ADVANCES IN MEDICAL NUTRITION: STRATEGIES AND INNOVATIONS IN DIETETICS, OBESITY MANAGEMENT, AND NUTRITIONAL SUPPORT

Inauguraldissertation
zur
Erlangung der Würde eines Doktors der Philosophie
vorgelegt der
Philosophisch-Naturwissenschaftlichen Fakultät
der Universität Basel

von

Katja Angela Schönenberger

2024

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät
auf Antrag von

Erstbetreuer: Prof. Dr. pharm. Stefan F. Mühlebach

Erstbetreuer: Prof. Dr. med. Zeno Stanga

Zweitbetreuer: Prof. Dr. Christoph R. Meier

Externer Experte: Prof. Dr. med. Cornel C. Sieber

Basel, den 20. Juni 2023

Prof. Dr. Marcel Mayor
(Dekan)

Dedicated to my family and partner,
whose belief in me has never wavered,
and whose support has enabled me
to pursue my academic endeavors.

"One cannot think well, love well, sleep well, if one has not dined well."
Virginia Woolf (1882-1941)

ACKNOWLEDGEMENTS

I am immensely grateful to all individuals and institutions who have provided invaluable support throughout my doctoral research. Prof. Dr. med. Zeno Stanga and Prof. Dr. pharm. Stefan Mühlebach have my sincerest appreciation for welcoming me into their "nutrition family" and for their expert guidance, encouragement, and inspiration. My gratitude also extends to Prof. Dr. phil. Christoph Meier for his exceptional supervision and mentorship, as well as Prof. Dr. med. Cornel Sieber for serving as the external expert. Special thanks to Dr. phil. Emilie Reber and Valentina Huwiler, who have been invaluable allies on this journey and provided generous support.

I would like to acknowledge the collaboration and support of numerous colleagues on various projects. To name but a few, I am grateful to PD Dr. med. Angelika Hammerer-Lercher for welcoming me to do the aluminum analysis in parenteral nutrition in her laboratory, and particularly to Christoph Saxer and Peter Neyer for their support and collaboration. Many thanks to Prof. Dr. med. et phil. Lia Bally for enabling and supervising the PBH Forecast study, and to all collaborators on this project. I extend my gratitude to Prof. Dr. med. David Fäh and Dr. phil. Giulia Pestoni for their supervision and guidance on the *menuCH* analyses. Additionally, I am grateful to Fresenius Kabi (Schweiz) AG and the collaborators of the eSwissHPN project, particularly Dr. med. Michèle Leuenberger, for their major contributions to its success.

I also wish to thank all my colleagues at the Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM) and beyond for their friendship and stimulating exchange. The administrative support provided by Laura Götschi and the research management board was invaluable and I am deeply grateful for the assistance of UDEM's study nurses. I would like to thank my students, Flurina von Blumenthal, Noah Näf, Stefanie Penitzka, Anne-Catherine Schüpfer, Céline Stebler, and Duy-Tan Vu, for their trust and dedication.

My heartfelt thanks go to my parents, Peter and Angela, my sister Nicole, and my partner Aurel, for their unwavering support and encouragement throughout my academic journey. Without their support, obtaining this PhD would have been impossible. Finally yet importantly, I extend my gratitude to all patients who have contributed to my research.

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

AIO	all-in-one
BMI	body mass index
CGM	continuous glucose monitoring
CIF	chronic intestinal failure
CLABSI	central line-associated bloodstream infection
CRBSI	catheter-related bloodstream infection
CRVT	catheter-related venous thrombosis
DGEM	German Society for Nutritional Medicine (in German: Deutsche Gesellschaft für Ernährungsmedizin)
EFFORT	Effect of early nutritional support on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial
EN	enteral nutrition
ESPEN	European Society for Clinical Nutrition and Metabolism
GLIM	Global Leadership Initiative on Malnutrition
GLP-1	glucagon-like peptide-1
HCP	health care professional
HPN	home parenteral nutrition
NNT	number needed to treat
NOURISH	Nutrition effect On Unplanned ReadmIssions and Survival in Hospitalized patients
NRS 2002	Nutritional Risk Screening 2002
NST	nutritional support team
ONS	oral nutritional supplements
PBH	post-bariatric hypoglycemia
PICC	peripherally inserted central catheter
PN	parenteral nutrition
PNALD	parenteral nutrition-associated liver disease
QOL	quality of life
RCT	randomized controlled trial
RYGB	Roux-en-Y gastric bypass
TEN	total enteral nutrition
TPN	total parenteral nutrition
UDEM	Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism

SUMMARY

This dissertation examines and adds to strategies and innovations in medical nutrition, covering more specifically the areas of dietetics, obesity management, and nutritional support. Medical nutrition encompasses all nutritional interventions under medical or nursing supervision as well as the structure, conception, and scientific derivation of these interventions. Medical nutrition overlaps with clinical nutrition but extends to nutritional care for selected healthy individuals.

1. Dietetics

Dietetics includes nutritional assessment and dietary advice with and without nutrition therapy to modify normal nutrition in cases of food allergies, intolerance, and disease, as well as secondary prevention and treatment of specific nutrient deficiencies. Within dietetics, we explored dietary fiber deficiency and its prevalence and found that 87% of the general Swiss population do not achieve the recommended intake of 30 g/day. Dietary fiber intake and ultra-processed food consumption exhibited an inverse dose-dependent association. Moreover, we examined the effects of potentially anti-inflammatory diets (Mediterranean, vegetarian, vegan, and ketogenic) on rheumatoid arthritis through a meta-analysis. These diets led to significant improvements in pain, health assessment questionnaire scores, and swollen joint counts, although the inflammatory markers did not improve.

2. Obesity Management

The clinical nutrition area of obesity management covers the prevention and treatment of obesity and related disorders, including bariatric surgery, and complements public health interventions. Post-bariatric hypoglycemia (PBH) is a frequent complication of bariatric surgery, particularly Roux-en-Y gastric bypass. This condition manifests as recurrent postprandial hypoglycemic events with potentially critical outcomes, such as loss of consciousness, and diminished quality of life (QOL). The PBH Forecast project aimed to prevent hypoglycemic events in patients with PBH and to establish a sustainable strategy for hypoglycemia correction. Hence, we collected data on continuous blood glucose levels, meal intake, symptoms, heart rate, and physical activity during a 50-day observational phase (n = 50). Concurrently, we conducted a randomized crossover clinical trial (n = 8) to investigate different nutritional strategies (15 g glucose vs. 5 g glucose vs. a combination of 10 g protein and 5 g carbohydrate) to correct mixed meal induced hypoglycemia. Our results suggested that diabetes-inspired guidelines for correcting

hypoglycemia with 15 g are not suitable for PBH and that an excessive glucose load may induce rebound hypoglycemia. While none of the tested strategies was unequivocally superior, a lower dose appears to adequately elevate glucose levels outside the critical range, and supplementary nutrients such as proteins may offer glycemia-stabilizing benefits. At present, a randomized controlled trial is testing an intervention for hypoglycemia prevention that combines a hypoglycemia prediction model developed using data from the above-mentioned observational phase with a preventive nutritional intervention, i.e. administering 10 g of glucose before reaching hypoglycemia at a time point dictated by the prediction model.

3. Nutritional Support

Nutritional support involves the provision of food or nutrients through conventional nutrition, special diets, food fortification, and medical nutrition therapy (oral nutritional supplements, enteral nutrition, and parenteral nutrition [PN]), as well as concurrent therapies to promote food intake, to prevent or treat malnutrition and improve clinical outcomes and QOL. If medical nutrition therapy is required over a long period, it can be administered outside the hospital, such as home PN (HPN). This requires specialized care and patient monitoring to prevent potentially life-threatening complications.

3.a) Improvements of Outcomes with eHealth

We explored the potential of eHealth to support and improve the QOL and quality of care of patients with HPN by distant monitoring and counseling. To this end, we conducted a multicenter survey on the attitudes and expectations of patients with HPN towards eHealth and substantiated the need for digital support in this population. Subsequently, we developed a smartphone application for patients and a web-based dashboard for health care professionals (HCPs), centered around a patient journal and videoconference consultations. This provides the data for remote monitoring and enables counseling through timely short consultations and interventions as needed despite physical distance, replacing the traditional model of infrequent lengthy consultations. This eHealth platform is currently undergoing evaluation in a nationwide multicenter project.

3.b) Risk Assessment of Toxic Aluminum Exposure Through Parenteral Nutrition

The long-term administration of PN increases the relevance of chronic exposure to potentially toxic contaminating components like aluminum. Currently, a new chapter of the European Pharmacopoeia (Ph. Eur.) is under development to limit the risk of

exposure to toxic levels of aluminum through PN. We developed an innovative and highly sensitive analytical method using inductively coupled plasma mass spectrometry to quantitatively measure aluminum and other elements in very low concentrations in commercial products used for all-in-one PN admixtures. Our findings reveal that commercial products can contain critical aluminum concentrations, emphasizing the necessity for regulatory measures to guarantee quality.

In summary, the evolving landscape of medical nutrition is placing an increasing emphasis on patient-reported outcomes and QOL to be supported by preventive actions. Customized digital solutions and eHealth have the potential to enhance patient-reported outcomes, patient safety, and the quality of care while demanding interprofessional collaboration and research among HCPs, scientists, engineers, legal experts, and end users. Such cooperation is required to produce a clinically useful tool that adheres to data security and privacy regulations as well as medical device regulations. These innovations have the potential to advance medical nutrition and to improve nutrition therapy and support. The thesis substantiated advances in medical nutrition in several projects in different populations as well as scientific lab investigations. The data are published or under review in peer-reviewed journals fulfilling the necessary scientific quality.

INTRODUCTION

Nutrition is a fundamental aspect of both daily life and medicine. A healthy diet is pivotal to long-term health, with the potential to prevent or delay the onset of non-communicable diseases. Conversely, acute and chronic diseases can affect food intake and metabolism, such as increasing catabolism, resulting in nutrition-related conditions associated with increased morbidity and mortality [1].

1. Terminology

1.1. Medical and Clinical Nutrition

Adherence to universally accepted, evidence-based professional jargon and standard terminology is crucial for addressing nutritional disease prevention and therapy [1]. However, as a naturally evolving field, nomenclature in nutrition is often inconsistent, posing challenges to professional and scientific discourse [2]. This dissertation is based on the terminology of clinical nutrition proposed by the German Society for Nutritional Medicine (DGEM), as illustrated in Figure 1.

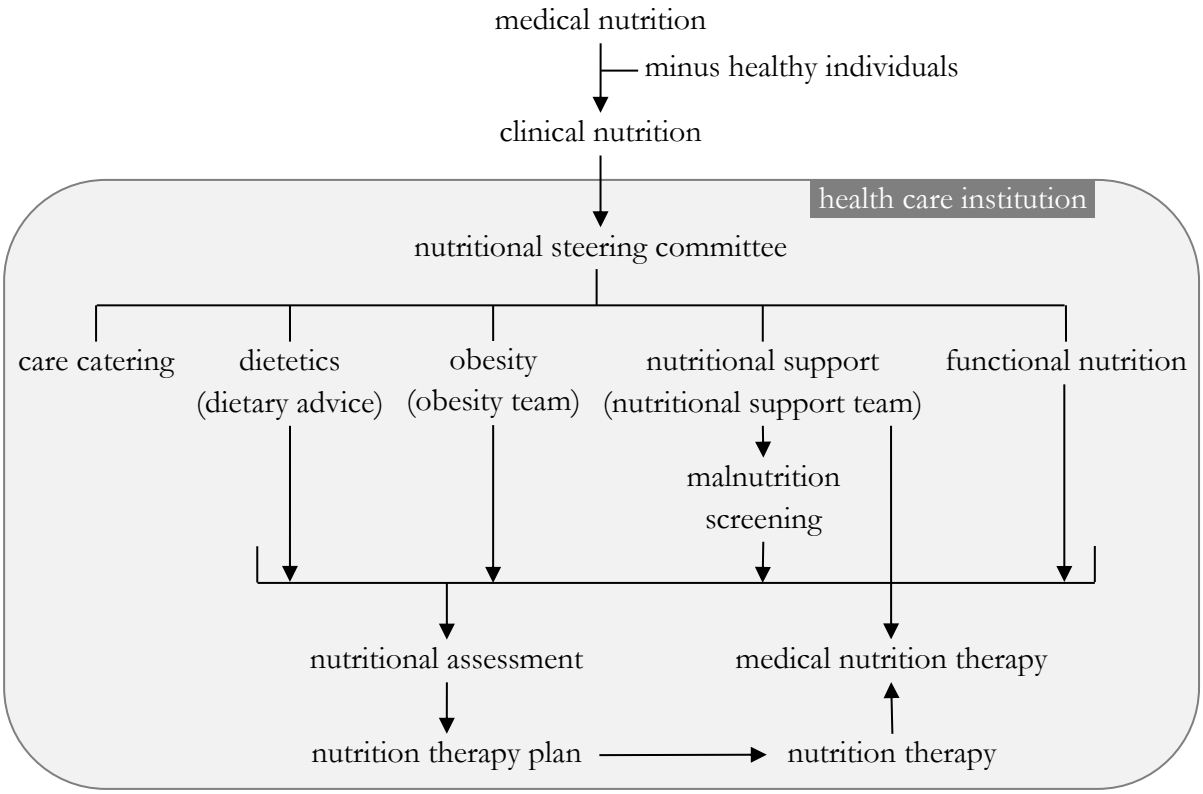


Figure 1: Taxonomy of terms in medical nutrition (adapted from [1, 3])

The term **medical nutrition** encompasses all nutritional interventions for both diseased and, in special cases, healthy individuals under medical or nursing supervision as well as their structure, conception, and scientific derivation. Medical

nutrition is almost synonymous with the term clinical nutrition but additionally includes nutritional care for select healthy individuals, provided that it occurs within the context of medical care. Examples of this include pregnant women and competitive athletes [2].

Clinical nutrition targets diseased patients and comprises "all research, practice, and theory of nutritional care provided by clinicians [physicians, pharmacists, dietitians, nurses] to inpatients, outpatients, or nursing home residents" [3]. The European Society for Clinical Nutrition and Metabolism (ESPEN) defines clinical nutrition as a "discipline that deals with the prevention, diagnosis, and management of nutritional and metabolic changes related to acute and chronic diseases and conditions caused by a lack or excess of energy and nutrients" [1]. Clinical nutrition aims to improve clinical outcomes, restore health, promote and accelerate recovery, maintain and enhance performance and maintain or improve quality of life (QOL) [2]. Within health care institutions, clinical nutrition can be divided into seven structural elements or responsibility areas: research, nutritional steering committee, care catering, dietetics, obesity, nutritional support, and functional nutrition (Figure 2) [2, 3]. The **nutritional steering committee** consists of institutional decision-makers and delegates from various clinical nutrition areas, creating institution-wide binding standards for clinical nutrition such as structure and processes [2]. **Care catering** is the provision of meal services in health care facilities (in-house or outsourced) according to the criteria of healthy nutrition or, in special cases, evidence-based criteria for disease-specific nutrition. Structural measures to facilitate food intake also fall into this area [2]. **Dietetics** includes nutritional assessment and dietary advice with and without nutrition therapy to modify normal nutrition in cases of food allergies, intolerances, and diseases. It involves modifying conventional nutrition for gastrointestinal symptom management, and secondary prevention and treatment of specific nutrient deficiencies [2]. **Nutrition therapy** is a nutritional intervention with a clear therapeutic goal to treat a nutrition-related condition [1, 2]. The **obesity** area is responsible for the individualized prevention and treatment of obesity and related disorders, including bariatric surgery, and complements public health interventions [2, 3]. **Nutritional support** is the provision of food or nutrients through oral nutrition (conventional nutrition, special diets, food fortification, or oral nutritional supplements [ONS]), enteral nutrition (EN), or parenteral nutrition (PN) to prevent or treat malnutrition and to improve clinical outcomes and QOL. Concurrent therapies to promote food intake, nutrient absorption, or metabolism are also a part of nutritional support (eg, enzyme substitution) [2]. **Functional nutrition** is the provision of food or specific nutrients to improve bodily functions such as disease-specific metabolism, specific organ and tissue functions, immunologic response,

disease activity, and systemic inflammatory processes [3]. It is important to note, as depicted in Figure 2, that these areas are not mutually exclusive, implying that a patient or disease may have nutrition-related issues spanning more than one area. An illustrative example is a malnourished obese patient who may require nutritional support. The research serving as the foundation for this dissertation belongs to or is relevant for dietetics, obesity management, or nutritional support. Consequently, the following chapters delve into these three domains, with an emphasis on aspects pertinent to the papers incorporated into the results section.

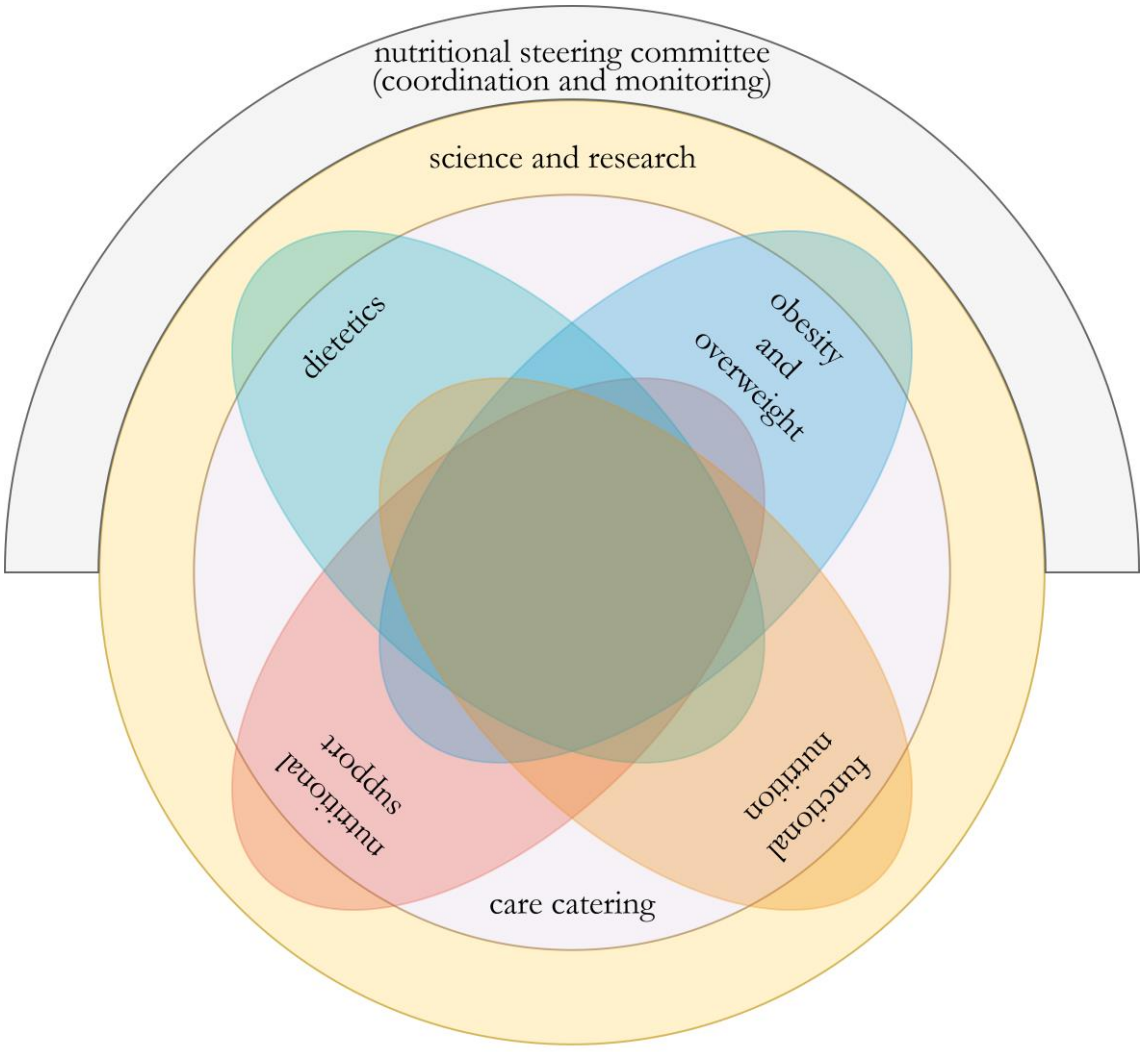


Figure 2: Structure of clinical nutrition in health care facilities (adapted from [4])

1.2. eHealth

Patients and health care professionals (HCPs) increasingly utilize technologies in health care with the potential to improve patient outcomes via better quality of care, easier and timely health care access, and reduced costs [5]. eHealth Suisse, the Swiss competence and coordination center of the confederation and the cantons, understands eHealth or electronic health services as the integrated use of information and communication technology to design, support and network all processes and

actors in the health care system [6]. Other frequently used terms include telehealth, telemedicine, and mHealth. The World Health Organization defines these as part of eHealth:

- "**eHealth** is the cost-effective and secure use of information and communications technologies in support of health and health-related fields, including health-care services, health surveillance, health literature, and health education, knowledge and research" [7].
- The synonyms **telehealth** and **telemedicine** [8] denote "the delivery of health care services, where patients and providers are separated by distance. Telehealth uses information and communications technologies for the exchange of information for the diagnosis and treatment of diseases and injuries, research, and evaluation" [9].
- **mHealth**, also known as mobile health, is the use of mobile devices, such as smartphones, patient monitoring devices [eg, continuous glucose monitoring (CGM)], and wireless devices, for medical and public health practice. mHealth applications include adherence, community mobilization, collection of community and clinical health data, wellness and self-care, chronic disease management, and remote patient monitoring [9].

2. Dietetics

Dietetics is a part of medical and clinical nutrition that encompasses nutrition history, dietary assessment, and dietary advice and counseling with or without nutrition therapy in order to modify the regular diet for various health conditions as well as secondary prevention and treatment of specific nutrient deficiencies [2, 3]. These conditions may include food allergies and intolerance, autoimmune diseases, congenital diseases, metabolic diseases, organ or tissue diseases, and gastrointestinal symptoms [2]. Dietetics aims to prevent or treat disease-specific disorders and maintain or improve QOL [2]. However, dietetics does not include nutritional care to prevent or treat obesity or disease-related malnutrition, which fall under obesity management (Chapter 3) and nutritional support (Chapter 4), respectively [3].

Dietary advice, which is the provision of recommendations or training on modifying food intake to improve nutrition or manage a disease, should be provided by qualified persons such as registered dietitians or professionals with equivalent qualifications and is typically prescribed by a physician [3]. A therapeutic diet is defined as prescribed food and fluid intake, where the type, quantity, or timing of food intake are regulated for therapeutic reasons [2]. Therapeutic diets aim to treat or prevent diseases or clinical conditions by eliminating, reducing, or increasing

certain substances in foods, such as gluten-free or lactose-free diets [2]. DGEM explicitly includes dietary modification for autoimmune diseases in the definition of dietetics [2], such as the Mediterranean, vegetarian, and vegan diets for rheumatoid arthritis investigated in this thesis.

2.1. National Nutrition Survey *menuCH*

Establishing a thorough understanding of the baseline diet is essential for effectively modifying the regular diet for therapeutic or preventive purposes. This involves a detailed nutritional assessment, including potential nutritional deficiencies and unfavorable dietary habits. Hence, it is important to study the diets of the general population. While this falls within the scope of nutrition sciences and public health and is thus a subject of practical and scientific work by nutritionists from non-medical backgrounds [2], the findings are highly relevant to the area of dietetics, especially for preventive measures.

The first national nutrition survey in Switzerland, *menuCH*, provided representative data on food consumption, lifestyle, and dietary behavior in the general population. Conducted from January 2014 to February 2015, it targeted 2000 men and women, aged 18 to 75 years, from all regions of Switzerland. The data collected were based on food recalls, questionnaires, and anthropometric measurements. The data allowed for the review and revision of current dietary recommendations, identifying potential food-related risks, and supporting research and development in nutrition, food, and behavioral sciences. The ultimate goal of *menuCH* was to explore and understand the dietary habits and physical activity of people living in Switzerland in order to enhance public health, food safety, and QOL.

3. Obesity and Post-Bariatric Hypoglycemia Management

Overnutrition is defined by ESPEN as "supplying nutrients in excess of requirements leading to increased storage of body stores" [10]. Such a surplus of macronutrient intake results in the accumulation of excessive energy in adipose tissue and obesity in the long-term [10]. Obesity is linked to alterations in body composition and function, increased risk of diseases including type 2 diabetes, cardiovascular disease, depression, arthritis, cancer, and decreased life expectancy. Furthermore, it is accompanied by a low-grade inflammatory state that exacerbates the metabolic changes. Increasingly, overnutrition is recognized as a form of malnutrition, implying that overweight and obese individuals can at the same time be malnourished [11].

The management of obesity incorporates nutritional care to treat or prevent obesity in both in- and outpatient settings. It comprises individualized, patient-centered, and

comprehensive weight management and lifestyle programs, taking into account comorbidities and behavioral, cultural, psychosocial, and economic factors [2]. Nutritional care to treat or prevent obesity and related disorders is complementary to public health interventions [3]. Obesity management also includes pre- and post-bariatric surgery care, with additional perioperative care, such as nutritional training, nutritional assessment, monitoring of nutritional status, and psychological support [2].

3.1. Bariatric Surgery

In cases of class III obesity (body mass index [BMI] of 40 kg/m^2 or higher), substantial weight loss can be achieved through bariatric surgery. The incidence of bariatric surgery has seen a global increase [12], with an approximate doubling in the number of such procedures over the past decade in Switzerland. Approximately 5000 surgeries are performed annually in Switzerland, with 80% being Roux-en-Y gastric bypasses (RYGB) [13].

RYGB involves creating a small stomach pouch (limiting food intake) and reconfiguring the small intestine (reducing nutrient absorption). Specific techniques and resulting limb lengths may vary among surgeons. Generally, the stomach is divided to form a pouch without a pylorus, and the small intestine is restructured into a Y-shape by cutting it 30-50 cm below the duodenojejunal junction (ligament of Treitz). The distal end is connected to the stomach pouch, forming the alimentary or Roux limb. The proximal end is reconnected through a side-to-side jejunojejunal anastomosis, forming the biliopancreatic limb [14].

Historically, bariatric surgeries have been categorized as purely restrictive, malabsorptive, or a combination of both, with the aim of limiting food consumption, decreasing nutrient absorption, or both. However, it is now understood that these anatomical changes influence gastrointestinal function, which, in turn, affects digestion and nutrient absorption. RYGB surgery reduces gastric acid production, accelerates liquid gastric emptying, and increases bile acid levels in the blood. However, its effects on intestinal pH, solid gastric emptying, intestinal transit time, gastric enzyme secretion, and surface area remain largely undetermined [14].

Despite the marked beneficial effects of bariatric surgery on diabetes, hypertension, and dyslipidemia remission [15], cancer incidence [16], and all-cause mortality [17, 18], adverse events may occur with a complication rate of 17% [15]. These include gastrointestinal and nutrition-related hospital admissions, malnutrition, nutritional deficiencies (eg, iron, calcium, and vitamins D, B12, B1, and B9), osteomalacia, and dumping syndrome, including post-bariatric hypoglycemia (PBH) [19].

3.2. Post-Bariatric Hypoglycemia

Postprandial hyperinsulinemic hypoglycemia after bariatric surgery or PBH is a metabolic disorder characterized by recurrent hypoglycemic events occurring after bariatric surgery and other upper gastrointestinal surgeries. Figure 3 shows 24-hour fluctuations in glucose levels in patients with PBH observed in work package 1 of the PBH Forecast study (chapter 3.2.4). The disorder typically manifests one year or more after surgery, with hypoglycemia occurring one to three hours after dietary intake, particularly when containing a high proportion of rapidly available carbohydrates [20]. Hypoglycemic episodes may present with typical autonomic symptoms (eg, trembling, anxiety, palpitations, perspiration), neuroglycopenic symptoms (eg, fatigue, concentration difficulties, confusion, vision changes), and nonspecific symptoms (eg, headache, nausea, sweating). Severe hypoglycemia can lead to serious consequences such as seizures, loss of consciousness, falls, traffic accidents, and even death. The disability and diminished QOL associated with PBH can be severe, and there is no evidence that the condition remits over time. The prevalence reported in the literature varies owing to differences in the diagnostic criteria. Recent studies suggest that approximately 30% of patients who have undergone bariatric surgery experience PBH [21], with a higher prevalence among those with RYGB [22]. Furthermore, a significant proportion of patients with PBH may be asymptomatic [21, 23-25], implying that the prevalence could be higher than estimated [26]. Asymptomatic hypoglycemia can have serious consequences for patients with PBH. For example, a recent study conducted at the Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM) of the Inselspital found no difference in symptom perception following the ingestion of 75 g glucose versus placebo (aspartame), yet driving performance was significantly impaired after glucose ingestion [27].

