

Supplementary Materials

Table S1: The search strategy of the umbrella meta-analysis.

Category	Search Terms
Smoking	"smoking" OR "smoked" OR "smokeless" OR "water pipeline smoking" OR "tobacco" OR "chewing tobacco" OR "betel quid" OR "betel nut" OR "areca nut" OR "dissolvable tobacco"
Alcohol	"alcohol" OR "drinking" OR "light drinking" OR "moderate drinking" OR "heavy drinking" OR "occasional drinking" OR "long term drinking"
Oral cancer	"oral cancer" OR "oral carcinoma" OR "oral squamous cell carcinoma" OR "OSCC" OR "mouth cancer" OR "oral cavity cancer" OR "lip cancer" OR "tongue cancer" OR "buccal cancer" OR "floor of mouth cancer" OR "gingival cancer" OR "oropharyngeal cancer" OR "head and neck cancer" OR "head and neck squamous cell carcinoma" OR "HNSCC"
Meta-analysis	"meta-analysis" OR "Meta-analysis" OR "meta-analysis" OR "Meta analysis" OR "Meta-Analysis" OR "meta-analyses" OR "meta-analyze" OR "Systematic Review" OR "Systematic Reviews as Topic" OR "Meta-Analysis as Topic"
Combination	("smoking" OR "smoked" OR "smokeless" OR "water pipeline smoking" OR "tobacco" OR "chewing tobacco" OR "betel quid" OR "betel nut" OR "areca nut") AND ("alcohol" OR "drinking" OR "light drinking" OR "moderate drinking" OR "heavy drinking" OR "occasional drinking" OR "long term drinking") AND ("meta-analysis" OR "Meta-analysis" OR "meta analysis" OR "Meta analysis" OR "Meta-Analysis" OR "meta-analyses" OR "meta-analyze" OR "Systematic Review" OR "Systematic Reviews as Topic" OR "Meta-Analysis as Topic") AND ("oral cancer" OR "oral carcinoma" OR "oral squamous cell carcinoma" OR "OSCC" OR "mouth cancer" OR "oral cavity cancer" OR "lip cancer" OR "tongue cancer" OR "buccal cancer" OR "floor of mouth cancer" OR "gingival cancer" OR "oropharyngeal cancer" OR "head and neck cancer" OR "head and neck squamous cell carcinoma" OR "HNSCC")

Table S2: Excluded meta-analyses.

Study	Reason for Exclusion
Thomas (1993) [1]	No overall quantification for oral cancer
Kulothungan (2024) [2]	No specific data for oral cancer
Batistella (2022) [3]	Only prevalence reported without OR or RR
Khalifeh. (2024) [4]	Reduction of oral cancer measured after smoking cessation
Ghasemiesfe (2019) [5]	The only study on marijuana (no comparability)
Lee (2013) [6]	Switch from cigarettes to snus
Lubin (2009) [7]	Outcome not measured in direct OR or RR
Li (2011) [8]	The only alcohol study measured the association in OR/lack of comparability

Table S3: Methodological quality of included systematic reviews and meta-analyses using AMSTAR 2.

