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In health and illness: does taste remain consistent? Exploring the influence of inflammation on taste perception through a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Dysgeusia is characterized by a loss of taste perception, leading to malnutrition. This situation affects inflammatory conditions such as respiratory and neurological conditions, obesity, cancer, chemotherapy, aging, and many others. To date, there is not much information on the prevalence and risk of dysgeusia in an inflammatory condition; also, it is unclear which flavor is altered.

MATERIALS AND METHODS: We systematically searched three databases from January 2018 to January 2023. Participants were children, adults, or elderly persons with an inflammatory condition and evaluated taste loss. A random effects model was used for statistical analysis to calculate the pooled odds ratio with its corresponding 95.0% confidence interval to estimate the probability of taste alteration (dysgeusia) in an inflammatory condition.

RESULTS: The data allowed us to conduct a systematic review, including 63 original articles and 15 studies to perform the meta-analysis. The meta-analysis indicated a heterogenicity of 84.7% with an odds ratio of 3.25 (2.66-3.96), indicating a significant risk of Alzheimer's disease, SARS-CoV-2, chemotherapy, and rhinosinusitis.

CONCLUSIONS: Inflammatory conditions and taste alterations are linked. Dysgeusia is associated with a higher risk of malnutrition and poorer general health status, especially in vulnerable populations.

Key Words:
Taste loss, Dysgeusia, Inflammation, Aging, Chronic disease.

Introduction

The sense of taste is described as a potential quality control mechanism that allows humans to distinguish between the quality and origin of the food ingested, absorbed, and metabolized to preserve health[1]. Taste is a complex sense that consists of 70% smell, 20% flavor, and 10% other perceptions. There are five known primary tastes, including sour, sweet, salty, bitter, and umami (savoriness). Fat has recently been identified as a taste[2]. Additionally, menthol is a taste stimulant in food and oral hygiene products, providing a cooling sensation[3]. Spicy flavor, another secondary taste bud stimulant activated by capsaicin, has been linked to a reduced preference for salty flavor[4]. In order to be detected by taste buds, tastants must be dissolved in the saliva or water in food[5,6].

Under healthy conditions, human papillae are renewed every ten days. Nonetheless, in diseases such as inflammatory conditions, these have been described[7] as at risk for a shorter life span and a loss due to the release of proinflammatory cytokines and the stimulation of the mitogen-activated protein (MAP) kinase pathway. This phenomenon is presented in three different ways: dysgeusia, a general alteration of taste perception; hypogeusia, which means a diminished taste perception; and finally, ageusia, referring to a total absence of taste perception. Several studies[8] have

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linked these alterations to the aggravation of the diseases inhibiting and activating metabolic and endocrine pathways, disturbing feeding behavior, and negatively affecting the nutritional status, leading to malnutrition. This state has been associated with older people and physiopathological conditions. To our knowledge, strong associations have yet to be established; thus, our first outcome was to conduct a systematic review[9-71]. Also, it is unclear which inflammatory condition has a higher risk of dysgeusia. Therefore, our secondary outcome was to assess this relation among the available data.

Materials and Methods

Search Strategy

A systematic review was conducted between December 2022 and January 2023, adhering to the Preferred Reporting Items for Systematic Reviews (PRISMA) method[72]. The databases enlisted to complete this research were PubMed Web of Science and Science Direct. We utilized the following search terms: taste loss AND inflammation, taste loss AND aging, and taste loss IN pathology.

Inclusion Criteria

The study focused on original articles written in the English language less than 5 years after publication. To perform this research, we included studies that indicated the evaluation of taste perception (objective, subjective, or mixed); study objects were required to be humans, mice, or rats, and inflammation inducers for the systematic review. Regarding meta-analysis, we included original cross-sectional and longitudinal studies that compared taste perception between control and experimental subjects and that indicated the number of participants with dysgeusia.

Exclusion Criteria

This systematic review and meta-analysis did not consider letters to the editor, narrative reviews, and published posters.

Data Extraction

The data extraction process was accomplished by extracting the author's first name, publication year, study design, sample size, type of sample, age of participants (when applicable), disease or inducer of inflammation, taste-loss assessment, and flavors not perceived.

