REVIEW

The Influence of Common Noncommunicable Diseases on Chemosensory Perception and Clinical Implications in Children and Adolescents

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ABSTRACT

An increased incidence of noninfectious chronic diseases, such as obesity, diabetes, and allergies, has been noted in the last century, especially in the last 2 to 3 generations. Evidence suggested that the interrelation among these chronic conditions in pediatric age (e.g., children and adolescents aged 4–16 y) is complex and still unknown, reinforcing the interest of pediatricians in these diseases. Of interest is the need to better understand the link between these pathologies and sensory perception, since the chemical senses of taste and smell, together with chemesthesis, are reported to have a role in food choices and may provide a novel target for intervention in the treatment of these pathologies. This review aims to explore the current evidence on the link between these chronic conditions and chemosensory perception (i.e., taste and smell). In addition, the putative role that chemosensory perception may have on food choices and eating behavior of children and adolescents affected by these diseases are highlighted. Furthermore, the review addresses the unexplored issues that need to be investigated in this area. The literature data search suggested that no clear relation between taste and smell perception and the aforementioned diseases in young population yet exists. However, some possible trends have been highlighted in the adult population, in whom the duration of disease might have affected the relation. There is a need for further, high-quality, hypothesis-led research, with robust measures of taste and smell functions as the primary outcomes, to strengthen or deny this evidence. *Adv Nutr* 2022;13:234–247.

Statement of Significance: The recent increase in noninfectious chronic diseases in pediatric population has reinforced the interest in research on these pathologies. One of the hotspots is the need to better understand the link between sensory perception, nutrition, and health status. In this review, we highlight the paucity of data and the urgent need for knowledge about this topic in children and summarize current data on the link between these chronic conditions and chemosensory perception (i.e., taste and smell). We also discuss the putative role that chemosensory perception may have on food choices and eating behavior of children and adolescents affected by obesity, diabetes, and allergies.

Keywords: taste, odor, eating behavior, obesity, diabetes, allergies

Introduction

An increased incidence of noninfectious diseases known as "civilization diseases" or "noncommunicable diseases" has been noted in the last century, especially in the last 2 to 3 generations (1). Moreover, obesity and diabetes among children have increased in recent decades. No indication of a stable and persistent decline in obesity prevalence has been noted, even though it has reached a plateau in recent years (2, 3). In addition, the prevalence of food allergies, the so-called second-wave allergy epidemic, has also risen in westernized countries in recent decades (4). Asthma and food allergy seem to be closely linked, and food allergy is a potential risk factor for asthma development and is associated with increased morbidity/mortality among children and adults who have both these conditions (5, 6).

Furthermore, an association between asthma and diabetes has recently been described in children (7), as well as a relation between overweight/obesity and asthma (8) and between overweight and food allergy (9). These data point to the existence of a complex interrelation among these chronic conditions, although knowledge of which is far from being understood. Of interest is the need to

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better understand the link between these pathologies and chemosensory perception, because the chemical senses of taste and smell, together with chemesthesis, are reported to have a role in food choices and may provide a novel target for intervention in the treatment of these pathologies. Thus, the NIH held the "Sensory Nutrition and Disease" Workshop (10) in November 2019 to explore and better understand the potential of sensory perception in influencing food preferences, intake, nutrition, and health. Such knowledge can be used to mitigate the risk of chronic disease and help develop interventions that promote healthier diets.

Sensory systems, particularly smell and taste, play a role in the sensory effects on appetite (11, 12), choice (13, 14), and intake (15, 16). The perception of food odors has a pre-consumption role, helping individuals in locating food sources and anticipating the content of foods that are to be eaten. Moreover, several studies have demonstrated that food odors could induce both general and specific appetite in anticipation of food consumption in adults (12, 16–19).

Among the food cues that could influence children's eating behavior, food odors are of particular interest, because olfaction is implicated in triggering emotions and memories, with an impact on defining early food-choice behavior. Orthonasal smell is involved in the anticipation of eating and retronasal smell during consumption, while the taste system comes into play while food is ingested.

Aside from contributing to the overall meal enjoyment, the taste system is responsible for regulating taste perception and aids individuals in evaluating the nutrient content of foods and in discriminating between those that are safe or poisonous (20, 21). Five taste modalities are perceived in humans: sweet, umami, salty, bitter, and sour. Moreover, it has been recently proposed that additional stimuli (i.e., fatty and metallic) may also be considered basic tastes (22). From birth, people are predisposed to crave sweet and salty tastes and to reject bitter foods, given that each taste modality is linked to different nutritional or physiological requirements (i.e., detecting calories, amino acids, and electrolytes) or indicates a potential dietary risk (22).

Some pathologies, such as the ones presented in this review, could affect the sensory systems and be among the causes of sensory impairment. Recent insights from animal models and humans suggest mechanisms for the taste dysfunction observed in patients with obesity or diabetes, as discussed more thoroughly in the following section. Consequently, taste or smell disturbances have been suggested to pose risks on multiple levels, and these dysfunctions can be frustrating, debilitating, and have an influence on enjoyment and interest in food, dietary habits, and quality of life (23). A diminished chemosensory perception makes it harder for people to appreciate and enjoy eating, causing them to avoid many foods, or may lead them to consume more to offset this impaired stimulation (24), setting the stage for generating a vicious circle in the illness state.

