Predictive factors of involuntary weight loss in patients with smell and taste disorders*

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Abstract

Background: Chemosensory dysfunction (olfaction, taste, and trigeminal) affects quality of life, potentially impacting eating behaviors. We investigated which factors are associated with weight loss in patients with smell and taste disorders.

Methods: Retrospective study of consecutive adult patients seen in the smell and taste clinic during a 10-year period. Patients were asked about smell, flavor and taste impairment. Psychophysically, smell was assessed with Sniffin' Sticks, flavor with a retronasal test, and taste with Taste Strips.

Results: A total of 554 patients (313 females) were included with a median age of 51 years (IQR 23). Seventy-six (13.7%) reported involuntary weight loss (median 6 kg, IQR 6) due to chemosensory disorders. The odds of losing weight were 2.1 times higher when patients reported subjective changes in flavor perception. Parosmia was a significant predictor of weight loss. Patients with symptoms lasting longer than two years were less likely to present with weight loss. Post-traumatic chemosensory dysfunction was a significant predictor of losing weight. On psychophysical testing, the probability of a patient losing weight increased by 8% for every 1-unit reduction in Taste Strips score.

Conclusion: Factors associated with weight loss were self-reported changes in flavor perception, parosmia, duration of symptoms for less than two years, head injury, and psychophysically measured low Taste Strips score. These data help to identify patients at risk of weight loss from smell or taste impairment.

Key words: olfaction disorders, taste disorders, flavor disorders, weight loss

Introduction

Chemical senses (olfaction, taste, and trigeminal) are important for eating, avoiding danger and social communication ⁽¹⁾. The trigeminal system senses pain, temperature, and nasal airflow. It perceives food and drink texture ^(2,3), whereas the basic tastes (salt, sweet, sour, bitter, and umami) are detected by the gustatory system ⁽⁴⁾. The olfactory system can discriminate between a vast array of odors (orthonasal pathway) and food aroma molecules streaming from the oral cavity to the nasopharynx and then to olfactory receptors in the nose. Activation of these receptors produces flavor perception beyond the basic taste qualities via the retronasal pathway ^(5,6). Smell and taste dysfunctions are common, affecting approximately 20% of the general population over the age of 40 years ^(7,8). Patients with these disorders may experience one or more of olfactory loss (complete or partial), parosmia (distorted odorant perception in odor source presence), phantosmia (smell perception without odor source), flavor loss or distortion

(diminished or distorted retronasal perception of food molecules), gustatory loss (complete or partial loss of salty, bitter, sweet, and/or sour perception), parageusia (distorted taste perception in stimulus presence) or phantogeusia (taste and oral sensation without stimulus). Subjective alteration of trigeminal sensation is rarely reported and not well characterized clinically ⁽⁹⁾. These symptoms may be caused by different etiologies, including sinonasal disease, head trauma, upper respiratory tract infection, drugs, neurological disorders, or can be idiopathic ⁽¹⁰⁾. Testing these senses separately is often required because self-reporting might be insufficient for localization and quantification of the deficit ^(11,12). For example, flavor is often confounded with gustatory function since flavor is commonly named taste, as patients are unfamiliar with this distinction ⁽¹³⁾.

Chemosensory dysfunction affects quality of life (14–17). One of the major impacts concerns eating behavior. Food perception is a multisensory experience; thus, chemosensory dysfunction can alter both anticipation (orthonasal smell) and experience of food and drink (retronasal smell and taste) (18). The relationship between chemosensory dysfunction and alteration of appetite and diet is well documented in the literature, with reported frequencies of 18-67% (10,17,19-25). Resultant changes in eating behavior may lead to altered nutrition and eventually to weight gain or loss. Some studies highlight the increased risk of malnutrition in individuals suffering from altered smell or taste ^(10,17,19,23,25-27). However, the evidence is scarce, and it is unclear which chemosensory changes put patients at higher risk for weight loss. For example, subjective flavor perception is a crucial component of food enjoyment ⁽²⁸⁾, but the association between subjective flavor loss and measured flavor function by a retronasal olfactory test and weight loss has never been tested. Based on our clinical experience and case reports ⁽²⁹⁾, we hypothesize that patients with true taste or gustatory dysfunction are more prone to weight loss.

