NEW INSIGHTS IN INTRA-ORAL HALITOSIS MANAGEMENT

PhD thesis

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„The first and greatest victory is to conquer yourself.”

Plato

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1. LIST OF ABBREVIATIONS

ClO_2	chlorine dioxide
C	correlation
c.c.	correlation coefficient
CI	confidence interval
CH_3SH	methyl mercaptan
$(CH_3)_2S$	dimethyl sulfide
DMF	number of decayed, filled, and missing teeth
F.n.	Fusobacterium nucleatum
GC/MS	Gas chromatography-mass spectrometry
GI	Gingival index
HSROC	Hierarchical summary receiver-operating characteristic
H_2S	hydrogen sulfide
IOH	intra-oral halitosis
NA	not available
$NaClO_2$	sodium chlorite
NPV	negative predictive value
mL	milliliter
MD	mean difference
MID	minimally important difference data
OLS	organoleptic testing score
OLT	organoleptic test
OM	organoleptic measurement
P.g.	Porphyromonas gingivalis
PI	Plaque index
PPV	positive predictive value
RCT	randomized clinical trials
ROC	receiver operating characteristic
SD	standard deviation
Se	Sensitivity
SIFT-MS	selective flow tube mass spectrometry
Sp	Specificity

S.m.	Streptococcus mutans
SMD	standardized mean difference
SROC	summary receiver operating characteristic
TCI	Tongue coating index
T.d.	Treponema denticola
TDI	Tongue discoloration index
T.f.	Tannerella forsythia
VSCs	volatile sulfur compounds

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to find and bring the best solution for diagnosing and managing halitosis for everyone. To reach my vision, my mission is to contribute to oral health and well-being by providing the best care to every patient.

My specific goals are to investigate chlorine dioxide's efficacy in intra-oral halitosis and find the most appropriate method to diagnose halitosis.

2.2. Scientometrics

Number of all publications:	5
Cumulative IF:	16.839
Av IF/publication:	3.368
Ranking (Sci Mago):	Q1: 4, Q4: 1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	7.35
Av IF/publication:	3.68
Ranking (Sci Mago):	Q1: 2
Number of citations on Google Scholar:	9
Number of citations on MTMT (independent):	6
H-index:	2

2.3. Future plans

I want to continue my research. We conducted a protocol for a trial, which will be a pilot randomized controlled trial about the efficacy of hyperpure chlorine dioxide (ClO_2) in halitosis. After the ethical approval, we started enrolling the patients in January of 2024. For this, we established a halitosis work group, and with continuous improvement, we would like to help these patients' well-being and quality of life. By the end of the trial, the following steps regarding our field of interest will be more apparent to us and the public.

In my clinical work, getting the subsequent specialization will be essential; it will also help me in patient care and teaching. In summary, continuous improvement is necessary in personal and professional life.

3. SUMMARY OF THE PHD

The prevalence of halitosis is 31.8%, and the most common type assumes an intra-oral origin. However, evidence-based treatment protocols and diagnostic methods still do not exist. We aimed to conduct two meta-analyses to facilitate this.

The first meta-analysis investigated the correlation and diagnostic test accuracy between OM (gold standard measurement) and the most used device-supported methods (sulfide monitors, gas chromatographs, and portable gas chromatographs), called halitometers.

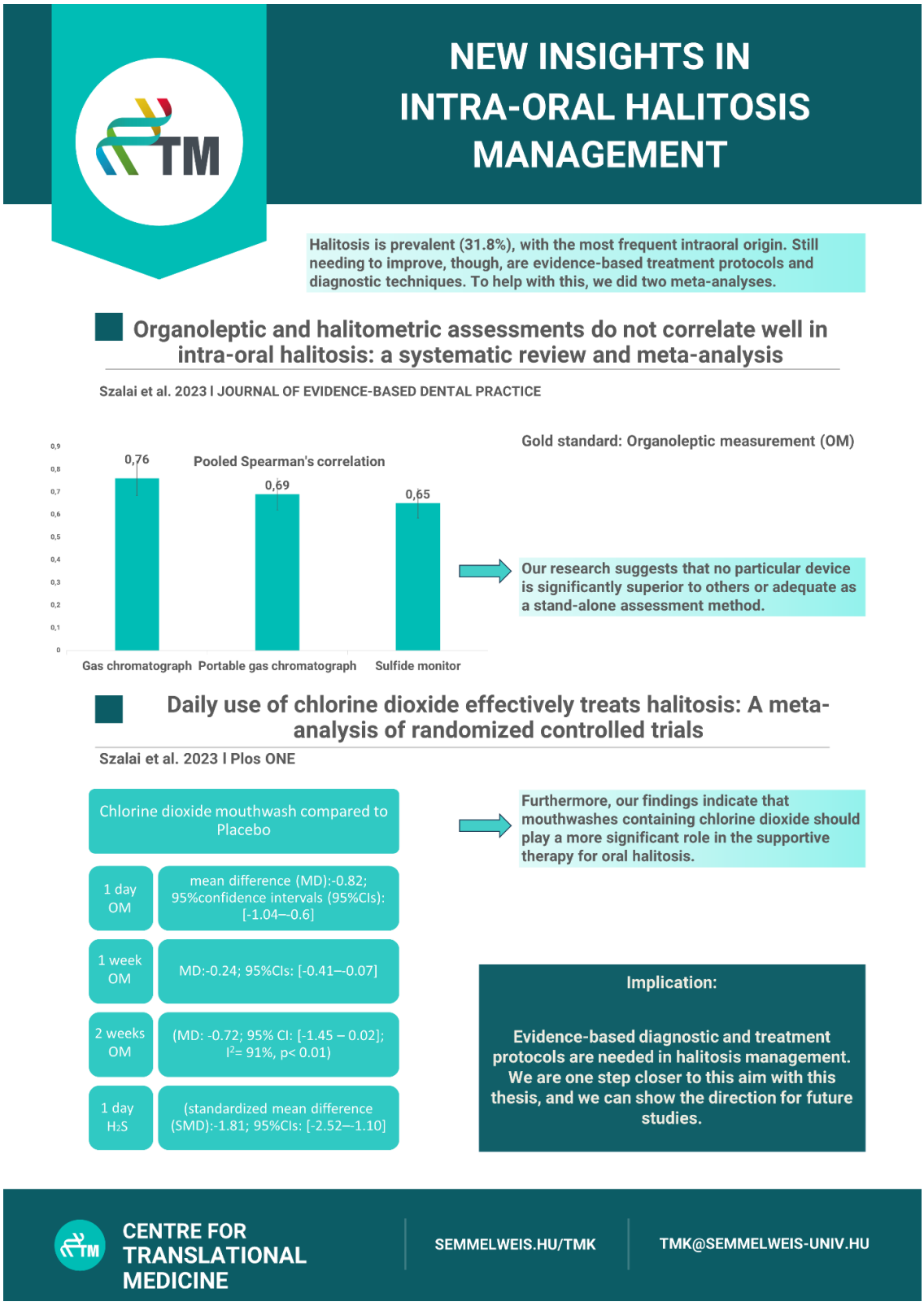
In the second meta-analysis, we investigated the efficacy of mouthwash products containing ClO_2 in halitosis. Primary outcomes were the changes in organoleptic measurement (OM) and volatile sulfur compounds.

The correlation analyses showed that the pooled Spearman's correlation coefficient with OM for sulfide monitors, portable gas chromatographs, and gas chromatographs was moderate.

The data showed a significant improvement in the ClO_2 group compared to the placebo group in the change of OM one-day, one-week, and changes in H_2S one-day data.

In conclusion, our data indicate that ClO_2 mouthwash may be a good supportive therapy in oral halitosis without known side effects in low concentration. Additionally, none of the most commonly used halitometers proved significantly superior to the others, and the correlation between them and OM needed to be stronger. Therefore, better devices must be developed as an alternative to OM for appropriate diagnosis.

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

We investigate the diagnosis options and chlorine dioxide mouthwash therapy for intra-oral halitosis.

5.1.2. What is the problem to solve?

In the field of intra-oral halitosis, there are no evidence-based diagnostic and treatment protocols; we would like to facilitate these missings.

5.1.3. What is the importance of the topic?

Oral hygiene has traditionally been associated with the privileged classes, but thankfully, perceptions and access to dental care are changing. A thorough examination is critical for diagnosing issues accurately. Halitosis, often linked to oral hygiene, can have deeper causes. When left undiagnosed or untreated, it can lead to severe psychological consequences, potentially causing isolation or even prompting thoughts of suicide. Recognizing that halitosis isn't always solely oral in origin is crucial, as it's often a symptom of underlying issues. This highlights the need for comprehensive healthcare that addresses oral health and its potential connections to broader health concerns. The significance lies in understanding the complexities of halitosis and its potential impacts and relations on a person as a whole.

5.1.4. What would be the impact of our research results?

We would facilitate our field of interest to get closer to the evidence-based guidelines in diagnosing and treating intra-oral halitosis. This can cause a significant improvement in patient care and quality of life in halitotic patients, and we can avoid the most serious consequences.

5.2. Understanding the complexity of halitosis plays a key role in the improvement of diagnosis and therapy

Halitosis research is increasingly important because patients' well-being is unimaginable with bad breath. Even the Egyptians were concerned about the problem and made an early form of a breath mint almost 3,000 years ago. The ancient Greeks and Romans used

various pastes, powders, and mouthwashes. Meanwhile, in the Far East, Buddhist principles regarded the mouth as the gateway to the body, so it is no coincidence that the tongue scraper became a popular utensil alongside the toothbrush (1). The Talmud mentions it as a significant disability and an acceptable reason for divorce and prohibits the priest from performing their duties with this condition (2). Today, halitosis can be a social isolation factor; in severe cases, people try to avoid social connection with halitotic people, and it also happens in the other direction to decrease uncomfortable reactions. This leads to depression and anxiety (3), so it causes secondary diseases. That can overwhelm the healthcare system if there is any capacity to work with these patients.

However, halitosis is a symptom, so finding the problem's origin is the main issue. Suppose doctors realize the problem and not just cure it but try to find the source and eliminate the pathological bad breath. In that case, patients' well-being will improve, and the overload of the healthcare system could decrease somewhat.

The prevalence of halitosis is between 20-71% (4-6). The various types of halitosis and the various diagnostic methods can explain the wide variety of prevalence. As we can see from the following figures, a new classification is raised approximately every ten years. Still, there is no consensus on the best definition and classification because they use different aspects.

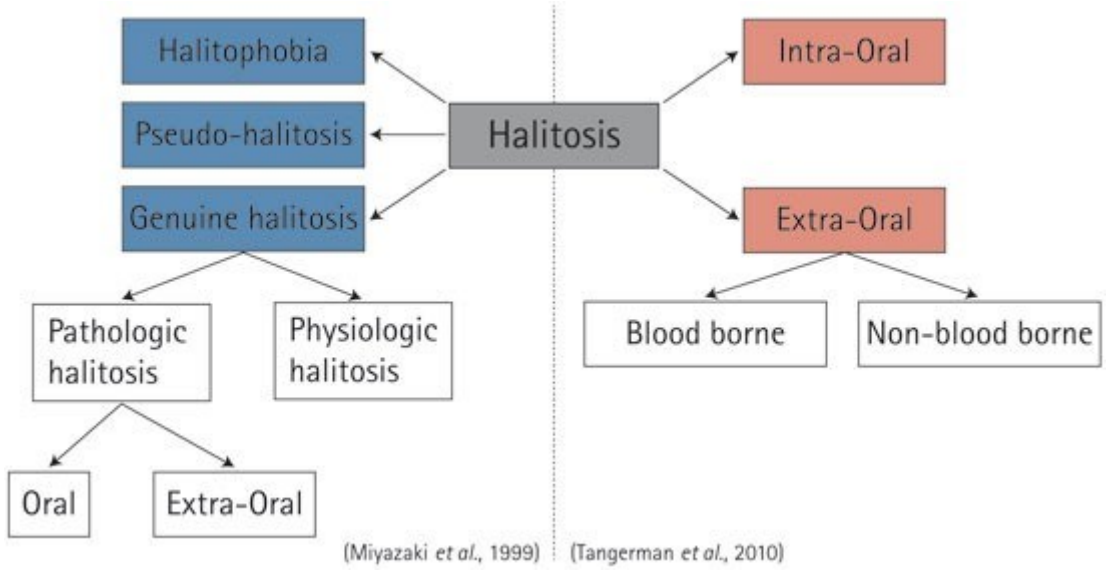


Figure 1. Previous classifications (1999, 2010) Original Figure from Aydin et al. (7)

After the Miyazaki et al. (8) (Figure 1.) classification, Tangerman et al. (9) tried to simplify it more clinically. Aydin et al. (7) suggested a new definition in 2014 and also a classification system for bad breath (Figure 2.) because previous ones may omit some aetiologies, and their diagnoses hinged on single-occasion halitometric and organoleptic findings. Halitometric diagnosis reflects the device-supported methods; meanwhile, the organoleptic measurement signs the sensory assessment of the breath. Based on the source of the bad breath, he distinguished it as Type 1 (oral), Type 2 (airway), Type 3 (gastroesophageal), Type 4 (blood-borne), or Type 5 (subjective) halitosis (7). Type 0 halitosis shows the sum of the physiological part of all five halitosis types present in every healthy patient to a small extent.

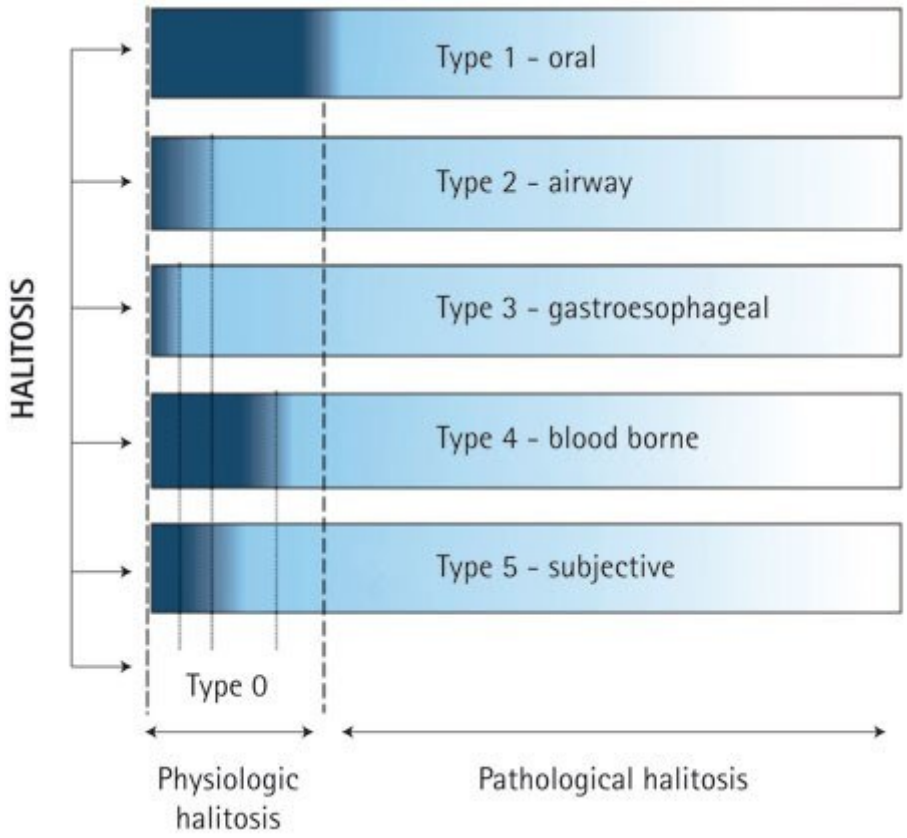


Figure 2. Halitosis classification (2014) by Aydin et al. (7)

Porter et al. mentioned (10), that the effectiveness of this classification will need to be tested. However, this classification makes it easier to understand the etiology of halitosis. Seemann et al. (11). suggested in the same year the following terminologies for general

dental practitioners (Table 1). Kapor et al. (12) further developed Miyazaki's variety, but the concept did not change (Figure 3).

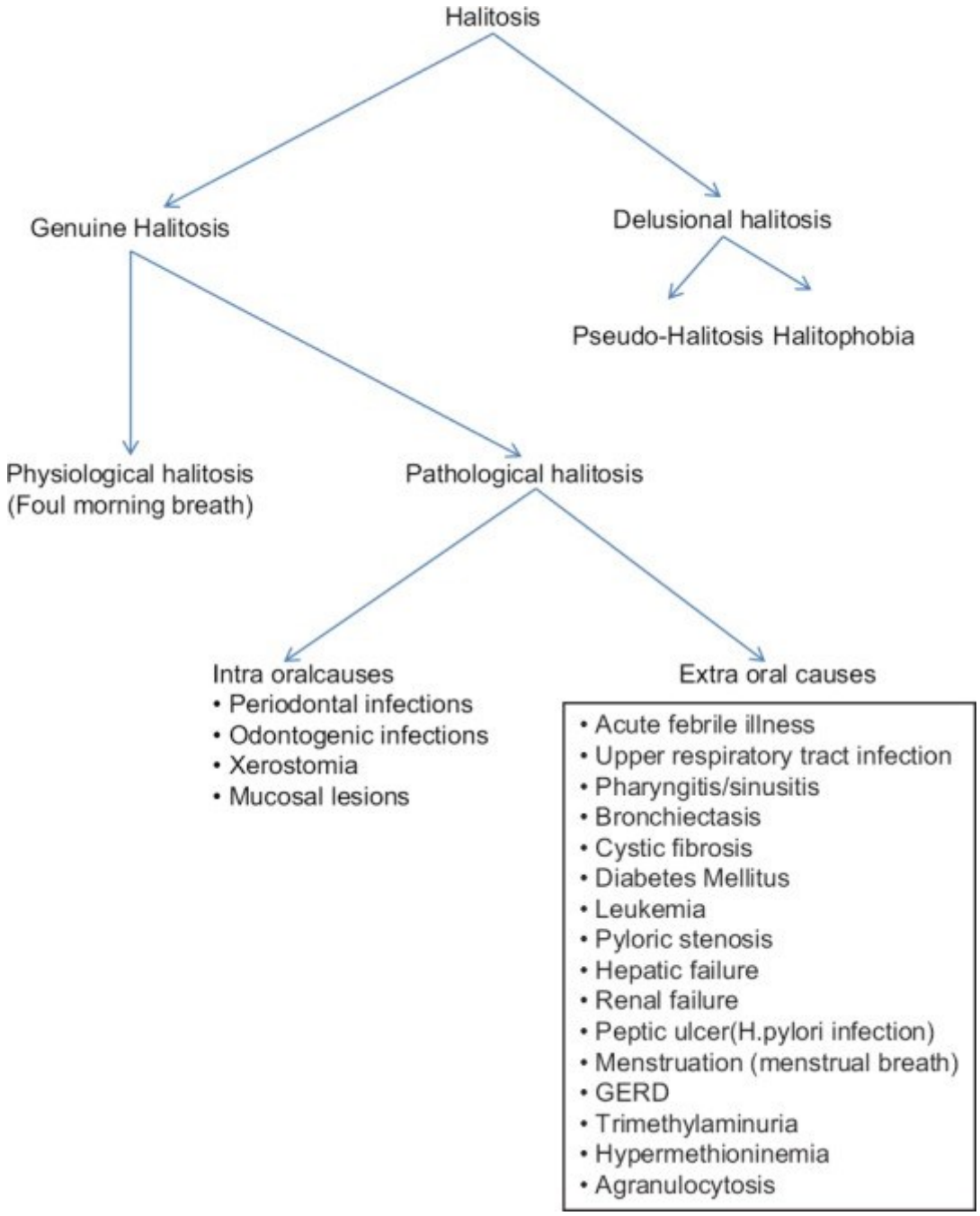


Figure 3. Latest halitosis classification (2016) by Kapoor et al. (12)

Table 1. The suggested terminologies that dental professionals can use to describe bad breath in their patients, given the typical circumstances of a general dental office (11, 13)

Diagnosis	Description
Temporary halitosis	The unpleasant smell we experience is caused by certain foods, such as garlic.
Intra-oral halitosis	An unpleasant smell that goes beyond socially acceptable levels and can affect personal relationships. This is usually caused by bacteria that accumulate on the back of the tongue or by a pathological condition or malfunction of oral tissues, such as periodontal disease. Several factors can affect the intensity of the malodor, including medication, smoking, and Sjögren's disease, which can influence the quality and quantity of saliva.
Extra-oral halitosis	Unpleasant odors can stem from pathological conditions beyond the mouth, including the nasal, paranasal, or laryngeal regions and the pulmonary or upper digestive tract. This type of odor is referred to as non-blood-borne extra-oral halitosis. Alternatively, in cases of blood-borne extra-oral halitosis, the unpleasant scent is released via the lungs and can be caused by disorders present anywhere in the body, such as hepatic cirrhosis.
Pseudo-halitosis	Patients may complain of persistent malodor despite a lack of objective evidence. This condition can often be improved with counseling and simple oral hygiene measures.
Halitophobia	After treatment for halitosis and pseudo-halitosis, the patient persists in believing they suffer from halitosis. No physical or social evidence supports this belief.

Intra-oral halitosis (IOH) is the most common; however, it can be mixed, which is probably why researchers avoid using any classifications.

5.2.1. Diagnostic methods

Not only is the classification so heterogeneous, but we can experience the same in the diagnostic methods. The organoleptic test (OLT) is considered the gold standard for diagnosing bad breath (14-16). The examiner sniffs the patient's breath and evaluates it from 0 to 5 (16). Most used this 6-point scale; when the breath is rated 0, patients have no bad breath, and 5 when it is very severe. However, the 4-point and 11-point scale also exist. The organoleptic method has several disadvantages; it is not just subjective (17) but nevertheless uncomfortable for the examiner and the patients (13). Another disadvantage of the process is that the training of organoleptic judges is complicated (18, 19). To the best of our knowledge, only University of the West of England Bristol organizes this course, leading to cost increases. Additionally, several factors can affect the olfactory sensation, leading to underestimation or overestimation, e.g., the examiner's emotional mood, gender, age, ethnicity, odor detection spectrum, threshold, climatic conditions, hormonal changes, olfactory fatigue, and COVID-19 infection (20, 21). However, the main disadvantage of OLT is the potential risk to human health or even life during any concomitant diseases, e.g., COVID-19, due to the nature of the examination process in potentially infectious situations (19).

Several diagnostic methods were developed to solve these problems. They can be direct and indirect. The most common way to measure IOH is to quantify the Volatile Sulfur Compounds (VSCs) from the breath produced by oral bacterial putrefaction (22). Principally, Gram-negative anaerobic bacteria produce (23) (*Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum, Tannerella forsythia, and Treponema denticola*) (24) these VSCs (hydrogen sulfide (H_2S), methyl mercaptan (CH_3SH), and dimethyl sulfide ($(CH_3)_2S$)) from sulfur-containing amino acids such as cysteine, cystine, methionine (25, 26). These bacteria localize mainly in deep pockets and the dorsum of the tongue (23). VSCs originate primarily from the tongue, secondary from the periodontal pockets (27), but patients with periodontitis display the highest concentrations of hydrogen sulfide in the deepest pockets (28). Bad breath also contains other molecules with an unpleasant odor, such as cadaverine and putrescine (29), although VSCs best characterize it, therefore primarily measured (30, 31).

Two common instruments to measure VSCs are electrochemical meters (e.g., Halimeter) and portable gas chromatographs (e.g., OralChroma) (26). They are considered objective, reliable and quantify the VSCs (17). The disadvantage of these instruments is that they cannot detect all kinds of volatiles, such as cadaverine and putrescine (29), which can also cause malodor. These items are also quite expensive (11).

Most researchers studying halitosis use more than one method to measure bad breath. On the one hand, they would like to perform a better diagnosis. On the other hand, it is a waste of time and money. Moreover, they use multiple different devices or techniques, which need to be standardized (32, 33). One article suggests device-supported measurement as a complementary diagnosing method (12), while another (34) suggests it as a primary method if it is a gas-chromatograph. Some diagnosing protocols also suggest more than one method to perform the diagnosis. Several studies were conducted to measure the correlation and diagnostic accuracy between OLT and device-assisted methods. The literature does not present a universally accepted measurement method that is considered appropriate and accurate (35, 36). Literature data must be compared, contrasted, and statistically assessed to understand halitosis measurement better. A 2007 review (14) also highlighted the need for meta-analyses to improve halitosis measurements. However, the need for evidence-based protocols is also present in the therapy.