Considering the lack of comprehensive literature on taste and smell perception at various clinical settings in children affected by noncommunicable diseases, PubMed, Medline, and Web of Science were searched from inception until January 2021 for relevant studies. The literature search included the following terms (with synonyms and closely related words): children, adolescents, obesity, diabetes mellitus, allergies, asthma, rhinitis, taste, gustatory, smell, olfactory, and olfaction. Searches were not restricted by study design. Further studies were identified by examining the reference lists of all included articles and using the expertise of the review team. This review deals with articles on these issues in children and adolescents, but a summary of the studies involving the adult population is also included.

This review aims to summarize the current knowledge of the link between these chronic conditions and chemosensory perception (i.e., taste and smell). In addition, the putative role that chemosensory perception may have on food choices and eating behavior of children and adolescents affected by these diseases, which can exert the pathological condition in these subjects, was highlighted. A brief overview of research on future perspectives for experimenters interested in this area was also included.

Current Status of Knowledge

Obesity

A dramatic increase in the amount of scientific literature on childhood obesity, exploring different aspects of this emerging disease, has recently been noticed. The pathophysiology of obesity is extremely complex and partially unknown. Weight gain is caused by elevated energy intake due to disproportionate diet composition (i.e., high in calories, fat, and sugars) and decreased physical activity and sedentarism. Moreover, genetic, biological, environmental, and behavioral factors could closely interact with each other and influence the pathogenesis of weight excess (25).

Chemosensory perception in obesity

The evidence of a link between taste perception and the development and persistence of obesity is currently unclear. Various psychophysical studies reported that adults with obesity have an altered taste/orosensory system (26–30). Some recent studies performed in animal models and in adults with obesity (31–34) reported that obesity causes a strong disruption in the homeostasis of taste buds, decreasing the number of circumvallate taste buds and fungiform papillae. Moreover, these differences in chemosensory perception have been linked to a reduction in expression of various taste cell markers in favor of several inflammatory markers, alongside a downregulation in the transcription

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Abbreviations used: CME, cow-milk exclusion diet; PROP, 6-n-propylthiuracil; T1D, type 1 diabetes; T2D, type 2 diabetes; T1R3, taste receptor type 1 member 3.

of classical taste markers responsible for regulating several taste sensations in obesity [e.g., taste receptor type 1 member 3 (T1R3) and cluster of differentiation 36 (CD36) that are linked to sweet/umami and fat detection, respectively] (34).

However, evidence is lacking in children and adolescents with obesity and taste perception in this target group has mostly been evaluated through the bitter responsiveness to the 6-n-propylthiouracil (PROP) compound, considered a general marker of taste sensitivity.

This review identified 23 psychophysical studies (**Tables 1** and **2**), which investigated whether differences in taste acuity or sensitivity for the 5 basic tastes, fat stimulus, and PROP exist among children and adolescents characterized by different nutritional statuses.

The ability of humans to taste bitter compounds varies widely among individuals, and the research on the effect of this interindividual variability on children's and adolescents' nutritional status has gained interest over the past 2 decades (35). Most studies (Table 1), which applied different methods to measure PROP responsiveness, did not support the relation between the bitterness perception of this compound and children's and adolescents' BMI (36–45). Some authors reported a relation, although other factors such as gender (46–49), impact of environment or socioeconomic status (50, 51), and ethnicity (52) have been suggested as a potential contributor to such findings. Therefore, further research is necessary to determine how current findings can be generalized. As previously stated, little is currently known about the sensitivity to bitter taste compounds other than PROP in the young population affected by obesity. This relation has been investigated only through the application of the "taste strips" method (53), whereby the filter paper strips are impregnated with 4 different concentrations of quinine hydrochloride. Of the studies reported in Table 2, 2 papers suggested no relation between bitter sensitivity and BMI (41, 54), whereas the other 2 reported a negative relation (55, 56).

Increased bitter sensitivity has been hypothesized for some time to be predictive of food preference and eating behaviors (57). For example, some authors reported that individuals with increased bitter taste sensitivity may avoid antioxidant-rich vegetables or bitter fruits because of their perceived bitterness (35, 58–60). These low-energy foods may be replaced by more energy-dense foods among subjects more sensitive to bitter taste (36, 61). Moreover, high sensitivity to bitter taste may cause food aversion and low-calorie intake (42, 62). Some studies showed that children who are nontasters had lower sucrose preferences than those who are tasters and exhibited some dietary differences (63). In addition, higher responsiveness to PROP was positively associated with food neophobia and negatively with the liking of fruit, vegetables, and fatty and spicy foods (36, 64, 65). However, others reported no such relation (40, 44, 66). The causal pathway between PROP responsiveness, dietary intake, and body weight in children and adolescents has been greatly investigated in the past decades. However, most studies investigated this relation independently, focusing the attention either on PROP responsiveness and dietary intake or on weight status and dietary intake. It is believed that only 2 studies applied a combined approach (45, 47), showing that bitterness sensitivity seems to play a role in the development of dietary patterns and weight differences in children. Although the role of bitterness responsiveness in shaping dietary preferences could be somehow suggestive, the potential interaction between bitterness sensitivity and actual food consumption remains unknown. Further investigations are required to clarify whether bitterness responsiveness alone dictates a meaningful impact and predictive validity on food preferences and food-intake behaviors in children and adolescents with obesity.

