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The waterpipe smoking and human health: a systematic review and meta-analysis of 191 observational studies

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Abstract

Background While growing evidence highlights the harmful effects of waterpipe smoking (WPS), detailed information about its association to chronic diseases remains limited. This systematic review and meta-analysis exploring the association between WPS and various health conditions.

Methods A systematic search of MEDLINE (via PubMed), Embase, Scopus, and Web of Science was conducted from inception to January 2025. Eligible observational studies on WPS and health outcomes were selected through a duplicate, independent process. Data extraction, including study details, participant characteristics, methods, and results, was performed independently by two reviewers using a standardized form. Methodological quality was assessed using the Newcastle–Ottawa scale (NOS), and studies were classified as high, moderate, or poor quality. The GRADE approach was applied to evaluate evidence certainty for each outcome, considering factors such as study design, risk of bias, consistency, precision, and publication bias.

Results A total of 191 studies with 807,174 participants were included, comprising 98 case–control, 77 cross-sectional, and 16 cohort studies from 24 countries. The median number of studies analyzed per outcome was 5, with a range of 3 to 30. Among the 62 outcomes evaluated, 31 (50%) demonstrated statistically significant effect sizes based on a random-effects model, with stroke, coronary artery disease (CAD), and cancer mortality exhibiting a significant prediction interval. Credibility evaluations identified low-quality evidence for birth weight, CAD, and cardiovascular and cancer mortality, whereas the evidence for the remaining outcomes was graded as very low quality. Significant associations were found between WPS and several health outcomes: gastric cancer, lung cancer, bladder cancer, esophageal cancer, CAD, stroke, diabetes, metabolic syndrome, overall mortality, cardiovascular mortality, cancer mortality, infertility, sperm normal form, sperm DNA fragmentation, chronic bronchitis, cough, sputum, low birth weight (LBW), spirometry parameters, and several dental health indicators.

Conclusion This study reveals strong links between WPS and adverse health outcomes, but low evidence quality calls for rigorous research and public health interventions to mitigate its effects.

Keywords Waterpipe tobacco smoking, Health effects, Systematic review, Meta-analysis

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Background

Waterpipe smoking (WPS) has steadily increased among all age groups, especially among young adults in the past two decades [1–3]. A systematic review in 2018, which included 129 studies reporting 355 estimates for 68 countries, shows sustained increasing patterns of WPS over time. Trends ranged between 0.3 and 1.0% per year among young adults in the United States (US), with some of the largest increasing trends (2.9%) seen among youth in Jordan [4].

According to the latest data from the National Youth Tobacco Survey in the USA in 2019 and the Global Youth Tobacco Survey (GYTS) in 2010–2019, the highest WPS prevalence rates were in the Eastern Mediterranean (10.7%) and European regions (10.9%), followed by South-East Asia (5.4%), the Americas (4.2%), Africa (4.2%), and the Western Pacific (1.9%). While young adults in the Eastern Mediterranean and European regions are the most affected by the WPS epidemic, its consumption today can be observed worldwide. Additionally, WPS has become prevalent among women and older adults, though these findings have primarily come from nonrepresentative samples [5].

Two comprehensive reviews are available on the effects of WPS on health-related outcomes [6, 7]. They elucidated that WPS is a risk factor for respiratory diseases, oral cancer, lung cancer, LBW, metabolic syndrome, cardiovascular disease (CVD), and mental health issues [6, 7]. However, the evidence available at the time was insufficient to either rule out or confirm an association between WPS and several important health-related outcomes, such as gastric cancer, bladder cancer, periodontitis, chronic bronchitis, sperm parameters, and lipid and hormone profiles. Therefore, the objective of this overview is to update and report the most precise and comprehensive estimates of the effects of WPS on health-related outcomes.

Methods

We adhered to the standard protocol for conducting the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [8]. We recorded the protocol for this systematic review and meta-analysis in the international prospective register of systematic reviews (PROSPERO) under CRD42023409108.

Search strategy and study selection

We systematically searched MEDLINE (via PubMed), Embase, Scopus, and Web of Science from their beginnings up to January 2025. The keywords employed in the search strategy are displayed in supplemental Table 1. Furthermore, we conducted a search for the reference lists and citations of selected articles to reduce the chance of missing any publications. We searched the gray literature using Google Scholar (https://scholar.google.com/) and tobacco-related sites. There were no limitations regarding the publication date or the language of the articles. Six independent researchers (Sh. R., H. G.-H., F. L., S. A., F. G. and Z. M.-P.) reviewed and compared titles, abstracts, and full texts based on predetermined eligibility criteria to identify potentially suitable studies. Any disagreements between the researchers were resolved through group discussion. If disagreements persisted, they were resolved through discussion with the third author (M. S.).

Eligibility criteria

Studies included in this meta-analysis were eligible if they met the following criteria: (1) observational studies (i.e., cohort, case control, and cross-sectional); (2) the exposure of interest was WPS; (3) the outcome was any health-related condition including those related to cardiovascular, cancer, metabolic, kidney, musculoskeletal, or metabolic risk markers; and (4) reported associations in the form of risk ratios (RRs), hazard ratios (HRs), odds ratios (ORs), standardized β coefficient or mean difference (MD) with 95% confidence intervals (CIs) between WPS (as exposure) and the risk of disease, or the mean of metabolic markers (as outcome). We excluded case reports, case series, and studies without a control group (non-smokers), studies not conducted in humans, qualitative studies, and abstracts. We also excluded cross-sectional studies that only calculated the prevalence of WPS without any outcome. Additionally, we excluded studies that assessed WP use for nontobacco smoking purposes (e.g., marijuana smoking and other recreational drug use), did not distinguish WPS from other forms of smoking, or did not report any measure of association. In the case of multiple reports on the same population or subpopulation, we considered the estimates from the most recent or most informative report.

Assessment and grading of evidence

We assessed the methodological quality of the included studies using the Newcastle–Ottawa scale (NOS). The NOS comprises three domains: selection, comparability, and outcome or exposure, depending on the study type. According to this scale, case–control and cohort studies can receive a maximum of 9 points, while cross-sectional studies can receive a maximum of 10 points. Methodological quality is categorized into three levels: poor, moderate, and high. Studies with 7 or more points for case–control and cohort studies, and 8 or more points for cross-sectional studies, were classified as high quality. Any discrepancies were resolved by consensus or discussion with another investigator (M. S.).

Table 1 Summary risk estimates of the association between waterpipe smoking and health-related outcomes

Outcome	Studies (*N*)	Participant (*N*)	Type of effect size metric	Effect size (95% *CI*)	I^2	95% *CI* prediction intervals	Publication bias	Largest study effect size	Small study effect	Certainty of the evidence (GRADE)
Anthropometric indices										
BMI	32	10,001	SMD	0.08 (−0.03, 0.20)	78.72	(−0.50, 0.66)	No	0.24 (−0.10, 0.57)	Yes	Very low
WC	8	4652	SMD	0.11 (−0.11, 0.33)	87.76	(−0.63, 0.85)	NA	0.34 (0.22, 0.46)	Yes	Very low
Weight	20	4198	SMD	0.43 (0.16, 0.70)	93.72	(−1.11, 2.01)	Yes	1.74 (1.51, 1.96)	No	Very low
Cancers										
Gastric	6	3764	OR	2.11 (1.02, 4.40)	84.47	(0.18, 25.34)	NA	1.86 (1.42, 2.42)	Yes	Very low
Lung	7	11,272	OR	2.61 (1.28, 5.34)	94.23	(0.22, 31.28)	NA	1.63 (1.30, 2.05)	No	Very low
Bladder	7	9131	OR	1.57 (1.14, 2.18)	72.08	(0.61, 4.02)	NA	1.42 (1.11, 1.82)	No	Very low
Esophageal	7	4783	OR	2.95 (1.36, 6.40)	92.42	(0.18, 48.15)	NA	2.06 (1.72, 2.47)	No	
Cardiovascular disease risk										
CVD	5	32,842	aOR	1.14 (0.95, 1.36)	12.77	(0.73, 1.77)	NA	1.29 (0.73, 2.27)	Yes	Very low
CAD	8	66,784	OR	1.56 (1.36, 1.79)	23.17	(1.17, 2.07)	NA	1.67 (1.25, 2.23)	No	Low
Stroke	5	6606	Crude OR	2.66 (2.02, 3.49)	0	(1.71, 4.13)	NA	1.06 (0.14, 7.97)	No	Very low
	4	2734	aOR	3.10 (2.20, 4.39)	0	(1.44, 6.65)	NA	2.47 (2.52, 4.01)	No	
SBP	21	19,491	SMD	0.14 (−0.37, 0.65)	99.07	(−2.38, 2.66)	No	0.01 (−0.06,0.06)	No	Very low
DBP	21	19,491	SMD	0.10 (−0.20, 0.40)	97.37	(−1.33, 1.53)	No	0.03 (−0.03,0.09)	No	Very low
Heart rate	16	16,882	SMD	0.14 (−0.08, 0.36)	92.65	(−0.80, 1.08)	No	0.04 (−0.02, 0.10)	No	Very low
Hypertension	13	40,598	OR	0.82 (0.64, 1.04)	72.72	(0.39, 1.71)	Yes	0.86 (0.66, 1.13)	No	Very low
Neurologic and psychiatric disorders										
Depression	4	85,361	aOR	1.09 (0.88, 1.34)	95.29	(−2.43, 2.77)	NA	1.30 (1.20, 1.40)	No	Very low
Multiple sclerosis	5	3477	Crude OR	1.37 (0.89, 2.20)	63.87	(0.31, 6.01)	NA	1.39 (1.11, 1.75)	Yes	Very low
	3	2287	aOR	1.46 (0.98, 2.18)	36.42	NA	NA	1.39 (1.11, 1.75)	Yes	Very low
Metabolic disease										
Diabetes	7	35,811	OR	1.42 (1.03, 1.95)	85.46	(0.53, 3.78)	NA	0.87 (0.71, 1.07)	Yes	Very low
Dyslipidemia	5	19,093	OR	0.96 (0.64, 1.45)	88.22	(0.22, 4.19)	NA	1.09 (0.92, 1.21)	No	Very low
Metabolic syndrome	4	16,184	OR	1.31 (1.17, 1.47)	24.73	(0.93, 1.85)	NA	1.38 (1.21, 1.57)	No	Very low
Mortality										
Overall	4	82,497	aHR	1.47 (1.23, 1.76)	65.73	(0.84, 2.58)	NA	1.30 (0.98, 1.73)	No	Very low
Cardiovascular disease	3	49,503	aHR	1.23 (1.01, 1.50)	0	(0.33, 4.56)	NA	1.10 (0.50, 1.42)	Yes	Low
Cancers	4	92,104	aHR	2.57 (2.10, 3.18)	0	(1.61, 4.10)	NA	1.75 (0.95, 3.22)	No	Low
Infertility and sperm parameters										
Infertility	3	849	OR	1.67 (1.05, 2.65)	0	(0.07, 36.80)	NA	4.22 (1.04, 17.14)	Yes	Very low
Semen volume	5	890	SMD	−0.50 (−1.29, 0.26)	94.79	(−3.41, 2.41)	NA	−1.90 (−2.09, −1.71)	No	Very low
Sperm active progressive motility	5	1403	SMD	0.33 (−3.04, 3.70)	99.74	(−13.06, 13.73)	NA	−3.72 (−3.99, −3.46)	No	Very low

Table 1 (continued)