Risk of Bias Assessment

Each study included in this meta-analysis was assessed using the Cochrane Collaboration's risk of bias for randomized trials (RoB-2) assessment tool[73]. This tool considers potential biases such as randomization, deviation from planned interventions, missing outcome data, outcome measurements, and the selection of reported results. Considering 5 domains, "low risk of bias" category indicates that the study is of high quality and that the results are likely to be reliable. The "some concerns" category indicates that there are some issues with the study that may affect its validity and reliability. The "high risk of bias" category indicates that the study has serious flaws that make its results inconclusive.

Statistical Analysis

A random effects model was employed to calculate the pooled odds ratio (OR) with its corresponding 95% confidence interval (95% CI) to estimate the risk of dysgeusia among the different inflammatory conditions. A p-value<0.05 was considered statistically significant. Also, we explored the effect of heterogeneity on estimates across the studies. Data was processed in SPSS Statistics 24 software (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9 (La Jolla, CA, USA).

Results

Figure 1 presents article selection procedures. The database search identified 7,592 studies, but the research included 63 studies[9-71] after removing duplicates and applying exclusion criteria. The outcomes of the studies included were diverse. Some aimed at describing or correlating taste loss with disease, age, or other inflammatory conditions.

Tables I and II describe the characteristics of the studies. The articles were published between 2018 and 2023; the majority (76.19%) were cross-sectional studies, followed by longitudinal cohort (20.63%) and case-control cohort (3.17%) studies.

The distribution of the included studies is summarized in Table III. Most studies comprised a human sample (92.06%) instead of a murine model (7.93%). The human sample consisted of participants of all ages. Regarding the animal models, the articles reported studying taste loss in albino rats[74], C57BL/6 mice[68,70], SAM mice[69], and ddY mice[71]. Also, the studies evaluated taste

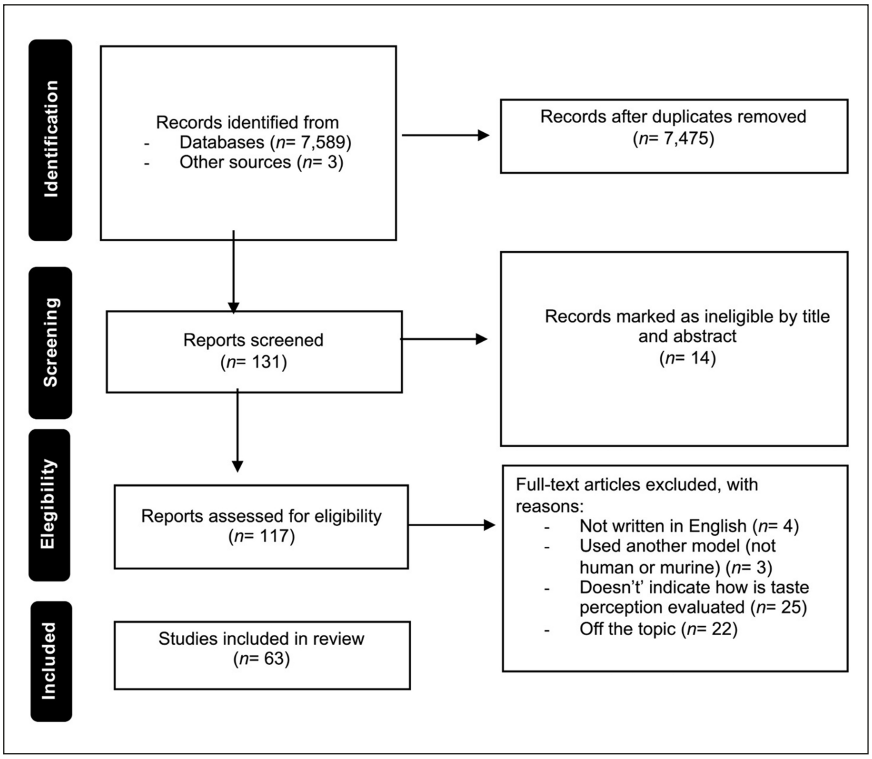

Figure 1. PRISMA flowchart of literature research.

loss in different ways, such as objective, subjective, and mixed. Participants discriminated the taste threshold in solutions or on taste strips in objective methods. DNA extraction, immunohistochemistry, saliva flow, extraction, and quantification of taste buds comprised other objective methods utilized to assess taste loss. With respect to the subjective methods, telephone interviews, self-report questionnaires, and face-to-face interviews were implemented. Our literature search yielded 9 studies[12,16,27,31,35,41,43,47,66] that met our inclusion criteria for meta-analysis. Nevertheless, 63 articles were assessed for the systematic review. Results regarding the risk of bias are shown in Figure 2. These studies investigated the association between dysgeusia and various diseases, including rhinosinusitis, type 2 diabetes, Alzheimer's disease, SARS-CoV-2, chemotherapy, Parkinson's disease, and obesity.