Author [ref]	Q1	Q2 (C)	Q3	Q4	Q5	Q6	Q7 (C)	Q8	Q9 (C)	Q10	Q11 (C)	Q12	Q13 (C)	Q14	Q15 (C)	Q16	Level of quality
Asthana (2019) [9]	Y	PY	Y	Y	Y	PY	N	Y	PY	N	Y	N	PY	Y	PY	Y	Low
Bagnardi (2015) [10]	Y	PY	Y	Y	Y	PY	N	Y	PY	N	Y	PY	Y	Y	PY	Y	Low
Choi (2018) [11]	Y	N	Y	Y	Y	PY	N	Y	Y	N	Y	N	PY	Y	N	Y	Critically low
Corrao (1999) [12]	Y	N	Y	Y	Y	PY	PY	Y	Y	N	Y	PY	Y	Y	Y	Y	Moderate
Dwivedi (2024) [13]	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	PY	PY	Y	Y	Y	Moderate
Gandini (2008) [14]	Y	N	Y	Y	N	N	N	Y	Y	N	Y	PY	Y	Y	Y	Y	Moderate
Guha (2014) [15]	Y	N	Y	Y	Y	Y	N	Y	PY	N	Y	PY	Y	Y	Y	Y	Low
Gupta (2014) [16]	Y	N	Y	Y	Y	Y	Y	Y	PY	N	Y	N	PY	Y	Y	Y	Moderate
Jayasekara (2016) [17]	Y	N	Y	Y	Y	Y	N	Y	PY	N	Y	N	PY	Y	Y	Y	Low
Jun (2024) [18]	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	PY	PY	Y	Y	Y	Moderate
Khan (2014) [19]	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	PY	PY	Y	N	Y	Low
Khan (2019) [20]	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	PY	PY	Y	N	Y	Low
Mariano (2022) [21]	Y	Y	Y	Y	Y	Y	PY	Y	Y	N	Y	PY	PY	Y	PY	Y	High
Mello (2019) [22]	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	High
Mu (2021) [23]	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	PY	PY	Y	Y	Y	Moderate
Petti (2013) [24]	Y	N	Y	Y	Y	Y	N	Y	PY	N	Y	N	Y	Y	Y	Y	Low
Prasad (2019) [25]	Y	N	Y	Y	N	N	N	Y	N	N	Y	N	N	Y	N	Y	Critically low
Rahman (2003) [26]	Y	N	Y	Y	N	N	N	Y	N	N	Y	N	PY	Y	Y	Y	Critically low
Sadri (2007) [27]	Y	N	Y	Y	Y	Y	N	Y	N	N	Y	N	N	Y	N	N	Critically low
Sinha (2016) [28]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	PY	PY	Y	Y	Y	High
Thomas (2007) [29]	Y	N	Y	PY	N	N	N	Y	N	N	Y	N	N	PY	N	Y	Critically low
Tramacere (2010) [30]	Y	N	Y	PY	Y	N	N	Y	N	N	Y	N	PY	Y	N	Y	Low

Table S3: continue

Turati (2010) [31]	Y	N	Y	Y	N	N	N	Y	PY	N	Y	PY	PY	Y	N	Y	Low
Turati (2013) [32]	Y	N	Y	Y	Y	Y	N	Y	PY	N	Y	PY	PY	Y	Y	Y	Moderate
Waziry (2017) [33]	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	PY	PY	Y	N	Y	Low
Weitkunat (2007) [34]	Y	N	Y	Y	N	N	N	Y	PY	N	Y	PY	PY	Y	PY	Y	Low
Xu (2024) [35]	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	PY	PY	Y	PY	Y	Moderate
Zhang (2015) [36]	Y	N	Y	Y	Y	Y	N	Y	N	N	Y	N	PY	Y	Y	Y	Low

(C): critical domain; PY: partially yes; N: no; Y: yes. Q1: PICO components in research question; Q2: protocol registered prior to review; Q3: justification for study designs; Q4: comprehensive literature search; Q5: study selection in duplicate; Q6: data extraction in duplicate; Q7: list of excluded studies with justification; Q8: included studies described in adequate detail; Q9: satisfactory technique for risk of bias assessment; Q10: funding sources reported; Q11: appropriate statistical combination; Q12: impact of RoB on results assessed; Q13: RoB accounted for in interpretation; Q14: heterogeneity discussed; Q15: publication bias investigated; Q16: conflict of interest reported.

Table S4: Corrected Covered Area (CCA) overlap analysis results by exposure category.

Category	k	r	Sci	CCA (%)	Interpretation
Overall	26	208	531	6.21%	Moderate
Smoking (smoked + smokeless)	16	151	301	6.62%	Moderate
Smoked	10	71	95	3.76%	Low
Smokeless	10	124	249	11.20%	High
Alcohol	6	63	187	39.37%	Very High
Alcohol + Smoking	4	34	43	8.82%	Moderate

k = number of meta-analyses; r = number of unique primary studies; Sci = total citations including cross-MA duplicates. Formula: $CCA = (Sci - r) / [r \times (k - 1)] \times 100$. CCA thresholds: slight <5%, moderate 5–10%, high 10–25%, very high $\geq 25\%$.

