The flavor of chemotherapy

THE FLAVOR OF CHEMOTHERAPY

Exploring smell and taste function in children with cancer

Mirjam van den Brink

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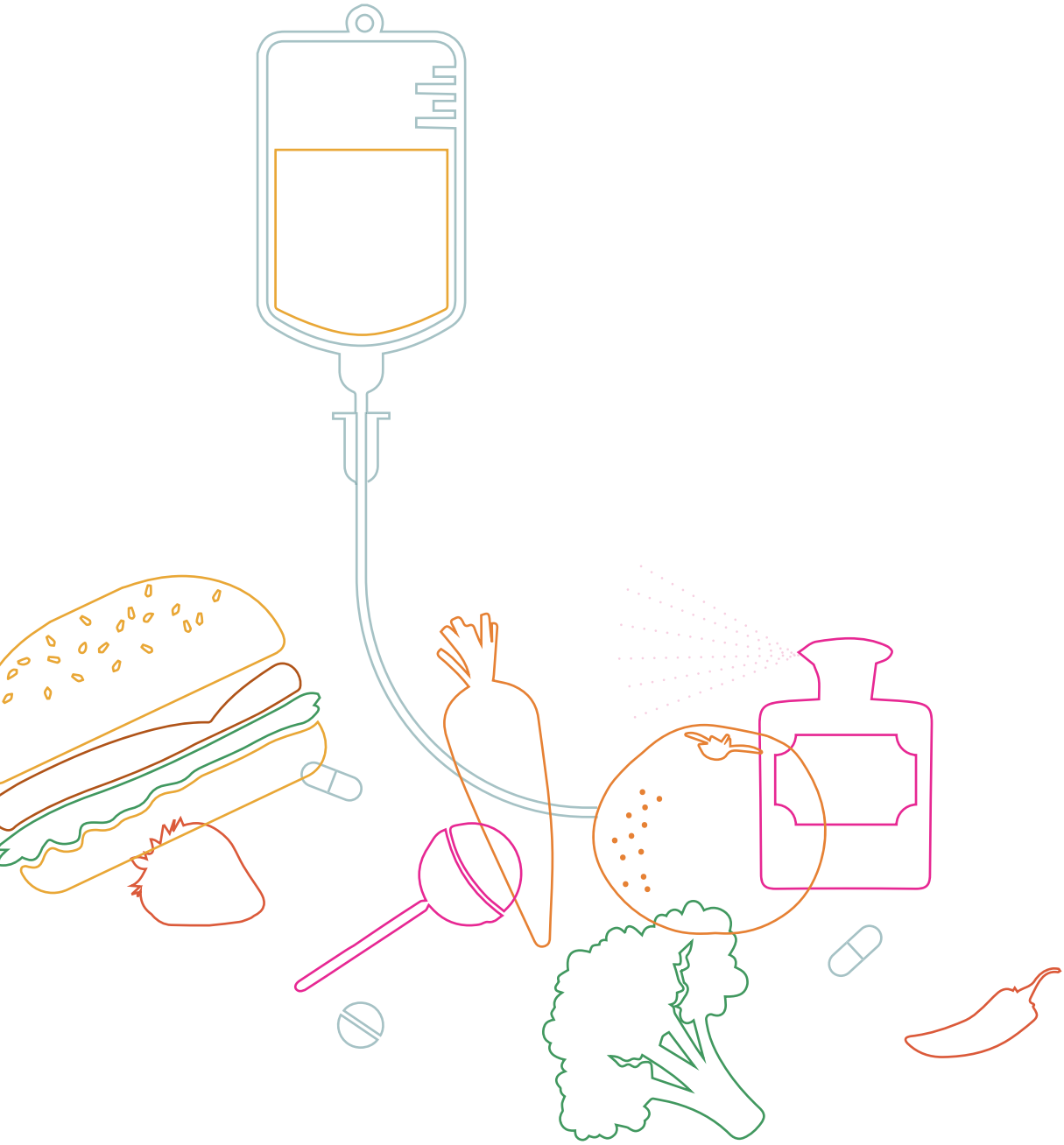

1

General introduction

PEDIATRIC ONCOLOGY

Although childhood cancer is a rare disease, it is a major cause of death among children in the Western world [1]. Each year, around 400,000 children are diagnosed with cancer worldwide, including 600 patients in the Netherlands [1, 2]. Childhood cancer can be roughly categorized into hematological, solid, and brain malignancies. More specifically, 12 diagnostic categories are defined by the International Classification of Childhood Cancers (ICCC) (Figure 1) [3]. Brain tumors and leukemia are the most prevalent types of childhood cancer in the Netherlands, accounting for 22% and 21% of all cancer cases respectively [2]. In the Netherlands, care for all childhood cancer patients is centralized in the Princess Máxima Center for Pediatric Oncology in Utrecht, which opened in June 2018.

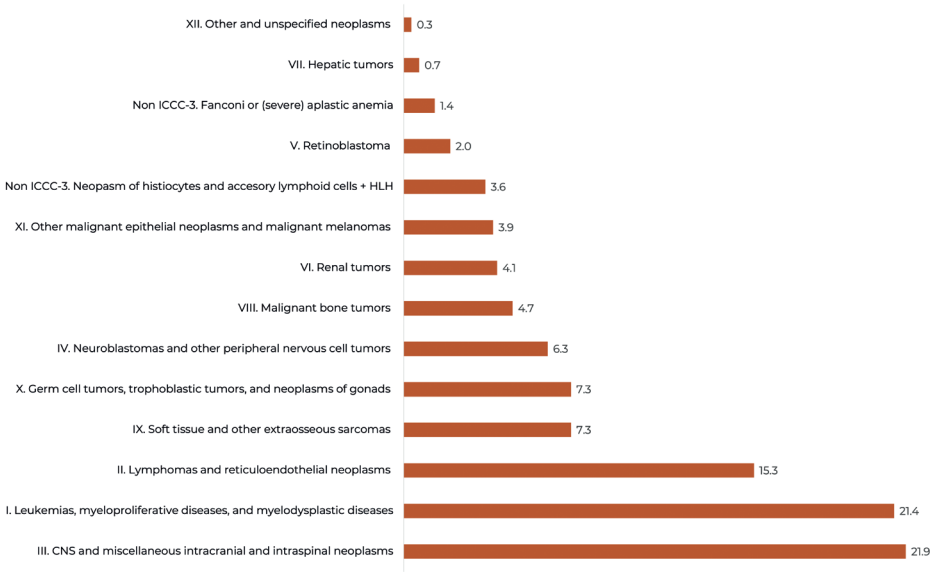

Figure 1. Incidence of childhood cancer in percentages in the Netherlands in 2020 [2].

To date, the exact etiology of pediatric cancers remains unclear. Cancer cells are faulty cells that grow uncontrollably. An accumulation of mutations may debilitate the control of cell division and proliferation, prompting a cell to become cancerous. Adult cancers are characterized by a high number of these so-called somatic mutations. However, this is not the case in children with cancer. Childhood cancer has a relatively low mutational burden, but a higher prevalence of germline alterations in cancer

predisposition genes [4]. Studies have started to unravel the complex underlying molecular mechanisms of childhood cancer, but these are still poorly understood.

Chemotherapy is the most common treatment modality across the various types of childhood cancer followed by surgery, radiation therapy, immunotherapy, and stem cell transplant [5]. Chemotherapy can be defined as a treatment regimen involving the use of cytostatic (inhibit cell division) and cytotoxic (induce cell death) drugs, designed to target rapidly dividing cancer cells. A distinction can be made between different drug classes, all having their own mechanism of action (Table 1) [6].

Table 1. Groups of most commonly used chemotherapeutic drugs in pediatric oncology [6].

Drug class	Examples of drugs used in pediatric oncology	Mechanism of action
Alkylating agents (including platinum agents)	· cyclophosphamide · ifosfamide · melfalan · busulfan · lomustine · cisplatin · carboplatin · dacarbazine · temozolomide	Add chemically reactive compounds to DNA strands, which causes cross-linking of DNA
Antimetabolites	· methotrexate · mercaptopurine · thioguanine · fludarabine · cytarabine · fluoruracil	Block synthesis of nucleotide precursors or are directly incorporated into DNA as fraudulent bases
Topoisomerase (I and II) inhibitors	· topotecan (I) · irinotecan (I) · doxorubicin (II) · daunorubicin (II) · mitoxantrone (II) · dactinomycin (II) · etoposide (II)	Interfere with DNA relegation, resulting in protein-associated DNA strand breaks
Tubulin inhibitors	· vincristine · vinblastine · vinorelbine · paclitaxel · docetaxel	Inhibit cell mitosis by binding to the protein tubulin, which blocks microtubule depolymerization
Miscellaneous agents	· arsenic trioxide · PEG-asparaginase · bleomycin · dexamethasone · prednisone	Apoptosis Asparagine depletion Free radical-mediated DNA breaks Receptor-mediated lympholysis

At present, 5-year survival of all pediatric cancers combined is approximately 80%, which was only 40% in the 1970s [7, 8]. Survival rates vary between types of childhood cancer – or stage of disease at diagnosis – with the most unfavorable prognoses being malignant brain tumors (high grade glioma, pontine glioma), neuroblastomas, and osteosarcomas [9]. Increased survival can be attributed to early diagnosis, development of novel treatments, intensified chemotherapeutic regimens, and improved supportive care. Unfortunately, for some childhood cancer types survival rates did not – or hardly – increase over the last years [9]. Especially for children with neuroblastomas, bone tumors, or particular brain tumors, much more improvement is necessary. New clinical trials are needed and these trials require international collaborations to be able to include enough participants from an already heterogeneous population [10].

Furthermore, supportive care clearly needs to receive more research attention. In recent decades, improvement of supportive have already resulted in better survival. For example, intense chemotherapy causes adverse side effects such as febrile neutropenia, leading to delay or reduction of chemotherapy dose, increased morbidity and mortality, and longer hospital stays [11, 12]. However, the introduction of hematopoietic growth factors, which promote the proliferation and activation of neutrophils in the bone marrow, has significantly reduced the duration of neutropenia and associated complications, allowing for more intensive treatment in children with cancer [13, 14]. Nowadays, for certain diagnoses (such as hematological malignancies), children are more likely to die from treatment-related mortality than disease progression [15]. Reducing treatment-related side effects such as bacterial infections, pain, and nausea has been associated with better survival and quality of life in children with cancer [16]. Therefore, interventions are needed to decrease these side effects in order to further increase overall survival, but also ensure that children tolerate their treatment physically and mentally as well as possible. In this way, supportive care research fits well within the mission of the Princess Máxima Center: '*Curing every child with cancer, with an optimal quality of life*'.

SUPPORTIVE CARE AND NUTRITIONAL STATUS

Supportive care can be defined as the prevention and management of the adverse effects of cancer and its treatment not only during treatment, but also

during survivorship or end of life care [17]. It encompasses physical and functional, psychological, social, and spiritual well-being, aiming to improve quality of life of patients and their relatives. In order to relieve the patients' symptoms and side effects, several specialists are involved including pediatric oncologists, nurses, pain specialists, physiotherapists, social workers, psychologists, and dietitians.

When focusing on nutritional status of children with cancer and nutritional support provided by dietitians, it is known that children treated for cancer are at risk for malnutrition. Malnutrition refers to an inadequate nutritional condition in which a deficiency or excess of energy, protein, or other nutrients causes adverse effects on the body and hence unfavorable clinical outcomes [18]. Almost all children suffer from treatment-related side effects interfering with food intake, such as oral mucositis, nausea, changes in taste, or less appetite, potentially leading to weight loss and undernutrition [19, 20]. In contrast, children with cancer can also be vulnerable to excessive weight gain during – and after – treatment [21-24]. In children with cancer, both undernutrition and overnutrition are associated with adverse outcomes such as toxicity, poor survival, and worse quality of life [25-27].

SMELL AND TASTE CHANGES

The importance of nutritional status is often underestimated in the treatment of cancer. Side effects that are even more often overlooked during treatment are changes in smell and taste [28]. Nevertheless, chemosensory changes are common among adult cancer patients treated with chemotherapy, showing occurrence rates between 45% and 84% for taste changes and between 5% and 60% for smell changes [29]. These changes not only contribute to inadequate food intake, but also reduce food enjoyment and social pleasure in the daily lives of adult cancer patients and their relatives [30-32] . Until recently, it was not known how often children with cancer experience such changes. However, evidence now suggests that changes in both smell and taste are common in children with cancer too and are often experienced as a very bothersome treatment effect [19]. In addition to being a very bothersome side effect of treatment, it may affect eating behavior (i.e., food choice and intake) and hence contribute to a poor nutritional status. Chemosensory function (i.e., smell and taste) and how it may suffer from cancer treatment is described in more detail in the following sections.

Smell function

The general role of smell – or olfaction – is to warn us of dangerous or life-threatening situations such as cooking accidents, ingestion of spoiled foods, and detecting fires or gas leaks [33]. Moreover, olfaction plays an important role in food intake by inducing appetite and shaping food choices [34]. For example, the smell of freshly baked bread that one smells when crossing a bakery. Such a smell induces appetite and may influence the decision of consuming that particular food. Furthermore, olfaction is also involved in social communication and sexual behavior, including partner choice [35, 36].

It is estimated that humans can detect more than 1 trillion smells [37]. Volatile compounds reach the olfactory epithelium of the nasal cavity through the nose, which is called orthonasal smelling, and from the mouth during eating, which is called retronasal smelling [38]. Within the nasal cavity, volatile molecules make contact with the mucus layer covering the olfactory receptor neurons where they bind with proteins to subsequently stimulate the cilia of the olfactory receptors [39]. From there, olfactory signals are transmitted via the olfactory nerve (Cranial Nerve I) to the olfactory bulb. Unlike other sensory modalities, olfactory signals are not relayed via the thalamus but transferred directly to the primary olfactory structures including the piriform cortex, entorhinal cortex, and amygdala [40]. Subsequently, olfactory information is sent to secondary olfactory structures composed of the insular cortex and orbitofrontal cortex.

Taste function

The sense of taste – or gustation – is mainly involved during eating and not in the anticipation of eating, like smell does. The importance of the gustatory system is to identify and consume nutrients, but also to protect humans of ingesting toxic substances [41]. It is important to note that taste is only one component of flavor. During eating, taste, smell, and mouthfeel sensations (including chemesthetic sensations such as pungency and astringency) are combined in the mouth, leading to a unitary percept called flavor [40]. Especially sensations that arise from retronasal smelling play a dominant role in flavor perception **(**Figure 2**)**, which is often confused or misused in everyday language. This is illustrated by the fact that aromas of chocolate, garlic or lemon are often attributed to the gustatory system, but in fact only five basic taste qualities have been identified: sweet, sour, salty, bitter, and umami. Each taste quality is associated with nutritional quality of food that helps guide food intake and food choice [41]. Sweet signals carbohydrates, and thereby the energy content

of food. Sour taste is linked to the pH of a food substance and guards acid-base balance in the body. Because sour taste is generally aversive (think about spoiled foods), we avoid ingesting excess acids. Salty taste is associated with various salts such as sodium chloride. Intake of sodium is important for maintaining the body's water and electrolyte balance. Many poisonous organic substances taste bitter. Bitter taste thus warns us against ingestion. Umami, the taste of glutamate, refers to the protein content of foods.

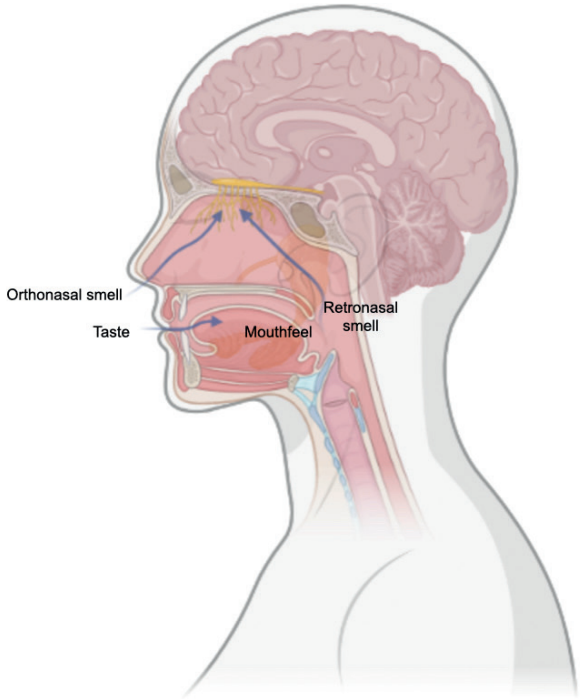

Figure 2. Different sensory modalities and pathways involved in food flavor perception. Image was created with BioRender.

Taste perception starts when taste receptor cells are activated by chemical stimuli. These taste receptors cells are modified epithelial cells, which are clustered in groups of 50 to 100 to form taste buds [42]. Taste buds are mostly located in gustatory papillae on the tongue, which can be fungiform, vallate, or foliate papillae. Each taste bud consist of several type cell types, each having their own function [41]. Type I cells, which are most abundant, are involved in ion redistribution and neurotransmitter clearance. Probably, type I cells play a role in salty taste perception. Type II cells are G-protein-coupled receptors that respond to sweet, bitter, and umami taste. Moreover, type II

cells induce the release of adenosine triphosphate (ATP). Type III cells are more neuron-like or pre-synaptic cells. These cells respond to sour taste molecules. Taste signals are distributed to the brain through the facial, glossopharyngeal, and vagus nerve (Cranial Nerve VII, IX, and X, respectively) that innervate the taste buds [42]. These gustatory nerves synapse in the nucleus of the solitary tract in the brainstem. From there the taste pathway continues to the insula and frontal operculum via the thalamus.

Smell and taste changes during chemotherapy

As described above, smell and taste changes appear to be common and very bothersome for childhood cancer patients. Distortions of the chemical senses can be categorized into quantitative and qualitative disorders. The former describes measurable changes in the detection threshold for odors or tastants through objective tests (such as Sniffin' Sticks and Taste Strips test), and the latter includes changes in the perceived quality of odors or tastants through subjective measures (usually a questionnaire) (Table 2).

Table 2. Overview of smell and taste disorders.

Quantitative smell disorders		**Quantitative taste disorders**	
Anosmia	Complete loss of smell function	Ageusia	Complete loss of taste function
Hyposmia	Reduced smell function	Hypogeusia	Reduced taste function
Hyperosmia	Enhanced smell function	Hypergeusia	Enhanced taste function
Qualitative smell disorders		**Qualitative taste disorders**	
Parosmia	Distorted smell perception	Dysgeusia	Distorted taste perception
Phantosmia	Smell perception in absence of a stimulus	Phantogeusia	Taste perception in absence of a stimulus

Smell and taste disorders may result from aging, viral infections, head trauma, neurological diseases, exposure to toxic substances or medication [43]. However, cancer itself – including side effects from its treatment – is another potential cause of smell and taste distortions [29]. It is not completely clear what causes these distortions, as previous studies were performed in heterogeneous populations regarding cancer type, stage of disease, and treatment regimen. Nonetheless, it is well-known that chemotherapy and radiotherapy kill rapidly dividing cells and, similar to cancer cells, smell and taste receptor cells have high turn-over rates. The average life span of a taste receptor cell is approximately 10 days, depending on cell type (i.e., type II

cells renew every 8 days, whereas type III cells have a longer half-life of 22 days on average), and renewal of olfactory receptor cells ranges between 30 and 90 days [44-47]. It is hypothesized that cell damage induced by radiotherapy or chemotherapy might cause either a decrease in the number of receptor cells, or a change in cell structure/receptor surface, or an interruption in neural coding [48]. In addition, other factors influencing taste function in cancer patients might be medications (such as antibiotics or antiemetics), poor oral hygiene, infections, or reduced saliva [49].

In adult cancer patients, studies have investigated chemosensory alterations in different patient populations such as patients with breast cancer, gynecologic malignancies, testicular cancer, or colorectal cancer [50-56]. A significant decrease in olfactory and gustatory function was found among women with breast cancer and gynecologic malignancies, which was completely restored three months after chemotherapy [50]. Salty taste was affected the most, comparable to a study in testicular cancer patients [50, 53]. Other studies did not find significant changes during treatment, or only in subjective perception [54, 55]. It is suggested that a broad range of cytotoxic drugs, including alkylating and platinum agents (cyclophosphamide, carboplatin, and cisplatin), tubulin inhibitors (vincristine), antimetabolites (mercaptopurine, methotrexate, and fluorouracil) as well as topoisomerase inhibitors (doxorubicin), are associated with taste changes but not with smell changes [29]. Moreover, a review summarizing the impact of chemosensory changes on eating behavior, showed that alterations in taste, but not smell, significantly affected food intake [57]. Particularly a reduced sweet taste sensitivity seems associated with a lower intake of energy and protein, avoidance of certain foods, and less appetite. It is important to keep in mind that when patients talk about taste changes, they may not be referring to a change in taste perception but to a more hedonic change. In such cases, food tastes like it always did, but that taste is no longer enjoyed.

When focusing on children with cancer, only a few studies regarding changes in smell and taste are available. Changes in taste have been found to be the third most common bothersome symptom among children with cancer during treatment, after feeling tired and feeling more or less hungry than usual [19]. Moreover, approximately 45% of the children with cancer reported any bothersome changes in taste and 9.6% reported severely bothersome changes in taste [58]. However, prevalence rates for taste changes were based on self-report and cross-sectional study designs. Another study found “changes in food taste” not the most frequent, but one of the most distressful

physical symptoms experienced by children and adolescents with cancer [59]. Only few studies measured taste function in small samples of children with cancer, comparing them with healthy controls but not studying the evolution of taste function during treatment. In those studies, higher recognition thresholds for all taste qualities have been found, as well as higher threshold for bitter or sour taste only [60-62]. Higher detection thresholds for sweet and salty have been found in children with leukemia specifically [60]. Smell function has been studied only once in 10 pediatric bone marrow transplantation patients, showing that 20% of the children had smell dysfunction at baseline and at 1 month post-transplant, but this was resolved within 2 months after transplantation [63]. Furthermore, the association between chemosensory changes and outcomes such as nutritional status, food intake, and quality of life has not been studied before in children with cancer.

SUMMARY AND KNOWLEDGE GAPS

In sum, hardly any evidence was available regarding smell and taste function in children with cancer undergoing treatment at the start of this research project. So far, most research was cross-sectional, conducted in small samples, limited to a specific cancer diagnosis, relying on self-report, and almost always limited to taste changes only. However, in clinical practice many children with cancer – and their parents – appear to have questions about nutrition, including how to deal with chemosensory alterations. Nutritional care should be prioritized in advancing care of children with cancer, potentially influencing clinical outcomes including infections, survival, and health-related quality of life. As smell and taste changes are believed to be of great influence on the daily (quality of) life of children with cancer, including the pleasure of eating, they need to be further investigated.

Several questions arise, such as: What are suitable research methods to investigate smell and taste function in seriously ill children and which tests are feasible? How big is the problem of smell and taste alterations in childhood cancer? Which children are most affected by smell and taste changes? Which smell and taste disorders do occur in children with cancer? What is the impact of chemosensory changes on children's live?

AIMS AND OUTLINE OF THIS THESIS

In response to above-mentioned knowledge gaps, we designed several studies (called Sensory and SENSORY-2) at the Princess Maxima Center in Utrecht, the Netherlands. The general aim of these studies was to explore smell and taste function in children with cancer undergoing chemotherapy. Knowledge regarding the prevalence, severity, duration, and impact of smell and taste changes in children with cancer undergoing chemotherapy allows for better information at the start of treatment on what to expect with regard to smell and taste changes. Ultimately, this research aimed to provide children and their parents with more science based nutritional recommendations, thereby improving patient-centered care.

In **chapter 2**, all available evidence regarding taste dysfunction in children and assessment methods is summarized in a review. Interestingly, a lot of research has been performed on olfactory (dys)function and available assessment tools in childhood [64, 65]. However, it was largely unclear which etiologies in childhood might cause taste dysfunction, which tests are available to quantify such a disorder in children, and what tools are suitable to use in clinical practice.

Chapter 3 describes the development of normative values for a taste test (i.e., "Taste Strips") in order to distinguish normal taste function from a reduced sense of taste in a pediatric clinical setting. Apart from establishing normative values, the influence of sex, age, and PROP taster status was investigated. As normative values for children were lacking for the Taste Strips test, results of this study bolster the clinical utility of this test.

In **chapter 4**, the presence and severity of self-reported nausea and nausea-related symptoms in children with cancer during their first year of treatment and its relationship with health related quality of life (HRQoL) is identified. In addition, potential risk factors are described. Data of the nausea scale of the PedsQL Cancer Module was used (proxy-report; 2-7 years, self-report; 8-21 years), consisting of the following items: nausea during medical treatment, food not tasting good, nausea while thinking of medical treatment, being too nauseous to eat, and nausea caused by food/smells. For this thesis, the items "food not tasting good" and "nausea caused by food/smells" were of special interest.

Chapter 5 shows the results of a feasibility study which aimed to investigate whether psychophysical smell and taste assessments can be obtained without unpleasant side effects in children with cancer. Taste and smell function, fungiform papillae density, and eating behavior were measured before (T1) and after (T2) a cycle of chemotherapy. In addition to feasibility assessment, smell and taste data of patients was compared 1) before and after a cycle of chemotherapy; and 2) to healthy controls.

In **chapter 6**, the results of a prospective longitudinal cohort study are described. Smell and taste function were assessed at several time points during active treatment and 3 months after the last chemotherapy (or during maintenance phase in the case of acute lymphoblastic leukemia; ALL). This study aimed to determine the dynamics of smell and taste function in children with cancer during and after chemotherapy, including factors contributing to these changes and whether any tested changes in taste and smell function correspond with self-reported changes in taste and smell.

Chapter 7 describes the results of our qualitative study into the impact of changes in smell, taste, and eating behavior in children with cancer. Children with cancer were invited to share their experiences about topics such as the nature and timing of smell and taste changes in semi-structured interviews. As it was still unclear what makes these changes bothersome to children with cancer and what impact they have on their daily lives, these aspects were also thoroughly investigated.

Chapter 8 consists of an overall summary and general discussion. Most relevant findings are summarized, the implications for clinical practice are thoroughly discussed, and future studies or perspectives are suggested. It also includes a discussion of the strengths, methodological considerations, and limitations of the studies described in this thesis.

Chapter 9 is the concluding chapter in which I briefly discuss the (potential) scientific impact of the research. The relevance and utility of the main findings for children with cancer and their families, society, and health care professionals is addressed, listing recommendations to improve children's quality of life and bolster professional quality of care, ending with an overall conclusion.

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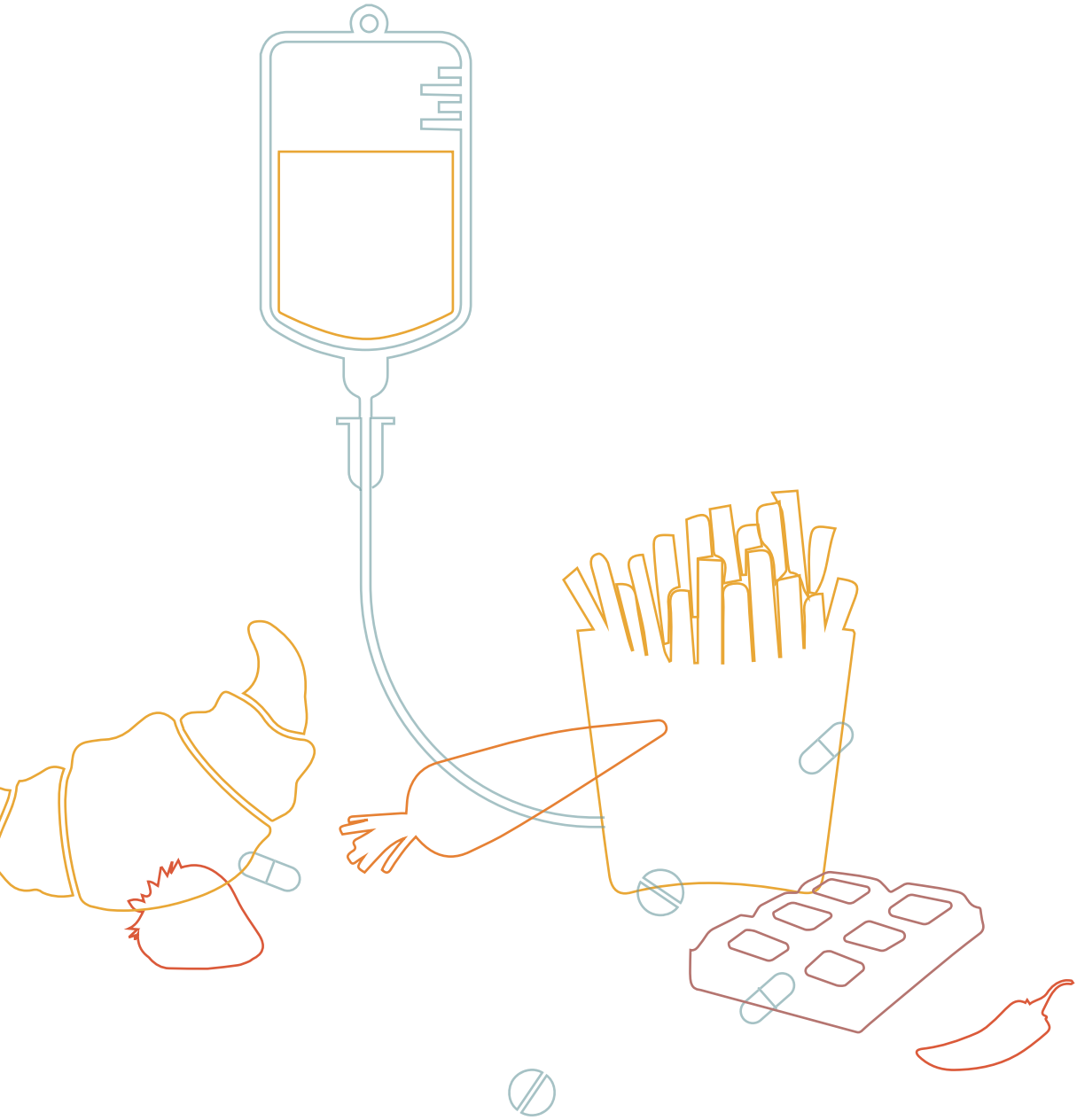

2

Taste dysfunction in children – a clinical perspective and review of assessment methods

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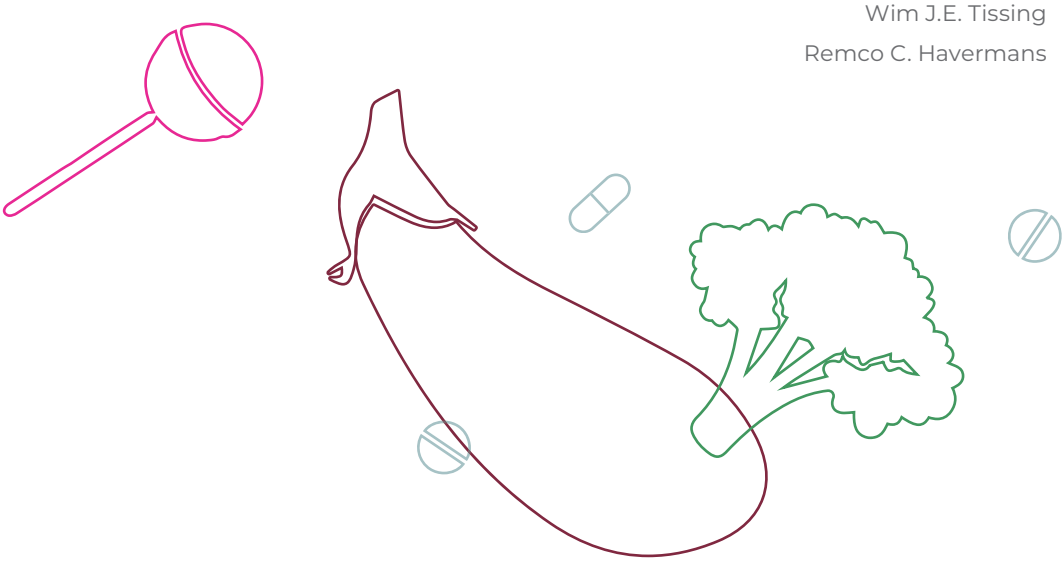

ABSTRACT

Taste dysfunction has been associated with aging and is therefore thought to be less common in children. However, children can face medical conditions influencing their taste function. Measuring and understanding taste dysfunction in children may foster the development of treatments/interventions mitigating the detrimental effects of taste dysfunction on children's appetite and quality of life. But measuring loss of taste function requires adequate tools. This review was conducted to 1) provide an overview of etiologies (i.e., disease and iatrogenic) associated with taste dysfunction in a pediatric population; 2) to investigate which tools (psychophysical tests and questionnaires) are available to assess taste function in children; and 3) to identify what tools can be and are actually used in clinical practice. It is concluded that only a minority of available tools to assess taste function in children are readily suitable for a pediatric clinical setting. Considering the profound impact of taste dysfunction in the pediatric setting, developing and implementing a standard taste test that is sensitive, simple, and practical to use with children is pertinent.

Keywords children, psychophysical test, taste, taste dysfunction, self-report

INTRODUCTION

The chemical senses – smell and taste – are important regarding food intake, safety, and quality of life [1, 2]. That is as true for children as it is for adults. However, most individuals do not acknowledge the importance of their chemical senses until they lose it. It should be noted that individuals complaining of taste problems often suffer from smell loss in the absence of any true taste dysfunction, as differentiating taste problems from smell loss is difficult [3]. In general, taste disorders are rare and have been reported in only 5% of the population [4]. Little is known about taste dysfunction in children. In general, it is thought to be very rare as taste disturbances are associated with aging and other factors such as (chronic) medication use or exposure to toxic substances [5].

Taste dysfunction is uncommon in the general population, but (temporary) loss of taste function is quite prevalent in the clinical setting as it can arise from a wide variety of diseases and/or treatments. Previous work in adults has shown that taste dysfunction is most often the result of disorders of the oral cavity, middle ear infections or surgery, trauma, Bell's palsy, systemic disturbances of metabolism such as diabetes mellitus, or cancer and its treatment [6]. More recently, taste loss has become an important symptom of the coronavirus disease 2019 (COVID-19) infection [7]. Further, several medications used alone or in combination have been reported to potentially change taste function or induce an unusual taste sensation. These include very different but commonly prescribed drugs like aspirin (an analgesic), simvastatin (an antilipidemic), and amoxycillin (an antibiotic) [8].

Like adult patients, children can suffer from a medical condition that will cause taste dysfunction, consequently affecting food intake and quality of life [9]. Presumably, the detrimental impact of such dysfunction might be larger in children, as their eating behavior and food preferences are still developing and are strongly influenced by input from the chemical senses. Therefore, the assessment of taste function in childhood is important, as diagnosis and characterization of taste loss may foster the development of more appropriate supportive strategies such as medication or dietary advice [10]. Note that a comprehensive assessment of taste function should also include measuring smell function as well (for reviews about measuring olfaction in children, see [11, 12]).

Over the past decades, several assessment methods have become available to assess taste function in adults. “Taste Strips” or taste solution drop tests are frequently used in a clinical setting to evaluate sensitivity to sweet, sour, salty, and bitter taste [13-16]. It should be noted that only Pingel and colleagues included a sample of children (age 5 – 15 years) with the development of their solution-based taste test and provided normative values for this age category.

Next to taste solutions tests, electrogustometry (EGM) is used to assess detection thresholds. With EGM, a probe is touched to the tongue through which a small electric current is applied that can evoke a sour/metallic taste sensation. EGM then does not depend on identifying taste qualities, but does allow for determining threshold measures [17]. In addition, questionnaires including patient-reported experiences can be useful for recognition of taste loss or further characterization of a taste disorder.

In sum, little is known about taste dysfunction in childhood. Some etiologies of taste dysfunction in adults may also apply to children, while others don’t. In addition, there seems to be a variety of taste function assessment tools available, at least for adults. However, the question remains what tools can be readily applied in a clinical setting where it is important to be able to diagnose potential taste dysfunction and to gain insight in the severity of any taste dysfunction. In other words, it is still unclear how taste function – or dysfunction – can be adequately assessed in a pediatric clinical setting. Therefore, this review was conducted to 1) provide an overview of etiologies associated with taste dysfunction in a pediatric population; 2) to investigate which tools (psychophysical taste tests measuring thresholds or identification scores and questionnaires) are available to quantify taste (dys)function in children; and 3) to identify what tools can be and are actually used in clinical practice. Taste tests including hedonic evaluation or taste intensity ratings are not discussed in this review as they are less frequently used for assessing taste function (or taste loss) in a clinical setting.

TASTE DYSFUNCTION IN CHILDHOOD

As displayed in Table 1, taste dysfunction is associated with several clinical disorders in children. Studies examining medical conditions that might influence taste function in children can be grouped into the following categories: otolaryngology, oncology, obesity, systemic diseases (excluding oncology and obesity), and other conditions. Some studies do show an association between a specific medical disorder (and/or its treatment) and taste function in children. However, results are not always clear-cut and occasionally no apparent association between disorder and taste function is found.

Regarding otolaryngology, taste loss is a potential risk as infections or surgical interventions may affect the gustatory nerves. However, children with recurrent tonsillitis showed no impaired taste function compared to controls [18]. This was an unexpected finding as repeated tonsillar infections might affect the glossopharyngeal nerve. Another study did show reduced taste ability in children with chronic otitis media as compared to controls. Chronic otitis media refers to inflammation of the middle ear cavity that injures the chorda tympanic nerve [19]. In addition, Leung and colleagues found a wide range of taste dysfunction (5 – 50%) among children who underwent otologic surgery, depending on the technique used, compared to taste dysfunction in the general pediatric population [20].

Childhood cancer and its treatment seems to change taste function in children with cancer. However, results are equivocal and hard to compare, as studies differ in assessment methods, timing of the measurements, and types of cancer. Four studies were performed in pediatric oncology patients, investigating the influence of chemotherapy or blood and marrow transplantation on taste function. A higher threshold for bitter taste, and more taste recognition errors, has been found among children receiving chemotherapy compared to controls [24]. In contrast, we found that children with a wide number of cancer diagnoses receiving chemotherapy are better at identifying sour taste than healthy controls. In addition, we found indications that bitter and sweet taste sensitivity increases in children from before to after a cycle of chemotherapy [27]. Regarding blood and marrow transplantation, a decreased taste function has been found in children with cancer shortly after blood and marrow transplantation, but this impaired sense of taste resolved within two and six months, respectively, after transplantation [25, 26].

Table 1. Etiologies associated with taste dysfunction in childhood.

Diagnosis	Author	Subjects (n)	Age (years)	Stimuli (number of solutions)	Taste test	Outcome
Asthma	Arias-Guillen et al.[21]	Patients (*n* = 46); controls (*n* = 45)	6 – 7	Sucrose (13); quinine hydrochloride (15)	DT using taste solutions, 2AFC staircase	Children with asthma required higher concentrations to discriminate between the tastant and distilled water.
Autism	Bennetto et al.[22]	Autism (*n* = 21); controls (*n* = 27)	10 – 18	Sucrose (1); sodium chloride (1); citric acid (1); quinine hydrochloride (1)	DT using EGM, 2AFC staircase; regional ID using taste solutions, 4AFC	Children with autism were less able to identify sour taste compared to controls. Detection thresholds were not different between groups.
Benign migratory glossitis	Vieira et al.[23]	Patients (*n* = 20); controls (*n* = 20)	8 – 18	Sucrose (3); sodium chloride (3); citric acid (3); quinine hydrochloride (3)	ID using Taste Strips, 5AFC	No differences were found between patients and controls regarding identifying taste stimuli.
Cancer *Chemotherapy*	Skolin et al.[24]	Patients (*n* = 10); controls (*n* = 10)	11 – 17	Sucrose (9); sodium chloride (9); citric acid (9); quinine hydrochloride (9)	RT using taste solutions, 5AFC staircase	The taste test was performed between two chemotherapy cycles, showing higher thresholds for bitter taste among patients. Also, patients made more taste recognition errors compared to controls.
Cancer *BMT*	Cohen et al.[25]	Patients (*n* = 10)	8 – 15	Sucrose (5); sodium chloride (5); citric acid (5); quinine hydrochloride (5)	ID using taste solutions, 3AFC	Taste tests were performed at baseline and after BMT (1-month, 2-month follow-up). Taste dysfunction was found among one third of the patients one month after BMT, but taste function was normalized two months after BMT for all patients.

Table 1. *(continued)*

Diagnosis	Author	Subjects (n)	Age (years)	Stimuli (number of solutions)	Taste test	Outcome
Cancer *HSCT*	Majorana et al.[26]	Patients (*n* = 51)	3 – 12	Sucrose (4); sodium chloride (4); citric acid (4); quinine hydrochloride (4)	ID using taste solutions, 5AFC	Taste tests were performed before, during, and after HSCT. During HSCT, threshold value means increased for the four stimuli. Six months after HSCT, taste function was normalized.
Cancer *Chemotherapy*	Van den Brink et al.[27]	Patients (*n* = 31); controls (*n* = 24)	6 – 18	Sucrose (4); sodium chloride (4); citric acid (4); quinine hydrochloride (4)	ID using Taste Strips, 5AFC	Taste tests were performed before and after a cycle chemotherapy, showing higher sweet, bitter, and total taste scores after a cycle of chemotherapy compared to before the start of that cycle. When compared to controls, patients had a higher sour taste score.
Cystic fibrosis	Laing et al.[28]	Patients (*n* = 42); controls (*n* = 42)	5 – 18	Sucrose (5); sodium chloride (5); citric acid (5); quinine hydrochloride (5)	ID using taste solutions, 3AFC	No significant differences in taste function were found between children with cystic fibrosis and controls.
Diabetes mellitus type I	Mameli et al.[29]	Patients (*n* = 31); controls (*n* = 31)	6 – 15	Sucrose (4); sodium chloride (4); citric acid (4); quinine hydrochloride (4)	ID using Taste Strips, 5AFC	Children with diabetes had lower bitter, sour, and total taste scores compared to controls.
Kidney disease	Armstrong et al.[30]	CKD 2 (*n* = 12); CKD 3 – 5 (*n* = 20); clinical controls (n =20); healthy controls (*n* = 20)	5 – 19	Sucrose (5); sodium chloride (5); citric acid (5); quinine hydrochloride (5)	ID using taste solutions, 3AFC	The ability to identify tastants by children with CKD diminishes as the eGFR decreases. This was observed for sweet and bitter taste and, to a lesser extent, for sour.

