SEMMELWEIS EGYETEM

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Ph.D. értekezések

3025.

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Fogorvostudományi kutatások
című program

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NEW INSIGHTS IN INTRA-ORAL HALITOSIS MANAGEMENT

PhD thesis

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Budapest

2024

„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,missing and filled 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	millilitre
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 achieve this 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:	7
Cumulative IF:	27.707
Av IF/publication:	3.958
Ranking (Sci Mago):	D1:1, Q1: 5, Q4: 1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	7.3
Av IF/publication:	3.68
Ranking (Sci Mago):	Q1: 2
Number of citations on Google Scholar:	15
Number of citations on MTMT (independent):	13
H-index:	3

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 was received, we started enrolling the patients in January of 2024. Therefore, we established a halitosis working group, and with continuous improvement, we would like to help these patients, to improve their 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. This specialization 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 organoleptic measurement (OM), gold standard measurement, and the most used device-supported methods (sulfide monitors, gas chromatographs and portable gas chromatographs), called halitometers.

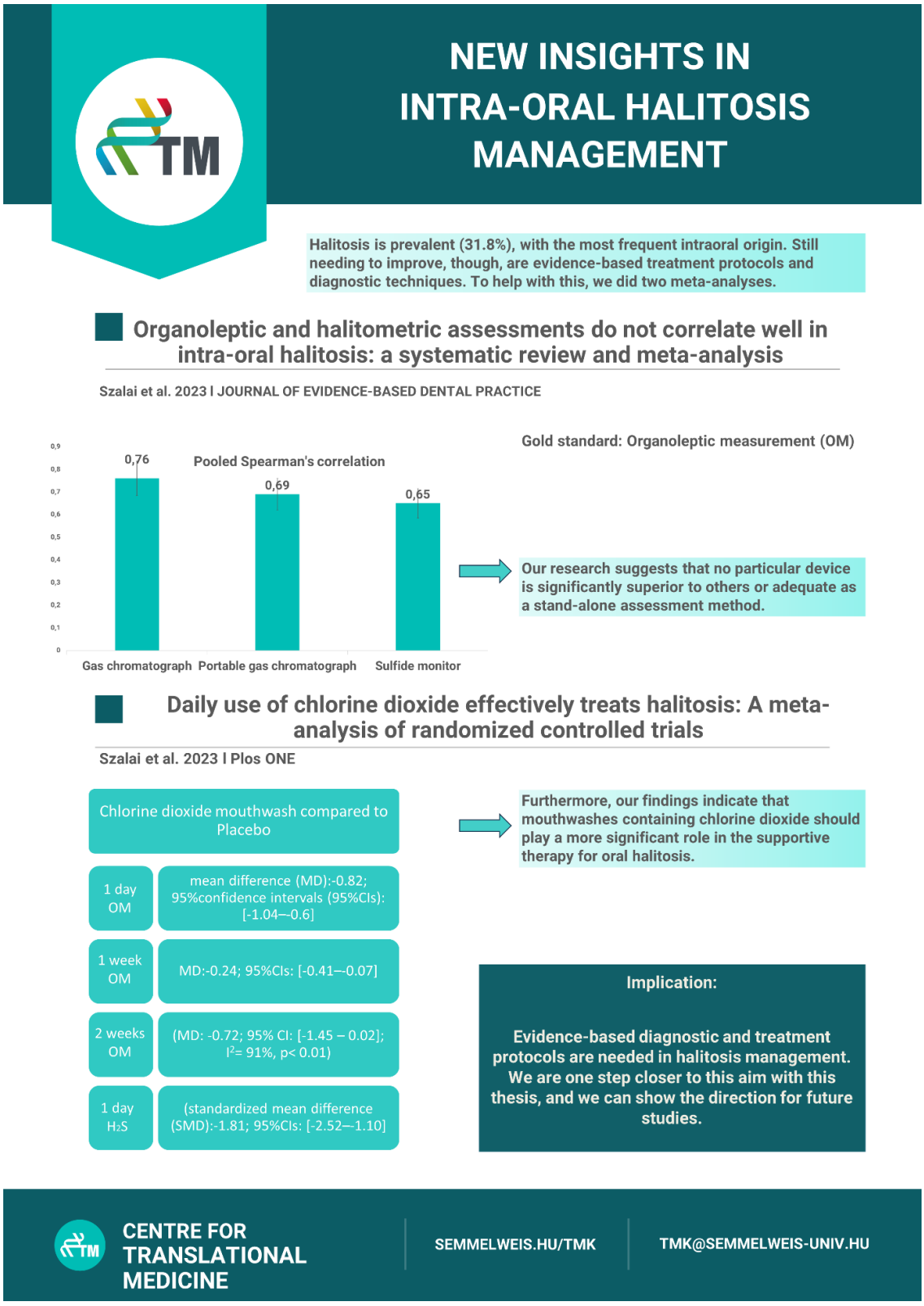
In the second meta-analysis, we investigated the efficacy of mouthwash products containing ClO_2 in halitosis. Primary outcomes were the changes in OM and volatile sulfur compounds.

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, or current devices need methodological improvement (e.g., OralChroma, Halimeter) 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 to fill these gaps.

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. Ancient Egyptians were also concerned about the problem and made 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.

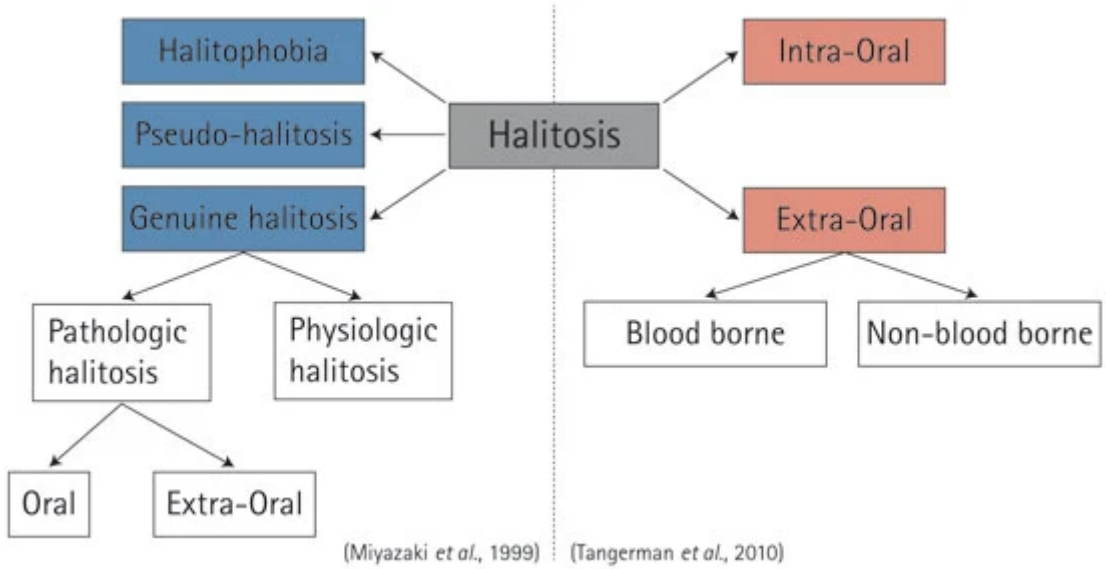


Figure 1. Previous classifications (1999, 2010) Original Figure from Aydin et al. (7)

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. The physiological component of each of the five types of halitosis, which are present to some degree in all healthy people, add up to type 0 halitosis (7).

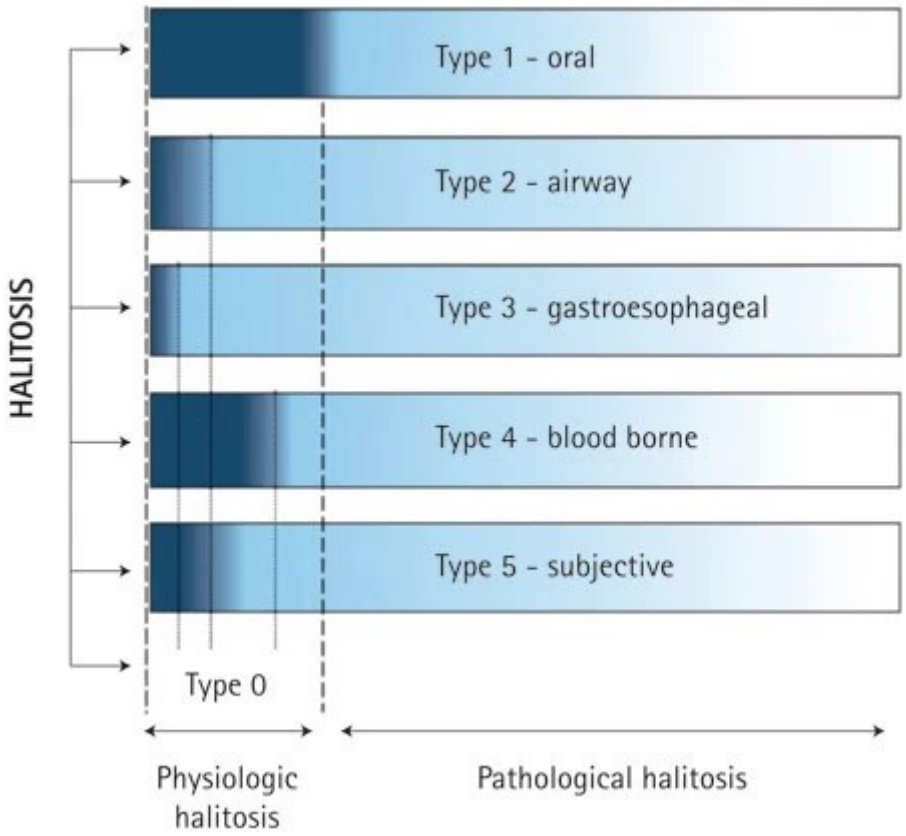


Figure 2. Halitosis classification (2014) by Aydin et al. (7)

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.).

