The influence of common non communicable diseases upon chemo-sensory perception and clinical implications in pediatric age

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Statement of significance: The recent increase of non-infectious chronic diseases in pediatric population reinforced the interest to make intriguing research on these pathologies. One of the hotspots is the need to better understand the role of sensory perception which could influences nutrition and health status. In this review, we highlighted the great lack of knowledge about the topic. We discussed the putative role that sensory perception may have on food choices and eating behavior of children and adolescents affected by obesity, diabetes and allergies.

Abstract

Over the course of the last century, but especially in the last 2–3 generations, there has been an increasing of non-infectious chronic diseases, such as obesity, diabetes and allergies. Evidence suggested that the inter-relationship among these chronic conditions in pediatric age is complex and far to be well known, reinforcing the interest of pediatricians on these diseases and makes intriguing research on these pathologies. One of the hotspots is the need to better understand the role of sensory perception, since the chemical senses of taste and smell, together with chemesthesis are reported to influences nutrition and diseases. In this review, we aimed to explore the current evidence on the influence of these chronic conditions on sensory perception (i.e., taste and smell). In addition, we highlight the putative role that sensory perception may have on food choices and eating behavior of children and adolescents affected by these diseases. Furthermore, we highlight the unexplored issues which need to be investigated by investigators interested in this research area.

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

Introduction

Over the course of the last century, but especially in the last 2–3 generations, there has been an increasing of non-infectious diseases known as ‘civilization diseases’ or ‘non communicable diseases’. Obesity and diabetes among children increased in recent decades. Even though the prevalence of obesity in some countries has plateaued in recent years, there is no indication of a stable and persistent decline [1, 2]. Therefore, many research sounds alarm again and defining obesity and diabetes a ‘sword of Damocles’ for future generations [3]. In addition, food allergy (FA) prevalence has also raised in westernized countries in recent decade the so called ‘second wave’ allergy epidemic [4]. An epidemiologic trend like food allergy occurred for allergic rhinitis [5] and asthma [6, 7]. Asthma and food allergy seem to be closely linked and FA has been found to be a potential risk factor for the development of asthma and is associated with increased morbidity/mortality among children and adults who have both these conditions [8, 9]. Furthermore, a relationship among asthma, diabetes and obesity has been reported, although the inter-relationship among these chronic conditions in pediatric age is complex and far to be well known [10]. These epidemiologic findings and the evidence of a complex, although not well understood relationship among them, reinforce the interest of pediatricians on these diseases and makes intriguing research on these pathologies. One of the hotspots and interest is the need to better understand the role of sensory perception, since the chemical senses of taste and smell, together with chemesthesis are reported to influences nutrition and diseases. On this regard, in November 2019 the NIH held the “Sensory Nutrition and Disease” Workshop [11] to explore and to better understand the potential of sensory perception in influencing food preferences, intake, nutrition and health. Such knowledge can be used to mitigate chronic disease risk and help develop interventions that promote healthier diets.

Sensory systems, particularly smell and taste, play a role in the sensory effects on appetite [e.g., 12, 13], choice [e.g., 14, 15] and intake [e.g., 16, 17]. The perception of food odors has a pre-consumption role, helping individuals in locating food sources, and anticipating the content of foods they are going to eat. Moreover, several studies have clearly demonstrated in adults that food odors could induce both general- and specific-appetite in anticipation of food consumption [13, 17-20].

Among the food cues that could influence children's eating behavior, food odors are of particular interest, since olfaction is implicated in triggering emotions and memories, with an impact on defining early food choice behavior. This may exert long-term effects over lifetime, such as changes in body weight, altered food preferences and intake and thereby affect health and nutritional status.

Ortho-nasal smell is involved in the anticipation of eating and retro-nasal smell during consumption, while the taste system comes into play while food is ingested. Besides contributing to the overall enjoyment of a meal, the taste system is responsible for the regulation of taste perception and aids individuals in evaluating the nutrient content of foods and in discriminating between those are safe or poisonous [21, 22]. It is well known that five taste modalities are perceived in humans: sweet, umami, salty, bitter, and sour and, recently, it has been proposed that additional stimuli, as fatty and metallic, might also be considered basic tastes [23]. From birth, people are predisposed to crave sweet and salty taste and reject bitter foods, given that each taste modality is linked with different nutritional or physiological requirements (i.e., detecting calories, amino acids, and electrolytes), or indicates a potential dietary risk [23]. Consequently, it has been suggested that taste or smell disturbances pose risks on multiple levels and these dysfunctions can be frustrating, debilitating, and have an influence on enjoyment and interest in food, nutritional status, dietary habits, and the quality of life [24]. A diminished chemo-sensory perception makes it more difficult for people to appreciate and enjoy eating, causing them to avoid many foods or, on the other hand, may lead them to consume more to offset this impaired stimulation [25].

In this review, we aimed to explore the current evidence on the influence of these chronic conditions on sensory perception (i.e., taste and smell). In addition, we highlight the putative role that sensory perception may have on food choices and eating behavior of children and adolescents affected by these diseases. We also include a brief overview of research future perspectives for experimenters interested in this area.

Available sensory methods to measure taste and smell perception

Sensory testing can be used to measure an individual's capability to perceive given stimuli and taste thresholds and supra-thresholds are the most used measurements. Threshold assessment permits comparisons of acuity to certain tastants among individuals, while supra-threshold measures examine the intensity of a perceived stimulus [26]. However, the study of taste thresholds and supra-thresholds in pediatric population is challenging and data in literature have highlighted a relatively confusing outcome, probably due to the difficulty in eliminating the influence of cognitive variables in those protocols [27]. Indeed, a staircase approach or n-alternative forced choice method could be affected by several biases since children, due to their ages, could exhibit limited attention spans and may suffer of fatigue from routine procedures. Moreover, scaling understanding may be somehow limited or required precise and adequate instruction [27-29]. A validated test called “Taste Strips” [30, 31], based on spoon-shaped filter paper strips impregnated with the basic taste qualities in four different concentrations, has been recently developed to overcome such limitations, to test the ability in recognizing the different taste qualities. Another measure often used is the responsiveness to bitter thiourea compounds such as phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP). It is well established that the capacity to perceive these compounds varies greatly among individuals due to genetic variation in TAS2R38 gene [32, 33]. There are two major forms of TAS2R38, PAV (Proline, Alanine, Valine) and AVI (Alanine, Valine, Isoleucine) haplotypes. This combination of alleles underpins the broad segregation of the population into three different phenotypes (PROP taste status) [34]: PROP Non-tasters (AVI/AVI alleles, less responsive), PROP medium-tasters (PAV/AVI alleles, medium responsive), and PROP Super-tasters (PAV/PAV alleles, most responsive). Subsequently, the PROP responsiveness has been linked to the heightened sensitivity to many other natural compounds and began to be considered as a general index of wider sensitivity to taste sensations [35-37]. However, the validity of PROP responsiveness as a general sensitivity index has been questioned by other authors who raised doubts on the idea that PROP responsiveness is sufficient to fully characterize the interindividual variability in response to oral stimulation [e.g., 38, 39].