The effect size of the analyzed studies is depicted in Figure 3 and Figure 4. The pooled OR for the association between dysgeusia and disease was 3.25 (95% CI, 2.66-3.96), indicating that individuals with an inflammatory condition are more than twice as likely to have dysgeusia ($p<0.05$). Inflammatory conditions with a higher risk of dysgeusia included chemotherapy, SARS-CoV-2, Alzheimer's disease, and rhinosinusitis.

Discussion

Results showed more research conducted on taste loss in humans than in murine models. Humans and mice share about 80% of their genomes, including how the immune system responds (cytokine release and signaling pathways)[75]. Although humans are the ideal model for studying dysgeusia, murine models are the basis that allows for a deeper evaluation of this phenomenon, which leads to applying a therapeutic approach to this condition[76].

Additionally, these results revealed a more objective evaluation of taste loss than subjective methods. Although subjective methods are potential sources of bias, it is essential to understand that they permit researchers to construct and describe the phenomena involved and to understand the psychosocial factors in participants[77,78]. In contrast, objective methods permit quantifying the incidence of the phenomena, correlating or comparing variables, and generalizing in larger

Table I. Characteristics of included articles in human sample.

Study	Study type	Sample size	Inflammation inducers	Taste perception evaluation	Flavors not perceived
Alvarenga da Silva et al[9]	Longitudinal	36	Age	Threshold test with solutions	Salty and bitter
Campagna et al[10]	Cross-sectional	243	Chemotherapy	Self-report questionnaire, Likert scale	Salty
Meirelles et al[11]	Cross-sectional	20	Hematologic disease	Recorded inverview	Not specified
Jin et al[12]	Cross-sectional	114	Chemomotheraphy	Self-report questionnaire	Not specified
Othieno et al[13]	Cross-sectional	68	Rhinosinusitis	Taste strips test	Bitter
Ramos-López et al[14]	Cross-sectional	474	Obesity	DNA methylation	Sweet
Roos et al[15]	Cross-sectional	63	Parkinson's disease	Taste strips test	No alteration
Walliczek-Dworschak et al[16]	Cross-sectional	84	Cochlear implant surgery	Taste strips test	Not specified
Archer et al[17]	Cross-sectional	36	Obesity	Taste buds density	Sweet
Brindisi et al[18]	Cross-sectional	18	Obesity and hyperglicemia	Two-alternative, forced-choice	Salty
Faccioli Sicchieri et al[19]	Case-control	43	Cancer	Taste strips test	Salty and sour
Fogel and Blisset[20]	Cross-sectional	99	Othitis	Self-report questionnaire	Sweet
Haehner et al[21]	Longitudinal	45	Parkinson diseas	Taste strips test	Not specified
Iijima et al[22]	Longitudinal	181	Chemotherapy	Self-report questionnaire	Not specified
Nolden et al[23]	Cross-sectional	1,329	Chemotherapy	Memorial Symptom Assessment Test	Not specified
Pushpass et al[24]	Cross-sectional	56	Age	Likert scale	Umami, menthol
Pushpass et al[25]	Cross-sectional	55	Age	Saliva flow	Not specified
Vignini et al[26]	Cross-sectional	41	Obesity	Taste strips test	Bitter, sweet, salty and sour
Sang et al[27]	Cross-sectional	300	Rhinosinusitis	Gustatory function test (YSK taste function test kit)**	Bitter and sweet
Alfaro et al[28]	Cross-sectional	40	Wolfram syndrome	*NIH Toolbox for Assessment of Neurological and Behavioral function	Sweet and salty
Árias-Guillén et al[29]	Cross-sectional	91	Asthma	Two-alternative, forced-choice	Sweet and bitter
Chatindiara et al[30]	Cross-sectional	16	Age	Recorded interviews	Not specified
Contri-Degiovanni et al[31]	Cross-sectional	120	Alzheimmer's disease	Taste strips test	Salty and sweet
Denda et al[32]	Longitudinal	41	Chemotherapy	Self-report questionnaire Taste strips test	Salty, sweet and umami
Uí Dhuibhir et al[33]	Longitudinal	31	Cancer	Self-report questionnaire Taste strips test	Salty and sweet
Epstein et al[34]	Longitudinal	10	Cancer	Liquid taste stimuli presented in drops Taste strips test	Fatty and sour
Izquierdo-Domínguez et al[35]	Cross-sectional	846	SARS-CoV-2	Visual analogue scale	Not specified
Márquez-Herrera et al[36]	Cross-sectional	75	Renal disease	Matched/paired method	Salty, sweet, bitter and sour
Migneault-Bouchard et al[37]	Cross-sectional	178	Rhinosinusitis	Taste strips test	Not specified

