Psychosocial risk factors associated with esophageal cancer in Chinese cohort
A systematic review and meta-analysis

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Abstract

Previous studies were controversial about the role of psychosocial factors in the pathogenesis of esophageal cancer (EC). This study aimed to systematically evaluate the effect size of psychosocial risk factors for EC in Chinese cohort.

A literature search was conducted in both English and Chinese databases, and odds ratios (OR) with the corresponding 95% confidence intervals (CI) were pooled using a random-effects model.

28 studies were identified with a total of 6951 EC cases and 7469 controls. The meta-analysis indicated a higher risk of EC among the individuals with psychological trauma (OR: 2.36, 95% CI: 1.71–3.26), Type A behavior (OR: 1.40, 95% CI: 1.17–1.67), depression (OR: 4.00, 95% CI: 2.44–6.55), melancholy (OR: 2.06, 95% CI: 1.32–3.20), always in sulks (OR: 2.49, 95% CI: 1.21–5.12), and irritable personality (OR: 2.13, 95% CI: 1.58–2.89). A lower EC risk was found in the individuals with good interpersonal relationship (OR: 0.35, 95% CI: 0.17–0.70) and outgoing personality (OR: 0.39, 95% CI: 0.19–0.78).

This meta-analysis suggested a potential association between psychosocial factors and EC risk. For the individuals with psychosocial risk factors, physicians should pay more attention to EC screening.

Abbreviations: EC = esophageal cancer, OR = odds ratio, CI = confidence interval.

Keywords: esophageal cancer, meta-analysis, psychosocial, risk factor

1. Introduction

Esophageal cancer (EC) is one of the most common cancers around the world, with an estimated 455,800 new cases and 400,200 deaths occurred per year.[1] EC was prevalent in China, with an incidence of 16.77 per 100,000, and ranked fifth among all cancers.[2] Moreover, the Chinese cohort contributed to 52.8% and 49.3% of the global EC incidence and mortality. Thus, it was necessary to illuminate the etiology or risk factors, and prevented the disease from the source, especially among those high-risk cohorts like Chinese. Multiple factors were reported in relation to the pathogenesis of EC, including smoking, drinking, hot-food eating, and high-temperature drinking.[3] Previous studies also found that psychosocial factors (e.g., psychological trauma and depression) could lower the immunity, and thus promote the carcinogenesis of multiple cancers.[4] However, the role of psychosocial risk factors was controversial in the pathogenesis of EC. In the population-based study of Shen et al, patients with generalized anxiety disorder (GAD) had a significant increased standardized incidence ratio (SIR) for overall cancer (1.14, 95% confidence interval (CI): 1.05–1.24), male lung cancer (1.77, 95% CI: 1.33–2.30) and prostate cancer (2.17, 95% CI 1.56–2.93), but it was not significant for EC (0.60, 95% CI: 0.19–1.40).[5] Schraub et al study did not suggested a role of life events, personality features, or depression in the onset of cancers, especially EC.[6] However, several Chinese studies indicated a potential involvement of these psychosocial factors in the pathogenesis of EC. No meta-analyses have focused on this controversy, and thus we conducted a systematic review and meta-analysis to evaluate the effect size of certain psychosocial risk factors (e.g., psychological trauma, Type A behavior, depression, melancholy, always in sulks and irritable personality) for EC in Chinese cohort.

2. Material and methods

2.1. Search strategy

The databases of PubMed, China Knowledge Resource Integrated Database (CNKI), China Wanfang Database, and China SinoMed Database were searched for relevant studies published up to July 1, 2020, using the key words ("psychological" OR "mental" OR "psychosocial") AND ("esophageal" OR "esophagus" OR "upper gastrointestinal tract") AND ("cancer" OR "carcinoma" OR "tumor" OR "malignancy"). Studies in languages other than English or Chinese were excluded.

Moreover, the references of related studies, reviews and meta-analyses were also reviewed for undetected original studies. This study was approved by the ethics committee of The Central Hospital of Enshi Tujia and Miao Autonomous Prefecture.

2.2. Study selection and exclusion

All the studies were reviewed independently by 2 investigators. Studies were included if they satisfied the following criteria:

1. observational studies published originally;
2. investigated at least one of the psychosocial factors (psychological trauma, Type A behavior, depression, melancholy, interpersonal relationship, always in sulks, outgoing personality, and irritable personality);
3. the association was evaluated by the effect sizes of relative risk (RR) or OR with 95% CI.

The exclusion criteria were as follows: animal studies, reviews, case reports, and studies without full-text or sufficient data.