Table 1. *(continued)*

Diagnosis	Author	Subjects (n)	Age (years)	Stimuli (number of solutions)	Taste test	Outcome
Kidney disease	Correa et al.[31]	CKD 3 – 5 (*n* = 12); clinical controls (*n* = 12)	5 – 18	Sucrose (5); sodium chloride (5); citric acid (5); quinine hydrochloride (5)	ID using taste solutions, 3AFC	Taste loss was more prevalent in children with CKD than in clinical controls.
Macroglossia *Tongue reduction*	Maas et al.[32]	Patients (*n* = 10)	5 – 18	Sucrose (4); sodium chloride (4); citric acid (4); quinine hydrochloride (4)	Regional ID using taste solutions, 5AFC	Taste was perceived on the different regions of the tongue, although not always correctly identified. Anterior tongue resection has no long-term consequences for taste function.
Obesity	Obrebowski et al.[33]	Obese (*n* = 30)	10 – 16	NA	DT using EGM	47% – 77% of the children with obesity have detection thresholds below the limit of normal range, depending on the electrode used.
Obesity	Pasquet et al.[34]	Obese (*n* = 39), controls (*n* = 48)	11 – 17	Sucrose (10); fructose (10); sodium chloride (12), citric acid (7)	RT using taste solutions, 5AFC staircase	Children with obesity had a higher sensitivity (lower RT) to sucrose and sodium chloride than controls.
Obesity	Overberg et al.[35]	Obese (*n* = 99); controls (*n* = 94)	6 – 18	Sucrose (4); sodium chloride (4); citric acid (4); quinine hydrochloride (4); MSG (4)	ID using Taste Strips, 6AFC	Children with obesity showed a lower ability in correctly identifying salty, umami, and bitter taste, resulting in lower total taste scores compared to controls.

Table 1. *(continued)*

Diagnosis	Author	Subjects (n)	Age (years)	Stimuli (number of solutions)	Taste test	Outcome
Obesity *Lifestyle intervention*	Sauer et al.[36]	Obese (*n* = 60); controls (*n* = 27)	9 – 17	Sucrose (4); sodium chloride (4); citric acid (4); quinine hydrochloride (4)	ID using Taste Strips, 5AFC	Before lifestyle intervention, children with obesity had a lower sour and total taste score compared to controls. After intervention, sour taste scores improved whereas sweet taste scores deteriorated.
Obesity	Mameli et al.[37]	Obese (*n* = 34); controls *(n* = 33)	6 – 14	Sucrose (4); sodium chloride (4); citric acid (4); quinine hydrochloride (4)	ID using Taste Strips, 5AFC	Children with obesity showed a lower ability in correctly identifying sweet, sour, and bitter taste, resulting in lower total taste scores compared to controls.
Obesity	Herz et al.[38]	Overweight/ obese (*n* = 27); controls (*n* = 26)	12 – 16	Sucrose (4); sodium chloride (4); citric acid (4); quinine hydrochloride (4)	ID using Taste Strips, 5AFC	No significant differences in taste function were found between adolescents with overweight/obesity and controls.
Obesity *Lifestyle intervention*	Kalveram et al.[39]	Obese (*n* = 102)	6 – 18	Sucrose (4); sodium chloride (4); citric acid (4); quinine hydrochloride (4); MSG (4)	ID using Taste Strips, 6AFC	Children with obesity identified sweet taste better compared to other taste stimuli. Total taste score, but also scores for bitter and umami, increased after lifestyle intervention.
Otitis media	Shin et al.[19]	Patients (*n* = 42); controls (*n* = 42)	3 – 7	Sucrose (4); sodium chloride (4); citric acid (4); quinine hydrochloride (4)	DT using EGM; ID using taste solutions	Patients showed higher thresholds for sweet and salty, but also higher thresholds on the anterior tongue (EGM), compared to controls.

Table 1. *(continued)*

Diagnosis	Author	Subjects (n)	Age (years)	Stimuli (number of solutions)	Taste test	Outcome
Otology *Otologic surgergy*	Leung et al.[20]	Patients (*n* = 99); controls (*n* = 61)	4 – 18	NA	DT using EGM	Taste dysfunction after otologic surgery range between 5 – 50 %, depending on the type of surgery, compared to 9% in controls.
Tonsillitis	Hill et al.[18]	Patients (*n* = 64); controls (*n* = 80)	6 – 17	Sucrose (4); sodium chloride (4); citric acid (4); quinine hydrochloride (4)	ID using Taste Strips, 5AFC	Scores for individual taste qualities and total taste were not different between patients and controls.

Abbreviations: BMI, Body Mass Index; BMT, blood and marrow transplantation; CKD, chronic kidney disease; DT, detection threshold; eGFR, estimated glomerular filtration rate; EGM, electrogustometry; HSCT, hematopoietic stem cell transplantation; ID, taste identification; MSG, monosodium glutamate; NA, not applicable; RT, recognition threshold; 3AFC, three-alternative forced-choice; 4AFC, four-alternative forced-choice 5AFC, five-alternative forced-choice; 6AFC, six-alternative forced-choice.

Taste function of children with obesity also seems to be different from healthy controls, but again, results are inconsistent and differ regarding taste qualities. Seven studies assessed the relation between obesity and taste function in children. In five studies, taste function of children with obesity was compared to healthy controls. Although results seem to differ regarding individual taste qualities, overall taste function of children with obesity is reported to be lower compared to controls in three studies [35-37]. In addition, 47% to 77% of the children with obesity showed taste detection thresholds below the normal range values as measured with electrogustometry [33]. More recently, Herz and colleagues failed to find differences in taste sensitivity between children who are overweight/obese and controls [38]. Moreover, in one study a higher sensitivity to sweet and salty taste among children with obesity was found [34]. The influence of a lifestyle weight management intervention on taste function in children with obesity has also been studied. Improved bitter sensitivity, umami sensitivity, and overall taste function was reported [39], whereas improvements in sour taste detection and deterioration in sweet taste detection have been reported after a lifestyle weight management intervention as well [36].

Systemic diseases in childhood (excluding oncology and obesity) that might influence taste function, and probably food preferences and dietary intake as well, include cystic fibrosis, diabetes mellitus type 1, and kidney disease. Taste identification of children with cystic fibrosis was similar to healthy children [28]. Children with type 1 diabetes, however, showed a lower ability to correctly identify taste qualities compared to controls, especially for bitter and sour taste [29]. Children with chronic kidney disease (CKD) exhibited a lower taste identification ability than clinical controls [31]. Another study found that taste function diminishes especially the ability to taste sweet and bitter, in children with CKD when their estimated glomerular filtration rate (eGFR) decreases [30].

Other conditions in which taste function might be impacted are summarized in this section. Detection thresholds of children with asthma were different from healthy children, requiring higher concentrations of sucrose and urea to perceive the taste for children with asthma [21]. Moreover, children with autism spectrum disorder can display extreme food selectivity [40], which perhaps is partly the result of abnormal taste function. But in children with autism, no differences in detection thresholds were found relative to controls, although they were less able to correctly identify sour taste [22]. BMG, an inflammatory disorder, affects the tongue. However, taste

function of children with BMG was not impaired [23]. Lastly, taste function after surgical tongue reduction was evaluated in children with an overgrowth disorder (Beckwith-Wiedemann syndrome) that causes macroglossia [32]. No long-term consequences regarding taste function were found in this group of patients either.

In sum, there is clear evidence that certain childhood diseases, conditions or medical treatments affect children's taste function. However, it is not always clear what that altered taste function comprises.

TASTE ASSESSMENT IN CHILDHOOD

General aspects

Taste cells begin to form at 7 or 8 weeks of gestation [41]. The sense of taste is anatomically well-developed at birth, however, it still develops over the lifespan. For example, neonates are already able to react to pleasurable (sweet) and aversive (bitter, sour) taste stimuli, but they react neutrally to salty taste. Liking for salt emerges a few months later [42, 43].

It remains unclear whether children have similar abilities as adults to detect various taste qualities. Some scholars found that children have similar taste thresholds as adults, whereas others report that children have a lower taste sensitivity than adults [44-46]. In addition, there is some evidence that gustation matures a bit faster in girls [46].

Table 2 provides an overview of psychophysical taste tests that have been developed or adapted for children by using detection thresholds (the lowest concentration of a solution consistently detected as being different from a control, usually water), recognition thresholds (the lowest concentration of a solution consistently recognized as the tastant) or taste identification. In general, these taste tests can be used in both clinical or research settings, although some differences between applications should be noted.

Table 2. Overview of psychophysical taste tests suitable for children.

Tool and author	Age (years)	Subtest	Presentation tastants	Stimuli (number of solutions)	Concentration (mmol/l)	Strengths	Weaknesses
Taste Detection Threshold test [47]	> 6 y	DT, 2AFC staircase	Taste solution in a cup (10 ml)	Sucrose (17)	0.1 – 1000	Extensive threshold procedure, protocol for preparation of taste solutions	Not commercially available, no normative data, long-lasting, not intended for clinical use or point-of-care testing
				Sodium chloride (17)	0.1 – 1000		
				Monosodium glutamate (17)	0.1 – 1000		
Magic water test [48]	3 – 4 *n = 140*	DT, 2AFC decreasing concentrations	Taste solution in a cup (20 ml)	Sucrose (4)	2.8 – 12.6	Reliable, large sample size, test include a game and fairy tile, several concentrations of each taste quality (including umami)	Not commercially available, no normative data, restricted to specific age category, not intended for clinical use or point-of-care testing
				Sodium chloride (4)	5.8 – 16.8		
				Citric acid (4)	1.04 – 1.98		
				Quinine hydrochloride (4)	0.004 – 0.012		
				Monosodium glutamate (4)	1.0 – 2.9		
Taste sensitivity test [49]	5 – 12 *n = 40*	ID, 5AFC increasing concentrations	Pipette with taste solution (2 ml)	Sucrose (2)	32, 320	Reliable, quick, for clinical use	Not commercially available, no normative data, small sample size, two concentrations of each taste quality
				Sodium chloride (2)	32, 320		
				Citric acid (2)	1, 10		
				Quinine hydrochloride (2)	0.032, 0.32		
European sensory perception test [50]	3 – 10 *n = 191*	DT, 2AFC increasing concentrations	Taste solution in a cup (20 ml)	Sucrose (5)	8.8 – 46.7	Reliable, large sample size, test include a board game, several concentrations of each taste quality (including umami)	Not commercially available, no normative data, not intended for clinical use or point-of-care testing
				Sodium chloride (5)	3.4 – 27.4		
				Caffeine (5)	0.3 – 1.3		
				Monosodium glutamate (5)	0.6 – 9.5		

Table 2. *(continued)*

Tool and author	Age (years)	Subtest	Presentation tastants	Stimuli (number of solutions)	Concentration (mmol/l)	Strengths	Weaknesses
Taste test after tongue reduction [51]	≥ 5 *n = 10*	ID, RT	Cotton swab with taste solution	Sucrose (ID:1, RT: 3)	ID: 2000 RT: 200, 20, 2	Quick, threshold concentrations according to literature, for clinical use	Reliability unknown, small sample size, restricted to specific patient population
				Sodium chloride (ID:1, RT: 3)	ID: 3500 RT: 350, 35, 3.5		
				Citric acid (ID:1, RT: 3)	ID: 200 RT: 20, 2, 0.2		
				Quinine hydrochloride (ID:1, RT: 3)	ID: 0.04 RT: 0.004, 0.0004, 0.00004		
Electrogustometry [20]	4 – 18 *n = 160*	DT	EGM	NA	Electrical current between -6 dB up to 30 dB	Commercially available, reliable, normative data, large sample size, for clinical use	EGM is restricted to regional testing
Screening test for gustatory function [52]	5 – 7 *n = 232*	ID, 3AFC	WM: taste solution in a cup (10 ml) R: cotton bud with taste solution	Sucrose (1)	WM: 360 R: 1000	Normative data, large sample size, whole-mouth and regional part, for clinical use	Reliability unknown, not commercially available, restricted to specific age category, one concentration of each taste quality (screening)
				Sodium chloride (1)	WM: 180 R: 1000		
				Citric acid (1)	WM: 9 R: 3.2		
				Quinine hydrochloride (1)	WM: 0.1 R: 1		

Table 2. *(continued)*

Tool and author	Age (years)	Subtest	Presentation tastants	Stimuli (number of solutions)	Concentration (mmol/l)	Strengths	Weaknesses
Taste sensitivity and aversion test [53]	3 – 6 *n = 45*	DT, 2AFC staircase	Taste solution in a cup (3 ml)	Sucrose (13) Urea (15)	1.5 – 300 3.8 – 3000	Test is introduced as fairy tile, extensive threshold procedure	Reliability for urea is unstable, not commercially available, no normative data, small sample size, not intended for clinical use or point-of-care testing
PROP threshold test [45]	5 – 7 *n = 34*	DT, 2AFC staircase	Taste solution in a cup	6-n-propylthiouracil (15)	0.006 – 3.2	Extensive threshold procedure	Reliability unknown, not commercially available, no normative data, small sample size, not intended for clinical use or point-of-care testing
Taste sensitivity test [54]	15 *n = 100*	RT, increasing concentrations	Taste solution in a cup (10 ml)	Sucrose (10) Sodium chloride (10) Citric acid (10) Quinine hydrochloride (10)	3.9 – 88. 4 2.8 – 62.5 0.02 – 0.49 0.0014 – 0.0313	Large sample size, extensive threshold procedure	Reliability unknown, not commercially available, no normative data, restricted to specific age category, not intended for clinical use or point-of-care testing

Abbreviations: DT, detection threshold; ID, taste identification; NA, not applicable; R, regional taste test; RT, recognition threshold; WM, whole mouth taste test; 2AFC, two-alternative forced-choice; 3AFC, three-alternative forced-choice; 5AFC, five-alternative forced-choice.

In a clinical routine, it is of great important that a taste test can be easily administered, renders individual scores that can be compared to normative data, has both high sensitivity and high specificity, and is relatively brief. In this setting, taste assessment largely focuses on the evaluation of the four taste qualities (i.e., sweet, sour, salty, and bitter) to screen or diagnose for taste dysfunction. Within the context of research, however, any patient taste test scores are often compared with scores from a matched, healthy comparison/control group. The goal in such research is not to diagnose taste dysfunction, but to qualify and quantify loss of taste function within a specific patient population versus healthy controls. In addition, the effects of genetics, age, or food habits on children's taste sensitivity are often studied for research purposes. Taste tests within such a research setting frequently focus on a specific taste quality (e.g., sweet taste). Nonetheless, these laboratory validated methods used to assess children's taste sensitivity might still have clinical utility and are discussed below alongside clinical tests.

Clinical assessment tools

We found four taste tests and one questionnaire that are available for investigating children's taste function in a clinical setting. Majorana and colleagues aimed to develop a standardized clinical evaluation of children's taste sensitivity (5 – 12 years) [49]. Two concentrations (high and low) of each taste quality are provided serially with pipettes and the child has to identify each tastant (sweet, salty, sour, bitter, or water). The lowest concentration of each taste quality that is correctly identified and distinguished from water is considered a child's taste threshold. Although this test seems reliable (test-retest reliability; $r = 0.74$), the low number of variations in taste concentrations makes it questionable whether this test can truly detect any taste dysfunction. Furthermore, data was obtained from a relatively small sample ($n = 40$) of healthy children and normative data are lacking.

Another simple taste test was developed for children with macroglossia, which is caused by an overgrowth disorder [51]. These children need to undergo a partial tongue reduction in early life, which might influence taste function. This test, which consists of two parts, can still evaluate taste function after surgery. The first part determines at what part of the tongue taste perception is optimal, by applying a concentrated solution of sucrose, sodium chloride, citric acid, and quinine hydrochloride on each of eight different regions. The second part determines correct identification of sweet, sour, salty, and bitter by using three solutions for each taste quality. Again, all eight

regions of the tongue are touched with a saturated cotton swab and the child is asked what taste is perceived.

A clinical gustatory screening test for school-age children, including a whole-mouth and regional task, was developed by Laing and colleagues [52]. During both tasks, a single suprathreshold taste solution is used for each taste quality which has to be identified by the child from a set of three photographs (one photo represents water in a glass, two represent tastants). During the whole mouth test, the child has to sip and identify the five samples (sucrose, sodium chloride, citric acid, quinine hydrochloride, and purified water). During the regional test, the four tastants and a water sample are presented to each of four regions on the dorsal surface of the tongue, resulting in a total of 20 presentations. This simple screening test includes normative data from a large sample (n = 232) and can be used to diagnose taste dysfunction in children.

Leung et al. assessed the reliability of electrogustometry in children, in order to investigate whether this tool is applicable in a pediatric otolaryngology setting [20]. Electrogustometry was found to be reliable (Cronbach alpha = 0.82) in children and, with exception of those under the age of six years, most children were able to understand instructions and complete the test.

Lastly, one questionnaire regarding taste function in children with cancer receiving chemotherapy is available: The Taste Alteration Scale for Children with Cancer Receiving Chemotherapy (TAS-CrC). This questionnaire aims to evaluate self-reported taste perception and taste alterations regarding sweet, sour, salty, and bitter among children with cancer aged 8 – 18 years [55]. This scale includes nine items rated on a 5-point Likert scale of which seven items address taste dysfunction and two address smell dysfunction. Items regarding taste alteration were obtained from a literature review and gathered into an item-pool, which was evaluated by experts. Moreover, a validity study (including content and construct validity) was performed among experts and a reliability study was performed to assess internal consistency of the scale. Both Cronbach's alpha reliability coefficient (alpha = 0.88) and test-retest reliability (r = 0.97, p < 0.01) were high. The TAS-CrC can thus be considered valid and reliable.

Other tools

Six other taste assessment methods are listed in Table 2, which can be used in children. Recently, an extensive protocol – the Taste Detection Threshold (TDT) test – for preparing and determining detection thresholds for sucrose, sodium chloride, and monosodium glutamate (MSG) was published and this protocol can be used in children as young as six years [47]. The TDT test uses a two-alternative forced-choice (2AFC) staircase procedure, which has already been employed in children in previous studies [56-58]. On average, it takes 15 minutes per tastant before a detection threshold is reached.

Another taste sensitivity test, focusing on very young children (3 – 6 years), has been developed in order to measure detection thresholds for sucrose and urea, also using a 2AFC staircase procedure [53]. Especially in young children, a forced-choice paradigm produces more valid results compared to a non-forced procedure. Although a fairy tale was used to enhance motivation and engagement during the test, a loss of interest over time was noticed by the authors in the participating children.

Engaging children (especially young children) in a taste test is not easy, but some researchers have developed interesting tests that attempt to involve the young child in a playful manner. Knof and colleagues [50], for example, developed a taste detection threshold test in which a board game is used and children are addressed as 'taste detectives'. For each tastant (sucrose, sodium chloride, caffeine, and monosodium glutamate), five concentration steps are investigated. Another taste test focuses on pre-schoolers (3 – 4 years) and uses a fairy tale to introduce five magic characters (tastants) who all drank magic water that differed in taste [48]. Although both these tests focus on taste sensitivity in healthy children, rather than identifying taste loss, these are attractive methods showing good test-retest reliability.

Lastly, two older methods are still frequently used or referred to when measuring taste function in children. Firstly, the threshold procedure from Anliker and colleagues focuses on the assessment of detection thresholds for the bitter compound 6-n-propylthiouracil (PROP) using 14 dilution steps by a 2AFC staircase procedure, but also includes a suprathreshold intensity rating test for PROP and sodium chloride [45]. Concentrations used in this test procedure are frequently chosen or adapted in later studies [59]. Secondly, Nilsson and Holm aimed to develop a quick and simple test method for investigating taste recognition thresholds, as they considered previous methods as too time-consuming and therefore not suitable for teenagers [54]. Their

whole-mouth test determines recognition thresholds for sweet, salty, sour, and bitter solutions by presenting 10 solutions of each tastant in increasing concentrations.

TESTS USED IN CLINICAL PRACTICE

The question arises whether taste tests developed for children, as described in Table 2, are actually used – or could be used – in clinical practice. From a clinical perspective, a test is preferably brief, easy to prepare and administer, and includes normative data to be able to diagnose potential dysfunction.

Regarding clinical assessment tools, taste loss in children can be reliably diagnosed by electrogustometry [20]. Further, normative data are available for the clinical gustatory screening test for children aged 5 – 7 years [52]. For this screening test, children aged 5 years should be able to identify at least three of the five taste substances, whereas 6- and 7-year-olds are expected to identify four substances. However, the screening test itself has not been used in later studies. Instead, an extended identification task including five different concentrations of each taste stimulus has been applied [25, 28, 30, 31]. Similar to the original screening test, children aged 5 years should be able to identify at least three concentrations of each tastant, and older children at least four concentrations of each tastant to be considered normogeusic. Unfortunately, an extensive description of this latter procedure is lacking, and its test-retest reliability does not appear to be very high (r = 0.52) [28, 30].

The other taste tests [49, 51] and validated questionnaire [55] described above lack normative data and thus seem to be rarely used in clinical practice. This might be due to the fact that those tools are restricted to specific patient groups (as is the case with the taste alteration scale for children with cancer) or are time-consuming to prepare (as is the case with various taste solution tests).

Another time-consuming approach is the Taste Detection Threshold test [47]. This test does include an extensive manual for preparing taste solutions. However, preparation requires laboratory skills and facilities which makes this test procedure not particularly convenient for the pediatric clinician (and patient) who would likely prefer to use a point-of-care (or bedside) test. Moreover, although detection thresholds do rely less on the verbal/cognitive skills of the child, staircase procedures

can be lengthy [45, 47, 53]. Test duration may not be overly problematic when assessing taste sensitivity of healthy children in a laboratory setting and when children can take a break in between sessions. However, in a clinical context where children are ill, the duration of testing should be kept to a minimum.

One convenient taste test that is ready made and does not require a lengthy procedure is the "Taste Strips" test. It is often used to assess taste function or taste loss in children [18, 23, 27, 29, 35-39]. This test is commercially available, has a long shelf-life, and is easy to use at the bedside. These features explain its appeal. However, this test has not been validated in children and available normative data are restricted to adults.

DISCUSSION AND CONCLUSIONS

Taste function is important for physical and psychological well-being, which is as true for children as it is for adults. The present review shows that several diseases (and treatment) in childhood are associated with taste dysfunction, but only a few standardized taste tests have been developed to assess or diagnose such taste dysfunction in a pediatric clinical setting. Their use is limited as most of these tests are not commercially available and often depend on self-prepared taste solutions. Furthermore, normative data are often lacking. This is not problematic when applying one of these tests in the context of academic research, but it does limit their clinical utility. Especially within a clinical setting, one wants to be able to quickly diagnose potential taste dysfunction if taste is expected to be compromised as a result of disease burden or treatment.

A standardized taste test is still needed that is suitable for children and can be easily applied in clinical practice. The "Taste Strips" test appears a suitable candidate for this purpose, however, normative values of the Taste Strips for children still need to be acquired. In addition, its relatively low test-retest reliability (r = 0.68, in adults) might hinder an accurate distinction between normogeusia and dysgeusia when tracking taste function over time and is thus of some concern.

Apart from the scarcity of convenient psychophysical taste tests for the pediatric clinical setting, there is also a lack of validated questionnaires concerning taste perception in children. Such a questionnaire only appears to exist for children with cancer [55]. Similar questionnaires would be very useful in clinical practice for quick screening

of taste function and associated problems in children. Further research is needed to develop questionnaires with which the clinician can quickly recognize or monitor taste loss/change in children in general. Self-reported taste dysfunction should always be followed up by a psychophysical test, given the relatively poor accuracy of self-report measures, but that does not obviate the utility of such a questionnaire [60].

To recapitulate, a variety of childhood diseases and disorders are associated with taste changes or even dysfunction. Impaired taste function is aversive and thus negatively impacts quality of life in pediatric patients. Furthermore, as taste dysfunction has important implications for food intake on the short term and for the development of dietary habits and food preferences on the longer term, monitoring taste function in pediatric clinical practice seems pertinent. Such screening, however, requires adequate taste testing instruments. Clearly, there is still a need for the development of a practical, reliable, and child-friendly taste test that accurately measures taste function and that can be used in clinical practice as a point-of-care test.

Author contributions

Mirjam van den Brink conceptualized the study, performed the literature search, selected articles, drafted the initial manuscript, and revised the manuscript. Irene IJpma, Wim Tissing, and Remco Havermans critically reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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The authors have no conflicts of interest relevant to this article to disclose.

Consent statement

Not applicable because human subjects were not involved in this review.

Category of study

Review article.

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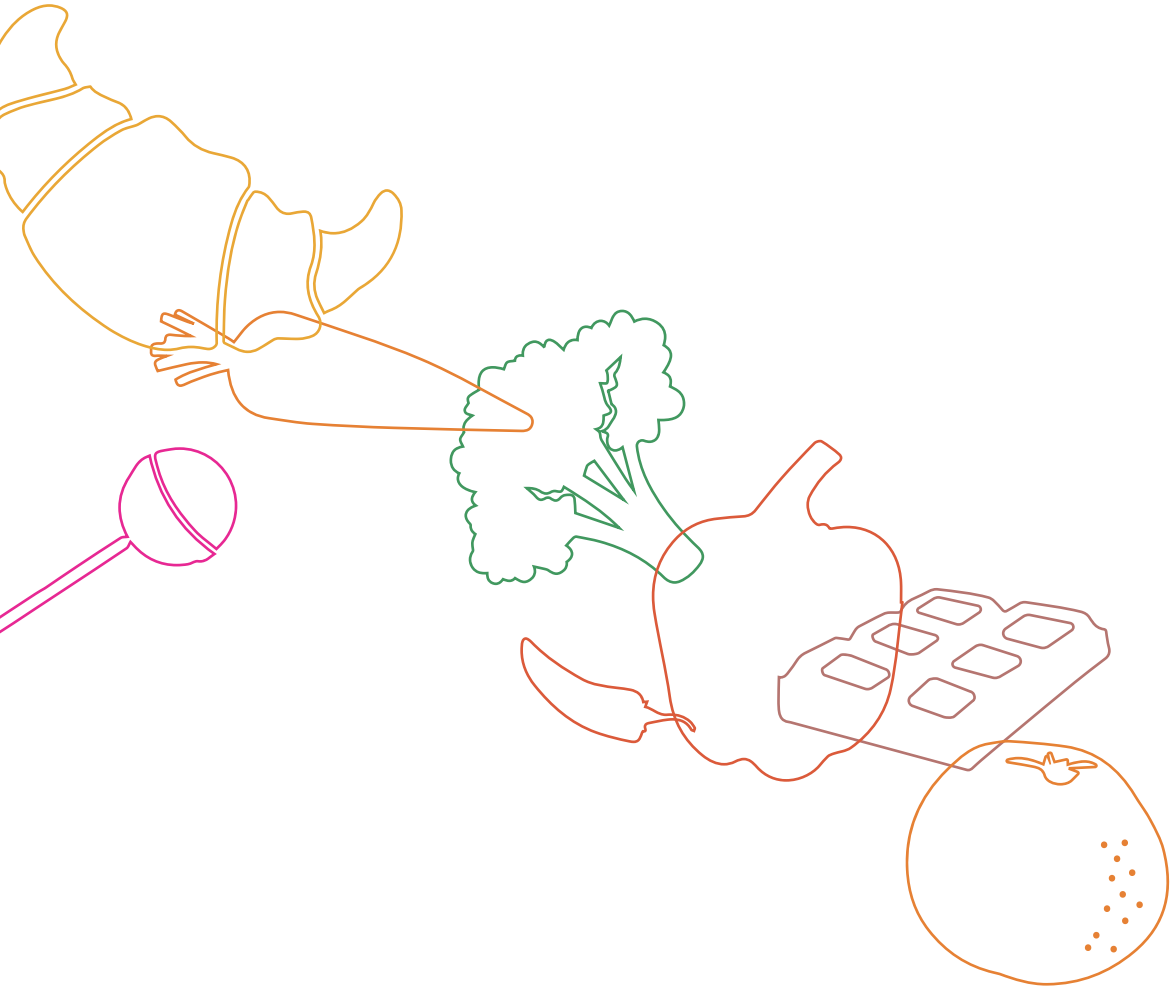

3

Taste function in children: normative values and associated factors

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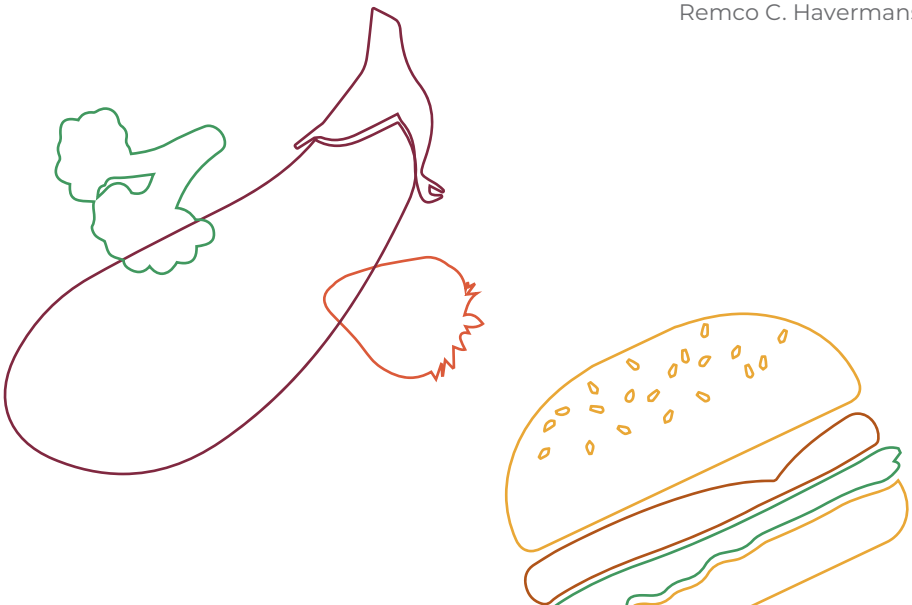

ABSTRACT

Background Although less frequent than in adults, taste loss also occurs in childhood. “Taste Strips” are frequently used for diagnosing taste dysfunction, however, normative values are lacking for children. In this study we will create normative values for the “Taste Strips” in children.

Methods This cross-sectional study included 609 children aged 6 – 15 years. “Taste Strips” were used to determine sweet, sour, salty, and bitter taste scores by a non-forced procedure. The 10th percentile was used to distinguish normal taste function from a reduced sense of taste. Multivariable Generalized Linear Models (GLM) were estimated to study the effect of age (group), sex, and 6-n-propylthiouracil (PROP) status on taste function.

Results Taste function changed with age, allowing for a distinction of three age groups: I) 6 – 7 years; II) 8 – 9 years; and III) 10 – 15 years. Normative values were created for the age groups and boys and girls separately. Additionally, GLM showed a significant effect of 1) age (group) on sweet, salty, bitter, and total taste scores; 2) sex on sweet, sour, and total taste scores; and 3) PROP status on total taste scores.

Conclusions This study provided normative values for the “Taste Strips” in children, highlighting age- and sex-related differences.

INTRODUCTION

Little is known about taste dysfunction in children. In general, it is thought to be rare as chemosensory problems are typically associated with aging [1]. Nevertheless, children are not safeguarded from health problems that affect their smell and taste function. Medical conditions such as cancer, diabetes mellitus, kidney disease, and obesity are only a few examples of etiologies associated with chemosensory dysfunction in children, consequently affecting food choice, dietary intake, and overall health status [2-6]. Measuring taste function may elucidate the exact relation between taste dysfunction and disease, fostering the development of more appropriate supportive strategies (e.g., medication, dietary advice) in treating disease[7]. Therefore, it is not a matter of debate that clinical assessment of taste function in children is needed.

In contrast to smell tests, few taste tests are available in a clinical setting. In part, this is due to the low prevalence of taste disorders (relative to smell disorders) [8]. Indeed, most patients complaining about taste dysfunction actually suffer from smell dysfunction [9]. The "Taste Strips" test is a frequently employed and well-validated clinical taste test [10]. Advantages of this test are its long shelf-life, easy administration, commercial availability, and short time of investigation. In the context of research, the "Taste Strips" have already frequently been used in children [11-13]. However, normative values are hitherto restricted to individuals aged 15 – 87 years [10, 14]. Especially within a clinical setting, if taste function is expected to be compromised as a result of disease burden and/or treatment, one needs to be able to determine a child's taste function and interpret these scores by using population specific normative values.

Several factors can modulate taste function in children which should be taken into account and needs further investigation concerning the "Taste Strips". First of all, taste function seems to improve as a child grows older, although results differ per tastant. For example, sucrose intensity has been reported to increase from childhood to adulthood, but sensitivity to bitter compounds was found to be similar between children and adults [15, 16]. Secondly, although most studies found no clear sex-related differences in taste function in children, there is some indication that girls outperform boys [17-20]. Thirdly, the ability to taste bitter compounds such as 6-n-propylthiouracil (PROP), which can be partly explained by genetic variations in TAS2R38 polymorphisms, correlates with an increased intensity perception to taste

stimuli and other orosensory sensations [21, 22]. However, it remains unclear whether PROP status is associated with taste scores as measured by "Taste Strips" in children.

Thus, the present study aimed to 1) provide normative values for the "Taste Strips" from a large sample of healthy children, 2) study the effect of age, sex, and PROP status on taste scores in children, and 3) identify to what extent scores on the "Taste Strips" test are associated with self-reported taste function in children.

METHODS

Participants

This study was performed at the NEMO Science Museum Amsterdam, the Netherlands. All consecutive visitors to the museum were asked to participate. Participants were eligible for participation if they were between 5 and 17.99 years of age, able to understand Dutch or English, and reported to be healthy. Exclusion criteria for participation were: having a cold, smoking, being pregnant or a self-reported allergy to quinine. Parents provided written informed consent.

Assessment of taste function

Taste Strips

Taste function was assessed by using "Taste Strips" (Burghart, Wedel, Germany). "Taste Strips" are filter-paper strips impregnated with a taste solution and determine sweet, sour, salty, and bitter taste scores. Four concentrations of each taste quality were used: sweet (0.05, 0.1, 0.2, and 0.4 g/ml sucrose), sour (0.05, 0.09, 0.165, and 0.3 g/ml citric acid), salty (0.016, 0.04, 0.1, and 0.25 g/ml sodium chloride), and bitter (0.0004, 0.0009, 0.0024, and 0.006 g/ml quinine hydrochloride). To each child, sixteen impregnated strips and two blank strips were presented in the same pseudo-randomized order starting with the lowest concentration.

Children were asked not to eat and drink except water one hour before the test. Before the test began, taste qualities were explained by presenting photographs (i.e., sweet like sugar, sour like lemon, salty like salt, bitter like coffee). "Taste Strips" were placed on the middle of the tongue, approximately 1.5 cm from the tip. Participants were then asked to close the mouth and indicate whether the perceived taste was sweet, sour, salty, bitter, or tasteless. Scores for each taste quality range from 0 to 4

and the total taste score was derived by summing the scores of each taste quality (range 0 – 16). A higher score represents a better taste function.

PROP test

PROP taster status was determined by a filter paper strip impregnated with 6-n-propylthiouracil (Sensonics International, NJ, United States, 20 µg/strip). Participants were instructed to place the strip on the dorsal surface of the tongue for approximately 30 seconds and were then asked whether they tasted anything (yes/no) [23]. Participants who answered "no" or reported that the strip "tastes like paper" were classified as "non-tasters". Children who indicated that the strip tasted "bitter", "sour", "bad", or "spicy" were classified as "tasters". In addition, participants who immediately removed the strip because of its "foul" taste or showed other signs of taste rejection were classified as "tasters" as well [24].

Self-report

Participants were asked to self-assess their taste function by rating their taste perception (on a 10-point scale: 1 "very bad" to 10 "very good") and by estimating their taste function relative to their peers on a 5-point Likert scale (1 "much worse than others" to 5 "much better than others").

Statistical analysis

Descriptive statistics are presented as median with interquartile range (IQR) and the number of participants (n) with percentage (%). The 10th percentile was used to distinguish normal taste function from a reduced sense of taste (i.e., hypogeusia) [10]. Non-parametric tests were used to assess differences between sex, age or self-reported measures in relation to taste scores. Bonferroni post-hoc procedure to adjust for multiple testing was used when required. To study the association between taste scores (i.e., sweet, sour, salty, bitter, and total) and the independent variables age (group), sex, and PROP status, multivariable generalized linear models (GLM) were estimated since the dependent variables were not normally distributed. To study the association between subgroups and outcome, interaction terms were created and included in the model if significant. An alpha level of 0.05 was used. Data analysis was performed with IBM SPSS Statistics (version 25.0).

RESULTS

Participant characteristics

In total, 645 children aged 5 – 17 years participated. Figure 1 shows a flowchart of the inclusion process. Four children did not complete the taste test. Among the 5-year-old children, identification rates for the highest concentration of sweet, sour, salty, and bitter taste were only 70%, 57%, 35%, and 61%, respectively, implying that the concentrations used in the "Taste Strips" test does not provide reliable results for <6-year-old children. Results of 5-year-old children were therefore excluded from analysis (*n* = 23), as well as the small number of 16-year-old (*n* = 5) and 17-year-old participants (*n* = 3). Thus, 609 participants aged 6 – 15 years were included for final analysis.

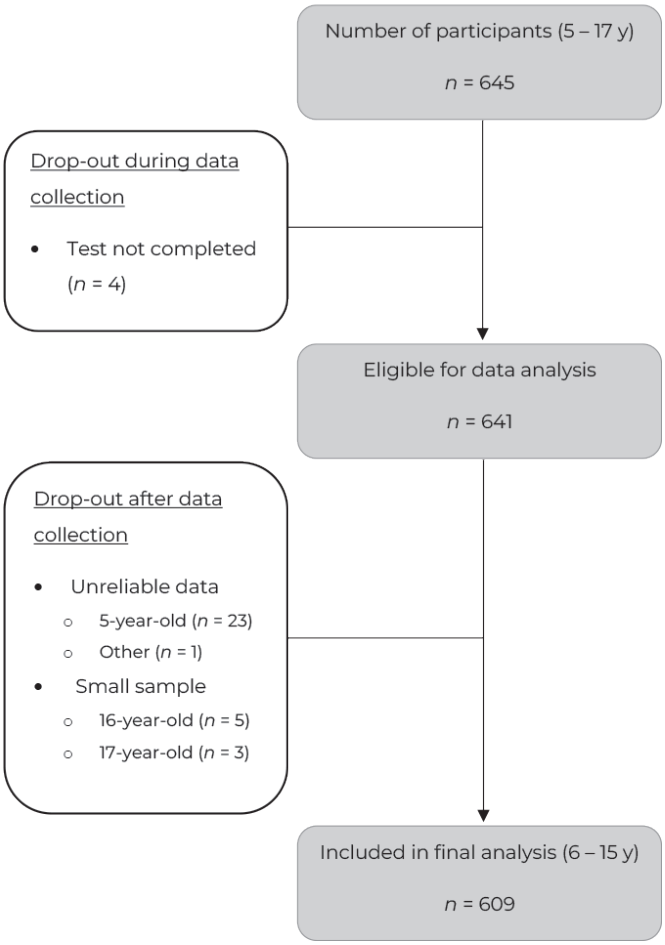

Figure 1. Flowchart of included children in the current study.

Participants' mean age was 9.3 ± 2.3 years; 365 of the participants were girls (60%). Overall, 541 participants (89%) were living in the Netherlands, 56 (9%) were living in other European countries, and 12 (2%) came from non-European countries.

Taste test results

Median scores (IQR) for the individual taste qualities were as follows: sweet 4.0 (3.0 – 4.0), sour 3.0 (2.0 – 3.0), salty 4.0 (2.5 – 4.0), and bitter 4.0 (3.0 – 4.0). Median total taste score (IQR) was 13.0 (11.0 – 14.0). In total, 373 children (61%) were PROP-tasters.

A sex difference ($p = 0.001$) and positive correlation ($r = 0.247$, $p < 0.001$) between age and total taste score was observed, showing major age- and sex related differences between 6 and 9 year of age. Based on these results, three arbitrary age groups were distinguished: group I, 6 to 7 years; group II, 8 to 9 years; group III, 10 to 15 years. A significant difference in sweet ($p < 0.001$), sour ($p = 0.044$), salty ($p < 0.001$), bitter ($p < 0.001$), and total taste score ($p < 0.001$) was found between the three age groups (Figure 2). Post-hoc testing indicated significant differences between group I and II and group I and III for sweet, salty, bitter, and total taste scores ($p < 0.001$). For sour taste, no significant differences were found between age groups when adjusted for multiple testing.

Normative values

Table 1 shows the distribution of taste scores separated for age and sex. According to the 10th percentile, a total taste score below the following values indicate hypogeusia: group I, <7.0 for girls and <6.0 for boys; group II, <10.0 for girls and <8.0 for boys; and group III, <9.9 for girls and <10.0 for boys.

Effect of age, sex, and PROP status on taste scores

Results based on the multivariable GLM models show the effect of age, sex, and PROP status on sweet, sour, salty, bitter, and total taste scores (Table 2). Adjusted for sex and PROP status, total taste scores of children aged 8 – 9 years and 10 – 15 years were, respectively, 1.3 and 1.8 points as high as children aged 6 – 7 years. In addition, higher salty and bitter scores were found in children aged 8 – 9 years compared to 6-7-year-old children and higher sweet, salty, and bitter scores were found in children aged 10 – 15 years compared to 6-7-year-old children when adjusted for sex and PROP status.