Continued

Table I *(Continued)*. Characteristics of included articles in human sample.

Study	Study type	Sample size	Inflammation inducers	Taste perception evaluation	Flavors not perceived
Parma et al[38]	Cross-sectional	4,039	SARS-CoV-2	Self-report questionnaire	Salty
Sakalli et al[39]	Cross-sectional	172	SARS-CoV-2	Self-report questionnaire	Not specified
Stieb et al[40]	Longitudinal	326	Radiation	Self-report questionnaire	Not specified
Szymandera-Buszka et al[41]	Cross-sectional	288	Crohn's disease	Threshold test with solutions	Bitter and sour
Türk et al[42]	Cross-sectional	88	Epilepsy	Taste strips test	Not specified
Yan et al[43]	Cross-sectional	1,480	SARS-CoV-2	Self-report questionnaire	Not specified
Amérigo et al[44]	Cross-sectional	234	SARS-CoV-2	Likert scale	Not specified
Arshad et al[45]	Cross-sectional	207	SARS-CoV-2	Telephone interview	Salty and bitter
Bozkurt et al[46]	Case-control	42	Rhinosinusitis	Taste strips test	Not specified
Catamo et al[47]	Cross-sectional	338	Type 2 diabetes	Taste strips test	Salty and sweet
Coelho et al[48]	Longitudinal	321	SARS-CoV-2	Online survey	Not specified
Husain et al[49]	Longitudinal	2,892	SARS-CoV-2	Face to face interview	Not specified
Jeyashree et al[50]	Cross-sectional	277	SARS-CoV-2	Threshold test with solutions	Not specified
Asadi et al[51]	Cross-sectional	57	SARS-CoV-2	Threshold test with solutions	Sweet, bitter and sour
Nigam et al[52]	Cross-sectional	92	Parkinson disease	Taste strips test	Not specified
Ninchritz-Becerra et al[53]	Cross-sectional	1,043	SARS-CoV-2	Self-report questionnaire	Not specified
Resuli and Oktem[54]	Longitudinal	96	SARS-CoV-2	Face to face interview	Not specified
Robino et al[55]	Cross-sectional	42	Obesity	DNA extraction	Sweet
Chen et al[56]	Cross-sectional	78	Renal chronic disease	Taste strips test	Not specified
Singer-Cornelius et al[57]	Longitudinal	41	SARS-CoV-2	Taste strips test	Sweet
Song et al[58]	Cross-sectional	1,172	SARS-CoV-2	Telephone Interview	Not specified
van den Brink et al[59]	Cross-sectional	609	Age	Taste strips test	Not specified
Henin et al[60]	Cross-sectional	16	SARS-CoV-2	Immunohistochemistry	Not specified
Sato et al[61]	Cross-sectional	81	Age	Threshold test with solutions	Salty
Turner and Rogers[62]	Cross-sectional	20	SARS-CoV-2	Semi-structured interview	Bitter and sweet
Yang et al[63]	Cross-sectional	54	Age	Threshold test with solutions	Sweet
Cattaneo et al[64]	Cross-sectional	168	Obesity	Dutch eating behaviour questionnaire	Sweet and salty
Drareni et al[65]	Longitudinal	100	Chemotherapy	Taste strips test	Not specified
Ponnusamy et al[66]	Cross-sectional	88	Obesity	The general labelled magnitude scale	Not specified

*NIH: National Institute of Health, United States of America; **YOF test, Kimex Co. Republic of Korea.

