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NUTRI-HAB
– Multidisciplinary nutritional rehabilitation and systematic assessment of rehabilitation needs in head and neck cancer survivors

PhD thesis

UNIVERSITY COLLEGE COPENHAGEN

REHPA
The Danish Knowledge Centre for Rehabilitation and Palliative Care

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Preface

This public sector industrial PhD project is a collaboration between the Bachelor's Degree Programme in Nutrition and Health at University College Copenhagen (UCC; previously Metropolitan University College) and REHPA, The Danish Knowledge Centre for Rehabilitation and Palliative Care (REHPA).

In hindsight, the very first seeds for this PhD were planted during my final year of the MSc. programme in Clinical Nutrition at University of Copenhagen in 2010-2011. In collaboration with a fellow student, I conducted an observational prospective clinical study on refeeding complications in head and neck cancer patients[1] as our MSc. thesis project. During six months of daily data collection at the Department of Otorhinolaryngology, Head and Neck Surgery & Audiology, Rigshospitalet, the wide-ranging consequences of eating problems in this population became evident to me. What also struck me was how easy needs for supportive care could go unrecognised if health professionals didn't address them directly, since many patients were hesitant to address the problems themselves.

In addition to acquainting me with the challenges of this patient group, the MSc. thesis project also triggered my interest in research. While being determined to apply for enrolment in the PhD programme one day, I decided to seek out other challenges immediately after completing my MSc. I was employed as lecturer and subsequently senior lecturer at UCC primarily teaching the future clinical dietitians and being involved in various smaller research, development, and student projects.

Through one of these, I was introduced to Ann-Dorthe Zwisler who was in the process of establishing REHPA. It led to collaboration on a study of current practice within dietary interventions in cardiac rehabilitation in Danish hospitals and municipalities[2]. Upon the decision of extending the collaboration to a PhD project, I had to admit, that despite having my curiosity for rehabilitation awakened through the project about services for patients with ischemic heart disease, my research heart was still with the head and neck cancer population.

Luckily, this idea for research topic was supported by UCC and REHPA, and a project group was established. The supervisors included Ann-Dorthe and Karin B. Dieperink from REHPA, Anne Marie Beck from UCC, and Irene Wessel from Rigshospitalet, who I also collaborated with on the MSc. thesis project. Together, we designed the NUTRI-HAB project and received funding from Innovation Fund Denmark through the public sector Industrial PhD Programme.

As an industrial PhD student, I have been employed by UCC throughout my PhD programme, and my working time has been divided by UCC and REHPA. Being an industrial PhD student, I have not had teaching obligations at University of Southern Denmark. Since I have five years of teaching experience at UCC prior to the PhD programme, it was decided that my teaching and dissemination activities, in addition to peer presentations at conferences etc., primarily should include patient education at REHPA and project-related supervision of students either during clinical/practical placements or during their BSc. thesis projects. Hence, throughout the PhD programme, I have been functioning as clinical dietitian at REHPA and delivered group-based patient education sessions on nutrition in relation to cancer and few individual dietary counselling sessions at REHPA's residential rehabilitation programmes for different groups of cancer patients and survivors. Furthermore, I have delivered the nutritional interventions in the studies included in the thesis with some assistance from colleagues and student assistants.

During the PhD programme, I have participated actively in relevant research environments and scientific networks. I spend five months with Professor Liz Isenring and the rest of Bond University Nutrition & Dietetics Research Group in Gold Coast, Australia. This collaboration has so far led to one published article[3] and one manuscript in preparation. Furthermore, I have participated actively in a newly established Danish multidisciplinary research network on late effects and quality of life in head and neck cancer[4], and since 2015, I have been a member of the board of the Danish Society for Clinical Nutrition and Metabolism.

The PhD programme has been completed from 1 May 2017 to 31 May 2020.

Marianne Boll Kristensen
Copenhagen, May 2020

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Furthermore, many people have contributed to the project's success, and I am grateful to every one of them. First, my sincere thanks to Cecilie Sveistrup, former head of the Bachelor's Degree Programme in Nutrition and Health at University College Copenhagen for giving me the opportunity to complete this PhD and for support along the way.

The last three years have been a rewarding journey, and this is not least because of my supervisors Ann-Dorthe Zwisler, Anne Marie Beck, Irene Wessel, and Karin B. Dieperink. I am sincerely grateful that you have taken me under your wings and shared your knowledge and expertise with me. Thank you for your invaluable support, encouragement, constructive feedback, and the inspiring discussions. I could not have asked for a better team, and I look forward to our collaboration in future projects.

The project would never have been possible without all the colleagues at REHPA. Thank you for your huge effort and for welcoming my project in the research clinic even though it meant lots of new routines and extra work. A special thanks to Dorthe Søsted Jørgensen who were clinical project manager on the NUTRI-HAB programmes, to Susan Dybkjær Johansson and Jan Børge Tofte who were course leaders, to Jens-Jakob Kjer Møller, Jan Christensen and Eva Jespersen for assistance with physical outcome measurements across the country, to Birthe Kargaard Jensen for administrative assistance, and to Tina Broby Mikkelsen for assistance with data management and analyses. Thank you, Annette Rasmussen, for prioritising the NUTRI-HAB programme again in 2020. I am grateful that we can continue this collaboration.

Thanks to the colleagues at University College Copenhagen for support and encouragement. A special thanks to Kim Skov Ustrup for assisting me in the NUTRI-HAB programme, to Berit Jelsbak Mortensen for assistance with project administration, and to head of programme Lasse Kristian Suhr for support and for some extra writing time in the final sprint of the PhD thesis.

To the students who have been involved in the project as a part of their practical placement or bachelor's thesis projects: thank you for your effort. It has been great to follow your progress and to learn together with you.

A warm thanks to Liz Isenring, Barbara van der Meij, Skye Marshall and rest of the Bond University Nutrition & Dietetics Research Group for welcoming me in the group and for five rewarding months. It was a great inspiration working with you, and I look forward to continuing the collaboration in the future.

My deepest gratitude goes to my family and friends for your support and for bearing over with me during busy times. I look forward to spending some more time with you all again.

Last but not least, a sincere thanks to all the study participants. I am grateful that you were willing to contribute with your valuable experiences and your time, and it has been rewarding to experience the unique atmosphere you created at REHPA during the NUTRI-HAB programmes.

Publications and manuscripts included in the thesis

Paper I-IV are included in appendices 1-4, and an overview of related publications and scientific contributions during the PhD programme is provided in Appendix 5.

STUDY 1	Paper I	Kristensen MB, Mikkelsen TB, Beck AM, Zwisler AD, Wessel I, Dieperink KB. **To eat is to practice – Managing eating problems after head and neck cancer.** *J Cancer Surviv*. 2019;13(5):792-803. https://doi.org/10.1007/s11764-019-00798-2. *In the online version of the thesis, only the post-peer-review, pre-copyedit version of the article is included.*
STUDY 2	Paper II	Kristensen MB, Beck AM, Zwisler AD, Dieperink KB, Wessel I. **Nutritional characteristics and associations with self-reported health-related quality of life in Danish head and neck cancer survivors 1-5 years after radiation therapy – results from the nationwide cross-sectional NUTRI-HAB Survey.** *Status: In manuscript 2020*
STUDY 3	Paper III	Kristensen, MB, Wessel I, Beck AM, Dieperink KB, Mikkelsen TB, Møller JJK, Zwisler AD. **Rationale and design of a randomised controlled trial investigating the effect of multidisciplinary nutritional rehabilitation for patients treated for head and neck cancer (the NUTRI-HAB trial).** *Nutr J* 19, 21 (2020). https://doi.org/10.1186/s12937-020-00539-7
	Paper IV	Kristensen, MB, Wessel I, Beck AM, Dieperink KB, Mikkelsen TB, Møller JJK, Zwisler AD. **Effects of a multidisciplinary residential nutritional rehabilitation programme in head and neck cancer survivors – Results from the NUTRI-HAB randomised controlled trial.** *Status: Submitted to Nutrients, May 2020.*

Summary

Nutrition impact symptoms and eating problems frequently affect quality of life and physical, psychological, and social function in head and neck cancer survivors and may occur or persist years after completion of treatment. Nutritional rehabilitation may ameliorate these adverse effects, but the evidence of different interventions is limited. And while national clinical guidelines prescribe that rehabilitation needs should be assessed systematically, lack of consensus and evidence on how this assessment should be performed may pose a risk of unrecognised and unmet rehabilitation needs.

The thesis aimed to strengthen the evidence base for multidisciplinary nutritional rehabilitation services in head and neck cancer survivors, and to create new knowledge on whether head and neck cancer survivors' needs for nutritional rehabilitation can be assessed systematically using existing nutrition screening and assessment tools.

The thesis is based on three studies that complement each other in the pursue of the overall aims, and a triangulation of research methods was used. In study 1, a multidisciplinary residential nutritional rehabilitation programme, the NUTRI-HAB programme, was pilot tested in 40 head and neck cancer survivors, and qualitative focus group interviews with participants were carried out. In study 2, a nationwide cross-sectional survey was conducted among all Danish head and neck cancer survivors who completed curatively intended radiation therapy 1-5 years prior to the survey, and 1190 (61.4%) head and neck cancer survivors completed the survey. In study 3, the effect of the NUTRI-HAB programme was tested in a randomised controlled trial including 71 participants.

Qualitative data from study 1 indicated that head and neck cancer survivors benefited from participation in the NUTRI-HAB programme, and qualitative data showed increased body weight and improvements in several quality of life measures. In the randomised controlled trial in study 3, the effect on body weight could not be replicated, thus no difference in changes in body weight was seen between the intervention and the control group, but overall trends towards greater improvements in physical function and quality of life were seen in the intervention group.

Study 1 illustrated how rehabilitation needs in relation to nutrition impact symptoms and eating problems in head and neck cancer survivors are far more wide-ranging than management of weight loss, and study 2 demonstrated that, that nutritional challenges and unmet rehabilitation needs are frequent among Danish head and neck cancer survivors 1-5 years posttreatment. Among selected nutrition screening and

assessment tools, the Scored Patient-Generated Subjective Global Assessment Short Form and M. D. Anderson Dysphagia Inventory were considered most relevant by participants in study 1, and these tools also showed strongest correlations to participants' quality of life in study 2.

In conclusion, the thesis has contributed to strengthen the evidence base for multidisciplinary nutritional rehabilitation services in head and neck cancer survivors and to create new knowledge on systematic assessment of head and neck cancer survivors' needs for nutritional rehabilitation.

The NUTRI-HAB programme appears to have effect on quality of life and physical function, while effect on body weight may be dependent on timing of the intervention. Future studies should explore the effects in different subgroups of head and neck cancer survivors and explore relevant inclusion criteria, timing and outcome.

The Scored Patient-Generated Subjective Global Assessment Short Form and M. D. Anderson Dysphagia Inventory are potentially able to capture head and neck cancer survivors' complex needs for nutritional rehabilitation, and future studies should explore whether the tools are able to identify head and neck cancer survivors with benefit of nutritional rehabilitation. Data for this purpose have been collected in study 3, and results will be published in the future.

Resumé

Ernæringsrelaterede symptomer og spiseproblemer påvirker ofte livskvalitet samt fysisk, psykologisk og social funktion hos hoved-halscanceroverlevere. Symptomerne kan vare ved eller opstå år efter endt behandling. Ernæringsinterventioner i rehabilitering kan potentielt mindske de negative konsekvenser, men evidensen for forskellige interventioner er begrænset. Og mens de nationale forløbsprogrammer foreskriver, at rehabiliteringsbehov skal vurderes systematisk, så medfører manglende konsensus og evidens for hvordan behovsvurderingen skal udføres risiko for at rehabiliteringsbehov ikke identificeres og imødekommes.

Formålet med afhandlingen er at styrke evidensgrundlaget for tværprofessionel ernæringsmæssig rehabilitering hos hoved-halscanceroverlevere samt at skabe ny viden om, hvorvidt hoved-halscanceroverleveres rehabiliteringsbehov kan vurderes systematisk ved hjælp af eksisterende ernæringsscreenings- og vurderingsredskaber.

Afhandlingen er baseret på tre studier der komplementerer hinanden, og triangulering af forskningsmetoder er anvendt. I studie 1, blev et tværprofessionelt ernæringsmæssigt internetrehabiliteringsophold (’Mad med glæde’) pilottestet blandt 40 hoved-halscanceroverlevere, og kvalitative fokusgruppeinterviews blev udført. I studie 2 gennemførtes en landsdækkende tværsnitsundersøgelse blandt alle hoved-halscanceroverlevere, der havde afsluttet kurative intenderet strålebehandling 1-5 år forinden, og 1190 (61.4%) besvarede det udsendte spørgeskema. I studie 3 blev effekten af ’Mad med glæde’ undersøgt i et randomiseret kontrolleret forsøg med 71 hoved-halscanceroverlevere.

Kvalitative data fra studie 1 indikerede at hoved-halscanceroverlevere havde gavn af at deltage i ’Mad med glæde’, og kvalitative data viste øget vægt og forbedringer i flere livskvalitetsmål. I det randomiserede kontrollerede forsøg i studie 3 sås der ingen forskel i vægtændringer mellem interventions- og kontrolgruppen, men der sås overordnede tendenser til større forbedringer i fysisk funktion og livskvalitet hos interventionsgruppen.

Studie 1 demonstrerede, at rehabiliteringsbehov som følge af ernæringsrelaterede symptomer hos hoved-halscanceroverlevere spænder væsentligt bredere end utilsigtet vægttab, og studie 2 viste, at ernæringsmæssige udfordringer og oversete rehabiliteringsbehov er hyppige hos danske hoved-halscanceroverlevere 1-5 år efter behandling. Blandt udvalgte ernæringsscreenings- og

vurderingsredskaber vurderede deltagerne i studie 1, at the Scored Patient-Generated Subjective Global Assessment Short Form and M. D. Anderson Dysphagia Inventory var mest relevante, og disse redskaber var desuden tættest korreleret til deltagernes livskvalitet i studie 2.

Afhandlingen har således bidraget til at styrke evidensgrundlaget for tværprofessionelle ernæringsinterventioner i rehabilitering og til at skabe ny viden om systematisk vurdering af hoved-halscanceroverleveres rehabiliteringsbehov.

'Mad med glæde' har formentlig effekt på livskvalitet og fysisk funktion, mens effekten på vægt kan afhænge af hvornår i forløbet indsatsen tilbydes. Fremtidige studier bør undersøge effekten blandt forskellige subgrupper af hoved-halscanceroverlevere og udforske relevante inklusionskriterier, timing og effektmål.

The Scored Patient-Generated Subjective Global Assessment Short Form og M. D. Anderson Dysphagia Inventory er potentielt egnede til at identificere hoved-halscanceroverleveres komplekse rehabiliteringsbehov, og fremtidige studier bør undersøge om redskaberne også er i stand til at identificere hoved-halscanceroverlevere, som vil have gavn af ernæringsmæssig rehabilitering. I studie 3 blev data til dette formål indsamlet, og disse resultater vil blive præsenteret i en fremtidig publikation.

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List of abbreviations

BMI	Body mass index
DAHANCA	Danish Head and Neck Cancer Group
EAT-10	Eating Assessment Tool
EORTC	The European Organization for Research and Treatment of Cancer
ESPEN	European Society for Clinical Nutrition and Metabolism
HADS	Hospital Anxiety and Depression Scale
HNC	Head and neck cancer
MDADI	M. D. Anderson Dysphagia Inventory
MUST	Malnutrition Universal Screening Tool
NRS 2002	Nutritional Risk Screening 2002
PG-SGA SF	Scored Patient-Generated Subjective Global Assessment Short Form
QOL	Quality of life
RcDallund	Rehabilitation Centre Dallund
REDCap	Research Electronic Data Capture
REHPA	REHPA, The Danish Knowledge Centre for Rehabilitation and Palliative Care

1. Introduction

Food, eating and meals have many essential functions in addition to providing an adequate supply of energy and nutrients. They also hold important social and cultural roles, bring people together, and are often important components of social gatherings. The German sociologist and philosopher Georg Simmel described how the shared meal elevate an event of physiological primitiveness into the sphere of social interaction[5].

"Hence, of all the things that people have in common, the most common is that they must eat and drink"

Georg Simmel, Sociology of the Meal, 1910[5]

Few people consider the importance of food and eating in their daily life, but it becomes painfully evident to head and neck cancer (HNC) survivors when side effects from an otherwise successful curative cancer treatment limit their eating ability. Eating becomes a full-time project, and social events including food and eating may be experienced as struggles rather than joyful events. Not knowing whether they will be able to eat the served food or fear of embarrassment when eating problems make it impossible to comply with widely accepted rules for table manners often make it easier to stay at home and withdraw from these social events. While some might consider the eating problems a small price to pay for a successful curative cancer treatment, they have substantial negative effects on the HNC survivor's daily life[6].

In Denmark, the incidence of HNC has been increasing during recent years, and at the same time the overall survival of the patient group has improved[7]. Hence, the population of HNC survivors is steadily increasing, and there will be an increased demand for proper rehabilitation services to support HNC survivors' coping with eating problems and other late effects and returning to their daily life when treatment is completed.

Currently, there is great variation in the offered rehabilitation services for HNC survivors across Denmark[8], and HNC survivors who participate in rehabilitation services are not necessarily the ones with the greatest rehabilitation needs[9]. Within nutritional rehabilitation, the differences across the country may partly be ascribed to a limited evidence base for the effect of different interventions. And while national clinical guidelines prescribe that rehabilitation needs should be assessed systematically[10,11], lack of consensus and evidence on how this assessment should be performed may pose a risk of unrecognised and unmet rehabilitation needs. This thesis will address some of these evidence gaps.

With rehabilitation services in Denmark as setting and framework, the thesis will focus on 1) multidisciplinary nutritional rehabilitation for HNC survivors and 2) systematic assessment of needs for nutritional rehabilitation.

Throughout the different chapters and studies of the thesis, these two aspects will be addressed separately or combined (Figure 1). In the 'Background' chapter, the population of interest, their nutritional challenges, the framework and setting will be presented along with a summary of existing evidence identifying the relevant knowledge gaps. In following chapters, aims, methods, and results of the included studies will be summarised and discussed leading to the overall conclusion of the thesis. Finally, perspectives on implications for clinical practice, future research, and usefulness of the project will be addressed.

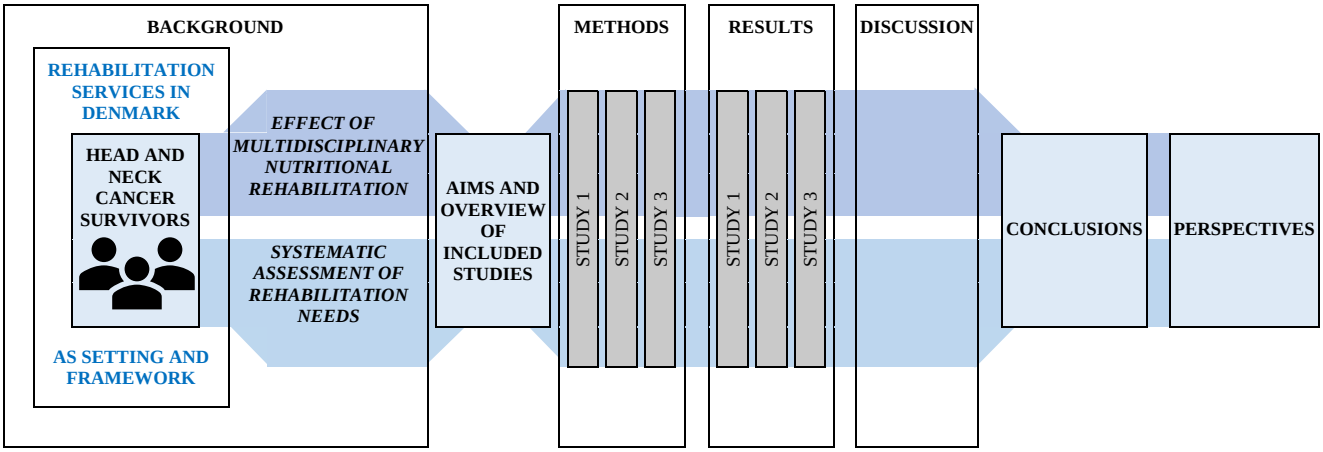

Figure 1: Overview of the NUTRI-HAB PhD thesis

2. Background

2.1. Danish head and neck cancer survivors

The population of interest in the thesis is Danish HNC survivors. The Danish Health Authority's definition of HNC comprise cancers of the pharynx, larynx, oral cavity, salivary glands, paranasal sinuses, nasal cavity, thyroid, and cervical metastases[12]. In contrast to definitions from some other countries, cancers of the lip and other skin tumours in the facial region are not included[12]. In the European Society for Clinical Nutrition and Metabolism's (ESPEN) guideline on nutrition in cancer patients[13], 'cancer survivors' are defined as patients who are cured from their cancer. Hence, in the thesis the term 'HNC survivors' refers to patients who have completed curatively intended HNC treatment.

2.1.1. Epidemiology of head and neck cancer in Denmark

Worldwide, HNCs are the sixth most common cancers with more than 900.000 new cases in 2018[7,14]. In Denmark, approximately 1600 individuals are diagnosed with HNC annually[15], and the most frequent HNC diagnoses are cancers of the pharynx (35%), thyroid (21%), oral cavity (18%), and larynx (14%)[15–19]. The incidence of HNC has increased in recent years, and from 1980 to 2014 the age-adjusted incidence rate in Denmark increased from 9.1 per 100.000 to 17.4 per 100.000 corresponding to an average annual percentage change of 2.1%. In the same time interval, the 5-year relative survival of the patient group increased from 49.0% to 62.4%[7]. Hence, the population of HNC survivors is steadily increasing.

Approximately two-thirds of Danish HNC patients are male[7], and HNC is often diagnosed around the age of 60[12]. The predominant risk factors for developing HNC are tobacco and alcohol consumption[20], and comorbidities related to the same risk factors are frequent[21]. A nationwide, population register-based study on variations in cancer incidence and survival by social position in Denmark observed a consistent increase in HNC incidence rates with shorter education and lower income[22]. Hence, compared to the general Danish population, a higher proportion of HNC patients have lower socioeconomic status. In addition to being associated with an increased risk of developing HNC, lower socioeconomic status is also associated with a poorer prognosis after HNC diagnosis. In population-based studies, Danish HNC patients with lower socioeconomic status have been observed to have higher risk of advanced HNC stage at diagnosis[23], poorer survival[22,24], and higher risk for early retirement and unemployment after curative HNC treatment[25].

In recent years there has been an increase in the numbers of HNC cases caused by Human Papillomavirus[20], especially in terms of increased oropharyngeal cancer incidence. In addition to an

increase in the total HNC incidence[20], the increasing proportion of virus-related cases has led to a shift in patient demographics. Individuals with virus-related HNC are often younger at diagnosis[26] with higher socioeconomic status[26,27]. Furthermore, Human Papillomavirus-related oropharyngeal cancer is associated with better treatment response and survival[28]. Hence, two subpopulations of HNC patients with distinct risk profiles and prognosis have emerged.

2.1.2. Head and neck cancer treatment in Denmark

In Denmark, HNC treatment and rehabilitation are tax-funded and free of charge for the patient. Denmark is politically divided into five regions who are responsible for hospital management, and all HNC treatment is offered at the hospitals, and hence at regional level. The Danish Health Authority has issued 'Integrated patient pathways' for HNC describing the preferred patient trajectory including roles and responsibilities of involved health actors from HNC suspicion through diagnosis, treatment, and follow-up[12]. Across the country, treatment follows the same principles based on the national clinical guidelines of the Danish Head and Neck Cancer Group (DAHANCA)[12].

Treatment modality varies with HNC diagnosis and stage. Both radiation therapy, surgery, and combinations of the two are used as primary treatment, and in some circumstances in combination with chemotherapy. Hence, for the majority of Danish HNC patients (53-75%) radiation therapy is a part of the initial treatment[12,15–19]. Modern techniques, such as intensity-modulated radiation therapy, allow for increasing radiation dose for the targeted tumour area while reducing dose for surrounding healthy tissue. Yet, early and late side effects to HNC treatment are still frequent[29].

2.2. Nutritional challenges of head and neck cancer survivors

Due to the location, HNC is associated with a high risk of nutritional challenges before, during and after treatment. Nutrition impact symptoms, defined as symptoms that affect dietary intake or nutritional status, are frequent[30–33]. They can be present at diagnosis due to the tumour location, and they may be the reason for the patient to consult the health system in the first place[12]. More frequently, nutrition impact symptoms occur as side effects to HNC treatment, and for some HNC patients, the nutrition impact symptoms persist and become chronic late effects. In others, the nutrition impact symptoms occur years after treatment completion[31–35]. The prevalence of nutrition impact symptoms varies with assessment method ans time interval posttreatment, but frequently reported nutrition impact symptoms in HNC survivors include xerostomia (dry mouth), dysphagia (swallowing difficulties), trismus (reduced mouth opening), dysgeusia (taste disturbances), and dental problems[31–33].

Xerostomia denotes the subjective sensation of dry mouth and is frequently associated with hyposalivation due to radiation-induced damage to the salivary glands. The volume, consistency and pH of the secreted saliva change towards thicker secretions with lower pH, resulting in the sensation of a dry mouth[36]. While xerostomia, oedema and mucositis impair the swallowing mechanism of HNC patients in the acute phase, long-term dysphagia in HNC survivors is perpetuated by radiation-induced tissue fibrosis and chronic oxidative stress[37]. In trismus, the ability to open the mouth fully is impaired due to a decreased range of motion in the mastication muscles. It is caused by surgery, radiation therapy or perioral fibrosis[36]. HNC treatment may lead to dysgeusia through damage to olfactory receptor cells and neuronal cells, and both radiation therapy and chemotherapy can potentially lead to formation of conditioned aversions and, hence, alter the pleasure produced by a given taste[38]. The majority (70-100%) of HNC patients develop dysgeusia during radiation therapy, and in most, dysgeusia recovery is seen 6-12 months after treatment[39]. In others, dysgeusia persist for years[32]. Dental problems are frequent after HNC treatment, and may occur a result of osteoradionecrosis, xerostomia[40] and a shift to a more cariogenic milieu.

Nutrition impact symptoms may lead to eating problems and decreased dietary intake[41,42]. For some HNC survivors, enteral nutrition or oral nutritional supplements will be indicated years after treatment completion[43–45], and in some the need for enteral nutrition becomes permanent[46].

The decreased dietary intake due to nutrition impact symptoms frequently leads to impaired nutritional status[31,42,47,48]. Furthermore, cancer-related metabolic derangements towards a catabolic state in the acute phase may increase the risk of critical weight loss, in particular loss of lean body mass[13]. Studies have reported significant weight loss (≥5% relative weight loss) in approximately 65% of HNC patients during

treatment[6,49,50]. This weight loss may continue up to years after treatment completion and be hard to reverse[47,51]. Weight loss and sarcopenia prior to and during HNC treatment have been associated with poorer prognosis in terms of increased treatment toxicity and poorer overall survival[52]. Furthermore, malnutrition in HNC has been associated with decreased physical function[53].

Both nutrition impact symptoms[31,54–58] per se and impaired nutritional status have been demonstrated to be associated with impaired health-related quality of life (QOL) in HNC[59]. Several studies have assessed the presence of nutrition impact symptoms in HNC survivors ≥1 year posttreatment[32–34,48,60–68]. Yet, only few studies[47,48,51,69] have assessed nutritional status or risk by other means than need for enteral nutrition or modified diet or have assessed how nutritional status is associated with QOL in this population. Hence, there is limited knowledge on how nutritional status or risk is affected in HNC survivors beyond 1 year posttreatment and how this relates to QOL.

In HNC survivors, QOL is most often assessed quantitatively[54,63,67,70,71]. Given the complexity of the topic, a qualitative approach may lead to a broader understanding of how nutrition impact symptoms and eating problems after HNC treatment affect the individual HNC survivors' daily life. A number of studies have used qualitative or mixed-methods to assess HNC survivors experiences of nutrition impact symptoms[72–76], eating problems, or the changed meaning of food after treatment[77–81]. These studies have found affected enjoyment with eating[79,81], a need for adaptive behavior[79,81], that HNC survivors experience feelings of loss[77,82], and that many of them feels left to themselves with eating problems after treatment[80]. Since meals are important components of social interaction, nutrition impact symptoms may also have profound negative effects on the HNCs survivor's social life. Several studies have reported social withdrawal in HNC survivors[72,79,81,83], which may affect psychological wellbeing.

However, to our knowledge, no previous studies have used focus groups to explore HNC survivors' experiences of everyday life with eating problems after treatment. With the benefit of using group interaction actively to stimulate discussion[84], this method may reveal new aspects and insights that are not being addressed in individual interviews.

2.3. Nutritional rehabilitation services for head and neck cancer survivors in Denmark

According to the World Health Organization, *"Rehabilitation addresses the impact of a health condition on a person's everyday life, by optimizing their functioning and reducing the experience of disability. Rehabilitation expands the focus of health beyond preventative and curative care, to ensure people with a*

health condition can remain as independent as possible and participate in education, work and meaningful life roles"[85].

With the aim of providing a general description and definition of the rehabilitation concept in a Danish context, a white paper was issued by the Danish Rehabilitation Forum and Marselisborg Centre in 2004 in collaboration with the Ministry of Social Affairs, the Danish Medical Association, the Danish Cancer Society, the Faculty of Health Sciences at The University of Southern Denmark (Master's degree in rehabilitation), The Danish Association of Occupational Therapists, The Association of Danish Physiotherapists, and the Danish Nurses' Organisation[86,87]. The following definition of rehabilitation was established: *"A goal-oriented, cooperative process involving a member of the public, his/her relatives, and professionals over a certain period of time. The aim of this process is to ensure that the person in question, who has, or is at risk of having, seriously diminished physical, mental and social functions, can achieve independence and a meaningful life. Rehabilitation takes account of the person's situation as a whole and the decisions he or she must make, and comprises co-ordinated, coherent, and knowledgebased measures"*[87].

These definitions of rehabilitation provide the theoretical framework for the thesis. Hence, nutritional rehabilitation is considered broader than merely securing adequate energy and protein intake; it also includes, but is not limited to, interventions aimed at managing nutrition impact symptoms and strengthening the HNC survivor's confidence in engaging in social activities including food, meals and eating. Despite the thesis' overall focus on nutritional rehabilitation, other rehabilitation needs of HNC survivors will also be addressed in the interventions in the included studies to allow for the holistic approach to the individual HNC survivor's life situation.

This subchapter will describe organisation of rehabilitation services for HNC survivors in Denmark, recommendations and current practice within nutritional rehabilitation.

2.3.1. Organisation of rehabilitation services for head and neck cancer survivors in Denmark

In addition to the five regions, Denmark is divided into 98 municipalities, and while rehabilitation during treatment is a regional responsibility, the municipalities hold the primary responsibility for posttreatment rehabilitation services[11].

As a part of the 'Integrated patient pathways', the Danish Health Authority has issued a diagnosis-specific follow-up programme[10] for HNC and a generic programme[11] for cancer rehabilitation and palliation as

guidelines for organising rehabilitation interventions. In these programmes, the roles and responsibilities of the hospitals and municipalities are described[10,11].

Until 2007, rehabilitation services were the hospitals' responsibility, but as a part of a political structural reform, the main responsibility for rehabilitation services was transferred to the municipalities[88]. The reform was in accordance with recommendations from the World Health Organization who encourages community-based outpatient health services in order to decrease the risk of social inequality in health, since the proximity to the patient may improve adherence among vulnerable patients[89,90].

Hence, in the 'Integrated patient pathways' it is defined, that municipalities hold the primary responsibility in relation to follow-up including rehabilitation, since a wide range of interventions offered by the municipalities may be needed. Furthermore, the required interventions may involve several municipal administrative areas, primarily healthcare, social services, employment and educational services[11].

In 2015, a national knowledge centre for rehabilitation was established. REHPA, The Danish Knowledge Centre for Rehabilitation and Palliative Care (REHPA) is a part of Odense University Hospital and Department of Clinical Research, University of Southern Denmark. As a national knowledge centre, REHPA aims to contribute to the development of evidence-based practice within rehabilitation and palliative care of individuals affected by life-threatening disease by sharing and developing knowledge. In addition to mapping and exploring current practice within rehabilitation and palliative care, the clinical activities at REHPA's research clinic aim to create evidence that can be used in the Danish municipalities and hospitals. Hence, all rehabilitation programmes offered at REHPA have a research-based purpose. The research clinic offers multidisciplinary residential rehabilitation programmes based on newest research and years of clinical experience from the previous, Rehabilitation Centre Dallund (RcDallund). From 2001-2015, RcDallund offered multidisciplinary residential rehabilitation programmes for cancer patients and cancer survivors, and the centre was a part of the Danish Cancer Society. When RcDallund closed in 2015, the centre's clinical function was transferred to the newly established REHPA[91].

The clinical studies included in the thesis were carried out at RcDallund and REHPA's research clinic.

2.3.1. Recommendations and current practice within nutritional rehabilitation for head and neck cancer survivors in Denmark

The diagnosis-specific follow-up programme emphasizes that patients with the same HNC diagnosis may have very different needs for rehabilitation and follow-up, and that planning of rehabilitation interventions

should be based on assessment of the individual patient's rehabilitation needs and continuous monitoring of the most frequent side effects.

Both the diagnosis-specific and the generic follow-up programme provide some suggestions and recommendations for rehabilitation aimed at nutritional problems. These are summarised in Table 1. Since nutritional problems and nutrition impact symptoms are highly interconnected, the follow-up programmes' recommendations and suggestions on both are included in the table.

Table 1: The Danish Health Authority's recommendations for follow-up and rehabilitation interventions aimed at nutritional problems and nutrition impact symptoms in head and neck cancer

	THE DIAGNOSIS-SPECIFIC FOLLOW-UP PROGRAMME FOR HEAD AND NECK CANCER[10]		THE GENERIC FOLLOW-UP PROGRAMME FOR CANCER REHABILITATION AND PALLITAION[11]
	Suggested rehabilitation interventions	**Responsibilities and coordination**	**Recommendations for rehabilitation interventions**
Nutritional problems	▪ Depending on the degree of weight loss, nutritional intake should be optimised through use of supplements or, possibly, by nasogastric tube or percutaneous endoscopic gastrostomy. ▪ Patients with persistent eating and/or swallowing problems after treatment completion should be referred to occupational therapy or physiotherapy for the purpose of training their eating ability. Most often this will be general physical rehabilitation that should be delivered by the municipality.	▪ Initially by nurse and/or clinical dietitian at the hospital. ▪ If long-term nutritional interventions or tube feeding is required, interventions should be delivered in cooperation with, or solely by, community nurse and municipal dietitian. ▪ In more severe cases, it may be advisable that treatment is carried out in hospital setting as specific rehabilitation.	▪ When assessing rehabilitation needs, it is recommended that individuals with cancer have their nutritional status assessed with focus on potential weight loss or weight gain. ▪ Based on the assessment, they should be offered nutritional counselling focusing on the general dietary advice or, if necessary, dietary treatment. ▪ Nutritional counselling and/or dietary treatment can be offered as a part of a rehabilitation intervention or as an independent intervention in the municipality or elsewhere. ▪ Nutritional interventions can often with benefit be supported by a multidisciplinary collaboration with relevant health professionals.
Dysphagia and eating problems	▪ For the individual patient, the degree of dysphagia should be assessed.	▪ Training related to trismus and motor skills in tongue and oral cavity are traditionally delivered by speech-language pathologist. ▪ If problems are located more distally, rehabilitation is delivered by occupational therapist in terms of respiratory-swallowing coordination exercises. ▪ There is a significant overlap between speech-language pathologists' and occupational therapists' areas of practice.	▪ Some groups, e.g. head and neck cancer patients, may have dysphagia and their needs for specific follow-up and training should be assessed. ▪ Interventions are partly preventive measures aimed at aspiration and partly oral and pharyngeal motor training as well as guidance on diet and fluid consistencies.
Xerostomia	▪ Information on moisturizing actions and products ▪ Patient-mediated symptom treatment (water, artificial saliva, sialagogues, and other measures that patients find helpful).	▪ Initial information on moisturizing actions are provided by hospital nurse and by municipal nurse. ▪ General practitioner or treating physician from hospital prescribe sialagogues.	
Trismus	▪ The patient should be referred to occupational therapy for guidance on stretching exercises, increased mouth opening, passive jaw mobilisation	▪ In the rehabilitation phase, treatment of trismus is performed in the municipality	
Teeth and jaw problems	▪ Patients are recommended to maintain good oral hygiene and to consult dentist every 2nd or 3rd month. ▪ Patients with osteoradionecrosis can be assessed for treatment with hyperbaric oxygen. Reconstruction can be performed when the condition allows it.	▪ Tooth extraction after radiation therapy should be performed in highly specialised oral and maxillofacial surgery departments.	

Despite national recommendations, nutritional rehabilitation services for HNC survivors vary greatly across the Danish municipalities. In a nationwide survey on cancer rehabilitation services in Danish hospitals and municipalities carried out in 2017[8], 10% of the municipalities responded that they did not offer nutritional interventions in their standard cancer rehabilitation services. Among the municipalities who did offer nutritional interventions, both individual (83%) and group-based (69%) nutritional interventions were being offered. The survey questions for the municipalities did not focus specifically on rehabilitation services for HNC survivors but for cancer patients and survivors in general, but when asked whether they offered diagnosis-specific rehabilitation services for HNC survivors, only 17% replied that they did[8]. Hence, most group-based nutritional interventions in the municipalities' rehabilitation services must be assumed to be for heterogenous groups of cancer patients and survivors or for other groups than HNC survivors.

In the survey, municipalities were not asked directly which health professionals delivered the nutritional interventions, but 84% responded that clinical dietitians were part of the multidisciplinary collaboration in their cancer rehabilitation services[8].

The survey only provides results on the municipalities' self-reported services within cancer rehabilitation on structural level. It does not provide information on the number of HNC survivors being referred to the existing nutritional rehabilitation services.

2.4. Effect of multidisciplinary nutritional rehabilitation in HNC survivors

While nutritional rehabilitation for HNC survivors in need hereof is recommended, evidence of the effect of different interventions is limited. A number of studies have demonstrated positive effects of nutritional interventions during HNC treatment[92–94], but few studies have assessed the effect of posttreatment nutritional interventions. Since the nutritional challenges may vary from the treatment phase to the posttreatment phase, so may the effect of nutritional interventions.

Considering the wide-ranging consequences of eating problems in HNC survivors, and the fact that rehabilitation per definition should focus on the individual's whole life situation, nutritional rehabilitation services should ideally address both the physical, psychological, and social consequences of eating problems. Yet, very few studies on effect of rehabilitation interventions have assessed these broad scoped interventions. In a systematic review from 2013, interventions for eating and drinking problems following treatment for HNC are reviewed. The authors identify 27 studies of which 15 focused on trismus, eight on

interventions to improve jaw mobility, and four on swallowing and jaw exercises. None of the included studies, intervened to address the complex combination of functional, physical and psychological problems associated with eating[95].

A more recent scoping review from 2019 examining the amount and nature of research activity in HNC rehabilitation (not restricted to nutritional rehabilitation), found few interventional studies (n=35). Among these, the most common interventions focused on chewing or swallowing (n=14). Authors concluded, that the literature is dominated by small (≤100 patients), outpatient-based observational studies, that more prospective studies in multidisciplinary domains across the cancer care continuum are needed, and that there is particular need for interventional studies and prospective observational studies[96].

Rehabilitation interventions for HNC survivors were furthermore reviewed in another scoping review published online in 2018[97]. The authors classified 12 studies as having interventions aimed at improving swallowing and nutrition[97]. But it seems as if only one of the studies included a nutritional intervention. In the given study, the nutritional intervention was initiated at the start of radiation therapy and continued for 12 weeks[94]. Among all studies, the scoping review only identify and classify three studies with comprehensive interdisciplinary rehabilitation interventions[97]. Interventions in these studies included an electronic health information support system[98], a weekly speech pathology/dietetic service model[99] delivered during treatment, and an 8-week interdisciplinary posttreatment outpatient nutrition-rehabilitation program[100]. The first study was a prospective evaluation study showing that the electronic health information support system was used intensively and highly appreciated by HNC patients. The second study was a service evaluation of the speech pathology/dietetic service model, and while results supported provision of a weekly speech pathology/dietetic service model[99], clinical effects of the service were not reported. In the third study, participants improved their results in 6-minute walk test, the majority increased or maintained their body weight, and clinically meaningful improvements were reported in distress and QOL. The authors concluded, that an interdisciplinary rehabilitation program may be beneficial after HNC treatment, but the effect should be assessed in a controlled trial[100]. Hence, the studies support multidisciplinary rehabilitation intervention, but evidence remains limited.

No studies exploring the effect of practical cooking interventions in HNC survivors have been identified, but in studies with other types of cancer survivors, practical cooking sessions have supported dietary changes and thereby improved health-related QoL[101,102].

Neither have any of the described studies assessed the effect of residential rehabilitation interventions. This type of intervention could be relevant to explore since they have the potential to create an environment for social eating among peers. In a pilot study on the effect of a 1-week residential psychoeducational program, researchers found high participant satisfaction and improvements in QOL in 14 HNC survivors[103]. However, the programme did not specifically target eating problems. Hence, the potential of residential nutritional rehabilitation interventions remains unexplored.

2.5. Assessment of rehabilitation needs in head and neck cancer survivors

As previously described, the diagnosis-specific follow-up programme emphasizes that rehabilitation should be based on assessment of the individual patient's rehabilitation needs since patients with the same HNC diagnosis may have very different needs for rehabilitation[10].

According to the follow-up programmes, the Danish hospitals are obliged to offer a systematic assessment of rehabilitation needs at the end of treatment and refer patients with identified rehabilitation needs to municipal rehabilitation services. The municipalities and general practitioners are obliged to follow up and to offer a reassessment if needed[10,11].

The follow-up programmes differentiate between two levels of assessment: the brief overall identification of a need for rehabilitation services and the more thorough assessment to identify which intervention should be initiated[10,11]. Yet, there is little evidence on how this systematic assessment of rehabilitation needs should be performed. The aforementioned nationwide survey on rehabilitation services in Danish hospitals' and municipalities showed that only 34% of hospitals had fully implemented systematic assessment of rehabilitation needs. There were great variances in how the systematic needs assessment was performed in different hospitals and municipalities[8].

Lacking or inconsistent assessment of rehabilitation needs may increase the risk of HNC survivors not getting the proper supportive care. There is a high risk that this will affect the most vulnerable individuals, since studies have shown, that the patients with the most rehabilitation needs are often not the ones to participate in the offered rehabilitation services[9,104].

The steadily increasing population of HNC survivors and the consequent increased demand for appropriate municipal rehabilitation services, make the systematic assessment of rehabilitation needs even more

important. Since extensive rehabilitation services are not indicated for all HNC survivors, systematic assessment of rehabilitation needs may contribute to optimise the use of resources while ensuring referral to rehabilitation for those in need.

2.5.1. Nutritional screening and assessment of head and neck cancer survivors

The obligation of systematic assessment of rehabilitation needs also comprise an obligation to assess the need for nutritional rehabilitation services.

When assessing needs for nutritional rehabilitation, the two levels of needs assessment described by the Danish Health Authority are comparable to nutritional screening and nutritional assessment. In ESPEN's guideline on nutrition in cancer patients[13], it is recommended that nutritional screening is performed at cancer diagnosis and repeated depending on the stability of the clinical situation. Furthermore, it is recommended that any nutritional intervention is preceded by a more thorough nutritional assessment of among others dietary intake and NIS[13]. ESPEN defines nutritional screening as *"a rapid process performed to identify subjects at nutritional risk",* while nutritional assessment *"should be performed in all subjects identified as being at risk by nutritional risk screening, and will give the basis for the diagnosis decision … , as well as for further actions including nutritional treatment."*[105]

These two levels can also be identified in the Nutrition Care Process and Model (Figure 2), a widely used structure model for nutritional interventions developed by The Academy of Nutrition and Dietetics[106] and recommended by The Danish Dietetic Association. The figure illustrates how an appropriate screening and referral system is crucial to initiation to any nutritional interventions.