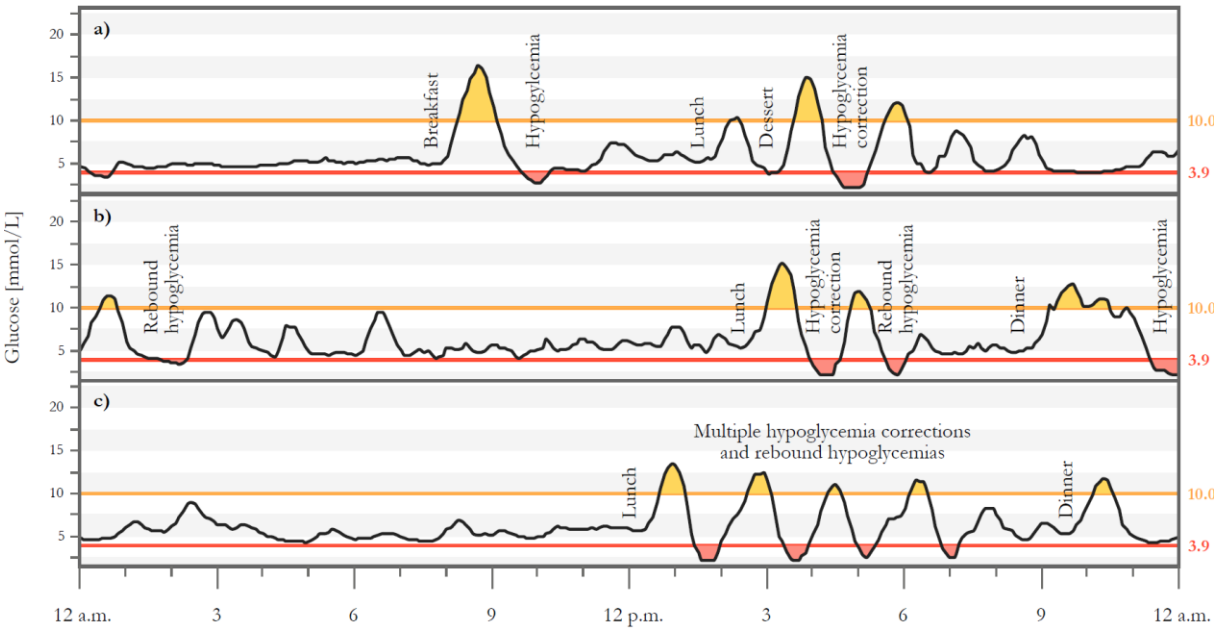


Figure 3: Fluctuations in glucose levels in patients with post-bariatric hypoglycemia traced using continuous glucose monitoring. a) Postprandial hypoglycemia after breakfast and lunch. b) Postprandial hypoglycemia after lunch and dinner, and correction-induced rebound hypoglycemia, with glucose fluctuations after dinner on the previous day extending into the night (hyperglycemia after midnight and rebound hypoglycemia between 2 and 3 a.m.). c) Postprandial hypoglycemia after lunch and multiple instances of correction-induced rebound hypoglycemia (yo-yo effect).

3.2.1. Pathophysiology

Although the understanding of the pathophysiology of PBH remains incomplete [26], it is hypothesized that a combination of factors, including accelerated nutrient absorption and increased secretion of insulinotropic gut factors such as glucagon-like peptide-1 (GLP-1), are associated with excessive postprandial insulin secretion in patients with PBH [28]. These factors are related to the altered gastrointestinal anatomy after bariatric surgery, particularly RYGB. Rapid nutrient delivery into the jejunum increases the rate of glucose absorption. After RYGB, 45% of glucose appears in the bloodstream within the first hour of oral ingestion of 75 g of glucose, compared with 30% preoperatively [29]. Over time, changes in glucose transporter density and intestinal epithelium (entero-plasticity) may further enhance glucose absorption [30]. The resulting early postprandial glucose peak stimulates pancreatic cells, and is amplified by insulinotropic gut factors, resulting in the incretin effect [20, 31-33]. This theory is supported by research indicating that symptoms do not occur and glucose and insulin curves remain normal when carbohydrates are administered via gastrostomy in the bypassed stomach [34]. Further mechanisms, such as reduced neuroendocrine counterregulation, altered bile acids, and reduced insulin clearance, may also contribute to PBH [35-38].

3.2.2. Diagnosis

As there are no universally accepted criteria for diagnosing PBH, a detailed history is required. Therefore, a comprehensive patient journal, including a diet record, hypoglycemia symptoms, and glucose level measurements, either through self-measured capillary glucose measurements or a CGM sensor, is imperative [39]. Glucose levels below 3.0 mmol/L are considered clinically significant hypoglycemia due to their association with neuroglycopenic symptoms and consequences in patients with diabetes [40], which is also applicable to PBH [41]. As neuroglycopenic symptoms may disappear with repeated hypoglycemia, leading to a high rate of hypoglycemia unawareness, the presence of symptoms is increasingly being questioned for relevance in diagnosis [24].

Provocative tests, such as mixed meal tolerance tests, can confirm a PBH diagnosis, whereas oral glucose tolerance tests have been found to be less useful in this population [39, 42, 43]. A mixed meal tolerance test involves the ingestion of a standardized meal of carbohydrates, protein, and fat (eg, a bread roll with butter and jam, and a sugar-sweetened yoghurt) in a fasted state. Glucose, insulin, and ideally glucagon levels are measured at baseline and at regular intervals thereafter, including upon detection of hypoglycemia.

Although there is no universally accepted definition of PBH, the following criteria may help to identify most patients:

- Postprandial hypoglycemia < 3.0 mmol/L one to three hours after meal intake (particularly after carbohydrate-rich meals)
- Normal fasting glucose and insulin levels
- Hyperinsulinemia before hypoglycemia with insufficient insulin suppression during hypoglycemia
- Inadequate glucagon response to hypoglycemia
- Asymptomatic presentation or with neuroglycopenic, autonomic, or nonspecific symptoms

PBH should be differentiated from early dumping syndrome and idiopathic reactive hypoglycemia. Early dumping syndrome typically presents within one hour (usually 15 to 30 minutes) after eating and is characterized by gastrointestinal (eg, bloating, abdominal pain, nausea, diarrhea) and vasomotor symptoms (eg, palpitations, perspiration, tachycardia, and hypotension) but lacks neuroglycopenic symptoms. This syndrome arises from rapid gastric emptying and hyperosmolar nutrient transition to the jejunum. Hyperosmolarity induces a shift of intravascular fluid into the intestinal lumen, and the resulting reduction in intravascular blood volume

coupled with intestinal wall distension leads to increased vagal tone. This, along with the release of various gastrointestinal peptide hormones, such as neurotensin and vasoactive intestinal peptides, triggers the characteristic symptoms [20]. In contrast, idiopathic reactive hypoglycemia affects individuals without bariatric surgery, predominantly normal-weight adolescents, and is characterized by recurrent symptomatic postprandial hypoglycemic episodes. The pathophysiology of this condition remains elusive [20].

3.2.3. Treatment and Management

Given that rapid glucose absorption is the central mechanism underlying PBH, the initial therapeutic approach centers on dietary modifications, particularly because there are no approved pharmacological treatments. Strategies to limit postprandial glucose peaks include reducing carbohydrate consumption, selecting low-glycemic index carbohydrates, and consuming carbohydrates along with other macronutrients [26]. Limiting meals to 30 g of carbohydrates in solid form or 28 g in liquid form with a low glycemic index can effectively prevent hypoglycemia in patients with PBH [44]. By increasing the protein content in meals, the nadir plasma glucose concentration can be increased by 13%, leading to reductions in insulin, GLP-1, and gastric inhibitory polypeptides as well as increased glucagon secretion [45]. Fats, serving as an alternative calorie source, do not trigger excessive insulin secretion and can stabilize postprandial glycemia [46]. Typically, meals for PBH patients should comprise 30% carbohydrates, 45-50% fats, and 20-25% protein. High fiber intake can slow glucose absorption, fluid intake should be separated from meals, and consumption of rapidly absorbed semi-solid or liquid meals should be limited [47-49]. Table 1 summarizes the nutritional strategies for managing PBH.

Hypoglycemia should be adequately corrected to increase the safety of patients with PBH. Importantly, standard dietary recommendations for diabetes are not suitable for PBH patients, necessitating tailored guidelines for hypoglycemia correction in the post-bariatric population [26]. Overcorrection of hypoglycemia with an excessively high glucose load can lead to rebound hypoglycemia, necessitating repeated corrections and possibly leading to a yo-yo effect (Figure 3) [50-52]. Additionally, appropriate correction strategies for PBH may involve the combined intake of glucose and amino acids or caffeine [45, 53-55].

Table 1: Dietary modifications for post-bariatric hypoglycemia (adapted from [26])

Carbohydrate quantity	– ≤ 30 g per meal – Several small meals spread throughout the day
Carbohydrate quality	– High-fiber starch sources (eg, whole grains, legumes) – Avoiding rapidly absorbed carbohydrates (eg, sugar/sweets) or substituting with sugar-free alternatives
Protein and fat	– Consistently combining carbohydrates with foods high in fat, protein, and vegetables/salad – Foods rich in protein/fat should provide > 70% of the energy per meal – Specific amino acids may increase endogenous glucagon (eg, arginine)
Meal pattern	– Dessert/snack 90 minutes after meals (to counter a rapid blood glucose decrease) – Avoiding liquids with meals
Soluble dietary fibers	– Addition of soluble dietary fiber (eg, guar/pectin) to decelerate carbohydrate absorption

3.2.4. PBH Forecast Project

The overall aim of the PBH Forecast project was to prevent hypoglycemic events in patients with PBH and to establish a sustainable strategy for hypoglycemia correction. This study consisted of three work packages (Figure 4):

1. Observational study: This phase involved fitting patients with a blinded CGM sensor for glucose level tracking, a smartwatch for tracking heart rate and physical activity, and a smartphone application for logging food intake and symptoms. The collected data were utilized to develop a model aimed at predicting postprandial hypoglycemia.
2. Randomized crossover trial: Three interventional visits to evaluate various nutritional strategies (5 g of glucose, 15 g of glucose, and a combination of 10 g of protein and 5 g of carbohydrates) in terms of achieving sustainable hypoglycemia correction, thereby minimizing the duration of hypoglycemia without causing rebound hyperglycemia and hypoglycemia.
3. Randomized controlled trial (RCT): One interventional visit to assess the efficacy of an intervention for hypoglycemia prevention that combines a hypoglycemia prediction model (developed using data from work package 1) with a preventative nutritional action (investigated in work package 2) versus hypoglycemia correction upon plasma glucose < 3.0 mmol/L.

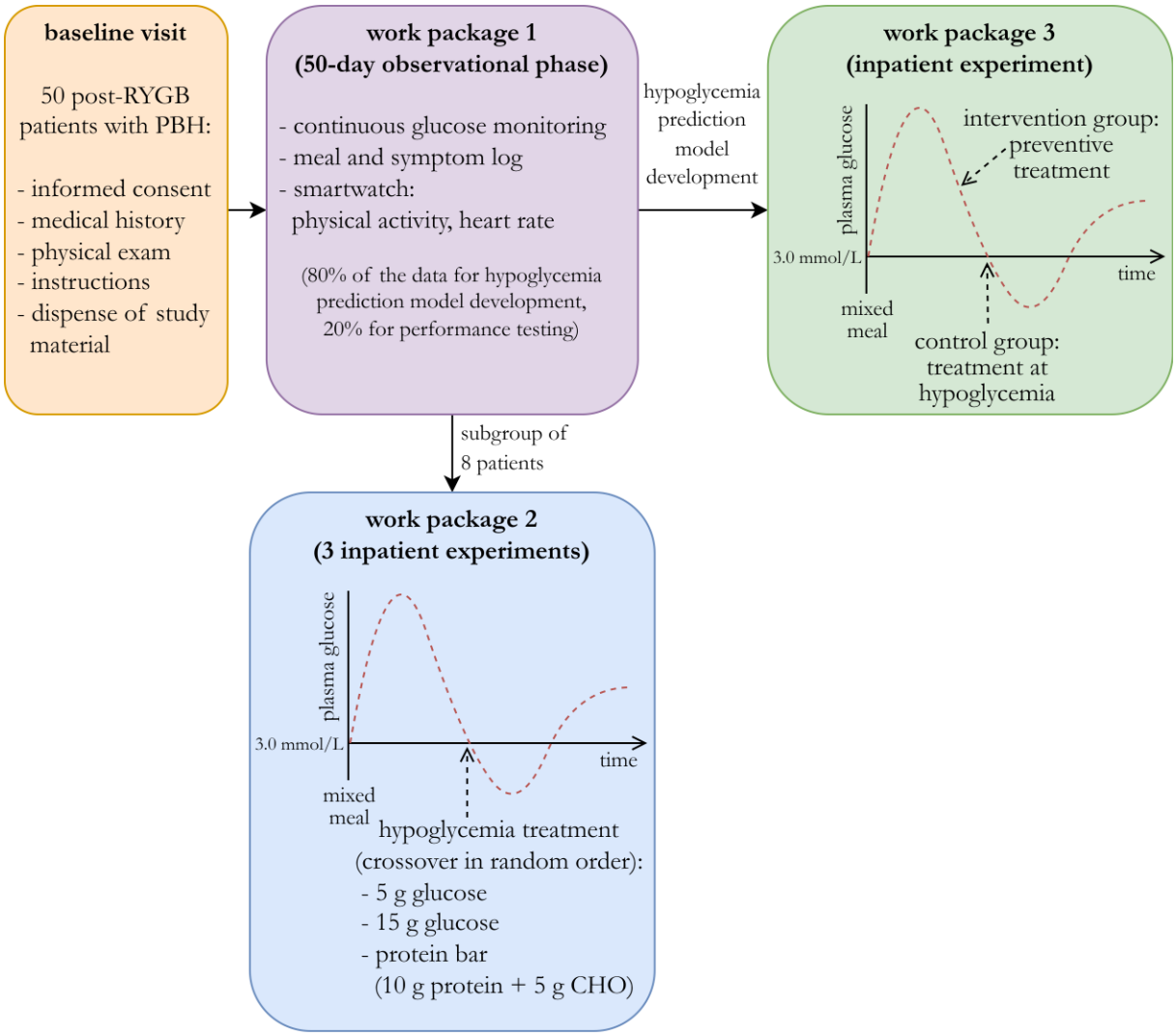


Figure 4: Overview of the PBH Forecast project
CHO, carbohydrate; PBH, post-bariatric hypoglycemia; RYGB, Roux-en-Y gastric bypass.

4. Nutritional Support

Nutritional support refers to the administration of nutrition or nutrients, primarily to prevent or treat disease-related malnutrition [3]. Adjunctive therapies to promote food intake, nutrient absorption, and metabolism are also a part of nutritional support (eg, enzyme replacement) [2]. Nutritional support can be provided orally (regular diet, therapeutic diet, fortified food, ONS), as EN, or as PN. Medical nutrition therapy, encompassing ONS, EN, and PN, is an essential component of nutritional support [1, 3]. EN and PN have historically been called artificial nutrition, but it is suggested to replace this term by medical nutrition therapy [1].

A multiprofessional nutritional support team (NST) should establish an indication for nutritional support through nutritional risk screening, nutritional assessment and malnutrition diagnosis, prescribe and administer nutritional support, and monitor therapy. Such a team typically consists of dietitians, nurses, physicians, and

pharmacists, with defined responsibilities and tasks. This interdisciplinary and interprofessional collaboration is essential for patient safety and quality of care [56].

4.1. Malnutrition

ESPEN defines malnutrition as "a subacute or chronic state of disordered nutrition in which a combination of varying degrees of over- or undernutrition and inflammatory activity has led to a change in body composition and diminished function" and undernutrition as "a state resulting from lack of uptake or intake of nutrition leading to altered body composition (decreased fat free mass and body cell mass) leading to diminished physical and mental function and impaired clinical outcome of disease" [11, 57]. A recent review of data from the United States of America and Europe showed that up to a third of patients are at risk of malnutrition upon hospital admission, and their nutritional status often declines during their stay due to disease-related loss of appetite, drug-related side effects, prescribed fasting for diagnostics, and the underlying disease [58]. Disease-associated malnutrition is also highly relevant in the outpatient sector. A 2019 systematic review and meta-analysis showed that the malnutrition prevalence in community-dwelling adults aged ≥ 65 years in Europe ranged from 3% to 30%, depending on the screening tool and setting [59].

4.2. Nutritional Risk Screening

To ensure adequate nutrition therapy, patients at risk of malnutrition must be identified using a standardized process. Upon detecting a risk for malnutrition, an in-depth nutritional assessment is required to evaluate nutritional needs and create an individualized nutrition therapy plan (Figure 1). To detect patients at risk of malnutrition, susceptible individuals, such as patients admitted to hospital, need to be screened systematically with validated nutritional screening tools. Various tools are available for different settings and populations. Commonly sought requirements for screening tools include ease of administration by HCPs or community care groups, noninvasiveness, and rapid execution (less than five minutes). There are a number of validated screening tools for different settings [60-65], with unintentional weight loss and reduced food intake being the most utilized factors.

The Nutrition Risk Screening 2002 (NRS 2002), the most widely used screening tool for patients in European hospitals [66] and recommended by ESPEN [67], is presented in Figure 5. It begins with four preliminary questions (Is BMI < 20.5 kg/m^2? Has the patient lost weight within the last three months? Has the patient had a reduced dietary intake in the last week? Is the patient severely ill?), and if any of these receive a positive response, the full NRS 2002 screening must be conducted [67]. The NRS 2002 considers nutritional status (0-3 points), disease

severity (0-3 points), and age (1 point for age ≥ 70 years). A total score is calculated, with three or more points signifying the risk or presence of malnutrition, necessitating a nutritional assessment [60]. The NRS 2002 has a sensitivity and specificity of 75% and 55%, respectively, as validated by a retrospective analysis of 128 RCTs on the effect of nutritional support versus no support or spontaneous intake on clinical outcome [60].

Impaired nutritional status	**Score**
Absent: Normal nutritional status	0
Mild: Weight loss > 5% in 3 months *or* food intake 50 to 70% of normal requirements in the last week	1
Moderate: Weight loss > 5% in 2 months *or* BMI 18.5 to 20.5 kg/m^2 and impaired general condition *or* food intake 25 to 50% of normal requirements in the last week	2
Severe: Weight loss > 5% in 1 month *or* BMI < 18.5 kg/m^2 and impaired general condition *or* food intake < 25% of normal requirements in the last week	3

+

Severity of disease (≈ stress metabolism)	**Score**
Absent: Normal nutritional requirements	0
Mild: Patient admitted to hospital due to complications associated with a chronic disease. The patient is weak but out of bed regularly. Protein requirement is increased but can be covered by oral diet or supplements in most cases.	1
Moderate: Patient confined to bed due to illness, eg, following major abdominal surgery or due to severe infection. Protein requirement is substantially increased but can be covered, although medical nutrition therapy is required in many cases.	2
Severe: Intensive care patient with assisted ventilation, inotropic drugs, etc. Protein requirement is increased to the extent that it cannot be covered by medical nutrition therapy in most cases, but protein breakdown and nitrogen loss can be attenuated significantly.	3

+

Age	**Score**
< 70 years	0
≥ 70 years	1

=

Nutritional risk total score

Figure 5: Nutritional Risk Screening 2002 (NRS 2002), adapted from [60]
Patients are scored in each of the two components impaired nutritional status and disease severity, according to whether symptoms are absent, mild, moderate, or severe, thereby giving a total score of 0 to 6. For patients aged 70 years or older, one extra point is added to account for potential frailty. A total score of three or more indicates that the patient is at nutritional risk [60]. BMI, body mass index.

4.3. Nutritional Assessment and Diagnosis of Malnutrition

Patients identified as at nutritional risk should undergo nutritional assessment to detect inadequate nutrient intake or malabsorption, altered body composition, diminished physical and mental function, and impaired clinical outcomes [1]. This comprehensive assessment of nutritional status involves evaluating anthropometric measures (eg, height, body weight, BMI, skinfold thickness, calf circumference), body composition (eg, determined by bioelectrical impedance analysis), and various biomarkers [2]. To estimate the required daily energy intake from resting energy expenditure, techniques such as indirect calorimetry or calculations using predictive weight, sex, and age-based equations, such as the Harris-Benedict equation, can be used [68]. Additionally, protein requirements can be estimated based on body weight, age, disease, and the extent of protein depletion [69]. Nutrition history should be consulted to assess potential nutrient deficits and limitations to food intake [1].

There has been a lack of consensus regarding how to diagnose malnutrition, and it has been handled inconsistently both in research and practice. Furthermore, the majority of malnutrition diagnostic standards have been verified for predicting adverse outcomes instead of identifying patients who may benefit from nutritional intervention [58]. Consequently, the Global Leadership Initiative on Malnutrition (GLIM) was established. In 2018, GLIM proposed a set of criteria to diagnose malnutrition [70]. Upon the detection of nutritional risk using a validated screening tool, the GLIM criteria are employed as a diagnostic assessment of malnutrition. The GLIM criteria consist of three phenotypic criteria (non- volitional weight loss, low BMI, and reduced muscle mass) and two etiologic criteria (reduced food intake or assimilation, and inflammation or disease burden). Diagnosis of malnutrition requires the presence of at least one phenotypic and one etiologic criterion. Malnutrition is classified as either moderate or severe depending on the manifestation of the phenotypic factors [70]. The GLIM criteria are continuously being validated and it is apparent that they have high prognostic value. However, it remains to be elucidated whether their sensitivity is sufficiently high to identify all patients who would benefit from nutritional support [71].

4.4. Nutritional Support Therapy

The outcome of the nutritional assessment provides the rationale for the indication for nutritional intervention and thus for the development of a detailed nutrition therapy plan, including nutritional support [2]. A fundamental principle of nutritional support is to fully utilize the oral (residual) capacity for food intake and choose the most natural nutritional access possible [2], as shown in Figure 6, starting with dietary modifications, including snacks or food fortification (eg, oil/fat, incorporating

maltodextrin, or protein powder into meals to provide additional energy and/or protein). If nutritional requirements cannot be met through these measures, medical nutrition therapy is indicated, with ONS if possible, followed by EN and PN. Therefore, ONS are indicated in malnourished patients with inadequate food intake not requiring EN or PN, EN in patients with a functional gut who have inadequate oral intake, and PN if the enteral route has insufficient capacity of function for adequate nutrition [72]. If these general indications for enteral and PN persist, it may be provided in the outpatient setting, referred to as home EN and PN (HPN). It is important to note that these levels of nutritional support are not mutually exclusive and can and should be used together.

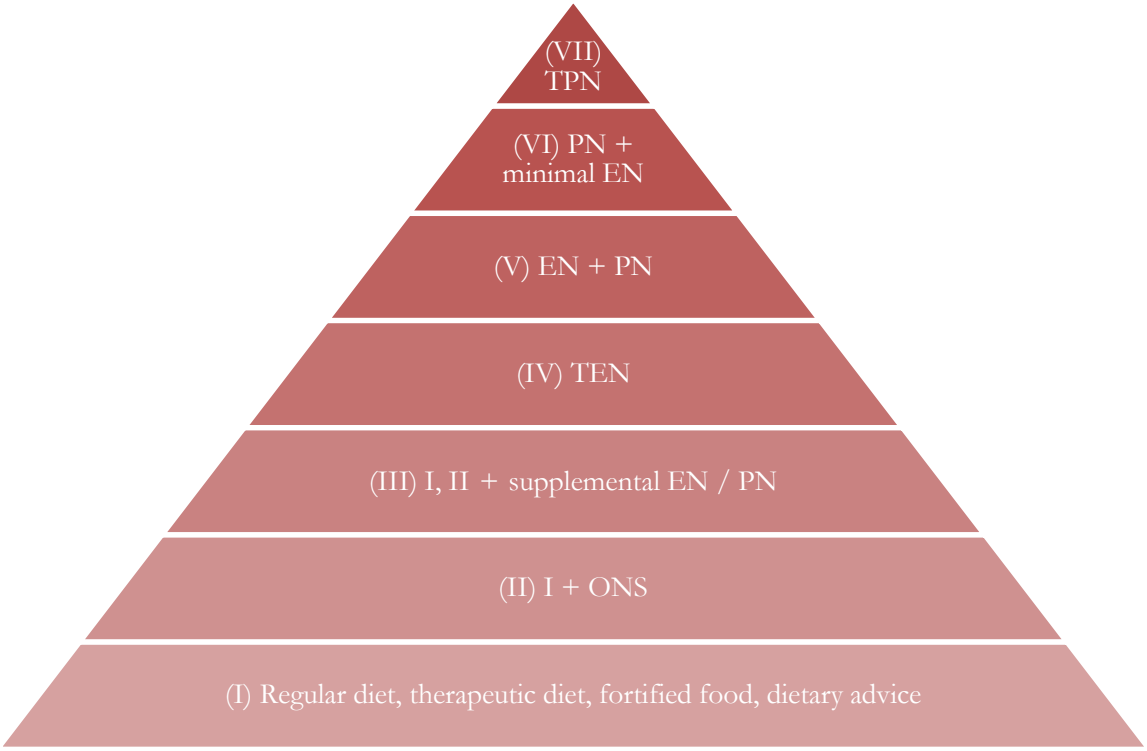


Figure 6: Levels of nutritional support (according to [2])
EN, enteral nutrition; ONS, oral nutritional supplements; PN, parenteral nutrition; TEN, total enteral nutrition; TPN, total parenteral nutrition

In recent years, several high-quality studies on nutritional support have been published, providing new evidence applicable in practice [73]. Two landmark multicenter RCTs demonstrated the high efficacy of adequate nutritional support in malnourished patients. The Effect of early nutritional support on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial (EFFORT) showed that disease-associated malnutrition is a modifiable risk factor to be addressed early in the hospital setting [74]. Early individualized nutritional support aimed at achieving protein and energy requirements in patients at nutritional risk or with manifest disease-related malnutrition significantly reduced 30-day mortality risk by 35%, improved QOL and functional outcomes. The number needed to treat

(NNT) was 37 for mortality and 25 for severe complications [74]. Similarly, convincing results in terms of mortality were obtained in the Nutrition effect On Unplanned ReadmIssions and Survival in Hospitalized patients (NOURISH) trial, which found that nutritional support significantly reduced the mortality risk with a NNT of 20 [75]. A subsequent meta-analysis including these two studies concluded that adequate nutrition therapy reduces the risk of mortality and non-elective rehospitalization by approximately 25% in malnourished patients [73].

4.5. Monitoring

Nutritional support necessitates monitoring to ensure the ongoing provision of nutrients, adequacy of intake, tolerance, and attainment of goals and anticipated outcomes. Individualized plans are essential for monitoring processes, with clearly defined nutritional objectives [1]. Such plans should include:

- Provision and intake of nutrients: Are the fluid, energy, and protein requirements met?
- Weight, anthropometry, and body composition: Are the changes occurring as expected?
- Functional parameters, which underline the importance of physical training in combination with nutrition to improve performance outcomes: Eg, hand grip strength, which has prognostic value regarding mortality and complication risks, and helps identify patients who benefit from nutritional support [76].
- QOL and patient-reported outcomes (eg, pain): Using validated tools or a visual analog scale for subjective factors.
- Biochemistry: Certain laboratory parameters can help identify malnourished patients; however, none of these markers specifically reflect nutritional deficiencies, and many non-nutritional factors, particularly inflammation, can cause significant changes in values. Consequently, laboratory values must always be interpreted in the clinical context [1, 77].

