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

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ABSTRACT

Smell and taste changes are bothersome treatment symptoms interfering with food intake. It remains unclear how and when children with cancer experience such changes during chemotherapy, and if the symptoms resolve after treatment. In this longitudinal study, we measured smell and taste function of 94 childhood cancer patients treated for hematological, solid, or brain malignancies. Smell and taste function were assessed using commercial Sniffin' Sticks and Taste Strips, respectively. For both tests, normative values were used to identify the presence of smell and taste abnormalities. Self-reported chemosensory and appetite changes were assessed using a questionnaire. Measurements were taken approximately 6 weeks (T0), 3 months (T1), 6 months after starting chemotherapy (T2), and 3 months after termination of chemotherapy or maintenance phase for children with acute lymphoblastic leukemia (ALL) (T3). We found that smell and taste scores did not change during active treatment (T0-2). However, approximately 20% of the patients suffered from decreased taste function according to normative values, particularly children with lymphoma or solid tumors. Changes in smell were predominantly characterized as increased rather than decreased. Self-reported changes were much more common than objectively measured, 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. In summary, 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 in children with cancer.

1. Introduction

Childhood cancer is a rare disease, but it is still the major cause of death among children in the Western world (Steliarova-Foucher et al., 2017). Each year, around 600 children are diagnosed with a variety of cancers in the Netherlands ("SKION Basistregistratie," 2020). In recent decades, new therapies and more intensive treatment regimens have resulted in survival rates of approximately 80% (Gatta et al., 2014; Kaatsch, 2010). However, these intensive cancer treatments have severe side effects such as infections, pain, nausea and vomiting (O'Connor et al., 2014). It is well-known that side effects are associated with worse survival and poor quality of life, highlighting the importance of supportive care (Baggott et al., 2011; Loeffen et al., 2019). 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 (Olver et al., 2020).

Nutrition plays an important aspect within supportive care, as a poor nutritional status – including both underweight and overweight – is associated with adverse clinical outcomes (Brinksma et al., 2015; Buturini et al., 2007; Joffe, Dwyer, Glade Bender, Frazier, & Ladas, 2019; Loeffen, Brinksma, Miedema, de Bock, & Tissing, 2015; Orgel et al.,

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2014a, 2014b, 2016). Maintaining an optimal nutritional status is challenging as many treatment-related side effects interfere with food intake (Dupuis et al., 2016). 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 (Johnston et al., 2018; Torres et al., 2019). 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 (Loves et al., 2019; van den Brink, Ter Hedde, van den Heuvel, Tissing, & Havermans, 2022). Moreover, a recent study showed that self-reported taste and smell alterations in children with cancer are also associated with impaired nutritional status (Grain et al., 2023).

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 (Comeau, Epstein, & Migas, 2001; Gamper et al., 2012)? Few studies have quantitatively investigated chemosensory changes in these patients before. Skolin and colleagues found that children with cancer ($n = 10$) had higher thresholds (lower sensitivity) for bitter taste and made more taste recognition errors compared to controls (Skolin et al., 2006), 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 (van den Brink et al., 2021), 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 medications to be most frequently associated with smell and taste disorders, namely docetaxel, paclitaxel, nab-paclitaxel, capecitabine, cyclophosphamide, epirubicin, anthracyclines, and oral 5-fluorouracil analogues (Buttiron Webber, Briata, DeCensi, Cevasco, & Paleari, 2023).

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.

2. Methods

2.1. 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 and associated anti cancer treatment, were able to understand Dutch, and were 6–18 years old. Children younger than 6 years were not considered for inclusion as the validity of chemosensory tests in younger children is limited (Cavazzana et al., 2017; van den Brink, IJpma, Fiocco, Tissing, & Havermans, 2022). 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.

2.2. 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 acute lymphoblastic leukemia (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 (Vaira et al., 2022). The measurement was then scheduled with the patient's visit to the outpatient clinic for a regular consultation. In addition, patients were asked whether they had suffered from smell and/or taste problems and whether they had recovered from them.