Table II. Characteristics of included articles in the murine sample.

Authors	Year	Study type	Sample size	Inflammation inducer	Taste perception evaluation	Flavors not perceived
Hassan et al[67]	2019	Cross-sectional	42	Alzheimmer's	Extraction of circumvallate papillae	Not specified
Kaufman et al[68]	2018	Cross-sectional	8	Obesity	Taste bud density Immunohistochemistry	Not specified
Narukawa et al[69]	2018	Cross-sectional	21	Age	Threshold test with solutions	Bitter
Sanjiv et al[70]	2019	Cross-sectional	24	Tissue damage	Cytokine quantification	Not specified
Takeuchi et al[71]	2021	Cross-sectional	NS*	Age	Electrophysiological response of taste receptor cells	Bitter and salty

*NS: not specified.

Table III. Distribution of sample, method, and inflammatory conditions associated with dysgeusia.

		n	%
Sample	Human	58	92.06
	Mouse/rat	5	7.93
Method	Objective	42	66.66
	Subjective	19	30.15
	Mixed	2	3.17
Inflammatory conditions	Age	9	14.28
	Neurological	6	9.52
	Respiratory	21	33.33
	Cancer	3	4.41
	Radiotherapy/Chemotherapy	7	11.11
	Cochlear implant surgery	1	1.58
	Gastrointestinal	1	1.58
	Hematologic	1	1.58
	Obesity/overweight	8	12.69
	Othitis	1	1.58
	Renal disease	2	3.17
	Tissue damage	1	1.58
	Insulin resistance	2	3.17

Percentage and frequency of sample, method, and inflammatory conditions in the studies included.

populations in terms of having a taste perception alteration in disease[79,80].

Figure 5 quantifies studies that include loss of taste perception in different flavors. Describing the available evidence on dysgeusia under inflammatory conditions, it was found that there is a more significant number of studies on respiratory diseases, which mainly included SARS-CoV-2 infection (16/21), leading to obesity. This is primarily due to the prevalence and importance of these conditions in recent years[81-83]. Despite this, it does not diminish the importance of other conditions that also cause an alteration in the perception of flavors. These inflammatory conditions entertain a common etiology; therefore, their treatment should aim to increase the proliferation of taste buds and inhibit apoptosis[84]. Notwithstanding this, more research involving this approach is needed to improve taste perception in vulnerable groups.

Results indicate a risk of taste alteration when individuals are found under vulnerable condi-

Figure 2. Risk of bias analysis and results of the included studies.

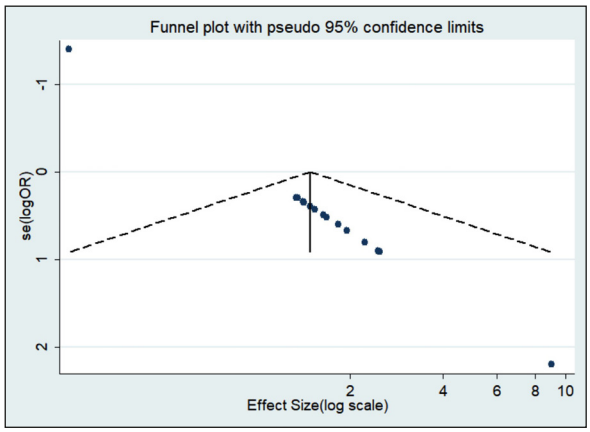

Figure 3. Funnel plot with an apparent asymmetry caused by the absence of negative or contrary to the hypothesis effects and with small sample sizes.

tions such as inflammation. Medical treatments, diseases, or senescence comprise risk factors contributing to a state of malnutrition that leads to a worse general health status. Acute inflammation such as SARS-CoV-2 promotes the release of a higher concentration of inflammatory biomarkers such as cytokines, growth factors, and chemokines, in which the alteration of taste perception may be immediately compared to chronic diseases including obesity, diabetes, and rhinosinusitis, in which these biomarkers are slowly but constantly released. Changes in taste perception are small and continuous, affecting long-term tissue remodeling, including taste buds[85,86].

