# NIH Workshop Report: sensory nutrition and disease

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**ABSTRACT**

In November 2019, the NIH held the "Sensory Nutrition and Disease" workshop to challenge multidisciplinary researchers working at the interface of sensory science, food science, psychology, neuroscience, nutrition, and health sciences to explore how chemosensation influences dietary choice and health. This report summarizes deliberations of the workshop, as well as follow-up discussion in the wake of the current pandemic. Three topics were addressed: *A*) the need to optimize human chemosensory testing and assessment, *B*) the plasticity of chemosensory systems, and *C*) the interplay of chemosensory signals, cognitive signals, dietary intake, and metabolism. Several ways to advance sensory nutrition research emerged from the workshop: *1*) refining methods to measure chemosensation in large cohort studies and validating measures that reflect perception of complex chemosensations relevant to dietary choice; *2*) characterizing interindividual differences in chemosensory function and how they affect ingestive behaviors, health, and disease risk; *3*) defining circuit-level organization and function that link and interact with gustatory, olfactory, homeostatic, visceral, and cognitive systems; and *4*) discovering new ligands for chemosensory receptors (e.g., those produced by the microbiome) and cataloging cell types expressing these receptors. Several of these priorities were made more urgent by the current pandemic because infection with sudden acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the ensuing coronavirus disease of 2019 has direct short- and perhaps long-term effects on flavor perception. There is increasing evidence of functional interactions between the chemosensory and nutritional sciences. Better characterization of this interface is expected to yield insights to promote health, mitigate disease risk, and guide nutrition policy. *Am J Clin Nutr* 2021;113:232–245.

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## Introduction

The foods and fluids a person ingests can satiate, nourish, and promote growth. They can also cause harm—either within

 

minutes or hours after swallowing or after longer periods of intermittent ingestion (1). The chemosensory receptors of the nose, mouth, and throat provide the brain with information about the composition of foods and fluids, which in turn influences the probability of ingestion or rejection (2). For this reason, the chemical senses of taste and smell, together with chemesthesis—the chemical sensitivity of the somatosensory system—play a role in body weight and nutritional state (3).

On 12–13 November, 2019, the NIH held the "Sensory Nutrition and Disease" Workshop (4) in Bethesda, Maryland, to engage a diverse group of basic science and clinical researchers working at the interface of sensory and nutrition sciences to explore the potential of chemosensory biology to influence food preferences, intake, and nutrition. Here, the workshop is summarized, identifying new research and approaches needed for understanding how the chemical senses ultimately influence nutrition and health. Such knowledge can be used to mitigate chronic disease risk and help develop interventions that promote healthier diets. This workshop summary also includes perspectives on priorities emerging from the coronavirus disease of 2019 (COVID-19) pandemic (5).

Three main topic areas were identified by workshop participants: *A*) the need to optimize human chemosensory testing and assessment, *B*) the plasticity of chemosensory systems, and *C*) the interplay of chemosensory signals, dietary intake, and metabolism. These topics highlight current overarching questions at the interface of taste, smell, and food choice. Eleven gaps and opportunities were identified in our current understanding of how chemosensory biology influences nutrition and disease, including those subsequently identified by the effects of COVID-19.

## Organization of the Chemosensory Systems

Each chemosensory system provides unique information to the brain. The olfactory system responds to thousands of different types of airborne molecules, whereas the gustatory system responds to a more limited set of chemicals in food and beverages, such as salts, sugars, amino acids, alkaloids, acids, and fats. The oronasal trigeminal system responds to chemicals in either volatile, liquid, or solid form via chemically sensitive receptors of the somatosensory system—a sensitivity referred to as chemesthesis (6). The signals from these different chemosensory systems interact [e.g., (7)] to form a flavor percept. This is the term for a composite perceptual integration of taste, smell, and chemesthesis and oral somatosensation, including food texture and temperature (8, 9).

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Abbreviations used: CCK, cholecystokinin; COVID-19, coronavirus disease of 2019; GLP-1, glucagon-like peptide 1; RNAseq, RNA sequencing.

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Although many factors influence dietary choice and consumption, flavor is a primary driver of the amount and type of food a person or other animal chooses to eat. Sensory nutrition is studied in controlled environments with model organisms, in laboratory settings with human participants and direct or indirect measures of intake and health, and eventually translated into community and population-based studies to test the generalizability of laboratory-based findings.

## Topics in Sensory Nutrition

Although there has been progress in understanding smell, taste, and chemesthesis, distillation of the presentations and discussion from the "Sensory Nutrition and Disease" Workshop highlighted 3 interconnected topic areas that warrant additional research (see **Table 1**): *1*) optimizing chemosensory testing with whole foods to complement research of simpler taste and smell stimuli; *2*) plasticity in smell, taste, and chemesthesis systems and effects on sensory and hedonic behaviors and responses; and *3*) the interplay of chemosensory signals, dietary intake, microbiome, and metabolism.