2.3. Measurements

2.3.1. Smell function

Sniffin' Sticks (Burghart, Wedel, Germany) were used to determine smell function (Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997). 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 3 s. 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 (Croy et al., 2009). The odor pens contained a solution of PEA in a propylene glycol solvent, starting with a 4% odor solution and the further 7 solutions diluted at a 1:4 ratio, corresponding to 1 (i.e., 4% odor), 3, 5, 7, 9, 11, 13, and 15 points. 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.

Odor 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 (Schriever et al., 2018). Pencils were randomly presented at each test session. 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) (Gellrich et al., 2019).

2.3.2. Taste function

Filter-paper strips (Taste Strips, Burghart, Wedel, Germany) were used to determine taste recognition thresholds (Mueller et al., 2003). The test contained of 2 blank strips and 16 impregnated strips, which were impregnated with 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). Taste qualities were randomized within a concentration and then 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)) (van den Brink, IJpma, et al., 2022).

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 or not taste PROP is the result of three single nucleotide polymorphisms in the *TASR38* gene, and generally correlates with increased sensitivity to taste stimuli and other orosensory sensations (Bajec & Pickering, 2008; Hayes, Bartoshuk, Kidd, & Duffy, 2008). For the current study, we were interested if PROP tasters still had better taste sensitivity or experienced less taste loss. 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) (Keller, Steinmann, Nurse, & Tepper, 2002). 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 (Steiner, Glaser, Hawilo, & Berridge, 2001).

2.3.3. 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.

2.3.4. Related factors

2.3.4.1. Patient characteristics. Patient characteristics were derived from medical records and included: age, sex, diagnosis, and treatment protocol. All data was used anonymously during analysis.

2.3.4.2. Treatment intensity. Treatment intensity was rated independently by Mirjam van den Brink and Wim Tissing 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" (Kazak et al., 2012).

2.3.4.3. 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. Due to the large heterogeneity of our population, many different treatment protocols have been used, each coming with their specific chemotherapeutic agents, although individual agents are used in multiple protocols. Given the large number of chemotherapeutic agents and variability in the distribution of cumulative doses (as the dosage depends on body surface), 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. Chemotherapy is mainly given intravenously (in shot or over several hours, except for corticosteroids, mercaptopurine, and methotrexate (intravenous or oral) which are given mostly orally. See Supplementary Table 1 for a complete overview of chemotherapeutic agents used in the current study, including their mechanism of action and potential relationship with smell and taste function (Blaney, Helman, & Adamson, 2020, pp. 239–302; Buttiron Webber et al., 2023; Gamper et al., 2012).

2.4. 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), changes in appetite (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 Strip threshold 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 size. All statistical analysis was performed with IBM SPSS Statistics (version 26.0). A 5% alpha level was used.

3. Results

3.1. 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. Of all patients, 41.4% were PROP tasters. During the study period, 8 more patients left the study because they passed away ($n = 5$) or experienced too much burden ($n = 3$) but data collected up to that moment could be used.

3.2. Smell function

3.2.1. Longitudinal evaluation of smell function

Fig. 1A shows odor 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) (Fig. 1B). During active treatment (T0-2), THR scores also did not

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 (ALL)	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)

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 Fig. 1C, $p = 0.012$), which was not the case for patients with other diagnoses 3 months after treatment (Fig. 1D).

Fig. 2A shows odor ID scores over time, which did not change during active treatment (T0-2) or during maintenance phase (T3; Fig. 2B) or 3 months after treatment (Fig. 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, with lower scores for boys, younger children, and those who received vincristine.

3.2.2. *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., higher score on THR test) 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.

When focusing on various diagnoses, we observed that an increased smell sensitivity (i.e., higher score on THR test) 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%).