From the 19th to the mid-20th century several olfactometry systems were developed. The sniff test with Elsberg–Levy's bottles (blast olfactometry) was developed in 1935 and offers the most precise measurement of individual's smell functionality by allowing an injection of a known concentration of odorous air under pressure into the nose [40]. Although this method is easy to use, today it is not performed in the clinical routine. Numerous olfactory tests were available in the past and used mainly to perform odor identification (for a review see [41]). In the last decades, new brief and easy use olfactory test have been developed and validated using normative data acquired on large samples of healthy and diseased subjects. The best-validated olfactory tests [42] include the University of Pennsylvania Smell Identification Test [43] a 'scratch and sniff' odor identification test, the 'sniffin' sticks' [44, 45], pen-like odor-dispensing devices which allows the odor identification (OI), discrimination (OD), and thresholds (OT) assessment, and the Connecticut Chemosensory Clinical Research Center Test (CCCRC test), a combined odor identification (OI) and odor threshold (OT) tests [46].

Current Status of Knowledge

Obesity

Nowadays we found a dramatic increase in the amount of scientific literature on childhood obesity in the past one or two decades, exploring different aspects of this emerging disease. Despite that the pathophysiology of obesity is extremely complex and partially unknown. Weight gain is caused by elevated energy intake, due to disproportionate composition of diet (i.e., high in calories-fat-sugars) and decreased physical activity and sedentarism. Moreover, genetic, biological, environmental, and behavioral factors could closely interact with each other and have an influence on the pathogenesis of weight excess [47].

Taste 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/oro-sensory system [e.g., 48-52]. Some recent studies performed in animal models and on adults with obesity [53-56], linked these differences in chemosensory perception to the expression of several inflammatory markers in the fungiform taste buds, alongside a downregulation in transcription of classical taste markers responsible for regulating several taste sensations in obese. However, evidence is lacking in children and adolescents with obesity and taste perception in this target group has been greatly evaluated through the bitter responsiveness to the 6-n-propylthiuracil (PROP) compound.

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

Bitter. It is well known that the ability of humans to taste bitter compounds varies widely among individuals and the research on the effect of this inter-individual variability on children and adolescents' nutritional status was worthy of interest over the past two decades [57]. Most studies (**Table 1**), which applied different methods to measure PROP responsiveness, did not support the relationship between the bitterness perception of this compound and children and adolescents' BMI [58-67]. Some authors reported a relationship, although other factors, such as ethnicity, gender, and the impact of environment or socio-economic status (SES) have been suggested as a potential contributor of such findings. Indeed, young children's BMI was reported to be higher only in either no-tasters male [68-70] or no-tasters female [71], in no-tasters living in unhealthy food environments and in supertasters children with a high [72] or low socio-economic status [73]. Ethnicity, as well, may play a role in influencing the relationship, since the frequency of no-tasters (less responsive to PROP) in different ethnic groups ranges from 3% to up 40% worldwide [74]. Therefore, further research is necessary to determine how well current findings can be generalized to other ethnic populations.

As previously stated, little is currently known about the sensitivity to bitter taste compounds other than PROP in young population affected by obesity. Indeed, this relationship has been investigated only through the application of 'Taste strips' method [30, 31], whereby the filter paper strips are impregnated with 4 different concentrations of quinine hydrochloride. Of the studies reported in **Table 2**, two papers suggested no relationship between bitter sensitivity and BMI [63, 75], whereas other two reported a negative relationship [76, 77].

It has been hypothesized for some time an increased bitter sensitivity may be predictive of subjects' food preference and eating behaviors [78]. As examples, some authors reported that individuals with increased bitter taste sensitivity might avoid antioxidant-rich vegetables or bitter fruits because of their perceived bitterness [e.g., 34, 57, 79, 80]. These low-energy foods may be replaced by more energy-dense foods among subjects more sensitive to bitter taste [58, 81]. On the other hand, high sensitivity to bitter taste may cause food aversion and low-calorie intake [64, 82]. Some studies showed that children who are no-tasters (less responsive) had lower sucrose preferences than tasters' subjects and exhibited some dietary differences [83], and higher responsiveness to PROP was positively associated with food neophobia and, negatively, with liking of fruit, vegetables, fatty and spicy foods [e.g., 58, 84, 85]. However, others reported no such relationship [62, 66, 86].

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 relationship independently, focusing the attention either on PROP responsiveness and dietary intake or on weight status and dietary intake. To our knowledge, only two studies applied a combined approach [67, 69], 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 little. 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.

Salt. Salt taste perception has been reported to be positively associated with sodium concentration and amount of salt added into foods [81, 87, 88]. Kim and Lee [87] reported an association between individuals' salty taste sensitivity and sodium-rich fast foods acceptance and consumption in a sample of Korean adolescents. Moreover, variation in salt perception was associated with differences in preferences to high-sodium foods and, indirectly, to sodium intake [88], as well as an increased consumption of bakery and salty baked products in subjects hyposensitive to salt taste [81]. Moreover, genetic variations in salty taste receptors (the ENaC and the TRPV1) have been reported to be associated with different perception and preference of salt in children, with influences on salty food intake [89, 90]. This implies the need to understand why children may be prone to consume high amounts of sodium, which far exceeds their biological need. Thus, various studies investigated sensitivity to salt taste in children and adolescents with obesity, to provide an insight into the physiological development of salt taste perception in this target group. Most of the reported studies showed no significant relationship between weight status and salt taste acuity [91], sensitivity [60, 92] or recognition abilities [63, 75, 77] (**Table 2**). An altered ability in recognize salty taste has been reported in children and adolescents with obesity by some investigators, with Overberg and colleagues [76] highlighting a negative relationship while Pasquet et al. [93] reported a higher sensitivity to salt taste, measured as suprathreshold differences, in children with an increased BMI.