It is important to note that current biochemical, functional, and QOL assessments may not be sufficiently sensitive to detect significant changes in nutritional status [1]. Nonetheless, serum proteins, such as plasma albumin and transthyretin/prealbumin concentrations, can be used primarily to indicate and track catabolic activity [1]. Upon hospital admission, these markers can predict mortality, but should not be employed to indicate nutritional intervention [78]. The American Society for Parenteral and Enteral Nutrition underlined these findings in a meta-analysis and consensus article, concluding that albumin should be used to assess disease severity rather than nutritional status [79, 80]. ESPEN recommends regular QOL

measurement using validated tools as part of routine clinical care, and quality of care should likewise be assessed regularly [81]. As PN can have potentially severe catheter-related complications requiring hospitalization, common indicators of the quality of care of patients with HPN include catheter-related infections, hospital readmission, and QOL [82, 83].

4.6. (Home) Parenteral Nutrition

PN delivers essential nutrients, including glucose, amino acids, lipids, electrolytes, vitamins, and trace elements, directly into the bloodstream via intravenous infusion. PN has two primary classifications: total (or exclusive) PN (TPN), which fulfills all nutritional requirements of a patient, and supplemental (partial or complementary) PN, which is combined with additional oral intake or EN [1]. The prevalence of HPN is comparable to that of rare diseases, with substantial variations between countries. It ranges from about 5 to 50 cases per million people per year, with an overall increasing tendency mainly in geriatric and oncologic patients [84-88]. The opposite trend is observed in the United States of America, where the prevalence decreased between 1992 and 2013 but is still higher than in Europe [88, 89].

4.6.1. Indications and Underlying Diseases

PN is required when the gut is not functional or accessible for EN, or when oral intake or EN are unsafe or unlikely to be effective. PN is no longer indicated when adequate and persistent oral intake or EN is possible [72].

A major indication for HPN is chronic intestinal failure (CIF). The formal ESPEN definition of intestinal failure is "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth" [90, 91]. Intestinal failure can be classified into five major pathophysiological conditions with various underlying gastrointestinal or systemic diseases. Several concomitant pathophysiological mechanisms may contribute to the severity of intestinal failure, but the primary conditions are [81, 90]:

1. Short bowel (< 200 cm remaining small bowel as a result of extensive surgical resection or congenital diseases): Malabsorption (reduced absorptive mucosal surface)
2. Intestinal fistula: Malabsorption (bypass of large areas of absorptive mucosal surface)
3. Intestinal dysmotility: Restricted oral intake and EN (feeding-related exacerbation of digestive symptoms or episodes of non-mechanical intestinal obstruction)
4. Mechanical obstruction: Restricted oral intake and EN (bowel rest)

5. Extensive small bowel mucosal disease: Malabsorption (inefficient absorptive and /or nutrient losing mucosal surface)

It is important to note that while many patients requiring HPN are affected by CIF, HPN may also be used to prevent or treat malnutrition despite a functional intestine, for example, when a patient declines medical nutrition therapy via the oral and enteral route. Thus, four clinical scenarios for the use of HPN can be distinguished [92]:

- HPN as an essential life-saving treatment for patients with CIF caused by a benign underlying disease
- HPN for CIF caused by a malignant disease (often temporarily during curative treatments)
- HPN incorporated within a palliative care plan for untreatable malignant conditions to prevent death due to undernutrition
- No-CIF scenario: HPN to prevent or treat malnutrition in patients with a functional gastrointestinal tract but refusing other forms of medical nutrition therapy

4.6.2. Formulation and Delivery Systems

PN delivers essential energy sources and building blocks for intermediary metabolism directly into the bloodstream in a low molecular form that is readily available to the body. In the normal digestive process, food is mechanically broken down by chewing, churning in the stomach, and segmentation in the small intestine. The smaller particles then undergo chemical digestion by digestive enzymes into soluble, low molecular weight, hydrophilic, or oil-in-water emulsified nutrients that are absorbed into the bloodstream and subsequently into organs and cells for metabolism or storage [93]. Thus, PN must deliver macro- and micronutrients as metabolizable small-molecular substrates to compensate for enteral digestion. It provides carbohydrates as monosaccharides, individual amino acids, emulsified lipids, fluids, electrolytes, and micronutrients, in a dissolved or dispersed state [93].

Complete PN admixtures contain all necessary macro- and micronutrients ideally in a ready-to-use single container as an all-in-one (AIO) admixture. They consist of up to 50 distinct, reactive or metastable components, resulting in a high susceptibility to physicochemical interactions and reactions. These can lead to deterioration of the components, generation of harmful byproducts, precipitation, and a decrease in the homogeneity with an increase in droplet size of the oil-in-water emulsion, resulting in limited stability [93]. Before the introduction of the single container AIO system incorporating all compatible components of PN in the nineteen-seventies [94], PN needed to be administered as a multi-bottle system, that is, each component in a

separate container and intravenous line [95]. Patients had an infusion stand with several bottles, containing a glucose solution, an amino acid solution, and a lipid emulsion, with compatible admixes of electrolytes for parallel or sequential infusion. Micronutrients were infused at separate times [96]. In contrast, AIO admixtures containing all required macro- and micronutrients are easier and safer to administer (reduced risk of administration errors and metabolic complications) and allow for a better nutrient utilization and assimilation [97]. AIO admixtures are available in two delivery systems: (1) ready-to-use individually compounded admixtures in a single container and (2) industrial multichamber bags to be admixed and completed prior to use. Compounded admixtures refer to PN manufactured for an individual patient in a hospital pharmacy or compounding center upon prescription. The major advantages of this system include individualized composition, convenience, ease of use, and sterile admixing compliant with good manufacturing practices. However, these AIO admixtures cannot be sterilized, and thus have very limited stability and require refrigerated transport and storage (cold chain). Furthermore, owing to their very limited storage time, they must be prepared on a near daily basis. This makes them highly susceptible to disruptions caused by shortages of stable starting materials. Trained staff and specific equipment, such as automated compounding devices, are required for safe compounding. Therefore, compounded PN admixtures are mostly used in patients who rely on individualized formulations, such as neonates, children or selected long-term patients. Industrially manufactured PN bags are compartmentalized into two or three chambers containing stable and sterile macronutrients to form binary (glucose and amino acids) or ternary mixtures (glucose, amino acids, and lipids). Such bags are usually available in different volumes and compositions, with and without electrolytes (in the glucose and/or amino acid solutions). Furthermore, ready-to-use PN admixtures with different osmolarities are available for peripheral and central venous administration (see also Chapter 4.6.3 Administration Methods). To obtain a ready-to-use AIO admixture from a multichamber bag, the seals separating the bag chambers are broken to mix the compartment contents mechanically. To complete the admixture, vitamins and trace elements must be supplemented into the bag (Figure 7) or infused separately. The key advantage of the industrial multichamber bags is their extended storage time at ambient temperature as the bag content is sterilized thereby offering increased logistic flexibility. Furthermore, large-scale industrial production is more cost effective than compounding and allows more extended quality control of the product [95]. However, there are certain drawbacks, such as the need for aseptic techniques and training for the admixing of chamber contents and the addition of vitamins, trace elements, individualized electrolyte doses, or other additives, which increases the risk of contamination. Additionally, industrial series production lacks customization for

specific patient requirements, however, they remain suitable for most adult patients upon initiation of PN. AIO admixtures, whether compounded or prepared from multichamber bags, have a restricted infusion time of 24 to maximally 48 hours at room temperature and need to be stored light-protected for stability reasons [92, 93, 98, 99].

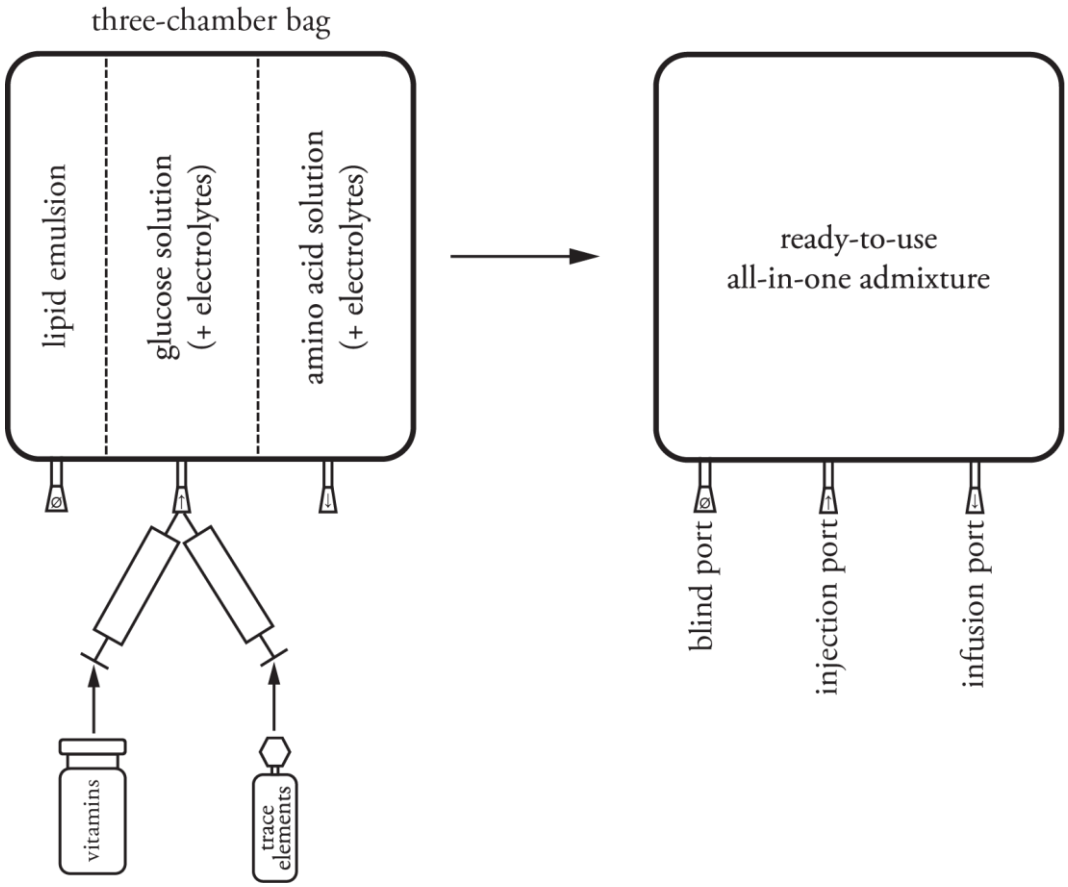


Figure 7: Ready-to-use all-in-one parenteral nutrition admixture prepared by breaking the seals of a multichamber bag and supplementing vitamins and trace elements with syringes via the bag's injection port

The maximum infusion rate of glucose in adults is 3 to 6 g/kg body weight/24 hours mostly limiting the administration rate of PN. Nonetheless, to reduce the volume of AIO PN admixtures, a highly concentrated hypertonic glucose solution is required, which results in elevated osmolarity [93, 100]. The lipid emulsion comprises various fatty acids and is stabilized using soy or egg yolk lecithin as an emulsifier prone to interactions with cationically charged PN components. Current and mostly used lipid emulsions include structured triglycerides, containing both medium and long-chain fatty acids esterified with glycerol. Combined fatty acids from soybeans, medium-chain triglycerides, olive oil, and fish oil are used. These lipid emulsions are isotonic and may contribute to reducing the osmolarity of AIO PN admixtures, eg, for peripheral administration [100]. Polyunsaturated fatty acids are prone to peroxidation and require protection from light and oxygen during storage and use, as degradation products may constitute free radicals [100]. Moreover, lipid droplet size is a crucial

safety parameter for the expiration time because droplet diameters exceeding 5 µm can induce lipid embolisms in small blood vessels [93, 100, 101]. Amino acid solutions for PN usually contain 10% crystalline L-amino acids, and the composition in terms of conditionally essential amino acids, such as glycine, varies among manufacturers [93].

4.6.3. Administration Methods

PN can be administered as a central or peripheral infusion. Central PN is delivered through a catheter or venous port with the tip positioned in a central vein (typically in the lower third of the superior vena cava or at the junction of the superior vena cava and right atrium) [93, 102]. Peripheral PN is provided via a cannula or catheter inserted into a peripheral vein, usually in the forearm. Additionally, arteriovenous shunts may be utilized when central venous catheterization is not feasible or if other veins are unavailable [102].

If the requirement for parenteral nutrients is high, a concentrated PN admixture is needed to remain within tolerable fluid volumes. When exceeding 900 mosmol/L, such hypertonic admixtures must be administered via a central vein in order to dilute the high tonicity of usual AIO PN admixtures (usually more than 2000 mosmol/L). Central PN is primarily delivered through a subcutaneously tunneled external catheter, fully implanted infusion device (port), or peripherally inserted central catheter (PICC). Each system offers specific advantages and disadvantages, and a multidisciplinary HPN team along with the patient should take the decision based on the particular situation and the local experience of the surgical team [81, 93]. For instance, a tunneled external catheter enables easy access, is ideal for self-administering PN, and facilitates infection treatment and external part repair compared with a fully implanted infusion device. However, it disrupts the body image more and is less suitable for swimming or bathing than a fully implanted infusion device. Disadvantages of a fully implanted infusion device further include the need for regular skin punctures for catheter use and the more difficult rinsing of the port to avoid clogging [103]. PICCs' main advantages include eliminating the risk of complications related to direct jugular or subclavian catheterization and ease of insertion and removal. Disadvantages include an increased risk of phlebitis, thrombosis, and infection, issues concerning self-administration of PN, and some interference with extremity use [81, 103].

By using peripheral PN, complications associated with central venous caterers can be avoided. Another advantage is the relative ease of venous access. However, the tolerance of PN infused into a peripheral vein is limited, depending on osmolarity, pH, and infusion rate, as well as on the cannula and catheter materials. PN is a

hypertonic fluid that irritates veins and may cause pain, phlebitis, and thrombosis [102]. The inclusion of lipid emulsions and increased water volume reduces osmolarity, and lipid emulsions seem to safeguard the vascular endothelium. For peripheral PN, a maximum osmolarity of around 850-900 mosmol/L is recommended [99, 104]. Consequently, PN admixtures for peripheral infusion rarely satisfy the nutritional needs of patients with high parenteral energy, protein, and/or electrolyte (particularly potassium) requirements, or those at risk of fluid overload. Moreover, peripheral venous access must be renewed every few days upon initial signs of phlebitis. Thus, peripheral PN is typically only an option for hospitalized patients who require PN for a short duration (usually anticipated duration less than 10 days) [105].

4.6.4. Complications

PN complications can be categorized into catheter-related and metabolic complications.

Catheter-Related Complications

Catheter-related complications encompass infections associated with the catheter, catheter occlusions, and thrombosis (Table 2). Preventing catheter-related infections necessitates proper education of HCPs, patients, and caregivers on proper catheter handling, care, and maintenance procedures. Both patients and HCPs must adhere to rigorous asepsis with good handwashing and disinfection practices to ensure that the hands are decontaminated before handling central-venous catheters, even when using sterile gloves. Furthermore, the hub connector should be disinfected upon each access, as should the catheter exit site, stopcock, catheter hubs, and other sampling ports. The intravenous administration sets must be changed regularly after use to maintain sterility. Finally, if patients have a stoma or fistula, it is essential to separate stoma and fistula care from catheter care to minimize cross-contamination [81]. Catheter lock with taurolidine has been shown to prevent infections and can be used in patients at risk for catheter-related bloodstream infections (CRBSI) [106]. Taurolidine inhibits microbial adhesion to catheter surfaces and hinders biofilm formation via an irreversible reaction between its metabolites and bacterial cell walls. It exhibits a broad spectrum of activities against bacterial and fungal pathogens. In-line filters, routine catheter replacement, antibiotic prophylaxis, and heparin locks are no longer recommended [107]. Minimizing venous damage during catheter insertion is crucial for the primary prevention of catheter-related venous thrombosis. Flushing catheters with saline and avoiding blood sampling through the catheter can prevent catheter occlusions [81].

Table 2: Catheter-related complications of parenteral nutrition

Catheter-related local infections	Exit site infection	Erythema, induration, and/or tenderness within 2 cm of the catheter exit site; may be associated with other signs and symptoms of infection, such as fever or purulent drainage emerging from the exit site, with or without concomitant bloodstream infection [81]
	Tunnel infection	Tenderness, erythema, and/or induration > 2 cm from the catheter exit site, along the subcutaneous tract of a tunneled catheter, with or without concomitant bloodstream infection [81]
	Pocket infection	Infected fluid in the subcutaneous pocket of a totally implanted intravascular device; often associated with tenderness, erythema, and/or induration over the pocket; spontaneous rupture and drainage, or necrosis of the overlying skin, with or without concomitant bloodstream infection [81]
Systemic bloodstream infections	Central line-associated bloodstream infection (CLABSI)	Positive blood culture and no apparent source for bloodstream infection (with the exception of the catheter) [108]
	Catheter-related bloodstream infection (CRBSI)	(Semi-)quantitative culture of the catheter (if the catheter is removed/exchanged) or paired quantitative or qualitative blood cultures from a peripheral vein and from the catheter, with continuous monitoring of the differential time to positivity (if the catheter is left in place) [104]
Catheter-related occlusions	Catheter occlusion	Mechanical, damage, clogging
	Catheter-related venous thrombosis (CRVT)	A thrombosis of a vein along the tract or at the tip of the catheter

Metabolic Complications

Numerous metabolic issues from insufficient or excessive nutrients or an inappropriate PN regimen can complicate PN. Metabolic complications can be classified as deficiencies or acute and chronic metabolic complications [109]. Among acute deficiencies, hypoglycemia, hypophosphatemia, hypokalemia, and thiamine deficiency are particularly relevant, as they are the primary features of the refeeding syndrome. Long-term essential nutrient deficiencies, including electrolytes, trace elements, vitamins, and essential fatty acids, can be detrimental. Regular monitoring of deficiency signs and, where applicable, biochemical monitoring are vital to ensure adequate provision of nutrients. Special consideration is necessary for patients with diabetes receiving PN [110]. Chronic metabolic complications of PN include intestinal failure-associated liver disease (multifactorial etiology), cholelithiasis and acalculous cholecystitis (due to decreased gallbladder motility and bile composition alterations) also known as PN-associated liver disease (PNALD), bone disease (long-term immobilization, vitamin D toxicity, low phosphate intake, excess amino acids, aluminum contamination, magnesium deficiency, heparin or corticoid

administration, low calcium and vitamin D intake), and chronic renal failure [109, 111].

4.6.5. eSwissHPN Project

The eSwissHPN project follows the SwissHPN-I [112] and II [85, 113] studies as the third nationwide project in patients with HPN conducted at UDEM. The aims of the SwissHPN-I [112] and II [85, 113] cohort studies were to gather representative nationwide data on adult HPN patients in Switzerland. The results revealed that complications related to HPN are frequent in Switzerland and that QOL is significantly impaired [85, 113]. Consequently, the eSwissHPN project aimed to explore eHealth solutions for HPN patients in Switzerland. The project was driven by a vision of an all-inclusive eHealth platform for HPN patients and their improved care. The envisioned features included: customizable access rights for the NST, patients, and caregivers; automatic data transfer from infusion pumps and Bluetooth-enabled devices (eg, wearables and scales), and potentially clinical information systems (eg, reports and laboratory values); manual data entry including pictures; and communication between and among patients, caregivers, and the NST. Communication among patients was envisioned, as some patients in the SwissHPN-II study indicated their interest in connecting with other HPN patients [85], and ESPEN suggests that patients should be encouraged to participate in organizations offering HPN education, assistance, and networking opportunities for members [81]. To work towards this vision, we conducted a survey among patients with HPN to elucidate their needs in relation to eHealth and developed a minimum viable product based on their feedback. Additionally, we made two patient testimonials movies [114] aiming to show patients starting HPN how it might progress and what they can expect from life with HPN.

AIMS AND OBJECTIVES

The overarching aim of the doctoral research underlying this dissertation was to investigate advances in medical nutrition in the areas of dietetics, obesity, and nutritional support (see Figure 1). To achieve this aim, the following specific objectives were pursued:

Dietetics:

- To determine whether there is a dietary fiber deficiency in conventional diets and to understand the role highly processed foods play in this.
- To assess whether anti-inflammatory diets can improve patient-reported and clinical outcomes in rheumatoid arthritis.

Obesity:

- To identify an effective and safe nutritional intervention strategy for correcting postprandial hypoglycemia in patients with PBH.

Nutritional support:

- To investigate the attitudes and expectations of patients with HPN towards eHealth for the monitoring of medical nutrition therapy.
- To evaluate whether commercial AIO PN admixtures for adults present a potential safety risk for aluminum toxicity.

RESULTS

The full-text papers included in this dissertation each address one of the objectives stated in the Chapter *Aims and Objectives*. Additional projects and publications that formed part of the doctoral research, and their relation to dietetics, obesity and nutritional support, are given in Table 3. The corresponding abstracts are included in Appendix B.

Table 3: Project involvement during the doctoral research and the relation to medical nutrition

Area	**Project / publication**
Dietetics (dietary advice to heal or treat a disease or a disease condition)	– Dietary fibre intake and its association with ultraprocessed food consumption in the general population of Switzerland: analysis of a population-based, cross-sectional national nutrition survey [115] – Dietary fibre intake in the adult Swiss population: a comprehensive analysis of timing and sources [forthcoming] – How prevalent is a cancer-protective lifestyle? Adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research cancer prevention recommendations in Switzerland [116] – Effect of anti-inflammatory diets on pain in rheumatoid arthritis: a systematic review and meta-analysis [117]
Obesity (obesity prevention or treatment, including bariatric surgery care)	– Prolonged isolated soluble dietary fiber supplementation in overweight and obese patients: a systematic review with meta-analysis of randomized controlled trials [118] – Nutrient and fluid requirements in post-bariatric patients performing physical activity: a systematic review [119] – Digital solutions to diagnose and manage postbariatric hypoglycemia [26] – Relationship between symptom perception and postprandial glycemic profiles in patients with post-bariatric hypoglycemia after Roux-en-Y gastric bypass surgery [120] – Nutritional strategies for correcting low glucose values in patients with post-bariatric hypoglycemia: a randomized controlled three-arm crossover trial [121] – Randomized, double-blind, placebo-controlled crossover trial of once daily empagliflozin 25 mg for the treatment of postprandial hypoglycemia after Roux-en-Y gastric bypass [122]

Nutritional support (disease-related malnutrition prevention or treatment)	– Mangelernährung: Ein Leichtgewicht mit Schwergewicht [123] – Nutritional risk screening in cancer patients: the first step toward better clinical outcome [124] – Ernährungsscreening in der Onkologie: Der erste Schritt zu einem besseren Outcome [125, 126] – Nutritional risk is a predictor for long-term mortality: 5-year follow-up of the EFFORT trial [127] – Nutritional assessment in adults with cystic fibrosis [128] – MEDPass versus conventional administration of oral nutritional supplements – a randomized controlled trial comparing coverage of energy and protein requirements [129] – The influence of patients' nutritional risk, nutritional status, and energy density in MEDPass versus conventional administration of oral nutritional supplements – a secondary analysis of a randomized controlled trial [130] – Should handgrip strength be considered when choosing the administration mode of oral nutritional supplements in geriatric patients? A secondary analysis of the MEDPass Trial [131] – The role of dietary fibre in enteral nutrition in sepsis prevention and therapy: a narrative review [132] – Management of hyperglycemia in hospitalized patients receiving parenteral nutrition [110] – Management of home parenteral nutrition: complications and survival [85] – Quality of life in the management of home parenteral nutrition [113] – Attitudes and expectations of patients on home parenteral nutrition towards eHealth: a multicenter survey [133] – Aluminum in parenteral nutrition components and all-in-one admixtures [134] – Stability of nanoparticular intravenous iron (Ferinject®) in commercial all-in-one parenteral nutrition: clinical potential for increased iron doses [forthcoming] – Physicochemical stability and compatibility testing of voriconazole in all-in-one parenteral nutrition admixtures [135] – Intravenous multivitamin shortage and the management for parenteral nutrition [forthcoming] – Refeeding-Syndrom: Wo stehen wir 2022? [Refeeding syndrome: Where do we stand in 2022?] [136] – Determinants of treatment toxicity in patients with soft tissue sarcomas [137] – Implementation of evidence-based clinical nutrition: usability of the new digital platform clinicalnutrition.science [forthcoming] – NutriPro™: a product-specific e-tool for healthcare professionals' guidance in clinical nutrition [forthcoming]

Paper 1 (peer-reviewed)

Katja A. Schönenberger, Valentina V. Huwiler, Emilie Reber, Stefan Mühlebach, Zeno Stanga, Giulia Pestoni, David Faeh. Dietary fibre intake and its association with ultraprocessed food consumption in the general population of Switzerland: analysis of a population-based, cross-sectional national nutrition survey. BMJ Nutrition, Prevention & Health. 2024;e000727. doi: 10.1136/bmjnph-2023-000727

Paper 2 (peer-reviewed)

Katja A. Schönenberger, Anne-Catherine Schüpfer, Viktoria L. Gloy, Paul Hasler, Zeno Stanga, Nina Kaegi-Braun, Emilie Reber. Effect of Anti-Inflammatory Diets on Pain in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Nutrients. 2021;13(12):4221. doi: 10.3390/nu13124221

Paper 3 (peer-reviewed)

Katja A. Schönenberger, Antonio Ferreira, Céline Stebler, Francesco Prendin, Joanna Gawinecka, Christos T. Nakas, Stefan Mühlebach, Zeno Stanga, Andrea Facchinetti, David Herzig, Lia Bally. Nutritional strategies for correcting low glucose values in patients with postbariatric hypoglycaemia: A randomized controlled three-arm crossover trial. Diabetes, Obesity and Metabolism. 2023;25(10)2853-2861. doi: 10.1111/dom.15175

Paper 4 (peer-reviewed)

Katja A. Schönenberger, Emilie Reber, Duy-Tan Vu, Claudia Krieger-Grübel, Philipp A. Gerber, Raphaela Muri, Valentina V. Huwiler, Stefan Mühlebach, Michèle Leuenberger, Zeno Stanga. Attitudes and expectations of patients on home parenteral nutrition towards eHealth: A multicenter survey. Clinical Nutrition ESPEN. 2022;52:445-449. doi: 10.1016/j.clnesp.2022.09.026

Paper 5 (peer-reviewed)

Katja A. Schönenberger, Christoph Saxer, Peter J. Neyer, Valentina V. Huwiler, Emilie Reber, Angelika Hammerer-Lercher, Zeno Stanga, Stefan Mühlebach. Aluminum and other chemical elements in parenteral nutrition components and all-in-one admixtures. Clinical Nutrition. 2023;42(12):2475-2483. doi: 10.1016/j.clnu.2023.10.012

Paper 1

Dietary Fibre Intake and its Association with Ultraprocessed Food Consumption in the General Population of Switzerland: Analysis of a Population-Based, Cross-Sectional National Nutrition Survey

Katja A. Schönenberger [1,2], Valentina V. Huwiler [1,2], Emilie Reber [1], Stefan Mühlebach [2], Zeno Stanga [1], Giulia Pestoni [3,4,*], David Faeh [4,5,*]

[1] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Bern, Switzerland

[2] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3] Nutrition Group, Health Department, Swiss Distance University of Applied Sciences (FFHS) / University of Applied Sciences and Arts of Southern Switzerland (SUPSI), Zurich, Switzerland

[4] Division of Chronic Disease Epidemiology, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland

[5] Health Department, Bern University of Applied Sciences, Bern, Switzerland

*Joint senior authors

BMJ Nutrition, Prevention & Health. 2024;e000727. doi: 10.1136/bmjnph-2023-000727

BMJ Nutrition, Prevention & Health

Dietary fibre intake and its association with ultraprocessed food consumption in the general population of Switzerland: analysis of a population-based, cross-sectional national nutrition survey

Katja A Schönenberger ,[1,2] Valentina V Huwiler ,[1,2] Emilie Reber ,[1] Stefan Mühlebach ,[2] Zeno Stanga ,[1] Giulia Pestoni ,[3,4] David Faeh [4,5]

To cite: Schönenberger KA, Huwiler VV, Reber E, *et al*. Dietary fibre intake and its association with ultraprocessed food consumption in the general population of Switzerland: analysis of a population-based, cross-sectional national nutrition survey. *BMJ Nutrition, Prevention & Health* 2024;**0**:e000727. doi:10.1136/bmjnph-2023-000727

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjnph-2023-000727).