Table S5: Causal relationship assessment using Bradford-Hill's criteria for the association of smoking and alcohol with oral cancer.

Bradford-Hill Criterion	Assessment
1. Strength of association	OR for smoking: 3.80; smokeless: 5.28; alcohol: 2.47; combined exposure: 10.16. Strong associations, especially for smokeless tobacco, heavy drinking, and combined smoking/alcohol.
2. Consistency	27 meta-analyses covering >500 studies from multiple regions confirm the association. Supported by IARC (Group 1 carcinogens for both tobacco and alcohol).
3. Specificity	Smoking and alcohol are risk factors for many cancers, but oral cancer shows strong and consistent associations, particularly for smokeless tobacco and heavy alcohol. Limitation: lack of absolute specificity due to multifactorial etiology.
4. Temporality	Cohort studies confirm exposure precedes cancer onset. Dose-response relationships (e.g., heavy drinking RR=5.4) further support temporality.
5. Biological gradient (Dose-response)	Smoking: risk increases with duration/intensity (e.g., OR=20.0 for >10x/day chewing). Alcohol: light (OR=1.37), moderate (OR=2.22), heavy (OR=4.94). Synergistic effect (OR=10.16) shows multiplicative risk.
6. Plausibility	Well-established mechanisms: Tobacco: DNA adducts, oxidative stress, immunosuppression. Alcohol: acetaldehyde, solvent effect for carcinogens, nutrient deficiencies. Combined: enhanced mutagenesis.
7. Coherence	Matches experimental data (e.g., mutagenicity of acetaldehyde), histopathology, and known biology of oral mucosa.
8. Experiment	Smoking and alcohol cessation reduce oral cancer risk. Animal models confirm carcinogenicity.
9. Analogy	Similar effects seen in cancers of the lung, esophagus, larynx, etc., due to similar exposures.
Conclusion	The evidence fulfills nearly all the criteria, especially strength, consistency, dose-response, plausibility, and temporality. The evidence supports a causal relationship between smoking, alcohol, and oral cancer, particularly for smokeless tobacco, heavy alcohol use, and their synergistic effects.