Sour. Sour taste may play a role in food selection and consumption (e.g., various fruits and vegetables), warning against spoiled or unripe foods. However, this taste was not extensively researched in the context of obesity. The studies summarized in this review suggested that sour perception seems not to be related to nutritional status [63, 76, 92, 93], except for two studies, whereby perception ability of sour taste was lower in children and adolescents with obesity [75, 77]. The potential relationship between sour taste perception, and subsequent influence on food choices in subjects with obesity remains to be explored.

Sweet. Humans present a universal preference for sweet substances, which elicit pleasant responses and occur to detect sugars and carbohydrates in foods [94]. Reduced sensitivity of glucose-sensing mechanisms, that may be involved in glucose homeostasis and/or energy balance, and decreased activation of food- reward circuits, may contribute to the over-consumption of energy [79, 95]. Additionally, different sweet liking patterns are observed across individuals [96]. The terms 'sweet tooth' or 'sweet likers' have been coined to describe people who 'prefer' sweets, implying either that these individuals usually prefer to eat sweet foods and beverages or that there is no such thing as too sweet for them and their liking increases as the concentration of sugar increases [97]. In a food environment abounding with sugars and sweetened foods and beverages, children's perception of and preference for sweets may make them prone to overconsumption, contributing to spread worldwide the prevalence of childhood overweight and obesity [98, 99].

Many studies have looked at taste perception and obesity, with a specific emphasis on sweet taste. In the studies selected for this review, three suggested no association between nutritional status and sweet sensitivity [60, 92] or perception abilities [63, 75]. One paper reported a reduced sensitivity only in male characterized as overweight or obese [60] and two papers reported a negative relationship [76, 77] between ability to recognize sweet taste and BMI (**Table 2**). Overberg and collaborators [76] found that children and adolescents with obesity showed a significantly lower ability in identifying sweet taste qualities in respect to non-obese subjects, and Mameli and colleagues [77], applying the same method, confirmed these results. On the contrary, Pasquet et al. [93] found that adolescents with obesity present lower recognition thresholds and higher taste sensitivity to sucrose but not fructose than non-obese adolescents. A few studies have investigated the effect of variations in sweet perception on sugar intake in young subjects with obesity. Pioltine and colleagues [100], performing a molecular study for the single nucleotide polymorphisms (SNPs) rs9701796 variations, which was associated with different sweet taste preference in children [89], stated that children with obesity carrying this variant have an increased waist-height ratio as well as presented a higher chocolate powder intake. However, it is still unclear whether, and to what extent, changes in thresholds and hedonic responses might be related to food intake.

Umami. The savory taste umami has been recognized as the fifth basic taste and contributes to a sense of satiety [101]. Despite its suggested role in signaling satiety, very little work to date has investigated the umami perception in childhood obesity. Two studies measured detection thresholds and sensitivity for monosodium glutamate (MSG). One study showing no relationship [91], whereas Overberg and colleagues [76] reported that participants with obesity are characterized by a lower perception ability in recognizing umami taste compared with normal weight children and adolescents.

Fat. Recently, in addition to the study of the perception of the five basic tastes, attention has been concentrated on the oro-sensory perception and sensitivity to fat stimulus, since the consumption of palatable, high-fat foods has been associated with increased risk for obesity [102]. A common explored hypothesis is that individuals with higher BMI present low sensitivity to palatable fatty texture (mouthfeel) and fatty acids (taste) and therefore need a greater concentration to detect fatty stimuli, leading to an excessive consumption of dietary energy and weight gain [103-105]. The results of one study supported this hypothesis [106] while one reported non-significant results [92]. Sayed and colleagues [106] found that children with obesity exhibited low oleic acid (OA) oral sensitivity (high detection threshold) and a positive correlation between waist size and increased oral detection threshold for fat taste was found in these children.

In summary, we reviewed 23 studies focused on children and adolescents' taste perception towards all taste qualities and PROP, highlighting that there was a lack of any clear trend between taste perception and obesity in young populations, and little is currently known about the perception of other compounds beside PROP. It has to be mentioned that methodological heterogeneity in the literature data negated meta-analysis, making difficult to draw clear conclusions, since the evidence appears to be inconclusive or incomplete. More longitudinal research is required to deepen the results obtained in the afore-mentioned cross-sectional studies. Nevertheless, the highlighted differences in taste perception are not sufficient to support a likely causal role in the development of eating behavior and diet related chronic conditions like obesity.

Odor perception in obesity

The relation between olfactory perception and obesity is the least understood. As reported above, olfaction plays an important role in food consumption, however it is still unclear whether olfactory abilities are related to weight gain and adiposity through direct influences on eating behavior. 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 [107] and are related almost exclusively to adults, while scientific evidence is scarce in the young population. In their meta-analysis, Peng and colleagues [107], suggested a trend of declining olfactory detection ability with increasing weight. Indeed, several studies which used the Sniffin' Sticks method (Burghardt Messtechnick GmbH, Wedel, Germany) for assessing olfactory function highlighted that adult subjects characterized by a higher BMI generally presented poorer detection abilities compared with the normal weight group. However, these differences have been detected only for odor detection and discrimination functions assessed by Sniffin' Sticks. On the other hand, an elegant 'externality-theory' originally proposed by Schachter [108], postulated that food external stimuli (e.g., sight, smell, taste) have a different influence on attitude toward foods in lean subjects and those with a higher BMI [109]. In particular, the latter present a 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, being prone to overeat [110-111]. In this perspective, "cue reactiveness" to external food stimuli has been reported to be stronger in obese than in normal-weight children, showing that their eating behavior is more often triggered by food cues [112, 113]. 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) [114] or increasing the intake of healthy and low-energy dense foods, suitable as part of a balanced diet, as recently demonstrated in adults [17].