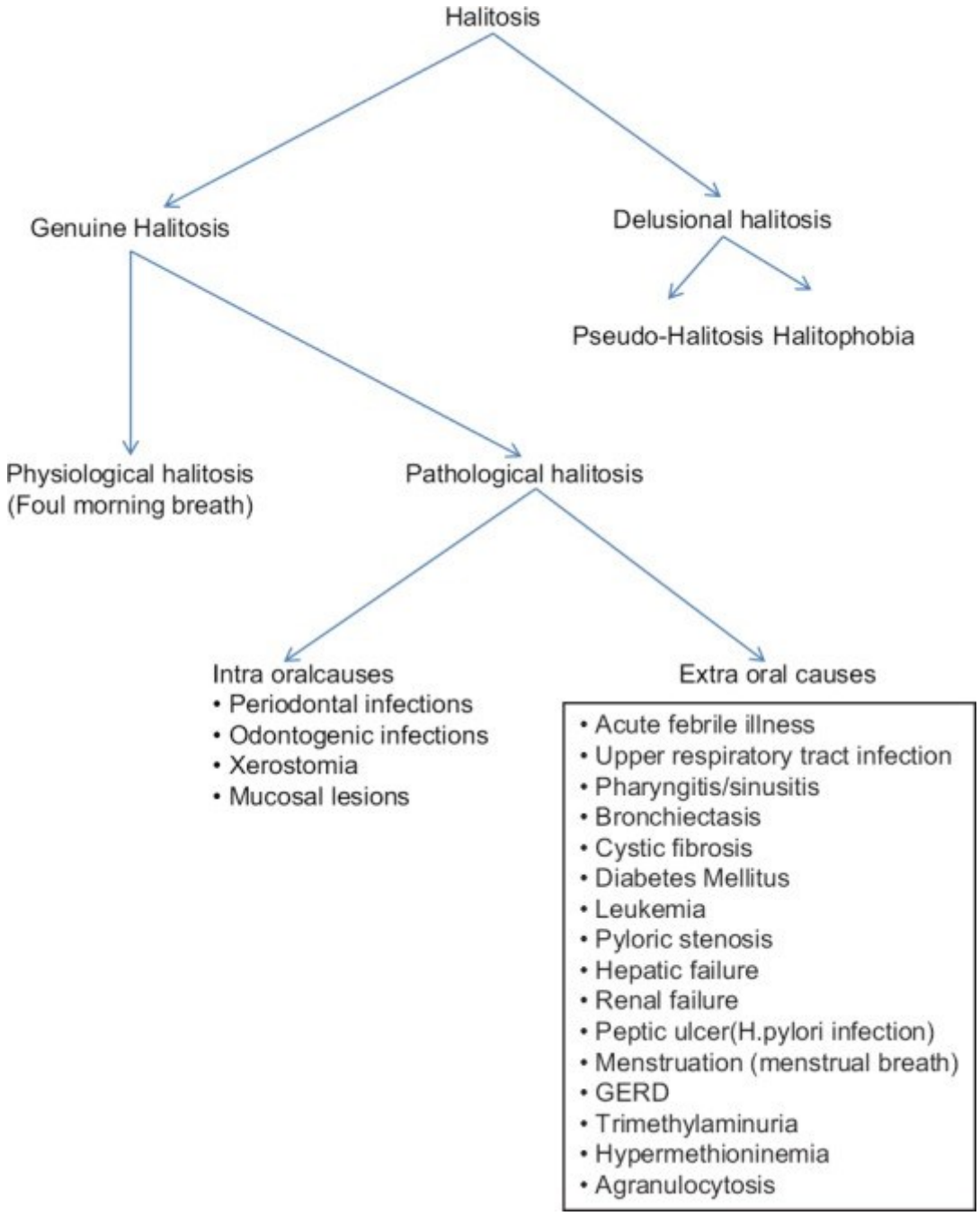


Figure 3. Latest halitosis classification (2016) by Kapoor et al. (12)

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 halitosis. Alternatively, in cases of blood-borne halitosis, diseases that affect any part of the body can release an unpleasant odor through the lungs, e.g., cirrhosis of the liver.
Pseudo-halitosis	Patients may complain of persistent malodor despite a lack of objective evidence. This condition can often be improved with counseling and basic procedures for dental hygiene.
Halitophobia	The patient continues to believe that they have halitosis even following therapy for bad breath and pseudohalitosis. There is no social or material evidence to support 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 the classification is 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 approach has many drawbacks and is not only subjective (17) but nevertheless embarassing for the tester 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. 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). The dorsum of the tongue and the deep pockets are the main areas where these bacteria are found. (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). Other unpleasant-smelling molecules, such as cadaverine and putrescine, are also present (29). Although VSCs best describe bad breath, it is primarily measured for VSCs (30, 31).

Diagnostic methods can be direct (OLT, gas chromatography, VSC measuring devices) or less commonly used indirect (saliva incubation test, ninhydrin method, etc.). 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). Gas chromatography is also used in research, but it is very complicated to use on a daily basis (14).

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), essential oils (42) or probiotics (43). Lifestyle changes can also help, such as avoiding smoking and alcohol and reducing onions, garlic, and spices in the diet. Patients should be encouraged to increase their fluid intake (44).

People buy anti-odor mouthwash for millions of dollars each year, and many different kinds of mouthwash are available on the market (45). Chlorhexidine-containing mouthwashes are considered the gold standard (46) 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 (46, 47). 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 (48). Unlike other oxidants, it interacts slightly with most elements in living beings (48). 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 (48). Furthermore, it oxidizes the precursors of VSCs, which increases its efficacy (14, 49). These antimicrobial mouthwashes are mainly effective against IOH.

The aqueous ClO_2 solution (50) is widely used in medicine for the disinfection of intra-oral areas (51-54) without side effects in small concentrations (55). A systematic review also could not find side effects in small concentrations (56,). However, the ClO_2 consumption in South America has discredited all products containing ClO_2 (57).

ClO_2 mouthwashes have already been the subject of several investigations into halitosis (54, 58-61); 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 intra-oral halitosis

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 ClO_2 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 (62) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA 2020) (63) 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 (64).

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 (65).

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 (66). **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 (67). 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 (68). Variance measure I^2 and Tau-squared (τ^2) statistics were applied to estimate the degree of heterogeneity among the studies (69, 70). 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 applied 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 (71, 72).

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 (73) because the thresholds varied among experiments. For the sake of clarification, we would like to point out that Harbord et al. (74) demonstrated that the method adopted is mathematically similar to the bivariate model (75, 76).

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 (77) was then used to determine the pooled sensitivity and specificity separately. Because so few papers were available, it was impossible to apply 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 using R [v4.1.2] (78) (79).

7.1.4. Bias assessment and quality of evidence

Two investigators worked independently with the quality assessment tool for diagnostic accuracy studies (QUADAS-2) (80) and QUADAS-C (81). 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 (82) method to calculate the test statistic as per Sterne et al. (83), 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 (84) tool to perform the evidence profile according to the GRADE Handbook (85).

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, comparators, 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 (62). 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 (62).

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 (78) 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 (86), 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 (85); we performed the summary of findings table with the GRADEpro (84) 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 (87). Finally, the qualitative analysis contained 76 studies (4, 35, 36, 88-160). However, ten studies (92, 108, 116, 117, 124, 140, 142, 144, 152, 159) 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.

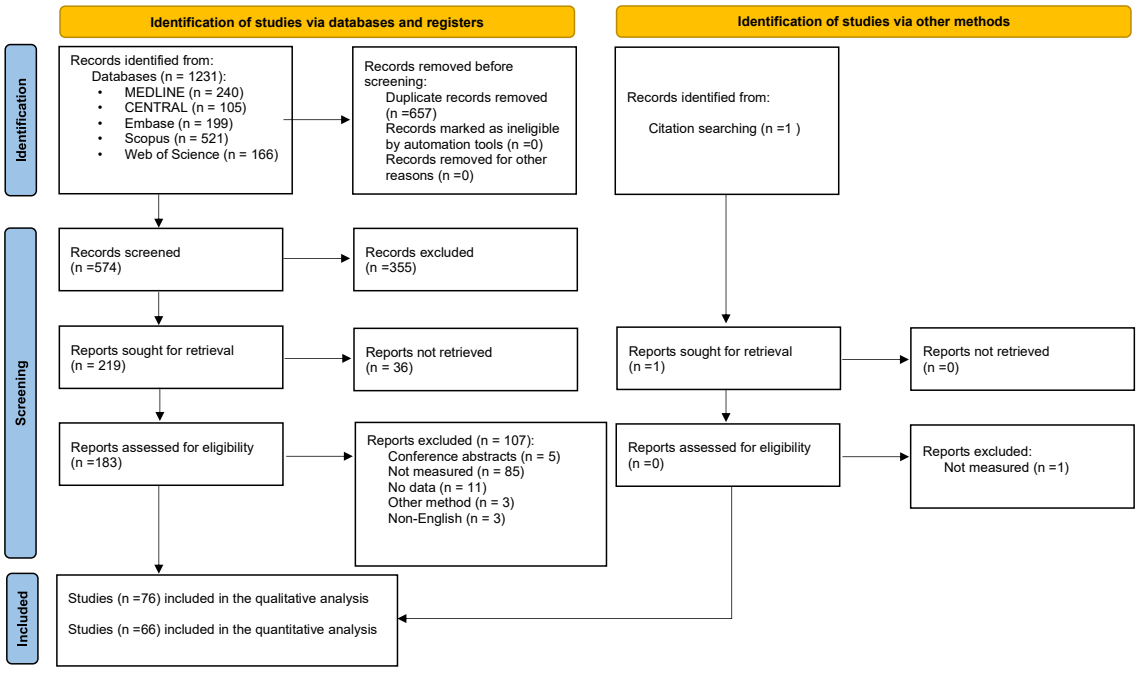


Figure 4. Prisma 2020 Flow Diagram of the screening and selection process (161)

