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Effect of physiological factors, pathologies, and acquired habits on the sweet taste threshold: A systematic review and meta-analysis

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Abstract

Sweet taste perception is a key factor in the establishment of the food pattern with nonstatic thresholds. Indeed, taste sensitivity can be influenced by physiological factors (age and sex), pathologies (obesity and type 2 diabetes mellitus), and acquired habits (tobacco and alcohol consumption). In order to elucidate how these variables influence the sucrose detection threshold (DT) and recognition threshold (RT), a systematic review and meta-analysis of the relevant literature were performed. After a comprehensive search in the PubMed and Scopus databases, a total of 48 studies were qualitatively considered, and 44 were meta-analyzed. The factors of aging (standard mean difference [SMD]: −0.46; 95% confidence interval (CI), −0.74 to −0.19; I^2: 73%; Tau^2: 0.18) and type 2 diabetes mellitus (SMD: 0.30; 95% CI, 0.06 to 0.55; I^2: 0%; Tau^2: 0.00) were found to significantly increase the sucrose RT, whereas the DT only increased in subjects with a higher body mass index (SMD: 0.58; 95% CI, 0.35 to 0.82; I^2: 0%; Tau^2: 0.00). No effects of sex and tobacco smoking were found, and associations with alcohol consumption could not be assessed, as it was included as a variable in only one study. Feasible mechanisms underlying changes in sucrose thresholds include the modulation of hormones involved in energy and body weight homeostasis, taste bud abundance, taste brain signaling, and the gut–brain axis. The present work provides insights into the variables that should be considered when

Nomenclature: AFC, alternative forced choice; BMI, body mass index; CI, confidence interval; DB, Downs and Black; DT, detection threshold; GLP-1, glucagon-like peptide 1; GLP-2, glucagon-like peptide 2; GLUT2, glucose transporter 2; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IV, inverse variance; LAGB, laparoscopic adjustable gastric banding; LSG, laparoscopic sleeve gastrectomy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PROP, 6-n-propylthiouracil; PTC, phenylthiocarbamide; RA, restrictive anorexia; RT, recognition threshold; RYGB, Roux-en-Y gastric bypass; SARS-COV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SD, standard deviation; SE, standard error; SG, sleeve gastrectomy; SGLT1, Na+/glucose cotransporter 1; SMD, standard mean difference; SNP, single-nucleotide polymorphism; T1R2 or TAS1R2, taste 1 receptor member 2; T1R3 or TAS1R3, taste 1 receptor member 3; T2DM, type 2 diabetes mellitus; T2R105, taste 2 receptornonbreakingspacemember 105; TR, taste receptor.

assessing sweet taste sensitivity, discusses the mechanisms underlying differences in sweet taste, and highlights the need for further research in the field of personalized nutrition.

KEYWORDS
chemoperception, detection threshold, personalized nutrition, recognition threshold, sucrose

1 | INTRODUCTION

Chemosensory perception (taste, smell, and chemesthesis) is essential for individual and species survival (Hawkes, 2001). The human sense of taste, which is limited to the oral cavity and mainly the tongue, is capable of identifying a wide variety of tastes (Smith & Margolskee, 2001). The two taste receptors (TRs) that are responsible for sweet taste stimulus detection and ligand selectivity, taste 1 receptor member 2 (T1R2) and taste 1 receptor member 3 (T1R3), belong to the G protein-coupled receptor family (Adler et al., 2000; Hoon et al., 1999; Matsunami, Montmayeur, & Buck, 2000). Sweetness response is triggered in the T1R2/T1R3 heterodimer (Nelson et al., 2001) and sucrose appears to bind to the Venus flytrap domain of T1R2/T1R3 (Chandrashekar, Hoon, Ryba, & Zuker, 2006). Sweet taste allows the identification of high-energy nutrients and, in general terms, indicates the presence of soluble carbohydrates. Nevertheless, a wide diversity of noncarbohydrate molecules, such as D-amino acids (e.g., D-phenylalanine, D-alanine, and D-serine) (Chandrashekar et al., 2006) and sweet testing proteins (e.g., monellin, thaumatin, curcullin, and brazzein), or noncaloric molecules such as artificial sweeteners (e.g., saccharine, sucralose, and aspartame) (Jiang et al., 2005) are also sweet as a consequence of interaction with T1R2 and T1R3 (Gamble, 2017; Lindemann, 2001).

The minimum concentration of a taste agent in an aqueous solution at which the stimulus solution can be distinguished from distilled water is referred to as the detection threshold (DT), whereas the lowest concentration that elicits the characteristic of taste is the recognition threshold (RT). These definitions were initially established for salty taste thresholds (Richter & MacLean, 1939) and were then generalized to all taste stimuli (O'Mahony, Hobson, Garvey, Davies, & Birt, 1976). Although this systematic review and meta-analysis has only been focused on DT and RT measurements, other parameters are commonly used to define human sensory perception. The measure of the perceived intensity of a concentration above the RT is known as suprathreshold intensity perception (Weiffenbach, Fox, & Baum, 1986). The differential threshold is defined as the minimum stimulus concentration by which taste intensity must be changed in order to produce a significant change in sensory experience (Galindo-Cuspinera et al., 2009), whereas the intensity of a stimulus from which its acceptance is altered, based on the transition point between sensory acceptance and rejection, refers to the rejection threshold (Lima Filho, Minim, Silva, Della Lucia, & Minim, 2015).

Chemical and physical methods, such as three alternative forced choice (3AFC) and electrogustometry (EGM), respectively, have been proposed for threshold determination, although taste tests based upon chemical substances is the preferred method for assessing sweet taste thresholds (Snyder, Prescott, & Bartoshuk, 2006). In a chemical taste test method, different tastant solutions are presented and participants must determine if taste is perceived or not, or even describe its taste quality.

Taste has the additional value of contributing to the overall pleasure and enjoyment of a meal (Chandrashekar et al., 2006). Moreover, sweet taste perception is an important phylogenetically preserved biological function (Kim, Wooding, Riaz, Jorde, & Drayna, 2006). In the context of genetics, health, and pathology, several variables that may affect the sweet taste and its perception have been described. They include T1R polymorphisms (Kim et al., 2006), age, sex, body mass index (BMI), smoking, consumption of alcohol, surgical interventions (Wasalathanthri, Hettiarachchi, & Prathapan, 2014), acute and chronic diseases such as otitis (Shin, Park, Kwon, & Yeo, 2011), cancer therapies with concomitant weight loss (Bolze, Fosmire, Stryker, Chung, & Flipse, 1982), chronic renal failure (Vreman, Venter, Leegwater, Oliver, & Weiner, 1980), and more recently, severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection (Lechien et al., 2020). Therefore, in the current study, we hypothesize that the sweet threshold in humans is not static, and it is influenced by physiological factors, pathologies, and acquired habits. A systematic review and meta-analysis on the influence of the usual descriptive physiological variables (e.g., age or sex), metabolic pathologies with the highest prevalence (e.g., obesity and type 2 diabetes mellitus (T2DM; Blüher, 2019; Glovaci, Fan, & Wong, 2019), and lifestyle habits most commonly described as perception modifiers (e.g., alcohol drinking and smoking habits; Da Ré et al., 2018; Silva et al., 2016) in sucrose DT and RT were performed, and the extent of the threshold differences was

discussed, with the aim of providing new evidence on this subject.

2 | MATERIALS AND METHODS

2.1 | Data sources and research method

Scientific literature was collected from the PubMed and Scopus databases (from the beginning of the database until July 2020). The search terms used were (sweet taste OR threshold) AND (T1R2 OR TAS1R2 OR T1R3 OR TAS1R3 OR sucrose). The search was restricted to the English language. In the PubMed database, the humans filter was used. In addition, manually selected reference articles and reviews were included. This work was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement (Supporting Information Table S1).