Aside from PROP, many studies have looked at taste perception and obesity with a specific emphasis on sweet and salty tastes. In the studies selected for this review, various studies suggested that salt taste acuity (67), sweet or salt sensitivity (38, 68), and perception abilities for both sweet (41, 54) and salt (41, 54, 56) tastes have no association with nutritional status. Few papers reported a negative relation between the ability to recognize sweet (55, 56) or salt (55) taste and BMI (Table 2). On the contrary, Pasquet et al. (69) found that adolescents with obesity present lower recognition thresholds and higher taste sensitivity to sodium chloride and sucrose but not fructose compared with adolescents without obesity.

Genetic variations in salty taste receptors [the epithelial sodium channel (ENaC) and transient receptor potential vanilloid 1 (TRPV1)] or in single nucleotide polymorphism rs9701796 associated with sweet taste receptors have been reported to be associated with different perception of and preference for salt and sweet tastes in children, with influences on related food intake (70–72). However, it is still unclear whether and to what extent changes in thresholds and hedonic responses may be related to food intake.

Sour and umami tastes were not extensively studied in the context of obesity. Sour taste plays a role in food selection and consumption (e.g., various fruits and vegetables), warning against spoiled or unripe foods, whereas umami contributes to a sense of satiety (73). The studies summarized in this review suggested that sour and umami perception seems to not be related to nutritional status (41, 55, 67–69). Few studies reported a lower perception ability in recognizing umami (55) or sour (54, 56) taste in children and adolescents with obesity compared with a normal-weight group. Thus, the potential relation between the perception of these 2 tastes and subsequent influence on food choices in subjects with obesity remains to be explored.

In addition to the study of the perception of the 5 basic tastes, attention has recently been focused on the orosensory perception and sensitivity to fat stimulus, because the consumption of palatable, high-fat foods has been associated with increased obesity risk (74). A common explored hypothesis is that individuals with higher BMI present low sensitivity to the palatable fatty texture (mouthfeel) and fatty acids (taste) and therefore need greater concentration to detect fatty stimuli, leading to excessive consumption of

TABLE 1 Relations between taste responsiveness to PROP and children's and adolescents' nutritional status[1]

Study	Cohort sample size	PROP status and body-weight groups	Methods	Main outcomes
Baranowski et al. 2010 (50)	1690 children and adolescents	• 331 non-tasters (NT) 225 underweight/normal-weight and 106 overweight/obese • 786 medium tasters (MT) 531 underweight/normal-weight and 255 overweight/obese • 573 supertasters (ST) 359 underweight/normal-weight and 214 overweight/obese	• Perceived intensity of PROP filter paper; (LMS)	• ST had the largest BMI percentile and *z*-score, but only among the group with highest socioeconomic status
Bell and Tepper 2006 (36)	65 children	• 24 tasters (T) • 41 non-tasters (NT) BMI%-for-age did not vary with taster status	• PROP forced-choice screening	• No relation with BMI
Borazon et al. 2012 (37)	120 adolescents	• 8 non-tasters (NT, mean BMI (kg/m^2): 17.2 ± 3.8) • 71 medium tasters (MT, mean BMI: 21.1 ± 4.8) • 41 supertasters (ST, mean BMI: 22.1 ± 7.7)	• Perceived intensity of PROP solutions; (LMS)	• No relation with BMI
Bouthoorn et al. 2014 (49)	5894 children	• 4564 tasters (T) • 1330 non-tasters (NT) (BMI not reported)	• PROP forced-choice screening	• NT girls had higher BMI *z*-score and body fat than T girls
Burd et al. 2013 (46)	120 children	• 85 tasters (T) 1.2% underweight, 51.8% normal-weight, 23.5% overweight, and 23.5% obese • 35 non-tasters (NT) 2.9% underweight, 57.1% normal-weight, 11.4% overweight, and 28.6% obese	• PROP forced-choice screening	• NT living in unhealthy food environment had higher BMI *z*-score
Feeney et al. 2017 (38)	525 children and adolescents	• 118 overweight • 66 obese • 341 lean • (BMI not reported)	• Perceived intensity of PROP filter paper (gLMS)	• No relation with BMI
Golding et al. 2009 (39)	5294 children	• 25% non-tasters (NT) • 25% medium tasters (MT) • 25% strong tasters • 25% super tasters (ST)	• Perceived intensity of PROP filter paper (VAS)	• No relation with BMI
Goldstein et al. 2007 (40)	65 children	• 20 non-tasters (NT) • 23 medium tasters (MT) • 22 supertasters (ST) 18.5% overweight (≥85th percentile weight/height)	• Perceived intensity of PROP filter paper (LMS)	• No relation with BMI
Herz et al. 2020 (41)	53 adolescents	• 27 overweight/obese (BMI percentile range: 85.6–99.7) • 26 lean (BMI percentile range: 11.1–83.9) 22.6% non-taster, 49.1% taster, and 28.3% supertaster	• Perceived intensity of PROP filter paper (gLMS)	• No relation with BMI
Keller and Tepper 2004 (47)	53 children	• 35 tasters (T) • 18 non-tasters (NT) 22.5% overweight (≥85th percentile weight/height) and 7.5% exceeding the 95th percentile of weight-for-height	• PROP forced-choice screening	• NT boys had higher BMI *z*-score than T boys • T girls had higher BMI *z*-score than NT girls