For numbered affiliations see end of article.

Correspondence to
Professor David Faeh; david.faeh@bfh.ch

GP and DF are joint senior authors.

Received 9 July 2023
Accepted 23 November 2023

ABSTRACT

Objectives The objective of this study was to describe the compliance to dietary fibre recommendations of the Swiss population and to investigate the association between dietary fibre intake and ultraprocessed food (UPF) consumption.

Methods Data were obtained from the cross-sectional Swiss National Nutrition Survey *menuCH*. We summarised the sociodemographic, lifestyle and anthropometric parameters as well as dietary data collected with two 24-hour dietary recalls for the whole population and subgroups according to absolute and relative dietary fibre intake. We analysed the associations between dietary fibre intake and UPF consumption by fitting multinomial logistic regression models. Data were weighted according to the *menuCH* weighting strategy to achieve a representation of the Swiss population.

Results Data obtained from 2057 adults were included in the analysis, of which 87% had a dietary fibre intake of <30 g/day. Participants with high UPF consumption had lower odds of being in the medium or high dietary fibre intake groups than participants with low UPF consumption. The odds of being in the medium or high dietary fibre intake groups decreased linearly across quartiles of UPF consumption (p for trend ≤0.004).

Conclusions Dietary fibre intake is insufficient in all population groups in Switzerland. UPF consumption is inversely and dose dependently associated with dietary fibre intake. To increase dietary fibre intake, public health measures should discourage UPF consumption and increase dietary fibre intake via unprocessed or minimally processed foods.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Scientific evidence has long emphasised the importance of dietary fibre, traditionally sourced from minimally processed or unprocessed foods, in promoting overall health. However, the rise of industrially manufactured ultraprocessed foods (UPFs) has introduced new challenges, as these products often incorporate dietary fibre due to market demands and various regulatory frameworks, even though their impact on health remains a concern.

WHAT THIS STUDY ADDS

⇒ Dietary fibre intake remains insufficient in 87% of the overall Swiss population and across all sociodemographic groups. In addition, dietary fibre intake shows an inverse and dose-dependent association with UPF consumption.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Achieving the recommended dietary fibre intake presents significant challenges and necessitates consumer-friendly guidelines promoting fibre-rich foods; UPFs are not effective sources for this. Therefore, strategies to enhance the appeal of unprocessed foods over UPFs are crucial to elevate fibre intake.

INTRODUCTION

Since the discovery of the association between diets low in dietary fibre and poor health outcomes almost half a century ago, numerous studies have investigated the impact of dietary fibre on chronic non-communicable diseases, mostly cardiometabolic disease and its risk factors, gastrointestinal diseases, and cancer.[1] Western countries have aimed to increase fibre intake in their populations and recommend an intake of approximately 25–35 g/day for adults.[1] Some countries indicate that recommendations refer to naturally occurring dietary fibre from foods such as fruits, vegetables, legumes, and grains.[1] However, there is little further guidance beyond the total amount of dietary fibre to be

consumed, such as types of dietary fibres or the proportions of different food sources that contain dietary fibre to achieve optimal intake.[1]

Industrially manufactured foods are processed in varying degrees. This includes fractioning whole foods into substances, physical modifications such as heat treatments or high pressure, chemical modification, assembly of foods, and frequent use of additives with the aim of producing highly profitable, convenient and extremely hyperpalatable products.[2] Ultraprocessed foods (UPFs) are 'formulations of ingredients, mostly of exclusive industrial use, that result from a series of industrial processes'.[2] The *NOVA* classification categorises foods according to the extent and purpose of food processing: group 1 consists of unprocessed or minimally processed foods; group 2 consists of processed culinary ingredients; group 3 consists of processed foods; and group 4 consists of UPFs.[3] UPFs typically have a high energy density and low satiating capacity, and their consumption is accompanied by an increased intake of added sugar and salt, hydrogenated/saturated fats, flavourings and preservatives.[4–7] Hence, UPFs lower the nutritional quality of the overall diet[5 6 8] and have been associated with all-cause mortality, overweight and obesity, high waist circumference, low high-density lipoprotein cholesterol, metabolic syndrome, cardiovascular disease, cerebrovascular disease, cancer, and depression.[9–11] In Switzerland, UPF consumption is similar to the European average, where daily UPF consumption assessed as average of dietary surveys conducted in the European adult population of 22 countries amounts to 328 g (12% of the total weight of daily food consumption) and 562 kcal (27% of energy intake).[7 12 13]

Food manufacturers often incorporate various forms of isolated dietary fibres or processed dietary fibre-rich foods to UPFs owing to their sales-promoting effect.[14] The European Commission and European Food Safety Authority have authorised a number of health claims for some dietary fibre types related to bowel function, reduction of postprandial glycaemic responses and maintenance of normal blood cholesterol concentrations.[15 16] These health claims underscore the perceived health benefits of specific isolated dietary fibre types. In addition, front-of-pack labels, such as the increasingly common Nutri-Score, consider dietary fibre content as a positive criterion.[17] Despite these considerations, the consumption of UPFs remains a risk factor for obesity, a concern that persists irrespective of the dietary fibre content within these products.[18 19]

From a public health perspective, it is important to gain further insights into how the population covers its dietary fibre needs in order to derive possible interventions and recommendations. Consequently, we aimed to analyse the compliance to dietary fibre recommendations of the overall Swiss population and describe the sociodemographic, anthropometric, lifestyle and dietary characteristics of the study population overall and by absolute and relative dietary fibre intake groups. Furthermore, we aimed to investigate the association between UPF consumption and dietary fibre intake.

METHODS

This work is reported using the Strengthening the Reporting of Observational Studies in Epidemiology—Nutritional Epidemiology guidelines.[20]

Study design and study population

We analysed data from the national nutrition survey *menuCH*, a population-based cross-sectional survey conducted among residents of Switzerland aged 18–75 years from January 2014 to February 2015.[21 22] The stratified random sample from the national sampling frame for person and household surveys was intended to be representative of seven major areas in Switzerland and five predefined age categories. A detailed description of participant recruitment and a flow diagram have been published elsewhere.[21 23] Of the 13 606 individuals invited to participate, 2086 agreed to participate and 2057 had a complete dietary assessment and were included in the analyses.[21]

Dietary assessment

Trained dieticians assessed food consumption through two non-consecutive 24-hour dietary recalls.[22 23] The interviews were distributed across weekdays and seasons.[21] The food consumption of participants was recorded using the trilingual Swiss version (V.0.2014.02.27) of the GloboDiet software (formerly EPIC-Soft, International Agency for Research on Cancer IARC, Lyon, France,[24] adapted for Switzerland by the Federal Food Safety and Veterinary Office, Bern, Switzerland). Data were cleaned after completion of data collection using an updated version (V.0.2015.09.28). Food group-specific descriptors included in the GloboDiet software allowed for standardised descriptions of foods and recipes.[21] FoodCASE software (Premotec GmbH, Winterthur, Switzerland) matched foods, recipes and ingredients from the GloboDiet software with the most appropriate item from the Swiss Food Composition Database (https://naehrwertdaten.ch/de/). The dietary fibre content of 2% of food items in the *menuCH* dataset was missing. We completed dietary fibre content using the Swiss Food Composition Database (https://naehrwertdaten.ch/de/) or manufacturer's nutrition facts label, the German Nutrient Database, or dietary fibre content of a similar product. Quality controls assessing compliance with survey-specific standard operating procedures and data cleaning have been described elsewhere.[21 23] Intake from dietary supplements was not considered.

Dietary fibre intake groups

We categorised the *menuCH* population into groups of low, medium, and high dietary fibre intake using absolute dietary fibre intake (<15 g/day, 15–30 g/day, and

≥30 g/day, respectively) and dietary fibre intake relative to energy intake (<10 g/1000 kcal/day, 10–14 g/1000 kcal/day, and ≥14 g/1000 kcal/day, respectively). We selected the cut-offs for dietary fibre intake according to the DACH (Germany, Austria, Switzerland) Reference Values for Nutrient Intake, reporting a reference value for dietary fibre of 30 g/day,[25 26] and according to the U.S. Food and Nutrition Board, reporting an adequate intake of 14 g/1000 kcal/day of dietary fibre.[27] The cut-offs for low-dietary fibre diets were based on the distribution of dietary fibre intake in the study population.

Food processing classification

The *NOVA* food classification system by Monteiro *et al* was used to classify food items according to the extent and purpose of food processing.[3] We categorised the *menuCH* food items into non-UPFs and UPFs (*NOVA* 4 category). The classification was based on the food and recipes included in each of the GloboDiet subcategories and using food group-specific descriptors. If the degree of processing was unclear, a conservative approach was adopted (ie, foods were classified as non-UPFs). A description of the *menuCH* food items categorised as UPFs has been published elsewhere.[13] We conducted the analyses using quartiles of UPF weight percentage (weight percentage of UPFs relative to the total weight of food consumed) and quartiles of UPF energy percentage (calorie percentage of UPFs relative to the total calories consumed).

Sociodemographic, lifestyle, and anthropometric characteristics

Participants completed a questionnaire providing information on sociodemographic and socioeconomic characteristics, education, self-reported health status, eating habits, smoking and physical activity behaviours.[22] Nationality was categorised into Swiss only, Swiss binational, and non-Swiss; net household income into <6000, 6000 to 13 000, and above 13 000 Swiss Francs/month; and general self-reported health into very bad to medium and good to very good. Physical activity was assessed using the short-form International Physical Activity Questionnaire (IPAQ) and categorised into low, moderate and high according to the IPAQ classifications.[28] The language region was determined based on the residency address.

During face-to-face interviews, body weight, height, waist circumference, and hip circumference were measured in a standardised manner.[22] We used measured body weight, height and waist circumference in our analyses, except for pregnant and lactating women or when measurements were impossible. Self-reported weight (before pregnancy, if applicable) was used in these cases. Body mass index (BMI) was calculated using body weight and height. We then divided the participants into four groups according to WHO definitions (underweight <18.5 kg/m^2, normal weight 18.5–24.9 kg/m^2, overweight 25.0–29.9 kg/m^2, obese >30.0 kg/m^2). We grouped waist circumference group into no increased risk (males ≤94 cm, females ≤80 cm), increased risk (males 94.1–101.9 cm, females 80.1–87.9 cm), and substantially increased risk (males ≥102 cm, females ≥88 cm).[29]

Dietary habits

The alternate healthy eating index (AHEI) was calculated as an index of overall diet quality.[30] The components included in the AHEI score were vegetables, fruits, whole grains, sugar-sweetened beverages and fruit juice, nuts and legumes, red and processed meat, *trans* fat, fish (as a proxy for long-chain *n*-3 fatty acids), polyunsaturated fatty acids, sodium and alcohol. A detailed description of the AHEI calculations for *menuCH* participants has been published previously.[31]

We used the four dietary patterns identified by Krieger *et al*[32] in our analysis. The Swiss traditional pattern was characterised by minimal variation to the average of the *menuCH* population, except for increased chocolate, milk and dairy consumption. Both Western patterns were characterised by a high intake of red and processed meat, with a high intake of soft drinks (Western-soft drinks) or high intake of alcoholic drinks and cereals and starchy food (Western alcohol). The prudent dietary pattern was characterised by a high intake of fruits, vegetables, white meat and fish.[32]

We distinguished between levels of meat consumption using subgroups published by Steinbach *et al*.[33] No-meat eaters reported meat avoidance according to the questionnaire and were corrected by intake recorded from the 24-hour dietary recalls. Low, medium and high meat eaters had an energy contribution from meat of 0%–2.4%, 2.4%–18.7% and 18.7%–48.4%, respectively.[33]

Statistical analysis

We calculated the mean food and nutrient intake of the two dietary recalls for each participant and subsequently used the mean for all statistical analyses. We explored the compliance to dietary fibre recommendations of the overall Swiss population and described the sociodemographic, anthropometric, lifestyle and dietary characteristics of the overall *menuCH* population as well as by absolute and relative dietary fibre intake groups using descriptive statistics. We fitted multinomial logistic regression models to examine the association between absolute and relative dietary fibre intake groups and quartiles of UPF consumption (weight percentage and energy percentage). The models were adjusted for sex, age, education, BMI, physical activity, smoking, recall season, and recall weekday. We calculated *p* values for trends using the medians of UPF quartiles as continuous variables in multinomial logistic regression models.

To make *menuCH* data representative of the general Swiss population, we applied the *menuCH* weighting strategy, as detailed elsewhere.[34] We weighted all statistical analyses for age, sex, marital status, major area of Switzerland based on home address, nationality and household size to consider the sampling design and non-response. We additionally weighted analyses of food and nutrient

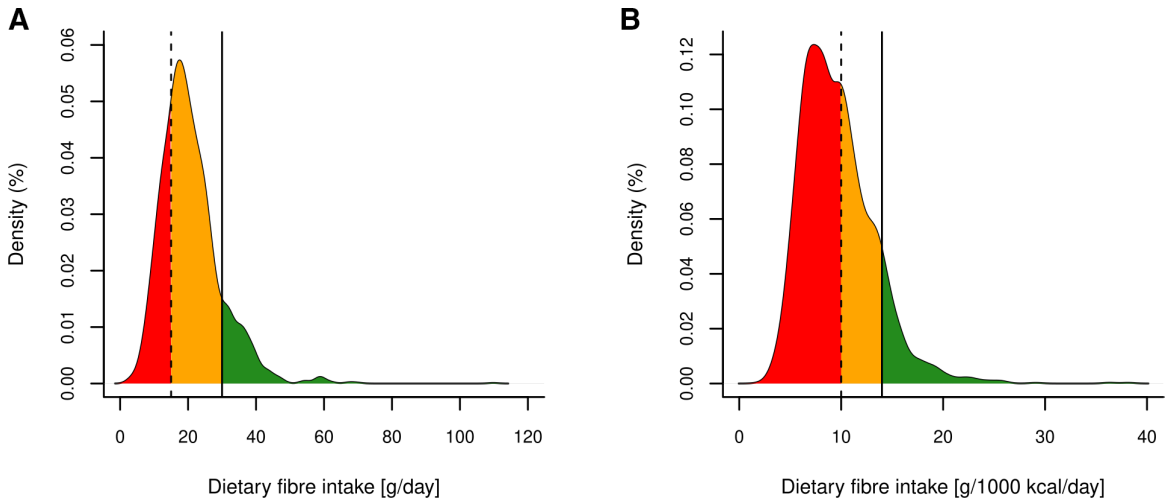


Figure 1 Density plots of absolute (A) and relative (B) dietary fibre intake. The density plot is a smoothed representation of a histogram and shows the distribution of a variable with a total area under the curve of 1. The density is weighted for age group, sex, marital status, major region of Switzerland, nationality, household size, season and weekday according to the *menuCH* weighting strategy.[34] Solid vertical lines represent the Swiss and DACH (Germany, Austria, Switzerland) reference value for dietary fibre of 30 g/day[25 26] and the adequate intake of total dietary fibre of 14 g/1000 kcal/day reported by the U.S. Food and Nutrition Board.[27] Dashed vertical lines represent 15 g/day and 10 g/1000 kcal/day.

intake for the recall season and weekday. For multinomial logistic regression models, we imputed missing data using multivariate imputation by chained equations (m=35). We calculated the variance inflation to detect potential multicollinearity in the regression models.

Statistical analyses were performed using R V.4.1.3[35] with the following packages: *questionr* (V.0.7.7) for weighted frequencies, *spatstat.geom* (V.2.3-1) for weighted median and IQR, *mice* (V.3.14.0) for multivariate imputation by chained equations, *nnet* (V.7.3-17) for multinomial logistic regression models, and *car* (V.3.1.0) for variance inflation factors. The significance level was $p \leq 0.05$ for all analyses.

RESULTS

The data obtained from 2057 individuals were included in the analysis. Figure 1 shows the distribution of absolute and relative dietary fibre intake. The absolute dietary fibre intake recommendation of 30 g/day[25 26] was met by 13% of the population, and the relative dietary fibre intake recommendation of 14 g/1000 kcal/day[27] was met by 11% of the population. Table 1 shows the sociodemographic, lifestyle and anthropometric characteristics of the overall population and stratified by absolute and relative dietary fibre intake. Additional participant characteristics are shown in online supplemental table 1. Compared with the overall study population, participants in the high absolute and relative dietary fibre intake groups tended to be Swiss, have tertiary education, be of normal weight, highly physically active, and non-smokers. In the high absolute dietary fibre intake group, participants tended to be male and between 30 and 59 years old, and participants in the high relative dietary intake group tended to be female and above 60 years old.

Table 2 shows the dietary parameters of the overall population, as well as the absolute and relative dietary fibre intake groups. Participants in the high absolute dietary fibre group tended to have a higher food intake (in weight and in energy) compared with the overall study population. Additionally, they tended to score higher on the AHEI and follow a prudent or Swiss traditional dietary pattern rather than a Western dietary pattern. They also tended to consume more fruits and nuts, vegetables, and cereals, and less meat. Additional dietary parameters are listed in online supplemental table 2.

The linear relationship between dietary fibre intake (absolute and relative) and UPF consumption (weight percentage and energy percentage) is displayed using scatter plots, shown in online supplemental figure 1. Table 3 shows the results of multinomial logistic regression models investigating the associations between dietary fibre intake (absolute and relative) and quartiles of UPF consumption (weight percentage and energy percentage). Participants consuming a high amount of UPFs had lower odds of being in the medium and high dietary fibre intake groups compared with participants consuming a low amount of UPFs. The magnitude of the OR was similar for UPF weight and energy percentage. The odds of being in the medium or high dietary fibre intake group decreased linearly across quartiles of UPF consumption (p for trend ≤0.004).

DISCUSSION

Based on the population-representative Swiss National Nutrition Survey *menuCH*, a large part of the Swiss population (87%) does not reach the national recommendation of 30 g dietary fibre intake per day. When considering dietary fibre intake relative to individual energy intake,

Table 1 Sociodemographic, lifestyle and anthropometric characteristics of the *menuCH* population, overall and by absolute and relative dietary fibre intake groups

		Absolute dietary fibre intake			Relative dietary fibre intake		
	menuCH	**<15 g/day**	**15–30 g/day**	**≥30 g/day**	**<10 g/1000 kcal/day**	**10–14 g/1000 kcal/day**	**≥14 g/1000 kcal/day**
Overall *menuCH* population*, *n* (weighted %)	2057 (100)	527 (25)	1268 (61)	262 (13)	1193 (59)	624 (30)	240 (11)
Sex, *n* (weighted %)							
Female	1124 (50)	327 (59)	692 (49)	105 (39)	565 (43)	399 (59)	160 (63)
Male	933 (50)	200 (41)	576 (51)	157 (61)	628 (57)	225 (41)	80 (37)
Age group, *n* (weighted %)							
18–29 years	400 (19)	105 (19)	255 (19)	40 (15)	266 (21)	100 (16)	34 (14)
30–44 years	533 (30)	146 (33)	315 (28)	72 (33)	338 (33)	138 (25)	57 (28)
45–59 years	625 (30)	163 (28)	376 (30)	86 (33)	357 (29)	193 (31)	75 (29)
60–75 years	499 (22)	113(20)	322 (23)	64 (19)	232 (17)	193 (28)	74 (28)
Language region, *n* (weighted %)							
German	1341 (69)	309 (64)	850 (71)	182 (72)	774 (69)	410 (68)	157 (71)
French	502 (25)	142 (28)	296 (24)	64 (25)	281 (25)	165 (27)	56 (22)
Italian	214 (5.6)	76 (7.6)	122 (5.2)	16 (3.1)	138 (5.9)	49 (4.5)	27 (6.6)
Nation group, *n* (weighted %)							
Swiss only	1492 (61)	378 (61)	914 (61)	200 (65)	860 (60)	452 (62)	180 (66)
Swiss binational	297 (14)	83 (16)	189 (14)	25 (8.7)	178 (14)	92 (14)	27 (11)
Non-Swiss	268 (25)	66 (24)	165 (25)	37 (26)	155 (25)	80 (24)	33 (24)
Education, *n* (weighted %)							
Primary	89 (4.7)	38 (7.0)	46 (4.3)	5 (2.0)	61 (5.7)	23 (3.7)	5 (2.0)
Secondary	968 (43)	276 (48)	589 (42)	103 (35)	567 (43)	287 (42)	114 (40)
Tertiary	997 (53)	213 (45)	630 (53)	154 (63)	563 (51)	314 (55)	120 (57)
NA	3 (0.15)	0 (0)	3 (0.24)	0 (0)	2 (0.21)	0 (0)	1 (0.23)
BMI group, *n* (weighted %)							
Underweight (<18.5 kg/m^2)	51 (2.4)	10 (2.5)	30 (2.1)	11 (3.6)	26 (2.2)	17 (2.5)	8 (3.1)
Normal weight (18.5–24.9 kg/m^2)	1115 (54)	248 (44)	704 (56)	163 (62)	601 (50)	365 (59)	149 (63)
Overweight (25.0–29.9 kg/m^2)	629 (31)	174 (35)	389 (30)	66 (25)	393 (33)	178 (29)	58 (24)
Obese (>30.0 kg/m^2)	262 (13)	95 (18)	145 (11)	22 (9.7)	173 (15)	64 (10)	25 (10)
Physical activity, *n* (weighted %)							
Low	219 (11)	66 (13)	130 (11)	23 (8.4)	152 (14)	53 (9.2)	14 (5.5)
Moderate	487 (24)	118 (24)	301 (24)	68 (27)	265 (22)	169 (28)	53 (25)

Continued

Table 1 Continued

	menuCH	Absolute dietary fibre intake			Relative dietary fibre intake		
		<15 g/day	15–30 g/day	≥30 g/day	<10 g/1000 kcal/day	10–14 g/1000 kcal/day	≥14 g/1000 kcal/day
High	827 (40)	179 (35)	524 (41)	124 (46)	449 (39)	264 (41)	114 (46)
NA	524 (24)	164 (29)	313 (24)	47 (18)	327 (25)	138 (22)	59 (23)
Smoking, *n* (weighted %)							
Current	451 (23)	135 (27)	271 (23)	45 (18)	308 (28)	105 (18)	38 (15)
Former	688 (34)	170 (32)	424 (34)	94 (36)	392 (33)	215 (34)	81 (33)
Never	914 (43)	222 (42)	569 (43)	123 (46)	490 (38)	304 (48)	120 (52)
NA	4 (0.22)	0 (0)	4 (0.35)	0 (0)	3 (0.32)	0 (0)	1 (0.23)
Currently on diet, *n* (weighted %)							
No	1940 (94)	486 (91)	1207 (96)	247 (93)	1139 (96)	586 (93)	215 (90)
Yes	113 (5.4)	41 (8.6)	57 (3.8)	15 (6.9)	51 (4.1)	38 (6.5)	24 (9.4)
NA	4 (0.22)	0 (0)	4 (0.35)	0 (0)	3 (0.32)	0 (0)	1 (0.23)

n are unweighted, percentages are weighted for age group, sex, marital status, major region of Switzerland, nationality and household size according to the *menuCH* weighting strategy,[34] NAs are shown only if any exist. If the percentages do not add up exactly to 100%, this is due to rounding differences.
*Representative for age range 18–75 years.
BMI, body mass index; NA, not applicable.

Table 2 Dietary parameters of the *menuCH* population, overall and by absolute and relative dietary fibre intake groups

	menuCH	Absolute dietary fibre intake			Relative dietary fibre intake		
	(*n*=2057)	<15 g/day (*n*=527)	15–30 g/day (*n*=1268)	≥30 g/day (*n*=262)	<10 g/1000 kcal/day (*n*=1193)	10–14 g/1000 kcal/day (*n*=624)	≥14 g/1000 kcal/day (*n*=240)
Dietary fibre intake (g/day), median (IQR)	19 (15–25)	12 (10–14)	20 (18–24)	36 (32–39)	17 (13–21)	23 (19–28)	31 (24–37)
Dietary fibre intake (g/1000 kcal/day), median (IQR)	9.2 (7.0–12)	6.8 (5.5–8.4)	9.5 (7.6–12)	14 (11–15)	7.4 (6.3–8.6)	12 (11–13)	16 (15–18)
Energy intake (kcal/day), median (IQR)	2111 (1702–2584)	1644 (1379–2023)	2168 (1818–2596)	2698 (2269–3305)	2256 (1813–2714)	1943 (1636–2380)	1833 (1418–2268)
Total intake (g/day), median (IQR)	3372 (2787–3988)	2906 (2382–3576)	3395 (2876–4019)	3948 (3485–4829)	3340 (2798–3959)	3368 (2744–3955)	3581 (2894–4335)
CHO energy percentage, median (IQR)	42 (36–48)	40 (34–47)	43 (37–48)	46 (40–50)	41 (35–47)	43 (38–48)	47 (40–52)
Fat energy percentage, median (IQR)	36 (31–41)	36 (31–42)	36 (31–41)	35 (30–40)	36 (32–41)	36 (31–41)	32 (28–38)
Protein energy percentage, median (IQR)	15 (13–17)	16 (13–19)	15 (13–17)	14 (12–16)	15 (13–17)	14 (13–17)	14 (12–17)
Protein intake(g/kg BW*/day), median (IQR)	1.1 (0.9–1.4)	0.9 (0.8–1.2)	1.1 (0.9–1.4)	1.3 (1.1–1.6)	1.1 (0.9–1.5)	1.1 (0.8–1.3)	1.0 (0.7–1.3)
UPF weight percentage, median (IQR)	9.7 (4.6–18)	11 (5.4–20)	9.8 (4.7–17)	7.1 (3.7–12)	13 (6.9–22)	6.8 (3.6–12)	3.9 (1.9–7.4)
UPF weight percentage quartile, *n* (weighted %)							
Q1	515 (25)	114 (21)	316 (24)	85 (35)	171 (14)	222 (34)	122 (53)
Q2	514 (24)	118 (21)	320 (25)	76 (26)	262 (21)	175 (28)	77 (28)
Q3	514 (25)	133 (25)	323 (26)	58 (22)	330 (27)	156 (25)	28 (13)
Q4	514 (26)	162 (33)	309 (26)	43 (17)	430 (38)	71 (12)	13 (5.5)
UPF energy percentage, median (IQR)	26 (16–37)	30 (18–41)	26 (16–37)	20 (12–29)	31 (20–41)	21 (13–31)	18 (10–23)
UPF energy percentage quartile, *n* (weighted %)							
Q1	515 (24)	99 (18)	325 (25)	91 (35)	194 (16)	214 (33)	107 (45)
Q2	514 (25)	125 (23)	304 (24)	85 (33)	259 (21)	175 (28)	80 (34)
Q3	514 (26)	134 (27)	327 (27)	53 (20)	342 (29)	136 (23)	36 (14)
Q4	514 (25)	169 (33)	312 (25)	33 (12)	398 (34)	99 (15)	17 (6.6)
AHEI†, median (IQR)	45 (36–54)	40 (34–47)	45 (36–54)	55 (46–65)	39 (32–46)	51 (44–59)	61 (52–68)
Dietary patterns‡, *n* (weighted %)							
Prudent	486 (24)	97 (19)	301 (23)	88 (35)	169 (14)	206 (35)	111 (45)
Swiss traditional	744 (35)	155 (29)	477 (36)	112 (41)	411 (33)	252 (38)	81 (32)
Western-soft drinks	383 (20)	129 (26)	233 (19)	21 (9.1)	317 (28)	56 (8.2)	10 (6.3)
Western alcohol	444 (22)	146 (26)	257 (22)	41 (15)	296 (24)	110 (19)	38 (17)
Meat consumption§, *n* (weighted %)							
None	92 (5.1)	13 (2.8)	51 (4.5)	28 (12)	22 (1.9)	36 (7.3)	34 (16)
Low	308 (14)	52 (8.0)	190 (15)	66 (26)	115 (8.6)	122 (21)	71 (27)
Medium	1349 (64)	330 (60)	863 (67)	156 (58)	819 (68)	408 (61)	122 (52)
High	308 (16)	132 (29)	164 (13)	12 (4.1)	237 (21)	58 (10)	13 (4.7)

Continued

Table 2 Continued

	menuCH	Absolute dietary fibre intake			Relative dietary fibre intake		
	(*n*=2057)	<15 g/day (*n*=527)	15–30 g/day (*n*=1268)	≥30 g/day (*n*=262)	<10 g/1000 kcal/day (*n*=1193)	10–14 g/1000 kcal/day (*n*=624)	≥14 g/1000 kcal/day (*n*=240)
Fruits and nuts (g/day), median (IQR)	116 (27–237)	48 (0.0–119)	132 (42–238)	290 (158–432)	69 (4.4–157)	200 (97–319)	290 (193–417)
Vegetables (g/day), median (IQR)	113 (53–197)	71 (28–125)	118 (60–199)	206 (124–295)	87 (41–159)	146 (80–227)	213 (116–313)
Cereals (g/day), median (IQR)	169 (101–259)	118 (69–183)	180 (117–269)	248 (159–410)	166 (100–253)	173 (105–263)	167 (96–253)

n are unweighted, all other results are weighted for age group, sex, marital status, major region of Switzerland, nationality, household size, season and weekday according to the *menuCH* weighting strategy.[34] If the percentages do not add up exactly to 100%, this is due to rounding differences.
*Measured body weight corrected for clothing, if measured body weight was unavailable, self-reported body weight was used (*n*=7), for pregnant and lactating women reported body weight before pregnancy was used (*n*=27)
†Minimum score=0, maximum score=110
‡According to Krieger *et al*.[32]
§According to Steinbach *et al*.[33]
AHEI, Alternate Healthy Eating Index; CHO, carbohydrate; NA, not available; Q, quartile; UPF, ultraprocessed food.

similar results were obtained. UPF consumption was inversely associated with dietary fibre intake in a dose-dependent manner, showing that dietary fibres mainly stem from non-UPFs.