Outcome	Studies (*N*)	Participant (*N*)	Type of effect size metric	Effect size (95% *CI*)	I^2	95% *CI* prediction intervals	Publication bias	Largest study effect size	Small study effect	Certainty of the evidence (GRADE)
Sperm count	6	1014	SMD	0.26 (−1.13, 1.65)	98.65	(−8.22, 5.96)	NA	3.60 (3.29, 3.91)	No	Very low
Sperm DNA fragmentation	3	712	SMD	3.36 (0.29, 6.43)	98.98	(−36.28, 42.99)	NA	6.43 (6.07, 6.83)	Yes	Very low
Sperm immotile	4	871	SMD	1.24 (−0.52, 3.01)	98.88	(−7.36, 9.84)	NA	0.36 (−0.08, 0.80)	No	Very low
Sperm total motility	3	767	SMD	−1.58 (−3.88, 0.72)	99.10	(−31.28, 28.12)	NA	−3.88 (−4.15, −3.61)	No	Very low
Sperm nonprogressive motility	3	767	SMD	0.01 (−0.46, 0.49)	83.28	(−5.70, 5.72)	NA	−0.38 (−0.54, −0.22)	No	Very low
Sperm normal form (NL morphology)	6	1509	SMD	−0.71 (−1.33, −0.10)	95.66	(−2.91, 1.49)	NA	−1.51 (−1.69, −1.33)	No	Very low
Respiratory symptoms and disease										
Asthma	4	71,081	OR	1.01 (0.39, 2.62)	82.92	(0.01, 69.10)	NA	1.53 (1.41, 1.65)	Yes	Very low
COPD	5	2627	OR	1.97 (0.88, 4.39)	79.70	(0.11, 34.55)	NA	2.03 (0.95, 4.33)	Yes	Very low
Chronic bronchitis	5	63,104	OR	3.61 (1.02, 12.72)	96.46	(0.03, 456.53)	NA	1.31 (1.03, 1.66)	Yes	Very low
Cough	4	61,584	OR	2.37 (1.17, 4.83)	93.02	(0.19, 29.51)	NA	1.25 (1.06, 1.47)	Yes	Very low
Dyspnea	3	61,250	OR	1.82 (0.58, 5.75)	94.73	NA	NA	1.16 (1.02, 1.32)	Yes	Very low
Sputum	3	61,730	OR	3.17 (1.49, 6.72)	54.53	NA	NA	1.99 (1.14, 3.47)	No	Very low
Wheeze	5	1844	OR	1.92 (0.82, 4.47)	85.52	(0.09, 41.59)	NA	0.46 (0.26, 0.82)	Yes	Very low
Spirometry parameters										
FEV1 (predicted)	14	3367	SMD	−0.35 (−0.59, −0.10)	90.17	(−1.33, 0.63)	Yes	−0.04 (0.19, 0.11)	No	Very low
FEV1 (volume)	7	2007	SMD	−0.31 (−1.02, 0.39)	97.93	(−2.87, 2.25)	NA	0.98 (0.82, 1.13)	No	Very low
FVC (predicted)	12	2825	SMD	−0.18 (−0.53, 0.17)	94.77	(−1.55, 1.19)	No	−0.03 (−0.18, 0.12)	No	Very low
FVC (volume)	7	2007	SMD	0.08 (−0.32, 0.48)	93.90	(−0.57, 2.17)	NA	1.05 (0.89, 1.21)	No	Very low
FEV1 on FVC fraction (observed)	6	1411	SMD	−0.10 (−0.40, 0.20)	81.23	(−1.07, 0.87)	NA	−0.18 (−0.33, −0.03)	No	Very low
FEV1 on FVC fraction (predicted)	9	2294	SMD	−0.58 (−1.03, −0.13)	95.57	(−2.26, 1.10)	NA	−2.09 (−2.31, −1.87)	No	Very low
PEF (predicted)	8	2093	SMD	−0.38 (−0.48, 0.08)	95.69	(−2.04, 1.28)	NA	0.41 (0.26, 0.56)	Yes	Very low
PEF (volume)	4	1678	SMD	0.08 (−0.61, 0.78)	97.78	(−3.30, 3.46)	NA	1.10 (0.94, 1.26)	Yes	Very low
FEF25–75 (predicted)	6	1506	SMD	−0.17 (−0.49, 0.16)	86.84	(−1.25, 0.99)	NA	0.01 (−0.15, 0.15)	No	Very low
FEF25–75 (volume)	3	1378	SMD	−0.63 (−0.44, 1.70)	98.67	(−19.85, 18.59)	NA	0.01 (−0.15, −0.15)	No	Very low
Neonatal anthropometry										
Birth weight	5	11,672	SMD	−0.51 (−0.83, −0.18)	93.55	(−1.84, 0.82)	NA	−0.04 (−0.14, 0.07)	No	Low
Low birth weight	3	8802	OR	1.53 (0.92, 2.55)	63.08	(0.01, 417.84)	NA	1.05 (0.73, 1.49)	Yes	Very low
Periodontal parameters										
PI	18	1638	SMD	3.25 (1.86, 4.65)	98.94	(−3.43, 9.93)	No	−0.18 (−0.73, 0.38)	No	Very low

Table 1 (continued)

Outcome	Studies (*N*)	Participant (*N*)	Type of effect size metric	Effect size (95% *CI*)	I^2	95% *CI* prediction intervals	Publication bias	Largest study effect size	Small study effect	Certainty of the evidence (GRADE)
Probing depth	16	1277	SMD	3.46 (2.02, 4.89)	98.54	(− 2.94, 9.86)	Yes	0.22 (− 0.34, 0.77)	No	Very low
Probing depth > 4 mm	4	419	SMD	4.24 (2.30, 6.19)	96.95	(− 5.97, 14.49)	NA	0.22 (− 0.34, 0.77)	No	Very low
Clinical attachment loss	7	675	SMD	3.12 (1.03, 5.22)	98.23	(− 4.57, 10.81)	NA	0.65 (0.09, 1.21)	Yes	Very low
Gingival index	5	469	SMD	10.21 (− 11.23, 31.64)	99.99	(− 74.70, 95.12)	NA	0.34 (0.03, 0.66)	No	Very low
BOP	14	1237	SMD	− 3.23 (− 5.32, − 1.14)	99.21	(− 12.17, 5.71)	Yes	− 0.38 (− 0.40, 0.18)	No	Very low
Distal MBL	7	487	SMD	7.92 (3.59, 12.24)	99.35	(− 7.97, 23.81)	NA	1.51 (1.03, 1.99)	No	Very low
Total distal CBL	4	282	SMD	7.39 (3.99, 13.83)	99.04	(− 15.32, 30.10)	NA	11.64 (9.80, 13.47)	Yes	Very low
Total mesial CBL	4	282	SMD	6.47 (1.23, 11.71)	99.11	(− 14.21, 27.15)	NA	15.78 (13.33, 18.24)	Yes	Very low
MBL	3	298	SMD	2.74 (0.67, 4.80)	97.42	(− 23.86, 29.24)	NA	3.32 (2.82, 3.83)	Yes	Very low
Mesial MBL	7	487	SMD	7.94 (3.81, 12.08)	99.22	(− 7.25, 23.13)	NA	1.97 (1.45, 2.49)	No	Very low
Infectious disease										
Hepatitis C	3	8946	aOR	1.05 (0.79, 1.38)	0	(0.22, 5.29)	NA	0.90 (0.40, 2.01)	No	Very low

BMI Body mass index, *WC* Waist circumference, *CVD* Cardiovascular disease, *CAD* Coronary artery disease, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *COPD* Chronic obstructive pulmonary disease, *FEV* Forced expiratory volume, *FVC* Forced vital capacity, *PEF* Peak expiratory flow, *FEF* Forced expiratory flow, *PI* Plaque index, *BOP* Bleeding on probing, *MBL* Marginal bone loss, *CBL* Crestal bone loss, *HCV* Hepatitis C virus, *SMD* Standardized mean difference, *OR* Odds ratio, *aOR* Adjusted odds ratio, *aHR* Adjusted hazard ratio

We utilized the GRADE system to evaluate and summarize the body of evidence for each outcome in the meta-analysis. This tool classifies evidence from systematic reviews and meta-analyses into four categories: "high," "moderate," "low," or "very low" [9]. The study's design, along with other methodological and statistical limitations, can either lower or raise the quality of the reported effect size. Two independent reviewers (Sh. R. and Z. M.-P.), with one author (M. S.) making the final decision in case of discrepancies, took into account the following factors for each outcome to assess the certainty of the estimate: study design, risk of bias, consistency, precision, directness, the presence of a large effect, dose–response gradient, and publication bias.

Data extraction

Two reviewers (Z. M.-P. and Sh. R.) utilized a standardized and pilot-tested form to independently extract data. Any disagreements were resolved through discussion or by consulting a third reviewer (M. S.). The following information was extracted from individual studies: (1) publication details (last name of the first author, publication year, and geographic location); (2) participant characteristics (total sample size, gender, age, and health status); (3) methods and study procedures (study design and methodological quality assessment); and (4) primary results (effect size with corresponding confidence interval (CI) and number of events in each group).

Statistical analysis

We conducted random-effects meta-analyses for the outcomes by pooling the appropriate data which could be extracted from at least three studies reporting effect estimates of their association with WPS that we considered to be sufficiently similar in their design and comparison groups. The variance between studies, which is crucial for the random-effects model, was estimated using the DerSimonian and Laird method and the restricted maximum likelihood (REML) method. The choice between these methods depends on factors such as sample size, study heterogeneity, computational resources, and the need for accurate between-study variance estimation. Effect sizes for categorical outcomes were expressed as ORs, RRs, and HRs with corresponding 95% CIs. For cohort studies, RRs and HRs were common measures of the associations of interest, with HRs treated as equivalent to RRs, assuming the relative risk remains constant over time. This assumption is generally valid when event rates are low and the follow-up period is not too long, indicating a stable likelihood of occurrence [10]. If cohort studies reported ORs, we converted them to RRs using the Zhang and Yu method, which approximates RR by adjusting the OR with the formula: $RR = \mathrm{OR}/[(1-\mathrm{P0})+(\mathrm{P0}\times\mathrm{OR})]$, where P0 is the incidence of the outcome in the nonexposed group [11]. When publications provided adjusted effect sizes for different outcomes, we extracted and reported both crude and adjusted outcomes separately. Effect sizes for continuous outcomes were measured as standardized mean differences (SMDs) with 95% CIs. To calculate SMD, we used Hedge's g, which adjusts for small sample sizes and is preferred in meta-analyses. SMD was determined by calculating the MD between intervention and control groups, divided by the pooled standard deviation. Hedge's g provides a more accurate estimate by correcting for small sample bias. If studies did not report standard deviations (SDs) of changes in continuous outcomes from baseline, we calculated them using the formula: $SD = \sqrt{[(\mathrm{SD\ pre\text{-}treatment})^2 + (\mathrm{SD\ post\text{-}treatment})^2 - (2\mathrm{R}\times\mathrm{SD\ pre\text{-}treatment}\times\mathrm{SD\ post\text{-}treatment})]}$, assuming a correlation coefficient (R) of 0.5. We utilized the I^2 statistic to measure heterogeneity across studies. In line with the Cochrane Handbook, we categorized I^2 values as follows: 0–40% (might not be important), 30–60% (moderate heterogeneity), 50–90% (substantial heterogeneity), and 75–100% (considerable heterogeneity). Funnel plots for parameters reported in more than 10 studies were interpreted as evidence of publication bias due to eventual asymmetry. Sensitivity analyses were conducted using a previously described "leave-one-out" approach which involved repeating the meta-analysis after dropping the outlying study that was responsible for the most changes in pooled effect size. All p-values were two-sided, with $p < 0.05$ considered as significant. All the above analyses were performed using the Stata software (Version 18, Stata Corp., College Station, TX, USA).

Results

Literature search

The flow diagram identifying the relevant studies in this study is presented in Fig. 1. A total of 28,858 articles were identified from the four database searches (11,086 from Medline, 9619 from Web of Science, 9294 from Scopus, and 615 from Embase). Additionally, 652 records were selected from websites, organizations, and citation searches of the relevant articles. Through title and abstract review, 632 full-text articles were assessed for eligibility. Finally, a total of 191 studies were included in qualitative and quantitative analysis.

