [41]. They in turn influence the risk of both diseases. For instance, emphysema is accorded with over-activated inflammation [42]; smoking can induce cell proliferation, apoptosis resistance, inflammation, and DNA alterations [43]; and metallic toxicants can trigger EMT in lung [44]. Given all descriptions above, these shared factors are all plausible causes of COPD and lung cancer. Therefore, they are objects that can be potentially controlled in prevention of both diseases.

Having considered that COPD acts as a risk factor for lung cancer, we used the lung cancer case–control studies to show the role of COPD on associations between above shared factors and lung cancer risk. Smokers, especially those smoked more than 20 packs per year, or biomass users, once suffer from COPD, would be more likely to develop lung cancer than those do not suffer from COPD because there was a significantly higher risk in smokers or biomass users with pre-existing COPD compared to those without, implying that COPD may modulate the effect of smoking and biomass burning on lung cancer risk. Likewise, the mediation model revealed that COPD had a significantly indirect effect on associations between smoking, passive smoking, biomass burning, and lung cancer risk. COPD explained about 12.0 % of effect smoking had, 9.9 % of effect more than 20 packs per year consumption had, 3.8 % of effect passive smoking had, and 6.1 % of effect biomass burning had on lung cancer risk. These mean that individuals who are smokers or consume more packs per year and those who use biomass as fuel are more likely to be COPD first, and in turn develop lung cancer. The indirect effect of COPD on smoking is much lower than a previous study that reported an indirect effect of 32.1 % [16]. This may be due to that in their study, the authors used physician-diagnosed emphysema as COPD, while we used much more rigorous criterion based on the Spirometry diagnosis. Also, there must be biased estimations of association between smoking and COPD, because the authors used the standard logistic regression to assess the regression coefficient of smoking-COPD association. This would cause biased evaluation of the indirect effect of COPD [27]. Moreover, we also observed that COPD has a mediation effect of pre-existing tuberculosis on lung cancer risk. However, it has been reported that tuberculosis increased the risk of COPD [45], COPD also increased the tuberculosis risk [46]. It was difficult for us to determine the causal sequence between COPD and tuberculosis. Thus, it was not conceivable that the mediation effect of COPD existed between pre-existing tuberculosis and lung cancer risk. Overall, we support that COPD screening for the

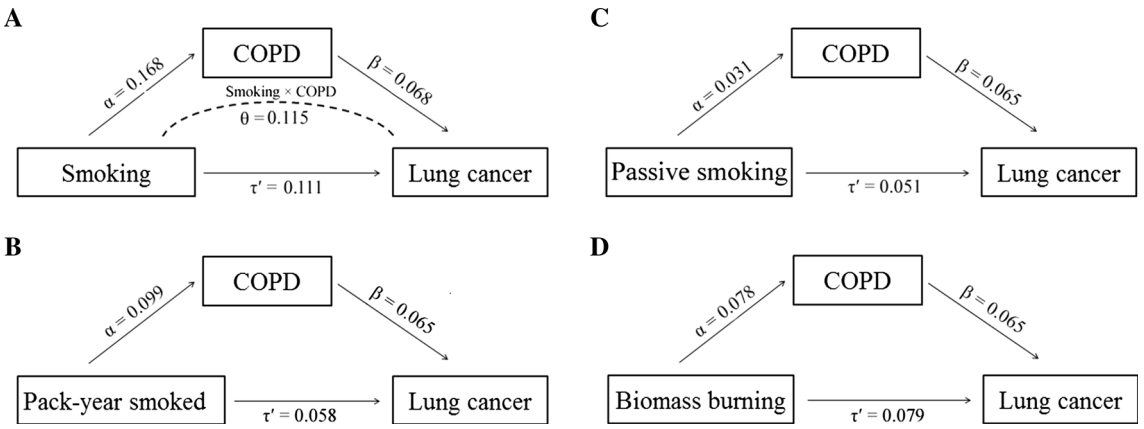

Fig. 1 Path models for the mediation effect of COPD on associations between the shared factors and lung cancer risk. **a** Smoking. **b** Pack-year smoked. **c** Passive smoking. **d** Biomass burning. The indirect effects of COPD were statistically significant as obtained from the Sobel test as that COPD explained about 12.0, 9.9, 3.8, and 6.1 % of the effect of the above factors in turn (p values were 0.005 for smoking, 0.006 for pack-year smoked, 0.041 for passive smoking, and 0.039 for biomass burning)

prevention of COPD and lung cancer should be conducted so long as it is feasible and should be initiated as early as possible in such high risk exposure individuals, so that they can take steps to reduce their predisposition to lung cancer such as quit smoking.

Our study has several unique aspects. First, we have discovered and validated the associations between these possible factors and two diseases risk by virtue of the southern and eastern populations. Second, the subjects were selected based on strict standards that all COPD cases and controls were chosen with the Spirometry test, and lung cancer patients were histopathologically confirmed. Third, the sample size in the current study was relatively large. Moreover, under an assumed 3 % measurement error rate in smoking, the sensitivity analysis still showed that the mediator role of COPD on smoking-caused lung cancer was valid. Finally, the standardization approach proposed by MacKinnon and Dawyer [47] was applied for a scenario with a presence of interaction in the current study for the first time. The approach seemed to be reasonable as supported by a recent study [48]. Nevertheless, limitations such as selection bias and information bias cannot be rule out owing to the fact that the study was based on case–control design restricted with Chinese Han population. Also, the mediation analysis used in the current study was based on no unmeasured confounding assumptions that included no exposure–outcome confounding, no mediator–outcome confounding, no exposure–mediator confounding, and no mediator–outcome confounders affected by the exposure. Thus, some omitted possible confounders might lead to biased estimates and incorrect results on the mediation effect of COPD [49]. In addition, because we only recognized these lung function diagnosed individuals with the Spirometry testing to be pre-existing COPD, it surely seems that the frequency of COPD is a little lower than the reality in the current study. This may underestimate the mediation effect of COPD on lung cancer development.

In conclusion, in the current case–control studies, we proposed eight factors that contribute to consistently increased risks of COPD and lung cancer. Among them, the effect of smoking or pack-year smoked, biomass burning on increasing lung cancer risk is modulated by COPD; and COPD acts as a mediating phenotype of the relationships between smoking, passive smoking, biomass burning and lung cancer development. Our data exhibited a shared spectrum of etiological factors for COPD and lung cancer in Chinese, which should be in consideration for prevention of both diseases.

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