However, other non-inflammatory conditions are not considered diseases that can cause dysgeusia. Tobacco consumption induces an alteration in the perception of flavors. The study by Berube et al[87] (2021) reports this relationship in North American patients; these authors evaluated smoking habits, such as the number of cigarettes per day, the age of the first cigarette, and the age at which the individuals became frequent smokers. The researchers found that participants who were nicotine-dependent, that

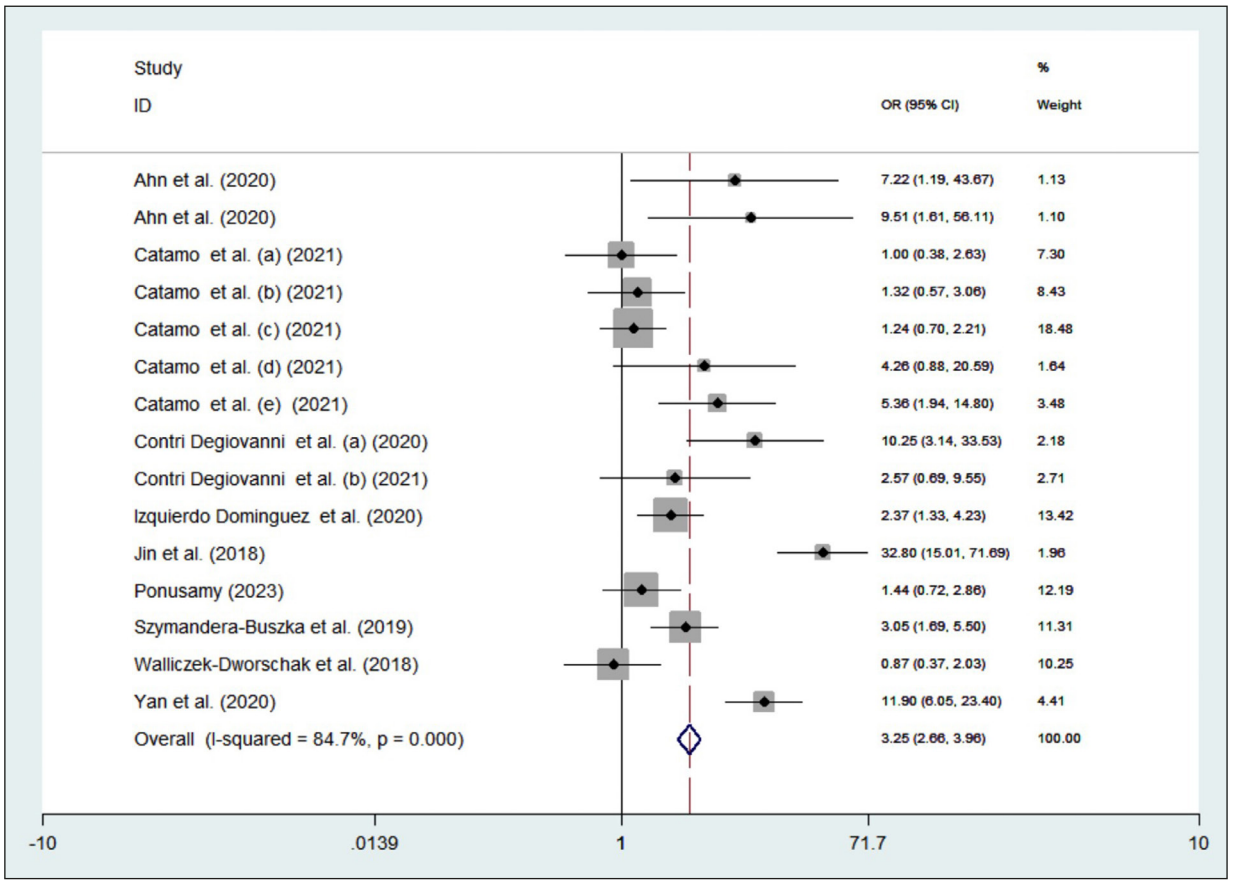

Figure 4. Forest plot showing study-specific estimates and meta-analysis results of disease effect on dysgeusia. Meta-analysis by OR with 95% CI and random effects model (OR: odds ratio; CI: confidence interval).