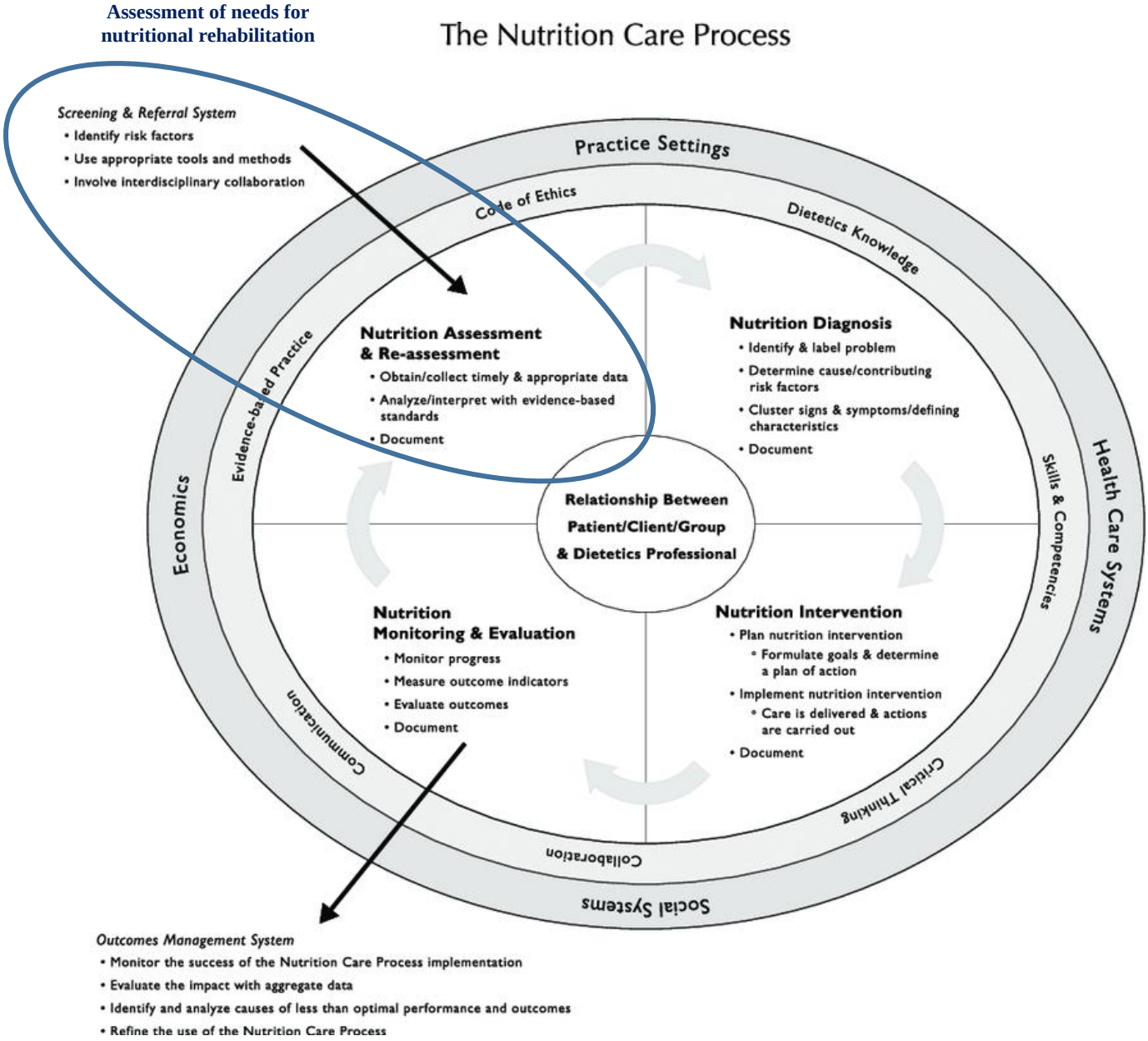

Figure 2: Assessment of needs for nutritional rehabilitation and The Nutrition Care Process and Model

(Adapted from Lacey and Pritchett 2003[106])

2.5.2. Nutritional screening and assessment tools and methods

There is no consensus on which method or tools to use for assessment of needs for nutritional rehabilitation in HNC survivors in Denmark or internationally.

In the disease-specific follow-up programme, it is recommended that nutritional status and dietary intake should be assessed at the beginning of treatment and weekly during treatment, but there is no recommendation on posttreatment assessment. The generic follow-up programme recommends that nutritional status should be assessed with focus on potential weight loss or weight gain, but no further recommendations are provided the assessment.

Several different tools and methods have been developed for nutritional screening and assessment. In Danish hospitals, the Nutritional Risk Screening 2002 (NRS 2002) is the recommended screening method, and it has been developed and validated to identify patients who will benefit from nutritional interventions[107]. It includes information on body weight history, dietary intake (amount consumed versus requirement), disease severity, and age in the assessment of nutritional risk. However, NRS 2002 has primarily been validated in admitted patients[107] who could possibly be assumed to be more affected by disease severity than curatively head and neck cancer survivors. Hence, it may be assumed that the recommended cut-offs of NRS 2002, will leave HNC survivors with needs of nutritional rehabilitation unidentified. In a study assessing the value of NRS 2002 as a nutritional risk screening method in pretreatment HNC patients, authors conclusively suggested that a cut-off value of 2 points instead of 3 should be used in this population[108].

In their guidelines on nutrition in cancer patients, ESPEN state that for nutrition risk screening, body mass index (BMI), weight loss, information on food intake may be obtained directly or through validated screening tools e.g. NRS 2002, Malnutrition Universal Screening Tool (MUST), Malnutrition Screening Tool, or Mini Nutritional Assessment Short Form Revised[13]. In their 2002 guideline on nutritional risk screening, NRS 2002 is recommended for screening at hospitals, while MUST is recommended in community settings[109]. Hence, MUST could potentially be more relevant in the assessment of HNC survivors' needs for nutritional rehabilitation in the Danish municipalities. To my knowledge, no previous studies have assessed whether NRS 2002 or MUST can be used to identify HNC survivors who will benefit from posttreatment nutritional rehabilitation services. In the guideline on nutrition in cancer patients, ESPEN concludes, that further research linking outcomes from current and future clinical trials with appropriate screening and assessment tools is needed[13].

Since nutrition impact symptoms are so frequent in HNC survivors, screening and assessment tools that include nutrition impact symptoms in their assessment may be more relevant than tools that merely focus on body weight changes and quantitative changes dietary intake. The Scored Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) further include presence of nutrition impact symptoms and performance in the assessment, and is widely used as a screening tool in cancer patients[110]. But while the tool has been found feasible and valid in HNC patients during treatment[111,112], evidence is limited on its applicability after treatment completion.

Tools specifically developed to assess nutrition impact symptoms could also be relevant to consider in the assessment of needs for nutritional rehabilitation. For the initial assessment of dysphagia in HNC patients and HNC survivors, the disease-specific follow-up programme from the Danish Health Authority[10] suggests body weight changes and M.D. Anderson Dysphagia Inventory (MDADI)[113] or Eating Assessment Tool (EAT-10)[114]. While EAT-10 is a symptom-specific outcome instrument for dysphagia, MDADI has been developed to assess dysphagia-specific QOL in terms of the physical, functional, and emotional impact of dysphagia in HNC[113]. Since neither MDADI or EAT-10 are typically being categorised as nutrition screening or assessment tools, their potential as such has not been explored.

To summarise, NRS 2002, MUST, PGSGA SF, MDADI, and EAT-10 could potentially all be relevant in the assessment of needs for nutritional rehabilitation in HNC survivors, but their potential has not yet been explored. The tools and methods are presented more detailed in Table 2.

Table 2: Overview of tools and methods that could potentially be relevant in the assessment of needs for nutritional rehabilitation in head and neck cancer survivors

Tool/method	Purpose	Description	Domains/subscales	Range	Interpretation
NRS 2002[107]	Identify patients at nutritional risk	Screening system developed for use by health professionals	*In secondary screening:* A-score for malnutrition, B-score for disease severity, age-adjustment if aged 70 years or above	A-score: 0-3 B-score: 0-3 Age-adjustment: 1	A higher score indicates greater nutritional risk. A score of ≥ 3 defines nutritional risk, and nutritional support should be initiated.
MUST[115]	Identify adults, who are malnourished/at risk of malnutrition (undernutrition), or obese	Screening system developed for use by health professionals	BMI score, weight loss score, acute disease effect score (or if there has been or likely will be no nutritional intake for >5 days)	BMI score: 0-2 Weight loss score: 0-2 Acute disease effect score: 2	0: Low risk: Routine clinical care 1: Medium risk: Observe (and increase nutritional intake if inadequate) ≥2: High risk: Treat (refer to dietitian, nutrition support team etc.) *Obesity (BMI>30): Underlying acute conditions are generally controlled before treating obesity*
PG-SGA SF[110]	Assess nutritional risk and nutritional deficit	Self-administered one-page instrument *(validated in Danish[116])*	Overall score based on weight changes, changes in dietary intake (amount or consistency), nutrition impact symptoms and performance status	Overall score: 0-36	A higher score indicates higher malnutrition risk. Nutrition triage recommendations*: - Score of 4-8: Intervention by dietitian and nurse/physician as indicated by symptoms - Score ≥ 9: Critical need for intervention
MDADI[113]	Assess dysphagia-specific QOL in head and neck cancer	Self-administered 20-item questionnaire (+4 extra items in Danish version[117]) *(validated in Danish[117])*	4 subscales: Global, emotional, functional and physical. 1 composite score: Weighted average of the emotional functional and physical subscales.	Subscales and composite score: 20-100	A higher score indicates a higher degree of functioning. Suggested cut-offs for composite score[118]: ≥ 80: Optimal swallowing function ≥60 - <80: Adequate swallowing function <60: Poor swallowing function
EAT-10[114]	Symptom-specific outcome instrument for dysphagia	Self-administered 10-item questionnaire *(validated in Danish)*	Overall score based on the 10 items	Overall score: 0-40	A higher score indicates higher degree of dysphagia. A score of ≥ 3 is suggested to define abnormal swallowing function

EAT-10: Eating Assessment Tool, MDADI: M. D. Anderson Dysphagia Inventory, NRS 2002: Nutritional Risk Screening 2002, PG-SGA SF: The Scored Patient Generated Subjective Global Assessment Short Form, QOL: Quality of life

*The nutrition triage recommendations are based on the full PG-SGA, not the short-form.

2.6. Summary of rationale

The knowledge gaps identified in this chapter and, hence, the rationale for the NUTRI-HAB thesis are summarised in table 3.

Table 3: Summary of knowledge gaps and rationale for the NUTRI-HAB project

Effect of multidisciplinary nutritional rehabilitation	**<u>What is the effect of different nutritional rehabilitation interventions in HNC survivors?</u>** ▪ What is the effect of multidisciplinary nutritional rehabilitation? ▪ Is residential nutritional rehabilitation relevant and effective? ▪ Are practical cooking interventions relevant and effective?
Assessment of rehabilitation needs	**<u>Which rehabilitation needs should be identified?</u>** ▪ Will qualitative focus group interviews provide new insights to how eating problems affect HNC survivors' everyday life? ▪ Which rehabilitation needs do Danish HNC survivors experience after treatment? ▪ How is nutritional risk and status affected in HNC survivors ≥1 year posttreatment, and how does this relate to QOL? **<u>How can needs for nutritional rehabilitation be assessed systematically?</u>** ▪ Are existing tools and methods such as NRS 2002, MUST, PG-SGA SF, MDADI, and EAT-10 relevant in this population? ▪ Can they be used to identify HNC survivors who will benefit from nutritional rehabilitation?

EAT-10: Eating Assessment Tool, HNC: Head and neck cancer, MDADI: M. D. Anderson Dysphagia Inventory, NRS 2002: Nutritional Risk Screening 2002, PG-SGA SF: The Scored Patient Generated Subjective Global Assessment Short Form, QOL: Quality of life

3. Aims, objectives and overview of included studies

With the ultimate goal of ensuring referral to proper nutritional rehabilitation services of HNC survivors in need hereof, the overall aims of the thesis were to strengthen the evidence base for multidisciplinary nutritional rehabilitation services in HNC survivors and to create new knowledge on whether HNC survivors' needs for nutritional rehabilitation can be assessed systematically using existing screening and assessment tools.

The thesis is based on three different studies with distinct objectives and methods that complement each other in the pursue of the overall aims. The objectives of each study are presented in Table 4

Table 4: Objectives of the studies included in the thesis

	STUDY 1	**STUDY 2**	**STUDY 3**
Effect of multidisciplinary nutritional rehabilitation	**Objective 1** To explore HNC survivors' experiences of a multidisciplinary residential rehabilitation programme with a primary focus on the physical, psychological and social aspects of eating problems after treatment for HNC. **Objective 2** To assess how HNC survivors' body weight and QOL develops during their participation in the multidisciplinary residential rehabilitation programme.		**Objective 1** To test the effect of a multidisciplinary residential nutritional rehabilitation programme compared to standard care on the primary outcome body weight and secondary outcomes health-related QOL, physical function and symptoms of anxiety and depression in patients curatively treated for HNC.
Assessment of rehabilitation needs	**Objective 3** To explore HNC survivors' experiences of everyday life with eating problems after treatment through focus group interviews. **Objective 4** To explore HNC survivors' experience of selected nutrition screening and assessment tools with regards to user friendliness and content relevance.	**Objective 1** To assess nutritional characteristics such as BMI, NRS 2002 score, MUST score, PG-SGA SF score, and MDADI scores of Danish HNC survivors 1-5 years after completion of radiation therapy. **Objective 2** To test whether respondents' BMI, NRS 2002 score, PG-SGA SF score, and MDADI scores is associated with their health-related QOL.	**Objective 2** To test for correlations between participants' development in outcome scores during their participation in the programme and their baseline scores in NRS 2002, PG-SGA SF, and MDADI and to assess sensitivity, specificity and predictive values of the three tools in relation to a clinically relevant improvement in outcome scores

BMI: Body mass index, HNC: Head and neck cancer, MDADI: M. D. Anderson Dysphagia Inventory, MUST: Malnutrition Universal Screening Tool, NRS 2002: Nutritional Risk Screening 2002, PG-SGA SF: Scored Patient-Generated Subjective Global Assessment Short Form, QOL: Quality of life.

For study 1, results from analyses of objective 1 and 3 have been published in paper I. For study 2, results from analyses of objective 1 and 2 are presented in paper II. For study 3, the trial protocol is published in paper III, and results from analysis of objective 1 are presented in paper IV. Results from analyses of objective 2 will be published in a separate publication.

An overview of the studies is provided in Figure 3, where it is furthermore illustrated how the individual studies complement each other.

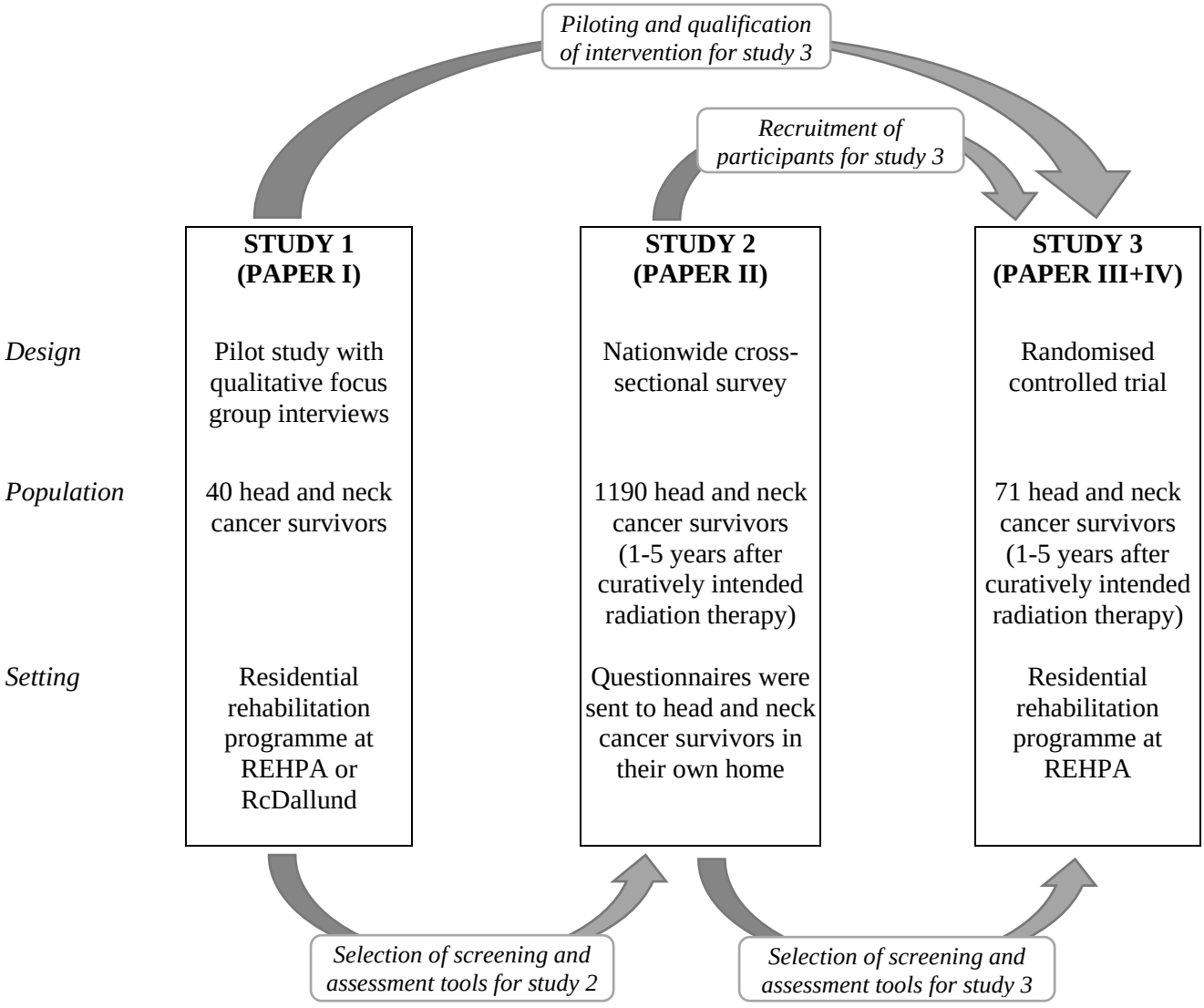

Figure 3: Overview of studies included in the thesis

4. Methods of included studies

Three distinct designs were used in the three studies, and methods are further summarised in Table 5.

Table 5: Summary of methods in included studies

	STUDY 1	STUDY 2	STUDY 3
RECRUITMENT	Referral from general practitioner or treating physician	Identification through DAHANCA's national clinical quality database	Recruitment among participants from study 2
ELIGIBILITY			
Inclusion criteria	▪ HNC diagnosis ▪ Completed curatively intended treatment ▪ Self-reliant[a] ▪ Experience self-reported eating problems and find themselves in need of rehabilitation	▪ HNC diagnosis (oral, laryngeal, pharyngeal cancer) ▪ Completed curatively intended radiation therapy 1-5 years before survey distribution ▪ Age ≥ 18 years	▪ Fulfil eligibility criteria for study 2 ▪ Interested in participating in a residential nutritional rehabilitation programme at specific dates and given permission to be contacted with further information ▪ Self-reliant[a]
Exclusion criteria		▪ No permanent address in Denmark ▪ Registered as protected from inquiries for scientific studies	▪ Self-reported active cancer or unknown cancer status
COLLECTED DATA			
Nutritional status, risk or presence of nutrition impact symptoms	▪ Body weight ▪ PG-SGA SF[b] ▪ MDADI[b] ▪ EAT-10[b]	▪ Body weight/body mass index ▪ NRS 2002 ▪ MUST ▪ PG-SGA SF ▪ MDADI ▪ Perception of own body weight ▪ Use of oral nutritional supplements/enteral nutrition.	▪ Body weight/body mass index ▪ NRS 2002 ▪ PG-SGA SF ▪ MDADI
Quality of life	▪ Qualitative focus group interviews ▪ EORTC QLQ-C30 ▪ EORTC QLQ-H&N35	▪ EQ-5D-5L ▪ EORTC QLQ-C30 ▪ EORTC QLQ-H&N35	▪ EQ-5D-5L ▪ EORTC QLQ-C30 ▪ EORTC QLQ-H&N35
Other outcome measures included in data analyses			Physical function: ▪ Maximal mouth opening ▪ Hand grip strength ▪ 30-second chair stand test ▪ 6-minute walk test Symptoms of anxiety and depression: ▪ HADS
DATA ANALYSES	<u>Qualitative data</u> ▪ Qualitative content analysis <u>Quantitative data</u> Summary of data: ▪ Descriptive statistics Changes from baseline to follow-up: ▪ Two-sided paired t-test ▪ Wilcoxon signed-rank test	Summary of data: ▪ Descriptive statistics Associations between nutrition score and QOL: ▪ Spearman's rank correlation coefficient Differences between subgroups: ▪ Kruskall Wallis H test ▪ Pearson's chi-squared ▪ Fisher's Exact test Assessment of selection bias: ▪ Two-sample two-sided t-test ▪ Pearson's chi-squared ▪ Fisher's Exact test	Summary of data: ▪ Descriptive statistics Differences between groups: ▪ Two-sample two-sided t-test (effect size: Cohen's d) ▪ Mann-Whitney U test (effect size *r*) ▪ Multiple linear regression Differences within groups: ▪ Two-sided paired t-test ▪ Wilcoxon signed-rank test Assessment of selection bias: ▪ Two-sample two-sided t-test ▪ Fisher's Exact test

DAHANCA: Danish Head and Neck Cancer Group, EAT-10: Eating Assessment Tool, EORTC: The European Organization for Research and Treatment of Cancer, HADS: Hospital Anxiety and Depression Scale, HNC: Head and neck cancer, MDADI: M. D. Anderson Dysphagia Inventory, MUST: Malnutrition Universal Screening Tool, NRS 2002: Nutritional Risk Screening 2002, PG-SGA SF: Scored Patient-Generated Subjective Global Assessment Short Form, QOL: Quality of life.

[a] Not requiring assistance with daily care

[b] Only assessed for participants recruited in 2018

4.1. Study designs

4.1.1. Study 1: Pilot study with qualitative focus group interviews (paper I)

In study 1, a multidisciplinary residential rehabilitation programme with a primary focus on the physical, psychological and social aspects of eating problems after treatment for HNC (hereinafter referred to as the "NUTRI-HAB programme") was pilot tested, and qualitative focus group interviews were carried out with participants.

In 2013 and 2014, RcDallund had offered the NUTRI-HAB programme twice with a maximum of 19 participants in each programme. The NUTRI-HAB programme was based on RcDallund's core model for residential rehabilitation programmes and adjusted through available evidence to meet the specific rehabilitation needs of HNC survivors. Due to the complexity of HNC survivors' rehabilitation needs, the programme was delivered as a coordinated multidisciplinary effort. The programme consisted of five days initial residential stay with two days follow-up residential stay after three months. In 2018, the NUTRI-HAB programme was offered once at REHPA with a maximum of 20 participants.

At RcDallund, different foods and drinks were used as stimulus materials in focus group interviews. With inspiration from participant-driven photo elicitation[119], participants at REHPA were encouraged to bring pictures of situations (own photos or pictures from websites, magazines etc.) where eating problems affected their everyday life. With participants' permission, these pictures were used as stimulus materials[6].

Participants in the NUTRI-HAB programme at REHPA were furthermore asked to complete selected nutrition screening tools, and their experiences of the tools regarding content relevance and user-friendliness were explored in the focus group interviews.

4.1.2. Study 2: Nationwide cross-sectional survey (paper II)

In study 2, a nationwide cross-sectional survey was carried out, and all Danish HNC survivors who had completed curatively intended radiation therapy for pharyngeal, laryngeal, or oral cancer 1-5 years before survey distribution were invited to participate[120]. The survey population was identified through the Danish Head and Neck Cancer Group's (DAHANCA) national clinical quality database. All hospital departments treating HNC are obliged to register patients in the database, and data can be obtained for research purposes upon application[121]. Updated contact information and permission to contact the population was obtained upon application to The Danish Health Data Authority.

The scope of the survey was broader than the objectives defined in study 2, and the 145-item survey questionnaire was composed of different validated questionnaires, items from other pre-tested questionnaires, and few purpose-designed items (Table 6).

Table 6: Content of the questionnaire used in the nationwide cross-sectional survey in study 2

	Domain	**Questionnaire/origin of items**	**Number of items**
Demographics	Current cancer status	Purpose-designed items	2
	Civil status and living arrangements	REHPA core questionnaire[122]	1
Health behaviour	Alcohol consumption	REHPA core questionnaire[122]	2
	Smoking	REHPA core questionnaire[122]	3
	Physical activity	The Danish National Health Survey (2013)[123]	2
		REHPA core questionnaire[122]	3
Nutritional status, nutritional risk and presence of nutrition impact symptoms	Nutritional risk or deficit.	PG-SGA SF[110]	4
		Purpose-designed items based on NRS 2002[107]	2
	Dysphagia-specific QOL	MDADI[113] (Danish version includes 4 extra items[117])	24
	Pre-cancer weight, weight loss, use of oral nutritional supplements/enteral nutrition.	Purpose-designed items	4
	Perception of own body weight	The Danish National Health Survey (2017)[124]	1
Health-related QOL	Generic health-related QOL	EuroQol EQ-5D-5L[125]	6
	Cancer-specific QOL	EORTC QLQ-C30[126,127]	30
	HNC-specific QOL	EORTC QLQ-H&N35[127,128]	35
Psychological wellbeing	Symptoms of anxiety and depression	HADS[129]	14
Rehabilitation	Rehabilitation needs	REHPA scale (adapted from the National Comprehensive Cancer Network® Distress Thermometer[130])	1
	Offered rehabilitation services and participation in these	Items from REHPA core questionnaire[122] adapted to HNC	2
	Experiences and perceptions of offered rehabilitation services	Purpose-designed items	3
Relatives	Perceived support from relatives	The Danish Cancer Society's barometer survey 2013[104]	1
	Perceived level of support for relatives from the health system	The Danish Cancer Society's barometer survey 2013[104]	3
NUTRI-HAB programme	Interest in participating in the NUTRI-HAB programme and in study 3	Purpose-designed item	1
	Request for permission to contact the individual with further information	Purpose-designed item	1

EORTC: The European Organization for Research and Treatment of Cancer, HADS: Hospital Anxiety and Depression Scale, HNC: Head and neck cancer, MDADI: M. D. Anderson Dysphagia Inventory, NRS 2002: Nutritional Risk Screening 2002, PG-SGA SF: Scored Patient-Generated Subjective Global Assessment Short Form, QOL: Quality of life.

4.1.3. Study 3: Randomised controlled trial (paper III and paper IV)

Study 3, the NUTRI-HAB trial, was a randomised controlled trial qualified by the results from the previous two studies. In the trial, effects of the NUTRI-HAB programme compared to standard care on body weight, QOL and physical function were tested.

Participants recruited among participants from study 2 were randomised to participation in the NUTRI-HAB programme at REHPA from baseline to 3-months follow-up or to a wait-list control group, that participated in the NUTRI-HAB programme from 3-months to 6-months follow-up (Figure 4). Groups were compared at 3-month follow-up to assess intervention effect[131].

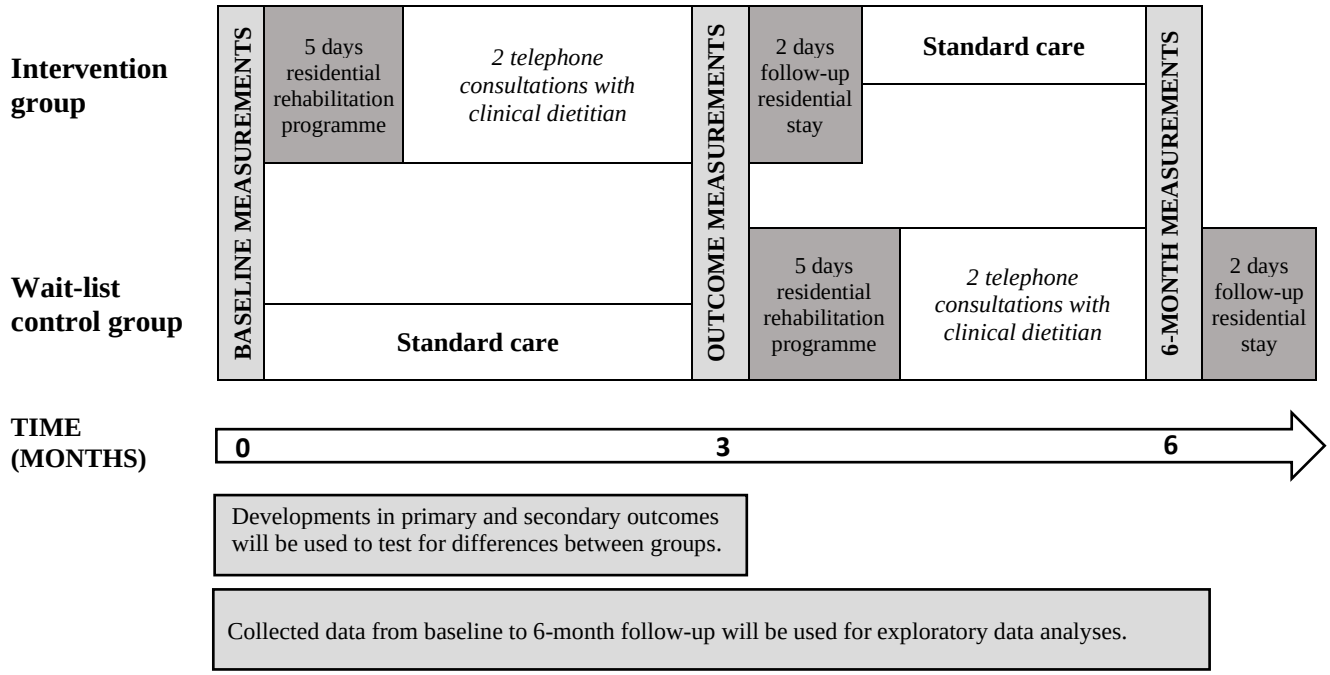

Figure 4: Timeline of the NUTRI-HAB trial

In study 1, the mean body weight change in percent during participation in the NUTRI-HAB programme was 1.74±2.37 when restricting to participants with cancer of the pharynx, larynx, or oral cavity who were 1-5 years posttreatment. Hence, to detect this difference between groups with a power of 80% and a significance level of 5%, 30 participants were required in each group in study 3. With an estimated withdrawal rate of 15%[6], the aim was to include 36 participants in each group[131].

4.2. Collected data

Data on nutritional status, risk or presence of nutrition impact symptoms, and quality of life were collected in all three studies (Table 5).

4.2.1. Nutritional status, nutritional risk and presence of nutrition impact symptoms

In all three studies, body weight was assessed as a crude measure of nutritional status. In study 1 and 3, body weight was measured by health professionals following strict protocols, whereas results from study 2 were based on self-reported body weight. Measures of nutritional status furthermore included body mass index, and weight loss, and in study 2, a question on participants evaluation of their current body weight was included.

Selected tools were used to assess nutritional risk or presence of nutrition impact symptoms. In study 1, participants at REHPA completed the PG-SGA SF, the MDADI, and the EAT-10. The three tools were selected because they, as described in 'Background' specifically assess or include nutrition impact symptoms in their assessment, because they have been translated and/or validated in Danish[116,117], and because MDADI and EAT-10 are suggested in the 'Integrated patient pathway'[10].

Based on results from study 1, PG-SGA SF and MDADI was included in the survey questionnaire for study 2 while EAT-10 was not. Items regarding dietary intake and magnitude of weight loss were included to allow for estimation of NRS 2002 score, since NRS 2002 is the recommended nutrition screening tool in Danish hospitals[132]. Furthermore, information on weight loss was used to assess MUST Score, since this screening tool has been developed by the Malnutrition Advisory Group of the British Association for Parenteral and Enteral Nutrition to detect malnutrition in all types of adult patients in all care settings[115].

In study 3, PG-SGA SF and MDADI were included based on their association with QOL in study 2. The NRS 2002 was again included as the recommended nutrition screening tool in Danish hospitals[132].

4.2.2. Quality of life

The World Health Organization defines QOL as *"an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical*

health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment"[133]. Hence, QOL covers many aspects, and it can be assessed in many ways.

In all three studies, cancer-specific QOL was assessed with The European Organization for Research and Treatment of Cancer's (EORTC) QLQ-C30[126,127], and the diagnosis specific EORTC QLQ-H&N35[127,128]. In study 2 and 3, generic QOL was assessed with EuroQol EQ-5D-5L[125]. In study 1, QOL in terms of how participants' daily life was affected was furthermore assessed through the qualitative focus group interview. The qualitative method has the advantage, that it may reveal new aspects of participants' QOL that are not being addressed in the standardised QOL-questionnaires and thus wouldn't become evident to the researchers when merely assessing QOL quantitatively.

4.2.3. Other outcome measures included in data analyses

In study 3, physical function in terms of maximal mouth opening, hand grip strength, 30-second chair stand test, and 6-minute walk test was measured, and Hospital Anxiety and Depression Scale (HADS)[129] was used to assess symptoms of anxiety and depression.

4.3. Data management

Research Electronic Data Capture (REDCap)[134] was used to distribute online questionnaires and to store outcome data. In study 2, data from paper-based questionnaires were entered in an electronic data sheet through optimal mark recognition scanning. In study 3, data from paper-based questionnaires and outcome data from physical measurements were entered in REDCap by one researcher, and then the entered data were doublechecked by another researcher[131].

4.4. Data analyses

4.4.1. Qualitative data analysis

Focus group interviews were audio recorded and transcribed verbatim[6]. Interview transcripts were analysed through qualitative content analysis[135] as illustrated in Table 7, where central themes related to the research objectives were derived. The software program NVivo 11 was used for the qualitative data analyses[6].

Table 7: Qualitative content analysis used in study 1

Meaning units related to the research objective	Condensed meaning units	Condensed meaning units abstracted/coded into researchers own word	Subthemes	Theme related to the research objective
"I also think I feel a development in myself, and I also see it among all the others. From last time, we were here and until now, we eat, we are actually seeking out new experiences. We will try this and that because, previously, we wouldn't dream of eating it, but we can just try. No harm is done by trying."	Participants have become more willing to try new food during the programme.	Increased courage to experiment with food.	Increased courage to eat.	***Increased courage to eat – A safe and supportive environment to practice eating skills.***
"When I think about food now, it actually makes me happy. Not that long ago it was just: I need it because otherwise I won't be able to stand. The opportunity to taste and try so many different things – and we are equal and all look strange when we eat – it has meant that we have dared – that I have dared to eat more things."	Opportunity to experiment and to eat with others in the same situation gave increased courage to eat new things.	New food experiences gave courage to further food experiments.		
		Eating with peers gave increased feeling of social acceptance, normality and courage to eat.		
"I have been living on tube feeding until Friday, where I said: 'So, now someone is taking care of me', so I dared to stop with the tube."	Being followed by health professionals in the programme made participant dare to stop with tube feeding.	Programme gave a feeling of safety.	Program was a safe environment.	

The table[6] illustrates examples of how themes related to head and neck cancer survivors' experiences of everyday life with eating problems after treatment were derived from identified meaning units in transcripts of focus group interviews in study 1.

4.4.2. Statistical analyses

In all three studies, descriptive statistics were used to summarise participant characteristics and quantitative data.

In study 1 and 3, differences within groups from baseline to follow-up were tested using two-sided paired t-test for normally distributed data and Wilcoxon Signed-rank test for other data.

Different statistical methods were used to assess differences between subgroups or groups in study 2 and 3 depending on variable characteristics, number of (sub)groups, and distribution of data. For categorical variables, differences were tested using Pearson's chi-squared test or, if any cells in the contingency table contained <5% of the observations, Fisher's Exact test. For continuous variables, differences between two groups were tested using a two-sample two-sided t-test for normally distributed data, and Mann-Whitney U test for other data. Differences in continuous variables between more than two (sub)groups were tested using Kruskall Wallis H test.

To assess intervention effect in study 3, changes in outcome variables were calculated for each participant and differences between groups were tested. Effect size was estimated with Cohens d[136] for normally distributed data, while effect size (r) was estimated for other data by dividing the z value obtained in the Mann Whitney U test with the square root of the number of observations[137]. In intention-to-treat analysis, multiple imputations were used to account for missing data in the primary endpoint, percentage change in body weight, under a missing at random assumption[138].

Simple linear regression was used to assess differences between groups in intention-to-treat analysis in study 3, while multiple linear regression was used for adjusted analyses.

Spearman's rank correlation coefficient was used to assess the relationship between participants' nutritional scores and QOL in study 2[120].

In study 3, a blinded researcher performed per protocol analyses of differences between groups in SAS® Enterprise Guide® 7.1, and the project group interpreted results before unblinding[131,139]. All other quantitative data in the studies were analysed in STATA/IC 15.0 (study 1) or STATA/IC 16.0 (study 2 and 3).

In correlation analyses in study 2, a significance level of 0.001 was applied to account for the multiple testing, while a significance level of 0.05 was applied for all other analyses[120].

4.5. Ethical considerations

The Regional Committees on Health Research Ethics for Southern Denmark concluded that none of the studies were subject to the duty to notify since no biological material was included (journal number 20182000-152 and 20182000-165).

The studies were registered by The Danish Data Protection Agency through the Region of Southern Denmark (study 1+3: registration number 2012-58-0018, approval number 18/14847, study 2: journal number 18/51739).

The studies were conducted in accordance with the Declaration of Helsinki[140]. Informed written consent was obtained from all participants in study 1 and 3, and they were informed verbally and in writing that participation was voluntary, and that they could withdraw their consent at any time. In study 2, individuals were informed that participation in the survey was voluntary. In the cover letter for the survey questionnaire, telephone number and email address of the principal researcher was included in case invited individuals had questions or wished to decline participation.

All personal data were kept confidential and presented so no individual participant can be identified.

To verify adherence to original intent, study 3 was registered in the database Clinical Trials (www.clinicaltrials.gov, NCT03909256) before inclusion of participants, and the detailed trial protocol (paper III) was published[131].

4.5.1. Patient and public involvement

Patient and public involvement has been used in several steps of the three studies. In study 1, participants contributed with ideas for further qualification of the intervention in study 3, and selection of nutrition and screening tools to include in study 2 and 3 was based on their evaluation. The preliminary trial protocol for study 3 was furthermore presented and discussed at a workshop for REHPA's user panel consisting of former participants in REHPA's programmes and patient organisation representatives. Input from patient involvement led to adjustments of the programme and to the decision that the NUTRI-HAB programme

would not be aimed at or include relatives for now, since patients were concerned that social interaction and candidness among participants would be affected.

Participants from study 3 will be invited to a symposium with presentation of the main results on the PhD project, and they will be welcome to contribute with suggestions for explorative analyses of patient interest to inform future research questions based the NUTRI-HAB study.

5. Results of included studies

5.1. Participants

For all three studies, participants were recruited from all over Denmark. Hence, the level of rehabilitation that they had received prior to participating in the given study varied. Except for one participant in study 1, all participants had been treated with radiation therapy. The survey in study 2 was distributed to 1937 individuals, and 1190 (61.4%) responded. Participant characteristics are presented in Table 8.

Table 8: Characteristics of participants included in the three studies

	STUDY 1 (n=40)	**STUDY 2 (n=1190)**	**STUDY 3 (n=71)**
Gender			
Male	20 (50.0%)	891 (74.9%)	46 (64.8%)
Female	20 (50.0%)	299 (25.1%)	25 (35.2%)
Age			
Mean ± SD	61.1 ±9.3	65.6 ± 9.1	64.3 ± 8.2
Median [range]	60.0 [39-80]	65.4 [32-91]	63.5 [35-85]
Cancer diagnosis			
Oral cavity	5 (12.5%)	100 (8.4%)	3 (4.2%)
Pharynx	23 (57.5%)	839 (70.5%)	59 (83.1%)
Larynx	1 (2.5%)	251 (21.1%)	9 (12.7%)
Esophagus	4 (10%)	0	0
Thyroid	1 (2.5%)	0	0
Salivary gland	1 (2.5%)	0	0
Unknown/other primary tumor with cervical metastases	5 (12.5%)	0	0
Time interval (months) from completion of radiation therapy			
Mean ± SD	19.2 ± 34.3[a]	34.3 ± 14.0	33.2 ± 14.5
Median [range]	7.2 [2.7-170.1][a]	33.0 [12-59]	33.2 [12-58]
0-11 months	25 (65.8%)[a]	0	0
12-23 months	9 (23.7%)[a]	345 (29.0%)	24 (33.8%)
24-35 months	0	296 (24.9%)	11 (15.5%)
36-47 months	1 (2.6%)[a]	267 (22.4%)	21 (29.6%)
48-59 months	0	282 (23.7%)	15 (21.1%)
> 48 months	3 (7.9%)[a]	0	0

[a] n=38 (one participant had not received radiation therapy, and for one participant information on time interval from radiation therapy was missing).

5.2. Summary of results

The main results of the three studies are presented in Table 9 and will be summarised in the following.

Table 9: Summary of main results of the included studies

	STUDY 1	STUDY 2	STUDY 3
Effect of multidisciplinary nutritional rehabilitation	**Results from analysis of objective 1** HNC survivors experienced the NUTRI-HAB programme as a safe and supportive environment to practice eating skills, and they benefitted from meeting peers. Through the programme, they gained knowledge and skills that many of them had been missing. **Results from analysis of objective 2** During the NUTRI-HAB programme, participants' body weight increased significantly (p=0.042), and significant improvements were seen in QOL scales 'Physical function (p=0.038), 'Swallowing' (p=0.034), 'Speech problems' (p=0.016), 'Trouble with social eating' (p=0.010), 'Feeding tube' (p=0.046), and 'Weight loss' (p=0.014).		**Results from analysis of objective 1** Compared to standard care, the NUTRI-HAB programme had no significant effect on body weight change. Overall trends towards greater improvements in the intervention group than in the control group were seen for physical function (hand grip strength: p=0.042, maximal mouth opening: p=0.072) and QOL domains ('Role functioning': p=0.041; 'Speech problems' p=0.040, 'Pain: p=0.048' and 'Fatigue' p=0.053). However, compared to the control group, the intervention group also had a significant greater increase in 'Felt ill' symptom level (p=0.020).
Assessment of rehabilitation needs	**Results from analysis of objective 3** Eating problems had substantial negative effects on HNC survivors' daily life. Often, they led to social withdrawal and challenged social relationships. Eating was experienced as an obligation or a training situation. **Results from analysis of objective 4** HNC survivors' experiences of selected nutrition screening and assessment tools: PG-SGA SF: ▪ User-friendly ▪ Relevant ▪ Content adequate for health professionals MDADI: ▪ Confusing for a few participants ▪ Relevant ▪ Gave rise to self-reflection EAT-10: ▪ Content not as relevant as in the other tools	**Results from analysis of objective 1** Nutritional characteristics are still adversely affected in Danish HNC survivors 1-5 years after RT: ▪ 12.2% had a PG-SGA SF score of ≥9 ▪ 15% had MDADI composite score<60 ▪ 48.4% had a current body weight <95% of their precancer body weight ▪ 17.3% considered their weight too low ▪ 11.7% required enteral nutrition **Results from analysis of objective 2** Statistically significant correlations (p<0.001) were seen between all QOL scales and NRS 2002 score, MUST score, PG-SGA SF score, MDADI global, and MDADI composite score. BMI only showed statistically significant correlation with 'Trouble with social eating'. Overall, PG-SGA SF and MDADI showed strongest correlations with QOL. Correlations were particularly strong with 'Trouble with social eating' (PG-SGA SF: r_s=0.63, MDADI composite: r_s=-0.75).	

BMI: Body mass index, HNC: Head and neck cancer, MDADI: M. D. Anderson Dysphagia Inventory, MUST: Malnutrition Universal Screening Tool, NRS 2002: Nutritional Risk Screening 2002, PG-SGA SF: Scored Patient-Generated Subjective Global Assessment Short Form, QOL: Quality of life, RT: Radiation therapy.

5.2.1. Effect of multidisciplinary nutritional rehabilitation

Results from qualitative data analyses in study 1, showed that HNC survivors benefitted from participation in the NUTRI-HAB programme[6]. Quantitative data from study 1, showed that during participation in the NUTRI-HAB programme, participants' body weight increased significantly (p=0.042), and improvements were seen in several QOL scales.

In study 3, no significant change was seen in body weight in the intervention group, and no significant difference was seen between intervention and control group in body weight change. There was an overall trends towards greater improvements in physical function and certain quality of life domains in the intervention group.

5.2.2. Assessment of rehabilitation needs

Qualitative data from study 1, illustrated the wide-ranging negative effects of eating problems on HNC survivors' everyday lives, Figure 5.

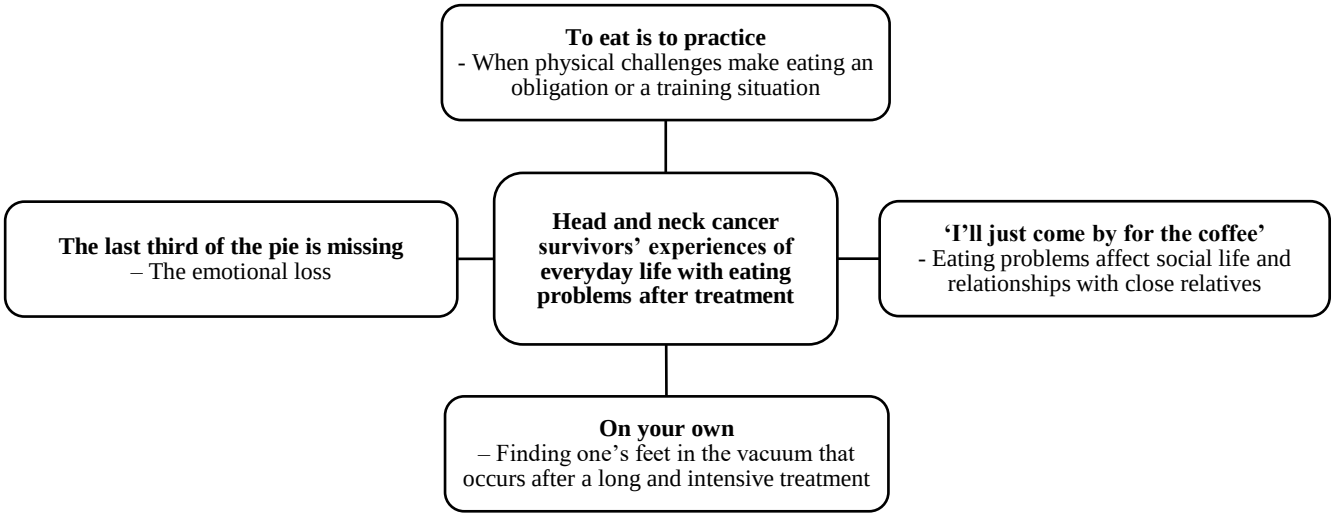

Figure 5: Head and neck cancer survivors' experiences of everyday life with eating problems after treatment[6]

Study 2 demonstrated that nutritional status and nutritional risk were still adversely affected 1-5 years after completion of radiation therapy, and only few differences were seen between subgroups based on time interval from treatment completion.