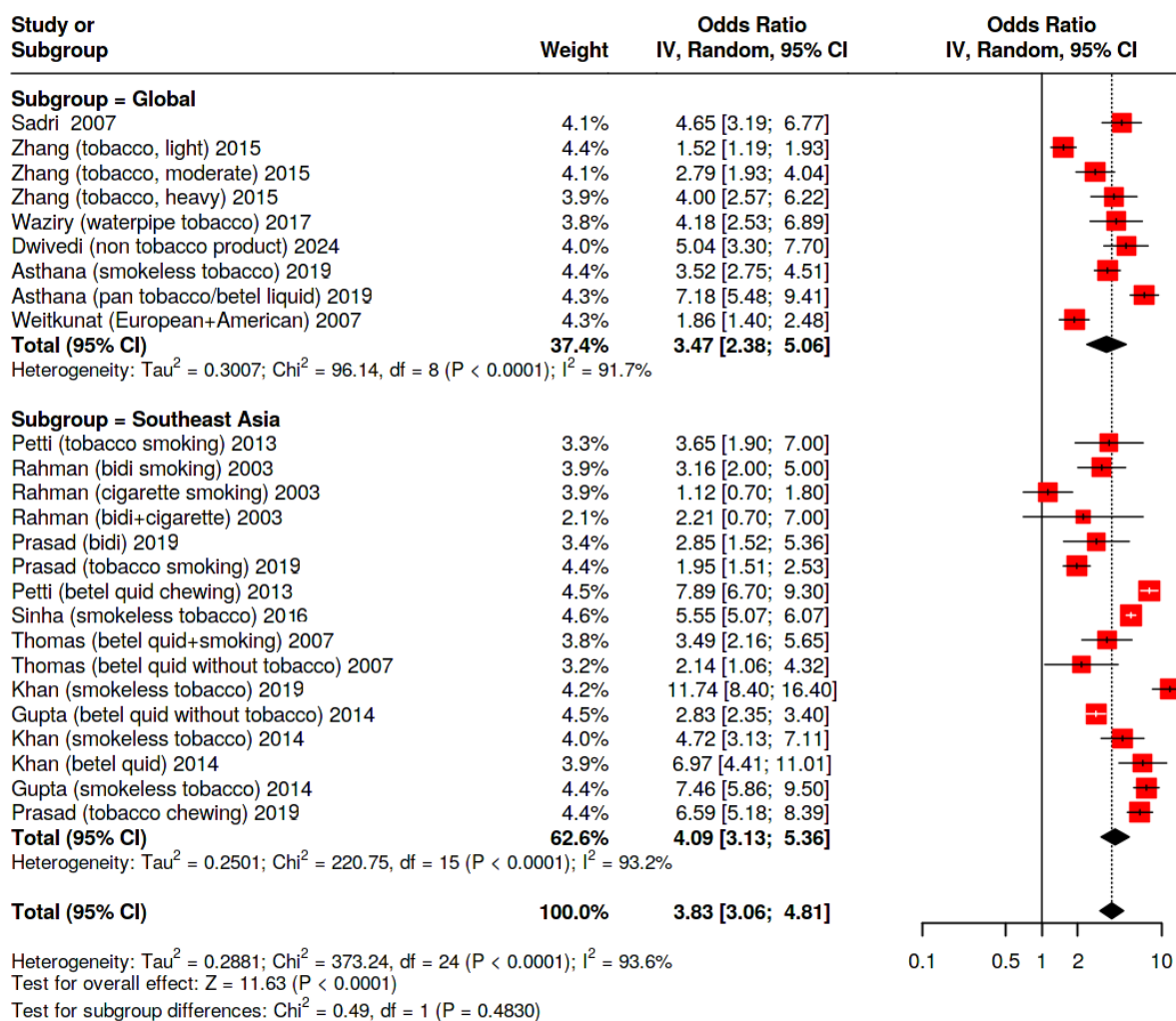


Figure S1: Forest plot of the association between smoking and oral cancer comparing global data with Southeast Asia.