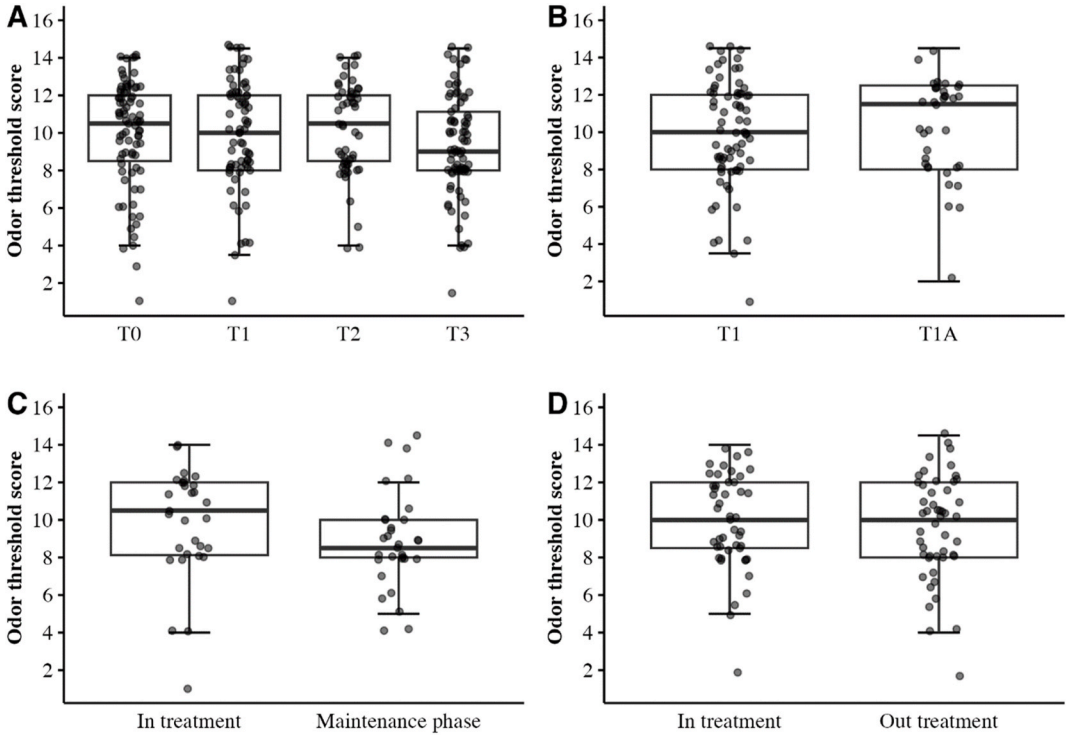

Fig. 1. Odor threshold scores during the study period at 6 weeks (T0), 3 months (T1), 6 months after starting chemotherapy (T2), and 3 months after termination of chemotherapy or maintenance phase for children with acute lymphoblastic leukemia (ALL) (T3) (panel A), for T1 and 7–21 days after T1 (T1A) specifically (panel B), separated for the last measurement in active treatment and maintenance phase for children with ALL (panel C, $n = 29$, $p = 0.012$), and for the last measurement in active treatment compared to 3 months after treatment for all other patients (panel D, $n = 47$). Boxplots show median score (midpoint of the scores), first quartile of the scores (Q1, lower boundary of the box), and 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.