2.3. Data extraction and quality assessment

Two authors extracted the data by a standardized collection form. All differences were resolved by discussion. In each study, the following information was extracted: first author, publication year, area, study design, number of cases and controls, effect sizes, and adjusted factors. The Newcastle-Ottawa Scale contained 9 terms with each term accounting for 1 score, and was widely chosen in meta-analyses to evaluate the methodological quality of case-

control deigned studies.[6] Thus, we used the Newcastle-Ottawa Scale to assess the methodological quality of included studies.

2.4. Statistical analysis

For the low incidence of EC, RR was roughly regarded as the OR in this study.[7] Pooled estimates of OR and 95% CI were used to evaluate the association between psychosocial factors and EC risk following the Mantel-Haenszel method.[8] A random-effects model was used as the pooled method, which considered both within-study and between-study variation. The heterogeneity between studies was estimated by Q test and I^2 statistic, and $I^2 > 50\%$ represented substantial heterogeneity. Egger test was used to detect publication bias.[9] All statistical analyses were performed using Stata SE12.0 software (StataCorp LP, College Station, TX), and all tests were sided with a significance level of 0.05.

3. Results

3.1. Study characteristics

The search strategy resulted in 1141 records: 186 from PubMed, 494 from Wanfang Database, 175 from SinoMed, and 286 from CNKI (Fig. 1). After excluding duplicated and irrelevant records, 27 studies were included in this meta-analysis with a total of 6951 EC cases and 7469 controls (Table 1).[10–36] In the included studies, most selected the healthy controls from the population. The studies were conducted in 12 provinces, covering the south, north, central, and northwest of China. Most studies were
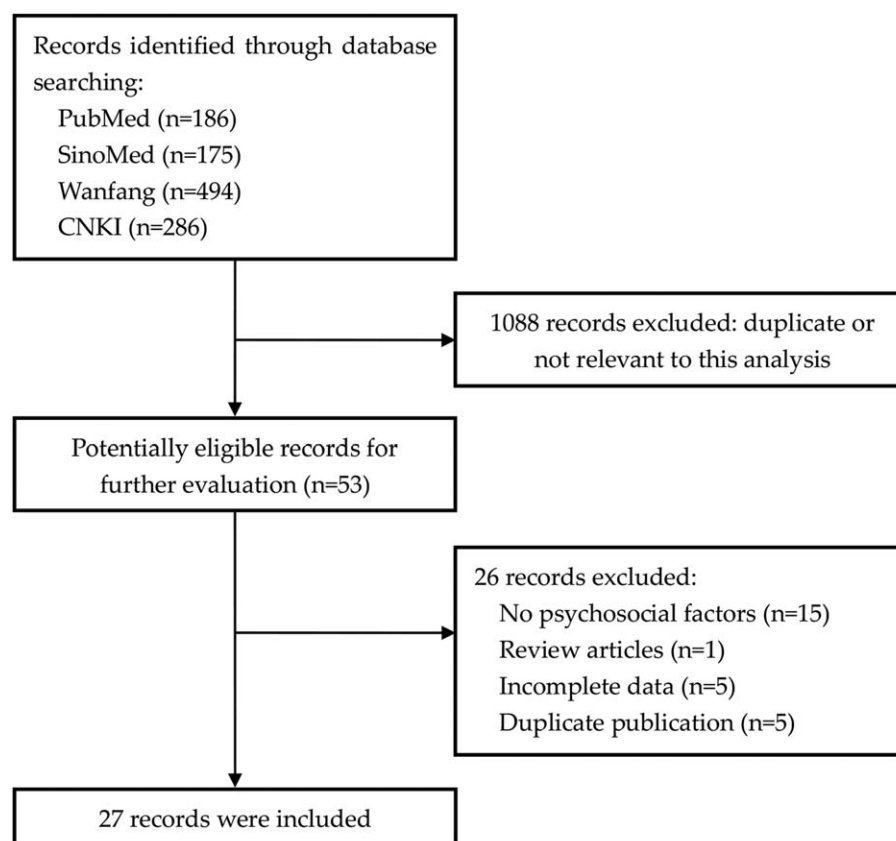

Figure 1. Flow chart of literature search.

Table 1

Characteristics of included studies.