The details of the methodological quality appraisal are presented in supplemental Table 2. Quality scores for case–control studies ranged between 1 and 9, with a median of six stars. There were 37 (37.8%) high-quality studies with an average NOS score of 7.45, while 52 (53.1%) displayed moderate quality with an average NOS score of 5.30. However, nine case–control studies (9.1%)

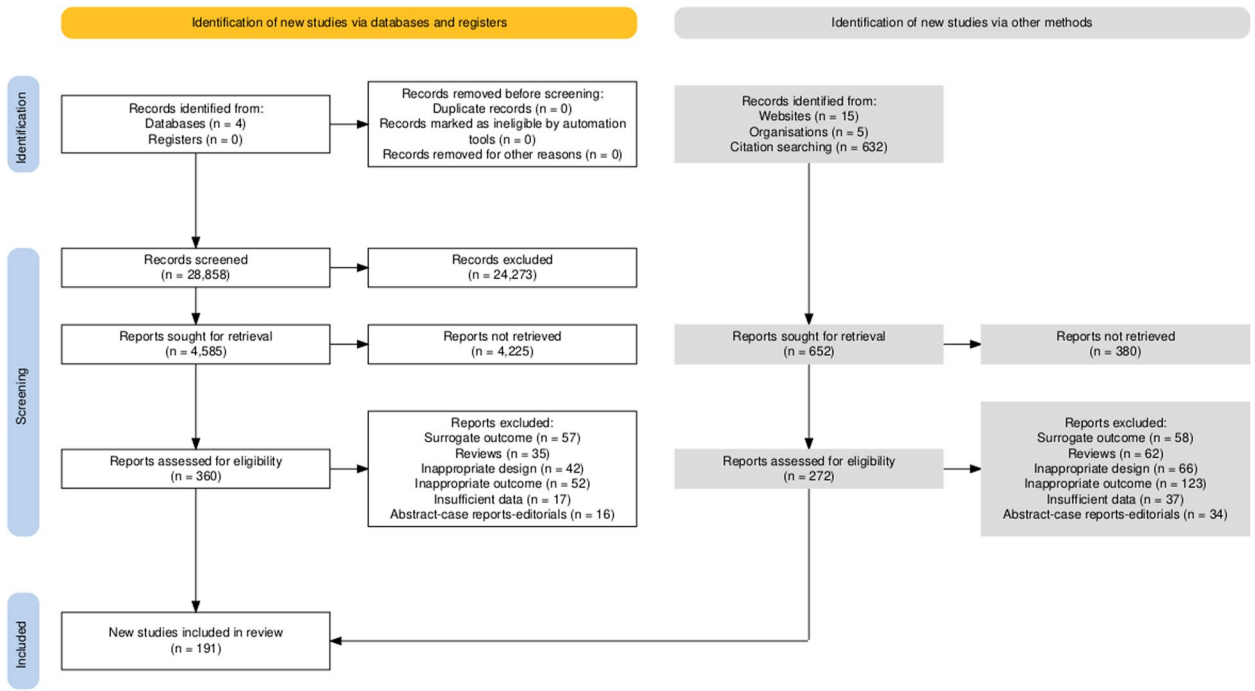

Fig. 1 PRISMA flowchart of study identification and selection

had a possible risk of poor quality. The main weaknesses in case–control studies were the representativeness of the cases and the selection of controls. The vast majority of the cohort studies (14, 87.5%) scored high quality, while the rest (2, 12.5%) scored fair quality. Quality scores for cohort studies ranged between 4 and 9, with a mean of 7.56 (median = 8). Cohort studies were characterized by their inefficiency in studying diseases with long latency, which was their main weakness. Quality scores for cross-sectional studies ranged between 3 and 9, with a median of seven stars (mean = 6.50). Among the cross-sectional studies, most were of high quality (42, 54.5%), while the rest were of fair (33, 42.9%) and low quality (2, 2.6%). The main weaknesses in cross-sectional studies were nonrespondents and inappropriate statistical analysis.

Study characteristics

The study characteristics are presented in supplemental Table 3. One-hundred and ninety-one studies with a total of 807,174 participants were included in our analysis. The sample size varied between 19 and 100,891. The studies were published between 1974 and 2024. Among the studies, 98 were case–control, 77 were cross-sectional, and 16 were cohort studies. These studies comprised samples from 5 WHO-defined regions in 24 countries. There were 155 studies (81.2%) from the Eastern Mediterranean region, 10 (5.2%) from the American region, 7 (3.7%) from the South-East Asia region, 10 (5.2%) from the Western Pacific region, 4 (2.1%) from the European region, and 5 (2.6%) from multiple countries. The countries with the most eligible studies were Iran (46 studies, 24.9%), Lebanon (24 studies, 13%), Saudi Arabia (22 studies, 11.9%), Egypt (16 studies, 8.6%), Jordan (12 studies, 6.5%), and the USA (10 studies, 5.4%). One-hundred and thirty-three studies (69.6%) were performed on healthy subjects, and 58 studies (30.4%) were performed on unhealthy subjects. In most studies (126, 66%), risk estimates were disclosed for both genders together, whereas 65 studies (34%) provided gender-specific associations (5.8% in females, 27.7% in males, and 0.5% in fetuses).

The included studies assessed the associations between WPS and the following outcomes: anthropometric indices (n = 60), gastric cancer (n = 6), lung cancer (n = 7), bladder cancer (n = 7), esophageal cancer (n = 7), pancreatic cancer (n = 1), oral cancer (n = 3), prostate cancer (n = 2), nasopharyngeal cancer (n = 2), head and neck cancer (n = 1), CVD (n = 5), coronary artery disease (CAD) (n = 8), stroke (n = 5), hypertension (n = 13), systolic blood pressure (SBP) (n = 21), diastolic blood pressure (DBP) (n = 21), heart rate (n = 16), depression (n = 4), diabetes (n = 7), dyslipidemia (n = 5), metabolic syndrome (n = 4), mortality from all diseases (n = 4), cardiovascular mortality (n = 4), cancer mortality (n = 4), mortality from respiratory disease (n = 1), mortality from stroke (n = 1), sperm parameters (n = 6), chronic obstructive pulmonary disease (COPD) (n = 5), chronic bronchitis (n = 5),

Table 2 Summary of studies published on health outcomes of waterpipe tobacco smoking

ID	Study	Design	Outcome(s)	Reported effect size (95% *CI*)
Cancers				
1.	Al-Awwad, 2021 [12]	Case control	Pancreatic cancer	*OR* = 0.65 (0.21, 1.67)
2.	Alharbi, 2018 [13]	Case control	Oral squamous cell carcinoma	*OR* = 53.16 (0.11, 76.77) *aOR* = 3.96 (0.24, 63.38)
3.	Collatuzzo, 2024 [14]	Case control	Colorectal cancer	*aOR* = 1.2 (0.9, 1.5)
4.	Collatuzzo, 2024 [14]	Case control	Colon cancer	*aOR* = 1.2 (0.8, 1.5)
5.	Collatuzzo, 2024 [14]	Case control	Rectum cancer	*aOR* = 1.2 (0.9, 1.7)
6.	Dwivedi, 2014 [15]	Case control	Prostate cancer	*OR* = 1.40 (0.50, 3.94)
7.	Feng, 2009 [16]	Case control	Nasopharyngeal cancer	*OR* = 0.49 (0.20, 1.23)
8.	Hosseini, 2010 [17]	Case control	Prostate cancer	*OR* = 7.0 (0.9, 56.9)
9.	Khlifi, 2013 [18]	Case control	Head and neck cancer	*aOR* = 2.73 (1.65, 4.41)
10.	Nguyen, 2023 [19]	Cohort	Nasopharyngeal cancer	*aHR* = 3.58 (1.32, 9.71)
11.	Quadri, 2015 [20]	Case control	Oral cancers	*aOR* = 4.20 (1.32, 13.34)
12.	Vora, 2019 [21]	Cross-sectional	Oral precancerous lesion	*aOR* = 3.50 (0.50, 27.40)
Hematologic section				
13.	Masoudkabir, 2024 [22]	Cross-sectional	Hyperlipidemia	*OR* = 0.82 (0.65, 1.04)
14.	Mohammed, 2025 [23]	Cross-sectional	Hematocrit	*MD* = 3.90 (1.20, 6.60)
ENT section				
15.	Kakaje, 2020 [24]	Cross-sectional	Reflux symptoms index	*OR* = 1.30 (0.91, 1.84)
Gastrointestinal section				
16.	Al Saadi, 2016 [25]	Cross-sectional	GERD	NA
			Irritable bowel syndrome (IBS)	NA
17.	Chatila, 2017 [26]	Cross-sectional	Irritable bowel syndrome (IBS)	*aOR* = 1.63 (1.04, 2.60)
18.	Etemadi, 2017 [27]	Cross-sectional	Any reflux	*aOR* = 1.07 (0.96, 1.20)
			Severe reflux	*aOR* = 1.14 (0.99, 1.32)
			Frequent reflux	*aOR* = 1.18 (1.03, 1.36)
			Severe and frequent reflux	*aOR* = 1.27 (1.04, 1.55)
19.	Islami, 2014 [28]	Cross-sectional	Severe symptoms of GERD	*aOR* = 1.34 (1.02, 1.75)
			Daily symptoms of GERD	*aOR* = 1.19 (0.92, 1.54)
			Any GERD symptom	*aOR* = 1.26 (1.01, 1.56)
Mental health section				
20.	Abu-Samak, 2019 [29]	Cross-sectional	Stress	
21.	Goodwin, 2014 [30]	Cross-sectional	Anxiety disorder	*OR* = 0.78 (0.48, 1.25)
			Substance dependence	*OR* = 1.08 (0.31, 3.71)
			Average stress	*OR* = 1.31 (0.76, 2.23)
			Greater than average tremendous stress	*OR* = 1.22 (0.72, 2.06)
22.	Grinberg, 2015 [31]	Cross-sectional	Stress	*MD* = 0.57 (−3.10, 4.24)
23.	Hallit, 2019 [32]	Cross-sectional	Stress score	*MD* = −2.58 (−4.48, −0.68)
24.	Hawari, 2019 [33]	Cross-sectional	General health	NA
			Physical health	NA
			Social health	NA
			Mental health	NA
25.	Nabhan, 2023 [34]	Cross-sectional	Poor sleep quality	*OR* = 7.89 (1.91, 32.57)

Table 2 (continued)