Three consistent themes emerged from all 3 topic areas. One theme was the historic reliance on simple chemosensory stimuli, such as single odorants or taste compounds dissolved in water, to study complex behavioral and physiological responses. These stimuli bear little relation to consumption of real-world foods, which integrate taste and smell and other sensory inputs into a compositive flavor experience. Another consistent theme was how the ability to taste and smell (especially in the experience of pleasure) changes with life events, including development and aging; illnesses such as bacterial or viral illness, including COVID-19 (10); age-related conditions (e.g., chronic health conditions, neurodegenerative disorders, polypharmacy); and diet [e.g., (11)]. The third involves interactions between sensation, hedonic value, and feeding state, for example, how the hedonic value of a food increases when a person or animal is hungry. These themes link each of the 3 topic areas discussed below.

### Optimizing chemosensory testing in sensory nutrition paradigms

With notable exceptions [e.g., (12–14)], most human research on the contribution of oronasal sensory signals to flavor and food preferences has largely relied on psychophysical studies with limited taste stimuli (15, 16) or noncommercial stimuli that provide investigators with better experimental control but limited ecological relevance. The dearth of research using real-world foods and beverages has impeded our understanding of flavor perception (17) and highlights the need for cross-talk between sensory psychologists, nutritionists, and food scientists for new research paradigms. As an example, using orally sampled real-world foods could capture relevant orthonasal and retronasal function (18), which could be used to better understand food pleasure (19) and dietary intake (20). Likewise, the flavor quality of low-calorie sweeteners differs depending on the type of food or beverage sweetened (21). New knowledge in this area may aid efforts to reformulate foods to make them

**TABLE 1** Sensory nutrition and disease: research topics and suggestions[1]

| Category | Description |
|---|---|
| Research topics | A) Optimizing human chemosensory testing and assessment |
| | B) Boundaries and mechanisms of chemosensory plasticity |
| | C) Interplay of chemosensory signals, food dietary intake, and metabolism |
| Research opportunities | 1) Chemosensory and hedonic biomarkers for food intake and food-related diseases |
| | 2) Multimodal evaluation of the response to food |
| | 3) Automating and standardizing methods to measure chemosensory behaviors |
| | 4) Connecting individual differences in genetics and experience of taste, smell, and ingestive behaviors |
| | 5) Clinical research in sensory nutrition |
| | 6) Capacity building for the study of big data in the sensory nutrition realm |
| | 7) Tracing neural circuits among peripheral chemosensory cells, gut, and brain across model organisms |
| | 8) Effects of chemosensory stimuli on visceral taste receptors |
| | 9) Microbiome and sensory receptor interactions |
| | 10) Deorphanization of chemosensory receptors, especially with nontraditional ligands |
| | 11) Single-cell RNAseq to define cell types that express chemosensory receptors |
| COVID-19 | i) Loss of taste and smell as a cardinal feature and future research directions |

[1]COVID-19, coronavirus disease of 2019; RNAseq, RNA sequencing.

healthier (e.g., reduce sugar) and more palatable (e.g., reduce bitterness).

New research approaches that enable systematic manipulation and measurement of sensory properties of foods and beverages are necessary to understand the contributions of flavor to the mechanisms of dietary choice. The development of defined but ecologically relevant food stimuli will pose technical challenges and complicate experimental designs and analyses, including for translation outside of laboratory settings. To meet these challenges, interdisciplinary collaborations are needed among researchers with expertise in food science and technology, the chemical senses, oral somesthesis, psychology, nutrition, and public health.

## Mechanisms of chemosensory plasticity

One burgeoning theme in chemosensory neurobiology is that chemosensory systems are highly plastic. For example, experience-dependent changes can occur at all levels of the olfactory system, including the olfactory epithelium. These changes include basic gain-control functions, where the system adjusts to environments with more or fewer odors (22–25). They also include strong associative plasticity (26). In animal models, pairing odors with strong positive (liked) or negative (disliked) stimuli causes radical changes in the numbers of neurons responsive to those odors in the olfactory epithelium (27, 28). In addition, stimulus–odor pairing causes alterations in the odor-evoked activity of the olfactory nerve (29, 30) and changes in the firing of neurons in the olfactory bulb (31–33), olfactory cortices (34, 35), and beyond. Similar experiences have been confirmed to induce perceptual changes in humans (36–38).