(*Continued*)

dietary energy and weight gain (75–77). The results of 1 study supported this hypothesis (78), whereas another study reported nonsignificant results (68).

The relation between olfactory perception and obesity is least understood. As reported in the Introduction, olfaction plays an important role in food consumption. However, whether olfactory abilities are related to weight gain and adiposity through direct influences on eating behavior is still unclear. Over the past decade, various studies have attempted to address this hypothesis by exploring olfactory abilities across different weight groups. However, findings have shown major inconsistencies to date (79) and are related almost exclusively to adults (80, 81), but scientific evidence is scarce in the young population. In their meta-analysis, Peng et al. (79) suggested a trend of declining olfactory detection ability with increasing weight. Moreover, an elegant externality theory, originally proposed by Schachter (82), postulated that food external stimuli (e.g., sight, smell, and taste) have a different influence on attitude toward foods in lean subjects and those with a higher BMI (83). In particular, the latter presents lower responsiveness to internal stimuli (e.g., hunger and satiation signals) and a higher susceptibility to external stimuli, leading them to increase their craving for foods and being prone to overeating (84, 85). In this perspective, cue reactiveness to external food stimuli has been reported to be stronger in obese children than in normal-weight children, showing that their eating behavior is more often triggered by food cues (86, 87). Food odor exposure could likewise be used to promote healthier food choices and consumption in young populations. Indeed, an appetizing and congruent olfactory cue could be promising in promoting better food choices (e.g., fruit vs. cake) (88) or increasing the intake of healthy and low-energy-dense foods, suitable as part of a balanced diet, as recently demonstrated in adults (16).

Because of the paucity of literature data, this review identified only 2 studies that investigated olfactory differences across weight groups of children and adolescents (41, 89). Obrębowski et al. (89) found that odor identification abilities and sensitivity were reduced in a sample of obese boys and girls aged 10–16 y. However, the study had a strong limitation because it involved 30 children and adolescents affected by obesity and their olfactory ability was estimated and compared with normal ranges, found in a previous study (90), without involving a control group of normal-weight children. On the contrary, a greater olfactory sensitivity (i.e., lower detection threshold) was found in adolescents with high BMI percentiles compared with normal-weight peers, as described by Herz et al. (41), applying the Sniffin' Stick method (Burghardt®, Wedel, Germany).

Aside from the olfactory functions measured through psychophysical studies, a cue exposure approach was used by Marty et al. (88) to investigate whether nonattentive food odor exposure may be predictive of food choices in obese children (91). The children ($n = 74$) were presented with 30 pairs of food images (a fatty sweet food picture vs. a fruit picture) and were asked to choose the food they most wanted

TABLE 1 (*Continued*)

Study	Cohort sample size	PROP status and body-weight groups	Methods	Main outcomes
Keller et al. 2010 (48)	72 children	• 52 tasters (T; mean BMI *z*-score: 1.0 ± 0.9) • 20 non-tasters (NT; mean BMI *z*-score: 1.2 ± 1.2)	• PROP forced-choice screening	• NT boys had higher BMI *z*-score than T boys
Keller et al. 2014 (42)	79 children	• 56 tasters (T; mean BMI *z*-score: 1.0 ± 0.9) • 23 non-tasters (NT; mean BMI *z*-score: 1.0 ± 1.2)	• PROP forced-choice screening	• No relation with BMI
Lumeng et al. 2008 (51)	81 children	• 63 tasters (T; mean BMI *z*-score: 0.99 ± 1.2) • 18 non-tasters (NT; mean BMI *z*-score: 0.03 ± 1.1)	• PROP forced-choice screening	• T had higher BMI *z*-score than NT
O'Brien et al. 2013 (43)	483 children	• 113 non-tasters (NT, mean BMI *z*-score: 0.6 ± 1.1) • 203 medium tasters (MT, mean BMI *z*-score: 0.5 ± 1.2) • 87 supertasters (ST, mean BMI *z*-score: 0.6 ± 1.3)	• Perceived intensity of PROP filter paper (gLMS)	• No relation with BMI
Oftedal and Tepper 2013 (44)	73 children	• 18 non-tasters (NT; mean BMI *z*-score: 0.2 ± 0.2) • 39 medium tasters (MT; mean BMI *z*-score: 0.4 ± 0.2) • 16 supertasters (ST; mean BMI *z*-score: 0.1 ± 0.3)	• Perceived intensity of PROP filter paper (LMS)	• No relation with BMI
Stoner et al. 2019 (45)	342 children	• 140 tasters (T; mean BMI *z*-score: 0.34 ± 1.23) 202 non-tasters (NT; mean BMI *z*-score: 0.45 ± 1.1)	• PROP forced-choice screening	• No relation with BMI

[1] LMS Labeled Magnitude Scale; gLMS General Labeled Magnitude Scale; PROP 6-n-propylthiouracil; VAS visual analogue scale.