Due to the paucity of literature data, this review identified only two studies which investigated olfactory differences across weight groups of children and adolescents [63, 115]. Obrębowski and colleagues [115] found that odor identification abilities and sensitivity were reduced in a sample of obese males and females ages 10–16 years. The authors tested odor detection thresholds (ODT) and odor identification thresholds (OIT) by blast injection method according to Elsberg–Levy's olfactometry, stimulating the nerve endings of both the olfactory and the trigeminal nerves. However, the study presented a strong limitation since the study involved 30 children and adolescents affected by obesity and their ODT and OIT were estimated and compared to normal ranges, found in a previous study [116], without involving a control group of normal weight. On the contrary, a greater olfactory sensitivity (i.e., lower detection threshold) were found in adolescents with high BMI percentiles in respect to normal weight peers, as described by Herz and colleagues [63] applying Sniffin' Stick methods.

Beside the olfactory functions measured through psychophysical studies, a cue exposure approach was used by Marty and colleagues [114] to investigate whether non-attentively food odors exposure may be predictive of food choices in obese children. 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 to eat'* for each pair. They performed the intention task three times, one for each olfactory condition: a fruity odor, a fatty-sweet odor or no odor, all non-attentively perceived. In children with obesity (n=29), the fruity odor increased the chance to choose the fruit picture compared to the no-odor condition, while the fatty-sweet odor had no effect on food choice. In children without obesity (n=45), both the fruity and the fatty-sweet odors decreased the chance of a fruit to be chosen in respect to 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. Indeed, Jansen and colleagues [117] found that overweight/obese children (n=16) failed to regulate their food intake and were more prone to overeat after being attentive exposed to the intense smell of tasty food, whereas normal-weight children (n=15) decreased their intake after this exposure.

As previously stated, the sense of smell is less explored in the context of childhood obesity. Inspection of the results from individual studies highlighted that little evidence exist to link BMI and increasing/decreasing olfactory thresholds. However, the lack of a substantial number of studies on this topic make difficult to draw any conclusion in younger population. In adults more solid evidence have been found which negatively correlated olfactory ability and body weight (for a review see [107]). The authors also highlighted that the existing literature suggests that changes in olfactory abilities is a common outcome of bariatric surgery, even if the mechanism behind these changes is still unclear.

When looking at the association with food liking and choices, evidence suggests that food odors could be considered predictors of eating behaviors [114, 118]. In this regard, overweight and obese children and adolescents might be more triggered by and susceptible to olfactory food cues, possibly overriding the internal signals of hunger and satiety [117], as reported in various studies whereby adult subjects have been involved [12, 17, 109].

Future research is required to further elucidate the relationship 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 [119]. In 2019, According to International Diabetes Federation Atlas children with diabetes represent 5-15% of 463 millions of total diabetic patients [120, 121]. Diabetes is also associated with high mortality and morbidity due to a broad range of complications, such as retinopathy, nephropathy, neuropathy, and cardiovascular disease [122]. Prevention and management of these complications have become major aspects of modern diabetes care.

Taste perception in diabetes

Diabetic neuropathy is the most common microvascular complication of diabetes mellitus with a wide-ranging spectrum of clinical forms. 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 [123]. 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 in microangiopathy of the taste buds [124-127]. Supporting this hypothesis, a recent study published by Pavlidis and colleagues [128] 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 condition of diabetics, as well, could induce sweet taste perception alterations as an adaptation of taste receptor cells to the elevated circulating concentrations of glucose [129].

Although evidence exists, these manifestations of diabetic neuropathy are less known and often overlooked. Moreover, psychophysical research into the association between DM and taste perception is limited to the adult population [123]. In the present review only one study regarding pediatric population has been reported. However, for the sake of completeness towards the readers a brief overview of studies related to taste perception involving adult populations with T1D and T2D has also been commented (**Supplemental Table 1**).

To the best of our knowledge, our study [130] is the unique which investigated whether differences in taste perception ability exist among children and adolescents with and without type 1 diabetes. The findings showed that children and adolescents with T1D presented a lower general ability to identify taste qualities compared to the control subjects, especially for bitter and sour perception. However, any causal inference cannot be made due to the lack of research in literature which investigated taste differences across diabetic children and adolescents.

Evidence in adult population seems to suggest a possible trend in higher prevalence of taste impairments in patients with type 1 and type 2 diabetes, compared to healthy controls. Studies between 1961 and 1981 revealed no differences in taste perception between people with or without diabetes [131, 132]. Later, most studies showed impaired taste ability in recognizing and perceiving different tastes in adult diabetic patients. Taste impairments have been found in diabetic patients (both T1D and T2D) compared to controls applying electro-chemical gustometry and taste impairment increased with duration of disease and degenerative complications, especially peripheral neuropathy, and nephropathy [126-128, 133-135]. Accordingly, in several studies wherein taste thresholds were tested using serially diluted solutions in both T1D [136] and T2D patients [137-140] a significant increase in taste threshold in diabetic patients compared to controls was observed, especially for sucrose. Same results have been obtained applying ‘Taste Strips’ method by some authors [141] but not others [142, 143]. Furthermore, one recent large cross-sectional, population based epidemiological study [144] was conducted in US population (n=3204 subjects, whose 428 affected by diabetes) and no differences were found between the diabetic and control groups.

It has to be mentioned that patients with diabetes (both T1D and T2D) regularly and attentively received medical nutrition therapy (e.g., avoid dietary sugars, increase the consumption of fruit and vegetables) as part of their disease management. This diet-related management tasks may have an impact on taste intensity perception and preferences for certain food categories. As examples, individuals who adopt a lowered-sodium diet for several weeks, may perceive more intensely saltiness in foods than it was before or come to prefer lower or higher concentrations of sodium depending on lower or higher salt intake, respectively [145-148]. The intake of sugars may affect sweetness perception of sugar-added foods in a similar fashion [159, 150]. 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.

Odor perception in diabetes

The sense of smell, likewise taste perception, has largely been overlooked in relation to diabetic conditions, with only a limited number of studies which investigated whether olfactory deficiencies affected diabetic patients [151]. Due to the paucity of data, the putative mechanisms for the potential olfactory dysfunction development and progression in diabetes are currently unknown, though several hypotheses have been proposed. The currently most accepted include microvascular [133, 152-154] and macrovascular [155] 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 [156], may modulate the individual response affecting olfactory bulb and mucosa [157-159].

Regarding the relationship between olfactory dysfunction and diabetes, the current literature is controversial, and most studies involved the adult population. As for the taste perception in diabetic patients, the present review reported only two studies related to smell perception involving pediatric populations. However, for the sake of completeness towards the readers a brief overview of studies which involved adult populations with T1D and T2D has also been commented (**Supplemental Table 2**).