As for the relevance of different nutrition screening and assessment tools, participants in study 1 agreed that screening and assessment tools could be useful to address rehabilitation needs. They considered the content of the PG-SGA relevant and adequate for the health professionals, and they found the tool user-friendly. While a few participants found the MDADI confusing, most participants found it relevant, and to some, it even gave rise to self-reflection. This self-reflection was mainly considered positive, but it could also lead to increased awareness of own limitations. Participants did not consider EAT-10 as relevant as the other tools, since it did not address activities and function and it gave no rise to self-reflection.

In study 2, NRS 2002 score, PG-SGA SF score and MDADI scores showed highly statistically significant correlations ($p<0.0001$) with all the QOL scales indicating that a high degree of nutritional challenges measured by the given tool was associated with a worse QOL. BMI was only weakly correlated to 'Trouble with social eating' and not to the other scales. Among the different screening and assessment tools, participants' scores in the PG-SGA SF and MDADI showed the strongest correlation with QOL.

6. Discussion

The overall aims of the thesis were to strengthen the evidence base for multidisciplinary nutritional rehabilitation services in HNC survivors and to create new knowledge on whether HNC survivors' needs for nutritional rehabilitation can be assessed systematically using existing screening and assessment tools. In this chapter, the results will be discussed followed by a discussion of methodological considerations, strengths, and limitations.

6.1. Effects of multidisciplinary nutritional rehabilitation

In study 1, qualitative results indicate that HNC survivors benefited from participation in the NUTRI-HAB programme, and quantitative data in a small sample of patients showed increased body weight and improvements in several QOL scales[6]. In the randomised controlled trial in study 3, the effect on body weight could not be replicated, thus no difference in changes in body weight was seen between the intervention and the control group, but overall trends towards greater improvements in physical function and QOL were seen in the intervention group[139].

As Table 10 illustrates, participants in study 3 were further ahead in their treatment trajectory than participants in study 1, and increased body weight was not a desired outcome for most of the participants in study 3. Since the counselling sessions with the clinical dietitian during the NUTRI-HAB programme was targeted the individual participant's desired outcome, no overall effect on body weight could be expected in the given sample.

Most of the improvements in QOL seen in study 1, were also seen within the intervention group in study 3, but the trial was not powered to detect differences in QOL between groups[139]. Furthermore, there tended to be a ceiling effect on several QOL scales in study 3, therefore improvements for many participants in these scales were not possible. This ceiling effect may occur due to the recruitment method. As discussed in paper IV, some participants accepted the invitation to participate in the NUTRI-HAB programme to support research despite few rehabilitation needs[139]. Still the significant changes occurring within groups and the trends towards greater improvements in the intervention group indicate, that the NUTRI-HAB programme has beneficial effect on certain QOL scales, but this should be confirmed in larger trials where relevant inclusion criteria should be applied.

As described in chapter 2, study 1 and 3 are the first studies to explore the effects of multidisciplinary residential nutritional rehabilitation programme in HNC survivors. Hammerlid et al. pilot tested the effect of a 1-week residential psychoeducational programme in 14 HNC survivors 12-22 months posttreatment, but the programme was not specifically aimed at managing eating problems. Yet, at follow-up they still saw the greatest improvements in the EORTC QLQ-H&N37 scales 'Trouble eating' and 'Problems enjoying your meals'[103]. Consistent with results from study 3, this could indicate that residential programmes support the HNC survivors' ability to cope with physical symptoms rather than reduce physical symptom severity.

An interesting finding of study 1, that might contribute to the effect of the residential rehabilitation programme, was participants' experiences of the programme as a safe environment to practice eating skills, and their benefit from eating together with peers[6]. No qualitative data collection was made in study 3, but judged from clinical experience during the present trial, the benefit of meeting peers and sharing experiences over the meals was as great in study 3 as in study 1. Other studies have described how HNC survivors benefit from meeting peers[80,141], but to our knowledge, no other studies have assessed HNC survivors' experiences of eating together with peers. This aspect is relevant to study further and to explore whether the same safe eating environment and candidness among peers can be created in other settings than the residential rehabilitation programme. Since participants also found the practical kitchen workshops useful, it could potentially be in weekly cooking clubs with social eating clubs.

6.2. Assessment of rehabilitation needs

Study 1 demonstrated the substantial negative effects of eating problems on HNC survivors' everyday life. Results illustrated how rehabilitation needs in relation to nutrition impact symptoms and eating problems in HNC survivors are far more wide-ranging than management of weight loss and impaired nutritional status[6], and supported the rationale for a multidisciplinary approach. Since an inclusion criterion for study 1 was that participants should find themselves in need of rehabilitation to manage eating problems, results could not be generalised to all Danish HNC survivors, and no conclusions on the magnitude of nutritional challenges among Danish HNC survivors could be made. However, the nationwide survey in study 2 confirmed, that nutritional challenges and unmet rehabilitation needs are not unique to participants in study 1. The study clearly demonstrate that nutritional challenges indeed are frequent among Danish HNC survivors 1-5 years posttreatment[120].

In study 2, only few differences were seen in nutritional characteristics and QOL between subgroups defined by time interval posttreatment[120]. This could indicate that few spontaneous improvements occur over time from 1 year posttreatment to 5 years posttreatment, which underpins the need for continuously assessment of needs for nutritional rehabilitation even in the late posttreatment phase. Since the study was cross-sectional study and not prospective, no firm conclusions can be drawn on this, but the study confirmed a high prevalence of unmet rehabilitation in Danish HNC survivors with one third of participants reporting that they found the offered rehabilitation services inadequate. Among these participants, unmet rehabilitation needs were most frequently reported in relation to management of late effects (68.8%) and management of dysphagia and other eating problems (47.7%).

Among screening and assessment tools, PG-SGA SF and MDADI were considered most relevant by participants in study 1, and they furthermore showed strongest correlations with participants' QOL in study 2. Despite being developed for different purposes, and MDADI not traditionally being categorised as a nutrition screening tool, both tools address nutrition impact symptoms in a broad assessment including both weight loss and measures of activities and function. Bearing in mind the wide-ranging nutritional rehabilitation needs of HNC survivors documented in study 1 and 2, the broad scope of PG-SGA SF and MDADI may very likely be the reason for their perceived relevance and their strong correlations with QOL in HNC survivors. Apparently, screening methods like MUST and NRS 2002 that primarily addresses weight loss and stress metabolism, were not broad enough to capture the complex rehabilitation needs of HNC survivors.

Yet, from results of study 1 and 2 it is still not possible to conclude whether PG-SGA SF or MDADI are able to identify HNC survivors who will benefit from nutritional rehabilitation. This should be tested in clinical studies, and it was in fact the secondary objective of study 3. Hence, these data will be analysed subsequently and published in the future.

The screening and assessment tools NRS 2002, MUST, PG-SGA SF, MDADI, and EAT-10 were included in the thesis since they are recommended by either the Danish Health Authority[132] or ESPEN[13,109], or because they are widely used in cancer patients[110]. Several other tools have been developed to assess nutritional risk and/or presence of nutrition symptoms[42,142], but evidence is limited on their applicability in systematic assessment of needs for nutritional interventions in HNC and other cancer patients and survivors in hospital and community-based health care settings. An overview of these tools and their validity would be useful for clinicians and researchers in both hospital and community-based health care settings in their decisions on tools to implement or test in clinical practice or clinical studies. We are

currently undertaking a systematic review[143] to provide this overview and to explore whether other tools could potentially be more relevant to include.

Based on participants' experiences and evaluation in study 1, MDADI and PG-SGA SF were chosen over EAT-10 for inclusion in the subsequent studies. While it is crucial to consider the perspectives of HNC survivors since they are the target group, they are not the only stakeholders whose opinion should be considered when selecting screening tools to implement in clinical practice. Implementation of nutritional screening in clinical practice may be affected by the health professionals' perceptions of the recommended screening tool[144], and while a positive perception of the tool may facilitate the implementation[145], a tool that is considered too complicated will not be used despite appropriate training[146]. Hence, if the future data analyses support the use of PG-SGA SF and MDADI in the needs assessment of HNC survivors, an exploration of whether the health professionals who will be performing and interpreting the screening find the tools meaningful and feasible should be carried out prior to deciding on any recommendations.

Since rehabilitation, and hence the assessment of rehabilitation needs, should consider the person's situation as a whole[87], it can be questioned whether it relevant to use tools that merely assess needs for nutritional interventions. However, it is not the intent that a selected nutrition screening tool should be used as a single measure. Rather it should be included as a part of the systematic assessment of rehabilitation needs in combination with validated screening tools covering other rehabilitation domains. Just as rehabilitation per se, the needs assessment should be a cooperative process, in which the individual HNC survivors' goals and wishes for their everyday life despite potential late effects are explored to ensure the most appropriate interventions.

6.3. Methodological considerations, strengths and limitations

A major strength of the PhD thesis is the triangulation of different research methods in three coherent well-designed studies that complement each other in the pursue of the overall aims. In study 1, objectives included exploration of HNC survivors' experiences, and hence, a qualitative approach was appropriate. In study 2, the cross-sectional design was suitable to assess the prevalence of nutritional challenges and their associations with QOL among Danish HNC survivors, and in study 3, the randomised controlled trial was the preferred study design to test the measurable effect of the NUTRI-HAB programme.

Study 1 and 3 are the first studies to explore the potential of multidisciplinary residential rehabilitation programmes, and the nationwide survey with a high response provides a unique and comprehensive data

material that creates new knowledge on the nutritional challenges, rehabilitation needs, and QOL of Danish HNC survivors.

In study 3, a well-designed a well-designed intervention with a multidisciplinary approach is delivered to meet the complex needs of the target group, and the study will be among few others who have reported comprehensive multidisciplinary interventions in HNC rehabilitation[97].

In the three studies, several efforts were made to strengthen the internal and external validity. To minimise information bias, all physical outcome measurements were performed by trained health professionals following strict protocols, and measures were taken to ensure correct data entry from measurements and paper-based questionnaires. Identification of the survey population through DAHANCA's national clinical quality database not only reduced the risk of selection bias, but also provided a comprehensive data material on patient characteristics allowing for detailed description of the population and assessment of potential selection bias. In study 3, randomisation reduces the risk of confounding, and blinded data analysis and interpretation of results minimise the risk of experimenter bias. Furthermore, the study was registered in clinicaltrials.gov, and the detailed protocol was published to verify that the trial and data analyses were performed in compliance with original intent.

6.3.1. Participant recruitment and inclusion criteria

Different recruitment strategies were used in study 1 and study 3. In study 3, recruitment through the nationwide survey could potentially reduce the risk of selection bias, but it also meant that participants were recruited later in their trajectory than would have been the case if recruitment had taken place at the hospitals. This also led to the observed differences between participants in the two studies in regards of time interval posttreatment. Yet, as the studies showed, some HNC survivors still had great rehabilitation needs even though they were years posttreatment.

The few inclusion criteria in study 3 may have affected results on intervention effect, since it can be assumed that individuals with few rehabilitation needs will have little effect of the intervention. Since the secondary objective of the trial was to explore relevant inclusion criteria through assessment of associations between participants score in the selected nutrition screening and assessment tools, and their effect of the intervention, it was not appropriate with further inclusion criteria.

6.3.2. Choice of primary outcome measure

As discussed in paper IV, changes in body weight was not a relevant outcome measure for most participants in study 3. The selection of body weight changes as primary outcome was based on results from study 1, where body weight was still an issue for many participants and significant increases were seen during the NUTRI-HAB programme. Study 2 further showed that approximately half of participants' body weight still amounted <95% of their precancer weight. Yet, many of them did not want to reach the precancer level, which can possibly be explained by the high prevalence of overweight and obesity even posttreatment. Hence, if the primary outcome should be an objective measure of nutritional status, a measure of body composition could possibly have been more relevant than body weight among participants in study 3.

The great variation in participants' nutritional risk dependent on screening method supported the hypothesis that participants needs for nutritional interventions concerned management of nutrition impact symptoms rather than weight loss[139]. Hence, a participant-reported outcome measure of how participants coped with the eating problems could possibly have been a more relevant primary outcome. With study 1 and other studies demonstrating the widespread consequences of eating problems on HNC survivors' social life, we suggest that the EORTC QLQ-H&N-35 symptom scale 'Trouble with social eating' could potentially be a more relevant outcome. In both study 1 and study 3, participants had significant improvements in this symptom scale, but study 3 was not powered to show any differences between groups. Other measures could also be relevant. Per definition, rehabilitation is a goal-oriented cooperative process that should consider the person's situation as a whole[87], and rehabilitation interventions should focus on goals and wishes of the individual partitipant[147]. In Goal Attainment Scaling, it is quantified to which extent a participant's individual goals are achieved during the intervention[148,149]. Goal Attainment Scaling has been applied in several health settings including mental health care settings, elderly care settings, and chronic pain rehabilitation[149], but to our knowledge, no studies have used Goal Attainment Scaling in HNC rehabilitation. Since rehabilitation interventions are complex health interventions undertaken in complex environments, Wade suggests that rehabilitation research, in contrast to traditional biomedical research, should include several primary outcomes to measure the distal effect of the intervention, and at least one intervening variable measure of the proximate effect[150]. Goal Attainment Scaling could potentially be used as measure of proximate effect or as primary outcome in combination with other relevant measures. However, the method should be pilot tested in the target group to assess its relevance and applicability. In study 1, HNC survivors were involved in selection of the nutrition screening tools to include in studies 2 and 3, but it would also have been relevant to involve them in selection of outcome measures, including patient-reported outcome measures.

6.3.3. Duration of the NUTRI-HAB trial

In study 3, the effect of the NUTRI-HAB programme was measured at 3-month follow-up, and hence did not assess the effect of clinical activities scheduled in the two days follow-up residential stay. In the design of the NUTRI-HAB programme, this was considered, and interventions primarily aimed at managing eating problems were schedules in the initial five days residential rehabilitation stay. A five-day rehabilitation intervention may seem inadequate to support HNC survivors in management of nutrition impact symptoms that has been challenging them for months or years, but the intervention was not intended to be limited to the residential stays. Rather, the aim was that participants considered the full three months as a coherent programme, where they continued working on the goals, they defined in their action plans in the end the five days initial residential stay. Goal Attainment Scaling[148] could potentially have been a part of the action plan to allow evaluation of progress at follow-up and during the telephonic consultations with the clinical dietitian from baseline to follow-up.

Wade emphasizes that effects of rehabilitation should ideally be measured long time after initiation of any intervention, since new behaviours are not necessarily transferable from one setting to another and since some effects of the complex interventions may be delayed. While an optimal time point cannot be provided, Wade argues that effect of rehabilitation should rarely be measured before 6 month after initiation of the intervention[150]. Hence, it can be questioned whether it was too early to measure the effect of the NUTRI-HAB programme at 3-month follow-up. Data collection was performed at 6-month follow-up for exploratory purposes, but since the wait-list control group received the intervention from 3-month to 6-month follow-up, it does not make sense to compare 6-month data across groups. Furthermore, while many participants in the intervention group still filled out questionnaires with patient-reported outcome measures, only 20 of the 36 participated in physical measurements at 6-month follow-up, and hence data are limited. The physical measurements were scheduled at three different outpatient clinics, and even though participants could choose the clinic closest to their home, some of them still had a long way to travel. With no other activities scheduled than the physical tests, it is likely that some of them did not consider the measurements worth the drive. In future studies, it should be considered how long-term follow-up can be optimised e.g. through measurements in participants' own home.

6.3.4. Statistical considerations

In study 3, 30 participants in each group were required sample size to detect a difference of 1.74±2.37 in percentage body weight change between groups. While multiple imputations were used to account for missing data in intention-to-treat analysis, only 29 participants in the intervention group had body weight

measurements performed at 3-month follow-up. Hence, per protocol analysis of the primary endpoint was slightly underpowered. However, from the results it seems very unlikely that a larger sample size would have changed results for primary outcome. This is consistent with the finding, that changes in body weight was not a relevant outcome measure for most participants. The study was not powered to show effects on secondary outcome, our results on intervention effect on these should be considered exploratory and be tested in a larger sample size.

In neither study 1 nor study 3, did we account for multiple testing, and results may be subject to type 1 errors, i.e. 'false positive' findings. Potentially, we could have accounted for this using e.g. Bonferroni correction, where the significance level is divided by the number of statistical tests[151], but this would have increased the risk of type 2 errors. Since the studies were exploratory, we did not want to miss potential effects on secondary outcome, and hence, no correction was made.

6.3.5. Trustworthiness of the qualitative study in paper 1

In the qualitative research tradition, different criteria are often used to assess validity or trustworthiness than in quantitative studies. Graneheim and Lundman suggest that for qualitative content analysis, the aspects credibility, dependability, and transferability should be considered[135]. Credibility describes confidence in how well the data and analyses address the intended focus[135]. Hence, it both refers to whether the selected respondents, context, and data collection method will provide a data material rich enough to explore the given topic, and to whether meaning units defined in the analysis process are suitable[135]. To strengthen credibility, a broad participant group in terms of diagnosis, time interval posttreatment, and place of residence (and hence treating hospital) was recruited in study 1, and identified meaning units and themes were discussed thoroughly between two researchers during the analysis. Dependability refers to taking into consideration changes in data or data collection method over time[135]. With the focus groups at RcDallund being carried out in 2013/2014 and the ones at REHPA being carried out in 2018, the semi-structured interview guides contributed to ensure consistent data collection over time. Instead of generalisability, the term transferability is suggested to describe the extent to which the finding of the qualitative content analysis can be transferred to other settings or groups than the one studied. Graneheim and Lundman emphasize, that the researcher can give suggestions about the transferability of the results, but reader decides whether results are transferable. Hence, to enhance transferability, the context, selection of participants, and methods for data collection should be described in detail, together with a rich description of findings supported by appropriate citations[135]. These detailed descriptions are provided in paper I in accordance with COnsolidated criteria for REporting Qualitative research (COREQ) Checklist[152]. With a relatively large number of participants, who covered a broad range

in terms clinical and demographic characteristics, we argue that the focus groups in study 1 provided a good insight into how posttreatment eating problems are experienced by Danish HNC survivors. Furthermore, these results were comparable with results from qualitative studies performed in other countries. Hence, we suggest that results regarding the impact of eating problems are transferable to other HNC survivors.

6.3.6. Generalisability of results

As discussed, generalisability is not necessarily an aim in qualitative studies, and even though the experiences of participants in study 1 were not unique to them, they could not necessarily be generalised to all Danish HNC survivors. However, results from study 2 demonstrated that the challenges were in fact shared by a large proportion of Danish HNC survivors.

It should be kept in mind, that only 13 participants recruited in 2018 participated in the evaluation of the nutrition screening and assessment tools, and their experiences and evaluations of the tools may not be generalisable. The ongoing systematic review on nutrition screening and assessment tools in cancer patients and survivors[143] may provide insights into, whether these experiences are unique to our participants.

Being a nationwide survey with a high response rate, participants in study 2 are likely to be representative for the population of Danish HNC survivors 1-5 years posttreatment, but as discussed in paper II, selection bias cannot be ruled out. This could potentially have affected the external validity and hence, the generalisability of results. In a future publication, the data from the nationwide survey will be linked to national registries to allow an even more detailed description of the population in terms of socioeconomic status, comorbidity, and delivered health services. Hence, a more detailed assessment of potential selection bias can be performed.

Since participants in study 3 were recruited among participants in study 2, potential selection bias from study 2 has been carried forward. Furthermore, additional selection bias may have been imposed. The NUTRI-HAB programme required participants to be self-reliant which may have excluded the most vulnerable HNC survivors. Hence, conclusions on residential rehabilitation programmes' effect are not generalisable to this subgroup. Yet, some of the elements that were found beneficial by participants in the NUTRI-HAB programme, e.g. meeting peers, are likely be beneficial to these individuals even though they would have to be delivered in another setup than the residential rehabilitation programme.

Residential programmes like the NUTRI-HAB programme are resource-demanding and may not be readily transferable in Danish municipalities. However, if future results prove them cost-beneficial, collaborations across municipalities could be established. This would allow for creating the opportunity to meet peers even in small municipalities with few HNC survivors. In the meantime, it would be relevant to explore how elements of the NUTRI-HAB programme e.g. social cooking and social meals can be implemented in municipal rehabilitation services.

7. Conclusions

Through triangulation of research methods, the thesis and its four enclosed papers have contributed to strengthen the evidence base for multidisciplinary nutritional rehabilitation services in HNC survivors and to create new knowledge on systematic assessment of HNC survivors' needs for nutritional rehabilitation.

From the studies it is concluded that nutrition impact symptoms and eating problems have substantial negative consequences on HNC survivors' everyday life, and nutritional challenges are still frequent in Danish HNC survivors 1-5 years after completion of curatively intended radiation therapy with potential consequences for their QOL. HNC survivors' rehabilitation needs are complex, and especially in the late posttreatment phase, needs for nutritional interventions comprise needs for support to manage nutrition impact symptoms rather than weight loss, indicating the need for a multidisciplinary approach in nutritional rehabilitation services.

For the first time, the effect of a multidisciplinary residential nutritional rehabilitation programme has been explored, and the NUTRI-HAB programme was experienced as a safe and supportive environment to practice eating skills, and participants experienced great benefit from meeting peers. In HNC survivors referred by physician, body weight increased significantly, and improvements were seen in QOL. Compared to standard care, the programme had no effect on changes in body weight in HNC survivors recruited based on self-reported interest in participation, but it possibly has effects on physical function and QOL. The effect on body weight is potentially dependent on time interval posttreatment, and patient-reported outcome measures on participants' coping with eating problems or achievement of their individual goals could potentially be more relevant outcome measures. Future studies should explore the effect of the NUTRI-HAB programme in different subgroups of HNC survivors and explore relevant inclusion criteria, timing and outcome.

Among selected nutrition screening and assessment tools, PG-SGA SF and MDADI were considered most relevant by HNC survivors, and these tools also showed strongest correlations to participants QOL. Screening methods that primarily addresses weight loss and stress metabolism such as NRS 2002 and MUST, were not broad enough to capture HNC survivors' complex needs for nutritional rehabilitation. Future studies should explore whether MDADI and PG-SGA SF are able to identify HNC survivors who will benefit from nutritional rehabilitation. Data for this purpose have been collected in the NUTRI-HAB trial, and results will be published in the future.

8. Perspectives

8.1. Implications for clinical practice

Since results from the thesis and the included studies will be presented widely both nationally and internationally, they can contribute to increase awareness of the challenges that HNC survivors are facing. Results describing the magnitude and nature of unmet rehabilitation needs in Danish HNC survivors are useful for planning future clinical approaches/research and organisation of rehabilitation services. Since the population of HNC survivors is increasing with a consequent increased demand for proper rehabilitation services, this is highly relevant.

The results underpin the need for a multidisciplinary approach in management of nutrition impact symptoms and other late effects in HNC survivors, and it provides promising results for the effect of such multidisciplinary interventions. Even though residential rehabilitation programmes may not be readily implementable in all municipalities, elements of the NUTRI-HAB programme could be implemented. With results showing how much participants benefited from meeting peers, diagnosis-specific group-based rehabilitation programmes could be considered as appropriate approaches in nutritional rehabilitation in the municipalities. With the national mapping of cancer rehabilitation services showing that only 17 of 98 municipalities offered diagnosis-specific rehabilitation services for HNC survivors in 2017, it becomes evident that the potential of peer support is not realised fully in the Danish municipalities.

The results confirm that assessment of rehabilitation needs in HNC survivors is crucial even years after treatment, and the assessment should be broader than simply assessing body weight, body mass index, or weight loss. Depending on the results of the future analyses of associations between PG-SGA SF or MDADI and intervention effect, the potential implementation of these in the systematic assessment of rehabilitation needs should be explored. As discussed, this include exploring the perspectives of the health care professionals who will be offering the needs assessment.

8.2. Future research perspectives

As concluded in the thesis, future studies should explore the effect of multidisciplinary nutritional rehabilitation in different subgroups of HNC survivors, and at what timepoint in the diseases trajectory it would be most appropriate to offer intervention. Since residential rehabilitation programmes may not be

readily implementable everywhere, additional methods of delivering multidisciplinary nutritional rehabilitation services should be explored.

Furthermore, relevant inclusion criteria for referral to multidisciplinary nutritional rehabilitation, and hence methods to assess needs for nutritional rehabilitation should be assessed. This includes further assessment of the applicability of different nutrition screening and assessment tools both in clinical studies and in the ongoing systematic review[143].

Given the social importance of meals and our participants' experiences of how eating problems affected the relationship with the relatives, future studies on how the social interactions in the family are affected and on how nutritional rehabilitation services could include the relatives without jeopardising the candidness among participants are relevant.

As for my future research career, funding for a postdoctoral study will be applied for to follow-up on remaining analyses and dissemination of results from the NUTRI-HAB project and to pursue some of the new research perspectives that have emerged throughout the project.

Data collected in study 3 will be used to pursue objective 2 defined in paper III: to assess whether effect of the NUTRI-HAB programme was associated with nutritional score at baseline and, hence, whether any of the included screening and assessment tools could potentially be relevant to assess HNC survivors' needs for nutritional rehabilitation.

Based on participants' experienced benefit of eating together in a safe and supportive environment, I will aim at exploring how elements of the NUTRI-HAB programme can be implemented in a municipal context in Denmark.

Finally, a comprehensive data material was collected in the nationwide survey in study 2, and only few of these data were included in the thesis. Remaining data will be published in future papers and include analyses of QOL, unmet rehabilitation needs, psychological well-being, and health behaviour of Danish HNC survivors 1-5 years after curatively intended radiation therapy. Publishing these data will be given high priority to ensure that the voice of the many HCN who shared their valuable insights and experience will be heard.

8.3. Usefulness of the public sector industrial PhD project

To be eligible as public sector industrial PhD projects, projects are evaluated by their usefulness to the host organisation, and by how the usefulness is realised and results are implemented. Usefulness for the organisation can be, e.g. knowledge building that directly improves the organisation's competences, systematic knowledge dissemination, and/or strengthening the quality of the product/service provided by the organisation[153].

Being a university college, UCC Nutrition and Health's primary service is education of the future nutrition professionals including clinical dietitians. With the strategy *'Together for excellent teaching'*, UCC's vision is to educate professionals who succeeds in and together with clinical practice in realising some of the society's ideals and solving some of its challenges. Aims included in the strategy are applied research that addresses challenges within the professions and the integration of more applied research and development in teaching of the future professionals[154]. More specifically, UCC's strategy for applied research include developing and testing tools, methods and interventions for professionals in practice and focusing on the potential to scale research projects to include several professionals[155].

With the NUTRI-HAB project exploring the effect of multidisciplinary nutritional rehabilitation it contributes to develop and test methods and interventions for nutrition professionals in a multidisciplinary collaboration. The project has furthermore tested different tools either to be used by the clinical dietitian in the nutritional assessment or to be used by other health professionals to screen for the need for referral to nutritional interventions.

With the initiation of the NUTRI-HAB project, a multidisciplinary group from different educational programmes at UCC and clinical practice took the initiative to establish a research network on late effects and QOL in head and neck cancer[4] to facilitate multidisciplinary and cross-sectoral collaboration. Hence, the project has contributed to strengthen collaboration across UCC's educational programmes with the prospect of future multidisciplinary research project.

During the 3-year project period, 10 students have been connected to the project either in practical placement or as a part of their BSc. thesis project. The students have been working with various tasks either directly as a part of the NUTRI-HAB project or as smaller related project e.g. developed recipe books and assisted with practical kitchen workshops at NUTRI-HAB programme or analysed data on nutritional interventions from REHPA's mapping cancer rehabilitation in Denmark[8] with a manuscript in

preparation. Hence, the students have had the opportunity to work with research and rehabilitation in practice and to strengthen their competences.

Furthermore, results and experiences from the project will be implemented in my future teaching. Returning to my position as senior lecturer, one of my first tasks is to develop a course on nutritional interventions including practical cooking and social eating in rehabilitation services for different patient groups as an elective course for our students. Eventually, continued education activities for trained health professionals will also be planned.

Through the NUTRI-HAB project a strong partnership between UCC and REHPA has been established. So far it has led to another project collaboration on a report on current practice and perspectives within nutritional rehabilitation in life-threatening disease[156] edited by REHPA and a colleague from UCC and with contributions from other colleagues from UCC myself included. This work has led to establishment of a professional network with representatives from REHPA, UCC, and other partners from clinical practice, educational institutions, and food service with the aim of developing practice within nutritional rehabilitation services in Denmark and to facilitate exchange of experiences and collaboration across the country.

Planned future collaboration between UCC and REHPA include planning and delivering the NUTRI-HAB programme again in September 2020 with the research-based purpose of qualifying ideas for future collaborative research projects.

Hence, the usefulness of the NUTRI-HAB project for UCC include all beforementioned aspects: knowledge building that directly improves the organisation’s competences, systematic knowledge dissemination, and strengthening the quality of the service provided by the organisation. While some of it has already been realised, other aspects of the usefulness will be realised in the future research and educational activities.

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1. Appendices

Appendix 1a: Paper I:

Kristensen MB, Mikkelsen TB, Beck AM, Zwisler AD, Wessel I, Dieperink KB.

To eat is to practice – Managing eating problems after head and neck cancer.

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Title page

Title

TO EAT IS TO PRACTICE – MANAGING EATING PROBLEMS AFTER HEAD AND NECK CANCER

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Abstract

Purpose: The purpose of this qualitative study was two-fold: 1) To explore head and neck cancer (HNC) survivors' experiences of everyday life with eating problems after cancer treatment and 2) To explore their experiences of participating in a multidisciplinary residential rehabilitation program with a primary focus on physical, psychological and social aspects of eating problems after treatment.

Methods: Semi-structured focus group interviews were conducted with 40 Danish HNC survivors who participated in a five day residential rehabilitation program with follow-up after three months. The transcribed interviews were analyzed through qualitative content analysis.

Results: Physical nutrition impact symptoms and unmet needs for support were frequent. Participants experienced a feeling of loss due to impaired eating abilities. Eating had become an obligation or a training situation, and the eating problems challenged the relationship with their relatives when well-meaning encouragement was perceived as a pressure. Social eating was a challenge and this often led to social withdrawal.

The residential program was a safe and supportive environment to practice eating skills and participants benefited from meeting peers. The program provided participants with knowledge and skills that many of them had been missing during and after treatment.

Conclusions: Eating problems after treatment have substantial effects on the everyday life of HNC survivors. A multidisciplinary residential rehabilitation program may be beneficial to meet their rehabilitation needs.

Implications for Cancer Survivors: The results are useful for future planning of rehabilitation services and clinical studies that may contribute to improving current clinical practice and benefit HNC survivors.

Key words

Head and neck cancer, survivorship, rehabilitation, nutrition impact symptoms, eating problems, quality of life

Abbreviations

HNC: head and neck cancer, NIS: Nutrition impact symptoms, QOL: quality of life

Introduction

For many head and neck cancer (HNC) survivors, the challenges do not end at completion of treatment. Nutrition impact symptoms (NIS) and eating problems may affect their everyday lives for years or, in some cases, for the rest of their lives [1].

Annually, approximately 900,000 people worldwide are diagnosed with HNC [2] making it a substantial contributor to morbidity and mortality. The incidence but also the survival has increased during recent years [3]. Hence, the population of HNC survivors is increasing and so is the requirement for appropriate rehabilitation services [4].

Frequent NIS after radiation therapy, surgery and/or chemotherapy in HNC are swallowing difficulties (dysphagia), dry mouth (xerostomia), taste disturbances (dysgeusia), poor dentition and mouth opening difficulties (trismus) [1]. NIS may occur or persist for years after treatment [1]. Nutrition problems have been found to be predictors of depression in HNC survivors [5] and NIS and eating problems may lead to social withdrawal [6-11] with consequences for social functioning in HNC survivors. Furthermore, a recent systematic review demonstrated that NIS and eating problems negatively affect dietary intake, everyday life and quality of life (QOL) in long-term HNC survivors [1].

Health-related QOL in HNC survivors is often assessed quantitatively [12-16]. However, eating problems and their effect on QOL is a complex topic and a qualitative approach may provide a broader understanding of the HNC survivor's experiences. In recent years, a growing number of studies have used qualitative methods in HNC survivors. Some of these [6,17-21] have focused broadly on HNC survivors' experiences and their everyday life after treatment or throughout the course of their care. Others have focused on HNC survivors' experiences of specific NIS e.g. dysphagia [7,22,23], xerostomia [24] or pain [25]. Finally, a few studies [8-11,26] have focused on HNC survivors' experiences of eating problems in general and/or the changed meaning of food after treatment. Findings from these studies include feelings of loss [8,26], affected enjoyment with eating [9,11], the need for adaptive behavior [9,11], and the experience of being left alone with eating problems after treatment [10]. However, to our knowledge no studies have used focus groups to explore HNC survivors' experiences of everyday life with eating problems. As this method uses group interaction to stimulate discussion [27] it may provide new insights into HNC survivors' experiences and rehabilitation needs that are not identified through individual interviews.

Management of NIS and eating problems have been shown to be some of the challenges where HNC survivors most frequently experiences need for supportive care or report unmet supportive care needs [5,28] and this should be reflected in rehabilitation services for this population. The World Health Organization defines rehabilitation as *"a set of measures that assist individuals, who experience or are likely to experience disability, to achieve and maintain optimum functioning in interaction with their environments"*, [29] and cancer rehabilitation services for HNC survivors should address the physical, psychological and social aspects of eating problems. This was also the conclusion of a systematic review from 2013, where none of the included studies addressed the complexity of eating problems in the target group [30]. A recent scoping review from 2018 on rehabilitation interventions used in studies with HNC survivors did identify and classify three studies with comprehensive interdisciplinary rehabilitation interventions [31]. These interventions included a weekly speech pathology/dietetic service model [32], an 8-week interdisciplinary outpatient nutrition-rehabilitation program [33] and an electronic health information support system [34]. The studies supported the need for interdisciplinary rehabilitation interventions [32], showed improvements in QOL [33] and showed that the given intervention was used and highly appreciated by participants [34]. None of the interventions included residential rehabilitation programs but since a major consequence of eating problems in HNC survivors is problems with social eating and the resulting social withdrawal [6-11], we hypothesize that a residential rehabilitation setting where the daily meals are a part of the intervention may be particularly beneficial for this population. To our knowledge, only one previous study has evaluated this type of intervention in HNC survivors [35]. In 1999, Hammerlid et al. reported a pilot study on the effect of a 1-week residential psychoeducational program in 14 HNC survivors and found high participant satisfaction and improvements in several QOL-variables [35]. However, it is not clear whether these improvements were statistically significant and the evidence on potential benefits of residential rehabilitation programs in HNC survivors is still sparse. Hence, it is relevant to explore participants' experiences of a multidisciplinary residential rehabilitation program with a primary focus on the physical, psychological and social aspects of eating problems in a larger study population.

The aim of this study was to contribute to the emerging qualitative evidence base on how eating problems affects HNC survivors' everyday life and to create new knowledge on which benefits this population experiences through participation in a multidisciplinary residential rehabilitation program. To address this aim, the following objectives were pursued:

1) To explore HNC survivors' experiences of everyday life with eating problems after treatment through focus group interviews.

2) To explore HNC survivors' experiences of a multidisciplinary residential rehabilitation program with a primary focus on the physical, psychological and social aspects of eating problems after treatment for HNC.

Methods

The study is a qualitative study based on data from focus group conducted and analyzed according to content analysis [36]. COREQ was used as a guideline for reporting study methods and results [37]. Study participants were HNC survivors who participated in a five day multidisciplinary residential rehabilitation program with a two day follow-up residential stay after three months. The program was offered three times; in 2013, 2014 and in 2018.

Participants

Study participants were sampled through self-selection sampling and HNC survivors could apply for participation in the multidisciplinary residential rehabilitation program if they met the following inclusion criteria:

- Participants should have completed curatively intended treatment for HNC.
- Participants should be experiencing self-reported eating problems and find themselves in need of rehabilitation or support to cope with these problems.
- Participants should be self-reliant as the program did not offer assistance with daily care.
- The participant's treating physician or general practitioner should complete and sign the referral form.

HNC survivors who did not speak and understand Danish were excluded from participation.

HNC survivors from all over the country could apply for participation, and information about the program was distributed to relevant hospital departments, relevant networks of health professionals and patient organisations. In 2013, esophageal cancer survivors with eating problems were invited to fill vacant places on the program at referral deadline even though they do not fall under the Danish Health Authority's definition of HNC [38].

The multidisciplinary residential rehabilitation program

The multidisciplinary residential rehabilitation program was a coordinated effort involving several specialists e.g. clinical dietitians, nurses, physiotherapists, psychologists and social workers. Through available evidence and more than 10 years' experience of offering multidisciplinary residential rehabilitation programs for more than 8000 cancer survivors, the rehabilitation center had developed a model for a five days program with two days follow-up that they used for heterogeneous groups of cancer survivors and other groups of cancer survivors than HNC. This model was

used as a template and the content was adjusted to include a primary focus on the physical, psychological and social aspects of eating problems after treatment for HNC. The program consisted of group sessions with patient education and a few individual activities. Sessions and activities related to the physical, psychological and social aspects of eating problems included group session with clinical dietitian on dietary advice to manage NIS and eating problems. A practical kitchen workshop was included to inspire and put theory into practice and take-home recipes were handed out. The evidence on the effect of practical kitchen sessions in HNC remains scarce, but practical kitchen sessions have been shown to support dietary changes and thereby improve health-related QOL in other cancer survivors [39, 40]. Furthermore, participants had an individual counselling session with a clinical dietitian, where counselling was adjusted to the individual's situation. An occupational therapist (in Denmark occupational therapists manage dysphagia) instructed participants in swallowing exercises and exercises for jaw and tongue mobility, as these may reduce trismus and dysphagia [41]. Participants were encouraged to continue doing these exercises in the period between the initial residential stay and the follow-up. Poor dentition is frequent after treatment for HNC [5] and a group session with dental hygienist on oral hygiene and dental reimbursement rules was included. As the program was residential, the participants stayed at the premises and all meals throughout the day were served in the dining room or in the café. At all meals, foods were of different textures and flavors to inspire participants and to allow them to experiment with different foods than they usually ate. The meals were also intended as social training since research has shown that some HNC survivors may have a tendency towards eating alone due to the eating problems [6,7,9].

Despite the primary focus on management of eating problems after treatment for HNC, other components of the rehabilitation center's core program was maintained as these have shown to be relevant and beneficial for other cancer survivors [42-44]. This included sessions with general physical activity e.g. yoga, session on fatigue, group session with psychologist on psychological consequences of cancer, group conversation with priest on existence, massage therapy and session on intimacy and sexuality. Furthermore, participants could have individual counselling sessions with relevant professionals (e.g. physician or social worker) depending on the individual's needs. On the last day of the five days initial stay, sessions on motivation and action plans were included to allow participants to reflect on, how they wanted to use the new inspiration and knowledge in their everyday life when they returned back home. A program for the initial residential stay and the follow-up is provided in the supplementary material.

Each of the three offered programs had a maximum of 20 participants. The program was free of charge for participants and an additional offer to existing rehabilitation services.

Focus group interviews

Each participant was invited to participate in two focus group interviews [27]; the first on the initial residential stay and the second at follow-up. The first focus group interview focused on the participants' experiences of everyday life with eating problems after treatment whereas the second focus group interview focused on the participants' experiences of the multidisciplinary residential rehabilitation program. Semi-structured interview guides with open-ended questions were developed based on the research questions. The interview guide for the focus group interviews at the initial residential stay included questions on how eating had changed since the cancer diagnosis, how eating problems affected their daily life, the meaning of food before and after treatment, the consequences of eating problems on wellbeing and social life, perceived support from health system and network and participants' coping strategies. In the focus groups carried out on the initial residential stay in 2013 and 2014, different foods such as chocolate milk, oral nutritional supplements and biscuits were used as stimulus materials in the focus groups on the initial residential stay to stimulate further elaboration of the questions in the interview guide. In 2018, participants were encouraged to bring photos of situations where their eating problems affected their daily life and with permission from participants, these photos were also used as stimulus material in the focus groups in the initial residential stay. Examples of motives in the photos were family dinners, restaurant menus and travel photos.

The interview guide for the focus group interviews at the follow-up included questions on participants' experienced benefits participating in the program, their motivation for participating, the value of the different activities, suggestions for improvement, their reflections on how to cope with the eating problems in the future and pros and cons of a residential program compared to other rehabilitation services. No stimulus materials were used in the focus group interviews at follow-up.

All focus group interviews were facilitated by an experienced researcher (KBD or MBK). A research assistant observed group interaction and registered non-verbal communication during the interviews. An overview of facilitators and observers of each interview is shown in supplementary material.

Even though participants had met the facilitators and observers during the residential stay and hence were familiar with them and the research project, the facilitators initiated each focus group by explaining the purpose of the study.

Focus group interviews were held at the rehabilitation center in a room that participants were familiar with. The interviews were carried out on day four or five of the initial five day residential stay to ensure that participants had reached a certain level of confidence in each other and would be willing to discuss difficult matters. Participants were

encouraged to be honest and candid throughout the interviews. All focus group interviews were audio recorded and transcribed verbatim. The duration of each focus group interview was approximately an hour.

Data analysis

The focus group interviews were analyzed using qualitative content analysis as described by Graneheim & Lundman [36] and central themes related to the research questions were derived from the interview transcripts. The analyses were carried out in a process that involved several steps. In the first step, all interview transcripts were read through to get an overall impression of the data. Second, the transcripts were reread, but this time meaning units related to the research objectives were identified. In the following steps, these meaning units were condensed and abstracted or coded into the researcher's words. In the last step, the coded meaning units were categorized and organized into subthemes and themes related to the research objectives. An example of how central themes were derived from identified meaning units is shown in Table 1.

The lead author (MBK) was primary coder and coding and organization into themes were discussed thoroughly with KBD during the process of analysis. The software program NVivo 11 was used in the data analysis. Citations in this article are translated from Danish.

MBK and KBD who performed the analyses were involved in the multidisciplinary residential rehabilitation programs, but were otherwise not involved in existing rehabilitation services for the target group. The results of the analyses were approved by co-authors.

Ethical considerations

Informed written consent was obtained from all individual participants before inclusion in the study. Participants were informed verbally and in writing that participation in the study was voluntary and that they could withdraw their consent at any time with no consequences for their participation in the multidisciplinary residential rehabilitation program. The study did not require approval from the ethical committee and was registered by The Danish Data Protection Agency, registration number 2012-58-0018, approval number 18/14847.

Results

Participants and data material

In total, 40 cancer survivors participated in the multidisciplinary residential rehabilitation programs of whom 10 participated in 2013, 17 participated in 2014 and 13 participated in 2018. As the maximum number of participants in

each program was not reached, all applications for participation were approved and no applicants were excluded.

All 40 cancer survivors gave informed consent to participate in the study during their participation in the program. The participant characteristics are shown in Table 2. Equal numbers of men and women participated, and pharyngeal cancer was the most frequent cancer diagnosis. All but one of the participants had been treated with radiation therapy, Table 2. Six participants did not participate in the follow-up stay. Reasons for not participating in the follow-up were: relapse of disease, scheduled surgery, personal matters and one participant did not respond. One participant didn't participate in the first focus group due to fatigue, but participated in the second focus group during follow-up.

In total, 10 focus group interviews were conducted with 4-14 participants in each focus group. The time points and number of participants for each focus group are shown in supplementary material.

HNC survivors' experiences of everyday life with eating problems after treatment

Through the qualitative content analysis, four themes related to HNC survivors' experiences of everyday life with eating problems were derived from the interview transcripts (Figure 1). The headlines of the four themes were 'To eat is to practice', 'The last third of the pie is missing', 'I'll just come by for the coffee' and 'On your own'.

To eat is to practice - When physical challenges make eating an obligation or a training situation

Even though many participants had experienced improvements in their symptoms, they still struggled with NIS including dysphagia, xerostomia, dysgeusia, trismus, poor dentition, anorexia and nausea. Participants had difficulties with certain textures and flavors and these difficulties could vary from day to day. It was a big disappointment when food tasted different than expected and a victory, when certain foods finally started to taste normal again.

> *"It was shocking to find out how difficult it was to eat - I was really looking forward to it. I like desserts, ice cream and sweet stuff … and it was just like getting a jellyfish into my mouth, both the taste and the texture."*

The majority of participants had received tube feeding at some point, and some participants were still reliant on the tube. Most participants had experienced significant weight loss, and only a few had retained their normal weight. Due to lack of appetite, most participants had to schedule small meals throughout the day, and the logistics around the meals were experienced as a full-time job. Eating was an obligation or a training situation rather than a pleasure.