2.2 | Inclusion and exclusion criteria

The study selection was performed independently by two authors (M.T-S. and D.A.S-A.). Full-text articles were selected according to the following inclusion criteria: (1) original studies; (2) studies reporting the measurement of sucrose DT and/or RT by a chemical taste test; (3) studies including and comparing at least two groups of the variables studied (age, sex, BMI, T2DM, tobacco, or alcohol consumption); and (4) outcomes containing the mean sucrose threshold of the group with its respective measure of dispersion (95% confidence interval [CI], standard deviation [SD] or standard error [SE] or exact *P* value for group comparison). The exclusion criteria were (1) duplicated studies; (2) in vitro or animal studies; (3) ecological studies, editorials, reviews, and meta-analyses; and (4) thresholds assessed by a method other than the chemical taste test.

2.3 | Data extraction and management

Discrepancies in data information from selected papers were discussed by M.T-S. and D.A.S-A. If no consensus was reached, J.J.M. was consulted. For each study, the extracted variable was classified as DT or RT. The data for each study included in this systematic review and meta-analyses were the following: (1) author, year, and country of the study; (2) Downs and Black (DB) score (quality assessment); (3) outcome (DT and RT); (4) population sample tested; (5) sample size; (6) taste test and conditions of data collection; (7) sucrose range and number of solutions; and (8) key findings regarding the variable evaluated.

2.4 | Study quality assessment

The quality of each study was independently checked and discussed by M.T-S. and D.A.S-A. Any controversy regarding inclusion, data extraction, and/or quality assessment was resolved with the support of a third person (J.J.M.). To evaluate the risk of bias in individual studies, two validated scales were used: the DB score (Downs & Black, 1998) and the Cochrane risk of bias scale (Higgins et al., 2011).

The checklist of the DB scoring system, which is appropriate for assessing both randomized and nonrandomized studies of health care interventions, comprises 26 questions to evaluate reporting, external validity, and internal validity (bias and confounding). For the present work, five questions (questions 8, 17, 19, 23, and 24) were omitted because most sensory studies do not consider the study characteristics related to these questions. Finally, 21 questions from the DB checklist were used to evaluate the quality of the studies selected. The last question, concerning statistical power, was adapted to: "Did the authors of the study provide any information concerning a sample size calculation? Yes/No" (Downs & Black, 1998).

In the second risk of bias assessment, the Cochrane scale was used, including all the categories except one, as established by another study in the field (Tucker et al., 2017), in order to adapt the scale to the study design. Five domains (selection, performance, attrition, reporting, and other) were judged as having a high, low, or unclear risk of bias.

2.5 | Evidence quality assessment

The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) scale was used to evaluate the overall strength of evidence for each outcome (Ryan & Hill, 2019). Starting with low evidence for the nonrandomized control trial design of studies included in this meta-analysis, outcomes were downgraded or upgraded depending on the GRADE criteria system.

2.6 | Statistical analysis

Before analyses, studies were classified by variable (e.g., age) and type of outcome (DT or RT). Each meta-analysis was performed by pooling the standard mean difference (SMD) derived from the difference in mean outcome between groups divided by the SD of outcomes among participants. Heterogeneity within studies was evaluated by the I^2 test, Tau^2, and 95% prediction intervals. Subgroup analyses were used to study heterogeneity in age, sex, and BMI variables. A random-effects model was used because of the nature of the studies, where the differences between populations or assessment of outcome may

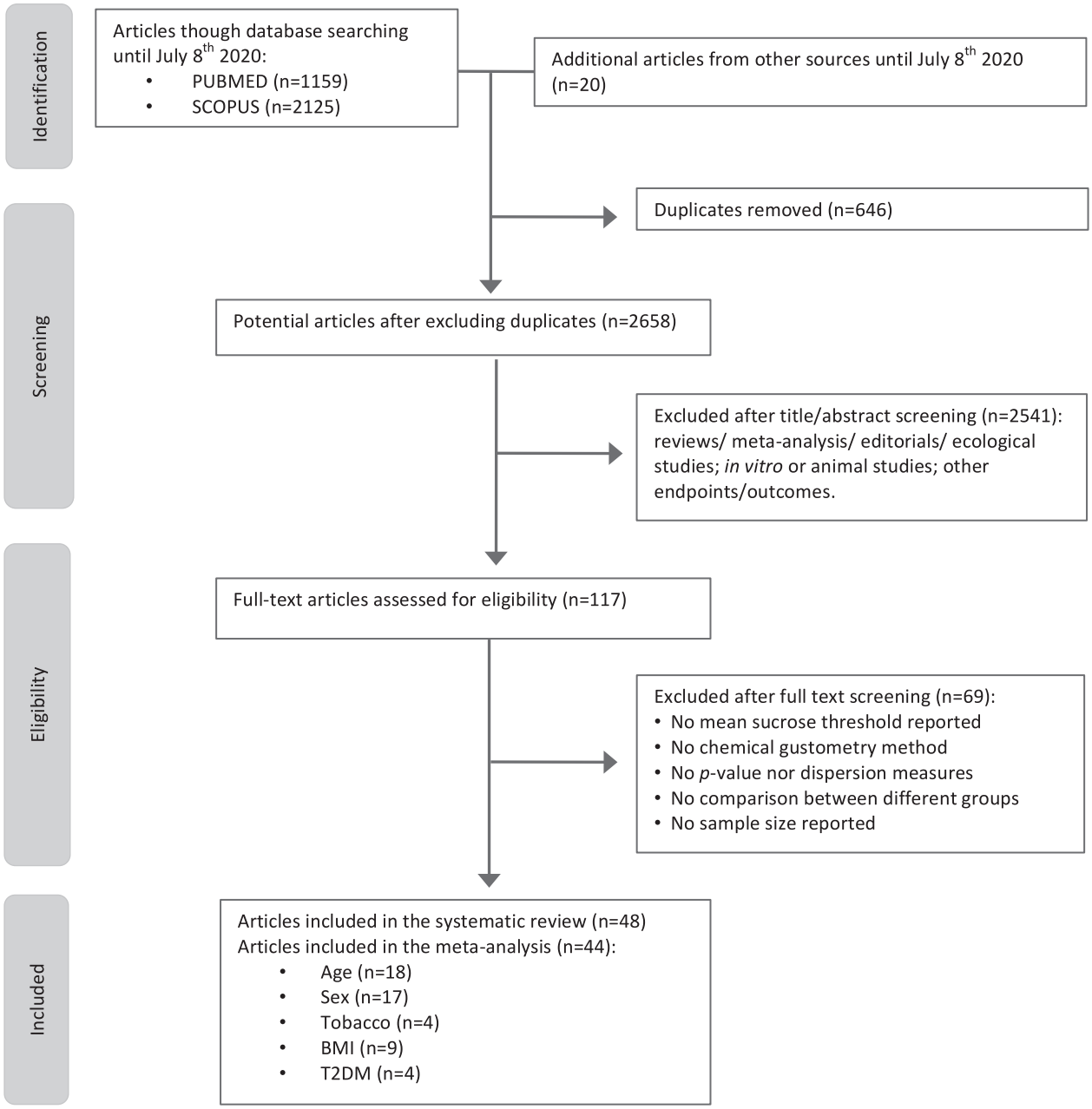

FIGURE 1 Flow chart of selected studies for the systematic review and meta-analyses

introduce variation between studies (Bouras, Tsilidis, Pounis, & Haidich, 2019). Meta-analyses and forest plots were performed with Review Manager (RevMan) Version 5.3 (The Cochrane Collaboration, 2014).