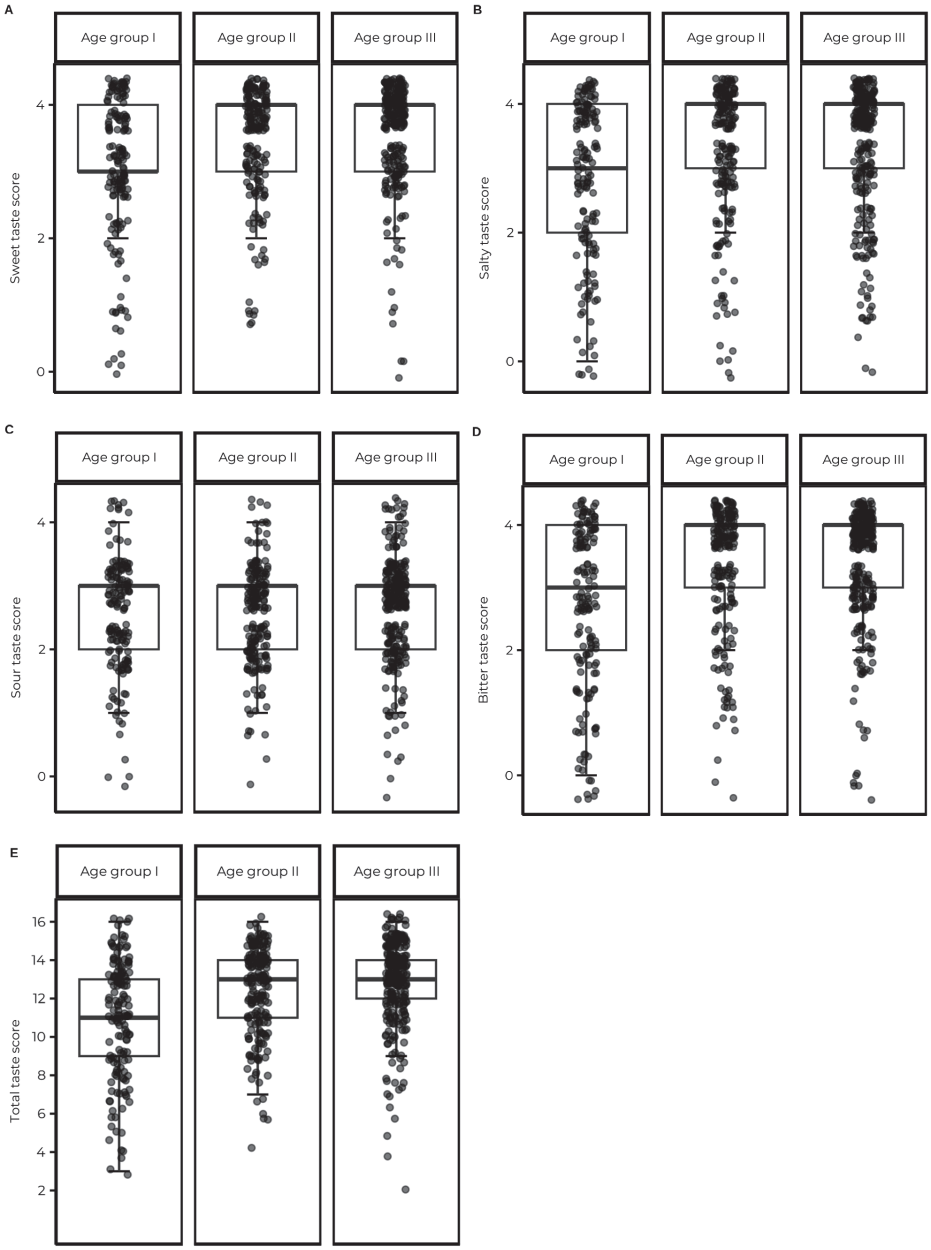

Figure 2. "Taste Strips" scores for the different age groups: sweet taste (a), salty taste (b), sour taste (c), bitter taste (d), and total score (e). Boxplots refer to the median score (midpoint of the scores), the first quartile of the scores (Q1, lower boundary of the box) and the third quartile of the scores (Q3, upper boundary of the box). The range of the box represents the interquartile range (IQR = Q3 − Q1) and the whiskers indicate what data points can be considered as outliers. The upper whisker extends to the most extreme score no more than 1.5 times the IQR above Q3, and the lower whisker extends to the most extreme score no more than 1.5 times the IQR below Q1. Note that, due to the limited range of possible scores for the individual taste qualities (0–4; a–d), some boxes (and whiskers) appear constricted.

Table 1. Distribution of taste scores separated for age and sex (*n* = 609).

		Sweet score		Sour score		Salty score		Bitter score		Total score	
Age 6 – 7 years		Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
N		65	89	65	89	65	89	65	89	65	89
Minimum		0	0	0	0	0	0	0	0	3	3
Maximum		4	4	4	4	4	4	4	4	16	16
Percentile	*10*	1.0	2.0	1.0	2.0	1.0	1.0	1.0	0.0	6.0	7.0
	25	2.0	3.0	2.0	2.0	2.0	2.0	1.5	2.0	8.0	9.0
	50	3.0	3.0	2.0	3.0	3.0	3.0	3.0	3.0	11.0	12.0
	75	4.0	4.0	3.0	3.0	4.0	4.0	4.0	4.0	13.0	13.0
	90	4.0	4.0	3.0	4.0	4.0	4.0	4.0	4.0	14.0	15.0
Age 8 – 9 years											
N		65	128	65	128	65	128	65	128	65	128
Minimum		1	1	0	1	0	0	0	0	4	6
Maximum		4	4	4	4	4	4	4	4	16	16
Percentile	*10*	1.6	3.0	1.0	2.0	1.0	2.0	1.0	2.0	8.0	10.0
	25	2.0	3.0	2.0	2.0	2.0	3.0	2.0	3.0	9.5	11.3
	50	3.0	4.0	2.0	3.0	3.0	4.0	3.0	4.0	12.0	13.0
	75	4.0	4.0	3.0	3.0	4.0	4.0	4.0	4.0	14.0	14.0
	90	4.0	4.0	3.0	4.0	4.0	4.0	4.0	4.0	15.0	15.0
Age 10 – 15 years											
N		114	148	114	148	114	148	114	148	114	148
Minimum		0	0	0	0	0	0	0	0	2	4
Maximum		4	4	4	4	4	4	4	4	16	16
Percentile	*10*	3.0	3.0	2.0	2.0	2.0	2.0	2.0	2.0	10.0	9.9
	25	3.0	3.0	2.0	2.0	2.8	3.0	3.0	3.0	12.0	12.0
	50	4.0	4.0	3.0	3.0	4.0	4.0	4.0	4.0	13.0	13.5
	75	4.0	4.0	3.0	3.0	4.0	4.0	4.0	4.0	14.0	15.0
	90	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	15.0	15.0

Girls outperformed boys by showing a total taste score of 0.7 points as high as boys, but also exhibit higher sweet and sour scores, when adjusted for age and PROP status. Except for sweet taste, the interaction between age and sex on the outcomes was not significant, implying that there is no different effect among subgroups on sour, salty, bitter, and total taste scores.

PROP status was associated with total taste score, with "tasters" having a total taste score of 0.6 points as high as "non-tasters", when adjusted for age and sex. Neither PROP status and age, nor PROP status and sex showed a significant interaction with the outcomes.

Self-report

The mean rating for taste function was 7.7 ± 1.4. No significant correlation was found between this rating and total taste scores in children. Additionally, self-reported taste function was rated to be "much better than others" by 18 participants (3%), "better than others" by 125 participants (21%), "similar to others" by 447 participants (73%), "worse than others" by 16 participants (3%), and "much worse than others" by 3 participants (<1%).

Table 2. Estimated parameters and confidence intervals based on GLM for dependent variables sweet, sour, salty, bitter, and total taste score.

	Sweet score (0 – 4)	**Sour score (0 – 4)**	**Salty score (0 – 4)**	**Bitter score (0 – 4)**	**Total taste score (0 – 16)**
Independent variables					
Age (reference: 6 – 7 years)					
8 – 9 years	0.21 (-0.08; 0.49)	-0.01 (-0.20; 0.16)	0.30 (0.05; 0.54)*	0.38 (0.15; 0.61)*	1.33 (0.75; 1.91)*
10 – 15 years	0.64 (0.38; 0.90)*	0.16 (-0.01; 0.33)	0.34 (0.11; 0.57)*	0.52 (0.30; 0.74)*	1.83 (1.28; 2.38)*
Sex (reference: boys)					
Girls	0.40 (0.13; 0.67)*	0.20 (0.02; 0.30)*	0.08 (-0.11; 0.27)	0.15 (-0.03; 0.33)	0.71 (0.25; 1.17)*
PROP status (reference: non-tasters)					
Tasters	0.07 (-0.08; 0.22)	0.06 (-0.08; 0.20)	0.08 (-0.11; 0.27)	0.14 (-0.04; 0;32)	0.62 (0.16; 1.01)*

Note: for sweet taste, the interaction between age and sex was significant and included in the model, showing an opposite effect for girls aged 10 – 15 year (B = -0.40, -0.80; -0.03). * $p < 0.05$

DISCUSSION

This is the first study that provides normative data for the "Taste Strips" from a large sample of children, divided into three age groups (6 – 7 years, 8 – 9 years, and 10 – 15 years) and separated for sex. The present study also shows that taste scores 1) increased with age for sweet, salty, bitter, and total taste; 2) was higher in girls

compared to boys for sweet, sour, and total taste scores; 3) was higher for PROP "tasters" compared to "non-tasters" regarding total taste scores; and 4) did not correlate with self-report.

Age- and sex differences in taste function among children were also found by James and colleagues, who showed higher detection thresholds for sucrose and sodium chloride in 8-9-year-old boys compared to 8-9-year-old girls when using freshly prepared taste solutions [20]. In addition, they compared 8-9-year-old children's taste function with adults, showing no significant differences in taste function between 8-9-year-old girls and adults, but 8-9-year-old boys showed a poorer ability to detect sweet, sour, and salty taste than adult males and a poorer ability to detect all four taste qualities than adult females. A similar trend can be found in the current study, when comparing children's taste scores with those previously found among adults [10]. Our results corroborates prior findings, suggesting that taste is functionally mature around an age of 10 years and that taste function matures a bit faster in girls [20, 25].

PROP status was associated with taste function in children, with higher total taste scores in "tasters" relative to "non-tasters". Although significant, this difference was moderate (0.6 points) and was not found for individual taste qualities. This is in line with a study that studied five common ways of measuring taste function (i.e., detection thresholds, recognition thresholds, suprathreshold intensity, PROP bitterness, and fungiform papillae) in women [26]. They found that detection thresholds and recognition thresholds for sweet, sour, salty, bitter, and umami did not correlate with PROP bitterness, but also not with fungiform papillae density. In general, only detection and recognition thresholds were related, which highlights the complexity of identifying taste function. Thus, the current study found PROP status to be associated with taste function, but not to the extent that it can be seen as a measure of overall taste function in children.

Self-reported taste function was not correlated with total taste scores. This indicates that children are not aware of their own taste function (or indeed dysfunction). One might argue that the absence of a correlation between self-reported taste function and performance on the "Taste Strips" test indicates that the "Taste Strips" are simply not valid, at least not in children. However, this also appears to be the case in adults as self-report of taste dysfunction has been shown inaccurate when using focused questions [27]. For that reason, self-reported taste abilities, which can provide

meaningful information to the clinician, should be always accompanied by a more objective test such as the “Taste Strips”.

Two methodological choices should be noted. First of all, a non-forced choice paradigm was used, according to the original protocol for the “Taste Strips” [10]. This allows the participant to indicate a strip as “tasteless”, instead of being forced to choose between sweet, salty, sour, or bitter. Forced choice testing has the advantage of limiting response bias and malingering [8, 28, 29]. The major disadvantage of a forced-choice method, however, is the inability to determine whether a “hit” or “miss” reflects an individual’s taste function or random guessing. As this information might be useful for the clinician if taste sensitivity is expected to be lost or changed, a non-forced choice method was chosen. Secondly, the 10th percentile was used to separate normogeusia from hypogeusia, according to the original protocol and originating from research into adults’ smell function [10, 14, 29, 30]. As we do not know how many children suffer from taste dysfunction, though presumably less than 10%, using the 10th percentile could lead to false-positive results and overdiagnosis. Using two standard deviations from the mean might be an alternative and more conservative approach [31]. However, if this remains unclear, we have chosen to apply the commonly used 10th percentile as a cut-off value for children’s taste function, additionally considering their self-report and clinical symptoms.

Strengths of our study were the large sample size and wide age-range of included participants. In addition to Dutch children, also children from other European countries were included which increases the generalizability of our findings. However, some limitations should be noted. As mainly European children were included, it is uncertain whether these normative values extend to children outside of Europe. Furthermore, body weight or body mass index was not reported or measured, which could be a confounding factor as obesity is associated with a lower taste sensitivity in children [11].

In conclusion, normative values for the “Taste Strips” were obtained for children aged 6 – 15 years, highlighting age and sex differences. These results bolster the clinical utility of the “Taste Strips” among children in a clinical setting, beyond its easy and quick administration.

Author contributions

Author contributions were as follows: Mirjam van den Brink participated in study design, collected data, conducted statistical analysis, and drafted the manuscript. Irene IJpma participated in study design, data collection, interpretation of the data, critical revision, and editing of the manuscript. Marta Fiocco participated in statistical analysis, interpretation of the data, critical revision, and editing of the manuscript. Wim Tissing participated in study design, interpretation of the data, critical revision, and editing of the manuscript. Remco Havermans participated in study design, interpretation of the data, critical revision and editing of the manuscript, and supervised its execution. All authors read and approved the final manuscript.

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Disclosure statement

The funding organizations had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript or decision to submit the manuscript for publication. The authors have no other conflicts of interest to disclose.

Consent statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from the Maastricht University Ethical Review Committee Inner City faculties (reference number ERCIC_162_09_12_2019). Parents provided written informed consent.

Impact statement

Taste dysfunction can be harmful and impacts quality of life, a topic that became increasingly important since the COVID-19 pandemic.

Although taste dysfunction is thought to be rare in childhood, the detrimental impact of such dysfunction might be large, as children's eating habits are strongly influenced by input from the chemical senses.

Measuring taste function may elucidate the relationship between taste dysfunction and disease, fostering the development of more appropriate supportive strategies. However, adequate tools are lacking for children.

Normative values of the "Taste Strips" are now available for children, which bolster the clinical utility of this test.

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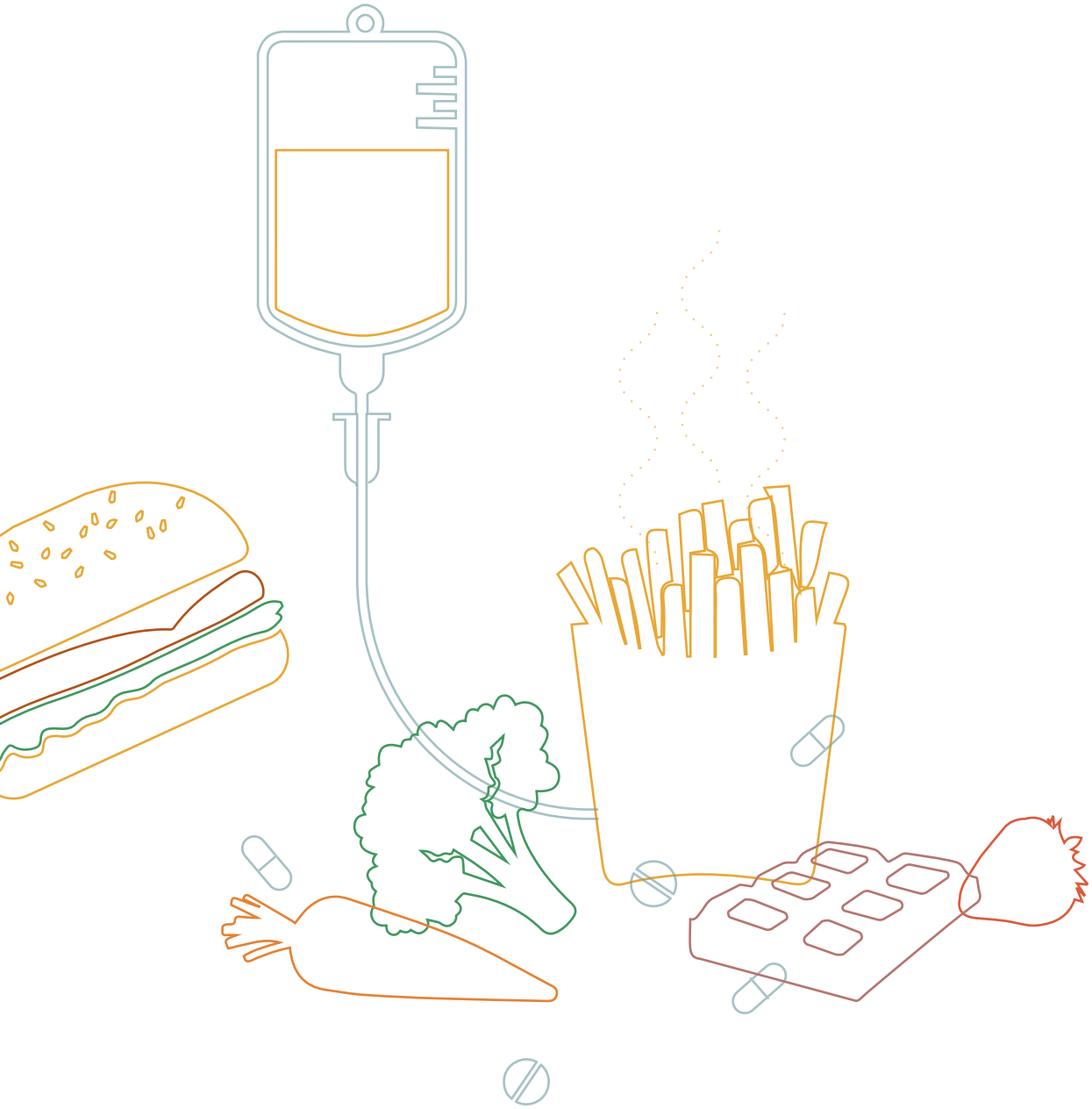

4

Nausea and nausea-related symptoms in children with cancer: presence, severity, risk factors and impact on quality of life during the first year of treatment

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ABSTRACT

Aims Identify 1) presence and severity of nausea and nausea-related symptoms during the first year of treatment, 2) associations between patient-related factors and nausea, 3) relationship between nausea-related symptoms and health-related quality of life (HRQoL) in children with cancer.

Methods A historical cohort study of 781 patients with cancer (2 – 21 years) was conducted. Presence and severity of nausea were assessed at 3, 6, 9, and 12 months after diagnosis using the nausea scale of the PedsQL3.0 Cancer Module, comprising 5 symptoms, using proxy-report (2 – 7 years) or self-report (8 – 21 years). Multivariable multilevel analyses were performed to evaluate the association between patient-related factors and nausea. Overall HRQoL (generic PedsQL) was compared between children with presence and absence of nausea related-symptoms.

Results The presence of nausea during medical treatment was highest at 6 months after diagnosis (42.9%). Highest symptom presence was seen on the item "food not tasting good" (range 51.6% – 62.8%). Pain, treatment anxiety, and worry were significantly associated with nausea in all children. In patients aged 8 – 21 years, male gender, a solid tumor, and BMI were associated with nausea. Patients with solid tumors were at higher risk of nausea compared to patients with hematological malignancies or brain/CNS tumors. Patients with a high BMI reported less nausea compared to patients with a normal BMI. For all nausea-related symptoms, average HRQoL scores were 9.9 – 14.4 points lower for patients with symptoms compared to patients without symptoms.

Conclusion Nausea is still a major problem in children with cancer and has a negative impact on HRQoL.

Keywords Childhood cancer, Nausea, Taste, Smell, Quality of life

INTRODUCTION

As a result of intensive therapies, almost all children with cancer experience physical and psychological symptoms, consequently interfering with health-related quality of life (HRQoL) [1-4]. Several studies have cited nausea as one of the most frequent and distressing symptoms among children with cancer with occurrence rates ranging from 13.4 to 100% [5-7]. Nausea is difficult to define, as it is a subjective feeling which is experienced differently in patients. Studies among adult patients have demonstrated that nausea is not just a single symptom but is frequently accompanied by a cluster of symptoms, such as anticipatory nausea, taste changes, and appetite loss [8-10]. Children with cancer explained how specific food and smells in the hospital can be a trigger for food aversions or anticipatory nausea [11].

Knowledge about potential risk factors might contribute to the prevention and targeted treatment of nausea and its related symptoms in children with cancer. A previous study showed higher prevalence rates of nausea in children with a solid tumor compared to children with leukemia or lymphoma [6]. Several studies in children with cancer showed that older age and intensive treatment are important risk factors [12-14]. Gender does not appear to be associated with the risk of nausea [6], although higher distress in a symptom cluster, which included nausea, was identified in boys compared to girls [10]. In adult cancer patients several risk factors including pain, anxiety, type of cancer, low social functioning, and a lower body mass index (BMI) seem to be associated with nausea [15-17].

As previous studies included small numbers of participants or were limited to one specific cancer diagnosis, the exact prevalence and risk factors for nausea and nausea-related symptoms in children with cancer, including its potential relationship with HRQoL, remains unclear and hamper targeted interventions to prevent or treat these symptoms. Therefore, we designed a study aiming to 1) determine the presence and severity of nausea and nausea-related symptoms during the first year of treatment, 2) identify risk factors for nausea, and 3) explore the relationship between nausea-related symptoms and HRQoL in children with cancer.

METHODS

Participants and procedures

In the Netherlands, all children with cancer are treated at the Princess Máxima Center for Pediatric Oncology in Utrecht. As part of standard care, the KLIK (Kwaliteit van Leven In Kaart, Dutch acronym for Quality of Life in Clinical Practice) patient-reported outcome measure (PROM) portal is used for monitoring QoL outcomes [18]. Cancer-specific and generic HRQoL questionnaires [19-21] are offered every three months during treatment prior to a doctor's appointment in the outpatient clinic, including proxy-report (2 – 7 years) or self-report (8 – 21 years). Families are informed regarding the use of these data for research purposes and patients (≥12 years) and caregivers are asked for informed consent. The Medical Ethics Committee has confirmed that the Medical Research Involving Human Subjects Act does not apply to this study.

For the current study, data from January 2016 to May 2021 were available. During this period, antiemetic treatment was provided according to the Multinational Association of Supportive Care in Cancer (MASCC) pediatric guideline for prevention of chemotherapy-induced nausea and vomiting (CINV) [22].

Children, or their parents, who completed the cancer-specific HRQoL questionnaire at least once during the first year of treatment, were included in this study.

Given some individual variation in timing of the KLIK assessments, we assigned the patients' collection time to the time points 3, 6, 9 and 12 months after diagnosis.

Measures

Nausea and nausea-related symptoms

Nausea and nausea-related symptoms were measured using the nausea scale of the PedsQL Cancer Module 3.0 [20]. This questionnaire consists of 27 items, measuring cancer-specific HRQoL on eight dimensions: pain, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance, and communication. The nausea scale includes five items: nausea during medical treatment, food not tasting good, nausea while thinking of medical treatment, being too nauseous to eat, and nausea caused by food/smells. Items are rated by the parent or child on a 5-point Likert scale, ranging from 0 (never a problem) to 4 (almost always a problem) reflecting the child's experiences in the last week prior to the outpatient

visit. Each answer is reversed scored and rescaled to 0 – 100. Higher scores indicate lower severity of nausea. Both the sum score on the nausea scale and the item scores were used separately for analyses. Cronbach's alphas of the nausea scale in this study ranged from .81 to .83 (proxy-report) and .76 to .82 (self-report).

Generic HRQoL

Generic HRQoL was measured using the PedsQL 4.0 Generic Core Scales [19, 21]. The questions are scored in the same way as the PedsQL Cancer Module. Higher scores indicate higher HRQoL.

Potential risk factors

Participants' characteristics

Clinical and demographic data were extracted from medical records, including age, gender, cancer type, length, weight, and BMI expressed as standard deviation scores (SDS; calculated from Dutch reference standards) [23] and categorized as "Low BMI" (<-2SDS), "Normal BMI" (-2SDS to +2SDS) and "High BMI" (>+2SDS).

Other risk factors

The sum scores of the subscales "pain", "treatment anxiety" and "worry" of the PedsQL Cancer Module were included in the analyses as potential risk factors. Scores range between 0 – 100, with higher scores indicating less symptom burden.

Statistical analysis

Statistical analyses were conducted in the Statistical Package for Social Sciences (SPSS) version 26.0. Demographical and clinical characteristics of the included participants were analyzed using descriptive statistics. Scores for the five items of the nausea scale were dichotomized and descriptive statistics (percentages) were calculated to identify the proportion of children with cancer reporting absence (''never-almost never'') or presence (''sometimes-often-almost always'') of nausea-related symptoms. For each item of the nausea scale, mean generic PedsQL total scores of both proxy- and self-report data were plotted against symptom presence (yes/no) to explore their impact on HRQoL.

Multivariable regression models were estimated to study the association between potential risk factors and nausea. To account for the presence of repeated measures, linear mixed models were estimated. All questionnaires completed during the first

year of treatment were included. Different models were estimated for proxy-report and self-report. For both analyses the sum score of the nausea scale was used as the dependent variable. The following potential risk factors were included: age, sex, diagnosis, time since diagnosis, BMI, pain, treatment anxiety, and worry. An unstructured correlation structure was used in both linear mixed models. Likelihood ratio tests were used to determine the best model for each analysis. P values <0.05 were considered statistically significant. To obtain standardized regression coefficients (β) in addition to regression coefficients (B), continuous variables were standardized. Effect sizes for potential risk factors were calculated [24].

RESULTS

Participants

Data of 781 unique patients were included, resulting in 1322 completed questionnaires during the first year of treatment. Hematological malignancies were the most common diagnosis (53.1%), followed by solid tumors (28.6%) and brain/CNS malignancies (18.3%). Median age of the patients was 6.8 years (range 2.0 – 21.0) and 42.4% were girl (Table 1).

Table 1. Patient demographic and clinical characteristics (*n* = 781)

Age at diagnosis, y, median (range)	6.8	2.0 – 21.0
	N	%
Gender		
Girls	331	42.4
Boys	450	57.6
Diagnosis[a]		
Hematological	415	53.1
ALL	255	32.7
AML	35	4.5
Hodgkin lymphoma	59	7.6
Non-Hodgkin lymphoma	50	6.4
LCH	16	2.0
Solid tumors	223	28.6
Renal	57	7.3
Soft tissue	53	6.8
Bone	41	5.2
Neuroblastoma	39	5.0
Germ cell (non-CNS)	13	1.7
Hepatic	10	1.3
Other	10	1.3

Table 1. *(continued)*

Brain/CNS tumors	143	18.3
LGG	61	7.8
Medulloblastoma	29	3.7
HGG	20	2.6
CNS germ cell	8	1.0
Craniopharyngioma	8	1.0
Ependymoma	7	0.9
Embryonal	2	0.3
PNET	1	0.1
DNET	1	0.1
Other	6	0.8

[a] Classified according to the Main Classification of the International Classification of Childhood Cancer (ICCC-3). ALL= acute lymphoblastic leukemia; AML= acute myeloid leukemia; LCH= Langerhans cell histiocytosis; CNS= central nervous system; LGG= low grade glioma; HGG= high grade glioma; PNET= primitive neuro-ectodermal tumor; DNET= dysembryoplastic neuroepithelial tumor.

Presence of nausea-related symptoms and severity of nausea

Nausea during medical treatment was present in 41.8% and 42.9% of the patients at 3 and 6 months after diagnosis respectively and gradually decreased to 24.8% at 12 months. Occurrence rates of all nausea-related symptoms were highest 6 months and lowest 12 months after diagnosis. Highest symptom presence was seen on the item “food not tasting good” (range 51.6 – 62.8%) and lowest symptom presence was found for anticipatory nausea (range 18.2 – 24.0%) (Figure 1). Results of symptom presence separately for patients aged 2 – 7 and 8 – 21 years can be found in the Supplement.

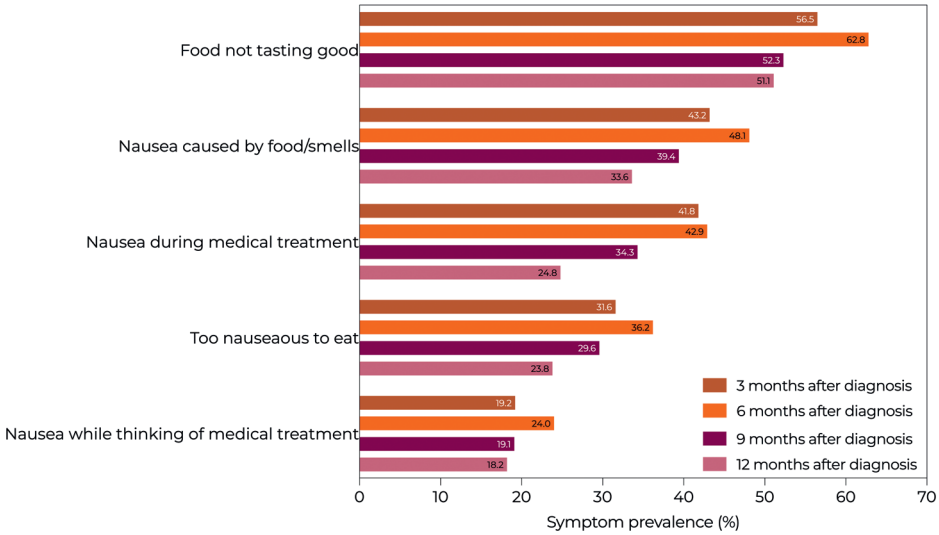

Figure 1. Occurrence rates of nausea-related symptoms at 3 (*n* = 354), 6 (*n* = 312), 9 (*n* = 277), and 12 (*n* = 307) months after diagnosis. Presence was defined as "sometimes-often-almost always" on an item of the nausea scale of the PedsQL Cancer Module. Proxy- and self-report were combined.

Figure 2 illustrates the severity of nausea (based on the mean of the nausea scale sum score). In young children, mean severity of nausea gradually improved from 67.6 (SD=23.3) to 76.6 (SD=20.8) at 3 and 12 months after diagnosis, respectively. In older children, nausea was reported to be most severe at 6 months after diagnosis 65.3 (SD=21.8) and then gradually improved to 74.3 (SD=21.3) at 12 months after diagnosis.

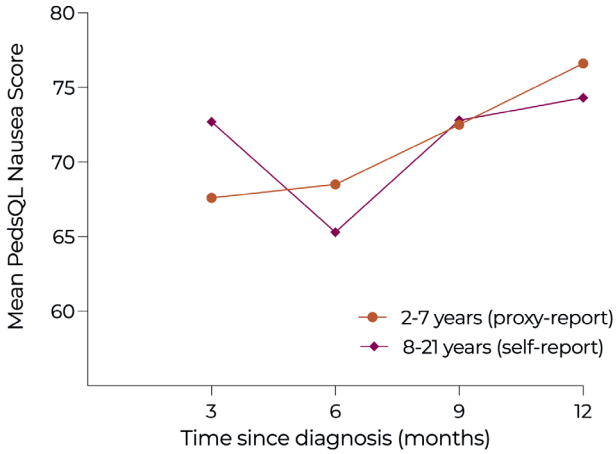

Figure 2. Severity of nausea, based on the mean sum score of the nausea scale of the PedsQL Cancer Module (self- and proxy-report) at 3, 6, 9 and 12 months after diagnosis. Higher scores indicate less nausea.

Risk factors for nausea

In children aged 2 – 7 years, time since diagnosis, pain, treatment anxiety, and worry were associated with nausea. Nausea scores improved gradually over the first year of treatment (B=7.01, SE=2.15). Pain (B=0.29, SE=0.03), treatment anxiety (B=0.18, SE=0.03) and worry (B=0.21, SE=0.05), were found to be risk factors for nausea as higher scores on these subscales are associated with less nausea (Table 2).

In patients aged 8 – 21 years, gender, BMI, diagnosis group, pain, treatment anxiety, and worry were significantly associated with nausea. Girls reported higher scores than boys (B=4.02, SE=1.91), indicating that girls suffer less from nausea than boys. Compared to patients with a solid tumor, higher scores were reported by patients with a hematological malignancy (B=8.42, SE=2.31) and patients with a brain/CNS tumor (B=11.13, SE=2.83) meaning that patients with hematological and brain/CNS malignancies suffer less from nausea than patients with a solid tumor. Patients with a high BMI reported less nausea (B=13.13, SE=3.64) compared to patients with a normal BMI. Furthermore, pain (B=0.17, SE=0.04), treatment anxiety (B=0.12, SE=0.05) and worry (B=0.25, SE=0.04) were found to be risk factors for nausea: higher scores on these subscales (meaning fewer problems with these symptoms) are associated with less nausea and vice versa. The results, including standardized regression coefficients and effect sizes, are summarized in Table 2.

Influence of nausea-related symptoms on HRQoL

In children aged 2 – 7 average HRQoL scores were 11.6 – 14.4 points lower for participants with symptom presence (yes/no) compared to participants without symptom presence (Figure 3A). Regarding patients aged 8 – 21 (Figure 3B), average HRQoL scores were 9.9 – 13.3 points lower for participants with symptom presence.

Table 2. Multivariable linear regression mixed model for patient-related factors and nausea

	2 – 7 years, proxy-report *n* = 413, 722 responses			**8 – 21 years, self-report** *n* = 368, 600 responses		
Variables	**B[a, d] (95% CI)**	**SE[b]**	**B[c, d, e]**	**B[a, d] (95% CI)**	**SE[b]**	**B[c, d, e]**
Time since diagnosis, year	7.01** (2.79;11.23)	2.15	0.31††	1.60 (-2.70;5.89)	2.19	0.07
Gender: girl vs boy[f]	2.40 (-0.89;5.69)	1.68	0.11	4.02* (0.27;7.77)	1.91	0.18
Age, y	-.47 (-1.54;0.61)	.55	-0.10†	0.28 (-0.33;0.90)	0.31	0.07
BMIz (-2≤ SDS ≤2[f])						
<2 SDS	2.84 (-4.83;10.51)	3.90	0.13	3.16 (-2.50;8.82)	2.88	0.14
>2 SDS	3.07 (-2.85;8.99)	3.01	0.14	13.13*** (5.97;20.29)	3.64	0.60††
Type of cancer (solid tumor[f])						
Hematological	2.74 (-0.98;6.45)	1.89	0.12	8.42*** (3.88;12.97)	2.31	0.39†
Brain/CNS	3.83 (-1.45;9.11)	2.68	0.17	11.13*** (5.57;16.70)	2.83	0.51††
PedsQL Cancer Module						
Pain	0.29*** (0.22;0.35)	0.03	0.30††	0.17*** (0.10-0.24)	0.04	0.18†
Treatment anxiety	0.18*** (0.12;0.24)	0.03	0.21†	0.12** (0.03;0.22)	0.05	0.11†
Worry	0.21*** (0.12-0.30)	0.05	0.15†	0.25*** (0.16;0.33)	0.04	0.25†

Dependent variable: sum score of the nausea scale of the PedsQL Cancer Module (range 0-100), higher scores indicate less symptom burden. Both linear-mixed models used a random intercept and fixed slope.

[a] Unstandardized regression coefficients

[b] Standard error for regression coefficients B

[c] Standardized regression coefficients

[d] Positive B/β coefficients indicate that the determinants are associated with less nausea. Negative B/β coefficients indicate that the determinants are associated with more nausea. As with the nausea scale, higher scores on the PedsQL Cancer Module scales "pain", "treatment anxiety" and "worry" mean a child is less bothered by the symptom.

[e] Effect sizes for differences between groups (regression coefficients of categorical variables) of .2, .5 and .8 and effect sizes for correlations between continuous variables (regression coefficients of continuous variables) of .1, .3 and .5 were considered small†, medium†† and large††† (30).

[f] Reference group

*p-value<0.05, **p-value<0.01, ***p-value<0.001

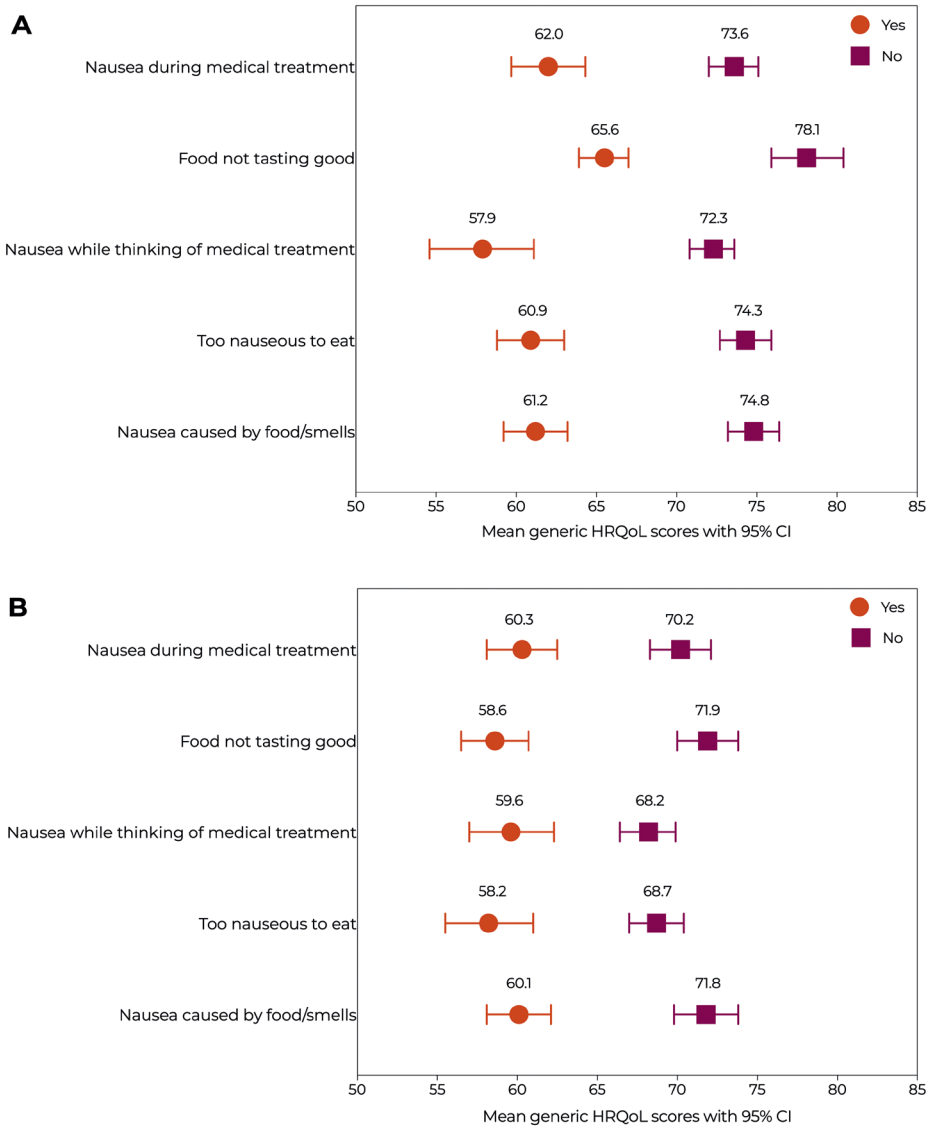

Figure 3. Mean generic HRQoL scores with 95% confidence intervals in children aged 2 – 7 years (proxy-report) with symptom presence (orange) or without symptom presence (blue) on nausea scale (A) and mean generic HRQoL with 95% confidence intervals scores in children aged 8 – 21 years (self-report) with symptom presence (orange) or without symptom presence (blue) on nausea scale (B).

DISCUSSION

This study showed that, despite standard supportive care treatment, many children with cancer suffer from nausea-related symptoms. The occurrence rate of nausea during medical treatment ranged between 24.5% and 42.9%. We identified pain, treatment anxiety, worry, a solid tumor diagnosis, and male gender as potential risk factors for nausea. In contrast, high BMI was associated with less nausea. Finally, the results of our study show that the presence of nausea-related symptoms was associated with a worse HRQoL.

These findings expand our knowledge regarding the presence of nausea and confirm that nausea is still an extensive problem. Generally, prevalence rates of nausea highly depend on the timing and method of symptom assessment [25]. In our study, nausea assessment was prior to an outpatient visit, generally a period of relatively less intensive treatment, and was administered longitudinally during a period of one year. This means that our results represent an average level of the presence of nausea-related symptoms during a less intensive phase of treatment, which at some times during treatment might even be higher.

The items “food not tasting good” and “nausea caused by food and smells” were the two most frequently reported symptoms, corresponding with previous research [26]. Moreover, taste changes have been found to be one of the most bothersome and distressful physical symptoms experienced by children with cancer [4, 27].

The high presence of nausea-related symptoms despite the use of antiemetic agents is concerning and underlines that prevention and treatment strategies of nausea need to be improved. Earlier recognition of nausea, using PROMs can help to realize better antiemetic treatment [28, 29]. Furthermore, a recent guideline provides new strategies for antiemetic treatment and highlights that prophylaxis for CINV should be adjusted from one chemotherapy block to the next, based on each patient’s history of CINV control [30].

The presence of nausea-related symptoms was highest at 6 months after diagnosis and nausea was also found to be most severe at that time point as reported by patients aged 8 – 21 years. Possible explanations for this pattern are that treatment is most intensive at 3 and 6 months, compared to later in treatment. Additionally,

children and/or parents may recognize the signs of nausea sooner over time, resulting in a faster and more targeted treatment of nausea.