To the best of our knowledge, only two studies investigated the relationship between olfactory dysfunction and diabetes in a pediatric population. Gellrich et al. [160] examined olfactory function in a cohort of 205 children and adolescents with various chronic diseases such as diabetes mellitus type 1 (n=43), hypothyroidism (n=34), and bronchial asthma in combination with allergic rhinitis (n=50) in comparison to healthy controls (n=78). Olfactory threshold using ‘Sniffin’ Sticks’ and odor identification using the ‘U-Sniff test’ [161] were evaluated in all participants. The authors reported no significant difference in olfactory function for any of the chronic diseases in children in comparison to healthy controls. Contrarily, Yilmaz et al. [162] measured the olfactory function of 30 T1D children and adolescents and 30 healthy controls, using the Pediatric Smell Wheel® (PSW) and demonstrated evident impaired smell functions in children with TID. In particular, the PSW scores were significantly lower in the patients with type 1 diabetes than in the controls (9.17 vs 10.37; $p < 0.0001$), although, in both cases, the scores fell within the normal range for individuals of their age (i.e., at or above 80%).

In regards of adult population, various authors highlighted that some degree of olfactory dysfunctions were found in diabetic patients (T1D, T2D or both) in respect to the control group [131, 133, 155, 163] while others not [164]. The authors who showed a poorer sense of smell in diabetics underlined the association with both microalbuminuria [133, 153] and microvascular complication such as neuropathy, nephropathy, and retinopathy [152, 155, 163]. More recent studies tested the olfactory performance of participants by the 'Sniffin' Sticks' validated tool, showing that patients with type 2 diabetes are characterized by a lower odor threshold, discrimination, and identification scores as well as lower TDI scores compared with participants without diabetes [154, 165]. Contrarily, some others did not report such association [142, 143, 166]. Furthermore, three large cross-sectional, population based epidemiological studies with identification tests were conducted in Sweden (n=1900; [167], Germany (n=1240; [168]) and US (n=3204; [144]). The first two mentioned studies did not show any odors impairments in diabetic patients compared to healthy controls, although it was generally reported that the incidence of anosmia increased with the presence of diabetes [167]. Moreover, the prevalence of smell impairment in US patients with diabetes (n=428) was significantly higher ($p < 0.001$) compared to the US controls: 22% *vs* 15%, and daily calorie intake appears to be reduced in people with smell impairment [144].

In summary, the current literature on pediatric population is scarce and the findings about olfactory dysfunctions and diabetes mellitus are still controversial. Taken together the whole evidence suggests a negligible effect of diabetes (both type 1 and 2) on smell perception, although peripheral neuropathy could have a possible impact on olfactory dysfunctions, as highlighted in some research. The variability in outcomes could be due to several methodological issues, such as differences in olfactory function tests performed, inconsistencies in the assessment of diabetic status as well as cross-sectional design with a relatively small sample size. Nevertheless, no evidence currently links these possible minor changes in perception to subsequent changes in food choice and behavior in children and adolescents affected by diabetes. Further studies are needed to clarify the controversial results found in children and to identify the possible underlying mechanisms behind smell dysfunction in patients with diabetes and its role in defying healthy/unhealthy eating patterns.

Allergic diseases

Allergic diseases represent a global public health concern, causing great burden in term of well-being and social life [169] and economic burden too [170]. While much more focus has been given to sensory perception and its potential implications in obesity and diabetes in childhood, this topic in relation to allergic diseases, especially food allergies, has not been sufficiently appreciated in the past. Hereby we report the studies focusing on this issue in respiratory allergic diseases and food allergy.

Chemo-sensory perception in patients with respiratory allergic diseases

Taste receptors have been identified in extra oral system, meaning that these receptors may have adapting function. Specifically, bitter taste receptors (TAS2Rs) and sweet receptors (T1R2/3) have been identified in the airway on a variety of cell types. More recently, they have been found to play a crucial role in the innate immune defense against pathogens [171-173]. Genetic dysfunction of these receptors is thought to partially contribute to the pathogenesis of chronic rhinosinusitis [174].

Overall, data in literature looking into the association between allergic respiratory diseases and chemo-sensory perception in pediatric age are scarce. Hereby, we describe the few studies assessing sensory perception in respiratory allergic diseases. As in the previous sections of this review a brief overview of studies involving adult populations has also been summarized.

So far, only two studies specifically focused the attention on a pediatric group of patients [160, 175]. Kutlug et al. [175] evaluated olfactory sensitivity of 77 children and adolescents with allergic and non-allergic rhinitis aged 6–18 years using the 'Sniffin' Sticks' kit. When compared with control group, children with allergic and non-allergic 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 to 78 control subjects [160]. Another couple of studies have to be mentioned, although both adolescents and adults have been recruited [176, 177]. Rydzewski, Pruszewicz and Sulkowski [177] examined a total of 240 patients aged from 7 to 79 years, suffering from hypersensitivity reactions. The 56.7% of the total sample suffered from perennial rhinitis. Both electrogustometry and olfactometry assessment according to Elsberg and Levy's method [40], 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, while smell disorders were predominantly identified in patients with 58.3% of cases of hyposmia and 90.5% cases of anosmia. In contrast with the previous studies, Avinćsal and colleagues [176] found significantly lower scores for odor threshold and identification tasks (using 'Sniffin' Stick' test) in adolescents and adults with perennial rhinitis, in accordance with previous studies involving only adult population [178-181]. To the best of our knowledge, this is also the first study which evaluated taste functions of patients, using Taste strips method for the 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 Bogadanov et al. [182], PROP responsiveness was evaluated in adult patients with asthma. Noteworthy, bitter and overall taste sensitivity decreased with increasing of asthma severity. This result agrees with those of previous study which found a negative correlation with bitter taste sensitivity and asthma severity [183]. In this context, taste and smell receptors' function may be considered a proxy of disease status, with potential clinical implications in term of diagnosis and therapy efficacy [184]. Furthermore, increasing understanding of taste perception and taste receptors may help to developing new treatment strategies (e.g., bitter taste agonist drugs). Considering the above few and contrasting results, further studies are warranted to investigate chemo-sensory perception in children and adolescent with allergic rhinitis and asthma, both ‘*per se*’ or in association.