3 | RESULTS

3.1 | Literature search and study characteristics

Figure 1 depicts a flow diagram for article selection. A total of 3,284 articles from the two databases analyzed were identified, and 20 articles were included from other sources (manual searching and reviews). After removing duplicates, 2,658 papers were potentially eligible, whereas 2,541 studies were excluded based on inclusion and exclusion criteria after title and abstract screening. Thus, 117 articles were examined in detail, and, finally, 48 papers were included for the qualitative review and 44 of those were also included in the quantitative meta-analysis.

Based on the literature search and discussion, the variables considered for the present study were age, sex, tobacco smoking habit, alcohol consumption, BMI, and T2DM. Other settings, such as pathologies, including cancer and radiation treatment (Sandow, Hejrat-Yazdi, &

Heft, 2006), neurological diseases (e.g., Parkinson's and Alzheimer's disease; Sakai, Ikeda, Kazui, Shigenobu, & Nishikawa, 2016; Tarakad & Jankovic, 2017), otitis media (Snyder & Bartoshuk, 2016), or depression (Nagai, Matsumoto, Endo, Sakamoto, & Wada, 2015), among others, influence sweet taste thresholds, but fall outside of the scope of the present study, which is limited to sensory analysis with variables commonly controlled in nutrition and metabolism studies.

3.2 | Qualitative review: Thresholds and factors

The qualitative review of the studies included is summarized in Supporting Information Tables S2 to S7. Only four studies were included in the qualitative review (Eiber, Berlin, De Brettes, Foulon, & Guelfi, 2002; Nagai et al., 2015; Park et al., 2015; Than, Delay, & Maier, 1994). Although these studies fit the inclusion criteria, the comparison of their study subgroups could not be matched with the others (Eiber et al., 2002; Nagai et al., 2015; Than et al., 1994) or the outcome measure and its dispersion was only reported graphically (Park et al., 2015).

3.3 | Quantitative review: Thresholds and factors

3.3.1 | Age

Eighteen studies involving 1,450 participants were included in the meta-analyses. The data obtained allowed DT and RT to be divided by sex groups, creating subgroups for females, males, and both sexes.

In the case of DT (Figure 2a), eight comparisons found significantly higher sucrose thresholds in older versus younger participants (Bales, Steinman, Freeland-Graves, Stone, & Young, 1986; Da Silva et al., 2014; Fukunaga, Uematsu, & Sugimoto, 2005; Kennedy, Law, Methven, Mottram, & Gosney, 2010; Mojet, 2001; Moore, Nielsen, & Mistretta, 1982; Spitzer, 1988; Yamauchi, Endo, & Yoshimura, 2002b), two described the opposite (James, Laing, & Oram, 1997; Stevens, 1996), and five reported no significant differences (James et al., 1997; Mojet, 2001; Mojet, Christ-Hazelhof, & Heidema, 2005; Wardwell, Chapman-Novakofski, & Brewer, 2009; Wiriyawattana, Suwonsichon, & Suwonsichon, 2018). However, based on the overall effect, differences in DT between age groups were not significant.

The RT (Figure 2b) was significantly higher among older people (SMD: −0.46; 95% CI, −0.74 to −0.19; I^2: 73%; Tau^2: 0.18). This outcome was supported by the results of eight studies that reported a significant direct relation between aging and sucrose RT (Dye & Koziatek, 1981; Easterby-Smith, Besford, & Heath, 1994; Fukunaga et al., 2005; Kennedy et al., 2010; Richter & MacLean, 1939; Wardwell et al., 2009; Wiriyawattana et al., 2018; Yamauchi et al., 2002b). In fact, only one study reported the contrary (Wayler, Perlmuter, Cardello, Jones, & Chauncey, 1990) and another did not find any significant result (Kalantari, Kalantari, & Hashemipour, 2017). Although the result is significant, the prediction interval of the meta-analysis is expected to be nonsignificant in around 95% of the population (Supporting Information Table S8).

3.3.2 | Sex

Figure 3 summarizes the effect of sex on sweet thresholds. Seventeen studies including a total of 2,347 participants were meta-analyzed, including 15 articles on the DT and nine on the RT. Subgroups were defined according to age, in which participants under 18 years were classified as "children," those aged 18 to 60 were "young adults" and "older adults" were over 60 years old. The age of 60 was used as the cutoff for older adults because of age-related losses and health conditions (de Carvalho, Epping-Jordan, & Beard, 2019).

No difference was found in the DT between males and females in the children subgroup, based on only four studies (Fogel & Blissett, 2019; James et al., 1997; Joseph, Reed, & Mennella, 2016; Yamauchi et al., 2002b). The DT was significantly higher in adult males in one study (Da Silva et al., 2014), whereas another study reported the opposite (Wardwell et al., 2009). Regarding the RT results, a significantly higher RT was found in males in three studies (Hong et al., 2005; Sanematsu, Nakamura, Nomura, Shigemura, & Ninomiya, 2018; Wardwell et al., 2009). The results of the study by Yamauchi et al. (2002b) differed among study subgroups, and other previously unmentioned studies did not report any significant findings (Chang, Chung, Kim, Chung, & Kho, 2006; Fogel & Blissett, 2019; Horio & Kawamura, 1990; Hwang et al., 2018; Kalantari et al., 2017; Kunka, Doty, & Settle, 1981; Mojet, 2001; Vreman et al., 1980; Yamauchi, Endo, Sakai, & Yoshimura, 2002a). To sum up, neither total nor age subgroups showed significant differences in DT and RT between sexes (Figure 3a and 3b).

3.3.3 | Tobacco consumption

A meta-analysis of both sucrose DT and RT was performed with the results of four studies including 645 participants. One of the studies divided the comparisons