TABLE 2 Relations between taste perception (measured as thresholds, suprathresholds, or tasting recognition abilities) and children's and adolescents' nutritional status[1]

Authors	Cohort sample size	Body-weight groups	Methods	Outcomes
Alexy et al. 2011 (68)	574 children and adolescents	• 94 overweight • 54 obese • 426 lean (BMI not reported)	• Sensitivity (suprathreshold) to sucrose, NaCl, citric acid, and fat measured using paired-comparison sensitivity tests	• No significant difference in sweet, salt, sour, and fat sensitivity among body-weight groups
Bobowski and Mennella 2015 (67)	97 children and adolescents	• 50 overweight/obese [mean BMI (kg/m^2): 25.0 ± 0.1] • 47 lean (mean BMI: 17.4 ± 0.3)	• Detection thresholds for NaCl and MSG using 2-alternative forced-choice staircase procedure	• No significant difference in salt and umami detection thresholds between body-weight groups
Feeney et al. 2017 (38)	525 children and adolescents	• 118 overweight • 66 obese • 341 lean (BMI not reported)	• Sensitivity (suprathreshold) sucrose and NaCl measured using the gLMS	• Overweight and obese males showing reduced sweet sensitivity compared with normal-weight males
Herz et al. 2020 (41)	53 adolescents	• 27 overweight/obese (BMI percentile range: 85.6–99.7) • 26 lean (BMI percentile range: 11.1–83.9)	• Ability to recognize sweet, sour, bitter, salt, using "taste strips" method Total taste score (TTS) calculated	• No significant difference in ability to recognize sweet, sour, bitter, and salt taste between body-weight groups
Mameli et al. 2019 (56)	67 children and adolescents	• 34 obese (mean BMI: 24.2 ± 2.3) • 33 lean (mean BMI: 17.5 ± 0.2)	• Ability to recognize sweet, sour, bitter, salt, using "taste strips" method Total taste score (TTS) calculated	• Lower ability to identify the correct taste qualities regarding the total score by subjects with obesity • Lower ability to identify bitter, sour, and sweet taste by subjects with obesity
Overberg et al. 2012 (55)	193 children and adolescents	• 99 obese (mean BMI: 29.9 ± 4.9) • 94 lean (mean BMI: 18.2 ± 2.4)	• Ability to recognize sweet, sour, bitter, salt, umami using "taste strips" method Total taste score (TTS) calculated	• Lower ability to identify the correct taste qualities regarding the total score by subjects with obesity • Lower ability to identify bitter, salty, umami taste by subjects with obesity
Pasquet et al. 2007 (69)	87 adolescents	• 39 obese (mean BMI: 39.5 ± 6.0) • 48 lean (mean BMI: 21.0 ± 2.5)	• Recognition thresholds for fructose, sucrose, NaCl, citric acid solutions using a staircase method • Sensitivity (suprathreshold) to sucrose and NaCl using 9-point scale	• Thresholds: lower recognition thresholds for sucrose and salt in subjects with obesity • Suprathresholds: higher perceived intensities for sucrose and salt in subjects with obesity
Sauer et al. 2017 (54)	87 children and adolescents	• 60 obese (BMI *z*-score: 2.5± 0.6) • 27 lean (BMI *z*-score: −0.2 ± 0.6)	• Ability to recognize sweet, sour, bitter, salt, using "taste strips" method Total taste score (TTS) calculated	• Lower ability to identify the correct taste qualities regarding the total score by subjects with obesity • Lower ability to identify sour taste by subjects with obesity
Sayed et al. 2015 (78)	116 children	• 57 obese (BMI *z*-score = 2.5 ± 0.5) • 59 lean (BMI *z*-score = −0.1 ± 0.6)	• Detection thresholds of oleic acid using 3-alternative forced-choice procedure	• Higher detection thresholds for fatty acid taste in children with obesity

[1] gLMS General Labeled Magnitude Scale; MSG, monosodium glutamate.

to eat for each pair. They performed the intention task 3 times, one for each olfactory condition (i.e., a fruity odor, a fatty sweet odor, or no odor), all nonattentively perceived. In children with obesity ($n = 29$), the fruity odor increased the chance of choosing the fruit picture compared with the no-odor condition, whereas the fatty sweet odor did not affect food choice. In children without obesity ($n = 45$), both the fruity and fatty sweet odors decreased the chance of a fruit to be chosen compared with the no-odor condition.