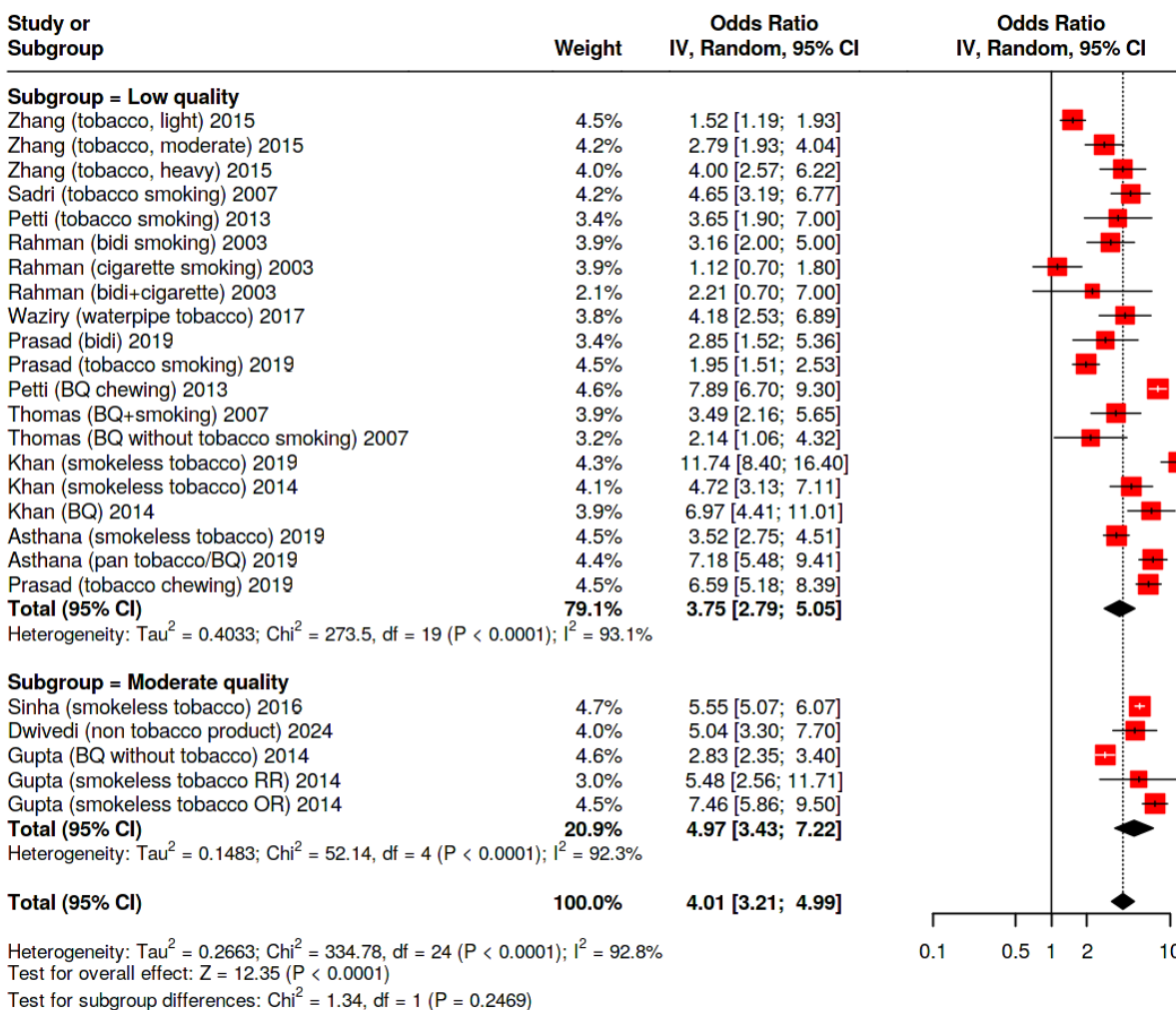


Figure S2: Forest plot of the association between smoking and oral cancer comparing low and moderate quality studies.