> *"It is really something you have to pull yourself together to do, the eating. It is a job, it is a training situation – it is not a pleasure!"*

Participants had to learn to eat again especially after a period of tube feeding. They had to experiment to find out which flavors and textures they found acceptable, and for some this experimental approach was difficult. Fear of eating difficult foods and the feeling of defeat, when an experiment wasn't a success contributed to this. For some, financial considerations also played a role, as they didn't want to buy food that they might not be able to eat.

The last third of the pie is missing – The emotional loss

The importance of food and being able to eat became apparent only when the ability to eat was affected, and many participants experienced a feeling of loss due to their eating problems.

> *"… If we take a pie, and we say that life is a three-piece pie … then the part about eating, it takes up almost a third. And if you can't do that, you nearly get depressed about it."*

Participants missed eating certain foods, eating with certain people or eating at certain occasions such as Christmas. Some participants reported that they were able to cope with the loss at certain times, whereas at other times, the situation seemed hopeless to them.

> *"There are some days when I think: 'Oh well, it is just food'. And other days you think: 'My world is going to come to an end because of this.'"*

'I'll just come by for the coffee' - Eating problems affect social life and relationships with close relatives

Many participants avoided social situations that included food or eating. Embarrassment and shame was experienced by some participants, even though they met understanding from their network. They described the difficulty of eating with others as a mental barrier.

> *"I have been feeling like: 'Argh, I will just come by for the coffee'. But it is … a mental thing you have to overcome. Because it is only a problem to yourself."*

Other participants found it stressful to eat with others, as they were eating slowly. Several participants ate in advance or after the social meal, as they weren't able to eat enough in the usual given timeframe. For some participants the stress of eating with others made their swallowing difficulties even more profound. Yet other participants avoided the social meals because they found it difficult to watch other people eat food that they couldn't eat themselves.

Meals outside the home were a challenge to most participants. The feeling of being a burden on the host or the feeling of defeat when not being able to eat the served food made some participants bring their own food or simply avoid the entire situation. However, most participants, who occasionally were eating out, stated that they generally met a great

willingness from hosts or restaurants to do whatever possible to prepare a suitable meal. They just had to overcome their modesty and ask for it or explain their difficulties; something that many of them found difficult.

Most participants received great support from their closest relatives, and often spouses or other family members assisted with the practical tasks around the meals. However, the well-meaning encouragement from relatives was often experienced as a pressure by the participants and could have the direct opposite effect and make it even more difficult to eat. This was often a cause of conflict, and most participants preferred that their relatives didn't address the eating problems or their food intake despite the well-meaning motive.

> *"It is so important that you get the right support. And the right support can be just to be present and not: 'Aren't you having a bit more? Try a piece of meat' You don't eat enough meat.' I am 54 years old. So do I still need to have my mother with me at the table?"*

On your own – Finding one's feet in the vacuum that occurs after a long and intensive treatment

For many participants the NIS worsened after completion of treatment, and while some participants had good support from the health system, many experienced that the support was limited. Some participants reported that they had to request the support themselves, but they did not necessarily have the required energy to do so. Hence, many participants felt left to themselves when the long and intensive treatment with close contact with health professionals ended:

> *"It is probably because you are used to driving to the hospital every day. Then you know that there is a team of nurses and doctors that takes care of you, if you have problems. And suddenly from one day to the other, you are finished. And then you just stand at home in such a strange vacuum. Now what?"*

HNC survivors' experiences of a multidisciplinary residential rehabilitation program with a primary focus on the physical, psychological and social aspects of eating problems

Through the qualitative content analysis, four themes related to HNC survivors' experiences of the multidisciplinary residential rehabilitation program with a primary focus on the physical, psychological and social aspects of eating problems were derived from the interview transcripts (Figure 2). The headlines of the four themes were 'All in the same boat', 'Increased courage to eat', 'A getaway from everyday life' and 'Focus on the specific problem but still on the whole person'.

All in the same boat – The importance of meeting peers

All participants found it beneficial to meet peers and many found relief and an increased feeling of normality in realizing that other people shared their challenges. For many participants, this was the first time they had talked to peers, even though they might have met other HNC patients during treatment. The common reasons for not communicating with peers during treatment was lack of energy, uninviting environment or the fear of facing another person with the same disease. Some participants feared meeting a peer with more progressive disease or symptoms because they were afraid that this would be their own future. They stated that this fear declined after completion of treatment. Participants regarded themselves as peers because of their eating problems and not because of their cancer. They wouldn't necessarily consider themselves as peers to other types of cancer survivors.

> *"It is a really good thing to focus on somebody, who has the same thing. I don't think, if there had been somebody with prostate cancer or liver cancer, I don't think I could have related to that the same way that we do now. … Then we wouldn't have known what they are experiencing.*
>
> *… And it is not the fact that we had cancer that is the problem. It is that we had cancer in the throat."*

Increased courage to eat – A safe and supportive environment to practice eating skills

The opportunity to experiment and to try different foods during the program was a breakthrough for many participants making them realize that there were many foods they were still able to eat. Furthermore, participants experienced it as a safe and supportive environment to practice eating skills. It was a positive experience that there was no pressure from relatives or the health care professionals at meals. In some situations participants put pressure on each other, but in contrast to the pressure from the relatives, this pressure wasn't regarded as negative. They knew that their peers actually understood how they felt. Several participants went from tube feeding to foods during the program. Some of these stated that tube feeding or oral nutritional supplements had become an easy and convenient solution. Others had developed a fear of eating and didn't feel confident to try real foods instead of tube feeds. Enrolment in the program and the contact with the health professionals made them feel safe and gave them the required push towards eating.

> *"I have been living on tube feeding until Friday, where I said: 'So, now someone is taking care of me', so I dared to stop with the tube."*

A getaway from everyday life – The value of a residential rehabilitation program

The residential program offered opportunities for participants to talk to each other outside the scheduled activities, which increased their feeling of unity. Participants, who previously had participated in out-patient rehabilitation, did not

experience the same feeling of unity in these services. Getting away from home was considered beneficial for the participant but also for the family.

> *"There was also something in getting away from home. Both for yourself, you were going somewhere else, but it was also a way of giving your family a break."*

When asked, participants said that they wouldn't have preferred to have their relatives with them on the program. It would affect the relationship with their peers and for some participants the program was an opportunity to address topics they wished to spare their relatives from.

Focus on the specific problem but still on the whole person – Knowledge and skills to cope with everyday life after treatment

Participants found it positive that the program focused specifically on their eating problems – a focus that most of them hadn't encountered in other rehabilitation services. Despite that, participants still experienced the program as holistic, which they also found important.

> *"The great thing about this is, that when the experts lets go of us, we become human beings again. The entire time the focus has been on repairing us. 'There is a problem. We should fix it.' And it is very tangible and physical. And here we experience that we can express our feelings and be honest with each other and there are no hidden agendas or anything … I think that it is very important that you, after you have been repaired, that you can follow up on some of the things inside."*

Participants experienced that they met a high degree of expertise among the health professionals in the program and that the health professionals took time to listen to their concerns, something some of them felt was missing in the busy health system. Participants valued the knowledge and skills they attained throughout the program. The practical cooking sessions and take-home recipes were found useful, and many participants continued to do the swallowing exercises in the period from the initial residential stay to the follow-up. Most participants found all parts of the program useful. However, some of the attained knowledge and skills were things that they would have liked to have earlier in their illness. Opinions were mixed on the optimal time point for participating in an intensive rehabilitation program like this. Some stated that the program could be too demanding if offered too close to treatment and others pointed out that they still benefitted even though they had completed their treatment years ago.

While many participants experienced a breakthrough in eating during the program, many were still experiencing physical NIS at follow-up. And while the program provided them with inspiration and skills to adjust to these physical symptoms and to maintain their eating skills, some participants also developed a greater acceptance of their situation.

They realized that it was okay to lower the bar and accept that some of their physical challenges might be chronic. Instead of focusing on the limitations, the focus was directed to the things that they were still capable of.

> *"But when you discover that you still have some social skills, then it means less whether you can eat. There are so many other things I can do."*

Discussion

This qualitative study with focus group interview with 40 cancer survivors showed that eating problems after treatment have substantial effects on everyday life in HNC survivors in various ways. It furthermore showed that a multidisciplinary residential rehabilitation program with focus on eating problems may strengthen the HNC survivor's ability to cope with these adverse effects.

HNC survivors' experiences of everyday life with eating problems after treatment

The physical NIS experienced by our study participants are very similar to the findings of other studies in HNC survivors [1,11] and so are the coping strategies of our participants. Semple et al. [6] and Nund et al. [45] described how their participants coped through 'active planning' and 'trial and error' and the latter was also described by McQuestion et al. [8]. Einarsson et al. found that HNC survivors up to 2 years after treatment used a variety of coping strategies e.g. liquids with the meal and choosing 'yes-foods' (easier to eat) over 'no-foods' (avoided foods) [11]. Ganzer et al. found that eating problems were still frequent ≥ 3 years after completion of chemo-radiation and participants still had to plan and alter their food choice. But despite this, all their participants stated that they enjoyed eating, enjoyed the social aspect of eating out and that eating had become easier over time [26]. In contrast, our participants and also participants in a study by Ottosson et al. [9] described how the pleasure of food had been limited and how some participants were eating only because they had to. However these participants' were not as far ahead in their trajectory as the participants in the study by Ganzer et al. This could indicate that the coping process may be an ongoing process that eventually leads to an adaptation to the new normal and that our participants were not as far ahead in their coping process. Consistent with this, Einarsson et al. described how participants had to force themselves to eat 3-6 months after treatment, that many participants still expressed problems that made eating a negative experience 1 year after treatment and that some still found eating a time-consuming activity two years after treatment [11]. In our study, our results indicated that many participants gradually moved towards adaptation and acceptance during the time interval from the initial residential stay to follow-up. However, it is not possible to conclude whether this can be attributed to the program or simply the time interval.

The feeling of loss due to the eating problems is not unique to our participants. Emotional, physical and/or social losses associated with eating problems have been identified by McQuestion et al. [8], Ganzer et al. [26] and Nund et al. [23]. The social withdrawal due to eating problems has been documented in several studies [6-11,25].

An interesting finding of our study was the balance between perceived support and perceived pressure from the relatives and how the well-meaning encouragement to eat often had the direct opposite effect. To our knowledge, this topic is well known in clinical practice in Denmark, but not frequently documented. Einarsson et al. described how support from relatives sometimes was experienced as unhelpful and led to conflicts if there was a lack of understanding from the relatives [11]. McQuestion et al. described participants´ frustration when food was being shoved at them during treatment [8], and Nund et al. described how some participants experienced that the relationship with their partner changed from being equal adults towards a mother-child relationship with the partner in the parental role [23]. But often it is the feeling of support from the relatives that HNC survivors describe through interviews [9,26]. The participants of our study also described how they were grateful for the support, but they also expressed frustrations, when they felt pressured and felt that their relatives didn't understand their struggle. Participants may feel they are ungrateful or it is unfair on their relatives when experiencing and expressing these feelings. The use of focus group interviews may have made it easier for the participants to address delicate topics, as they realized that other participants were experiencing the same frustrations.

The feeling of being on their own and being unprepared for life after treatment is not unique to our participants or to Danish HNC survivors [6,10,45,46]. Many studies find that HNC survivors have unmet needs for support to cope with their eating problems after treatment [5,8,10,28,46] and it may affect their coping process [46].

HNC survivors' experiences of a multidisciplinary residential rehabilitation program with a primary focus on the physical, psychological and social aspects of eating problems

The participants in our study valued the coordinated effort and the holistic approach of the program and meeting with dedicated health professionals who took the time to listen and answer questions. Consistent with our results, Larsson et al. described how their participants, despite often regarding the treatment period as a safe period with daily contact with health professionals at the hospital, often felt that there was not enough time to ask all of their questions [10]. Participants felt less abandoned and more safe if they were referred to support services after treatment (e.g. dental hygienist), but still they felt like these experts were only taking care of their own area of specialty and did not take the

person's entire situation into account [10]. This supports the value of a coordinated and multidisciplinary effort in rehabilitation services for HNC survivors.

Consistent with our study, other studies have described how HNC patients and/or survivors benefit from meeting peers [10,45]. However, many participants in this study described how they were not ready to meet peers during treatment, but that their readiness matured over time when they completed the treatment. This should be considered when planning supportive services during treatment. Another interesting finding was that our participants considered themselves peers due to their eating problems and not due to the fact that they were cancer survivors. And with a nationwide survey in 2017 showing that only 17 of the 98 Danish municipalities (responsible for post-treatment rehabilitation [38]) offered diagnosis specific post-treatment rehabilitation services for HNC survivors [47], it can be questioned whether the potential of peer support is being effectively used.

Other studies [7,19,23,24] have described HNC patients and survivors experiencing fear of eating or fear of choking when eating, and our results indicate that creating a safe and supportive eating environment with support from health professionals and peers may help HNC survivors overcome this fear.

Strengths and limitations

The qualitative approach used in this study gives a broader perspective on the everyday challenges of HNC survivors than a quantitative study on QOL would have done. With a relatively high number of participants for qualitative interviews and a low drop-out rate, our study provides a good insight into the experiences of Danish HNC survivors. An equal number of men and women participated, which does not reflect the actual distribution of HNC in the Danish population, where HNC more frequently affects men than women [3]. This could potentially have affected the representativeness of our study population. Furthermore, the multidisciplinary residential rehabilitation program required that participants were self-reliant and able to participate in the planned activities, which may have excluded the most vulnerable HNC survivors.

Even though our participants experienced the multidisciplinary residential rehabilitation program as beneficial to meet their rehabilitation needs, no firm conclusions on the effect of the program can be drawn from this qualitative study. The current study will serve as a pilot study for a future randomized clinical trial.

Conclusion

Eating problems affect the everyday life of HNC survivors in various ways. For many HNC survivors eating becomes an obligation or a training situation, and the eating problems challenge their relationships with their relatives and may

lead to social withdrawal. Unmet needs for support to cope with the eating problems are frequent, and HNC survivors often feel left by themselves after completion of treatment.

HNC survivors found the multidisciplinary residential rehabilitation program with a primary focus on the physical, psychological and social aspects of eating problems, as beneficial to meet their rehabilitation needs. Furthermore, participants experienced the residential rehabilitation program as a safe environment to experiment and practice eating skills, and they benefited from meeting peers. The program provided participants with knowledge and skills that many of them had been missing during and after treatment.

Ultimately, no firm conclusions on the effect of the multidisciplinary residential rehabilitation program can be drawn from this qualitative study, but the results generates hypotheses that should be tested in a randomized clinical trial to contribute to future planning of multidisciplinary rehabilitation services for HNC survivors.

Compliance with ethical standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical 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.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1: Examples of how themes related to head and neck cancer survivors' experiences of everyday life with eating problems after treatment were derived from identified meaning units in transcripts of focus group interviews with 40 Danish head and neck cancer survivors.

<table>
<tr><th>Meaning units related to the research objective</th><th>Condensed meaning units</th><th>Condensed meaning units abstracted/coded into researchers own word</th><th>Subthemes</th><th>Theme related to the research objective</th></tr>
<tr><td>"I also think I feel a development in myself, and I also see it among all the others. From last time, we were here and until now, we eat, we are actually seeking out new experiences. We will try this and that because, previously, we wouldn't dream of eating it, but we can just try. No harm is done by trying."</td><td>Participants have become more willing to try new food during the program.</td><td>Increased courage to experiment with food.</td><td rowspan="2">Increased courage to eat.</td><td rowspan="3">Increased courage to eat – A safe and supportive environment to practice eating skills.</td></tr>
<tr><td>"When I think about food now, it actually makes me happy. Not that long ago it was just: I need it because otherwise I won't be able to stand. The opportunity to taste and try so many different things – and we are equal and all look strange when we eat – it has meant that we have dared – that I have dared to eat more things."</td><td>Opportunity to experiment and to eat with others in the same situation gave increased courage to eat new things.</td><td>New food experiences gave courage to further food experiments.
Eating with peers gave increased feeling of social acceptance, normality and courage to eat.</td></tr>
<tr><td>"I have been living on tube feeding until Friday, where I said: 'So, now someone is taking care of me', so I dared to stop with the tube."</td><td>Being followed by health professionals in the program made participant dare to stop with tube feeding.</td><td>Program gave a feeling of safety.</td><td>Program was a safe environment.</td></tr>
</table>

Table 2: Characteristics of the 40 cancer survivors who participated in a multidisciplinary residential rehabilitation program with a primary focus on the physical, psychological and social aspects of eating problems after treatment for head and neck cancer.

	All participants (n=40)
Gender	
- Male	50% (20/20)
- Female	50% (20/20)
Age	
Mean ± SD	61 ±9.3
Median [range]	60 [39;80]
Cancer diagnosis	
- Oral cavity	12% (5/40)
- Pharynx	58% (23/40)
- Larynx, salivary gland, thyroid, esophagus	18% (7/40)
- Unknown or other primary tumor with cervical metastases	12% (5/40)
Treatment	
- Radiation therapy	98% (39/40)
- Surgery	48% (19/40)
- Chemotherapy	55% (22/40)
Time interval (months) from completion of radiation therapy	
Mean ± SD	19 ±34.3[a]
Median [range]	7 [3;170][a]
Civil status	
- Married or living with partner	57% (23/40)
- Living alone	43% (17/40)
Occupational status	
- Working	23% (9/40)
- Retired	47% (19/40)
- On sick-leave	30% (12/40)

[a] n=38

Figures

Figure 1: Themes related to head and neck cancer survivors' experiences of everyday life with eating problems after treatment derived from the analysis of focus group interviews with 40 Danish head and neck cancer survivors.

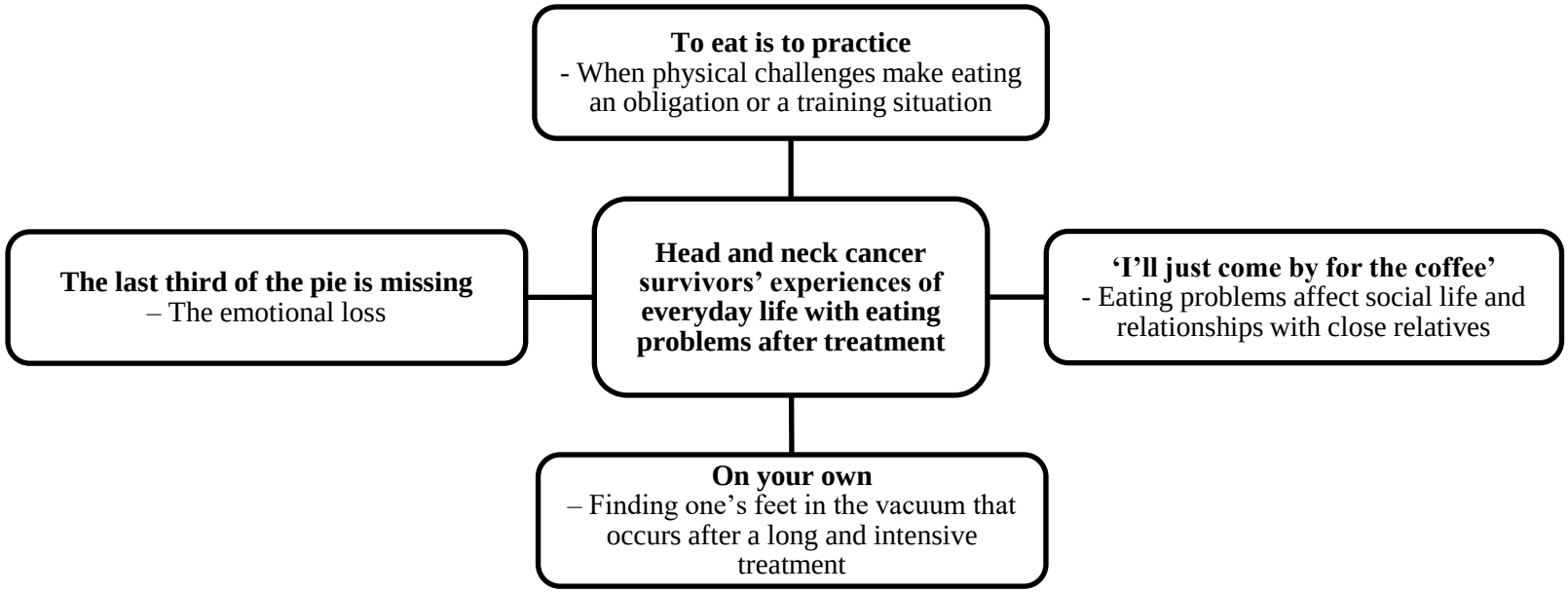
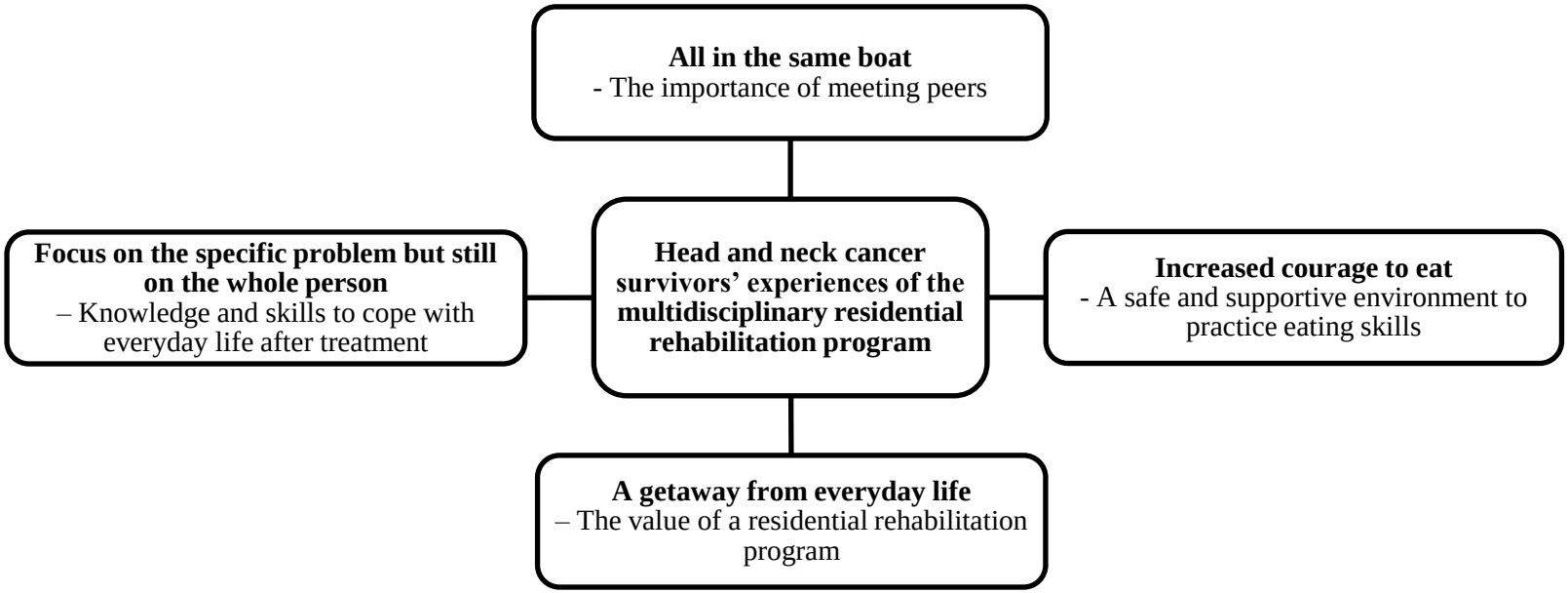


Figure 2: Themes related to head and neck cancer survivors' experiences of a multidisciplinary residential rehabilitation program with a primary focus on the physical, psychological and social aspects of eating problems after treatment derived from the analysis of focus group interviews with 40 Danish head and neck cancer survivors.



Appendix 1b: Supplementary material for paper I

Supplementary tables

Table 1: Course program for the initial five days of the multidisciplinary residential rehabilitation program with a primary focus on the physical, psychological and social aspects of eating problems after treatment for head and neck cancer.

TIME	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
7.30		BREAKFAST BUFFET	BREAKFAST BUFFET	BREAKFAST BUFFET	BREAKFAST BUFFET
8.45		MORNING ASSEMBLY	MORNING ASSEMBLY	MORNING ASSEMBLY	MORNING ASSEMBLY
9.00	Arrival and registration Welcome and presentation of the program (course leader) Walk and talk	Practical kitchen workshop (clinical dietitian)	Fatigue and late effects (nurse) Oral hygiene and dental treatment reimbursement rules (dental hygienist)	Focus group interview (researcher) Physical activity (physiotherapist)	Physical activity (physiotherapist) Motivation, change processes and action plans (course leader) Individual work on action plans (course leader)
12.00	LUNCH BUFFET	LUNCH BUFFET	LUNCH BUFFET	LUNCH BUFFET	LUNCH BUFFET
13.00	Participant introduction round Theoretical session on eating problems (clinical dietitian)	Physical tests (physiotherapist)	Swallowing exercises (occupational therapist) Individual counseling (clinical dietitian)	Psychological reactions to cancer (psychologist) Individual counseling (depending on the participant's needs) Massage (massage therapist)	Group discussion of action plans (course leader) Closing session and farewell (course leader)
18.00	DINNER	DINNER	DINNER	DINNER	
	Social activity	Group conversation on existence (priest)	(Possibility to go for a walk, watch movies, play games etc.)		

Table 2: Example of a program for the two days follow-up three months after the initial five days of the multidisciplinary residential rehabilitation program with a primary focus on the physical, psychological and social aspects of eating problems after treatment for head and neck cancer.

TIME	DAY 1	DAY 2
7.30		BREAKFAST BUFFET
8.45		MORNING ASSEMBLY
9.00	Arrival and registration Welcome and presentation of the program (course leader) What's new within the last three months? (course leader)	Physical tests (physiotherapist) Focus group interview (researcher)
12.00	LUNCH BUFFET	LUNCH BUFFET
13.00	Sexuality, intimacy, relationship and single life (sexologist) Individual counseling (clinical dietitian) Physical/social activity (course leader)	Individual work and group discussion on action plans (course leader) Closing session and farewell (course leader)
18.00	DINNER	

Table 3: Overview of focus group interviews conducted during the multidisciplinary residential rehabilitation programs with a primary focus on the physical, psychological and social aspects of eating problems after treatment for head and neck cancer.

Interview	Time point for the interview	Setting of the interview	Number of informants (n)	Facilitator (Initials; gender; title(s))	Observer
1	December 2013	During the five day residential rehabilitation program	4	KBD; female; RN, PhD	TBM; female; PhD
2	December 2013	During the five day residential rehabilitation program	5	KBD; female; RN, PhD	TBM; female; PhD
3	March 2014	During the two day follow-up	9 (Participants from interviews 1+2)	KBD; female; RN, PhD	TBM; female; PhD
4	April 2014	During the five day residential rehabilitation program	8	KBD; female; RN, PhD	TBM; female; PhD
5	April 2014	During the five day residential rehabilitation program	9	KBD; female; RN, PhD	TBM; female; PhD
6	August 2014	During the two day follow-up	14 (Participants from interviews 4+5)	KBD; female; RN, PhD	TBM; female; PhD
7	March 2018	During the five day residential rehabilitation program	7	MBK; female; RD, PhD Fellow	AK; female; Nutrition student
8	March 2018	During the five day residential rehabilitation program	6	MBK; female; RD, PhD Fellow	NS; female; Nutrition student
9	June 2018	During the two day follow-up	5 (Participants from interviews 7+8)	MBK; female; RD, PhD Fellow	KBD; female; RN, PhD
10	June 2018	During the two day follow-up	6 (Participants from interviews 7+8)	MBK; female; RD, MSc., PhD Fellow	KBD; female; RN, PhD

Appendix 2a: Paper II

Kristensen MB, Beck AM, Zwisler AD, Dieperink KB, Wessel I.

Nutritional characteristics and associations with self-reported health-related quality of life in Danish head and neck cancer survivors 1-5 years after radiation therapy – results from the nationwide cross-sectional NUTRI-HAB Survey.

Status: In manuscript 2020

Title

Nutritional characteristics and associations with self-reported health-related quality of life in Danish head and neck cancer survivors 1-5 years after radiation therapy – results from the nationwide cross-sectional NUTRI-HAB Survey

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Abstract

Background & Aims: Head and neck cancer (HNC) survivors may experience nutrition impact symptoms years after treatment, but few studies have assessed nutritional characteristics and their association with health-related quality of life (HRQOL) ≥1 year posttreatment. Study objectives were: 1) To assess nutritional characteristics such as body mass index (BMI), Nutritional Risk Screening 2002 (NRS 2002), Malnutrition Universal Screening Tool (MUST), the Scored Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF), and M.D. Anderson Dysphagia Inventory (MDADI) scores of Danish HNC survivors 1-5 years posttreatment and 2) To test associations between self-reported HRQOL and nutritional characteristics.

Methods: The study was a nationwide cross-sectional survey. All Danish HNC survivors who completed curatively intended radiation therapy within 1-5 years (n=1937) were invited. In addition to above mentioned nutritional characteristics, information on precancer weight, own evaluation of current body weight, and use of oral nutritional supplements/enteral nutrition was registered. Correlations between self-reported HRQOL measured by EQ-5D-5L, The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, and EORTC QLQ-H&N35 and nutritional scores were tested using Spearman's rank correlation coefficient.

Results: In total, 1190 (61.4%) responded. While 4.6% were underweight (BMI<18.5), 17.3% considered their body weight too low. In 48.4%, current body weight amounted <95% of precancer weight. According to NRS 2002, 7.8% were at nutritional risk, 12.2% had a PG-SGA SF score ≥9, and hence a critical need for intervention, and MUST categorised 6.9% as being at high risk of malnutrition. Oral nutritional supplements were required by 10%, and 11.7%, and 10% required enteral nutrition. NRS 2002, MUST, PG-SGA SF, and MDADI were significantly correlated with HRQOL ($p<0.0001$) indicating that a higher degree of nutritional challenges was associated with

worse HRQOL. Correlations were strongest for PG-SGA SF (r_s= ±0.40-0.63) and MDADI (global score: r_s= ±0.35-0.64; composite score: r_s= ±0.38-0.75).

Conclusions: Nutritional characteristics are still adversely affected in head and neck cancer survivors 1-5 years after treatment with potential consequences for HRQOL. Among selected screening tools, PG-SGA SF and MDADI showed strongest correlations to self-reported HRQOL.

Keywords:

Head and neck cancer survivors, NRS-2002, MUST, PG-SGA SF, MDADI, quality of life

Abbreviations:

BMI: Body mass index, DAHANCA: Danish Head and Neck Cancer Group, EORTC: The European Organization for Research and Treatment of Cancer, HNC: head and neck cancer, HRQOL: health-related quality of life, MUST: Malnutrition Universal Screening Tool, NRS 2002: Nutritional Risk Screening 2002, PG-SGA SF: the Scored Patient-Generated Subjective Global Assessment Short Form, MDADI: M. D. Anderson Dysphagia Inventory, QOL: quality of life.

1 Introduction

Head and neck cancer (HNC) survivors frequently experience dysphagia, xerostomia and other nutrition impact symptoms[1–3] that may affect nutritional status[3–5] and health-related quality of life (HRQOL)[3,6]. Several studies have documented the magnitude of nutrition impact symptoms in HNC survivors beyond 1 year posttreatment[1,2,7–17], but only few studies have used other means than need for enteral nutrition or modified diet to report how nutritional status or nutritional risk is affected in this population. Methods to asses nutritional status or risk vary across these studies[5,7,18,19], and while several methods exist, evidence is scarce on their relevance in HNC survivors ≥1 year posttreatment. Crude measures of nutritional status include body mass index (BMI), while tools like Nutritional Risk Screening 2002 (NRS 2002)[20] and Malnutrition Universal Screening Tool (MUST)[21] also include weight loss, decreased dietary intake and disease severity. The Scored Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF)[22] further include performance status and presence of nutrition impact symptoms in the screening, and M.D. Anderson Dysphagia Inventory (MDADI)[23] specifically assess the physical,

functional, and emotional impact of dysphagia. While nutritional interventions in rehabilitation services may ameliorate the negative consequences of nutrition impact symptoms in HNC survivors[24–26], inconsistent screening of nutritional status or nutritional risk may lead to unrecognised rehabilitation needs. Many aspects can be considered when evaluating the relevance of different screening methods. In nutritional interventions, HRQOL is often used as an outcome measure, while a chosen screening method is used as inclusion criteria. Hence, associations between HRQOL and screening results are relevant to consider. To our knowledge, no previous studies have assessed how HRQOL is associated with BMI, NRS 2002 score, MUST score, and PG-SGA SF score in HNC survivors ≥ 1 year posttreatment.

Thus the objectives of this study were: 1) To assess nutritional characteristics such as BMI, NRS 2002 score, MUST score, PG-SGA SF score, and MDADI scores of Danish HNC survivors 1-5 years after completion of radiation therapy and 2) To test whether participants' HRQOL measured by EuroQOL's EQ-5D-5L, The European Organization for Research and Treatment of Cancer's (EORTC) QLQ-C30, and EORTC QLQ-H&N35 is associated with their nutritional characteristics.

2 Materials and methods

The study is based on data from the Danish nationwide cross-sectional NUTRI-HAB Survey on nutritional characteristics, HRQOL, and rehabilitation needs of Danish HNC survivors 1-5 years after completion of radiation therapy.

2.1 Participants

The survey population should meet the following inclusion criteria: 1) have been diagnosed with cancer of the pharynx, larynx or oral cavity, 2) have been treated with curatively intended radiation

therapy and have completed the treatment between 1st March 2014 and 28th February 2018, and 3) age ≥ 18 years. Individuals were excluded if they: 1) had no permanent address in Denmark, and 2) were registered as protected from inquiries for scientific studies.

The population was identified through the Danish Head and Neck Cancer Group's (DAHANCA) national clinical quality database[27], from which selected data are available for researchers upon application.

2.2 Survey distribution

The survey questionnaire was distributed electronically or through postal mail. The online survey was conducted using Research Electronic Data Capture (REDCap)[28]. A link was sent to e-Boks, a secure digital mailbox linked to the individual's civil registration number. Individuals who were exempted from having e-Boks received a paper-based questionnaire and a stamped reply envelope through postal mail. For both the online and the paper-based questionnaire, a cover letter with participant information was included. In the cover letter of the paper-based questionnaires, the link for a website and a personal code was included in case the participant wanted to complete the survey online. Individuals who initially received the link for the online survey in their e-Boks and didn't feel confident in filling out the questionnaire online, received a paper-based questionnaire upon request.

One week after distribution of the link to the online survey, an electronic reminder was sent, and after another three weeks, all non-responders received a paper-based questionnaire with a stamped reply envelope through postal mail. For individuals who initially received the questionnaire through postal mail, a reminder was sent through postal mail after four weeks.

2.3 Collected data

An overview of collected data is provided in Supplementary file 1.

2.3.1 Data obtained through databases and registries

Information on age, gender, cancer diagnosis, and treatment was obtained from DAHANCA's national clinical quality database[27], while updated contact information and information on place of residence was obtained from the Danish civil registry system upon application to The Danish Health Data Authority.

2.3.2 Self-reported data collected through survey questionnaires

The study included self-reported data on current cancer status, nutritional characteristics, and HRQOL.

2.3.2.1 Nutritional characteristics

Questions on current body weight and height were included to allow for calculation of BMI (body weight in kg divided by squared height in metres). Furthermore, nutritional risk and presence of nutrition impact symptoms were assessed with NRS 2002[20], MUST[21], PG-SGA SF[22], and MDADI[23]. An overview of content and interpretation of the different tools is included in Table 1. Since NRS 2002 and MUST were not developed as questionnaires to be filled out by the patient, modified versions were used. Questions on recent changes in body weight and dietary intake were included in the survey questionnaire, to allow for estimation of the NRS 2002 A-score. Since participants were 1-5 years posttreatment, it was assumed that the majority no longer would be stress metabolic. Hence, participants were assigned 1 point in NRS 2002 B-score if they responded that they had active cancer at the time of the survey, but disease severity from potential

comorbidities was not assessed. When estimating the NRS 2002 A-score, a BMI ≤20.5 can result in a higher score if associated with an impaired general condition that can be ascribed to undernutrition[20]. In the present study, participants with BMI ≤20.5 were defined as having impaired general condition ascribed to undernutrition if their current body weight was lower than their precancer body weight, and they reported limitations in doing their usual activities in the EQ-5D-5L[29] questionnaire (level 2-5 in the dimension 'Usual activities').

Questions on recent weight loss and BMI were furthermore used to estimate MUST score. The weight loss score in MUST is originally based on unintentional weight loss[21]. However, we had no information on whether a participant's potential weight loss was intentional or unintentional. Hence, in the present study, the weight loss score in MUST as based on any weight loss exceeding the given cut-offs. No participants were assigned an acute disease effect score, since they were all 1-5 years posttreatment.

The Danish version of the PG-SGA SF has been translated, cross-culturally adapted, and linguistically validated[30]; and was used with permission. When using the full Scored Patient-Generated Subjective Global Assessment instead of the short form, the nutrition triage recommendations prescribe that a score of 4-8 requires intervention by dietitian in conjunction with nurse or physician as indicated by symptoms, and a score ≥ 9 indicates a critical need for intervention. Since the PG-SGA SF was designed to reflect approximately 80–90% of the full Scored Patient-Generated Subjective Global Assessment score[22], these cut-offs are also used in the present study.

The Danish translation of MDADI, which has been cross-culturally adapted and found reliable in terms of internal consistency and test–retest reproducibility[31], was included in the survey questionnaire, and participants' results on MDADI global and composite score are presented in this study. In accordance with other studies, MDADI composite score below 60 was categorised as

'poor' swallowing function, a score of 60-<80 as 'adequate' swallowing function, and a score ≥80 as 'optimal' swallowing function[32,33].

In addition to BMI and the selected screening tools, the survey questionnaire addressed weight loss during cancer trajectory, participants' precancer weight, participants' own evaluation of their current body weight and use of oral nutritional supplements and enteral nutrition.

2.3.2.2 Self-reported health-related quality of life

With permissions, the Danish translations of the EQ-5D-5L[29], the EORTC QLQ-C30[34,35], and the diagnosis specific EORTC QLQ-H&N35[35,36] were used to assess HRQOL. Details of the tools are shown in Table 1. In the present study, only selected scales of the tools were included in the analyses. These were the EQ-5D-5L summary index score, EQ-5D-5L VAS-score, and EORTC QLQ-C30 'Global health status/QOL' and functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning). Furthermore, the QLQ-H&N35 symptom scale 'Trouble with social eating' was included in analyses, because previous studies have shown that social withdrawal due to eating problems have substantial effects on HNC survivors' everyday lives[26,37,38].

2.4 Ethical statement

Participants were informed that their participation in the survey was voluntary, that all personal information would be kept confidential, and that data would be presented so no individual participant could be identified. Telephone number and email address of the principal researcher was included in the cover letter in case invited individuals had questions or if they wished to decline participation.

Based on Danish legislation, the Regional Committees on Health Research Ethics for Southern Denmark committees concluded that the survey did not need approval since no intervention was carried out and no biological material was included (journal number 20182000-152). The survey was registered by The Danish Data Protection Agency through the Region of Southern Denmark, journal number 18/51739.

2.5 Data analysis and statistical considerations

Descriptive statistics were used to summarise data. For categorical variables, frequencies are presented in numbers and percentages. For age, mean and standard deviation are presented, and for other continuous variables, median and interquartile ranges are presented.

Data on nutritional characteristics and HRQOL are summarised for all participants combined, and for subgroups based on the time interval from participants' treatment completion to survey distribution (12-23, 24-35, 36-47 and 48-59 months). In exploratory analyses, differences between subgroups were tested using Kruskall Wallis H test for continuous variables and Pearson's chi-squared or Fisher's Exact test for categorical variables. The latter was used if any cells in the contingency table contained <5% of the observations. Spearman's rank correlation coefficient (r_s) was used to assess the relationship between participants' HRQOL scores and their BMI, NRS 2002 score, MUST score, PG-SGA SF score, and MDADI scores. An r_s of 1 correspond to a perfect increasing monotone relationship between the ranks of the two variables indicating that a higher value on the X-axis (nutrition score) is associated with a higher value on the Y-axis (HRQOL), whereas an r_s of -1 correspond to a perfect inverse monotone relationship, indication that a higher value on the X-axis is associated with a lower value on the Y-axis. An r_s of 0 indicate that there is no monotone relationship between the two variables.

Due to the number of statistical tests, a statistical significance level of 0.001 was applied in Spearman's rank correlation analyses, while a significance level of 0.05 was applied in all other data analyses. STATA/IC 16.0 was used for the statistical analyses. Since missing data occurred, the number of observations (n) included in each analysis is stated in result tables.

To assess potential selection bias, participants and non-respondents were compared with regards to age, gender, cancer diagnosis, time interval since treatment completion and place of residence. Potential differences in age were tested using a two-sample two-sided t-test, while differences in categorical variables were tested using Pearson's chi-squared test or Fisher's Exact test.

3 Results

3.1 Response rate and participants

In total, 1937 individuals fulfilled the inclusion criteria, and were invited for participation in the survey. Of these, 1190 (61.4%) completed the survey questionnaire (Figure 1). Most participants (73.6%) completed the questionnaire online, while 26.4% completed paper-based questionnaires. The mean age was 65.6 ± 9.1 years, and 74.9% of participants were male (Table 2). Pharyngeal cancer was the most frequent HNC diagnosis (70.5%), while cancer of the oral cavity only accounted for 8.4% of the cases. The majority of participants (78.4%) were successfully curatively treated and had no active cancer at the time of the survey.

No significant differences were seen between participants and non-respondents in age, gender, time interval since treatment completion and place of residence (Table 2). Compared to non-respondents, the proportion of participants with a diagnosis of pharyngeal cancer was greater, while the proportion of participants with laryngeal cancer was smaller ($p<0.001$). Lymph node stage differed significantly ($p=0.003$), but no differences were seen in overall cancer stage.

3.2 Nutritional characteristics

Participants' median BMI was 24.9, and while 4.6% were categorised as underweight (BMI<18.5), 48.9% were categorised as either overweight (BMI 25.0-29.9) or obese (BMI≥30) (Table 3). Based on NRS 2002, 7.8% of participants were at nutritional risk (≥3 points), and according to MUST, 9.9% were at medium risk of malnutrition, and 6.9% were at high risk. The median PG-SGA SF score was 2, and 12.2% had a score ≥ 9 points and hence, a critical need for intervention according to the nutrition triage recommendation. Based on the MDADI composite score, 15% were categorised as having poor swallowing function, 26% as having adequate function, and 59% as having optimal swallowing function. No significant differences between subgroups (categorised by the time interval from completion of radiation therapy) were seen in BMI, NRS 2002, MUST, PG-SGA SF, or MDADI scores.

Most participants (89.5%) had experienced weight loss during their cancer trajectory, and in 48.4%, the current body weight amounted less than 95% of their precancer body weight. The body weight in percentage of precancer body weight differed significantly between subgroups (p=0.002). Median values were lowest in the '12-23 months' and '24-35 months' (94.4% and 94.6%) and highest in the '36-47 months' subgroup (96.8%). Approximately one in six participants (17.3%) considered their current body weight too low, while 37.4% considered it too high.

At the time of the survey, 10.0% were using oral nutritional supplements (but not enteral nutrition), 8.9% were using enteral nutrition (but not oral nutritional supplements), and 2.8% were using both. Significant differences in current use of oral nutritional supplements were seen between subgroups (p=0.012) with 14.1% in the '12-23 months' subgroup decreasing to 6.1% in the '48-59 months' subgroup. No significant difference was seen between subgroups in use of enteral nutrition.

3.3 Health-related quality of life

Participants median scores on the included HRQOL scales are presented in Supplementary file 2. A significant difference in the EORTC QLQ-H&N35 symptom scale 'Trouble with social eating' was seen between subgroups defined by time interval from completion of radiation therapy (p=0.0057). However, there was no clear pattern indicating a gradual improvement or worsening over time from completion of radiation therapy. No significant differences in other HRQOL scales were seen between subgroups.

3.4 Correlations between nutritional characteristics and HRQOL

Except for EORTC QLQ-H&N35 scale 'Trouble with social eating', BMI was not significantly correlated with HRQOL. Lower BMI was associated with higher 'Trouble with social eating' symptom level, but the correlation was weak (r_s= -0.25, p<0.0001), Table 4.

NRS 2002 score showed statistically significant correlations (p<0.0001) with all HRQOL scales indicating that a higher NRS 2002 score was associated with a worse HRQOL. However, the correlations were weak, and the strongest correlation was seen for 'Physical functioning' (r_s= -0.35).

Statistically significant correlations for all HRQOL scales (p<0.0001) also indicated that a higher MUST score was associated with worse HRQOL, even though the correlations were weak. The strongest correlation was seen for 'Trouble with social eating' (r_s= 0.29) while the weakest was seen for 'Cognitive functioning' (r_s= -0.12).

For PG-SGA SF, significant correlations with all HRQOL (p<0.0001) indicated that a higher PG-SGA SF score was associated with worse HRQOL. The correlation with the 'Trouble with social

eating' symptom scale was rather strong (r_s= 0.63), while correlations with other HRQOL scales were moderate (r_s ranging from -0.40 for 'Cognitive functioning' to -0.57 for 'Global health status/QOL').