ID	Study	Design	Outcome(s)	Reported effect size (95% *CI*)
26.	Primack, 2013 [35]	Cross-sectional	Anxiety	*OR* = 1.2 (1.1, 1.3) *aOR* = 1.3 (1.2, 1.4)
			Sleeping disorder	*OR* = 1.5 (1.3, 1.6) *aOR* = 1.5 (1.4, 1.7)
			Eating disorder	*OR* = 1.6 (1.3, 1.8) *aOR* = 1.7 (1.4, 1.9)
			Attention-deficit disorder	*OR* = 1.8 (1.6, 1.9) *aOR* = 1.7 (1.5, 1.8)
			Attention disorder	*OR* = 2.5 (2.2, 2.9) *aOR* = 2.4 (2.0, 2.8)
			Tremendous stress	*OR* = 1.0 (0.9, 1.1) *aOR* = 1.1 (1.02, 1.2)
			Overall health fair or poor	*OR* = 1.3 (1.2, 1.4) *aOR* = 1.4 (1.2, 1.5)
			Severely inadequate sleep	*OR* = 1.05 (0.99, 1.1) *aOR* = 1.08 (1.02, 1.14)
27.	Ramji, 2018 [36]	Cross-sectional	Stress	*MD* = 0.78 (0.48, 1.08) *SD* = 0.15
			Sleep quality	*MD* = −0.57 (−0.85, −0.29) *SD* = 0.14
28.	Tavafian, 2009 [37]	Cross-sectional	Mental component summary	*OR* = 1.88 (1.36, 2.60)
			Physical component summary	*OR* = 2.15 (1.56, 2.96)
			General health	*MD* = −6.30 (−9.45, −3.15) *SD* = 1.61
			Mental health	*MD* = −6.70 (−9.33, −4.07) *SD* = 1.34
			Social function	*MD* = −5.00 (−7.94, −2.06) *SD* = 1.50
Mortality section				
29.	Etemadi, 2017 [27]	Cohort	Mortality from respiratory disease	*aHR* = 0.40 (0.05, 3.15)
30.	Wu, 2013 [38]	Cohort	Mortality from stroke	*aHR* = 0.91 (0.56, 1.46)
Musculoskeletal section				
31.	Hemmati, 2021 [39]	Cross-sectional	Osteopenia	*OR* = 1.85 (0.30, 19.68)
			Osteoporosis	*OR* = 1.31 (0.93, 18.30)
32.	Tajvar, 2023 [40]	Cross-sectional	Musculoskeletal disorders in neck	*OR* = 1.54 (0.98, 2.41)
33.	Tajvar, 2023 [40]	Cross-sectional	Musculoskeletal disorders in shoulder	*OR* = 1.38 (0.86, 2.22)
34.	Tajvar, 2023 [40]	Cross-sectional	Musculoskeletal disorders in elbow	*OR* = 1.49 (0.96, 2.31)
35.	Tajvar, 2023 [40]	Cross-sectional	Musculoskeletal disorders in hand and wrist	*OR* = 0.95 (0.61, 1.47)
36.	Tajvar, 2023 [40]	Cross-sectional	Musculoskeletal disorders in upper back	*OR* = 1.52 (0.93, 2.47)
37.	Tajvar, 2023 [40]	Cross-sectional	Musculoskeletal disorders in lower back	*OR* = 2.23 (1.27, 3.90)
38.	Tajvar, 2023 [40]	Cross-sectional	Musculoskeletal disorders in hip	*OR* = 1.32 (0.86, 2.04)
39.	Tajvar, 2023 [40]	Cross-sectional	Musculoskeletal disorders in knee	*OR* = 1.90 (1.17, 3.10)
40.	Tajvar, 2023 [40]	Cross-sectional	Musculoskeletal disorders in feet/ankles	*OR* = 1.08 (0.70, 1.66)
41.	Valeh, 2020 [41]	Cross-sectional	Osteoporosis	*PR* = 1.14 (0.79, 1.63)
Prenatal outcomes				
42.	Eftekhar, 2007 [42]	Case control	Intrauterine growth retardation	*OR* = 3.50 (1.10, 12.60)
43.	El-Shahawy, 2021 [43]	Cohort	Low birth weight and/or preterm birth	*OR* = 9.55 (2.17, 42.00)
44.	Lotfi, 2018 [44]	Case control	Gestational diabetes mellitus	*OR* = 3.30 (1.06, 10.40)

Table 2 (continued)

ID	Study	Design	Outcome(s)	Reported effect size (95% *CI*)
45.	Tamim, 2008 [45]	Cohort	Gestational diabetes mellitus	*OR* = 0.8 (0.3, 2.1)
			Hypertensive disorders of pregnancy	*OR* = 0.9 (0.4, 2.3)
			Preterm delivery	*OR* = 1.4 (0.8, 2.5)
			Small for gestational age	*OR* = 0.8 (0.5, 1.3)
Respiratory section				
46.	Akiki, 2021 [46]	Cross-sectional	Physician-diagnosed asthma	*aOR* = 0.17 (0.04, 0.67)
47.	Boskabady, 2014 [47]	Cross-sectional	Tightness	NA
48.	Hawari, 2019 [33]	Cross-sectional	Episode of cough and phlegm lasting more than 3 weeks	NA
			Phlegm during day or night	NA
			Phlegm when you wake up	NA
			Shortness of breath when walking fast	NA
			Shortness of breath while active	NA
49.	Hill Rice, 2019 [48]	Cross-sectional	Frequent sore throats (> 2/year)	*OR* = 1.18 (0.67, 2.08)
			Frequent colds (> 2/year)	*OR* = 1.54 (0.94, 2.54)
50.	She, 2014 [49]	Cross-sectional	Abnormal lung function	*OR* = 7.15 (4.61, 11.10)
51.	Wake, 2009 [50]	Cross-sectional	Physician diagnosed respiratory disease	*aOR* = 1.95 (0.99, 4.05)
Periodontal section				
52.	Abdu, 2023 [51]	Cross-sectional	Gingivitis	*OR* = 0.27 (0.06, 1.25)
			Periodontitis stage I	*OR* = 1.02 (0.30, 3.44)
			Periodontitis stage II	*OR* = 2.99 (0.96, 9.33)
			Periodontitis stage III	*OR* = 2.43 (0.28, 21.37)
			Periodontitis stage IV	*OR* = 1.71 (0.09, 33.40)
53.	Al Kawas, 2021 [52]	Case control	Periodontitis (no/mild)	NA
			Periodontitis (moderate/severe)	NA
54.	Baljoon, 2003 [53]	Cross-sectional	Periodontal disease	*OR* = 2.90 (1.20, 7.00)

MD Mean difference, *SD* Standard deviation, *aOR* Adjusted odds ratio, *OR* Odds ratio, *RR* Risk ratio, *HR* Hazard ratio, *aHR* Adjusted hazard ratio, *PR* Prevalence ratio, *GERD* Gastroesophageal reflux disease

respiratory symptoms ($n=9$), spirometry parameters ($n=14$), gastroesophageal reflux disease (GERD) ($n=3$), irritable bowel syndrome (IBS) ($n=1$), mental health ($n=8$), osteopenia ($n=1$), osteoporosis ($n=1$), infertility ($n=3$), adverse pregnancy outcomes ($n=4$), asthma ($n=1$), gingivitis ($n=1$), periodontal parameters ($n=16$), and periodontitis ($n=3$).

Quantitative analysis

Evidence synthesis

We displayed the findings and the level of evidence for each outcome in Table 1. The median number of studies analyzed per outcome was 5, with a range of 3 to 30. Among the 62 outcomes evaluated, 31 (50%) demonstrated statistically significant effect sizes based on a random-effects model, with stroke, CAD, and cancer mortality exhibiting a significant prediction interval. Credibility evaluations identified low-quality evidence for birth weight, CAD, and cardiovascular and cancer mortality, whereas the evidence for the remaining outcomes was graded as very low quality (Table 1). Detailed GRADE assessment and justification for downgrades of each outcome were presented in supplemental Table 4.

Anthropometric parameters

A total of 32 studies (16 cross-sectional and 16 case control) with 10,001 participants evaluated the association between WPS and body mass index (BMI). In a random-effects model, the pooled SMD was 0.08 (95% *CI*: −0.03, 0.20), indicating no association between WPS and BMI. There was substantial between-study heterogeneity ($I^2=78.72\%$) and no evidence of funnel plot asymmetry (no publication bias, Supplemental Fig. 1 and Table 1). The association between WPS and weight was evaluated in 20 studies involving 4198 subjects (1803 exposed and 2395 nonexposed subjects). The pooled SMD was 0.43 (95% *CI*: 0.16, 0.70), indicating a significant association between WPS and weight ($I^2=93.72\%$). There was evidence of publication bias in this regard (evidence of funnel plot asymmetry, Supplemental Fig. 1 and Table 1).

Eight studies with a total number of 4652 participants evaluated the association between WPS and waist circumference (WC). The pooled analysis indicated no association between WPS and WC (SMD = 0.11; 95% *CI*: −0.11, 0.33; I^2 = 87.76%, Table 1).

Gastric cancer

Six studies (5 case control and 1 cohort) including 3764 participants evaluated the association between WPS and gastric cancer with ORs ranging from 0.45 (95% *CI*: 0.19, 1.05) to 6.69 (95% *CI*: 3.20, 14.02). Pooling results from six studies showed a significant association between WPS and gastric cancer (*OR* = 2.11; 95% *CI*: 1.02, 4.40; I^2 = 84.47%, Table 1). Sensitivity analysis suggested that one study [12] substantially influenced the pooled estimate.

Lung cancer

Seven case–control studies including 11,272 participants evaluated the association between WPS and lung cancer with ORs ranging from 0.53 (95% *CI*: 0.20, 1.42) to 11.49 (95% *CI*: 5.31, 24.89). People who smoke WP demonstrated higher odds of developing lung cancer compared to people who did not smoke WP (*OR* = 2.61; 95% *CI*: 1.28, 5.34; I^2 = 94.23%, Table 1).

Bladder cancer

Seven case–control studies including 9131 participants evaluated the association between WPS and bladder cancer with ORs ranging from 1.04 (95% *CI*: 0.77, 1.40) to 15.68 (95% *CI*: 0.81, 304.76). Pooling results from seven studies showed a significant association between WPS and bladder cancer (*OR* = 1.57; 95% *CI*: 1.14, 2.18; I^2 = 72.08%, Table 1).

Esophageal cancer

In total, seven case–control studies including 4783 participants reported the association between WPS and esophageal cancer. The pooled OR for the association of WPS with esophageal cancer diagnosis was 2.95 (95% *CI*: 1.36, 6.40; I^2 = 92.42%, Table 1).

Cardiovascular disease

A total of five studies (3 cross-sectional and 2 case control) with 32,842 participants evaluated the association between WPS and CVD. Comparing WP smokers with never smokers, the combined OR for the development of CVD for the five studies was 1.14 (95% *CI*: 0.95, 1.32) using the random-effects model. There was low heterogeneity between studies (I^2 = 12.77%, Table 1).

Coronary artery disease

Eight studies (5 cross-sectional, 1 cohort, and 2 case control) including 66,784 participants evaluated the association between WPS and CAD with ORs ranging from 1.13 (95% *CI*: 0.69, 1.84) to 11.64 (95% *CI*: 3.33, 40.66). Compared to never smokers, current WP smokers had significantly higher odds of developing CAD (*OR* = 1.56; 95% *CI*: 1.36, 1.79; I^2 = 23.17%, Table 1).

Heart rate

The association between WPS and heart rate was examined using data from 16 studies (10 cross-sectional, 1 cohort, and 5 case control), including 16,882 participants. The pooled SMD was 0.14 (95% *CI*: −0.08, 0.36), indicating no significant association between WPS and heart rate (I^2 = 92.65%, Table 1).

Stroke

A total of five studies (2 cross-sectional and 3 case control) with 6606 participants evaluated the association between WPS and stroke. The included case–control studies reported crude and adjusted estimates of OR, but only one of the included cross-sectional studies reported an adjusted estimate of OR. The crude estimate of OR ranged widely, from 1.06 (95% *CI*: 0.14, 7.97) to 5.17 (95% *CI*: 1.08, 24.74). The pooled crude OR was 2.66 (95% *CI*: 2.02, 3.49) without heterogeneity (I^2 = 0%). Overall, the pooled multivariable-adjusted OR indicated the strong association between WPS and stroke (*n* = 4, participants: 2734; *aOR* = 3.10; 95% *CI*: 2.20, 4.39; I^2 = 0%, Table 1).

Hypertension

Thirteen studies, with data from 1 cohort and 12 cross-sectional studies that included 40,598 individuals (4066 exposed and 36,532 non-exposed), reported on the odds of hypertension in current WP smokers compared with never smokers. No evidence of an increased odds was present among current WP smokers compared with never smokers (*OR* = 0.82; 95% *CI*: 0.64, 1.04; I^2 = 72.72%, Table 1).

Systolic and diastolic blood pressure

Twenty-one studies (8 cross-sectional, 1 cohort, and 12 case control) with 19,491 participants were entered in order to assess the association between WPS and blood pressure. After pooling the amounts of SMD, it was shown that WPS leads to a nonsignificant increase in the absolute level of SBP (*SMD* = 0.14; *CI*: −0.37, 0.65; I^2 = 99.07%) and DBP (*SMD* = 0.10; *CI*: −0.20, 0.41; I^2 = 97.37%, Supplemental Fig. 1 and Table 1).