Moreover, one other study supported the hypothesis that children with a higher BMI show higher external eating styles, which means that their intake is more often triggered by food cues like the smell of food. Jansen et al. (92) found that overweight/obese children ($n = 16$) failed to regulate their food intake and were more prone to overeat after being attentively exposed to the intense smell of tasty food, whereas normal-weight children ($n = 15$) decreased their intake after this exposure.

Future research is required to further elucidate the relation between body weight and odor perception in children and adolescents and to specifically address whether the influence of food cues can positively interfere with their attitudes toward foods, modifying both preparatory and satiety-related components of ingestion.

Diabetes

Diabetes is defined as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (93). Children with diabetes represent 5–15% of 463 million total patients with diabetes in 2019 according to the International Diabetes Federation Atlas (94, 95). Diabetes is also associated with high mortality and morbidity due to a broad range of complications (e.g., retinopathy, nephropathy, neuropathy, and cardiovascular disease) (96). The prevention and management of these complications have become major aspects of modern diabetes care.

Chemosensory perception in diabetes

Diabetic neuropathy is the most common microvascular complication of diabetes mellitus with a wide-ranging spectrum of clinical forms. Furthermore, several oral complications, including periodontitis, xerostomia (i.e., dry mouth), burning mouth syndrome, and taste disorders and impairments, have been reported to occur in individuals diagnosed with diabetes (97). Some authors suggested that hyperglycemia and glucotoxicity may mediate downstream metabolic and microvascular effects that result in progressive peripheral nerve fiber damage and loss and microangiopathy of the taste buds (98–101). Supporting this hypothesis, a recent study published by Pavlidis et al. (102) found that the gustatory anatomical structures containing taste buds (i.e., the fungiform papillae) are reduced in number and the morphology and vascularization of these structures are adversely affected in patients with diabetes. Hyperglycemia conditions of patients with diabetes, as well, could induce sweet taste perception alterations as an adaptation of taste receptor cells to the elevated circulating concentrations of glucose (103).

Although evidence exists, these manifestations of diabetic neuropathy are less known and often overlooked. Moreover, psychophysical research into the association between diabetes and taste perception is limited to the adult population (97). In the present review, only 1 study regarding the pediatric population has been discussed. However, a brief comment on studies related to taste perception involving adult populations with type 1 diabetes (T1D) and type 2 diabetes (T2D) has also been reported for the sake of completeness for the readers (for a more complete summary of studies, see **Supplemental Table 1**).

In the only study to our knowledge to investigate perception ability in children and adolescents with and without T1D, Mameli and colleagues (104) found that children and adolescents with T1D presented a lower general ability to identify taste qualities compared with the control subjects, especially for bitter and sour perception. However, any causal inference cannot be made because of the cross-sectional nature of the study and the general lack of research in the literature investigating taste differences across children and adolescents with diabetes.

Evidence in the adult population seems to suggest a possible trend in a higher prevalence of taste impairments in patients with T1D and T2D, compared with healthy controls (100–102, 105–113). Few studies revealed no differences in taste perception between people with or without diabetes (114–117), as reported in 1 recent large cross-sectional, population-based epidemiological study (118) conducted in the US population ($n = 3204$ subjects, with 428 affected by diabetes). Generally, taste impairments seem to increase with disease duration and degenerative complications, especially peripheral neuropathy and nephropathy. Moreover, weight excess can confound the true connection between diabetes and chemosensory response as there exists a strong correlation between obesity and T2D.

Patients with diabetes (both T1D and T2D) regularly and attentively receive medical nutrition therapy (e.g., avoid dietary sugars and increase fruit and vegetable the consumption) as part of their disease management. These diet-related management tasks may have an impact on taste intensity perception and preferences for certain food categories (e.g., foods with added salt and sugar) (119–124). However, more work is needed to determine whether controlled dietary intakes through diet manipulation shift perception and preferences for sweet or salty foods with transient or long-lasting effects.

The sense of smell has largely been overlooked concerning diabetic conditions, with only a limited number of studies that investigated whether olfactory deficiencies affected patients with diabetes (125). Because of the paucity of data, the putative mechanisms for the potential olfactory dysfunction development and progression in diabetes are unknown, although several hypotheses have been proposed.

The currently most accepted include microvascular (105, 126–128) and macrovascular (129) complications related to glucose toxicity and oxidative stress. Moreover, the action of various metabolic molecules (e.g., ghrelin, insulin, and leptin) involved in the regulation of food intake as well as in modulating olfactory function (130) may modulate the individual response affecting the olfactory bulb and mucosa (131–133).

With regard to the relation between olfactory dysfunction and diabetes, the current literature is controversial, and most studies involved the adult population. As for the taste perception in patients with diabetes, the present review reported only 2 studies related to smell perception involving pediatric populations. However, a brief comment on studies related to smell perception involving adult populations with T1D and T2D has also been reported for the sake of completeness for the readers (for a more complete summary of studies, see **Supplemental Table 2**).