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 applied 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 (144, 152, 156), 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 (161)

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Acar B (88)	2019	RCT	Turkey	36	0-5	Halimeter	C
Aimetti M (89)	2015	cross-sectional	Italy	744/ 250	0-5	OralChroma	C
Aliyev B (90)	2021	cross-sectional	Turkey	75	0-5	Halimeter	C
Alqumber MA (91)	2014	blind, crossover	Saudi Arabia	20	0-5	Halimeter	C
Amano A (92)	2002	cross-sectional	Japan	61	0-3	GC-14B	C
Amou T (93)	2014	cross-sectional	Japan	94	0-5	GC	C
Apatzidou A (94)	2013	cross-sectional	Greece	78	0-5	Halimeter, RH-17	C
Awano S (95)	2004	cross-sectional	Japan	127	0-5	G2800 GC	C, Se, Sp, NPV, PPV
Ayo-Yusuf O (96)	2011	cross-sectional	South Africa	889	0-5	Halimeter	C
Baharvand M (97)	2008	cross-sectional	Iran	77	0-3	Halimeter	C, Se, Sp, NPV, PPV
Bodrumlu E (98)	2011	cross-sectional	Turkey	107	0-5	Halimeter	C
Bolepalli AC (99)	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 (100)	1994	cross-sectional	Canada	127	0-5	Halimeter, Interscan 1170 portable sulfide monitor	C
Brunner F (101)	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 (102)	2012	cross-sectional	Belgium	100	0-5	OralChroma	C
Donaldson AC (103)	2007	cross-sectional	UK	37	0-3	Halimeter	C
Doran AL (104)	2007	cross-sectional	UK	24	0-5	Halimeter	C
Du M (105)	2019	cross-sectional	China	205	0-5	Halimeter	C
Falcão DP (106)	2017	cross-sectional	Brasil	34	0-5	Halimeter, Breth Alert	C, Se, Sp, NPV, PPV
Faveri M (107)	2006	RCT, blinded	Brazil	19	0-3	Halimeter	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Figueiredo LC (108)	2002	cross-sectional	Brazil	21	0-4	Halimeter	C
Greenstein RB (109)	1997	RCT	Israel	123	0-5	Halimeter	C
Guentsch A (110)	2014	controlled clinical trial	Germany	30	0-5	Halimeter	C
Hunter CM (111)	2005	RCT, double-blind, parallel	US	13	0-5	GC Agilent 6890	C
Iatropoulos A (112)	2016	cross-sectional	Greece	18	0-5	OralChroma	C
Iwamura Y (113)	2016	randomized, double-blind pilot study	Japan	29	0-5	OralChroma	C
Iwanicka-Grzegorek K (114)	2005	cross-sectional	Poland	88	0-5	Halimeter	C
Jerv-Storm PM (115)	2019	RCT, cross-over	Germany	17	0-5	OralChroma, CHM-1	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Kameyama A (116)	2015	cross-sectional	Japan	359	0-5	OralChroma	C
Kim DJ (117)	2009	cross-sectional	Korea	52	0-4	Halimeter, gas chromatography, HP 5890	C
Laleman I (118)	2018	retrospective	Belgium	476	0-5	Halimeter, OralChroma	C, Se, Sp, NPV, PPV
Laleman I (119)	2020	retrospective	Belgium	570	0-5	Halimeter, OralChroma CHM-1, OralChroma CHM-2	C, Se, Sp, NPV, PPV
Lee ES (120)	2016	cross-sectional	Korea	99	0-5	OralChroma	C
Lee ES (121)	2016	cross-sectional	Korea	103	0-5	OralChroma	C
Liu XN (122)	2006	cross-sectional	China	2000	0-5	Halimeter	C
Lu HX (123)	2014	cross-sectional	China	911	0-5	Halimeter	C
Marchetti E (124)	2015	RCT	Italy	20	0-5	Bionote, OralChroma	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Matarazzo F (125)	2013	cross-sectional	Brazil	13	0-3	Halimeter	C
Morita M (126)	2001	cross-sectional	US	20	0-5	Halimeter,Tongue sulfide probe	C
Morita M (127)	2001	cross-sectional	US	81	0-5	Halimeter	C
Musić L (128)	2021	pilot study	Croatia	10	0-5	Halimeter	C
Nonaka A (129)	2005	cross-sectional	Japan	66	0-5	FF-1 odor discrimination analyzer, GC	C
Quirynen Q (130)	2009	retrospective	Belgium	2000	0-5	Halimeter	C
Roldán S (131)	2005	prospective case series	Spain	19	0-5	Halimeter	C
Roldán S (132)	2004	RCT- double-blind, cross-over	Spain	10	0-5	Halimeter	C
Roldán S (133)	2003	RCT	Spain, Netherlands	40	0-5	Halimeter	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Romano F (134)	2020	retrospective non-interventional clinical study	Italy	504	0-5	OralChroma	C
Rosenberg M (135)	1992	RCT	Israel	60	0-5	Interscan 1170, portable sulfide monitor	C
Rosenberg M (136)	1991	cross-sectional	Canada	41	0-5	Interscan 1170, portable sulfide monitor	C
Rosenberg M (162)	1991	cross-sectional	Canada	75	0-5	Interscan 1170, portable sulfide monitor	C
Ross B (138)	2009	cross-sectional	Canada	18	0-5	Halimeter	C
Saad S (139)	2011	RCT	UK	14	0-5	Halimeter, OralChroma	C
Schmidt NF (140)	1978	cross-sectional	US	66	0-3	gas-liquid chromatography	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Seemann R (141)	2016	RCT	Germany	34	0-5	Halimeter, OralChroma	C
Shimura M (142)	1997	cross-sectional	Japan	94	0-4	VSC monitor (New Cosmos Electric)	C
Song Y (143)	2021	cross-sectional	Korea	111 / 330	0-5	portable GC (TwinBreasor)	C
Sopapornamorn P (144)	2006	cross-sectional	Japan	260	0-5	Breathtron sulfide monitor, GC- 8A	C, Se, Sp, NPV, PPV
Southward K (145)	2013	case-study	Canada	649	0-5	Halimeter, OralChroma	C
Stamou E (146)	2005	cross-sectional	Israel	71	0-5	Halimeter	C
Sterer N (147)	2002	cross-sectional	Israel	64	0-5	VSC monitor, interscan modell 1170	C
Sterer N (148)	2008	cross-sectional	Israel	42	0-5	Halimeter	C, Se, Sp, NPV, PPV
Suzuki N (149)	2011	cross-sectional	Japan	368	0-5	GC 14B	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Takeuchi H (150)	2010	cross-sectional	Japan	823	0-5	GC 14B	C
Talebian A (151)	2008	cross-sectional	Iran	222	0-5	OralChroma	C
Tamaki N (153)	2011	cross-sectional	Japan	30	0-5	B/B Checker, GC 14B	C, Se, Sp, NPV, PPV
Tanda N (152)	2007	cross-sectional	Japan	46	0-4	Breathtron sulfide monitor, GC- 7A	C, Se, Sp
Tangerman A (154)	2007	cross-sectional	Nether-lands	75	0-5	Halimeter, GC	C
Tsai CC (155)	2008	cross-sectional	Taiwan	72	0-5	OralChroma	C
Ueno M (156)	2008	cross-sectional	Japan	475	0-5	Breathtron sulfide monitor, GC- 8A	C, Se, Sp, NPV, PPV
Van den Velde S (157)	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 (158)	2010	RCT	Germany	42	0-5	Oralchroma	C
Willis CL (159)	1999	cross-sectional	UK	30	1-10	Halimeter	C

First Author	Year	Design	Country	Population	Reference	Index test	Outcomes
Yasukawa T (160)	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). The correlation analysis can be used to identify the device that is most similar to the sensory evaluation.