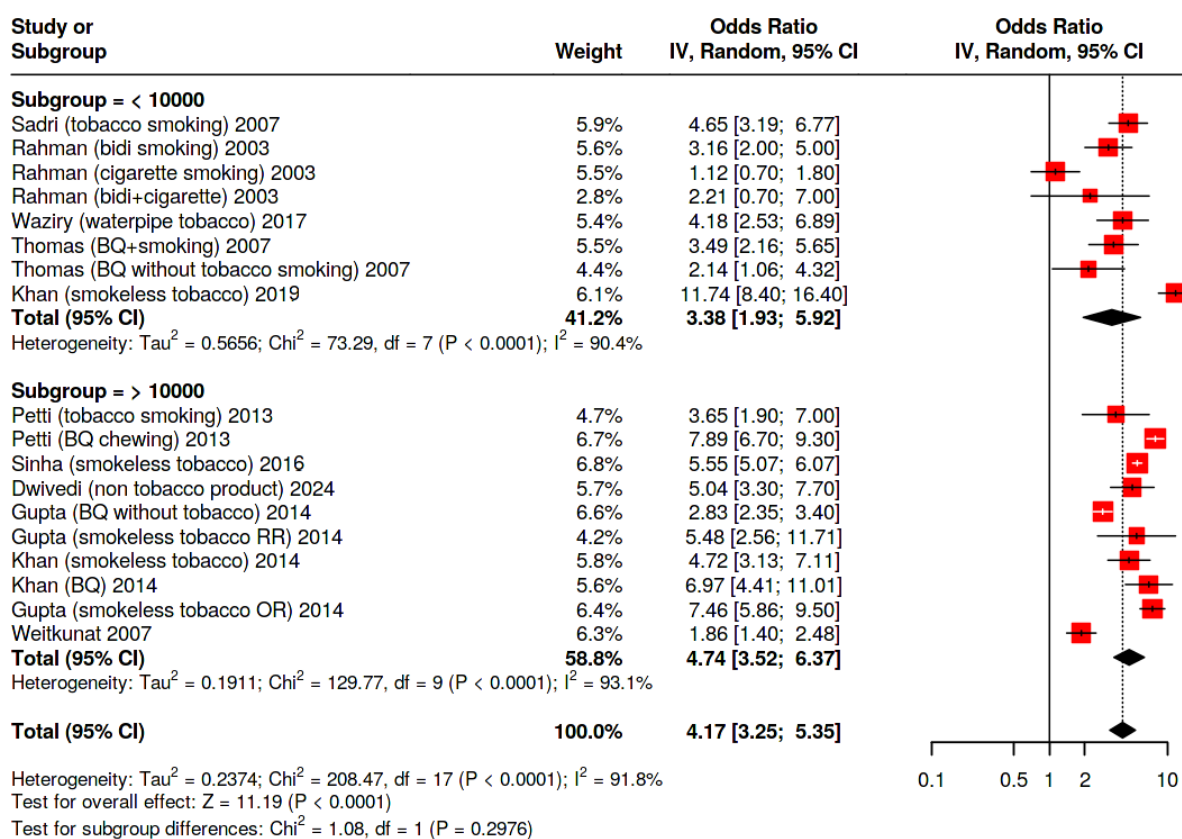


Figure S3: Forest plot for the association between smoking and oral cancer comparing small vs. large sample studies.

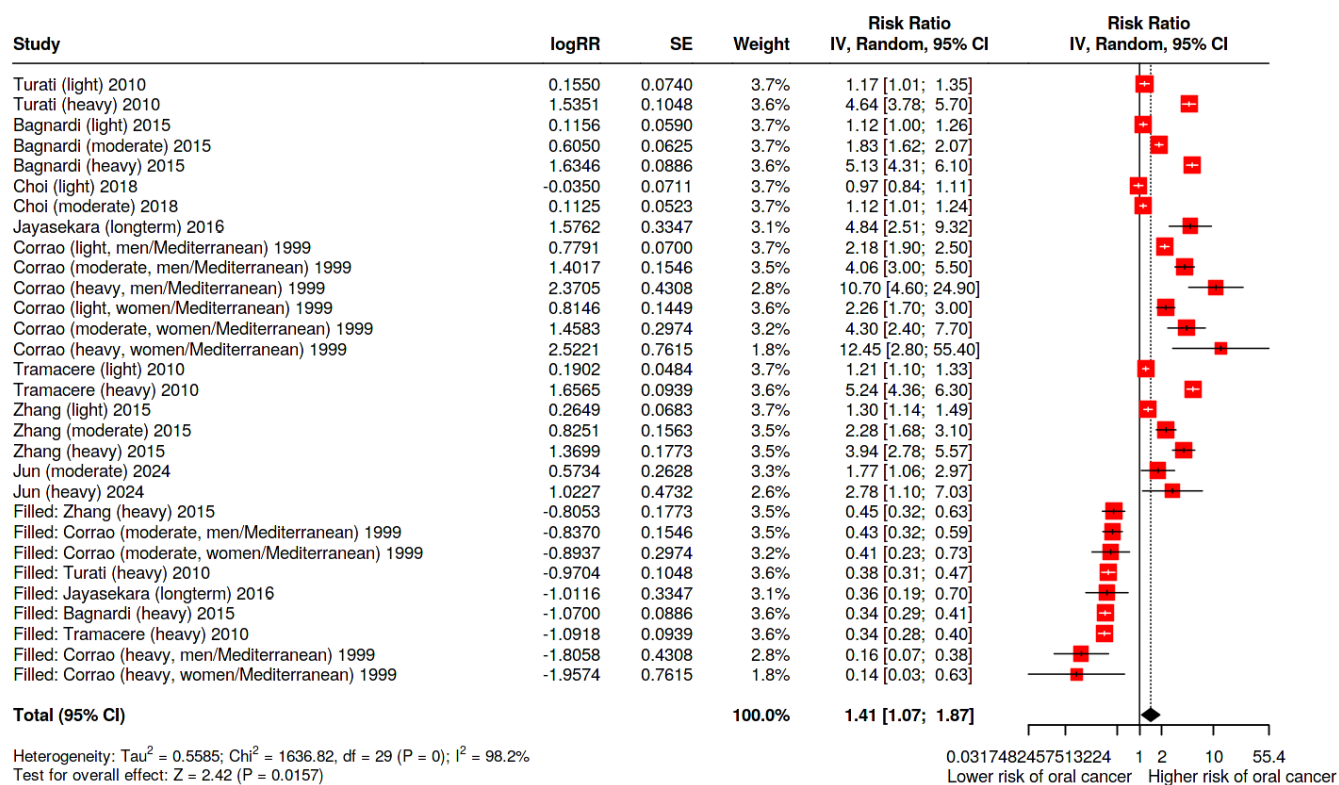


Figure S4: Trim and fill analysis for the association between alcohol consumption and oral cancer in cohort studies.