5.2.2. Therapeutic possibilities and the chlorine dioxide mouthwashes

Bad breath still lacks a definitive treatment protocol, and the Cochrane review (15) found insufficient evidence to support any intervention. A protocol states that everything starts with proper oral hygiene (12). As concluded by Wylleman et al. (37) in a systematic review, it has been shown that cleaning the tongue, in addition to toothbrushing, can effectively reduce oral malodor. If proper oral hygiene does not alleviate symptoms and the underlying condition has been adequately treated (e.g., periodontitis), additional treatment may be necessary (38, 39), namely, the use of mouthwashes (38, 40, 41) or probiotics (42). People buy anti-odor mouthwash for millions of dollars each year, and many different kinds of mouthwash are available on the market (43). Chlorhexidine-containing mouthwashes are considered the gold standard (44) mouthwashes. Although they are effective, they have several side effects, e.g., tooth or tongue staining, increased tartar, mouth or throat irritation, dry mouth, and change in taste of food or drink may

occur (44, 45). There is an obvious need to find a mouthwash that supports halitosis treatment effectively and without adverse events.

ClO_2 is a selective oxidizing agent (46). Unlike other oxidants, it interacts slightly with most elements in living beings (46). Cysteine, tyrosine, and tryptophan are the three amino acids that ClO_2 reacts with most quickly. Due to its interactions with the three aforementioned amino acids and their acid residues in proteins and peptides, ClO_2's anti-halitotic activity has an antibacterial impact (46). Furthermore, it oxidizes the precursors of VSCs, which increases its efficacy (14, 47). These antimicrobial mouthwashes are mainly effective against IOH.

The aqueous ClO_2 solution (48) is widely used in medicine for the disinfection of intra-oral areas (49-52) without side effects in small concentrations (53). A systematic review also could not find side effects in small concentrations (54,). However, the ClO_2 consumption in South America makes it look not good (55).

ClO_2 mouthwashes have already been the subject of several investigations into halitosis (52, 56-59); however, these individual studies need more power.

We can see there needs to be an understanding of the whole halitosis. We need to understand every process, and this area is a bit underestimated; however, if more investigation could bring more knowledge, we could be closer to guidelines and evidence-based diagnostic and treatment protocols. Consequently, more doctors could treat these patients, and the prevalence of bad breath and its consequences could decrease.

6. OBJECTIVES

6.1. Study I. - Investigating the diagnostic value of the device-supported measurement in IOH

We aimed to find and recommend the best method for the device-supported measurement of oral malodor. We seek the answer to the following clinical questions:
Are halitometers suitable for measuring IOH as OMs?
We hypothesized that the halitometers are as appropriate as the organoleptic method to measure the level of halitosis.

6.2. Study II. - Investigating the efficacy of chlorine dioxide in intra-oral halitosis

In Study II, we wanted to understand: Are mouthwashes containing c effective in patients with IOH?
We hypothesized that mouthwashes containing ClO_2 are more effective than placebos and as effective as other mouthwashes in reducing oral malodor.

7. METHODS

Both meta-analyses were registered at the International Prospective Register of Systematic Reviews (PROSPERO), using the registration numbers CRD42022320024 (Study I.) and CRD42021281195 (Study II.).

The Cochrane Handbook for Systematic Reviews (60) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA 2020) (61) led to the processing of the meta-analyses.

7.1. Study I. - Investigating the diagnostic value of the device-supported measurement in intra-oral halitosis

7.1.1. Systematic search

The following PIRD (Population, Inex test, Reference Test, Diagnosis) framework was used as an inclusion criteria for the study topic. We aimed to quantify IOH. Hence, we excluded known systemic disorders from the population. The traditional reference test, OM, was contrasted with eNoses, gas chromatographs, portable gas chromatographs, and electrochemical meters. The correlation coefficient (c.c.) was the primary outcome, while the devices' specificity and sensitivity came in second. When correlations were calculated between the VSC and organoleptic testing scores (OLS), clinical trials were included.

Case reports, non-English conference papers, in vitro or animal research, and non-English publications were rejected. We didn't include children in our population. (62).

The literature search was done in the five databases (MEDLINE, CENTRAL, Embase, Scopus, and Web of Science) on 23rd March 2022. The search key used was the following:

(halitosis OR "bad breath" OR "oral malodor" OR "oral malodour" OR "morning breath" OR "fetor oris" OR "foetor oris" OR "fetor ex ore" OR "foetor ex ore") AND (organoleptic OR "organoleptic measurements" OR "organoleptic measurement" OR OLT OR OT OR "organoleptic scale" OR "organoleptic test" OR "organoleptic scores" OR "organoleptic score") AND (Halimeter OR Breathtron OR OralChroma OR eNose OR "putative odorant" OR "sulfide detector" OR "gas chromatography" OR "gas chromatograph" OR GC OR Volatilization OR "gas sensor" OR "hydrogen sulfide" OR "methyl mercaptan" OR " dimethyl sulfide" OR VSC OR VSCs OR "Volatile sulfur

compounds" OR "Volatile sulfur compound" OR "Volatile sulphur compounds" OR "Volatile sulphur compound") AND (correlation OR "correlation coefficient" OR relationship OR association OR accuracy OR correlation OR utility OR comparison OR compare OR association OR assessment OR reliability)

We followed the same protocol in Studies I and II. during the selection process:
After automatic and manual duplicate elimination, two researchers independently checked each record for appropriate titles and abstracts. Then, they determined which full texts were eligible. In the event of a dispute, a third investigator was brought in. Cohen's Kappa was also used in both events to calculate the inter-rater agreements. We scanned the grey literature, review papers, and articles that met the eligibility requirements' reference lists. The selection process was visualized with the PRISMA2020 flow diagram (63).

7.1.2. Data collection process and data items

All available data was collected in predefined tables by two investigators who worked independently. The following data items were collected: first author, year of publication, study design, demographic data of the population, type of index and reference tests, type of correlations, c.c., exclusion of extraoral halitosis and children, sensitivity, specificity, threshold, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC). In those articles where correlations were available for multiple dates, only one (preferably the baseline) was included in the analyses.

7.1.3. Effect measure and synthesis methods

A meta-analysis of correlations and a diagnostic meta-analysis are both included in Study I.

1. **Pearson's correlation, Spearman correlation, Kendall tau correlation**, and correlations whose type of correlation was not mentioned in the paper were all present in all analyses. The most common sort of correlation is **Pearson's c.c.** However, it functions correctly if there is a linear correlation between the variables (64). **Kendall's tau-b c.c.** is a rank correlation analogous to the **Spearman correlation**. The range of the correlation was -1 to +1. The perfect positive correlation indicates that both variables move in the same direction. The two variables appear to move in opposition to one another, according

to the perfect negative correlation. In the absence of a linear relationship, 0, the two variables are unrelated.

The standard errors of each obtained correlation might be approximated using the study sample sizes after Fisher's z-transformation was applied to each obtained correlation (65). Correlations were then retransformed for the meta-analyses.

Subgroup analyses were used to examine the various associations in order to improve accuracy and reduce bias in the calculations.

The Hartung-Knapp adjustment was used to do random-effects meta-analyses on the various datasets since we predicted significant between-study heterogeneity (66). Variance measure I^2 and Tau-squared (τ^2) statistics were employed to estimate the degree of heterogeneity among the studies (67, 68). With the Q profile approach, the constrained maximum-likelihood estimator was used to estimate the variance for the confidence interval (CI). Based on the association noted previously, additional subgroup analyses of the correlations were also carried out because their combined analysis is troublesome. In order to determine whether or not systemic disorders were present in the subgroups, the sorts of correlations were further examined.

Forest plots were employed to graphically represent the results. Where appropriate, we also provided the results' prediction ranges or the projected range of their influence on subsequent investigations. Outlier and influence analyses were carried out (69, 70).

2. The studies for the **Halimeter** and **OralChroma** diagnostic tools were retrieved, together with the corresponding thresholds of the continuous results underlying the diagnostics. The values for the true positive, false positive, false negative, and true negative entries in the contingency tables were usually generated from other data, such as the overall number of patients under investigation, sensitivity, specificity, and PPV.

The **Halimeter** tool's summary receiver operating characteristic (SROC) curve was fitted using the non-Bayesian variant of the method (71) because the thresholds varied among experiments. For the sake of clarification, we would like to point out that Harbord et al. (72) demonstrated that the method adopted is mathematically similar to the bivariate model (73, 74).

Two thresholds' worth of findings from two investigations were published. We only used one threshold from these investigations to fit the SROC curve. We weren't really sure

whether the objective of the other two experiments was to find OLS ≥ 2 conditions. We also performed the analysis again without these studies for this reason.

For the **OralChroma** diagnostic tool, there were just three studies available. From each of these research, we gathered contingency tables corresponding to the same threshold usage ((H_2S 112 ppb or CH_3SH 23 ppb or $(CH_3)_2S$ 8 ppb). The generalized mixed-effect univariate method (75) was then used to determine the pooled sensitivity and specificity separately. Because so few papers were available, it was impossible to employ the bivariate technique. The resulting Halimeter SROC curve, the OralChroma summary point, the study-level estimations, and their CIs were all shown on a similar ROC plot.

The meta [5.2.0] package and the R script of the online tool were used to conduct all statistical analyses (Team, 2021) using R [v4.1.2] (76) (77).

7.1.4. Bias assessment and quality of evidence

Two investigators worked independently with the quality assessment tool for diagnostic accuracy studies (QUADAS-2) (78) and QUADAS-C (79). When a more comprehensive range of comparable index tests are available, we applied QUADAS-C, which is an extension of QUADAS-2. The purpose of these tools is to assess the risk of potential bias in several areas, including patient selection, index tests, reference standards, time and flow, and applicability.

Publication bias was assessed with Egger's test using the classical Egger's (80) method to calculate the test statistic as per Sterne et al. (81), and contour-enhanced funnel plots were also created to give visual aid. The analysis results were critically handled if the study number was below ten or the study effects showed high heterogeneity.

Two reviewers (E.S., P.T.) used the GRADEpro (82) tool to perform the evidence profile according to the GRADE Handbook (83).

7.2. Study II. - Investigating the efficacy of chlorine dioxide in intra-oral halitosis

7.2.1. Eligibility criteria

We used the PICO framework (population, intervention, comparator, and outcome) for eligibility. Adults with odorous breath and no systemic disorders comprised the included population. A mouthwash containing ClO_2 was used as the intervention, while other mouthwashes, placebo, or no therapy were used as the comparison. Changes in OLT

results or VSCs' levels were the outcomes of the interest. We didn't set an upper age limit; the population was over the age of 18. OLS ≥ 1 was used to define bad breath. Only randomized controlled studies were included. No language or time limitations had been placed throughout our search.

We did not include patients with systemic diseases or children as a population, nor in vitro or animal trials. We also did not include experiments where mouthwash contained ClO_2 and zinc together in the same mouthwash.

7.2.2. Search strategy and study selection

The literature search was conducted on 14 October 2021 and updated on 23 September 2022 in the same five databases that we used in Study I.

The search key used was the following:

("chlorine dioxide" OR "chlorinedioxide" OR "chlorine-dioxide" OR ClO2 OR "oxohalogen oxidant" OR "Chlorine dioxide containing mouthwash" OR "Chlorine dioxide containing mouthwash*") AND (halitosis OR "bad breath" OR "oral malodor" OR "oral malodour" OR "morning breath" OR "fetor oris" OR "foetor oris" OR "fetor ex ore" OR "foetor ex ore" OR VSC OR VSCs OR "Volatile sulfur compounds" OR "Volatile sulfur compound" OR "Volatile sulphur compounds" OR "Volatile sulphur compound")

We utilized customized search phrases in diverse databases and scrutinized each reference list of the included research and relevant reviews both manually and with Scopus automation.

We applied the same method for the study selection as Study I.

7.2.3. Data collection process and data items

The following data from the eligible articles were extracted: population characteristics, interventions, comparator, measurement methods, and outcomes. We analyzed the outcomes of OLT scores and VSCs' levels by pooling the data from all available time points. The studies presented VSC data in either ppb (parts per billion) or ng/10mL (nanograms per 10 milliliters), with some providing total VSC data while others separated the data into H_2S, CH_3SH, and $(CH_3)_2S$. To ensure comparability, we converted the ppb measurements into ng/10 mL by dividing them by ten.

7.2.4. Effect measures and synthesis methods

The data were analyzed by mean difference (MD) and standardized mean difference (SMD) meta-analyses with a 95% confidence level. When all available data were measured with identical techniques, tools, and scales, the MD meta-analysis was carried out. In contrast, the SMD meta-analysis was used when different instruments were used to measure the same parameter. Because researchers used various tools to measure them, we used the MD on the OLS data and the SMD on the VSC data. Studies without Standard Deviations (SD) or with uncomputable SDs from OLS data were excluded from meta-analyses. We formed subgroups based on changes in outcome data over various time periods: one-day, one-week, and two-week data are demonstrated separately by OLS subgroups.

In crossover studies, only first-period results were used to avoid distorting data with dependent study populations.

If the SD of the measurements changes across the follow-up times was not specified, the Cochrane guidelines were implemented. In cases where only a CI was provided for the change, we calculated the difference between the upper and lower CI limits and divided it by 3.92, which corresponds to the value for a 95% CI (60). In studies where the SD of the change was available, a c.c. was computed by using the SD values of both the intervention and control groups from that study. The missing SDs of other studies were then calculated using this c.c. value (60).

The weight that each study carried in the meta-analysis was determined by its SDs and sample size. If a study had larger SDs or smaller sample sizes, it was assigned a lower weight. Conversely, a study with smaller SDs or larger sample sizes was assigned a higher weight. The I-squared test was used to calculate statistical heterogeneity. Since the population of studies was expected to be heterogeneous, random effects models were used for the meta-analyses. All statistical analyses were performed using the R statistics software (76) and its meta package. The results of the meta-analyses were presented through forest plots.

7.2.5. Bias assessment

The Cochrane Risk of Bias 2 (ROB-2) Tool (84), individually randomized, parallel-group trials, and crossover trials were used for risk of bias assessment. They have the following

domains: bias arising from the randomization process, bias arising from the period and the carryover effects, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in selecting the reported results. The difference between the two ROB 2 Tools applied is the bias domain due to period and carryover effects, which only applies to crossover trials. The two investigators discussed and settled the disagreements.

Due to the small number of articles, we were unable to conduct funnel plots and heterogeneity analysis.

7.2.7. Certainty assessment

The certainty assessment was evaluated according to the GRADE Handbook (83); we performed the summary of findings table with the GRADEpro (82) tool.

8. RESULTS

8.1. Study I. - Investigating the diagnostic value of the device-supported measurement in intra-oral halitosis

8.1.1. Search and selection

1,231 records were downloaded from the databases (Figure 4). The inter-examiner agreement between the reviewers was κ=0.95 at the title abstract selection and κ=0.968 at the full-text selection, resulting in 76 articles. The reference checking yielded only one additional record (85). Finally, the qualitative analysis contained 76 studies (4, 35, 36, 86-158). However, ten studies (90, 106, 114, 115, 122, 138, 140, 142, 150, 157) could not be included in the quantitative synthesis due to the use of a different OLS scale or the lack of similar comparator devices. In the quantitative synthesis, 66 studies were included.

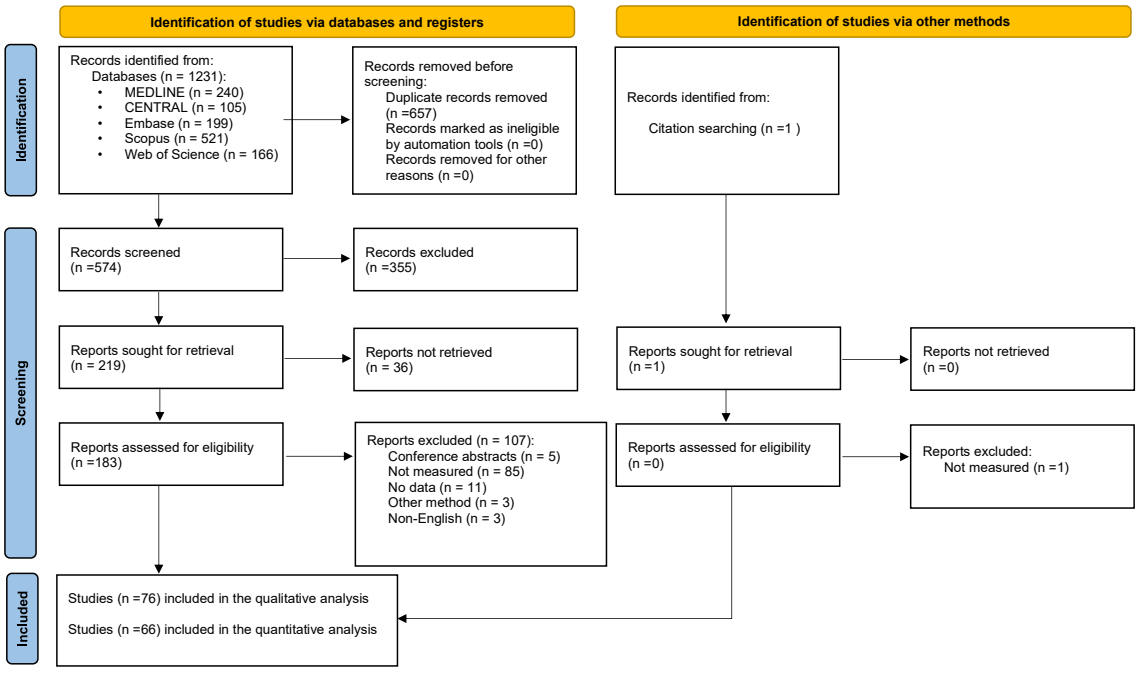


Figure 4. Prisma 2020 Flow Diagram of the screening and selection process (159)

8.1.2. Basic characteristics of included studies

The main characteristics of the 76 studies are shown in Table 2. 13 of the research were randomized controlled trials, and the majority used cross-sectional designs. They include

information gathered from across the globe. The majority of the study utilized a six-point scale (0-5) for sensory testing, but a few papers also employed four (0-3), five (0-4), or eleven points (0-10). Most of the secondary outcomes of the investigations were c.c. Halimeter, OralChroma, and gas chromatographs are all included in this meta-analysis, although we were unable to distinguish between the newer and older devices. Three studies investigated the Breathtron (142, 150, 154), a modified sulfide monitor; however, the quantitative synthesis was not feasible.

Table 2. Main characteristics of the included studies in the systematic review and meta-analysis (159)

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Acar B (86)	2019	RCT	Turkey	36	0-5	Halimeter	C
Aimetti M (87)	2015	cross-sectional	Italy	744/ 250	0-5	OralChroma	C
Aliyev B (88)	2021	cross-sectional	Turkey	75	0-5	Halimeter	C
Alqumber MA (89)	2014	blind, crossover	Saudi Arabia	20	0-5	Halimeter	C
Amano A (90)	2002	cross-sectional	Japan	61	0-3	GC-14B	C
Amou T (91)	2014	cross-sectional	Japan	94	0-5	GC	C
Apatzidou A (92)	2013	cross-sectional	Greece	78	0-5	Halimeter, RH-17	C
Awano S (93)	2004	cross-sectional	Japan	127	0-5	G2800 GC	C, Se, Sp, NPV, PPV
Ayo-Yusuf O (94)	2011	cross-sectional	South Africa	889	0-5	Halimeter	C
Baharvand M (95)	2008	cross-sectional	Iran	77	0-3	Halimeter	C, Se, Sp, NPV, PPV
Bodrumlu E (96)	2011	cross-sectional	Turkey	107	0-5	Halimeter	C
Bolepalli AC (97)	2015	cross-sectional	India	240	0-5	Halimeter	C, Se, Sp, NPV, PPV

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Bornstein MM (4)	2009	cross-sectional	Switzer-land	419	0-5, 0-3	Halimeter	C
Bosy A (98)	1994	cross-sectional	Canada	127	0-5	Halimeter, Interscan 1170 portable sulfide monitor	C
Brunner F (99)	2010	cross-sectional	Switzer-land	100	0-5	Halimeter, Halitox, and Fresh Kiss	C
Dadamio J (35)	2013	cross-sectional	Belgium	96	0-5	Halimeter, OralChroma, BB Checker	C, Se, Sp, NPV, PPV
Dadamio J (100)	2012	cross-sectional	Belgium	100	0-5	OralChroma	C
Donaldson AC (101)	2007	cross-sectional	UK	37	0-3	Halimeter	C
Doran AL (102)	2007	cross-sectional	UK	24	0-5	Halimeter	C
Du M (103)	2019	cross-sectional	China	205	0-5	Halimeter	C
Falcão DP (104)	2017	cross-sectional	Brasil	34	0-5	Halimeter, Breth Alert	C, Se, Sp, NPV, PPV
Faveri M (105)	2006	RCT, blinded	Brazil	19	0-3	Halimeter	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Figueiredo LC (106)	2002	cross-sectional	Brazil	21	0-4	Halimeter	C
Greenstein RB (107)	1997	RCT	Israel	123	0-5	Halimeter	C
Guentsch A (108)	2014	controlled clinical trial	Germany	30	0-5	Halimeter	C
Hunter CM (109)	2005	RCT, double-blind, parallel	US	13	0-5	GC Agilent 6890	C
Iatropoulos A (110)	2016	cross-sectional	Greece	18	0-5	OralChroma	C
Iwamura Y (111)	2016	randomized, double-blind pilot study	Japan	29	0-5	OralChroma	C
Iwanicka-Grzegorek K (112)	2005	cross-sectional	Poland	88	0-5	Halimeter	C
Jerv-Storm PM (113)	2019	RCT, cross-over	Germany	17	0-5	OralChroma, CHM-1	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Kameyama A (114)	2015	cross-sectional	Japan	359	0-5	OralChroma	C
Kim DJ (115)	2009	cross-sectional	Korea	52	0-4	Halimeter, gas chromatography, HP 5890	C
Laleman I (116)	2018	retrospective	Belgium	476	0-5	Halimeter, OralChroma	C, Se, Sp, NPV, PPV
Laleman I (117)	2020	retrospective	Belgium	570	0-5	Halimeter, OralChroma CHM-1, OralChroma CHM-2	C, Se, Sp, NPV, PPV
Lee ES (118)	2016	cross-sectional	Korea	99	0-5	OralChroma	C
Lee ES (119)	2016	cross-sectional	Korea	103	0-5	OralChroma	C
Liu XN (120)	2006	cross-sectional	China	2000	0-5	Halimeter	C
Lu HX (121)	2014	cross-sectional	China	911	0-5	Halimeter	C
Marchetti E (122)	2015	RCT	Italy	20	0-5	Bionote, OralChroma	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Matarazzo F (123)	2013	cross-sectional	Brazil	13	0-3	Halimeter	C
Morita M (124)	2001	cross-sectional	US	20	0-5	Halimeter,Tongue sulfide probe	C
Morita M (125)	2001	cross-sectional	US	81	0-5	Halimeter	C
Musić L (126)	2021	pilot study	Croatia	10	0-5	Halimeter	C
Nonaka A (127)	2005	cross-sectional	Japan	66	0-5	FF-1 odor discrimination analyzer, GC	C
Quirynen Q (128)	2009	retrospective	Belgium	2000	0-5	Halimeter	C
Roldán S (129)	2005	prospective case series	Spain	19	0-5	Halimeter	C
Roldán S (130)	2004	RCT- double-blind, cross-over	Spain	10	0-5	Halimeter	C
Roldán S (131)	2003	RCT	Spain, Netherlands	40	0-5	Halimeter	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Romano F (132)	2020	retrospective non-interventional clinical study	Italy	504	0-5	OralChroma	C
Rosenberg M (133)	1992	RCT	Israel	60	0-5	Interscan 1170, portable sulfide monitor	C
Rosenberg M (134)	1991	cross-sectional	Canada	41	0-5	Interscan 1170, portable sulfide monitor	C
Rosenberg M (160)	1991	cross-sectional	Canada	75	0-5	Interscan 1170, portable sulfide monitor	C
Ross B (136)	2009	cross-sectional	Canada	18	0-5	Halimeter	C
Saad S (137)	2011	RCT	UK	14	0-5	Halimeter, OralChroma	C
Schmidt NF (138)	1978	cross-sectional	US	66	0-3	gas-liquid chromatography	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Seemann R (139)	2016	RCT	Germany	34	0-5	Halimeter, OralChroma	C
Shimura M (140)	1997	cross-sectional	Japan	94	0-4	VSC monitor (New Cosmos Electric)	C
Song Y (141)	2021	cross-sectional	Korea	111 / 330	0-5	portable GC (TwinBreasor)	C
Sopapornamorn P (142)	2006	cross-sectional	Japan	260	0-5	Breathtron sulfide monitor, GC- 8A	C, Se, Sp, NPV, PPV
Southward K (143)	2013	case-study	Canada	649	0-5	Halimeter, OralChroma	C
Stamou E (144)	2005	cross-sectional	Israel	71	0-5	Halimeter	C
Sterer N (145)	2002	cross-sectional	Israel	64	0-5	VSC monitor, interscan modell 1170	C
Sterer N (146)	2008	cross-sectional	Israel	42	0-5	Halimeter	C, Se, Sp, NPV, PPV
Suzuki N (147)	2011	cross-sectional	Japan	368	0-5	GC 14B	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Takeuchi H (148)	2010	cross-sectional	Japan	823	0-5	GC 14B	C
Talebian A (149)	2008	cross-sectional	Iran	222	0-5	OralChroma	C
Tamaki N (151)	2011	cross-sectional	Japan	30	0-5	B/B Checker, GC 14B	C, Se, Sp, NPV, PPV
Tanda N (150)	2007	cross-sectional	Japan	46	0-4	Breathtron sulfide monitor, GC- 7A	C, Se, Sp
Tangerman A (152)	2007	cross-sectional	Nether-lands	75	0-5	Halimeter, GC	C
Tsai CC (153)	2008	cross-sectional	Taiwan	72	0-5	OralChroma	C
Ueno M (154)	2008	cross-sectional	Japan	475	0-5	Breathtron sulfide monitor, GC- 8A	C, Se, Sp, NPV, PPV
Van den Velde S (155)	2009	cross-sectional	Belgium	80	0-5	Halimeter, OralChroma	C
Vandekerckhov B (36)	2009	cross-sectional	Belgium	280	0-5	Halimeter, OralChroma	C, Se, Sp, NPV, PPV
Wilhelm D (156)	2010	RCT	Germany	42	0-5	Oralchroma	C
Willis CL (157)	1999	cross-sectional	UK	30	1-10	Halimeter	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Yasukawa T (158)	2010	cross-sectional	Japan	62	0-5	Halimeter, GC	C

RCT: randomized clinical trials; C: correlation; Se: Sensitivity; Sp: Specificity; NPV: negative predictive value; PPV: positive predictive value; NA: not available; GC: gas chromatograph

8.1.3. Results of the synthesis

8.1.3.1. Correlation between the halitometers and OLS

The qualitative analysis could involve 14,635 participants.