The dietary fibre intake in the *menuCH* study (19 g/day) is comparable to that reported in other European national nutrition surveys. Overall, the recommendation of 30 g dietary fibre per day is hardly reached at the population level.[1 36] For example, the median dietary fibre intake of adults is 24 g/day in Germany[37] and 19 g/day in the UK.[38] In addition, we analysed dietary fibre intake relative to energy intake and found similar results. Even with potentially lower recommendations or recommendations relative to energy intake, a large proportion of the population in our study would still have had insufficient dietary fibre intake.

Altogether, we found that participants with a higher overall food intake and a generally healthy lifestyle were more represented in the group with a high dietary fibre intake. For example, male and younger participants were more likely to be in the high absolute dietary fibre intake group; however, this is mainly attributed to their higher overall food consumption. In contrast, when looking at the relative dietary fibre intake, women and older participants consumed more dietary fibre. Our results suggest that especially people with a low education level, obesity, smokers and, in general, people with a particularly unhealthy lifestyle belong to the group with low fibre intake. Studies that investigated the determinants of low dietary fibre intake reported results consistent with our findings.[39 40]

We observed an inverse and dose-dependent relationship between UPF consumption and dietary fibre intake, suggesting that dietary fibres are mainly consumed via non-UPFs. In the analyses of relative dietary fibre, we observed small OR for the extreme groups (ie, UPF quartile 4 and dietary fibre intake ≥14 g/1000 kcal/day), which must be interpreted with caution. We built these groups despite a rather small *n* (see table 2), caused by the large variability in dietary fibre intake between participants, as we aimed to reflect the recommendations for dietary fibre intake. Using tertiles instead of cut-off values in line with recommendations increased the number of participants in the groups, but did not influence the magnitude of the OR, suggesting the robustness of our findings (data not shown). Nevertheless, when interpreting our results, the focus should be on the overall negative association between UPF consumption and dietary fibre intake. Our results are not aligned with those of a previous ecological study from Europe, which found no association between UPF consumption (in terms of energy percentage) and dietary fibre intake.[12] However, this study analysed country-level data rather than individual consumption data, possibly leading to an ecological fallacy and results not directly comparable to ours.

To improve the intake of dietary fibres in the population, public health measures may aim to increase dietary fibre intake through unprocessed or minimally processed

Table 3 Association between dietary fibre intake and ultraprocessed food consumption

	Absolute dietary fibre intake			Relative dietary fibre intake				Absolute dietary fibre intake			Relative dietary fibre intake		
	<15 g/d	15–30 g/d	≥30 g/d	<10 g/1000 kcal/d	10–14 g/1000 kcal/d	≥14 g/1000 kcal/d		<15 g/d	15–30 g/d	≥30 g/d	<10 g/1000 kcal/d	10–14 g/1000 kcal/d	≥14 g/1000 kcal/d
UPF weight percentage	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**UPF energy percentage**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Q1 0.0–4.5	1 –	1 –	1 –	1 –	1 –	1 –	Q1 0.0–16	1 –	1 –	1 –	1 –	1 –	1 –
Q2 4.5–9.3	1 –	0.97 (0.70–1.33)	**0.57** **(0.37–0.87)**	1 –	**0.56** **(0.42–0.75)**	**0.31** **(0.21–0.46)**	Q2 16–26	1 –	0.79 (0.57–1.09)	0.74 (0.49–1.12)	1 –	**0.62** **(0.46–0.82)**	**0.62** **(0.43–0.90)**
Q3 9.3–17	1 –	0.99 (0.72–1.36)	**0.47** **(0.31–0.73)**	1 –	**0.44** **(0.33–0.58)**	**0.14** **(0.09–0.22)**	Q3 26–36	1 –	**0.73** **(0.53–1.00)**	**0.41** **(0.26–0.63)**	1 –	**0.39** **(0.29–0.51)**	**0.18** **(0.11–0.28)**
Q4 17–92	1 –	**0.67** **(0.49–0.92)**	**0.22** **(0.14–0.35)**	1 –	**0.15** **(0.10–0.20)**	**0.04** **(0.02–0.07)**	Q4 26–95	1 –	**0.59** **(0.43–0.81)**	**0.17** **(0.10–0.29)**	1 –	**0.22** **(0.16–0.30)**	**0.07** **(0.04–0.13)**
p for trend	–	**0.004**	**<0.001**	–	**<0.001**	**<0.001**	*p* for trend	–	**<0.001**	**<0.001**	–	**<0.001**	**<0.001**

Results displayed as OR and 95% CI, statistically significant results printed in bold.
Results are derived from multinomial logistic regression models adjusted for sex, age, education, body mass index (BMI), physical activity, smoking, recall season, recall weekday and weighted for age group, sex, marital status, major region of Switzerland, nationality, household size, season and weekday according to the *menuCH* weighting strategy.[34] *p* for trend was calculated by using the medians of the UPF quartiles as continuous variable in the multinomial logistic regression model.
d, day; Q, quartile; UPF, ultraprocessed food.

foods. Our results suggest that population groups with a low socioeconomic status or unhealthy lifestyle need to be particularly targeted. Therefore, it would be useful to develop alternative or complementary recommendations with practical implications for these groups. Furthermore, recommendations for dietary fibre intake need to be translated into advice that can be easily realised. In fact, it is difficult for consumers to estimate their dietary fibre intake. The benefit of a recommendation without advice on how to achieve an intake of 30 g dietary fibre per day is questionable, and recommendations on the food group level may be more practical. For example, foods with a particularly high dietary fibre content can be promoted by recommending starchy fibre-rich foods such as legumes and whole grains, nuts and seeds, in addition to five portions of fruit and vegetables per day. At the same time, discouraging UPF consumption, for example, through food taxation/subsidisation or labelling of UPFs, might be beneficial to increase consumption of minimally processed or unprocessed foods.

Since 2019, the Swiss Federal Food Safety and Veterinary Office has supported the Nutri-Score, a food-labelling system with a coloured scale from A (green=balanced) to E (red=unbalanced). The score is determined using a scientifically validated formula, in which positive criteria include the content of fruits, vegetables, legumes, nuts, certain oils, dietary fibre, and protein, and negative criteria include sugar, salt, saturated fat and energy.[17] Therefore, adding dietary fibre leads to a 'greener' Nutri-Score,[17] providing an incentive for food manufacturers to add isolated dietary fibres or ultraprocessed fibre rich foods to their products. However, increasing the dietary fibre content by adding dietary fibre at the cost of higher UPF consumption is not likely to benefit consumers. For example, a previously published study reported that adding dietary fibre to ultraprocessed cereal flakes did not affect total postprandial blood glucose or satiety in a healthy population.[41] Currently, the widely used Nutri-Score does not consider the degree of food processing,[17] and UPFs can be found in all Nutri-Score categories. More than a quarter of Nutri-Score A products and more than half of Nutri-Score B products belong to *NOVA* class 4.[42] Front-of-pack labelling with the Nutri-Score could be complemented with an indicator for the processing level, such as the new graphically modified Nutri-Score recently tested by Srour *et al*.[43] Finally, dietary fibre content should be included in the nutrition facts labels to allow consumers identifying fibre-rich products and estimate dietary fibre intake (eg, 5–8 g fibre/100 g).

Strengths and limitations

The association between UPFs and dietary fibre intake has been poorly studied. We used individual consumption data, and due to the applied weighting strategy, the sample is representative of the Swiss population aged 18–75 years. The 24-hour dietary recalls allowed for a more accurate classification of non-UPFs versus UPFs than food frequency questionnaires. Furthermore, we conducted data analysis with both UPF energy and weight percentage, taking energy-free UPFs into account.

Besides the cross-sectional design and residual confounding, the study might be limited by participation bias, since participants might have been more interested in health-related topics than the general population. If our results were affected by participation bias, we may have overestimated dietary fibre intake and underestimated UPF consumption. 24-hour dietary recalls can be limited by under-reporting or over-reporting and recall bias. Furthermore, the degree of food processing was sometimes unclear, leading to potential misclassification of some food items within the ultraprocessed and non-ultraprocessed groups. In instances of uncertainty, we adopted a conservative approach which would lead to an underestimation of the observed association.

CONCLUSION

Based on the recommendation of consuming 30 g of dietary fibre per day, our study showed that dietary fibre intake is insufficient in the Swiss population. Similarly, dietary fibre intake relative to energy intake was also insufficient. The recommendation of 30 g of dietary fibre per day is difficult to implement and needs to be translated into consumer-friendly advice for foods that are particularly high in dietary fibre. Our results showed that UPFs are not a good source of dietary fibre. By increasing the proportion of minimally processed or unprocessed products and correspondingly decreasing UPF consumption, we expect an increase in fibre intake. Therefore, it is desirable to make unprocessed products more attractive than UPFs. This could be achieved through public health measures such as food taxation/subsidisation or labelling of UPFs and educational approaches about dietary fibre intake and UPF consumption in schools and the community.

Author affiliations
[1]Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), University Hospital and University of Bern, Bern, Switzerland
[2]Department of Pharmaceutical Sciences, Division of Clinical Pharmacy and Epidemiology, University of Basel, Basel, Switzerland
[3]Health Department, Nutrition Group, Swiss Distance University of Applied Sciences (FFHS) / University of Applied Sciences and Arts of Southern Switzerland (SUPSI), Zurich, Switzerland
[4]Epidemiology, Biostatistics and Prevention Institute, Division of Chronic Disease Epidemiology, University of Zurich, Zurich, Switzerland
[5]Health Department, Bern University of Applied Sciences, Bern, Switzerland

Twitter Giulia Pestoni @GiuliaPestoni

Acknowledgements We thank Dr. sc. nat. Julia Braun, Division of Chronic Disease Epidemiology, Epidemiology, Biostatistics and Prevention Institute, University of Zurich for the statistical consulting.

Contributors Conceptualisation: KAS, ZS, GP and DF. Data curation: KAS and GP. Formal analysis: KAS. Funding acquisition: KAS, SM, ZS and DF. Methodology: KAS, GP and DF. Supervision: SM, ZS, GP and DF. Visualisation, writing – original draft: KAS. Writing – review and editing: all authors. DF is responsible for the overall content as the guarantor.

Funding This work was supported by the SV Foundation; a third-party grant of the Division of Clinical Pharmacy and Epidemiology, University of Basel (grant number FO119900); and the Department of Diabetes, Endocrinology, Nutritional Medicine

and Metabolism, Inselspital, Bern University Hospital (research fund number WFE-012). The SV Foundation had no role in the design, analysis or writing of this article.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Cantonal ethics committee of Vaud, ref: Protocol 26/13. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed by Angeline Chatelan, Geneva School of Health Sciences, Switzerland.

Data availability statement Data may be obtained from a third party and are not publicly available. Data may be obtained from the Swiss Federal Food Safety and Veterinary Office.

ORCID iDs
Katja A Schönenberger http://orcid.org/0000-0002-2122-4746
Valentina V Huwiler http://orcid.org/0000-0002-0357-6887
Emilie Reber http://orcid.org/0000-0001-8799-2708
Stefan Mühlebach http://orcid.org/0000-0002-8471-7513
Zeno Stanga http://orcid.org/0000-0002-8630-2477
Giulia Pestoni http://orcid.org/0000-0002-5933-7439
David Faeh http://orcid.org/0000-0003-2630-8102

REFERENCES

1 Stephen AM, Champ MM-J, Cloran SJ, *et al*. Dietary fibre in Europe: current state of knowledge on definitions, sources, recommendations, intakes and relationships to health. *Nutr Res Rev* 2017;30:149–90.
2 Monteiro CA, Cannon G, Levy RB, *et al*. Ultra-processed foods: what they are and how to identify them. *Public Health Nutr* 2019;22:936–41.
3 Monteiro CA, Cannon G, Levy R, *et al*. NOVA. The star shines bright. *World Nutr J* 2016;7:28–38.
4 Fardet A. Minimally processed foods are more satiating and less hyperglycemic than ultra-processed foods: a preliminary study with 98 ready-to-eat foods. *Food Funct* 2016;7:2338–46.
5 Moubarac J-C, Batal M, Louzada ML, *et al*. Consumption of ultra-processed foods predicts diet quality in Canada. *Appetite* 2017;108:512–20.
6 Louzada ML da C, Ricardo CZ, Steele EM, *et al*. The share of ultra-processed foods determines the overall nutritional quality of diets in Brazil. *Public Health Nutr* 2018;21:94–102.
7 Bertoni Maluf VA, Bucher Della Torre S, Jotterand Chaparro C, *et al*. Description of ultra-processed food intake in a Swiss population-based sample of adults aged 18 to 75 years. *Nutrients* 2022;14:4486.
8 Martínez Steele E, Popkin BM, Swinburn B, *et al*. The share of ultra-processed foods and the overall nutritional quality of diets in the US: evidence from a nationally representative cross-sectional study. *Popul Health Metr* 2017;15:6.
9 Pagliai G, Dinu M, Madarena MP, *et al*. Consumption of ultra-processed foods and health status: a systematic review and meta-analysis. *Br J Nutr* 2021;125:308–18.
10 Bonaccio M, Di Castelnuovo A, Ruggiero E, *et al*. Joint association of food nutritional profile by nutri-score front-of-pack label and ultra-processed food intake with mortality: Moli-Sani prospective cohort study. *BMJ* 2022;378:e070688.
11 Wang L, Du M, Wang K, *et al*. Association of ultra-processed food consumption with colorectal cancer risk among men and women: results from three prospective US cohort studies. *BMJ* 2022;378:e068921.
12 Mertens E, Colizzi C, Peñalvo JL. Ultra-processed food consumption in adults across Europe. *Eur J Nutr* 2022;61:1521–39.
13 Pestoni G, Habib L, Reber E, *et al*. Ultraprocessed food consumption is strongly and dose-dependently associated with excess body weight in Swiss women. *Obesity (Silver Spring)* 2021;29:601–9.
14 Yangilar F. The application of dietary fibre in food industry: structural features, effects on health and definition, obtaining and analysis of dietary fibre: a review. *J Food Nutr Res* 2013;1:13–23.
15 European Commission. Commission Regulation (EU) no 432/2012 of 16 may 2012 establishing a list of permitted health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health. *Off J Eur Union* 2012;136:1–40.
16 EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific opinion on the substantiation of health claims related to dietary fibre (ID 744, 745, 746, 748, 749, 753, 803, 810, 855, 1415, 1416, 4308, 4330) pursuant to article 13(1) of regulation (EC) no 1924/2006. *EFSA Journal* 2010;8:1735.
17 Chantal J, Hercberg S, World Health Organization. Development of a new front-of-pack nutrition label in France: the five-colour nutri-score. *Public Health Panor* 2017;3:712–25.
18 Hall KD, Ayuketah A, Brychta R, *et al*. Ultra-processed diets cause excess calorie intake and weight gain: an inpatient randomized controlled trial of ad libitum food intake. *Cell Metab* 2019;30:67–77.
19 Monteiro CA, Moubarac J-C, Levy RB, *et al*. Household availability of ultra-processed foods and obesity in nineteen European countries. *Public Health Nutr* 2018;21:18–26.
20 Lachat C, Hawwash D, Ocké MC, *et al*. Strengthening the reporting of observational studies in epidemiology-nutritional epidemiology (STROBE-nut): an extension of the STROBE statement. *PLoS Med* 2016;13:e1002036.
21 Chatelan A, Beer-Borst S, Randriamiharisoa A, *et al*. Major differences in diet across three linguistic regions of Switzerland: results from the first national nutrition survey menuCH. *Nutrients* 2017;9:1163.
22 Bochud M, Chatelan A, Blanco J-M. Anthropometric characteristics and indicators of eating and physical activity behaviors in the Swiss adult population: results from menuCH 2014-2015. 2017. Available: http://www.bag.admin.ch/dam/bag/de/dokumente/npp/forschungsberichte/forschungsberichte-e-und-b/schlussbericht-menuch-chuv.pdf.download.pdf/MenuCH1_Report_March2017.pdf [Accessed May 2022].
23 Chatelan A, Marques-Vidal P, Bucher S, *et al*. Lessons learnt about conducting a multilingual nutrition survey in Switzerland: results from menuCH pilot survey. *Int J Vitam Nutr Res* 2017;87:25–36.
24 Slimani N, Casagrande C, Nicolas G, *et al*. The standardized computerized 24-H dietary recall method EPIC-soft adapted for Pan-European dietary monitoring. *Eur J Clin Nutr* 2011;65 Suppl 1:S5–15.
25 Sieber R, Reinli K. Verbrauch an Kohlenhydraten und Nahrungsfasern in der Schweiz. In: *Kohlenhydrate in der Ernährung: Stellungnahme und Empfehlungen der Eidgenössischen Ernährungskommission (EEK) 2009*. 2009. Available: http://www.blv.admin.ch/dam/blv/de/dokumente/das-blv/organisation/kommissionen/eek/kohlenhydrate-in-der-ernaehrung/expertenbericht-kohlenhydrate-ernaehrung.pdf.download.pdf/Kohlenhydrate_de.pdf
26 D-A-CH Referenzwerte Für die Nährstoffzufuhr. Bonn, Germany Deutsche Gesellschaft für Ernährung (DGE), Österreichische Gesellschaft für Ernährung (ÖGE), Schweizerische Gesellschaft für Ernährung (SGE); 2021.
27 Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC, USA: The National Academies Press, 2005.
28 IPAQ Research Committee. Guidelines for data processing and analysis of the International physical activity questionnaire (IPAQ) – short and long forms; 2005.
29 Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. *BMJ* 1995;311:158–61.
30 Chiuve SE, Fung TT, Rimm EB, *et al*. Alternative dietary indices both strongly predict risk of chronic disease. *J Nutr* 2012;142:1009–18.
31 Pestoni G, Krieger J-P, Sych JM, *et al*. Cultural differences in diet and determinants of diet quality in Switzerland: results from the National nutrition survey menuCH. *Nutrients* 2019;11:126.
32 Krieger J-P, Pestoni G, Cabaset S, *et al*. Dietary patterns and their sociodemographic and lifestyle determinants in Switzerland: results from the National nutrition survey menuCH *Nutrients* 2018;11:62.
33 Steinbach L, Rohrmann S, Kaelin I, *et al*. No-meat eaters are less likely to be overweight or obese, but take dietary supplements more

often: results from the Swiss National nutrition survey menuCH. *Public Health Nutr* 2021;24:4156–65.
34 Pasquier J, Chatelan A, Bochud M. *Weighting strategy*. Lausanne, Switzerland: Institute of Social and Preventive Medicine (IUMSP), 2017.
35 R Core Team. R: A language and environment for statistical computing. Vienna, Austria R Foundation for Statistical Computing; 2022. Available: https://www.R-project.org
36 Rippin HL, Hutchinson J, Jewell J, *et al*. Adult nutrient intakes from current national dietary surveys of European populations. *Nutrients* 2017;9:1288.
37 Ergebnisbericht Teil 2: Nationale Verzehrsstudie II, . 2008Available: http://www.mri.bund.de/fileadmin/MRI/Institute/EV/NVSII_Abschlussbericht_Teil_2.pdf [Accessed Jul 2022].
38 Public Health England, Food Standards Agency. National diet and nutrition survey rolling programme years 9 to 11 (2016/2017 to 2018/2019. 2020. Available: http://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/943114/NDNS_UK_Y9-11_report.pdf [Accessed Jul 2022].
39 Fayet-Moore F, Cassettari T, Tuck K, *et al*. Dietary fibre intake in Australia. Paper I: associations with demographic, socio-economic, and anthropometric factors. *Nutrients* 2018;10:599.
40 Seljak BK, Valenčič E, Hristov H, *et al*. Inadequate intake of dietary fibre in adolescents, adults, and elderlies: results of slovenian representative SI. *Nutrients* 2021;13:3826.
41 Hlebowicz J, Wickenberg J, Fahlström R, *et al*. Effect of commercial breakfast fibre cereals compared with corn flakes on postprandial blood glucose, gastric emptying and satiety in healthy subjects: a randomized blinded crossover trial. *Nutr J* 2007;6:22.
42 Romero Ferreiro C, Lora Pablos D, Gómez de la Cámara A. Two dimensions of nutritional value: nutri-score and NOVA. *Nutrients* 2021;13:2783.
43 Srour B, Hercberg S, Galan P, *et al*. Effect of a new graphically modified nutri-score on the objective understanding of foods' nutrient profile and ultraprocessing: a randomised controlled trial. *BMJ Nutr Prev Health* 2023;6:108–18.

Paper 2

Effect of Anti-Inflammatory Diets on Pain in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

Katja A. Schönenberger [1,2] , Anne-Catherine Schüpfer [1], Viktoria L. Gloy [3], Paul Hasler [4], Zeno Stanga [1], Nina Kaegi-Braun [5], Emilie Reber [1]

[1] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Bern, Switzerland

[2] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3] Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland

[4] Division of Rheumatology, Medical University Department, University of Basel Medical Faculty, Kantonsspital Aarau, Aarau, Switzerland

[5] Division of General Internal and Emergency Medicine, Medical University Department, University of Basel, Medical Faculty, Cantonal Hospital Aarau, Aarau, Switzerland

Nutrients. 2021;13(12):4221. doi: 10.3390/nu13124221

nutrients

MDPI

Systematic Review

Effect of Anti-Inflammatory Diets on Pain in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

Katja A. Schönenberger [1,2,*], Anne-Catherine Schüpfer [1], Viktoria L. Gloy [3], Paul Hasler [4], Zeno Stanga [1], Nina Kaegi-Braun [5] and Emilie Reber [1]

1 Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland; anne-catherine.schuepfer@students.unibe.ch (A.-C.S.); zeno.stanga@insel.ch (Z.S.); emilie.reber@insel.ch (E.R.)
2 Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, 4031 Basel, Switzerland
3 Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, 4031 Basel, Switzerland; viktoria.gloy@usb.ch
4 Division of Rheumatology, Medical University Department, University of Basel Medical Faculty, Kantonsspital Aarau, 5001 Aarau, Switzerland; paul.hasler@ksa.ch
5 Division of General Internal and Emergency Medicine, Medical University Department, University of Basel Medical Faculty, Kantonsspital Aarau, 5001 Aarau, Switzerland; nina.kaegi@ksa.ch
* Correspondence: katja.schoenenberger@extern.insel.ch; Tel.: +41-31-664-21-05

Abstract: Various nutritional therapies have been proposed in rheumatoid arthritis, particularly diets rich in ω-3 fatty acids, which may lead to eicosanoid reduction. Our aim was to investigate the effect of potentially anti-inflammatory diets (Mediterranean, vegetarian, vegan, ketogenic) on pain. The primary outcome was pain on a 10 cm visual analogue scale. Secondary outcomes were C-reactive protein levels, erythrocyte sedimentation rate, health assessment questionnaire, disease activity score 28, tender/swollen joint counts, weight, and body mass index. We searched MEDLINE (OVID), Embase (Elsevier), and CINAHL for studies published from database inception to 12 November 2021. Two authors independently assessed studies for inclusion, extracted study data, and assessed the risk of bias. We performed a meta-analysis with all eligible randomized controlled trials using RevMan 5. We used mean differences or standardized mean differences and the inverse variance method of pooling using a random-effects model. The search retrieved 564 unique publications, of which we included 12 in the systematic review and 7 in the meta-analysis. All studies had a high risk of bias and the evidence was very low. The main conclusion is that anti-inflammatory diets resulted in significantly lower pain than ordinary diets (−9.22 mm; 95% CI −14.15 to −4.29; $p = 0.0002$; 7 RCTs, 326 participants).

Keywords: anti-inflammatory diet; arthralgia; ketogenic diet; Mediterranean diet; pain; rheumatoid arthritis; vegan diet; vegetarian diet

Citation: Schönenberger, K.A.; Schüpfer, A.-C.; Gloy, V.L.; Hasler, P.; Stanga, Z.; Kaegi-Braun, N.; Reber, E. Effect of Anti-Inflammatory Diets on Pain in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *Nutrients* **2021**, *13*, 4221. https://doi.org/10.3390/nu13124221

Academic Editor: Dirkjan van Schaardenburg

Received: 27 September 2021
Accepted: 22 November 2021
Published: 24 November 2021

1. Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory disorder that primarily affects the joints. Clinical manifestations of RA include joint pain, stiffness, swelling, as well as joint destructions, and systemic manifestations. RA may cause progressive joint damage and disability. Risk factors for RA are genetic and non-genetic, including smoking, changes in the microbiota, female sex, Western diet, and ethnic factors [1]. The global burden of disease study 2019 showed a global prevalence of 0.22%; 0.31% in females and 0.13% in males [2]. RA treatment comprises a multimodal approach. The pharmacologic therapy consists of disease-modifying anti-rheumatic drugs (DMARDs) and anti-inflammatory therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids [1]. The non-pharmacologic measures include patient education, physiotherapy, and nutritional therapy, among others [3].

Nutritional therapy for RA aims to attenuate inflammation by altering the ratio of ω-6 to ω-3 fatty acids and increasing antioxidants. The reduction of arachidonic acid (AA), an ω-6 fatty acid, is particularly relevant. AA is the precursor of eicosanoids, which are involved in a variety of cellular functions and reactions. Eicosanoids are also mediators of inflammation, and the amount of AA released from the cell membrane determines the intensity of inflammation. When less AA is present in the cell membrane, less AA is released, and fewer eicosanoids are formed [4].

Endogenous biosynthesis produces AA and thus eicosanoids from linoleic acid adjusted to physiologic requirements. In contrast, in developed countries, AA in cell membranes mostly originates from the diet, while endogenous biosynthesis is very low, the median daily AA intake being about 210–250 mg [5]. Vegetarian diets contain less AA than diets with meat, whereas vegan diets contain virtually no AA. There is evidence from population studies that nutrients of animal origin, as consumed in high amounts in the Western diet, correlate with the occurrence of RA [6,7]. Therefore, vegetarian and vegan diets may favorably influence inflammation.