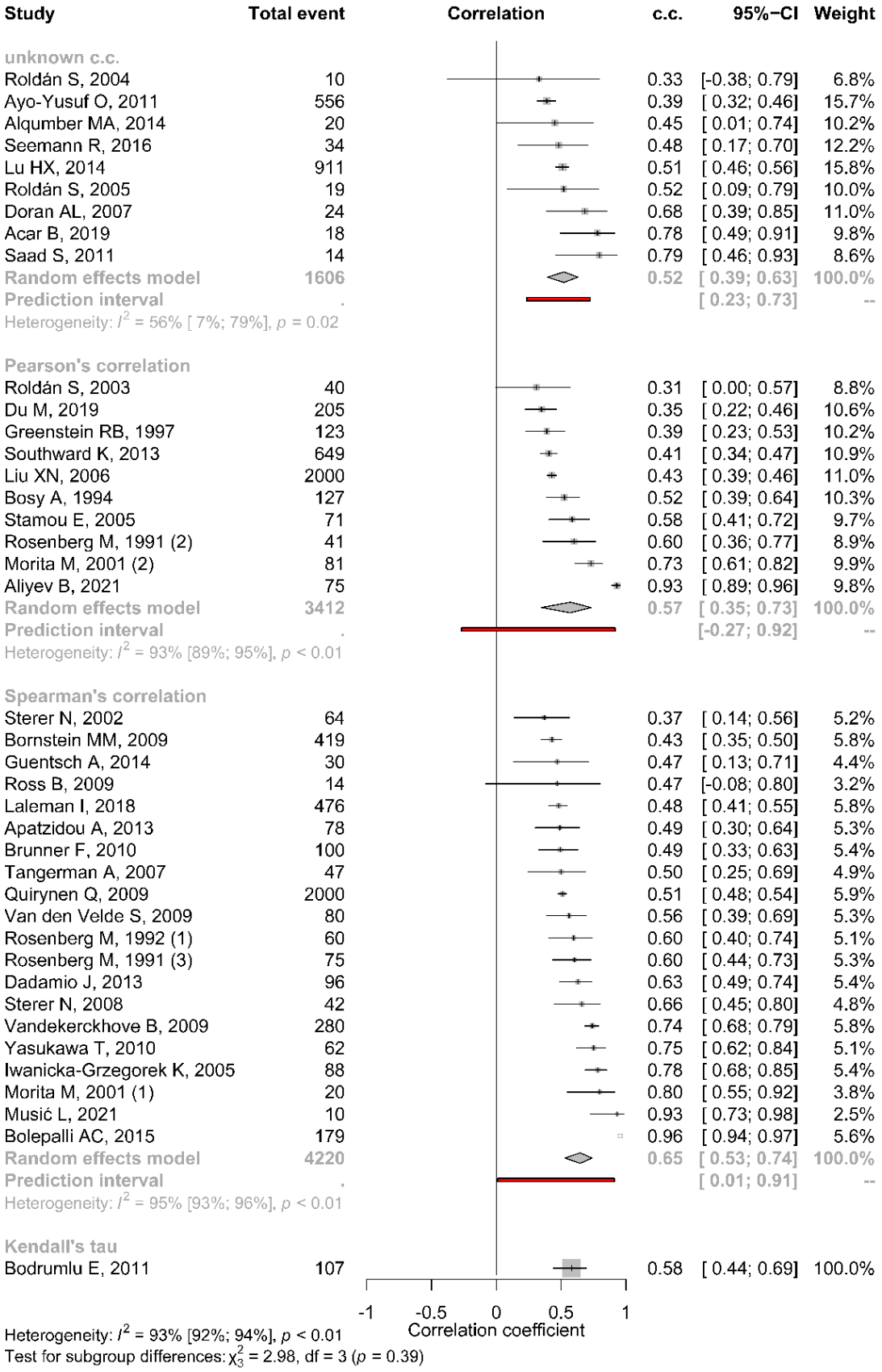


Figure 5. Forest plot of the pooled correlations between the sulfide monitor devices and OLS (161)

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).

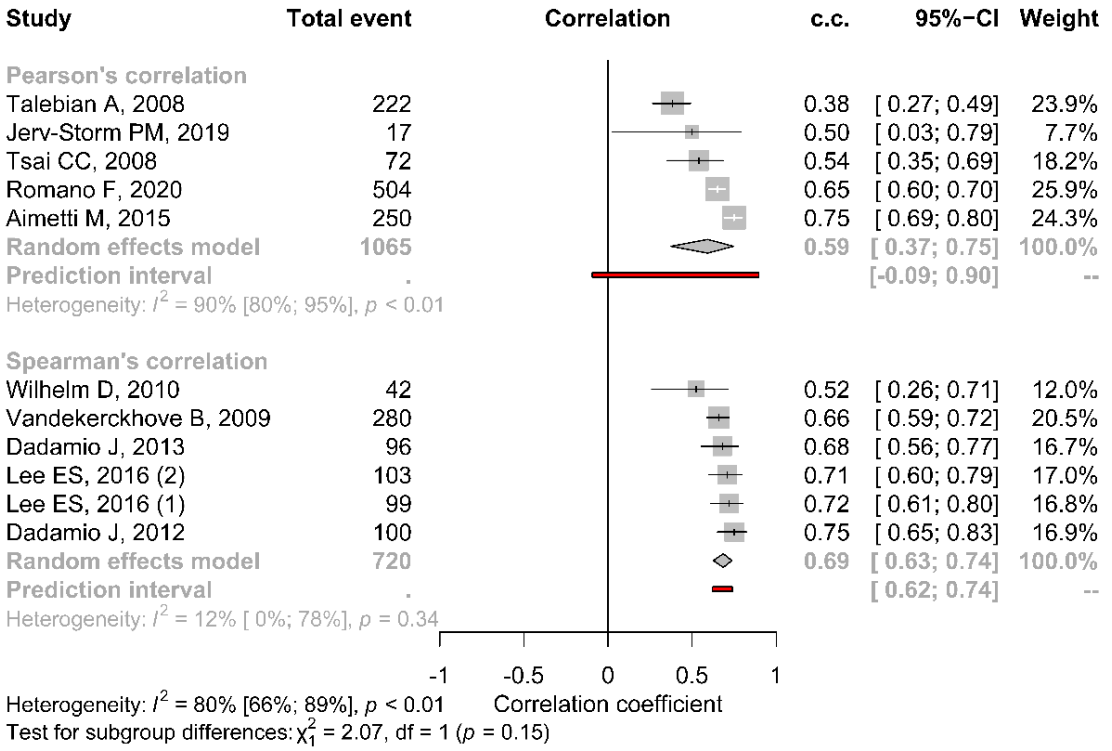


Figure 6. Forest plot of the pooled correlations between the portable gas chromatographs and OLS (161)

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) (161).

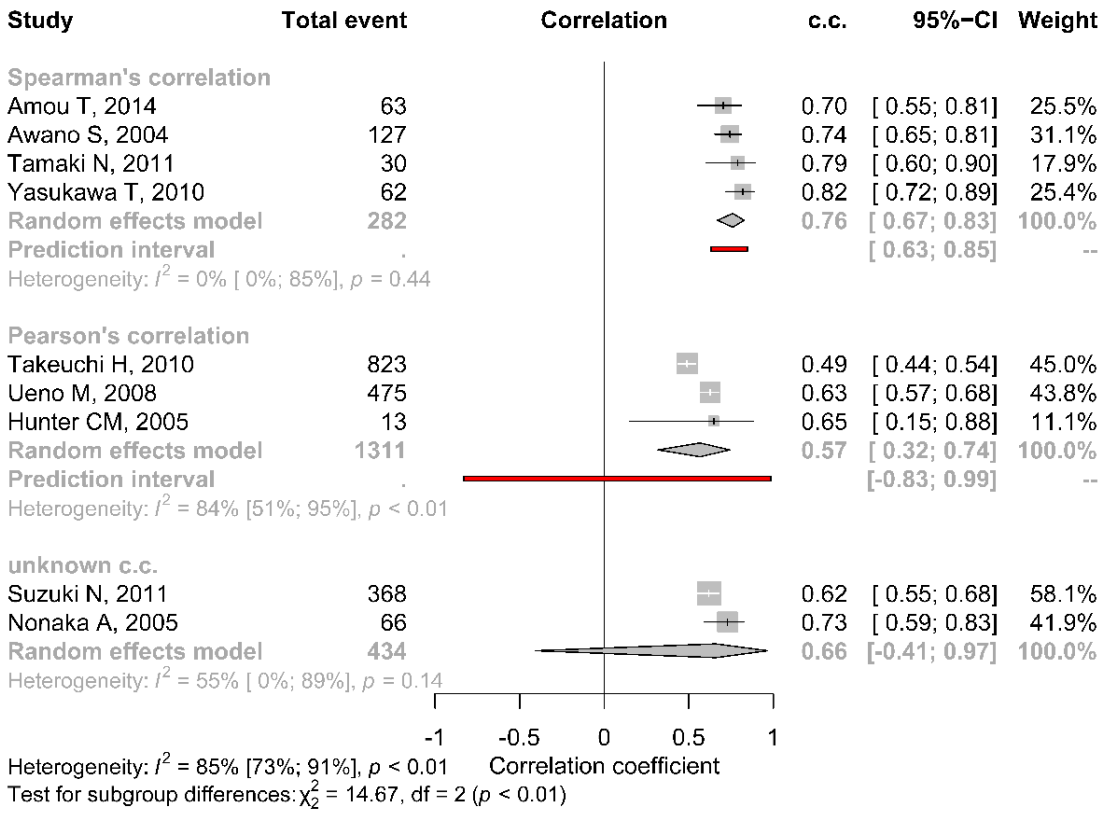


Figure 7. Forest plot of the pooled correlations between the gas chromatographs and OLS (161)

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) (161).