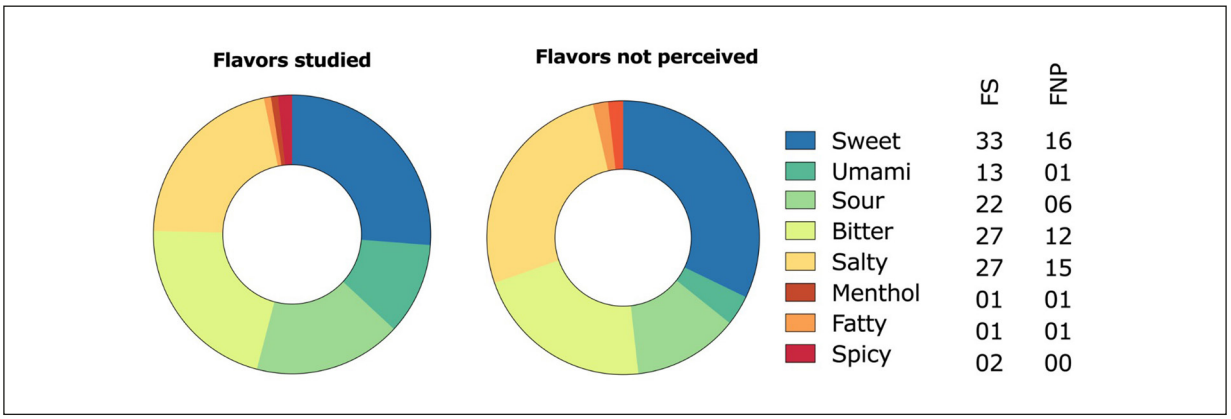

Figure 5. Comparison of flavors studied *vs.* flavors not perceived. FS: Flavors Studied, FNP: Flavors not Perceived.

is, those who smoked one cigarette within one-half hour of waking up and who smoked more than 20 packs of cigarettes per year, had lower perceptions of bitter tastes and salty tastes than non-smokers[87].

Even during the gestation stage, there is an alteration in the perception of flavors. In a study by Choo et al[88] (2021), the authors performed a preference test of sucrose solutions at different concentrations with a randomized block in C57BL/6 female mice. The number of licks before, during, and after pregnancy was quantified. From this, the authors found significant differences in the consumption of sucrose solutions in the gestation stage of female mice: pregnant mice tended to consume a more considerable amount of the higher concentration sucrose solution[88]. This study opens the possibility that alteration in taste perception during pregnancy should be considered since the type of diet that the pregnant person consumes could define the development of diseases such as gestational diabetes mellitus in predisposed women[89,90].

Moreover, zinc deficiency has been associated with taste loss. Badahdah et al[91] (2022) related taste impairment in patients with COVID-19 with and without dysgeusia by comparing saliva zinc levels in Saudi Arabia patients. Results showed lower zinc concentrations in patients with dysgeusia and COVID-19 patients than in non-infected and infected patients with no dysgeusia. This is mainly because the enzyme phospholipase (PLC), which metabolizes sweet, bitter, and umami flavors depending on the G protein-associated receptor, uses zinc as a co-enzyme. A decrease in this element leads to less uptake and, therefore, less nervous impulse for flavor transduction[92].

Conclusions

Inflammatory conditions and taste alterations are linked. Dysgeusia is associated with a higher risk of malnutrition and poorer general health status, especially in vulnerable populations. From this, we can conclude that further research needs to be done to increase taste buds' proliferation and prevent apoptosis to improve taste perception in patients with risk.

Finally, these results invite health professionals to consider dysgeusia as a potential risk of negatively affecting feeding behavior and nutritional status. Therefore, it is necessary to approach pharmacological, nutritional, and behavioral fields to improve health conditions.

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Conflicts of Interest
The authors declare that they have no conflict of interest to declare.

Ethics Approval
Not applicable due to the design of the study.

Informed Consent
Not applicable due to the design of the study.

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Availability of Data and Materials
Datasets used for this study can be obtained from the corresponding author upon a reasonable request.

Authors' Contributions
All authors have significantly contributed to the manuscript's research. SCLS and JMVP designed and performed the original idea. SCLS wrote the paper; SCLS and HAEG identified and collected data for the systematic review. JMVP and MEFS reviewed the integrity of the data collected, and FEH and SCLS designed and performed the statistical analysis. All the authors reviewed the final version of the manuscript and agreed with its content.

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