Chronic disease-related malnutrition increases morbidity and mortality with socioeconomic impacts ⁽³⁰⁾. This study aims to investigate the association between weight loss and self-reported chemosensory complaints, chemosensory test results, and putative etiologies.

Materials and Methods

Study design

This is a retrospective study based on the extended version of a questionnaire created by the German Working Group for Taste and Smell Disorders (see Supplementary Material) to assess patients' smell and taste complaints ⁽³¹⁾. This questionnaire was given to all patients seen in the Smell and Taste Clinic at Geneva University Hospitals (tertiary care facility) in Switzerland between 2003-2012. The study was approved by the institutional ethics review board and was conducted according to the Declaration of Helsinki on Biomedical Research Involving Human Subjects (Institutional review board approval No: 13-161).

Subjects

Five hundred fifty-five consecutive adult patients presenting with chemosensory complaints completed the questionnaire. Patients who reported weight loss for reasons other than chemosensory dysfunction were excluded.

Outcome measures

Questionnaire

This two-part questionnaire completed by the patient (part I) and the physician (part II) is an extension of an existing questionnaire ⁽³¹⁾. Part I includes detailed questions about chemosensory complaints and symptoms such as olfactory dysfunction, parosmia, phantosmia, subjective flavor loss, flavor distortion, gustatory loss, para- or phantogeusia, unusual oral sensation, and duration of symptoms. The physician recorded self-reported involuntary weight loss (in kilograms) due to the chemosensory problem, comorbidities, physical examination findings, chemosensory psychophysical test scores (orthonasal smell, retronasal smell, and taste), and putative etiology. The questionnaire is available in the Supplementary Material in its original French form.

Orthonasal smell test

We performed the Sniffin' Sticks test (Burghart, Wedel, Germany), which comprises olfactory threshold (T), discrimination (D), and identification (I) subtests ⁽³²⁾. The TDI score was calculated as the sum of the results obtained from the three subsets. In the case of results for each nostril separately, we chose the best side's score as the overall value.

Retronasal smell test

We assessed retronasal olfactory function by applying the standardized "taste powder" tool. This tool uses food-related flavors in powder form applied at the posterior part of the tongue. The participants then select the corresponding flavor from four descriptors ⁽³³⁾. The retronasal score is the sum of the correct answers from ten trials.

Taste test

Taste evaluation was based on filter paper Taste Strips (Burghart, Wedel, Germany) impregnated with four concentrations of the four basic taste qualities. We applied the test stimuli in random order with four increasing concentrations for each of the four tastes and on both sides of the anterior third of the extended tongue. A total score was obtained by summing the correct answers ^(34,35).

Statistical analysis

We used Pearson's chi-square and Mann-Whitney test to uncover differences between patients with and without weight loss regarding age, gender, chief complaint, chemosensory symptoms, duration, putative etiologies, diagnosed depression, and Table 1. Logistic regression models for weight loss prediction based on chief complaints, symptoms and putative etiologies (n = 508).

	1	Univariable analysis Multivariable ana			ultivariable analy	sis
Variables	OR	95% CI	p-value	OR	95% CI	p-value
Smell loss (yes / no)	1.79	0.88, 3.62	0.11			
Flavor complaint (yes / no)	2.2	1.25, 3.88	0.006	2.1	1.15, 3.83	0.012
Taste complaint (yes / no)	1.7	1.02, 2.86	0.043	1.42	0.83, 2.44	0.2
Parosmia (yes / no)	2.06	1.17, 3.63	0.013	2.22	1.17, 4.2	0.015
Phantosmia (yes / no)	0.67	0.35, 1.26	0.21	0.51	0.25, 1.01	0.052
Etiologies (reference group = idiopathic)			0.005			0.003
Sinonasal	0.45	0.16, 1.27	0.132	0.46	0.16, 1.32	0.15
Post-traumatic	2.17	1.1, 4.25	0.025	2.08	1.04, 4.16	0.039
Post-infectious	1.07	0.47, 2.44	0.868	0.76	0.32, 1.81	0.54
Others	1.96	0.93, 4.16	0.078	2.26	1.04, 4.91	0.04
Duration of symptoms (> 2 years / < 2years)	0.44	0.23, 0.85	0.014			
Age (in years)	1.01	0.99, 1.03	0.21			
Depression (yes / no)	0.99	0.32, 3.05	0.99			

OR odds ratio, CI confidence interval.