Significant correlations were also seen for MDADI scores and all HRQOL scales ($p<0.0001$) indicating that lower MDADI scores were associated with worse HRQOL. For MDADI global score, a rather strong correlation was seen with 'Trouble with social eating' (r_s= -0.64), while correlations with remaining HRQOL scales were moderate with r_s ranged from 0.35 ('Cognitive functioning') to 0.54 ('Global health status/QOL'). The same pattern was seen for MDADI Composite score, where r_s for the correlation with 'Trouble with social eating' was -0.75.

4 Discussion

This study based on data from a nationwide cross-sectional survey showed that nutritional characteristics are still adversely affected in Danish HNC survivors 1-5 years after radiation therapy. Associations between HRQOL and nutritional characteristics indicated that a higher degree of nutritional challenges was associated with worse QOL. Among selected screening tools, PG-SGA SF and MDADI were most strongly correlated to self-reported HRQOL.

4.1 Nutritional characteristics

Based on BMI, 4.6% of participants were underweight compared to 2.4% in the general Danish population[39]. In comparison, Ottosson et al. found that 10% of 101 HNC survivors 71.6 (±28.3) months after radiation therapy were underweight (BMI < 20; BMI<22 if age ≥70)[5]. The higher prevalence can possibly be ascribed to different cut-offs.

BMI does not consider body composition or weight history, and individuals can be at nutritional risk despite a high BMI. Depending on the screening method, 6.9-12.2% of participants in the present study were at nutritional risk and, hence required nutritional intervention according to guidelines[40]. The high nutritional risk may not be unique to our participants. Participants' MUST classification (9.9% medium risk, 6.9% high risk) was almost identical with results from a small study by van den Berg et al. who assessed 32 HNC survivors 14-68 months after chemoradiation and found 13% at medium risk, and 6% at high risk[7].

Poor swallowing function (MDADI composite score <60) was seen in 15% of participants. Twelve and 24 months after radiation therapy, Goepfert et al. reported poor swallowing function (composite score <60) in 13% and 7% of locoregionally advanced oropharyngeal carcinoma survivors[33] and in 15% and 9% of patients with "Low-Intermediate Risk" oropharyngeal carcinoma[32]. Dixon et al. reported poor swallowing function (composite score <60) in 38% of oropharyngeal carcinoma survivors 2.0-5.5 years after chemoradiotherapy[11]. With no data on potential concurrent chemotherapy in the present study, we cannot conclude whether differences between studies can be ascribed to differences in treatment or population.

Nearly all participants (89.5%) had lost weight during their cancer trajectory. Other studies have reported significant weight loss in approximately 65% during HNC treatment[26,41,42]. In these studies, significant weight loss was defined as ≥5%[26,41,42], whereas we assessed any weight loss. The median for current body weight in percentage of precancer weight was lowest in the '12-23 months' and '24-35 months' subgroups. The latter subgroup was furthermore most likely to consider their current body weight too low (20.6% compared to 6% in the general Danish population[39]). Kramer et al. found, that body weight declined by 17% in average in 74 HNC patients from diagnosis to two-years follow-up, and that mean body weight reached a minimum two years after treatment[18]. Based on mean values instead of medians, body weight in percentage of

precancer weight was also lowest in the ’24-35 months’ subgroup in the present study (93.3% vs. 94.1% in ’12-23 months’ subgroup and >95% in remaining subgroups), even though the average weight loss appeared smaller. Ottosson et al. reported that weight started to increase 11 months posttreatment without returning to pretreatment level at their final follow-up (71.5 ± 28.3 months)[5].

Even 5 years after treatment, 11.6% of participants required enteral nutrition, and 17.7% required either enteral nutrition or oral nutritional supplements. Dependency of oral nutritional supplements seemed to decrease over time, which was not the case for enteral nutrition. The few significant differences seen between subgroups according to time interval posttreatment could indicate that only few spontaneous improvements in nutritional characteristics occur in the time interval from 1 to 5 years after radiation therapy.

4.2 Correlations between nutritional characteristics and HRQOL

BMI only showed weak correlation with one HRQOL scale. Consistent with this, Egestad & Nieder examined BMI and HRQOL (EORTC QLQ-C30 and QLQ-H&N35) in 60 HNC patients in the beginning and end of radiation therapy and saw no difference between participants with BMI≥25 and BMI<25[43]. Since BMI does not necessarily reflect nutritional risk, this finding is not surprising. Hence, even though BMI is a widely used measure of nutritional status, it should be used in combination with e.g. weight loss to identify nutritional characteristics with consequences for HRQOL in HNC survivors.

Among screening tools, PG-SGA SF and MDADI were most strongly correlated to participants’ self-reported HRQOL. Previous studies have tested correlations between PG-SGA (albeit not the short form) or MDADI, and HRQOL measured by EQ-5D-5L or EORTC QLQ-C30 in HNC

patients or HNC survivors. Even though only one of them included HNC survivors ≥1 year after treatment, results are consistent with ours. The MD Anderson Head and Neck Cancer Symptom Working Group found a positive correlation between EQ-5D VAS and MDADI composite score (r_s= 0.50; p<0.0001) in 714 oropharyngeal cancer survivors ≥12 months after radiotherapy[44]. Isenring et al. found negative correlations between PG-SGA and EORTC QLQ-C30 'Global health status/QOL' in 60 patients prior to radiation therapy to the head and neck, abdominal or rectal area (r= -0.66, p<0.001) and after 4 weeks of radiotherapy (r= -0.61, p<0.001)[45]. Mulasi et al. also reported a negative correlation between PG-SGA score and EORTC QLQ-C30 'Global health status/QOL' in 19 HNC patients undergoing chemoradiotherapy even though the association was weaker (r= -0.37, p= 0.012)[46]. Since PG-SGA SF was designed to reflect approximately 80–90% of the full PG-SGA score[22], we find results comparable with ours.

Previous studies have documented how social consequences of eating problems have profound effect on HNC survivors' everyday lives[26,37,38], and nutritional interventions in rehabilitation services should address this[47]. In the present study, PG-SGA SF score and MDADI scores showed rather strong correlations with the EORTC QLQ H&N35 scale 'Trouble with social eating'. We consider this a valuable finding indicating that these tools may be relevant in HNC survivors. Future clinical studies should investigate whether PG-SGA SF and MDADI can identify HNC survivors who will benefit from nutritional interventions in rehabilitation services, and whether nutritional interventions leading to improvements in the given nutrition score also lead to improvements in HRQOL.

4.3 Strengths and limitations

Major strengths include a rich data material from a cross-sectional nationwide survey with a high response rate. Identification of respondents through a national clinical quality database enables detailed description of the population and assessment of potential selection bias. A health system free of charge for patients reduces the risk of socioeconomic groups not being accounted for. Despite this, studies always pose a risk of selection bias. Kjær et al. found that Danish HNC survivors who accepted to participate in a study were younger with higher educational level than non-participants, and they reported better HRQOL and less symptoms than those who declined participation but agreed to fill out a questionnaire[48]. If the most challenged individuals were less likely to respond, the present study could underestimate the magnitude of nutritional challenges in HNC survivors. The fact that individuals with pharyngeal cancer were more likely to respond than individuals with laryngeal cancer could support this, since the increase in HPV-related oropharyngeal cancer has led to a shift towards higher socioeconomic status and less alcohol and tobacco abuse in this population[49]. Conversely, individuals who do not experience nutritional challenges could find the survey irrelevant and be less likely to respond. We saw no differences between participants and non-respondents in age, gender, time interval posttreatment and place of residence, but we have no data to assess differences in socioeconomic demographics. All nutritional data are self-reported, and only some of the included screening methods are designed for self-completion by patients. However, self-reported weight and height have been shown to correlate highly with measured weight and height in the general Danish population[50], and we expect that this also applies to our HNC population.

5 Conclusion

This study based on data from a nationwide cross-sectional survey showed that nutritional characteristics including nutritional status and risk are still adversely affected in Danish HNC survivors 1-5 years after curatively intended radiation therapy. Nutritional interventions are required by up to 12%, and inconsistent screening of nutritional risk may lead to unrecognised nutritional rehabilitation needs.

While the screening tools NRS 2002, MUST, PG-SGA SF and MDADI are all significantly correlated to HRQOL, PG-SGA SF and MDADI showed strongest correlations. Future clinical studies should assess the tools' ability to identify HNC survivors who will benefit from nutritional intervention, and nutritional interventions improving the given nutrition score also leads to improvements in HRQOL.

Statement of Authorship

All authors were involved in the design of the NUTRI-HAB Survey, and the survey was conducted by Marianne Boll Kristensen and Ann-Dorthe Zwisler. Marianne Boll Kristensen analysed the data for the present study. Results were interpreted by Marianne Boll Kristensen, Irene Wessel, and Anne Marie Beck who drafted the manuscript with contribution to content from all authors. The final version of the manuscript was approved by all authors.

Conflict of Interest Statement

The authors have nothing to declare.

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Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

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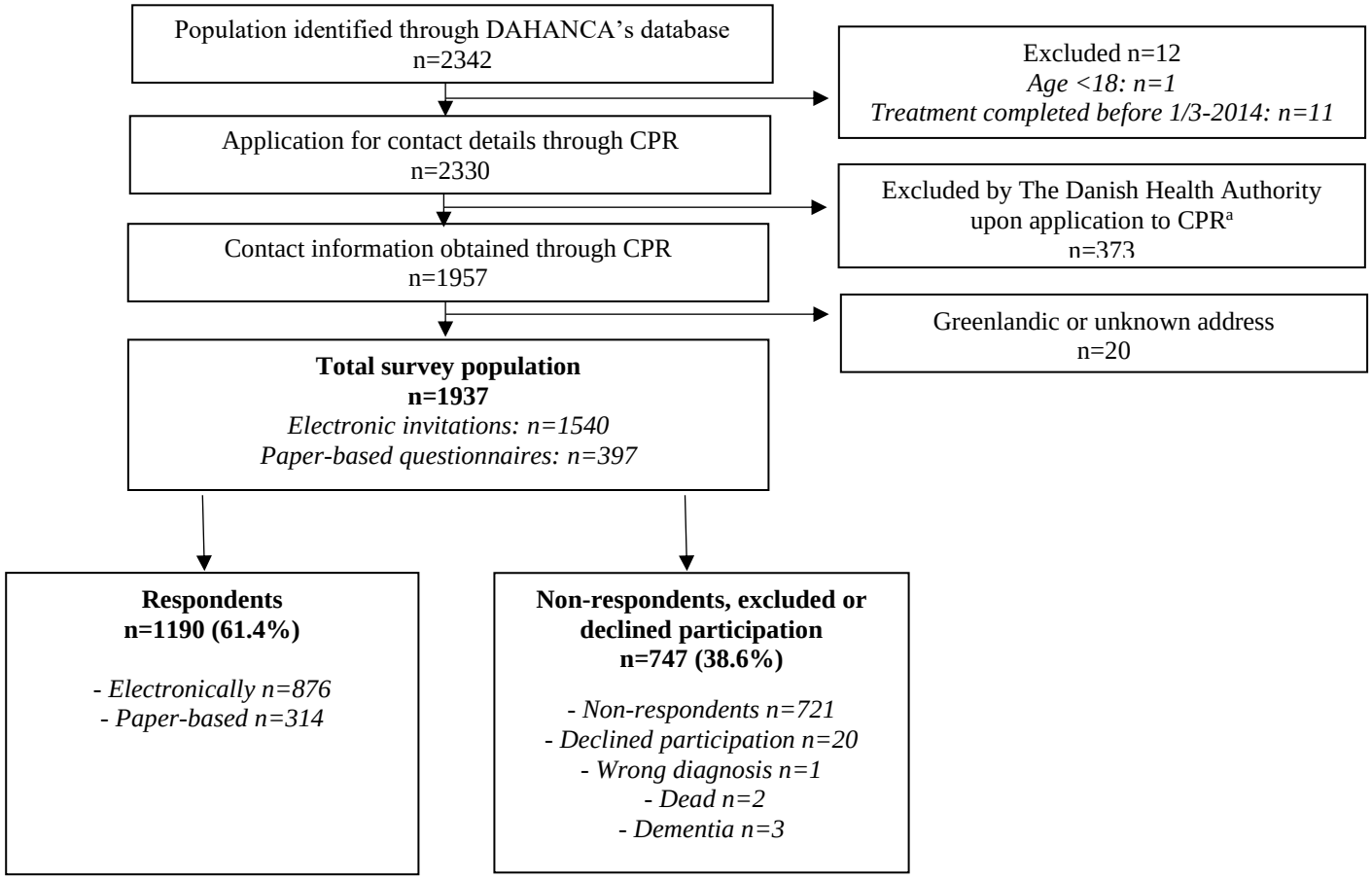
Figure 1: The NUTRI-HAB survey flow diagram



DAHANCA: The Danish Head and Neck Cancer Group, CPR: The Danish Civil Registry System.

[a] Individuals excluded by The Danish Health Authority upon application to CPR are individuals without permanent address in Denmark, individuals who were registered as protected from inquiries for scientific studies, and individuals who were no longer alive at the time for application.

Table 1: Overview of tools and methods used to assess nutritional risk and health-related quality of life in the NUTRI-HAB survey

Tool/method	Purpose	Description	Domains/subscales	Range	Interpretation
NRS 2002[1]	Identify patients at nutritional risk	Screening system developed for use by health professionals	*In secondary screening:* A-score for malnutrition (based on weight loss history, dietary intake, and BMI), B-score for disease severity, age-adjustment if aged 70 years or above	A-score: 0-3 B-score: 0-3 Age-adjustment: 1	A higher score indicates greater nutritional risk. A score of ≥ 3 defines nutritional risk, and nutritional support should be initiated.
MUST[2]	Identify adults, who are malnourished/at risk of malnutrition (undernutrition), or obese	Screening system developed for use by health professionals	BMI score, weight loss score, acute disease effect score (or if there has been or likely will be no nutritional intake for >5 days)	BMI score: 0-2 Weight loss score: 0-2 Acute disease effect score: 2	0: Low risk: Routine clinical care 1: Medium risk: Observe (and increase nutritional intake if inadequate) ≥2: High risk: Treat (refer to dietitian/nutrition support team) *Obesity (BMI>30): Underlying acute conditions are generally controlled before treating obesity*
PG-SGA SF[3]	Assess nutritional risk and deficit	Self-administered one-page instrument	Overall score based on weight changes, changes in dietary intake (amount or consistency), nutrition impact symptoms and performance status	Overall score: 0-36	A higher score indicates higher malnutrition risk. Nutrition triage recommendations*: - Score of 4-8: Intervention by dietitian and nurse/physician as indicated by symptoms - Score ≥ 9: Critical need for intervention
MDADI[4]	Assess dysphagia-specific QOL in head and neck cancer	Self-administered 20-item questionnaire (+4 extra items in Danish version[5])	1 global score (based on 1 item) 3 subscales: Emotional, functional and physical (based on remaining 19 items) 1 composite score: Weighted average of the emotional functional and physical subscales.	Subscales and composite score: 20-100	A higher score indicates a higher degree of functioning. Suggested cut-offs for composite score[6]: ≥ 80: Optimal swallowing function ≥60 - <80: Adequate swallowing function <60: Poor swallowing function
EQ-5D-5L[7]	Generic measure of health status	Self-administered 6-item questionnaire	5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Summary index score of the five dimensions based on societal preference weights for the health state. Overall health measured by visual analogue scale (VAS)	Dimensions: 1-5 Summary index score (Danish values): -0.624 to 1.0 VAS: 0-100	A higher score in the five dimensions indicates higher level of problem. A higher score in summary index score or VAS represents a better self-rated health.
EORTC QLQ-C30[8]	Cancer-specific QOL	Self-administered 30-item questionnaire	1 global health status/QOL scale 5 functional scales: physical, role, emotional, cognitive, social functioning 9 symptom scales/items: fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties	All scales/items: 0-100	A higher score represents a higher response level. Thus, a high score for in global health status or functional sales indicates a high level of functioning whereas a high score on a symptom scale represents a high symptom level.
EORTC QLQ-H&N35[9]	Head and neck cancer-specific QOL	Self-administered 35-item questionnaire	18 symptom scales/items: pain, swallowing, senses problems, speech problems, trouble with social eating, trouble with social contact, less sexuality, teeth, opening mouth, dry mouth, sticky saliva, coughing, felt ill, pain killers, nutritional supplements, feeding tube, weight loss, weight gain	All scales/items: 0-100	A higher score represents a higher symptom level.

EORTC: European Organization for Research and Treatment of Cancer, MDADI: M. D. Anderson Dysphagia Inventory, MUST: Malnutrition Screening Tool, NRS 2002: Nutritional Risk Screening 2002, PG-SGA SF: The Scored Patient Generated Subjective Global Assessment Short Form, QOL: Quality of life

*The nutrition triage recommendations are based on the full Scored Patient Generated Subjective Global Assessment, not the short-form.

Table 2: Demographics of participants and non-respondents of the NUTRI-HAB Survey

	Participants (n=1190)	Non-respondents (n=747)	Difference between groups *p-value*
Age			
- Mean ± SD	65.6 ± 9.1	65.9 ± 9.6	0.504
Gender			
- Male	891 (74.9%)	585 (78.3%)	0.084
- Female	299 (25.1%)	162 (21.7%)	
Cancer diagnosis			
- Larynx	251 (21.1%)	226 (30.3%)	
- Pharynx	839 (70.5%)	451 (60.4%)	<0.001**
- Oral cavity	100 (8.4%)	70 (9.4%)	
Overall cancer stage	*(n=1182)*	*(n=744)*	
I	226 (19%)	127 (17%)	
II	194 (16%)	136 (18%)	0.577
III	197 (17%)	124 (17%)	
IV	565 (48%)	357 (48%)	
Tumour (T) stage			
T1	378 (31.8%)	222 (29.7%)	
T2	481 (40.4%)	299 (40.0%)	
T3	201 (16.9%)	125 (16.7%)	0.385
T4	121 (10.2%)	97 (13.0%)	
TX	9 (0.8%)	4 (0.5%)	
Lymph node (N) stage	*(n=1189)*	*(n=744)*	
N0	406 (34.2%)	310 (41.7%)	
N1	228 (19.2%)	113 (15.2%)	
N2	539 (45.3%)	305 (41.0%)	0.003*
N3	15 (1.3%)	15 (2.0%)	
NX	1 (0.1%)	1 (0.1%)	
Metastasis (M) stage			
M0	1185 (99.6%)	744 (99.6%)	1.000
M1	5 (0.4%)	3 (0.4%)	
Time interval from completion of radiation therapy			
- 12-23 months	345 (29.0%)	194 (26.0%)	
- 24-35 months	296 (24.9%)	213 (28.5%)	0.106
- 36-47 months	267 (22.4%)	183 (24.5%)	
- 48-59 months	282 (23.7%)	157 (21.0%)	
Current cancer status			
- No active cancer	933 (78.4%)	-	
- Active HNC	39 (3.3%)	-	
- Active cancer (other than HNC)	60 (5.0%)	-	
- Active cancer (HNC + other cancer)	13 (1.1%)	-	
- Cancer status unknown	145 (12.2%)	-	
Place of residence			
- Capital Region of Denmark	322 (27.1%)	223 (29.9%)	
- Region Zealand	234 (19.7%)	140 (18.7%)	
- North Denmark Region	135 (11.3%)	83 (11.1%)	0.777
- Central Denmark Region	243 (20.4%)	147 (19.7%)	
- Region of Southern Denmark	256 (21.5%)	154 (20.6%)	

*p≤0.05, **p ≤0.001

HNC: Head and neck cancer.

Data are presented as numbers and (percentages) unless otherwise stated. Differences between groups were tested using a two-sample two-sided t-test for the continuous variable ‘Age’, Pearson’s chi-squared test for the categorical variables ‘Gender’ and ‘Time interval from completion of radiation therapy’, and Fisher’s Exact test for the categorical variables ‘Cancer diagnosis’ and ‘Place of residence’.

Table 3: Nutritional characteristics of 1190 Danish head and neck cancer survivors 1-5 years after completion of radiation therapy

	All respondents	12-23 months after RT	24-35 months after RT	36-47 months after RT	48-59 months after RT	Difference between subgroups *p-value*
BODY MASS INDEX (BMI)	***(n=1067)***	*(n=317)*	*(n=262)*	*(n=233)*	*(n=255)*	
Median (IQR)	**24.9 (5.2)**	24.9 (5.6)	24.7 (5.2)	25.3 (6.0)	24.8 (4.6)	0.157
- Underweight (BMI <18.5)	**49 (4.6%)**	15 (4.7%)	17 (6.5%)	10 (4.3%)	7 (2.8%)	
- Normal weight (BMI 18.5-24.9)	**498 (46.6%)**	149 (47.0%)	122 (46.4%)	99 (42.3%)	128 (50.2%)	-
- Overweight (BMI 25.0-29.9)	**378 (35.4%)**	108 (34.1%)	91 (34.6%)	87 (37.2%)	92 (36.1%)	
- Obesity (BMI ≥30)	**144 (13.5%)**	45 (14.2%)	33 (12.6%)	38 (16.2%)	28 (11.0%)	
NRS 2002	*(n=1047)*	*(n=314)*	*(n=254)*	*(n=227)*	*(n=252)*	
Median (IQR)	**0 (1)**	0 (1)	0 (1)	1 (1)	0 (1)	0.602
NRS 2002 score=0	**528 (50.4%)**	161 (51.3%)	129 (50.8%)	107 (47.1%)	131 (52.0%)	
NRS 2002 score=1	**344 (32.9%)**	110 (35.0%)	77 (30.3%)	77 (33.9%)	80 (31.8%)	
NRS 2002 score=2	**93 (8.9%)**	19 (6.1%)	30 (11.8%)	24 (10.6%)	20 (7.9%)	-
NRS 2002 Score ≥3	**82 (7.8%)**	24 (7.6%)	18 (7.1%)	19 (8.4%)	21 (8.3%)	
MUST	*(n=1034)*	*(n=303)*	*(n=255)*	*(n=227)*	*(n=249)*	
Low risk (0 point)	**861 (83.3%)**	251 (82.8%)	208 (81.6%)	190 (83.7%)	212 (85.1%)	
Medium risk (1 point)	**102 (9.9%)**	31 (10.2%)	27 (10.6%)	23 (10.1%)	21 (8.4%)	0.961
High risk (≥2 points)	**71 (6.9%)**	21 (6.9%)	20 (7.8%)	14 (6.2%)	16 (6.4%)	
PG-SGA-SF	*(n=1134)*	*(n=331)*	*(n=278)*	*(n=254)*	*(n=271)*	
Median (IQR)	**2 (5)**	3 (5)	3 (5)	2 (4)	2 (4)	0.057
PG-SGA-SF score of 4-8	**321 (28.3%)**	110 (33.2%)	77 (27.7%)	61 (24.0%)	73 (26.9%)	0.087
PG-SGA-SF score ≥ 9	**138 (12.2%)**	40 (12.1%)	37 (13.3%)	31 (12.2%)	30 (11.1%)	0.889
MDADI	*(n=1163)*	*(n=340)*	*(n=286)*	*(n=266)*	*(n=271)*	
Global score (Median (IQR))	**80.0 (40.0)**	80.0 (40.0)	80.0 (40.0)	90.0 (20.0)	80.0 (40.0)	0.222
	(n=1179)	*(n=342)*	*(n=294)*	*(n=267)*	*(n=276)*	
Composite score (Median (IQR))	**84.2 (24.2)**	84.2 (25.3)	84.2 (23.6)	86.3 (23.2)	84.2 (26.3)	0.564
Swallowing function:						
- Optimal (composite score≥80)	**693 (59%)**	196 (57%)	170 (58%)	164 (61%)	163 (59%)	
- Adequate (composite score ≥60-<80)	**308 (26%)**	95 (28%)	78 (27%)	66 (25%)	69 (25%)	0.948
- Poor (composite score <60)	**178 (15%)**	51 (15%)	46 (16%)	37 (14%)	44 (16%)	
WEIGHT LOSS DURING CANCER TRAJECTORY	*(n=1187)*	*(n=342)*	*(n=296)*	*(n=267)*	*(n=282)*	
Prevalence	**1062 (89.5%)**	307 (89.8%)	265 (89.5%)	232 (86.9%)	258 (91.5%)	0.377
CURRENT BODY WEIGHT VS. PRECANCER BODY WEIGHT	*(n=1089)*	*(n=320)*	*(n=275)*	*(n=240)*	*(n=254)*	
Percent (Median (IQR))	**95.2 (11.3)**	94.4 (12.1)	94.6 (12.9)	96.8 (9.9)	95.6 (11.0)	0.002*
<95%	**527 (48.4%)**	168 (52.5%)	140 (50.9%)	103 (42.9%)	116 (45.7%)	
95-105%	**444 (40.8%)**	131 (40.9%)	114 (41.5%)	103 (42.9%)	96 (37.8%)	
>105%	**118 (10.8%)**	21 (6.6%)	21 (7.6%)	34 (14.2%)	42 (16.5%)	
RESPONDENT'S EVALUATION OF CURRENT BODY WEIGHT	*(n=1188)*	*(n=344)*	*(n=296)*	*(n=266)*	*(n=282)*	
- Much too low	**56 (4.7%)**	14 (4.1%)	19 (6.4%)	17 (6.4%)	6 (2.1%)	
- A little too low	**150 (12.6%)**	52 (15.1%)	42 (14.2%)	28 (10.5%)	28 (9.9%)	
- Appropriate	**538 (45.3%)**	167 (48.6%)	125 (42.2%)	114 (42.9%)	132 (46.8%)	
- A little too high	**353 (29.7%)**	98 (28.5%)	84 (28.4%)	78 (29.3%)	93 (33.0%)	
- Much too high	**91 (7.7%)**	13 (3.8%)	26 (8.8%)	29 (10.9%)	23 (8.2%)	
USE OF ONS AND EN						
- Use of ONS at any time during the cancer trajectory	*(n=1181)* **1007 (85.3%)**	*(n=342)* 300 (87.7%)	*(n=294)* 249 (84.7%)	*(n=267)* 223 (83.5%)	*(n=278)* 235 (84.5%)	0.464
- Use of EN at any time during the cancer trajectory	*(n=1184)* **555 (46.9%)**	*(n=344)* 151 (43.9%)	*(n=296)* 143 (48.3%)	*(n=264)* 116 (43.9%)	*(n=280)* 145 (51.8%)	0.165
Current use of ONS and/or EN	***(n=1177)***	*(n=341)*	*(n=293)*	*(n=266)*	*(n=277)*	
- Currently using ONS (but not EN)	**118 (10.0%)**	48 (14.1%)	28 (9.6%)	25 (9.4%)	17 (6.1%)	0.012*
- Currently using EN (but not ONS)	**105 (8.9%)**	36 (10.6%)	19 (6.5%)	24 (9.0%)	26 (9.4%)	0.329
- Currently using ONS and EN	**33 (2.8%)**	13 (3.8%)	9 (3.1%)	5 (1.9%)	6 (2.2%)	0.483

*p<0.05
RT: Completion of radiation therapy, BMI: Body mass index, IQR: Interquartile range, NRS 2002: Nutritional Risk Screening 2002, MUST: Malnutrition Universal Screening Tool, PG-SGA SF: The Scored Patient Generated Subjective Global Assessment Short Form, MDADI: M. D. Anderson Dysphagia Inventory, ONS: Oral nutritional supplements, EN: Enteral nutrition.

Data are presented as numbers and (percentages) unless otherwise stated. Differences between subgroups in continuous variables were tested using Kruskall-Wallis H test. Difference between subgroups in use of enteral feeding at any time during the cancer trajectory was tested using Pearson's chi-squared test, while differences in other categorical variables were tested using Fisher's Exact test.
The PG-SGA SF score can range from 0-36, and MDADI scales range from 20-100. For NRS 2002, MUST, and PG-SGA-SF a high score indicates a high risk of malnutrition, and a high score on the MDADI scales indicates a high level of functioning.

Table 4: Correlations between nutritional scores and health-related quality of life in 1190 Danish head and neck cancer survivors 1-5 years after completion of radiation therapy

		EQ-5D-5L		EORTC QLQ-C30						EORTC QLQ-H&N35
		VAS-score	Summary index score	Global health status/QOL	Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning	Trouble with social eating
Body Mass Index	n	1058	1055	1066	1061	1060	1064	1065	1066	1064
	r_s	0.05	0.06	0.05	0.06	0.06	0.07	0.03	0.09	-0.25
	p-value	0.1165	0.0628	0.1000	0.0641	0.0508	0.0164	0.3656	0.0053	<0.0001*
NRS 2002	n	1039	1036	1046	1042	1041	1044	1045	1045	1045
	r_s	-0.24	-0.21	-0.23	-0.35	-0.26	-0.14	-0.15	-0.22	0.26
	p-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*
MUST	n	1020	1015	1026	1021	1020	1024	1025	1026	1025
	r_s	-0.21	-0.20	-0.23	-0.26	-0.19	-0.17	-0.12	-0.21	0.29
	p-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	0.0001*	<0.0001*	<0.0001*
PG-SGA SF	n	1126	1124	1133	1130	1127	1132	1132	1132	1131
	r_s	**-0.53**	**-0.55**	**-0.57**	**-0.53**	**-0.53**	**-0.46**	**-0.40**	**-0.51**	0.63
	p-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*
MDADI Global score	n	1155	1151	1162	1159	1159	1160	1161	1161	1162
	r_s	0.50	0.48	0.54	0.44	0.47	0.43	0.35	0.50	-0.64
	p-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*
MDADI Composite score	n	1171	1165	1178	1174	1174	1176	1177	1177	1176
	r_s	0.51	0.51	0.54	0.45	0.45	**0.46**	0.38	**0.51**	**-0.75**
	p-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*

*p≤0.001

EORTC: European Organization for Research and Treatment of Cancer, QOL: Quality of life, NRS 2002: Nutritional Risk Screening 2002, MUST: Malnutrition Universal Screening Tool, PG-SGA SF: The Scored Patient Generated Subjective Global Assessment Short Form, MDADI: M. D. Anderson Dysphagia Inventory.

Correlations were tested Spearman's rank correlation coefficient. The strongest correlation for each health-related QOL scale is highlighted in bold.

On the EQ-5D-5L scales, the MDADI scales and the EORTC QLQ-C30 global health status and functional scales, a high score indicates a high level of functioning whereas a high score on the EORTC symptom scale 'Trouble with social eating' indicates a high prevalence of the given symptom. For NRS 2002, MUST and PG-SGA-SF a high score indicates a high risk of malnutrition.

Appendix 2b: Supplementary material for paper II

Supplementary file 1: Data collection for the present study on nutritional characteristics and their association with health-related quality of life in Danish head and neck cancer survivors 1-5 years after completion of radiation therapy

	Data obtained from DAHANCA's clinical quality database	Data obtained from the Danish civil registry system	Self-reported information collected in the NUTRI-HAB Survey
DEMOGRAPHIC DATA			
- Age	X		
- Gender	X		
- Cancer diagnosis	X		
- Time interval from completion of radiation therapy	X		
- Current cancer status			X
- Place of residence		X	
NUTRITIONAL CHARACTERISTICS			
- Body mass index			X
- NRS 2002			X
- MUST			X
- PG-SGA SF			X
- MDADI			X
- Respondent's evaluation of current body weight			X
- Weight loss during cancer trajectory			X
- Precancer body weight			X
- Use of oral nutritional supplements			X
- Use of enteral nutrition			X
HEALTH-RELATED QUALITY OF LIFE			
- EQ-5D-5L			X
- EORTC QLQ-C30			X
- EORTC QLQ-H&N35			X

DAHANCA: The Danish Head and Neck Cancer Group, NRS 2002: Nutritional Risk Screening 2002, MUST: Malnutrition Universal Screening Tool, PG-SGA SF: The Scored Patient Generated Subjective Global Assessment Short Form, MDADI: M. D. Anderson Dysphagia Inventory, EORTC: European Organization for Research and Treatment of Cancer.

Supplementary file 2: Health-related quality of life in 1190 Danish head and neck cancer survivors 1-5 years after completion of radiation therapy

	All respondents	12-23 months after RT	24-35 months after RT	36-47 months after RT	48-59 months after RT	Difference between groups *p-value*
EQ-5D-5L						
VAS-score	*(n=1179)* **80.0 (25.9)**	*(n=344)* 80.0 (20.0)	*(n=292)* 80.0 (27.0)	*(n=264)* 80.0 (25.0)	*(n=279)* 80.0 (24.0)	0.673
Summary index score	(n=1175) **0.824 (0.258)**	(n=342) 0.824 (0.258)	(n=289) 0.802 (0.277)	(n=266) 0.847 (0.255)	(n=278) 0.833 (0.245)	0.315
EORTC QLQ-C30						
Global health status/QOL	*(n=1188)* **83.3 (33.3)**	*(n=344)* 83.3 (33.3)	*(n=296)* 83.3 (41.7)	*(n=267)* 75.0 (83.3)	*(n=281)* 83.3 (16.7)	0.9145
Physical functioning	*(n=1183)* **93.3 (26.7)**	*(n=343)* 93.3 (20.0)	*(n=293)* 86.7 (26.7)	*(n=267)* 86.7 (26.7)	*(n=280)* 93.3 (20.0)	0.0847
Role functioning	*(n=1182)* **100.0 (33.3)**	*(n=343)* 100.0 (33.3)	*(n=296)* 100.0 (33.3)	*(n=267)* 100.0 (33.3)	*(n=276)* 100.0 (33.3)	0.3204
Emotional functioning	*(n=1186)* **91.7 (25.0)**	*(n=344)* 91.7 (25.0)	*(n=295)* 91.7 (33.3)	*(n=267)* 91.7 (33.3)	*(n=280)* 91.7 (25.0)	0.3852
Cognitive functioning	*(n=1187)* **83.3 (33.3)**	*(n=344)* 83.3 (16.7)	*(n=296)* 83.3 (33.3)	*(n=267)* 83.3 (33.3)	*(n=280)* 83.3 (33.3)	0.0665
Social functioning	*(n=1187)* **100.0 (33.3)**	*(n=344)* 100.0 (33.3)	*(n=295)* 100.0 (33.3)	*(n=267)* 100.0 (33.3)	*n=281)* 100.0 (33.3)	0.9481
EORTC QLQ-H&N35						
- Trouble with social eating	*(n=1185)* **8.3 (25.0)**	*(n=343)* 8.3 (25.0)	*(n=296)* 8.3 (29.2)	*(n=267)* 0.0 (25.0)	*(n=279)* 8.3 (25.0)	0.0057*

* $p < 0.05$

Data are presented as medians (interquartile range). Differences between groups were tested using Kruskall-Wallis H test.

The EORTC scales and the EQ-5D-5L VAS range from 0-100, and the EQ-5D-5L summary index score ranges from -0.624-1.0. On the EQ-5D-5L scales, the MDADI scales and the EORTC global health status and functional scales, a high score indicates a high level of functioning whereas a high score on the EORTC symptom scale 'Trouble with social eating' indicates a high prevalence of the given symptom.

Appendix 3a: Paper III

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Rationale and design of a randomised controlled trial investigating the effect of multidisciplinary nutritional rehabilitation for patients treated for head and neck cancer (the NUTRI-HAB trial)

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Abstract

Background: Eating problems frequently affect quality of life and physical, psychological and social function in patients treated for head and neck cancer (HNC). Residential rehabilitation programmes may ameliorate these adverse effects but are not indicated for all individuals. Systematic assessment of rehabilitation needs may optimise the use of resources while ensuring referral to rehabilitation for those in need. Yet, evidence lacks on which nutrition screening and assessment tools to use. The trial objectives are: 1) To test the effect of a multidisciplinary residential nutritional rehabilitation programme compared to standard care on the primary outcome body weight and secondary outcomes health-related quality of life, physical function and symptoms of anxiety and depression in patients curatively treated for HNC and 2) To test for correlations between participants' development in outcome scores during their participation in the programme and their baseline scores in Nutritional Risk Screening 2002 (NRS 2002), the Scored Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF), and M. D. Anderson Dysphagia Inventory (MDADI) and to assess sensitivity, specificity and predictive values of the three tools in relation to a clinically relevant improvement in outcome scores.

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Methods: In a randomised controlled trial, 72 patients treated for HNC recruited through a nationwide survey will be randomised to a multidisciplinary residential nutritional rehabilitation programme or to a wait-list control group. Data are collected at baseline, three and six months. Primary outcome is change in body weight, and secondary outcomes include changes in quality of life, physical function and symptoms of anxiety and depression. Potential correlations between intervention effect and baseline scores in NRS 2002, PG-SGA-SF and MDADI will be tested, and sensitivity, specificity and predictive values of the three tools in relation to a clinically relevant improvement in outcome scores will be assessed.

Discussion: This is the first randomised controlled trial to test the effect of a multidisciplinary residential nutritional rehabilitation programme in patients treated for HNC. Recruitment through a nationwide survey gives a unique possibility to describe the trial population and to identify potential selection bias. As the trial will explore the potential of different nutrition screening and assessment tools in the assessment of rehabilitation needs in patients treated for HNC, the trial will create knowledge about how selection and prioritisation of nutritional rehabilitation aimed at patients treated for HNC should be offered. The results may contribute to a better organisation and use of existing resources in benefit of patients treated for HNC.

Trial registration: The trial is registered by The Danish Data Protection Agency (registration 2012-58-0018, approval number 18/14847) and the Regional Committees on Health Research Ethics for Southern Denmark (journal number 20182000–165). ClinicalTrials.gov Identifier: NCT03909256. Registered April 9, 2019.

Keywords: Head and neck cancer, Rehabilitation, Survivorship, Eating problems, Quality of life, Assessment of rehabilitation needs, Nutritional assessment, Nutrition screening

Background

The incidence of head and neck cancer (HNC) has increased to approximately 900.000 new cases worldwide in 2018 [1, 2]. With a simultaneous increase in the relative survival [3], the population of patients treated for HNC is increasing.

Many patients treated for HNC feel unprepared for the life that awaits them after cancer treatment [4–7] when eating problems and other late effects may persist for years or even become chronic [8]. These include dysphagia (swallowing difficulties), xerostomia (dry mouth), dysgeusia (taste disturbances), and trismus (reduced mouth opening) [8]. The negative effects of eating problems on quality of life (QOL) and everyday life in patients treated for HNC have been documented in quantitative [8–13] and qualitative [5, 14–19] studies. Based on existing studies [4–7, 18, 20, 21] it is suggested that appropriate rehabilitation services can strengthen the patient's ability to cope with eating problems and thereby reduce the negative consequences. Yet, unmet rehabilitation needs are widely documented in this population [4, 5, 7, 16, 22, 23].

A frequent strategy for patients treated for HNC to cope with eating problems is the trial-and-error approach [4, 6, 16, 20] with continuous experiments to find tolerated foods as this varies over time. The process may be complicated by fear of choking [4, 15, 19] and feelings of defeat when experiments are unsuccessful [4, 16]. Residential group based rehabilitation programmes, where the daily meals are part of the intervention, may be particularly effective to support patients treated for HNC in this coping process as they can provide a safe environment to practice eating skills [4, 21]. High participant satisfaction and improvements in QOL scales were seen among patients treated for HNC participating in a pilot study testing a 1-week residential psychoeducational programme [21]. In another pilot study, qualitative data showed that patients treated for HNC benefitted from participating in a multidisciplinary residential nutritional rehabilitation programme [4]. Unpublished quantitative data from the latter pilot study (included in Additional file 1) showed significant improvements in body weight and several QOL scales at 3-month follow-up. With no control group in the pilot study, the results should be tested in a randomised controlled trial on the effect of the multidisciplinary residential nutritional rehabilitation programme.

The increasing population of patients treated for HNC may present a challenge to existing health care systems through increased rehabilitation costs. Residential rehabilitation programmes and other specialised rehabilitation services aimed at eating problems may be costly, and may not be indicated for all patients treated for HNC. Systematic screening and/or assessment of rehabilitation needs in patients treated for HNC may optimise the use of existing resources while ensuring referral to appropriate rehabilitation services for those in need.

The European Society for Clinical Nutrition and Metabolism recommends that nutritional screening is performed at cancer diagnosis and repeated regularly depending on the stability of the clinical situation [24]. Several tools have been developed to screen and assess nutritional risk, nutritional status and nutrition impact

symptoms [24–28]. Nutritional Risk Screening 2002 (NRS 2002), [26] is validated to identify patients, regardless of their diagnosis, who will benefit from nutritional intervention. Yet, to our knowledge no studies have validated NRS 2002 in patients treated for HNC after treatment, and even for patients with HNC prior to treatment, it has been suggested to use a modified version with a different cut-off value [29]. Furthermore, NRS 2002 only assesses dietary intake as the consumed amount in relation to requirements [26]. It does not assess nutrition impact symptoms, which would be highly relevant in this population. The Scored Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) includes information on nutrition impact symptoms and changes in dietary intake (amount or consistency) in the assessment of nutritional risk and nutritional deficit [27], but no validation studies have been carried out in patients after treatment for HNC. The M. D. Anderson Dysphagia Inventory (MDADI) [28] is developed to assess dysphagia-specific QOL in patients with HNC. But so far, no clinical studies have investigated associations between MDADI score and intervention effect. Hence, the evidence is scarce on the three tools' ability to identify patients treated for HNC who will benefit from posttreatment nutritional rehabilitation.

Trial objectives

The objectives of the trial are:

- To test the effect of a multidisciplinary residential nutritional rehabilitation programme compared to standard care on the primary outcome body weight and secondary outcomes health-related QOL, physical function and symptoms of anxiety and depression in patients curatively treated for HNC
- To test for correlations between participants' development in outcome scores during their participation in the programme and their baseline scores in NRS 2002 [26], PG-SGA SF [27], and MDADI [28] and to assess sensitivity, specificity and predictive values of the three tools in relation to a clinically relevant improvement in outcome scores

Methods

Trial design

The trial is a randomised controlled trial with recruitment through a nationwide survey. Participants will be randomised into either an intervention group or a wait-list control group. Data will be collected at baseline, at three, and at six months (Fig. 1).

Differences between groups at 3-month follow-up will be tested to assess the effect of the intervention. Exploratory analyses will be based on all data collected from baseline to 6-month follow-up. They will include analyses of the long-term effect of the intervention and of whether the selected nutrition screening tools are labile and able to reflect changes over time.

The SPIRIT (Standard Protocol Items for Randomized Trials) 2013 [30, 31] statement, the CONSORT (Consolidated Standards of Reporting Trials) extension for reporting trials of nonpharmacologic treatments [32] and the TIDieR (template for intervention description and replication) [33] checklist and guide have been used

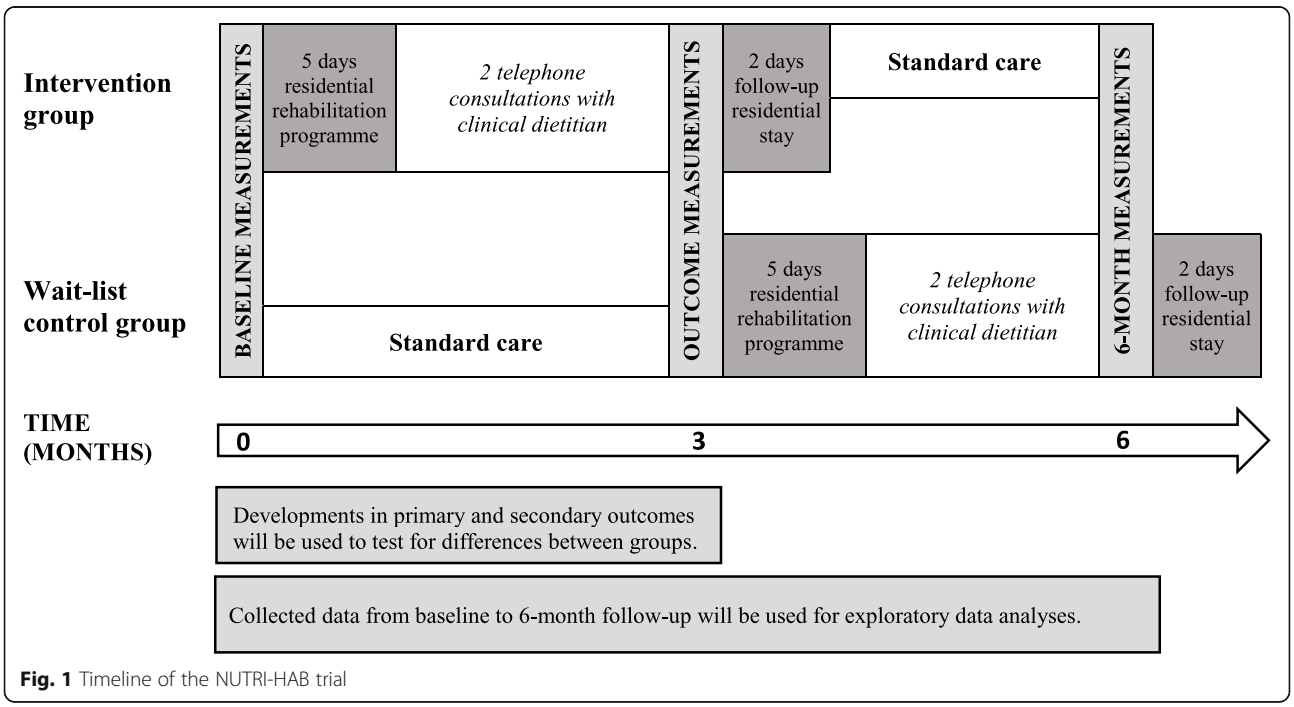

Fig. 1 Timeline of the NUTRI-HAB trial

as guidelines for developing the trial protocol. The SPIRIT checklist is included in Additional file 2, and descriptions of all physical and informational materials used in the trial and how to assess these are included in Additional file 3.