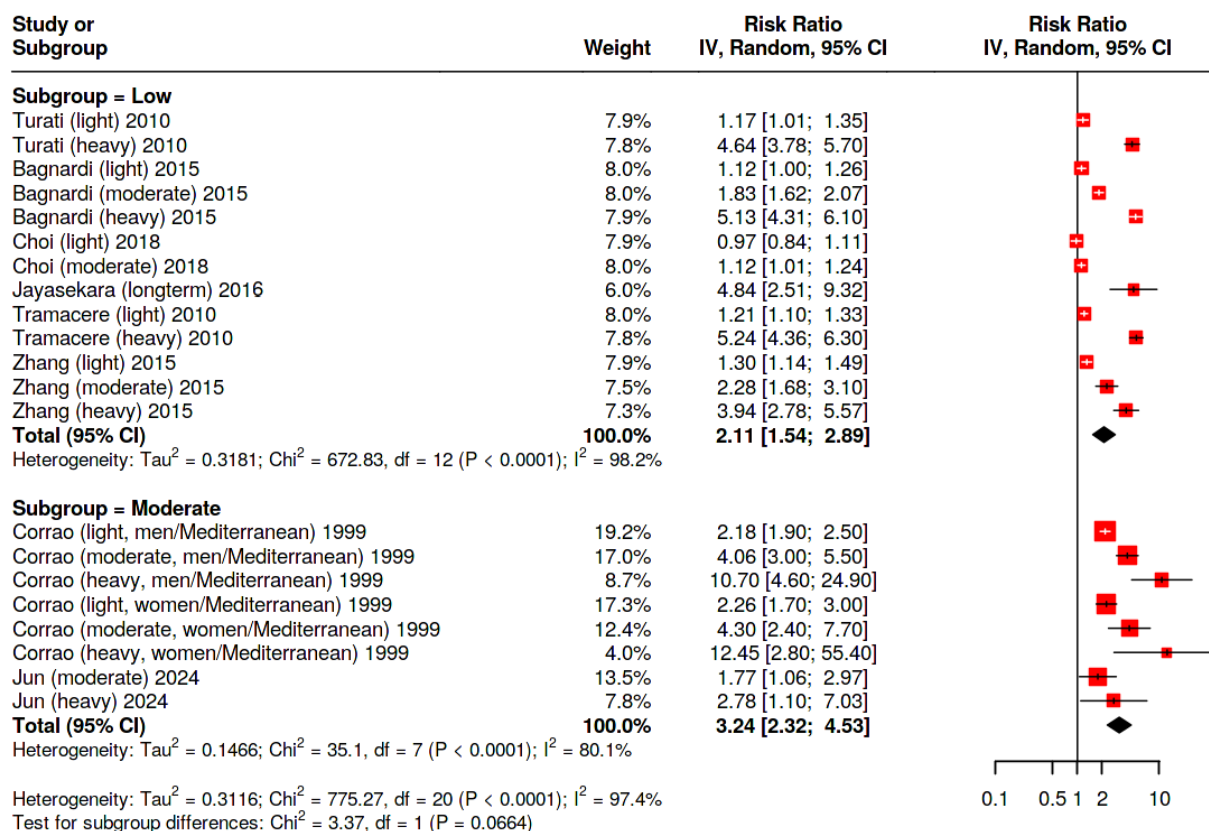


Figure S5: Forest plot of the association between alcohol consumption and oral cancer comparing low and moderate quality papers.