The pooled Spearman's c.c. for the sulfide monitor devices was 0.65; 95% CIs: [0.53 – 0.74]; I^2= 95%, p<0.01, and the pooled Pearson c.c. for the sulfide monitor devices was 0.57; 95% CIs: [0.35 – 0.73]; I^2= 93%, p<0.01 (Figure 5).

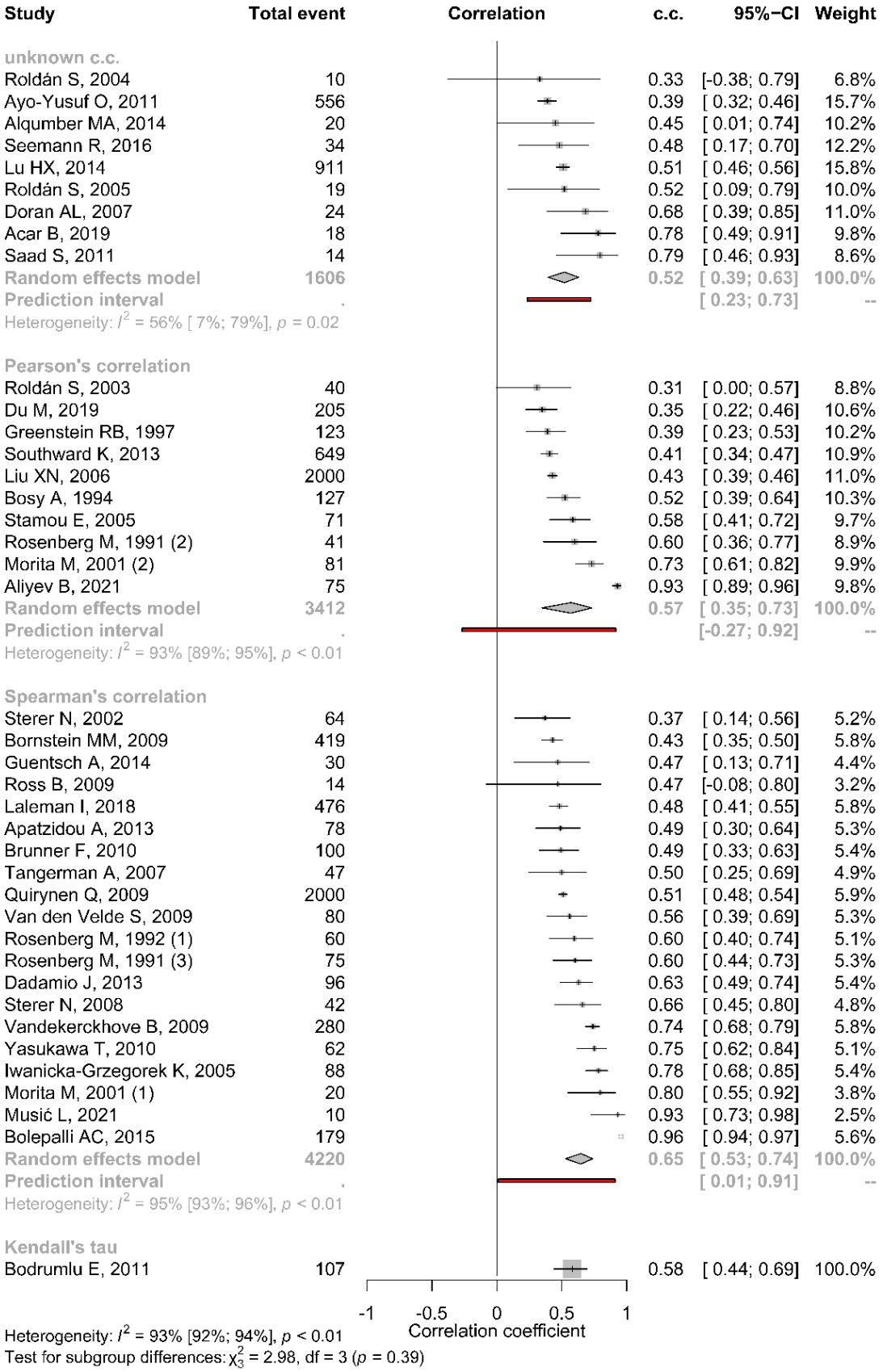


Figure 5. Forest plot of the pooled correlations between the sulfide monitor devices and OLS (159)

The pooled Spearman's c.c. for portable gas chromatographs was 0.69; 95% CIs: [0.63 – 0.74]; I^2= 12%, p<0.01, and the pooled Pearson c.c. for portable gas chromatographs was 0.59; 95% CIs: [0.37 – 0.75]; I^2= 90%, p<0.01 (Figure 6).

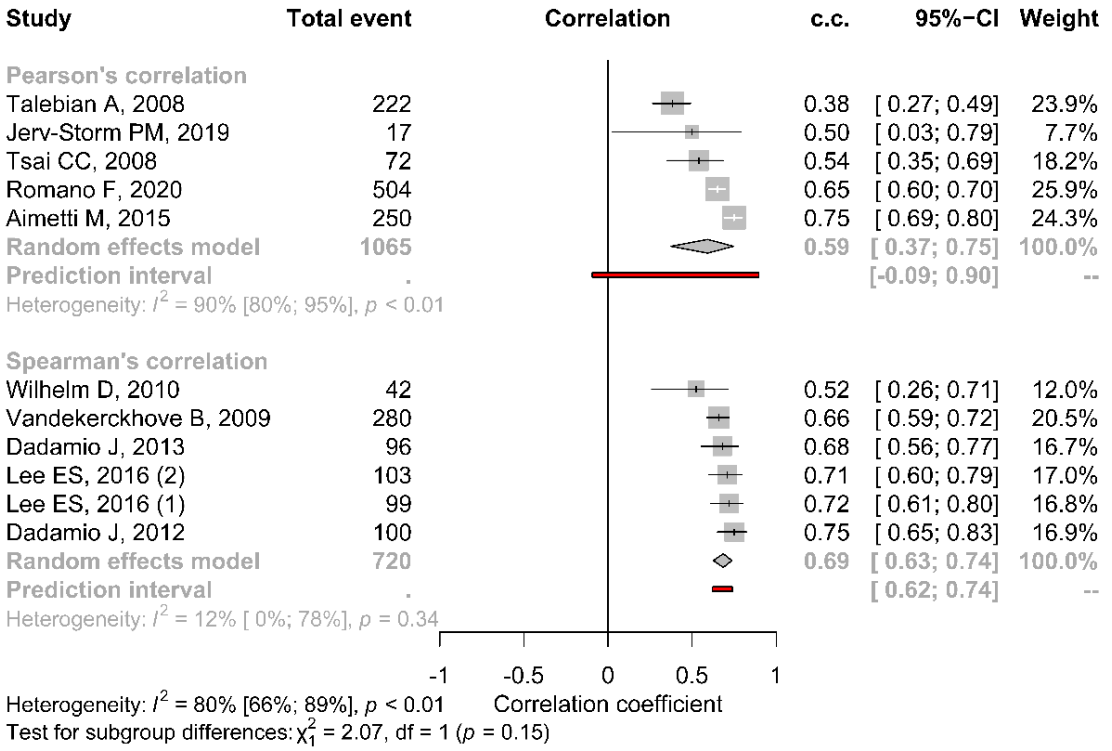


Figure 6. Forest plot of the pooled correlations between the portable gas chromatographs and OLS (159)

The pooled Spearman's c.c. for the gas chromatographs was 0.76; 95% CIs: [0.67 – 0.83]; I^2= 0%, p<0.01, and the pooled Pearson c.c. for gas chromatographs was 0.57; 95% CIs: [0.32 – 0.47]; I^2= 84%, p<0.01 (Figure 7) (159).

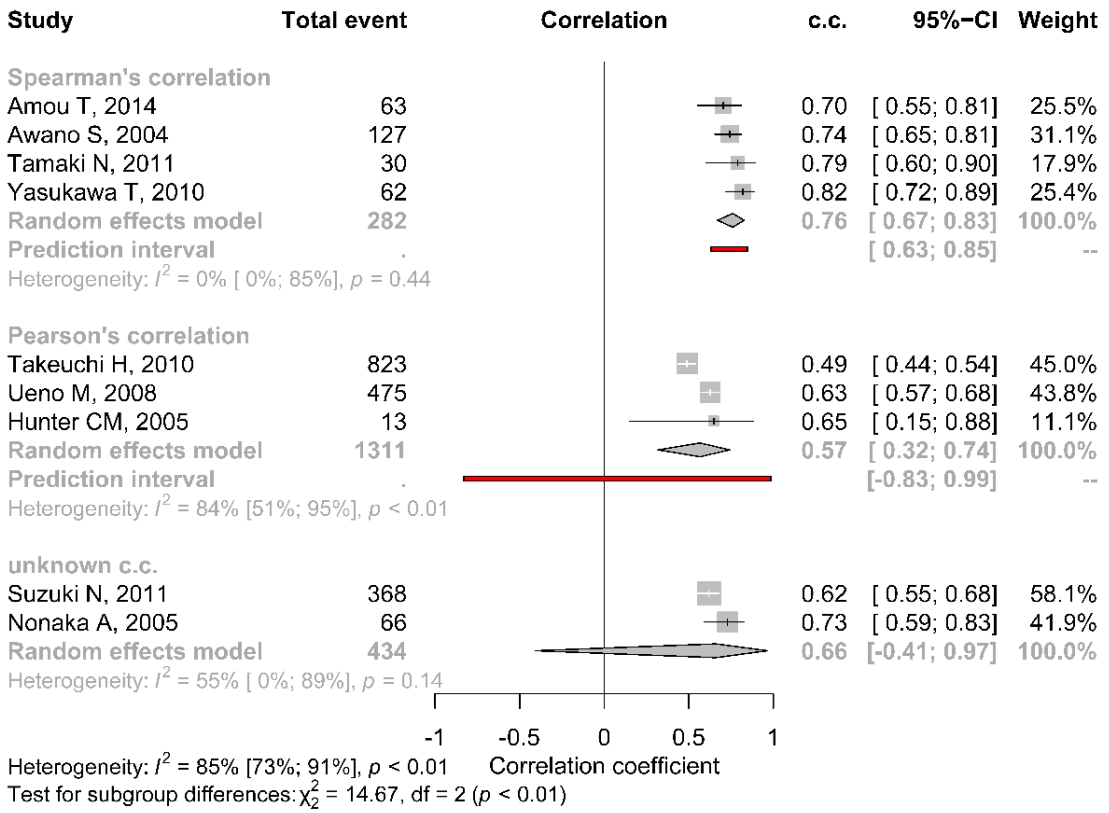


Figure 7. Forest plot of the pooled correlations between the gas chromatographs and OLS (159)

In the subgroups of sulfide monitor data where the exclusion of systemic diseases was unknown, the correlation was significantly lower ($p<0.05$) compared to the subgroup where systemic diseases were excluded. The pooled Spearman's c.c. for sulfide monitors without systemic diseases was 0.72; 95% CIs: [0.56 – 0.83]; I^2= 80%, $p<0.01$ and without the information on the exclusion or inclusion of systemic diseases the pooled Spearman's c.c. was 0.50; 95% CIs: [0.44 – 0.54]; I^2= 34%, $p<0.01$ (Figure 8) (159).

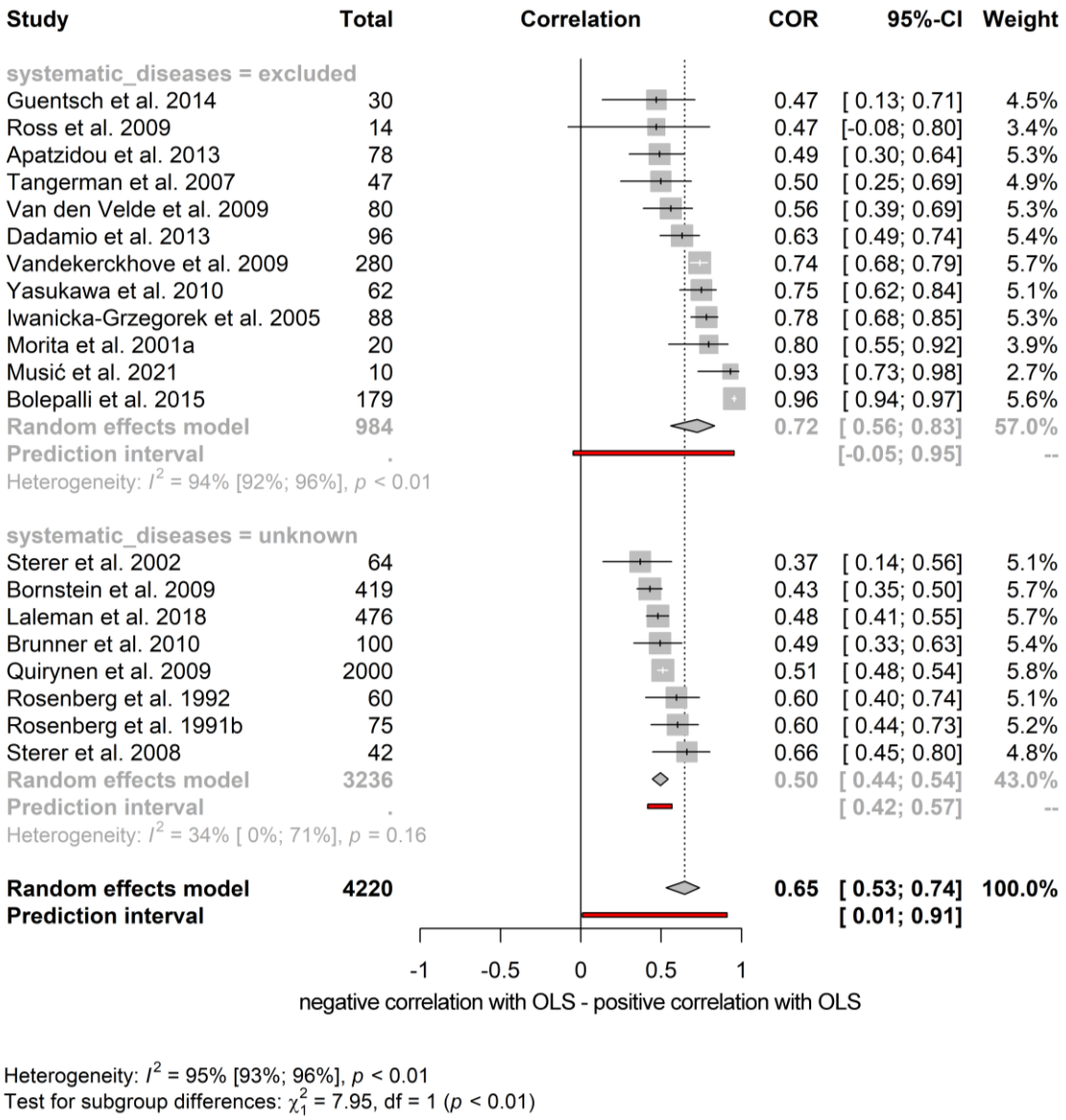


Figure 8. Forest plot of the pooled correlations regarding the inclusion of extraoral halitosis between the sulfide monitors and OLS (159)

The pooled Spearman's correlations with the OralChroma for the H_2S was 0.59; 95% CIs: [0.51 – 0.66]; I^2= 93%, p<0.01 (Figure 6). The pooled Spearman's c.c. for the CH_3SH was 0.58; 95% CIs: [0.45 – 0.68]; I^2= 97%, p<0.01 (Figure 9).

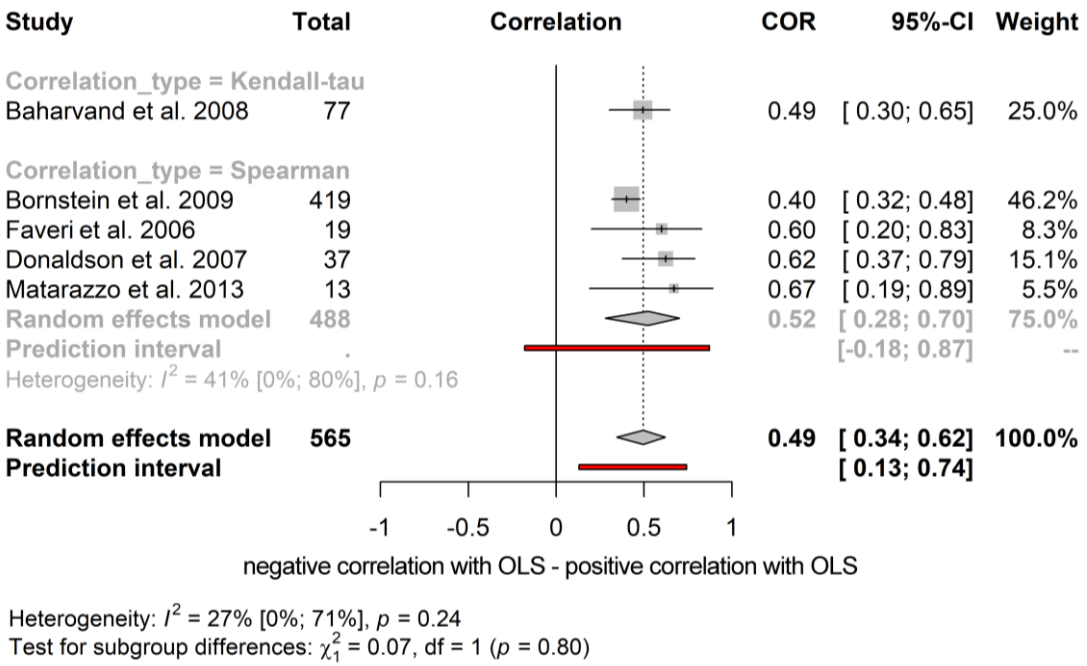


Figure 9. Forest plot of the pooled correlations for the methyl mercaptan between portable gas chromatographs and OLS (159)

The pooled Spearman's c.c. for the $(CH_3)_2S$ was 0.24; 95% CIs: [0.09 – 0.39]; I^2= 80%, p<0.01 (Figure 10). H_2S and CH_3SH correlated significantly (p<0.05) better to OLS than $(CH_3)_2S$ (159).

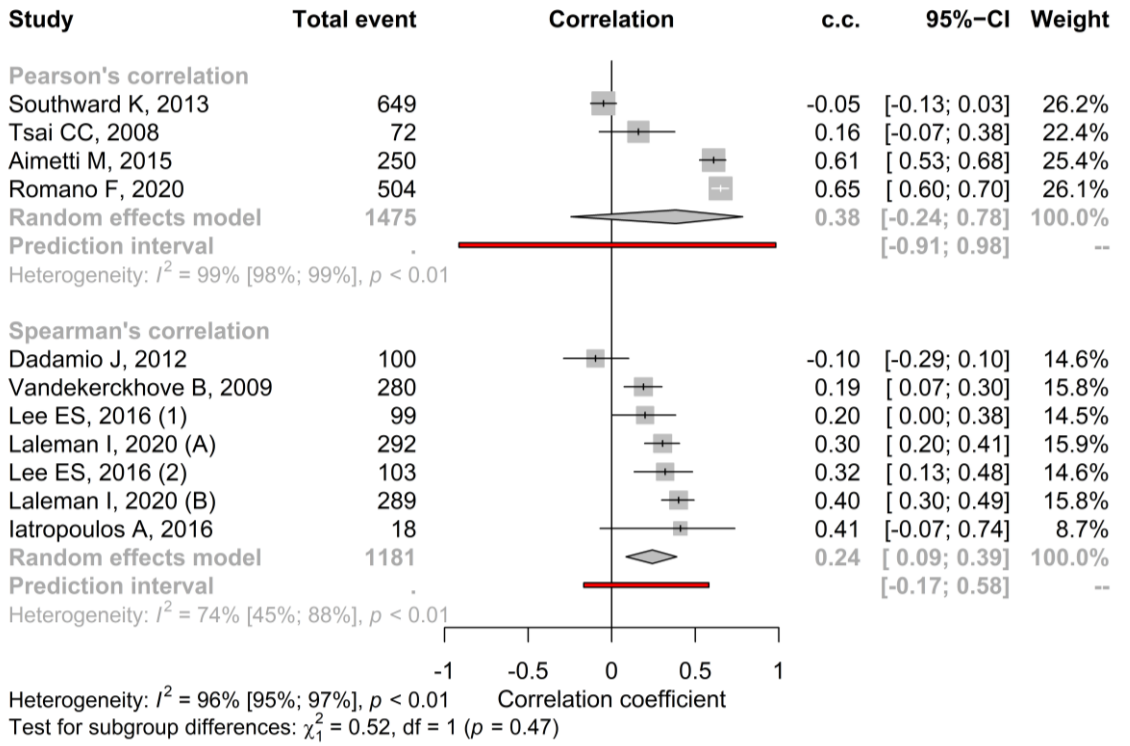


Figure 10. Forest plot of the pooled correlations for the dimethyl sulfide between portable gas chromatographs and OLT (159)

The pooled Spearman's c.c. between the portable gas chromatographs and sulfide monitors was 0.55; 95% CIs: [0.50 – 0.59]; I^2= 0%, p<0.01 (Figure 11).