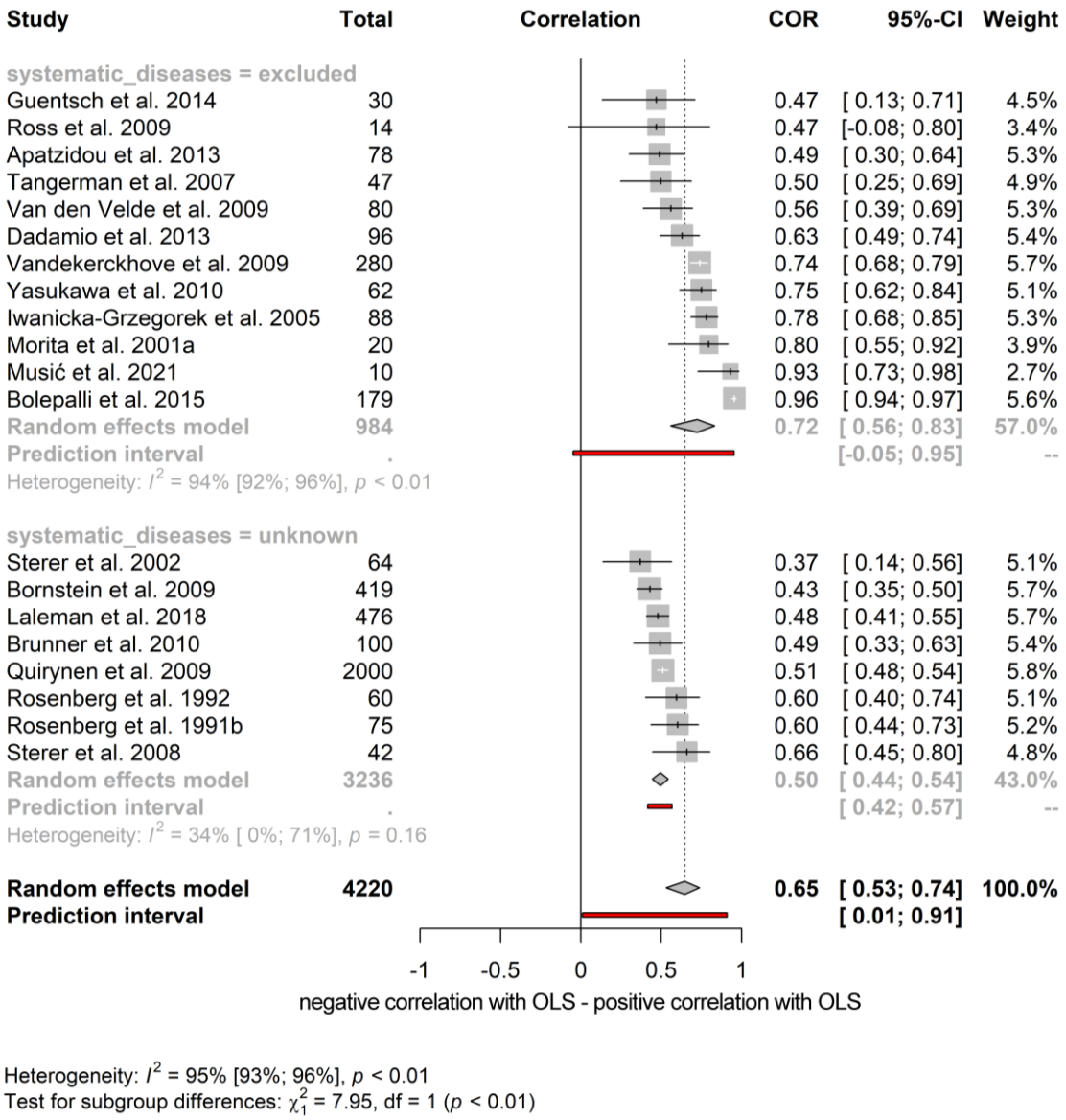


Figure 8. Forest plot of the pooled correlations regarding the inclusion of extraoral halitosis between the sulfide monitors and OLS (161)

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).

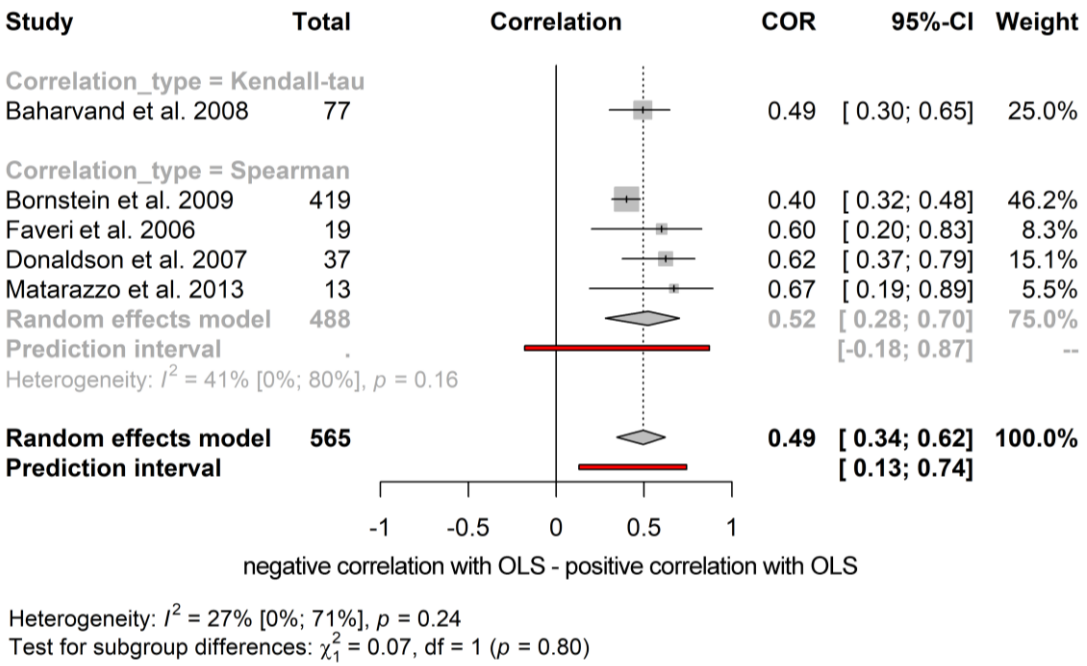


Figure 9. Forest plot of the pooled correlations for the methyl mercaptan between portable gas chromatographs and OLS (161)

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 $(CH_3)_2S$ (161).

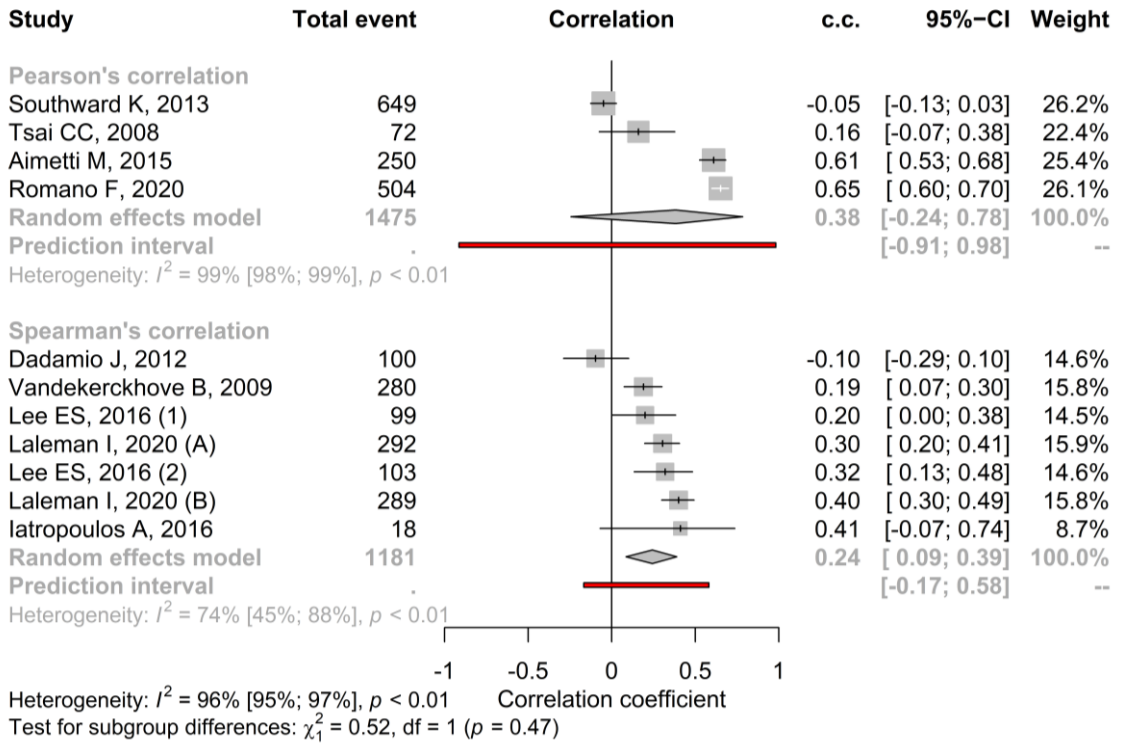


Figure 10. Forest plot of the pooled correlations for the dimethyl sulfide between portable gas chromatographs and OLT (161)

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).