Pain, treatment anxiety, and worry were found to be associated with nausea. Especially regarding anticipatory nausea, it is well-known that cancer patients with high levels of anxiety experience more anticipatory nausea [31-33]. Our results expand this evidence by showing that treatment anxiety and worry are also associated with nausea in general (not only anticipatory nausea). This implies that in addition to pharmacological interventions, cognitive-behavioral interventions are important in controlling nausea [34]. Our study shows that pain is associated with nausea in children with cancer, as was demonstrated in adult cancer patients before [16]. Therefore, good pain management might help reduce nausea. However, it is also known that some pain medication can introduce nausea [35].

Patients aged 8 – 21 with solid tumors reported significantly more nausea compared to patients with hematological malignancies and brain tumors, which is in line with previous research [6]. An obvious explanation is that these patients receive more intensive treatment with more emetogenic medication. Moreover, children aged 8 – 21 years with a high BMI experienced less nausea than children with a normal BMI. Apparently, BMI has an influence on nausea, which is in line with a previous study reporting that undernourished children with cancer were more nauseous than well-nourished children [36].

HRQoL of children who experienced nausea-related symptoms was lower compared to children without symptom presence. It is known that children with cancer have a reduced quality of life in comparison with healthy children [26, 37, 38] and nausea reduces their quality of life even more. This is supported by a study among children with advanced cancer [39]. Our results emphasize the importance of good symptom management and adequate nausea control to support optimal quality of life.

Strengths of the current study were the large cohort, inclusion of all types of childhood cancer, wide age range, and availability of data at several time points. However, several limitations should be mentioned. Firstly, we were unable to include the exact phase and type of treatment, as data were retrospectively retrieved. Consequently, no distinction could be made between the degree of nausea in children who did receive chemotherapy in the week prior to the doctor's appointment and children who did

not. Secondly, heterogeneity of the sample can be seen as a limitation because treatment regimens vary widely in terms of emetogenicity, which could have influenced the results. On the other hand, heterogeneity increases generalizability of our findings. Lastly, in more than half of the patients, only one measurement was available which might have influenced patterns of nausea over time. Future research, preferably a prospective study, is recommended to determine relationships between treatment protocol, severity and duration of nausea, effects of antiemetic therapy, and patient characteristics.

In conclusion, nausea in children with cancer is still a major problem. Management of nausea and nausea-related symptoms should be priority of care, potentially leading to a better HRQoL. Adequate symptom management should not only focus on pharmacological treatment, but should also include pain management and cognitive-behavioral interventions to deal with nausea and nausea-related symptoms.

Author contributions

Mirjam van den Brink: conceptualization, formal analysis, methodology, visualization, writing-original draft, writing-review and editing. Rosanne Been: conceptualization, formal analysis, methodology, visualization, writing-original draft, writing-review and editing. Martha A. Grootenhuis: data curation, writing-review and editing. Marloes van Gorp: data curation, writing-review and editing. Jolanda Maaskant: writing-review and editing. Marta Fiocco: formal analysis, writing-review and editing. Remco C. Havermans: writing-review and editing. Evelien de Vos-Kerkhof: writing-review and editing. Wim J.E. Tissing: supervision, writing-review and editing. Aeltsje Brinksma: conceptualization, formal analysis, methodology, supervision, writing-review and editing.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

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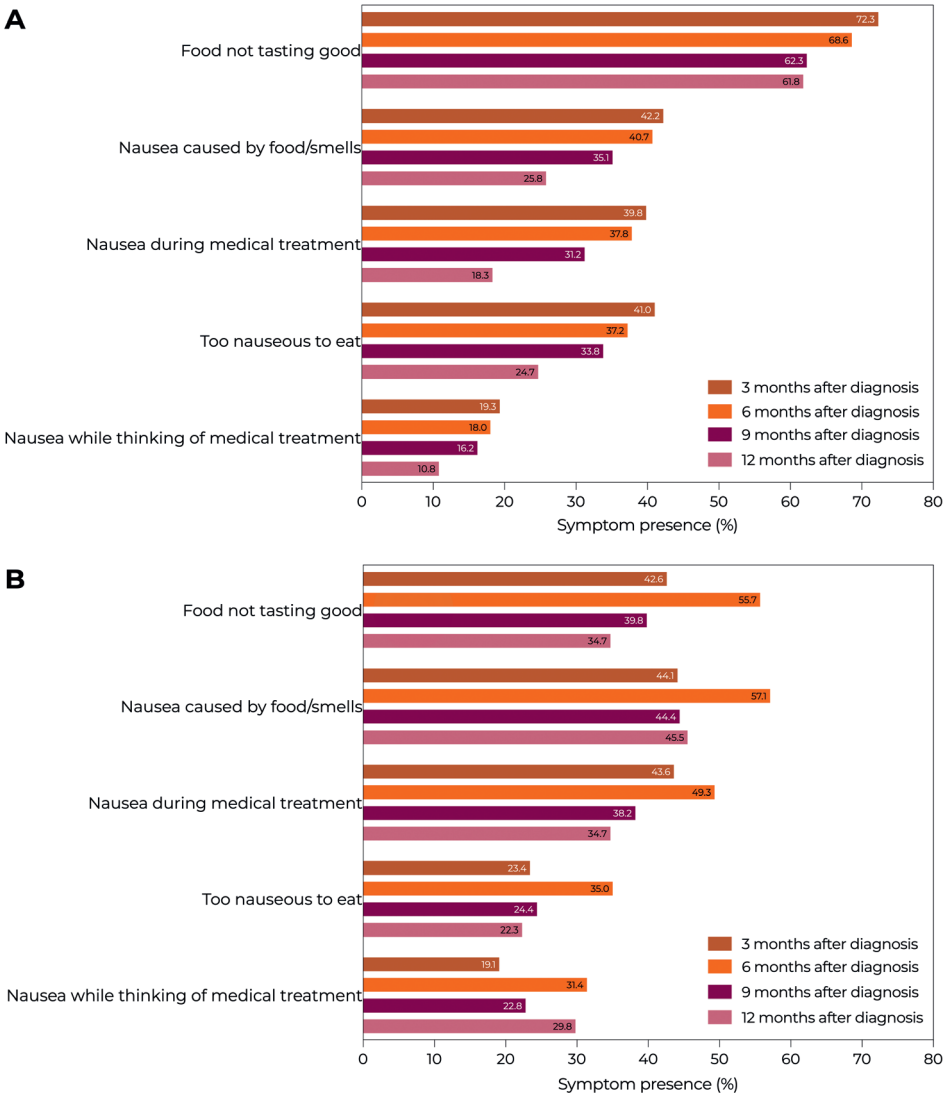
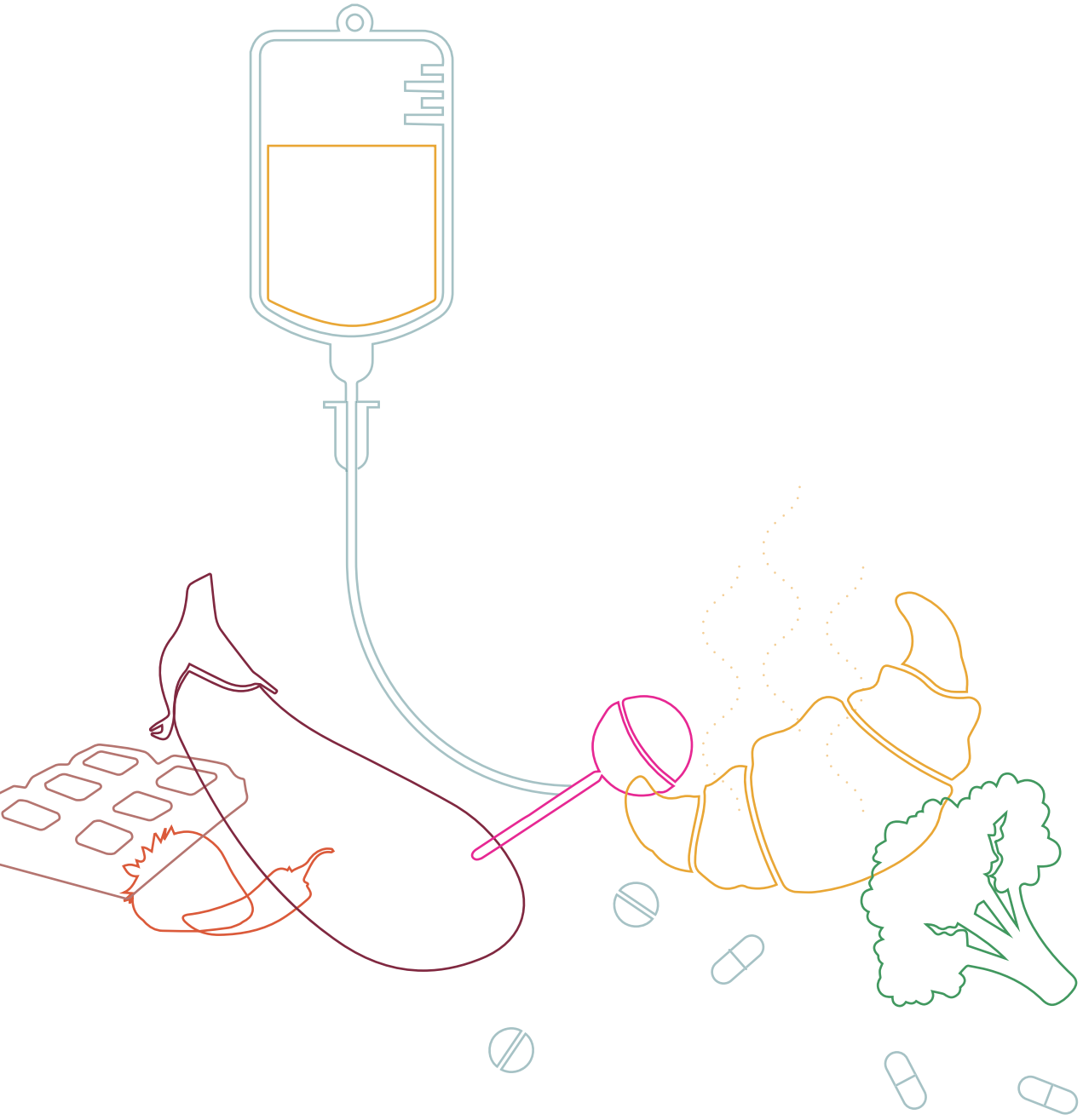
SUPPLEMENT



Supplemental Figure 1. Occurrence rates of nausea-related symptoms at 3 (n = 166), 6 (n = 172), 9 (n = 154), and 12 (n = 186) months after diagnosis separate in children aged 2 – 7 years (proxy-report, A) and occurrence rates of nausea-related symptoms at 3 (n = 188), 6 (n = 140), 9 (n = 123), and 12 (n = 121) months after diagnosis in children aged 8 – 21 years (self-report, B). Presence was defined as ''sometimes-often-almost always'' on an item of the nausea scale of the PedsQL Cancer Module.



5

Smell and taste function in childhood cancer patients: a feasibility study

Support Care Cancer. 2021;29(3):1619-28

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ABSTRACT

Purpose Chemotherapy can affect smell and taste function. This has never been investigated in childhood cancer patients during chemotherapy. The objective of this study was to determine whether psychophysical smell and taste tests are suitable for children with cancer. Taste and smell function, fungiform papillae density, and eating behavior were measured before (T1) and after (T2) a cycle of chemotherapy, and compared with healthy controls.

Methods Thirty-one childhood cancer patients treated for a hematological, solid, or brain malignancy (median age: 12 years, 16 girls) and 24 healthy controls (median age: 11 years, 10 girls) participated. Smell function was measured using Sniffin' Sticks, including a threshold, discrimination, and identification test. Taste Strips were used to determine recognition thresholds for sweet, sour, salty, and bitter taste. Papillae density was investigated by counting the fungiform papillae of the anterior tongue. Eating behavior was assessed using the Behavioral Pediatrics Feeding Assessment Scale (BPFAS).

Results Smell and taste function could be investigated in more than 90% of the patients, while fungiform papillae density could be determined in 61% of the patients. A significant difference in smell threshold was found between patients and controls ($p = 0.001$), showing lower thresholds in patients. In patients, sweet taste ($p < 0.001$), bitter taste ($p = 0.028$), and total taste function ($p = 0.004$) were significantly different after a cycle of chemotherapy, with higher scores at T2.

Conclusion The assessment of smell, taste, and fungiform papillae density is feasible in children with cancer. Results of the current study suggest that smell and taste sensitivity increased in children with cancer.

Keywords smell, taste, childhood cancer, chemotherapy

INTRODUCTION

Childhood cancer survival rates have markedly improved in recent decades [1]. Increased survival can be attributed to providing more intensive therapies. However, as a result, almost all such children suffer from bothersome or severe treatment-related side effects [2]. Nausea, vomiting, and loss of appetite are well-known side effects among childhood cancer patients, interfering with food intake [3]. Taste changes have been found to be the third most common bothersome symptom (prevalence 60.3%) [2]. These changes are an often overlooked side effect contributing to inadequate food intake, which in turn affects nutritional status [4]. Poor nutritional status in children with cancer is associated with increased infections, poor survival, and impaired health-related quality of life [5, 6].

Studies investigating changes in smell and taste among childhood cancer patients are rare. Skolin and colleagues found that children with cancer undergoing chemotherapy had significant lower scores for bitter taste and made more taste-recognition errors compared to controls [7]. However, this cross-sectional study was heterogeneous regarding chemotherapy (i.e., patients receiving doxorubicin, methotrexate, ifosfamide, cytarabine, procarbazine, dacarbazine, cisplatin, or cyclophoshamide per protocol depending on diagnosis and treatment phase) and only ten patients (median age 14.5 years) underwent a taste test. Qualitative studies indicated that changes in taste were the predominant cause of eating problems and altered food preferences in children with cancer, although specific food choices were highly variable [7, 8]. Changes in taste are often accompanied by changes in smell function. This has been found in adult patients undergoing various chemotherapy regimens (e.g., anthracycline, taxane, platinum containing) but has not been studied in childhood cancer patients during chemotherapy [9]. Only one study evaluated both smell and taste function in pediatric patients (n = 10) after bone marrow transplantation, but not during chemotherapy [10]. As current evidence comes from small studies and lack the assessment of smell function in childhood cancer patients during chemotherapy, prospective studies are needed to measure smell and taste function in children with cancer during chemotherapy.

Before investigating smell and taste changes in childhood cancer patients extensively, it must be considered whether psychophysical smell and taste assessments can be obtained without unpleasant side effects. For example, if children with cancer

are rather sensitive to odors, which is regularly seen in adult patients, they might experience nausea when certain odors are presented [11]. Therefore, this study aimed to examine whether measurements of smell, taste, and fungiform papillae density are feasible (i.e., completed by more than 60% of the patients) in children with cancer and if those tests require adjustments. Furthermore, smell and taste function, fungiform papillae density, and eating behavior were evaluated during chemotherapy (i.e., before and after a cycle) and compared with healthy controls, results of which contribute to a burgeoning understanding of smell and taste changes and their consequences in children with cancer.

METHODS

Participants

This study was performed at the Princess Máxima Center for Pediatric Oncology in Utrecht, the Netherlands. Eligible patients were children diagnosed with a hematological, solid, or brain malignancy, currently treated with chemotherapy. Treatment regimens supplied during the study period can be found in Table 1.

Patients were compared to healthy controls, matched by age and gender. Controls were recruited among siblings and friends of the patients. Participants were eligible for participation if they were between 6 and 18 years, and able to understand Dutch. Exclusion criteria were: isolated congenital anosmia (ICA) or a self-reported allergy to quinine.

Procedure and feasibility assessment

Patients were measured twice whereas controls were measured only once. A measurement was postponed in the case of severe oral mucositis or having a cold. During the first measurement in patients (T1), which was performed at day one of a cycle of chemotherapy somewhere during treatment protocol, feasibility of the tests was assessed. A test was considered feasible if at least 60% of the patients could complete the test without unpleasant side effects. Additionally, patients were asked to rate the tests by using smileys regarding the following topics: fun, difficulty level, concentration, and time duration.

Table 1. Characteristics of childhood cancer patients and healthy controls.

Characteristics	Patients (*n* = 31)	Controls (*n* = 24)	*p* value
Gender, female (n, %)	16 (51.6)	10 (41.7)	0.464
Age, (median, range)	12 (7 – 17)	11 (6 – 18)	0.658
6 – 8 years (n, %)	7 (22.6)	5 (20.8)	
9 – 14 years (n, %)	14 (45.2)	13 (54.2)	
15 – 18 years (n, %)	10 (32.2)	6 (25.0)	
Diagnosis			
Hematologic malignancy (n, %)	*16 (51.6)*		
ALL	8 (25.8)		
AML	1 (3.2)		
Lymphoma	7 (22.6)		
Brain tumor (n, %)	*3 (9.7)*		
Medulloblastoma	3 (9.7)		
Solid tumor (n, %)	*12 (38.7)*		
Bone	9 (29.0)		
Rhabdomyosarcoma	3 (9.7)		
Chemotherapy regimen *(n, %)*[*]			
Alkylating agents[a]	14 (53.8)		
Anthracyclines[b]	7 (26.9)		
Platinum agents[c]	4 (15.4)		
Vinca alkaloids[d]	15 (57.7)		
Antimetabolites[e]	11 (42.3)		
Epipodophyllotoxins[f]	5 (19.2)		
Other[g]	11 (42.3)		
Intensity of Treatment Rating (ITR)			
Moderate intensive (n, %)	11 (35.5)		
Very intensive (n, %)	17 (54.8)		
Most intensive (n, %)	3 (9.7)		

ALL= acute lymphoblastic leukemia; AML= acute myeloid leukemia.
[*] Provided chemotherapy between T1 and T2, *n* = 26
[a] Cyclophosphamide, dacarbazine, ifosfamide, lomustine; [b] Doxorubicin; [c] Carboplatin, cisplatin; [d] Vincristine; [e] Methotrexate, 6-mercaptopurine; [f] Etoposide; [g] Asparaginase, dactinomycin, dexamethasone, prednisone

If the first measurement in patients was considered viable, a second measurement (T2) was performed to assess potential changes in smell and taste within a cycle of chemotherapy. When a patient was admitted to the hospital for at least four days, the second measurement was taken on the last day of admission. In case of a shorter hospital stay, the second measurement was performed on the first day of the following chemotherapy cycle (usually 21 days later).

Measurements

Smell function

Sniffin' Sticks (Burghart, Wedel, Germany) were used to determine smell function [12]. This test comprises three parts: odor threshold (THR), discrimination (DIS), and identification (ID). All odorants are presented in pen-like odor dispensing devices, which are positioned 2 cm in front of the patient's nostrils for approximately three seconds. For the THR-test, a modified set of eight dilutions of phenyl ethyl alcohol (PEA; rose-like smell) was used [13]. Each time, three pens, of which one contained PEA and two contained a non-odorous solvent, were presented to the blindfolded participant. The participant had to distinguish the odor-containing pen in a staircase up-down procedure by starting with the lowest concentration of PEA. Reversal of the staircase was triggered by two correct or one false identification until seven reversals were obtained or until five reversals if attentiveness waned. The average of the last four reversal points was used as threshold score and ranged between 1 and 15. For the DIS-test, 16 triplets, containing two equal odorants and one different odorant, were presented in a randomized order. Participants, who were blindfolded, had to determine which pen smelled differently. ID was assessed by presenting sixteen common odorants and participants had to identify these odorants by using a four-choice task. For DIS and ID, a correct response resulted in one point and scores range between 0 and 16.

Taste function

Filter-paper strips (Taste Strips, Burghart, Wedel, Germany) with impregnated concentrations of sweet, sour, salty, and bitter were used to determine taste recognition thresholds [14]. Each time, one of four concentrations of sweet taste (0.05, 0.1, 0.2, and 0.4 g/ml sucrose), sour taste (0.05, 0.09, 0.165, and 0.3 g/ml citric acid), salty taste (0.016, 0.04, 0.1, and 0.25 g/ml sodium chloride), or bitter taste (0.0004, 0.0009, 0.0024, and 0.006 g/ml quinine hydrochloride) were presented in an order of increasing concentrations. Before the test began, the highest concentration of each taste was given to familiarize participants with the taste qualities. Taste strips were placed on the middle of the tongue for whole-mouth testing. Participants were then asked whether the perceived taste was sweet, sour, salty, bitter, or tasteless. Scores for each taste quality range from 0 to 4 and the total taste score was derived by summing the scores of each taste quality (range 0 – 16).

Subjective smell, taste, and appetite

Participants were asked to self-assess their smell, taste, and appetite on a 5-point Likert scale (1 “very bad” to 5 “very good”). In addition, participants rated their smell, taste, and appetite (1 “much worse” to 5 “much better”) compared to the start of chemotherapy (patients) or to the last month (controls).

Fungiform papillae density

Fungiform papillae density was investigated by staining the tongue with a 0.9% Brilliant Blue food dye (Pomona Aroma, Hedel, the Netherlands), diluted to a concentration of 1:10 at which fungiform papillae remain pink [15]. Participants were asked to extend their tongue and secure it gently between their teeth and lips. Subsequently, the tongue was dried with filter paper, stained with blue food dye, and dried again. Then, a 15 mm diameter Whatman circular filter paper Grade 1 (GE Healthcare Life Science, Chalfont St Giles, UK) with a 6 mm diameter circular cut-out (area 0.283 cm^2) was placed on the anterior of the left side of the tongue, next to the midline [16]. At least three close-up images of the tongue were taken by a digital camera (Canon Powershot SX70 HS, Tokyo, Japan). Afterwards, the clearest image was further investigated in Fiji, a distribution of ImageJ software (National Institutes of Health, Bethesda, USA) [17]. The Denver Papillae Protocol (DPP) was used for counting fungiform papillae [18].

Eating behavior

Eating behavior was assessed using the Behavioral Pediatrics Feeding Assessment Scale (BPFAS) [19]. The BPFAS is a 35-item parent-report questionnaire that consists of 25 items that focus on child eating behavior and 10 items that focus on parents’ feeding strategies. For each statement, parents reported how often the particular behavior occurred on a 5-point Likert scale (1 “never” to 5 “always”). They were also asked to indicate whether they believed this behavior was problematic or not. Four scores are thus generated: Child Behavior-Frequency (CBF) and Parent Behavior-Frequency (PBF) (which refer to how often the specific child and parent behavior occur), and Child Behavior-Problems (CBP) and Parent Behavior-Problems (PBP) (which reflect the number of behaviors seen as problematic). Higher scores indicate more eating/feeding problems [20].

Treatment intensity

Treatment intensity was rated with the Intensity of Treatment Rating scale (ITR-3), a psychometrically valid classification of pediatric cancer treatment, into one of four

levels ranging from 1 “minimally invasive” (e.g., in case of stage 1 Wilm’s tumor) to 4 “most invasive” (e.g., in case of a brain tumor with treatment requiring HSCT) [21].

Statistical analysis

Descriptive statistics are presented as median with interquartile range (IQR) or number of participants (N) with percentage (%) for both groups. The Mann-Whitney U Test was used to compare smell, taste, fungiform papillae density, and BPFAS scores between controls and patients at T1. The Wilcoxon signed-rank test was used to compare changes in smell, taste, and fungiform papillae density between the two measurements in patients. Spearman’s test was employed to investigate correlations between taste function and fungiform papillae density, and taste function and eating behavior in patients at T1. A 5% alpha level was used. Data analysis was performed with IBM SPSS Statistics (version 25.0).

RESULTS

Participant characteristics

Thirty-one patients and 24 healthy controls were included in this study (Table 1). After the first measurement, five patients left the study because they completed their treatment (n = 2), continued treatment somewhere else (n = 1), or became too ill (n = 2). Median time interval between T1 and T2 was 21 days (IQR 14 – 37). Six patients underwent the second measurement more than 37 days later due to postponed admissions or severe complications.

Feasibility assessment in patients

Twenty-nine patients (94%) performed the THR-test and for 23 of them (79%) a THR-score could be obtained after seven reversals of the staircase. For the remaining six patients, the THR-score was calculated after five reversals of the staircase as their attentiveness waned. For DIS and ID, 28 (90%) and 30 (97%) patients could complete these tests, respectively. Thirty patients (97%) finished the taste test. One DIS-test and taste test were prematurely terminated due to nausea. For papillae density, six patients (19%) did not undergo the measurement. Reasons for not participating in this test were: nausea/gagging (n = 2), anxiety/tension (n = 2), or logistical reasons (n = 2). From the remaining 25 patients, six photos were of insufficient quality to count the fungiform papillae. Overall, fungiform papillae density could be calculated for 19 (61%) of the patients.

Concerning patients' experiences, 81% reported that they really liked the overall assessment and 84% reported that they did not experience any problems concerning concentration. Difficulty of the tests was qualified by 71% of the patients as "a bit difficult". In addition, 39% of the patients reported time of the assessment as "long lasting".

Smell and taste function

Figure 1 shows smell function of the childhood cancer patients and controls. A significant difference in smell threshold was found between patients and controls (p = 0.001), showing lower thresholds in patients. DIS and ID were not significantly different between the two groups. In patients, no significant differences in smell function were found between the two measurements.

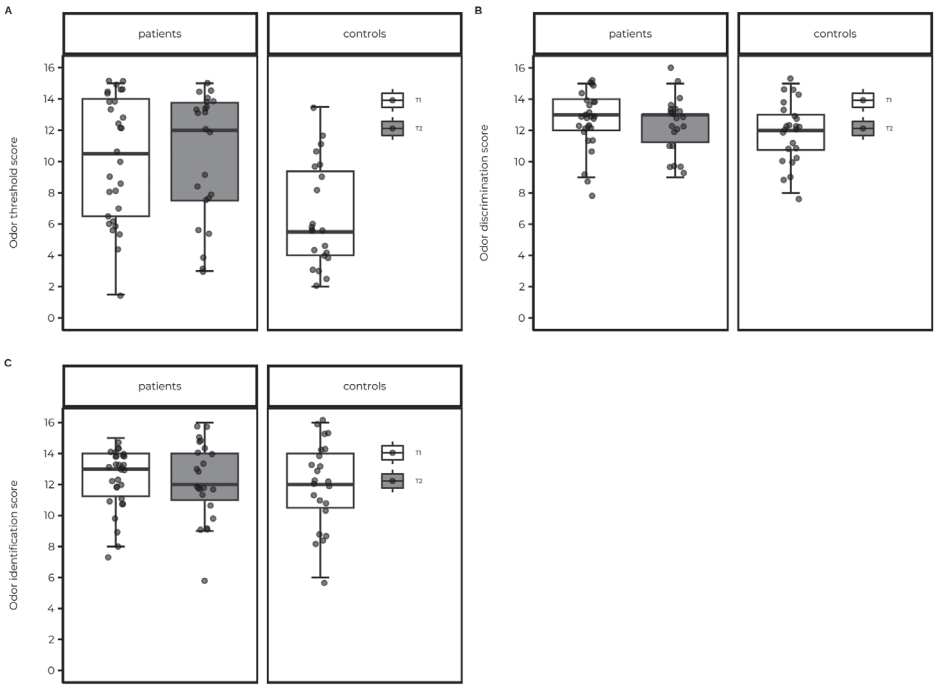

Figure 1. Boxplots for the three different smell tests: odor threshold (a), odor discrimination (b), and odor identification (c). The boxplots refer to the median score (midpoint of the scores), the first quartile of the scores (Q1, lower boundary of the box), and the third quartile of the scores (Q3, upper boundary of the box). The range of the box represents the interquartile range (IQR = Q3 – Q1), and the whiskers indicate what data points can be considered outliers. The upper whisker extends to the most extreme score no more than 1.5 times the IQR above Q3, and the lower whisker extends to the most extreme score no more than 1.5 times the IQR below Q1. Note that the data points represent individual scores and that these points were slightly jittered to avoid overplotting.

Compared to controls, patients had a different sour taste threshold ($p = 0.042$) (Figure 2). Regarding the other taste qualities, no significant differences were found between patients and controls. In patients, sweet taste ($p < 0.001$), bitter taste ($p = 0.028$), and total taste function ($p = 0.004$) were significantly different after a cycle of chemotherapy, showing higher scores at T2.

Table 2 shows subjective smell, taste, and appetite of childhood cancer patients at T1. Twelve patients (39%) reported changes in smell and 11 patients (36%) reported taste changes, reflecting both increased and decreased perceptions. In addition, 24 patients (77%) reported alterations in appetite.

Table 2. Subjective smell, taste, and appetite among childhood cancer patients at T1 ($n = 31$).

Rating	Number of patients (%)	Changes since start chemotherapy	Number of patients (%)
Smell			
Very good	8 (25.8)	Much better	2 (6.4)
Good	19 (61.3)	Better	6 (19.4)
Moderate	4 (12.9)	Unchanged	19 (61.3)
Bad	0 (0.0)	Worse	4 (12.9)
Very bad	0 (0.0)	Much worse	0 (0.0)
Taste			
Very good	6 (19.4)	Much better	1 (3.2)
Good	20 (64.5)	Better	4 (12.9)
Moderate	3 (9.7)	Unchanged	20 (64.5)
Bad	2 (6.4)	Worse	6 (19.4)
Very bad	0 (0.0)	Much worse	0 (0.0)
Appetite			
Very good	8 (25.8)	Much better	0 (0.0)
Good	12 (38.7)	Better	11 (35.5)
Moderate	6 (19.4)	Unchanged	7 (22.6)
Bad	3 (9.7)	Worse	10 (32.2)
Very bad	2 (6.4)	Much worse	3 (9.7)

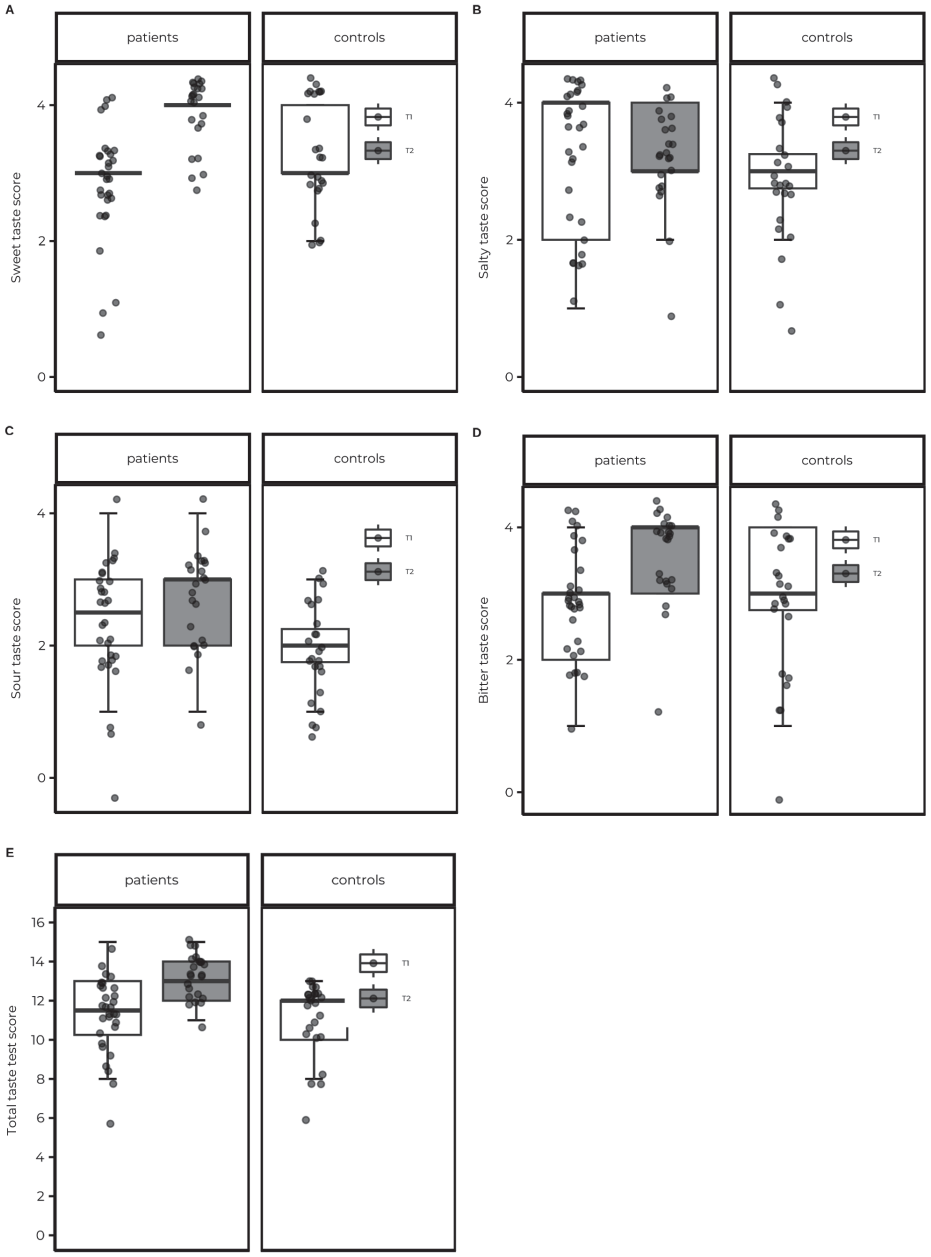

Figure 2. Boxplots for the "Taste Strips" test scores: sweet taste (a), salty taste (b), sour taste (c), bitter taste (d), and total score (e). Note that due to the limited range of possible scores for the individual taste qualities (0–4; a–d), some boxes (and whiskers) appear constricted.

Fungiform papillae density

Fungiform papillae density was neither significantly different between patients and controls, nor between the two measurements in patients (Table 3). Fungiform papillae density was not significantly correlated with taste function in children with cancer.

Table 3. Median scores (IQR) of fungiform papillae in childhood cancer patients and healthy controls.

	Controls (*n* = 17)	**Patients (T1) (*n* = 19)**	**Patients (T2) (*n* = 18)**	***p* value***
Number of papillae	15.0 (12.5 – 24.0)	20.0 (15.0 – 28.0)	20.5 (17.8 – 25.8)	0.327
Papillae density	53.1 (44.2 – 84.9)	70.7 (53.1 – 99.0)	72.5 (62.8 – 91.1)	0.294

IQR = Interquartile range.
* *p* value between T1 and T2 within patients.

Eating behavior

No significant differences were found in BPFAS scores and the prevalence of eating disorders between patients and controls (Table 4). In patients, total taste function at T1 was negatively correlated with PBF (r = - 0.402, p = 0.042), meaning that a better taste function is associated with less frequently reported 'poor' feeding strategies. Additionally, a difference in taste function (T1 vs T2; i.e., increased sensitivity in this case) was positively correlated with CBF (r = 0.469, p = 0.037). Thus, increased taste function in children with cancer was associated with eating disorders.

Table 4. Comparisons of BPFAS scores across childhood cancer patients and healthy controls.

	Patients (*n* = 26)		**Controls (*n* = 20)**	
	Median (IQR)	*N* disorder (%)	Median (IQR)	*N* disorder (%)
Child Behavior – Frequency (CBF)	43.0 (38.5 – 47.3)	3 (11.5)	37.0 (34.3 – 45.8)	2 (10.0)
Child Behavior – Problem (CBP)	0.0 (0.0 – 0.8)[a]	3 (12.5)	0.0 (0.0 – 0.0)[b]	0 (0.0)
Parent Behavior – Frequency (PBF)	16.0 (13.0 – 18.0)	3 (11.5)	14.0 (12.0 – 16.0)	0 (0.0)
Parent Behavior – Problem (PBP)	0.0 (0.0 – 0.0)[a]	3 (12.5)	0.0 (0.0 – 0.0)[b]	1 (5.9)

IQR = Interquartile range.
[a] n = 24; [b] n = 17

DISCUSSION

The present study has shown that assessing smell, taste, and fungiform papillae density is feasible in children with cancer, as more than 60% of the patients were able to complete the tests. Although feasible, some adaptions are deemed necessary regarding time duration and difficulty level of the tests. Furthermore, we showed that taste function increased in childhood cancer patients during chemotherapy, especially for sweet and bitter taste. Lower smell thresholds were found in patients compared with healthy controls, which suggest that both smell and taste sensitivity increased in children with cancer.

Regarding smell function, a wide step method was used for the threshold test to enhance concentration and reduce time of investigation. This method has never been used in children, but has been shown reliable in adults [13]. Due to the size of our control group, and its distribution across different age categories, it was not possible to compare the threshold scores with those derived from a regularly used narrow step method [22]. Still, the wide step method provides an advantage for threshold testing in participants where time of investigation should be kept as short as possible [13]. Although only one discrimination test was prematurely terminated due to nausea, several patients noted that they did not like the intensity and large number of odorants either. Concerning odor identification, children were often not familiar with some of the odorants (e.g., turpentine, apple) from the odor identification test. This finding is consistent with a study among German children [23]. The Universal Sniff Test, a recently developed international odor identification test for children, will be more suitable as odorants are selected on familiarity [24]. This test is now commercially available, including normative values for children aged 6 – 17 years [22].

As smell thresholds are less influenced by age, contribute to a large extent to the diagnosis of smell loss, and seem affected the most in our study population, the assessment of smell function in children with cancer should include at least an odor threshold test [25, 26]. However, the assessment of several components of smell function, instead of a single component, is preferred. Therefore, a suitable odor identification task for children, such as the Universal Sniff Test, should be added. Odor discrimination does not seem to have much added value in children with cancer and child-friendly tasks are lacking. Removing this task will save at least ten minutes.

Investigating taste function and papillae density can be considered feasible, although the assessment of papillae density was more problematic in children with cancer. The main obstacle was not the measurement, which relatively few children disliked**,** but rather obtaining a proper photograph of the tongue. Photographs regularly failed due to movement of the tongue or being taken in poorly lit rooms. Sometimes, fungiform papillae were invisible because of a white layer on the surface of the tongue. So-called oral thrush, or oral candidiasis, is common among people with a weakened immune system [27]. In addition, papillae density was not significantly different between the groups nor correlated with taste function in patients. Although feasible, the limitations and current results do not warrant further investigation of fungiform papillae density in children with cancer. Practical issues need to be overcome first to reduce the burden on children with cancer.

Results of our study seem to indicate that smell function sensitizes in children with cancer, showing lower smell thresholds compared to controls. Smell function did not change significantly after a cycle of chemotherapy in patients. Our findings are in contrast with those of previous studies who examined adults receiving chemotherapy. For example, women undergoing chemotherapy for breast cancer or gynecological malignancies showed increased smell thresholds during chemotherapy [9]. In addition, men undergoing chemotherapy for testicular cancer showed no changes in smell function [28]. Although there was no measurement before diagnosis, and it cannot be ruled out that lower smell thresholds were already present before diagnosis, several children with cancer (n = 8) reported a better or much better smell perception since the start of chemotherapy. This may well be an underestimation. Increased smell sensitivity was typically judged as negative. Possibly, some children conflated their evaluation of their altered sense of smell with their altered smell sensitivity leading them to rate their sense of smell as 'worse' after chemotherapy. Future research on subjective smell and taste sensitivity in children with cancer requires more careful instruction and phrasing of questions.

The current study showed increased sweet, bitter, and total taste function after a cycle of chemotherapy. So far, evidence regarding smell and taste function in childhood cancer patients during chemotherapy is limited to cross-sectional studies with small sizes. Those studies generally show reduced taste perception for all taste qualities, or bitter taste only, in children with cancer compared to healthy controls [7, 29]. When reviewing prospective studies among adults receiving chemotherapy,

changes in sweet taste and, to a lesser extent, bitter taste seem more common than changes in salt or sour perception [30]. However, taste changes in the current subset of childhood cancer patients were characterized by increased perception of sweet and bitter taste, while adults generally experience a decreased perception of these taste qualities during chemotherapy. Maybe other pathways are involved in children compared to adults.

The etiology of smell and taste changes during chemotherapy is not fully understood. In general, damage to sensory receptor cells and abnormal neuronal activity are thought to be the major cause of these distortions [31]. Smell and taste receptor cells have high turnover rates, as do cancer cells, and particularly rapidly dividing cells are affected by chemotherapy. With respect to specific chemotherapeutic substances, drugs such as methotrexate, vincristine, cisplatin, carboplatin, doxorubicin, cyclophosphamide, 6-mercaptopurine, and 5- fluorouracil all seem to be associated with taste changes in adults but not necessarily with smell changes [32]. Taste changes may be also related to oral mucositis, poor oral hygiene, infections, or a dry mouth. In addition, it is presumed that cancer-related inflammation can trigger apoptosis of the taste bud cells through cytokine signaling pathways and thereby contributing to the development of taste disorders [33]. An enhanced ability to smell during chemotherapy, potentially resulting in food aversions and nausea, might be a strengthened defense mechanism of the sensory organ to avoid ingestion of potentially harmful substances into the body [34]. However, many questions remain regarding smell and taste changes during chemotherapy.

Taste function was correlated with eating behavior and feeding strategies in children with cancer. This is in line with qualitative studies that already highlighted the influence of taste changes on food preferences and eating behavior [7, 8, 35]. Since eating behavior and food preferences are still developing in children, and are strongly influenced by the chemical senses, it is suggested that the impact of smell and taste changes in the long term could be large as well [36, 37]. To prevent children with cancer from inadequate food intake and bad dietary habits due to this phenomenon, longitudinal studies are needed to identify the course of smell and taste changes and its consequences regarding food intake and eating behavior during and after chemotherapy.

This study aimed to investigate feasibility of smell, taste, and papillae density assessment in children with cancer. Therefore, the current results regarding smell

and taste function do not allow for strong conclusions and should be considered as tentative. Even if it is the largest study to date, the size of the current study is small, lacks a measurement at diagnosis, and vary in time intervals between measurements. Nevertheless, the prospective study design and control group make the results of this feasibility study already useful for a burgeoning understanding of smell and taste changes in children with cancer during chemotherapy.

In conclusion, the assessment of smell and taste function and fungiform papillae density is feasible in children with cancer. Future longitudinal studies should focus on smell (threshold and identification) and taste function in children with cancer, whereas the assessment of fungiform papillae density should be omitted. In addition, results of the current study suggest a remarkable increased smell and taste sensitivity in children with cancer, which was an unexpected finding and requires further investigation.