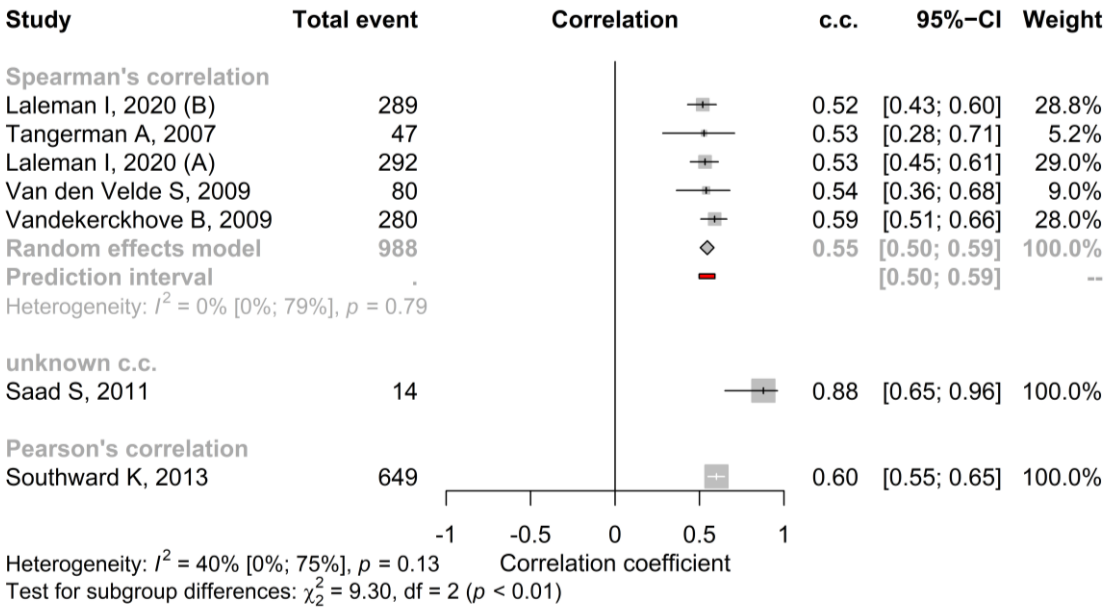


Figure11. Forest plot of the correlation between portable gas chromatographs and sulfide monitors (159)

The pooled Spearman's c.c. for sulfide monitors on the 4-point sale was 0.52; 95% CIs: [0.28 – 0.70]; I^2= 41%, p<0.01 (Figure 12) (159).

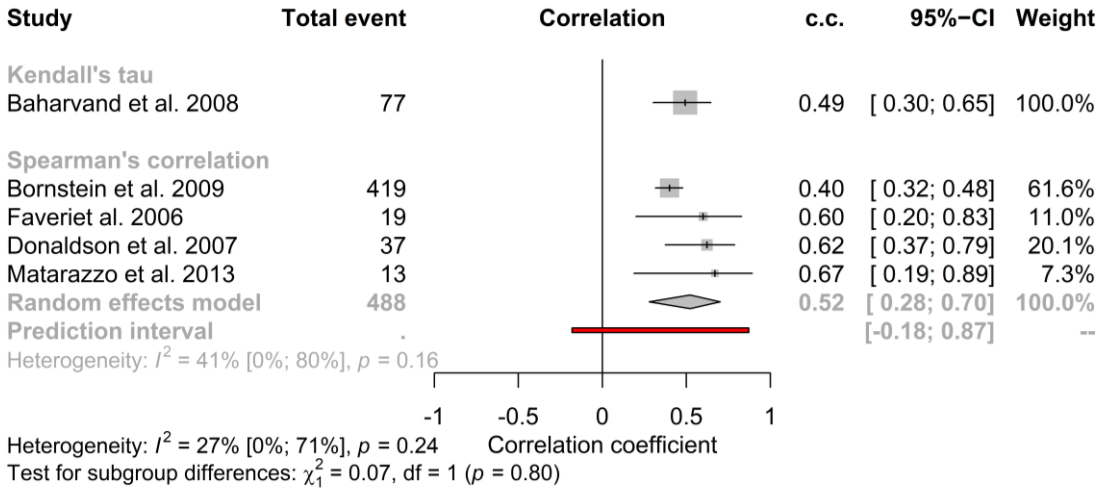


Figure 12. Forest plot of the pooled correlations between sulfide monitors and 4-point scale (159)

8.1.3.2. Specificity and sensitivity

The SROC curve for the Halimeter was based on data from six articles (35, 36, 97, 104, 117, 146) (Figure 13). Light blue crosses show the individual study data with Halimeters.

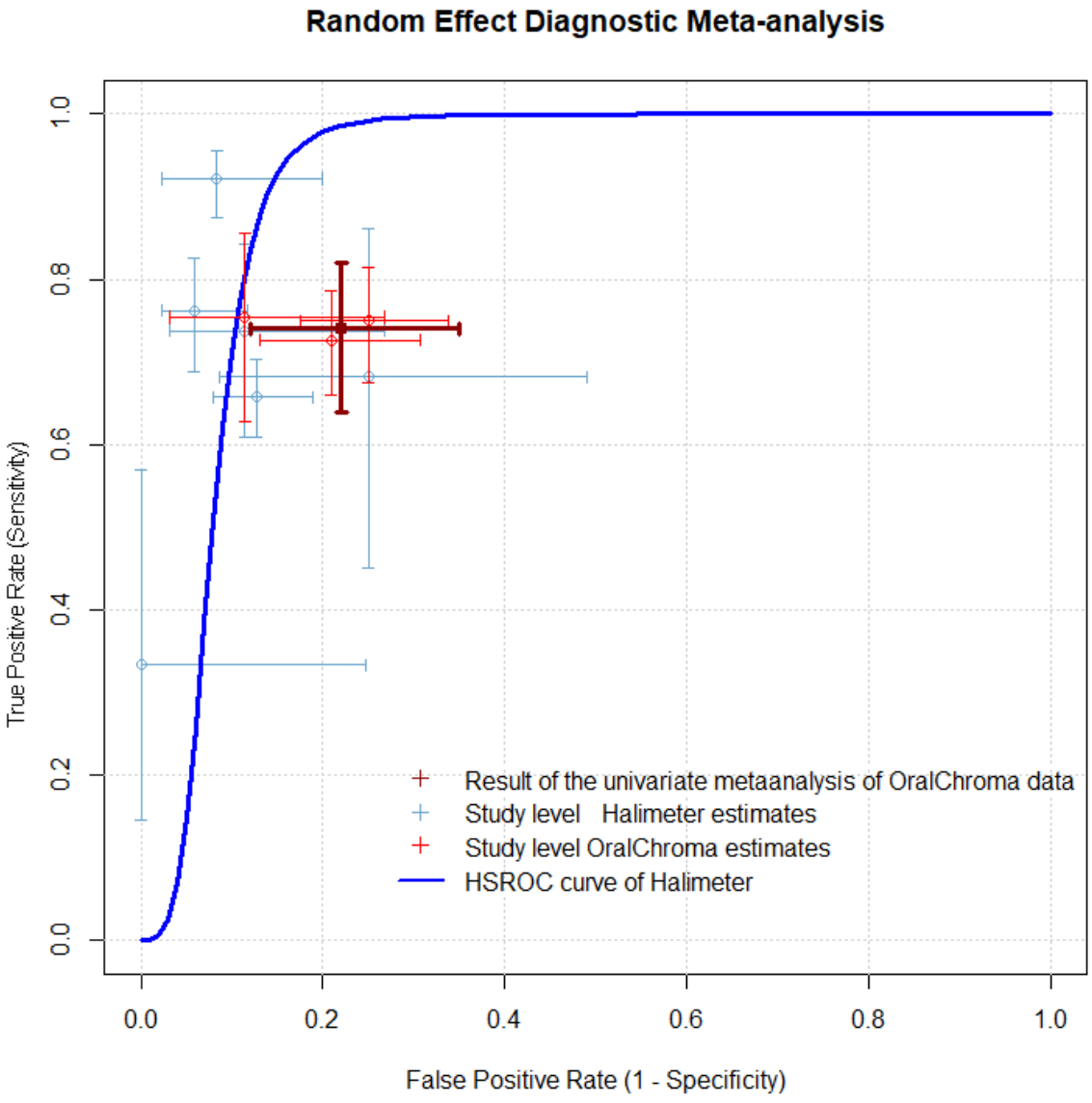


Figure 13. ROC plot visualizing the diagnostic performance of Halimeter and OralChroma diagnostic tools (original running with six articles) (159)

HSROC: Hierarchical summary receiver-operating characteristic

The repeated analysis excluded two studies (97, 104), where the aim of detecting OLS ≥ 2 conditions (Figure 14) (159).

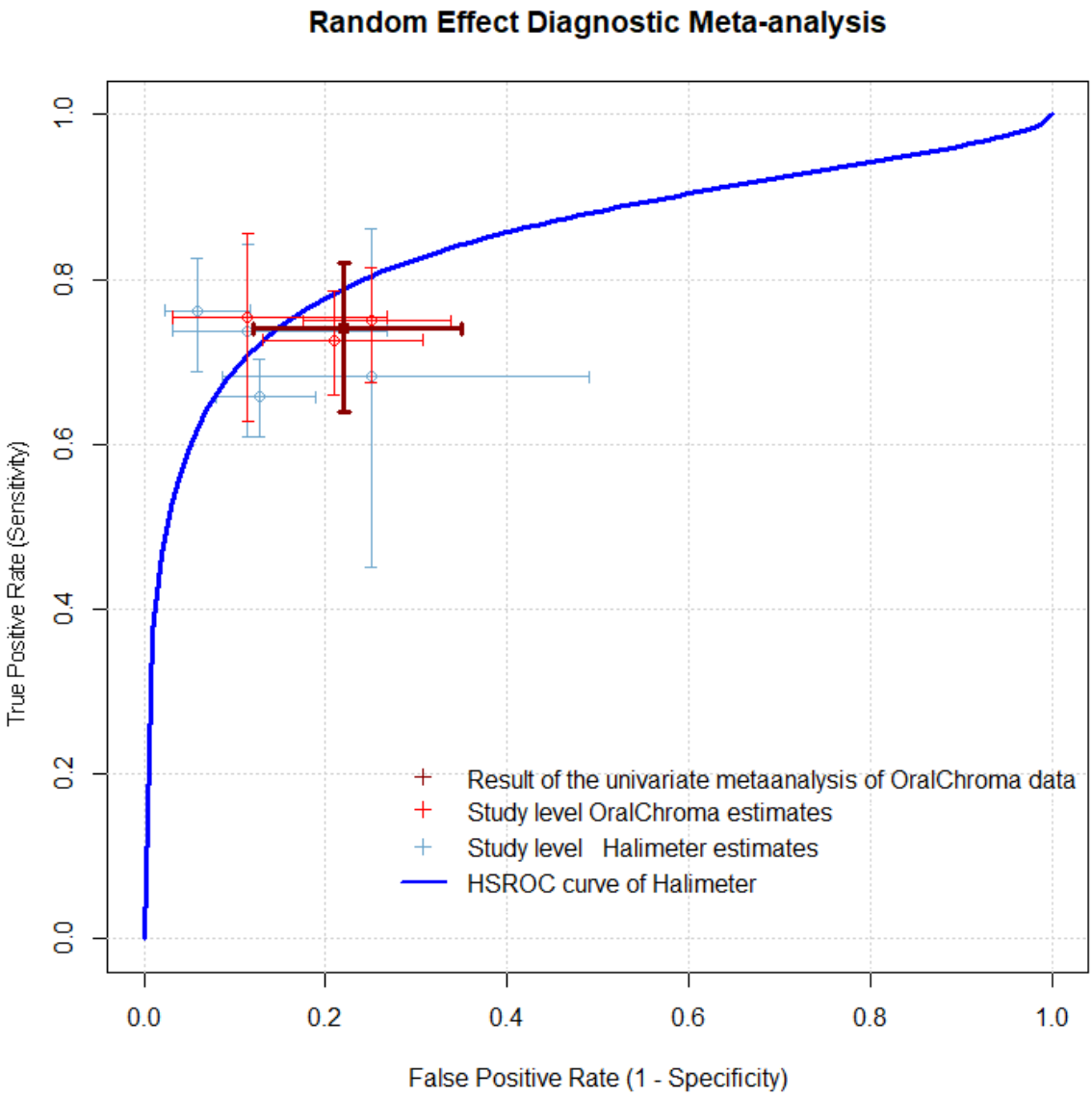


Figure 14. ROC plot visualizing the diagnostic performance of Halimeter and OralChroma diagnostic tools (original running with four articles) (159).

Only three studies (35, 36, 117) were available for the OralChroma-CHM-1 diagnostic tool, and it was not possible to test the difference between the devices as they require different analysis types. Despite the model fitting being more uncertain and the visual difference decreasing with four articles instead of six, the truth may still be reflected due

to the number of articles. This is because the aim was pre-specified as OLS ≥ 2 with four articles (Figure 14) (159).

8.1.4. Risk of bias assessment

In terms of QUADAS-2 patient selection, flow and timing domain, and application concerns, the publications typically showed a low risk of bias. Because there was no information indicating the knowledge of the other test findings in some cases, the risk of the reference standard or index test results was unclear. The majority of the studies' non-diagnostic test accuracy is thought to be the reason these data weren't published. Additionally, it increased the risk of QUADAS-C; nonetheless, the subgroup analysis used this comparison. Despite our index tests' objectivity, we think the studies would benefit by considering the pre-determined threshold.

8.1.5. Publication bias and heterogeneity

The findings of the publishing bias evaluation were visualized with funnel plots. Publication bias may exist in the case of sulfide monitors (Egger's test: $p = 0.0289$). The varied threshold selections may lead to considerable heterogeneity in sulfide monitor cases. With Spearman's c.c., heterogeneity tends less.

8.1.6. Certainty of evidence

Due to study designs and considerable variability, the GRADE evidence table displayed extremely low certainty of evidence for the major outcomes. Due to the small number of studies, the evidence for the secondary outcomes should be treated with caution.

8.2. Study II. - Investigating the efficacy of chlorine dioxide in intra-oral halitosis

8.2.1. Study selection

Three hundred fifty-two articles were downloaded from the databases. See the detailed selection process on Figure 15 (161).

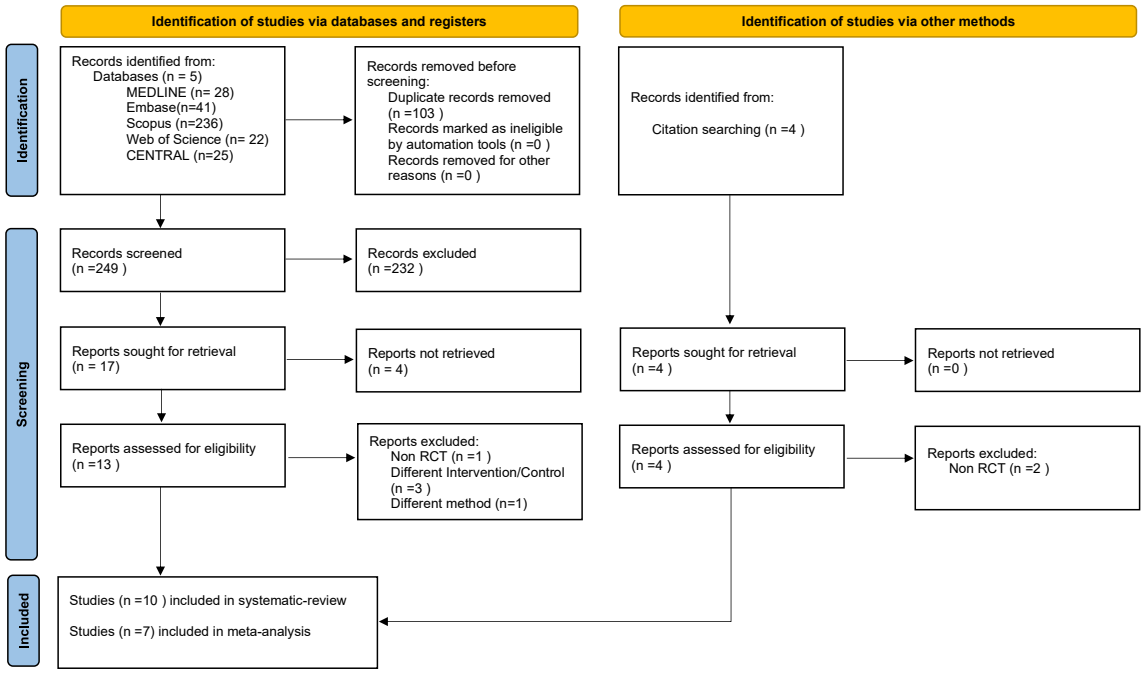


Figure 15. Prisma 2020 Flow Diagram of the screening and selection process (161)

After the selection process, a total of ten articles were included in the qualitative synthesis (41, 162-170).

8.2.2. Characteristics of the included studies

Table 3 lists the major characteristics of the included studies. With the exception of one trial (170), placebo was utilized in the comparator groups. Women were excluded from four studies because their menstrual cycles might impact the findings (41, 167, 168, 170). The corresponding author of two studies (163, 164) confirmed that the included populations varied. Then, we summarized the data for one day, one week, and two weeks. We had to leave out three papers (41, 165, 170) from the quantitative synthesis since there weren't enough comparison studies for the VSC 1-week and 2-week data. Patients who were included in one-day follow-up studies used the experimental mouthwashes on the morning of the measurement day, and on the one-week and two-week follow-ups, they

were instructed to use them twice daily. No other treatment or intervention was permitted for these patients. The eligible reports applied the six-point OLS scale from Greenman (18). We did not examine secondary outcomes like the effect on gingivitis and periodontitis because Kerémi et al. (50) further investigated.

First Author / Year of Publication	Country	Study Design	Population	N0 of Patient	Sex (F/M)	N° of Patient	Care product	Main content	Outcomes			Time points
									O	T	VS C	
Shinada et al. 2010 (168)	Japan	RCT, double-blind, crossover	healthy	15	0/15	8	ClO_2 Fresh	0.1% ClO_2	yes		GC 8A	Baseline 1-week
						7	Placebo					
Aung et al. 2015 (41)	Myanmar	RCT, single-blind, parallel	healthy, VSCs > 250 ppb	30	0/30	15	Fresh	ClO_2	no		Breathtron	Baseline, 1, 2, 3, 4, 5 week
						15	just tooth brushing					
Pham et al. 2018 (166)	Vietnam	RCT, double-blind, crossover	healthy students, OM>2	39	19/20	17	Thera-Breath®	0.1% ClO_2	yes		Oral-Chroma	Baseline, 12-hour, 2-week
						22	placebo	sodium chloride 0.9%				
Peruzzo et al. 2007 (165)	Brazil	RCT double-blind, crossover	dental students	14	8/6	7	SaudBucal®	0.1% ClO_2	no		Halimeter	Baseline, 4-day
						7	placebo	NA				
Shetty et al. 2013 (170)	India	RCT, double-blind, crossover	healthy men	18	0/18	9	Thera-Breath®	0.1% stabilized ClO_2	no		Halimeter	Baseline, 7-day
						9	CHX	chlorhexidine 0.2 %				
Grootveld et al. 2018 (169)	UK	RCT, double blind, crossover	healthy patients	30	13/17	NA		0.10% $NaClO_2$	no		Oral-Chroma	Baseline, 0,33, 4, 8 and 12-hour
						NA	H2O					

First Author / Year of Publication	Country	Study Design	Population	N0 of Patient	Sex (F/M)	N⁰ of Patient	Care product	Main content	Outcomes				Time points
									O	PI	VS	C	
Shinada et al. 2008 (167)	Japan	RCT, double-blind, crossover	healthy men	15	0/15	8	ClO2 fresh	0.16% $NaClO_2$	yes		GC		Baseline, 0,5, 2, 4-hour
						7	Placebo						
Bestari et al. 2017 (162)	Indonesia	RCT, single-blind	NA	40	NA	20	Oxyfresh ®	ClO_2	yes		Oral-Chroma		Baseline, 0,5, 2, 4, 6-hour
						20	Placebo	dest. water					
Lee et al. 2021 (164)	USA	RCT, double-blind, crossover	healthy patients, OM>2.6	48	34/14	24	CloSYS	0.1% stabilized ClO_2	yes		no		Baseline, 1,2,3-week
						24	Placebo						
Lee et al. 2018 (163)	USA	RCT, double-blind, crossover	healthy patients, OM>2.6	48	30/18	23	CloSYS	0.1% ClO_2	yes		no		Baseline, 0,5, 2, 4-hour
						25	Placebo						

Table 3. Main characteristics of the included studies (161)

RCT: randomized clinical trials; OLS: organoleptic testing scores; SD: standard deviation; ClO_2: chlorine dioxide; $NaClO_2$: sodium chlorite; NA: not available, GC: gas chromatograph; PI: Plaque index; GI: Gingival index, TCI: Tongue coating index; TDI: Tongue discoloration index, DMF: number of decayed, filled, and missing teeth *T.f.: Tannerella forsythia, F.n.: Fusobacterium nucleatum; P.g.: Porphyromonas gingivalis, T.d.: Treponema denticola; S.m.: Streptococcus mutans*

8.2.3. Results of the synthesis

The quantitative analysis comprised 234 patients in total. There were no patient-reported adverse events mentioned in any of the studies. When compared to the control (placebo) group, the ClO_2 group's organoleptic ratings significantly improved in our forest plots (Figure 16. a, b) (161).

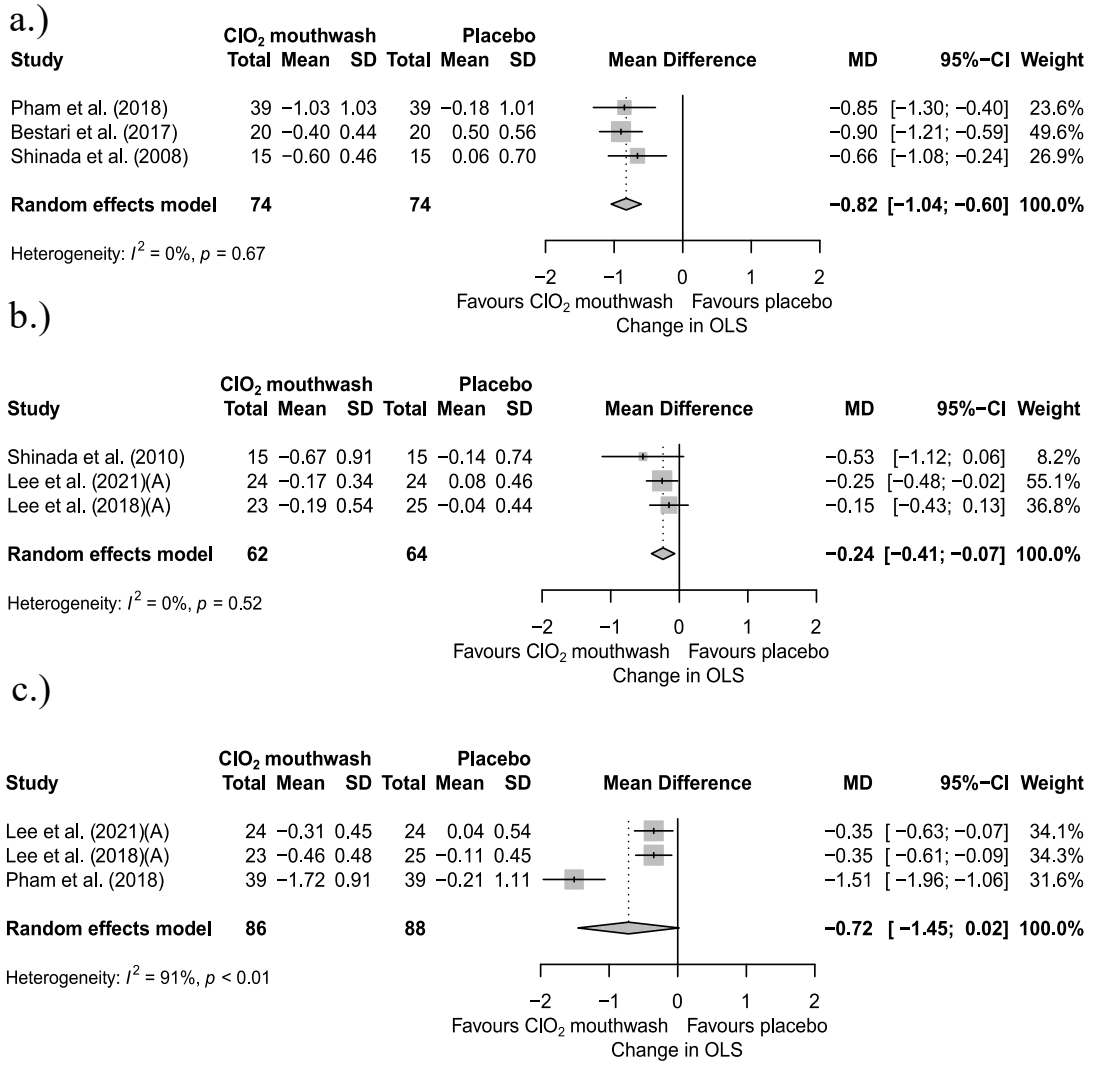


Figure 16. Changes of organoleptic measurement (161)

a. between baseline and within one day with and without ClO_2 mouthwash

b. between baseline and within one week with and without ClO_2 mouthwash

c. between baseline and within two weeks with and without ClO_2 mouthwash

One-day OLS data were pooled from three articles (162, 166, 167) after 4, 6, and 12 hours. The data from the study indicates that ClO_2 was successful in achieving its intended

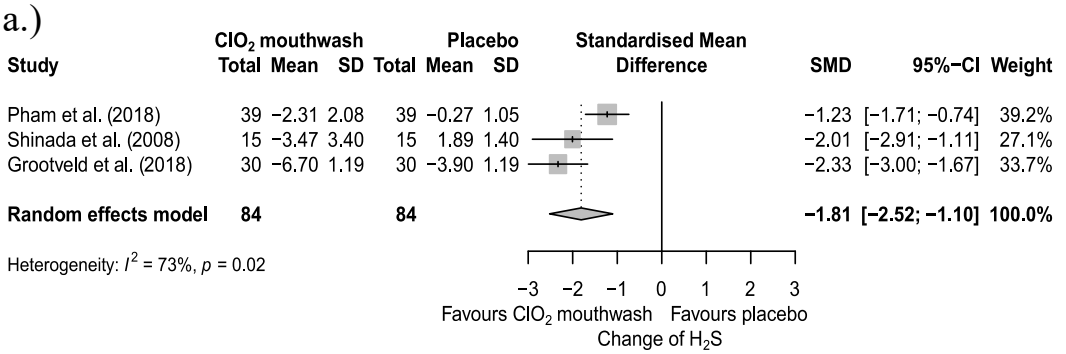
purpose within a single day (MD: -0.82; 95% CIs): [-1.04 – -0.6]; heterogeneity: I^2= 0%, p= 0.67) (Figure 16. a) (161).