The taste system is also plastic (39–44) and changes over time (45, 46), for example, with age (47–49), as a result of illness (50, 51), or with changes in diet (52). These changes may affect individual eating habits. For example, it is commonly believed that eating a low-sugar diet makes people more sensitive to sucrose (53), which may in turn reduce the liking for high-sugar foods. Testing this idea experimentally is topical because of the public health pressure to reduce intake of sugar (as well as salt and fat), with the expectation that people will acclimate over time, with foods with lower salt, sugar, or fat eventually becoming more palatable or even preferred. In humans, the best-studied taste effect based on dietary change is salt reduction: when people adopt a diet lower in sodium, they gradually adjust and come to prefer lower levels of saltiness (54). The same has been shown for fat (55, 56). Similar studies to evaluate the effects of low-sugar diets are under way.

Similarly, experience-dependent changes in liking and preference for hot and spicy foods are well known (57) but not well understood. The lack of understanding no doubt is due to the involvement of multiple factors (58), ranging from desensitization of chemesthetic receptors that occurs with frequent exposure (59) to personality variables (60). In addition, the possible contribution of postingestive nutrient effects to increases in liking of hot and spicy foods over time, such as flavor-nutrient conditioning (61), has not been investigated.

When studying the plasticity of the chemosensory systems, a few methodological details warrant particular attention. First, using sodium reduction as an example, all studies carried out to date have used abrupt reductions in salt consumption, whereas a gradual reduction of salt consumption is recommended (54). Thus, dietary change studies need to consider the rate of change as well as the final magnitude of reduction. Another aspect of experimental design is choice of outcome measures. In addition to taste and the habitual aforementioned intake and choice measures, other outcome measures usually comprise body weight and/or other measures related to metabolic disease (e.g., fasting or postprandial plasma glucose concentration). However, building on animal studies, these measures should be expanded to include less obvious but equally important outcomes, such as cognitive performance (62–66). Another consideration is the period of study. For example, studies of hedonic shifts indicate they require 8–12 wk to manifest and may be reversible in similar time spans. Similarly, changes in taste preferences after bariatric surgery are a model system for human taste plasticity, but the period of measurement has been limited to several months, and it is unclear whether favorable changes postsurgery persist beyond that brief window of study (67). In contrast, viral and bacterial infections, which are among the most common causes of taste and

smell disorders, may evoke rapid changes (68), requiring methods sensitive to the detection of short-term shifts. Such infections may also result in longer-term chemosensory dysfunction, so longitudinal studies are a needed area of research.

The inability to assess the response of the chemosensory cells and nerves to stimuli has been an obstacle in understanding the mechanisms of chemosensory plasticity and its implications for food choice and intake. However, studies in animal models from fruit flies to rodents have quantified the responses of the taste buds and the sensory neurons to stimuli in animals exposed to varying diet compositions. These studies have shown that exposure to diets high in sugar and fat decreases or alters the physiological responses of the taste buds and sensory neurons to stimuli or changes their number (39–44, 69), and 2 recent studies were able to uncouple the effects of weight gain from those of diet composition (42, 44) on the taste system. Further research in model organisms will capitalize on new methods to study old questions about chemosensory plasticity and rapidly generate hypotheses to be tested in human studies.

### The interplay of chemosensory signals, dietary intake, and metabolism

Chemosensory plasticity is intertwined with endocrine responses because metabolism is in constant flux in response to meals, as well as longer-term dietary and lifestyle changes. There is a bidirectional relation between metabolism and chemical sensing (70): taste, smell, and chemesthesis affect what animals choose to eat, and what animals eat may influence their chemosensory sensitivities. The nutritional status of an animal or human modulates the relevance and valence of sensory stimuli (71, 72).

The influence of feeding state on taste, smell, and eating may be a key driver of ingestive behavior. As an example, the olfactory epithelium and olfactory bulb express metabolic signaling molecules and receptors, including orexins, ghrelins, neuropeptide Y, insulin, leptin, glucagon-like peptide 1 (GLP-1), cholecystokinin (CCK), and cannabinoid receptors 1 and 2 (73). Caution in interpretation is needed, however, because although these molecules play a role in some cells and tissues as a metabolic signal, here they may only be neuromodulators involved in synaptic transmission at different brain sites underlying functions that have nothing to do with metabolism. However, insulin and leptin both increase spontaneous activity and decrease odor-evoked activity in olfactory sensory neurons in the olfactory epithelium, which points to a direct role in metabolism (74). The activity of mitral cells, a type of neuron in the olfactory bulb, is influenced by insulin, glucose, and GLP-1 (71, 72, 75, 76). The olfactory bulb receives orexin-expressing projections from the lateral hypothalamus (77, 78), whereas some mitral cells from the bulb project to the arcuate nucleus (79). The olfactory bulb and cortex are also interconnected with affective and motivational centers that can play a role in eating behavior, including the amygdala, ventral hippocampus, and orbitofrontal cortex (80–92). In free-living animals and humans, the neural signals are not linear or immutable; context may modulate each step. For example, sweet taste stimuli typically have a positive valence and trigger a feeding response, yet satiety may dampen or even eliminate feeding by modulating central pathways (93–95). In turn, changes in the central processing of sensory stimuli could affect the early steps of the satiety cascade and result in alterations in food intake (96, 97).