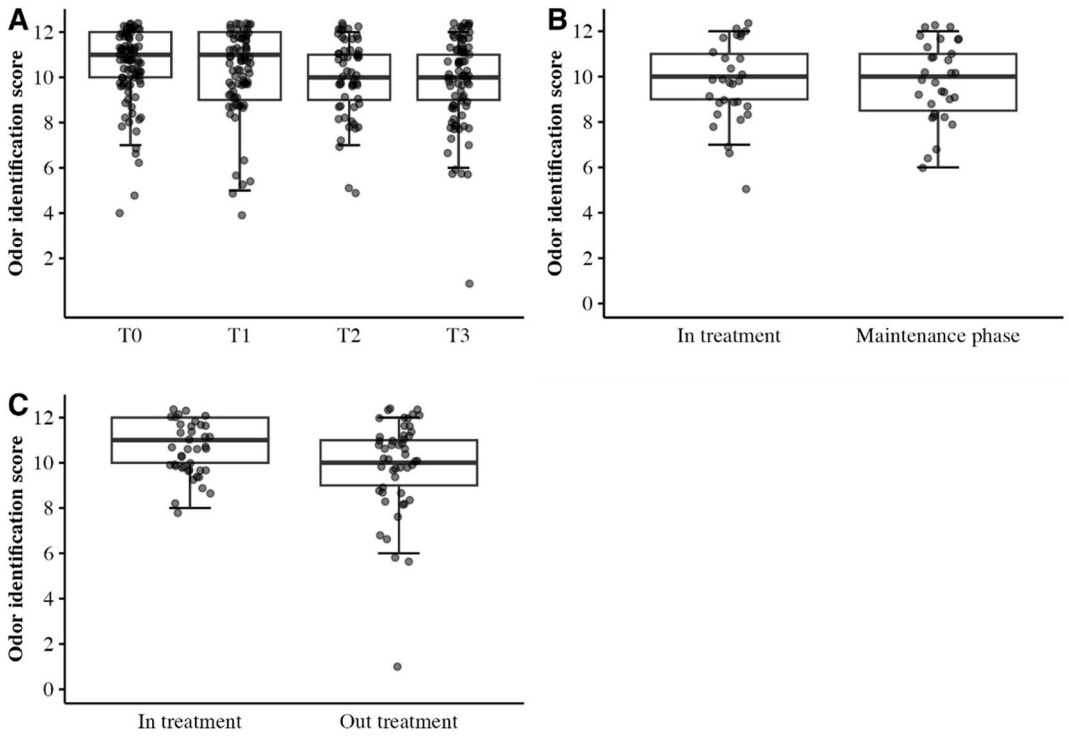

Fig. 2. Odor identification scores during the study period at 6 weeks (T0), 3 months (T1), 6 months after starting chemotherapy (T2), and 3 months after termination of chemotherapy or maintenance phase for children with acute lymphoblastic leukemia (ALL) (T3) (panel A), separated for the last measurement in active treatment and maintenance phase for children with ALL (panel B, $n = 29$), and for the last measurement in active treatment compared to 3 months after treatment for all other patients (panel C, $n = 40$).

Table 2
Percentage of smell function 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, $n = 50$.

3.2.3. 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%).

3.3. Taste function

3.3.1. Longitudinal evaluation of taste function

Fig. 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 (Fig. 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, with girls and PROP tasters having higher taste scores than boys and non-tasters, respectively. Administration of etoposide ($B = -1.0$, $SE = 0.5$, $p = 0.035$) in the past month has been associated with lower total taste scores, whereas corticosteroids ($B = 1.1$, $SE = 0.3$, $p = 0.001$) and mercaptopurine ($B = 1.0$, $SE = 0.4$, $p = 0.021$) were associated with higher total taste scores compared to children not receiving those drugs. Total taste scores were significantly higher at T3 (i.e., during maintenance phase (Fig. 3C, $p = 0.023$), or after treatment (Fig. 3D, $p = 0.005$)) relative to T2. Also, sweet, sour, salty, and bitter taste thresholds 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 Fig. 1.