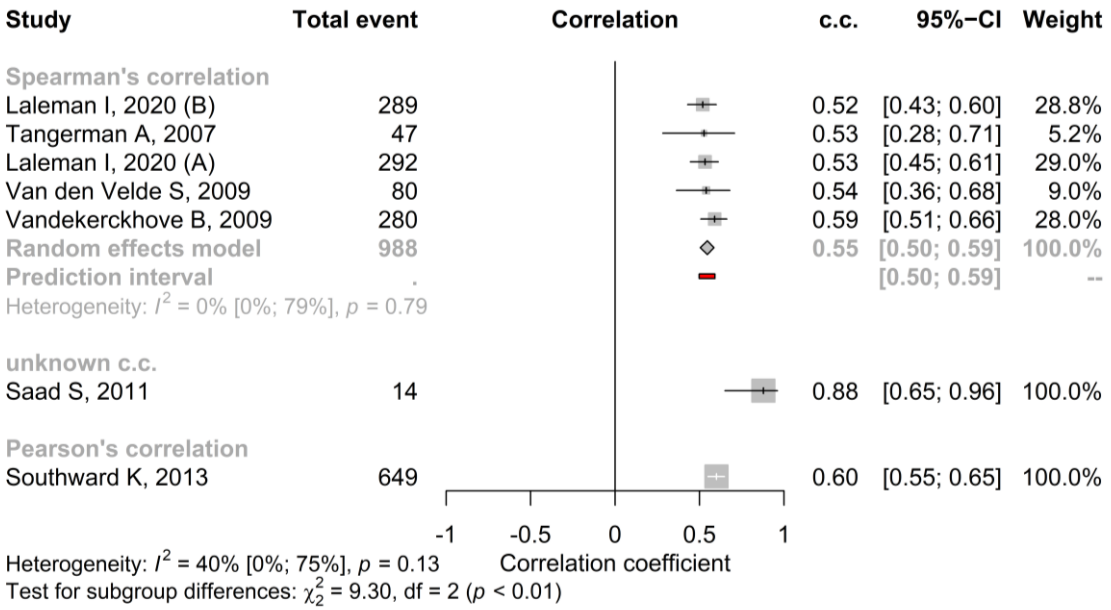


Figure11. Forest plot of the correlation between portable gas chromatographs and sulfide monitors (161)

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) (161).

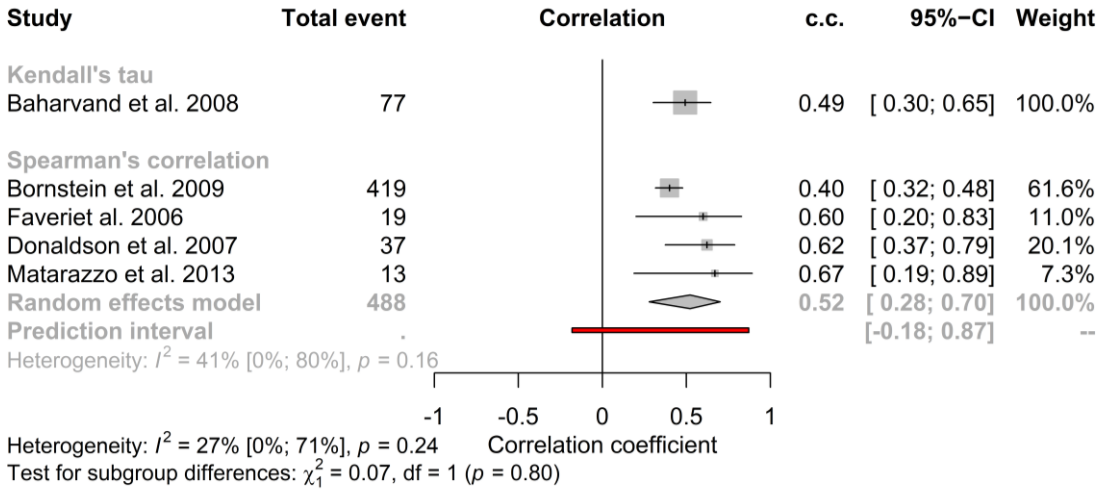


Figure 12. Forest plot of the pooled correlations between sulfide monitors and 4-point scale (161)

8.1.3.2. Specificity and sensitivity

The diagnostic test accuracy can demonstrate the effectiveness of diagnosing patients with or without the condition, assuming that the OLS is the appropriate gold standard. The SROC curve for the Halimeter was based on data from six articles (35, 36, 99, 106, 119, 148) (Figure 13). Light blue crosses show the individual study data with Halimeters.

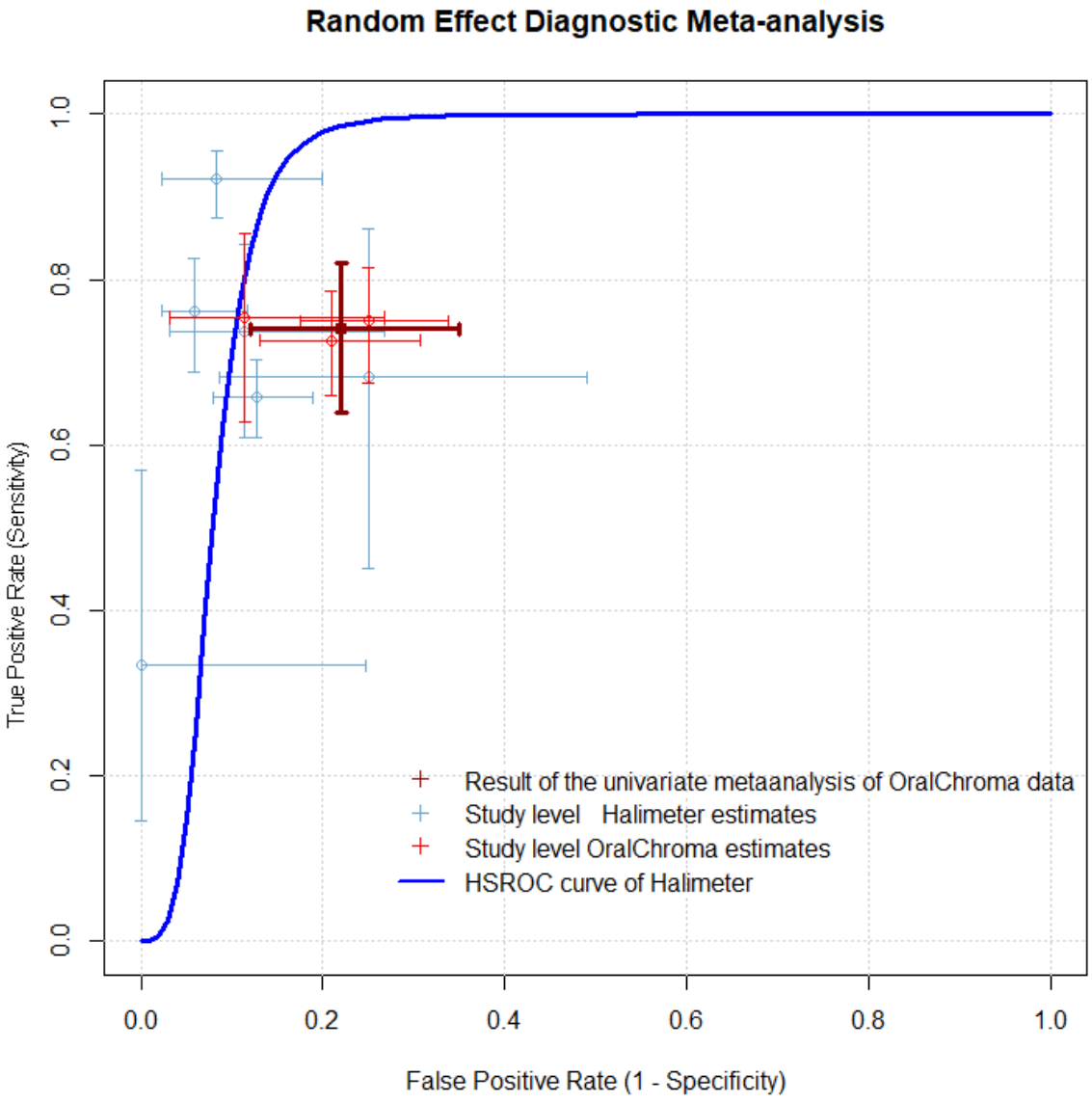


Figure 13. ROC plot visualizing the diagnostic performance of Halimeter and OralChroma diagnostic tools (original running with six articles) (161)

HSROC: Hierarchical summary receiver-operating characteristic

The repeated analysis excluded two studies (99, 106), where the aim of detecting OLS ≥ 2 conditions (Figure 14) (161).