The interactions between sensory systems and metabolism may also occur directly in the gut. What we eat may influence gut metabolism acting through chemoreceptors. For example, some bitter taste receptors are upregulated in gut mucosal chemoreceptor cell subtypes of people with obesity and in the gut mucosa of mice with high-fat diet-induced obesity (98, 99), suggesting an interaction with diet or diet-induced intraluminal changes. Also, the chemicals produced by the gut, especially by the microbiome, may affect the brain (100) and may even result in changes in food preferences and choice behavior. Finally, metabolic signaling pathways could act on cells autonomously to directly modulate the responsiveness of the chemosensory neurons, as has been shown in invertebrates (42, 101). Overall, understanding the ability to sense foods via chemosensory receptors in response to metabolic changes may help inform disease treatment and suggest directions for public health policy relating to food and nutrition.

## Specific Suggestions to Address Gaps in Sensory Nutrition Research

This section describes specific suggestions to address current challenges and gaps in sensory nutrition research. In particular, we focus on methods or approaches that are expected to improve the tempo and nature of research in the aforementioned topic areas. These suggestions, summarized in Table 1, are organized hierarchically, starting with the study of whole animals (e.g., behavioral measures), followed by tissues and circuits, and then individual cells.

### Chemosensory and hedonic biomarkers for food intake and food-related diseases

People differ in their ability to smell and taste, owing to such factors as genetics, nutritional state, and age. Effort has been made to translate time-consuming, classical psychophysical tests into brief measures to study individual differences in chemosensation (102, 103), including those designed to measure taste preferences and taste-related behaviors (104). However, chemosensory and hedonic measures are needed that are useful, feasible, and represent complex flavor sensations for population-based studies, to allow us to generalize findings from experimental and clinical studies to the general population. Summaries of a number of population-based studies that have measured smell and taste are provided in **Tables 2** and **3**, respectively. In the United States, brief and standardized measures of smell and taste from the NIH Toolbox were further standardized and included in the 2011–2014 NHANES for adults ≥40 y of age (105). NHANES is a continuous, cross-sectional, multifaceted, nationally representative assessment of the health and diet of the US population, collected via in-home visits and mobile examination centers. The 2011–2014 data provide an opportunity to examine the strength of taste and smell associations across a broad array of diseases and conditions (e.g., cardiovascular, diabetes, kidney disease, obesity, oral health, and respiratory tract), environmental exposures, and behaviors (e.g., dietary, physical activity).

**TABLE 2** Major population-based studies with olfactory data [modified from Yang and Pinto (106)][1]

| Name | Country | Years | Design | Sample | Measure | Brief description of outcome | Reference |
|---|---|---|---|---|---|---|---|
| Betula | Sweden | 1988–2014[a] | Long | Healthy adults | ID | Dysfunction correlated with cognition | (107) |
| Honolulu-Asia Aging | USA | 1991–2012 | Long | Older men | ID | 75% dysfunction; dysfunction as a risk factor for future PD | (108) |
| Rush Memory & Aging Project | USA | 1997–2014 | Long | Cohort of older adults | ID | 55% olfactory impairment; dysfunction correlated with AD | (109) |
| Epidemiology of Hearing Loss Study, Beaver Dam | USA | 1998–2000 | Long | Older adults in 1 US community | ID | 24.5% impairment; increased risk with sinonasal disease, smoking, respiratory infection | (110) |
| Skövde population-based study | Sweden | 2001 | CS | Nationally representative adults | ID | 19.1% dysfunction; increased risk with nasal polyps | (111) |
| Blue Mountain Eye Study | Australia | 2002–2004 | CS | Sydney residents | ID | Dysfunction related to BMI (in $kg/m^2$), cognition | (112) |
| Washington Heights/Inwood Columbia Aging Project | USA | 2004–2010[b] | Long | Older adults in 1 US community | ID | Dysfunction as biomarker of cognitive decline and AD dementia | (113) |
| National Social Life, Health & Aging Longitudinal | USA | 2005[c] | Long | Nationally representative older adults | ID, Thsh | 3% severe dysfunction; dysfunction strong predictor of mortality | (114) |
| Kailuan study | China | 2006 | Long | Adults 18–98 y old; subset | SR | Alteration correlated with larger increases in BP | (115) |
| KNHANES | South Korea | 2009–2011 | CS | Nationally representative | SR | 5% dysfunction; dysfunction correlated with mental health | (116) |
| US NHANES | USA | 2011–2014 | CS | Nationally representative of adults ≥40 y old | ID, SR | 12.4% dysfunction, 6.5% phantom odors | (105, 117) |