In addition, the low intake of the ω-3 fatty acid eicosapentaenoic acid (EPA) in Western societies favors the accumulation of AA. EPA lowers the AA content in cell membranes by replacing AA [8]. This results in less AA available for oxidation to inflammatory mediators. In addition, EPA is a competitive inhibitor of cyclooxygenase and lipoxygenase, two enzymes relevant to eicosanoid biosynthesis [4]. The Mediterranean diet includes weekly fish consumption but little dairy products, eggs, and red meat, thus, more fish oil (rich in ω-3 fatty acids EPA and docosahexaenoic acid (DHA)) and less AA than in the Western diet. Indeed, the role of fish oil supplements in the treatment of RA is well studied [9–11]. This may contribute to an anti-inflammatory effect of the Mediterranean diet.

The impact of dietary fibers on the composition and metabolic activity of the gut microbiome further contributes to the anti-inflammatory effect of vegetarian, vegan or Mediterranean diets. In RA patients, a high-fiber diet increases anti-inflammatory short-chain fatty acids, decreases pro-inflammatory cytokines, and favorably alters the gut microbiome composition [12].

The ketogenic diet may reduce eicosanoid formation through the lower generation of reactive oxygen species (ROS) of the ketone metabolism compared to the glucose metabolism [13]. ROS activate phospholipase A2 in the cell membrane of immune cells, which exclusively cleaves AA from phospholipids of the cell membrane. ROS also serve as substrates for the oxidation of AA and lead to excessive eicosanoid formation [14]. In addition, the ketogenic diet increases adenosine, which may alleviate pain and have an anti-inflammatory effect [13,15].

Our aim was to synthesize the evidence and pool the effect of the above-mentioned anti-inflammatory diets (Mediterranean, vegetarian, vegan, and ketogenic) on pain in rheumatoid arthritis in a systematic review and a meta-analysis.

2. Methods

We conducted this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16].

Studies comparing the effect of a Mediterranean, vegetarian, vegan, or ketogenic diet vs. an ordinary omnivorous diet on pain in adults with RA were eligible. We included randomized and non-randomized, controlled and uncontrolled trials (including before-after studies), and observational studies (including cohort and case-control studies). We excluded reviews, conference abstracts, case reports, editorials, letters, and notes. Inclusion criteria for the studied population were adults ≥18 years of age with RA. We excluded studies on patients with non-rheumatic disorders or rheumatic disorders other than RA, and adolescents and children <18 years of age. We included studies identifying their intervention as Mediterranean, vegetarian, vegan, or ketogenic diet. We excluded non-whole diet interventions, i.e., single food items, nutrients, or supplements. The control

intervention was an ordinary omnivorous diet. We included studies published in English, German, or French with no restrictions on the publication date.

We searched the electronic bibliographic databases MEDLINE via OVID, Embase via Elsevier, and CINAHL with Full Text via EBSCOhost. The last search date for all databases was 12 November 2021. In addition, we screened the reference lists of relevant publications. The search strategy included terms relating to RA-related pain and Mediterranean, vegetarian, vegan, or ketogenic diets. We searched for MeSH terms, Emtree terms, and CINAHL Subject Headings in MEDLINE, Embase, and CINAHL, respectively, and text words in title, abstract and keywords. Appendix A shows the full electronic search strategies.

Two authors independently screened titles and/or abstracts of records identified from database searches or additional sources, to identify those potentially meeting the inclusion criteria. We retrieved the full text of potentially eligible studies and two authors independently assessed them for eligibility. We resolved any disagreement over the eligibility of particular studies through discussion with a third reviewer.

We used a standardized, pilot-tested data extraction form, including information on study size, population, intervention, comparison, outcomes, study design, intervention period, and results for the main and secondary outcomes of this meta-analysis. Two authors extracted the data independently and resolved discrepancies through discussion, where necessary with a third author. We requested missing data from study authors via email. We sought baseline and endpoint data for the primary outcome pain score on a 10 cm visual analog scale (VAS) and the following secondary outcomes: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), health assessment questionnaire (HAQ) [17], disease activity score 28 (DAS28) [18,19], swollen joint count (SJC), tender joint count (TJC), weight and BMI. In addition, we sought data for the following variables: participant characteristics (number, age, sex, height), intervention and comparison characteristics, concomitant medication, and study design.

Two authors independently assessed the risk of bias in individual studies using version 2 of the Cochrane tool for assessing risk of bias in randomized trials (RoB 2) [20] and the risk of bias in non-randomized studies—of interventions (ROBINS-I) tool [21].

If possible, we summarized outcome results quantitatively in meta-analyses by using the inverse variance method based on random-effects models. We analyzed the data using RevMan 5 [22]. The principal summary measures were mean differences or standardized mean differences for outcomes measured with different instruments or on different scales (SJC and TJC). We included only randomized controlled trials (RCTs) in the meta-analysis. If the change-from-baseline SD was missing, we imputed it using a correlation coefficient from another study in the meta-analysis [23–25]. We assessed heterogeneity using the χ^2 test and the I^2 and τ^2 statistic.

Since there were less than ten studies included in the meta-analysis, the risk of publication bias by evaluating the symmetry of funnel plots remained undetected [26].

Finally, we performed a transparent assessment and rating of the quality of evidence with the grading of recommendations assessment, development, and evaluation (GRADE) approach [27], using GRADEpro software [28].

3. Results

Figure 1 depicts the number of studies screened, assessed for eligibility, and included in the review. Table 1 shows the characteristics of the included studies. No studies assessing the effect of a ketogenic diet on pain in RA were eligible. The interventions varied in terms of included therapies (e.g., physical and drug therapy), but were usually constant over the study period.

In 1979, Sköldstam and colleagues conducted the first RCT on the effect of 7–10 days fasting followed by 9 weeks lactovegetarian diet in RA [29]. Of the 14 patients in the diet group, 8 (57%) had less pain than at baseline and planned to continue the lactovegetarian diet after the trial. However, as a group they showed no change in pain, stiffness, or use of analgesics. In 1991, Kjeldsen-Kragh and colleagues published another landmark RCT [30].

A diet group of 27 patients initially fasted (800–1260 kJ/day) for 7–10 days, followed by an individually adjusted gluten-free vegan diet for 3–5 months. Then, they gradually changed to a lactovegetarian diet for the remainder of the total study period of one year. Compared with the 26 patients in the control group, who ate ordinary mixed food, the diet group reported significant improvements in pain, duration of morning stiffness, SJC, TJC, ESR, and CRP levels, among others. In 1979, Sköldstam and colleagues conducted the first RCT on the effect of 7–10 days fasting followed by 9 weeks lactovegetarian diet in RA [29]. Of the 14 patients in the diet group, 8 (57%) had less pain than at baseline and planned to continue the lactovegetarian diet after the trial. However, as a group they showed no change in pain, stiffness, or use of analgesics. In 1991, Kjeldsen-Kragh and colleagues published another landmark RCT [30]. A diet group of 27 patients initially fasted (800–1260 kJ/day) for 7–10 days, followed by an individually adjusted gluten-free vegan diet for 3–5 months. Then, they gradually changed to a lactovegetarian diet for the remainder of the total study period of one year. Compared with the 26 patients in the control group, who ate ordinary mixed food, the diet group reported significant improvements in pain, duration of morning stiffness, SJC, TJC, ESR, and CRP levels, among others.

Hafström and colleagues published a RCT in 2001, in which they assessed the clinical effects of one year gluten-free vegan diet vs. non-vegan diet according to the American College of Rheumatology (ACR) response criteria (ACR20) [31]. They found a significant improvement in all clinical variables included in the ACR20 except CRP in the vegan group as compared with the non-vegan group.

In 2003, Sköldstam and colleagues conducted another RCT with 51 RA patients [32]. This time, they compared 12 weeks of Mediterranean diet with usual diet in Swedish participants. At the end of the study, patients on the Mediterranean diet reported significant decreases in pain, DAS28, HAQ score, SJC, and CRP compared to the control group. This difference was apparent only in the second half of the trial.

García-Morales and colleagues conducted the largest RCT so far [33]. RA patients were randomized in four groups: Mediterranean diet + dynamic exercise program (n = 26), dynamic exercise program (n = 37), Mediterranean diet (n = 40), and control (n = 31). The dynamic exercise program consisted of 80–90 min training sessions twice a week. After 24 weeks, the scores of physical function, vitality, mental health, bodily pain, and global health domains showed significant improvement in the dynamic exercise program group compared with the other groups.

The pooled results showed that overall patients on anti-inflammatory diets reported significantly less pain than patients in the control groups (mean difference (MD) −9.22 mm, 95% CI −14.15 to −4.29 mm; p = 0.0002; 7 RCTs, 326 participants, Figure 2), improved HAQ (−0.20 points, 95% CI −0.36 to −0.05 points; p = 0.01; 4 RCTs; 202 participants, Figure S2), and lower SJC (standardized mean difference (SMD) −0.60, 95% CI −1.08 to −0.11; p = 0.02; 4 RCTs; 214 participants, Figure S3). In addition, patients on anti-inflammatory diets lost more weight than patients in the control groups (MD −3.73 kg, 95% CI −5.45 to −2.01 kg; $p < 0.0001$; 6 RCTs; 286 participants, Figure S5) and BMI decreased (MD −1.28 kg/m^2, 95% CI −1.89 to −0.67 kg/m^2; $p < 0.0001$; 4 RCTs; 209 participants, Figure S6). There were no significant differences in CRP (Figure 3), ESR (Figure S1), and TJC (Figure S4). Since only two RCTs reported DAS28, we did not perform a meta-analysis for this outcome.

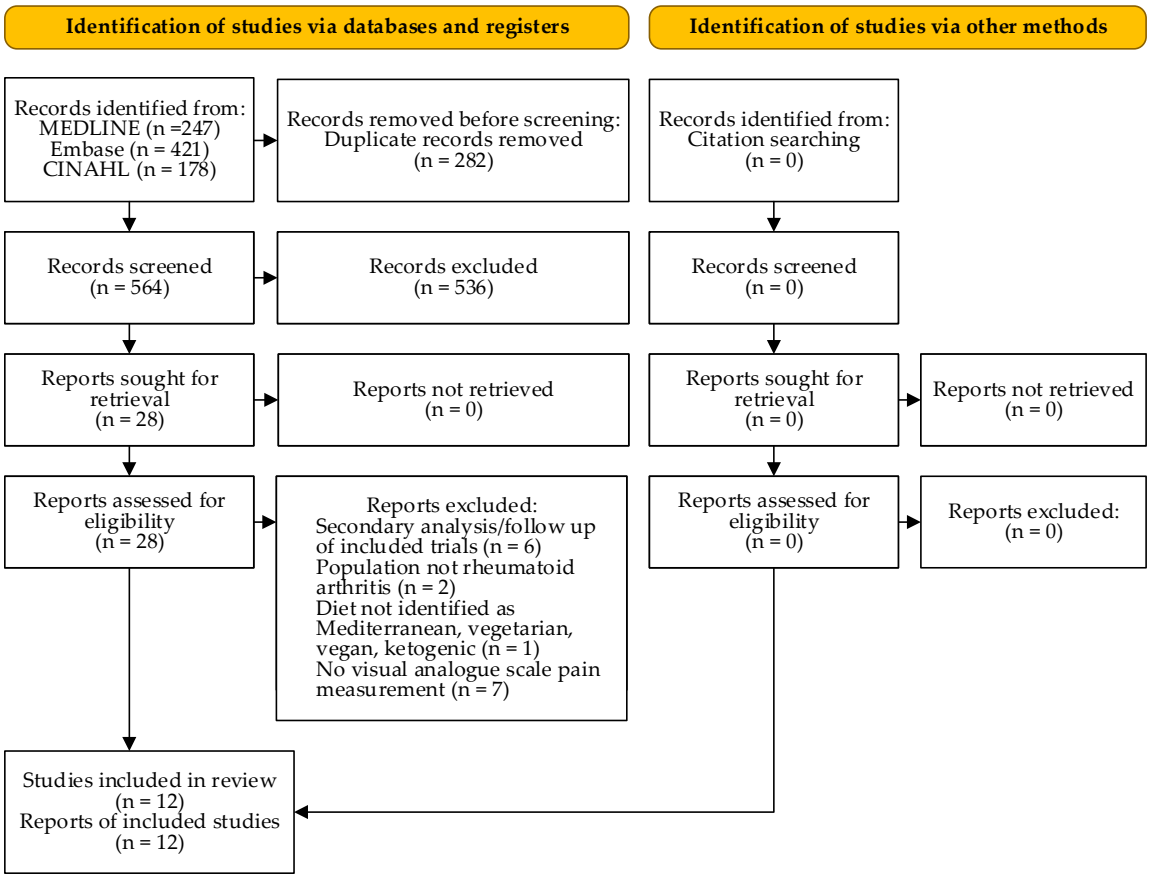


Figure 1. PRISMA flow diagram (according to [16]).

Table 1. Study characteristics.

Author Year	Population: n (% female) Age, Mean (SD/Range/IQR), y	Intervention vs. Control	Diet	Outcome, Mean (SD) Baseline; Endpoint			Study Design
					Intervention	Control	
Abendroth et al. 2010 [34]	MED: n = 28 (93%) Age: 60 (SD 12)	2 weeks MED vs. 7-day fasting	MED according to Leitzmann [35]: normocaloric, mostly vegetarian, whole grain diet, fruit, and vegetables 7 p/day, abundant intake of whole grain bread, pasta and rice, fish 2 p/week, exclusive use of olive and canola oil	Pain, mm CRP, mg/L HAQ DAS28 BMI, kg/m^2	35 (27); 33 (26) 20 (27); 16 (22) 2.4 (0.8); 2.2 (0.8) 5.4 (1.4); 4.5 (1.3) 25.5 (5.8); NA	NA	non-randomized intervention study
Adam et al. 2003 [36]	AID + corn oil: n = 30 (93%) Age: 58 (SD 13) WD + corn oil: n = 30 (93%) Age: 57 (SD 13)	WD vs. AID with menhaden oil vs. corn oil crossover, 3 months each	AID: modified lactovegetarian diet, only plant-derived fats and oils, no egg yolk, dairy products with reduced fat, meat maximum 2 × 120 g/week WD: usual diet, characteristic for industrialized countries, meat, and meat products >2×/week	Pain, mm CRP, mg/L SJC, n TJC, n Weight, kg BMI, kg/m^2	AID + corn oil 48 (21); 39 (16) 16 (15); 15 (15) 35 (4.9); 30 (4.5) 34 (5.1); 30 (4.7) 65 (11); 63 (9.3) 24.9 (0.7); 24.1 (0.7)	WD + corn oil 44 (18); 44(17) 22 (25); 22 (24) 34 (2.8); 36 (4.7) 36 (4.9); 36 (4.7) 62 (10); 63 (8.0) 23.2 (0.7); 23.3 (0.7)	RCT
García-Morales et al. 2020 [33]	MED: n = 40 (100%) Age: 46 (SD 13) Control: n = 31 (100%) Age: 49 (SD 12)	24 weeks MED + DEP vs. DEP vs. MED vs. control	MED: individualized according to Harris-Benedict BMR [37], 50% carbohydrates, 30% fats, 20% proteins, olive or canola oil as main dietary fat, whole grains (1–2 p/meal), fruits (2–4 p/day), vegetables (2–3 p/meal), fish (>2 p/week), oilseeds (1–2 p/day), legumes (>2 p/week), red meat (<2 p/week) Control: general nutritional recommendations	Pain, mm CRP, mg/L ESR, mm/h HAQ DAS28 SJC, n TJC, n Weight, kg BMI, kg/m^2	MED: 45 (32); 35 (30) 6 (9); 6 (11) 11 (9); 11 (12) 0.5 (0.5); 0.5 (0.6) 2.2 (1.1); 2.4 (0.6) 1.0 (1.6); 0.9 (1.5) 1.4 (2.0); 2.9 (2.6) 67 (10); 64 (10) 27.2 (3.6); 26.5 (3.7)	Control: 51 (27); 52 (25) 4 (4); 9 (10) 16 (10); 18 (16) 0.9 (0.7); 0.8 (0.6) 2.6 (0.9); 2.4 (0.7) 1.4 (1.9); 2.0 (2.3) 1.5 (1.7); 0.7 (1.2) 64 (8.3); 66 (16) 27.1 (4.2); 27.6 (6.2)	RCT

Table 1. *Cont.*

Author Year	Population: n (% female) Age, Mean (SD/Range/IQR), y	Intervention vs. Control	Diet	Outcome, Mean (SD) Baseline; Endpoint			Study Design
					Intervention	Control	
Hafström et al. 2001 [31]	Vegan: *n* = 38 Age: 50 (SD 9.6) Control: *n* = 28 Age: 51 (SD 12)	1 year gluten-free vegan diet vs. non-vegan diet	Gluten-free vegan: vegetables, root vegetables, nuts and fruits, buckwheat, millet, corn, rice, and sunflower seeds. Unshelled sesame seeds in the form of sesame milk were a daily source of calcium. Non-vegan diet: variety of foods from all food groups	Pain, mm CRP, mg/L HAQ Weight, kg	46 (19); 33 (28) 23 (19); 18 (28) 1.4 (0.4); 1.1 (0.7) 66 (13); 61 (10)	46 (21); 44 (26) 25 (22); 18 (20) 1.3 (0.5); 1.2 (0.5) 68 (20); 66 (15)	RCT
Ingegnoli et al. 2020 [38]	*n* = 205 (80%) Age: Mdn 53 (IQR 44–59)	N/A (observational study on the association between the MED score and RA disease impact, activity, and comorbidities)		Pain CRP HAQ DAS28-CRP SJC TJC BMI	Univariate analysis: association between outcomes (dependent variables) and the adherence to MED (independent variable) regression coefficient (95% CI) −0.08 (−0.15, −0.01) 0.01 (−0.03, 0.05) −0.01 (−0.02, −0.001) −0.01 (−0.04, 0.01) −0.01 (−0.03, 0.01) −0.02 (−0.06, 0.02) −0.04 (−0.15,0.07)		observational, cross-sectional study
Kjeldsen-Kragh et al. 1991 [30]	Vegetarian: *n* = 27 (89%) Age: 53 (range 26–63) Control: *n* = 26 (81%) Age: 56 (range 38–78)	13 months vegetarian vs. usual diet	Vegetarian: initial 7–10 days fast (800–1260 kJ/day), afterwards reintroduction of a new food item every 2nd day, during the first 3–5 months no gluten, meat, fish, eggs, dairy products, refined sugar, citrus fruits, salt, strong spices, preservatives, alcoholic beverages, tea, coffee, afterwards reintroduction of milk, other dairy products Control: ordinary mixed food	Pain, mm HAQ Weight, kg	NA; 36 (27) NA; 1.0 (0.6) NA; 65 (11)	NA; 55 (24) NA; 1.1 (0.6) NA; 67 (11)	RCT

Table 1. *Cont.*

Author Year	Population: n (% female) Age, Mean (SD/Range/IQR), y	Intervention vs. Control	Diet	Outcome, Mean (SD) Baseline; Endpoint			Study Design
					Intervention	Control	
McDougall et al. 2002 [39]	Vegan: *n* = 24 (92%) Age: 54 (SD 11)	4 weeks vegan diet	Low-fat, vegan diet: no animal products or added fats and oils of any kind, ad libitum menus based on common starches, such as beans, breads, corn, pastas, potatoes, sweet potatoes, and rice, fresh or fresh-frozen fruits and vegetables, dehydrated cereals, soups, main entrees	Pain, mm CRP, mg/L ESR, mm/h SJC, n TJC, n Weight, kg	49 (20); 34 (20) 21 (18); 17 (17) 50 (30); 50 (28) 27 (9); 22 (8) 24 (12); 17 (16) 68 (19); 65 (18)	NA	uncontrolled, pre-post intervention study
McKellar et al. 2007 [40]	MED: *n* = 75 (100%) Age: 54 (IQR 47–64) Control: *n* = 55 (100%) Age: 53 (IQR 45–61)	6 months MED vs. healthy eating	MED: 6-week cookery course on Medi-terranean-type diet, weekly 2 h cookery class, written information on a Medi-terranean-type diet, healthy eating and recipes promoting fruits, vegetables and legumes, substitution of saturated fat with olive oil or spreads containing olive oil Control: readily available written information on healthy eating	Pain, mm CRP, mg/L ESR, mm/h HAQ DAS28 SJC, n TJC, n Weight, kg BMI, kg/m^2	Median: 50; 50 10; 10 19; 16 1.8; 1.6 4.7; 4.4 6; 4 5; 4 66; 65 25.9; 25.4	Median: 55; 63 8.5; 8.0 19; 16 1.8; 1.9 5.0; 4.8 6; 5 6; 6 70; 73 27.7; 28.2	non-randomized intervention study

Table 1. *Cont.*

Author Year	Population: n (% female) Age, Mean (SD/Range/IQR), y	Intervention vs. Control	Diet	Outcome, Mean (SD) Baseline; Endpoint			Study Design
					Intervention	Control	
Nenonen et al. 1998 [41]	Vegan: *n* = 22 (82%) Age: 49 (SD 7) Control: *n* = 20 (95%) Age: 56 (SD 11)	2–3 months vegan vs. omnivorous diet	Vegan living food diet according to Hänninen [42]: uncooked, rich in lacto-bacilli, no animal products, no refined substances, no added salt, majority of food items soaked and sprouted (seeds and grains), fermented, bread is blended and dehydrated. Control: previous omnivorous diet	Pain, mm CRP, mg/L ESR, mm/h SJC, n TJC, n Weight, kg BMI, kg/m^2	36 (14); 23 (18) 13 (16); 16 (22) 33 (16); 41 (22) 3.4 (2.5); 3.6 (3.0) 8.6 (4.7); 6.5 (4.7) 68 (10); 62 (9) 25.5 (4.0); 23.4 (3.5)	38 (15); 25 (13) 17 (24); 12 (19) 40 (26); 43 (26) 3.9 (3.6); 3.8 (2.8) 9.6 (4.6); 9.6 (5.2) 64 (12); 64 (11) 23.5 (3.4); 23.7 (3.5)	RCT
Sköldstam et al. 1979 [29]	Vegetarian: *n* = 16 (63%) Age: 52 (range 35–66) Control: *n* = 10 (90%) Age: 54 (range 43–65)	9 weeks vegetarian vs. normal diet	Vegetarian: initial 7–10 days fast (800 kJ/day, 3 L fruit and vegetable juices), followed by plain lactovegetarian diet, no animal or fish protein (including egg), yoghurt allowed freely, fresh milk and cream discouraged, no alcohol, tobacco, coffee, tea, restriction on salt, sugar, white flour, small quantities of grain products Control: normal diet	Pain, mm ESR, mm/h Weight, kg	35 (19), Δ-12 (32) 41 (23), Δ2.3 (11) 71 (15), Δ−2.6 (2.1)	27 (17), Δ-3 (21) 41 (20), Δ0.7 (14) 69 (9.5), Δ0.6 (2.0)	RCT
Sköldstam 1986 [43]	*n* = 20 (90%) Age: range 35–68	4 months vegan diet vs. ordinary diet	Vegan: initial 7–10 days fast, followed by diet excluding meat, fish, eggs and dairy products, refined sugar, corn flour, salt, strong spices, preservatives, alcoholic beverages, tea, coffee Control: ordinary diet	Pain, mm CRP, mg/L ESR, mm/h Weight, kg	45 (NA); 36 (NA) No change No change Δ−4.8 (0.7)	NA	uncontrolled, pre-post intervention study

Table 1. *Cont.*

Author Year	Population: n (% female) Age, Mean (SD/Range/IQR), y	Intervention vs. Control	Diet	Outcome, Mean (SD) Baseline; Endpoint			Study Design
					Intervention	Control	
Sköldstam et al. 2003 [32]	MED: *n* = 26 (81%) Age: 58 (range 33–73) Control: *n* = 25 (80%) Age: 59 (range 35–75)	12 weeks MED vs. usual diet	Cretan MED according to de Lorgeril [44]: olive and canola oil for cooking, canola-based margarine, reduced consumption of dairy products or low-fat dairy products, green or black tea Control: ordinary hospital food followed by usual diet at home.	Pain, mm	32 (20); 20 (13)	31 (20); 34 (21)	RCT
				CRP, mg/L	17 (20); 12 (15)	15 (14); 15 (12)	
				ESR, mm/h	24 (15); 25 (15)	23 (15); 25 (19)	
				HAQ	0.7 (0.5); 0.6 (0.4)	0.8 (0.6); 0.8 (0.6)	
				DAS28	4.4 (1.2); 3.9 (1.2)	4.3 (1.4); 4.3 (1.5)	
				SJC, n	7.0 (5.6); 5.2 (5.1)	6.9 (5.0); 7.5 (5.7)	
				TJC, n	6.8 (5.9); 4.5 (5.1)	6.9 (6.3); 6.1 (6.4)	
				Weight, kg	79 (14); 76 (14)	73 (13); 73 (13)	
				BMI, kg/m^2	28.4 (4.9); 27.3 (4.6)	25.7 (3.6); 25.6 (3.6)	

AID, anti-inflammatory diet; BMR, basal metabolic rate; CRP, C-reactive protein; DAS28, disease activity score 28 [18]; DAS28-CRP, disease activity score 28 based on C-reactive protein [19]; DEP, dynamic exercise program; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire [17]; IQR, interquartile range; Mdn, median; MED, Mediterranean diet; NA, not applicable or not available; p, portions; RA, rheumatoid arthritis; RCT, randomized clinical trial; SJC, swollen joint count; TJC, tender joint count; WD, Western diet; y, years.

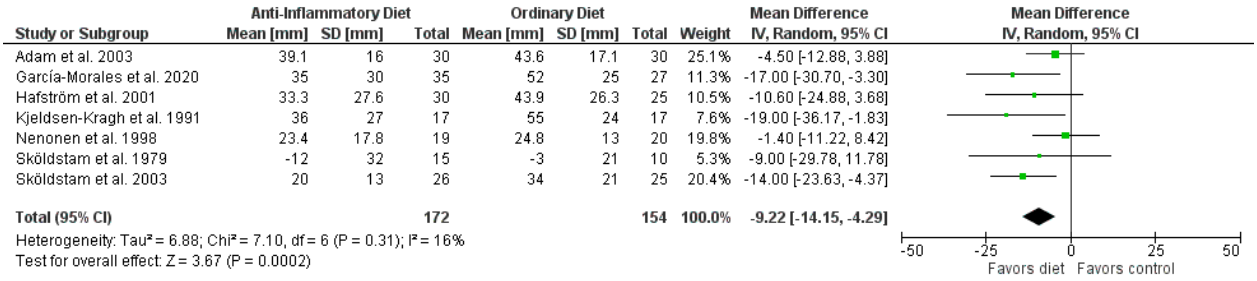


Figure 2. Forest plot summarizing the effect of anti-inflammatory diets on pain.

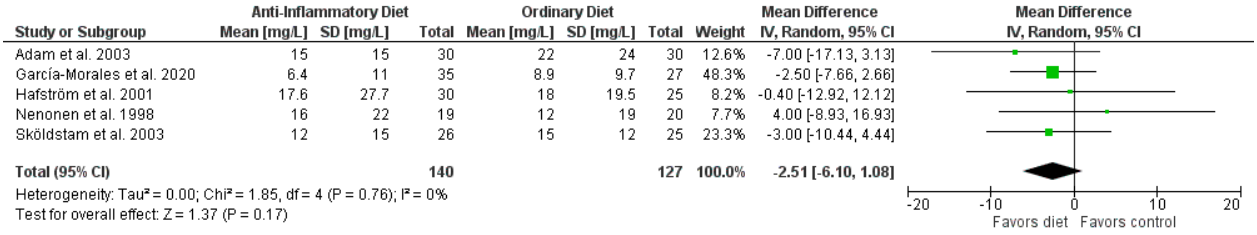


Figure 3. Forest plot summarizing the effect of anti-inflammatory diets on C-reactive protein levels.