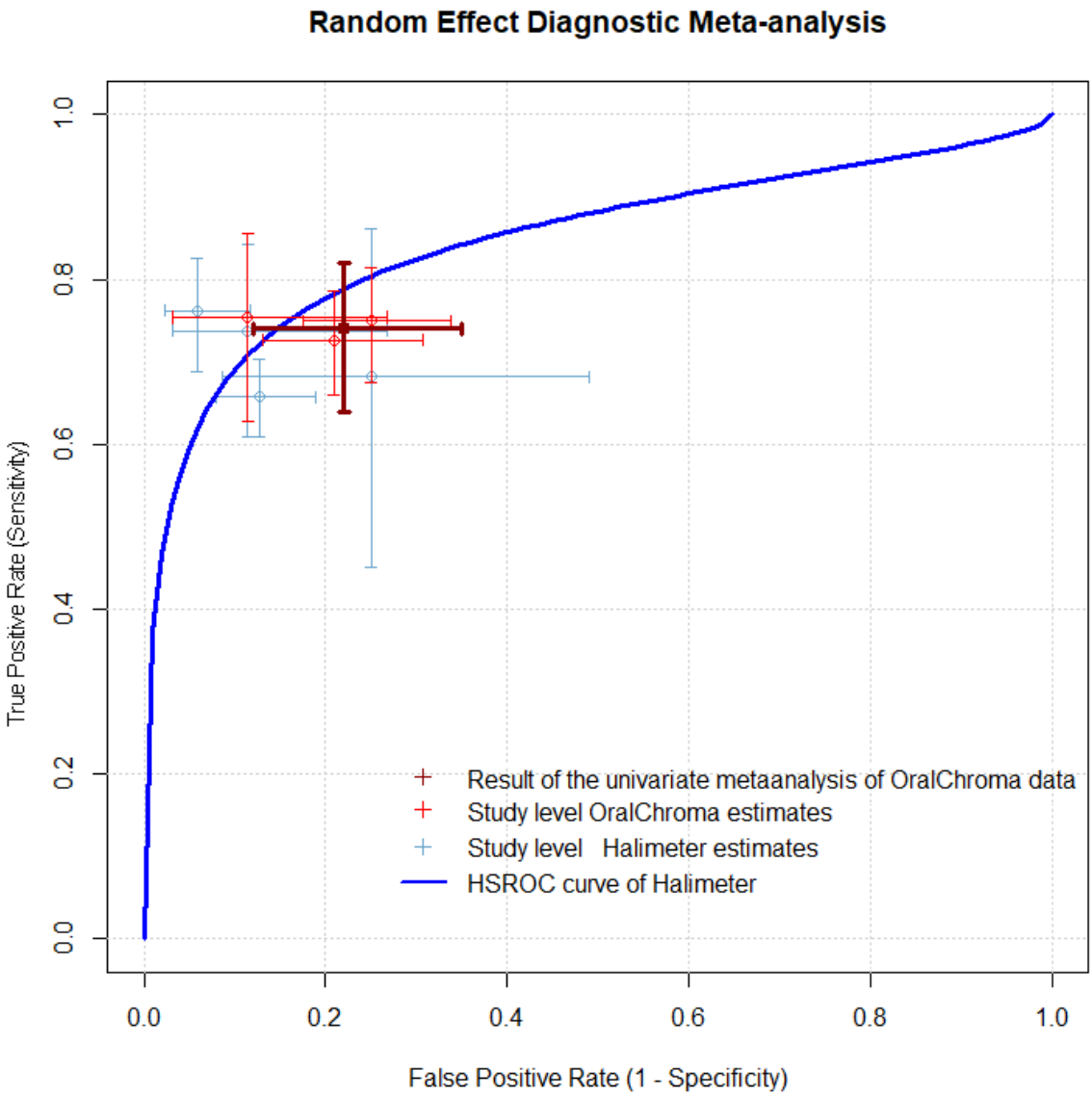


Figure 14. ROC plot visualizing the diagnostic performance of Halimeter and OralChroma diagnostic tools (original running with four articles) (161).

Only three studies (35, 36, 119) 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) (161).

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 (163).

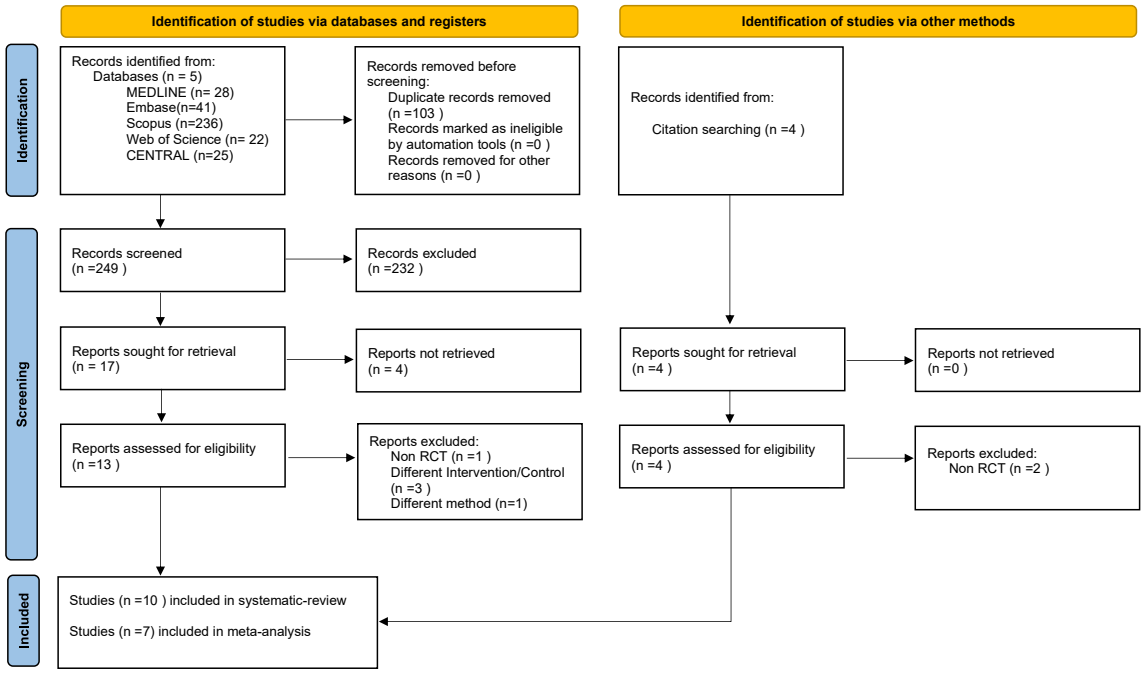


Figure 15. Prisma 2020 Flow Diagram of the screening and selection process (163)

After the selection process, a total of ten articles were included in the qualitative synthesis (41, 164-172).

8.2.2. Characteristics of the included studies

Table 3 lists the major characteristics of the included studies. With the exception of one trial (172), placebo was utilized in the comparator groups. Women were excluded from four studies because their menstrual cycles might impact the findings (41, 169, 170, 172). The corresponding author of two studies (165, 166) 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, 167, 172) 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. (52) further investigated.

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	[illegible]	VS C	
Shinada et al. 2010 (170)	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 (168)	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 (167)	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 (172)	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 (171)	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)	N° of Patient	Care product	Main content	Outcomes				Time points
									O	PI	VS	C	
Shinada et al. 2008 (169)	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 (164)	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 (166)	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 (165)	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 (163)

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, missing and filled 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) (163).

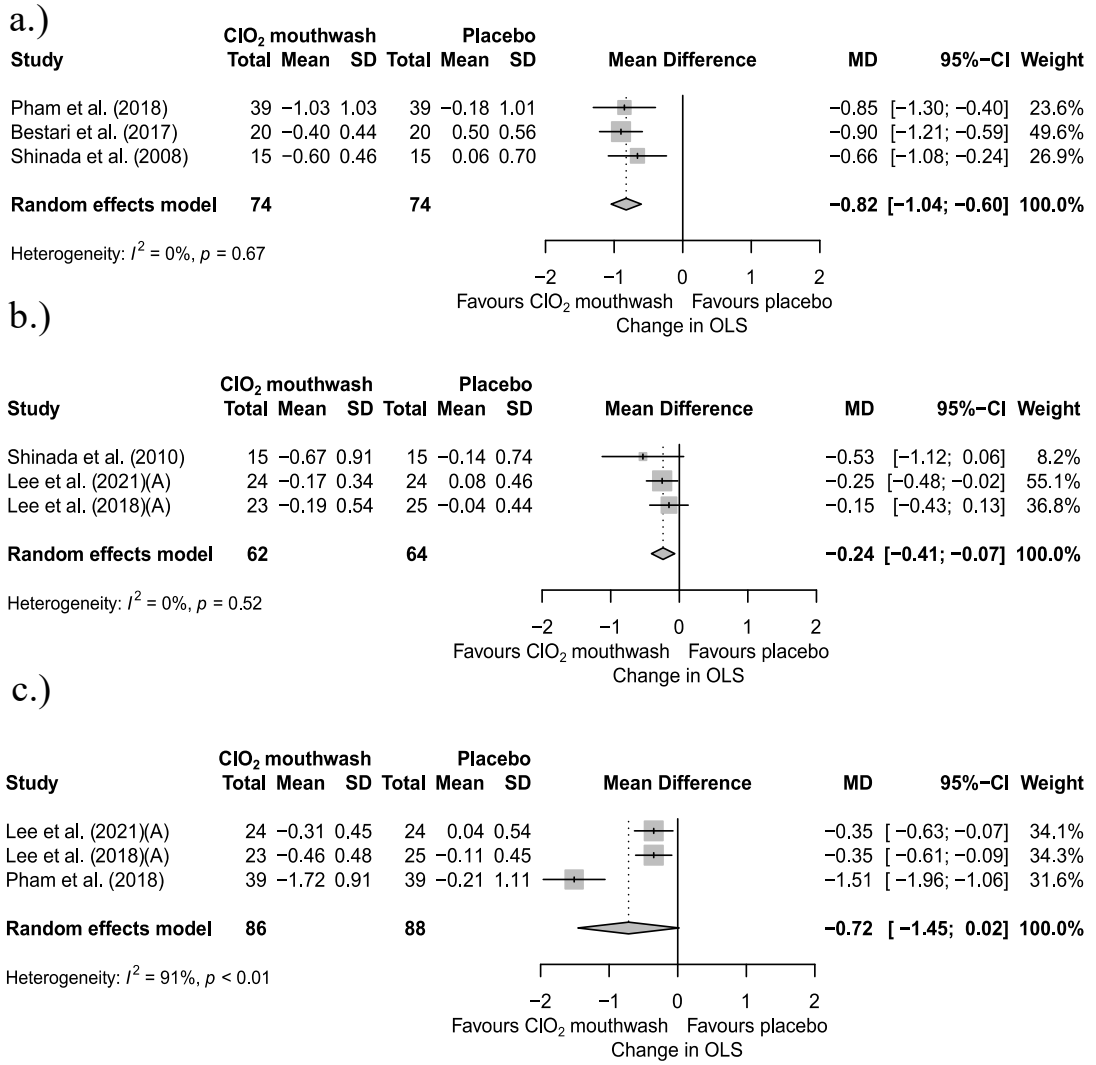


Figure 16. Changes of organoleptic measurement (163)