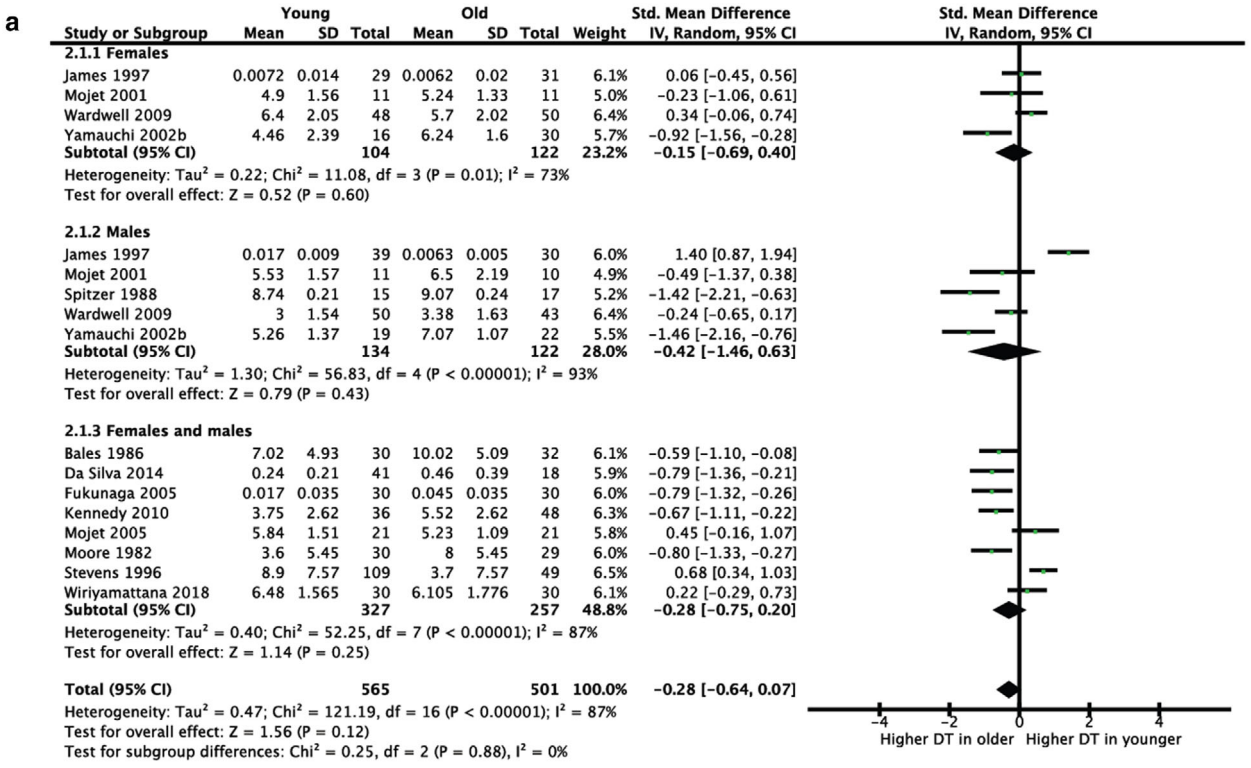

FIGURE 2 Forest plot of studies investigating the association between age and sucrose taste thresholds. SMD and 95% CI from the random model. (A) DT (B) RT. F: females; IV: inverse variance; M: males; SD: standard deviation. *Comparisons between higher versus lower. >18 years old noninstitutionalized age group categories were made when more than two study groups were available

into age groups (Yamauchi et al., 2002b). For the DT outcome (Figure 4a), 449 participants from two different studies were included in the meta-analysis. The study reporting single data found a significantly higher DT in 21- to 40-year-old women smokers (Pepino & Mennella, 2007), whereas DT differences between smokers and nonsmokers increased in parallel with age among the age subgroups (Yamauchi et al., 2002b). Nevertheless, no

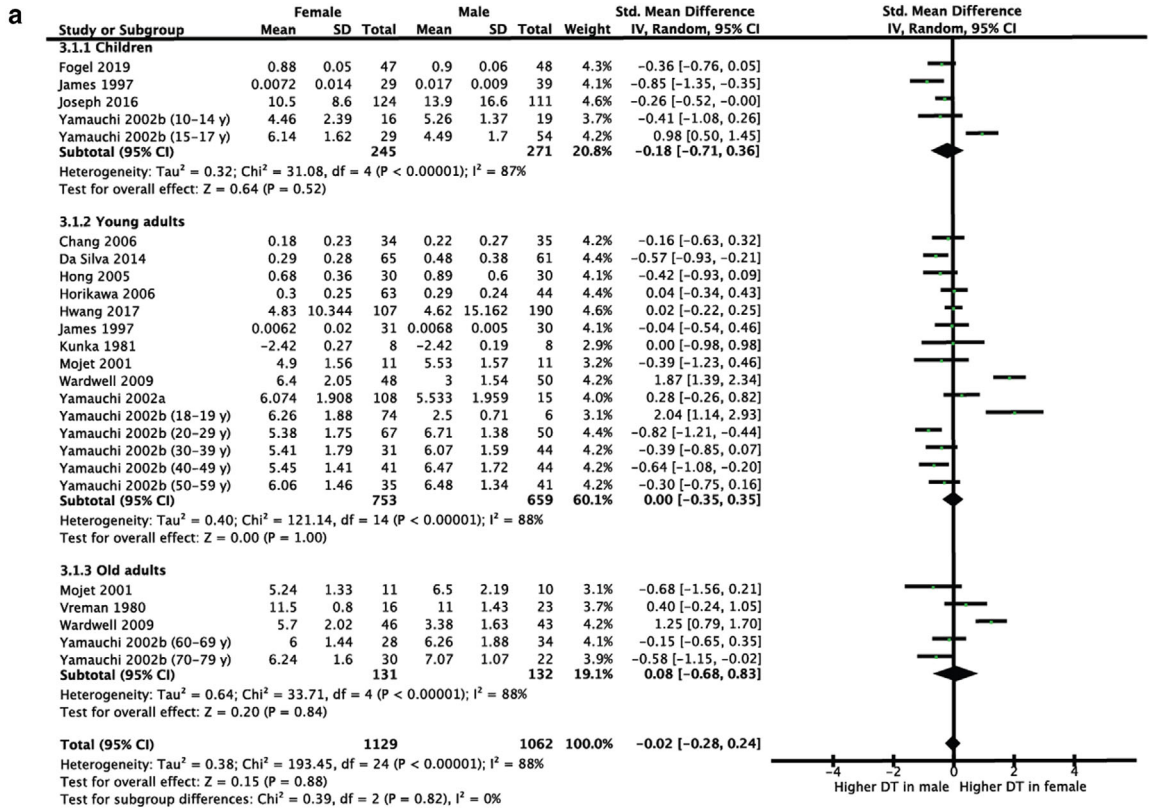

FIGURE 3 Forest plot of studies investigating the association between sex and sucrose taste thresholds. SMD and 95% CI from the random model. (A) DT and (B) RT. IV: inverse variance; SD: standard deviation; y: years old

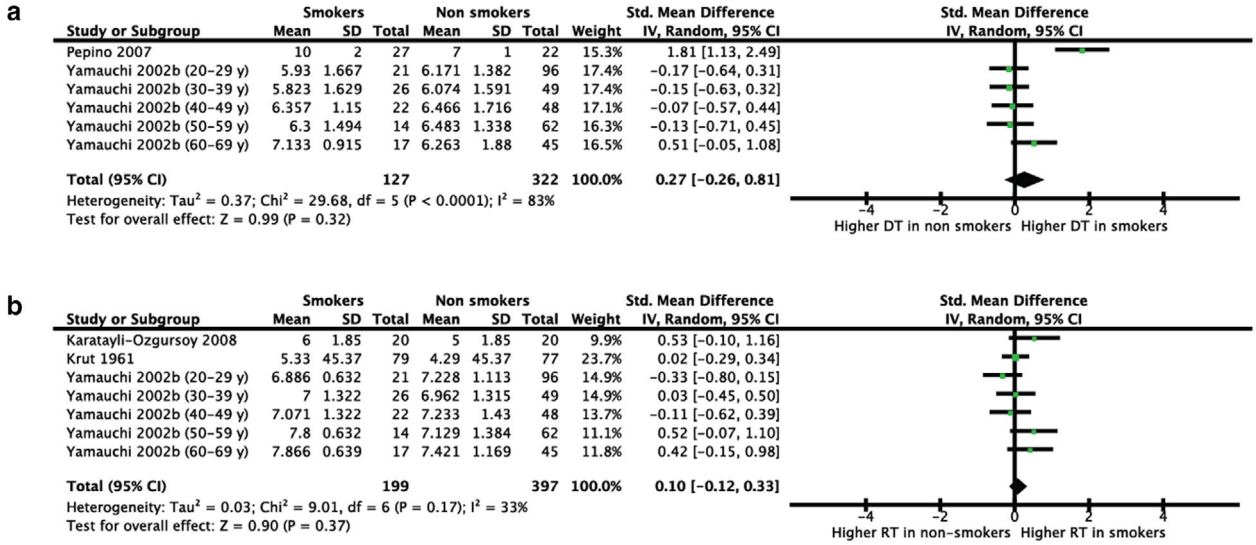

FIGURE 4 Forest plot of studies investigating the association between smoking and sucrose taste thresholds. SMD and 95% CI from random model. (A) DT and (B) RT. IV: inverse variance; SD: standard deviation; y: years old

significant differences were observed in the global result. The RT meta-analysis (Figure 4b) included three studies involving 596 participants (Karatayli-Ozgursoy, Ozgursoy, Muz, Kesici, & Akiner, 2009; Krut, Perrin, & Bronte-Stewart, 1961; Yamauchi et al., 2002b), and similarly, no significant differences were observed between groups.