Gellrich et al. (134) examined olfactory function in a cohort of 205 children and adolescents with various chronic diseases such as T1D ($n = 43$), hypothyroidism ($n = 34$), and bronchial asthma in combination with allergic rhinitis ($n = 50$) in comparison with that in healthy controls ($n = 78$). Olfactory threshold using Sniffin' Sticks and odor identification using the U-Sniff test (135) were evaluated in all participants. The authors reported no significant difference in olfactory function for any of the chronic diseases in children in comparison with that in healthy controls. On the contrary, Yilmaz et al. (136) measured the olfactory function of 30 children and adolescents with diabetes and 30 healthy controls using the Pediatric Smell Wheel® (Sensonics International, Haddon Heights, NJ, USA) and demonstrated evident impaired smell functions in children with T1D.

Evidence is contrasting in the adult population. Although some observational studies found some degree of olfactory dysfunctions in patients with diabetes (T1D, T2D, or both) with respect to the control group (105, 114, 118, 128, 129, 137, 138), others did not (116, 117, 137, 139–142). Chemosensory impairment has been hypothesized to be due to microalbuminuria (105, 127) and microvascular damage associated with neuropathy, nephropathy, and retinopathy (126, 129, 137).

Allergic diseases

Allergic diseases represent a global public health concern, causing a great burden in terms of well-being and social life (143) as well as the economy (144). Although more focus has been given to obesity and diabetes and their potential implications in children's chemosensory perception, this topic concerning allergic diseases, especially food allergies, has not been sufficiently appreciated previously. Hereby, studies focusing on chemosensory perception in respiratory allergic diseases and food allergy have been reported.

Chemosensory perception in patients with respiratory allergic diseases

Taste receptors have been identified in the extraoral system, meaning that these receptors may have an adapting function. Specifically, bitter taste receptors (TAS2Rs) and sweet receptors [taste receptor type 1 member 2 (T1R2) and T1R3] have been identified in the airway on a variety of cell types. They have been found to play a crucial role more recently in the innate immune defense against pathogens (145–147). Genetic dysfunction of these receptors is thought to partially contribute to the pathogenesis of chronic rhinosinusitis (148).

Overall, data in the literature looking into the association between allergic respiratory diseases and chemosensory perception in the pediatric age are scarce. Hereby, the few studies assessing chemosensory perception in respiratory allergic diseases have been described. As in the previous sections of this review, a brief comment on studies involving adult populations has also been reported (for a more complete summary of studies, see **Supplemental Table 3**).

Only 2 studies have specifically focused attention on a pediatric group of patients (134, 149). Kutlug et al. (149) evaluated the olfactory sensitivity of 77 children and adolescents with allergic and nonallergic rhinitis aged 6–18 y using the Sniffin' Sticks kit. When compared with a control group, children with allergic and nonallergic rhinitis were not found to have reduced olfactory function. These outcomes have been confirmed in another study, wherein 50 children and adolescents affected by bronchial asthma in combination with allergic rhinitis did not present smell impairments in comparison with 78 control subjects (134). Another couple of studies have to be mentioned, although both adolescents and adults were recruited (150, 151). Rydzewski et al. (151) examined 240 patients aged 7–79 y, suffering from hypersensitivity reactions. Moreover, 56.7% of the total sample suffered from perennial rhinitis. Both electrogustometry and olfactometry assessments according to the method of Elsberg and Levy (152) were performed. The study revealed that the incidence of taste and smell disorders in patients with allergic rhinitis is 31.2% and 21.4%, respectively. Electrogustometry revealed no correlations between the taste thresholds and pathological patient status, and smell disorders were predominantly identified in patients, with 58.3% of cases of hyposmia and 90.5% cases of anosmia. In contrast to the previous studies, Avinćsal et al. (150) found significantly lower scores for odor threshold and identification tasks (using the Sniffin' Sticks test) in adolescents and adults with perennial rhinitis, following previous studies involving only the adult population (153–156). It is believed that this is the first study that evaluated taste functions of patients, using the taste strips method for taste identification functionality. They reported that taste recognition ability was decreased for all the basic tastes in adolescent and adult patients with allergic rhinitis. In a recent clinical prospective study by Bogdanov et al. (157), PROP responsiveness was evaluated in adult patients with asthma. It is noteworthy that bitter and overall taste sensitivity decreased with increasing asthma severity. This result agrees with that of a previous study that found a negative correlation between bitter taste sensitivity and asthma severity (158). In this context, taste and smell receptors' function may be considered a proxy of disease status, with potential clinical implications in terms of diagnosis and therapy efficacy (159). Furthermore, increasing understanding of taste perception and taste receptors may help develop new treatment strategies (e.g., bitter taste agonist drugs). Considering the aforementioned few and contrasting results, further studies are warranted to investigate the chemosensory perception in children and adolescents with allergic rhinitis and asthma, both separately or in an association.