OLS data was collected over a period of one week and was sourced from three different articles. (163, 164, 168) The findings suggest that the group undergoing the experiment achieved a positive result (MD: -0.24; 95% CI : [-0.41 – -0.07]); I^2= 0%, p= 0.52) (Figure 16. b) (161).

OLS data was collected over two weeks and was sourced from three different articles (163, 164, 166). The results also favor CLO_2 mouthwashes in halitosis (MD: -0.72; 95% CI: [-1.45 – 0.02]; I^2= 91%, p< 0.01) (Figure 16. c) (161).

Changes in H_2S and CH_3SH on one-day data were collected from three articles (166, 168, 169). Significant differences were found in H_2S data (SMD: -1.81; 95% CI: [-2.52 – -1.10]; I^2= 73.4%, p= 0.02) (Figure 17. a). The result of CH_3SH one-day data was (SMD: -7.26; 95% CI: [-18.93 – 4.4]; I^2= 98.0%, p< 0.01) (Figure 17. b) (161).

a.)



b.)

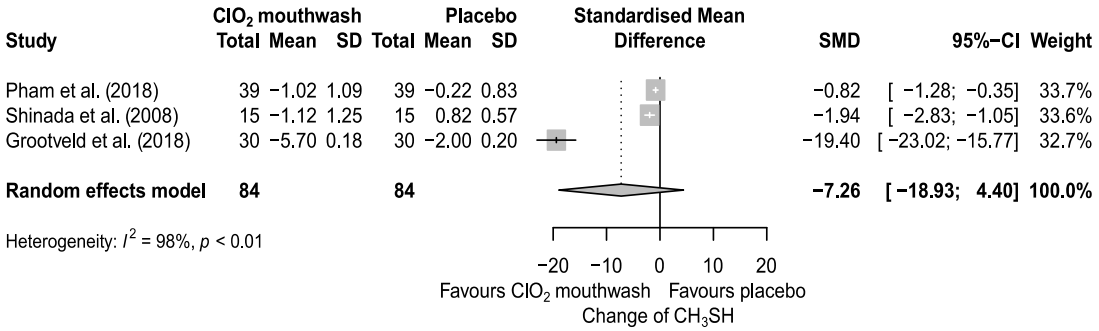


Figure 17.a. Changes of hydrogen sulfide concentration between baseline and within one day with and without ClO_2 mouthwash (161)

Figure 17. b. Changes of methyl mercaptan within concentration between baseline and one day with and without ClO_2 mouthwash (161)

8.2.4. Risk of bias in studies

All included studies presented in high quality, but due to Domain 5, we have to consider the overall risk to be of some concern. Even though the studies published the trial protocols, they did not provide a pre-specified analysis plan. Therefore, we rated all of them as having some concern in Domain 5 on the selection bias of the presented results.

8.2.5. Publication bias and heterogeneity

The one-day and one-week data's heterogeneity might not be important, but the two-week OLS data's heterogeneity might be considerable. There was substantial statistical heterogeneity in H_2S data and considerable statistical heterogeneity in CH_3SH data (161).

8.2.6. Certainty of evidence

Very low to moderate evidence certainty was received in the certainty rating of the researched outcomes. The findings needed to be downgraded because of statistical heterogeneity, risk of bias assessment, and imprecision. The statistical estimation expanded the CI, which raised the degree of imprecision.

9. DISCUSSION

9.1. Summary of findings, international comparisons

Study I. focused on the evaluation of various diagnostic methods for measuring halitosis. It assessed the correlation between different halitosis measuring devices and the OLS, the gold standard assessment of bad breath. The study found that the data obtained from these devices does not correlate strongly with the OLS, and the correlations are only moderately positive. This finding is not in line with the initial hypothesis, and some previous studies (4, 171-173) also questioned the strong correlation. These findings support the challenges of correlating these methods. The better results may originate, the better, more accurate diagnosing methods.

The analysis concluded that none of the tested halitometers is significantly superior to the others, not just in the correlation but in the diagnostic test accuracy analysis. We could show the device that is most similar to the sensory evaluation with the correlation analysis. Meanwhile, with the diagnostic test accuracy, we could show how well we can diagnose the patients with or without the condition if the OLS is the proper gold standard. Gas chromatographs showed the highest correlation with OLS. Therefore, we agree with Yaegaki et al. and van den Broek et al. (14, 34), who suggested using gas chromatographs in halitosis research. Furthermore, the gas chromatograph was recognized as the gold standard (174). Additional studies are needed to assess the accuracy of gas chromatography for detecting halitosis because we could not perform the analysis. It is also important to note that the instrumentation of this method is expensive, complicated, and time-consuming (175); however, it is constantly changing (176). E. g. Gas chromatography-mass spectrometry (GC/MS) is an instrumental technique comprising a gas chromatograph coupled to a mass spectrometer, by which complex mixtures of chemicals can be separated, identified, and quantified by a trained person, who will calibrate the device with a specific gas mixture.

Numerous devices were ineligible for our quantitative study because of a lack of comparing data. Due to its speed in monitoring non-VSC gases, studies using selective flow tube mass spectrometry (SIFT-MS) or eNoses can be a potential diagnostic method in halitosis research. The current SIFT-MS device has been lacking with the OLS correlation (14, 136). The correlations were 0.78-0.81 with electrical sensing (122, 127); however, e.g., the Cyranose device, without methodological improvement of the

software, can only recognize a pattern, so it's more suitable to diagnose a yes-no question than intensity or concentration. Despite their potential benefits, these devices are not currently more advantageous than the most commonly used ones (177). This is because there is a lack of quantitative measurements of the gases, which hinders their effectiveness (122).

A few test results are available for the following devices: FreshKiss (r=0.283) (99), tongue sulfide monitor (r=0.768) (124), Breathtron (r=0.65) (150), and Tanita (ROC=0.473) (178), MX6 (179, 180), Breath-Alert (104). As a result, even though the most excellent device might already be in use, we could not find it. Furthermore, both sensory and halitometric breath tests are highly technique-sensitive procedures. The particular steps taken to do the study, including thresholds, calibration, the timing of the comparison, gathered sample size's volume, and sample collection, are often not described in depth in research publications, which can cause biases.

Probably, the public's primary concern is determining when their breath smells bad, regardless of origin. There is a massive need for a reliable self-assessment tool that people can use to quickly and affordably evaluate their breath for odor, as seen by the wide variety (181) of self-assessment tools available on the market.

When we compared our correlation analysis to the interrater agreement of the organoleptic judges, we found similar diversity between the examiners (from 0.559 (156) to 0.743 (95)), probably because of the method's subjectivity.

There was less heterogeneity in the correlation between the portable gas chromatographs and the sulfide monitor devices. Nevertheless, the two devices measuring the same compounds using two methods showed a weaker correlation than predicted.

The correlation between OLS and the indirect methods was usually weaker: (spectrophotometric analysis of saliva (182), combined plaque fluorescence score (118), the concentration of the saliva's *Solobacterium moorei* (183), the colorimetric chair-side test (100)). These results indicate that, for the time being, direct diagnostic methods are more appropriate.

Our data shows sulfide monitors had a significantly worse correlation when extraoral halitosis was present. We could explain this with the following literature data. Firstly, sulfide monitors are less sensitive to $(CH_3)_2S$ and less effective at identifying extraoral halitosis (152, 184). Secondly, the mouth area holds approximately 25 mL of air; one

issue with using devices to measure halitosis is that they often pull more than 25 mL of air during their processing (e.g., Halimeter); therefore, the additional air coming up and being analyzed is usually from the lungs. Once lung air is included in the assessment, extra-oral content is evaluated.

Our data recommend against using sulfide monitors in patients with extraoral halitosis or known systemic disorders. The cysteine induction method (185) or nasal breath analysis (152) can be used to distinguish between extraoral and oral halitosis. On the other hand, extra-oral halitosis may coexist with intra-oral halitosis.

The diagnostic test accuracy of our meta-analysis showed that these devices could correctly diagnose 70 percent of the patients with IOH. Of course, this lower success could be due to inadequate threshold selection (36), limitation of the software (186), and the insensitivity of the devices for cadaverine, indoles, and skatoles (13), or the sensitivity of Halimeter for acetone, ethanol, and methanol (187), resulting in an incorrect diagnosis that shows false negative results. It is significant because a single compound can change the level of IOH (188) and increase the false negative and positive results.

A newer type of OralChroma instrument (CHM-2) could not be included in the diagnostic test accuracy analysis. However, it performed even worse in that one study (117) than the older version (CHM-1), which was included in the analysis. The Halimeter slightly outperformed the OralChroma (CHM-1) in our investigation of sensitivity and specificity levels, but it was not significant.

Due to COVID-19, the OLT has been less frequently employed as a diagnostic tool over the past three years. Patients could smell their bad breath through their masks; however, it's possible that the diagnosis and subsequent treatment were delayed. Before the pandemic, the OM was essential for determining the cause of bad breath (11), and every doctor could diagnose with it (189). The safety apprehensions regarding inhaling other people's breath have increased due to the pandemic. In line with Laleman et al. (190), the OLT is the gold standard despite its disadvantages. However, it is necessary to investigate with a statistical method whether it is a proper gold standard. Our data suggest there is no given halitometer that is better than others or sufficient to use as a stand-alone assessment method.

Study II. asserts that mouthwashes containing ClO_2 effectively reduce halitosis levels in both OLS and VSC measurements. Our research demonstrated that, among VSCs, ClO_2 primarily lowers H_2S. Additionally, H_2S may indicate future development and severe disorders such as periodontitis and oxidative stress (191, 192). In contrast with our study, one study (57) found that ClO_2 mainly lowers $(CH_3)_2S$. However, we could not perform a meta-analysis from $(CH_3)_2S$ data. Takeshita et al. (193) emphasized separating VSCs is not necessary to assess the total impact. However, targeted therapy may improve patients' health-related quality of life (194).

ClO_2 demonstrated almost the same efficacy as chlorhexidine compared to the only eligible article with a mouthwash comparator containing chlorhexidine (170). However, two systematic reviews found low-certainty evidence to support the effectiveness of any interventions for managing halitosis (15, 195). Another meta-analysis conducted on probiotics found probiotics effective, but they reduced only OLT results (196). A few clinical trials (197-199) found different kinds of herbal mouthwashes to be effective. However, the trials have several limitations.

Some patients mentioned an unpleasant taste (170). However, no other article mentioned side effects in low concentrations and short term. This is probably because ClO_2 selective toxicity (Noszticzius et al., 2013) favors ClO_2's clinical advantages over other disinfectants (200). A systematic review (201) strengthened the same. However, they include some overdosed, posing cases. Chlorhexidine and mouthwashes with alcohol are known to have adverse effects (44, 202, 203). Additionally, a different meta-analysis (204) concluded that patients should limit their long-term use with low evidence.

Several factors may have caused the heterogeneity of the included studies. There were slight variations in the study designs, protocols, and follow-up periods. Furthermore, we hypothesized additional confounding factors besides the small number of studies. Variations in rinsing protocols could be the cause of the moderate statistical heterogeneity. While Lee et al. (163, 164) advised patients to gargle with 15 mL of mouthwash for 30 seconds only, Pham et al. (166) advised their patients to rinse with 15 mL of mouthwash for 30 seconds, spit and continue gargling with 15 mL of mouthwash for 15 seconds. The longer mandatory mouth closure before measurement—5 minutes for Grootveld et al. (169) and 3 minutes for the other studies—may cause the remarkably high statistical heterogeneity of the CH_3SH data. Additional explanations could include

the fact that *Porphyromonas gingivalis* is primarily responsible for the concentration of methyl mercaptan (205) and that racial variations can lead to variations in the composition of bacteria (206); two of these articles (166, 167) are from Asia, and the other is from the UK (169). Moreover, increased CH_3SH concentration is widely associated with periodontal disease (30); however, Grootveld et al. (169) do not include periodontopathic patients. Primarily, we should exercise caution when using our assumptions to explain the heterogeneity of measurement readings because of the small number of included studies.

Although it primarily depends on the brand of mouthwash chosen, the cost of this therapy is comparable to or slightly greater than therapy with other mouthwashes. We believe that our findings are encouraging and that ClO_2 is a viable option.

9.2. Strengths

Both analyses were conducted with a rigorous methodology and represented the first meta-analyses. Study I. includes a large number of publications, as well as findings from the most widely used tools for correlation and diagnostic test accuracy. On the other hand, all of the included articles in Study II. are randomized controlled trials (RCTs). We were able to track the mid-term impacts by collecting data at multiple time points for organoleptic assessment. Additionally, we believe that independent VSC results are valuable in evaluating the efficacy of ClO_2.

9.3. Limitations

Study I. admits that variations in study designs, methods, thresholds, and patient groups could cause study heterogeneity. Due to a lack of information, we sometimes could not exclude patients with extraoral halitosis and the immature population, just like in real life. In Study II., comparing ClO_2 mouthwashes with other active components was impossible because only one study was found.

10. CONCLUSIONS

1. We answered our clinical question with the following: no particular halitometer is superior to others or adequate as a stand-alone assessment method in IOH. Despite its limitations, OLS is the recommended diagnostic technique. Our null hypothesis that the halitometers are as appropriate as the organoleptic method to measure the level of halitosis is rejected.

2. Our findings indicate that mouthwashes containing ClO_2 may should play a more significant role in the supportive therapy for oral halitosis. The evidence suggests that it is more effective than a placebo in the short term for treating halitosis. Our null hypothesis was partially rejected because we can not prove that mouthwashes containing ClO_2 are as effective as other mouthwashes in reducing oral malodor because of a lack of data. A personalized treatment plan is particularly beneficial for patients with elevated levels of H_2S, as ClO_2 is more effective against this molecule.

11. IMPLEMENTATION OF PRACTICE

Study I. indicates that patients with extra-oral halitosis should be handled carefully if the diagnosis is made using sulfide monitors. In the indirect comparison, the rarely-used OLS 4-point scale appears to be adequate for measuring halitosis accurately; however, we advise using the more common 6-point scale.

Study II. has practical implications for the management of halitosis. It suggests that mouthwashes containing ClO_2 are a viable treatment option for patients with oral halitosis. The side-effect-free nature of ClO_2 mouthwashes is highlighted, in contrast to potential adverse effects associated with other mouthwashes containing alcohol or chlorhexidine.

12. IMPLEMENTATION OF RESEARCH

Instead of focusing on device correlations, we recommend that future research highlight the accuracy of diagnostic tests based on specific devices. It would be advantageous to do a ROC analysis and give results corresponding to various thresholds of continuous device readings for both existing and new device enhancements. If OLS is the gold standard, that should be further researched. It is clear that a low-cost, device-supported diagnostic technique is needed.

We hope our findings will facilitate further research into various mouthwashes for halitosis treatment. We recommend that future research present their data in total VSCs with SD in order to make them comparable because the SD is lost when we sum the H_2S, CH_3SH, and $(CH_3)_2S$ data. In addition, it's crucial to specify the difference that matters. To determine whether the statistical evidence is consistent with the clinical evidence, defining the minimally important difference data (MID) is necessary.

13. IMPLEMENTATION OF POLICYMAKERS

Policymakers need to recognize and emphasize the importance of prevention and the need to integrate evidence-based therapies into health systems as soon as possible. This will allow care systems to be more financially efficient, indirectly leading to further improvements, which is in the interest of both the care system and patients.

14. FUTURE PERSPECTIVES

Evidence-based diagnostic and treatment protocols are needed in halitosis management. We are one step closer to this aim with this thesis, and we may show the direction for future studies, such as improving the diagnostic methods of IOH or comparing the ClO_2 with other mouthwashes in IOH.

Therefore, we wrote a pilot protocol for a randomized controlled trial in the field of IOH to continue this work. The protocol has been approved by the National Institute of Pharmacy and Nutrition (OGYÉI) (838), and we started the enrollment in January of 2024. With this, we also started to treat and observe patients with IOH. We hope with continuous improvement in the field of our interest, we can help these patients and the dentists' society.

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16. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

16.1. Publications related to the thesis

1. **Szalai, E.**, Tajti, P., Szabó, B., Kói, T., Hegyi, P., Czumbel, L. M.,Varga, G., Kerémi, B. (2023). Organoleptic and halitometric assessments do not correlate well in intra-oral halitosis: a systematic review and meta-analysis. **JOURNAL OF EVIDENCE-BASED DENTAL PRACTICE**. http://doi.org/10.1016/j.jebdp.2023.101862

Q1, IF: 3.6

2. **Szalai, E.**, Tajti, P., Szabó, B., Hegyi, P., Czumbel, L. M., Shojazadeh, S.,Varga, G., Németh, O., Kerémi, B. (2023). Daily use of chlorine dioxide effectively treats halitosis: A meta-analysis of randomised controlled trials. **PLOS ONE**, 18(1). http://doi.org/10.1371/journal.pone.0280377

Q1, IF:3.752

16.2. Publications not related to the thesis

1. Sólyom, E., **Szalai, E.**, Czumbel, M. L., Szabó, B., Váncsa, Sz., Mikulás, K., Radóczy-Drajkó, Zs., Varga, G., Hegyi, P., Molnár, B., Fazekas, R. (2023). The use of autogenous tooth bone graft is an efficient method of alveolar ridge preservation – meta-analysis and systematic review. **BMC ORAL HEALTH**. https://doi.org/10.1186/s12903-023-02930-2

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Q1, IF: 5.2

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REVIEW

ORGANOLEPTIC AND HALITOMETRIC ASSESSMENTS DO NOT CORRELATE WELL IN INTRA-ORAL HALITOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background

The gold standard method for diagnosing oral halitosis is the subjective organoleptic measurement. Device-supported methods are also widespread worldwide. The challenges and safety concerns around performing organoleptic measurements during pandemics and the diversity of measuring device alternatives raised our clinical question: which halitometer is the most suitable for diagnosing halitosis?

Methods

This systematic review was registered in PROSPERO (ID CRD42022320024). The search was performed on March 23, 2022 in the following electronic databases: MEDLINE, Embase, Scopus, Web of Science, and CENTRAL. Adult populations with or without halitosis were included, and patients with systemic diseases were excluded. Organoleptic (subjective) measurement and the device-supported (objective) methods were compared; the primary outcome was the correlation coefficient, and the secondary was the specificity and sensitivity of the devices. QUADAS-2 and QUADAS-C were used to evaluate the risk of bias in the studies. Random–effects meta analyses were performed on the outcomes, and the secondary outcomes were plotted on a common ROC plot.

Results

A total of 1231 records were found in the 5 databases. After the selection process, 76 articles were eligible for the systematic review, and 14,635 patients were involved in the qualitative analysis. The pooled Spearman's correlation coefficient (c.c.) for sulfide monitors was 0.65; 95% CIs: [0.53-0.74]; $I^2 = 95\%$, $P < .01$. The pooled Spearman's c.c. for portable gas chromatographs was 0.69; 95% CIs: [0.63-0.74]; $I^2 = 12\%$, $P < .01$. The pooled Spearman's c.c. for gas chromatographs was 0.76; 95% CIs: [0.67-0.83]; $I^2 = 0\%$, $P < .01$.

Discussion

None of the most commonly used halitometers proved to be significantly superior to the others. Halimeter and OralChroma measurements did not correlate well with the organoleptic level of oral halitosis in adults. Therefore, better halitometers need to be developed as an alternative to organoleptic measurements.

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KEYWORDS

Malodor, Sensitivity, Halitometer, Volatile sulfur compounds, H_2S, Organoleptic assessment

Abbreviations: c.c., Correlation coefficient; NPV, Negative predictive value; OLS, Organoleptic testing score; OLT, Organoleptic test; PPV, Positive predictive value; ROC, receiver operating characteristic; SROC, summary receiver operating characteristic; VSC, volatile sulfur compound.

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INTRODUCTION

Of all halitosis cases, 76%-90% originate from the oral cavity,[1–3] called Type 1 halitosis.[4] The main consequences of halitosis are feelings of inadequacy, depression, anxiety,[5] society's negative perception of the patient, and, accordingly, lower self-esteem.[6] In the long term, it generates social isolation; additionally, without addressing the underlying cause, exacerbation of the underlying disease is expected.[6] These threats to mental health could be avoided with timely diagnosis and treatment.[7] Additionally, diagnosis also supports the differentiation of pseudo-halitosis and halitophobia.[8]

Several direct[9] and indirect (chemical and enzymatic)[10] methods have been developed to measure halitosis. However, the gold standard method for diagnosing halitosis involves sensory assessment using one of several scales. One of the most widely used sensory scales is the organoleptic test (OLT).[11–14] The examiner sniffs the patient's breath and evaluates the smell from 0 to 5.[14] The examiner rates it 0 when the patient has no halitosis, and 5 when it is very severe. This method has several disadvantages; it is not only subjective,[15] but also uncomfortable for the examiner and the tested person.[16,17] Moreover, training organoleptic examiners is complicated[18] and nonstandard.[17] Additional shortcomings of the method are insufficient reliability, irreproducibility, lack of calibration, less specificity, and accuracy.[14,17,19] Additionally, hormonal changes, age,[17] and COVID-19 infection can affect the olfactory sensation, leading either to underestimation[20] or overestimation.[21] However, the main disadvantage of the OLT is that, due to the nature of the examination process, it can endanger human health or even life in potentially infectious situations during COVID-19.[17] Because of these problems, reliable halitometers are needed in halitosis diagnostics. The most widespread halitometers quantify volatile sulfur compounds (VSC), which originate from oral microbiological putrefaction.[2] Mainly Gram-negative anaerobic bacteria produce[22] VSCs such as hydrogen sulfide (H_2S), methyl mercaptan (CH_3SH), and dimethyl sulfide ($(CH_3)_2S$).[23] These VSCs are primarily responsible for oral malodor.[24]

The most common instruments to measure VSCs are electrochemical sensors (eg, Halimeter) and portable gas chromatographs (eg, OralChroma).[23] They are considered objective, reliable, easy to handle,[11] and quantify the gases.[15] The disadvantage of these instruments is that they cannot detect all kinds of volatiles, such as cadaverine and putrescine,[25] and they are also expensive.[26] OralChroma measures the 3 most common VSCs separately whereas the Halimeter evaluates them together.[11] In the research field, gas chromatographs are also used as an accurate method. However, it is a sensitive and expensive technique, requiring a trained person.[11,27]

Most researchers studying halitosis use more than 1 method to measure it for better diagnosis. On the other hand, it is time-consuming, and the results are only sometimes comparable by a meta-analysis[28] because multiple different devices and/or techniques are used[29] to measure halitosis.[30] Several studies have measured the correlation between OLT and device-supported methods. However, there is no consensus on the most appropriate and accurate measurement method. Several controversies exist amongst the studies.[31,32] To unravel the problem, all relevant literature data must be compared, contrasted, and statistically assessed to identify the differences and find correlations between various halitosis measurement methodologies. To improve precision in halitosis measurements, an important review has already emphasized the need for meta-analyses.[12]

Therefore, the aim of this study is to find and recommend a halitometer that may replace the OLT. We also sought the answer to the following clinical question: are VSC measuring instruments as suitable for measuring oral halitosis as organoleptic measurements? We hypothesized that halitosis measurements with halitometers are strongly correlated with subjective sensory or organoleptic halitosis measurements.