Study	Location	Participants (cases/controls)	Design	Psychosocial factors	OR (95% CI)	Adjusted factors
Zhou CF 1999	Haian, Jiangsu	548 (274/274)	Population-based	Psychological trauma	2.119 (1.259–3.566)	Age, sex, residence, education, cooking, eating fresh food, intake of salted fish and meat, overeating and overdrinking, eating fast, eating irregularly, eating with anger, psychological stress
Chen ZY 2000	Rugao, Jiangsu	200 (100/100)	Population-based	Psychological trauma	10.49 (2.46–44.78)	Age, sex, residence
				Always in sulks	10.14 (1.84–55.66)	
				Irritable personality	1.92 (0.85–3.76)	
Zhang GS 2000	Cixian, Hebei	700 (350/350)	Population-based	Psychological trauma	2.86 (1.6–5.12)	Age, sex, residence
Qi GY 2001	Pizhou, Jiang	206 (103/103)	Population-based	Type A behavior	1.33 (0.97–1.83)	Age, sex, residence, eating fast, intake of salted food, intake of
				Psychological trauma	2.77 (1.42–5.41)	mildew food, garlic intake, fruit intake, smoking, gastric diseases
Ding BG 2003	Taixing, Jiangsu	601 (204/397)	Population-based	Psychological trauma	2.000 (1.258–3.168)	Age, sex, residence
				Outgoing personality	0.200 (0.072–0.423)	
Wang J 2005	Yakeshi, Neimenggu	150 (50/100)	Hospital-based	Psychological trauma	6.6015 (5.0274–7.2164)	Age, sex, residence, ethnicity, hospitalization, drinking, smoking, fruit intake, melena, harmonious neighborhood, marital status, illness or death of family members, income
				Interpersonal relationship	0.2216 (0.1379–0.4327)	
Li ZF 2007	Changzhi, Shanxi	402 (201/201)	Hospital-based	Psychological trauma	1.74 (1.01–3.00)	Age, sex, residence, ethnicity, hospitalisation, egg and meat intake, smoking, eating hot-food, eating hard food, EC family history
Dai LP 2009	Xinxiang, Henan	3422 (1711/1711)	Population-based	Psychological trauma	1.91 (1.26–2.88)	Age, sex, residence, eating fast, eating hot-food, eating smoked food, eating fried food, eating hard food, symptoms of upper gastrointestinal tract
Ding HM 2013	Tengzhou, Shandong	177 (86/91)	Hospital-based	Psychological trauma	2.36 (1.54–4.50)	Age, sex, residence, hospitalization, intake of meat and eggs, intake of soybean products, education, eating hot food, eating hard food, drinking, smoking, eating salted food, family history of esophageal cancer, seething, harmonious interpersonal relationship
				Always in sulks	1.84 (0.96–3.51)	
				Interpersonal relationship	0.38 (0.24–0.64)	
Duan PF 2015	Changzhi, Shanxi	308 (143/165)	Hospital-based	Psychological trauma	3.45 (1.84–6.50)	Age, sex, hospitalization, education, eating hot food, eating hard food, intake of salted food, gene-type
Zhu DS 2019	Zhucheng, Shandong	240 (120/120)	Hospital-based	Psychological trauma	1.395 (1.102–1.766)	Hospitalization
				Melancholy	2.277 (1.231–4.212)	
				Outgoing personality	0.644 (0.306–1.355)	
Lu JB 2000	Linzhou, Henan	704 (352/352)	Population-based	Type A behavior	1.82 (1.20–2.77)	Age, sex, residence
				Psychological trauma	1.44 (1.04–2.00)	
				Depression	3.552 (1.95–6.46)	
Liu XM 2001	Tianjin	330 (165/165)	Population-based	Psychological trauma	2.07 (1.18–3.61)	Age, sex, residence, ethnicity, education
Li SP 2001	Taixing, Jiangsu	1182 (591/591)	Population-based	Psychological trauma	1.96 (1.38–2.80)	Age, sex, residence
				Melancholy	5.52 (2.77–11.28)	
				Depression	2.80 (1.98–3.96)	
				Interpersonal relationship	0.73 (0.58–0.93)	
Liu YT 2002	Huaian, Jiangsu	244 (122/122)	Population-based	Psychological trauma	2.12 (1.22–3.69)	Age, sex, residence, ethnicity, marital status, education, job, income, smoking, drinking
				Introverted personality	4.74 (2.56–8.78)	

(continued)

Table 1

(continued).