3.3.4 | Alcohol intake

A meta-analysis could not be carried out as only one study reporting chemically assessed thresholds in alcohol drinkers and nondrinkers was found. Furthermore, no significant differences between groups were reported (Than et al., 1994).

3.3.5 | BMI

Nine studies involving 343 participants were included in this meta-analysis. The BMI was used as an indicator of the degree of obesity. Although waist circumference and the waist-to-height ratio are better predictors of obesity (Bosello, Donataccio, & Cuzzolaro, 2016), the BMI was more extensively determined. Participants of the articles included were candidates for bariatric surgery, patients with metabolic syndrome, or were even described as obese in the original article.

Regarding the DT (Figure 5a), subgroup analyses were defined according to weight loss after nonsurgical intervention (Umabiki et al., 2010), bariatric surgery (Abdeen, Miras, Alqhatani, & le Roux, 2018; Bueter et al., 2011; Nance, Eagon, Klein, & Pepino, 2017; Nishihara et al., 2019; Pepino et al., 2014), or by two parallel comparison groups (Bueter et al., 2011). In the studies in which the variable studied was weight loss, the participants constituted their own comparative group. Two studies revealed a significantly higher threshold in subjects with a higher BMI (Umabiki et al., 2010), whereas the remaining studies did not report any significant differences. Nonetheless, the overall outcome was that the sucrose DT increased with the BMI (SMD: 0.58; 95% CI, 0.35 to 0.82; I^2: 0%; Tau^2: 0.00). Indeed, the true size effect in about 95% of the population is predicted to range from 0.30 to 0.86 and thus remains significant (Supporting Information Table S8).

Although two studies described a significantly higher RT in subjects with a lower BMI (Hardikar, Höchenberger, Villringer, & Ohla, 2017; Pasquet, Frelut, Simmen, Hladik, & Monneuse, 2007) and one did not observe any significant difference (Green, Jacobson, Haase, & Murphy, 2015), the total effect indicated no significant differences in sucrose RT among BMI groups (Figure 5b).

3.3.6 | T2DM

The outcomes of the four studies, including 263 participants, allowed comparison of sucrose RT (Figure 6). Although only one (De Carli et al., 2018) of the four studies (De Carli et al., 2018; Dye & Koziatek, 1981; Wasalathanthri et al., 2014; Yazla et al., 2018) reported a significant difference between groups, the global effect showed that patients with T2DM have a significantly higher RT than nondiabetic subjects (SMD 0.30; 95% CI, 0.06 to 0.55; I^2: 0%; Tau^2: 0.00). However, the prediction interval is expected not to be significant in about 95% of the whole population (Supporting Information Table S8).

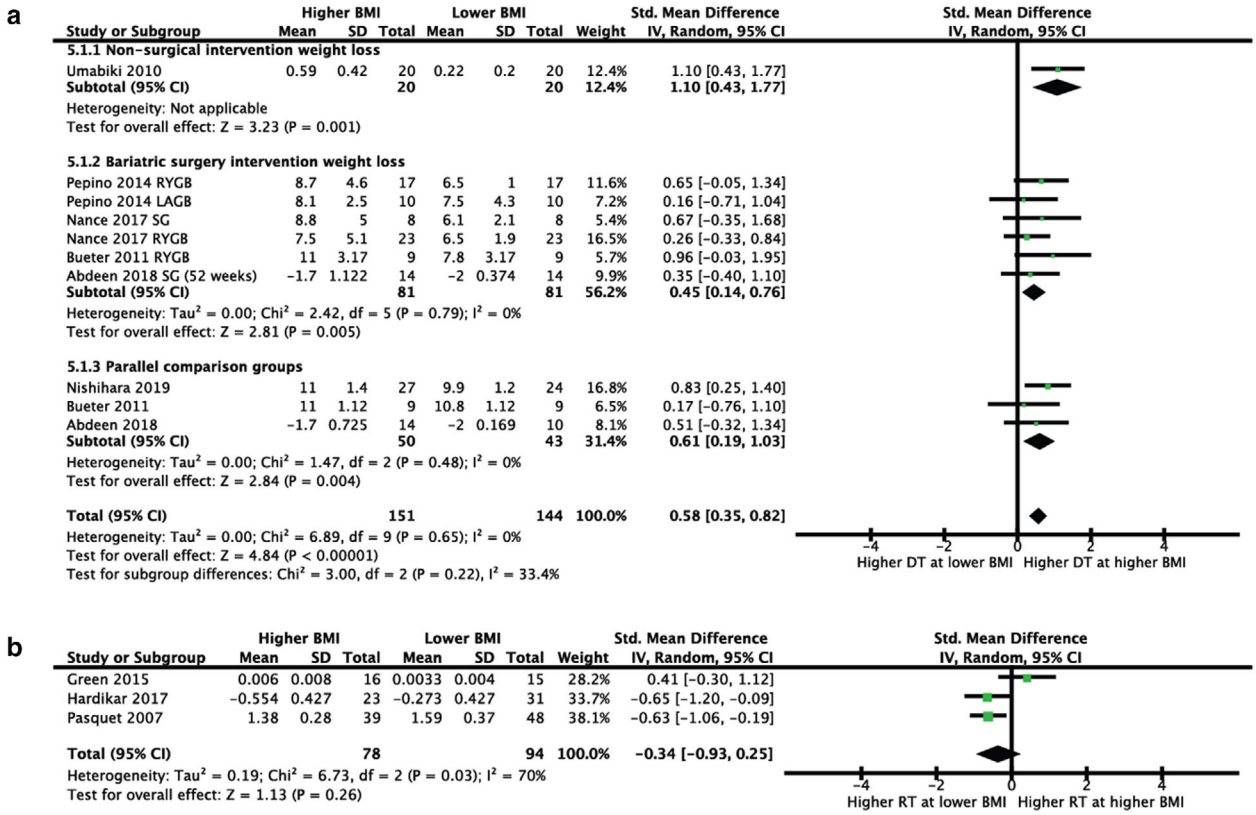

FIGURE 5 Forest plot of studies investigating the association between BMI and sucrose taste thresholds. SMD and 95% CI from random model. (A) DT and (B) RT. IV: inverse variance; LAGB: laparoscopic adjustable gastric band; RYGB: Roux-en-Y gastric bypass; SD: standard deviation; SG: sleeve gastrectomy

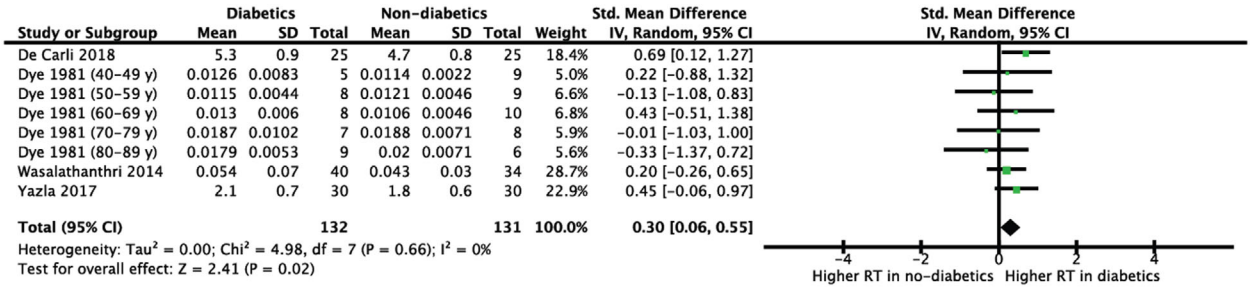

FIGURE 6 Forest plot of studies investigating the association between type II diabetes mellitus and sucrose taste RT. SMD and 95% CI from the random model. IV: inverse variance; SD: standard deviation; y: years old

3.4 | Study quality and overall strength of evidence

According to the DB scoring system, the quality of the individual studies ranged from 11 to 22 points out of a total possible score of 22. Many studies failed to blind the persons measuring the main outcomes and did not describe the staff, places, and facilities where the patients were treated. Information about a sample size calculation was also missing in most of the studies included. Additionally, taste-testing studies are at risk of bias due to nonrandom subject selection and the inability to blind researchers and participants to the purpose of the study.