METHODS

This meta-analysis was preregistered in the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42022320024.

The Cochrane Handbook for Systematic Reviews[33] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA 2020)[34] (Supplementary Table 1) guided our meta-analysis.

Systematic Search

The following population-intervention-comparison-outcomes framework was applied as an inclusion criterion regarding the research question. The searched population was exempted from known systemic diseases because we aimed to measure only intra-oral halitosis. The standard organoleptic measurement was compared to the VSC measuring devices, halitometers such as gas chromatographs, portable gas chromatographs (OralChroma), electrochemical sensors (Halimeter), and eNoses. The primary outcome was the correlation coefficient, and the secondary was the specificity and sensitivity of the devices. Clinical trials were included when the VSC and organoleptic testing scores (OLS) were measured, and the correlation coefficient was reported.

In vitro or animal studies, non-English or conference papers, and case reports were excluded. Regarding our population, we excluded children.[35]

The literature search date for the databases MEDLINE, CENTRAL, Embase, Scopus, and Web of Science was March 23, 2022. The different search keys used can be found in Supplementary Document 1.

The reference lists of eligible articles, review articles, and grey literature were also examined.

After EndNote's automatic and manual duplicate removal, 2 independent researchers (E.S., P.T.) screened the records for eligible titles and abstracts. Afterward, they identified the eligible full texts. In case of a disagreement, they involved a third investigator (B.K.). Interrater agreements were also calculated in both cases with Cohen's Kappa.

The selection process was visualized with the PRISMA2020 flow diagram.[36]

Data Collection Process and Data Items

Two authors (E.S., P.T.) independently collected all available data in predefined tables. The following data items were collected: first author, year of publication, study design, demographic data of the population, type of index and reference tests, type of correlations, correlation coefficient (c.c.), exclusion of extra-oral halitosis and children, sensitivity, specificity, threshold, positive prediction value (PPV), and negative prediction value (NPV). In the event of missing information, E.S. contacted the corresponding authors. In articles where correlations were available for multiple dates, only 1 (preferably the baseline) was included in the analyses.

Study Risk of Bias Assessment

Two reviewers, working independently from one another, utilized the quality assessment tool for diagnostic accuracy studies with QUADAS-2[37] and QUADAS-C.[38] QUADAS-C is an extension to QUADAS-2 that is used if more comparable index tests are available. These tools help evaluate the risk with signaling questions in patient selection, index tests, reference standards, time and flowing, and applicability's.

Effect Measure and Synthesis Methods

The current study contains 2 main types of meta-analyses: a meta-analysis of correlations and a diagnostic meta-analysis. The methodologies are detailed in Supplementary Documentum 2.

In all studies, correlations belonging to the categories Pearson's c.c., Spearman's c.c., Kendall's tau, and those whose type of c.c. were not mentioned in the article. Pearson c.c. is the most commonly used type of correlation. However, it works properly only if the type of correlation is linear between the variables. Kendall's tau-b c.c. is a rank correlation, similar to the Spearman correlation.[39] The correlation is measured from −1 to +1. The perfect positive correlation shows that both variables move in the same direction. The perfect negative correlation suggests that the 2 variables move in the opposite direction. 0 indicates no linear relationship between the 2 variables.

Fisher's z-transformation was carried out on each obtained c.c., so the standard errors of each obtained correlation could be approximated using the sample sizes of the studies.[40] Correlations were then retransformed for the meta-analyses.

The correlations were analyzed using subgroup analyses to increase reliability and decrease bias within calculations.

As we anticipated considerable between-study heterogeneity, random-effects meta-analyses were performed on datasets using the Hartung-Knapp adjustment.[41]

Reporting Bias Assessment and Quality of Evidence

Publication bias was assessed with Egger's test using the classical Egger's[42] method to calculate the test statistic as per Sterne et al.,[43] and contour-enhanced funnel plots were also created to give visual aid. Analysis results were critically handled if the study number was below 10 or the study effects showed high heterogeneity.

Two reviewers (E.S., P.T.) used the GRADEpro[44] tool to perform the evidence profile according to the GRADE Handbook.[45]

RESULTS

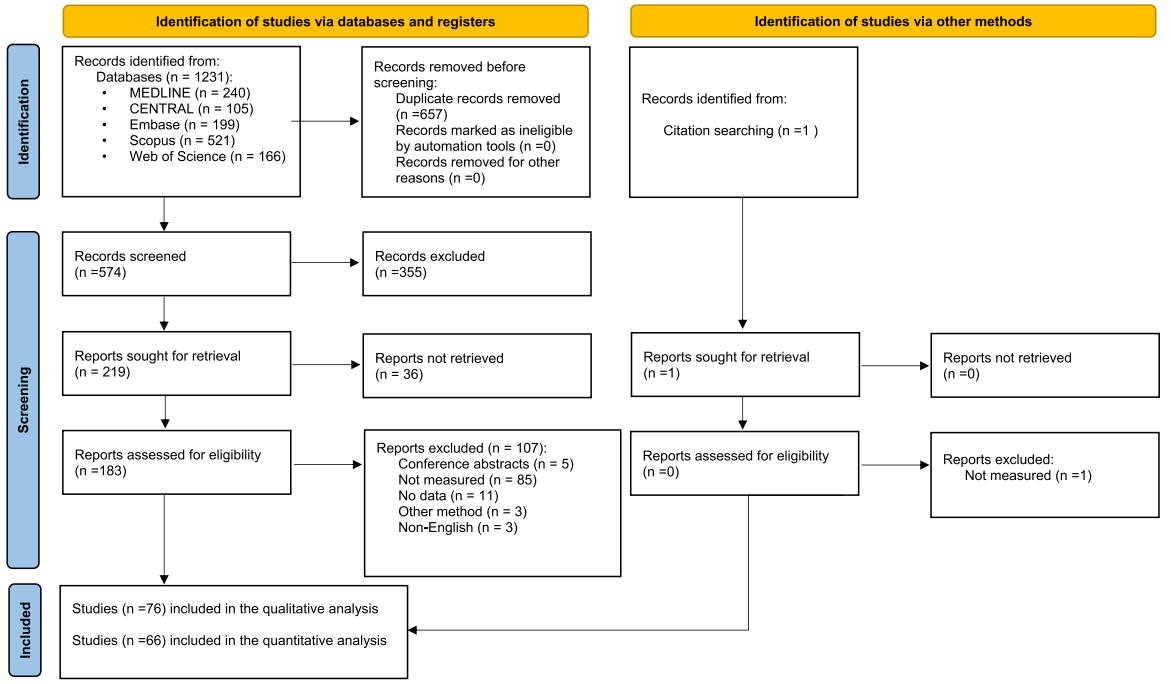
Search and Selection

A total of 1231 records were imported into EndNote[46] from the MEDLINE, CENTRAL, Embase, Scopus, and Web of Science databases (Figure 1). The inter-examiner agreement between the reviewers was $\kappa = 0.95$ at the title abstract selection and $\kappa = 0.968$ at the full-text selection, resulting in 76 articles. While during the full-text selection process, we had to exclude 36 reports[27,47–81] because the full texts were not available. Five were conference abstracts[82–86] and 85 studies[24,87–170] had not measured the correlation. Another 11 articles did not contain data,[171–181] 3 reports[182–184] were not in English, and 3[185-187] used different methods. In 1 article,[188] there was an overlapping population; however, only nonoverlapping data were used. A literature search via additional methods and search of grey literature yielded only 1 additional record.[189] Finally, the qualitative analysis contained 76 studies. However, 10 studies[190–199] could not be included in the quantitative analysis due to the use of a different OLS scale or the lack of similar comparator devices. In the quantitative analysis, 66 studies were included.

Basic Characteristics of Included Studies

The main characteristics of the studies[19,31,32,188,190–261] are displayed in Supplementary Table 2. Most of the studies had cross-sectional designs, a few of them investigated diagnostic test accuracy, and 13 were randomized controlled

Figure 1. Prisma 2020 Flow Diagram of the screening and selection process.



trials. The studies represent data from all over the world. Most of the studies used a 6-point scale (0-5) to perform sensory testing, but there were also a few articles with 4 (0-3), 5 (0-4), or 11-point sensory scales (0-10). Correlation coefficients were secondary outcomes of most studies. The following devices are included in this meta-analysis: Halimeter, OralChroma, and gas chromatographs, but we could not differentiate between the newer and older devices. Three studies investigated the Breathtron,[197,198,258] a modified sulfide monitor, which also correlated well, but the quantitative analysis was not feasible. Other devices, such as the eNose and different types of sulfide monitors, were included in the qualitative analysis.

Correlation Between Halitometers and OLS

We could include 14,635 patients in the qualitative analysis.

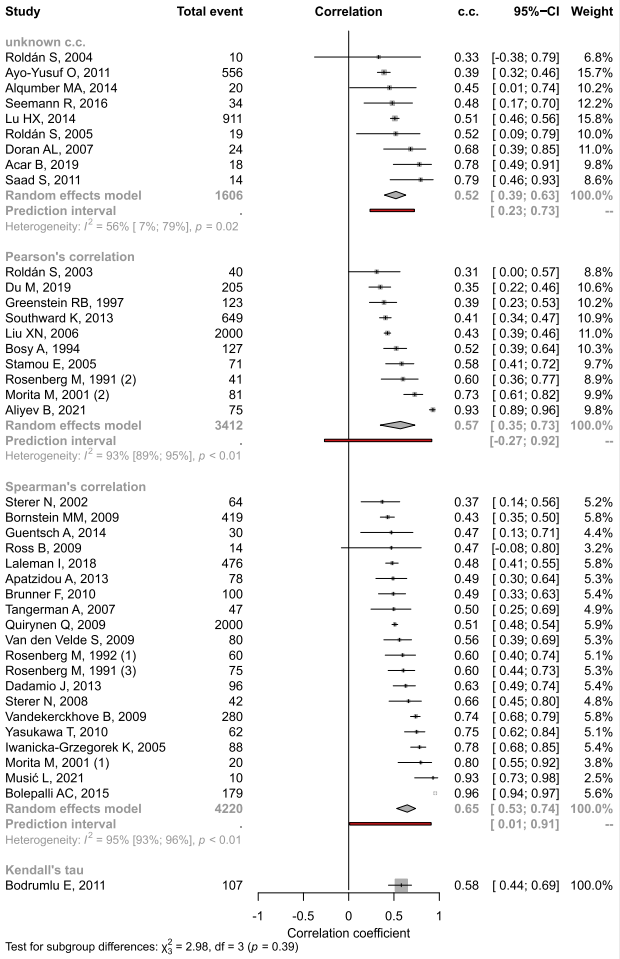
The pooled Spearman's c.c. for the sulfide monitors was 0.65; 95% CIs: [0.53-0.74]; $I^2 = 95\%$, $P < .01$, and the pooled Pearson c.c. for the sulfide monitors was 0.57; 95% CIs: [0.35-0.73]; $I^2 = 93\%$, $P < .01$ (Figure 2). The pooled Spearman's c.c. for portable gas chromatographs was 0.69; 95% CIs: [0.63-0.74]; $I^2 = 12\%$, $P < .01$, and the pooled Pearson c.c. for portable gas chromatographs was 0.59; 95% CIs: [0.37-0.75]; $I^2 = 90\%$, $P < .01$ (Figure 3). The pooled Spearman's c.c. for the gas chromatographs was 0.76; 95% CIs: [0.67-0.83]; $I^2 = 0\%$, $P < .01$, and the pooled Pearson c.c. for gas chromatographs was 0.57; 95% CIs: [0.32-0.47]; $I^2 = 84\%$, $P < .01$ (Figure 4).

For sulfide monitor data, the correlation was significantly ($P < .05$) lower in the study subgroup, where the exclusion was unknown regarding systemic diseases, compared to the subgroup where systemic diseases were excluded. The pooled Spearman's c.c. for sulfide monitors without systemic diseases was 0.72; 95% CIs: [0.56-0.83]; $I^2 = 80\%$, $P < .01$ and without the information on the exclusion or inclusion of systemic diseases the pooled Spearman's c.c. was 0.50; 95% CIs: [0.44-0.54]; $I^2 = 34\%$, $P < .01$ (Figure 5).

The pooled Spearman's c.c. with the OralChroma for the H_2S, was 0.59; 95% CIs: [0.51-0.66]; $I^2 = 93\%$, $P < .01$ (Figure 6). The pooled Spearman's c.c. for the CH_3SH was 0.58; 95% CIs: [0.45-0.68]; $I^2 = 97\%$, $P < .01$ (Supplementary Figure 1). The pooled Spearman's c.c. for the $(CH_3)_2S$ was 0.24; 95% CIs: [0.09-0.39]; $I^2 = 80\%$, $P < .01$ (Supplementary Figure 2). H_2S and CH_3SH correlated significantly ($P < .05$) better to OLS than $(CH_3)_2S$.

The pooled Spearman's c.c. between the portable gas chromatographs and sulfide monitors was 0.55; 95% CIs: [0.50-0.59]; $I^2 = 0\%$, $P < .01$ (Supplementary Figure 3).

Figure 2. Forest plot of the pooled correlations between the sulfide monitor devices and organoleptic test scores. c.c., correlation coefficient; CI, confidence interval. The grey squares show the correlations between the organoleptic testing scores and the halitometers from the individual studies, and horizontal lines represent the CIs. The overall result illustrates by the grey diamond.

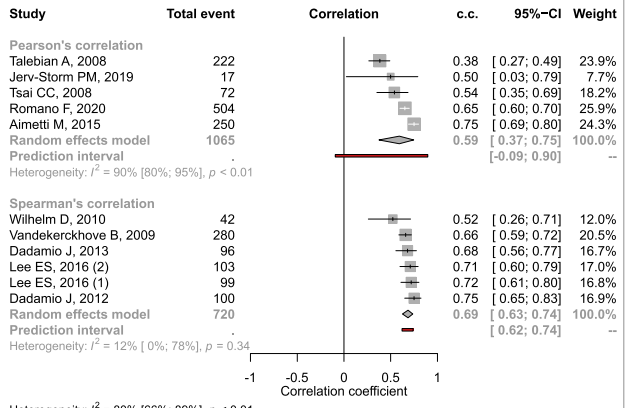


Test for subgroup differences: χ^2_3 = 2.98, df = 3 (p = 0.39)

Heterogeneity: I^2 = 93% [92%; 94%], p < 0.01

c.c.: correlation coefficient; CI: confidence interval
The grey squares show the correlations between the organoleptic testing scores and the halitometers from the individual studies, and horizontal lines represent the CIs. The overall result illustrates by the grey diamond.

Figure 3. Forest plot of the pooled correlations between the portable gas chromatographs and organoleptic test scores, c.c., correlation coefficient; CI, confidence interval. The grey squares show the correlations between the organoleptic testing scores and the halitometers from the individual studies, and horizontal lines represent the CIs. The overall result illustrates by the grey diamond.



Heterogeneity: I^2 = 80% [66%; 89%], p < 0.01

Test for subgroup differences: χ^2_1 = 2.07, df = 1 (p = 0.15)

c.c.: correlation coefficient; CI: confidence interval
The grey squares show the correlations between the organoleptic testing scores and the halitometers from the individual studies, and horizontal lines represent the CIs. The overall result illustrates by the grey diamond.

The pooled Spearman's c.c. for sulfide monitors on the 4-point sale was 0.52; 95% CIs: [0.28-0.70]; I^2= 41%, P < .01 (Supplementary Figure 4).

Specificity and Sensitivity

In the case of the Halimeter, the SROC curve was fitted using 6 articles[31,32,210,218,227,251] (Supplementary Figure 5). The analysis was repeated without 2 studies,[210,218] where it was unclear whether the aim was to detect OLS ≥2 conditions (Figure 7).

In the case of the OralChroma-CHM-1 diagnostic tool, only 3 studies[31,32,227] were available. The difference between the Halimeter and the OralChroma could not be tested because a different analysis type was required for the 2 devices. So even though the model fitting is more uncertain, and the visual difference is reduced for 4 articles rather than with 6, due to the number of articles, it may still reflect the truth (Figure 7, Supplementary Figure 5) as the target aim was prespecified as OLS ≥2 for 4 articles.

Risk of Bias Assessment

The risk of bias in all included studies is displayed in a tabular view (Supplementary Table 3). The articles generally represented a low risk of bias in applicability concerns, QUADAS-2 patient selection, and flow and timing domain. In some cases, the risk of the reference standard or index test results was unclear because there was no information on the knowledge of the other test results. The presumed reason why these were not reported may have been that most studies had non-diagnostic test accuracy. Moreover, there was a high risk of QUADAS-C; however, this comparison was used

Figure 4. Forest plot of the pooled correlations between the gas chromatographs and organoleptic test scores. c.c., correlation coefficient; CI, confidence interval. The grey squares show the correlations between the organoleptic testing scores and the halitometers from the individual studies, and horizontal lines represent the CIs. The overall result illustrates by the grey diamond.

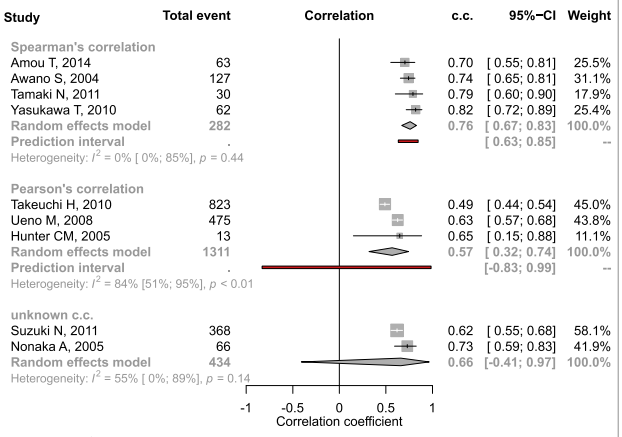
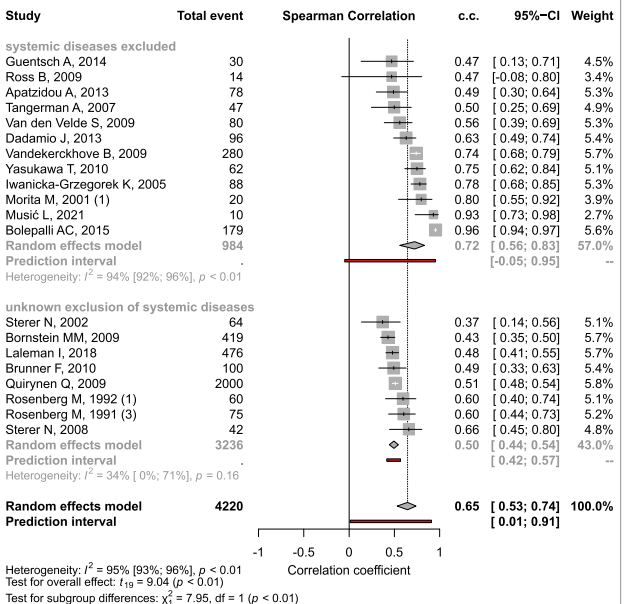


Figure 5. Forest plot of the pooled correlations regarding the inclusion of extraoral halitosis between the sulfide monitors and organoleptic test scores. c.c., correlation coefficient; CI, confidence interval. The grey squares show the correlations between the organoleptic testing scores and the halitometers from the individual studies, and horizontal lines represent the CIs. The overall result illustrates by the grey diamond.



in the subgroup analysis. Although our index tests were objective, we believe that noting the prespecified threshold could strengthen the studies.

Publication Bias and Heterogeneity

Funnel plots display the results of the publication bias assessment (Supplementary Figures 6-8). In the case of sulfide monitors, publication bias may be present (Egger's test: $P = .0289$). In the case of sulfide monitors, the choice of different thresholds can lead to considerable heterogeneity. Heterogeneity is usually lower for Spearman's c.c.

Certainty of Evidence

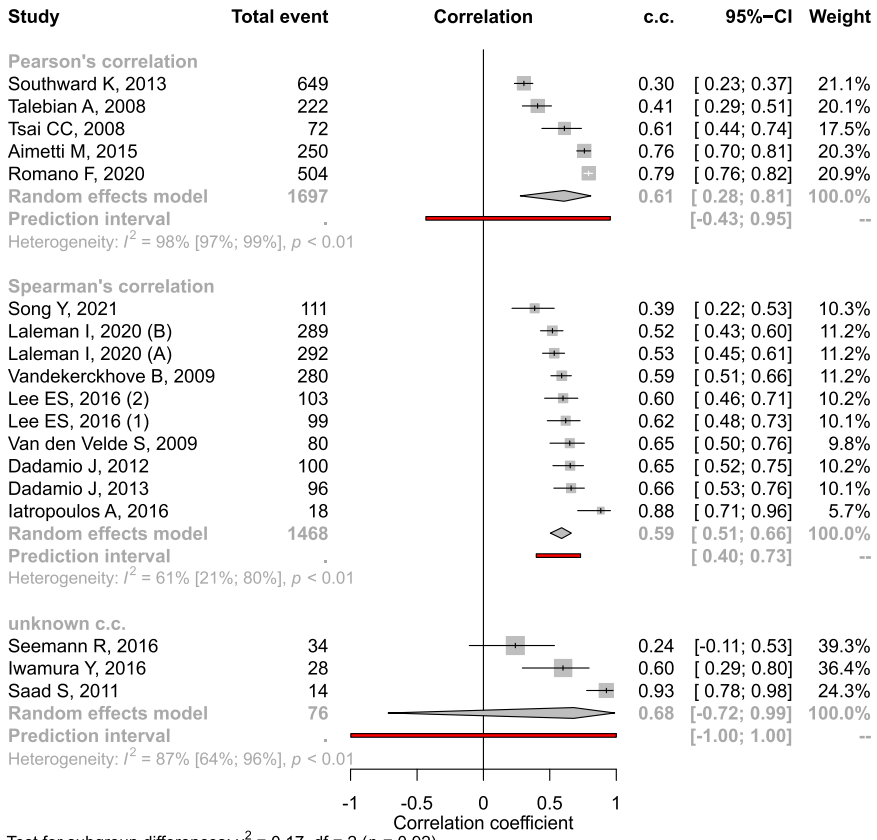
The GRADE evidence table (Supplementary Table 4) shows very low certainty of evidence for primary outcomes due to study designs and high heterogeneity. For secondary outcomes, the evidence should be treated with caution due to the low number of studies (Supplementary Tables 5 and 6).

DISCUSSION

The results showed that the data obtained with the halitosis measuring devices did not correlate closely with the organoleptic method. In all cases, the correlations were moderately positive compared to the 6-point scale of the OLS, which is particularly advantageous when comparing halitometers to a subjective process. However, this level of correlation is insufficient in the case of comparing 2 diagnostic methods. Therefore, the original hypothesis had to be rejected; this is in line with some papers that question the significant correlation between the OLS and the different device-supported methods.[141,161,180,211] Moreover, the best instrumental diagnostic method could not be revealed. The primary outcome allows us to propose the most similar device to OLT.