Study	Location	Participants (cases/controls)	Design	Psychosocial factors	OR (95% CI)	Adjusted factors
Luo R 2008	Zhangye, Gansu	1034 (488/546)	Hospital-based	Psychological trauma	3.89 (1.71–8.78)	Education, smoking, drinking, intake of vegetables and hot-food, EC family history, psychological trauma
Huang LW 2014	Putian, Fujian	200 (40/160)	Population-based	Psychological trauma	1.31 (0.65–1.94)	Age, sex, residence, ethnicity, education, job, esophagitis history, cancer family history, smoking, drinking, psychological trauma, depression, intake of fruits, vegetables and red meat
Pan Y 2017	Huaian, Jiangsu	308 (154/154)	Population-based	Melancholy Psychological trauma	1.04 (0.38–1.93) 1.542 (0.612–3.885)	Age, sex, residence, smoked food intake, cancer family history, history of digestive diseases
Yuan Y 2001	Anyang, Henan	144 (48/96)	Population-based	Type A behavior Interpersonal relationship	1.475 (0.873–2.491) 0.15 (0.04–0.49)	Age, sex, residence
Wu T 2003	Wuhan, Hubei	116 (58/58)	Hospital-based	Type A behavior	1.60 (0.59–4.34)	Age, sex, hospitalization, smoking, intake of vegetables, fruits and smoked food
Zhao JK 2005	Yancheng, Jiangsu	290 (145/145)	Population-based	Depression Outgoing personality	10.24 (0.90–116.91) 0.728 (0.432–1.226)	Age, sex, residence, income, pollution, eating fast, sauce intake, tea intake, EC family history
Tan L 2010	Laiwu, Shandong	231 (113/118)	Hospital-based	Irritable personality	2.285 (1.234–4.521)	Hospitalization, intake of hot-food, mildew food and vegetables, pollution
Liu ZQ 2011	Jining, Shandong	324 (162/162)	Population-based	Depression Always in sulks	27.747 (7.152–149.853) 3.692 (2.678–4.684)	Age, sex, residence, smoking, drinking,eating fast, eating mildew food, EC family history
Xie ZP 2013	Nanning, Guangxi/Zhanjiang, Guangdong	397 (196/201)	Hospital-based	Irritable personality	2.141 (1.456–3.151)	Hospitalization, residence, smoking, drinking, intake of tea, hot-food, salted fish, fruits and vegetables
Zhai M 2014	Jining, Shandong	304 (152/152)	Population/ hospital-based	Melancholy Melancholy	1.693 (1.176–2.438) 1.726 (1.015–2.934)	Age sex
Zhang X 2018	Nanyang, Henan	1158 (573/585)	Hospital-based	Always in sulks	1.04 (0.83–4.01)	Hospitalization, smoking, intake of egg, milk, meat, fruits, salted food, hot-food, family history
Yan HQ 2019	Ningde, Fujian	500 (250/250)	Population-based	Type A behavior Depression	1.386 (0.972–1.976) 3.405 (2.232–6.768)	Residence, ethnicity, smoking, drinking, intake of hard food, hot-food, mildew food, fruits, vegetables, meat, egg, milk and soybean, family history

CI = confidence interval, EC = esophagus cancer, OR = odds ratio.

adjusted by age, sex and residence, and several studies were also adjusted by certain EC risk factors, like drinking, eating fast, and intake of hot and salted food. In quality assessment, the included studies had an average score of 7.09.

3.2. Psychological trauma and EC risk

Eighteen studies investigated the association between psychological trauma and EC risk, with a total of 5254 cases and 5702 controls. Individuals with history of psychological trauma had a higher risk of EC (OR: 2.36, 95% CI: 1.71–3.26; $I^2 = 88.9\%$) (Fig. 2). Egger test detected no obvious publication bias ($P = .158$).

3.3. Type A behavior and EC risk

Five studies investigated the association between Type A behavior and EC risk, with a total of 1164 cases and 1164 controls. Individuals with Type A behavior had a higher risk of

EC (OR: 1.40, 95% CI: 1.17–1.67; $I^2 = 0.0\%$) (Fig. 3). Egger test detected no obvious publication bias ($P = .172$).

3.4. Depression and EC risk

Five studies investigated the association between depression and EC risk, with a total of 1364 cases and 1369 controls. Individuals with depression had a higher risk of EC (OR: 4.00, 95% CI: 2.44–6.55; $I^2 = 56.9\%$) (Fig. 4). Egger test detected no obvious publication bias ($P = .057$).