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Authors' contribution

Author contributions were as follows: Mirjam van den Brink participated in study design, collected data, conducted statistical analysis, and drafted the manuscript. Irene IJpma participated in study design, interpretation of the data, and helped to draft the manuscript. Britt van Belkom collected data. Marta Fiocco participated in statistical analysis, interpretation of the data, critical revision and editing of the manuscript. Remco Havermans participated in study design, supervised its execution, helped with interpretation of the data, and helped to draft the manuscript. Wim Tissing participated in study design, supervised its execution, helped with interpretation of the data, and helped to draft the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

The authors have declared no relevant conflict of interest.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Medical Ethics Review Committee of the University Medical Center Groningen (UMCG) determined that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study.

Informed consent

Written informed consent was obtained from the parents and children ≥12 years.

Consent for publication

Not applicable.

Availability of data and material

Data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability

Not applicable.

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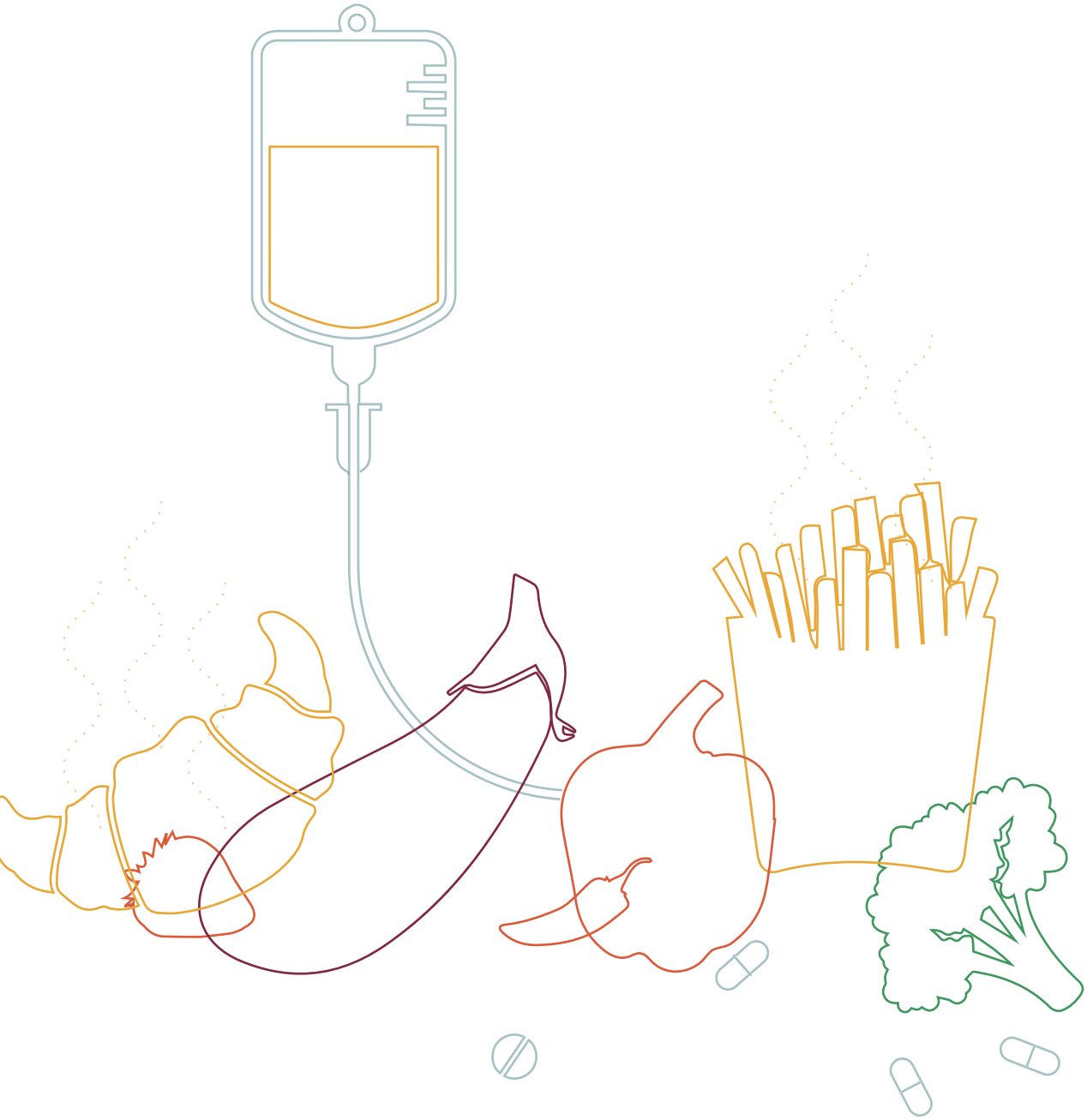

6

A longitudinal evaluation of smell and taste function in children with cancer during and after treatment with chemotherapy

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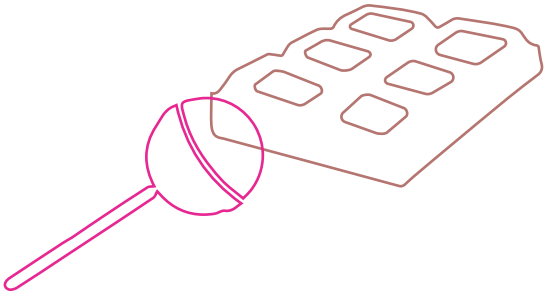

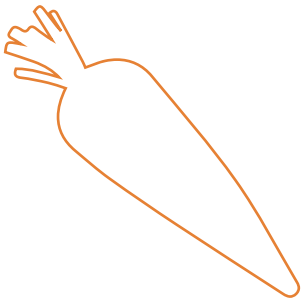

ABSTRACT

Background & aims Smell and taste changes are bothersome treatment symptoms interfering with dietary intake and quality of life. It remains unclear how and when children with cancer experience such changes during chemotherapy, and if they resolve after treatment. Therefore, our aim was to get insight into the dynamics of smell and taste function in children with cancer both during and after treatment with chemotherapy.

Methods A prospective longitudinal study with 94 childhood cancer patients treated for hematological, solid, or brain malignancies was performed. Smell and taste function were assessed using Sniffin' Sticks (odor threshold and identification) and Taste Strips, respectively. For both tests, normative values were used to identify the presence of smell and taste abnormalities. Self-reported smell and taste changes were assessed using a questionnaire. Measurements were taken at approximately 6 weeks (T0), 3 months (T1), 6 months after starting chemotherapy (T2), and 3 months after the stop of chemotherapy or maintenance phase for children with acute lymphoblastic leukemia (ALL) (T3). Linear mixed models were estimated to analyze smell and taste function during active treatment (T0-2). Wilcoxon signed rank tests were used to compare data between the last time point in active treatment to T3.

Results Smell and taste scores did not change during active treatment (T0-2). However, the proportion of children showing normal smell (i.e., odor identification) and taste function during active treatment was significantly lower than expected based on normative values. Approximately 20% of the patients suffered from decreased taste function, particularly children with lymphoma or solid tumors. Changes in smell were predominantly characterized as increased rather than decreased, specifically among children with hematological malignancies. Self-reported changes were much more common than objectively measured, but heterogeneous, with smell changes ranging from 26 to 53% and taste changes up to 80% during treatment. After active treatment, odor threshold scores decreased in children with ALL during maintenance phase, whereas total taste scores increased in all children at T3.

Conclusion Objectively measured smell and taste function remained stable during active treatment, while at the individual level a fairly large number of children suffered from chemosensory distortions which comprised either increased or

decreased sensitivity. Individual dietary advice and coping strategies are warranted to prevent detrimental effects on food intake and improve quality of life of children with cancer.

Keywords smell, taste, childhood cancer, chemotherapy

INTRODUCTION

Childhood cancer is a rare disease, but it is still the major cause of death among children in the Western world [1]. Each year, around 600 children are diagnosed with cancer in the Netherlands [2]. In recent decades, new therapies and more intensive treatment regimens have resulted in survival rates of approximately 80% [3, 4]. However, these intensive cancer treatments have severe side effects such as infections, pain, nausea and vomiting [5]. It is well-known that side effects are associated with worse survival and poor quality of life, highlighting the importance of supportive care [6, 7]. Supportive care can be defined as the prevention and management of the adverse effects of cancer and its treatment, aiming to ensure patients withstand their treatment physically and mentally as well as possible [8].

Nutrition plays an important aspect within supportive care, as a poor nutritional status – including both underweight and overweight – is associated with adverse clinical outcomes [9-15]. Maintaining an optimal nutritional status is challenging as many treatment-related side effects interfere with food intake [16]. Although frequently overlooked in clinical practice, children with cancer report taste changes as being one of the most frequent, unpleasant, and distressful side effects during treatment [17, 18]. This is corroborated by qualitative studies in which children with cancer interviewed during or after chemotherapy report that treatment-induced changes in taste and smell negatively impact their daily lives [19, 20]. Moreover, a recent study showed that self-reported taste and smell alterations in children with cancer are also associated with impaired nutritional status [21].

Cancer treatment (particularly chemotherapy) impacts childhood cancer patients' chemical senses: smell and taste. The question arises how smell and taste are affected during treatment. Is there a loss of smell and taste, as it is often seen in adults with cancer during chemotherapy, or rather a heightened sensitivity or distorted chemosensory perception [22, 23]? Few studies have quantitatively investigated taste and smell changes in these patients before. Skolin and colleagues found that children with cancer (n = 10) had higher thresholds for bitter taste and made more taste recognition errors compared to controls [24], suggesting a negative impact of cancer treatment on taste function. In contrast, our feasibility study showed that childhood cancer patients (n = 31) became more sensitive to sweet and bitter taste after a cycle of chemotherapy and had lower smell thresholds

compared to controls [25], suggesting heightened taste and smell sensitivity in children with cancer. These contradictory findings might be explained by the large heterogeneity in chemotherapeutic treatment regimens used in pediatric oncology. Conceivably, some chemotherapeutic agents might have a detrimental effect on taste and smell function whereas other agents increase taste and smell function. A recent review found the following drugs to be most frequently associated with smell and taste disorders, namely docetaxel, paclitaxel, nab-paclitaxel, capecitabine, cyclophosphamide, epirubicin, anthracyclines, and oral 5-FU analogues [26].

As previous studies were performed with small samples and consisted of only one or two measurements, it remains unclear how, when, and among which types of childhood cancer changes in smell and taste are experienced during treatment. Note that the focus is primarily on chemotherapeutic treatment since children with cancer are typically treated with chemotherapy and much less often with radiotherapy. Therefore, we conducted a prospective cohort study among children with cancer in their first year of treatment and measured smell and taste function at several time points during and after treatment with chemotherapy. We aimed to get insight into the dynamics of smell and taste function both during and after the course of treatment, as well as the general occurrence of smell and taste dysfunction investigated through objective measures and self-report.

METHODS

Participants

This study was performed at the Princess Máxima Center for Pediatric Oncology in Utrecht, the Netherlands. All children newly diagnosed with cancer and treated with chemotherapy were asked to participate in a prospective cohort study called SENSORY-2 between November 2020 and January 2022. The follow-up period ended in March 2023. Eligible patients had no prior diagnosis of cancer, were able to understand Dutch, and were 6 to 18 years old. Children younger than 6 years were not considered for inclusion as the validity of chemosensory tests in younger children is limited [27, 28]. Exclusion criteria were isolated congenital anosmia and (self-reported) allergy to quinine. Ethical approval was obtained from the Medical Ethics Review Committee of the University Medical Center Utrecht (METC N19.809). Written informed consent was obtained from the parents, and from children ≥ 12 years.

Procedure

Smell and taste function were assessed at four time points, so-called "main study visits": within six weeks of diagnosis (T0), 3 months (T1) after starting chemotherapy, 6 months (T2) after starting chemotherapy, and 3 months (T3) after ending chemotherapy. For children with ALL, T3 was performed during the maintenance phase (approximately 12 months after diagnosis) when children receive a much gentler form of chemotherapy (typically comprising oral mercaptopurine and methotrexate, with additional vincristine and dexamethasone for some patients) that does not require hospital admissions. To investigate possible changes in taste and smell function directly after a cycle of chemotherapy, participating children were asked for an extra measurement of their taste and smell function 7 – 21 days (T1A) after T1. All measurements were performed during regular visits to the hospital to make study participation as practical as possible for patients.

Measurements at T0-T2 mainly took place during the first waves of the COVID-19 pandemic, when children were less likely to become infected than adults. However, the later omicron variant also affected many children – including children with cancer. Since COVID-19 can affect the sense of smell and taste, T3 measurements were postponed for 3 months for those patients who had had a recent infection. The measurement was then scheduled with the patient's visit to the outpatient clinic for a regular consultation [29]. In addition, patients were asked whether they had suffered from smell and/or taste problems and whether they had recovered from them.

Measurements

Smell function

Sniffin' Sticks (Burghart, Wedel, Germany) were used to determine smell function [30]. We investigated two parts of smell function: odor threshold (THR) and odor identification (ID). All odorants were presented in pen-like odor dispensing devices, which were positioned 2 cm in front of the patient's nostrils for approximately three seconds. For the THR-test, a modified set of eight dilutions (instead of 16 dilutions) of phenylethyl alcohol (PEA; rose-like smell) was used to reduce time of investigation, taking potential fatigue into account. This wide step method has been shown to be reliable in adults [31]. Each separate trial, three pens, of which one contained PEA and two contained a non-odorous solvent, were presented to the blindfolded participant. The participant had to distinguish the odor-containing pen in a staircase up-down procedure by starting with the lowest concentration of PEA. Reversal of the staircase

was triggered by two correct or one false identification until seven reversals were obtained (or five reversals if attentiveness waned). The average of the last four reversal points was used as the threshold score and could range between 1 and 15.

ID was assessed by presenting twelve familiar odorants to children and they had to identify each odorant by using a 4-alternatives forced choice task [32]. For ID, a correct response resulted in one point and scores could thus range between 0 and 12. Normative values were used to distinguish between normal and altered smell function (i.e., decreased (<10th percentile) or increased (>90th percentile) sensitivity/ ability to identify smells) [33].

Taste function

Filter-paper strips (Taste Strips, Burghart, Wedel, Germany) with impregnated concentrations of sweet, sour, salty, and bitter were used to determine taste recognition thresholds [34]. Each time, one of four concentrations of sweet taste (0.05, 0.1, 0.2, and 0.4 g/ml sucrose), sour taste (0.05, 0.09, 0.165, and 0.3 g/ml citric acid), salty taste (0.016, 0.04, 0.1, and 0.25 g/ml sodium chloride), or bitter taste (0.0004, 0.0009, 0.0024, and 0.006 g/ml quinine hydrochloride) was presented in an order of increasing concentrations. Taste strips were placed on the middle of the tongue for whole-mouth testing. Children were then asked whether the perceived taste was sweet, sour, salty, bitter, or tasteless. Scores for each taste quality range from 0 to 4 and the total taste score was derived by summing the scores of each taste quality (range 0-16). Normative values were used to distinguish between normal and altered taste function (i.e., decreased (<10th percentile) or increased perception (>90th percentile)) [28].

Apart from the taste recognition threshold scores, 6-n-propylthiouracil (PROP) taster status was determined by a filter paper strip impregnated with PROP (Sensonics International, NJ, United States, 20 µg/ strip). The ability to taste PROP is genetically controlled and correlates with increased sensitivity to taste stimuli and other orosensory sensations [35, 36]. Participants were instructed to place the strip on the dorsal surface of the tongue for approximately 30 s and were then asked whether they tasted anything (yes/no) [37]. Participants who answered “no” or reported that the strip “tastes like paper” were classified as “non-tasters.” Children who indicated that the strip tasted “bitter”, “sour”, “bad”, or “spicy” were classified as “tasters”. In

addition, participants who immediately removed the strip because of its "foul" taste or showed other signs of taste rejection were classified as "tasters" as well [38].

Subjective smell, taste, and appetite

Participants rated their smell, taste, and appetite on a 5-point Likert scale (1 "very bad" to 5 "very good". In addition, participants were asked whether their smell, taste, and appetite had changed (yes/no) since chemotherapy. Regarding smell and taste, follow-up questions included specifying whether taste and smell changed in terms of intensity and/or quality.

Related factors

Patient characteristics

Patient characteristics were derived from medical records and included: age, sex, diagnosis, and treatment protocol.

Treatment intensity

Treatment intensity was rated by MB and WT using the Intensity of Treatment Rating scale (ITR-3), a psychometrically valid classification of pediatric cancer treatment, into one of four levels ranging from 1 "minimally invasive" to 4 "most invasive" [39].

Chemotherapeutic agents and corticosteroids

For each child, the actual given cumulative dose of chemotherapy and corticosteroids was calculated (mg/m^2) for each time point. Given the large number of chemotherapeutic agents and variability in the distribution of cumulative doses in our population, the eight most frequently prescribed agents in the last month before our study measurement (i.e., vincristine, doxorubicin, cyclophosphamide, methotrexate, cytarabine, etoposide, mercaptopurine, asparaginase) were used as a binary variable (yes/no) for analysis.

Statistical analysis

Descriptive statistics are presented as mean with standard deviation (SD), median with interquartile range (IQR) or number of participants (N) with percentage (%). Due to the presence of repeated measurements, linear mixed models for longitudinal data were estimated to investigate the association of smell (ID, THR) and taste (total score) with age, sex, intensity of treatment rating, chemotherapeutic agents (y/n), corticosteroids (y/n), nausea (y/n), and PROP taster status (y/n, only for model

including taste) during active treatment (T0-2). Linear mixed models were also estimated for sweet, sour, salty, and bitter taste to study whether the individual taste qualities change over time (T0-2), but without any other covariates. An autoregressive order 1 (AR1) covariance structure was used.

Wilcoxon signed rank tests were used to: 1) compare smell (i.e., THR) and taste function (i.e., total Taste Strips scores) at study visit T1A to patients' smell and taste at T1; 2) compare THR, ID, and Taste Strips scores (i.e., sweet, sour, salty, bitter, and total scores) of patients with ALL in active treatment (last time point, usually T2) to maintenance phase (T3); and 3) compare THR, ID, and Taste Strips scores (i.e., sweet, sour, salty, bitter, and total scores) of all other patients in active treatment (last time point, usually T2) to 3 months after treatment (T3).

At each time point (T0-3), we conducted separate binomial tests to assess whether the proportion of children showing normal chemosensory function deviated from the expected normative values (≥80%) for the THR and ID smell tests as well as the total Taste Strips score. Bonferroni correction was applied to account for multiple comparisons. We also analyzed differences in chemosensory function (both increased and decreased) among different diagnosis groups which included ALL, lymphoma, myeloid malignancies, and solid tumors. Brain tumors were excluded from this analysis due to the small sample. All statistical analysis was performed with IBM SPSS Statistics (version 26.0). A 5% alpha level was used.

RESULTS

Patient characteristics

A total of 96 patients were included in this study. Two participants left the study before any data was collected and therefore, results are described for 94 children diagnosed with a hematological (74.5%), solid (21.3%), or brain (4.3%) malignancy (Table 1). Median age was 12 years (range 6 – 17) and 51.1% were girls. During the study period, 8 more patients left the study because they died (n = 5) or experienced too much burden (n = 3) but data collected up to that moment could be used.

Smell function

Longitudinal evaluation of smell function

Figure 1A shows THR scores at the four main study visits (T0-3). On short-term, THR scores did not change significantly between T1 (median 10.0; IQR 8.0 – 12.0) and T1A (median 11.5; IQR 8.0 – 12.5) (Figure 1B). During active treatment (T0-2), THR scores also did not change and none of the covariates nor chemotherapeutic agents were associated with odor threshold. However, THR scores of children with ALL were significantly lower during maintenance phase (T3) compared to the last measurement in active treatment (T2; see Figure 1C, $p = 0.012$), which was not the case for patients with other diagnoses 3 months after treatment (Figure 1D).

Table 1. Patient characteristics ($n = 94$)

Sex, girl (n, %)	48 (51.1)
Age (median, range)	12 (6 – 17)
Diagnosis	
Hematological malignancy (n, %)	*70 (74.5)*
Acute lymphoblastic leukemia	34 (36.2)
Myeloid malignancies	11 (11.7)
Malignant lymphoma	25 (26.6)
Solid tumors (n, %)	*20 (21.3)*
Bone tumor	11 (11.7)
Neuroblastoma	2 (2.1)
Soft tissue tumor	3 (3.2)
Other solid tumors	4 (4.3)
Brain tumors (n, %)	*4 (4.3)*
Intensity of Treatment Rating (n, %)	
Moderate intensive	45 (47.9)
Very intensive	40 (42.6)
Most intensive	9 (9.6)
Chemotherapeutic agents (n, %)	
Vincristine	67 (71.3)
Doxorubicin	55 (58.5)
Cyclophosphamide	55 (58.5)
Methotrexate	55 (58.5)
Cytarabine	51 (54.3)
Etoposide	36 (38.3)
Mercaptopurine	35 (37.2)
Asparaginase	35 (37.2)
Corticosteroids (n, %)	80 (85.1)

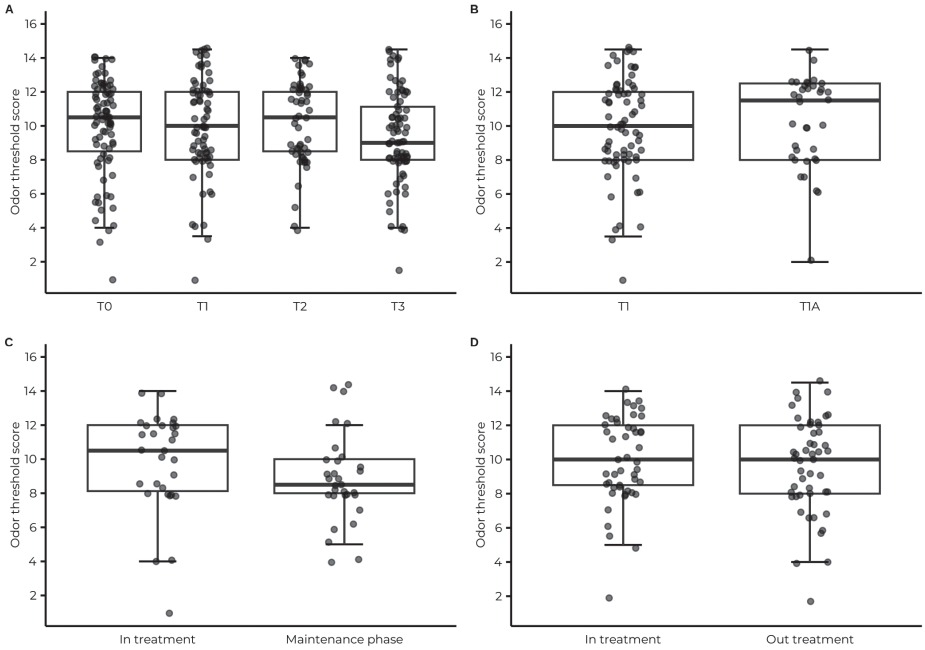

Figure 1. Odor threshold scores during the study period (a), for T1 and T1A specifically (b), separated for the last measurement in active treatment and maintenance phase for children with ALL (c, n = 29, p = 0.012), and for the last measurement in active treatment compared to 3 months after treatment for all other patients (d, n = 47).

Figure 2A shows ID scores over time, which did not change during active treatment (T0-2) or during maintenance phase (T3; Figure 2B) or 3 months after treatment (Figure 2C). Sex (B = -1.0, SE = 0.2, p < 0.001), age (B = 0.2, SE = 0.0, p < 0.001), and receiving vincristine in the past month (B -0.5, SE 0.2, p = 0.012) were associated with ID scores.

Smell dysfunction according to normative values

Table 2 shows the percentage of decreased, normal, and increased smell function during and after treatment (T0-3). At each time point, the proportion of children showing normal smell sensitivity (i.e., THR scores) was not significantly different from expected based on normative values. However, when using cut-off values of the ID test, a normal ability to identify odors ranged between 53.8% and 64%, which was significantly lower than expected based on normative values.

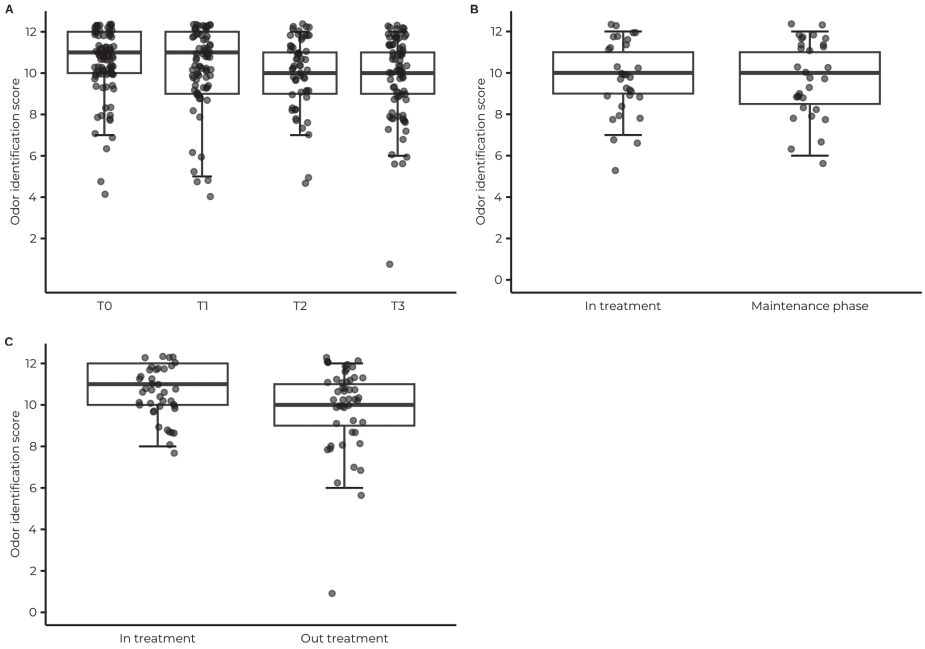

Figure 2. Odor identification scores during the study period (a), separated for the last measurement in active treatment and maintenance phase for children with ALL (b, *n* = 29), and for the last measurement in active treatment compared to 3 months after treatment for all other patients (c, *n* = 40).

When focusing on various diagnoses, we observed that an increased smell sensitivity (i.e., THR scores) during active treatment (T0-2) is most common among children with lymphoma (ranging from 5 to 60%) and myeloid malignancies (ranging from 0 to 40%). In contrast, a decreased smell sensitivity was rarely observed among diagnoses (ranging from 0 to 11.5%). An increased ability to identify odors was most common among children with hematological malignancies during active treatment (T0-2), particularly among those with lymphoma (ranging from 20 to 41.7%) and myeloid malignancies (ranging from 18.2 to 40%). A decreased ability to identify odors was more common among children with ALL (ranging from 9.4 to 34.5%) and solid tumors (ranging from 0 to 26.7%).

Self-reported smell changes

Self-reported changes in smell function ranged between 26.3% and 52.5% during active treatment (T0-2) (Table 2). According to the patients, this change was mainly described as an increased sensitivity (range 63.6 – 86.7%) to odors rather than a decrease (range 0 – 19.0%) during treatment. Of the children with abnormal smell scores (i.e., decreased

or increased) according to the THR and ID test, a minority reported smell changes at each time point (THR: range 25.0 – 60.0%); ID: range 29.2 – 42.9%).

Table 2. Percentage of smell dysfunction according to validated tests vs self-reported smell changes**.**

	T0	T1	T1A	T2	T3[a]	T3[b]
Odor threshold (THR score)						
Decreased sensitivity to odors (n, %)	5 (6.2)	5 (6.9)	1 (2.8)	2 (3.8)	2 (6.4)	3 (6.1)
Normal sensitivity to odors (n, %)	69 (85.2)	57 (79.2)	31 (86.1)	45 (84.9)	26 (83.9)	42 (85.7)
Increased sensitivity to odors (n, %)	7 (8.6)	10 (13.9)	4 (11.1)	6 (11.3)	3 (9.7)	4 (8.2)
Odor identification (ID score)						
Decreased ability to identify odors (n, %)	9 (10.1)	14 (18.0)	-	12 (21.4)	7 (22.6)	8 (16.3)
Normal ability to identify odors (n, %)	57 (64.1)	42 (53.8)	-	31 (55.4)	17 (54.8)	31 (63.3)
Increased ability to identify odors (n, %)	23 (25.8)	22 (28.2)	-	13 (23.2)	7 (22.6)	10 (20.4)
Self-reported changes in smell						
Smell changes y/n (n, %)	27 (29.7)	30 (38.0)	21 (52.5)	15 (26.3)	11 (34.4)	11 (22.0)
· Decreased sensitivity (n, %)	2 (7.4)	3 (10.0)	4 (19.0)	0 (0.0)	1 (9.1)	3 (27.3)
· Increased sensitivity (n, %)	21 (77.8)	21 (70.0)	15 (71.4)	13 (86.7)	7 (63.6)	5 (45.5)
· Changes in quality (n, %)	8 (29.6)	8 (26.7)	5 (23.8)	4 (26.7)	4 (36.4)	5 (45.5)

[a] maintenance phase (ALL), *n* = 32
[b] 3 months after treatment, *n* = 50

6

Taste function

Longitudinal evaluation of taste function

Figure 3A shows total taste scores at the four main study visits. Between T1 and T1A, taste sensitivity did not change significantly with median total taste scores being 11.0 (IQR 9.0 – 14.0) at T1 and 12.5 (IQR 8.0 – 14.0) at T1A (Figure 3B). During active treatment (T0-2), taste scores did not change significantly. Sex (B = -1.8, SE = 0.4, p <0.001) and PROP taster status (B = 0.9, SE = 0.4, p = 0.040) was significantly associated to taste function. Moreover, administration of etoposide (B = -1.0, SE = 0.5, p = 0.035), corticosteroids (B = 1.1, SE = 0.3, p = 0.001), and mercaptopurine (B = -1.0, SE = 0.4, p = 0.021) in the past month has been associated with total taste scores. Total taste scores were significantly higher at T3 (i.e., during maintenance phase (Figure 3C, p = 0.023), or after treatment (Figure 3D, p = 0.005)) relative to T2.

Also, sweet, sour, salty, and bitter taste did not change significantly during active treatment (T0-2). Sweet (p = 0.016) and bitter taste (p = 0.026) were significantly higher at T3 after treatment relative to T2, which was not the case for children with

ALL during maintenance phase. A comparison of the individual taste qualities can be found in Supplementary Figure 1.

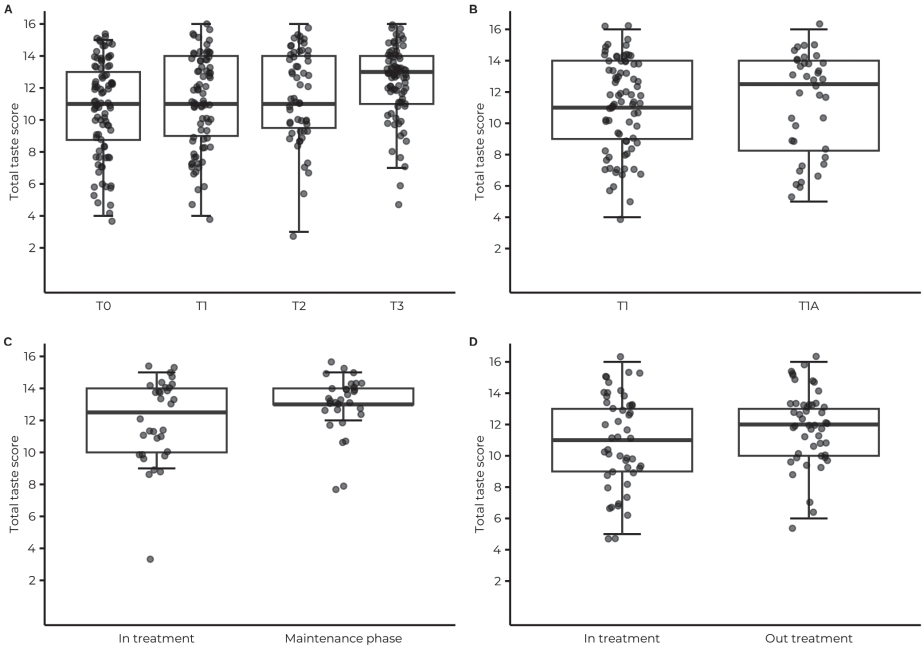

Figure 3. Total taste scores during the study period (a), for T1 and T1A specifically (b), separated for the last measurement in active treatment and maintenance phase for children with ALL (c, n = 31, p = 0.023), and for the last measurement in active treatment compared to 3 months after treatment for all other patients (d, n = 47, p = 0.005).

Taste dysfunction according to normative values

Table 3 shows taste abnormalities according to age – and sex-related normative values. At each time point during active treatment (T0-2), the proportion of children showing normal taste function was significantly lower than expected based on normative values. No disproportionately large occurrence of abnormal taste function was found at T3, after treatment or during maintenance phase (for the children with ALL). During active treatment (T0-2), an increased taste sensitivity was not seen in children with solid tumors, but particularly present in children with ALL (ranging from 16.7 to 24.2%), lymphoma (ranging from 4.2 to 40%) and myeloid malignancies (ranging from 0 to 60%). In contrast, taste loss was also frequently present in children with lymphoma (ranging from 37.5 to 41.7%) and solid tumors (ranging from 17.6 to 37.5%) specifically.

Table 3. Percentage of taste dysfunction according to validated test vs self-reported taste changes

	T0	T1	T1A	T2	T3[a]	T3[b]
Total taste score						
Decreased taste perception (n, %)	19 (21.6)	18 (23.4)	10 (26.3)	11 (20.0)	1 (3.2)	6 (12.5)
Normal taste perception (n, %)	60 (68.2)	50 (64.9)	23 (60.5)	34 (61.8)	25 (80.7)	34 (70.8)
Increased taste perception (n, %)	9 (10.2)	9 (11.7)	5 (13.2)	10 (18.2)	5 (16.1)	8 (16.7)
Self-reported changes in taste						
Taste changes y/n (n, %)	69 (75.8)	52 (65.8)	32 (80.0)	35 (61.4)	20 (62.5)	19 (38.0)
· Decreased sensitivity (n, %)	17 (24.6)	11 (21.1)	4 (12.5)	10 (28.6)	4 (20.0)	3 (15.8)
· Increased sensitivity (n, %)	15 (21.7)	14 (26.9)	7 (21.9)	8 (22.9)	4 (20.0)	6 (31.6)
· Changes in quality (n, %)	46 (66.6)	33 (63.4)	18 (56.3)	20 (57.2)	12 (60.0)	12 (63.1)

[a] maintenance phase (ALL), *n* = 32
[b] 3 months after treatment, *n* = 50

Self-reported taste changes

Self-reported taste changes ranged between 61.4% and 80.0% during active treatment (T0-2) and was lowest 3 months after treatment (38.0%, T3[b]). These changes were described both as an increase or decrease, but much more often as tastes being very different from before (in terms of quality; ranging from 57.2 to 66.6%). The percentage of all patients with abnormal taste scores (i.e., increased or decreased according to self-report) ranged from 45 to 78.6% at each time point. Interestingly, even among patients with a normal taste perception according to normative values, more than half reported experiencing taste changes (ranging from 50.8 to 82.6%).

DISCUSSION

This study primarily aimed to gain insight into potential changes or fluctuations in taste and smell function in children with cancer during and after chemotherapy. Objectively measured smell and taste function remained stable during active treatment. However, we observed a decrease in smell sensitivity among children with ALL during maintenance phase, which suggest better smell sensitivity during active treatment. In contrast, taste sensitivity was higher during maintenance phase and in all other children with cancer 3 months after their last chemotherapy, suggesting decreased taste function during active treatment. Furthermore, a fairly large number of children suffered from chemosensory distortions somewhere during treatment, which comprised either increased or decreased sensitivity.

Changes in smell

Smell sensitivity of children with ALL was higher during active treatment compared to maintenance phase. Although a real baseline measurement before chemotherapy is lacking, this suggests an increased smell sensitivity during treatment, similarly to our previous results showing better smell sensitivity in children with cancer compared to healthy controls [25]. In contrast, studies among adults undergoing chemotherapy did not find changes in smell sensitivity or showed a decrease during treatment and an increase afterwards [40-42]. According to normative values, an increased smell sensitivity was more prevalent than decreased sensitivity among children with cancer. Interestingly, this occurred mainly in children with hematological cancers, in particular lymphoma and myeloid malignancies. Together with increased smell sensitivity that children with ALL show during active treatment, this suggests a role for corticosteroids, which are particularly administered in hematological treatment regimens. Although we did not find an association between cumulative dose of corticosteroids and smell function, a study in dexamethasone-treated rats showed higher responsiveness to complex odorant mixtures [43]. Moreover, it has been suggested that chemotherapy might induce a neuro-endocrine stress response to protect the body from danger, consequently leading to the release of glucocorticoid hormones (e.g., cortisol) promoting a state of hypervigilance [44, 45]. Olfactory performance can thus be sensitized either through stress-induced release of endogenous glucocorticoid hormones or administration of exogenous corticosteroids.

Building on this topic, some children indicated overall sensory sensitization, that is, being overly sensitive to tastes and smells but also to visual, auditory, and haptic stimuli. Several mothers of the included children recognized their child's state of "hyperolfaction", comparing it to their sense of smell during pregnancy. Although there is little evidence for increased smell sensitivity during pregnancy, pregnant women do perceive changes in their smell function, rating odors as more intense and finding most odors less pleasant [46-49]. It has been suggested that a heightened awareness to odors in pregnancy may lead to a perceived increment in smell sensitivity in the absence of increased sensory acuity, which may also occur in children with cancer [46, 50].

Odor identification ability did not change during and after treatment with chemotherapy. Of course, we cannot rule out a learning effect, which is a well-known phenomenon when nonverbal tasks are repeatedly assessed resulting in better performance. However, the latter does not appear to be the case in our study. Age and gender

significantly influenced odor identification during treatment, with a better performance among older children and girls compared to boys, which is a well-known phenomenon in healthy children as well [51]. Interestingly, vincristine was associated with lower odor identification ability. Such an association between psychophysically measured smell and a specific chemotherapeutic agent has not been previously found [42, 52].

Changes in taste

Taste sensitivity of children with cancer was lower during active treatment compared to 3 months after the last chemotherapy or maintenance phase in children with ALL. Although a measurement before chemotherapy is lacking, this seems to indicate that taste sensitivity declines shortly after starting chemotherapy and recovers within 3 months after its stop. Such a pattern has been also found among adult patients undergoing chemotherapy [42]. Although taste receptor cells can renew quickly in healthy individuals, our results suggest that repeated cycles of chemotherapy may not provide enough time for full recovery of potential damage to receptor cells. However, recovery does occur once chemotherapy has been stopped for some time or if the dose has been reduced.

Several chemotherapeutic agents were associated with taste function in the current study, but not in the same manner. Children receiving etoposide (e.g., children with lymphoma or solid tumor) had lower taste sensitivity compared to children that did not receive those agents. In contrast, administration of mercaptopurine (in particular children with ALL) resulted in higher taste sensitivity. Anthracyclines and mercaptopurine have been associated with taste alterations more often than etoposide in previous studies, although a specific direction of such changes is frequently left unmentioned [23, 26]. In addition, corticosteroids were associated with better taste function. Similar to olfactory sensitivity, the use of glucocorticoids might enhance taste sensitivity. It might even counteract chemotherapy-induced taste loss. For example, taste loss disappeared in 5 out of 7 colorectal cancer patients treated with 5-fluorouracil and leucovorin when pretreated with dexamethasone [53]. Unfortunately, the current sample size does not allow for testing possible interactions between cytotoxic agents. We also could not distinguish high-dose corticosteroids (as part of treatment) and the administration of a much lower dose of corticosteroids intended as antiemetics. Our results, therefore, only tentatively suggest that certain chemotherapeutic agents are associated with certain taste changes in certain children with cancer.

According to normative values, taste loss was present in approximately 20% of all children with cancer. In contrast, self-reported taste changes ranged between 60 – 80%. But these changes were often described as "tastes being very different from before" rather than changes in sensitivity per se. Regardless, objective measures of both smell and taste function did not seem to correspond with self-reported smell and taste function. Another reason for this poor correspondence between measures is the well-known finding that people tend to experience taste loss when they actually suffer from smell loss [54, 55]. Further, in our previous qualitative study, we showed that children with cancer when talking about taste (changes), frequently talked about taste preferences or the food they like, rather than experienced changes in sensitivity of the taste qualities [20]. These subjective chemosensory – or hedonic – alterations largely impacted the quality and daily lives of children undergoing chemotherapy. Perhaps it is not taste function that changes much with chemotherapy, but the valence attributed to taste, smell, and flavors, highlighting the importance of subjective testing in addition to objective, psychophysical tests. The poor correspondence between objective and subjective measures for smell and taste cannot be readily explained in terms of children being unable to reliably verbalize their complaints as previous studies among adult patients undergoing chemotherapy also did not find associations between objective and subjective measures of chemosensory function [40, 41].

Strengths, limitations, and future directions

This is the first study to describe the trajectories of changes in smell and taste function in a prospective cohort of children with different types of cancer both during and after chemotherapy. As hardly any evidence was available, the results of this study are useful for educating children and parents as well as developing future interventions. Some limitations should be noted. First of all, the sample size of children with particular malignancies, such as brain tumors, was small. Secondly, it proved to be impossible to measure children's smell and taste function before they received their first cycle of chemotherapy. Therefore, the current study lacks a proper baseline measurement. However, we felt the need for a baseline measurement did not outweigh the burden such a measurement would impose on children having just learned they have cancer. Thirdly, it should be noted that this study was performed amid the COVID-19 pandemic. COVID-19 can impair chemosensory function, particularly smell. Although chemosensory function measurements were

always performed at least 3 months after a potential COVID-19 infection, we cannot completely rule out that it may have had an impact on our study results.