The analysis showed that none of the devices were significantly superior to the others. However, gas chromatographs showed the highest correlation with OLS. Therefore, the results are in agreement with those of Yaegaki et al.[166] and van den Broek et al.[12] who suggested the use of gas chromatographs in halitosis research. Moreover, Murata et al.[9] regarded the gas chromatograph to be the gold standard. However, more research is necessary to evaluate the real accuracy of gas chromatography for halitosis detection. It is also important to note that the instrumentation of this

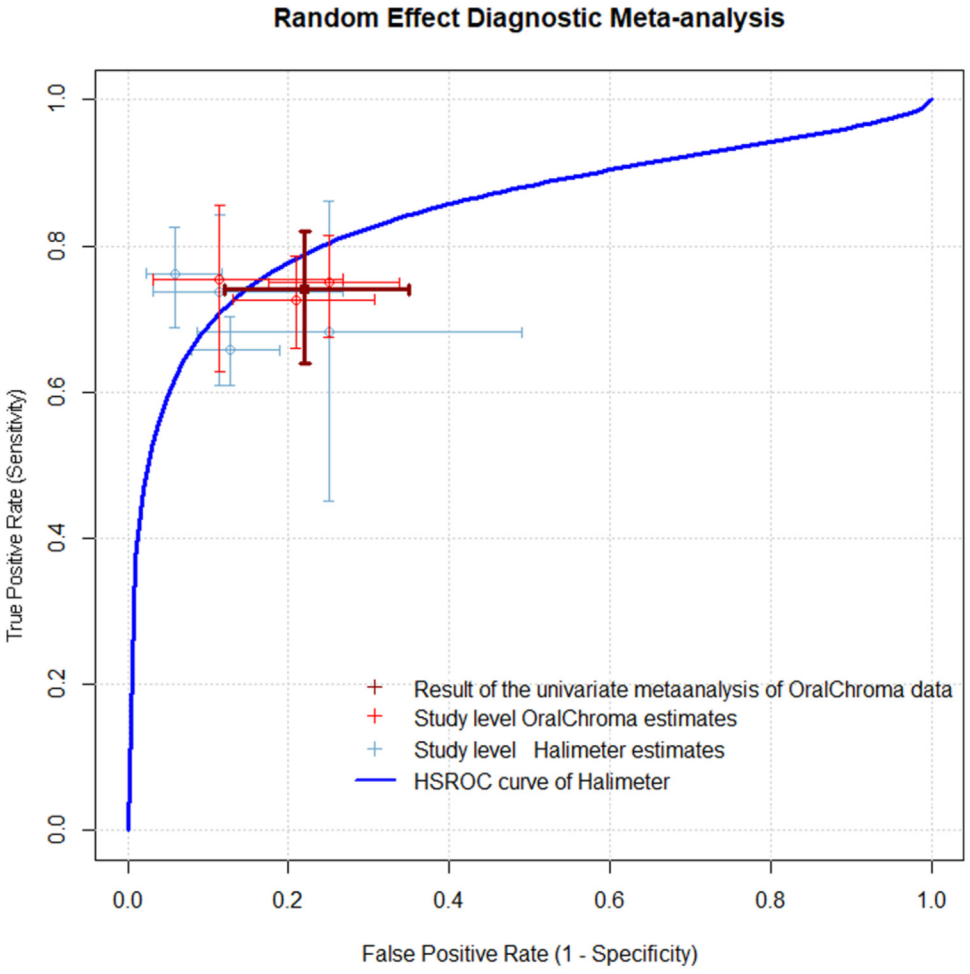
Figure 6. Forest plot of the pooled correlations for the hydrogen sulfide measured by OralChroma and organoleptically assessed values. c.c., correlation coefficient; CI, confidence interval. The grey squares show the correlations between the organoleptic testing scores and the halitometers from the individual studies, and horizontal lines represent the CIs. The overall result illustrates by the grey diamond.



method is expensive, complicated, and time-consuming[262]; however, it is constantly evolving.[263] Many devices could not be included in the quantitative analysis. Thus, the best device may already exist, but this study could not identify that; hence it is not widely used. Furthermore, the correct breath analyses, both sensory and halitometric, are very technique-sensitive methods. Research reports in many instances did not report in detail the exact way how they performed the analysis regarding thresholds, calibration, the timing of the comparison, or how they collected the samples. The volume of the collected sample size is also often missing.

The data suggest that an important reason for the controversies between the studies could be that sulfide monitors represented a significantly worse correlation when extra-oral halitosis was not excluded (Figure 5). It has been reported that sulfide monitors are less sensitive to detecting extra-oral halitosis as they are less sensitive to $(CH_3)_2S$.[27,256,264] Therefore, the results suggest excluding patients with known systemic disorders or extra-oral halitosis when using sulfide monitors. However, it is difficult to estimate what differential diagnostic criteria were applied to distinguish intra- or extra-oral halitosis during case selection of included literature reports. For this reason, it is possible that some halitometric or organoleptic measurements evaluated are associated with extra-oral halitosis. Extra-oral halitosis could be differentiated by the cysteine induction method, as described by Aydin et al.[265] or by examining the nasal breath.[256]

Figure 7. ROC plot visualizing the diagnostic performance of Halimeter and OralChroma diagnostic tools (original running with 4 articles). HSROC, Hierarchical summary receiver-operating characteristic. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



HSROC, Hierarchical summary receiver-operating characteristic. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

OLS correlated significantly better to H_2S and CH_3SH than to $(CH_3)_2S$ (Supplementary Figure 2) with OralChroma devices in our analysis, supporting the statement of Tozenteich et al.[2] that VSCs are defined as 90% H_2S and CH_3SH.

The interrater agreement of organoleptic examiners in the literature, was similarly heterogeneous (Spearman c.c. was 0.559[260]; Cohen's Kappa was ($\kappa = 0.69$)[266]; Kendall's tau-b c.c. was 0.743[208]) as the results of the included studies, mainly because of the subjectivity of the method. Cohen's Kappa measures interrater agreement between 0 and 1; a value above 0.81 indicated a near-perfect agreement.

The correlation between sulfide monitors and portable gas chromatographs showed lower heterogeneity. Still, the correlation was weaker than expected between the 2 devices measuring the same compounds with 2 different methods.

Further studies with selective flow tube mass spectrometry (SIFT-MS) or new versions of eNoses are needed in halitosis research, as they measure non-VSC gases rapidly. However, the presently available SIFT-MS application reports lacked correlation with OLS.[12,244] Electrical sensing is a constantly evolving field[267] with various devices available,[194,236] correlations were between 0.78 and 0.81. However, the lack of quantitative measurements of gases does not make them superior to the most commonly used devices.[194]

MX6 is a portable multigas detector, separately measuring volatile organic compounds, such as NH_3, SO_2, H_2S, and H_2.[268,269] Breath-Alert[218] could be a cheap diagnostic alternative with high sensitivity and specificity.[270] Only a few test results are available for the following devices: FreshKiss ($r = 0.283$),[213] tongue sulfide monitor ($r = 0.768$),[233] Breathtron ($r = 0.65$),[198] and Tanita (ROC = 0.473).[271] The wide range of self-assessment devices on the market is indicative of the tremendous demand for a cheap, fast, suitable diagnostic device that individuals can use to reliably check their own breath for odor.

Correlations between OLS and less frequently used indirect methods were also moderately positive or even weaker; for example, with the spectrophotometric analysis of saliva,[187] or with the combined plaque fluorescence score,[228] or with the concentration of *Solobacterium moorei* in saliva,[158] or with the colorimetric chair-side test.[214] These data suggest that more diagnostic test accuracy studies are necessary to detect differences between methods more accurately.

The diagnostic test accuracy of our meta-analysis revealed that the sensitivity and specificity of device-supported measurement could be more outstanding. Our data showed that these devices could correctly diagnose 70% of the patients with halitosis. Of course, this could be due to inadequate threshold selection[32] and the insensitivity of the devices for cadaverine, indoles, and skatoles,[16] causing a false-negative diagnosis. As Greenman et al.[272] pointed out, single-compound contributions to halitosis depend on the odor power and the threshold concentration.[272] False-positive diagnosis can be caused by acetone, ethanol, and methanol in exhaled air measured with the Halimeter.[273]

A newer type of OralChroma instrument (CHM-2) could not be included in the diagnostic test accuracy meta-analysis because we found only 1 eligible article. This instrument performed even worse in the article[227] than the older version (CHM-1), which was included in the analysis. Although there is no significant difference between the devices, the Halimeter performed slightly better on sensitivity and specificity levels than the OralChroma (CHM-1) in the analysis. However, these are based on secondary outcomes from a limited number of articles. This could be due to software limitations that need to be improved in the future,[274] which could lead to significant improvements.

The OLT has been used less frequently as a diagnostic tool in the last 3 years due to COVID-19. Patients could detect halitosis under their masks, but the diagnosis may have been delayed and, consequently, the treatment was delayed, too. Before the pandemic, Seeman et al.[26] suggested that organoleptic measurement was mandatory in diagnosing halitosis, and could be performed by all dentists.[275] The pandemic situation has increased safety concerns about inhaling people's breath. We agree with Laleman et al.[11] that the OLT is currently the gold standard. On the basis of data that could be included in the present meta-analysis, we cannot recommend a particular halitometer that is better than others or that would be sufficient for use as a stand-alone assessment method.

The strengths of our meta-analysis are the high number of articles included, the results obtained with 3 different popular devices, and the fact that no meta-analysis has been published on this topic.

The limitations are the potentially interesting articles; 35 reports could not be retrieved. Most of the included studies had cross-sectional study designs. Therefore, the evidence could not be more robust than low, indicating a very low level of evidence following the GRADE evaluation. Another weakness could be that the comparison was made using a subjective method. The low number of studies included in our secondary outcome analysis and the inadequate, unknown thresholds in the primary analysis could also cause biases.

In some cases, as in real life, patients with extra-oral halitosis, and the under-aged population was not excluded as planned due to the lack of information.

Clinical and Research Implication

The data suggest that patients with extra-oral halitosis should be excluded if the diagnosis is made with sulfide monitors. The rarely-used 4-point scale of OLS does not appear to be inappropriate for the measurement of halitosis accurately in indirect comparison; however, this study recommends the use of using the 6-point scale.

Further studies should focus on the accuracy of device-based diagnostic tests rather on the examination of correlations between devices. For existing and new device improvements, it would be useful to perform ROC analysis and report results corresponding to different thresholds of continuous device measurements would be beneficial. Researchers should investigate whether OLS is indeed the gold standard.

CONCLUSION

None of the most commonly used halitometers proved to be significantly superior to the others. Halimeter and OralChroma measurements did not correlate well with the organoleptic level of oral halitosis in adults. Therefore, better halitometers need to be developed as an alternative to organoleptic measurements.

ETHICAL APPROVAL

No ethical approval was required for this meta-analysis, as all data had already been published in peer-reviewed journals.

The datasets used in this study can be found in the published full-text articles included in the systematic review and meta-analysis.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jebdp.2023.101862.

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PLOS ONE

RESEARCH ARTICLE

Daily use of chlorine dioxide effectively treats halitosis: A meta-analysis of randomised controlled trials

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Abstract

Objectives

We aimed to conduct a systematic review on published data in order to investigate the efficacy of mouthwash products containing chlorine dioxide in halitosis.

Study design

Systematic review and meta-analysis

Methods

Our search was conducted on 14th October 2021. We searched the following electronic databases: MEDLINE, Embase, Scopus, Web of Science, and CENTRAL. We analysed data on adults with halitosis, included only randomised controlled trials and excluded *in vitro* and animal studies. The interventional groups used chlorine dioxide, and the comparator groups used a placebo or other mouthwash. Our primary outcomes were changes in organoleptic test scores (OLS) and Volatile Sulfur Compound (VSC) levels from baseline to the last available follow-up.

Results

We found 325 articles in databases. After the selection process, ten articles were eligible for qualitative synthesis, and 7 RCTs with 234 patients were involved in the meta-analysis. Our findings showed a significant improvement in the parameters of the chlorine dioxide group compared to the placebo group in OLS one-day data (mean difference (MD): -0.82; 95% confidence intervals (95% CIs): [-1.04 –-0.6]; heterogeneity: $I^2 = 0\%$, $p = 0.67$); and one-

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week OLS data (MD: -0.24; 95% CIs: [-0.41 –-0.07]; I^2 = 0%, p = 0.52); and also changes in H_2S one-day data (standardised mean difference (SMD): -1.81; 95% CIs: [-2.52 –-1.10]); I^2 = 73.4%, p = 0.02).

Conclusion

Our data indicate that chlorine dioxide mouthwash may be a good supportive therapy in oral halitosis without known side effects.

Introduction

Halitosis or bad breath, defined as "malodor with intensity beyond a socially acceptable level, perceived" [1], is an unpleasant condition that most people experience or notice in others. Halitosis may result in higher anxiety levels, feelings of inadequacy, depression, sensitivity, anger, and stress [2].

Oral microbial putrefaction of proteins is the leading cause of Type 1(oral) halitosis [3]. This process results in the formation of volatile sulfur compounds (VSCs). The main VSCs involved in oral halitosis are hydrogen sulfide (H_2S), methyl mercaptan (CH_3SH), and dimethyl sulfide ($(CH_3)_2S$) [4]. The first two compounds are responsible for approximately 90% of VSCs [5]. These VSCs are mainly produced by gram-negative anaerobic oral bacteria (*Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Tannerella forsythia*, and *Treponema denticola*) [6–8] from sulfur-containing amino acids such as cysteine, cystine, and methionine [4, 9].

There is still no evidence-based, definitive treatment protocol for bad breath. As mentioned in a systematic review by Wylleman et al. [10], it was proved that tongue cleaning is effective in reducing oral malodor in addition to toothbrushing. If measures do not help and the supposed cause was also treated well (e.g., periodontitis), further treatment might be necessary [11, 12]; namely, the use of mouthwashes (e.g. Halita™, meridol® [11], stannous fluoride and zinc lactate [13] or chlorine dioxide mouthwashes [14]) or probiotics (e.g. *Lactobacillus salivarius*, *Lactobacillus reuteri* [15–17], *Bifidobacterium lactis* and *Lactobacillus acidophilus* [18]). There are various types of mouthwash on the market, and people spend millions of dollars annually on anti-malodor mouthwash products [19]. Chlorhexidine-containing mouthwashes are considered to be the gold standard [20] mouthwashes. Although they are effective, they have several side effects [20, 21]. There is an obvious need to find a mouthwash that treats halitosis effectively and without side effects.

Chlorine dioxide (ClO_2) is a selective oxidizing agent [22]. Unlike other oxidants, it reacts poorly with most substances in living organisms [22]. However, it rapidly responds with three amino acids: cysteine, tyrosine, and tryptophan. The anti-halitotic activity of ClO_2 is primarily an antibacterial effect due to its reactions with the three amino acids mentioned above and their acid residues in proteins and peptides [22]. Furthermore, it oxidises the precursors of VSCs [23, 24]. These antimicrobial mouthwashes are mainly effective against Type 1 halitosis.

The aqueous chlorine dioxide solution [25] is widely used in medicine for disinfection of intraoral areas [26–29], without any recorded side effects [30]. Several studies have already been conducted to investigate chlorine dioxide mouthwashes in halitosis [29, 31–34]; however, these individual studies lack high power, and there is imprecision in the data. Cochrane review [35] did not find sufficient evidence to support the effectiveness of any interventions for managing halitosis and had certain limitations in its data sets. It justifies the rationale for conducting this review.

We aimed to investigate the efficacy of chlorine dioxide mouthwashes in patients with halitosis. We hypothesised that mouthwashes containing chlorine dioxide are as efficient as other mouthwash products and more efficient than placebos in reducing oral malodor.

Methods

Protocol and registration

We conducted the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [36] statement (S1 Table) and the guidance of the Cochrane Handbook for Systematic Reviews of Interventions [37].

The protocol of this meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42021281195.

Eligibility criteria

For eligibility, we applied the PICO (population, intervention, comparator, and outcome) framework as the reference standard. The included population were as follows: adults without systemic diseases who had bad breath; the intervention: chlorine dioxide-containing mouthwash; the comparator: other mouthwashes, placebo, or no-treatment groups; outcomes: changes in organoleptic test scores or volatile sulfur compound levels. The included population was above 18 years of age, and we did not apply any upper age limit. Bad breath was defined as OLS $\geq$ 1. We included only randomised controlled trials. We did not apply any language or time restrictions in our search.

We excluded in vitro and animal studies as well as patients with systemic disease or children as a population. We also excluded studies where the mouthwash with chlorine dioxide or the comparator mouthwash contained multiple active ingredients, such as chlorine dioxide and zinc.

Information sources and search strategy

The literature search was conducted on 14th October 2021 and updated on 23rd September 2022. The search covered the following databases: MEDLINE, Embase, Scopus, Web of Science, and CENTRAL.

We used individualised search terms in different databases and examined every relevant reference list of included studies and relevant systematic reviews manually and automatically (Scopus).

Study selection

EndNote 20 software was used for record management [38]. After duplicate removal, two investigators (E.S., P.T.) separately made the title and abstract selection to be followed by full-text selection. After the title, abstract, and full-text selection, the inter-rater agreement was measured between the investigators with Cohen's kappa. In case of disagreement, a third author (B.K.) was also involved. If a full text could not be obtained, it was requested from the authors or libraries by E.S.

Data collection process and data items

Two authors (E.S, P.T.) independently extracted the following data from the eligible articles and cross-checked them: population characteristics, interventions, comparator, measurement methods, and outcomes.

The primary outcome domains were organoleptic testing (OLT) scores and volatile sulfur compounds (VSCs) levels. We pooled these data from all available time points. Studies presented VSC data in either ppb or ng/10mL; some of them had total VSC data, and some separated data into H_2S, CH_3SH, and $(CH_3)_2S$. The ppb measurements were converted into ng/10 mL for comparison with a division of ten.

In cases of missing data, E.S. contacted the corresponding authors.

Risk of bias in individual studies

For risk of bias assessment, the Cochrane Risk of Bias 2 Tool [39], individually-randomized, parallel-group trials, and crossover trials were used, including the following domains: bias arising from the randomisation process, bias arising from the period and the carryover effects, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in selecting the reported results. The domain of bias arising from the period and the carryover effects is the difference between the two applied Risk of Bias 2 Tools. This domain is included for crossover trials only. The two reviewers (E.S., P.T.) who made the assessments discussed and settled the disagreements. In cases of a lack of agreement, a third author was also involved.

Effect measures

Mean-difference and standardised mean-difference meta-analyses were performed on the data with a predefined confidence interval of 95%. The mean-difference meta-analysis was performed in cases when all available data were measured using the same methods and instruments and were on the same scale. On the other hand, the standardised mean-difference meta-analysis was utilised in cases where the same parameter was measured, but the instruments differed. We applied the mean difference on the OLS data and the standardised mean difference on the VSC data because researchers used different devices to measure them. Studies that did not include Standard Deviations (SD) for either measurement and those with SDs that were not computable from the OLS data or with the latter mentioned methods were excluded from the meta-analyses and were used only for the 'qualitative results' part of this study. We also calculated the changes in the outcome data in various periods; this was the criteria to form subgroups. The OLS subgroups demonstrate one-day, one-week, and two-week data separately.

In the case of crossover studies, only the results of the first phases were utilised as a conservative and cautious approach. It was thus ensured that there was no distortion due to the inclusion of dependent study populations.

In cases where the standard deviation of changes in the measurements for the different follow-up times was not given, Cochrane guidelines [37] were used. When researchers gave only a confidence interval (CI) for the change, we divided the difference between the upper and lower CI limits by 3.92 (the value for 95% CI) [37]. When there was an available SD of the change in any study, a correlation coefficient was calculated using the SD value for the intervention and the control groups of the study, and the missing SDs of the other studies were calculated using this correlation coefficient value [37].

Synthesis methods

The weight of each study in the meta-analysis was based on its standard deviations and sample size. Larger SDs or a smaller sample size resulted in a lower weight assigned to the specific study. In contrast, studies with small SDs or a high sample size received higher weights in the analyses. Statistical heterogeneity was calculated using the I-squared test. For the meta-analyses, random-effects models were used, as the population of the studies was expected to be

heterogeneous. All statistical analyses were carried out using R-statistics [40] and its "meta" package. The results of the meta-analyses were presented using forest plots.

Reporting bias assessment

Funnel plot analyses and heterogeneity analysis could not be appropriately performed due to the low number of articles.

Certainty assessment

The certainty assessment was evaluated according to the GRADE Handbook [41]; we performed the summary of findings table with the GRADEpro [42] tool. Two reviewers (E.S., P. T.) assessed the certainty of evidence individually, the discrepancies were discussed, and consensual decisions were made.

Results

Study selection

352 articles were downloaded: MEDLINE (n = 28), Embase (n = 41), Scopus (n = 236), Web of Science (n = 22), and CENTRAL (n = 25). After duplicate removal, we had 249 articles (Fig 1).

For full-text selection, 17 abstracts were selected. Eight articles remained after we compared our choices from the eligible full texts. The first Cohen's kappa was 1, and the second was 0.88. Four articles were excluded because the full texts were not available [29, 33, 34, 43]; one report was excluded [44] because it was not a randomized controlled trial; three other articles were

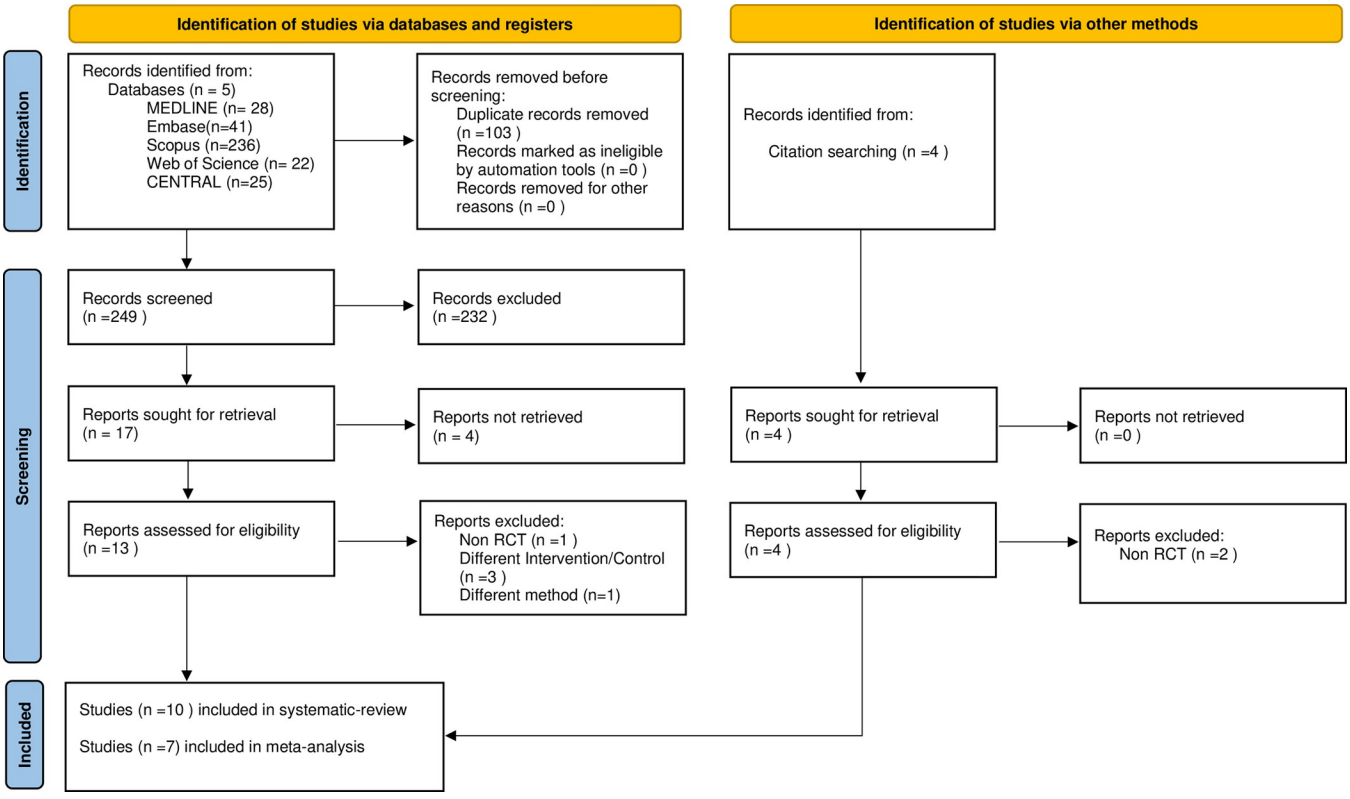

Fig 1. Prisma 2020 flow diagram of the screening and selection process.