3.5. Melancholy and EC risk

Five studies investigated the association between melancholy and EC risk, with a total of 1099 cases and 1224 controls. Individuals with melancholy had a higher risk of EC (OR: 2.06, 95% CI: 1.32–3.20; $I^2 = 66.0\%$) (Fig. 5). Egger test detected no obvious publication bias ($P = .654$).
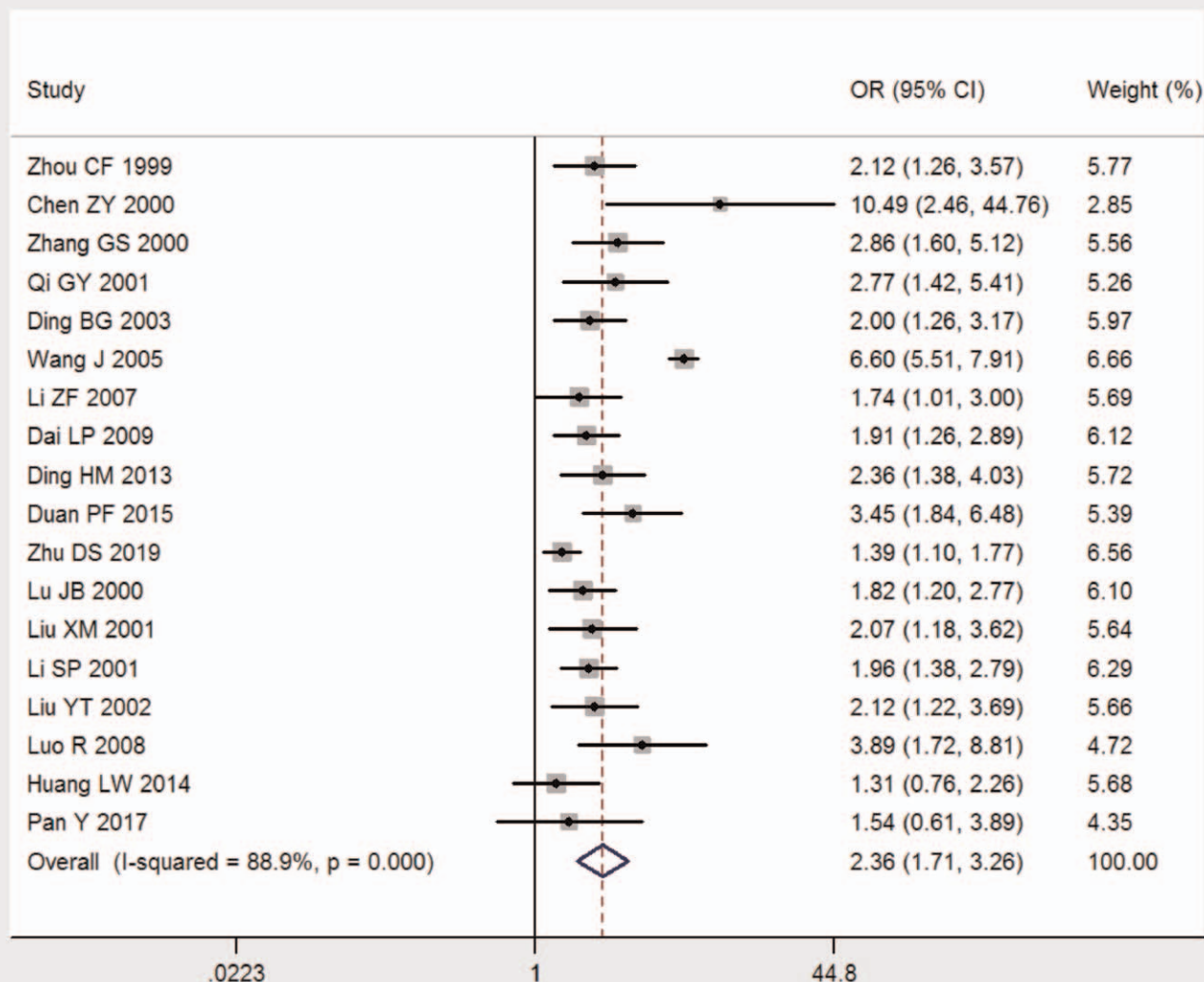