Table 2. Logistic regression models for weight loss prediction based on psychophysical test scores (n = 144).

		Univariable analys	Multivariable analysis			
Variables	OR	95% CI	p-value	OR	95% CI	p-value
Sniffin' Sticks TDI score	0.99	0.96, 1.02	0.41	1	0.96, 1.05	0.71
Retronasal "powder tool" score	1.01	0.89, 1.13	0.99	1.06	0.88, 1.27	0.48
Taste Strips score	0.93	0.89, 0.98	0.006	0.92	0.87, 0.98	0.006

OR odds ratio, CI confidence interval, TDI threshold, discrimination and identification.

chemosensory test results. When the expected frequencies were small, we used Fisher's exact test instead of Pearson's chi-square test. Post-hoc analysis for Pearson's chi-square was performed using squared adjusted residuals (or z-square), which were transformed into p-values using a formula integrated into SPSS. To reject the null hypothesis, the p-value of 0.05 was divided by the number of associations to determine the adjusted p-value cut-off as described by Beasley et al. (36). We used univariable logistic regressions to verify these associations, and by consulting stepwise regression, we created two multivariable regression models. However, to have adequate statistical power for the model in Table 1 we could reasonably accommodate, at most, eight independent variables (putative etiologies accounted for four independent variables), and thus we created a nested model by removing smell loss and duration variables. We ran a likelihood ratio test comparing the model with more predictors (full model, Akaike information criterion AIC=395.09) with the model with fewer predictors (nested model, AIC=395.29), and we found that smell loss and duration did not give extra information to predict weight loss when all other variables were taken into account

(p-value=0.12). All assumptions for the logistic regression model were checked and satisfied. We performed subgroup analysis based on etiology, but no additional information was obtained. We employed SPSS version 26 and an up-to-date version of R (version 1.2.5033, "https://www.r-project.org"). The statistical significance was defined as p<0.05 (two-sided). Figures were created with Prism 8.0 and Adobe Illustrator. Data of patients who did not answer, answered "I do not know", gave uninterpretable answers (e.g., multiple choices selected

gave uninterpretable answers (e.g., multiple choices selected when only one was authorized), or did not undergo chemosensory tests were considered as missing values. The remaining data regarding weight loss were n=554, while data for 508 participants were free of missing values for all the variables assessed in the model of Table 1. Missing values were detected for patients who did not undergo the full TDI battery test (remaining=512), retronasal test (remaining=460), and Taste Strips test (remaining=198) and thus, data for 144 participants were free of missing values for the three chemosensory tests in the model of Table 2.

Table 3. Population characteristics and comparisons.

	Weight loss			
Variables	Yes	No	p-value	
Age in years, median (IQR)	52 (22.5)	50 (23.75)	0.28	
Gender, No. (%, female)	42/76 (55)	271/478 (57)	0.82	
Chief complaint, No. (%)				
Smell	62/76 (82)	423/475 (89)	0.06	
Flavor	55/76 (72)	265/475 (56)	0.008	
Taste	32/76 (42)	138/475 (29)	0.024	
Chemosensory symptoms, No. (%)				
Parosmia	22/76 (29)	75/478 (16)	0.006	
Phantosmia	13/76 (17)	113/478 (24)	0.21	
Smell loss	63/76 (83)	387/478 (81)	0.77	
Flavor loss	50/76 (66)	334/478 (70)	0.55	
Flavor distortion	52/70 (74)	295/459 (64)	0.1	
At least one basic taste altered	26/76 (34)	155/478 (32)	0.55	
Qualitative taste complaint and oral sensation, No. (%)				
Burning	9/75 (12)	59/478 (12)	0.9	
Bitter	12/75 (16)	54/478 (11)	0.29	
Salty	4/75 (5)	30/478 (6)	0.99	
Sour	6/75 (8)	43/478 (9)	0.75	
Xerostomia	29/75 (39)	138/478 (29)	0.06	
Foreign body	6/75 (8)	37/478 (8)	0.99	
Etiologies, No. (%)			0.006	
Sinonasal	5/56 (9)	91/404 (23)	0.019+	
Post-traumatic	23/56 (41)	88/404 (22)	0.002+	
Post-infectious	10/56 (18)	74/404 (18)	0.93+	
Idiopathic	18/56 (32)	151/404 (37)	0.45+	
Duration > 2 years, No. (%)	13/76 (17)	148/457 (32)	0.01	
Depression, No. (%)	4/76 (5)	26/478 (5)	0.99	
Median psychophysical test scores, median (IQR)				
Sniffin' Sticks TDI score	19.12 (17.12)	20 (17.5)	0.53	
Threshold	2.25 (3.5)	2.25 (5.25)	0.3	
Discrimination	8 (6)	8 (7)	0.67	
Identification	8 (8)	9 (7)	0.6	
Taste Strips score	18 (15)	20 (10)	0.027	
Retronasal "powder tool" score	5 (4)	5 (4)	0.88	