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excluded because the intervention [31, 45] or a comparator [32] contained Zn, an active component not considered in our analysis. Another study was excluded because cysteine was used to induce halitosis [46]. We found four articles [47–50] by citation search. Two were eligible for full texts [48, 50]. The other two articles from the citation search were not RCTs [47, 49] and were thus excluded.

After the selection process, a total of ten articles were included in the qualitative synthesis [14, 48, 50–57], and seven in the quantitative synthesis. Three articles could not be included in the statistical analysis because we did not have enough comparable data [14, 50, 54].

Characteristics of the included studies

Key characteristics of the included studies are presented in Table 1. Placebo was used in the comparator groups, except for one study [50], where it was chlorhexidine.

Four studies did not involve women because their menstruation cycles could influence the results [14, 50, 56, 57]. All the studies were written in English. We included two articles by Lee et al. [52, 53]; the corresponding author confirmed that the applied populations differed. After that, we summarised one-day, one-week, and two-week data. In the VSC 1-week and 2-week data, we did not have enough comparative articles, so we had to exclude three articles from the quantitative synthesis [14, 50, 54]. The one-day follow-up patients used the experimental mouthwashes in the morning of the measurement day, and on the one-week and two-week follow-ups, they used them twice a day. No other intervention was allowed for the patients.

All of the included studies used the six-point OLS scale [58]. The organoleptic method measures the intensity of halitosis from 0 to 5, where 0 means no malodor, and 5 indicates very severe malodor [58].

We did not analyse secondary outcomes because Kerémi et al. [27] further performed a meta-analysis of our secondary outcomes.

Results of individual studies and the results of the synthesis

Altogether, 234 patients were included in the quantitative analysis. None of the studies reported any side effects experienced by the patients. Our forest plots show a significant improvement in the parameters of the chlorine dioxide group compared to the control (placebo) group in organoleptic scores (Fig 2A and 2B).

One-day OLS data were pooled from three articles [51, 55, 56] after 4, 6, and 12 hours. The results show the effectiveness of chlorine dioxide in the one-day data (mean difference (MD): -0.82; 95% confidence intervals (95% CIs): [-1.04 –-0.6]; heterogeneity: $I^2 = 0\%$, $p = 0.67$) (Fig 2A).

One-week OLS data pooled from three articles [52, 53, 57] and the results are also in favor of the experimental group (MD: -0.24; 95% CI: [-0.41 –-0.07]); $I^2 = 0\%$, $p = 0.52$) (Fig 2B).

Two-week OLS data were collected from three articles [52, 53, 55], and the results also show the effect of chlorine dioxide-containing mouthwashes in halitosis (MD: -0.72; 95% CI: [-1.45–0.02]; $I^2 = 91\%$, $p < 0.01$) (Fig 2C).

Changes in H_2S and CH_3SH one-day data were pooled from three articles [48, 55, 57]. We also found significant differences in H_2S data (standardized mean difference: (SMD): -1.81; 95% CI: [-2.52 –-1.10]; $I^2 = 73.4\%$, $p = 0.02$) (Fig 3A), but we did not find significant differences in the CH_3SH one-day data (SMD: -7.26; 95% CI: [-18.93–4.4]; $I^2 = 98.0\%$, $p < 0.01$) (Fig 3B).

Risk of bias in studies

All the included crossover studies [48, 50, 52–57] had a low risk of bias in Domains 1–4, except for two [48, 50]. We evaluate bias arising from the period, the carryover effects, and deviations

Table 1. Main characteristics of the included studies.

Publication Data			Population	Age			N0 of Patients	Sex (Female/ Male)	N° of Patients/ Groups	Care product	Main content	Outcomes			Time points
First Author / Year of Publication	Country	Study Design		Mean	SD	Range						OLT	VSC	Other	
Shinada et al. 2010	Japan	RCT, double-blind, crossover	healthy	22,9	6,2	19–38	15	0/15	8	ClO_2 Fresh	0.1% ClO_2	yes	GC8A gas chromato-graph	PI, GI, TCI, TDI, Resting saliva, F.n., T.d., T. f., P. g.	Baseline 1-week
									7	Placebo					
Aung et al. 2015	Myanmar	RCT, single-blind, parallel	healthy VSCs more than 250 ppb	19,8	2,9	18–30	30	0/30	15	Fresh	ClO_2	no	Breathtron	DMF, DI, BOP, TC, Ph of saliva, flow	Baseline, 1, 2, 3, 4, 5 week
									15	just tooth brushing					
Pham et al. 2018	Vietnam	RCT, double-blind, crossover	healthy students, OM>2	NA	NA	19–23	39	19/20	17	Thera-Breath®	0.1% ClO_2	yes	Oral-Chroma	PI, GI, TCI, T.f., F.n., P. g., T.d, salivary pH and flow rate	Baseline, 12-hour, 2-week
									22	placebo	sodium chloride 0.9%				
Peruzzo et al. 2007	Brasil	RCT double-blind, crossover	dental students	NA	NA	18–25	14	08/06	7	SaudBucal®	0.1% ClO_2	no	Halimeter	NA	Baseline, 4-day
									7	placebo	NA				
Shetty et al. 2013	India	RCT, double-blind, crossover	healthy men	NA	NA	18–35	18	0/18	9	Thera-Breath®	0.1% stabilised ClO_2	no	Halimeter	PI, GI	Baseline, 7-day
									9	CHX	chlorhexidine 0.2%				
Grootveld et al. 2018	UK	RCT, double blind, crossover	healthy patients	NA	NA	24–55	30	13/17	NA		0.10% $NaClO_2$	no	Oral-Chroma	NA	Baseline, 0,33, 4, 8 and 12-hour
									NA	H2O					
Shinada et al. 2008	Japan	RCT, double-blind, crossover	healthy men	22,9	6,2	19–38	15	0/15	8	ClO2 fresh	0.16% $NaClO_2$	yes	gas chromato-graph	DMF, PI, GI	Baseline, 0,5, 2, 4-hour
									7	Placebo					
Bestari et al. 2017	Indonesia	RCT, single-blind	NA	NA	NA	NA	40	NA	20	Oxyfresh® "Oxygene® "	ClO_2	yes	Oral-Chroma	NA	Baseline, 0,5, 2, 4, 6-hour
									20	Placebo	dest. water				
Lee et al. 2021	USA	RCT, double-blind, crossover	healthy patients, 4.5>OM>2.6	39,4	13,3	21–65	48	34/14	24	CloSYS	0.1% stabilized ClO_2	yes	no	NA	Baseline, 1,2,3-week
									24	Placebo					
Lee et al. 2018	USA	RCT, double-blind, crossover	healthy patients, 4.5>OM>2.6	45,4	13,5–14,4	21–65	48	30/18	23	CloSYS	0.1% ClO_2	yes	no	NA	Baseline, 0,5, 2, 4-hour
									25	Placebo					

RCT: randomised clinical trials; OLS: organoleptic test scores; SD: standard deviation; ClO_2: chlorine dioxide; $NaClO_2$: sodium chlorite; NA: not available, PI: Plaque index; GI: Gingival index, TCI: Tongue coating index; TDI: Tongue discolouration index, DMF: number of decayed, filled, and missing teeth T.f.: Tannerella forsythia, F.n.: Fusobacterium nucleatum; P.g.: Prphyromonas gingivalis, T.d.: Treponema denticola; S.m.: Streptococcus mutans

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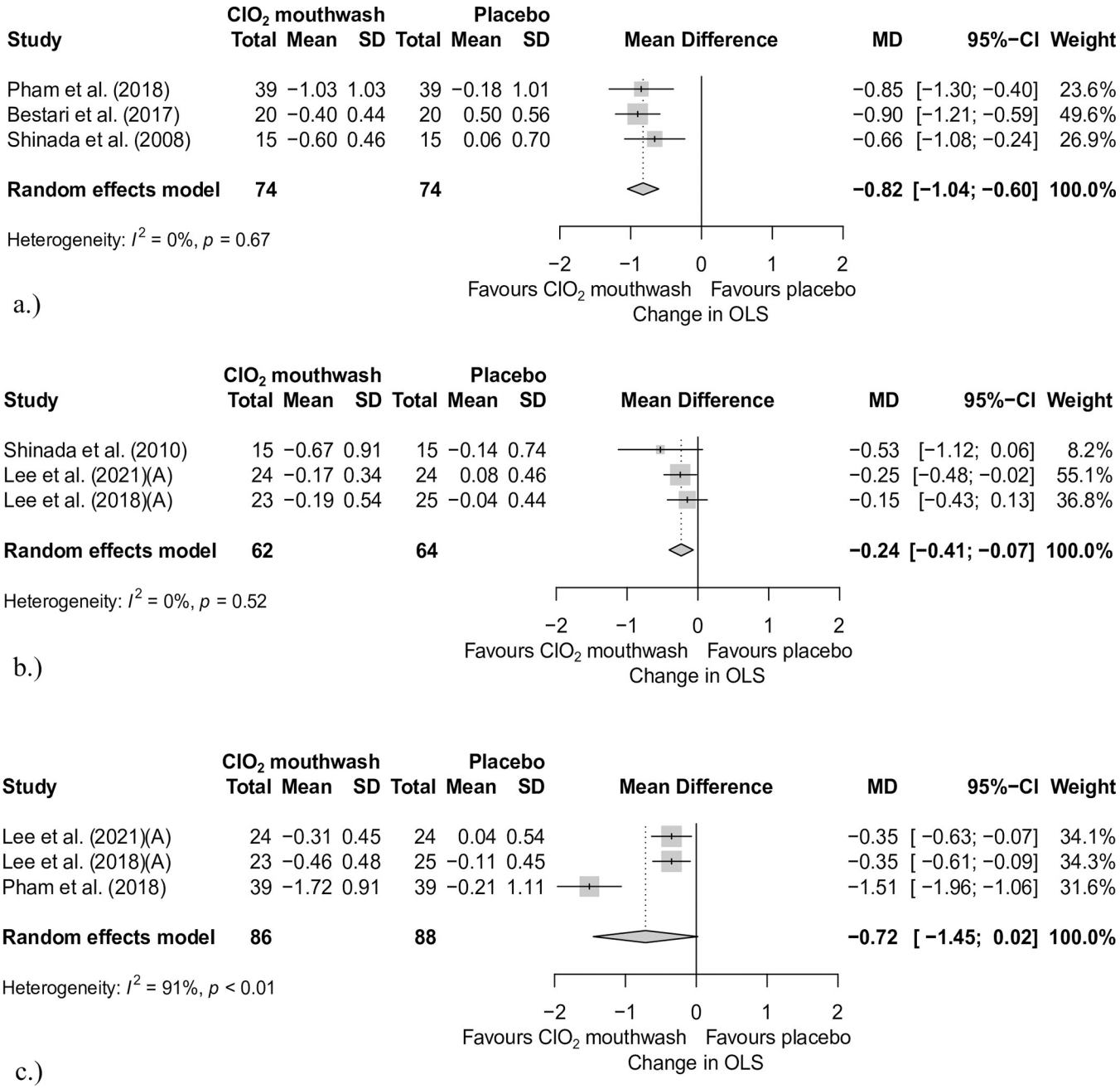

Fig 2. Forest plot analysis of the changes of organoleptic measurement. a. between baseline and within one day with and without ClO_2 mouthwash. b. between baseline and within one week with and without ClO_2 mouthwash. c. between baseline and within two weeks with and without ClO_2 mouthwash. MD: Mean difference; CI: Confidence interval; SD: Standard deviation; ClO_2: chlorine dioxide; OLS: organoleptic test scores.

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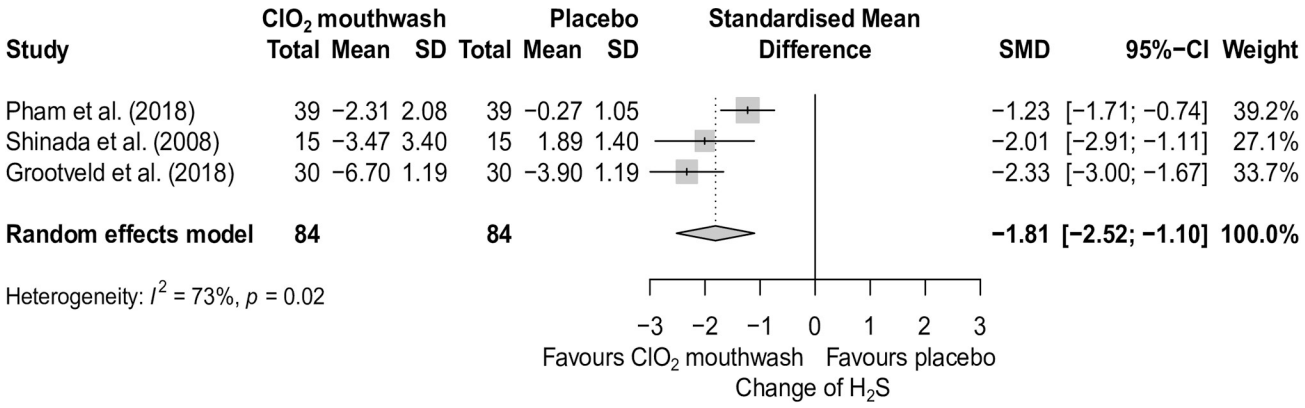
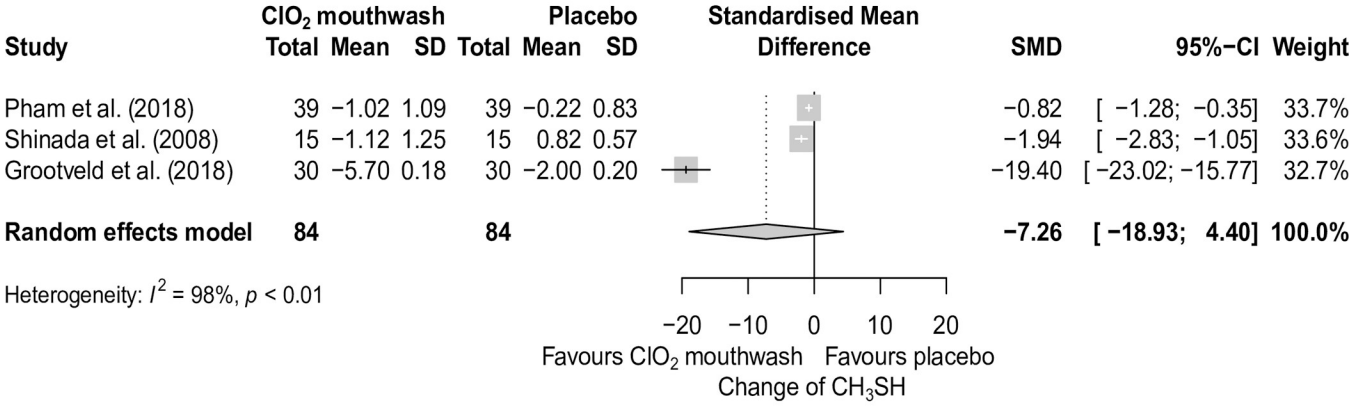
from the intended interventions, such as some concerns because we do not have any information about it in the article by Grootveld et al. [48]. Shetty et al. [50] did not give detailed information about randomisation, so we evaluated some concerns in the first domain. We considered two articles as cluster-randomized trials [14, 51]. Bestari et al. [51] received some concerns about the risk of bias because of missing information in the related question due to deviations from intended interventions and bias in selecting the reported result. In Domain 5,



a.)



b.)

Fig 3. a. Forest plot analysis of the changes of hydrogen sulfide concentration between baseline and within one day with and without ClO_2 mouthwash. b. Forest plot analysis of the changes of methyl mercaptan within concentration between baseline and one day with and without ClO_2 mouthwash. SMD: Standardized mean difference; CI: Confidence interval; SD: Standard deviation; ClO_2: chlorine dioxide.

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the bias of selection of the reported results, we evaluated all the studies as of some concern because even if they published the trial protocols, these did not contain the pre-specified analysis plan. All included studies represented good quality, but we had to evaluate the overall risk as of some concern because of Domain 5 (S1 and S2 Figs).

Publication bias and heterogeneity

The heterogeneity might not be important in the one-day and one-week data; however, the two-week OLS data may represent considerable heterogeneity. There was substantial statistical heterogeneity in H_2S data and considerable statistical heterogeneity in CH_3SH data.

Certainty of evidence

The certainty assessment of the investigated outcomes displays very low to moderate certainty of evidence (S1 Table). We had to downgrade our results, primarily because of statistical heterogeneity, the risk of bias assessment, and imprecision. The statistical estimation caused a higher confidence interval, which increased imprecision.

Discussion

The study aimed to investigate the efficacy of mouthwashes containing chlorine dioxide. On the basis of our results, mouthwashes containing chlorine dioxide effectively reduce the level of halitosis against placebos in OLS and VSCs measurements in the short term in one-day and one-week data. In one-day and two-week data, chlorine dioxide decreased the halitosis level by almost one in a five-degree scale, which means that bad breath decreased. Significant results in hydrogen sulfide data support it because it is the main component of oral malodor. Articles that could not include quantitative synthesis had a similar conclusion [14, 32, 54]. The one eligible article with a mouthwash comparator containing chlorhexidine showed chlorine dioxide to be almost as efficient as chlorhexidine [50], but it was unfeasible to carry out a meta-analysis. A few patients reported an unpleasant mouthwash taste [50], but researchers concluded that this problem was treatable with a masking agent [50]. Moreover, patients did not experience side effects in the short term (2 weeks) and when using lower concentrations (0.1% chlorine dioxide). Similar results were found about the adverse effect of chlorine dioxide in another systematic review [59]. However, the experimental mouthwash's overuse (with 24–48 h incubation time) can be cytotoxic or apoptotic on human cells [60].

Heterogeneity in the studies included could originate from various factors. The study designs and protocols were slightly different, and we included studies with various follow-up periods. Furthermore, in the case of moderate or substantial heterogeneity, we supposed other confounding factors besides the low number of studies. We hypothesised that the reason for a moderate statistical heterogeneity was the difference in rinsing protocols. Pham et al. [55] instructed their patients to rinse with 15 mL of mouthwash for 30 sec, then spit and continue to gargle with 15 mL of mouthwash for 15 sec, whereas Lee et al. [52, 53] instructed patients to gargle with 15 mL for 30 sec only. The reason for the extremely high statistical heterogeneity of CH_3SH data may be the longer compulsory mouth closing before measurement, which Grootveld et al. [48] applied for 5 minutes, while in the other studies it was applied for 3 minutes only. Further explanations may be that methyl mercaptan concentration depends mainly on *Porphyromonas gingivalis* [61], and that racial differences can cause differences in bacterial composition [62]; two articles [55, 56] are from Asia, and one is from the UK [48]. Furthermore, elevated CH_3SH concentration in periodontal disease [63, 64] is well-known, but Grootveld et al. [48] exclude periodontopathic patients. However, due to the low number of included studies, our assumptions to explain the heterogeneity of measurement readings should be handled with care.

Our investigations proved that out of VSCs, chlorine dioxide reduces mainly hydrogen sulfide. Furthermore, H_2S may predict further progress and severe conditions [65], like periodontitis, and oxidative stress [65, 66]. Takeshita et al. [67] suggest that higher CH_3SH or H_2S levels originate from different bacteria, and it is unnecessary to separate VSCs in order to check the overall effect. We believe that targeted therapy facilitates patient well-being. Additionally, Ademovski et al. [32] mentioned that chlorine dioxide primarily reduces dimethyl sulfide. We did not have a synthesised result from dimethyl sulfide data. However, we are certain that dimethyl sulfide is not the main component of VSCs.

As we know, we do not have an evidence-based treatment protocol for malodor. We agree with the systematic review by Nagraj et al. [35], who found low-certainty evidence to support the effectiveness of interventions for managing halitosis compared to a placebo or control for the OLT [35, 68]. On the basis of our results, mouthwash containing chlorine dioxide may be effective in halitosis and is free of known side effects. The efficacy is visible both on OLT and VSC data when compared to another meta-analysis conducted on probiotics, which reduced only OLT results [69]. The side effects of chlorhexidine and alcohol-

containing mouthwashes are well-known [20, 70]. Moreover, another meta-analysis [71], which investigated the carcinogenic effect of alcohol-containing mouthwashes, did not find sufficient evidence. However, it concluded that patients should minimise their long-term use. The selective toxicity of chlorine dioxide, based on its mechanism of action [22], is the most significant point supporting its clinical benefits over other disinfectants [72]. The cost of this therapy is similar to or a bit higher than therapy with other mouthwashes, although it depends mainly on the brand of the selected mouthwash. We think our results are promising, and our findings suggest that chlorine dioxide is a valid alternative. For the above reasons, we suggest using mouthwashes containing chlorine dioxide rather than chlorhexidine against intraoral halitosis.

Strengths and limitations

Our meta-analysis's strengths are the pre-registered, well-documented methodology and the fact that all the included studies are RCTs. Another strength is that we had organoleptic measurement data in more time points, which can follow the mid-term effects. We also think that separated VSC results help to understand chlorine dioxide's efficacy better.

The main limitation of our paper is the relatively small number of included studies. Other significant limitation, there are not enough comparable results with other mouthwashes containing active ingredients. Four studies could not be retrieved. We could not perform a meta-analysis from the total VSC data, and long-term effect follow-ups are missing. Furthermore, physiological and pathological halitosis could not be adequately differentiated when conducting the meta-analysis. Due to the low number of studies, the results of the analyses must be handled with caution, as the inclusion of further studies could easily change the results acquired.

Implications for research

We believe our findings will facilitate further investigations of other mouthwashes in halitosis therapy. We suggest that further studies should present their data also in total VSCs with SD so as to be make them comparable because if we summarise the H_2S, CH_3SH, and $(CH_3)_2S$ data, we lose the SD. Furthermore, it is necessary to define the minimally important difference data (MID) to conclude whether the statistical evidence is in line with the clinical evidence as well.

Implications for practice

Patients with oral halitosis are easily treatable with side-effect-free chlorine dioxide mouthwashes. Based on our investigation, chlorine dioxide-containing mouthwashes may be preferable to other mouthwashes, and consequently, they can be the first choice of dentists and patients. We also think chlorine dioxide could play a prominent role in targeted therapy for H_2S.

Conclusion

The findings suggest that chlorine dioxide mouthwashes should receive a more prominent role in the supportive therapy of oral halitosis. Our results show that it is effective against halitosis in the short term compared to the placebo. Especially patients with an elevated H_2S level can benefit from a targeted treatment because chlorine dioxide demonstrates greater efficacy in that compound.

Supporting information

S1 Fig. Risk of bias-2 assessment of the included crossover studies. The domains and the overall risk of bias were marked using the following traffic light system: red signified high risk, yellow indicated some concerns, and green represented a low risk of bias.
(PDF)

S2 Fig. Risk of bias-2 assessment of the included parallel study. The domains and the overall risk of bias were marked using the following traffic light system: red signified high risk, yellow indicated some concerns, and green represented a low risk of bias.
(PDF)

S1 Table. PRISMA checklist. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. DOI: 10.1136/bmj.n71s. For more information, visit: http://www.prisma-statement.org/.
(DOCX)

S2 Table. Summary of evidence table. CI: confidence interval; **MD:** mean difference; **SMD:** standardised mean difference. Explanations. a. Statistical heterogeneity I^2 = 73%. b. Statistical heterogeneity I^2 = 91%. c. Statistical heterogeneity I^2 = 96%. d. Funnel plot analysis was performed.
(DOCX)

S3 Table. Data included in the meta-analysis. Note: CI: Confidence interval; SD: Standard deviation.
(PDF)

Author Contributions

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Validation: Bence Szabó.

Visualization: Bence Szabó.

Writing – original draft: Eszter Szalai.

Writing – review & editing: Péter Tajti, Bence Szabó, Péter Hegyi, László Márk Czumbel, Saghar Shojazadeh, Gábor Varga, Orsolya Németh, Beata Keremi.

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