Since nutritional status of children with cancer is already vulnerable, it is important to recognize smell and taste changes in time before they might have any detrimental effects. Educating children and parents at the start of treatment and providing effective coping strategies regarding chemosensory changes will have a large influence on the daily (quality of) life of children with cancer, on their pleasure of eating, and food intake. An association between chemosensory function and dietary intake or nutritional status has been found among adult cancer patients, as well as children with cancer [21, 56-58]. Therefore, future studies regarding chemosensory changes in children with cancer should include dietary assessment as well. Moreover, it would be highly relevant to develop interventions – and study their effectiveness – for children with cancer experiencing smell and taste changes. However, this should include an individual, tailored approach, as both objective and subjective smell and taste changes were found to vary (in intensity, direction, and essence) between patients in the current study.

CONCLUSION

This study showed that objective measures of smell and taste function did not change in children with cancer during active treatment. However, at each time point quite a number of patients significantly suffered from altered taste function. In particular, a decreased taste sensitivity was present among children with lymphoma and solid tumors. After active treatment, taste function increased among patients in maintenance phase (ALL) or 3 months after the stop of chemotherapy (other diagnosis). Changes in smell were mainly presented in terms of increased sensitivity, specifically among children with hematological malignancies. In addition, smell sensitivity of children with ALL decreased in maintenance phase, which implies increased smell sensitivity during active treatment. So, chemosensory changes were heterogeneous, making it difficult to unravel potential mechanisms. Given their high prevalence, they might impact eating behavior and dietary intake. To maintain or improve nutritional status of children with cancer, it is beneficial to provide them with both general recommendations and individual dietary advice, considering any possible changes in their sense of smell and taste.

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Authors' contribution

Mirjam van den Brink: conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing-original draft, writing-review and editing. Remco C. Havermans: conceptualization, methodology, supervision, writing-review and editing. Marta Fiocco: formal analysis, writing-review and editing. Wim J.E. Tissing: conceptualization, methodology, supervision, writing-review and editing.

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Conflict of interest

The authors have declared no relevant conflict of interest.

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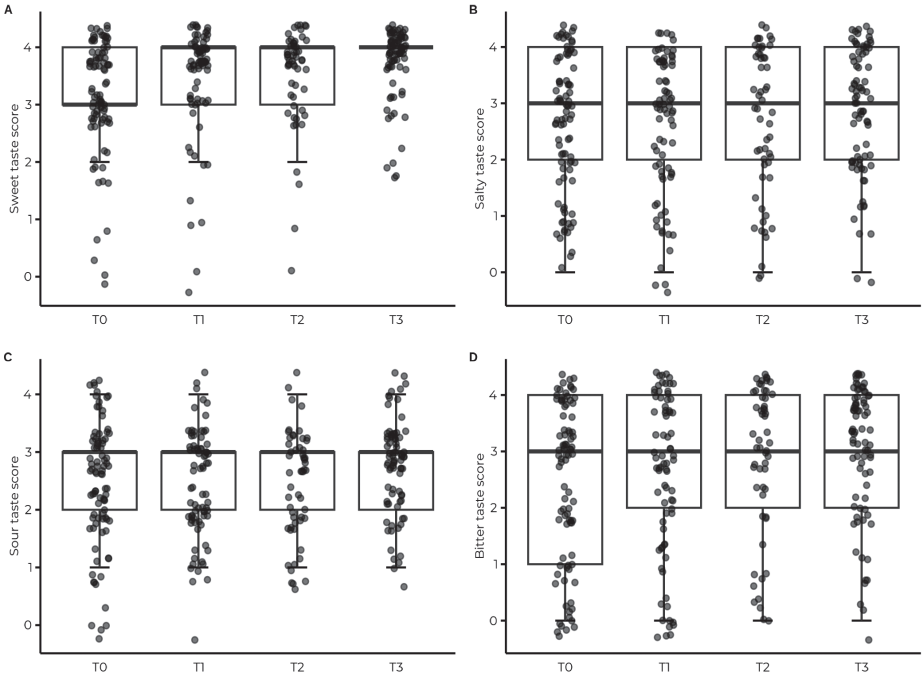
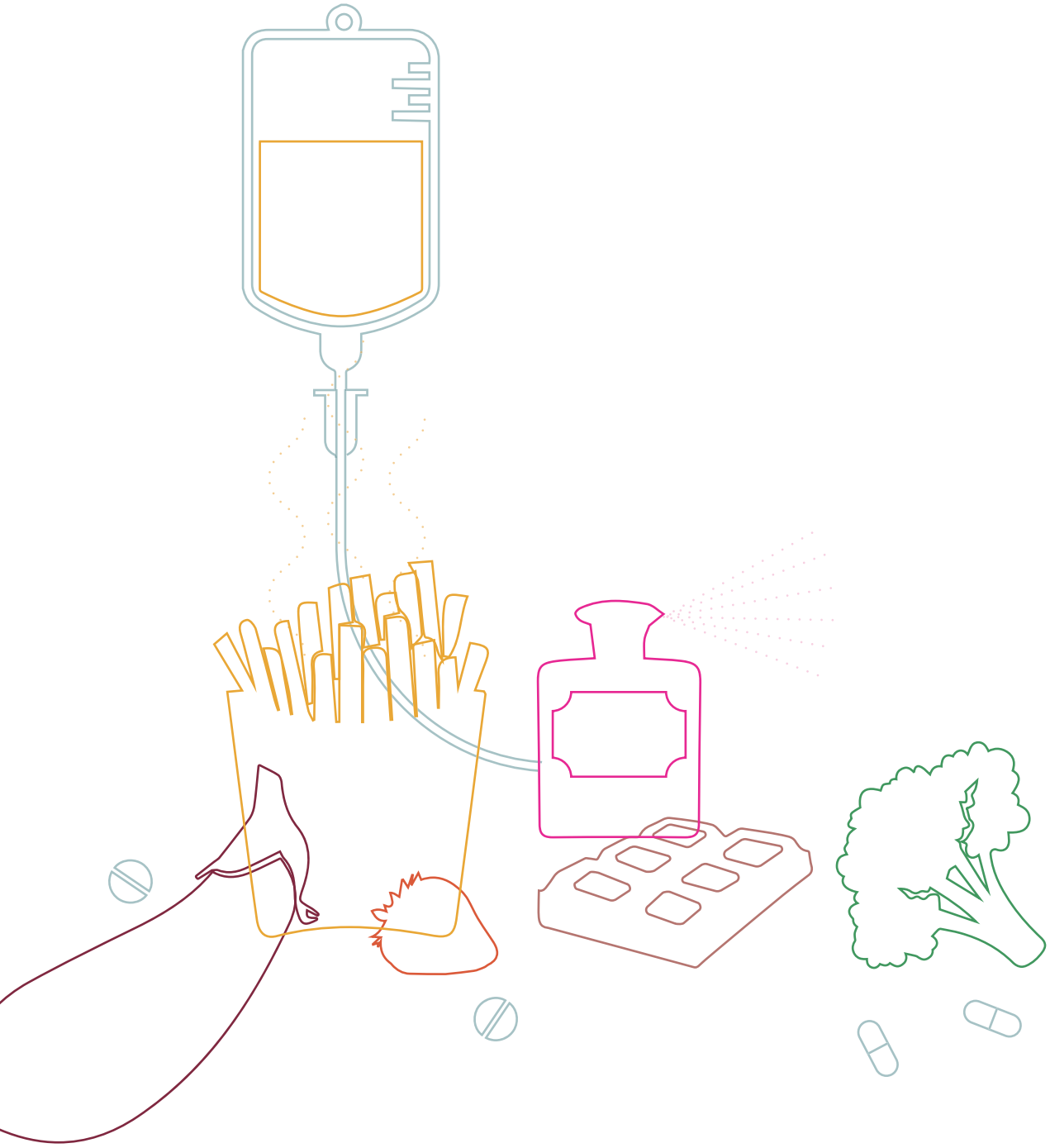
SUPPLEMENT



Supplementary Figure 1. Boxplots for the "Taste Strips" test scores during the study period: sweet taste (a), salty taste (b), sour taste (c), and bitter taste (d).



7

The impact of changes in taste, smell, and eating behavior in children with cancer undergoing chemotherapy: a qualitative study

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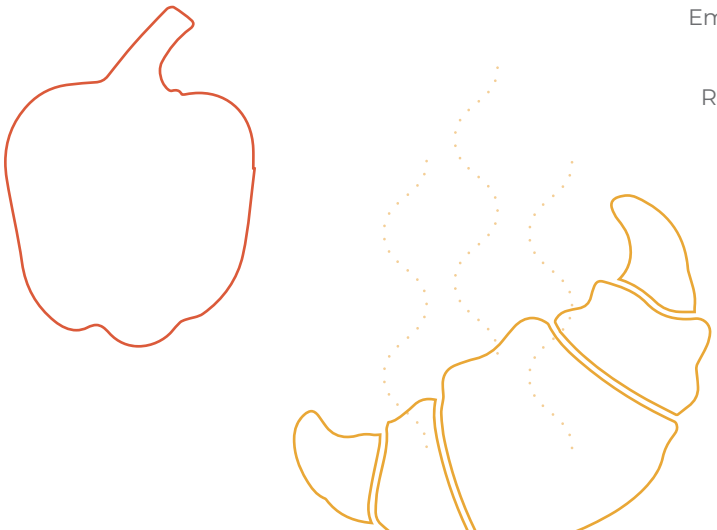

ABSTRACT

Background & Aims Taste changes are the third most common bothersome symptom during treatment in children with cancer. However, it is still unclear what the essence of these taste changes are, to what degree concomitant changes in sense of smell qualify this bothersome treatment symptom and how much of an impact these changes have on the life of children with cancer. The aim of this study was to explore characteristics of both taste and smell changes and to gain insight into the impact of these changes in children with cancer receiving chemotherapy.

Methods Semi-structured interviews were performed until data saturation was achieved in each age group (6 – 12 years, 13 – 17 years). This resulted in an in-depth description of taste and smell changes, including its impact on the life of 27 children with various cancer types receiving chemotherapy. Thematic analysis of interview data was performed.

Results Interview data could be grouped into three main themes, namely changes in 1) taste, 2) smell, and 3) eating behavior. As expected, most children reported experiencing taste and smell changes just after start of treatment, but changes varied greatly between children; that is, some reported changes in intensity (increased or decreased), whereas others reported different perceptions or preferences (from sweet to savory). Taste and smell changes (regardless of direction) negatively impacted quality of life, with these changes commonly described as “disappointing” or “frustrating”. Interestingly, particular chemotherapeutic agents were frequently mentioned regarding taste and smell changes, prompting sensory-specific coping strategies. Children’s eating behavior changed in terms of alterations in food liking and appetite, sometimes due to chemosensory changes, but children also mentioned specific medication or hospital food being responsible for their altered eating behavior.

Conclusions Both taste and smell changes are common in children with cancer. The essence of these changes varies widely, but taste and smell changes are generally considered bothersome treatment symptoms. Ways to cope with taste or smell changes specifically were described by the children warranting further research and offering the opportunity for enhancing patient-centered care.

Keywords taste, smell, eating behavior, quality of life, childhood cancer

INTRODUCTION

Children with cancer receiving chemotherapy often experience bothersome symptoms, such as nausea and pain. Taste changes have been found to be the third most common bothersome symptom during treatment, reported by 60.3% of the children [1]. Several studies indicate that taste changes are indeed common in children with cancer [2-4]. However, experienced changes in taste do not reflect a change in taste function per se. Decreased smell function (anosmia/hyposmia) for instance, is often mistaken for loss of taste function in the general population [5]. Colloquially, taste refers to a multisensory percept (flavor); that is, the integrated chemosensory experience of gustatory, olfactory, and somesthetic stimulation [6]. So, smell and taste, and their combined perception of flavor, are all important characteristics of food that determine liking and preferences and play a distinct but related role in eating behavior [7]. However, little is known whether smell changes also occur in children with cancer undergoing treatment, and if so, to what extent.

When exploring chemotherapy-induced chemosensory changes in adult cancer patients, a systematic review suggests that there is insufficient evidence that chemotherapy influences taste in a uniform manner when focusing on sensitivity and intensity of taste qualities [8]. However, it seems that the changes in liking for foods and other aspects of flavor perception have the greatest influence on the perception of food during chemotherapy. This is confirmed by a qualitative study among adults with cancer, showing that patients experience a range of symptoms which they identify as “taste” problems during chemotherapy which in fact mostly relate to the broader phenomena of flavor and hedonics [9]. Among children with cancer, taste changes have been previously described in a heterogeneous way, mostly referring to hedonics (food tasting “different” or “bad”) [10]. In addition, flavors could be experienced blander or more extreme in children receiving cancer treatments. However, it is still unclear what exactly a child with cancer means when it talks about “taste” problems. Does it reflect a shift in taste function? Does a possible change in taste function lead to a concomitant shift in food preferences? Is the sense of smell affected? If so, does that play a likely role in food enjoyment and the degree of perceived taste changes? Until now, these aspects are understudied as most studies solely focus on taste changes in children with cancer. For that reason, changes in smell and other aspects potentially influencing eating behavior should be explored as well, because

a complete overview of chemosensory problems might facilitate the development of effective strategies to manage these changes.

It should be noted that taste and smell changes associated with anti-cancer treatments (notably chemotherapy) affect food intake and nutritional status in adult patients [11, 12]. In addition to that, chemosensory changes seriously impact adult patients' daily life and well-being [9, 13]. This appears to be just as true in the case of childhood cancer. In a recent study, adolescents with cancer (12 – 18 years) most frequently reported cancer-specific health-related quality of life (HRQoL) problems related to chemosensory changes such as "food not tasting good" (54.3%) and "nausea caused by food and smells" (61.4%) [14]. Again, it is unclear what qualities define the essence of these food-related changes experienced by children with cancer. At the moment, we are still working on a longitudinal study in which we quantitatively measure taste and smell function in children with cancer. However, if we measure taste and smell changes it is largely unclear what makes these changes bothersome and what impact they have on the daily lives of so many children undergoing chemotherapy. These are meaningful questions as qualifying children's experiences with taste and smell changes during treatment offers the opportunity to enhance patient-centered care. Therefore, we interviewed children with cancer, as part of the longitudinal study, asking them about their experiences with changes in taste and/or smell while receiving chemotherapy and how these changes impact(ed) their daily lives.

METHODS

Study design

This is a qualitative study to explore experiences with and the impact of taste and smell changes in children with cancer undergoing chemotherapy, using semi-structured interviews. Interviews were held between January and September 2021.

Participants and recruitment

This study was performed at the Princess Máxima Center for Pediatric Oncology in Utrecht, the Netherlands. All children newly diagnosed with cancer, consecutively admitted to the Princess Máxima Center, were asked to participate in a prospective cohort study called SENSORY-2, including several quantitative measurements of

taste and smell function during treatment. Children in the SENSORY-2 study needed to be between 6 and 17 years old, diagnosed with a hematological, solid, or brain malignancy, and currently treated with chemotherapy.

As quantitative measurements alone do not inform us on all aspects concerning children's chemosensory disturbances, all children within SENSORY-2 were invited to participate in the current study comprising a semi-structured interview. At the time of the interview, these children had already undergone chemotherapy for at least 3 months so that they were sufficiently able to talk about their potential experiences with taste and smell changes. Children were not purposefully selected on reporting changes in taste and smell function (convenience sampling) and interviews were held with the children who were first enrolled in SENSORY-2 (pending data saturation).

Data collection

MB carried out the semi-structured interviews. We planned to enroll at least 10 children in each age group (6 – 12 years, 13 – 17 years). After interviewing ~20 participants, we decided that data saturation was achieved if no new information was obtained from the three subsequent interviews in each age group, resulting in a total of 27 interviewees. Interviews were held during (day)admission at the Princess Máxima Center and lasted between 10 – 27 minutes. During the interviews, children were often accompanied by a parent who was allowed to participate in the conversation, preferably at the end of the interview to make any additions. The interview guide was developed in collaboration with a pediatric oncologist, nutritional scientist/dietitian, health scientist, representative of the patient organization, and two psychologists and was based on key topics from literature and experiences from a previous study [4]. Interviews covered descriptions of changes in taste, smell, or preferences, timing of these changes, its association with specific treatments or interventions, the impact (practical, social) on daily life, and strategies to handle these changes. Interviews were audio recorded.

The youngest children (6 – 12 years) were invited to use the 'write and draw technique' [15]. School-age children are familiar with drawings and writings and this technique is therefore considered a child-friendly method to collect data from children. Children who wanted to use this technique, were given paper and pencils and were asked to draw or write: 1) their favorite foods; 2) foods that taste differently; and 3) smells that have changed or became unpleasant since treatment with chemotherapy.

Afterwards, children were asked to talk about their drawings and writings, followed by further questions about their experiences.

Data analysis

Data were analyzed using thematic analysis, a qualitative method for identifying, analyzing and reporting themes [16, 17]. Thematic analysis was chosen to provide a rich description of the data. All digitally recorded interviews were transcribed verbatim and imported as text documents in ATLAS.ti (Scientific Software Development GmbH, Berlin, Germany), a qualitative analysis program. MB and MH initially coded all transcripts (open coding), compared coding, and resolved discrepancies. RH then reread all coded transcripts and supplemented feedback to create a coding manual that was finalized after feedback from EH. Afterwards, all transcripts were coded again using the final coding manual. Themes were derived from the data in an inductive way.

The team had regular discussions throughout the duration of the project. Further, MB presented findings and tentative conclusions for further discussion with other experts at a research meeting. These discussions were conducted with the intent to avoid that our conclusions being particular to the perspective of just one researcher. However, it should be noted that several members of the team (MB, WT, RH) have previously investigated taste and smell changes in children with cancer, which may have influenced the interviewing and coding of the data.

Ethical consideration

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Medical Ethics Review Committee of the University Medical Center Utrecht (UMCU), the Netherlands, approved this study as subpart of the SENSORY-2 study (METC N19.809). Written informed consent was obtained from the parents, and from children ≥ 12 years. A 15-point checklist of criteria for good thematic analysis was used for reporting and writing [17].

RESULTS

Twenty-seven children with cancer were included in this study. Participant demographics and clinical characteristics can be found in Table 1. During the interviews, the majority of children reported both taste and smell changes (*n* = 20, 74.1%), whereas only one girl did not report any changes in taste or smell perception. When focusing on taste and smell separately, it can be noticed that taste changes (*n* = 23, 85.2%) and smell changes (*n* = 22, 81.5%) are frequently reported since the start of treatment.

Thematic analysis identified three overarching main themes, namely 1) changes in taste; 2) changes in smell, and 3) altered eating behavior. In discussing changes in taste and smell, interview data could be grouped into five sub-themes: *nature, timing, association, impact, and coping*. Data regarding altered eating behavior was grouped into two sub-themes: *food liking and appetite* (Table 2). Each theme and sub-theme are explored using illustrative quotes from the children to illuminate findings.

Table 1. Characteristics of the included childhood cancer patients.

Characteristics	**Patients (*n* = 27)**
Sex, female (n, %)	14 (51.9)
Age (median, range)	12 (6 – 17)
6 – 12 years (n, %)	14 (51.9)
13 – 17 years (n, %)	13 (48.1)
Diagnosis	
Hematologic malignancy (n, %)	23 (85.2)
Brain tumor (n, %)	1 (3.7)
Solid tumor (n, %)	3 (11.1)
Months since diagnosis (median, range)	3.7 (2.3 – 5.3)
Taste changes since treatment (n, %)	23 (85.2)
Smell changes since treatment (n, %)	22 (81.5)
Both taste and smell changes since treatment (n, %)	20 (74.1)
Nausea in last 2 days (n, %)	6 (22.2)
Mucositis in last 2 days (n, %)	1 (3.7)

Table 2. Themes.

1) Taste changes	2) Smell changes	3) Altered eating behavior
I. Nature · Intensity · Quality · Bad taste · Preference	I. Nature · Intensity · Quality · Hedonics	I. Food liking · Less desired foods · More desired foods · Home-cooked meals · Fluctuation of food choices
II. Timing · Onset · Transience	II. Timing · Onset · Transience	II. Appetite · Changes in appetite · Corticosteroids
III. Association · Mucositis · Specific chemotherapeutic agent · Treatment-related intervention	III. Association · Nausea · Specific chemotherapeutic agent · Treatment-related intervention · Negative experience	
IV. Impact · Frustration · Dissapointment	IV. Impact · Irritation	
V. Coping · Adding (strong) flavors · Trying foods · Brushing teeth · Eating sweets · Drinking	V. Coping · Avoiding unpleasant smells · Covering unpleasant smells	

Taste changes

Nature

To understand how children describe possible taste changes, we first asked them about their definition of taste. This was described in a uniform way, namely: how something (food or drink) tastes, how strong it tastes, and whether it is tasty or not.

Then we continued the conversation about taste changes during chemotherapy. Children described a variety of taste changes, most often expressed by alterations in intensity, quality, preferences, or the presence of a bad taste. Taste perception in terms of intensity could be either increased or decreased:

> *"Everything tastes much stronger" (girl, 11 years)*
>
> *"My taste was then completely gone, I couldn't taste anything" (boy, 17 years)*

Children also mentioned that some foods tasted very different (quality) than before chemotherapy or than they were used to. Others experienced a bad taste in their mouth:

> *"Sometimes it has a completely different flavor, for example my father always makes soup on Sundays and suddenly the zucchini soup tasted like chicken soup or something. Not really a recognizable soup" (girl, 11 years)*
>
> *"I often have a very bad taste in my mouth the whole day long and it doesn't matter what I eat or drink, that taste just stays the whole time" (boy, 16 years)*

A majority of the children noticed a change in their taste preference, with sweet being less preferred and a remarkable preference for salty or savory foods:

> *"I would now rather eat something savory than something sweet, that is a really big change" (boy, 16 years)*
>
> *"When I had chemotherapy, I leaned much more towards salty. I really liked chips, or those salty pretzels" (girl, 17 years)*

Timing

In general, taste changes were experienced since the start – or in the first month – of treatment:

> *"When I had chemo for the first time" (girl, 9 years)*

The course of these changes was relatively heterogeneous with some children describing that these changes are mainly present in the first week after a cycle of chemotherapy and then gradually normalizes, while others describing taste changes as being continuously present since the start of treatment:

> *"I think that after 1 or 2 days you already notice it and that lasts for about the first week. Then you really notice it, your tongue also feels a bit numb. Then after a week and a half you may have it [normal sense of taste] back, but then you have half a week to taste your food and then you have a new course [of chemotherapy]" (boy, 17 years)*

Association

When it comes to treatment-related symptoms associated with taste changes, oral mucositis was mentioned by some of the children being responsible for their altered taste perception:

> *"My mucous membranes were completely damaged. The taste change is because of that" (boy, 15 years)*

In addition, specific chemotherapeutic agents (methotrexate) or chemotherapy cycles (e.g., OEPA, consisting of vincristine, doxorubicin, prednisone, and etoposide) were mentioned regarding a decreased perception of taste intensity. Furthermore, dexamethasone (a corticosteroid) was mentioned by several children in relation to changes in taste preferences:

> *"During the first two OEPA courses I experienced it [change in taste] badly. My taste was then really just gone" (boy, 17 years)*
>
> *"That was very strange, he only wanted savory when he was on the dexa[methasone]" (mother of 6-year old boy)*

Moreover, a lot of children notice a flavor or retronasal smell during saline flushing of their central venous line which was reported to be like "glue", "medicine" or "salty":

> *"A salty, uh yes... it's really a kind of smell that you taste in your mouth. It's really odd" (girl, 14 years)*

Impact

Taste changes negatively influence daily lives of most children, with these changes commonly described as "frustrating" or "disappointing":

> *"It was extremely frustrating. I smelled yummy food everywhere, but when it ended up in my mouth, I didn't like it. It was just really annoying to go through that, it makes you not want to eat" (girl, 17 years)*
>
> *"I really noticed that I couldn't really enjoy my food because those flavors didn't come out properly. I didn't like that at the time either" (girl, 14 years)*

Coping

Children tried several things to manage changes in taste. Coping strategies included adding (strong) flavors or trying (new) foods when suffering from any form of changes in taste:

> *"If we have chips, I'll have sweet chili sauce with them, and I'll dip the chips in it. That has a very strong flavor which I could taste" (girl, 13 years)*
>
> *"I try to eat some things more often to get used to the new taste" (girl, 11 years)*

A bad taste in the mouth, especially when not eating, was resolved by brushing teeth, eating sweets, or drinking something:

> *"I just tried rinsing my mouth and brushing my teeth quite often, but nothing helped at that point" (girl, 17 years)*
>
> *"When I eat lollipops, I don't taste the bad taste" (boy, 17 years)*

Smell changes

Nature

Smell changes were most often expressed by alterations in intensity, quality, or hedonics. Similar to taste, smell perception could be either increased or decreased in intensity:

> *"Well I burned a scented candle recently but that also smelled too strong" (girl, 14 years)*
>
> *"My nose doesn't smell things far away but does smell things close to my nose" (boy, 6 years)*

Sometimes, smells were perceived differently compared to before chemotherapy:

> *"I remember how that perfume smelled in the past, it was always a bit sweet but now it just smells very different, a bit like sweat" (boy, 12 years)*

A majority of the children indicated that they perceived unpleasant smells since the start of treatment, mainly concerning food odors, body odors, and hospital odors:

> *"Dinner just stinks, but nothing else" (boy, 17 years)*
>
> *"Your breath stinks; she never said that before" (mother of 17-year old girl)*
>
> *"At one point I had troubles with the smell of that disinfectant stuff. The smell was just continuously present" (girl, 17 years)*

Timing

Changes in smell intensity – increased or decreased – were most often noticed since the start of treatment. However, the perception of unpleasant smells, especially food odors and hospital odors, was only experienced after several visits to the hospital. From that moment on, these odors were continuously experienced as unpleasant, while, for example, a decreased smell intensity was mainly experienced in the two weeks after a cycle of chemotherapy and then slowly recovered:

> *"In the first two weeks, I also had a lot of smell loss. It also took a long time to come back, maybe two weeks" (boy, 17 years)*
>
> *"At the beginning of treatment she said she didn't like it (smell of alcohol) very much, but then it wasn't so dominant. I think it started in the middle of treatment, after 6 or 7 cycles" (mother of 10-year old girl)*

Association

Although a majority of the children also experienced taste alterations besides changes in smell, these concepts were rarely linked to each other. However, nausea was often mentioned in relation to smell. On the one hand, children indicated that unpleasant odors cause nausea, but on the other hand, it was also noted that smells are poorly tolerated when you already feel nauseous:

> *"On a normal day it's okay if I smell fries or something, but on a day when I'm nauseous I think: go away" (girl, 17 years)*
>
> *"The smell of food makes me nauseous and usually makes me vomit" (girl, 11 years)*

In addition to nausea, the use of corticosteroids (dexamethasone and prednisone) was mentioned a few times in relation to increased smell sensitivity or perception of body odors:

> *"What struck me is that whenever she had prednisone or dexa[methasone], if I had had coffee she would say: Gross, your breath stinks" (mother of 12-year old girl)*

Moreover, a lot of children stated not liking the smell of ethanol on their central venous catheter patch, which is generally only experienced by themselves:

> *"When they change that PICC line patch, I can smell it for a few days afterwards but mommy doesn't smell it" (girl, 14 years)*

Odorants are frequently linked to specific experiences or locations. In this case, children with cancer described that certain smells, for example from soup or hand sanitizer, directly remind them of the hospital which is unpleasant

> *"They often eat soup here [at the hospital], and then I smell, you know, the scent of soup. And then when I'm home and I smell tomato soup, I start to think about the hospital. It just makes me nauseous" (boy, 17 years)*

Impact

Changes in smell, in whatever form they appear, are mostly experienced as "irritation". Children also describe unpleasant food and hospital odors being continuously present, which has a negative impact on their mood:

> *"It's kind of an irritation. You want to get rid of that smell. It follows you and that's not fun, it's not nice and it has to go" (girl, 17 years)*
>
> *"It's a bit of an issue because she starts to breathe really strange and nothing helps which makes her unhappy. It makes her a bit grumpy" (mother of 10-year old girl)*

Coping

Children generally described coping strategies for managing unpleasant smells, rather than solutions for a decreased or increased smell sensitivity. Coping strategies include avoiding and covering of unpleasant smells:

> *"I often say at dinner time: give me only potatoes with Greek yogurt. I just can't tolerate the smell of other things being cooked" (girl, 17 years)*
>
> *"I usually ran upstairs around dinner time because it smells so bad but I can still smell it [food being cooked] upstairs. Then I spray deo[dorant], that suddenly smells very nice" (girl, 11 years)*

Altered eating behavior

Food liking

Children commonly described a decrease in food liking for certain foods, such as vegetables and chocolate. Sometimes, this reduction in food desire was linked to perceived changes in taste or attributed to the smell of that particular food, but this was not always clear:

> *"Well I really think: disgusting. I don't feel like that. Chocolate, yuck, no. While I normally think: oh yum, chocolate" (girl, 17 years)*

On the other hand, fruits and fatty snacks, such as chips, fries, and noodles, were often referred to as more desirable foods. A lot of children also explicitly stated that they prefer home-cooked meals:

> *"I started eating noodles more often" (girl, 14 years)*
>
> *"Well, I really don't like the hospital food, I just like our own food" (girl, 14 years)*

Additionally, desired foods seem to fluctuate during treatment as mentioned by the following participant:

> *"Sometimes I like fruit, then candy and then, a few days later, I like something else and then candy doesn't taste good anymore" (boy, 17 years)*

Appetite

Children noticed their appetite changed since the start of treatment, with some children experiencing a decreased appetite and others having an increased appetite. Particularly dexamethasone and prednisone were mentioned when it comes to an insatiable appetite and binge eating:

> *"I have the feeling that the signal between her head and tummy is just turned off" (mother of 8-year old girl)*
>
> *"During the first two courses I ate a lot, a lot more. But that's because of the prednisone, you're much hungrier then" (boy, 17 years)*

DISCUSSION

This qualitative study provided an in-depth exploration of how children with cancer experience changes in taste and smell, but also eating behavior, and the impact these changes have on their daily lives. As expected, most children reported experiencing taste and smell changes right after the start of treatment, but changes varied greatly between children; that is, some reported changes in intensity (increased or decreased), whereas others reported different perceptions or preferences. Taste and smell changes often affect the daily lives of children with cancer, with these changes commonly described as "disappointing", "frustrating" or "annoying". Interestingly, particular chemotherapeutic agents (e.g., methotrexate, corticosteroids) were frequently mentioned regarding taste and smell changes, prompting sensory-specific coping strategies. Children's eating behavior changed in terms of alterations in food liking and appetite, sometimes due to chemosensory changes, but children also mentioned specific medication or hospital food being responsible for their altered eating behavior.

In our study, taste changes were heterogeneously experienced and described by children with cancer. This is in accordance with a previous qualitative study, in which pediatric patients noted that food tasted "different" or "not right", but could also be experienced in terms of food tasting "bland" while others experienced more extreme flavors [10]. Like that study, taste changes were described to start with treatment initiation and coping strategies, such as sucking on candy, brushing teeth, and

modifying food choices, were mentioned by our patients as well. Although children with cancer try to resolve taste changes, the current study emphasizes that these changes seriously reduce food enjoyment and affect daily life in various ways. In contrast to the study from Loves and colleagues, we also investigated changes in smell which have been shown to have a major impact on the eating experience of children with cancer as well. Further research should focus on how children and parents want to be supported on this topic. Interestingly, a recent feasibility study investigating nutrition education and cooking workshops for families of children with cancer, showed that the workshop "changes in taste during cancer therapy" was most useful to parents [18]. This underscores how much difficulty parents and children have with taste changes and that providing ways to deal with these changes is very valuable.

A shift from sweet to savory foods was a common finding among children in our study. Previous qualitative reports describe a similar pattern among children with cancer undergoing chemotherapy, in which children repeatedly indicated that they avoid chocolate and candy since the start of treatment [3, 10, 19]. The mechanism for such a change in taste preference (from sweet to savory) is not clear. A comparative analysis exploring taste perception and food behavior among adults undergoing chemotherapy showed that a reduced sweet sensitivity is indeed most common, consequently affecting food intake [20]. The authors suggest that sweet taste receptors might be more susceptible to chemotherapy or that neural responses to sweet ligands are altered. In contrast, increased sweet taste sensitivities have also been found in breast cancer patients and children with cancer undergoing chemotherapy, which may also explain why sweet dishes appear to be less preferred during chemotherapy [4, 21]. Further research is needed to verify these changes in sweet preference and/or sensitivity in cancer patients receiving chemotherapy.

A follow-up study from Loves and colleagues among 108 pediatric cancer patients suggested that optimizing chemotherapy-induced nausea and vomiting control, but also mucositis prevention, may reduce taste changes [22]. Children in our study also associate nausea and mucositis with changes in smell and taste, respectively. Interestingly, nausea was explicitly mentioned in relation to smell. That is, smells from food might cause nausea or exacerbate existing nausea, which in turn leads to the child not wanting to eat. Adequate symptom management might help in the case of existing nausea, but might not be a solution for nausea induced by (food) odors

that can appear at any time. The question however is, whether an intervention to control nausea improve taste changes (in terms of increased or decreased sensitivity) or rather prevent a child with cancer from conditioned taste aversions (CTA). It is well-known that nausea can reinforce a strong aversion for a food stimulus (its smell and/or taste), allowing children with cancer to develop a CTA [23]. This too highlights the importance of exploring not only taste changes, but also smell sensitivity, during treatment with chemotherapy.

In general, extreme sensitivities to specific odorants such as perfume, cleaning solutions, food cooking, and hand sanitizer have been reported by adult cancer patients receiving cancer treatment [11]. Children in our study gave similar examples of unpleasant smells they had experienced during treatment, but also frequently noted that they were much more likely to perceive their own body odor – or someone else's – than they were used to before chemotherapy. Further research should clarify if corticosteroids might cause these alterations or heightened sensitivity, as some children and parents indicated. The impact of smell changes is most apparent around meals. In contrast to adults, children with cancer did not talk about its social implications such as the inability to eat with family and friends [13, 24]. However, they do use coping strategies such as the elimination of strong-smelling foods or eating in another room to deal with this unpleasant situation.

Applying thematic analysis as a method to explore the experiences of children with cancer undergoing chemotherapy resulted in a rich description of food-related changes and its impact on children's daily lives. This study also includes a broad range of experiences, as we did not purposefully select participants who reported smell or taste changes before. Furthermore, this is the first study that explores children's experiences with changes in smell during treatment with chemotherapy. Like taste changes, changes in smell also have a major impact on the eating experience and social lives of children with cancer, which requires more attention in the future. Moreover, a relatively large number of children participated in this study at the same time point in their treatment. However, our findings must be interpreted in the light of several study limitations. Similar to adults, children in the current study frequently confused the concepts of taste and smell. This is the result of inductive analysis where we wanted to have an open view on how children themselves describe their chemosensory disorders. However, explaining the definitions of taste and smell could have facilitated the interpretation of the

results. Moreover, childhood cancer represents a heterogeneous set of diseases among children of various ages. Nevertheless, the majority of our participants were children with hematological malignancies, which may have consequences for drawing general conclusions. In addition to this qualitative study, changes in taste and smell need further investigation through quantitative measurements, including its consequences regarding nutritional status and quality of life.

CONCLUSIONS

In conclusion, our findings show that both taste and smell changes are highly prevalent and diverse in children with cancer receiving chemotherapy, but are generally considered bothersome treatment symptoms. Ways to cope with these changes were extensively described, including adding (strong) flavors or covering unpleasant smells for taste and smell changes, respectively. Future research should explore ways to manage taste and smell changes in children with cancer undergoing chemotherapy. In the meantime, current findings can be used to improve patient-centered care.

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Authors' contribution

Author contributions were as follows: MB conceptualized and designed the study, collected data, reviewed data, participated in interpretation of the data, drafted the initial manuscript and revised the manuscript. MH reviewed data, participated in interpretation of the data, and helped to draft the manuscript. EH reviewed data, participated in interpretation of the data, and critically reviewed the manuscript for important intellectual content. WT participated in study design, supervised its execution, helped with interpretation of the data, and critically reviewed the manuscript for important intellectual content. RH participated in study design, supervised its execution, reviewed data, helped with interpretation of the data, and

critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Review Committee of the University Medical Center Utrecht (UMCU), the Netherlands. Written informed consent was obtained from the parents, and from children 12 years and under.

Data availability statement

The original contributions presented in the study are included in the article/ Supplementary materials, further inquiries can be directed to the corresponding author.

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SUPPLEMENT 1: INTERVIEW GUIDE SENSORY-2

Introduction (grand-tour question)

Think of your favorite foods. What would you like to eat at the moment?

Part 1: taste

- What do you think of when you hear the word "taste"?
- Have you noticed that certain foods taste differently or that your taste has changed with receiving chemotherapy?
  - Prompts: what exactly changed? (loss of taste, change of intensity or quality, or otherwise)
- Have you noticed that you now like certain foods more – or less?
  - Prompts: what do you like (or dislike) about it? How did it happen?
- Can you tell me when you first noticed this?
- Can you tell me when this is most noticeable or what makes it worse?
  - Prompts: before/during/after chemotherapy? Related to location (hospital/home setting)?
- Thinking of your changes in taste, how did these changes affect you?
  - Prompts: how do you notice those changes everyday? What do you find difficult/stupid/fun about it?
- Have you tried any strategies to make the taste changes less annoying or bothersome?
  - Prompts: did you change your diet? If so, what foods do you eat more/less?
- Do you ever have a (bad) taste in your mouth even when you are not eating?
  - Prompts: how would you describe this taste?

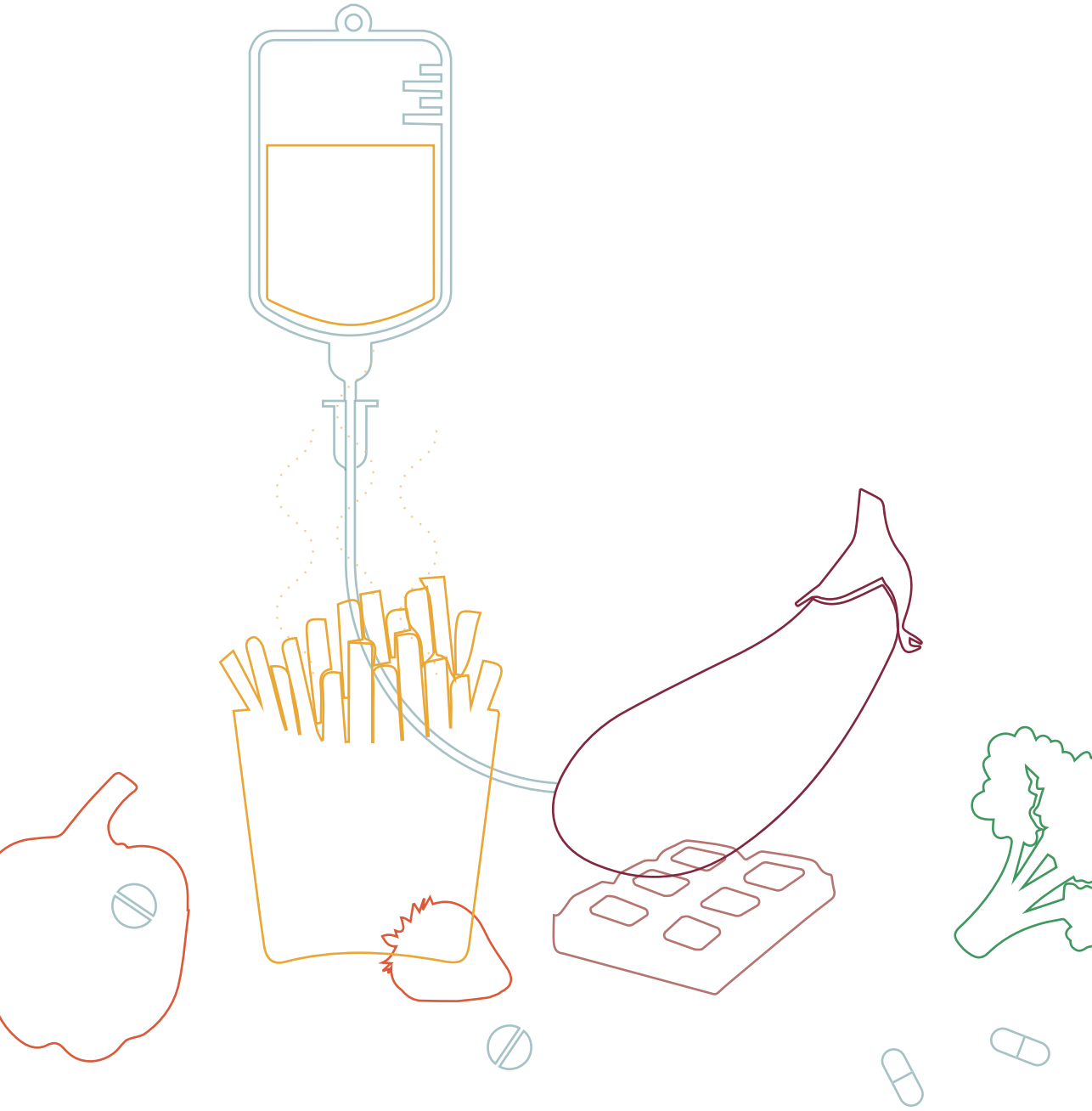
Part 2: smell

- Have you noticed that your smell has changed with receiving chemotherapy?
  - Prompts: what exactly has changed? (loss of smell, change of intensity or quality, hedonics/aversions, or otherwise)
- Can you tell me when you first noticed this?
- Can you tell me when this is most noticeable or what makes it worse?
  - Prompts: before/during/after chemotherapy? Related to location (hospital/home setting)?

- Thinking of your changes in smell, how did these changes affect you?
  - Prompts: how do you notice those changes every day? What do you find difficult/stupid/fun about it?
- Have you tried any strategies to make the smell changes less annoying or bothersome?