Figure 2. Forest plot of meta-analysis between psychological trauma and esophageal cancer risk.
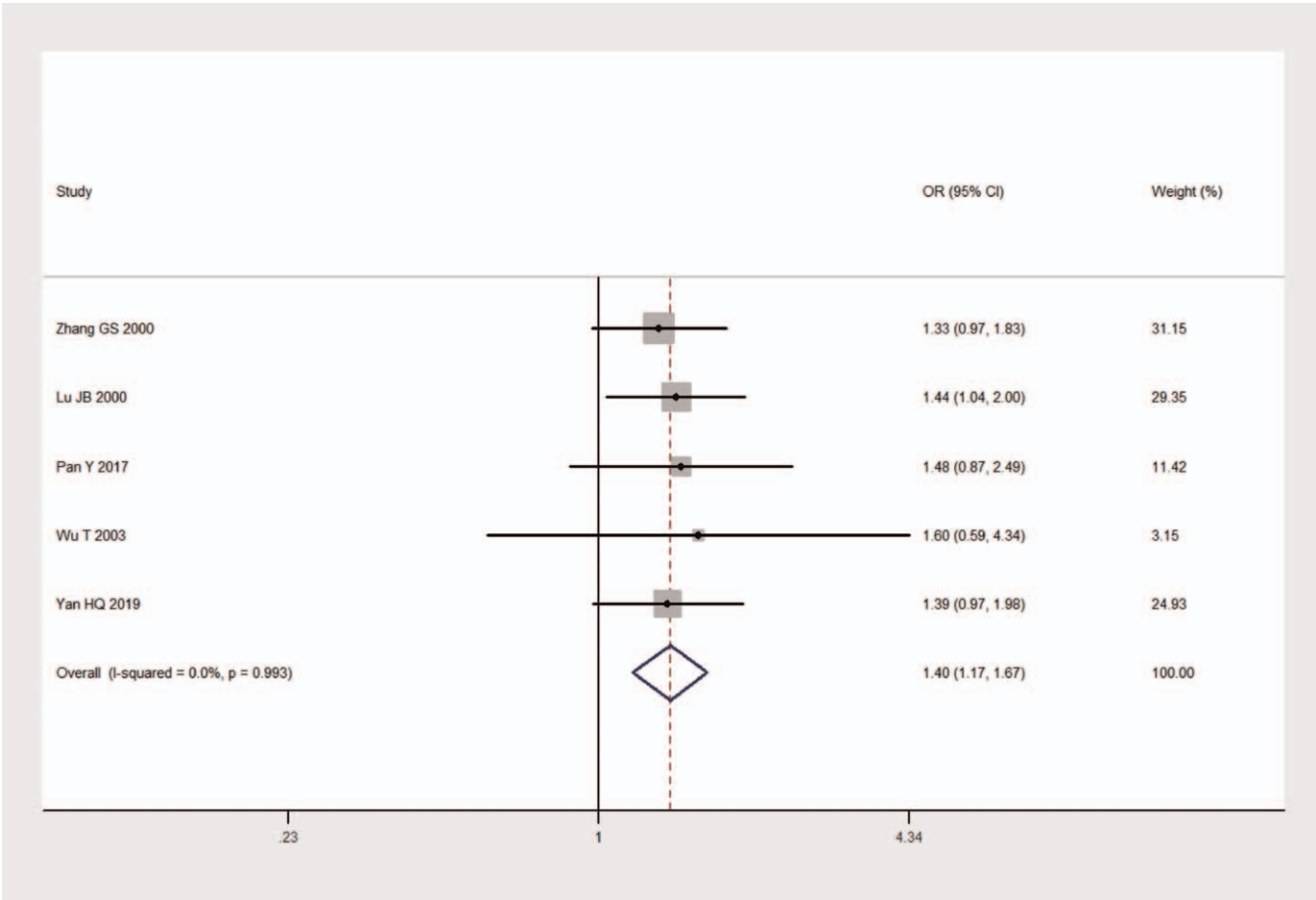
Figure 3. Forest plot of meta-analysis between Type A behavior and esophageal cancer risk.

3.6. Interpersonal relationship and EC risk

Four studies investigated the association between interpersonal relationship and EC risk, with a total of 775 cases and 878 controls. Individuals with good interpersonal relationship had a lower risk of EC (OR: 0.35, 95% CI: 0.17–0.70; $I^2 = 86.1\%$). Egger test detected no obvious publication bias ($P = .081$).

3.7. Always in sulks and EC risk

Four studies investigated the association between frequent sulks and EC risk, with a total of 921 cases and 938 controls. Individuals always in sulks had a higher risk of EC (OR: 2.49, 95% CI: 1.21–5.12; $I^2 = 77.3\%$). Egger test detected no obvious publication bias ($P = .637$).

3.8. Outgoing personality and EC risk

Four studies investigated the association between outgoing personality and EC risk, with a total of 591 cases and 784 controls. Individuals with outgoing personality had a lower risk of EC (OR: 0.39, 95% CI: 0.19–0.78; $I^2 = 77.0\%$). Egger test detected no obvious publication bias ($P = .511$).

3.9. Irritable personality and EC risk

Four studies investigated the association between irritable personality and EC risk, with a total of 409 cases and 419 controls. Individuals with irritable personality had a higher risk of EC (OR: 2.13, 95% CI: 1.58–2.89; $I^2 = 0.0\%$). Egger test detected no obvious publication bias ($P = .818$).