Setting

The trial will be carried out at REHPA, the Danish Knowledge Centre for Rehabilitation and Palliative Care in Nyborg, Denmark, between May 2019 and December 2019.

In Denmark, cancer treatment and rehabilitation are funded by government taxes and free of charge for patients. While cancer treatment and rehabilitation services during treatment are offered at the hospitals, posttreatment rehabilitation is primarily a municipal responsibility [34]. Denmark comprise 98 municipalities with great variation between their rehabilitation services [35, 36]. Only 17 Danish municipalities offered diagnosis specific rehabilitation services for patients treated for HNC in 2017 [36]. Hence, the level of rehabilitation that participants have received prior to their participation in the trial may vary, and information on which rehabilitation services participants have been offered and participated in will be registered.

Participants

Participants will be recruited among respondents of a nationwide survey on late effects and health-related QOL in Danish patients treated for HNC 1–5 years following radiation therapy. The survey population was identified through The Danish Head and Neck Cancer Group's (DAHANCA) national clinical quality database [37].

The survey was distributed in March 2019. Patients treated for HNC will be eligible for participation in the trial if they meet the following inclusion criteria:

Register-based information:

- Have been diagnosed with cancer of the larynx, pharynx, or oral cavity
- Have completed curatively intended treatment with radiation therapy 1–5 years before survey distribution (1st of March 2014 to 28th of February 2018)
- Are aged ≥18 years

Self-reported information collected through the survey:

- Have no active HNC or any other active cancer at the time for completion of the survey
- Are self-reliant. Survey respondents are defined as self-reliant if they answered "Not at all" on the question "Do you need help with eating, dressing, washing yourself or using the toilet?" in The European Organization for Research and Treatment of Cancer's (EORTC) QLQ-C30 questionnaire [38] on health-related QOL
- Are able to speak and understand Danish
- Have confirmed that they are interested in participating in a multidisciplinary residential nutritional rehabilitation programme at specific dates and given their permission to be contacted with further information. This inclusion criterion has been established to obtain permission and contact details for telephone contact and to narrow down the population for inclusion since the nationwide survey was distributed to almost 2000 individuals. By giving survey respondents the possibility to opt out for further contact regarding the trial, we reduce the number of inquiries to each respondent.

Potential recurrence of cancer during the trial will not lead to exclusion of participants. In the event of cancer recurrence in one or more participants, sensitivity analyses will be made to investigate whether this affects the trial results.

Intervention

The intervention is a multidisciplinary residential nutritional rehabilitation programme with a primary focus on the physical, psychological and social aspects of eating problems after treatment for HNC. The programme will comprise five days initial residential stay and two days follow-up residential stay after three months (Fig. 1). The rehabilitation centre has developed a core programme model through available evidence and more than 10 years' experience in offering multidisciplinary residential rehabilitation programmes for heterogeneous groups of patients with cancer [39, 40]. To meet the specific rehabilitation needs of patients treated for HNC, the core programme was further developed through available evidence, patient involvement and a pilot study including 40 patients treated for HNC [4]. Components of the rehabilitation centre's core programme will be included even though they are not specifically aimed at eating problems. Yet, these activities have shown to be relevant and beneficial to other groups of patients with cancer [39–41]. The programme consists of group sessions with patient education and a few individual activities. The content of these sessions and activities are shown in Table 1 while a detailed schedule of the programme is shown in Additional file 4.

As described in the background section, patients treated for HNC frequently use the trial-and-error approach [4, 6, 16, 20] to cope with their eating problems. The programme aims to support participants in this coping process in various ways. Participants will stay at the premises during the residential stays and all meals will be served in the dining room and break areas. Meals

Table 1 Patient education sessions in the multidisciplinary residential nutritional rehabilitation programme [42] in the NUTRI-HAB trial

SESSION	DURATION (minutes)	CONTENT	SESSION LED BY
Welcome session with presentation of the programme[a,d]	30	The aim of the welcome session is to make participants feel safe and comfortable in the environment in which they will be spending the next five days. This may contribute to increased motivation and willingness to participate actively throughout the programme [43, 44].	Course leader[f] and clinical dietitian
Presentation round[a,d]	60	In the presentation round, participants will share information about their background and cancer diagnosis, and they will be encouraged to use selected picture cards to narratively describe their expectations and desired outcomes of participation. The aim of the session is to enhance group formation and to establish a sense of community among participants since this may facilitate patient empowerment [45]. Central staff members (course leader, physician, clinical dietitian, and evening hostess) participate.	Course leader
Social activity[a,d]	60	A social activity including music and movement will be scheduled on the first evening of the programme to support group formation and candidness among participants.	Music therapist
Theoretical session on eating problems[a,d]	105	The session will include dietary advice to manage different nutrition impact symptoms e.g. choice of foods, texture and flavour modification [24, 46]. Exchange of experiences between participants will be encouraged.	Clinical dietitian
Individual dietary counselling[c,d,e]	30 (20 at follow-up)	In the individual dietary counselling, dietary advice will be tailored to the individual participant [24].	Clinical dietitian
Practical kitchen workshop[b,d]	180	In the practical kitchen workshop, participants will prepare foods of different textures and flavours, and take-home recipes will be handed out. The aim of the workshop is to inspire and put theory into practice [4], and practical kitchen sessions have supported dietary changes in studies with other types of cancer survivors [47, 48].	Clinical dietitian
Swallowing exercises[b,d]	90	Participants will be instructed in different swallowing exercises and exercises for jaw and tongue mobility, since these types of exercises may reduce dysphagia and trismus [46, 49]. Participants will receive an exercise manual and a training diary, and will be encouraged to continue doing the exercises, when they come home.	Occupational therapist
Dental problems and oral hygiene[b,d]	75	Dental problems are frequent after treatment for head and neck cancer [22]. The session will include information on how to maintain good oral hygiene and on dental reimbursement rules in relation to cancer treatment.	Dental hygienist
Physical activity[a,d,e]	75	Physical activity may contribute to ameliorate late effects associated with decreased physical function in cancer survivors [50–53]. In the physical activity sessions, participants will be introduced to different kinds of physical activity that they can do at home e.g. balance or resistance training exercises. Exercises will be adjusted to the participants' training level.	Physiotherapist
Yoga[b,d]	60	Yoga may contribute to improve quality of life and to reduce fatigue and symptoms of distress and anxiety in cancer survivors [54, 55]. The yoga session will be based on principles from Hatha yoga and Physioflow yoga. Special attention will be given to exercises aimed at releasing tensions in the head and neck area.	Physiotherapist certified as yoga instructor
Psychological reactions to cancer[b,d]	150	The session will be based on a psychoeducational approach [56, 57] and will aim at supporting participants' coping of everyday life after cancer. The session will comprise psychologist's presentation of frequent psychological reactions to cancer and discussions in small groups.	Psychologist
The existential dimension of rehabilitation[a,d]	90	The session is a group conversation on questions of existential and spiritual character that often follow the diagnosis of a life-threatening disease [58, 59].	Priest
Massage therapy[c,d]	45	Massage therapy may contribute to short term reduction of pain and anxiety even though the level of evidence is very low [60]. Each participant will receive 45 min of relaxing massage therapy and will have to choose between a full body relaxing massage or special attention given to a certain area e.g. tensions in the neck.	Massage therapist
Vocational counselling[b,d]	75	Optional session. Vocational counselling session will aim to support return-to-work processes and hence participants functioning in accordance with the World Health Organization's International Classification of Functioning, Disability and Health (ICF) [61]. The session will include information on rights and obligations according to Danish legislation.	Social worker

Table 1 Patient education sessions in the multidisciplinary residential nutritional rehabilitation programme [42] in the NUTRI-HAB trial *(Continued)*

SESSION	DURATION (minutes)	CONTENT	SESSION LED BY
Fatigue and sleep problems[b,d]	75	Optional session on reasons for and management of cancer-related fatigue [52, 62] and sleep problems [63, 64].	Nurse
Motivation, goal setting and action plans[a,d]	100	Based on principles of motivational interviewing [65], the session will allow participants to reflect on, how they will implement new inspiration and knowledge gained through the programme, when returning back home.	Course leader
Intimacy and sexuality[b,e]	90	Optional session. Based on the PLISSIT model [66], the session will address how sexuality and intimacy can be affected by cancer and cancer treatment [67, 68] and provide advice for management of potential challenges. Participants will be divided into groups by gender for the session.	Sexologist
Meaning and values in life[b,e]	90	Optional session. Based on principles of acceptance and commitment therapy [69], the session will aim to support participants in re-establishing meaning in life through reflections on values and sources to meaning in lif e[70, 71].	Psychologist
Individual counselling[c,d,e]	30–45	Individual counselling with relevant health professionals (e.g. speech pathologist, physician) will scheduled depending on participants' needs.	Depending on need

[a] Group session with a maximum of 20 participants; [b] Group session with a maximum of 10 participants; [c] Individual session; [d] Session is offered at the initial five days residential stay; [e] Session is offered at the two days follow-up residential stay after three months; [f] Course leader (nurse, physiotherapist or social worker) coordinates all activities during the week and is the participants' primary contact person
Rehabilitation Centre Dallund and REHPA, The Danish Knowledge Centre for Rehabilitation and Palliative Care have developed the core model for the residential group-based rehabilitation programme as a best practice patient-centred rehabilitation model for heterogeneous groups of cancer survivors. The rationale, evidence base and content of the model and the specific activities are described in details elsewhere [42]. The core model has been adjusted to meet the rehabilitation needs of the population in the NUTRI-HAB trial

will be served as self-service buffets, and foods of different textures and flavours will be served to inspire and to allow participants to experiment. The menu plan for the entire residential stay will be presented on the first day and will be available in the dining room. If a participant has specific dietary preferences or requirements that are not met in the menu plan for a given meal, the kitchen staff will find alternatives together with the participant. The meals are furthermore intended as social training since eating problems often lead to social withdrawal [4, 15, 17, 20]. Individual counselling sessions with relevant professionals (e.g. speech pathologist or physician) will be scheduled depending on the individual participant's needs assessed by baseline questionnaires and outcome data.

Between the initial stay and the two days follow-up, participants will have two telephone consultations with a clinical dietitian. These will be scheduled in week 4 and week 8. The aims of these consultations are to follow up on topics addressed in the individual consultation at the residential stay, to answer potential questions that have emerged, and to encourage the participant to continue with any activities or changes that they planned to implement after the residential stay.

The programme will be free of charge for participants and an additional offer to existing rehabilitation services. Participants will be asked to fill out an evaluation form in which they will evaluate the overall residential stay, the different sessions and indicate whether they participated in the specific session.

Wait-list control group

Between baseline and 3-month follow-up, the wait-list control group will receive no intervention other than standard care. Since participants will be from all over the country, standard care may vary. Participants will not be restricted from participating in other rehabilitation services during the trial period. After 3-month follow-up, participants in the wait-list control group will be offered participation in the multidisciplinary residential nutritional rehabilitation programme.

Inclusion and randomisation

Figure 2 shows the flow of the inclusion and randomisation process. Individuals who have responded to the nationwide survey within nine weeks from survey distribution and who meet the inclusion criteria will be randomised into invitation lists for intervention group or wait-list control group. The allocation ratio will be 1:1, and allocated individuals will be placed in random order on the numbered invitation list. Four residential rehabilitation programmes are scheduled, and each has a maximum capacity of 20 participants. Hence, a maximum of 40 participants in each group can be included. The first 40 individuals on each invitation list will receive further information about the trial and be invited to participate. Invitations will be sent electronically to e-Boks, a secure digital mailbox linked to the individual's civil registration number. In Denmark, it is mandatory to have e-Boks unless a citizen applies for exemption. Individuals without e-Boks will receive the invitation through postal mail. If the invitation is declined, the next person on the given invitation list will be invited. If invited individuals do not respond, they will be contacted by telephone.

Randomisation will be stratified by need for rehabilitation services measured by the REHPA scale adapted from the National Comprehensive Cancer Network® Distress Thermometer [72]. On the REHPA Scale, participants indicate how close or how far they are from living the life they want after or in spite of their disease. A higher score indicates greater rehabilitation needs. The REHPA Scale was included in the nationwide survey. A certain score on the REHPA scale is not an inclusion criteria for the present trial, but randomisation will be stratified to ensure similar proportions of individuals with a score of ≥3 across the invitation lists. Participants will be randomised in STATA/IC 15.1 by a blinded researcher (TBM) who is not involved in the trial intervention or assessment of outcomes.

Outcome measures and data collection

Outcome measures will be collected at entry, at three, and at six months (Fig. 1). Baseline measurements of the wait-list control group and 6-month follow-up measurements of the intervention group will be performed in one of three regional outpatient clinics depending on the participant's place of residence. All other measurements will be performed at the rehabilitation centre. Data collected at different time points are shown in Table 2.

Trained health professionals will perform all physical measurements and tests following strict protocols. Patient reported outcome measures and other patient reported data will be collected through electronic questionnaires distributed through Research Electronic Data Capture (REDCap) [73] to participants' e-Boks one week before the scheduled physical measurements. Participants without e-Boks will be asked to fill out the questionnaire on a computer on the location of the measurement. Participants who are not confident in filling out the questionnaires electronically will fill out a paper-based questionnaire.

Data from paper-based questionnaires and results from physical measurements and tests will be entered in REDCap by one researcher, and the entered data will be double-checked by a second researcher.

Demographic data

Register-based data Information on age, gender, cancer diagnosis and treatment was obtained from DAHANCA's

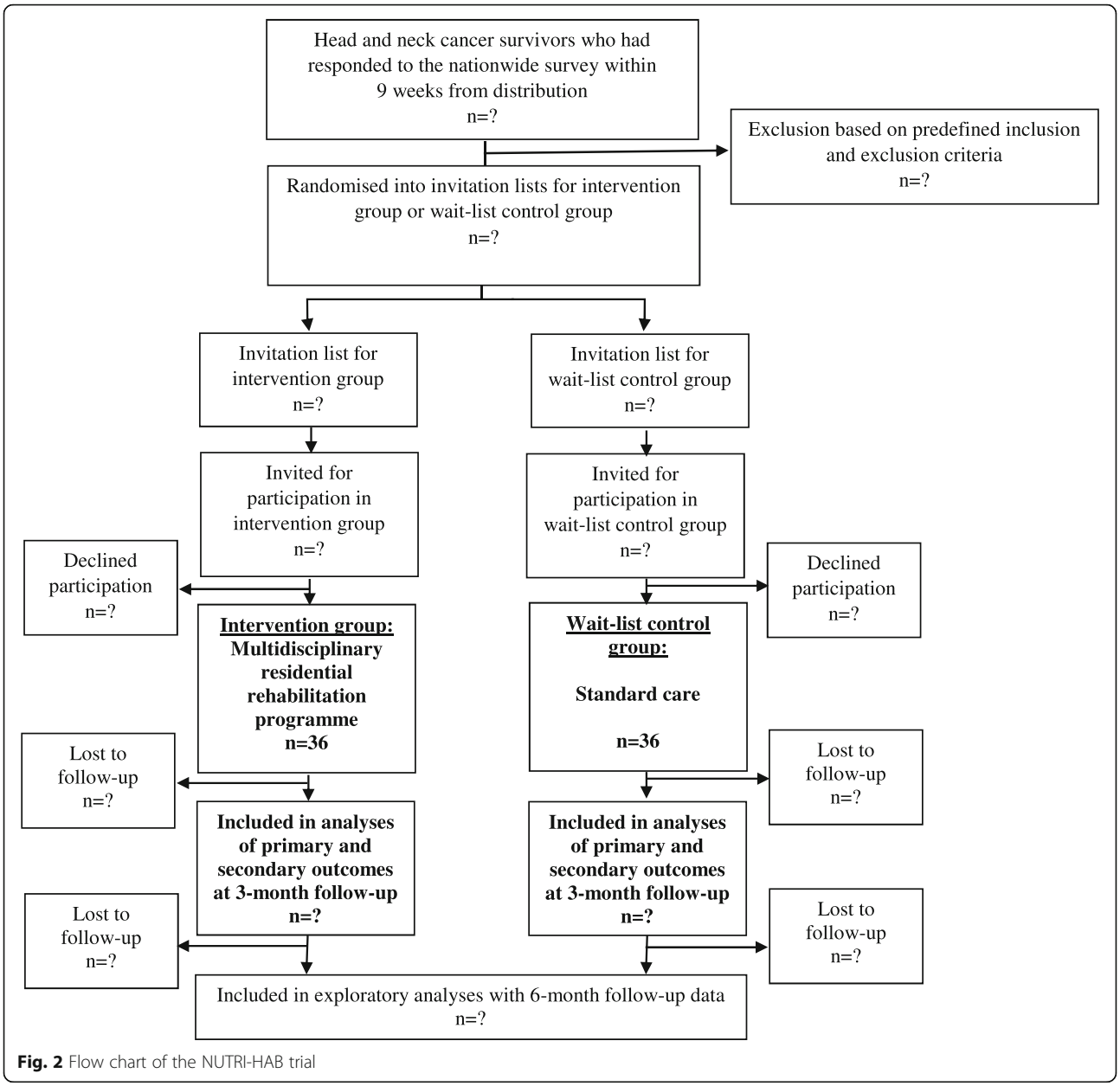

Fig. 2 Flow chart of the NUTRI-HAB trial

national clinical quality database [37] before the nationwide survey was sent out.

Self-reported data Questions on civil status, educational level, occupational status, will be included in the electronic questionnaire at baseline. Questions on current cancer status and participation in other rehabilitation services prior to baseline was included in the nationwide survey. At 3-month and 6-month follow-up information on this will be collected through individual counselling sessions with the clinical dietitian.

Nutritional risk and presence of nutrition impact symptoms at entry of the rehabilitation programme

Nutritional risk screening 2002 The NRS 2002 has been developed and validated to identify admitted patients who will benefit from nutritional intervention [26]. Screening with NRS 2002 comprises a primary screening and, dependent on the result, a secondary screening. The primary screening assesses the presence of recent weight loss, body mass index < 20.5, decreased dietary intake in the preceding week and severe disease. In the secondary screening, the overall score comprises an A-score for nutritional status, a B-score for disease

Table 2 Data collection at the different time points in the NUTRI-HAB trial

	TIMEPOINT		
	Baseline	3-month follow-up	6-month follow-up
DEMOGRAPHIC DATA			
Register-based information			
- Age	X		
- Gender	X		
- Cancer diagnosis	X		
- Time interval since treatment	X		
Self-reported information			
- Civil status	X		
- Educational level	X		
- Occupational status	X		
- Current cancer status	(X)	(X)	(X)
- Participation in other rehabilitation services	(X)	(X)	(X)
NUTRITIONAL RISK AND PRESENCE OF NUTRITION IMPACT SYMPTOMS			
- NRS 2002	X	(X)	(X)
- PG-SGA SF	X	(X)	(X)
- MDADI	X	(X)	(X)
REHABILITATION NEEDS MEASURED BY THE REHPA SCALE			
	(X)	(X)	(X)
PRIMARY OUTCOME			
- Body weight	X	X	(X)
SECONDARY OUTCOMES			
Patient-reported outcome measures			
Quality of life			
- EQ-5D-5 L	X	X	(X)
- EORTC QLQ-C30	X	X	(X)
- EORTC QLQ-H&N35	X	X	(X)
Symptoms of anxiety and depression			
- HADS	X	X	(X)
Physical measurements and tests[a]			
- Body mass index	X	X	(X)
- Maximal mouth opening	X	X	(X)
- Hand grip strength	X	X	(X)
- 30-second chair stand test	X	X	(X)
- 6-minute walk test	X	X	(X)

X: Data will be collected for primary analyses, (X): Data will be collected for exploratory analyses
[a]The physical performance tests will be made in a standardised order as follows: 30-second chair stand test, hand grip strength, and 6-minute walk test
EORTC: European Organization for Research and Treatment of Cancer, HADS: Hospital Anxiety and Depression Scale, NRS 2002: Nutritional Risk Screening 2002, PG-SGA SF: The Scored Patient Generated Subjective Global Assessment Short Form, MDADI: M. D. Anderson Dysphagia Inventory

severity and an extra point if aged 70 or above. A higher score indicates greater nutritional risk [26]. Hence, questions on recent changes in body weight and dietary intake will be included in the questionnaire.

The scored patient-generated subjective global assessment short form The PG-SGA SF is a one-page instrument that assesses nutritional risk and nutritional deficit [27]. It includes questions on weight changes, changes in dietary intake (amount or consistency), nutrition impact symptoms and performance status [27]. The PG-SGA SF score ranges from 0 to 36, and a higher score indicates a higher risk of malnutrition. The Danish version has been translated, cross-culturally adapted,

and linguistically validated [74]; and is used with permission.

M. D. Anderson dysphagia inventory The MDADI is a self-administered questionnaire on dysphagia-specific QOL in patients with HNC [28]. The Danish version has been translated and culturally adapted, and has been found reliable in terms of internal consistency and test–retest reproducibility [75]. The original version of MDADI consists of 20 items. One item covers overall QOL whereas remaining 19 items form three subdomains: emotional, functional and physical. In addition to a score for each subdomain, a composite score is calculated for the 19 items. The scales range from 20 to 100, and a high score indicates a high degree of functioning. The Danish version contains four additional items concerning specific mechanisms that affect deglutition [75].

Rehabilitation needs measured by the REHPA scale

As described under 'Inclusion and randomisation', the REHPA Scale is a numerical score of how close or far an individual is from living the life they desire after their disease. The scale ranges from 1 to 9, and a higher score indicate greater rehabilitation needs. In addition to the numerical score, the participant can mark the challenges that prevent them from achieving their goals. Challenges listed in the questionnaire include different practical problems, work-related problems, family problems, physical symptoms, psychological problems and existential problems.

Primary outcome

The primary outcome is percentage change in body weight from baseline to 3-month follow-up. Body weight will be measured to the nearest 0.1 kg on calibrated Seca 877/878 scales. In accordance with National Institute for Health Research Southampton Biomedical Research Centre Procedure for Measuring Adult Weight [76], body weight measurements will be continued until three consecutive measurements within 100 g of each other are obtained. The mean of the three will be used in the analyses. Participants will be asked to limit their food and fluid intake two hours before the weighing and to empty their bladder immediately before. For each participant, body weight measurements will be performed at the same time of day (before/after noon) at baseline and 3-month follow-up.

Secondary outcomes: patient reported outcome measures

Health-related quality of life Health-related QOL will be measured using the Danish translations of the EuroQol 5D-5 L (EQ-5D-5 L) [77], the EORTC QLQ-C30 [38, 78], and the diagnosis specific EORTC QLQ-H&N35 [78, 79].

The EQ-5D-5 L covers the dimensions mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a low score indicates a high level of functioning in the given dimension. Overall health is measured with an index score based on the five dimensions and by visual analogue scale (VAS). The index score ranges from − 0.624-1.0 and the VAS scale ranges from 0 to 100. A higher score represents a better self-rated health [77].

Participants' scores in QLQ-C30 and QLQ-H&N35 will be calculated according to the manual [80]. The tools comprise one global QOL scale, five functional scales and 27 symptom scales. All scales range from 0 to 100, and a high score represents a higher response level. Thus, a high score for a functional scale or global QOL represents a high level of functioning/QOL whereas a high score on a symptom scale represents a high level of symptoms.

Symptoms of anxiety and depression Symptoms of anxiety and depression will be measured with the Danish translation of the Hospital Anxiety and Depression Scale. The scale consists of two subscales for anxiety and depression. The subscales range from 0 to 21, and a high score indicates a high symptom level [81].

Secondary outcomes: physical measurements and physical performance tests

Body mass index Body mass index will be calculated as body weight (kg) divided by squared height (m). Height will be measured to the nearest 0.5 cm using a Seca 222 stadiometer.

Maximal mouth opening To assess trismus, maximal mouth opening will be measured in mm using a TheraBite® Range-Of-Motion ROM Scale. Participants will be seated on a chair during the test. The notch of the scale will be placed on the left lower front tooth, and the participant will be asked to open the mouth as widely as possible without discomfort. While still touching the lower front tooth, the scale will be rotated until it also touches the left upper front teeth, and the measuring point will be registered. Three measurements will be performed, and the highest measurement will be used for data analyses.

Hand grip strength Hand grip strength will be measured in kg using a calibrated Jamar hand dynamometer. The measurement protocol is based on recommendations from Roberts et al. [82]. Measurements will be made with the hand dynamometer in the second handle position. Three consecutive measurements in each hand

will be performed, and the highest measurement for each hand will be used for data analyses.

30-second chair stand test The 30-second chair stand test assesses lower body strength [83]. It measures the number of times a person can sit and rise to full standing position from a chair in 30 s. The test protocol follows the method described by Jones et al. [83]. The participant will be instructed to be fully seated between the stands and encouraged to complete as many full stands as possible during the 30 s without using their hands. The final score will be the total number of stands executed correctly. If participants are unable to rise without using their hands, it will be registered that the test is completed in a modified version.

6-minute walk test The 6-minute walk test is considered a measure of the submaximal level of functional capacity [84].

The test will be performed on a 30-m walking course. Participants will be instructed to walk as many laps as possible during the six minutes without jogging or running. Each minute, the tester will inform the participant about the remaining time, but otherwise the test will be performed in silence. After six minutes, the participant will be asked to stop, and completed distance of the final lap will be measured to the nearest metre. The score will be the total distance walked in metres.

Sample size

The sample size calculation is based on quantitative data from the previous pilot study [4]. The mean weight change in percent was 1.74 ± 2.37 when restricting to participants with cancer of the pharynx, larynx, or oral cavity and who had completed radiation therapy 1–5 years prior to participation. Based on these data, 30 participants are required in each group to achieve a power of 80% and a significance level of 5%. Thus with an estimated withdrawal rate of 15% [4], we will include 36 participants in each group.

Data analysis

The statistical analysis plan for the trial is shown in Additional file 5. Data will be analysed in SAS® Enterprise Guide® 7.1 by both per protocol and intention-to-treat principle [85]. Data analyses will not be commenced until all data collection is completed. A blinded researcher (TBM) will analyse the data, and the project group will interpret results before unblinding. Development in outcome scores from baseline to 3-month follow-up will be calculated for each participant, and differences between intervention group and wait-list control group will be tested using a two-sample two-sided t-test for normally distributed data and Mann-Whitney U test for non-normally distributed data. A significance level of 5% will be applied. Effect size will be estimated with Cohens d [86]. Multiple linear regression will be used to assess the influence of potential confounding variables (e.g. time interval from completion of treatment) on intervention effect. Mean baseline values for outcome scores in both groups will be presented in result tables. Simple linear regression will be used to test correlations between developments in outcome scores and baseline scores in NRS 2002, MDADI or PG-SGA SF. Sensitivity, specificity and predictive values of different cut-offs in NRS 2002, MDADI or PG-SGA SF at baseline in relation to a clinically relevant improvement in outcome scores during participation in the programme will be assessed. To avoid missing data, participants who drop out of the trial will be encouraged to participate in follow-up measurements. The percentage and patterns of missing values in outcome variables will be examined. If data are missing at random and the percentage of missing data is not substantial [87], multiple imputation techniques will be used in the intention-to-treat analyses.

Patient and public involvement

Patients have been involved in several steps of the trial development. A pilot study was conducted [4], where participants through focus groups contributed with ideas for further qualification of the intervention. Furthermore, they contributed to the selection of the nutrition screening and assessment tools for this trial. The preliminary trial protocol was presented at a workshop for REHPA's user panel. The panel consists of former participants in REHPA's programmes and representatives from patient organisations. The discussion at the workshop focused on the intervention and on pros and cons of including participants' relatives. Input from patient involvement led to adjustments of the programme including possibility for counselling with a speech pathologist, optional session with a sexologist, optional session with vocational counselling, and adjustment of breaks during the days. Furthermore, it was decided that the intervention in the present trial will not be aimed at or include relatives, since patients were concerned that it would affect social interaction and candidness among participants.

When the trial is completed, participants will be invited to a symposium with presentation of the main results. Participants will be welcome suggest secondary explorative analyses of patient interest to inform future research questions based on the findings of the NUTRI-HAB trial.

Ethics and dissemination

The trial will be conducted in accordance with the Declaration of Helsinki [88]. Informed written consent will be obtained from all participants before inclusion. Participants will be informed verbally and in writing that

participation is voluntary, and that they can withdraw their consent at any time. Participants will receive no payment for their participation, and their only expenses associated with participation will be transportation costs to the rehabilitation centre. For ethical reasons, we will use a wait-list control group, who also receives the intervention after 3-month follow-up. Based on the prior pilot study [4] it is expected that participants will benefit from participation, and there are no expected risks associated with participation. The Regional Committees on Health Research Ethics for Southern Denmark have assessed the duty to notify for the present trial (journal number 20182000–165). Based on Danish legislation, the committees concluded that the trial is not subject to the duty to notify since no biological material is included. The trial is registered by The Danish Data Protection Agency, registration number 2012-58-0018, approval number 18/14847, and registered in the database Clinical Trials (www.clinicaltrials.gov, NCT03909256). Amendments to the protocol will be made public at clinicaltrials.gov.

Results will be published in international peer-reviewed journals and presented at national and international conferences.

Within the confines of Danish legislation, anonymised data from the trial will be available for other researchers upon reasonable request when results have been published.

Discussion

This is the first randomised controlled trial to test the effect of a multidisciplinary residential nutritional rehabilitation programme in patients treated for HNC. While residential rehabilitation programmes may be beneficial for patients treated for HNC, the residential rehabilitation programme in this trial is also intensive and requires participants to be self-reliant and to participate actively. Hence, the residential rehabilitation programme is distinct from typical inpatient rehabilitation services, and participants may be of better health than in other inpatient rehabilitation services. Requiring participants to be self-reliant may exclude the most vulnerable patients from participating and pose a risk of selection bias. In the present trial, recruitment through a nationwide survey gives a unique possibility to describe the trial population and to identify potential selection bias.

Additional methodological strengths of the trial include randomisation, blinded data analysis and blinded interpretation of results. The use of a wait-list control group may enhance trial adherence, and it meets the ethical challenges of using a non-intervention control group. However, the improvement typically seen among individuals in a non-intervention control group tend to be smaller among individuals in a wait-list control group. Hence, concerns have been raised that trials using wait-list control groups may overestimate the effect of intervention [89]. This will be considered when interpreting the results.

Multidisciplinary residential rehabilitation programmes are resource-intensive, and they may not be readily implementable in existing municipal or community-based rehabilitation services everywhere. This may affect the applicability of the trial results. However, establishing residential rehabilitation programmes across municipalities or institutions could allow for offering group-based diagnosis specific rehabilitation services even in small municipalities or communities with few patients treated for HNC. Hence, this trial will serve as a proof-of-concept trial, while future studies on the potential implementation of residential rehabilitation services in existing health services may be relevant depending on trial results.

As the trial will explore the potential of different nutrition screening and assessment tools in the assessment of rehabilitation needs in patients treated for HNC, the trial will create knowledge about how selection and prioritisation of nutritional rehabilitation aimed at patients treated for HNC should be offered. The results may contribute to a better organisation and use of existing resources in benefit of patients treated for HNC.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12937-020-00539-7.

Additional file 1. Mean body weight and quality of life scores at baseline and 3- month follow-up in patients treated for head and neck cancer who participated in the pilot study of the intervention.

Additional file 2. SPIRIT checklist.

Additional file 3. Overview and description of physical and informational materials used in the NUTRI-HAB trial.

Additional file 4. Course programme for the initial five days and the two days follow-up of the multidisciplinary residential nutritional rehabilitation programme in the NUTRI-HAB trial.

Additional file 5. Statistical analysis plan for the NUTRI-HAB trial.

Abbreviations

EORTC: The European Organization for Research and Treatment of Cancer; HNC: head and neck cancer; MDADI: M. D. Anderson Dysphagia Inventory; NRS 2002: Nutritional Risk Screening 2002; PG-SGA SF: The Scored Patient-Generated Subjective Global Assessment Short Form; QOL: Quality of life; REDCap: Research Electronic Data Capture

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Authors' contributions

MBK, ADZ, AMB, KBD and IW designed the trial and developed the protocol. TBM, MBK and ADZ developed the national survey set-up and the statistical analysis plan. JJKM developed the protocols for the physical tests. MBK and

ADZ drafted the manuscript, which was revised critically by all authors. All authors approved the final version to be published.

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Availability of data and materials
Within the confines of Danish legislation, the anonymised data from the trial will be available for other researchers upon reasonable request when results have been published.

Ethics approval and consent to participate
The Regional Committees on Health Research Ethics for Southern Denmark have assessed the duty to notify for the present trial (journal number 20182000–165). Based on Danish legislation, the committees concluded that the trial is not subject to the duty to notify. The trial is registered by The Danish Data Protection Agency, registration number 2012-58-0018, approval number 18/14847. Informed written consent to participate will be obtained from all participants before inclusion.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

Appendix 3b: Supplementary material for paper III

Additional file 1: Body weight and health related quality of life (QOL) at baseline and at 3-month follow-up in Danish patients treated for head and neck cancer who participated in a multidisciplinary residential nutritional rehabilitation programme[a].

	Baseline	3-month follow-up	p-value[b]
Body weight (n=34)	65.0 ±15.1	66.0 ±15.5	0.042*
EORTC QLQ-C30			
Global health status/QOL (n=32)	59.4 ±22.7	58.1 ±19.8	0.558
Functional scales			
- Physical functioning (n=32)	77.5 ±16.7	82.7 ±13.2	0.038*
- Role functioning (n=32)	68.8 ±26.4	72.9 ±27.7	0.312
- Emotional functioning (n=32)	65.4 ±21.6	71.9 ±22.7	0.154
- Cognitive functioning (n=32)	72.4 ±21.8	75.0 ±25.8	0.233
- Social functioning (n=31)	68.8 ±25.0	76.9 ±16.7	0.210
Symptom scales/items			
- Fatigue (n=32)	42.0 ±23.2	41.3 ±25.1	0.719
- Nausea and vomiting (n=32)	13.0 ±18.8	7.3 ±11.9	0.066
- Pain (n=32)	25.5 ±26.1	28.1 ±27.3	0.382
- Dyspnoea (n=32)	20.8 ±30.2	15.6 ±25.4	0.195
- Insomnia (n=32)	36.5 ±27.3	32.3 ±32.2	0.194
- Appetite loss (n=31)	47.3 ±35.3	36.6 ±31.5	0.054
- Constipation (n=32)	14.6 ±22.3	11.5 ±16.1	0.366
- Diarrhoea (n=32)	14.6 ±20.6	11.5 ±23.4	0.432
- Financial difficulties (n=32)	10.4 ±17.9	11.5 ±24.8	0.948
EORTC QLQ-H&N35			
Symptom scales/items			
- Pain (n=31)	31.7 ±22.8	28.2 ±24.4	0.760
- Swallowing (n=30)	35.8 ±23.4	30.0 ±24.3	0.034*
- Sensory problems (n=31)	35.5 ±25.7	30.6 ±25.1	0.059
- Speech problems (n=31)	22.2 ±21.1	15.4 ±16.4	0.016*
- Trouble with social eating (n=30)	47.8 ±31.3	38.4 ±27.3	0.010*
- Trouble with social contact (n=30)	12.9 ±15.4	11.8 ±17.1	0.508
- Less sexuality (n=26)	37.2 ±38.7	33.3 ±36.2	0.873
- Teeth (n=30)	42.2 ±36.0	41.1 ±39.8	0.873
- Opening mouth (n=30)	25.6 ±32.4	27.8 ±35.1	0.964
- Dry mouth (n=31)	73.1 ±29.1	71.0 ±30.7	0.629
- Sticky saliva (n=30)	51.1 ±36.9	50.0 ±35.8	0.719
- Coughing (n=31)	31.2 ±29.7	31.2 ±33.3	0.992
- Felt ill (n=31)	21.5 ±20.3	23.7 ±27.5	0.392
- Pain killers (n=31)	51.6 ±50.8	38.7 ±49.5	0.103
- Nutritional supplements (n=30)	33.3 ±47.9	40.0 ±49.8	0.527
- Feeding tube (n=28)	25.0 ±44.1	10.7 ±31.5	0.046*
- Weight loss (n=29)	41.4 ±50.1	20.7 ±41.2	0.014*
- Weight gain (n=27)	22.2 ±42.4	33.3 ±48.0	0.257

[a] Only participants with both a baseline and a follow-up measurement of the given variable were included in the analyses and thus in the table. The included numbers of participants are presented for each variable.
[b] Differences between body weight at baseline and follow up were tested using a two-sided paired t-test while differences between QOL scores at baseline and follow-up were tested using the Wilcoxon sign rank test.
*$p<0.05$

Data are presented as mean values and standard deviations. The European Organization for Research and Treatment of Cancer's (EORTC) QLQ-C30 and QLQ-H&N35 were used to assess QOL. All scales and single-item measures range in score from 0 to 100. A high score represents a higher response level. Thus a high score for a functional scale or global QOL represents a high level of functioning/QOL whereas a high score on a symptom scale represents a high level of symptoms.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4+21
	2b	All items from the World Health Organization Trial Registration Data Set	4+21+24
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1+2+24
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	12+21
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9+10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	19-20
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7+8+12 (Fig 1+2)

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12+13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13+19
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	19

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-18 +additional file 3
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	19

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13-14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19-20
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	21

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13+21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23-24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	23
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

Additional file 3: Overview and description of physical and informational materials used in the NUTRI-HAB Trial.

Trial materials (with the exception of copyrighted validated questionnaires) are available upon request to the corresponding author (mabk@kp.dk). All trial materials are in Danish.

	Description of material(s)	***How will the material(s) be distributed/administered?***
MATERIALS FOR PARTICIPANT RECRUITMENT, INCLUSION AND RETENTION		
- Invitation letter	1-page invitation letter with information on the trial and the dates on which the individual recipient is invited to participate in the programme, the follow-up and the outcome measurements in the regional outpatient clinics.	Sent electronically to e-Boks[a] or through postal mail to individuals on the invitation lists for intervention group or wait-list control group.
- Programme leaflet	4-page leaflet with information on the multidisciplinary residential nutritional rehabilitation programme.	Sent together with 'Invitation letter'.
- Consent form for participating in the NUTRI-HAB Trial	3-page form with 2 pages of information regarding participation in the trial and trial registration details and 1 page to be signed by the participant and the researcher.	Handed out to participants (and signed form collected with copy provided to participant) on the first day of the residential stay for the intervention group, and on the day of the outcome measurements in the outpatient clinics for the control group.
- Consent form for registration in the rehabilitation centre's clinical research database	3-page form with 2 pages of information regarding the rehabilitation centre's clinical research database and 1 page to be signed by the participant and the researcher.	Handed out to participants (and signed form collected with copy provided to participant) on the first day of the residential stay for the intervention group, and on the day of the outcome measurement in the outpatient clinics for the control group.
- Welcome letter (five days residential stay)	1-page letter with practical information on arrival etc.	Sent to individuals who accepted invitation to participate. Sent electronically to e-Boks or through postal mail prior to the five days residential stay.

- Leaflet about the rehabilitation centre	4-page folder with practical information about the residential rehabilitation centre.	Sent to participants together with 'Welcome letter (five days residential stay)'.
- Welcome letter (two days follow-up residential stay)	1-page letter with practical information on arrival etc.	Sent electronically to e-Boks or through postal mail prior to the two days follow-up residential stay.
- Invitation for outcome measurements in the regional outpatient clinics	1-page letter with information on date, time, and place for the outcome measurement, and instructions to wear comfortable clothes and to limit food and fluid intake the last two hours prior to the measurements.	Sent electronically to e-Boks or through postal mail prior to the outcome measurement in the outpatient clinics.
INTERVENTION MATERIALS		
- Course programme (five days residential stay)	An overall course programme (not including individual activities)	Sent to participants together with 'Welcome letter (five days residential stay)'.
- Course programme (two days follow-up residential stay)	An overall course programme (not including individual activities)	Sent to participants together with 'Welcome letter (two days follow-up residential stay)'.
- Individualised course programme (five days residential stay)	A detailed individualised course programme with scheduled individual activities and selected optional sessions.	Handed out to participants on the first day of the five days residential stay.
- Individualised course programme (two days follow-up residential stay)	A detailed individualised course programme with scheduled individual activities and selected optional sessions.	Handed out to participants on the first day of the two days follow-up residential stay.
- 'Participant book'	The participant book includes a training manual with 16 different swallowing exercises, a training dairy where participants can register their training, space for taking notes throughout the programme, and dates for telephone consultations with the clinical dietitian.	Handed out to participants on the five days residential stay immediately before the session with 'Swallowing exercises'.

Materials from the different patient education sessions in the programme		
- Materials from 'Theoretical session on eating problems'	Handouts of the PowerPoint slides used in the session.	Sent to participants after the five days residential stay.
- Materials from the 'Kitchen workshop'	A recipe book with 45 different recipes and information about the five basic tastes and how they complement each other. An apron with the Danish name of the programme and logos of the collaborating institutions printed on it.	Recipe book: Handed out in the session. Apron: Handed out in the session for intervention group and handed out on the day of the outcome measurements in the outpatient clinics for control group.
- Materials from the session 'Swallowing exercises'	Handouts of the PowerPoint slides used in the session.	Sent to participants after the five days residential stay.
- Materials from the session 'Dental problems and oral hygiene'	Handouts of the PowerPoint slides used in the session and a 2-page summary with take-home messages.	Sent to participants after the five days residential stay.
- Materials from the session on 'Psychological reactions to cancer'	Handouts of the PowerPoint slides used in the session.	Sent to participants after the five days residential stay.
- Materials from the session on 'Fatigue and sleep problems'	Handouts of the PowerPoint slides used in the session.	Sent to participants after the five days residential stay.
- Materials from the session on 'Motivation, goal setting and action plans'	Handouts of the PowerPoint slides used in the session. A 2-page template for the participants' action plans.	The action plan template: Handed out in the session. The handouts of PowerPoint slides: Sent to participants after the five days residential stay.

DATA COLLECTION FORMS **Forms/questionnaires to be filled out by participants**		
- Questionnaire with outcome measures	A 117-item questionnaire comprising EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-H&N35, PG-SGA SF, MDADI, HADS, and questions on body weight history, dietary intake, civil status, educational level, and occupational status.	Sent electronically to e-Boks one week prior to the five days residential stay, the two days follow-up residential stay, and the outcome measurements in the outpatient clinics. Participants without e-Boks: Possibility to fill out electronically or in paper on the location of the measurement.
- Questionnaire with information prior to participation in the five days residential stay	Questionnaire with practical information required by the rehabilitation centre: specific dietary requirements, comorbidities, emergency contact, expectations for the programme, specific challenges they want to address, and which optional activities they want to participate in.	Sent electronically to e-Boks or through postal mail together with 'Welcome letter (five days residential stay)'.
- Questionnaire with information prior to participation in the two days follow-up residential stay	Questionnaire with practical information required by the rehabilitation centre: specific dietary requirements, expectations for the follow-up, and which optional activities they want to participate in.	Sent electronically to e-Boks or through postal mail together with 'Welcome letter (two days follow-up residential stay)'.
- Evaluation form (five days residential stay)	1-page evaluation form where participants will be asked to evaluate the overall residential stay, the different sessions and indicate whether they participated in the specific session.	Handed out to participants on the first day of the five days residential stay and collected from participants on the last day.
- Evaluation form (two days follow-up residential stay)	1-page evaluation form where participants will be asked to evaluate the overall residential stay, the different sessions and indicate whether they participated in the specific session.	Handed out to participants on the first day of the two days follow-up residential stay and collected from participants on the last day.

Data collection forms to be used by health professionals		
- Form to enter results from physical test and measurements	1-page standardised form to register measured weight, height, maximal mouth opening, hand grip strength, 30-second chair stand test, 6-minute walk test, and initials of the physiotherapist performing the measurements.	Used by physiotherapists at the five days residential stay, the two days follow-up residential stay, and the outcome measurements in the outpatient clinics.
- Standardised form for the individual counselling with clinical dietitian (five days residential stay – intervention group)	2-page form with space for summary of relevant outcome measurements, participant's evaluation of own weight, and a summary of the individual counselling.	Used by dietitians at the five days residential stay.
- Standardised form for the individual counselling with clinical dietitian (five days residential stay – control group)	2-page form with space for summary of relevant outcome measurements, participant's evaluation of own weight, changes in health status, participation in other rehabilitation services, and a summary of the individual counselling.	Used by dietitians at the five days residential stay.
- Standardised form for summary of the telephone consultations with clinical dietitian	1-page form with space for summary of the two telephone consultations.	Used by dietitians for the telephone consultations between the five days residential stay and the two days follow-up residential stay.
- Standardised form for the individual counselling with clinical dietitian (two days follow-up residential stay)	2-page form with space for summary of previous and current counselling, relevant outcome measurements, changes in health status, participation in other rehabilitation services, and experiences of participating in the programme.	Used by dietitians at the two days follow-up residential stay.

[a] e-Boks is a secure digital mailbox linked to the individual's civil registration number. In Denmark, it is mandatory to have e-Boks unless a citizen applies for exemption.

EORTC: European Organization for Research and Treatment of Cancer, PG-SGA SF: The Scored Patient Generated Subjective Global Assessment Short Form, HADS: Hospital Anxiety and Depression Scale, MDADI: M. D. Anderson Dysphagia Inventory.