IQR interquartile range, TDI threshold, discrimination and identification. + The adjusted level of significance is p < 0.0063 for Pearson's chi-square posthoc analysis.

Results

Demographics and clinical findings in patients with and without weight loss

The median age in patients with (n=76) and without (n=478) weight loss was 52 (IQR 22.5) and 50 (IQR 23.75) years, respectively. Both groups had a balanced number of females. In these

groups, we analyzed the association between weight loss and subjective chief complaints (smell, flavor/aroma, taste), disease duration, type of chemosensory symptoms (an/hyposmia, a/hypogeusia, parosmia, phantosmia, little or no flavor/aroma perception, burning mouth, xerostomia, sensation of oral foreign body), depression, putative etiologies, and psychophysical tes-



Figure 1. Findings of chemosensory workup between patients with (blue) and without (white) weight loss. (a) Comparison of relative frequencies between patients' chief complaints and weight loss. (b) Association between qualitative olfactory dysfunctions (parosmia and phantosmia), duration of symptoms and weight loss. (c) Comparison between chemosensory dysfunction putative etiologies and weight loss. Pearson's chi-square test results indicate an association between weight loss and etiologies. Post-hoc analysis yielded a significant difference only in the post-traumatic group. (d) Presentation of chemosensory test scores with violin plots in patients with and without weight loss. (e) Absolute frequency of subjects presenting different degrees of weight loss in kilograms since the onset of the chemosensory complaint. Significant differences between the two groups are indicated by asterisks (* p-value < 0.05 for all analyses except post-hoc analysis in Figure 1c, where the adjusted level of significance is p-value < 0.0063). TDI threshold, discrimination, and identification.

ting of orthonasal (TDI), retronasal smell and taste (Taste Strips) function. Figure 1 illustrates the significant associations, while Table 3 provides detailed information on these associations. Regarding putative etiologies, only trauma was associated with weight loss (squared adjusted residuals=10, p-value=0.002, ad-justed p-value cut-off=0.0063) (Figure 1c). Although the median Taste Strips scores were close (18 vs. 20), the two groups showed different distributions (bi-modal vs. uni-modal, respectively), and this difference in medians was significant (p-value=0.027) (Figure 1d). The median weight loss was 6 kilograms (IQR 6) over 3 months (n=15), 4-6 months (n=9), 6-12 months (n=25), 12-24 months (n=11), and 36 months (n=1). One patient lost 60 kilograms after bariatric surgery and was excluded. Measured overall olfactory function (TDI score) and subscores (T, D and

I) did not differ between groups (Table 3). TDI patterns such as low threshold and elevated discrimination and identification or inverse have been described to help diagnose etiologies ⁽³⁷⁾. In our series, little doubt about diagnosis existed, and few patients had clear patterns. As a consequence, no TDI pattern analysis was done.

Univariable analysis and multivariable logistic regression to predict weight loss

For subjective chief complaint, we found that the odds of losing weight were 2.2 and 1.7 times higher for patients who reported alteration of flavor and taste, respectively (p-value=0.006; 95% Cl 1.25-3.88 and p-value=0.043; 95% Cl 1.02-2.86). Regarding symptoms, the odds of weight loss were twice as high for