[1]AD, Alzheimer disease; BP, blood pressure; CS, cross-sectional; ID, measured identification of odorants; KNHANES, Korean National Health and Nutrition Examination Survey; Long, longitudinal; PD, Parkinson disease; SR, self-report; Thsh, odorant threshold.

[a]Measured in the third wave; [b]measured in the first wave, continuing; [c]measured in the fourth wave, continuing.

**TABLE 3** Sampling of population-based studies with taste data[1]

| Study | Country | Design | Sample | Measure | Brief description of outcome | Reference |
|---|---|---|---|---|---|---|
| Beaver Dam Offspring Study | USA | Long | 1981 adults | Taste/papillae | Taste correlated with body weight changes | (118, 119) |
| National Social Life, Health and Aging Project | USA | Long | Nationally representative older adults | Taste strip identification | 74% gustatory deficit | (120, 121) |
| Swedish 1942 birth cohort | Sweden | 20-y cohort | 6346 adults | Reported taste distortion | 7%; distortions correlated with poor oral and overall health | (122) |
| SONIC | Japan | Long | 621 older adults | Recognition threshold | Gender and cognitive effects on function | (123) |
| Dallas Heart Study/Dallas Biobank | USA | CS | >10,000 | PTC taste | Race and PTC effects on smoking | (124) |
| Genetically isolated village of Carlantino | Italy | CS | 540 healthy inhabitants | PROP taste | Nontasters heavier than tasters; interaction with dietary restraint | (125) |
| UK Women's Cohort Study | United Kingdom | Long | 5500 adult women | PTC taste | Tasters correlated with cancer risk | (126) |
| Silk Road | Asia | CS | 496 adults across 6 countries | PROP taste | PROP related to food preference | (127) |
| Brisbane Longitudinal Twin Study | Australia | Long | 1576 adolescents | Sweet intensity | Sweet–BMI association | (128) |
| IDEFICS cohort | Europe | PCS | 1861 children | Taste/papilla/ preference | Preferences associated with body weight | (129) |
| Generation R Study | Netherlands | Birth cohort | 5585 children | PROP taste | Few PROP–diet/food associations; PROP–body weight associations | (130) |
| US NHANES | USA | CS | Nationally representative adults ≥40 y old | Bitter/salt intensity—whole mouth and regional | 5.24% dysgeusia | (49, 105) |

[1]CS, cross-sectional; IDEFICS, Identification and Prevention of Dietary- and Lifestyle-Induced Health Effects in Children and Infants; Long, longitudinal; PCS, prospective cohort study; PROP, propylthiouracil; PTC, phenylthiocarbamide; SONIC, Septuagenarians, Octogenarians, Nonagenarians Investigation with Centenarians.

The majority of smell tests measure odorant identification (e.g., amyl acetate smells like a banana), which often relates to cognitive function and may not be a sensitive method to understand how smell function affects food intake. In contrast, many taste tests measure intensity responses to a single compound or quality, such as bitterness evoked by propylthiouracil or phenylthiocarbamide. These compounds are often used because of the wide range of responses they evoke (131, 132), but broadening taste testing to other compounds representing other taste qualities and mixtures of compounds to reflect the flavor percept would enrich knowledge of sensory nutrition as it relates to short-term (e.g., viral infection) and chronic (e.g., diabetes) disease. Of particular importance is work on hedonic responses to tastants, because this facet of chemosensory function is probably the strongest determinant of food choice (133).

There are several benefits to developing validated chemosensory measurement tools that are faster and more reliable than current methods as well as standardizing current methods so that results of large-scale studies can be compared directly. In addition, methods are needed to facilitate collection and analysis of large amounts of data [e.g., the All of Us precision medicine initiative and related efforts (105, 134)] to enrich hypothesis generation.

Overall, there is a critical need to optimize chemosensory testing that is feasible for population-based studies and that has relevance to dietary behaviors. Such olfactory and taste methods could produce measures that become biomarkers of long-term dietary behaviors, which, in turn, would enhance understanding of the connections between diet and chronic disease (135).