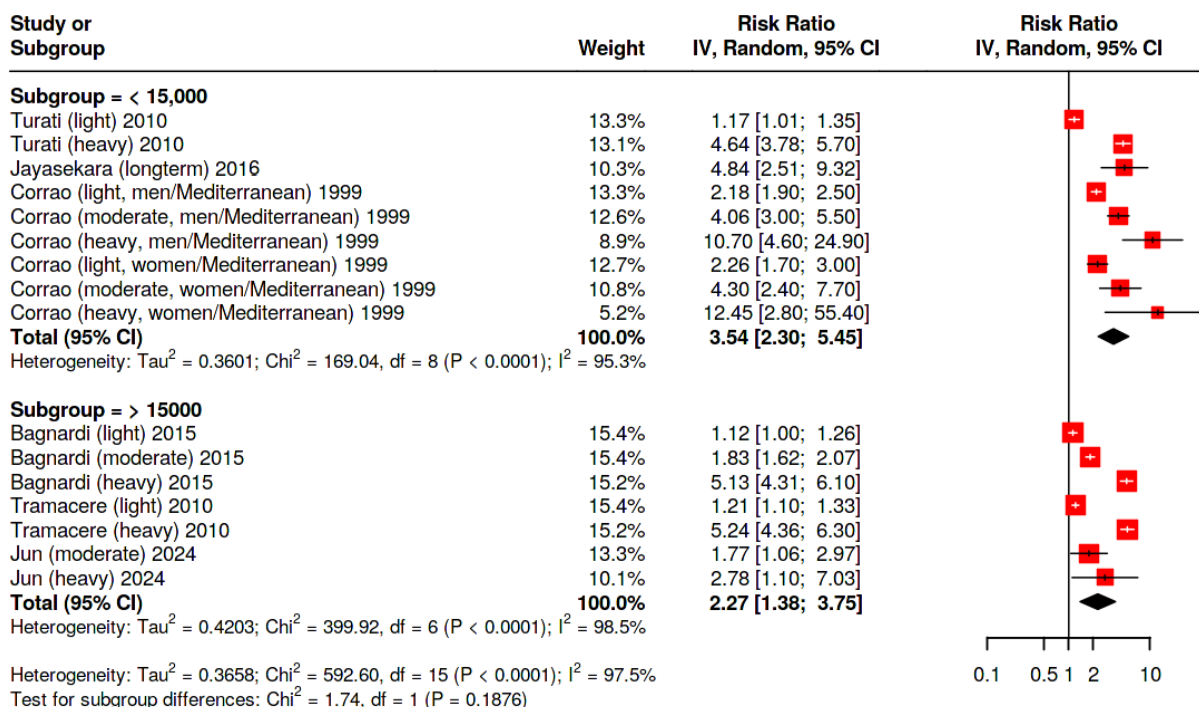


Figure S6: Forest plot of the association between alcohol consumption and oral cancer comparing small and large sample sized papers.

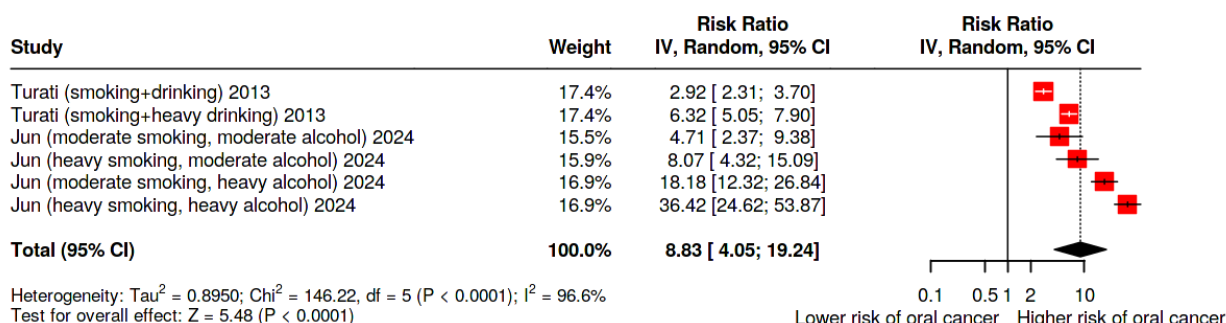


Figure S7: Forest plot of the association between combined smoking and alcohol intake with oral cancer.

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