Sensory science in food allergy: going beyond liking?

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 to be understood. Much of the published research, which is not extensive, focused the attention on liking and preference of infant formulas and how they impact on later flavor likes and dislikes. Normally, children’s food choices are often guided by their preferences [185]. However, infants and children with food allergy have to learn new food preferences, as specific food groups need to be avoided [186, 187]. 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 [188, 189]. Thus, it is likely that early sensory experiences with these formulas affect infants' taste acceptance patterns later in life. Indeed, previous studies demonstrated that infants who had been fed with casein hydrolyzed 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 [186, 190].

On the other hand, although infants and children diagnosed with food allergies from an early age seems to be unconventionally more willing to accept such taste and flavors, at the same time it is likely that they have never acquired certain taste preferences and therefore 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 do not introduce the food after a negative oral food challenge [191] and why many teenagers stated that they did not have a desire to consume the foods they were allergic to, often because they would taste “horrible” and strange, as recently reported [192]. Only two studies were identified in the literature which 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’s milk proteins (e.g., milk and derivatives) during infancy [193, 194]. Sausenthaler and colleagues [192] found a positive association between feeding hydrolyzed formula during infancy and the acceptance of extensively hydrolyzed casein formula at age 10 year [192]. A more recent study [193] found that children who had consumed a cow’s 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 products intake, which was lower in children who had consumed an avoidance diet during infancy. Noteworthy, almost double the number of children in the CME group were overweight/obese compared to the control group, although this difference was not statistically significant [193]. This study provides preliminary evidence suggesting a long-term effect of avoidance diet on taste perception and food intake, as well as a potential long-term effect on the risk of being overweight and obese. However, due to small sample size, both issues need further investigation for their potential clinical implication. Beyond the specific aversion toward the offending food, a decreased interest for foods in general has also been observed in children suffering from one or more food allergies [194], which fact may be a barrier to maintaining a varied diet necessary to support adequate growth and health [195]. If this phenomenon might be underlined by a biological basis is thus 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 the early selection and preferences of certain types foods, whereas the low threshold (and low desensitization) for noxious substances may minimizes the consumption of other types [196], especially at early stage of life. Thus, further studies focusing on sensory perception, and not only acceptance or liking, in children with one or multiple food allergies on exclusion diet are required.

Summary and conclusions

Multi-factorial causes underpin the nowadays most important chronic diseases, such as obesity, diabetes, and allergies. Among all these factors, the hypothesis that chemo-sensory perceptions of foods may play a role in food choices, nutritional and health outcomes have been largely supported. In this review we have summarized outcomes from the pertinent studies, showing that evidence for the relationship between sensory perception and these diseases is still greatly controversial. With respect to the studies that have looked at children and adolescents, no clear evidence suggests a relationship between taste and smell perception and the aforementioned diseases in young population. However, some possible trends have been highlighted in adult population, in whom the duration of disease might have affected the relationship. 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 these evidences. Nevertheless, it should be considered that biological bases and genetics alone do not explain the complexities of these pathologies. Dietary and socio-economic 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 relationship and relevance in the progression of such diseases as well as in the definition of dietary habits.

Moreover, a special attention should be paid to another player, the collective human microbiome. Microorganisms of our body are not just passive residents but are responsible for a range of biological functions (via their secondary metabolites) linked with nutrition and individual well-being [197, 198]. Dysbiosis (i.e., the imbalance of the human microbial community), has been linked with several diseases, showing that the microbial community has the capability to reflect health status and functionality [199-201], and could be used as a potential diagnostic tool. Indeed, differences in both nasal and oral microbial community have been recently linked to interindividual differences in smell and taste perception [77, 81, 202-206].

To provide further insights into variables related to these diseases and improving the quality of life of frail subjects' groups both the scientific community and society needs the expertise of professionals belonging to a wide range of fields, such as food scientists, nutritionists, clinicians, molecular biologists, and neuroscientists, to solve such a multidisciplinary task.

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Table 1. Summary table of the literature evidence (alphabetical order) for the relationships between taste responsiveness to PROP and children and adolescents nutritional status.

Authors	Cohort sample size	Prop status and body weight groups	Methods	Main Outcomes
Baranowski et al. 2010	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 socio-economic status
Bell and Tepper 2006	65 children	• 24 tasters (T) • 41 non-tasters (NT) BMI%-for-age did not vary with taster status	• PROP forced-choice screening	• No relationship with BMI
Borazon et al. 2012	120 adolescents	• 8 non-tasters (NT, mean BMI: 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 relationship with BMI
Bouthoorn et al. 2014	5894 children	• 4564 tasters (T) • 1330 non-tasters (NT) (BMI not reported)	• PROP forced-choice screening	• NT girls had higher BMIz and body fat than T girls
Burd et al. 2013	120 children	• 85 tasters (T) 1.2% underweight, 51.8% normal-weight, 23.5% overweight and 23.5% obese • 35 non-tasters (NT)	• PROP forced-choice screening	• NT living in unhealthy food environment had higher BMI z-score

		2.9% underweight, 57.1% normal-weight, 11.4% overweight and 28.6% obese		
Feeney et al. 2017	525 children and adolescents	• 118 overweight • 66 obese • 341 lean • (BMI not reported)	• Perceived intensity of PROP filter paper; (gLMS)	• No relationship with BMI
Golding et al. 2009	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 relationship with BMI
Goldstein et al. 2007	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 relationship with BMI
Herz et al. 2020	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 relationship with BMI
Keller and Tepper 2004	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

Keller et al. 2010	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	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 relationship with BMI
Lumeng et al. 2008	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	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 relationship with BMI
Oftedal and Tepper 2013	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 relationship with BMI
Stoner et al. 2019	342 children	• 140 tasters (T; mean BMI: 0.34±1.23) 202 non-tasters (NT; mean BMI z-score: 0.45±1.1)	• PROP forced-choice screening	• No relationship with BMI

Table 2. Summary table of the literature evidence (alphabetical order) for the relationships between taste perception (measured as thresholds, supra-thresholds or tasting recognition abilities) and children and adolescents' nutritional status.