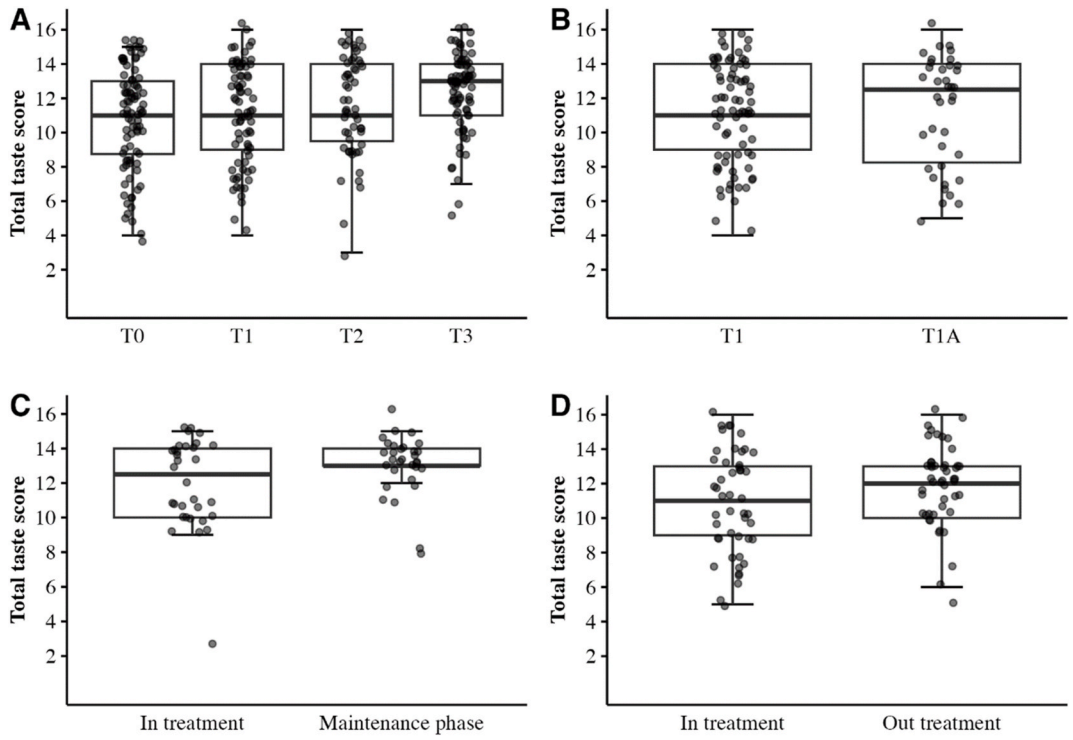

Fig. 3. Total taste scores during the study period at 6 weeks (T0), 3 months (T1), 6 months after starting chemotherapy (T2), and 3 months after termination of chemotherapy or maintenance phase for children with acute lymphoblastic leukemia (ALL) (T3) (panel A), for T1 and 7–21 days after T1 (T1A) specifically (panel B), separated for the last measurement in active treatment and maintenance phase for children with ALL (panel C, $n = 31$, $p = 0.023$), and for the last measurement in active treatment compared to 3 months after treatment for all other patients (panel D, $n = 47$, $p = 0.005$).

3.3.2. *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, a decrease in taste perception was 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 function 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, $n = 50$.

3.3.3. *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 taste perception 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%).

3.4. *Appetite*

The presence of self-reported appetite changes varied between 69.0% and 88.6% during active treatment (T0-2) and was lowest 3 months after treatment (54.0%, T3[b]) (see Table 4). These changes were described both as an increase or decrease, with the presence of less appetite gradually decreasing with time and more appetite increasing over time. Changes in appetite were not associated with smell and taste function during active treatment.

4. 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

Table 4
Self-reported changes in appetite.

	T0	T1	T1A	T2	T3[a]	T3[b]
Appetite ranking						
Very good (n, %)	11 (12.1)	8 (10.1)	5 (12.5)	8 (13.8)	6 (18.8)	10 (20.0)
Good (n, %)	34 (37.4)	35 (44.3)	21 (52.5)	36 (62.1)	23 (71.9)	30 (60.0)
Moderate (n, %)	27 (29.7)	25 (31.6)	12 (30.0)	9 (15.5)	2 (6.3)	5 (10.0)
Bad (n, %)	13 (14.3)	10 (12.7)	1 (2.5)	4 (6.9)	1 (3.1)	3 (6.0)
Very bad (n, %)	6 (6.6)	1 (1.3)	1 (2.5)	1 (1.7)	0 (0.0)	2 (4.0)
Self-reported changes in appetite						
Appetite changes y/n (n, %)	77 (84.6)	70 (88.6)	29 (72.5)	40 (69.0)	21 (65.6)	27 (54.0)
(Much) more than before (n, %)	21 (27.3)	20 (28.6)	13 (44.8)	18 (45.0)	11 (52.4)	11 (40.7)
As before (n, %)	7 (9.1)	11 (15.7)	1 (3.5)	6 (15.0)	6 (28.6)	2 (7.4)
(Much) less than before (n, %)	49 (63.6)	39 (55.7)	13 (44.8)	16 (40.0)	4 (19.0)	14 (51.9)

[a] Maintenance phase (ALL), $n = 32$.
[b] 3 months after treatment, $n = 50$.