Additional file 4: Example of the course programme for the initial five days and the two days follow-up of the multidisciplinary residential nutritional rehabilitation programme in the NUTRI-HAB Trial.

INITIAL RESIDENTIAL STAY					FOLLOW-UP RESIDENTIAL STAY AFTER 3 MONTHS	
DAY 1	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**	**DAY 1**	**DAY 2**
	BREAKFAST BUFFET	BREAKFAST BUFFET	BREAKFAST BUFFET	BREAKFAST BUFFET		BREAKFAST BUFFET
	MORNING ASSEMBLY	MORNING ASSEMBLY	MORNING ASSEMBLY	MORNING ASSEMBLY		MORNING ASSEMBLY
Arrival Welcome session with presentation of the programme (course leader and clinical dietitian) Walk and talk	Practical kitchen workshop (clinical dietitian)	Psychological reactions to cancer (psychologist)	Physical activity (physiotherapist) Optional session: Fatigue and sleep problems (nurse) *OR* Vocational counselling (social worker)	Motivation, goal setting and action plans (social worker and course leader) Individual work and group discussion on action plans (social worker and course leader)	Arrival Welcome and presentation of the program (course leader and clinical dietitian) What's new within the last three months? (course leader and clinical dietitian)	Physical activity (physiotherapist) Optional session: Sexuality and intimacy (sexologist) *OR* Meaning and values in life (psychologist)
LUNCH BUFFET	LUNCH BUFFET	LUNCH BUFFET	LUNCH BUFFET	LUNCH BUFFET	LUNCH BUFFET	LUNCH BUFFET
Introduction round (course leader and central health professionals) Theoretical session on eating problems (clinical dietitian)	DATA COLLECTION Physical tests (physiotherapist) Yoga (physiotherapist)	Swallowing exercises (occupational therapist) Individual dietary counselling (clinical dietitian)	Dental problems and oral hygiene (dental hygienist) Individual counselling (depending on the participant's needs) Massage therapy (massage therapist)	Closing session and farewell (course leader and clinical dietitian)	DATA COLLECTION Physical tests (physiotherapist) Individual dietary counselling (clinical dietitian)	Closing session and farewell (course leader and clinical dietitian)
DINNER	DINNER	DINNER	DINNER		DINNER	
Social activity	Group conversation on existence (priest)	(Possibility to go for a walk, watch movies, play games etc.)				

Additional file 5: Statistical analysis plan (SAP) for The NUTRI-HAB trial.

ADMINISTRATIVE INFORMATION	
Title	Statistical analysis plan (SAP) for a randomised controlled trial investigating the effect of multidisciplinary nutritional rehabilitation for patients treated for head and neck cancer (the NUTRI-HAB Trial)
Trial registration details	• ClinicalTrials.gov Identifier: NCT03909256 • The Danish Data Protection Agency: registration number 2012-58-0018, approval number 18/14847 • The Regional Committees on Health Research Ethics for Southern Denmark: journal number 20182000-165
Principal investigator	Marianne Boll Kristensen, PhD Fellow, RD, *REHPA, The Danish Knowledge Centre for Rehabilitation and Palliative Care &* *Department of Nursing and Nutrition, University College Copenhagen &* *OPEN, Odense Patient data Explorative Network, Odense University Hospital*
Data analyst	Tina Broby Mikkelsen, PhD, *REHPA, The Danish Knowledge Centre for Rehabilitation and Palliative Care*
SAP developed by	Tina Broby Mikkelsen, Marianne Boll Kristensen.
SAP version date	15/10-2019 *(Minor revisions based on reviewers' comments carried out 5/2-2020)*
SAP version approval	SAP version approved by the project group 28/10-2019.
TRIAL INFORMATION	
Objectives	The objectives of the trial are: • To test the effect of a multidisciplinary residential nutritional rehabilitation programme compared to standard care on the primary outcome body weight and secondary outcomes health-related quality of life, physical function and symptoms of anxiety and depression in patients curatively treated for head and neck cancer • To test whether a potential effect of a multidisciplinary residential nutritional rehabilitation programme is associated with the participants' nutritional status, nutritional risk or presence of nutrition impact symptoms measured by measured by Nutritional Risk Screening 2002 (NRS 2002)[1], the Scored Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF)[2], and the M. D. Anderson Dysphagia Inventory (MDADI)[3] at entry to the programme.
Trial design	The trial is a randomised controlled trial with recruitment through a nationwide survey. Participants will be randomised into either intervention group or a wait-list control group in a 1:1 allocation ratio.
Trial setting	The trial will be carried out at REHPA, the Danish Knowledge Centre for Rehabilitation and Palliative Care in Nyborg, Denmark between May 2019 and December 2019
Participants	Participants will be recruited among respondents of a nationwide survey in Danish patients treated for head and neck cancer. The following inclusion criteria apply: *Register-based information* • Have been diagnosed with cancer of the larynx, pharynx, or oral cavity • Have completed curatively intended treatment with radiation therapy 1-5 years before survey distribution (1st of March 2014 to 28th of February 2018) • Are aged ≥ 18 years *Self-reported information collected through the survey* • Have no active head and neck cancer or any other active cancer at the time for completion of the survey

	• Are self-reliant • Are able to speak and understand Danish • Are willing to participate in a multidisciplinary residential nutritional rehabilitation programme
Sample size	The sample size calculation is based on quantitative data from a previous pilot study[4] and an expectation to see a difference of 1.74±2.37 in primary outcome (weight change in percent) between groups. 30 participants are required in each group to achieve a power of 80% and a significance level of 5%. Thus with an estimated withdrawal rate of 15%, 36 participants will be included in each group.
Randomisation and inclusion	Individuals who meet the inclusion criteria will be randomised into invitation lists for intervention group or wait-list control group. The allocation ratio will be 1:1, and allocated individuals will be placed in random order on the numbered invitation list. Individuals will be invited for participation in the order they appear on the given invitation list. Data analyst, who is not involved in the study intervention or outcome assessment, will randomise participants in STATA/IC 15.1.
Blinding	Data analysis will be blinded. A trial-independent researcher codes the data set prior to analyses, and the code will be kept in a sealed envelope. The project group will interpret the blinded results before unblinding.
TIMELINE OF THE TRIAL AND DATA ANALYSES	
Trial timeline	The trial is expected to run from May 2019 to early December 2019. For half of the intervention group and half of the wait-list control group, baseline measurements will be in May 2019, and 6-month follow-up measurements will be late October 2019. For the other half of the participants, baseline measurements will be in June 2019, and 6-month follow-up measurements will be late November 2019.
Timeline for data collection	Data is collected at baseline, 3-month follow-up and 6-month follow up. The last physical measurements are planned to late November 2019 (27/11-2019). As an effort to minimise missing data, data collection will not be considered completed until early December 2019 (09/12-2019) allowing for eight extra work days to obtain data from potential no-show participants.
Timeline for data preparation and analysis	The data set will be prepared immediately after data collection is considered completed and will be sent to data analyst mid December 2019 (16/12-2019). Data analyses will be completed no later than early January 2020 (07/01-2019), where the blinded results will be interpreted by the project group.
GENERAL STATISTICAL CONSIDERATIONS	
Significance level	A significance level of 5% will be applied.
Protocol violations and exclusions from the trial	Protocol deviations and exclusions from the trial (including reasons for exclusion) will be reported for each group of the trial. Data on primary and secondary outcomes will be analysed by both the intention-to-treat principle and per protocol, and results from both types of analysis will be presented in publications. In analyses by the intention-to-treat principle, all participants will be analysed in the trial group to which they were randomised even if they do not receive the allocated treatment. In the per protocol analyses, only participants who received the allocated treatment is included.

Missing data	All efforts will be made to minimise missing data. Participants who drop out of the trial will be encouraged to participate in follow-up measurements and to complete follow-up questionnaires. In the event of missing data, the percentage and patterns of missing values in outcome variables will be examined. If data are missing at random and the percentage of missing data is not substantial[5], multiple imputation techniques will be used in the intention-to-treat analyses.
Statistical software	Data will be analysed in SAS® Enterprise Guide® 7.1
DATA PREPARATION	
Data entry	Patient reported data will primarily be collected through electronic questionnaires distributed through REDCap. In the event that participants fill out a paper-based questionnaire instead, the data will be entered in REDCap by one researcher, and the entered data will be double-checked by a second researcher.
Preparation of data set	Principal investigator will prepare the data set and remove all possible identifiers including dates and time stamps.
Coding	A trial-independent researcher will code the prepared data set and put the code in a sealed envelope.
DATA ANALYSES	
Descriptive statistics	Descriptive statistics will be used for baseline characteristics of participants in the intervention and wait-list control group. The following variables will be included in the presentation of baseline characteristics: • Age • Gender • Cancer diagnosis (pharynx, larynx, oral cavity) • Time (months) interval since completion of radiation therapy • Civil status • Educational level • Occupational status • Rehabilitation needs measured by the REHPA scale (≥3 point, <3 point) Numerical variables will be presented as median [range] or mean (SD) and categorical variables as number of participants (%).
Assessment of selection bias	To assess potential selection bias, it will be tested whether the trial population differ from the remaining survey population (including non-responders) with regards to the following variable: age, gender, cancer diagnosis and time interval since completion of radiation therapy.
Analysis of primary outcome	The primary outcome is percent change in body weight from baseline to 3-month follow-up. Differences between group means will be tested using a two-sample two-sided t-test, and effect size will be estimated with Cohens d[6]. An estimate of the difference between groups along with a 95% CI and a two-sided p value for the null hypothesis of no difference between groups will be reported. The mean body weight in each group at the different time points will be presented in publications.

	Multiple linear regression will be used to assess the influence of potential confounding variables (e.g. time interval from completion of treatment) on intervention effect
Analyses of secondary outcome measures	Secondary outcomes include changes from baseline to 3-month follow up in the following outcome measures: Patient reported outcome measures: • EQ-5D-5L[7] • EORTC QLQ-C30[8,9] • EORTC QLQ-H&N35[9,10] • Hospital Anxiety and Depression Scale[11] Physical test and measurements: • Maximal mouth opening • Hand grip strength • 30-second chair stand test • 6-minute walk test All patient-reported outcome measures will be scored according to manuals. Differences between group means will be tested using a two-sample two-sided t-test or Mann-Whitney U test depending on distribution of data. Effect size will be estimated with Cohens d[6]. For all analyses on secondary outcome, an estimate of the difference between groups along with a 95% CI and a two-sided p value for the null hypothesis of no difference between groups will be reported. For all secondary outcomes, the mean score in each group at the different time points will be presented in publications.
Analysis between intervention effect and nutrition screening/assessment scores at baseline and	Linear regression will be used to test potential associations between developments in outcome scores from baseline to 3-month follow-up and baseline scores in NRS 2002, MDADI or PG-SGA SF. Sensitivity, specificity and predictive values of different cut-offs in NRS 2002, MDADI or PG-SGA SF at baseline in relation to a clinically relevant improvement in outcome scores during participation in the programme will be assessed.
Planned subgroup analyses	Subgroup analyses will be performed to investigate whether the intervention has different effects on different subgroups of participants e.g. grouped by time from treatment completion.
Exploratory analyses	All data collected from baseline to 6-month follow-up will be used for relevant exploratory analyses including analyses of the long-term effect of the intervention and of whether the selected nutrition screening tools are labile and able to reflect changes over time.
INTERPRETATION OF RESULTS	
Interpretation of results	Data analyst will present the blinded results on a meeting with the rest of the project group and involved clinicians. Baseline characteristics and number of participants in each group for the different analyses will not be displayed at the presentation, as these data may reveal the coding of the groups to the clinicians, who delivered the intervention.

	The project group initially interprets the blinded results on the assumption that one specific group is the intervention group, and afterwards on the assumption that the other group is the intervention group. The group writes down the conclusions for both possible scenarios.
Unblinding	When the conclusions for the two possible scenarios have been written down, the principal investigator will open the sealed envelope and reveal the blinding code.

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Appendix 4a: Paper IV

Kristensen, MB, Wessel I, Beck AM, Dieperink KB, Mikkelsen TB, Møller JJK, Zwisler AD.

Effects of a multidisciplinary residential nutritional rehabilitation programme in head and neck cancer survivors – Results from the NUTRI-HAB randomised controlled trial.

Status: Submitted to Nutrients, May 2020.

TITLE PAGE

Title

Effects of a multidisciplinary residential nutritional rehabilitation programme in head and neck cancer survivors – Results from the NUTRI-HAB randomised controlled trial

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Abstract

Head and neck cancer survivors frequently experience nutritional challenges, and proper rehabilitation should be offered. Trial objective was to test the effect of a multidisciplinary residential nutritional rehabilitation programme addressing physical, psychological, and social aspects of eating problems after treatment. In a randomised controlled trial, 71 head and neck cancer survivors recruited through a nationwide survey were randomised to the programme or a wait-list control group. Inclusion was based on self-reported interest in participation. Primary outcome was change in body weight, and secondary outcomes included physical function, quality of life, and symptoms of anxiety and depression. Differences between groups at 3-month follow-up were tested. No significant differences were seen in body weight change, but there were overall trends towards greater improvements in physical function (hand grip strength: p=0.042; maximal mouth opening: p=0.072) and quality of life ('Role functioning': p=0.041; 'Speech problems': p=0.040; 'Pain': p=0.048') in the intervention group. To conclude, a multidisciplinary residential nutritional rehabilitation programme had no effect on body weight in head and neck cancer survivors with self-reported interest in participation, but it may have effect on physical function and quality of life. Further research on relevant inclusion criteria and the programme's effect in different subgroups is needed.

Keywords: Head and neck cancer, rehabilitation, survivorship, eating problems, late effects, quality of life.

Abbreviations: DAHANCA: Danish Head and Neck Cancer Group, EORTC: European Organization for Research and Treatment of Cancer, HADS: Hospital Anxiety and Depression Scale, HNC: Head and neck cancer, NRS 2002: Nutritional Risk Screening 2002, PG-SGA SF: the Scored Patient-Generated Subjective Global Assessment Short Form, QOL: Quality of life, REDCap: Research Electronic Data Capture.

1 Introduction

In 2018, approximately 900.000 individuals worldwide were diagnosed with head and neck cancer (HNC) [1]. The incidence has increased in recent years [1,2] with a simultaneous increase in the relative survival [3], but despite the prospect of a successful curatively treatment result, many HNC survivors feel unprepared for the life that awaits them after treatment [4–7]. Nutrition impact symptoms such as dysphagia, xerostomia, trismus, and dysgeusia are frequent [8–10] and may persist years after treatment [8–12]. These symptoms lead to eating problems, which have substantial negative consequences for HNC survivors' nutritional status, quality of life (QOL), and daily lives [5,10,13–18]. Group-based residential rehabilitation programmes, where the daily meals are part of the intervention, can provide a safe environment for HNC survivors to practice eating skills [4,19]. Hence, they may be particularly effective to support HNC survivors in the trial-and-error approach; a frequently used coping strategy with continuous experiments to find tolerated foods as the eating problems vary over time [4,6,20,21]. A process that may otherwise be complicated by fear of choking [4,22,23] and feelings of defeat associated with unsuccessful experiments [4,20].

To our knowledge, very few studies have explored the potential of group-based residential rehabilitation programmes in HNC survivors. In a pilot study testing a 1-week residential psychoeducational programme in HNC survivors, high participant satisfaction and improvements in QOL scales were reported [19]. In another pilot study conducted by the researchers behind the present trial, qualitative data showed that HNC survivors benefitted from participating in a multidisciplinary residential nutritional rehabilitation programme [4], and significant improvements in body weight and several QOL scales were seen at 3-month follow-up [24]. With no control group in any of the pilot studies, the effect of residential rehabilitation programmes in HNC survivors should be tested in randomised controlled trials. Thus we designed the NUTRI-HAB trial [24]. The primary objective of the trial was to test the effect of a multidisciplinary residential nutritional rehabilitation programme compared to standard care on the primary outcome body weight and secondary outcomes physical function, health-related QOL, and symptoms of anxiety and depression in HNC survivors.

Secondary exploratory objectives and analyses were further predefined in the trial protocol [24]. These will be approached in future publications.

2 Materials and methods

2.1 Trial design

A randomised controlled trial was carried out from May 2019 to December 2019. Participants were randomised to either an intervention group participating in a multidisciplinary residential nutritional rehabilitation programme from baseline to 3-month follow-up or a wait-list control group. For the primary objective, data were collected at baseline and 3-month follow-up (Figure 1). Further data collected for explorative objectives will be presented in future publications.

The detailed trial protocol [24] was developed in accordance with the SPIRIT (Standard Protocol Items for Randomized Trials) 2013 [25,26] statement, the CONSORT (Consolidated Standards of Reporting Trials) extension for reporting trials of nonpharmacologic treatments [27] and the TIDieR (template for intervention description and replication) [28] checklist and guide. An overview of trial materials and information on how to obtain these have been published with the trial protocol [24]. The CONSORT 2010 Statement [29] and the CONSORT extension for reporting trials of nonpharmacologic treatments [27] were used as guidelines for reporting trial results.

2.2 Participants and setting

Participants were recruited among respondents of the nationwide cross-sectional NUTRI-HAB survey on nutritional challenges, late effects and QOL in HNC survivors. The survey population was identified through The Danish Head and Neck Cancer Group's (DAHANCA) national clinical quality database [30] and included all Danish individuals ≥ 18 years treated with curatively intended radiation therapy for oral, pharyngeal, or laryngeal cancer 1-5 years before survey distribution (n=1937). Since rehabilitation interventions should be based on the wishes and goals of the individual patient [31], a crucial inclusion criteria in the present trial was individuals' self-reported interest in participating in the programme. Hence, based on self-reported information collected through the NUTRI-HAB survey, respondents were considered eligible for participation

in the present trial if they met the following inclusion criteria: 1) had no active HNC or other cancer at the time for completion of the survey, 2) were self-reliant (defined as having answered "Not at all" on the question "Do you need help with eating, dressing, washing yourself or using the toilet?" in The European Organization for Research and Treatment of Cancer's (EORTC) QLQ-C30 questionnaire [32]), 3) were able to speak and understand Danish, and 4) had confirmed that they were interested in participating in a multidisciplinary residential nutritional rehabilitation programme at specific dates and given their permission to be contacted with further information.

All individuals who had responded within nine weeks from survey distribution and who met the inclusion criteria were randomised and placed in random order on numbered invitation lists for intervention group or wait-list control group in an allocation ratio of 1:1. In the recruitment process, the first individuals on each invitation list received further information about the trial and were invited to participate, and if an individual declined the invitation, the next person on the given invitation list was invited.

Randomisation was performed in STATA/IC 15.1 by a blinded researcher who was not involved in the trial intervention or outcome assessment. Randomisation was stratified by need for rehabilitation services measured by the REHPA scale [33], a numerical scale where participants indicate how close or how far they are from living the life they want after or despite their disease [34]. A score of 1 indicates "Very close" whereas a score of 9 indicates "Infinitely far away". Randomisation was stratified to ensure similar proportions of individuals with a score of ≥3 across invitation lists.

The trial was carried out at REHPA, the Danish Knowledge Centre for Rehabilitation and Palliative Care in Nyborg, Denmark, and the intervention was an additional offer to existing rehabilitation services. In Denmark, cancer treatment and rehabilitation services are funded by government taxes and free of charge for patients, and while rehabilitation during treatment is offered at the hospitals, posttreatment rehabilitation is primarily a municipal responsibility [35]. Denmark comprise 98 municipalities with great variation between their rehabilitation services [36,37].

2.3 Intervention

The trial intervention was a multidisciplinary residential nutritional rehabilitation programme with a primary focus on the physical, psychological and social aspects of eating problems after treatment for HNC. The programme comprised five days initial residential stay and two days follow-up residential stay after three months and consisted of group-based patient education sessions and few individual activities. The programme is based on REHPA's and former Rehabilitation Centre Dallund's core programme developed through available evidence and more than 10 years' experience in offering multidisciplinary residential rehabilitation programmes for heterogeneous groups of cancer survivors [34,38,39]. The core model was further developed to meet the specific rehabilitation needs of HNC survivors through available evidence, patient involvement and a pilot study including 40 HNC survivors [4]. The programme is described in further details in the trial protocol [24], and a schedule of activities during the residential stays is provided in Table 1. Sessions specifically aimed at managing eating problems included group session with clinical dietitian on dietary advice, individual counselling with clinical dietitian, practical kitchen workshop with take-home recipes, group session on oral hygiene and dental reimbursement rules, and instruction in swallowing exercises by occupational therapist, who typically are responsible for dysphagia management in Denmark [40]. Participants received an exercise manual and a training diary, and were encouraged to continue doing the exercises, when they came home. During the residential stays, participants stayed at the premises, and all meals were served there. Foods of different flavours and textures were served to allow participants to experiment and to support their trial-and-error coping process as described in introduction [4,6,20,21]. Other activities included sessions with physical activity and restorative yoga, group sessions with psychologist, session on motivation and action plans, group conversation with priest on existence, massage therapy and optional sessions on vocational counselling, fatigue, and sexuality and intimacy. Individual counselling sessions with relevant professionals (e.g. speech pathologist or physician) were scheduled depending on the individual participant's needs assessed through patient-reported outcome measures. Between the initial stay and the two days follow-up, all participants had two telephone consultations with a clinical dietitian scheduled in week 4 and week 8 to follow up on individual consultation at the residential stay, to answer potential emerging questions, and to encourage the participant to continue with any activities or changes that they planned to implement after the residential stay.

Each scheduled programme had a maximum capacity of 20 participants. The programme was free of charge for participants.

2.4 Wait-list control group

From baseline to 3-month follow-up, the wait-list control group received no intervention other than standard care. In Denmark, HNC patients attend follow-up visits at oncological tertiary centres every 6 month for the first 2 years and annually for the next 3 years. As needed and on referral, they can participate in the municipal rehabilitation services, which as described vary across municipalities. Hence, with participants being from all over the country, standard care could vary, and participants were not restricted from participating in other rehabilitation services during the trial. The wait-list control group were offered participation in the multidisciplinary residential nutritional rehabilitation programme from 3-month follow-up.

2.5 Data collection and outcome measures

All physical measurements and tests were performed by authorised health professionals following strict protocols [24]. Blinding of health professionals performing the measurements was not possible. For the intervention group, baseline and 3-month follow-up physical measurements were performed at REHPA in the beginning of their five days and two days residential stay. The same was the case for the 3-month measurement in the control group. The baseline physical measurement in the control group was performed in one of three outpatient clinics depending on the participant's place of residence. Patient-reported outcome measures were assessed through online or paper-based questionnaires distributed to participants one week before the physical tests. Research Electronic Data Capture (REDCap) [41] was used for online questionnaires and data storage. Data from paper-based questionnaires and physical measurements were entered in REDCap by one researcher, and the entered data was doublechecked by another researcher.
To reduce missing data, participants who dropped out of the trial were still encouraged to participate in follow-up measurements. Hence, if participants from the intervention group did not participate in the follow-up residential stay, they were encouraged to participate in physical measurements in the nearest outpatient clinic instead, and the same was the case for individuals in

the wait-list control group, if they chose not to participate in residential rehabilitation programme at 3-month follow-up. If they were unable to participate in the physical measurements, they were still encouraged to fill out the questionnaires.

2.5.1 Participant characteristics at baseline

Information on age, gender, cancer diagnosis and time interval since treatment was already obtained from DAHANCA's national clinical database [30]. Questions on current cancer status and respondents' participation in other rehabilitation services prior to baseline was included in the NUTRI-HAB survey. At follow-up, this information was collected in the consultations with the clinical dietitian to allow for sensitivity analyses on effect of potential cancer relapse or participation in other nutritional rehabilitation programmes on intervention effect.

Nutritional risk was assessed with Nutritional Risk Screening 2002 (NRS 2002) and the Scored Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF). In the secondary screening with NRS 2002, the overall score comprises an A-score for nutritional status, a B-score for disease severity and an extra point if aged 70 or above. A higher score indicates greater nutritional risk [29]. The PG-SGA SF includes questions on weight changes, changes in dietary intake (amount or texture), nutrition impact symptoms and performance status [30]. The score ranges from 0-36, and a higher score indicates a higher risk of malnutrition. The Danish version has been translated, cross-culturally adapted, and linguistically validated [47]; and was used with permission.

The REHPA Scale was included in the baseline questionnaires with patient-reported outcome measures. In addition to the numerical scale, participants could mark the challenges preventing them from achieving their goals. In combination with the other patient-reported outcome measures, this information was used to target the intervention to the individual participant's rehabilitation needs.

2.5.2 Primary outcome

The primary endpoint was percentage change in body weight. Body weight was measured to the nearest 0.1 kg using calibrated and levelled Seca 877/878 scales, and participants were instructed to minimize their food and fluid intake two hours before the weighing.

2.5.3 Secondary outcomes

Secondary outcomes included changes in measures of physical function, patient-reported outcome measures of health-related QOL, and symptoms of anxiety and depression.

Measures of physical function were maximal mouth opening, hand grip strength, 30-second chair stand test, and 6-minute walk test. Maximal mouth opening was measured in mm using a TheraBite® Range-Of-Motion ROM Scale. Hand grip strength was measured in kg using a calibrated Jamar hydraulic hand dynamometer. All measurements were made with the hand dynamometer in the second handle position, and three consecutive measurements in each hand were performed. The highest of the six measurement was used in data analyses [42]. The 30-second chair stand test was used to assess lower body strength [43], and the registered score was the number of full stands from a chair during 30 seconds without using the hands. If participants were unable to rise without using their hands, it was registered that the test was completed in a modified version and the following tests for that participant were completed in the modified version. The 6-minute walk test was used to measure the submaximal level of functional capacity [44]. The test was performed on a 30-metre walking course, and the score was the total distance walked in metres.

Health-related QOL was measured using the Danish translations of the EuroQol 5D-5L (EQ-5D-5L) [45], the EORTC QLQ-C30 [32,46], and the diagnosis specific EORTC QLQ-H&N35 [46,47]. The EQ-5D-5L covers mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and overall health is measured by visual analogue scale (VAS) and with a summary index score based on the five dimensions and on societal preference weights for the health state. The VAS scale ranges from 0-100, and the summary index score calculated based on Danish values ranges from -0.624 to 1.0. A higher score indicates a better self-rated health [45]. The EORTC QLQ-C30 comprise one global QOL scale, five functional scales and nine symptom scales, whereas the QLQ-H&N35 comprise 18 symptom scales. All EORTC scales range from 0-100. A higher score indicates a higher response level. Thus, a high score for a functional scale or global QOL indicates a high level of functioning/QOL, and a high score on a symptom scale indicates a high symptom level [32,46,47].

Symptoms of anxiety and depression were measured with the Danish translation of the Hospital Anxiety and Depression Scale (HADS). The two subscales for anxiety and depression range from 0-21 points, and a higher score indicates a higher symptom level [48].

2.6 Sample size

Based on results from a previous pilot study [4,24], a sample size of 30 individuals in each group was required to detect a difference of 1.74±2.37 in percentage body weight change with a power of 80% and a significance level of 5%. Hence, with an estimated withdrawal rate of 15% [4] the aim was to include 36 participants in each group.

2.7 Statistical analyses

Descriptive statistics were used to summarise baseline data. Intervention effect on the primary outcome, percentage change in body weight, was analysed by both intention-to-treat principle and per protocol principle, whereas intervention effect on other outcome measures were analysed by per protocol principle.

In the intention-to-treat analysis of intervention effect on primary outcome, multiple imputations (m=20) were used to account for missing data under a missing at random assumption [49]. Missing observations in body weight at 3-month follow-up were imputed using the following variables: baseline body weight, treatment arm (group), age, gender, cancer diagnosis, time interval posttreatment, and REHPA scale score <3/≥ 3 at inclusion. In per protocol analyses, only participants with baseline and follow-up measurements of the given outcome were included.

Development in outcome scores from baseline to 3-month follow-up were calculated for each participant, and differences between intervention group and wait-list control group were tested. In intention-to-treat analysis, difference between groups in percentual change from baseline to follow-up was assessed using linear regression. In per protocol analyses, differences were tested using a two-sample two-sided t-test for normally distributed data and Mann-Whitney U test for non-normally distributed data. As described in trial protocol [24], effect size for normally

distributed data was estimated with Cohen's d [50]. However, for non-normally distributed data, where differences were tested using Mann-Whitney U test, it was more appropriate to estimate effect size (*r*) by dividing the z value obtained in the Mann Whitney U test with the square root of the number of observations [51]. It is suggested, that Cohen's d values of 0.8, 0.5, and 0.2 represents large, medium, and small effect sizes, while the corresponding values for *r* are 0.5, 0.3 and 0.1 [50,51].

Adjusted analyses were performed using multiple linear regression to adjust for gender, time interval (months) posttreatment, and REHPA scale score.

In addition to the analyses defined in the trial protocol, differences within groups from baseline to follow-up were tested with two-sided paired t-test for normally distributed data and with Wilcoxon signed-rank test for non-normally distributed data. For outcomes on physical function where evidence on minimal clinically relevant change was available, it is indicated in result tables mean changes within groups from baseline to follow-up are greater than this cut-off. The relevant cut-off's were defined as 5% for body weight [52] , 5 kg for hand grip strength [53], and 14 metres for 6-minute walk test [54].

Participants who had relapse of their cancer during the trial were not excluded from data analyses, but in accordance with trial protocol [24], sensitivity analyses were performed to assess whether this affected results.

A statistical significance level of 5% was applied. Per protocol analyses of differences between groups were performed in SAS® Enterprise Guide® 7.1 by a blinded researcher, and the project group interpreted results before unblinding. STATA/IC 16.0 was used for other data analyses.

2.8 Ethical statement

The trial was conducted in accordance with the Declaration of Helsinki [55]. Informed written consent was obtained from all participants, and they were informed verbally and in writing that participation was voluntary, and that they could withdraw their consent at any time. The Regional Committees on Health Research Ethics for Southern Denmark assessed the duty to notify for the

trial (journal number 20182000-165) and concluded, based on Danish legislation, that the trial was not subject to the duty to notify since no biological material was included. The trial was registered by The Danish Data Protection Agency, registration number 2012-58-0018, approval number 18/14847, and registered in the database Clinical Trials (www.clinicaltrials.gov, NCT03909256) before inclusion of participants. Furthermore, a detailed trial protocol was published to verify adherence to original intent [24].

3 Results

In total, 71 individuals were included of whom 36 were randomised to the intervention group, and 35 were randomised to the control group. Participant baseline characteristics are shown in Table 2.

In both groups, three participants were lost to follow-up between baseline and 3-month follow-up (Figure 2). In the intervention group, additional six participants did not participate in the two days follow-up residential stay at 3-month follow-up, but they still completed patient-reported outcome questionnaires and/or participated in physical measurements at the outpatient clinics. These participants still had telephone consultations with the clinical dietitian in week 4 and week 8. Since outcome measurements for all participants in the intervention group were scheduled in the beginning of the two days follow-up residential stay, and hence, not measured the effect of the two days, the six participants were categorised as having completed the intervention from baseline to 3-month follow-up and included in per protocol analyses.

Three participants from intervention group and one participant from control group had relapse of their cancer. Two of them were among the three participants, that were lost to follow-up in the intervention group, whereas follow-up data was available for the remaining two.

An overview of the intervention group's scheduled individual counselling sessions with other professionals than clinical dietitian during the five days residential stay and their choices of optional group sessions is provided in Appendix A.

3.1 Intervention effect on primary outcome

In intention-to-treat analysis, the primary endpoint, percentage change in body weight, was almost identical across groups (0.46% in intervention group vs. 0.38% in control group), and the adjusted p-value for differences between groups was 0.795 (Table 3). The per protocol analysis yielded similar results (adjusted p=0.752). No statistically significant or clinically relevant changes within groups were seen.

3.2 Intervention effect on secondary outcomes

For changes in maximal hand grip strength, significant differences (p=0.038) were seen between groups with a mean increase of 1.3 kg in intervention group, while a slight decrease (-0.6 kg) was seen in control group. With Cohen's d of 0.55, this corresponded to a medium effect. The differences remained significant in the adjusted analyses (Table 3). In 30-second chair stand test, improvements were greater in control group than in intervention group (2.3 vs. 0.5, d= -0.69, adjusted p-value = 0.008). For maximal mouth opening and 6-minute walk test, tendencies were seen towards greater improvements in intervention group (mouth opening: d=0.46; p=0.088; 6-minute walk test: d=0.51; p=0.061), but in the adjusted analyses the tendency was no longer present for 6-minute walk test. In the intervention group, a statistically significant and clinically relevant improvement in 6-minute walk test (p<0.001) was seen from baseline to follow-up (Appendix B, Table B1). In the control group, the result of the 30-second chair stand test improved significantly (p<0.001).

No significant differences were seen between groups or within groups in EQ-5D-5L scores (Table 4).

In the EORTC QLQ-C30 scales, significant differences were seen between groups in 'Role functioning' (r=0.28; p=0.024, adjusted p=0.041) and 'Pain' (r= -0.27, p=0.029, adjusted p=0.048) indicating greater improvements in the intervention group. The same was the case for 'Fatigue' (r= -0.24, p=0.050), but in adjusted analysis, only a tendency was seen (Table 4). For 'Physical functioning', a tendency towards greater improvement in the intervention group was seen (r=0.22, p=0.070), but in adjusted analysis this tendency was no longer present. In the intervention group, a

significant improvement in 'Cognitive functioning' was seen from baseline to follow-up (p=0.034), while no significant changes were seen in control group.

In the EORTC QLQ-H&N35 scales, improvements in 'Speech problems' were greater in the intervention group (r=-0.18, adjusted p=0.040), but so was the increase in 'Felt ill' symptom level (r=0.29, adjusted p=0.020) and use of 'Nutritional supplements' (r=0.31, adjusted p=0.005). From baseline to follow-up, the intervention group had significant improvements in the symptom scales 'Swallowing' (p=0.032), 'Speech problems' (p=0.009), 'Trouble with social eating' (p=0.027), 'Teeth' (p=0.023), 'Opening mouth' (p=0.020), and 'Dry mouth' (p=0.029). From baseline to follow-up, the control group had significant decreases in symptom level in 'Swallowing' (p=0.010)' and 'Senses problems' (p=0.007), 'Coughing' (p=0.038), and 'Nutritional supplements' (p=0.025) (Table 4).

For HADS scores, a tendency towards greater improvements in the anxiety subscale was seen for the intervention group (adjusted p=0.061), but no ignificant differences were seen between groups or within groups (Table 4).

3.3 Sensitivity analyses

Sensitivity analyses of differences between groups when excluding participants with relapse of their cancer did not change the overall results (Appendix B, Table B2). Since none of the participants participated in other nutritional rehabilitation services during the trial period, no sensitivity analyses were required to account for this.

4 Discussion

This is the first randomised controlled trial to test the effect of a multidisciplinary residential nutritional rehabilitation programme compared to standard care in HNC survivors. The trial showed no effect on the primary outcome, percentage weight in body mass, but there was an overall trend towards greater improvements physical function and QOL in the intervention group.

In the pilot study of the intervention, a significant increase in body weight was seen [4,24], and several factors may contribute to why no effect on body weight was seen in the present trial. Since participants were 1-5 years posttreatment, it can be questioned, whether changes in body weight

was the most relevant primary outcome. It was chosen because it is an objective measure, and in the nationwide survey that preceded participant recruitment, approximately half of HNC survivors 1-5 years posttreatment had not regained their habitual weight. This was also the case for trial participants, but while 51% had a current body weight lower than 95% of their precancer weight, only 11% considered their current weight too low, and 46% considered it too high (Table 2 and Appendix C, Table C1). Hence, for most participants, increases in body weight was not a desired outcome. The individual counselling sessions with the clinical dietitian were tailored to the individual participant, which meant that for some participants it included strategies for weight gain while for others, it included strategies for weight loss. Hence, no overall effect on body weight was seen. Yet, nutritional rehabilitation may still be indicated even though the weight is stable. According to the nutrition triage recommendations for the full Scored Patient-Generated Subjective Global Assessment, individuals with a score of 4-8 require intervention by dietitian in conjunction with nurse or physician as indicated by symptoms, while a score ≥ 9 indicates a critical need for intervention. Since the PG-SGA SF is designed to reflect approximately 80–90% of the full Scored Patient-Generated Subjective Global Assessment score[56], the same cut-offs can potentially be used for the PG-SGA SF. Baseline data showed that 44% of participants in the intervention group had a PG-SGA SF score of 4-8 and 14% had a score of ≥9 and hence, according to PG-SGA SF, 48% required intervention by dietitian. In comparison, NRS 2002 only classified 11% as being at nutritional risk. While the malnutrition score in NRS 2002 is primarily based on weight loss and decreased dietary intake, the PG-SGA SF furthermore includes information on nutrition impact symptoms and diet texture, and the different results obtained with the two tools may indicate, that nutritional rehabilitation needs in this population primarily concerns support to manage nutrition impact symptoms rather than support to gain weight. Hence, outcome measures of how individuals cope with nutrition impact symptoms may be more relevant.

Studies have shown that eating problems in HNC survivors frequently lead to social withdrawal [4,18,20], and in the pilot study of the intervention in the present trial, participants gained 'Increased courage to eat' from the programme [4]. Hence, the EORTC QLQ-H&N35 scale 'Trouble with social eating' might have been a more relevant primary outcome. Significant improvement in this scale was seen in the intervention group, but with only 65 participants having complete data in this scale, the trial was not powered to show any difference between groups. Based on data from

the present trial, 36 observations in each group would be required to detect a difference of 10 points (corresponding to a medium clinically relevant effect [57]) between groups with a power of 80% and a significance level of 5%. To detect a small effect (a difference between groups of 5 points), 141 participants would be required in each group.

Analyses of effect on secondary outcomes indicated tendencies towards greater improvements in physical function in the intervention group except for 30-second chair stand test, where a statistically significant improvement was seen in the control group. The same overall trend towards greater improvements in the intervention group was seen for several QOL scales and symptoms of anxiety, and the intervention group showed significant changes in approximately twice as many QOL scales than the control group. Notably, compared to the control group, participants in the intervention group had greater increases in the symptom scale 'Felt ill'. While eight participants in the intervention group had an increase in symptom level on this scale, the same was the case for one participant in the control group (data not shown). This scale is based on a single item and refers to whether the individual has been feeling ill during the preceding week. With the wording of the Danish EORTC QLQ-H&N35, feeling ill can either refer to acute illness or to a more generalised feeling of being categorised as suffering from a disease. Bearing in mind that most participants were 1-5 years posttreatment and their focus on the cancer and its late effects may have decreased over time, participating in an intensive rehabilitation programme increases this focus again. This could potentially lead to an increased feeling of being affected by the cancer. This feeling is not uncommon in cancer rehabilitation which for some individuals comprise the acceptance of the long-term rehabilitation aim being coping with late effects rather than curing them [58].

The significant improvements seen in QOL scales in the pilot study of the intervention [4,24] were also seen in the intervention group of the present trial in addition to improvements in several other QOL scales. In their pilot study on the effect of a 1-week residential psychoeducational programme at 4-weeks follow-up, Hammerlid et al. saw the greatest improvements in the EORTC QLQ-H&N37 scales 'Trouble eating' and 'Problems enjoying your meals' in HNC survivors 12-22 months posttreatment [19]. These scales do not directly translate to the current QLQ-H&N35

scales, but consistent with our results this could indicate that the residential programmes support the HNC survivors' ability to cope with physical symptoms rather than reducing physical symptom severity.

Another factor that could possibly have affected results of the present trial, is the mode of participant recruitment and inclusion criteria. While recruitment in the pilot study was dependent on referral from physicians, inclusion in the present trial was based on self-reported interest in participation, and no further selection based on nutritional screening was performed. It can be hypothesised that some of the trial participants in the given study would have no measurable benefit of rehabilitation services no matter how effective the intervention, since they had relatively few or no late effects. Restricting inclusion to individuals who met certain criteria for nutritional status, nutritional risk, or presence of nutrition impact symptoms could potentially have led to other results. However, evidence is scarce on what these criteria optimally should be. Most nutrition screening tools validated in cancer patients are validated in the acute phase of the trajectory [52,59,60], and their applicability in HNC survivors >1-year posttreatment is unstudied. In the present trial, differences in baseline nutritional risk were seen when comparing NRS 2002 and PG-SGA SF. A secondary objective of trial was in fact to test associations between participants' development in outcome scores and their baseline scores in selected nutrition screening tools [24], and hence to assess the applicability of the different tools in this population. This secondary objective will be approached in future publications but could not have been pursued properly with further inclusion criteria in the trial. Inclusion through self-referral poses a risk that included participants are not necessarily the ones with greatest rehabilitation needs. This is already seen in existing rehabilitation services in Denmark even upon referral from health professionals [61,62]. Furthermore, being invited to participate in the rehabilitation programme as a part of clinical study may have encouraged individuals to participate to support research despite few rehabilitation needs. However, compared to other NUTRI-HAB survey respondents, a greater proportion of trial participants (69% vs. 48%, p=0.007, Appendix C, Table C1) had a REHPA scale score of 3 or above which is REHPA's inclusion criteria for their standard residential rehabilitation programmes. The results of the present work highlight the need for further explorative studies on

relevant inclusion criteria for residential rehabilitation programmes and support that access to rehabilitation services should be based on referral from health professionals rather than self-referral.

Since the programme required participants to be self-reliant and to participate actively, the most vulnerable HNC survivors may have been excluded. Recruitment through a nationwide survey gives a unique possibility to assess potential selection bias. Compared to the remaining survey population, more trial participants were female (p=0.032), and more were diagnosed with pharyngeal cancer while fewer were diagnosed with oral or laryngeal cancer (p=0.011, Appendix C, Table C1). A great proportion of pharyngeal cancers are related to Human Papillomavirus, and these individuals tend to have a higher socioeconomic status and less alcohol and tobacco abuse [63]. Hence, their symptom level and rehabilitation needs may differ from oral or laryngeal cancer survivors'.

In addition to recruitment through a nationwide survey with data from a national clinical quality database, methodological strengths of the trial include randomisation, blinded data analysis, and blinded interpretation of results. The use of a wait-list control group may have reduced participant drop-out, and with a relatively low attrition rate (8%) equally distributed across groups, the risk of attrition bias is considered low. Since concerns have been raised that wait-list control may overestimate intervention effect in randomised controlled trials [64], and the number of statistical tests in the present trial poses a risk of type 1 errors, no firm conclusions on intervention effect on secondary outcomes can be drawn.

5 Conclusion

A multidisciplinary residential nutritional rehabilitation programme had no effect on body weight in HNC survivors included based on self-reported interest in participation, but it may have effect on physical function and QOL. Further research on relevant inclusion criteria for referral to nutritional rehabilitation and the programme's effect in different subgroups of HNC survivors is needed.