Neurologic and psychiatric disorders

A total of four studies investigated the association of WPS and depression, of which 2 (50%) found evidence to support this association, while 2 (50%) found no evidence of an association. The pooled aOR was 1.09 (95% *CI*: 0.88, 1.34; $I^2 = 95.29\%$) by the random-effects model. Five studies with 3477 participants were suitable for inclusion in the random-effects model of WPS and multiple sclerosis (MS) risk. This showed a nonsignificant increased risk of MS associated with WPS with high heterogeneity (*OR* = 1.37; 95% *CI*: 0.89, 2.20; $I^2 = 63.87\%$). Overall, the pooled multivariable-adjusted OR indicated a nonsignificant odds of MS associated with WPS (*aOR* = 1.46; 95% *CI*: 0.98, 2.18; $I^2 = 36.42\%$). Sensitivity analysis suggested that one study (Mortazavi, 2023) is substantially influencing the pooled estimates (crude and adjusted, Table 1).

Diabetes

The search yielded seven studies (6 cross-sectional and 1 case control) which included a total of 35,811 subjects. Meta-analysis of the seven included studies using the random-effects model suggested an increased risk of type 2 diabetes in WP smokers compared to non-smokers (*OR* = 1.42; 95% *CI*: 1.03, 1.95; $I^2 = 85.46\%$). The pooled OR was not substantially influenced by omitting any of the individual studies (Table 1).

Metabolic syndrome

Four studies (2 cross-sectional, 1 cohort, and 1 case control) with 16,184 participants were included in the assessment of the association between WPS and metabolic syndrome. The four independent effect sizes for metabolic syndrome resulted in a summary OR forever use of WP of 1.31 (95% *CI*: 1.17, 1.47), with low homogeneity between studies ($I^2 = 24.73\%$). The pooled OR was not substantially influenced by omitting any of the individual studies (Table 1).

Dyslipidemia

A total of five cross-sectional studies with 19,093 participants evaluated the association between WPS and dyslipidemia. No evidence of an increased risk was present among current users compared to non-smokers (*OR* = 0.96; 95% *CI*: 0.64, 1.45; $I^2 = 88.22\%$). The pooled OR was not substantially influenced by omitting any of the individual studies (Table 1).

Mortality

A total of four cohort studies were retrieved; all of them reported all-cause mortality (*N* = 82,497), while four studies reported cancer (*N* = 92,104), and three studies reported cardiovascular (*N* = 49,503) mortality. WPS was associated with a 47% increment in overall mortality (*aHR* = 1.47; 95% *CI*: 1.23, 1.76; $I^2 = 65.73\%$). The pooled aHR was not substantially influenced by omitting any of the individual studies. Compared to never smokers, current WP smokers had a significant 23% higher risk of developing cardiovascular mortality (*aHR* = 1.23; 95% *CI*: 1.01, 1.50; $I^2 = 0\%$). Meta-analyses showed that WPS was associated with a higher risk of cancer mortality (*aHR* = 2.57; 95% *CI*: 2.10, 3.18; $I^2 = 0\%$) (Table 1).

Infertility and sperm parameters

Three studies (2 case control and 1 cohort) reported information on infertility, including 849 participants. Compared to never smokers, current WP smokers had a significantly higher risk of developing infertility (*OR* = 1.67; 95% *CI*: 1.05, 2.65; $I^2 = 0\%$, Table 1). Eight studies (two cross-sectional and six case control) reported sperm parameters. Men who were current WP smokers demonstrated higher mean sperm DNA fragmentation index (SDF) (*n* = 3, participants: 712; *SMD* = 3.36; 95% *CI*: 0.29, 6.43, $I^2 = 98.98\%$, Table 1) and normal sperm morphology (*n* = 6, participants: 1509; *SMD* = −0.71; *CI*: −1.33, −0.10; $I^2 = 95.66\%$, Table 1) compared to never smokers. No significant differences between WP smokers and non-smokers were found for semen volume (*n* = 5, participants: 890; *SMD* = −0.50; *CI*: −1.29, 0.26; $I^2 = 94.79\%$, Table 1), sperm active progressive motility (*n* = 5, participants: 1403; *SMD* = 0.33; *CI*: −3.04, 3.70; $I^2 = 99.74\%$, Table 1), sperm nonprogressive motility (*n* = 3, participants: 767; *SMD* = 0.01; *CI*: −0.46, 0.49; $I^2 = 83.28\%$, Table 1), and sperm count (*n* = 6, participants: 1014; *SMD* = 0.26; *CI*: −1.13, 1.65; $I^2 = 98.65\%$, Table 1).

Respiratory symptoms and diseases

Fourteen studies (10 cross-sectional and 4 case control) reported respiratory symptoms and diseases related to WPS. A pooled analysis of the included studies showed that WPS use was associated with an increased risk for chronic bronchitis (*n* = 5, participants: 63,104; *OR* = 3.61; 95% *CI*: 1.02, 12.72; $I^2 = 96.46\%$, Table 1), cough (*n* = 4, participants: 61,584; *OR* = 2.37; 95% *CI*: 1.17, 4.83; $I^2 = 93.02\%$, Table 1), and sputum (*n* = 3, participants: 61,730; *OR* = 3.17; 95% *CI*: 1.49, 6.72; $I^2 = 54.53\%$, Table 1). Additionally, we found no significant association between current WPS and asthma (*n* = 4, participants: 71,081; *OR* = 1.01; 95% *CI*: 0.39, 2.62; $I^2 = 82.92\%$, Table 1), COPD (*n* = 5, participants: 2627; *OR* = 1.97; 95% *CI*: 0.88, 4.39; $I^2 = 79.70\%$, Table 1), dyspnea (*n* = 3, participants: 61,250; *OR* = 1.82; 95% *CI*: 0.58, 5.75; $I^2 = 94.73\%$, Table 1), and wheeze (*n* = 5, participants: 1844; *OR* = 1.92; 95% *CI*: 0.82, 4.47; $I^2 = 85.52\%$, Table 1). Sensitivity analysis suggested that one study is substantially influencing the pooled estimate in all nonsignificant outcomes.

Spirometry parameters

Fifteen studies (7 cross-sectional and 8 case control) satisfying the inclusion/exclusion criteria were identified. Compared with no smoking, WPS was associated with a statistically significant reduction in forced expiratory volume (FEV1) predicted ($n=14$, participants: 3367; $SMD=-0.35$; 95% CI: −0.59, −0.10, $I^2=90.17\%$, Table 1) and FEV1/ forced vital capacity (FVC) predicted ($n=9$, participants: 2294; $SMD=-0.58$; 95% CI: −1.03, −0.13, $I^2=95.57\%$, Table 1). There was evidence of publication bias for FEV1 predicted, considering the asymmetry of the funnel plot (Supplemental Fig. 1). There was no statistically significant difference in other parameters including FEV1 volume ($n=7$, participants: 2007; $SMD=-0.31$; 95% CI: −1.02, 0.39, $I^2=97.93\%$, Table 1), FVC predicted ($n=12$, participants: 2825; $SMD=-0.18$; 95% CI: −0.53, 0.17, $I^2=94.77\%$, Table 1), FVC volume ($n=7$, participants: 2007; $SMD=0.08$; 95% CI: −0.32, 0.48, $I^2=93.90\%$, Table 1), FEV1/FVC observed ($n=6$, participants: 1411; $SMD=-0.10$; 95% CI: −0.40, 0.20, $I^2=81.23\%$, Table 1), PEF predicted ($n=8$, participants: 2093; $SMD=-0.38$; 95% CI: −0.48, 0.08, $I^2=95.69\%$, Table 1), PEF volume ($n=4$, participants: 1678; $SMD=0.08$; 95% CI: −0.61, 0.78, $I^2=97.78\%$, Table 1), FEF25–75 predicted ($n=6$, participants: 1506; $SMD=-0.17$; 95% CI: −0.49, 0.16, $I^2=86.84\%$, Table 1), and FEF25–75 volume ($n=3$, participants: 1378; $SMD=-0.63$; 95% CI: −0.44, 1.70, $I^2=98.67\%$, Table 1). There was an evidence of publication bias for FVC predicted, considering the asymmetry of the funnel plot (Supplemental Fig. 1).

Neonatal anthropometry

Five studies were included in the meta-analysis, resulting in a sample of 11,672 pregnant women who smoked WP during pregnancy. The risk of LBW (LBW, < 2500 g) was not increased in infants of WPS-exposed women ($n=3$, participants: 8802; $OR=1.53$; 95% CI: 0.92, 2.55; $I^2=63.08\%$), but after pooling the amounts of SMD, it was shown that WPS leads to a significant decrease in birth weight ($SMD=-0.51$; CI: −0.83, −0.18; $I^2=93.55\%$). Sensitivity analysis suggested that one study [45] is substantially influencing the pooled estimate of LBW. After removing this study and reanalyzing, the pooled effect size became significant ($OR=2.27$; 95% CI: 1.33, 3.89) (Table 1).

Periodontal parameters

Meta-analysis results for changes in periodontal parameters demonstrated an increase in plaque index (PI) ($n=18$, participants: 1638; $SMD=3.25$; 95% CI: 1.86, 4.65, $I^2=98.94\%$, Table 1), probing depth ($n=16$, participants: 1277; $SMD=3.46$; 95% CI: 2.02, 4.89, $I^2=98.54\%$, Table 1), probing depth > 4 mm ($n=4$, participants: 419; $SMD=4.24$; 95% CI: 2.30, 6.19, $I^2=96.95\%$, Table 1), clinical attachment loss ($n=7$, participants: 675; $SMD=3.12$; 95% CI: 1.03, 5.22, $I^2=98.23\%$, Table 1), bleeding on probing (BOP) ($n=14$, participants: 1237; $SMD=-3.23$; 95% CI: −5.32, −1.14, $I^2=99.21\%$, Table 1), distal marginal bone loss (MBL) ($n=7$, participants: 487; $SMD=7.92$; 95% CI: 3.59, 12.24, $I^2=99.35\%$, Table 1), total distal crestal bone loss (CBL) ($n=4$, participants: 282; $SMD=7.39$; 95% CI: 3.99, 13.83, $I^2=99.04\%$, Table 1), total mesial CBL ($n=4$, participants: 282; $SMD=6.47$; 95% CI: 1.23, 11.71, $I^2=99.11\%$, Table 1), MBL ($n=3$, participants: 298; $SMD=2.74$; 95% CI: 0.67, 4.80, $I^2=97.42\%$, Table 1), and mesial MBL ($n=7$, participants: 487; $SMD=7.94$; 95% CI: 3.81, 12.08, $I^2=99.22\%$, Table 1) in WP smokers compared to non-smokers. There was no statistically significant difference in the gingival index ($n=5$, participants: 469; $SMD=10.21$; 95% CI: −11.23, 31.64, $I^2=99.99\%$, Table 1). There was no evidence of publication bias for PI, considering the symmetry of the funnel plot, but we found evidence of publication bias for probing depth and BOP, considering the asymmetry of the funnel plot (Supplemental Fig. 1).

Hepatitis C

The combined result based on the adjusted ORs from the three studies in which WP smokers were compared with never smokers among the HCV-negative subjects was 1.05 (95% CI: 0.79, 1.38, $I^2=0\%$) (Table 1).

Qualitative analysis

Pancreatic cancer

One case–control study ($n=578$, quality score: 5) evaluated the association between WPS and pancreatic cancer in Jordan. The OR for the association of WPS with pancreatic cancer was 0.65 (95% CI: 0.21, 1.67) (Table 2, Supplemental Table 3) [12].