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.

4.1. Changes in smell

Smell sensitivity of children with ALL was higher during active treatment compared to maintenance phase. Such an increased smell sensitivity during treatment seems in line with our previous results showing better smell sensitivity in children with cancer compared to healthy controls (van den Brink et al., 2021). In contrast, studies among adults undergoing chemotherapy did not find changes in smell sensitivity or showed a decrease during treatment and an increase afterwards (IJpma et al., 2017; Postma, Kok, de Graaf, Kampman, & Boesveldt, 2020; Steinbach et al., 2009). An increased smell sensitivity occurred mainly in children with hematological cancers, which suggests a role for corticosteroids. 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 (Meunier et al., 2020). 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 (Huang et al., 2012; Ishinaga et al., 2018). It is important to note that, in addition to the anti-inflammatory activity, corticosteroids may improve olfaction through increasing nasal patency and modulate the function of olfactory receptor neurons (Wolfensberger & Hummel, 2002). 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 tactile stimuli. Particularly "hyperolfaction" also seems to occur during pregnancy. Although there is little evidence for increased smell sensitivity, pregnant women do perceive changes in their smell function, rating odors as more intense and finding most odors less pleasant (Cameron, 2014; Hummel, von Mering, Huch, & Kölble, 2002; Nordin et al., 2005, 2007). 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 (Hummel et al., 2002; Olofsson, Broman, Wulff, Martinkauppi, & Nordin, 2005).

Odor identification ability showed no significant 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. We found a better performance among older children and girls compared to boys, which is a well-known phenomenon in healthy children as well (Cameron, 2018). 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 (Ovesen, Sørensen, Hannibal, & Allingstrup, 1991; Steinbach et al., 2009).

4.2. Changes in taste

Although the current study lacks a measurement before chemotherapy, taste sensitivity appears to decrease shortly after starting chemotherapy and recovers within 3 months after its stop. Such a pattern has been also found among adult patients undergoing chemotherapy (Steinbach et al., 2009). 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. 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 (Buttiron Webber et al., 2023; Gamper et al., 2012). 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 (Tirgan, 2005). Unfortunately, the current sample size does not allow for testing possible interactions between cytotoxic agents. We also could not take dosage into account or 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.

Some taste loss was present in approximately 20% of all children with cancer, whereas self-reported taste changes ranged between 60 and 80%. Similar to adult patients undergoing chemotherapy, objective measures of smell and taste function did not seem to correspond with self-report in children with cancer (Ijpma et al., 2017; Postma et al., 2020). It is well-known that people tend to experience taste loss when they actually suffer from smell loss which in turn could affect the flavor of food (Deems et al., 1991; Soter et al., 2008). 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 (van den Brink, Ter Hedde, et al., 2022). 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.

4.3. Strengths, limitations, and future directions

This is the first study to describe longitudinal changes in smell and taste function in a prospective cohort of children with different types of cancer both during and after chemotherapy. 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, taste function was measured using taste recognition thresholds only. However, suprathreshold tests (i.e., higher stimuli concentrations) may correspond better with real life taste exposures and could possibly identify taste confusions in cancer patients. Lastly, 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 on food intake. 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 (de Vries et al., 2017; DeWys & Walters, 1975; Grain et al., 2023; Nolden, Hwang, Boltong, & Reed, 2019). 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.

4.4. Conclusions

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 few 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 termination 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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Ethical statement

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.

CRediT authorship contribution statement

Mirjam van den Brink: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Remco C. Havermans:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Marta Fiocco:** Writing – review & editing, Methodology, Formal analysis. **Wim J.E. Tissing:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

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Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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