Author Contributions:

Conceptualization and methodology, M.B.K, A.D.Z., A.M.B, K.B.D and I.W; investigation, M.B.K and J.J.K.M..; data curation, T.B.M. and M.B.K.; formal analysis, T.B.M. and M.B.K.; writing—original draft preparation, M.B.K. and A.D.Z.; writing—review and editing, A.M.B., K.B.D., and I.W.; supervision, A.D.Z.; project administration, M.B.K.; funding acquisition, M.B.K, A.D.Z., A.M.B, K.B.D and I.W. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest:

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Figure 1: Timeline of the NUTRI-HAB Trial from baseline to 3-month follow-up

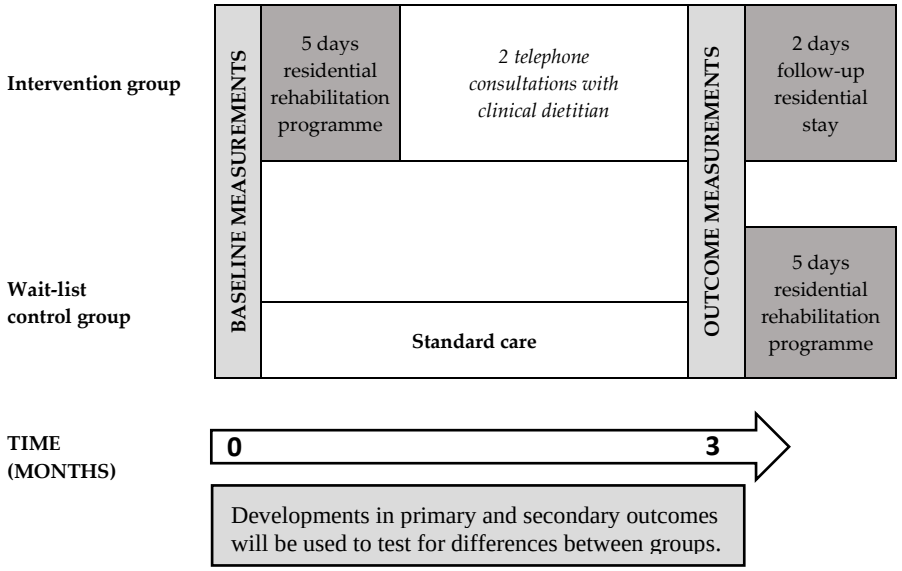

Figure 2: Flow chart of the NUTRI-HAB trial from baseline to 3-month follow-up

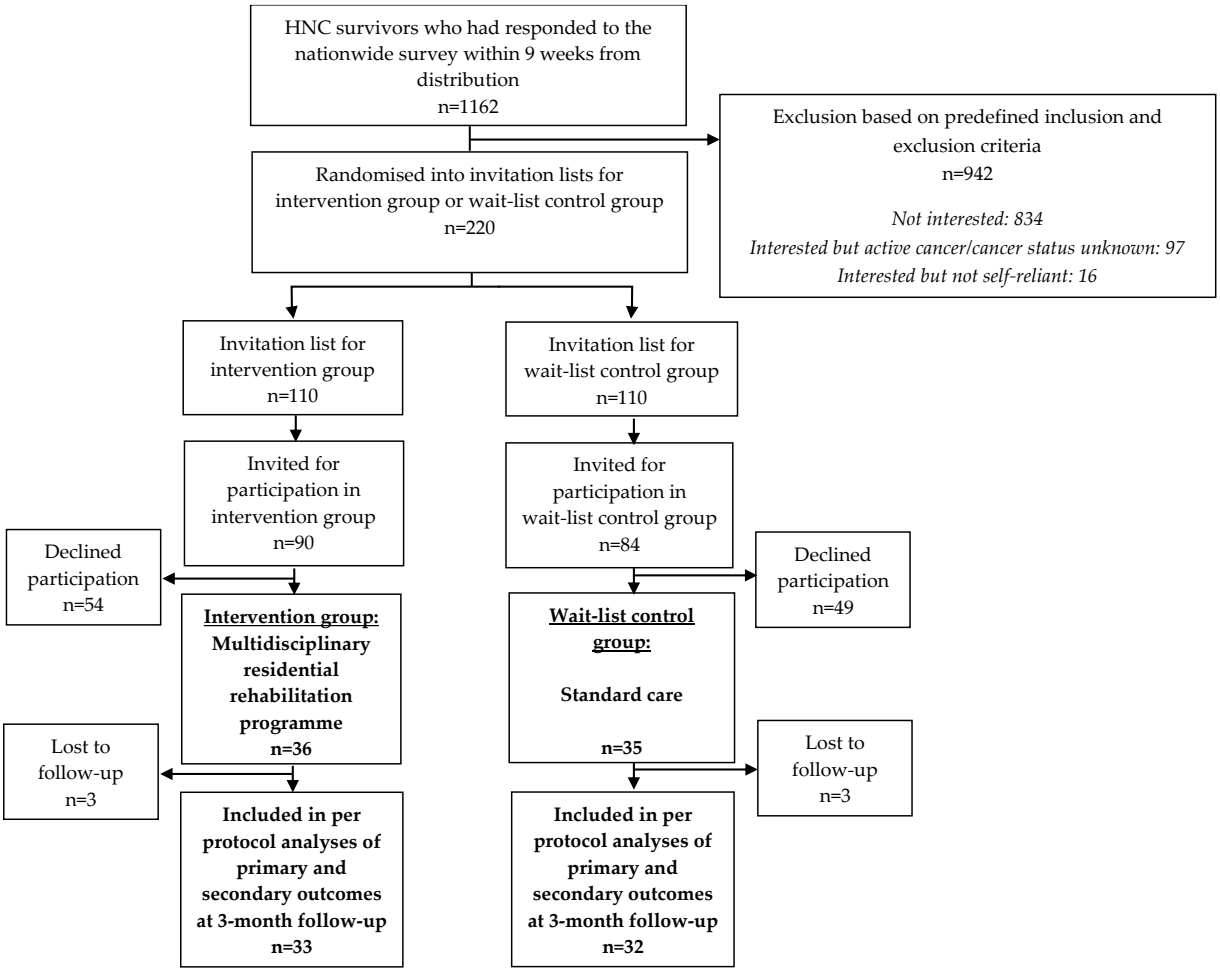

Table 1: Schedule for the initial five days and the two days follow-up of the multidisciplinary residential nutritional rehabilitation programme in the NUTRI-HAB trial.

INITIAL FIVE DAYS RESIDENTIAL STAY					**FOLLOW-UP RESIDENTIAL STAY AFTER 3 MONTHS**	
DAY 1	***DAY 2***	***DAY 3***	***DAY 4***	***DAY 5***	***DAY 1***	***DAY 2***
	BREAKFAST					*BREAKFAST*
	MORNING ASSEMBLY					*MORNING ASSEMBLY*
Arrival Welcome session and presentation of the programme *(course leader and clinical dietitian)* Walk and talk	Practical kitchen workshop *(clinical dietitian)*	Psychological reactions to cancer *(psychologist)*	Physical activity *(physiotherapist)* <u>Optional sessions:</u> Fatigue and sleep problems *(nurse)* *OR* Vocational counselling *(social worker)*	Motivation, goal setting and action plans *(social worker and course leader)* Individual work and group discussion on action plans *(social worker and course leader)*	Arrival Welcome session and presentation of the programme *(course leader and clinical dietitian)* What's new within the last three months? *(course leader and clinical dietitian)*	Physical activity *(physiotherapist)* <u>Optional sessions:</u> Sexuality and intimacy *(sexologist)* *OR* Meaning and values in life *(psychologist)*
LUNCH					*LUNCH*	
Introduction round *(course leader and central health professionals)* Theoretical session on management of eating problems *(clinical dietitian)*	***<u>DATA COLLECTION</u>*** ***Physical tests and measurements (physiotherapist)*** Yoga *(physiotherapist)*	Swallowing exercises *(occupational therapist)* Individual dietary counselling *(clinical dietitian)*	Dental problems and oral hygiene *(dental hygienist)* Individual counselling *(depending on participant's needs)* Massage therapy *(massage therapist)*	Closing session and farewell (course leader and clinical dietitian)	***<u>DATA COLLECTION</u>*** ***Physical tests and measurements (physiotherapist)*** Individual dietary counselling *(clinical dietitian)*	Closing session and farewell *(course leader and clinical dietitian)*
DINNER					*DINNER*	
Social activity	Group conversation on existence *(priest)*					

Table 2: Baseline characteristics of participants in the NUTRI-HAB trial

	Intervention group (n=36)	Control group (n=35)
Age (years)	64.5 ± 6.7	64.0 ± 9.6
Gender		
Male	26 (72%)	20 (57%)
Female	10 (28%)	15 (43%)
Cancer diagnosis		
Larynx	6 (17%)	3 (9%)
Pharynx	30 (83%)	29 (83%)
Oral cavity	0	3 (9%)
Overall cancer stage		
I	6 (17%)	3 (9%)
II	7 (19%)	5 (14%)
III	5 (14%)	8 (23%)
IV	18 (50%)	19 (54%)
Tumour (T) stage		
T1	12 (33%)	8 (23%)
T2	9 (25%)	14 (40%)
T3	12 (33%)	9 (26%)
T4	3 (8%)	4 (11%)
Lymph node (N) stage		
N0	12 (33%)	8 (23%)
N1	4 (11%)	6 (17%)
N2	20 (56%)	21 (60%)
N3	0	0
Metastasis (M) stage		
M0	36 (100%)	35 (100%)
M1	0	0
Time interval from completion of radiation therapy		
12-23 months	13 (36%)	11 (31%)
24-35 months	6 (17%)	5 (14%)
36-47 months	7 (19%)	14 (40%)
48-59 months	10 (28%)	5 (14%)
Rehabilitation needs measured by the REHPA scale[a,b]		
< 3	13 (36%)	9 (26%)
≥ 3	23 (63%)	26 (74%)
Nutritional risk (NRS 2002)		
≥ 3 points	4 (11%)	2 (6%)
Nutritional risk and deficit (PG-SGA SF)		
4-8 points	16 (44%)	14 (40%)
≥ 9 points	5 (14%)	6 (17%)
BMI category		
Underweight (BMI <18.5)	0	0
Normal weight (BMI 18.5-24.9)	17 (47%)	15 (43%)
Overweight (BMI 25.0-29.9)	13 (36%)	10 (29%)
Obese (BMI ≥ 30.0)	6 (17%)	10 (29%)
Current body weight vs. precancer body weight[a]		
<95%	18 (53%)	17 (50%)
95-105%	14 (41%)	13 (38%)
>105%	2 (6%)	4 (12%)
Participant's own evaluation of current body weight[a]		
Too low	3 (8%)	5 (14%)
Appropriate	18 (50%)	12 (34%)
Too high	15 (42%)	18 (51%)

NRS 2002: Nutritional Risk Screening 2002, PG-SGA SF: The Scored Patient Generated Subjective Global Assessment Short Form, BMI: Body mass index.

Data are presented as means ± standard deviations or numbers and (percentages). The PG-SGA SF score can range from 0-36, and NRS 2002 score can range from 0-7. On both scales, a higher score indicates a greater nutritional risk. REHPA scale ranges from ranges from 1-9, and a higher score indicates greater rehabilitation needs.

a Self-reported data collected through the nationwide cross-sectional NUTRI-HAB survey prior to inclusion.
b Used for stratification of randomisation.

Table 3: Changes in in physical measurements and tests from baseline to 3-month follow-up in the NUTRI-HAB trial

	BASELINE VALUES		CHANGES FROM BASELINE TO 3-MONTH FOLLOW-UP					
	Intervention group	Control group	Intervention group	Control group	Difference between groups[a] *p-value*	Effect size Cohen's d [95% confidence interval]	Adjusted model[b] β	*p-value*
PRIMARY OUTCOME								
Intention-to-treat analysis								
Body weight (kg) *(36/35)*[c]	78.8 ± 2.3	79.3 ± 2.8	0.46 ± 0.43[d]	0.38 ± 0.56[d]	0.910		0.194	0.795
Per protocol analysis								
Body weight (kg) *(29/30)*[c]	80.4 ± 12.8	77.8 ± 16.5	0.45 ± 1.66[d]	0.41 ± 3.06[d]	0.958	0.01 [-0.50, 0.52]	0.215	0.752
SECONDARY OUTCOMES								
Physical measurements and tests								
Body mass index (kg/m²) *(29/30)*[c]	26.7 ± 4.4	27.0 ± 5.1	0.45 ± 1.66[d]	0.41 ± 3.06[d]	0.958	0.01 [-0.50, 0.52]	0.215	0.752
Maximal mouth opening (mm) *(29/29)*[c]	47.7 ± 7.1	42.8 ± 10.1	0.6 ± 1.6	-0.3 ± 2.1	0.088	0.46 [-0.07, 0.98]	0.962	0.072
Maximal hand grip strength (kg) *(29/30)*[c]	39.4 ± 9.2	39.3 ± 13.0	1.3 ± 3.8	-0.6 ± 3.3	**0.038**	0.55 [0.03, 1.07]	1.950	**0.042**
30-second chair stand test (number of repetitions) *(28/29)*[c]	15.1 ± 4.2	13.8 ± 4.1	0.5 ± 2.3	2.3 ± 3.1*	**0.012**	-0.69 [-1.22, -0.15]	-2.074	**0.008**
6-minute walk test (m) *(28/28)*[c]	562.7 ± 72.1	572.9 ± 115.7	34.6 ± 43.4*,#	8.5 ± 57.7	0.061	0.51 [-0.02, 1.04]	18.620	0.192

Baseline values and changes within groups are shown as means ± standard deviations (standard error in intention-to-treat analysis). Significant p-values are highlighted in bold.

[a] Differences between groups are tested with linear regression in intention-to-treat analysis and with two-sample two-sided t-test in per protocol analyses.

[b] Differences between groups assessed in a multiple linear regression model including gender, time interval (months) posttreatment, and rehabilitation needs assessed by the REHPA scale.

[c] n included in analyses in (intervention/control) groups.

[d] Changes in body weight and body mass index from baseline to 3-month follow-up is shown in percent.

* Statistically significant change ($p<0.05$) within group from baseline to 3-month follow-up tested with paired two-sided t-test in per protocol analyses. Results are shown in Appendix B, Table B1.

Clinically relevant change within group from baseline to 3-month follow-up defined as a difference between mean value at baseline and 3-month follow up of minimum 5% for weight [1], 5 kg for hand grip strength [2], and 14 metres for 6-minute walk test [3].

Table 4: Changes in health-related quality of life and symptoms of anxiety and depression from baseline to 3-month follow-up in the NUTRI-HAB trial

	BASELINE VALUES		CHANGES FROM BASELINE TO 3-MONTH FOLLOW-UP					
	Intervention group	Control group	Intervention group	Control group	Difference between groups[a] *p-value*	Effect size (r)	Adjusted model[b] β	*p-value*
EQ-5D-5L								
VAS *(32/32)*[c]	79.0 (52.0;87.5)	75.0 (61.1;85.5)	1.5 (-1.0;10.0)	3.5 (-6.0;6.5)	0.672	0.05	2.319	0.523
Summary Index Score *(32/32)*[c]	0.783 (0.719;0.859)	0.787 (0.740;0.847)	0.0 (-0.008;0.043)	0.0 (-0.280;0.034)	0.440	0.10	0.012	0.548
EORTC QLQ-C30								
Global health status/QOL *(33/32)*[c]	66.7 (58.3;83.3)	66.7 (54.2;83.3)	0.0 (0;16.7)	0.0 (0;12.5)	0.870	-0.02	-0.310	0.943
Functional scales								
Physical functioning *(33/32)*[c]	86.7 (80.0;100)	93.3 (76.7;100)	0.0 (0;6.7)	0.0 (-6.7;0)	0.070	0.22	4.622	0.102
Role functioning *(33/32)*[c]	83.3 (66.7;100)	83.3 (66.7;100)	0.0 (0;16.7)	0.0 (-16.7;0)	**0.024**	0.28	9.630	**0.041**
Emotional functioning *(33/32)*[c]	83.3 (66.7;100)	83.3 (66.7;95.8)	0.0 (0;0)	0.0 (0;8.3)	0.416	-0.10	-2.740	0.464
Cognitive functioning *(33/32)*[c]	83.3 (50.0;83.3)	83.3 (66.7;91.7)	0.0 (0;16.7)*	0.0 (0;0)	0.100	0.20	5.756	0.088
Social functioning *(33/32)*[c]	83.3 (66.7;100)	100.0 (75.0;100)	0.0 (0;16.7)	0.0 (0;0)	0.211	0.16	5.525	0.238
Symptom scales/items								
Fatigue *(33/32)*[c]	33.3 (11.1;44.4)	27.8 (11.1;33.3)	0.0 (-11.1;0)	0.0 (0;11.1)	**0.050**	-0.24	-8.161	0.053
Nausea and vomiting *(33/32)*[c]	0.0 (0;0)	0.0 (0;8.3)	0.0 (0;0)	0.0 (-8.3;0)	0.723	0.04	1.054	0.787
Pain *(33/32)*[c]	16.7 (0;33.3)	16.7 (0;33.3)	0.0 (-16.7;0)	0.0 (0;16.7)	**0.029**	-0.27	-8.536	**0.048**
Dyspnoea *(33/32)*[c]	0.0 (0;33.3)	0.0 (0;33.3)	0.0 (0;0)	0.0 (0;0)	0.978	-0.003	1.284	0.750
Insomnia *(33/32)*[c]	33.3 (0;33.3)	33.3 (0;50.0)	0.0 (0;0)	0.0 (0;0)	0.856	0.02	0.663	0.907
Appetite loss *(33/32)*[c]	0.0 (0;33.3)	0.0 (0;33.3)	0.0 (-33.3;0)	0.0 (0;0)	0.879	-0.02	-5.582	0.383
Constipation *(33/32)*[c]	0.0 (0;33.3)	0.0 (0;33.3)	0.0 (0;0)	0.0 (0;0)	0.785	0.03	0.222	0.965
Diarrhoea *(33/32)*[c]	0.0 (0;0)	0.0 (0;0)	0.0 (0;0)	0.0 (0;0)	0.776	0.04	0.297	0.943
Financial difficulties *(33/32)*[c]	0.0 (0;33.3)	0.0 (0;33.3)	0.0 (0;0)	0.0 (0;0)	0.807	0.03	1.425	0.766
EORTC QLQ-H&N35								
Symptom scales/items								
Pain *(33/32)*[c]	25.0 (8.3;33.3)	16.7 (8.3;37.5)	0.0 (-8.3;0)	0.0 (-8.3;8.3)	0.507	-0.08	-5.046	0.316
Swallowing *(33/32)*[c]	16.7 (8.3;33.3)	25.0 (12.5;25.0)	0.0 (-8.3;0)*	-8.3 (-12.5;0)*	0.760	0.04	-1.409	0.691
Senses problems *(33/32)*[c]	33.3 (16.7;50.0)	25.0 (8.3;66.7)	0.0 (-16.7;0)	0.0 (-16.7;0)*	0.592	0.07	3.336	0.366
Speech problems *(33/32)*[c]	22.2 (11.1;33.3)	11.1 (5.6;22.2)	0.0 (-11.1;0)*	0.0 (0;0)	0.136	-0.18	-6.306	**0.040**
Trouble with social eating *(33/32)*[c]	25.0 (0;33.3)	16.7 (0;33.3)	0.0 (-16.7;0)*	0.0 (-8.3;0)	0.276	-0.14	-6.188	0.110
Trouble with social contact *(33/32)*[c]	0.0 (0;20.0)	3.3 (0;16.7)	0.0 (-6.7;0)	0.0 (-6.7;0)	0.764	-0.04	0.135	0.965
Less sexuality *(31/31)*[c]	33.3 (0;66.7)	33.3 (0;66.7)	0.0 (-16.7;16.7)	0.0 (-33.3;0)	0.534	0.08	0.808	0.925
Teeth *(33/32)*[c]	0.0 (0;66.7)	16.7 (0;33.3)	0.0 (-33.3;0)*	0.0 (0;0)	0.198	-0.16	-8.512	0.144
Opening mouth *(33/32)*[c]	0.0 (0;33.3)	0.0 (0;33.3)	0.0 (-33.3;0)*	0.0 (0;0)	0.148	-0.18	-5.607	0.256
Dry mouth *(33/32)*[c]	66.7 (33.3;100)	66.7 (33.3;100)	0.0 (-33.3;0)*	0.0 (0;0)	0.202	-0.16	-10.064	0.102
Sticky saliva *(32/32)*[c]	33.3 (33.3;66.7)	50.0 (33.3;100)	0.0 (-16.7;0)	0.0 (-33.3;0)	0.629	0.06	4.182	0.521
Coughing *(33/32)*[c]	33.3 (0;33.3)	33.3 (33.3;33.3)	0.0 (-33.3;0)	0.0 (-33.3;0)*	0.300	0.13	10.130	0.149
Felt ill *(33/32)*[c]	0.0 (0;33.3)	0.0 (0;33.3)	0.0 (0;0)	0.0 (0;0)	**0.020**	0.29	10.395	**0.020**
Pain-killers *(33/32)*[c]	0.0 (0;100)	100 (0;100)	0.0 (0;0)	0.0 (0;0)	0.755	0.04	1.515	0.887

Nutritional supplements *(33/32)*[c]	0.0 (0;0)	0.0 (0;100)	0.0 (0;0)	0.0 (0;0)*	0.013	0.31	31.465	**0.005**
Feeding tube *(33/32)*[c]	0.0 (0;0)	0.0 (0;0)	0.0 (0;0)	0.0 (0;0)	0.313	-0.13	-7.271	0.240
Weight loss *(33/32)*[c]	0.0 (0;0)	0.0 (0;0)	0.0 (0;0)	0.0 (0;0)	0.443	-0.10	-9.273	0.462
Weight gain *(33/32)*[c]	0.0 (0;0)	0.0 (0;100)	0.0 (0;0)	0.0 (0;0)	0.155	0.18	16.499	0.226
HADS								
Anxiety *(32/32)*[c]	4.5 (2.0;8.0)	4.0 (1.0;8.5)	-1.0 (-2.0;1.0)	0.0 (-1.0;1.0)	0.094	-0.21	-1.230	0.061
Depression *(32/32)*[c]	4.0 (1.0;7.5)	5.0 (2.0;8.5)	0.0 (-1.0;0.5)	0.0 (-2.0;1.0)	0.789	0.03	-0.228	0.694

EORTC: European Organization for Research and Treatment of Cancer, HADS: Hospital Anxiety and Depression Scale.

Baseline values and changes within groups are shown as medians and quartiles (Q1;Q3). Significant p-values are highlighted in bold.

The EQ-5D-5L VAS ranges from 0-100, and the summary index calculated based on Danish values ranges from -0.624 to 1.0. A higher score indicates a better self-rated health. The EORTC QLQ-C30 and QLQ-H&N35 scales range from 0-100. A higher score indicates a higher response level. Thus, a high score for a functional scale or global QOL indicates a high level of functioning/QOL and a high score on a symptom scale indicates a high symptom level. The HADS subscales range from 0-21, and a higher score indicates higher symptom level.

[a] Differences between groups are tested with Mann Whitney U test.

[b] Differences between groups assessed in a multiple linear regression model including gender, time interval (months) posttreatment, and rehabilitation needs assessed by the REHPA scale.

[c] n included in analyses in (intervention/control) groups.

* Statistically significant change ($p<0.05$) within group from baseline to 3-month follow-up tested with Wilcoxon signed-rank test. Results are shown in Appendix B, Table B1.

Appendix 4b: Supplementary material for paper IV

Appendix A: Scheduled individual activities during the programme

Table A1: Overview of scheduled individual counselling sessions and optional sessions attended by participants in the intervention group of the NUTRI-HAB trial

	Number of participants attending
INDIVIDUAL COUNSELLING SESSIONS	
During the five days residential stay (n=36)	
Clinical dietitian	36
Physician	6
Nurse	4
Psychologist	7
Social worker	1
Speech pathologist	9
Occupational therapist	1
Physiotherapist	3
Priest	1
OPTIONAL GROUP SESSIONS	
During the five days residential stay (n=36)	
Fatigue and sleep problems (nurse)	24
Vocational counselling (social worker)	7
During the two days follow-up residential stay (n=27)	
Meaning and values in life (psychologist)	16
Sexuality and intimacy (sexologist)	11

All participants had individual counselling sessions with clinical dietitian whereas other individual counselling sessions were scheduled depending on the individual participant's needs assessed through patient-reported outcome measures.

Appendix B: Results from exploratory and sensitivity analyses

Table B1: Tests of within group differences in body weight, physical function, health-related quality of life, and symptoms of anxiety and depression from baseline to 3-month follow-up

	INTERVENTION GROUP			CONTROL GROUP		
	Baseline	Changes from baseline to 3-month follow-up	p-value [a]	Baseline	Changes from baseline to 3-month follow-up	p-value [a]
PRIMARY OUTCOME						
Body weight *(29/30)*[b]	80.4 ± 12.8	0.45 ± 1.66[c]	0.165	77.8 ± 16.5	0.41 ± 3.06[c]	0.638
SECONDARY OUTCOMES						
Physical measurements and tests						
Body mass index (kg/m²) *(29/30)*[b]	26.7 ± 4.4	0.45 ± 1.66[c]	0.174	77.8 ± 16.5	27.0 ± 4.9[c]	0.582
Maximal mouth opening (mm) *(29/29)*[b]	47.7 ± 7.1	0.6 ± 1.6	0.073	-0.3 ± 2.1	42.5 ± 10.3	0.449
Maximal hand grip strength (kg) *(29/30)*[b]	39.4 ± 9.2	1.3 ± 3.8	0.064	-0.6 ± 3.3	38.7 ± 13.4	0.326
30-second chair stand test (number of repetitions) *(28/29)*[b]	15.1 ± 4.2	0.5 ± 2.3	0.288	2.3 ± 3.1	16.1 ± 4.4	**<0.001**
6-minute walk test (m) *(28/28)*[b]	562.7 ± 72.1	34.6 ± 43.4	**<0.001**	8.5 ± 57.7	581.4 ± 111.6	0.445
EQ-5D-5L						
VAS *(32/32)*[b]	79.0 (52.0;87.5)	1.5 (-1.0;10.0)	0.081	75.0 (61.1;85.5)	3.5 (-6.0;6.5)	0.303
Summary Index Score *(32/32)*[b]	0.783 (0.719;0.859)	0.0 (-0.008;0.043)	0.218	0.787 (0.740;0.847)	0.0 (-0.280;0.034)	0.712
EORTC QLQ-C30						
Global health status/QOL *(33/32)*[b]	66.7 (58.3;83.3)	0.0 (0;16.7)	0.209	66.7 (54.2;83.3)	0.0 (0;12.5)	0.090
Functional scales						
Physical functioning *(33/32)*[b]	86.7 (80.0;100)	0.0 (0;6.7)	0.307	93.3 (76.7;100)	0.0 (-6.7;0)	0.102
Role functioning *(33/32)*[b]	83.3 (66.7;100)	0.0 (0;16.7)	0.104	83.3 (66.7;100)	0.0 (-16.7;0)	0.110
Emotional functioning *(33/32)*[b]	83.3 (66.7;100)	0.0 (0;0)	0.885	83.3 (66.7;95.8)	0.0 (0;8.3)	0.357
Cognitive functioning *(33/32)*[b]	83.3 (50.0;83.3)	0.0 (0;16.7)	**0.034**	83.3 (66.7;91.7)	0.0 (0;0)	0.792
Social functioning *(33/32)*[b]	83.3 (66.7;100)	0.0 (0;16.7)	0.053	100.0 (75.0;100)	0.0 (0;0)	0.816
Symptom scales/items						
Fatigue *(33/32)*[b]	33.3 (11.1;44.4)	0.0 (-11.1;0)	0.098	27.8 (11.1;33.3)	0.0 (0;11.1)	0.332
Nausea and vomiting *(33/32)*[b]	0.0 (0;0)	0.0 (0;0)	0.611	0.0 (0;8.3)	0.0 (-8.3;0)	0.396
Pain *(33/32)*[b]	16.7 (0;33.3)	0.0 (-16.7;0)	0.188	16.7 (0;33.3)	0.0 (0;16.7)	0.066
Dyspnoea *(33/32)*[b]	0.0 (0;33.3)	0.0 (0;0)	0.655	0.0 (0;33.3)	0.0 (0;0)	0.739
Insomnia *(33/32)*[b]	33.3 (0;33.3)	0.0 (0;0)	0.725	33.3 (0;50.0)	0.0 (0;0)	0.983
Appetite loss *(33/32)*[b]	0.0 (0;33.3)	0.0 (-33.3;0)	0.198	0.0 (0;33.3)	0.0 (0;0)	0.091
Constipation *(33/32)*[b]	0.0 (0;33.3)	0.0 (0;0)	0.247	0.0 (0;33.3)	0.0 (0;0)	0.115
Diarrhoea *(33/32)*[b]	0.0 (0;0)	0.0 (0;0)	0.458	0.0 (0;0)	0.0 (0;0)	0.706
Financial difficulties *(33/32)*[b]	0.0 (0;33.3)	0.0 (0;0)	0.734	0.0 (0;33.3)	0.0 (0;0)	1.000
EORTC QLQ-H&N35						
Symptom scales/items						
Pain *(33/32)*[b]	25.0 (8.3;33.3)	0.0 (-8.3;0)	0.068	16.7 (8.3;37.5)	0.0 (-8.3;8.3)	0.470
Swallowing *(33/32)*[b]	16.7 (8.3;33.3)	0.0 (-8.3;0)	**0.032**	25.0 (12.5;25.0)	-8.3 (-12.5;0)	**0.010**
Senses problems *(33/32)*[b]	33.3 (16.7;50.0)	0.0 (-16.7;0)	0.070	25.0 (8.3;66.7)	0.0 (-16.7;0)	**0.007**
Speech problems *(33/32)*[b]	22.2 (11.1;33.3)	0.0 (-11.1;0)	**0.009**	11.1 (5.6;22.2)	0.0 (0;0)	0.248
Trouble with social eating *(33/32)*[b]	25.0 (0;33.3)	0.0 (-16.7;0)	**0.027**	16.7 (0;33.3)	0.0 (-8.3;0)	0.294

Trouble with social contact *(33/32)*[b]	0.0 (0;20.0)	0.0 (-6.7;0)	0.170	3.3 (0;16.7)	0.0 (-6.7;0)	0.434
Less sexuality *(31/31)*[b]	33.3 (0;66.7)	0.0 (-16.7;16.7)	0.672	33.3 (0;66.7)	0.0 (-33.3;0)	0.149
Teeth *(33/32)*[b]	0.0 (0;66.7)	0.0 (-33.3;0)	**0.023**	16.7 (0;33.3)	0.0 (0;0)	0.494
Opening mouth *(33/32)*[b]	0.0 (0;33.3)	0.0 (-33.3;0)	**0.020**	0.0 (0;33.3)	0.0 (0;0)	0.423
Dry mouth *(33/32)*[b]	66.7 (33.3;100)	0.0 (-33.3;0)	**0.029**	66.7 (33.3;100)	0.0 (0;0)	0.764
Sticky saliva *(32/32)*[b]	33.3 (33.3;66.7)	0.0 (-16.7;0)	0.329	50.0 (33.3;100)	0.0 (-33.3;0)	0.153
Coughing *(33/32)*[b]	33.3 (0;33.3)	0.0 (-33.3;0)	0.424	33.3 (33.3;33.3)	0.0 (-33.3;0)	**0.038**
Felt ill *(33/32)*[b]	0.0 (0;33.3)	0.0 (0;0)	0.055	0.0 (0;33.3)	0.0 (0;0)	0.180
Pain killers *(33/32)*[b]	0.0 (0;100)	0.0 (0;0)	0.414	100 (0;100)	0.0 (0;0)	0.180
Nutritional supplements *(33/32)*[b]	0.0 (0;0)	0.0 (0;0)	0.157	0.0 (0;100)	0.0 (0;0)	**0.025**
Feeding tube *(33/32)*[b]	0.0 (0;0)	0.0 (0;0)	0.317	0.0 (0;0)	0.0 (0;0)	1.000
Weight loss *(33/32)*[b]	0.0 (0;0)	0.0 (0;0)	0.480	0.0 (0;0)	0.0 (0;0)	0.706
Weight gain *(33/32)*[b]	0.0 (0;0)	0.0 (0;0)	0.132	0.0 (0;100)	0.0 (0;0)	0.706
HADS						
Anxiety *(32/32)*[b]	4.5 (2.0;8.0)	3.5 (0.5;7.5)	0.116	4.0 (1.0;8.5)	4.0 (1.0;8.5)	0.864
Depression *(32/32)*[b]	4.0 (1.0;7.5)	3.0 (1.0;7.0)	0.329	5.0 (2.0;8.5)	4.0 (2.0;7.0)	0.156

EORTC: European Organization for Research and Treatment of Cancer, HADS: Hospital Anxiety and Depression Scale.

Data are presented as means ± standard deviations or medians and quartiles (Q1;Q3). Significant p-values are highlighted in bold. The EQ-5D-5L VAS ranges from 0-100, and the summary index calculated based on Danish values ranges from -0.624 to 1.0. A higher score indicates a better self-rated health. The EORTC QLQ-C30 and QLQ-H&N35 scales range from 0-100. A higher score indicates a higher response level. Thus, a high score for a functional scale or global QOL indicates a high level of functioning/QOL and a high score on a symptom scale indicates a high symptom level. The HADS subscales range from 0-21, and a higher score indicates higher symptom level.

[a] Differences within groups are tested with two-sided paired t-test for primary outcome and other physical tests and measurements, while Wilcoxon signed-rank test was used for EQ-5D-5L, EORTC, and HADS data.

[b] n included in analyses in (intervention/control) groups.

[c] Changes in body weight and body mass index from baseline to 3-month follow-up is shown in percent.

Table B2: Sensitivity analyses of differences between intervention and control group excluding participants with cancer relapse between baseline and 3-month follow up

	CHANGES FROM BASELINE TO 3-MONTH FOLLOW-UP				
	Intervention group	Control group	Difference between groups[a] *p-value*	Effect size Cohen's d [95% confidence interval]	Effect size r
PRIMARY OUTCOME					
Body weight (%) *(29/29)*[b]	0.45 ± 1.66	0.60 ± 2.93	0.808	-0.06 [-0.58-0.45]	
SECONDARY OUTCOMES					
Physical measurements and tests					
Body mass index (kg/m²) *(29/29)*[b]	0.45 ± 1.66	0.60 ± 2.93	0.808	-0.06 [-0.58, 0.45]	
Maximal mouth opening (mm) *(29/28)*[b]	0.6 ± 1.6	-0.2 ± 2.1	0.116	0.42 [-0.10, 0.95]	
Maximal hand grip strength (kg) *(29/29)*[b]	1.34 ± 0.70	-0.62 ± 0.62	**0.038**	0.55 [0.03, 1.08]	
30-second chair stand test (number of repetitions) *(28/28)*[b]	0.5 ± 2.3	2.3 ± 3.2	**0.017**	-0.66 [-1.20, -0.12]	
6-minute walk test (m) *(28/27)*[b]	34.6 ± 43.4	7.3 ± 58.5	0.055	0.52 [-0.10, 1.07]	
EQ-5D-5L					
VAS *(31/31)*[b]	2.0 (-1.0;10.0)	4.0 (-6.0;7.0)	0.612		0.06
Summary Index Score *(31/31)*[b]	0.0 (-0.002;0.044)	0.0 (-0.042;0.035)	0.357		0.12
EORTC QLQ-C30					
Global health status/QOL *(32/31)*[b]	0.0 (0;16.7)	0.0 (0;16.7)	0.864		-0.02
Functional scales					
Physical functioning *(32/31)*[b]	0.0 (0;6.7)	0.0 (-6.7;0)	0.056		0.24
Role functioning *(32/31)*[b]	0.0 (0;16.7)	0.0 (-16.7;0)	0.018		0.30
Emotional functioning *(32/31)*[b]	0.0 (0;4.2)	0.0 (0;8.3)	0.416		-0.10
Cognitive functioning *32/31)*[b]	0.0 (0;16.7)	0.0 (0;0)	0.101		0.21
Social functioning *(32/31)*[b]	0.0 (0;16.7)	0.0 (0;0)	0.201		0.16
Symptom scales/items					
Fatigue *(32/31)*[b]	0.0 (-11.1;0)	0.0 (0;11.1)	0.029		-0.27
Nausea and vomiting *(32/31)*[b]	0.0 (0;0)	0.0 (-16.7;0)	0.719		0.05
Pain *(32/31)*[b]	0.0 (-16.7;0)	0.0 (0;16.7)	**0.040**		-0.26
Dyspnoea *(32/31)*[b]	0.0 (0;0)	0.0 (0;0)	0.770		-0.04
Insomnia *(32/31)*[b]	0.0 (0;0)	0.0 (0;0)	0.857		0.02
Appetite loss *(32/31)*[b]	0.0 (-33.3;0)	0.0 (0;0)	1.000		0.00
Constipation *(32/31)*[b]	0.0 (0;0)	0.0 (0;0)	0.976		0.003
Diarrhoea *(32/31)*[b]	0.0 (0;0)	0.0 (0;0)	0.763		0.04
Financial difficulties *(32/31)*[b]	0.0 (0;0)	0.0 (0;0)	0.809		0.03
EORTC QLQ-H&N35					
Symptom scales/items					
Pain *(32/31)*[b]	0.0 (-8.3;0)	0.0 (-8.3;8.3)	0.511		-0.08
Swallowing *(32/31)*[b]	-8.3 (-12.5;0)	-8.3 (-8.3;0)	0.978		0.003
Senses problems *(32/31)*[b]	0.0 (-16.7;0)	0.0 (-16.7;0)	0.358		0.12
Speech problems *(32/31)*[b]	0.0 (-11.1;0)	0.0 (0;0)	0.277		-0.14
Trouble with social eating *(32/31)*[b]	0.0 (-16.7;0)	0.0 (-8.3;0)	0.322		-0.12
Trouble with social contact *(32/31)*[b]	0.0 (-6.7;0)	0.0 (-6.7;0)	0.918		-0.01
Less sexuality *(30/30)*[b]	0.0 (-16.7;16.7)	0.0 (-33.3;0)	0.470		0.09
Teeth *(32/31)*[b]	0.0 (-33.3;0)	0.0 (0;0)	0.196		-0.16
Opening mouth *(32/31)*[b]	0.0 (-33.3;0)	0.0 (0;0)	0.148		-0.18
Dry mouth *(32/31)*[b]	0.0 (-33.3;0)	0.0 (0;0)	0.190		-0.17

Sticky saliva *(31/31)*[b]	0.0 (0;0)	0.0 (-33.3;0)	0.493	0.19
Coughing *(32/31)*[b]	0.0 (-33.3;0)	0.0 (-33.3;0)	0.435	0.10
Felt ill *(32/31)*[b]	0.0 (0;0)	0.0 (0;0)	**0.032**	0.27
Pain killers *(32/31)*[b]	0.0 (0;0)	0.0 (0;0)	0.755	0.04
Nutritional supplements *(32/31)*[b]	0.0 (0;0)	0.0 (0;0)	**0.013**	0.31
Feeding tube *(32/31)*[b]	0.0 (0;0)	0.0 (0;0)	0.564	-0.07
Weight loss *(32/31)*[b]	0.0 (0;0)	0.0 (0;0)	0.444	-0.10
Weight gain *(32/31)*[b]	0.0 (0;0)	0.0 (0;0)	0.226	0.15
HADS				
Anxiety *(31/31)*[b]	-1.0 (-2.0;1.0)	0.0 (-1.0;1.0)	0.062	-0.24
Depression *(31/31)*[b]	0.0 (-1.0;0)	0.0 (-2.0;1.0)	0.925	0.01

EORTC: European Organization for Research and Treatment of Cancer, HADS: Hospital Anxiety and Depression Scale.

Changes within groups are shown as means ± standard deviations (standard error for intention-to-treat analysis) or medians and quartiles (Q1;Q3). Significant p-values are highlighted in bold. The EQ-5D-5L VAS ranges from 0-100, and the summary index calculated based on Danish values ranges from -0.624 to 1.0. A higher score indicates a better self-rated health. The EORTC QLQ-C30 and QLQ-H&N35 scales range from 0-100. A higher score indicates a higher response level. Thus, a high score for a functional scale or global QOL indicates a high level of functioning/QOL and a high score on a symptom scale indicates a high symptom level. The HADS subscales range from 0-21, and a higher score indicates higher symptom level. Thus, increases in EQ-5D-5L and EORTC QLQ-C30 global QOL and functional scores indicate improvements in self-reported QOL whereas increased scores on EORTC symptom scales and HADS indicate increased symptom level.

[a] Differences between groups are tested with two-sample two-sided t-test for primary outcome and other physical tests and measurements, while Mann-Whitney U was used for EQ-5D-5L, EORTC, and HADS data.
[b] n included in analyses in (intervention/control) groups.

Appendix C: Assessment of potential selection bias

Table C1: Characteristics and differences between participants in the NUTRI-HAB trial and the NUTRI-HAB survey population

	Participants in the NUTRI-HAB trial	Respondents of the NUTRI-HAB survey (excl. trial participants)		Survey population of the NUTRI-HAB survey (excl. trial participants, incl. non-responders)	
	(n=71)	(n=1119)	p-value[a]	(n=1866)	p-value[a]
Age (years)	64.1 ± 8.2	65.7 ± 9.1	0.138	65.8 ± 9.3	0.125
Gender					
Male	46 (65%)	845 (76%)	**0.049**	1430 (77%)	**0.032**
Female	25 (35%)	274 (25%)		436 (23%)	
Cancer diagnosis					
Larynx	9 (13%)	242 (22%)		468 (25%)	
Pharynx	59 (83%)	780 (70%)	0.062	1231 (66%)	**0.011**
Oral cavity	3 (4%)	97 (9%)		167 (9%)	
Overall cancer stage		*(n=1111)*		*(n=1855)*	
I	9 (13%)	217 (20%		344 (19%)	
II	12 (17%)	182 (16%)	0.549	318 (17%)	0.648
III	13 (18%)	184 (17%)		308 (17%)	
IV	37 (52%)	528 (48%)		885 (48%)	
Time interval from completion of radiation therapy					
12-23 months	24 (34%)	321 (29%)		515 (28%)	
24-35 months	11 (15%)	285 (25%)	0.148	498 (27%)	0.117
36-47 months	21 (30%)	246 (22%)		429 (23%)	
48-59 months	15 (21%)	267 (24%)		424 (23%)	
Rehabilitation needs measured by the REHPA scale[b]		*(n=1108)*			
< 3	22 (31%)	521 (47%)			
≥ 3	49 (69%)	536 (48%)	**0.007**		
No goals	0	11 (1%)			
Don't know	0	40 (4%)			
Nutritional risk (NRS 2002)[b]		*(n=976)*	0.648		
≥ 3 points	4 (6%)	78 (8%)			
Nutritional risk and deficit (PG-SGA SF)[b]	*(n=70)*	*(n=1064)*			
4-8 points	30 (43%)	291 (37%)	**0.009**		
≥ 9 points	10 (14%)	128 (12%)	0.571		
BMI category[b]		*(n=998)*			
Underweight (BMI <18.5)	1 (1%)	48 (5%)			
Normal weight (BMI 18.5-24.9)	34 (48%)	464 (47%)	0.643		
Overweight (BMI 25.0-29.9)	25 (35%)	353 (35%)			
Obese (BMI ≥ 30.0)	11 (15%)	133 (13%)			
Current body weight vs. precancer body weight[b]	*(n=68)*	*(n=1021)*			
<95%	35 (51%)	492 (48%)			
95-105%	27 (40%)	417 (41%)	0.859		
>105%	6 (9%)	112 (11%)			
Participant's evaluation of own body weight[b]		*(n=1117)*			
- Too low	8 (11%)	198 (18%)			
- Appropriate	30 (42%)	508 (45%)	0.191		
- Too high	33 (46%)	411 (37%)			

NRS 2002: Nutritional Risk Screening 2002, PG-SGA SF: The Scored Patient Generated Subjective Global Assessment Short Form, BMI: Body mass index.

Data are presented as means ± standard deviations or numbers and (percentages). Significant p-values are highlighted in bold. The PG-SGA SF score can range from 0-36, and NRS 2002 score can range from 0-7. On both scales, a higher score indicates a greater nutritional risk. REHPA scale ranges from ranges from 1-9, and a higher score indicates greater rehabilitation needs.

[a] Differences between NUTRI-HAB trial participants and the given population is tested with two-sample two-sided t-test for weight and Fisher's Exact test for other variables.
[b] Self-reported data collected through the NUTRI-HAB survey

Appendix 5: Related publications and scientific contributions during the PhD programme

Appendix 5: Related publications and scientific contributions during the PhD programme

Peer-reviewed articles

Kristensen MB, Wessel I, Ustrup KS, Dieperink KB, Zwisler AD. **Nutrition screening and assessment tools for cancer patients and cancer survivors: a systematic review protocol.** *Manuscript in review for BMJ Open.*

Kristensen MB, Isenring E, Brown B. **Nutrition and swallowing therapy strategies for patients with head and neck cancer**. *Nutrition*. 2020;69:110548. https://doi.org/10.1016/j.nut.2019.06.028

Other publications

Kristensen MB. **Rehabilitering gennem mad og måltider kan hjælpe, når hoved-halskræft giver skår i madglæden** [Nutritional rehabilitation helps when head and neck cancer affects enjoyment with eating] Diætisten. 2019. 27;161:16-17.

Kristensen MB. **Mennesker med hoved-halskræft har store problemer med at spise. De mister glæden ved mad og savner livskvalitet** [Individuals with head and neck cancer have substantial eating problems. They lose the enjoyment with eating and lack quality of life], in: Rasmussen A, Skov Ustrup K, Fly Haastrup A, Zwisler AD (ed.) MAD, MÅLTIDER & LIVSKVALITET: Ernæringsrehabilitering til mennesker med livstruende sygdom [Food, Meals and Quality of Life - Nutritional rehabilitation for individuals with life threatening disease] , REHPA Videncenter for Rehabilitering og Palliation, sep. 2019,6-9.

Contributions to scientific conferences

Oral presentations

Kristensen MB, Mikkelsen TB, Beck AM, Zwisler AD, Wessel I, Dieperink KB.
To eat is to practice - Everyday Challenges of Head and Neck Cancer Survivors.
Annual congress in The Australasian Society of Parenteral and Enteral Nutrition (AuSPEN), Sydney, Australia, November 2018.

Kristensen MB, Dieperink KB, Rossau HK, Egholm CL, Viggers L, Bertelsen BM, Zwisler AD.
Dietary interventions in cardiac rehabilitation – the gap between guidelines and clinical practice,
Nordic Implementation Conference, Copenhagen, Denmark, May 2018.

Kristensen MB, Dieperink KB, Zwisler AD; **Nutritional challenges in cancer survivors**,
Annual meeting in Danish Society for Clinical Nutrition and Metabolism (DAPEN), Copenhagen, Denmark, May 2018.

Accepted abstracts

Kristensen MB, Zwisler AD, Dieperink KB, Beck AM, Wessel I.
Danish head and neck cancer survivors have adapted to the high symptom burden 1-5 years after radiation therapy – results from a nationwide cross-sectional survey on health-related quality of life.
Accepted for oral presentation at European Congress of Head and Neck Oncology (ECHNO) 2020, Brussels, Belgium (postponed due to COVID-19).

Kristensen, MB, Mikkelsen TB, Wessel I, Beck AM, Dieperink KB, Møller JJK, Zwisler AD.
Effect of a multidisciplinary residential nutritional rehabilitation programme in head and neck cancer survivors - The NUTRI-HAB RCT.
Accepted for e-poster presentation at 2020 Annual Meeting of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO), Seville, Spain (postponed to 2021 due to COVID-19).

Kristensen, MB, Dieperink KB, Beck AM, Wessel I, Zwisler AD.
Unmet rehabilitation needs of Danish head and neck cancer survivors.
Accepted for oral presentation at Rehabilitation International World Congress 2020, Copenhagen, Denmark (postponed to 2021 due to COVID-19).