Authors	Cohort sample size	Body weight groups	Methods	Outcomes
Alexy et al. 2011	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	97 children and adolescents	• 50 overweight/obese (mean BMI: 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	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 than normal weight males
Herz et al. 2020	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, Cattaneo, Panelli et al. 2019	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	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 and taste by subjects with obesity
Pasquet et al. 2007	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 • Supra-thresholds: Higher perceived intensities for sucrose and salt in subjects with obesity
Sauer et al. 2017	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	116 children	• 57 obese (BMI z-score=2.5±0.5) • 59 lean (BMI z-score=−0.1±0.6)	• Detection thresholds oleic acid using 3-alternative forced-choice procedure	• Higher detection thresholds for fatty acid taste in children with obesity

Supplementary materials

Supplementary Table 1. Summary table of the literature evidence related to taste perception (measured as electogustometry, thresholds, supra-thresholds or tasting recognition abilities) in adult patients suffering from type 1 (T1D) and 2 (T2D) diabetes mellitus.

Authors	Cohort sample size	Diabetes type	Methods	Main outcomes
Altundag et al. 2017	70 subjects	• 39 T1D with no complication • 31 control subjects	• Ability to recognize sweet, sour, bitter, salt, umami; Total taste score (TTS) calculated	• No significant difference in ability to recognize sweet, sour, bitter and salt taste between groups
De Carli et al. 2018	50 subjects	• 25 T2D • 25 control subjects	• Recognition thresholds for sucrose, NaCl, citric acid and quinine hydrochloride solutions using a forced-choice ascending-series method	• Higher recognition threshold for sweet, salt, sour and bitter taste in T2D
Dye and Koziatek 1981	79 subjects	• 37 T2D • 42 control subjects	• Sensitivity for 5 sucrose solutions	• No significant difference in sweet sensitivity between groups
Gondivkar et al. 2009	120 subjects	• 40 controlled T2D • 40 uncontrolled T2D • 40 control subjects	• Whole-mouth above-threshold taste test for sucrose, NaCl, citric acid and quinine hydrochloride solutions measured using a staircase-method	• Higher thresholds for salt, sour and sweet taste in subjects with T2D • Hypogeusia was reported among 62.5% of the diabetic patients versus 12.5% of control subjects

Jongensen and Buch 1961	62 patients aged	- T1D	- Electrogustometry	- No significant difference in thresholds between values of diabetics and those of a control group in Kristensen and Zilstroff-Pedersen (1953)
Khobragade et al. 2012	140 subjects	- 70 T1D - 70 control subjects	- Recognition thresholds for glucose, NaCl, citric acid and quinine sulfate solutions using a forced-choice ascending-series method	- Higher recognition thresholds for sweet, salt, sour and bitter in T1D subjects
Latha	120 subjects	- 60 T2D - 60 control subjects	- Recognition thresholds for glucose, NaCl, monosodium glutamate, citric acid, quinine sulfate solutions using a forced choice and up-down tracking procedure	- Higher recognition threshold for sweet, and salt taste in T2D -
Le Floch et al. 1989	95 subjects	- 57 T1D - 38 control subjects	- Electrogustometry - Chemical gustometry	- Taste impairment in the diabetic group relative to the control group - Hypogeusia was found among 73% of the diabetic patients *vs* 16% of the control subjects
Le Floch et al. 1990	100 subjects	- 50 T1D - 50 control subjects	- Electrogustometry	- Higher electrogustometric threshold in the diabetic group than in the control group - Electric hypogeusia was found among 54% of the diabetic patients *vs* 2% of the control subjects

Naka et al. 2010	76 subjects	• 29 T2D/T1D with no complication (Group 1) • 24 T2D/T1D with microangiopathy and/or macroangiopathy (Group 2) • 23 patients with complicating diseases (Group 3) • 29 control subjects (Group 4)	• Ability to recognize sweet, sour, bitter, salt, umami; Total taste score (TTS) calculated	• No significant difference in ability to recognize sweet, sour, bitter and salt taste across groups
Pavlidis et al. 2014	62 subjects	• 14 T1D • 22 T2D • 36 control subjects	• Electrogustometry	• Higher electrogustometry thresholds in T1D and T2D groups than in the control group • The fungiform papillae density was significantly reduced in groups with diabetic patients compared to control group
Perros et al. 1996	51 subjects	• 20 patients before and after treatment of hyperglycemia (group 1) • 20 control subjects (group 2) • 11 patients with long duration of diabetes and advanced peripheral neuropathy (group 3)	• Electrogustometry • Detection and recognition thresholds for glucose, fructose, NaCl, urea solutions	• Higher electrogustometric threshold in group 1 and group 3 than in the control group • Detection thresholds for glucose and recognition thresholds for glucose and salt were elevated in group 1 and 3 compared with control group
Pugnaloni et al. 2020	64 subjects	• 32 T2D • 32 healthy subjects	• Ability to recognize sweet, sour, bitter, salt, umami; Total taste score (TTS) calculated	• Lower ability to identify the correct taste qualities regarding the total score by subjects with T2D • Lower ability to identify bitter, sour and sweet taste by subjects with T2D

Rasmussen et al. 2018	3204 subjects	• 428 with diabetes (type not reported) • 2776 control subjects	• NHANES tongue tip taste and whole-mouth taste tests for sensitivity to quinine and NaCl rated through gLMS	• No significant difference in salt and bitter sensitivity between groups
Stolbovà et al. 1999	125 subjects	• 73 T2D • 11 T1D • 12 obese without DM • 29 control subjects	• Electrogustometry	• Hypogeusia was found in 40% T2D patients, 33% T1D and 25% patients with obesity • No hypogeusia was found in control group
Wasalathanthri, Hettiarachchi and Prathapan 2014	114 subjects	• 40 pre-diabetics (Group 1) • 40 T2D (Group 2) • 34 control subjects (Group 3)	• Detection and recognition thresholds for sucrose • Sensitivity for sucrose solutions using 3-alternative forced-choice procedure	• Thresholds: higher detection threshold for sucrose in group 2 • Supra-thresholds: lower sensitivity in group 2

Supplementary Table 2. Summary table of the literature evidence related to smell perception (measured as odor threshold, odor detection, odor identification) in patients suffering from type 1 (T1D) and 2 (T2D) diabetes mellitus.