Closing questions

- Is there anything else about your smell and taste changes that you feel we didn't talk about?
- Do you have any advice for the Princess Máxima Center? For example, should we pay more attention to certain foods, (hospital) smells, et cetera?



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Summary and general discussion

Changes in smell and taste during treatment with chemotherapy are well-known problems in adult cancer patients. However, little was known if and how chemotherapy impacts smell and taste function in children with cancer. Therefore, the general aim of the present dissertation was to assess smell and taste function in children with cancer receiving treatment. Do smell and taste typically change during treatment, and if so, how bothersome are these treatment symptoms? Are experienced changes in smell and taste associated with eating problems? To answer these questions (and more), it was first necessary to gain further insight into children's taste function, how it develops, and how to measure it (chapters 2 and 3). Next, I studied smell and taste function in children with cancer through analyzing questionnaire data, measuring smell and taste function, and interviewing childhood cancer patients (chapters 4 – 7).

In this chapter, I will first give an overview of the main findings in this thesis. Subsequently, the findings regarding changes in smell and taste in children with cancer are discussed in the wider context of previous research. Next, implications of the main findings for both research and clinical practice are discussed, and the methodological strengths and limitations are considered. Finally, I conclude that changes in smell and taste are prevalent, bothersome, and relevant but that these changes can include either increased or decreased chemosensory function.

SUMMARY OF MAIN FINDINGS

Chapter 2 reviews available evidence regarding taste dysfunction in children and methods for assessing such taste dysfunction. The review indicates that there is clear evidence for various medical conditions (e.g., cystic fibrosis, diabetes mellitus, kidney disease, autism, asthma, et cetera) negatively affecting children's taste function. However, the number of tools to adequately measure taste function in a pediatric clinical setting was small. Most studies reporting taste dysfunction in pediatric patients relied on taste tests conducted in controlled laboratory settings, tests that are largely unsuitable for point-of-care (or bedside) testing. Only one standardized and commercially available taste test (i.e., "Taste Strips"; Burghart, Wedel, Germany) that can be used in a pediatric clinical setting was found, although it lacked age-related normative data [1].

In **Chapter 3**, we measured taste function in a large cohort of healthy children (aged 6 – 15 years) using the Taste Strips test to obtain age-related normative values for this test. “Taste Strips” are filter-paper strips impregnated with a taste solution to determine sweet, sour, salty, and bitter taste scores, using four concentrations of each taste quality. This chapter further describes the association of age, gender, and PROP taster status with children’s taste function (as measured with the Taste Strips test).

We found that taste function increases with age, which allowed us for distinguishing three meaningful age groups (6 – 7, 8 – 9, and 10 – 15 years). Further, the total Taste Strips score was higher in girls compared to boys. This study then resulted in age- and sex-specific cut-off values for the Taste Strips test scores to distinguish children’s normal taste function from a reduced sense of taste using the 10th percentile, thereby extending the utility of the Taste Strips test to children in a clinical setting. In addition, this study revealed that PROP-tasters (sometimes referred to as supertasters) had higher Taste Strips scores compared to non-tasters, which might indicate the validity of the Taste Strips test when measuring taste function in children. However, children’s self-reported impression of how well they can taste did not correlate with the Taste Strips scores [2].

The study described in **Chapter 4** identified the presence and severity of nausea and nausea-related symptoms in children with cancer during the first year of treatment and its relationship with health-related quality of life (HRQoL). In addition, potential risk factors for the outcomes of interest were described. For this study, retrospective data of the PedsQL Cancer Module (i.e., nausea, pain, treatment anxiety, and worry scales) and PedsQL 4.0 Generic Core Scales (generic total HRQoL score) was available from 781 patients (between 2 and 21 years old). These questionnaires are offered every three months during treatment prior to a doctor’s appointment in the outpatient clinic, using the online portal KLIK (Kwaliteit van Leven In Kaart, Dutch acronym for Quality of Life in Clinical Practice). For this study, we focused on data from the nausea scale which consist of the following items assessing nausea-related symptoms: nausea during medical treatment, food not tasting good, nausea while thinking of medical treatment, being too nauseous to eat, and nausea caused by food/smells. Data included proxy-report (i.e., parent report for children 2 - 7 years old) or self-report (i.e., children > 7 years old).

The presence of nausea during medical treatment was highest at 6 months after diagnosis. The symptom “food not tasting good” was reported most frequently (range 51.6%-62.8%), followed by “nausea caused by food/smells” (range 33.6%-48.1%). Pain, treatment anxiety, and worry were significantly associated with reported nausea in all children. Additionally, male gender, a solid tumor, and BMI were associated with self-reported nausea in patients aged 8-21 years. Lastly, the occurrence of nausea-related symptoms was negatively associated with average HRQoL scores. In other words, experienced nausea – especially in relation to tasting and smelling food – is common and negatively impacts quality of life in children with cancer [3].

Next, in **Chapter 5**, we explored feasibility of psychophysical smell (i.e., Sniffin’ Sticks: odor threshold, discrimination, and identification tasks) and taste (i.e., Taste Strips, papillae density) measurements in children with cancer. In addition to feasibility, we investigated smell and taste function before and after a cycle of chemotherapy and compared results with healthy controls. Also, eating behavior was assessed using the Behavioral Pediatrics Feeding Assessment Scale (BPFAS). Thirty-one children with cancer and 24 healthy controls (sibling or friend) between 6 and 18 years old participated in this study.

First, we found that the assessment of smell and taste function was feasible in children with cancer (i.e., completion of tests by ≥ 60% of the patients), although some adaptions (i.e., omitting papillae density measurement and odor discrimination test) were deemed opportune for future studies to limit the risk of overly burdening children. Second, we compared smell and taste function before and after a cycle of chemotherapy and found taste function to be increased in childhood cancer patients, especially for sweet and bitter taste. Thirdly, results were compared against smell and taste scores of healthy controls, showing that the group of children with cancer had lower smell thresholds (i.e., higher sensitivity). Lastly, we found taste function to be correlated with eating behavior, but not with papillae density [4].

Chapter 6 describes a longitudinal study including a cohort of 94 children with cancer (between 6 and 18 years old) undergoing chemotherapy. Smell (i.e., odor threshold and identification) and taste function were assessed at several time points during active treatment (T0-T2) and 3 months after the last chemotherapy (T3). In case of children with acute lymphoblastic leukemia (ALL), the last measurement at T3 was performed during the so-called maintenance phase when children receive a much gentler form

of chemotherapy (typically comprising oral mercaptopurine and methotrexate) that does not require hospital admissions. The aim of this study was to determine the occurrence of smell and taste changes during treatment, whether they resolve after treatment, and to examine which factors are associated to these changes.

Linear mixed models showed that smell sensitivity (i.e., odor threshold) did not change during active treatment but decreased in maintenance phase (children with ALL). The proportion of children showing normal smell sensitivity was not significantly different from expected based on normative values. However, when comparing children with an increased, normal, or decreased smell sensitivity we found differences per diagnosis group, particularly children with myeloid malignancies and lymphoma showed an increased smell sensitivity, whereas a decreased smell sensitivity was hardly present among all diagnosis. Similarly, self-reported smell sensitivity was more often increased than decreased. Interestingly, of all children with an increased or decreased performance on either the odor threshold or odor identification test, only a minority reported as such. Odor identification changed neither during active treatment nor at T3 during maintenance phase or 3 months after treatment, but sex, age, and receiving vincristine were associated with odor identification ability.

Taste Strips test scores did not change during active treatment but increased at T3 in the maintenance phase (for the children with ALL) or 3 months after the last cycle of chemotherapy (for the children with myeloid malignancies, lymphoma, solid tumor, or brain tumor). However, a significantly lower percentage of children than expected scored within a normal range of taste function measured throughout treatment, as taste loss was present among approximately 20% of all children with cancer, and in particular among children with lymphomas and solid tumors. This suggests that chemotherapy affects taste, especially considering that 3 months after the last chemotherapy and during maintenance phase the relative frequency of children with cancer having normal taste function no longer deviated from what one would expect based on established taste function in a general sample of children. Etoposide was found to be negatively associated with taste function, whereas mercaptopurine and corticosteroids were associated with higher taste sensitivity. Interestingly, self-reported taste changes were much more common (range: 60 – 80%) and additionally revealed that taste changes are most often described as “tastes being very different from before” rather than changes in sensitivity [5].

Finally, **chapter 7** describes the results of a qualitative study. Although objectively measuring smell and taste changes is insightful, it does not elucidate what makes these changes so bothersome to children with cancer and what impact changes in smell and taste have on their daily lives. Therefore, children who already participated in the longitudinal SENSORY-2 study described in chapter 6 were asked to be interviewed regarding their experiences with smell and taste changes during treatment. Semi-structured interviews were performed until data saturation was achieved in each age group (6 – 12 years, 13 – 17 years), resulting in 27 participants. Interview data was analyzed through thematic analysis.

We found that changes in smell and taste were common and varied greatly between children. These changes were generally considered bothersome symptoms described as "disappointing" or frustrating". Children reported various strategies for managing their smell and taste changes such as regularly brushing their teeth and avoiding or masking unpleasant smells. Regarding eating behavior, some children stated adding strong flavors to their food, or frequently trying (new) foods [6].

INCREASED OR DECREASED SENSITIVITY?

Changes in smell

In adults with cancer undergoing chemotherapy changes in odor thresholds were either not found or shown to increase during treatment (i.e., meaning decreased sensitivity) [7-9]. Based on these findings, I initially hypothesized that children with cancer would have decreased smell sensitivity. However, smell loss was hardly present in children with cancer. In contrast, children with cancer's sense of smell (odor threshold) was more sensitive than smell sensitivity of healthy controls (chapter 5) and more sensitive during treatment than out of treatment, at least in children with ALL in the maintenance phase of treatment (chapter 6). Moreover, smell sensitivity seemed to increase shortly after a cycle of chemotherapy (chapters 5 and 6). Children too often reported experiencing increased smell sensitivity rather than a loss of smell (chapter 6). The question arises what mechanisms might explain smell changes in children with cancer – changes that apparently contrast treatment effects on adult cancer patients' sense of smell. These contrasting changes in smell might be due to age-related factors (e.g., growth and development), life-style related factors (e.g., differences in the occurrence of smoking and overweight/obesity), or differences in

treatment protocol (e.g., differences in cytotoxic agents, supportive medication, and overall treatment intensity).

Cell turnover and regeneration of the olfactory epithelium is known to decrease with aging [10, 11]. Moreover, olfactory receptor cells are more susceptible to toxic substances at an older age [12]. This was shown in a study in adults with gynecologic and breast malignancies, showing olfactory function to be more affected (i.e., decreased smell sensitivity) in older patients (> 46 years) compared to younger patients (20 – 45 years) [7]. Presumably, olfactory receptor cells are renewed more quickly in children, regardless of administration of chemotherapy, making children less susceptible to any treatment-induced smell loss compared to adults. However, that still does not fully explain why smell function appears to increase in children with cancer during chemotherapeutic treatment.

Another potential factor contributing to increased smell sensitivity is stress. It is well-known that the sense of smell is important for detecting potential danger. Physiological stress responses activate the hypothalamic–pituitary–adrenal axis, leading to secretion of corticotrophin-releasing hormone (CRH), which in turn sends messages through the release of adrenocorticotropic hormone (ACTH) stimulating the cortex of the adrenal glands to release glucocorticoid hormones (e.g., cortisol) into the bloodstream [13]. This neuro-endocrine stress response has been associated with enhanced olfactory performance, including better odor identification performance, higher odor intensity ratings, and improved odor detection [14-18]. Chemotherapy in children may evoke a similar stress response and the release of specific hormones, potentially promoting a state of hypervigilance [19, 20]. Interestingly, some children with cancer included in the studies indicated overall sensory sensitization, that is, being overly sensitive to not just tastes and smells but also to visual, auditory, and haptic stimuli. Such heightened sensory sensitivity has not been previously reported in children with cancer, but could be related to increased stress and cortisol levels as seen in children with autism [21]. A study among adult cancer patients showed that self-reported “change in the way food tastes” as investigated by the Memorial Symptom Assessment Scale, has been associated with stress by reporting higher scores on hyperarousal [22]. Future studies regarding smell and taste changes in children with cancer should therefore be expanded to include analysis of sensory sensitivity in general as well as experienced stress and the measurement of cortisol levels.

Stress may contribute to enhanced smell sensitivity observed in our population, but it may not be its sole cause. The potential effect of glucocorticoids (i.e., dexamethasone and prednisone) should be noted. Glucocorticoids are an important element in treatment regimens of particularly pediatric hematological malignancies, since they induce apoptosis in lymphoblastic cells [23]. The influence of glucocorticoids on chemosensory function in adult patients with ALL has not been previously investigated, as most studies included patients with solid tumors that are more common in adulthood. Children with ALL, who are treated with high dose of dexamethasone during the first year after diagnosis, showed heightened smell sensitivity during active treatment compared to maintenance phase but we did not find an association between administration of corticosteroids and odor threshold (chapter 6). Interestingly, in a previously conducted animal study, dexamethasone-treated rats showed significantly higher responsiveness to complex odorant mixtures [24]. In sum, olfactory performance might thus be sensitized either through stress-induced release of endogenous glucocorticoid hormones or through administration of high-dose exogenous corticosteroids like dexamethasone during treatment for ALL.

Interestingly, several mothers I interviewed linked their child's heightened smell sensitivity to their own experience during pregnancy. Indeed, many pregnant women note a change in smell sensitivity and scholars have proposed that hyperosmia during pregnancy, especially during the first trimester, is fetus protective through limiting the risk of ingesting toxic substances, foods that could be hazardous when eaten in large quantities (e.g., coffee, or certain spices), and foods that spoil easily (e.g., animal-based, protein-rich foods such as meat, fish, and eggs) [25]. However, several studies showed that there is no evidence for objectively measured increased smell sensitivity during pregnancy [26, 27]. Pregnant women do perceive changes in smell, rating odors to be more intense and finding most odors less pleasant (or unpleasant) but are not necessarily better at detecting or identifying odors [28, 29]. It has been suggested then that pregnant women have a heightened awareness of odors, which is perceived as an increment in smell sensitivity in the absence of truly increased sensory acuity [26, 30]. This also seems to be the case in children with cancer, as many more cases of heightened smell sensitivity were identified through self-report than with objective tests (chapter 6). Furthermore, in the qualitative study described in chapter 7, several children reported having developed an aversion to the smell of spicy food and coffee.

Lastly, it has been shown that adult patients with advanced cancer significantly recognize more odors compared to age-matched controls [31]. The authors of this study suggest that an ongoing inflammatory response – caused by the disease itself regardless of treatment – especially in patients with weight loss, sensitize afferent nerves including chemosensory pathways [31, 32]. We did not collect blood samples to allow us to study inflammation in our studies. However, children with cancer mentioned that changes in smell (but also taste) almost always started with the first cycle of chemotherapy or later during active treatment, indicating that an increased (or changed) smell function is most likely caused by chemotherapy and not by the cancer itself in our population.

Changes in taste

In the aforementioned study in adult patients with advanced cancer, patients not only recognized more odors compared to controls, but also showed improved bitter sensitivity, again particularly in patients with weight loss [31]. This finding was independent of the administration of chemotherapy or radiotherapy. Weight fluctuations are common in children with cancer receiving treatment. However, caution is warranted regarding causality between taste changes and weight status, as it can go both ways. We did not study the influence of weight (loss) on children's taste perception in chapter 6, but this should be further investigated in future studies.

Chapter 6 describes the first longitudinal study tracking taste function in children with cancer during and after chemotherapy and concludes that taste function remains stable during active treatment, although lower compared to maintenance phase or after stop of chemotherapy. However, in the feasibility study described in chapter 5, we found an increase of sweet, bitter, and total taste function shortly after a cycle of chemotherapy in children with cancer. A similar pattern of elevated taste sensitivity (though not statistically significant) shortly after a cycle of chemotherapy can be discerned in the longitudinal study described in chapter 6. Taken together, these results suggest a fluctuating pattern of changes in taste function during active treatment with short-lived, increased taste sensitivity briefly after a cycle of chemotherapy, which then deteriorates to a more stable state of lowered taste sensitivity. Factors related to this pattern of taste changes are unclear but this might be related to specific cytotoxic agents and corticosteroids. Nevertheless, taste function does recover after the end of intense chemotherapy treatment.

In adult cancer patients undergoing chemotherapy, taste function is usually decreased [33]. However, some studies have reported increased taste sensitivity (to umami and bitter tastes specifically) as well as increased intensity judgements for sweet, salty, and bitter taste [34, 35]. Studies in children with cancer also show inconsistent findings regarding the effects of treatment on taste function. Most studies cross-sectionally compared patients with healthy controls. Higher recognition thresholds for all taste qualities were found by Wall et al, while other researchers found higher threshold for bitter or sour taste only [36-38]. Wall and colleagues also found higher detection thresholds for sweet and salty taste in children with leukemia specifically [36]. We also found higher recognition thresholds for sour taste in children with cancer compared to healthy controls, as described in chapter 5. Thus, there clearly is an impact of chemotherapy on the sense of taste in children but its direction tends to vary between studies. One reason for these heterogeneous findings may be the use of different psychophysical taste testing methods.

Decreased taste sensitivity during treatment as described in chapter 6 suggest chemotherapy-induced damage to taste receptor cells [39]. As taste receptor cells are renewed every 10 days (approximately), such relatively rapid turnover of cells is easily disrupted by cytotoxic agents. We found etoposide to be associated with lower taste sensitivity, whereas mercaptopurine was associated with higher taste sensitivity. Particularly mercaptopurine has been previously found to interfere with taste function, although the direction of that change is not exactly clear [40]. Moreover, an inflammatory state and a corresponding release of cytokines can prompt apoptosis of taste receptor cells and hence promote taste-related disorders [41]. In addition, multi-modal anti-emetic treatment (i.e., being prescribed an NK-1 receptor antagonist with two other antiemetics) next to chemotherapy has been found to negatively contribute to self-reported “changes in the way food taste” in adult cancer patients, but this might be explained by the fact that multimodal antiemetics are only prescribed for highly emetogenic cytostatic drugs which are usually associated with more taste problems [42].

Hypergeusia, increased taste sensitivity, was also present in several childhood cancer patients (range 10.2 – 18.6%), although this seemed to be largely limited to children with hematological malignancies. In accordance with this, children receiving corticosteroids in the past month had higher taste sensitivity compared to those not receiving corticosteroids (chapter 6). Like olfaction, the administration

of glucocorticoids (e.g., dexamethasone and prednisone) might enhance taste sensitivity. A clinical trial among colorectal cancer patients treated with 5-fluorouracil and leucovorin showed that taste disturbances (i.e., loss of taste) disappeared in 5 out of 7 patients when pretreated with dexamethasone [43]. Also, a qualitative study focusing on taste changes in children undergoing chemotherapy or stem cell transplantation found that dexamethasone made food taste better as a child noted "It tastes better with dex. When you're on the dex, when you're on the steroid everything tastes 1000x better" [44]. Unfortunately, the current sample does not allow to distinguish high-dose corticosteroids (as part of treatment) and the administration of a much lower dose of corticosteroids (intended as antiemetics), which may provide more clarity on which patients are likely to experience such taste disturbances.

Interestingly, in our interviews many children with cancer mentioned (sometimes to their own surprise) that they prefer sweet foods much less since the start of treatment (see chapter 7). This might be caused by a temporarily increased sweet sensitivity after a cycle of chemotherapy, as described in chapter 5, which has been found in breast cancer patients as well [45]. A study among adult cancer patients showed that patients undergoing chemotherapy were also less likely to prefer (high levels of) sucrose compared to those not undergoing chemotherapy, but sweet preference in these patients was also associated with their degree of appetite [46]. In other words, the question remains whether an increased sweet sensitivity negatively affects sweet preference in childhood cancer patients.

Another potential cause for a loss in sweet taste preference is the effect that intense chemotherapy may have on growth and development. One of many long-term effects of chemotherapy in childhood cancer survivors is short stature as chemotherapy impedes rapid skeletal development, and also corticosteroids have been associated with impaired bone health [47, 48]. Interrupted bone growth may be relevant for understanding children's starkly reduced sweet preference. Normally, children, relative to adults, have a clear sweet preference [49]. This preference has been associated with biomarkers (i.e., type I collagen cross-linked N-telopeptides (NTx)) for skeletal growth in children [50, 51]. Possibly, these biomarkers also function as neural signals promoting children's sweet preference and thus, in the absence of these signals, sweet preference is reduced. Such a reduction in sweet preference occurs with normal maturation but in children with cancer may occur as the result of chemotherapy interrupting bone growth. Future studies should investigate whether

NTx levels, derived from urine samples, is associated with sweet preference, and may change throughout treatment in children with cancer undergoing chemotherapy.

Factors affecting smell and taste, other than chemotherapy

Chemotherapy is clearly associated with changes in smell and taste in children with cancer, but these changes (i.e., deviations from normal smell and taste) comprised either increased or decreased function and could not be fully linked to specific chemotherapeutic agents or dose. It is important to note that a cycle of chemotherapy is never administered in isolation. A single cycle usually comprises more than one cytotoxic agent and the typically relative high dose of these agents requires (medical) management of acute toxicities like pain, nausea, and vomiting [52, 53]. Further, chemotherapy in children induces neutropenia, compromising immune function and increasing the risk for infections. Therefore, children receiving chemotherapy typically receive many drugs other than chemotherapy, such as analgesics (to manage pain), various anti-emetic drugs (to manage nausea and vomiting), antipyretic drugs (to manage fever), and prophylactic antibiotics (to limit the risk of bacterial/fungal infections). All aforementioned types of drugs are known to possibly affect smell and/or taste, even at fairly modest therapeutic doses [54]. However, our studies were too small to take other drugs into account. Furthermore, the amount and composition of saliva influences chemosensory perception, which is known to alter with chemotherapy and its associated chronic polypharmacy [55]. Saliva is essential for taste as taste molecules dissolve in saliva which then transports taste molecules to the taste buds located predominantly on the gustatory papillae in the oral cavity. Polypharmacy and its myriad effects on taste, smell, and salivation makes it virtually impossible to parse any specific effects of chemotherapy on children's sense of smell and taste.

Apart from polypharmacy, individual differences clearly play a role in how and to what degree chemotherapy impacts childhood cancer patients' smell and taste function. Previous research has shown that younger patients are less susceptible to smell and taste disorders during cancer treatment [7]. Further, girls typically outperform boys on the Taste Strips test (see chapter 3), and this was also found among children with cancer; that is, during chemotherapy girls exhibited higher (i.e., better) taste and smell (i.e., odor identification) than did boys (chapter 6). Girls' sense of smell and taste seems to mature earlier. This might mean that girls are more likely to experience smell and taste changes – particularly increased sensitivity – during chemotherapy

than do boys, but whether this is the case requires further research. In adult patients, though, it was already found that women have higher sensitivity to sweet and bitter taste during chemotherapy compared to men [56]. Lastly, genetic variations in the expression of olfactory and gustatory receptor cells lead to inter-individual variation in smell and taste function, respectively [57-59]. For example, the ability to taste PROP depends on the expression of certain taste receptors and may result in a different degree of susceptibility to changes in taste function during chemotherapy, as we found PROP-tasters having higher taste sensitivity during chemotherapy compared to non-tasters in chapter 6 [39, 60].

OBJECTIVE OR SUBJECTIVE MEASURES?

Both objective and subjective measures can be used to assess (potential changes in) smell and taste function. One can simply ask children how well they can still smell and taste, or to what degree they feel their sense of smell and taste has changed. Apart from these subjective methods, one can use psychophysical tests to objectively assess children's capacity to smell and taste. In the present thesis, I used one or both methods in different studies (chapters 3 – 6). These methods clearly do not substitute for one another as objective and subjective measures of taste/smell function neither corresponded in healthy children (chapter 3) nor in children with cancer (chapter 6).

It is well-known that individuals have difficulties distinguishing a loss of smell from a loss of taste, as smell and taste are integrated in flavor perception [61, 62]. Studies among adults with cancer undergoing chemotherapy also showed that objective and subjective measures of smell and taste function did not correspond [8, 9, 63]. This may simply mean that people are not particularly able in estimating or monitoring their own sensory function. However, self-reported changes in smell and taste function correlated with eating behavior, while objective measures did not, suggesting that most objective tests of smell and taste function lack sensitivity and/or validity [9]. It should be noted that the reliability of the Taste Strips test has not yet been established in children but test-retest reliability of the Taste Strips in adults is moderate at best (r = 0.68) [64]. It is a practical test, but it is also a crude test that may not be able to detect more subtle (yet meaningful) changes in taste function. Further, even if a taste or smell threshold test accurately measures a person's taste or smell sensitivity/acuity, the changes that cancer patients typically experience and

report may not necessarily encompass changes in taste/smell sensitivity. Patients might still be able to smell and taste certain foods as well as before, but these foods may now have a different flavor quality. Or foods may still smell and taste the same as before except that these same flavors are now evaluated differently, as disliked, or even disgusting.

It is not only hard for children to distinguish potential smell problems from having taste problems, but also difficult to distinguish analytic sensation (*how well can you detect and distinguish taste/smell intensities?*) and hedonic evaluation of taste stimuli (*how much do you like certain flavors?*). This became clear during the interviews with children with cancer, described in chapter 7, as their thoughts regarding the concept of "taste" often referred to foods they like or prefer to eat rather than their taste ability [65]. The same chapter also revealed that changes in smell and taste perception are frequently described in terms of distortions (a qualitative impairment). For example, one boy remarked that "coke tastes like vomit". Another one mentioned "that perfume smells like sweat now". Qualitative taste/smell disorders, such as parosmia (i.e., distorted odor perception in the presence of a triggering source) and phantosmia (i.e., odor perception in the absence of any odor) have also been reported in adult patients undergoing chemotherapy [7]. Recently, a new method came available to detect qualitative smell disorders. This new test (Sniffin' Sticks Parosmia Test, SSParoT) is based on the already existing Sniffin' Sticks odor identification task and uses hedonic estimates of two oppositely valenced odors (pleasant versus unpleasant smells) [66]. Subjects receive odors in pairs of Sniffin' Sticks to evaluate on 9-point hedonic scales. Across pairs, hedonic range (i.e., hedonic distance between two oppositely valenced odors such as pleasant pineapple odor versus unpleasant smell of turpentine) and hedonic direction (i.e., indicator for overall hedonic experience of odors in daily life: positive, neutral or negative) can then be determined based on the hedonic ratings. It seems a valuable tool to investigate a shift in hedonic olfactory evaluation in healthy and diseased individuals. This might also include children with cancer, although to date, the SSParoT includes normative data for people aged 18 – 35 years only. Moreover, a similar test for evaluating qualitative taste disorders has not been developed yet.

In sum, the observed disconnect between self-reported smell and taste changes and objectively measured changes in smell/taste function as found in our population, suggest that the effects of chemotherapy on smell and taste are wider in scope

than only changes in smell/taste acuity. The full extent and essence of these changes warrant further research. Clearly, regardless of whether there are changes in chemosensory function (objective) or perception (subjective), an experienced change in smell and taste in children with cancer receiving treatment is common, bothersome, and impacts eating behavior, food enjoyment, and quality of life (as described in chapters 4 and 7).

LEARNED FOOD AVERSIONS – THE ROLE OF CLASSICAL CONDITIONING

Changes in smell and taste may often encompass a change in liking for smells and tastes. As described above, more often than not, these changes in hedonic evaluation are negative. Of course, these negative hedonic shifts may be the direct results of changes in smell/taste sensitivity and/or smell/taste perception. However, nausea and learned food aversions may also play an important role in promoting children's dislikes for food smells and tastes. As described in chapter 4, nausea is still a common side effect of chemotherapy with occurrence rates ranging between 24.8% and 42.9% during the first year of treatment, despite the availability and use of multimodal antiemetic agents. In general, patients report eating less food and preferring dry, bland foods when nauseated [67]. Apart from influencing appetite and the perceived palatability of food directly, nausea can also induce the learning of strong and long-lasting food aversions.

Nausea can function as an unconditioned stimulus that becomes associated with a food (its smell and taste) eaten before the onset of nausea [68]. The smell and taste of that food then comes to function as a conditioned stimulus, signaling nausea and thus promoting further avoidance of that food. The smell and taste of the food itself become highly disliked. Unlike most forms of classical conditioning, these smell and taste aversions are rapidly acquired and are unusually resistant to unlearning [69]. Chemotherapy, through inducing nausea and/or gastro-intestinal distress, can condition potent taste aversions in children with cancer. Bernstein and colleagues performed a controlled study among children with cancer, exposing these children to a rather unusual ice cream flavor (Mapletoff) shortly before receiving chemotherapy [70]. Two other groups served as controls, with the first group of children eating the ice cream in between treatments, and the second group receiving toys instead

of ice cream at the start of chemotherapy. Of these three groups of children with cancer, only the first group acquired an aversion for Mapletoff ice cream. Such a conditioned aversion is not limited to ice cream with an unusual flavor – it also was shown to extend to a hospital test meal and other food items consumed prior to receiving chemotherapy [71, 72]. Chapter 7 describes how for several children specific foods and smells had become highly aversive after exposure to these flavors and odors during their admission in hospital. It is conceivable that self-reported smell and taste changes among children with cancer included conditioned smell and taste aversions. However, it remains unclear to what extent conditioned smell and taste aversions play a role in childhood cancer patients' perceived smell and taste problems, eating problems, and quality of life. This too deserves further research.

EVERYTHING TASTES DIFFERENTLY – HOW TO COPE WITH THAT?

A recent review nicely showed that smell and taste alterations (i.e., hypo – and hypersensitivity) in adult patients influence food behavior during chemotherapy [73]. For adults undergoing chemotherapy, various treatment options for chemosensory problems have already been investigated, such as the administration of zinc. However, the efficacy of most of these treatments is still either moot, or disappointingly limited [74, 75]. Dietary and educational counselling has been proven to significantly reduce (though not abolish) taste problems in adult cancer patients and remains the best approach to date [76, 77]. The findings described in this thesis may serve as input for similar dietary (or sensory) counselling for the management of smell and taste problems in children with cancer (chapter 7). Food has no nutritional value when left uneaten and thus advice on how to cope with smell and taste problems would be a valuable addition to dietary advice on nutritional requirements. In the qualitative study described in chapter 7, children listed various strategies to manage or cope with smell and taste problems.

Regarding smell, children frequently mentioned coping strategies for dealing with unpleasant smells, either through avoiding or masking these smells. Masking unpleasant smells can be done by using another strong smell that is found to be pleasant, such as deodorant. The need to avoid smells seems more often related to the smell of food or body odors. For example, kitchen cooking smells can be

unpleasant to the extent that the child feels compelled to eat dinner as far away from the kitchen as possible (e.g., upstairs). Some children found it impossible to tolerate certain perfume fragrances worn by either family members or health care professionals. Children do not always feel comfortable requesting family, friends, or hospital staff to stop using a specific perfume or deodorant. Sometimes, children spoke for the first time about this topic in the interviews. If everyone involved is aware that children with cancer may experience this discomfort, it will be easier to discuss this topic and ask others to pay attention to it.

Regarding taste, coping strategies for a variety of changes have been suggested as listed in Table 2. Children who suffer from taste loss, frequently seen among children with a solid tumor or lymphoma, could benefit from adding strong flavors and seasonings (e.g., hot chili sauce, pepper, tabasco) causing trigeminal stimulation. Conversely, when tastes are perceived as much more intense, neutral/bland foods could be recommended. When food tastes differently, it might help to repeatedly try this food to get used to its altered flavor or to try and find new favorite foods. Some children chose to just avoid products for a period trusting that these foods would eventually taste good to them again. Several children constantly experienced a bad taste in their mouth. Coping strategies to deal with this annoying symptom can be found in Table 2. Please note that eating sweets and lollipops can also have adverse effects on the teeth, which should be carefully considered by patients and their caregivers. Regardless of taste changes as mentioned above, food preferences and eating behavior may change during treatment and may even vary from day to day. If this is the case, children and parents mentioned that it is important to acknowledge these changes and look for other products that may still taste good.

IMPLICATIONS FOR CLINICAL PRACTICE

Changes in smell and taste frequently occur during treatment for childhood cancer. However, they are easily overlooked in clinical practice as they are non-life-threatening treatment effects. But smell and taste changes are certainly bothersome to children and by playing a key role in appetite can be considered a risk factor for malnutrition. Malnourished children with cancer have a significantly greater risk for morbidity and mortality [78]. In other words, the limited clinical attention for the occurrence of smell and taste problems in children with cancer is unjustified and highlights the urgent

need to raise more awareness about smell and taste changes among healthcare providers such as doctors, nurses, and dietitians. This also includes practical tips such as not wearing perfume during working hours, which is unpleasant for many children. Furthermore, I advocate standard referral to a dietitian for both nutrition and sensory counselling to optimize coping with any smell and taste problems, thus reducing the need for complementary (tube) feeding and limiting the risk of malnutrition and weight fluctuations in patients during treatment. In the Princess Máxima Center, every three months a HRQoL questionnaire including topics "food not tasting good" and "nausea caused by food/smells" is filled in by patients in KLIK and evaluated during consultation with the pediatric oncologist. If patients show poor scores on items pertaining to the perception of food smell and taste, additional advice from a dietitian might be beneficial.

Table 1. (Dietary) recommendations when experiencing chemotherapy-induced taste changes.

Taste changes	Recommendations
Increased taste sensitivity	try bland or neutral foods (e.g., yoghurt, cracker, boiled potatoes) avoid strong food smells serve foods cold or at room temperature
Decreased taste sensitivity	try different (strong) flavors enhance flavors (e.g., adding salt or herbs) add spicy toppings to dishes (e.g., raw onion, capers, chili sauce)
Food tasting different	frequently try those foods to get used to new taste try different foods to find new favorites avoid foods that became disgusting
Bad taste in mouth	frequently brushing teeth drinking (e.g., water or lemonade) sucking on a candy or lollipop

Information to parents and patients about the occurrence of smell and taste changes should be provided at the start of treatment. Several parents mentioned that they had not expected such severe smell and taste changes in their child and thought that their child's smell and taste problems was exceptional. Since this topic receives little or no attention during consultations with doctors or nurse practitioners, parents do not know just how frequent and bothersome smell and taste changes can be. Furthermore, the neglect of these smell and taste problems in consultations means that often parents try several strategies at home in their attempt to manage these problems. However, this coping through trial and error is often accompanied by a

lot of frustration, which can be prevented if parents and their children are informed on these treatment effects in advance.

Taste changes are the main reason for losing interest in food and skipping meals in adult cancer patients. Nutritional/educational counseling in these patients reduces severity of taste problems and positively influences other outcomes such as nutritional intake, morbidity, quality of life, and self-care behavior [76, 77, 79]. Although I did not explicitly study the influence of smell and taste changes on dietary intake yet, several children claimed that their eating behavior and food choices changed due to chemosensory changes (chapter 7) and that it impacted their daily lives. In line with these claims, results described in chapter 5 show that taste function and eating behavior in children with cancer are correlated. Therefore, I believe that there is an important role for the dietitian at the pediatric oncology ward/center too, as children with cancer also often experience smell and taste problems and accompanying eating problems. At present, hardly any pediatric oncology dietitian pays much attention to smell and taste problems (SIOP international survey of pediatric oncology nutritional practices in high income countries, *preliminary data*). This might be the result of insufficient awareness and knowledge of smell and taste problems in children with cancer and chemosensory perception in general [80]. That gap in knowledge can however be remedied with appropriate education allowing the pediatric oncology dietitian to deliver more appropriate and patient-centered dietary advice.

RECOMMENDATIONS FOR FUTURE RESEARCH

The discussion of the results from this thesis indicates several directions for future research. First of all, it would be highly relevant to investigate whether referral to a dietitian for counselling regarding smell and/or taste abnormalities improves dietary intake, nutritional status, and the quality of life in children with cancer. At the moment, sensory counselling by a dietitian is not part of standard care. A study comparing usual care with standard care-plus-dietary-counselling for smell and/or taste abnormalities specifically could indicate whether such counselling is indeed beneficial.

Secondly, it would be interesting to study whether culinary adaptations including flavor enhancements are feasible and effective in children with cancer. In adult

cancer patients, flavor enhancements seem to increase food acceptance in patients with self-reported smell and/or taste abnormalities [81]. However, flavor enhancement seems particularly appropriate in case of taste *loss*, which may not be the case in all children with cancer. Of course, lower taste sensitivity have been found during active treatment, but this does not necessarily indicate hypogeusia in all cases. In contrast, providing more neutral food products might be an effective strategy to cope with other taste distortions, such as increased taste sensitivity. Such a study should adapt sensory properties of food in various way, suitable for children with cancer specifically.

Thirdly, the relationship between chemosensory changes and nutrition-related outcomes such as dietary intake and nutritional status remains unclear. In adults, it has been shown that changes in smell and taste function not only affect food liking, but also dietary intake and body weight [82]. Moreover, a recent study showed that self-reported smell and taste alterations in children with cancer are associated with impaired nutritional status [83]. It would be interesting to study whether objective measures of smell and taste function are also associated with other clinical outcomes such as infections and survival in children with cancer. Preferably, these studies also include analysis of cytokines, cortisol, and NTx levels, as well as the degree of chronic polypharmacy (e.g., composition, duration, and dose).

Lastly, while we already performed measurements of smell and taste function after chemotherapy, follow up on longer term should be considered. Both smell and taste function seemed to normalize in children after ending intense chemotherapy. However, it is unclear if it fully recovers in most children. There is reason to doubt that it does. One of the most frequent questions that pediatric oncology dietitians at the Princess Maxima Center receive from childhood cancer survivors is “when will my sense of taste return to normal again?” (personal communication). It has been shown in a cross-sectional study that some smell and taste dysfunction is still common among childhood cancer survivors (at least five years in remission), although others found that taste function of childhood cancer patients after completing treatment no longer differed from healthy controls [84, 85]. More research is needed here.

METHODOLOGICAL CONSIDERATIONS

Some methodological considerations need to be taken into account when interpreting the results. Overall, there are some clear strengths of the studies. The results described in chapters 5 and 6 of this thesis are the first prospective evaluations of smell and taste function in children undergoing chemotherapy. In addition, the longitudinal study design as described in chapter 6 includes measurements both during and after treatment and is the largest study among children with cancer regarding smell and taste function to date. Another strength of this thesis lies in the use of both quantitative and qualitative data, which allows for a deeper discussion and richer understanding of both the extent and probable causes of perceived smell and taste problems in children with cancer. Apart from these strengths there are, however, a number of limitations to consider.

First, we were not able to establish a true baseline measurement in the longitudinal study examining smell and taste function in children with cancer during and 3 months after intense chemotherapy (chapter 6). All children had already received chemotherapy before the first measurement at T0, some 6 weeks after diagnosis. Since the impact of a childhood cancer diagnosis is large, and treatment is often started within hours or days after diagnosis, we felt it was unethical to recruit children for participating in this study at time of diagnosis. Therefore, results cannot rule out that the presumed changes in smell and taste during active treatment are not at all the result of chemotherapy.

Moreover, smell and taste tests were always performed at the first day of administering chemotherapy, when children are in a relatively good condition, having recovered from the previous cycle of chemotherapy some weeks before. One could argue that measurements at T0-T2 then do not represent a chemotherapy effect on smell and taste but rather the effect of recovery from chemotherapy. The rationale behind the decision to nonetheless plan these measurements always at the start of a chemotherapy cycle was to minimize the influence of acute treatment side effects, such as nausea and oral mucositis, and to limit the risk of study attrition (i.e., children no longer wanting to participate due to general malaise associated with intense chemotherapy).

Another limitation is the heterogeneity of the study samples in both the feasibility study and the longitudinal study. Childhood cancer refers to many very different types of cancer and this variety is reflected in the samples of patients included in the aforementioned studies. Children with brain malignancies were hardly present in our studies, whereas a hematological cancer diagnosis (ALL, myeloid malignancies, and lymphoma) was dominant. I experienced that especially children with brain tumors were hard to include in the studies and more frequently refrained from participation. This might be due to the fact that surgery of the brain tumor is often planned soon after diagnosis, followed by 6 weeks of (proton) radiotherapy trajectory at the University Medical Center Groningen, outside the Princess Máxima Center. Overall, the heterogeneity of the sample, and the small number of children per diagnosis group, prevented us from examining a clear association between smell and taste changes and type of cancer diagnosis. For the same reason, we could not investigate possible interactions between cytotoxic agents. However, our results tentatively suggest children with hematological malignancies, at least children with ALL, having an increased smell sensitivity whereas taste loss appears to be particularly common in children with solid tumors and lymphoma. Receiving vincristine was associated with lower odor identification ability. Moreover, etoposide was associated with lower taste sensitivity, whereas mercaptopurine and corticosteroids seem to be associated with higher taste sensitivity.

One more methodological consideration concerns the use of the smell and taste measurement tools. Firstly, for measuring odor identification, we used a test with 16 Sniffin' Sticks for adults in chapter 5, but another validated child-friendly version with 12 Sniffin' Sticks including normative values became available a little later and was therefore used in chapter 6. Secondly, we used a wide step method (8 staircases instead of 16) for the odor threshold test to limit time and burden of investigation in these children. This method has never been used in children but has been shown to be reliable in adults [86]. However, cut-off values for the odor threshold test were based on the original test having 16 staircases, potentially leading to an underestimation of increased smell sensitivity. For measuring taste function, we relied on the Taste Strips test, which is practical but is not a genuine taste threshold test and a test that has only modest reliability. Nonetheless, this test did allow us to measure taste recognition ability in children with cancer and to compare their scores against normative values, making it the best test available for assessing taste function in children.

CONCLUSION

In this thesis, I aimed to get insight into smell and taste function of children with cancer. We found that changes in smell and taste are very common but rather heterogeneous in its presentation. That is, smell and taste sensitivity can be either decreased or increased or perceived as completely different than before. Especially these latter changes are not always measurable with psychophysical tests, highlighting the importance of self-report. In general, I can conclude that smell sensitivity seems higher during treatment (based on objective measures of smell identification and self-report), specifically in children with ALL. In contrast, taste sensitivity seems lower during active treatment with chemotherapy. Moreover, most cases of taste loss were found among children with lymphomas and solid tumors specifically. This heterogeneity in results lack explanation at present, but regardless of the direction of smell and taste changes I can conclude they are common, bothersome, and impact the quality of life in children with cancer receiving chemotherapy.