The risk of detection bias was high due to the characteristics of the sensory studies, in which the investigator usually knows the concentrations of the stimuli tested. On the contrary, attrition and reporting biases were low, whereas a few articles were judged to be highly biased in terms of selection, performance, and other aspects. Figures showing the risk of bias according to the Cochrane scale are provided in Supporting Information Figures S1 and S2.

Few studies including tobacco smoking, alcohol consumption, and T2DM outcomes were identified. Due to the low number of studies quantified in some analyses, high or moderate heterogeneity was observed in most of the meta-analyses performed. The risk of bias or indirectness was not detected. Thus, according to the GRADE scale, the evidence available for the association between the modifiable and nonmodifiable factors and the sucrose thresholds is of low certainty.

4 | DISCUSSION

4.1 | Principal findings

Sweet taste thresholds are a measure related to the first contact of high-energy nutrients with the subject's metabolism, and their assessment may be important within nutritional and general health settings. Our findings indicating that older people have a higher sucrose RT are in line with a previous meta-analysis that addressed the effect of age on thresholds of five tastes (Methven, Allen, Withers, & Gosney, 2012). Some determinants hypothesized to explain taste loss in the elderly are internal factors, such as a diminishing number of taste buds, shorter lifespan of sensorial cells, and lower hyposalivation flow rate, or external factors, such as smoking, pharmaceutical or denture use, dietary habits, and difficulties in maintaining oral health (Sergi, Bano, Pizzato, Veronese, & Manzato, 2017; Wiriyawattana et al., 2018).

The effect of age on taste has also been investigated in animal models. The mRNA expression of the bitter taste 2 receptor 105 (T2R105) and gustducin significantly decreased with aging in mice, although other molecules tested for other tastes did not show significant changes in expression (Narukawa, Kamiyoshihara, Kawae, Kohta, & Misaka, 2018). This situation may be relevant when multiple taste stimuli are presented together, with the expression of a TR being important in taste–taste interactions (Keast & Breslin, 2003; Mojet, Heidema, & Christ-Hazelhof, 2004). In addition, no significant differences in the turnover rates of taste bud cells were observed between older versus younger experimental groups (Narukawa et al., 2018). Similarly, the number of taste buds, in old and young monkeys, has been reported as not being significantly different (Bradley, Stedman, & Mistretta, 1985). These experimental results suggest that the changes in taste thresholds due to aging are caused by factors other than degenerative changes in lingual taste buds, such as aging-related changes in serum components or alterations in neural mechanisms (Bradley et al., 1985; Narukawa et al., 2018).

Anatomical differences of the gustatory system between sexes have also been found, with women having more fungiform papillae and more taste buds than men (Chang et al., 2006; Hong et al., 2005; Hwang et al., 2018). Notably, in a previous article, estrogens seemed to reduce the attraction of sucrose for rats, but only at low concentrations (Curtis, Stratford, & Contreras, 2005). In addition, brain responses to sweet stimuli do not differ under low (ovariectomized animals), moderate (diestrous), or high estrogen (pregnancy animals) circulating conditions, suggesting that female sex hormones have organized but not activated sweet gustatory processing (Di Lorenzo & Monroe, 1989). On the other hand, lower thresholds have been observed among women in the preovulation phase of the menstrual cycle (Than et al., 1994) and the effects of hormonal changes during menopause such as mucosal dryness, a burning sensation, and taste disorders have also been described (Kalantari et al., 2017). However, the sex factor is not associated with differences in sucrose taste thresholds. This result is in agreement with a recent mini-review by Martin and Sollars (2017). More studies assessing the effect of menstrual cycle on sweet taste thresholds are required to understand the implications of female sex hormones in sensory perception.

The effect of tobacco consumption on taste threshold changes has been studied, and it has been reported that there smoking may have a slight influence (Da Ré et al., 2018). It is thought that nicotine may alter the perception of quinine hydrochloride, a molecule commonly used as a bitter tastant (Krut et al., 1961), indicating that bitter taste is the taste type most likely affected (Chéruel, Jarlier, & Sancho-Garnier, 2017). A lower sensitivity in smokers might be due to poorer oral hygiene with a concomitant increased risk of periodontal diseases and whole mouth complaints (Taybos, 2003). Other nicotine-associated mechanisms have been described, such as the inhibition of neurons in the nucleus of the salivary tract and alterations in serotonin and consequent modulation of cellular responses of TRs. However, one study concluded that a higher sucrose DT in smokers is related to the smoking dose in packs per year rather than acute exposure to nicotine. Accordingly, the greater the dose, the lower is the sucrose sensitivity. Moreover, this study demonstrated that the cigarette dose in pack-years was the variable that best predicts the sucrose threshold in current smokers, more than the current age or the age at which regular smoking began (Pepino & Mennella, 2007). Nevertheless, our results suggest that sucrose thresholds do not differ between tobacco smokers and nonsmokers. Nevertheless, further investigation is needed, due to the lack of evidence. In fact, the study reporting significant results showed a higher score in the quality assessment, using the most

robust taste test method and a more homogeneous sample (Pepino & Mennella, 2007).

Interestingly, it has been suggested that taste is the primary signal for ethanol detection in a beverage (Mattes & DiMeglio, 2001). It is of note that sugar alcohols elicit sweet taste through T1R2/T1R3 activation (Feeney, O'Brien, Scannell, Markey, & Gibney, 2011). Consequently, a strong relation between alcohol beverages and the threshold index for sweet taste has been described (Silva et al., 2016).

Zinc is a component of gustin, a protein present only in the parotid saliva in humans (Silva et al., 2016). One underlying explanation for lower sweet sensitivity may be zinc deficiency caused by the excessive consumption of alcohol and subsequent atrophy of the taste buds, which leads to dysgeusia, glossodynia, and hypogeusia (Cerchiari et al., 2006). Moreover, a deterioration in taste discernment has been described in drinkers in comparison with nondrinkers, using different methods, such as EGM and chemical taste responses (Lelièvre, Le Floch, Perlemuter, & Peynègre, 1989). Different protein salivary concentrations have also been proposed as a contributor factor (Silva et al., 2016).

No statistical differences were reported with alcohol intake and sucrose RT in the study included, but other studies have described that the consumption of alcohol over a long period might negatively affect the perception of sweetness (Silva et al., 2016). Indeed, Silva et al. (2016) concluded that alcohol intake may lead to increased consumption of sweetened substances, thereby affecting the nutritional status and even contributing to thiamine deficiency and T2DM. A sensory preference for sweet taste has also been linked to alcoholism and is considered as a risk factor (Mennella, Pepino, Lehmann-Castor, & Yourshaw, 2010; Silva et al., 2016). These discrepancies between studies might be due to the lack of connection between absolute taste thresholds (DT/RT) and sensory perception up to the suprathreshold concentrations of alcoholic beverages. More research is needed about the relationship between DT/RT and alcohol consumption, in order to obtain conclusive results.