Authors	Cohort sample size	Diabetes type	Methods	Main Outcomes
Altundag et al. 2017	70 subjects	• 39 T1D with no complications • 31 control subjects	• Odor thresholds, odor detection and odor identification tests using 'Sniffin' Sticks' kit TDI score calculated	• No differences in olfactory functions between the two groups
Brady et al. 2013	70 subjects	• 51 diabetic patients 19 with non-complicated DM (Group 1) 15 with DPN-NoP (diabetic peripheral neuropathy without neuropathic pain) (Group 2) 21 with DPN-P (diabetic peripheral neuropathy with neuropathic pain) (Group 3) • 19 control participants (Group 4)	• Odor thresholds, odor detection and odor identification tests using 'Sniffin' Sticks' kit	• Lower odor detection thresholds, reduced ability to discriminate between odor qualities, reduced ability to identify the odor in diabetic patients
Brämerson et al. 2004	1900 subjects	• Not reported	• Olfactory function was assessed with the Scandinavian Odor Identification Test (SOIT)	• No odors impairments in diabetic patients
Duda-Sobczak et al. 2017	136 subjects	• 106 T1D • 30 control subjects	• Identification test using 'Sniffin' Sticks' kit	• Hyposmia was found in 72 diabetic patients (67.9%) compared to 16 subjects (53.3%) in the control group.

Falkwoski et al. 2020	113 subjects	• 113 T1D	• Screening smell test using 'Sniffin' Sticks' kit	• 5 patients (4.4%) were diagnosed with anosmia and 51 with hyposmia (38.3%)
Gascon et al. 2013	61 subjects	• 61 diabetic patients (type not reported)	• Detection and identification thresholds and percentage of correct responses (i.e. accuracy) of the 29 components of the Barcelona Smell-taste Test-24 (BAST-24)	• Reduced percentage of correct responses in the olfactory test in diabetic patients
Gouveri et al. 2014	154 subjects	• 119 T2D • 35 control subjects	• Odor thresholds, odor detection and odor identification tests using 'Sniffin' Sticks' kit TDI score calculated	• Lower odor threshold, odor discrimination, odor identification and TDI scores in T2D patients than control subjects.
Jorgensen and Buch 1961	58 subjects	• 58 T1D	• Odor detection and identification thresholds tested by blast injection method according to Elsberg–Levy's olfactometry	• 35 diabetic patients (60%) showed an impaired sense of smell, including 24 with severe impairment
Landis et al. 2004	1240 subjects	• 51 with diabetes (type not reported) • 1189 control subjects	• Odor identification test using Sniffin' Sticks' kit	• No altered olfactory function in diabetic patients
Le Floch et al. 1993	98 subjects	• 17 T1D • 51 T2D • 30 control subjects	• Quantification of olfactory performance through Smell Recognition Score (SRS)	• The SRS was significantly lower in diabetic patients than in control subjects
Naka et al. 2010	76 subjects	• 29 T2D/T1D with no complication (Group 1) • 24 T2D/T1D with microangiopathy and/or macroangiopathy (Group 2)	• Odor identification short screen-test using five items from the 'Sniffin' Sticks' kit	• Lower identification scores in Group 3 than Group 1 patients and control subjects

		• 23 patients with complicating diseases (Group 3) • 29 control subjects (Group 4)		
Patterson, Turner and Smart 1966	118 subjects	• 59 with diabetes (type not reported) • 59 control subjects	• Odor detection thresholds tested by blast injection method according to Elsberg–Levy's olfactometry	• No differences highlighted in olfactory functions between the two groups
Rasmussen et al. 2018	3204 subjects	• 428 with diabetes (type not reported) • 2776 control subjects	• Identification test using NHANES Pocket Smell Test	• The prevalence of smell impairment in patients with diabetes (22%) was significantly higher compared to the non-diabetic control population (15%)
Seraj et al 2015	60 subjects	• 30 diabetic patients (type not reported) • 30 control subjects	• Odor detection threshold using 'absorbent perfumer's paper strips' method with phenylethyl alcohol as the odorant and propylene glycol as the solvent	• 60% of diabetics were found to have some degree of olfactory dysfunction and a significant difference in the olfactory threshold between diabetics and control group
Weinstock, Wright and Smith 1993	111 subjects	• 111 T1D and T2D	• Quantification of olfactory performance through the Odorant Confusion Matrix	• Olfactory ability was overall impaired in diabetic patients (67.8% of correct identifications) in respect to the control group (80% of correct identifications).

Supplementary Table 3. Summary table of the literature evidence related to sensory perception (both taste and smell perception) in patients suffering allergic rhinitis, chronic rhinosinusitis or asthma.

Authors	Cohort sample size	Group type	Methods	Main Outcomes
Becker et al. 2012	105 subjects	• 72 patients with seasonal/perennial allergic rhinitis • 33 control subjects	• Odor threshold, odor detection and odor identification tests using 'Sniffin' Sticks' kit TDI score calculated	• Lower odor threshold, odor detection and odor identification scores in patients with rhinitis in comparison with the control group
Bogadanov et al. 2020	127 subjects	• 65 with asthma • 62 control subjects	• Taste sensitivity assessed with the suprathreshold 'Taste Sprays' test (perceived/not perceived) • Ability to recognize sweet, sour, bitter, salt using 'Taste strips' Total taste score (TTS) calculated • Responsiveness to PROP using paper strips	• Patients with asthma had significantly lower sensitivity for bitter, salty, and umami tastes and for PROP than control subjects
Cowart et al. 1993	171 subjects	• 91 with symptoms of allergic rhinitis • 80 control subjects	• Odor detection threshold using phenylethyl alcohol	• Higher olfactory thresholds in allergic patients than in control subjects • 23.1% of the patients demonstrating a clinically significant smell loss
Guilemany et al. 2009	109 subjects	• 49 with persistent allergic rhinitis • 60 control subjects	• Detection and identification thresholds and percentage of correct responses (i.e. accuracy) of 20 components for the olfactory CN and 4 components for the trigeminal CN of the Barcelona Smell-taste Test-24 (BAST-24)	• Smell detection, identification, and accuracy tests were significantly worse in allergic patients than in healthy controls for the odors related to the olfactory and trigeminal CN.

Simola et al. 1988	209 subjects	• 104 with perennial allergic rhinitis • 101 control subjects	• Odor detection thresholds tested with a commercially available kit of squeeze-bottle pairs	• Impaired sense of smell in subjects with perennial rhinitis • 15% patients with moderate anosmia