patients who reported parosmia (p-value=0.013; 95% Cl 1.17-3.63). Furthermore, patients with symptoms for more than two years were 56% less likely to lose weight compared to patients with symptoms for less than two years (p-value=0.014; 95% CI 0.23-0.85). Regarding putative etiologies, post-traumatic patients were at greater risk for developing weight loss (OR 2.17; p-value=0.025; 95% CI 1.1-4.25) when compared with the reference group (idiopathic). We controlled for age as a possible predictor of weight loss, but the association was non-significant (p-value=0.21; 95% CI 0.99-1.03). Thirty patients were diagnosed with depression; we found no association between depression and weight loss (p-value=0.99; 95% CI 0.32-3.05). After controlling for the other variables of the multivariable model in Table 1, subjective changes in flavor perception remained a significant predictor of weight loss (OR 2.1; p-value=0.012; 95% CI 1.15-3.83). However, subjective changes in taste perception proved non-significant (p-value=0.2; 95% CI 0.83-2.44). Regarding chemosensory symptoms, self-reported parosmia continued to be a significant predictor (OR 2.22; p-value=0.015; 95% CI 1.17-4.2), while phantosmia remained non-significant (p-value=0.052; 95% CI 0.25-1.01). The post-traumatic group was twice as likely to lose weight than the reference group (p-value=0.039; 95% CI 1.04-4.16) (Table 1).

We examined measured function by means of TDI, retronasal, and Taste Strips scores as predictors of weight loss in a multivariable model. The probability of weight loss increased by 8% for every 1-unit reduction in Taste Strips score adjusted for all other variables (p-value=0.006; 95% CI 0.87-0.98). We did not find a significant association between weight loss and other psychophysical test scores (Table 2).

Discussion

The main findings of this study were twofold: first, approximately 15% of patients with chemosensory disorders lost weight; and second, self-reported impaired flavor perception, parosmia, duration of symptoms less than two years, low measurable gustatory function, and post-traumatic etiology were associated with weight loss. In contrast, reduced psychophysically measured olfactory function did not favor weight loss. These findings may help to identify patients at risk of weight loss from chemosensory disorders.

One in seven patients with chemosensory disorders experienced weight loss and thus, in line with previously published data ^(17,19), the majority of patients with chemosensory disorders do not lose weight. However, when considering that 20% of the general population has smell and taste disorders, it is important to detect those at risk. This study aimed to identify findings in smell and taste workup that may predict weight loss, with its resultant socioeconomic impact and increased morbidity and mortality. Evidence in the literature is scarce; results and methods are heterogeneous, leading to clinical uncertainty about how to identify patients at risk of weight loss.

Although altered nutrition has been studied with orthonasal smell and taste tests, there is a lack of evidence in the literature about the link between flavor perception, measured by psychophysical tests, and weight loss. We found that patients with flavor issues as chief complaint were 2.1 times more likely to lose weight even after controlling for confounding factors. However, this finding was not supported by retronasal smell testing results, which may be due to the rather limited ten-item screening test. More extended retronasal testing may reveal an association between weight loss and retronasal function. It is also worth noting that flavor, as perceived by the retronasal route, is generally confused with basic taste detected in the oral cavity as the general population is unfamiliar with this distinction ⁽¹³⁾. The question used might be too vague for patients to understand the concept of flavor. However, further detailed questions about taste and flavor loss or distortion did not show differences between patients with and without weight loss. It remains possible that taste dysfunction, as measured by Taste Strips, could explain this finding.

Regarding taste and its impact on weight loss, we analyzed other modalities contributing to flavor perception because these chemical senses interact closely. The hypothesis of mutual chemosensory weakening is based on the projection of the three chemical senses to the orbitofrontal cortex, which is considered the secondary olfactory and gustatory cortex (38,39). Mazzola et al. found that the mid-dorsal insula, which plays an essential role in flavor perception, has a spatial overlap between olfactory, gustatory, and oral somatosensory representation ⁽⁴⁰⁾. Migneault-Bouchard et al. previously showed that the three chemical senses tend to decrease proportionally across different smell loss etiologies (41). By controlling for ortho- and retronasal smell with psychophysical tests, which contribute highly to flavor perception, we identified the predominant effect of taste dysfunction in weight loss. Our results suggest a negative association between weight loss and Taste Strips score. This contrasts with findings from Roos et al., who did not find a significant correlation between Taste Strips score and body mass index (BMI) (27), and De Jong et al., who conducted a study in an elderly population and found no association between taste score and energy intake or BMI ⁽²⁰⁾. However, they used an unvalidated taste test composed of commercially available products, potentially triggering multiple aspects of the chemical senses. Both studies had sample sizes too small to detect subtle differences in taste function. In contrast, the present study was powered to detect a smaller effect size, and the test used was more extensive and validated. In line with our clinical experience in daily practice, we bring new evidence that a low Taste Strips score could be an independent risk factor for weight loss. While patients with taste-related complaints exhibited a higher risk of weight loss in the univariable model, this association did

not reach statistical significance in the multivariable model. As previously mentioned, a possible explanation could be the confounding of flavor and taste, highlighting the critical importance of precise psychophysical measurement of both senses individually to identify patients at risk.