Prostate cancer

Two case–control studies evaluated the association between WPS and prostate cancer: one from Iran ($n=137$, quality score: 8) and one from India ($n=570$, quality score: 6). The reported ORs were 7.0 (95% CI: 0.9, 56.9) and 1.40 (95% CI: 0.50, 3.94), respectively (Table 2, Supplemental Table 3) [15].

Oral cancer and precancerous lesion

Two case–control and one cross-sectional study evaluated the association between WPS and oral cancer, as well as precancerous lesions. Both case–control studies were conducted in Saudi Arabia. One found that WP smokers have higher odds of oral cancer compared to non-smokers (aOR: 4.20, 95% CI: 1.32, 13.34), while another found no significant association between WPS

and oral cancer [13, 20] (*aOR*: 3.96, 95% *CI*: 0.24, 63.38). Additionally, the cross-sectional study results showed no significant association between WPS and precancerous lesions [21] (*aOR*: 3.50, 95% *CI*: 0.50, 27.40) (Table 2, Supplemental Table 3).

Nasopharyngeal cancer

Two studies (one case control and one cohort) evaluated the association between WPS and nasopharyngeal cancer. One multicenter case–control study evaluated the association between WPS and nasopharyngeal cancer in Algeria, Morocco, and Tunisia. The incident cases ($n=636$) were selected from 5 hospitals by clinicians in the oncology and radiotherapy departments from 2001–2004. The frequency-matched controls ($n=615$) were selected from 15 non-cancer hospital departments or friends and family members of non-nasopharyngeal cancer patients. Based on conditional logistic regression, there was no significant association between WPS and nasopharyngeal cancer [16] (*OR*: 0.49, 95% *CI*: 0.20, 1.23). A cohort study followed up with 20,144 eligible man participants from 9 northern Vietnam communes between 2007 and 2019. They found a strong positive association between WPS and nasopharyngeal cancer according to intensity (over 10 smokes per day) (*aHR*: 3.58, 95% *CI*: 1.32, 9.71), duration (over 25 years) (*aHR*: 3.10, 95% *CI*: 1.16, 8.26), age of smoking initiation (over 25) (*aHR*: 3.37, 95% *CI*: 1.31, 8.67), and cumulative number of smoking lifetime [19] (over 300) (*aHR*: 3.65, 95% *CI*: 1.33, 10.06) (Table 2, Supplemental Table 3).

Colorectal cancer

A multicenter hospital-based case–control study investigated the association between waterpipe use and colorectal cancer in an Iranian population. The study population included 3215 controls and 848 cases, comprising 455 colon cancers and 393 rectal cancers. The results indicate no association between WPS and colorectal cancer (*OR*: 1.2, 95% *CI*: 0.9, 1.5), colon cancer (*OR*: 1.2, 95% *CI*: 0.8, 1.5), and rectal cancer [14] (*OR*: 1.2, 95% *CI*: 0.9, 1.7) (Table 2, Supplemental Table 3).

Head and neck cancer

One case–control study evaluated the association between WPS and head and neck cancer (HNC) in Tunisia. The case–control study population consisted of 169 patients (97 laryngeal cancer, 48 nasopharyngeal cancer, 11 pharyngeal cancer, 6 tongue cancer, and 7 cheek cancer) with histologically confirmed HNC and 351 cancer-free control subjects. The adjusted OR for the association of WPS with HNC was 2.73 (1.65, 4.41) [18] (Table 2, Supplemental Table 3).

Hematologic section

One cross-sectional study assessed the association between WPS and hyperlipidemia. This study involved a retrospective analysis of patients who underwent diagnostic coronary angiography at the Tehran Heart Center from April 2021 to May 2022. The medical records of 8699 patients were reviewed, including 380 waterpipe smokers. The results indicate no association between WPS and hyperlipidemia [22] (*OR*: 0.82, 95% *CI*: 0.65, 1.04). A comparative cross-sectional study involved 120 smokers and non-smokers adult male participants. This study was carried out in 12 Khartoum North city social smoking centers between September and December 2022. The mean hematocrit of the waterpipe smokers was 47.1% (± 3.9%), whereas that of the non-smokers was 43.2% (± 4.5%), with a significant statistical difference [23] (*MD*: 3.90, 95% *CI*: 1.20, 6.60) (Table 2, Supplemental Table 3).

Gastroesophageal reflux disease

The characteristics of the three cross-sectional studies on WPS and the risk of gastroesophageal reflux disease (GERD) are presented in Table 2 and Supplemental Table 3. The studies were published from 2014 to 2017. Two studies were conducted in Iran and one in Syria. The included studies divided the subjects into different groups according to disease types. In a cross-sectional analysis of the baseline data from a population-based cohort study of 50,000 individuals in Golestan Province, Iran, Islami et al. found WPS to be positively associated with severe symptoms of GERD (*OR*: 1.34, 95% *CI*: 1.02, 1.75) and any GERD symptom (*OR*: 1.26, 95% *CI*: 1.01, 1.56), but not daily symptoms of GERD [28] (*OR*: 1.19, 95% *CI*: 0.92, 1.54). Another cross-sectional study using baseline data from the Pars cohort study conducted in southern Iran by Etemadi et al. found WPS positively associated with frequent reflux (*OR*: 1.18, 95% *CI*: 1.03, 1.36) and severe and frequent reflux (*OR*: 1.27, 95% *CI*: 1.04, 1.55), but did not find a significant association between WPS and any reflux [27] (*OR*: 1.07, 95% *CI*: 0.96, 1.20). Additionally, a cross-sectional study on 320 students at a campus of Damascus University in Syria showed no significant association between WPS and GERD [25] ($\chi^2=3.74$, $p=0.442$). A cross-sectional study that included 734 responders found no clear association between WPS and GERD [24] (*OR*: 1.30, 95% *CI*: 0.91, 1.84).

Irritable bowel syndrome

Two cross-sectional studies reported IBS related to WPS. One study was conducted in Syria and the other in Lebanon. A cross-sectional study conducted in July–September 2015 at a campus of Damascus University in Syria showed no significant association between WPS and IBS ($\chi^2 = 3.19$, $p = 0.525$). Another cross-sectional study including a convenience population of bank employees in different geographical areas in Lebanon found that compared to never smokers, current WP smokers had a significantly higher risk of developing IBS [26] (*aOR* = 1.63; 95% *CI*: 1.04, 2.60).

Psychological disorders

Stress

Three cross-sectional studies [31] (USA, Lebanon, and Sweden) including 2461 participants assessed the association between WPS and stress. Using a nationally representative dataset of adults aged 18–30 years in the USA in 2015, Grinberg et al. found no significant association between WPS and stress (*MD*: 0.57, 95% *CI*: − 3.10, 4.24). Paradoxically, another cross-sectional study conducted between October 2016 and February 2017, enrolling 308 patients from four laboratories in Lebanon, showed WPS decreased the stress score [32] (*MD*: − 2.58, 95% *CI*: − 4.48, − 0.68). Another cross-sectional study enrolling 1006 adolescents in grades 9–12 in Sweden by Ramji et al. reported a higher mean score of stress among students who smoke WP compared to non-smokers [36] (*MD*: 0.78, 95% *CI*: 0.48, 1.08).

Quality of life

Three cross-sectional studies including 4614 participants evaluated the association between WPS and QOL. One cross-sectional study using a multistage cluster sample ($n = 2201$) across Lebanon found that WPS is associated with lower respiratory quality of life, as evidenced by the Clinical COPD Questionnaire (CCQ) [32] (*SMD*: 0.83, 95% *CI*: 0.55, 1.11). In a cross-sectional study in Iran, Tavafian et al. interviewed all eligible participants using the Short-Form Health Survey (SF-36) questionnaire. All scales showed a statistically significant difference between WP smokers and non-smokers, except for emotional role: general health (*MD*: − 6.30, 95% *CI*: − 9.45, − 3.15), mental health (*MD*: − 6.70, 95% *CI*: − 9.33, − 4.07), and social function [37] (*MD*: − 5.01, 95% *CI*: − 7.94, − 2.06). Another cross-sectional study on college campuses across four countries (Egypt, Jordan, Morocco, and Oman) showed WP smokers have significantly lower scores in two domains of QOL relative to non-smokers (general health *SMD*: − 0.25, 95% *CI*: − 0.45, − 0.05; physical health [33] *SMD*: − 0.13, 95% *CI*: − 0.34, − 0.07).

Sleeping disorder

Three cross-sectional studies (USA, Lebanon, and Sweden) including 102,168 participants assessed the association between WPS and sleeping disorder. A cross-sectional study utilizing a snowball sampling method was conducted in Lebanon from January to March 2023. A total of 350 healthcare professionals were included in the study. WPS showed a significant association with poor sleep quality, indicated by an adjusted odds ratio of 7.89 [34] (95% *CI*: 1.91 to 32.57). A cross-sectional study in the USA analyzed data collected from 152 academic institutions that participated in the National College Health Assessment during the 2008–2009 academic year to examine associations between WPS and mental health problems among college students ($N = 100{,}891$). Severely inadequate sleep was associated with waterpipe use [35] (*aOR* = 1.5; 95% *CI*: 1.4, 1.7). A cross-sectional study using a purposeful sample of adolescent high-school students, aged 16–19 years in Umea, Sweden, assessed mental well-being with three separate validated items, which assessed stress, mental energy, and sleep quality. The results indicated a lower mean score for sleep disorders among students who smoke WP, compared to non-smokers [36] (*MD*: − 0.57, 95% *CI*: − 0.85, − 0.29).

Musculoskeletal section

Two cross-sectional studies including 20,883 participants evaluated the association between WPS and osteoporosis, both conducted in Iran. Neither study found a statistically significant association between WPS and osteoporosis. Valeh et al., enrolling a total of 2377 participants (1225 women), revealed no significant association between WPS and osteoporosis [41] (prevalence ratio (PR): 1.14, 95% *CI*: 0.79, 1.63). Similarly, Hemmati et al., including a simple random sampling of 850 postmenopausal women aged 50–65 years, reported non-significant results [39] (*OR*: 1.31, 95% *CI*: 0.93, 1.83). A cross-sectional study comprised 351 urban service workers employed in Bandar Abbas City, Iran, and examined musculoskeletal disorders over the past 12 months using the Nordic questionnaire in each of the nine body parts. Musculoskeletal disorders in waterpipe smokers revealed a significant difference in two areas of the body compared to non-smokers. The affected areas include the lower back, with an odds ratio (OR) of 2.23 (95% confidence interval [CI]: 1.27 to 3.90), and the knees, with an OR of 1.90 [40] (95% *CI*: 1.17 to 3.10).

Adverse pregnancy outcomes

Four studies (two case–control and two cohort studies) including 9248 women evaluated the association between WPS and adverse pregnancy outcomes. A retrospective cohort study from August 2000 to August 2003 in

6 major hospitals in Lebanon, enrolling 8592 women, reported all pregnancy outcomes as non-significant, including gestational diabetes mellitus (GDM) (*OR*: 0.81, 95% *CI*: 0.31, 2.10), hypertensive disorders of pregnancy (*OR*: 0.91, 95% *CI*: 0.41, 2.31), preterm delivery (*OR*: 1.41, 95% *CI*: 0.81, 2.51), and small for gestational age [45] (*OR*: 0.81, 95% *CI*: 0.51, 1.31). A case–control study including 120 women (60 cases and 60 controls) in Iran found that current WP smokers had a significantly higher odds of developing intrauterine growth retardation compared to never smokers [42] (*OR* = 3.50; 95% *CI*: 1.10, 12.60). Another case–control study in Iran, carried out on 168 women with gestational diabetes and 168 controls, found that compared to never smokers, current WP smokers had a significantly higher risk of developing gestational diabetes [44] (*OR* = 3.30; 95% *CI*: 1.06, 10.40). In a cohort study in Egypt, 200 pregnant women were recruited during their last trimester from antenatal clinics in Cairo from June 2015 to May 2016. WP smokers during pregnancy had greater odds of premature birth and/or LBW babies compared to non-smokers [43] (*OR* = 9.55; 95% *CI*: 2.17, 42.01).