4. Discussion

The etiology of EC was still unclear, and several meta-analyses have focused on the epidemiological data to identify potential risk factors. Though this method, anticancer recommendations would be made and prevent the cancer from the source. For example, increased consumption of green tea, citrus fruit, and beverage could reduce EC risk, as well as micronutrients of total iron, zinc, folate, and fiber.[37–41] On the other hand, high intake of hot food and meat could increase the risk.[42]

However, few studies focused on the effects of psychosocial factors in the development of EC, especially among the high-risk cohorts like Chinese. Barrett esophagus was a chronic esophageal condition in association with an increased risk of EC. The chronic condition negatively impacted the patients' life quality, and was associated with increased levels of psychological distress.[43] Thus, we thought there existed a potential relationship between psychosocial factors and later EC risk. In this meta-analysis, we indicated risk factors of psychological trauma, Type A behavior, depression, melancholy, always in sulks and irritable personality in the development of EC, and protective factors of interpersonal relationship and outgoing personality.
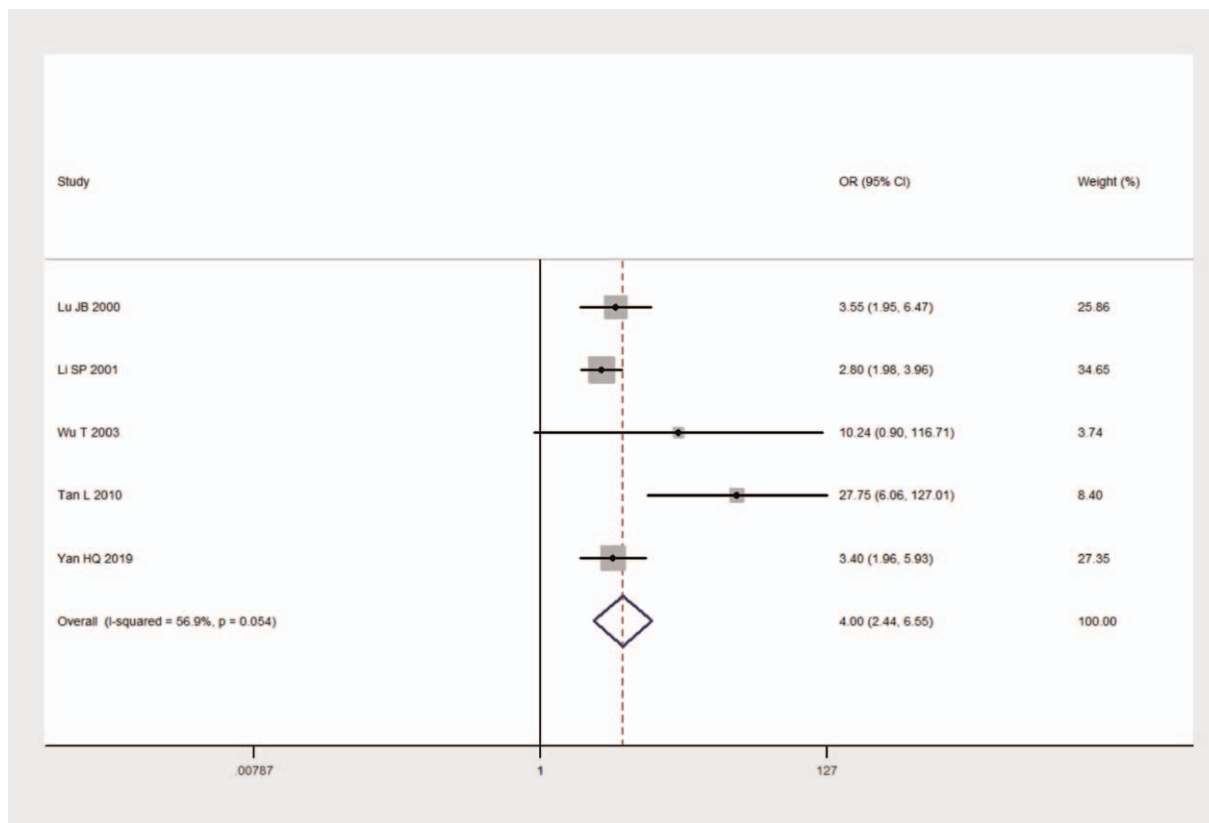
Figure 4. Forest plot of meta-analysis between depression and esophageal cancer risk.
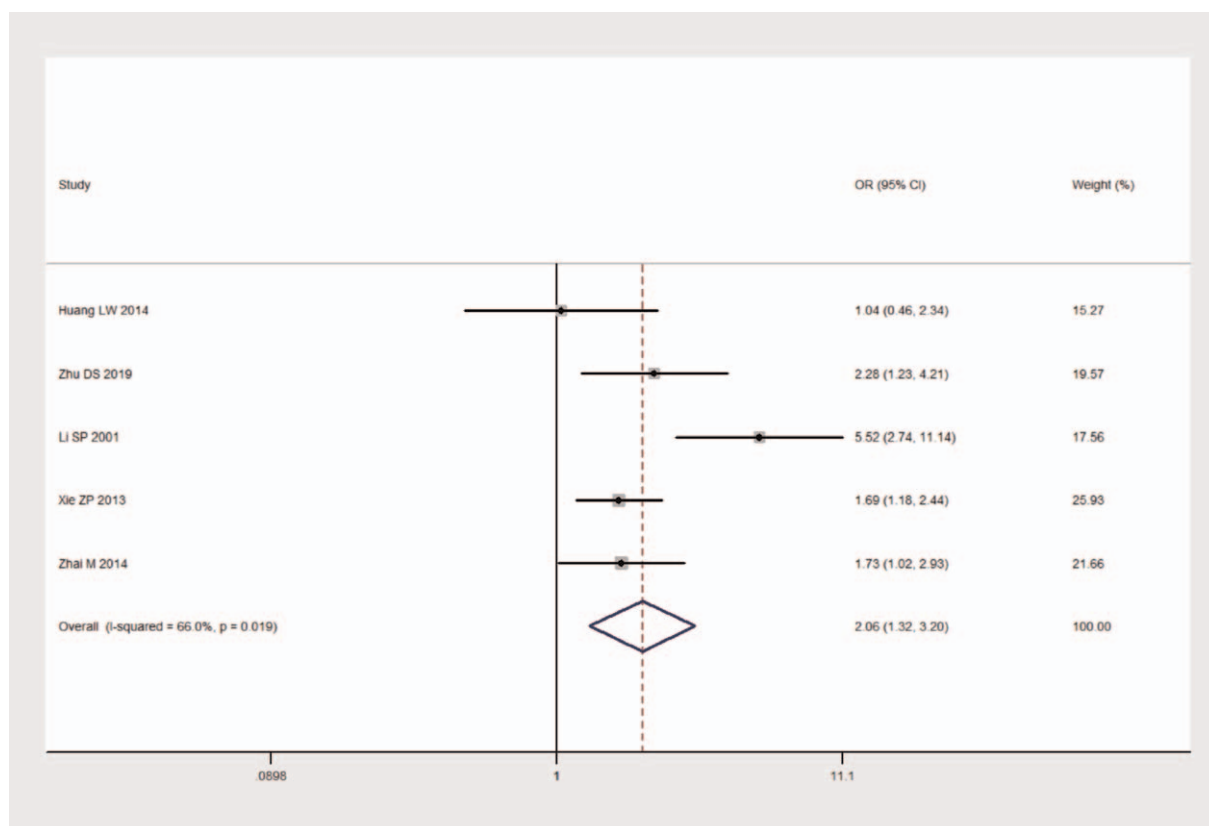