Sensory science in food allergy: where we have been and where we should move

Sensory research in the field of food allergy and allergic diseases, in general, is still in its infancy, and the mechanisms underlying sensory perception are far from being understood. Much of the published research, which is not extensive, focused attention on the liking and preference of infant formulas and how they impact later flavor likes and dislikes. Normally, children's food choices are often guided by their preferences (160). However, infants and children with food allergies have to learn new food preferences as specific food groups need to be avoided (161, 162). In some cases, infants need to be fed with a hypoallergenic formula (e.g., hydrolyzed formulas), which has a more pronounced sour, savory, and bitter taste than regular formulas (163, 164). Thus, it is likely that early sensory experiences with these formulas affect infants' taste-acceptance patterns later in life. Previous studies demonstrated that infants who had been fed with casein-hydrolyzed formulas in the first months of life, and consequently have had more experiences with bitter, sour, and astringent stimuli, were later more willing to accept them in beverages (e.g., fruit juice) or savory cereals than infants not exposed to these formulas in infancy (161, 165).

Although infants and children diagnosed with food allergies from an early age seem to be more willing to accept bitter, sour, and savory foods, it is likely they never acquired certain taste preferences. Therefore, they also do not have the feeling of missing out on foods they were not allowed to eat. This would explain why children previously diagnosed with food allergy continue to not introduce the offending food even after resolution of their allergy (166) and why many teenagers stated that they did not have a desire to consume the foods they were allergic to, often because it would taste horrible and strange (167). Only 2 studies were identified in the literature that assessed how long potential effects of taste programming (i.e., how early taste/flavor exposure influence later food preferences) endure in children who avoided cow-milk proteins (e.g., milk and derivatives) during infancy (168, 169). Moreover, Sausenthaler et al. (167) found a positive association between feeding hydrolyzed formula during infancy and the acceptance of extensively hydrolyzed casein formula at age 10 y (167). A more recent study (168) found that children who had consumed a cow-milk exclusion diet (CME) during infancy had a significantly higher preference for bitter taste than those in the control group. Moreover, an inverse correlation was also found between bitter taste and dairy product intake, which was lower in children who had consumed an avoidance diet during infancy. It is noteworthy that almost double the number of children in the CME group were overweight or obese compared with those in the control group, although this difference was not statistically significant (168). This study provides preliminary evidence suggesting a long-term effect of an avoidance diet on taste perception and food intake, as well as a potentially long-term effect on the risk of being overweight and obese. However, due to the small sample size, both issues need further investigation for their potential clinical implication. Beyond the specific aversion toward the offending food, a decreased interest in foods in general has also been observed in children suffering from 1 or more food allergies (169), which may be a barrier to maintaining a varied diet necessary to support adequate growth and health (170). Whether this phenomenon may be underlined by a biological basis is not yet clear: different reactivity of taste receptor mechanisms (e.g., bitter and sweet) could be relevant in the pathways of nutrient detection and evaluation of food quality before, during, and after ingestion. The high threshold (and strong desensitization) of nutrient sensors may promote early selection and preferences of certain types of foods, whereas the low threshold (and low desensitization) for noxious substances may minimize the consumption of other types (171), especially at the early stage of life. Thus, further psychophysiological studies focusing on chemosensory perception, rather than just acceptance or liking, in children with 1 or multiple food allergies on an exclusion diet are required.

Summary and Conclusions

Multifactorial causes currently underpin the most important chronic diseases (e.g., obesity, diabetes, and allergies). Among all of these factors, the hypothesis that chemosensory perceptions of foods may be linked to disease status has been largely supported. This review has summarized the outcomes from the pertinent studies, showing that evidence for the relation between chemosensory perception and these diseases is still greatly controversial. Concerning the studies that have looked at children and adolescents, no clear evidence suggests a relation between taste and smell perception and the aforementioned diseases, probably due to the cross-sectional nature of the reported studies and the methodological heterogeneity in the literature data. However, some possible trends have been highlighted in the adult population, in whom the duration of disease may have affected the relation. There is a need for further, high-quality, hypothesis-led research, with robust measures of taste and olfactory functions as the primary outcomes, to strengthen or deny this evidence. Nevertheless, biological bases and genetics alone do not explain the complexities of these pathologies. Dietary and socioeconomic environment, as well as cultural and learned factors, should be considered. Cohort studies are needed to evaluate the changes in taste abilities and understand their relation and relevance in the progression of such diseases as well as in the definition of dietary habits. Although not the focus of this review, the collective human microbiome should be taken into consideration. The microorganisms of the body not only are passive residents but also are responsible for a range of biological functions (via their secondary metabolites) linked to nutrition and individual well-being (172, 173). Dysbiosis (i.e., the imbalance of the human microbial community) has been linked to several diseases, showing that the microbial community can reflect health status and functionality (174–176) and could be used as a potential diagnostic tool. Differences in both nasal and oral microbial communities have been recently linked to interindividual differences in smell and taste perception (56, 61, 177–181).

To provide further insights into variables related to these diseases and improve the quality of life of susceptible subject groups, both the scientific community and society need the expertise of professionals belonging to a wide range of fields (e.g., food scientists, nutritionists, clinicians, molecular biologists, and neuroscientists) to solve such a multidisciplinary task.

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