Periodontitis and gingivitis

Three studies (2 cross-sectional and 1 case control) including 599 participants reported the adverse effects of WPS on periodontitis and gingivitis. A cross-sectional study enrolling a sample of 355 individuals aged 17 to 60 years in Saudi Arabia demonstrated a statistically significant association between WPS and periodontitis [53] (*OR* = 2.90; 95% *CI*: 1.20, 7.01). However, two other studies did not show a statistically significant association between WPS and periodontitis. A case–control study enrolling non-smokers seeking dental treatment at the University Dental Hospital in Sharjah, United Arab Emirates, found no significant association between WPS and periodontitis [52] (*OR* = 1.00; 95% *CI*: 0.01, 87.11). A cross-sectional study including 322 medically fit volunteers consecutively enrolled at the diagnostic center at Cairo University's Faculty of Dentistry found that WP smokers had a nonsignificant highest prevalence of periodontitis stages II and III, while non-smokers had the highest prevalence of healthy periodontium as well as gingivitis [51].

Discussion

We conducted a systematic review of the medical literature to examine the deleterious effects of WPS on health-related outcomes. Our findings indicated that WPS is linked to spirometry parameters, respiratory diseases such as chronic bronchitis, cough, and sputum. Additionally, it is associated with gastric cancer, lung cancer, bladder cancer, esophageal cancer, CAD, stroke, diabetes, metabolic syndrome, sperm parameters, periodontal parameters, birth weight, all-cause, CVD, and cancer mortality. However, the existing evidence did not support an association with BMI, WC, hypertension, heart rate, depression, dyslipidemia, asthma, COPD, hepatitis C, and MS.

The systematic review and meta-analysis conducted by Reem Waziry et al. in 2017 provided a foundational understanding of the health impacts associated with WPS. Their findings indicated significant associations between WPS and respiratory diseases such as COPD, bronchitis, and wheezing due to passive exposure. Additionally, they reported correlations with oral cancer, lung cancer, LBW, metabolic syndrome, CVD, and mental health disorders. Notably, their analysis found no significant associations between WPS and several other conditions, including esophageal cancer, gastric carcinoma, bladder cancer, prostate cancer, hepatitis C infection, periodontal disease, GERD, nasopharyngeal carcinoma, infertility, or overall mortality. Our updated study builds on the work of Waziry et al., extending the breadth and depth of the investigation into the health outcomes associated with WPS. One of the critical differences between the two studies is our identification of significant associations with a broader range of health conditions. Specifically, our findings indicated that WPS is linked to adverse spirometry parameters and a variety of respiratory diseases, including COPD, chronic bronchitis, cough, and wheezing, aligning with the respiratory impacts identified in the 2017 review [7]. However, our study further identified significant associations with several cancers, including gastric cancer, lung cancer, bladder cancer, and esophageal cancer, expanding the oncological impacts beyond those previously reported.

In contrast to the findings of Waziry et al., our study established a significant link between WPS and CVD beyond just the general cardiovascular disease category, including stroke. We also identified associations with metabolic disorders like diabetes and metabolic syndrome, corroborating the earlier study but providing additional specificity regarding the nature of these metabolic impacts. Our research further identified significant associations with reproductive outcomes, such as changes in sperm parameters and infertility, reinforcing concerns about the broader reproductive health implications of WPS. Moreover, our study provided new insights into mortality risks associated with WPS, including both all-cause, CVD, and cancer-specific mortality, findings not supported in the earlier review. This substantial evidence underscores the severe and potentially fatal consequences of long-term WPS exposure, adding a critical dimension to the understanding of WPS's health impacts. Despite these expanded findings, our study also noted

conditions where no significant associations with WPS were observed, aligning in some respects with the previous review. Both studies found no significant association between WPS and certain conditions like BMI, WC, hypertension, heart rate, and dyslipidemia. However, our study uniquely highlighted the lack of association with depression, and dyspnea, adding to the nuanced understanding of WPS's health impacts.

The harmful constituents of WPS elucidate the molecular and pathological mechanisms underlying these associations. WPS contains a myriad of carcinogenic substances, including polycyclic aromatic hydrocarbons (PAHs) [54, 55], nitrosamines [56], volatile organic compounds (VOCs) [57], and heavy metals [58]. PAHs, produced during the incomplete combustion of tobacco and charcoal, are potent carcinogens that form DNA adducts, leading to mutagenesis and carcinogenesis [59, 60]. Similarly, nitrosamines, generated during tobacco curing, are highly carcinogenic, causing critical genetic mutations that disrupt cell regulation and promote malignancy [61]. VOCs such as benzene and formaldehyde are well-documented carcinogens implicated in lung cancer development [62, 63]. Heavy metals like arsenic, cadmium, and lead, present in WPS, cause DNA damage directly or through oxidative stress, contributing to cancers of the stomach, lungs, bladder, and esophagus [64–66].

CVD and stroke are major health concerns associated with WPS. Carbon monoxide (CO) in WPS binds to hemoglobin with greater affinity than oxygen, reducing oxygen delivery to tissues and exacerbating cardiovascular conditions [67, 68]. Nicotine, a central component of WPS, acts as a stimulant, increasing heart rate and blood pressure and promoting atherosclerosis and thrombosis, thereby elevating the risk of CVD and stroke [69]. Additionally, particulate matter in WPS penetrates deep into the lungs and enters the bloodstream, causing systemic inflammation and oxidative stress, which further contribute to cardiovascular pathology [70, 71].

The association between WPS and metabolic disorders, including diabetes and metabolic syndrome, can be attributed to nicotine and tobacco-specific nitrosamines (TSNAs) [72]. Nicotine is known to induce insulin resistance and dyslipidemia, key factors in the pathogenesis of type 2 diabetes and metabolic syndrome [73]. TSNAs, on the other hand, impair glucose metabolism and insulin sensitivity, exacerbating metabolic dysfunctions. These mechanisms highlight the multifaceted impact of WPS on metabolic health, underscoring the need for targeted interventions to mitigate these risks.

Reproductive health is adversely affected by WPS, with heavy metals and nicotine playing pivotal roles. Lead and cadmium, prevalent in WPS, negatively impact sperm quality, including count, motility, and morphology [74–77]. Nicotine further impairs sperm function and contributes to reduced fetal growth by affecting placental function, leading to adverse reproductive outcomes such as LBW [78, 79]. These findings emphasize the detrimental effects of WPS on reproductive health and the potential for intergenerational health impacts.

Respiratory diseases, including COPD, bronchitis, and wheezing, are strongly linked to WPS due to the presence of tar and reactive oxygen species (ROS) in the smoke [71]. Tar, a complex mixture of chemicals, damages the respiratory tract, leading to chronic respiratory conditions [80]. ROS cause oxidative stress and inflammation, further compromising respiratory health [81]. Additionally, ROS contribute to periodontal disease by damaging periodontal tissues, highlighting the broader systemic effects of WPS on respiratory and oral health [82, 83].

The association between WPS and increased mortality, particularly all-cause and cancer-specific mortality, is underscored by the chronic exposure to CO and various carcinogens in the smoke. Chronic CO exposure leads to long-term cardiovascular and respiratory issues, contributing to higher mortality rates. Carcinogens such as PAHs, nitrosamines, and heavy metals significantly elevate the risk of cancer-related deaths, reflecting the severe and multifaceted health impacts of WPS [84].

Periodontal disease is characterized by inflammation and destruction of the supporting structures of the teeth, including the gingiva, periodontal ligament, and alveolar bone. The pathophysiology of periodontal disease in the context of WPS involves complex interactions between microbial, immune, and inflammatory responses, exacerbated by the components of WPS [52, 85, 86].

One of the primary mechanisms by which WPS affects periodontal health is through its impact on the oral microbiome [52]. WPS contains a myriad of toxic substances, including nicotine, tar, carbon monoxide, and various heavy metals. These substances can alter the composition of the oral microbiota, promoting the growth of pathogenic bacteria such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*, collectively known as the "red complex." These pathogens are key contributors to periodontal disease as they possess virulence factors like proteases, lipopolysaccharides, and fimbriae, which facilitate tissue invasion and immune evasion [87, 88].

Nicotine, a major component of WPS, plays a significant role in modulating the host immune response. Nicotine can suppress the function of neutrophils, macrophages, and lymphocytes, which are critical for the initial immune defense against periodontal pathogens. Additionally, nicotine stimulates the release of pro-inflammatory cytokines such as interleukin-1β, tumor necrosis factor-alpha, and interleukin-6, leading to a

sustained inflammatory response. This chronic inflammation results in the destruction of connective tissue and alveolar bone, hallmark features of periodontitis [89, 90].

Oxidative stress is another crucial mechanism through which WPS exacerbates periodontal disease. The combustion of tobacco in WP generates a high concentration of ROS, which can cause direct damage to cellular components, including lipids, proteins, and DNA. In periodontal tissues, ROS can enhance the expression of matrix metalloproteinases, particularly MMP-8 and MMP-9, which degrade extracellular matrix components such as collagen and elastin. This enzymatic degradation weakens the structural integrity of the periodontal ligament and alveolar bone, facilitating disease progression [91, 92].

Furthermore, WPS-induced hypoxia can contribute to periodontal tissue destruction. The high levels of carbon monoxide in WPS can bind to hemoglobin, reducing its oxygen-carrying capacity and leading to localized tissue hypoxia. Hypoxic conditions can further promote the release of inflammatory mediators and enhance osteoclast activity, resulting in increased bone resorption and periodontal attachment loss [93, 94].

In addition to these molecular mechanisms, WPS can also impair the healing and regenerative capacity of periodontal tissues. Nicotine and other toxicants in WPS can inhibit the proliferation and differentiation of gingival fibroblasts and periodontal ligament cells, which are essential for tissue repair and regeneration. This inhibition can delay wound healing and exacerbate tissue destruction in the context of periodontal disease [95].

The quality of evidence in our systematic review and meta-analysis was evaluated using the GRADE system, which allowed us to rigorously assess the robustness of our findings. The GRADE system classifies evidence into four categories: high, moderate, low, and very low. This classification is based on several factors, including study design, risk of bias, consistency, precision, directness, and the presence of a large effect, dose–response gradient, and publication bias [96]. Despite identifying significant associations between WPS and numerous adverse health outcomes, credibility assessment criteria showed one outcome presented low evidence (birth weight), while other outcomes presented very low evidence.

The observational studies included in our meta-analysis, encompassing case–control, cross-sectional, and cohort designs, are inherently subject to several limitations that can affect the validity and reliability of our findings. One major limitation is the presence of confounding factors, where unmeasured or inadequately controlled variables may influence both the exposure (waterpipe smoking) and the outcomes, leading to biased estimates. For example, lifestyle factors such as diet, physical activity, and exposure to other forms of tobacco smoke or environmental pollutants, were not consistently accounted for across studies [97]. Additionally, recall bias is a significant concern, particularly in case–control and cross-sectional studies, as participants' self-reported data on smoking habits and health outcomes may be inaccurate or influenced by their current health status [98]. Selection bias is another issue, where the participants included in the studies may not be representative of the general population, limiting the generalizability of the results. The cross-sectional nature of many included studies also precludes the establishment of temporal relationships between WPS and health outcomes, hindering causal inferences.