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 (164, 168, 169) after 4, 6 and 12 hours. The data from the study indicates that ClO_2 was successful in achieving its intended

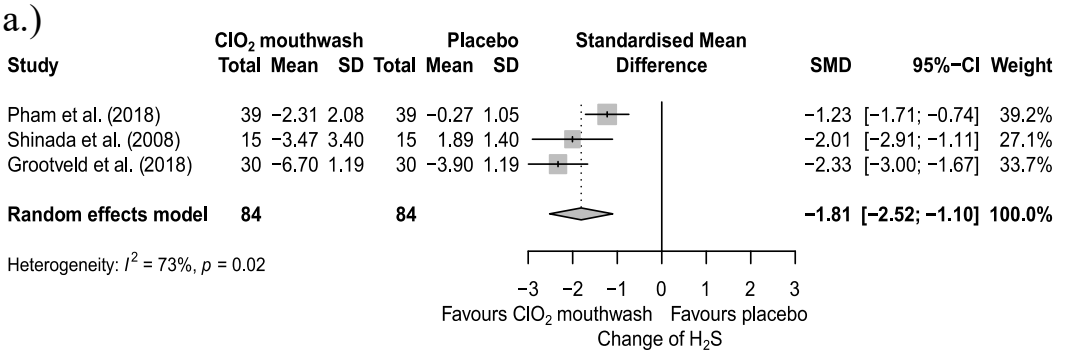
purpose within a single day (MD: -0.82; 95% CIs): [-1.04 – -0.6]; heterogeneity: I^2= 0%, p= 0.67) (Figure 16.a) (163).

OLS data was collected over a period of one week and was sourced from three different articles. (165, 166, 170) 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) (163).

OLS data was collected over two weeks and was sourced from three different articles (165, 166, 168). 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) (163).

Changes in H_2S and CH_3SH on one-day data were collected from three articles (168, 170, 171). 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) (163).

a.)



b.)

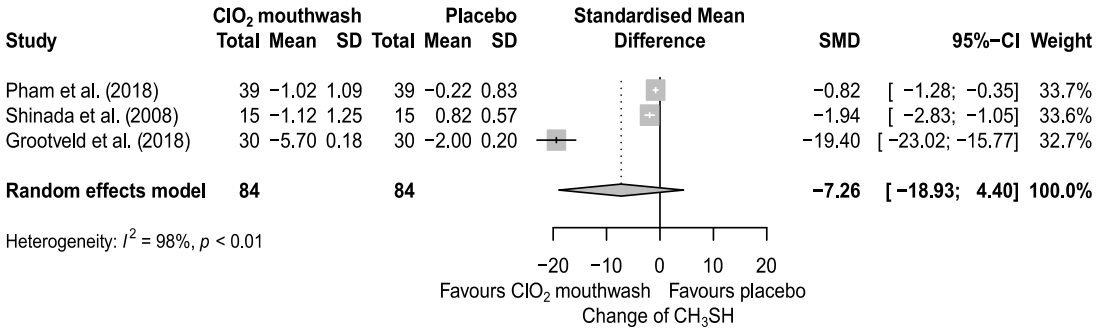


Figure 17.a. Changes of hydrogen sulfide concentration between baseline and within one day with and without ClO_2 mouthwash (163)

Figure 17.b. Changes of methyl mercaptan within concentration between baseline and one day with and without ClO_2 mouthwash (163)

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 (163).

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, 173-175) 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 (gas chromatograph) 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 (176). 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 (177); however, it is constantly changing (178). E. g. Complex chemical mixtures can be broken down, identified and measured using an analytical method known as gas chromatography-mass spectrometry (GC/MS), which consists of a gas chromatograph connected to a mass spectrometer.

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, 138). The correlations were 0.78-0.81 with electrical sensing (124, 129); 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 (179). This is because there is a lack of quantitative measurements of the gases, which hinders their effectiveness (124).

A few test results are available for the following devices: FreshKiss (r=0.283) (101), tongue sulfide monitor (r=0.768) (126), Breathtron (r=0.65) (152), Tanita (ROC=0.473) (180), MX6 (181, 182), Breath-Alert (106). 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 (183) 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 (158) to 0.743 (97)), 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 (184), combined plaque fluorescence score (120), the concentration of the saliva's *Solobacterium moorei* (185), the colorimetric chair-side test (102)). 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 (154, 186). 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 (187) or nasal breath analysis (154) 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 (188), and the insensitivity of the devices for cadaverine, indoles and skatoles (13), or the sensitivity of Halimeter for acetone, ethanol and methanol (189), resulting in an incorrect diagnosis that shows false negative results. It is significant because a single compound can change the level of IOH (190) 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 because there were not enough comparable articles. However, it performed even worse in that one study (119) 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 applied as a diagnostic tool over the past 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 (191). The safety apprehensions regarding inhaling other people's breath have increased due to the pandemic. In line with Laleman et al. (192), 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 (193, 194). In contrast with our study, one study (59) 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. (195) emphasized separating VSCs is not necessary to assess the total impact. However, targeted therapy may improve patients' health-related quality of life (196).

ClO_2 demonstrated almost the same efficacy as chlorhexidine compared to the only eligible article with a mouthwash comparator containing chlorhexidine (172). However, two systematic reviews found low-certainty evidence to support the effectiveness of any interventions for managing halitosis (15, 197). Another meta-analysis conducted on probiotics found probiotics effective, but they reduced only OLT results (198). A few clinical trials (199-201) found different kinds of herbal mouthwashes to be effective. However, the trials have several limitations.

Some patients mentioned an unpleasant taste (172). 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 (202). A systematic review (203) strengthened the same. However, they include some overdosed, posing cases. Chlorhexidine and mouthwashes with alcohol are known to have adverse effects (46, 204, 205). Additionally, a different meta-analysis (206) 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. (165, 166) advised patients to gargle with 15 mL of mouthwash for 30 seconds only, Pham et al. (168) 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. (171) 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 (207) and that racial variations can lead to variations in the composition

of bacteria (208); two of these articles (168, 169) are from Asia, and the other is from the UK (171). Moreover, increased CH_3SH concentration is widely associated with periodontal disease (30); however, Grootveld et al. (171) do not include periodontopathic patients. Primarily, we should be cautious 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 play a more significant role in supportive therapy for intra-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 accepted 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 FOR 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 FOR RESEARCH

Instead of focusing on device correlations, we recommend that future research should 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 FOR 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 enrolment 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** 23 : 3 Paper: 101862 , 20 p.
http://doi.org/10.1016/j.jebdp.2023.101862

Accepted in D1, Published in 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 Paper: e0280377 , 16 p.
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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** 23 : 1 Paper: 226 , 11 p.
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Q1, IF: 5.2

4. Tarján, D., **Szalai, E.**, Lipp, M., ; Verbói, M., Kói, T., Erőss, B., Teutsch, B., Faluhelyi, N., Hegyi, P., Mikó, A. (2024). Persistently High Procalcitonin and C-Reactive Protein Are Good Predictors of Infection in Acute Necrotizing Pancreatitis: A Systematic Review and Meta-Analysis. **INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES** 25 : 2 Paper: 1273 , 14 p.
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D1, IF: 6.208

5. Borbély, R. Zs., **Szalai, E. Á.**, Mangalath P. B., Dobszai, D., Teutsch, B., Zolcsák, Á., Veres, D. S., Erőss, B., Gellért, B., Hegyi, P. J., Hegyi, P., Faluhelyi, N. (2024). The risk of developing splanchnic vein thrombosis in acute pancreatitis increases 3 days after symptom onset: A systematic review and meta-analysis. **UNITED EUROPEAN GASTROENTEROLOGY JOURNAL**
https://doi.org/10.1002/ueg2.12550

Q1,IF: 6.866

17. ACKNOWLEDGEMENTS

I am grateful that I could work with the following people. Without them, my scientific work would not have been possible.

Primarily, I would like to express my appreciation, Beáta Kerémi DMD, PhD, deputy director of the Department of Restorative Dentistry and Endodontics, Semmelweis University. My research and writing of this thesis would not have been possible without her constant professional and personal support. Her commitment motivated and inspired me and constantly made me feel we were a team. It was a pleasure to work together.

I want to thank János Vág DMD, PhD, the chair of the Department of Restorative Dentistry and Endodontics, Semmelweis University, for giving me the chance to join the Centre for Translational Medicine PhD Program.

I want to express my appreciation to Péter Hegyi, MD, PhD, D.Sc., MAE, the director of the Centre for Translational Medicine. The program gave me the opportunity to become a part of a motivating research team. It showed me the importance of high-quality research work and the importance of constant development.

I would also like to thank Gábor Varga, PhD, D.Sc., MAE, the head of the doctoral program, for supporting my scientific work.

I want to express my gratitude to the following persons for their invaluable contribution: Brigitta Teutsch, MD, Márk László Czumbel, DMD, PhD, Bence Szabó PhD, Tamás Kói PhD, Péter Tajti DMD, Eleonóra Sólyom DMD, Orsolya Németh DMD, PhD, Zsolt M. Lohinai DMD, PhD, Boglárka Szántai DMD, Réka Németh DMD, Adél Galvács, Viktória Babay and Saghar Shojazadeh DMD who elevated the quality of my research.

I want to say thank you to Gábor Gerber, DMD, PhD, D.Sc, the dean of the Faculty of Dentistry, to gave us the opportunity and supporting our work with Faculty Grants.

I want to special thank my husband, parents and kids, especially for their flexibility and constant support during my PhD studies.