Subgroup analysis showed that Mediterranean diets tended to have a greater effect on pain than vegetarian or vegan diets did (−14.99 mm, 95% CI −22.87 to −7.11 mm; $p = 0.0002$; 2 RCTs, 113 participants vs. −6.13 mm, 95% CI −11.46 to−0.80 mm; $p = 0.02$; 5 RCTs, 213 participants; test for subgroup differences $p = 0.07$, Figure S7). In addition, studies with a longer intervention period tended to have greater effects (intervention period ≤3 months −6.71 mm, 95% CI −12.52 to −0.90 mm; $p = 0.02$; 4 RCTs, 175 participants vs. intervention period >3 months −15.19 mm, 95% CI −23.76 to −6.63 mm; $p = 0.0005$; 3 RCTs, 151 participants; test for subgroup differences $p = 0.11$, Figure S8).

Tables 2 and 3 summarize the risk of bias assessment of the RCTs and non-randomized studies, respectively, for the outcome pain. All studies had a high risk of bias in the domain measurement of the outcome, since it is not possible to blind the dietary intervention and pain is a subjective, self-reported outcome. For objectively measured secondary outcomes, all RCTs had some concerns overall, since there was no information on whether the data that produced this result were analyzed in accordance with a pre-specified analysis plan. Consequently, the GRADE assessment resulted in very low or low certainty for all outcomes (Appendix B).

A search on ClinicalTrials.gov (accessed on 2 September 2021) revealed four studies by the Physicians Committee for Responsible Medicine with a vegan diet intervention in RA patients. Two of the studies are active (NCT01700881 and NCT03580681), while the others were completed in 2012 (NCT01544101) and 2018 (NCT03417648). The researchers were not able to share the unpublished results at this point, but they are summarizing and publishing the findings from several replications of the same study [45].

Table 2. Risk of bias assessment of randomized controlled trials for the primary outcome pain.

Author Year	Randomization Process	Deviations from Interventions	Missing Outcome Data	Outcome Measurement	Selection of the Reported Result	Overall Bias
Adam et al. 2003 [36]	Some concerns	Low	Low	High	Some concerns	High
García-Morales et al. 2020 [33]	Low	Low	Low	High	Some concerns	High
Hafström et al. 2001 [31]	Some concerns	Low	Low	High	Some concerns	High
Kjeldsen-Kragh et al. 1991 [30]	Some concerns	Low	Low	High	Some concerns	High
Nenonen et al. 1998 [41]	Some concerns	Some concerns	Low	High	Some concerns	High
Sköldstam et al. 1979 [29]	Low	Some concerns	Low	High	Some concerns	High
Sköldstam et al. 2003 [32]	Low	Some concerns	Low	High	Some concerns	High

Table 3. Risk of bias assessment of non-randomized studies for the primary outcome pain.

Author Year	Confounding	Selection of Participants	Intervention Classification	Deviations from Interventions	Missing Outcome Data	Outcome Measurement	Selection of the Reported Result	Overall Bias
Abendroth et al. 2010 [34]	Serious	Low	Moderate	No information	No information	Serious	Moderate	Serious
Ingegnoli et al. 2020 [38]	Serious	Moderate	Low	No information	Low	Serious	Low	Serious
McDougall et al. 2002 [39]	Low	Low	Low	Low	Low	Serious	Low	Serious
McKellar et al. 2007 [40]	Low	Low	Low	No information	Low	Serious	Low	Serious
Sköldstam 1986 [43]	Low	Low	No information	Low	No information	Serious	Low	Serious

4. Discussion

Our meta-analysis showed a significant improvement in pain in RA patients on anti-inflammatory diets compared with ordinary diets. Stauffer et al. determined that for a baseline VAS of 30–49 mm, the minimal clinically important difference for improvement was 7–11 mm [46]. Therefore, the mean difference of our meta-analysis (−9.22 mm) is clinically relevant, although the 95% CI (−14.15 to −4.29 mm) might refute this. Non-randomized trials support our findings [38,39,43]. Given the level of evidence for the outcome pain, the actual effect could deviate from the estimated effect.

Subgroup analysis showed that Mediterranean diets tended to have a greater effect on pain than vegetarian or vegan diets did. However, only two RCTs intervened with a Mediterranean diet. The observational, cross-sectional study by Ingegnoli et al. found a significant negative association between Mediterranean diet adherence and pain [38]. Special consideration should be given when recommending the Mediterranean diet to RA patients, as gluten sensitivity is more common in patients with rheumatic diseases than in the general population [47], and the Mediterranean diet contains high amounts of whole

grain products. None of the eligible studies investigated the effect of a ketogenic diet, which comes close to fasting in terms of metabolism, but is difficult to follow because it is restrictive in everyday life.

RCTs with significant effects tended to have a longer intervention period (13 months [30], 6 months [33], 12 weeks [32]) than RCTs with insignificant effects (3 months [36], 2–3 months [41], 9 weeks [29]). Studies investigating ω-3 fatty acids in RA found similar results [48]. This indicates that effects of dietary interventions for RA occur from three months onwards.

Intervention group patients with a higher baseline BMI [32,33] appeared to have a greater improvement in pain than patients with normal weight or borderline overweight [36,41]. However, improvement in pain did not correlate with weight loss. A previous meta-analysis concluded that obesity negatively impacts disease activity and patient-reported outcomes in RA [49].

The significant and clinically relevant improvement in the secondary outcomes HAQ and SJC confirmed the perceived improvement in pain. However, although CRP and ESR show a tendency for improvement, these results were not significant and therefore we cannot assume an underlying pathophysiological mechanism for the improved pain. Furthermore, the physician-assessed SJC improved significantly, while the TJC did not.

The effect of exercise in RA is well established [50,51]. García-Morales et al. [33] conducted a multi-arm study, including a control group without any intervention and intervention groups receiving a dynamic exercise program or Mediterranean diet only or both. There was no additional benefit of the Mediterranean diet and exercise over exercise only, suggesting that the observed effect might be the result of any lifestyle intervention vs. no intervention. Likewise, all patients in the study of Sköldstam et al. [29] participated in the usual physiotherapy and physical training on the ward and the decrease in pain was not significantly greater in the intervention group. Conversely, all participants in the study of Kjeldsen-Kragh et al. [30] were offered physiotherapy three times a week during the first four weeks of the study, yet the decrease in pain was greater in the diet group after the first month of the study. Similarly, Sköldstam et al. [32] found a significantly greater decrease in pain in the diet than the control group, although they recruited patients from the outpatient-based rehabilitation program, which includes patient education, strength and fitness training, and individual physiotherapy and occupational therapy.

The studies included mainly female patients (92%). Of note, the RA prevalence is two to three times higher in women than in men [2]. The studies included in this systematic review did not investigate differences between male and female patients. Therefore, the information is insufficient to make any conclusions.

A Cochrane review of 14 RCTs involving 837 RA patients on different diets provided little evidence of their effectiveness. However, the results of studies with different interventions and follow-up lengths were not pooled. Consequently, each study was reported individually in a separate forest plot [52]. Another meta-analysis included studies with interventions termed as low-inflammatory diet, anti-inflammatory diet, Mediterranean diet or synonyms of these in patients with osteoarthritis, RA, and seronegative arthropathies. While the physical outcome measures as well as pain scores did not favor either diet overall, the effect was significant in RA. Thus, their results were similar to the present meta-analysis in terms of patient-reported outcomes and quality of evidence, but they found a significant effect of diet on the inflammatory biomarkers interleukin-6 and CRP [3].

In the context of multimodal therapy, diets are one of many possibilities that should be offered to patients. Perception of pain varies from individual to individual and is highly subjective, and there may be a placebo effect in many patients. The influence of other factors cannot be investigated based on the current data, but it is probably high. Nevertheless, we chose perceived pain as the primary outcome of this meta-analysis because it has a positive effect on the disease burden and quality of life. Many RA patients seek adjuvant therapies to pharmacotherapy and are mainly looking for symptom and specifically pain relief [53]. Hence, the effect of nutritional therapy on pain is not only essential for patient outcome but also for compliance. We assume, however, that the effect of diet is greater with high disease

activity and low medication therapy. Especially when drug therapy is exhausted, diet can be a valuable therapeutic modality with few side effects. This is particularly relevant with regard to chronic opioid use and addiction, for which RA patients are especially susceptible [54–56].

The limitations of this meta-analysis are in the nature of the research question, as it is not possible to blind dietary interventions and pain measured by VAS is a subjective self-reported outcome. Therefore, all studies had a high risk of bias for the primary outcome pain. In addition, publication bias was difficult to assess due to the small number of published RCTs. Apart from the two unpublished completed trials registered in ClinicalTrials.gov (accessed on 2 September 2021), there were no indications for publication bias. The risk of bias in the individual studies together with the width of the CI resulted in very low certainty of evidence in the GRADE rating.

We pooled the results of dietary interventions with Mediterranean, vegetarian, and vegan diet in this meta-analysis. Our rationale for this was that the definition of these diets differed across the studies (see Table 1). Moreover, the implementation and monitoring of diet adherence was heterogeneous. In spite of this, all studies investigated an intervention with an anti-inflammatory diet as defined in the protocol of this meta-analysis. Finally, this heterogeneity assumingly represents the actions and implementation by patients in clinical practice outside of a study setting better than strict definitions and separations of the diets. Therefore, we chose to perform a pragmatic and explorative, yet statistically more powerful meta-analysis to investigate the potential of nutritional therapy with anti-inflammatory diets. Nevertheless, we conducted a subgroup analysis on the effect of the different diet forms for the main outcome pain (Figure S7).

In conclusion, the decreased subjective pain rating of patients on anti-inflammatory diets compared with patients on ordinary diets was clinically relevant. Vegetarian, vegan, and Mediterranean diets might be beneficial for some RA patients. However, due to lack of blinding, effects on the patient-reported outcome pain might be biased.

5. Other Information

We registered this systematic review and meta-analysis on the international prospective register of systematic reviews (PROSPERO, registration number CRD42021223712). An additional protocol was not prepared. There were no amendments to information provided at registration.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/nu13124221/s1, Figure S1: Forest plot summarizing the effect of anti-inflammatory diets on erythrocyte sedimentation rate, Figure S2: Forest plot summarizing the effect of anti-inflammatory diets on health assessment questionnaire score, Figure S3: Forest plot summarizing the effect of anti-inflammatory diets on swollen joint count, Figure S4: Forest plot summarizing the effect of anti-inflammatory diets on tender joint count, Figure S5: Forest plot summarizing the effect of anti-inflammatory diets on weight loss, Figure S6: Forest plot summarizing the effect of anti-inflammatory diets on body mass index decrease, Figure S7: Forest plot summarizing the subgroup analysis on the effect of Mediterranean vs. vegetarian or vegan diets on pain, Figure S8: Forest plot summarizing the subgroup analysis on the effect of intervention duration on pain.

Author Contributions: Ideation, K.A.S., P.H., Z.S., N.K.-B. and E.R.; literature search, K.A.S. and A.-C.S.; data extraction, K.A.S. and A.-C.S.; risk of bias assessment, K.A.S. and A.-C.S.; formal analysis, K.A.S.; GRADE assessment, K.A.S. and V.L.G.; writing—original draft preparation, K.A.S.; writing—review and editing, V.L.G., P.H., Z.S., N.K.-B. and E.R.; visualization, K.A.S.; supervision, Z.S. and E.R. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by a third-party grant of the Division of Clinical Pharmacy and Epidemiology, University of Basel, grant number FO119900, and the Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Inselspital, Bern University Hospital, research fund number WFE-002. The APC was funded by the Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Inselspital, Bern University Hospital.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in this article and corresponding supplementary materials.

Acknowledgments: We thank the medical information specialist of the University Medical Library, University of Basel, for the advice on the search strategy. We appreciate the methodologic and statistic consulting by the Department of Clinical Research, University of Basel.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A.

Appendix A.1. Search Strategy: MEDLINE (OVID)

((Arthritis, Rheumatoid/ or Arthritis/ or (rheuma* or arthrit* or polyarthrit*).ti,ab,kw.) and (exp Diet, Vegetarian/ or exp Vegetarians/ or exp Diet, Mediterranean/ or exp Diet, Ketogenic/ or (vegetarian* or lactovegetarian* or pescovegetarian* or pescatarian* or ovovegetarian* or ovolactovegetarian* or lactoovovegetarian* or vegan* or plant-based or (Mediterranean adj3 diet) or MedDiet or (MIND adj3 diet) or (keto* adj3 diet) or (low adj3 carb*) or (carb* adj3 restricted) or (high adj3 fat adj3 diet)).ti,ab,kw.)) not (exp Animals/ not Humans.sh)

Appendix A.2. Search Strategy: Embase (Elsevier)

('rheumatoid arthritis'/de OR 'arthritis'/de OR 'rheumatic disease'/de OR (rheuma* OR arthrit* or polyarthrit*):ti,ab,kw) AND ('vegetarian diet'/exp OR 'vegetarian'/exp OR 'Mediterranean diet'/exp OR 'ketogenic diet'/exp OR (vegetarian* OR lactovegetarian* OR pescovegetarian* OR pescatarian* OR ovovegetarian* OR ovolactovegetarian* OR lactoovovegetarian* OR vegan* OR plant-based OR (Mediterranean NEAR/3 diet) OR MedDiet OR (MIND NEAR/3 diet) OR (keto* NEAR/3 diet) OR (low NEAR/3 carb*) OR (carb* NEAR/3 restricted) OR (high NEAR/3 fat NEAR/3 diet)):ti,ab,kw) NOT (('animal'/de OR 'animal experiment'/exp OR 'nonhuman'/de) NOT ('human'/exp OR 'human experiment'/de)) NOT 'conference abstract'/it

Appendix A.3. Search Strategy: CINAHL with Full Text (EBSCOhost)

(MH (Arthritis, Rheumatoid OR Arthritis OR Rheumatic Diseases) OR TI (rheuma* OR arthrit* OR polyarthrit*) OR AB (rheuma* OR arthrit* OR polyarthrit*)) AND (MH (Vegetarianism OR Plant-Based Diet OR Mediterranean Diet OR Diet, Ketogenic OR Diet, Low Carbohydrate) OR TI (vegetarian* OR lactovegetarian* OR pescovegetarian* OR pescatarian* OR ovovegetarian* OR ovolactovegetarian* OR lactoovovegetarian* OR vegan* OR plant-based OR (Mediterranean N3 diet) OR MedDiet OR (MIND N3 diet) OR (keto* N3 diet) OR (low N3 carb*) OR (carb* N3 restricted) OR (high N3 fat N3 diet)) OR AB (vegetarian* OR lactovegetarian* OR pescovegetarian* OR pescatarian* OR ovovegetarian* OR ovolactovegetarian* OR lactoovovegetarian* OR vegan* OR plant-based OR (Mediterranean N3 diet) OR MedDiet OR (MIND N3 diet) OR (keto* N3 diet) OR (low N3 carb*) OR (carb* N3 restricted) OR (high N3 fat N3 diet))).

Appendix B

Table A1. Grading of Recommendations Assessment, Development and Evaluation (GRADE) rating.

Outcome	Certainty Assessment							No. of Patients		Absolute Effect (95% CI)	Certainty
	No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Anti-Inflammatory Diet	Ordinary Diet		
Pain	7	randomized trials	very serious [a]	not serious	not serious	serious [b]	none	172	154	MD 9.22 lower (14.15 lower to 4.29 lower)	⊕◯◯◯ very low
CRP	5	randomized trials	serious [c]	not serious	not serious	very serious [d]	none	140	127	MD 2.51 lower (6.10 lower to 1.08 higher)	⊕◯◯◯ very low
ESR	4	randomized trials	serious [e]	not serious	not serious	serious [f]	none	95	82	MD 2.9 lower (7.67 lower to 1.87 higher)	⊕⊕◯◯ low
HAQ	4	randomized trials	very serious [g]	not serious	not serious	serious [f]	none	108	94	MD 0.20 lower (0.36 lower to 0.05 lower)	⊕⊕◯◯ low
SJC	4	randomized trials	very serious [h]	serious [i]	not serious	not serious	none	112	102	SMD 0.6 lower (1.08 lower to 0.11 lower)	⊕◯◯◯ very low
TJC	4	randomized trials	very serious [h]	very serious [j]	not serious	serious [f]	none	110	102	SMD 0.39 lower (1.17 lower to 0.39 higher)	⊕◯◯◯ very low
Weight loss	6	randomized trials	serious [k]	very serious [j]	not serious	not serious	none	152	134	MD 3.73 lower (5.45 lower to 2.01 lower)	⊕◯◯◯ very low
BMI decrease	4	randomized trials	serious [l]	very serious [j]	not serious	not serious	none	93	99	MD 1.28 lower (1.89 lower to 0.67 lower)	⊕◯◯◯ very low

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; MD, mean difference; SJC, swollen joint count; SMD, standardized mean difference; TJC, tender joint count. [a] All 7 trials had high risk of bias, overall. Some concerns were noted regarding the randomization process in 4 trials. Some concerns were noted due to deviations from the intended intervention in 3 trials. In all 7 trials a high risk of bias was noted regarding the outcome measurement. [b] Imprecision was downgraded by 1 level because the 95% confidence interval of the mean difference was sufficiently wide that the estimate could also refute the effectiveness of the intervention assuming a clinically important difference of 7–11 units on the VAS. [c] All 5 trials had some concerns regarding the overall bias. Some concerns were noted regarding the randomization process in 3 trials. Some concerns were noted due to deviations from the intended intervention in 2 trials. [d] Imprecision was downgraded by 2 levels because the 95% confidence interval of the mean difference was sufficiently wide that the estimate could also refute the effectiveness of the intervention and the sample size of the meta-analysis was too small. [e] All 4 trials had some concerns regarding the overall bias. Some concerns were noted regarding the randomization process in 1 trial. Some concerns were noted due to deviations from the intended intervention in 3 trials. [f] Imprecision was downgraded by 1 level because the 95% confidence interval of the mean difference was sufficiently wide that the estimate could also refute the effectiveness of the intervention. [g] All 4 trials had high risk of bias overall. Some concerns were noted regarding the randomization process in 2 trials. Some concerns were noted due to deviations from the intended intervention in 1 trial. In all 4 trials high risk of bias was noted regarding the outcome measurement. [h] All 4 trials had high risk of bias overall. Some concerns were noted regarding the randomization process in 2 trials. Some concerns were noted due to deviations from the intended intervention in 2 trial. In all 4 trials a high risk of bias was noted regarding the outcome measurement. [i] Inconsistency was downgraded by 1 level because the I^2 statistic may represent substantial heterogeneity. [j] Inconsistency was downgraded by 2 levels because the I^2 statistic may represent substantial heterogeneity and confidence intervals for the results of individual studies have poor overlap. [k] All 6 trials had some concerns regarding overall bias. Some concerns were noted regarding the randomization process in 3 trials. Some concerns were noted due to deviations from the intended intervention in 3 trials. [l] All 4 trials had some concerns regarding the overall bias. Some concerns were noted regarding the randomization process in 2 trials. Some concerns were noted due to deviations from the intended intervention in 2 trials.

References

1. Smolen, J.S.; Aletaha, D.; Barton, A.; Burmester, G.R.; Emery, P.; Firestein, G.S.; Kavanaugh, A.; McInnes, I.B.; Solomon, D.H.; Strand, V.; et al. Rheumatoid arthritis. *Nat. Rev. Dis. Primers* **2018**, *4*, 18001. [CrossRef]
2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet* **2020**, *396*, 1204–1222. [CrossRef]
3. Genel, F.; Kale, M.; Pavlovic, N.; Flood, V.M.; Naylor, J.M.; Adie, S. Health effects of a low-inflammatory diet in adults with arthritis: A systematic review and meta-analysis. *J. Nutr. Sci.* **2020**, *9*, e37. [CrossRef]
4. Calder, P.C. n-3 Polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am. J. Clin. Nutr.* **2006**, *83*, 1505S–1519S. [CrossRef] [PubMed]
5. Forsyth, S.; Gautier, S.; Salem, N., Jr. Global Estimates of Dietary Intake of Docosahexaenoic Acid and Arachidonic Acid in Developing and Developed Countries. *Ann. Nutr. Metab.* **2016**, *68*, 258–267. [CrossRef]
6. Grant, W.B. The role of meat in the expression of rheumatoid arthritis. *Br. J. Nutr.* **2000**, *84*, 589–595. [CrossRef]
7. Pattison, D.J.; Symmons, D.P.; Lunt, M.; Welch, A.; Luben, R.; Bingham, S.A.; Khaw, K.T.; Day, N.E.; Silman, A.J. Dietary Risk Factors for the Development of Inflammatory Polyarthritis: Evidence for a Role of High Level of Red Meat Consumption. *Arthritis Rheum* **2004**, *50*, 3804–3812. [CrossRef]
8. Siriwardhana, N.; Kalupahana, N.S.; Moustaid-Moussa, N. Health Benefits of n-3 Polyunsaturated Fatty Acids: Eicosapentaenoic Acid and Docosahexaenoic Acid. *Adv. Food Nutr. Res.* **2012**, *65*, 211–222. [CrossRef] [PubMed]
9. James, M.; Proudman, S.; Cleland, L. Fish oil and rheumatoid arthritis: Past, present and future. *Proc. Nutr. Soc.* **2010**, *69*, 316–323. [CrossRef] [PubMed]
10. Lee, Y.H.; Bae, S.C.; Song, G.G. Omega-3 Polyunsaturated Fatty Acids and the Treatment of Rheumatoid Arthritis: A Meta-analysis. *Arch. Med. Res.* **2012**, *43*, 356–362. [CrossRef]
11. Miles, E.A.; Calder, P.C. Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. *Br. J. Nutr.* **2012**, *107* (Suppl 2), S171–S184. [CrossRef]
12. Dürholz, K.; Hofmann, J.; Iljazovic, A.; Häger, J.; Lucas, S.; Sarter, K.; Strowig, T.; Bang, H.; Rech, J.; Schett, G.; et al. Dietary Short-Term Fiber Interventions in Arthritis Patients Increase Systemic SCFA Levels and Regulate Inflammation. *Nutrients* **2020**, *12*, 3207. [CrossRef]
13. Masino, S.A.; Ruskin, D.N. Ketogenic Diets and Pain. *J. Child. Neurol.* **2013**, *28*, 993–1001. [CrossRef]
14. Korbecki, J.; Baranowska-Bosiacka, I.; Gutowska, I.; Chlubek, D. The Effect of Reactive Oxygen Species on the Synthesis of Prostanoids From Arachidonic Acid. *J. Physiol. Pharmacol.* **2013**, *64*, 409–421. [PubMed]
15. Cronstein, B.N.; Sitkovsky, M. Adenosine and adenosine receptors in the pathogenesis and treatment of rheumatic diseases. *Nat. Rev. Rheumatol.* **2017**, *13*, 41–51. [CrossRef]
16. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [CrossRef] [PubMed]
17. Fries, J.F.; Spitz, P.; Kraines, R.G.; Holman, H.R. Measurement of Patient Outcome in Arthritis. *Arthritis Rheum* **1980**, *23*, 137–145. [CrossRef] [PubMed]
18. Prevoo, M.L.; van 't Hof, M.A.; Kuper, H.H.; van Leeuwen, M.A.; van de Putte, L.B.; van Riel, P.L. Modified Disease Activity Scores That Include Twenty-eight-joint Counts: Development and Validation in a Prospective Longitudinal Study of Patients with Rheumatoid Arthritis. *Arthritis Rheum* **1995**, *38*, 44–48. [CrossRef]
19. Fransen, J.; Welsing, P.; de Keijzer, R.; van Riel, P. Disease activity scores using C-reactive protein: CRP may replace ESR in the assessment of RA disease activity. *Ann. Rheum. Dis.* **2004**, *62*, 151.
20. Sterne, J.A.C.; Savovic, J.; Page, M.J.; Elbers, R.G.; Blencowe, N.S.; Boutron, I.; Cates, C.J.; Cheng, H.Y.; Corbett, M.S.; Eldridge, S.M.; et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* **2019**, *366*, l4898. [CrossRef]
21. Sterne, J.A.; Hernan, M.A.; Reeves, B.C.; Savovic, J.; Berkman, N.D.; Viswanathan, M.; Henry, D.; Altman, D.G.; Ansari, M.T.; Boutron, I.; et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* **2016**, *355*, i4919. [CrossRef]
22. Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020. RRID:SCR_003581. Available online: www.training.cochrane.org/online-learning/core-software-cochrane-reviews/revman (accessed on 23 November 2021).
23. Follmann, D.; Elliott, P.; Suh, I.; Cutler, J. Variance Imputation for Overviews of Clinical Trials with Continuous Response. *J. Clin. Epidemiol.* **1992**, *45*, 769–773. [CrossRef]
24. Abrams, K.R.; Gillies, C.L.; Lambert, P.C. Meta-analysis of heterogeneously reported trials assessing change from baseline. *Stat. Med.* **2005**, *24*, 3823–3844. [CrossRef] [PubMed]
25. Higgins, J.P.T.; Li, T.; Deeks, J.J. Choosing effect measures and computing estimates of effect. In *Cochrane Handbook for Systematic Reviews of Interventions*; Version 6.2 (updated February 2021); Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A., Eds.; Cochrane, 2021; Chapter 6; Available online: www.training.cochrane.org/handbook (accessed on 23 November 2021).