Patients suffering from parosmia are at greater risk of weight loss, even when controlling for other chemosensory symptoms and putative etiologies. Mattes et al. highlighted the greater risk of dietary dissatisfaction and weight loss due to smell and taste distortions compared to complete or partial loss of these functions ⁽²³⁾. They argued that distortions are more challenging to cope with, and patients begin to develop aversions to specific foods. Patients who report parosmia have a more significant reduction in quality of life than individuals with simple loss of smell (16,42,43). Anecdotal reports show that parosmia may induce near-life-threatening weight loss that can only be overcome by wearing a nose clip during eating (44). Parosmia patients present with higher rates of mild depression and more difficulty coping with their olfactory dysfunction ⁽¹⁶⁾. According to our results, depression is not a confounding factor between weight loss and parosmia. This supports the current literature that parosmia is an independent risk factor for weight loss.

Olfaction is an important component of food perception and enjoyment. Approximately 70% of people with smell dysfunction report reduced pleasure in eating ^(14,22–24). This reduction in food enjoyment forces patients to change their eating behavior and develop strategies to enhance food perception. Common strategies include adding more spices, sweeteners, or salt and focusing on food texture ^(15,45). These strategies may be sufficient for individuals with simple olfactory loss, to alter their diet and prevent malnutrition.

Our results suggest that symptom duration for more than two years reduces the risk of weight loss. The importance of chemosensory senses in everyday life may decrease as a result of a "response shift", defined as a recalibration of internal values over time to incorporate a loss of function after neurological injury ⁽⁴⁶⁾. Our data are consistent with most previous findings (10,20,22,23,25). Neither self-reported smell loss nor low TDI score is associated with weight loss. Aschenbrenner et al. speculated that decreased or absent olfactory function could result in decreased weight ⁽¹⁹⁾. However, patients with isolated congenital anosmia have no weight difference to age-matched controls (47). Roos et al. measured TDI scores in patients with Parkinson's disease and found a positive correlation between TDI score and BMI (27). However, the authors controlled only for disease duration, not energy expenditure, which has been shown to increase during the course of the disease and is probably the main reason for weight loss (48).

Post-traumatic patients were at higher risk of losing weight compared to other putative etiologies, regardless of the impact of chemosensory symptoms. In these patients, chemosensory disorders may be the result of sinonasal olfactory tract disruption, injury of the olfactory nerve or of the primary and secondary cortex (49). Interestingly, Crenn and colleagues showed in a longitudinal study that 30% of patients with severe head trauma lose weight. They argue that this may be due to disruption of pathways regulating food intake ⁽⁵⁰⁾. In our study, 20% of patients with post-traumatic chemosensory loss lost weight, which seems to be independent of other chemosensory symptoms. Our study has several limitations. A retrospective study has known inherent biases. We minimized selection bias by including consecutive patients. Data were carefully and regularly reported in the study database. However, weight loss was self-reported in a single consultation and not measured and documented in follow-up visits. Additionally, we did not ask patients about weight gain, which could also result from altered dietary behavior. Although several confounders were included in our regression models, we cannot exclude others that may influence our conclusions, such as trigeminal dysfunction. Also, we have to critically interpret the external validity of our analysis. Although one in five people in the general population have chemosensory disorders, only a few are seen in specialized clinics. These patients may be more motivated because of greater functional impact. As a result, conclusions can be drawn for patients seeking medical help for their chemosensory complaints but not necessarily for the general population.

Conclusion

We highlight the specific findings in chemosensory disorders that are more likely to be associated with weight loss, namely self-reported changes in flavor perception, parosmia, duration of symptoms for less than two years, head injury, and when the Taste Strips score is low. These patients may need dietician review to avoid malnutrition.

Authorship contribution

Conceptualization, Methodology: DD, JWH, BNL, Data acquisition, analysis and interpretation: DD, JWH, BNL, MH, JR; Writing original draft preparation: DD, JWH; Writing - review and editing: All authors; Supervision: GC, JR, BNL.

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Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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