Further, I conclude that individual (dietary) advice is probably the best approach to manage smell and taste problems. To ensure that childhood cancer patients are referred to a dietitian for such counselling, healthcare providers will have to be educated on the occurrence of smell and taste changes and on the consequences of these changes for children's appetite and quality of life. Notably, pediatric oncology dietitians too need to be educated on chemosensory function and its relation to appetite before they can provide optimal dietary/sensory counselling to children with cancer. Future research should focus on the hypothesized benefits of such dietary counselling interventions for children with cancer.

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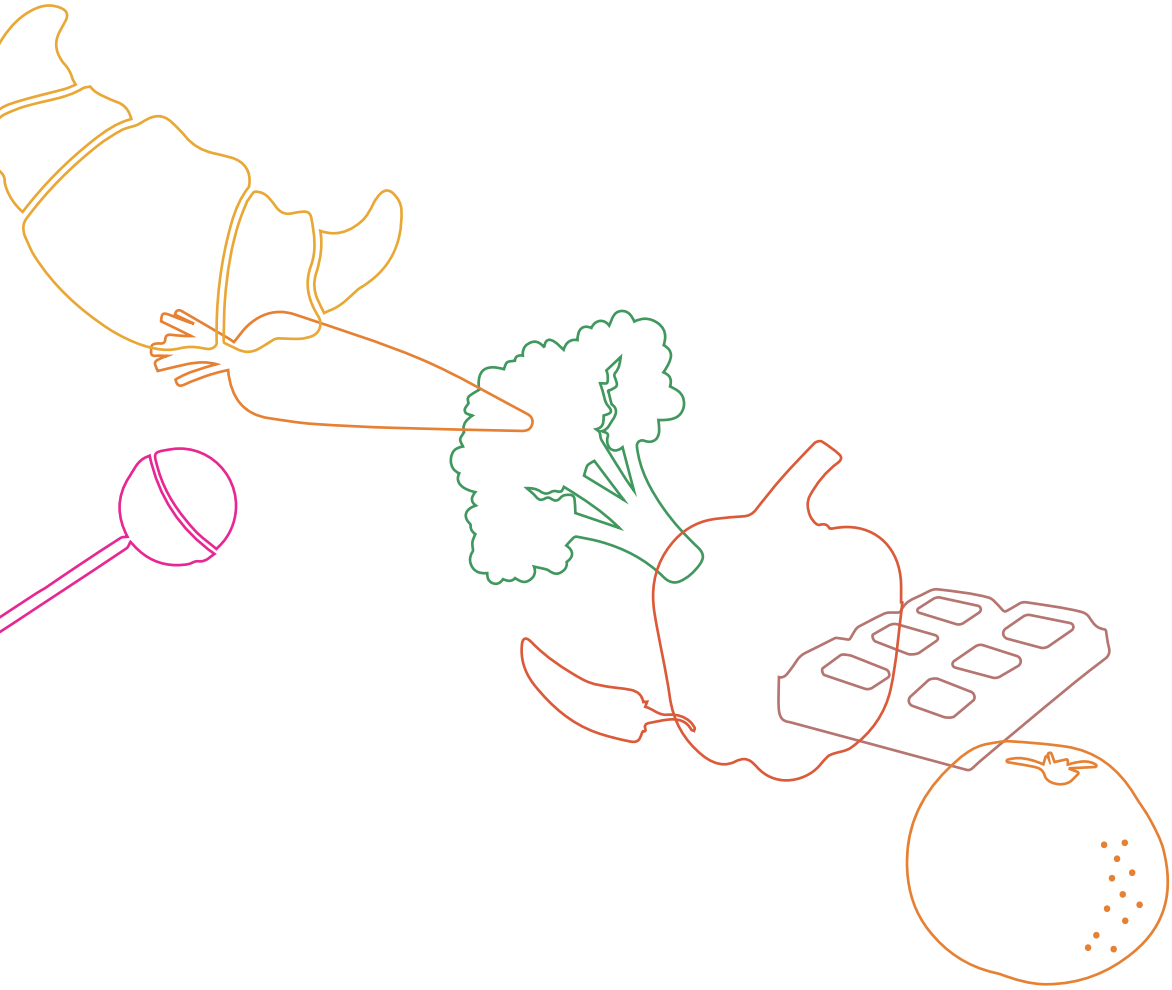

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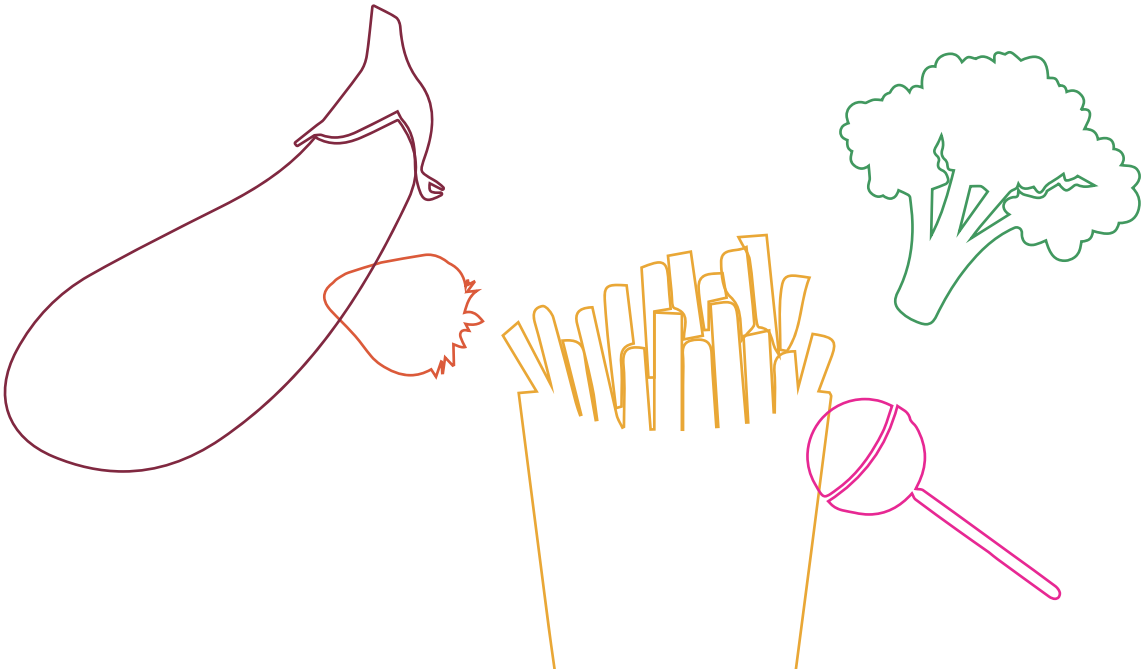

A cancer diagnosis and subsequent treatment have an enormous impact on a child's life. Consequently, physical, psychological, social, and spiritual well-being of the child is affected [1]. Survival rates of children with cancer have increased over the past decades and as a result, pediatric oncology care is no longer focused solely on survival [2-4]. Surviving childhood cancer requires very intense treatment and can have both acute and longer-term effects on a child's health and well-being [5-7]. Therefore, more attention is directed towards managing side effects during treatment and late effects in survivorship, which is reflected in the mission statement of the Princess Máxima Center: '*Curing every child with cancer, with an optimal quality of life*'.

Nutritional care should be highly prioritized in advancing care of children with cancer, as it can have a profound impact on both short- and-long-term outcomes [8-10]. Such nutritional care or counseling should be provided taking potential taste and smell changes into account. Unfortunately, this is not a fixture of (pediatric oncology) clinical practice yet. Developing and implementing such counseling seems timely. Until recently, hardly any data was available regarding changes in smell and taste in children with cancer, but since the COVID-19 pandemic the potential impact of such chemosensory changes on eating behavior and quality of life are more readily recognized [11-14].

The aim of this dissertation was to expand our knowledge and understanding of children's changes in smell and taste during treatment for childhood cancer. Apart from contributing to a body of scientific evidence, the results described in this thesis may lead to the development of new interventions and (dietary) recommendations in the future. In this chapter, I will discuss the scientific impact of our research by addressing its relevance for children with cancer and their families specifically, but also for health care professionals and society. Moreover, the dissemination of our knowledge is addressed, ending with an overall conclusion.

RELEVANCE FOR CHILDREN WITH CANCER – QUALITY OF LIFE

The results of this thesis are relevant for the child with cancer. I found that smell and taste disturbances are highly present among children with cancer, although these disturbances vary between individuals. Some patients displayed heightened chemosensory function, whereas other patients had decreased chemosensory function.

Smell sensitivity seems increased during treatment, particularly for children with ALL receiving corticosteroids. However, this was not a consistent finding across studies. While our feasibility study indicated heightened smell sensitivity in patients compared to controls, our longitudinal study did not show significant changes in smell sensitivity during treatment (although an increase in maintenance phase in children with ALL). However, we did find that an experienced (i.e., self-reported) increase in smell sensitivity was highly prevalent as well as a generally increased ability to identify odors (relative to norm scores) at each time point.

Sweet, bitter, and overall taste scores tended to increase shortly after a cycle of chemotherapy, but in contrast to smell function, taste function generally seems lowered in children during active treatment with chemotherapy. Based on the Taste Strips test, taste loss had an occurrence rate of approximately 20%. Self-reported changes in taste occurred in nearly 80% of the children during treatment, although these changes were often described as “food tasting different than before” rather than changes in taste sensitivity or perceived taste intensity. Regardless of their presentation, chemotherapy-induced taste (and smell) changes affect eating behavior and (quality of) daily lives of children with cancer and their families.

In the Netherlands, children and their parents do not receive any standardized information regarding the changes in smell and taste that occur during chemotherapy. This is perhaps not very surprising. When a child has just received a cancer diagnosis, the parents’ main focus is on questions regarding prognosis, type of treatment, hospital admissions, medication, lab results, and so on. Most parents are initially unaware of the risk for nutritional complications, including changes in smell and taste, that are associated with chemotherapy. Further, as chemosensory changes are non-life threatening, they are rarely discussed during regular consultations. Therefore, children and parents end up experimenting; that is, trying out several strategies to cope with taste, smell, and eating problems. They manage through trial and error but not without unnecessary disappointments and frustration. The present results give valuable input for educating children and parents at the start of treatment so that they know what to expect and are provided with effective coping strategies. I believe that this research will have a large influence on the daily (quality of) life of children with cancer, on their pleasure of eating, and on their nutritional status and clinical outcomes.

Unlike older adults who survive cancer, childhood cancer survivors have a whole life ahead of them. Their adult life is marked by an increased risk for various non-communicable diseases. For example, childhood cancer survivors have an additional risk of developing cardiometabolic disease [15-17]. Treatment trajectories for childhood cancer appear to be a period in which children develop unhealthy eating habits and food preferences [18]. Parents are already happy if their child eats something, even if it is just ice cream or fries. Studies suggest that long-term changes in chemosensory function and appetite may affect eating habits in survivorship [19]. In addition, adverse effects during treatment (e.g., nausea, vomiting, mucositis) have been associated with reduced dietary intake and pleasure, consequently changing dietary patterns which may become longer-term habits [20-23]. Unfortunately, such acquired unhealthy eating habits (e.g., decreased fruit and vegetable intake, increased junk food consumption and portion sizes) have been proven difficult to unlearn in survivorship [18, 24, 25]. Therefore, research into the development of tailor-made dietary recommendations to alleviate treatment-related side effects, but also adequate nutrition education during and after treatment, is relevant for patients as well as their families and society.

RELEVANCE FOR HEALTH CARE PROFESSIONALS – QUALITY OF CARE

The findings of this thesis also apply to pediatric oncology health care professionals including doctors, nurses, dietitians, nutrition assistants, chefs, psychologists, pedagogical staff, and all other team members involved. Apart from informing and educating patients and their parents, health care professionals should be educated too. At the moment, there is little knowledge and awareness about smell and taste changes in children with cancer undergoing chemotherapy. Therefore, it is necessary to share the results of this thesis at the various departments of the Princess Máxima Center, as well as its shared care centers (i.e., pediatric departments within hospitals across the Netherlands that closely work with the Princess Máxima Center) and the Children's Comfort Team (i.e., health care professionals providing home care), to provide the best possible quality of care.

AND NOW?

All studies including children with cancer as described in this thesis were designed in close collaboration with parents of patients via the Dutch Childhood Cancer Organization (VKN). For example, patient information letters and interview guides were reviewed and commented upon by the VKN before I used these forms and letters in the studies. Since this thesis has been finalized, we will share our results and knowledge with this audience via their monthly newsletter and quarterly magazine (Attent). Moreover, a section about changes in smell and taste will be added to the information diary that children and parents receive at the start of treatment.

Apart from sharing our knowledge at several departments and shared care center of the Princess Máxima Center, as mentioned before, our results will be (and have been) shared through publications in peer-reviewed journals and presentations at international congresses.

Lastly, I will collaborate with Institute Paul Bocuse in Lyon to further work on exploring culinary adaptations for children with cancer specifically. Through this, we hope to find approaches to alleviate the detrimental effects of chemosensory changes on food intake, thereby improving nutritional status and quality of life of children with cancer.

CONCLUSION

In sum, this dissertation enhances our understanding of how smell and taste function might change in children with cancer undergoing chemotherapy. Although our findings warrant further investigation, they can be used to educate patients, their families, and health care professionals regarding expectations and coping strategies of smell and taste alterations. Moreover, it provides a useful starting point for new (dietary) recommendations and interventions, including studying whether counseling by a dietitian regarding smell and taste changes is effective in improving food intake, nutritional status, and quality of life of children with cancer.

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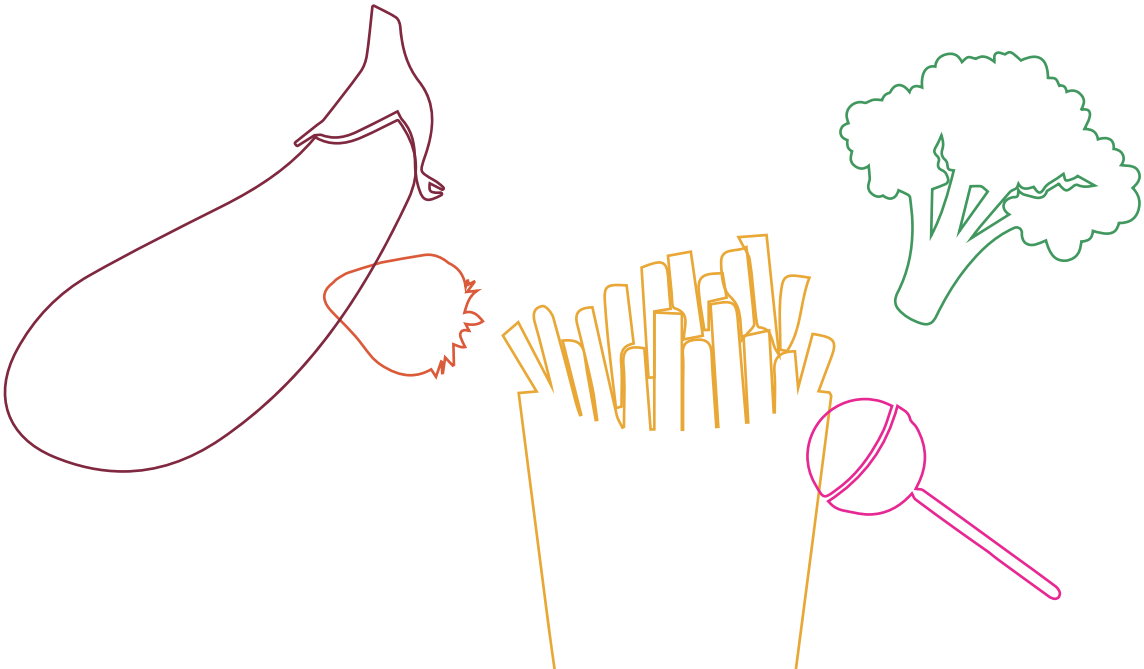
Appendices

Nederlandse samenvatting
Curriculum Vitae
List of publications
PhD portfolio
Dankwoord



NEDERLANDSE SAMENVATTING

Toen we in 2018 begonnen met dit onderzoek, was er nauwelijks iets bekend over reuk – en smaakveranderingen bij kinderen met kanker. Dat het een onderwerp was dat leefde, bleek wel uit de vragen die artsen, verpleegkundigen en diëtisten hierover kregen. In datzelfde jaar verscheen er voor het eerst een artikel dat liet zien hoeveel kinderen met kanker hiermee te maken krijgen. Tot wel 60% van de kinderen rapporteert smaakveranderingen en noemt dit één van de meest vervelende klachten tijdens de behandeling voor kinderkanker. Over reukveranderingen bij kinderen met kanker wisten we nog helemaal niets. Werk aan de winkel dus.

In **hoofdstuk 1,** de algemene inleiding, wordt verder ingegaan op de achtergrond en doelen van dit proefschrift. In de afgelopen decennia is de behandeling van kinderkanker dusdanig verbeterd, dat de overlevingskansen zijn toegenomen tot ongeveer 80%. Echter gaan deze behandelingen wel gepaard met bijwerkingen, zoals misselijkheid, braken en mucositis, die de voedingsinname beïnvloeden en het risico op ondervoeding vergroten. Een slechte voedingstoestand – dit omvat zowel ondergewicht als overgewicht – wordt geassocieerd met meer infecties, een verminderde overleving en lagere kwaliteit van leven bij kinderen met kanker. Het is dus belangrijk dat een kind met kanker goed gevoed is – en blijft – tijdens de behandeling.

Naast de eerdergenoemde bijwerkingen, kunnen ook reuk– en smaakveranderingen de voedingsinname in gevaar brengen. De behandeling van kinderkanker bestaat naast chirurgie en radiotherapie hoofdzakelijk uit chemotherapie, dat als doel heeft om snel delende kankercellen te doden. Er wordt verondersteld dat chemotherapie ook andere snel delende cellen aantast, zoals reuk– en smaakreceptoren. Bij volwassen patiënten die chemotherapie kregen, lijkt dit met name te resulteren in reuk en/of smaakverlies. Het reukvermogen speelt, naast het herkennen van gevaar, een belangrijke rol in het opwekken van eetlust. Daarnaast is de smaak van eten één van de belangrijkste aspecten bij de keuze om een voedingsmiddel wel of niet te consumeren. Op het moment dat (een van) deze zintuigen aangetast zijn, heeft dit logischerwijs invloed op de hoeveelheid die er gegeten wordt of de mate van plezier waarmee er gegeten wordt.

Het doel van dit onderzoek was om reuk en smaakfunctie bij kinderen met kanker te onderzoeken. Hiervoor zijn diverse studies opgezet. Allereerst wilden we meer inzicht krijgen in smaakfunctie van kinderen in het algemeen, hoe dit zich ontwikkelt in hun jonge jaren en hoe dit het beste te meten is (hoofdstukken 2 en 3). Vervolgens is retrospectieve data van Nederlandse kinderen met kanker gebruikt om een inzicht te krijgen in misselijkheid en daaraan gerelateerde symptomen (zoals veranderingen op het gebied van reuk en smaak, hoofdstuk 4). Daarnaast is gekeken of het meten van reuk– en smaakfunctie haalbaar is bij kinderen met kanker (hoofdstuk 5) en of dit verandert tijdens behandeling met chemotherapie (hoofdstuk 6). Tenslotte zijn kinderen met kanker geïnterviewd over hun ervaringen met reuk– en smaakveranderingen en de impact hiervan op hun dagelijks leven (hoofdstuk 7).

Hoofdstuk 2 is een overzichtsartikel waarin de beschikbare literatuur over smaakverlies bij kinderen en de daarvoor geschikte meetinstrumenten wordt samengevat. Dit artikel laat zien dat er diverse medische aandoeningen zijn die de smaakfunctie van kinderen kunnen beïnvloeden. Denk hierbij, naast kinderkanker, aan taaislijmziekte, diabetes type 1, nierfalen, astma en autisme. Er zijn echter maar weinig smaaktesten geschikt om bij kinderen af te nemen in een klinische setting. De zogenaamde “Taste Strips test” bleek de enige smaaktest die gemakkelijk is te verkrijgen en af te nemen. Voor deze test waren alleen nog geen normaalwaarden voor kinderen beschikbaar, wat het gebruik ervan beperkt in de kliniek.

Vervolgens wordt in **hoofdstuk 3** de smaakfunctie van 609 gezonde kinderen (6 – 15 jaar) gemeten met behulp van de Taste Strips om normaalwaarden te creëren voor deze smaaktest. Taste Strips zijn papieren strips waarbij de smaken zoet, zuur, zout en bitter in diverse concentraties zijn geïmpregneerd. Dit hoofdstuk beschrijft, naast leeftijd en geslacht, ook de relatie met gevoeligheid voor de bittere stof 6-n-propylthiouracil (PROP) en smaakfunctie van kinderen.

Resultaten toonden dat de smaakfunctie toeneemt naarmate kinderen ouder worden, waarbij we 3 leeftijdsgroepen van elkaar konden onderscheiden, namelijk kinderen van 6 – 7 jaar, 8 – 9 jaar en 10 – 15 jaar. Daarnaast bleek dat meisjes beter proeven dan jongens. Dit resulteerde in normaalwaarden specifiek voor leeftijd en geslacht, waarbij het 10^{e} percentiel gebruikt wordt als afkappunt om een normale smaakfunctie te onderscheiden van een verminderde smaakfunctie. Ook vonden we dat kinderen die PROP kunnen waarnemen, ook wel “supertasters” genoemd, een betere smaakfunctie

hebben dan kinderen die PROP niet kunnen waarnemen. Ten slotte bleek dat de mate waarin kinderen hun eigen smaakfunctie beoordelen (subjectief) niet samenhangt met smaakscores zoals gemeten met de Taste Strips (objectief).

In **hoofdstuk 4** wordt een retrospectief cohortonderzoek beschreven naar de aanwezigheid en ernst van misselijkheid en misselijkheid-gerelateerde symptomen bij kinderen met kanker tijdens het eerste jaar van hun behandeling. Daarnaast hebben we gekeken naar mogelijke risicofactoren en hebben we de invloed van misselijkheid en misselijkheid-gerelateerde symptomen op de kwaliteit van leven bij kinderen met kanker onderzocht. We hebben hiervoor gebruik gemaakt van kwaliteit van leven vragenlijsten die elke 3 maanden worden aangeboden in KLIK (Kwaliteit van Leven In Kaart) zolang kinderen in behandeling zijn. Voor deze studie hebben we ons gefocust op de 'misselijkheidsschaal' uit deze vragenlijst, welke bestaat uit de volgende onderdelen: misselijk worden tijdens medische behandelingen, eten dat niet goed smaakt, misselijk worden bij het denken aan medische behandelingen, te misselijk zijn om te eten, misselijk worden van voedsel/geuren. In totaal vulden 781 kinderen met kanker (2 – 21 jaar) of hun ouders deze vragenlijsten in tussen 2016 en 2021.

De resultaten toonden aan dat misselijkheid tijdens de medische behandeling het meest voorkomt rond 6 maanden na de diagnose. Wanneer er gekeken wordt naar de individuele onderdelen van de 'misselijkheidsschaal', dan blijkt dat 'eten dat niet goed smaakt' het vaakst wordt genoemd (52 – 63%), gevolgd door 'misselijkheid veroorzaakt door voedsel/geuren' (34 – 48%). Pijn, angst voor de behandeling en zorgen werden bij alle kinderen met kanker gerelateerd aan misselijkheid. Bij patiënten van 8 tot 21 jaar werd daarnaast gevonden dat het mannelijke geslacht, een solide tumor en een laag BMI van invloed zijn op het ervaren van misselijkheid. Ten slotte hebben misselijkheid-gerelateerde symptomen een negatieve invloed op de kwaliteit van leven van kinderen met kanker. Met andere woorden, misselijkheid – vooral in relatie met de smaak en geur van eten – komt vaak voor en heeft een negatieve invloed op de kwaliteit van leven bij kinderen met kanker.

In **hoofdstuk 5** wordt gekeken naar de haalbaarheid van het meten van reuk en smaak, met behulp van respectievelijk de Sniffin' Sticks en Taste Strips, bij kinderen met kanker. Naast haalbaarheid is er ook gekeken of reuk – en smaakscores daadwerkelijk veranderden na een chemokuur en of deze anders waren dan de scores van gezonde kinderen. Ook werd de dichtheid van de smaakpapillen gemeten

en het eetgedrag in kaart gebracht door middel van een vragenlijst. Eenendertig kinderen met kanker en 24 gezonde broertjes/zusjes of vriendjes/vriendinnetjes tussen de 6 en 18 jaar deden mee met dit onderzoek.

Allereerst vonden we dat het meten van reuk en smaak met objectieve testen haalbaar was bij kinderen met kanker (d.w.z. het voltooien van de testen door ≥60% van de kinderen). Echter bleken er wel wat aanpassingen nodig te zijn voor toekomstig onderzoek om de totale duur van de testen wat in te korten, zoals het achterwege laten van zowel de geur discriminatietest als het bepalen van de dichtheid van de smaakpapillen. Vervolgens vonden we dat de totale smaakscore, inclusief de scores voor zoet en bitter, hoger was na een chemokuur en dat kinderen met kanker gevoeliger zijn voor geuren dan gezonde kinderen. Tenslotte bleek dat smaakfunctie samenhangt met eetgedrag maar niet met de dichtheid van smaakpapillen.

Hoofdstuk 6 beschrijft een longitudinale studie waarbij 94 kinderen met kanker (6 – 18 jaar) werden gevolgd tijdens en na de behandeling met chemotherapie. Reuk (omvat gevoeligheid voor – en herkennen van geuren) en smaakfunctie werden gemeten op verschillende tijdstippen tijdens de behandeling (6 weken, 3 maanden en 6 maanden na diagnose) en 3 maanden na de laatste chemokuur. Bij kinderen met acute lymfoblastische leukemie (ALL) werd de laatste meting uitgevoerd tijdens de zogenaamde onderhoudsfase, waarbij kinderen een veel mildere vorm van chemotherapie krijgen (doorgaans bestaande uit orale mercaptopurine en methotrexaat, aangevuld met dexamethason en vincristine voor sommige patiënten) waarvoor geen ziekenhuisopname nodig is. Het doel van dit onderzoek was om vast te stellen in hoeverre reuk– en smaakveranderingen tijdens de behandeling optreden, of deze na de behandeling weer verdwijnen, en welke factoren er mogelijk samenhangen met deze veranderingen.

Als het gaat om het reukvermogen, dan was er geen verandering in reukgevoeligheid en het herkennen van geuren tijdens de actieve behandeling. Wel nam reukgevoeligheid af in de onderhoudsfase (kinderen met ALL). Aangezien we geen uitgangsmeting konden uitvoeren voor de start van chemotherapie, suggereert dit een verhoogde reukgevoeligheid tijdens de actieve behandeling met chemotherapie bij kinderen met ALL. Het aantal kinderen met kanker met een normale reukgevoeligheid was niet anders dan dat we zien bij gezonde kinderen

(normaalwaarden), wat wel het geval was voor het herkennen van geuren. Terwijl een verminderde reukgevoeligheid nauwelijks voorkomt bij kinderen met kanker, is er wel een deel van de kinderen dat geuren minder goed herkent alsook een deel dat geuren beter herkent ten opzichte van de normaalwaarden. We zagen daarbij ook verschillen per diagnosegroep, vooral kinderen met myeloïde maligniteiten en lymfomen hadden een verhoogde reukgevoeligheid en konden geuren beter herkennen. Zelfrapportage laat ook zien dat kinderen met kanker vaker een toename dan een afname van hun reukvermogen ervaren, echter correspondeert dit maar beperkt met de uitkomsten van een objectieve test.

Smaakfunctie veranderde niet tijdens de actieve behandeling, maar nam toe tijdens de onderhoudsfase of 3 maanden na de laatste chemokuur. Aangezien we geen uitgangsmeting konden uitvoeren voor de start van chemotherapie, suggereert dit een verminderde smaakfunctie tijdens de actieve behandeling met chemotherapie. Het aantal kinderen met kanker dat normaal scoort op de smaaktest was lager dan we zouden verwachten op basis van normaalwaarden bij gezonde kinderen. Bij ongeveer 20% van de kinderen met kanker was er sprake van smaakverlies, in het bijzonder bij kinderen met lymfomen en solide tumoren. Dit duidt op een negatieve invloed van chemotherapie op het smaakvermogen, vooral gezien het feit dat drie maanden na de laatste chemokuur en tijdens de onderhoudsfase het aantal kinderen met kanker met een normale smaakfunctie niet langer afwijkt van wat we zouden verwachten op basis van normaalwaarden bij gezonde kinderen. Etoposide hangt samen met een verminderde smaakfunctie, terwijl mercaptopurine en corticosteroïden de smaakfunctie verbeteren. Zelf gerapporteerde smaakveranderingen kwamen veel vaker voor (60 – 80%) en werden hoofdzakelijk beschreven als “smaken zijn anders dan voorheen” in plaats van veranderingen in intensiteit of gevoeligheid.

Tenslotte beschrijft **hoofdstuk 7** de resultaten van een kwalitatief onderzoek. Hoewel het objectief meten van reuk – en smaakveranderingen verhelderend is, wordt op deze manier niet duidelijk wat deze veranderingen zo hinderlijk maakt voor kinderen met kanker en welke impact het heeft op hun dagelijks leven. Daarom werden kinderen die al deelnamen aan de longitudinale studie, beschreven in hoofdstuk 6, geïnterviewd over hun ervaringen met reuk – en smaakveranderingen tijdens de behandeling. Er werden semi-gestructureerde interviews afgenomen tot er informatieverzadiging werd bereikt in elke leeftijdsgroep (6 – 12 jaar, 13 – 17 jaar), wat

resulteerde in een totaal van 27 deelnemers. De interviews werden geanalyseerd door middel van thematische analyse.

Uit de interviews bleek dat veranderingen in reuk en smaak vaak voorkomen bij kinderen met kanker, maar sterk kunnen variëren. Deze veranderingen werden over het algemeen als hinderlijke symptomen beschouwd en beschreven als “teleurstellend” of frustrerend”. Kinderen rapporteerden verschillende strategieën om met reuk– en smaakveranderingen om te gaan, zoals regelmatig hun tanden poetsen en onaangename geuren vermijden of maskeren. Met betrekking tot het eten, gaven kinderen aan dat ze sterke smaken aan hun eten toevoegen of vaak (nieuw) voedsel proberen om gewend te raken aan de nieuwe smaak.

CONCLUSIE

Dit proefschrift is een eerste aanzet om reuk– en smaakverandering bij kinderen met kanker beter te begrijpen. We vonden dat veranderingen in reuk en smaak heel vaak voorkomen bij kinderen met kanker, maar zeer heterogeen zijn. Dat wil zeggen dat geuren en smaken beter of slechter kunnen worden waargenomen, alsook compleet anders dan voorheen. Vooral de laatstgenoemde veranderingen zijn lastig te meten met objectieven testen, wat het belang van zelfrapportage benadrukt. Over het algemeen concluderen we dat de reukgevoeligheid hoger lijkt tijdens de behandeling (zowel objectief als subjectief), vooral bij kinderen met ALL en ook ten opzichte van gezonde kinderen. Daarentegen lijkt smaakfunctie verminderd te zijn tijdens actieve behandeling met chemotherapie. Smaakverlies lijkt relatief vaker voor te komen bij kinderen met lymfomen en solide tumoren. Alhoewel de heterogeniteit in onze resultaten op dit moment evenveel vragen oproept als beantwoordt, concluderen we dat ongeacht de richting van de reuk– en smaakveranderingen, deze vaak voorkomen, hinderlijk zijn en van invloed zijn op de kwaliteit van leven bij kinderen met kanker die chemotherapie krijgen.

Op dit moment is individueel (voedings)advies waarschijnlijk de beste aanpak om met reuk– en smaakveranderingen om te gaan. Om ervoor te zorgen dat kinderen met kanker voor dergelijke begeleiding naar een diëtist worden verwezen, zullen zorgverleners moeten worden voorgelicht over het optreden van reuk– en smaakveranderingen en over de gevolgen van deze veranderingen voor de eetlust

en de kwaliteit van leven van kinderen met kanker. Ook scholing aan diëtisten die werkzaam zijn in de kinderoncologie is belangrijk, voordat zij optimale begeleiding kunnen bieden op het gebied van reuk– en smaakveranderingen bij kinderen met kanker. Toekomstig onderzoek moet uitwijzen of dergelijk begeleiding effectief is en bijvoorbeeld de voedingsinname en kwaliteit van leven van kinderen met kanker verbetert.

CURRICULUM VITAE

Mirjam van den Brink was born on June 8th 1992 in Arnhem, the Netherlands. She graduated from secondary school in 2010 (Atheneum, Ichthus college Veenendaal), after which she co mpleted a Bachelor of Science in Nutrition and Dietetics in 2015 at the University of Applied Sciences Amsterdam. Her interest in research started while writing her bachelor thesis at the gender outpatient clinic, studying the effects of cross-sex hormone therapy on resting energy expenditure, body composition, and energy-intake in transgender people.

From 2015 until 2017, Mirjam worked as a clinical dietitian at the Amsterdam University Medical Center at the departments of oncological surgery, gastroenterology, and internal medicine. At the same time, she started a premaster in Health Sciences at the VU University Amsterdam. In September 2017, she started studying Health Sciences (specialization Nutrition & Health). During her masters, she wrote a master thesis at the department of Human Nutrition at Wageningen University & Research, studying smell and taste function in relation to food preference and body weight in colorectal cancer survivors treated with chemotherapy. After obtaining her master's degree, Mirjam worked for two months at the National Institute for Medical Research in Tanzania as a research assistant.

Mirjam started her PhD project in September 2018 at the Laboratory of Behavioural Gastronomy at Maastricht University Campus Venlo in collaboration with the Princess Máxima Center for pediatric oncology in Utrecht. During her PhD project, she worked on several projects aiming to get a better insight into smell and taste changes in children with cancer under supervision of Prof. dr. Remco Havermans, Prof. dr. Wim Tissing, and Prof. dr. Marta Fiocco. Mirjam combined her work as a PhD student with working on several projects regarding nutrition in children with cancer in collaboration with dietitians and other experts at the Princess Máxima Center. Internationally, she is part of the SIOP nutrition in High Income Countries network. Mirjam attended several courses, leadership trainings, and presented her work at international conferences. Moreover, she was involved in supervising several BSc and MSc students. Mirjam will continue her work as postdoctoral researcher at the Princess Máxima Center.

Mirjam is married to Roel van Marle and they are proud parents of their son Boaz.

LIST OF PUBLICATIONS

This thesis

van den Brink M, IJpma I, Tissing WJE, Havermans RC. Taste Dysfunction in Children-A Clinical Perspective and Review of Assessment Methods. *Chemical senses. 2021;46:bjab035*.

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van den Brink M, Havermans RC, Fiocco M, Tissing WJE. A longitudinal evaluation of smell and taste function in children with cancer during and after treatment with chemotherapy. *Appetite. 2024;193:107174*.

Other

Parma V, Ohla K, Veldhuizen MG, Niv MY, Kelly CE, Bakke AJ,...,**van den Brink M**,...,et al. More Than Smell-COVID-19 Is Associated With Severe Impairment of Smell, Taste, and Chemesthesis. *Chemical senses. 2020;45(7):609-22*.

Parma V, Ohla K, Veldhuizen MG, Niv MY, Kelly CE, Bakke AJ, ,...,**van den Brink M**,...,et al. Corrigendum to: More Than Smell-COVID-19 Is Associated With Severe Impairment of Smell, Taste, and Chemesthesis. *Chemical senses. 2021;46*.

Van den Brink M*, Van Roessel IMAA*, Dekker J, Ruitenburg-van Essen BG, Tissing WJE, van Santen HM. Efficacy and feasibility of dietary and lifestyle interventions for hypothalamic obesity during childhood: a systematic review. *Under review*.

Van den Brink M, Tissing WJE, Fiocco M, Havermans RC. Taste and smell are associated with dietary intake in children with cancer. *In preparation*.

Noij LCE, **van den Brink M**, Brackel-Kosterink CLH, Lap CR, Biesbroek G, van Houten M, Maitland-van der Zee AH, Hashimoto S, Terheggen-Lagro SWJ. Long-term olfactory dysfunction in children with post-COVID syndrome: towards a standardized approach. *In preparation*.

Gordon E, **van den Brink M**, van der Linden N, Smith K, Gardiner B, Alford A. An international survey of pediatric oncology nutritional practices in high income countries. *In preparation*.

PHD PORTFOLIO

Courses and workshops	Year
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoeker (BROK)	2018
Bijscholing 'Professionals in de kinderoncologie'	2018
Scientific writing in English	2019
Introduction in principles of PBL	2020
Mentoring skills	2020
Examiner training	2020
Workshop KNAW 'Ga eens buiten je boekje'	2020
Bijscholing 'Voeding bij het zieke kind'	2020
Using R for data analysis	2020
Slimme Gasten	2021
Analysis for repeated measurements	2022
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoeker (BROK)	2022
Energy Metabolism and Body Composition	2024

Presentations	Year
Oral, Congress of the International Society of Paediatric Oncology (SIOP)	2020
Oral, Congress of the European Chemoreception Research Organization (ECRO)	2020
Poster, Quality of Life symposium Princess Máxima Center	2020
Poster, Congress of the Multinational Association of Supportive Care in Cancer (MASCC)	2021
Poster, Congress of the British Feeding and Drinking Group (BFDG)	2021
Oral, research meeting Institute Paul Bocuse	2021
Oral, Altered Taste Symposium	2022
Oral, Congress of the British Feeding and Drinking Group (BFDG)	2022
Poster, Congress of the Multinational Association of Supportive Care in Cancer (MASCC)	2022
Poster, Congress of the International Society of Paediatric Oncology (SIOP)	2022
Poster, SKION day Princess Máxima Center	2022
Oral, Congress of the International Society of Paediatric Oncology (SIOP)	2023
Oral, Princess Maxima Research Retreat	2023

(inter)national conferences and seminars	Year
Scientific symposium Princess Máxima Center	2018
Summerschool on Human Olfaction	2019
Women in Olfactory Science (WIOS)	2019
TULIPS jonge onderzoekerdag	2019
Research retreat Princess Máxima Center	2019
Congress of the International Society of Paediatric Oncology (SIOP)	2020
Congress of the European Chemoreception Research Organization (ECRO)	2020
Congress of the Multinational Association of Supportive Care in Cancer (MASCC)	2021
Congress of the British Feeding and Drinking Group (BFDG)	2021
Amsterdam Kinder Symposium	2021
Research retreat Princess Máxima Center	2021
Altered Taste Symposium	2022
Research retreat Princess Máxima Center	2022
Congress of the British Feeding and Drinking Group (BFDG)	2022
Congress of the International Society of Paediatric Oncology (SIOP)	2022
Scientific symposium Princess Máxima Center	2023
Congress of the International Society of Paediatric Oncology (SIOP)	2023
Research retreat Princess Máxima Center	2023

Personal development and skills	Year
2-year PhD program Training Upstanding Leaders In Pediatric Science (TULIPS)	2020 - 2022
9-day Essentials Seminar European Nutrition Leadership Platform (ENLP)	2022

Supervising	Year
Britt van Belkom, Master student Health Food Innovation Management	2019
Charlotte Beddows, Bachelor student Medicine	2020
Minke ter Hedde, Master student Health Food Innovation Management	2021
Valerie Bontan, Bachelor student Nutrition and Dietetics	2021
Jacqueline Heijnen, Bachelor student Nutrition and Dietetics	2021
Nienke Hartman, Master student Health Food Innovation Management	2022

Other activities	Year
Website nutrition in pediatric oncology, Princess Máxima Center	2019 -
SIOP HIC Nutrition working group	2020 -
Member Global Consortium for Chemosensory Research (GCCR)	2020 - 2022
Journalclub with dietitians, Princess Máxima Center	2021 -

Media	Year
Interview BNR 'Waarom onderzoek naar verlies reuk- en smaakvermogen hard nodig is'	2020
Interview de Limburger 'Ruikt azijn anders? Mogelijk signaal voor coronabesmetting'	2020

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Lieve **pap & mam**, dank voor jullie onvoorwaardelijke liefde en steun. Nu ik zelf moeder ben, snap ik nog iets beter hoe diep dat kan gaan. Jullie zijn er altijd voor mij geweest – en nog steeds – maar hebben me ook ontzettend vrij gelaten in de keuzes die ik maakte. Jullie hadden het vertrouwen dat ik niet in zeven sloten tegelijk zou lopen en vonden het bijvoorbeeld prima dat ik als veertienjarige op fietsvakantie ging met Ilonka. Het kwam ook altijd goed en ik ben ervan overtuigd dat deze basishouding van vertrouwen (en geen wantrouwen of angst) mijn wereldbeeld en zelfbeeld positief hebben gevormd tot op de dag van vandaag. Daar ik ben ik

ontzettend dankbaar voor! Ik geniet er ook van om jullie nu te zien in een nieuwe rol van opa en oma, Boaz boft maar met zulke grootouders.

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Save the best for last: de twee belangrijkste mannen uit mijn leven.

Lieve **Boaz,** mama worden van jou was het absolute hoogtepunt van de afgelopen 5 jaar! Ik geniet er elke dag van om te zien hoe je de wereld ontdekt – en hoe deze steeds een beetje groter wordt voor jou. Je bent een heerlijk lief, open en energiek ventje. Ik hoop dat je je bij ons veilig zult voelen en dat je weet dat je echt altijd bij ons terecht kunt. Ik kijk uit naar alles wat we samen met elkaar mee gaan maken. Je bent ontzettend geliefd ♡

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