Inconsistency is a critical factor affecting the quality of evidence in our systematic review and meta-analysis, particularly as assessed through the GRADE framework. Consistency refers to the degree to which similar results are obtained across different studies [99]. In our analysis, we evaluated inconsistency using the I^2 statistic, which quantifies the percentage of variation across studies that is due to heterogeneity rather than chance [100]. High I^2 values indicate substantial inconsistency among the included studies. Our findings revealed significant heterogeneity in the effect sizes reported across different studies for many health outcomes. This inconsistency may arise from several sources, including differences in study populations, variations in WPS exposure definitions (e.g., frequency, duration, and intensity of smoking), and methodological disparities across studies. Variability in the demographic characteristics of study participants, such as age, gender, socioeconomic status, and geographic location, can contribute to inconsistent findings. Additionally, differences in study design and quality, such as how outcomes were measured and controlled for confounding factors, further exacerbate heterogeneity. For example, some studies may have employed more rigorous methodologies or had more comprehensive adjustments for potential confounders, leading to differences in reported effect sizes. The inconsistency reflected by high I^2 values necessitates caution in interpreting the pooled estimates from our meta-analysis. It suggests that the observed associations may not be universally applicable, and that individual study results should be considered in their specific contexts.

The I^2 statistic is a widely accepted index for evaluating heterogeneity between studies. It quantifies the proportion of total variation due to heterogeneity rather than within-study sampling error. However, interpreting I^2 can be challenging due to within-study sampling error, which complicates its application. According to the grading approach, an I^2 value greater than 50% may indicate substantial heterogeneity, suggesting that the evidence should be downgraded. Unfortunately, the I^2

statistic does not reveal the actual heterogeneity between studies or the extent of variation in effect size. Instead, it indicates the proportion of observed variance that would likely remain if sampling error was eliminated. It is important to note that I^2 is a proportion, not an absolute value [101, 102]. The prediction interval provides additional information about the variability in effect size. It represents the range within which a true effect is likely to fall, roughly between plus or minus two standard deviations. This interval offers a clear and intuitive measure of the absolute amount of dispersion [103].

Directness is a crucial component of evidence quality in the GRADE framework, referring to how closely the evidence aligns with the specific research question or the population, intervention, comparator, and outcomes of interest [104]. In our systematic review and meta-analysis, evaluating the directness of the evidence involved assessing whether the included studies directly addressed the health impacts of WPS in the populations and contexts of interest. One challenge in assessing directness was the variation in how WPS was defined and measured across studies. Differences in frequency, duration, and intensity of waterpipe smoking can significantly influence health outcomes, yet these aspects were not uniformly reported or standardized. Some studies might have defined WPS as occasional use, while others considered regular or daily use, leading to potential discrepancies in the observed associations. Moreover, the populations studied in the included research varied widely in terms of age, gender, socioeconomic status, and geographical location. While this diversity can enhance the generalizability of the findings, it can also introduce variability that affects the directness of the evidence. For instance, cultural differences in smoking practices and exposure to other environmental risk factors may impact the applicability of the results to different populations. The comparators used in the studies also influenced the directness of our findings. While some studies compared WPS users to non-smokers, others included comparisons with cigarette smokers or users of other tobacco products. These different comparators can yield varying insights into the relative risks associated with WPS, complicating the synthesis of a clear and direct understanding of its health impacts. Additionally, the outcomes measured in the studies covered a wide range of health effects, from various cancers and cardiovascular diseases to respiratory conditions and reproductive issues. While these outcomes are all relevant to understanding the health impacts of WPS, the breadth of outcomes studied means that not all results directly pertain to every specific research question about WPS. For example, some studies focused on short-term respiratory effects, while others examined long-term cancer risks, each requiring different considerations in terms of directness.

Imprecision is a critical factor in the GRADE framework, reflecting the uncertainty around effect estimates [105]. In our systematic review and meta-analysis on the health impacts of WPS, one of the primary indicators of imprecision was the prediction interval. Unlike confidence intervals, which estimate the range within which the true effect lies based on the included studies, prediction intervals provide a range where the effect estimate is expected to fall for a new study. This distinction is crucial for assessing the consistency and reliability of our findings [103].

Among the various health outcomes assessed, three outcomes (stroke, CAD, and cancer mortality) showed a prediction interval that excluded the null effect, indicating a statistically significant finding. This suggests that the observed association with WPS is less likely to be due to random chance and is more likely to represent a true effect. In contrast, for other outcomes such as cancers, cardiovascular diseases, and respiratory conditions, the prediction intervals were wide, encompassing both significant and nonsignificant effects. This wide variability underscores the uncertainty surrounding these associations and suggests that the true effects of WPS on these outcomes may vary widely across different populations and study contexts. The wide prediction intervals can be attributed to several factors. First, the included studies varied significantly in their sample sizes, methodologies, and populations. This heterogeneity can lead to inconsistent effect estimates, contributing to broader prediction intervals. Additionally, differences in how WPS was defined and measured across studies (e.g., variations in frequency, duration, and intensity of use) further exacerbate this variability, making it challenging to obtain precise and reliable estimates. Moreover, the prediction intervals also reflect the influence of potential confounding factors and biases within the included studies. For example, studies with different levels of control for confounders, such as other tobacco use, environmental exposures, and lifestyle factors, can produce varying effect sizes. These discrepancies are captured in the wide prediction intervals, indicating that the true effect of WPS may differ depending on the study design and context.

The presence of wide prediction intervals necessitates caution in interpreting the pooled effect estimates from our meta-analysis. It underscores the need for more standardized research methodologies and larger, well-conducted studies to reduce variability and improve the precision of the effect estimates. Additionally, future research should aim to explore and account for potential sources of heterogeneity to narrow the prediction intervals and provide more definitive conclusions.

The presence of a large effect and dose–response gradients was considered when assessing the evidence quality [106]. For several outcomes, such as gastric cancer, lung cancer, CAD, and stroke, the effect sizes were substantial, suggesting a strong association with WPS. However, the evidence was often downgraded due to methodological limitations and potential biases in the included studies. Additionally, while some studies reported dose–response relationships, the overall evidence was insufficient to robustly establish this gradient across all outcomes.

Publication bias is a concern in meta-analyses, including ours on the health impacts of WPS, as it can distort the overall findings by favoring the publication of studies with significant results. To assess publication bias in our study, we followed guidelines outlined in the Cochrane Handbook by examining the symmetry of funnel plots. In our meta-analysis, we visually inspected funnel plots for each outcome to assess for potential publication bias. We found that funnel plot asymmetry was observed in several analyses, indicating possible publication bias. Specifically, there appeared to be a lack of small studies with nonsignificant results, which could suggest that studies reporting no association between WPS and certain health outcomes may not have been published or included in our analysis. This asymmetry suggests that our results may overestimate the true effect size of WPS on these outcomes [107, 108].

A significant limitation of our study is the inability to conduct subgroup analyses based on study design, age categories, and gender. The primary reason for this limitation is the low number of studies available for most outcomes, with the majority of outcomes being supported by only 3–5 studies. Conducting subgroup analyses with such limited data would lead to insufficient statistical power, resulting in wide confidence intervals and unreliable estimates. Additionally, the variation in study design was minimal, as most of the included studies for each outcome were of a similar design, such as cross-sectional or case–control studies. This homogeneity in study design further precluded meaningful subgroup analyses. Furthermore, the included studies predominantly focused on male participants and young to middle-aged adults, leading to an underrepresentation of females and older populations. This lack of diversity in study populations limited our ability to assess potential variations in associations across different age and gender groups. While the consistency in study design and participant demographics enhances comparability within outcomes, it also restricts the generalizability of our findings to broader populations. These limitations highlight the need for future research to include a greater diversity in study designs and participant characteristics to enable comprehensive subgroup analyses and provide more nuanced insights into the associations between waterpipe smoking and health outcomes. We have acknowledged these constraints in the discussion section to ensure transparency and to inform readers about the interpretive boundaries of our findings.

One of the primary strengths of our systematic review and meta-analysis is the comprehensive nature of our literature search. We meticulously screened a wide array of databases and included a significant number of studies, ensuring that our findings are based on a broad and diverse set of data. This extensive search strategy enhances the generalizability of our results and provides a robust overview of the health impacts of WPS. Additionally, we employed rigorous inclusion and exclusion criteria, which ensured that only high-quality observational studies were included in our analysis. This methodological rigor enhances the credibility of our findings and reduces the risk of bias. The use of a random-effects model in our meta-analyses further accounted for the variability among the included studies, providing a more accurate estimate of the associations between WPS and various health outcomes. Our review also benefits from the detailed assessment of a wide range of health outcomes. By examining not only respiratory diseases and cancers but also cardiovascular diseases, metabolic parameters, reproductive health, and periodontal diseases, our study provides a comprehensive understanding of the multifaceted impacts of WPS on human health. This holistic approach allows for a more nuanced interpretation of the risks associated with WPS. Moreover, we conducted thorough sensitivity analyses to identify any studies that might have disproportionately influenced our pooled estimates. This approach adds to the robustness of our findings, as it ensures that our conclusions are not unduly affected by any single study.

Conclusions

In conclusion, our systematic review and meta-analysis provide compelling evidence that WPS is significantly associated with a broad spectrum of adverse health outcomes. Notably, WPS is linked to various respiratory diseases, including COPD, chronic bronchitis, and respiratory symptoms such as cough and sputum. Furthermore, our findings reveal a significant association between WPS and several types of cancer, including gastric, lung, bladder, and esophageal cancers. The analysis also indicates that WPS contributes to CAD, stroke, diabetes, metabolic syndrome, and adverse reproductive health outcomes, such as impaired sperm parameters. Moreover, WPS is associated with increased periodontal disease severity and a higher risk of LBW. Importantly, our study highlights a substantial increase in all-cause mortality and cancer-specific

mortality among waterpipe smokers. While our meta-analysis provides important insights into the health risks associated with WPS, the predominantly low to very low quality of evidence highlights the need for further high-quality research. Future studies should focus on minimizing biases, increasing sample sizes, standardizing exposure and outcome measurements, and exploring dose–response relationships to strengthen the evidence base. High-quality, well-conducted cohort studies are essential to better understand the causal association and inform effective public health policies to mitigate the harms of WPS.

Abbreviations

WPS	Waterpipe smoking
US	United States
GYTS	Global Youth Tobacco Survey
CVD	Cardiovascular disease
LBW	Low birth weight
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
PROSPERO	Prospective register of systematic reviews
RR	Risk ratios
HR	Hazard ratios
OR	Odds ratios
MD	Mean difference
CI	Confidence intervals
NOS	Newcastle-Ottawa scale
REML	Restricted maximum likelihood
SMDs	Sandardized mean differences
SDs	Standard deviations
CAD	Coronary artery disease
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
COPD	Chronic obstructive pulmonary disease
GERD	Gastroesophageal reflux disease
IBS	Irritable bowel syndrome
MS	Multiple sclerosis
SDF	Sperm DNA fragmentation
FEV	Forced expiratory volume
FVC	Forced vital capacity
PI	Plaque index
BOP	Bleeding on probing
MBL	Marginal bone loss
CBL	Crestal bone loss
PR	Prevalence ratio
GDM	Gestational diabetes mellitus
WC	Waist circumference
PAHs	Polycyclic aromatic hydrocarbons
VOCs	Volatile organic compounds
CO	Carbon monoxide
TSNAs	Tobacco-specific nitrosamines
ROS	Reactive oxygen species

Supplementary Information

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Supplementary Material 1: Supplemental Table 1. Search strategy. Supplemental Table 2. The methodological quality assessment of included studies. Supplemental Table 3. Summary of included studies. Supplemental Table 4. Detailed GRADE Assessment and Justification for Downgrades of Each Outcome.

Supplementary Material 2: Figure 1.

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Not applicable.

Authors' contributions
MS, SR, and WM contributed to the conceptualization. MS, SR, and HG contributed to the literature searches with HG, SA, FG, FL, ZM, and SR contributing to the data curation and extraction. MS and SR conducted the formal analyses. MS, SR, and WM led the writing of the manuscript. All authors commented on and contributed text to the manuscript. MS and SR accessed and verified the data.

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Data availability
All data relevant to the study are included in the article or uploaded as supplementary information.

Declarations

Ethics approval and consent to participate
This study is a systematic review and meta-analysis of previously published observational studies. As it does not involve any new human or animal subjects, ethics approval and informed consent were not required.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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