Several studies have evaluated the effect of weight, BMI, body fat mass, or obesity status on sucrose taste thresholds (Abdeen et al., 2018; Bueter et al., 2011; Nance et al., 2017; Pepino et al., 2014; Umabiki et al., 2010), including subjects with diseases such as anorexia and bulimia (Eiber et al., 2002). Studies on waist circumference, a strong predictor of obesity, and taste sensitivity have also been performed (Ileri-Gurel, Pehlivanoglu, & Dogan, 2013; Low, Lacy, McBride, & Keast, 2016, 2017). In fact, maltodextrin DT was not significantly correlated to BMI, whereas participants who were more sensitive to complex carbohydrates had a higher waist circumference (Low et al., 2017). Other studies did not find any association between sweet taste function and waist circumference (Low et al., 2016) or the waist-to-hip ratio (Ileri-Gurel et al., 2013). A recent study found an inverse association between taste intensity perception and body weight, as well as waist circumference, BMI, and obesity (Coltell et al., 2019).

Along the same line, impairment of taste sensation has been described in patients with T2DM, especially in relation to sweetness (Wasalathanthri et al., 2014). Higher taste thresholds have been associated with hyperglycemia (Bustos-Saldaña et al., 2009), with a significant correlation between the sweet taste threshold and the blood glucose concentrations, suggesting diminished sweet taste response in patients with T2DM (Gondivkar, Indurkar, Degwekar, & Bhowate, 2009). However, although a direct relationship has been reported between blood glucose levels and sweet taste thresholds, other older studies concluded the contrary (Chochinov, Ullyot, & Moorhouse, 1972; Perros, MacFarlane, Counsell, & Frier, 1996). In the euglycemia state, T1R2 expression in humans increased in both healthy and diabetic subjects after intraduodenal glucose infusion, whereas during hyperglycemia, lower T1R2 expression was observed in healthy controls, and in diabetics there were no variations (Young et al., 2009). More recently, one study performed in 2020 reported significant differences in the ability to recognize sweet taste between T2DM patients and healthy controls, independently of their sex, glycemic control, and time since diagnosis (Pugnaloni et al., 2020).

The results of this meta-analysis show that a higher BMI and T2DM are linked with a higher sucrose DT and RT, respectively. On the other hand, differences in sucrose RT between subjects with higher and lower BMI are not conclusive, possibly because of the low number of studies and their heterogeneity.

Feasible mechanisms underlying changes in the sucrose DT include the modulation of incretin secretion with anorexigenic and glucose-regulatory effects triggered by T1R2/T1R3 or a reduction in taste bud abundance, among others (Kaufman, Choo, Koh, & Dando, 2018; K. R. Smith et al., 2016). The T1R2/T1R3, which mediate sweet taste sensing in the tongue, are also expressed in the gut, pancreas, and adipose tissue, suggesting a physiological contribution to whole body nutrient sensing and metabolism (Smith et al., 2016). In the digestive tube, sugars act through α-gustducin on the T1R2/T1R3 of neuroendocrine K cells, which release glucagon-like peptides (GLP-1 and GLP-2) and the peptide tyrosine–tyrosine. They also act on L cells that release glucose-dependent insulinotropic polypeptide (Jang et al., 2007; Raka, Farr, Kelly, Stoianov, & Adeli, 2019), thereby regulating energy homeostasis. Notably, sucralose can also induce GLP-1 secretion (Margolskee et al., 2007), and together with saccharin and

stevia it can modify the microbiota of consumers (Ruiz-Ojeda, Plaza-Díaz, Sáez-Lara, & Gil, 2019), with these events being involved in obesity and T2DM (Górowska-Kowolik & Chobot, 2019). It should be noted that the regulation of the gut–brain neuroendocrine axis involves other molecules and receptors besides the activation of T1R2/T1R3. Indeed, satiety induced by protein intake could be a main contributor to weight maintenance due to the release of satiety hormones such as peptide tyrosine–tyrosine, cholecystokinin, and GLP-1 (Raka et al., 2019).

In addition, chronic low-grade inflammatory response associated with obesity was found to reduce the density of taste buds in gustatory tissues of mice (Kaufman et al., 2018), explaining taste dysfunction in obese populations. The results of a longitudinal human study demonstrated that human fungiform papillae, the structures housing taste buds, decrease in abundance with increasing adiposity (Kaufman, Kim, Noel, & Dando, 2020).

Another plausible mechanism described for a reduction in taste sensitivity in obesity has been the influence of diet-induced obesity on the reduction of responsiveness to sweet taste stimuli in the peripheral taste cells, and thus, changes in the central taste system (Maliphol, Garth, & Medler, 2013). Glucose sensors are present in the brain, and T1Rs expression is regulated by nutritional status (Calvo & Egan, 2015). In comparison, the levels of T1Rs expression in hypothalamus neurons of obese mice were lower than those in lean mice (Laubach, Pierce, Shuler, & Hopkins, 2009), whereas nutrient deprivation has been linked to increased T2Rs expression (Calvo & Egan, 2015).

Glucose absorption also seems to be controlled by gastrointestinal nutrient-sensing mechanisms involving the Na^+/glucose cotransporter-1 (SGLT1) and the glucose transporter 2 (GLUT2), which are the two main mediators of dietary glucose absorption at the apical membrane of enterocytes (Gorboulev et al., 2012). SGLT1 expression has been shown to be regulated by intestinal expression of T1R2/T1R3 in response to glucose delivery (Shirazi-Beechey, Daly, Al-Rammahi, Moran, & Bravo, 2014). When glucose is sensed by intestinal T1R2/T1R3, GLP-2 is secreted from L cells to mediate increased SGLT1 expression in adjacent enterocytes (Sangild et al., 2006; Shirazi-Beechey et al., 2014; Tsai, Hill, Asa, Brubaker, & Drucker, 1997). GLUT2 is also upregulated in the presence of luminal sugars or sweeteners, but not in knockout mice lacking T1R3 and α-gustducin (Mace, Affleck, Patel, & Kellett, 2007; Margolskee et al., 2007). Thus, gastrointestinal sweet sensing seems to be a critical regulator of SGLT1 and GLUT2 expression and glucose uptake (Mace et al., 2007; Margolskee, 2007; Raka et al., 2019).

Leptin, another molecule involved in satiety, seems to be related to threshold differences between normal versus overweight subjects. Leptin levels significantly decrease after weight loss in obese females, and may be associated with decreasing sweet taste thresholds (Umabiki et al., 2010). It has been shown that leptin receptors in taste cells respond to systemic leptin, causing a decrease in responsiveness to sweet stimuli without affecting responses to sour, salty, and bitter substances. This suggests that post-ingestion hormone release is capable of regulating the peripheral gustatory apparatus by modulating the responsiveness of sweet stimuli (Depoortere, 2014). Receptors of adiponectin, a metabolic hormone that mediates insulin sensitivity, adipocyte development, and fatty acid oxidation, have also been found to be expressed in T1Rs, suggesting that adiponectin signaling could also impact sweet signaling (Crosson et al., 2019).

4.2 | Strengths and limitations

The general search term criterion used constitutes one of the strengths of the present study, as it allowed the identification of a large number of relevant papers and minimized the exclusion of potentially eligible studies. The manual search for papers based on the bibliography of reviews and articles further reduced the possibility of missing studies. However, studies with significant data but with a main goal other than sweet taste threshold evaluation or in which the abstract did not refer to threshold assessment may have been omitted.