## Multimodal evaluation of the response to food

Taste and smell have most often been studied in isolation, but their interaction is essential to understand how flavor affects consumption (136), especially hyperpalatability (137) or the idea that some foods [e.g., combinations of fat and sugar (138)] are so hedonically rewarding that overconsumption is inevitable. Moreover, chemesthesis and somatosensory (texture) qualities of flavor also play a role in palatability, food selection, and consumption.

Thus, sensory testing needs to integrate the myriad sensory qualities of foods and beverages. Filling this gap in the field will require interdisciplinary research that considers taste, smell, chemesthesis, vision, audition, and somatosensation not as separate contributors but as essential components of the flavor gestalt that guides food selection and intake.

## Automating and standardizing methods to measure chemosensory behaviors

Animals and humans alike have characteristic behaviors that are objective signs of food and drink enjoyment or rejection (139), but more effort is needed to connect common methods of measuring these behaviors in animals (licking rate, facial expressions, sniffing) with corresponding human behaviors. Facial expressions are an example of how to forge these connections [e.g., (139)], but most human studies rely on food intake and verbal reports of liking, preference, or intensity. Thus, validated and reliable behavioral measures that have direct

correlates between humans and animals would enhance research in this area.

Ideal methods for monitoring and automatically classifying behavior, such as oral movements (licking and swallowing) and feeding behavioral assays, will be practical and compatible with other types of measurement, such as brain function using functional MRI and optical neurophysiological methods (140–142). In humans, neuroimaging methods, particularly functional and structural MRI, have the potential to reveal nutritional effects on the neural substrates of taste, smell, and ingestion. Application of neuroimaging methods to understanding brain mechanisms underlying eating behavior in populations at risk of earlier morbidity and mortality, such as those people who have obesity or diabetes, will be of particular interest (143, 144). The development of these methods should serve as a translational bridge, logically linking findings between animal models and humans.

### Connecting individual differences in genetics and experience to taste, smell, and ingestive behaviors

People differ in how they perceive and respond to the sight, smell, and taste of food. For example, there are well-studied person-to-person differences in bitter perception (145), salivary composition (146), and cephalic-phase insulin responses to the sensory properties of food (147). Studies are needed to determine whether this variability reflects heritable differences across subjects, experience-induced plasticity, or their interaction and whether these effects are larger for certain flavors and tastes such as sweetness and bitterness.

Historically, the extent of genetic compared with other influences was determined by comparing biological relatives—often twins, in the case of humans (148), and inbred, selectively bred, and hybrid strains in animal models (149, 150). More recently, genome-wide association studies, which use large numbers of unrelated people, have inferred heritability by the association of a trait (e.g., the consumption of particular foods or foods with a specific taste quality) with a genetic variant (151, 152). As our knowledge of associations between food-related behaviors expands (153), genotype becomes a standard variable to consider (similarly to age or sex) when assessing taste, smell, chemesthesis, and somatosensation and their relations to food intake.

### Clinical research in sensory nutrition

More than 200,000 people visit a doctor each year for problems with their chemical senses (154). Furthermore, just over 1 in 5 adults in the United States with a smell or taste disorder sought medical care for this disorder according to data from the 2014–2016 NHANES and the baseline for one of the HealthyPeople 2030 goals (155). Clinical studies of the chemesthetic senses are needed because impairments in these senses have important implications for health and quality of life. Few clinical studies have assessed chemosensory measures or clinical guidelines for treatments, and, as aforementioned, we need to optimize rapid, standardized measures for the clinical setting that could extend to nonclinical settings. In addition, existing treatment strategies for taste and smell disorders are limited and often ineffective (156). More studies are also needed to connect chemosensory alterations to other clinical disorders such as diabetes, obesity, and cancer, and we need increased support for chemosensory clinician-scientists to foster interdisciplinary collaborations.

### Building capacity to facilitate the use of big data in the sensory nutrition realm

Very large data sets are being generated that could expand our understanding of sensory–nutrition interactions. Some examples are the UK Biobank (157), the Million Veteran Program (158), and All of Us (159), which are large-scale efforts to study hundreds of thousands to millions of people through health records, surveys, biological samples, and other physiological indexes, as well as genetic data. Studies based on these data sources could further inform us about how flavor affects food choice and how variation in taste and smell receptor genes affects human health.

Thus, new large-scale collaborative initiatives and training programs in artificial intelligence and data science are needed for chemosensory scientists in the biomedical workforce. It will also be important to offer retraining programs for established scientists hoping to gain skills in these new computational areas. Finally, support for interdisciplinary teams is needed to fully mine the chemosensory data and direct analyses of chemosensory-related genes.