Figure 5. Forest plot of meta-analysis between melancholy and esophageal cancer risk.

To our knowledge, this was the first meta-analysis to investigate the association between psychosocial factors and EC risk. Second, EC was prevalent in China, and there were enough cases and studies for the meta-analysis to illuminate the relationship. Third, during the past decades of rapid economic development, the Chinese society experienced a huge change, which caused an imbalance among different social classes. Life events like death of family members, job frustration, and family or interpersonal dissension might make huge effects on certain classes and affect individual health. In our meta-analysis, we found a significant association between psychosocial factors and EC risk. For the individuals with psychosocial risk factors, physicians should pay more attention to EC screening.

Several limitations in this study should be also considered. First, the number of cases and controls in each study was relatively small. Second, the obvious heterogeneity between studies was observed. Third, all included studies were case-control designed. Large-scale prospective designed studies were needed to warrant our findings.

In conclusion, this meta-analysis suggested a potential association between psychosocial factors and EC risk. For the individuals with psychosocial risk factors, physicians should pay more attention to EC screening.

Author contributions

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Software: Li-Li Xiang.
Supervision: Li-Li Xiang.
Visualization: Jie Xiang.
Writing – original draft: Lei Lei, Jie Xiang.
Writing – review & editing: Lei Lei, Xu Li.

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