Chemical taste response was the only sucrose threshold assessment method considered. Although EGM is especially suitable for testing the integrity of the whole taste sensory chain, including ionotropic transduction mechanisms, it excludes metabotropic transduction mechanisms that rely on sweet, bitter, or umami taste (Chaudhari & Roper, 2010). Additionally, the characteristics of the taste agent aqueous matrix (e.g., viscosity or mineral content), as well as the amount of stimulus solution and the time between solution administration, together with other factors, differ among studies and may bias the outcome of threshold assessment (Gonázlez Viñas, Salvador, & Martin-Alvarez, 1998; Murphy, Cardello, & Brand, 1981; Stone & Oliver, 1966; Whelton, Dietrich, Burlingame, Schechs, & Duncan, 2007). Although standardized methods for chemical taste threshold assessment are available (e.g., British Standard ISO), their use is limited to a few studies. Despite the wide variety of assessing methods, SMDs were used to standardize the results of the studies into a uniform scale before meta-analysis. However, methodological differences may have a direct impact on the individual results.

One of the influencing factors analyzed was diabetes, but only studies on T2DM were included, thereby

excluding the possible effects of type 1 diabetes mellitus on sweet taste thresholds. Regarding the effect of age, the groups were not identical among studies, which may have influenced the results. In addition, the study by taste sensory analysis in any pathological condition has a higher potential bias related to the difference in the duration, control, and treatment of the pathology among the study samples of the studies meta-analyzed.

Moreover, as the scope of this work was limited to physiopathological conditions related to the field of nutrition, other reported modifiers of the sweet taste threshold, such as nonnutritional-related pathologies, were not considered.

Threshold values were used because they allow comparability among studies. Nevertheless, as thresholds do not provide information about sensory perception across the full dynamic range of sensation, it has been argued that suprathreshold scales provide a more realistic perspective of sensory function (Snyder et al., 2006). Although each sweetener has its own affinity to heterodimer T1R2/T1R3, a strong correlation has already been described between DT/RT and caloric sweeteners across people (Low, McBride, Lacy, & Keast, 2017). Thus, the authors believe that the result of this systematic review and meta-analysis should be the same even with glucose or other caloric sweeteners.

In conclusion, the present study provides significant findings, although the assessment of biases, absence of randomized clinical trials, the small sample size, and heterogeneity may have obscured more consistent relationships between sucrose thresholds and the variables analyzed.

4.3 | Implication for sensory analysis and clinicians

Some authors have reported that DT/RT has limited utility in the prediction of food behavior and hedonic liking, when most of the sweet foods are within the sweetness-intensity perception range (Jayasinghe et al., 2017; Low et al., 2016). Moreover, the use of sucrose concentrations above the threshold cannot reveal a direct relation between DT/RT and sweet taste intensity (Jayasinghe et al., 2017). Thus, the relation between DT/RT and intensity perception in suprathreshold concentrations and sweet dietary intake is still not clearly defined (Hardikar et al., 2017; Tan & Tucker, 2019). However, alimentary patterns and enhanced hedonic liking of sweetness at high concentrations may result in a higher consumption of sweet food (dos Santos, Marreiros, da Silva, de Oliveira, & Cruz, 2017; Duffy, Hayes, Sullivan, & Faghri, 2009). Additionally, a dose-dependent relationship has been described between suprathreshold intensity perception and hedonic liking (Jayasinghe et al., 2017). On the contrary, a recent study reported a significantly negative correlation between sucrose DT and suprathreshold sensitivity, whereas sucrose DT and sweet preference had a weak positive correlation, eliciting hedonic liking (Chamoun et al., 2019). More studies are needed to elucidate evidence in taste sensitivity and food preferences and eating behavior.

It is notable that the decline in taste sensitivity with age occurs to a greater extent with sour, salty, and bitter than with sweet flavors, indicating that sweet taste sensitivity is a robustly preserved function over the lifetime (Yoshinaka et al., 2015). Although the exact mechanisms by which taste sensitivity decreases with age are still unknown, its measurement is a useful tool in personalized nutrition. Knowledge on how to overcome alterations in taste senses could have implications in the health-related quality of life of elderly people and may also be useful in the new food industry. Moreover, the identification of sensory loss is important as a predictive factor for neurodegenerative diseases (e.g., Parkinson's and Alzheimer's disease) and other conditions (Da Silva et al., 2014).

Early studies suggested that the frequency of phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP) tasters is higher in females than in males (Martin & Sollars, 2017; Prutkin et al., 2000) and among nonsmokers (Ye et al., 2011). As the PTC/PROP tasting mechanism has been linked to sweet liking (Kaczor-Urbanowicz et al., 2017; Yeomans, Tepper, Rietzschel, & Prescott, 2007), unequal distribution of this taste phenotype could be a potential explanation (Gondivkar et al., 2009) for different sweet-eating behaviors. Indeed, these differences between sexes could explain different dietary habits, as well as smoking behavior and alcohol consumption (Chang et al., 2006; Hong et al., 2005).

This meta-analysis demonstrates that a decrease in BMI after bariatric surgery or a behavioral intervention is associated with a reduction in sucrose DT. This result brings to light the idea that intraindividual changes in DT/RT during weight loss can be a potential consideration in the monitoring of obesity treatment. In addition, T2DM increases the sucrose RT, and this effect seems to increase among uncontrolled diabetic patients (Gondivkar et al., 2009; Yazla et al., 2018). To sum up, sucrose threshold measurement and its changes might be a marker of the severity of obesity and T2DM, independent of their influence or not in hedonic liking or dietary patterns, and a useful tool in personalized nutrition in the treatment of these disorders. However, to prove causality, prospective controlled studies need to be performed.

Although environmental factors have an influential role in sweet thresholds, T1R genes present multiple polymorphisms, which are thought to be associated with variations

in sweet taste perception (Kim et al., 2006; Tarragon & Moreno, 2018). Indeed, T1R2 is within the top 5% to 10% of all human genes with regard to the reported number of polymorphisms (Kim et al., 2006), and geographical and evolutionary differences in the distribution of genetic variants such as single-nucleotide polymorphism have been established (Yamauchi et al., 2002b). For example, T1R3 gene promoters rs307355 and rs3574481 explain about 16% of the variability in taste sensitivity and have different frequencies according to the population and geographical location (Fushan, Simons, Slack, Manichaikul, & Drayna, 2009).

5 | CONCLUSIONS

Chemosensory perception is not a static measurement due to environmental, physiological, and genetic factors. Indeed, our results suggest that aging and T2DM are factors that significantly increase the sucrose RT, whereas only subjects with a higher BMI have a higher DT. Sex and smoking showed no effect, whereas the effects of alcohol consumption or even alcohol abuse are still unknown.

Because TR may be involved in the release of orexigenic/anorexigenic and energy-metabolism-modulator molecules, further studies are required to relate sucrose thresholds with the levels of the hormones involved in energy homeostasis. Knowledge as to how the sweet DT and RT are affected by physiological and pathophysiological factors may be of interest when analyzing their roles in the pathogenesis of high prevalence pathologies such as obesity and T2DM, as has been recently reported with T2Rs (Tarragon & Moreno, 2020).

Although more research is needed, these results imply the appearance of a new way of optimizing the clinical practice of nutritionists and understanding the complexity of dietary practice and human beings.

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AUTHOR CONTRIBUTIONS

J. J. Moreno designed the study. M. Trius-Soler and D. A. Santillán-Alarcón collected data, performed statistical analysis, interpreted results, and drafted the manuscript. J. J. Moreno, M. Martínez-Huélamo, and R. M. Lamuela-Raventós interpreted the study results and performed the writing–review of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflict of interest in relation to this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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