### Tracing neural circuits among peripheral chemosensory cells, gut, and brain across model organisms

The interplay of taste, smell, chemesthesis, somatosensation, and digestion arises from neural connections between the nose, oral cavity, gut, and brain. One example of this interplay is the cephalic-phase response, which arises when food-related sensory inputs stimulate centers in the brainstem (e.g., the dorsal motor vagal nucleus), which in turn initiate parasympathetic and/or sympathetic response pathways. Another example of this interplay is between nutrient-sensing responses in the gut and the brain–gut axis connections. However, the nature of the effective stimuli, afferent pathways to the brainstem, integrating centers in the brainstem, and efferent pathways to the periphery remain largely unknown. Thus, knowledge about the interaction between the cephalic chemosensory systems, the viscera, and the gustatory system would close this knowledge gap concerning neural circuits. A better understanding of this neural circuitry in different model organisms would inform the interplay of chemosensation, food intake, and metabolism.

One challenge to the study of chemosensory brain circuitry in mammals is its unfavorable anatomy. For instance, gustatory areas pose unique challenges to their study in rodent models. Subcortical and cortical regions are small, cytoarchitecturally heterogeneous, and located in inaccessible anatomical positions (95). Thus, the anatomy of the taste system makes it hard to measure the responses of specific types of taste cells to stimuli in awake, behaving animals. Development of multisite neural recording methods and stimulation approaches suitable for the taste-related brain areas is critical to delineate the complex interconnectivity of the gustatory system with central circuits. Further, it will be important to continue leveraging the advances in knowledge brought by studies in invertebrate model organisms,

with research informed by hypotheses relevant to and formulated from human and preclinical models.

### Effects of chemosensory stimuli on visceral taste receptors

Many chemosensory receptors are expressed in the gut and viscera, and their function has been only partially characterized. Current data suggest that these sensory pathways contribute to nutrient digestion and metabolism, and ultimately to obesity, diabetes, and other diet-related diseases. For example, hyperglycemia downregulates sweet taste receptor expression in $\beta$-cells, leading to compensatory alterations in insulin secretion in obese and diabetic mouse models (160). Likewise, in patients with type 2 diabetes, intestinal sweet taste receptor mRNA levels are inversely correlated with fasting glycemia (161). These sweet taste receptors are dysregulated in response to high luminal glucose (162) and by acute high-sucrose feeding (163). These observations suggest that taste receptors may be, in part, responsible for adaptive responses to imbalances in nutrient availability (e.g., diabetes and refined carbohydrate intake, coronary artery disease, and high saturated fat intake) and signal the need for additional research to explore the function of chemosensory receptors in the viscera.

### Microbiome and sensory receptor interactions

The role of the microbiota in health and disease is ever-expanding, with its application to sensory nutrition inevitable at least in part because the microbiota in the upper airway and gastrointestinal tract, starting with the tongue, are a rich source of chemical signals. One new research avenue is the study of sometimes subtle changes in the diet and how they affect the gut microbiome [e.g., (164, 165)], perhaps reshaping it over generations. For example, rats selectively bred for high sweet preference reliably differ in the pattern of their gut microbiota compared with rats bred for low sweet preference (150). Another avenue of research is to study microbes that can produce chemicals that influence behavior (166–169) and to determine whether chemosensory bitter taste receptors detect these signals in the gut (as they do in the nose) (170). These chemical signals could be similar to or the same as neurochemicals produced by the host and affect host behavior (100, 171), for example, by getting the host to eat more of the type of food that members of the gut microbiota can easily metabolize (172). The nose and tongue also contain a diverse microbiome (173, 174), which may affect taste and smell directly. Currently, most studies of the microbiome are correlative, but the challenge ahead is to test these microbiome–host interactions experimentally. Another challenge is to have hypotheses in advance of the analysis of the very large data sets generated by most microbiome sequencing studies and to rapidly incorporate new knowledge about how to translate raw DNA sequencing data into more accurate descriptions of the microbiome [e.g., (175)].

### Deorphanization of chemosensory receptors, especially with nontraditional ligands

Taste and smell receptors are part of a large family of G-protein-coupled receptors that sense extracellular chemicals and initiate responses that result in conscious perception. However, many of these receptor proteins selectively respond to ligands that are not traditional taste or smell stimuli, including those produced in the host's own body, such as metabolites, bacterial metabolites, hormones, and neurotransmitters. Likewise, proteins identified in other tissues because of their role in metabolite sensing (e.g., sugar transporters) can act as noncanonical taste sensors (176).

Ecnomotopic taste and olfactory receptors continue to be identified, but their significance often remains unknown. For example, a mouse bitter receptor has been reported to abide in gastric parietal and chief cells (177), and a human bitter taste receptor has been described in subtypes of enteroendocrine cells of the colon, including GLP-1, peptide YY, and CCK cells (98). Another bitter taste receptor has been observed in epithelial cells of the rodent small intestine (178), and yet another bitter receptor has been described in mouse Paneth cells and goblet cells (179, 180). Their functional roles in these locations have yet to be characterized.

This broad distribution of receptors in various cell types across the gut supports the concept that these chemosensory receptors serve as modulators of several functions, such as glucose homeostasis, gut motility and secretion, nutrient sensing, and secretion of hormones with purported appetitive properties (181, 182). Identifying the ligands of these receptors and sensors may uncover novel therapeutic opportunities. For instance, treatment with selective bitter agonists might target intestinal receptors and constitute a nonsurgical approach with the same benefits as bariatric surgery. However, these types of therapeutic opportunities will be easier to accomplish if the entire receptive range of these receptors is known, rather than focusing on classic taste and smell ligands (183, 184). Studies to identify this broad range of ligands also need to include those for receptors of model organisms, especially rodents, because there is often limited conservation of receptors between humans and model organisms (185). For preclinical animal studies to predict effects in humans, a functional human counterpart—in both its response to the specific compound of interest and its pattern of tissue expression—needs to be identified.

Thus, research programs to match both canonical and non-canonical chemosensory receptors to ligands should expand to include ligands beyond classic taste and smell stimuli (e.g., metabolites, hormones) and to include model organisms (e.g., fly, worm, mouse) in addition to human receptors. This new knowledge would pave the way for potent and selective pharmacological tools to study these receptors and their potentially broad role in human health and disease.

### Single-cell RNA sequencing to define cell types that express chemosensory receptors

Chemosensory receptors were originally identified and characterized in taste and olfactory receptor cells, but how many additional cell types contain these receptors and their function in these different cell types are unknown. As is often the case with receptor proteins, the low expression of chemosensory receptors or their expression in a few rare cell types within a tissue hinders their detection, and they are seldom found in global RNA sequencing (RNAseq) analyses (186) or in proteomic studies (187).

Single-cell RNAseq methods provide a more sensitive approach to identify the cell-specific expression of taste and

olfactory receptors throughout the body. Analysis of even a single tissue using these methods reveals many more cell types than previously identified [e.g., (188)] and allows investigators to construct more informed hypotheses to test their function. Large-scale efforts to examine the cellular composition of common tissues are under way (189), but taste, smell, and chemesthetic tissues are often ignored by large-scale projects [for an exception, see (190)]. These single-cell studies would be most useful with a complementary effort to get validated antibodies to confirm the presence of certain markers in particular sensory cell types. Olfactory receptor proteins are hard to measure (187) and validated antibodies for chemosensory cells are often lacking (191). The goal of defining the cell types that express chemosensory receptors is made more urgent by an emerging appreciation that receptor functions can differ based on the number and type of chemosensory receptors expressed in a given cell type (192). Therefore, methods that define and validate taste and olfactory receptor cell types are a current priority.

## COVID-19 and Sensory Nutrition: Gaps and Opportunities

Several months after the NIH conference was held, the US CDC declared an outbreak of SARS-CoV-2 (i.e., sudden acute respiratory syndrome coronavirus 2), which leads to COVID-19, a pandemic (5). Abrupt loss of taste and smell is among the most reliable predictors of COVID-19 (193, 194), which highlights the urgent need for practical tests of chemosensory loss that are standardized, valid, and reliable (195). Taste and smell loss with COVID-19 is fully or partially regained, but it is currently unclear what the long-term consequences will be on flavor perception, food preferences, food intake, and broader disease risks. Especially relevant are the high rates of parosmia (distortions of smell) or phantosmia (smelling something that is not present) in those with COVID-19 (10), which may have long-term consequences for nutritional health.

## Summary

Understanding the determinants and consequences of an unhealthy diet is critical because it is the root of many chronic diseases, including obesity, diabetes, and heart disease. Similarly, disorders affecting chemosensory functions may compromise diet quality, predisposing individuals to health complications. To understand these complex relations, the study of sensory influences on nutrition will require the collective efforts of teams comprising diverse expertise in a wide range of fields, such as food scientists, nutritionists, psychologists, neuroscientists, geneticists, molecular biologists, microbiologists, statisticians, and computer scientists, working on multiple model organisms. Such multidisciplinary research teams will move the field forward by expanding markers, inputs, and methods to use in chemosensory and metabolism research. Establishing connections in big data, neural circuitry, and individual genetics and behaviors to identify the chemosensory stimuli, receptors, and cell types that contribute to food choice and metabolism will jumpstart this effort. Collecting robust, reproducible data will facilitate better prediction and mitigation of disease risk and guide sound nutrition policy.

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