26. Page, M.J.; Higgins, J.P.T.; Sterne, J.A.C. Assessing risk of bias due to missing results in a synthesis. In *Cochrane Handbook for Systematic Reviews of Interventions*; Version 6.2 (updated February 2021); Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A., Eds.; Cochrane, 2021; Available online: www.training.cochrane.org/handbook (accessed on 23 November 2021).
27. The GRADE Working Group. *GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations*; Updated October 2013; Schünemann, H., Brożek, J., Guyatt, G., Oxman, A., Eds.; The GRADE Working Group, 2013; Available online: www.guidelinedevelopment.org/handbook (accessed on 23 November 2021).
28. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2020 (developed by Evidence Prime, Inc.). RRID:SCR_021308. Available online: www.gradepro.org (accessed on 23 November 2021).
29. Sköldstam, L.; Larsson, L.; Lindström, F.D. Effect of Fasting and Lactovegetarian Diet on Rheumatoid Arthritis. *Scand. J. Rheumatol.* **1979**, *8*, 249–255. [CrossRef] [PubMed]
30. Kjeldsen-Kragh, J.; Haugen, M.; Borchgrevink, C.F.; Laerum, E.; Eek, M.; Mowinkel, P.; Hovi, K.; Førre, O. Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. *Lancet* **1991**, *338*, 899–902. [CrossRef]
31. Hafström, I.; Ringertz, B.; Spångberg, A.; von Zweigbergk, L.; Brannemark, S.; Nylander, I.; Rönnelid, J.; Laasonen, L.; Klareskog, L. A vegan diet free of gluten improves the signs and symptoms of rheumatoid arthritis: The effects on arthritis correlate with a reduction in antibodies to food antigens. *Rheumatology* **2001**, *40*, 1175–1179. [CrossRef]
32. Sköldstam, L.; Hagfors, L.; Johansson, G. An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. *Ann. Rheum. Dis.* **2003**, *62*, 208–214. [CrossRef]
33. Garcia-Morales, J.M.; Lozada-Mellado, M.; Hinojosa-Azaola, A.; Llorente, L.; Ogata-Medel, M.; Pineda-Juarez, J.A.; Alcocer-Varela, J.; Cervantes-Gaytan, R.; Castillo-Martinez, L. Effect of a Dynamic Exercise Program in Combination With Mediterranean Diet on Quality of Life in Women With Rheumatoid Arthritis. *J. Clin. Rheumatol.* **2020**, *26*, S116–S122. [CrossRef]
34. Abendroth, A.; Michalsen, A.; Ludtke, R.; Ruffer, A.; Musial, F.; Dobos, G.J.; Langhorst, J. Changes of Intestinal Microflora in Patients with Rheumatoid Arthritis during Fasting or a Mediterranean Diet. *Forsch Komplementmed* **2010**, *17*, 307–313. [CrossRef]
35. Von Koerber, K.; Männle, T.; Leitzmann, C. 4.5 Ernährung und Mikroflora des Verdauungstrakts. In *Vollwert-Ernährung: Konzeption einer zeitgemäßenund nachhaltigen Ernährung*, 10th ed.; Haug: Stuttgart, Germany, 2004; pp. 93–98.
36. Adam, O.; Beringer, C.; Kless, T.; Lemmen, C.; Adam, A.; Wiseman, M.; Adam, P.; Klimmek, R.; Forth, W. Anti-inflammatory effects of a low arachidonic acid diet and fish oil in patients with rheumatoid arthritis. *Rheumatol. Int.* **2003**, *23*, 27–36. [CrossRef]
37. Harris, J.A.; Benedict, F.G. A Biometric Study of Human Basal Metabolism. *Proc. Natl. Acad. Sci. USA* **1918**, *4*, 370–373. [CrossRef] [PubMed]
38. Ingegnoli, F.; Schioppo, T.; Scotti, I.; Ubiali, T.; de Lucia, O.; Murgo, A.; Marano, G.; Boracchi, P.; Caporali, R. Adherence to Mediterranean diet and patient perception of rheumatoid arthritis. *Complement Ther. Med.* **2020**, *52*, 102519. [CrossRef] [PubMed]
39. McDougall, J.; Bruce, B.; Spiller, G.; Westerdahl, J.; McDougall, M. Effects of a Very Low-Fat, Vegan Diet in Subjects with Rheumatoid Arthritis. *J. Altern. Complement. Med.* **2002**, *8*, 71–75. [CrossRef] [PubMed]
40. McKellar, G.; Morrison, E.; McEntegart, A.; Hampson, R.; Tierney, A.; Mackle, G.; Scoular, J.; Scott, J.A.; Capell, H.A. A pilot study of a Mediterranean-type diet intervention in female patients with rheumatoid arthritis living in areas of social deprivation in Glasgow. *Ann. Rheum. Dis.* **2007**, *66*, 1239–1243. [CrossRef]
41. Nenonen, M.T.; Helve, T.A.; Rauma, A.L.; Hänninen, O.O. Uncooked, Lactobacilli-rich, Vegan Food and Rheumatoid Arthritis. *Br. J. Rheumatol.* **1998**, *37*, 274–281. [CrossRef]
42. Hänninen, O.; Nenonen, M.; Ling, W.H.; Li, D.S.; Sihvonen, L. Effects of Eating an Uncooked Vegetable Diet for 1 Week. *Appetite* **1992**, *19*, 243–254. [CrossRef]
43. Sköldstam, L. Fasting and Vegan Diet in Rheumatoid Arthritis. *Scand. J. Rheumatol.* **1986**, *15*, 219–221. [CrossRef]
44. De Lorgeril, M.; Renaud, S.; Mamelle, N.; Salen, P.; Martin, J.L.; Monjaud, I.; Guidollet, J.; Touboul, P.; Delaye, J. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* **1994**, *343*, 1454–1459. [CrossRef]
45. Kahleova, H. (Physicians Committee for Responsible Medicine, Washington, DC, USA). Personal communication, 2021.
46. Stauffer, M.E.; Taylor, S.D.; Watson, D.J.; Peloso, P.M.; Morrison, A. Definition of Nonresponse to Analgesic Treatment of Arthritic Pain: An Analytical Literature Review of the Smallest Detectable Difference, the Minimal Detectable Change, and the Minimal Clinically Important Difference on the Pain Visual Analog Scale. *Int. J. Inflam.* **2011**, *2011*, 231926. [CrossRef]
47. Coenen, M.J.; Trynka, G.; Heskamp, S.; Franke, B.; van Diemen, C.C.; Smolonska, J.; van Leeuwen, M.; Brouwer, E.; Boezen, M.H.; Postma, D.S.; et al. Common and different genetic background for rheumatoid arthritis and coeliac disease. *Hum. Mol. Genet.* **2009**, *18*, 4195–4203. [CrossRef] [PubMed]
48. Goldberg, R.J.; Katz, J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. *Pain* **2007**, *129*, 210–223. [CrossRef]
49. Liu, Y.; Hazlewood, G.S.; Kaplan, G.G.; Eksteen, B.; Barnabe, C. Impact of Obesity on Remission and Disease Activity in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *Arthritis Care Res.* **2017**, *69*, 157–165. [CrossRef]
50. Geneen, L.J.; Moore, R.A.; Clarke, C.; Martin, D.; Colvin, L.A.; Smith, B.H. Physical activity and exercise for chronic pain in adults: An overview of Cochrane Reviews. *Cochrane Database Syst. Rev.* **2017**, *4*, CD011279. [CrossRef] [PubMed]

51. Hurkmans, E.; van der Giesen, F.J.; Vliet Vlieland, T.P.; Schoones, J.; van den Ende, E.C. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. *Cochrane Database Syst. Rev.* **2009**, CD006853. [CrossRef]
52. Hagen, K.B.; Byfuglien, M.G.; Falzon, L.; Olsen, S.U.; Smedslund, G. Dietary interventions for rheumatoid arthritis. *Cochrane Database Syst. Rev.* **2009**, CD006400. [CrossRef] [PubMed]
53. Heiberg, T.; Finset, A.; Uhlig, T.; Kvien, T.K. Seven year changes in health status and priorities for improvement of health in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* **2005**, *64*, 191–195. [CrossRef] [PubMed]
54. Day, A.L.; Curtis, J.R. Opioid use in rheumatoid arthritis: Trends, efficacy, safety, and best practices. *Curr. Opin. Rheumatol.* **2019**, *31*, 264–270. [CrossRef]
55. Kim, S.C.; Choudhry, N.; Franklin, J.M.; Bykov, K.; Eikermann, M.; Lii, J.; Fischer, M.A.; Bateman, B.T. Patterns and predictors of persistent opioid use following hip or knee arthroplasty. *Osteoarthr. Cartil.* **2017**, *25*, 1399–1406. [CrossRef]
56. Kuo, Y.F.; Raji, M.A.; Chen, N.W.; Hasan, H.; Goodwin, J.S. Trends in Opioid Prescriptions Among Part D Medicare Recipients From 2007 to 2012. *Am. J. Med.* **2016**, *129*, 221.e21–221.e30. [CrossRef]

Paper 3

Nutritional Strategies for Correcting Low Glucose Values in Patients with Postbariatric Hypoglycaemia: A Randomized Controlled Three-Arm Crossover Trial

Katja A. Schönenberger [1,2], Antonio Ferreira [1], Céline Stebler [1], Francesco Prendin [3], Joanna Gawinecka [4], Christos T. Nakas [5,6], Stefan Mühlebach [2], Zeno Stanga [1], Andrea Facchinetti [3], David Herzig [1], Lia Bally [1]

[1] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Bern, Switzerland

[2] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3] Department of Information Engineering, University of Padova, Padova, Italy

[4] Institute of Clinical Chemistry, University Hospital Zurich, University of Zurich, Zurich, Switzerland

[5] Laboratory of Biometry, Department of Agriculture Crop Production and Rural Environment, School of Agriculture, University of Thessaly, Volos, Greece

[6] University Institute of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Diabetes, Obesity and Metabolism. 2023;25(10)2853-2861. doi: 10.1111/dom.15175

Received: 4 April 2023 | Revised: 19 May 2023 | Accepted: 26 May 2023

DOI: 10.1111/dom.15175

ORIGINAL ARTICLE

WILEY

Nutritional strategies for correcting low glucose values in patients with postbariatric hypoglycaemia: A randomized controlled three-arm crossover trial

Katja A. Schönenberger MSc[1,2] | Antonio Ferreira MD[1] | Céline Stebler BSc[1] | Francesco Prendin PhD[3] | Joanna Gawinecka PhD[4] | Christos T. Nakas PhD[5,6] | Stefan Mühlebach PharmD[2] | Zeno Stanga MD[1] | Andrea Facchinetti PhD[3] | David Herzig PhD[1] | Lia Bally MD[1]

[1]Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[2]Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3]Department of Information Engineering, University of Padova, Padova, Italy

[4]Institute of Clinical Chemistry, University Hospital Zurich, University of Zurich, Zurich, Switzerland

[5]Laboratory of Biometry, Department of Agriculture Crop Production and Rural Environment, School of Agriculture, University of Thessaly, Volos, Greece

[6]University Institute of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Correspondence
Lia Bally, MD, Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 15, 3010 Bern, Switzerland.
Email: lia.bally@insel.ch

Funding information
Department of Information Engineering, University of Padova; Division of Clinical Pharmacy and Epidemiology, University of Basel, Grant/Award Number: FO119900; Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung, Grant/Award Number: PCEGP3_186978

Abstract

Aim: To evaluate the efficacy of nutritional hypoglycaemia correction strategies in postbariatric hypoglycaemia (PBH) after Roux-en-Y gastric bypass (RYGB).

Materials and methods: In a randomized, controlled, three-arm crossover trial, eight post-RYGB adults (mean [SD] 7.0 [1.4] years since surgery) with PBH ingested a solid mixed meal (584 kcal, 85 g carbohydrates, 21 g fat, 12 g protein) to induce hypoglycaemia on three separate days. Upon reaching plasma glucose of less than 3.0 mmol/L, hypoglycaemia was corrected with 15 g of glucose (G15), 5 g of glucose (G5) or a protein bar (P10, 10 g of protein) in random order. The primary outcome was percentage of time spent in the target plasma glucose range (3.9-5.5 mmol/L) during 40 minutes after correction.

Results: Postcorrection time spent in the target glucose range did not differ significantly between the interventions ($P = .161$). However, postcorrection time with glucose less than 3.9 mmol/L was lower after G15 than P10 ($P = .007$), whereas time spent with glucose more than 5.5 mmol/L, peak glucose and insulin 15 minutes postcorrection were higher after G15 than G5 and P10 ($P < .001$). Glucagon 15 minutes postcorrection was higher after P10 than after G15 and G5 ($P = .002$ and $P = .003$, respectively). G15 resulted in rebound hypoglycaemia (< 3.0 mmol/L) in three of eight cases (38%), while no rebound hypoglycaemia occurred with G5 and P10.

Conclusions: Correcting hypoglycaemia with 15 g of glucose should be reconsidered in post-RYGB PBH. A lower dose appears to sufficiently increase glucose levels outside the critical range in most cases, and complementary nutrients (e.g. proteins) may provide glycaemia-stabilizing benefits.

Registration number of clinical trial: NTC05250271 (ClinicalTrials.gov).

KEYWORDS
nutrition, postbariatric hypoglycaemia, Roux-en-Y gastric bypass

1 | INTRODUCTION

Hypoglycaemia after bariatric surgery, also known as postbariatric hypoglycaemia (PBH), is an increasingly recognized complication of bariatric surgery, particularly after Roux-en-Y gastric bypass (RYGB).[1,2] The condition typically manifests as recurrent episodes of hypoglycaemia after meals containing carbohydrates with a high glycaemic index.[3] The key pathophysiological features of PBH include excessive insulin secretion because of rapid glucose absorption and stimulation of insulinotropic factors from the gut.[4]

Dietary management is the cornerstone treatment to prevent the occurrence of PBH.[5,6] In addition, an essential part of education to improve patient safety is acute treatment of hypoglycaemia. Current guidelines, based on recommendations for managing hypoglycaemia in individuals with diabetes,[7,8] suggest correcting low glucose levels using the 'rule of 15'. This involves the consumption of 15 g of fast-acting carbohydrates or glucose.[9] Although this treatment protocol aims to increase glucose levels quickly to improve safety, rapid spikes in blood glucose can increase glucose variability and possibly even trigger later 'rebound' hypoglycaemia in PBH. Currently, there are no hypoglycaemia correction strategies tailored to the specific needs of patients with PBH. As the nature of hypoglycaemia in PBH essentially differs from that of individuals with diabetes on insulin therapy, lower doses of glucose may be more appropriate. In addition, because of its stimulatory effect on glucagon secretion,[10,11] protein also a potential corrective strategy in PBH.

The current study aimed to assess the effectiveness of alternative nutritional strategies for correcting low blood glucose levels in adults with PBH after RYGB. We hypothesized that 15 g of glucose may not be an adequate hypoglycaemia correction strategy for patients suffering from PBH and may even predispose them to rebound hypoglycaemia.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was a three-arm, randomized, controlled, crossover clinical trial conducted at Bern University Hospital. After a screening and baseline visit, participants received three different interventions for hypoglycaemia correction in a random order during in-clinic visits. These visits were spaced at least 48 hours apart. All the participants provided written informed consent. This clinical trial was approved by the Ethics Commission of the Canton of Bern (BASEC ID 2021-02086) and was conducted in accordance with the Declaration of Helsinki. This clinical trial was registered at ClinicalTrials.gov (NTC05250271).

2.2 | Study population

Participants were eligible for inclusion if they were aged 18 years or older with a history of RYGB and a clinical diagnosis of PBH (symptomatic postprandial plasma or sensor glucose levels < 3.0 mmol/L, as defined by the International Hypoglycaemia Study Group[12]). The exclusion criteria were other causes of hypoglycaemia, pregnancy or lactation, medical contraindications to study procedures, drugs interfering with blood glucose regulation during the time of investigation, and inability or incapacity to follow study procedures or provide informed consent, as judged by the investigator.

2.3 | Interventions

The three interventions for hypoglycaemia correction under investigation were glucose tablets (intact Expert Dextrose, sanotact GmbH, Münster, Germany) in doses of 15 g (G15) and 5 g (G5), and one-half of a commercial low-sugar protein bar (High Protein Bar Double Chocolate Cookie, Premier Protein, Active Nutrition International GmbH, München, Germany), which contained 10 g of protein and 5 g of carbohydrates as polyols (P10). The nutritional details of the protein bars are provided in Appendix S1. Polyols, also known as sugar alcohols, are a group of reduced-calorie, low-digestible, low-glycaemic carbohydrates.

2.4 | Randomization and blinding

The order of the three interventions was allocated by simple randomization using a computer-generated sequence. The randomization list was generated before the start of the study and implemented using the randomization module in the Research Electronic Data Capture (REDCap) software. Randomization remained concealed until the interventions were assigned. Blinding of the nutritional interventions was not possible because of technical constraints. However, the participants remained blinded to the intervention until they received the hypoglycaemia correction. Additionally, patients were blinded to their glucose levels throughout the experiment.

2.5 | Procedures

After study inclusion, the participants attended a baseline visit at the clinical research facility for medical history and anthropometric assessment. On the day of the intervention, participants reported to the clinical facility after a 10-hour overnight fast and had an antecubital vein cannula fitted for frequent blood sampling. After a baseline blood draw, participants consumed a standardized breakfast consisting of bread with butter and jam, and fruit yogurt (584 kcal, 85 g of carbohydrates, of which 40 g of sugar, 21 g of fat, 12 g of protein) to induce postprandial hypoglycaemia. When plasma glucose levels fell below 3.0 mmol/L, hypoglycaemia correction was performed according to the assigned nutritional intervention. Patients were excluded from the study if their plasma glucose levels did not fall below 3.0 mmol/L during the first visit. If they did not reach this threshold during subsequent visits, hypoglycaemia correction was administered

once the plasma glucose levels stopped decreasing. Plasma glucose was sampled 5 minutes before the meal, then at 10, 20, 30, 45, 60 and 90 minutes after the start of the meal. After 90 minutes, plasma glucose was sampled every 5 minutes until 40 minutes after hypoglycaemia correction. Blood samples for insulin and glucagon measurements were collected at baseline, at the time of hypoglycaemia correction, and 15 minutes after correction. These samples were immediately centrifuged, separated and stored at −80°C until analysis. Because the primary outcome was assessed within 40 minutes after initial hypoglycaemia correction, no further corrections for ineffective hypoglycaemia correction were performed during the 40 minutes after the initial correction, except in cases of clinical signs of severe hypoglycaemia. At the end of the visit, participants were advised to ingest a meal or snack containing slowly digestible carbohydrates of their choice to allow for stable glucose levels at the time of discharge. At the end of the third interventional visit, the patients were verbally asked about their preferred hypoglycaemia correction.

2.6 | Biochemical analyses

Plasma glucose levels were measured in duplicate using a Biosen C-line glucose analyser (EKF-diagnostic GmbH, Barleben, Germany). Glucose-regulating hormones were measured using commercial immunometric assays (Elecsys Insulin assay, Roche Diagnostics GmbH, Mannheim, Germany; Mercodia AB Glucagon assay, Uppsala, Sweden).

2.7 | Outcomes

All outcomes were assessed within 40 minutes after hypoglycaemia correction. The primary outcome was the percentage of time spent in the target glucose range (defined as plasma glucose 3.9-5.5 mmol/L). Secondary outcomes were percentage of time with plasma glucose less than 3.0 mmol/L, less than 3.9 mmol/L, more than 5.5 mmol/L and more than 10.0 mmol/L, peak plasma glucose, time to euglycaemia (plasma glucose 3.9 mmol/L), proportion of participants with rebound hypoglycaemia (plasma glucose < 3.0 mmol/L following successful primary hypoglycaemia correction defined as plasma glucose ≥ 3.9 mmol/L), plasma insulin and glucagon concentrations 15 minutes after hypoglycaemia correction. Outcomes within 150 minutes after hypoglycaemia correction were not assessed because patients had lunch immediately after the inpatient visit.

Exploratory outcomes included percentage of time spent with plasma glucose 3.5-5.5 mmol/L and less than 3.5 mmol/L, time to plasma glucose of 3.5 mmol/L and of 3.0 mmol/L, proportion of participants with rebound hypoglycaemia following plasma glucose of 3.5 mmol/L and higher, and treatment failure (plasma glucose never reaching ≥ 3.0 mmol/L during 40 minutes postcorrection). Furthermore, we analysed insulin and glucagon concentrations at the time of hypoglycaemia correction, and the change between 0 and 15 minutes after hypoglycaemia correction. Finally, the patients' preference for hypoglycaemia correction was recorded.

2.8 | Sample size

Because of the lack of preliminary data, no formal sample size calculation was applicable, and we defined the sample size based on practical feasibility. Specifically, with a sample size of eight participants, the study detects an effect size (f) of 0.5 with a power of 80% at an alpha level of 5% (assuming a correlation among repeated measures of 0.6). Power was calculated for a repeated-measure analysis of variance with within-subject factors using GPower (version 3.1.9.7). New participants replaced dropouts until eight participants completed all three treatment arms.

2.9 | Statistical analyses

We preprocessed the plasma glucose values before calculating the outcomes by linearly interpolating the mean of the duplicate plasma glucose measurements. For outcomes based on time spent in specified glucose ranges, peak plasma glucose levels and hormonal responses, we assessed treatment differences using linear mixed-effects models. We used Kaplan–Meier curves to describe the time to reach specified plasma glucose levels and assessed treatment differences using Cox mixed-effects models. Visits with hypoglycaemia correction administered above these specified levels (one visit with correction at plasma glucose ≥ 3.5 mmol/L and four visits with correction at ≥ 3.0 mmol/L) were excluded from the Kaplan–Meier curves and Cox mixed-effects models. We used generalized linear mixed-effects models for the occurrence of rebound hypoglycaemia. All models were adjusted for the period effect and accounted for within-subject correlations arising from the crossover design (period was considered as a fixed effect and subjects as a random effect). In addition, we performed a sensitivity analysis in which all models were further adjusted to account for plasma glucose levels at the time of hypoglycaemia correction. In the case of a significant treatment effect (assessed using Wald chi-square tests), marginal means were compared pairwise using the Tukey method for *P* value adjustment. An identity link was used for the linear mixed-effects models, and a logit link was used for the occurrence of rebound hypoglycaemia. Statistical analysis was conducted using R version 4.2.2[13] with the packages *tidyverse* version 1.3.2,[14] *lme4* version 1.1.31,[15] *lmerTest* version 3.1.3,[16] *survival* version 3.4.0,[17,18] *coxme* version 2.2.18.1,[19] *car* version 3.1.1[20] and *emmeans* version 1.8.2.[21] Data are presented as *n* (%) for categorical variables and mean (SD) for continuous variables, unless otherwise specified. Statistical significance was set at *P* less than .05 (two-tailed).

3 | RESULTS

We recruited participants from 11 January to 13 July 2022, and the study ended when a predefined number of participants was reached. Of the 10 participants who were randomized, eight completed all three mixed meal tests. One participant did not experience hypoglycaemia

TABLE 1 Participant characteristics

Characteristic	*n* (%) or mean (SD)
N	8
Female	6 (75.0%)
Age, y	46.5 (12.5)
BMI, kg/m^2	26.0 (4.24)
Waist circumference, cm	84.9 (10.8)
HbA1c,	
%	5.4 (0.2)
mmol/mol	35.4 (2.6)
Time since surgery, y	7.0 (1.4)
Pre-RYGB BMI, kg/m^2	39.5 (2.1)
Total weight loss after RYGB, %	36.2 (12.6)
History of severe hypoglycaemia and neurological symptoms:	
None	1 (12.5%)
Loss of consciousness	3 (37.5%)
Seizure	4 (50.0%)
Hospitalization because of syncope	2 (25.0%)
Current or previous pharmacological treatment for PBH:	
Acarbose	3 (37.5%)
GLP-1 receptor agonists	1 (12.5%)
None	5 (62.5%)
Invasive treatment for PBH:	
Laparoscopic pouch resizing	3 (37.5%)
Endoscopic suturing for transoral outlet reduction	1 (12.5%)
Charlson Comorbidity Index	0.13 (0.35)

Abbreviations: BMI, body mass index; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated hemoglobin; PBH, postbariatric hypoglycaemia; RYGB, Roux-en-Y gastric bypass.

during the first visit and another withdrew from the study before the first visit. The consort flow diagram is shown in Figure **S1**. One visit of one patient was excluded from the analysis of outcomes affected by an additional rescue correction 25 minutes after the initial correction (see section 3.4). Participant characteristics are reported in Table 1.

3.1 | Glucose trajectories

The plasma glucose trajectories following the three corrections are illustrated in Figure 1, and the results of the plasma glucose outcomes are shown in Table 2. There were no significant differences in the percentage of time spent in the target glucose range after the three hypoglycaemia treatments ($P = .161$). The analysis revealed a treatment effect for the time spent at less than 3.0 mmol/L and less than 3.9 mmol/L. Specifically, G15 resulted in a shorter time at less than 3.9 mmol/L than P10 ($P = .007$). Marginally non-significant differences were observed for the comparisons between G15 and G5 ($P = .083$ for time < 3.0 mmol/L and $P = .082$ for time < 3.9 mmol/L) and between G15 and P10 ($P = .059$ for time < 3.0 mmol/L). While none of the interventions led to plasma glucose values of more than 10.0 mmol/L, G15 resulted in the highest glucose peaks. In addition, hypoglycaemia correction with G15 led to the longest time with glucose values of more than 5.5 mmol/L. Results obtained by the models adjusted for plasma glucose at the time of hypoglycaemia correction were in line with the unadjusted results (Table **S1**).

Treatment effects were observed for time to euglycaemia (3.9 mmol/L) and 3.5 mmol/L or higher ($P = .04$ and $P = .003$, respectively). While pairwise comparisons did not reach statistical significance for time to euglycaemia (a marginally non-significant difference was observed for G15 vs. P10, $P = .052$), time to glycaemia of 3.5 mmol/L was shorter for G15 than for G5 ($P = .020$) and P10 ($P = .007$). Figure 2 shows Kaplan–Meier curves illustrating time to glucose values above 3.0 mmol/L, and treatment failures (plasma glucose never reaching 3.0 mmol/L during 40 minutes postcorrection). Time to 3.0 mmol/L was not statistically significantly different after the three hypoglycaemia treatments. No treatment failures occurred with G15, but did in two (29%) and three (38%) participants after G5 and P10, respectively. Rebound hypoglycaemia after reaching plasma levels of 3.9 and 3.5 mmol/L occurred in three out of eight cases (38%) after G15, but did not occur after G5 and P10 ($P = 1.00$).

Participants usually had lunch shortly after the end of the visit (at the end of the 40-minute plasma glucose collection posthypoglycaemia), which limits the interpretability of the sensor-based follow-up glucose trajectories up to 150 minutes. Therefore, the outcomes based on sensor glucose were not calculated.

3.2 | Hormonal responses

The levels of insulin and glucagon measured during the experiment are listed in Table 3. Insulin levels were highest after G15, whereas glucagon levels were highest after P10 (both $P < .001$). Hormone levels at baseline and at the time of hypoglycaemia (before correction) were comparable in all conditions.

3.3 | Participants' preferences

Of the eight participants, seven preferred hypoglycaemia correction with P10, whereas the remaining participant preferred G5. As clarified by additional comments, their responses reflected the perceived discomfort after correction with G15 and the more pleasant taste of the protein bar compared with dextrose tablets.

3.4 | Safety events

One participant required rescue correction with 5 g of additional glucose 25 minutes after the initial correction with G5 because of clinically relevant signs of neuroglycopaenia, such as sleepiness and slurred

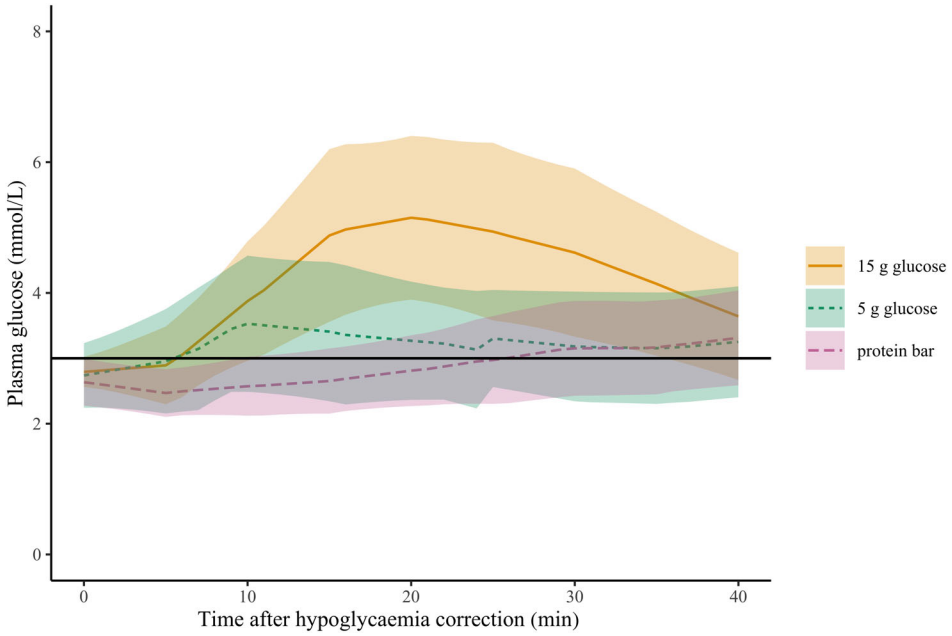


FIGURE 1 Plasma glucose trajectories during 40 minutes after hypoglycaemia correction. Mean (line) and SD (ribbon) of linearly interpolated glucose values. The solid line represents a plasma glucose value of 3.0 mmol/L.

TABLE 2 Plasma glucose outcomes during 40 minutes posthypoglycaemia correction

	Estimated mean (95% CI)			*P* value			
Outcome	G15	G5	P10	Overall	G15 versus G5	G15 versus P10	G5 versus P10
Time with plasma glucose 3.9-5.5 mmol/L, %	27.3 (9.3 to 45.2)	19.4 (0.6 to 38.3)	10.3 (−8.2 to 28.7)	.161	N/A		
Time with plasma glucose < 3.0 mmol/L, %	24.7 (−0.8 to 50.2)	53.4 (26.5 to 80.2)	58.3 (32.0 to 84.6)	.012	.083	.059	.931
Time with plasma glucose < 3.9 mmol/L, %	50.8 (29.4 to 72.2)	77.1 (54.3 to 99.9)	95.9 (73.6 to 118.2)	< .001	.082	.007	.321
Time with plasma glucose > 5.5 mmol/L, %	21.9 (14.3 to 29.6)	3.6 (−4.7 to 11.9)	−6.2 (−14.3 to 1.9)	< .001	.006	< .001	.204
Peak plasma glucose, mmol/L	5.6 (4.8 to 6.4)	3.8 (2.9 to 4.6)	3.2 (2.4 to 4.1)	< .001	.002	< .001	.449
Time with plasma glucose 3.5-5.5 mmol/L, %	43.7 (24.5 to 62.8)	29.1 (9.2 to 49.0)	28.6 (9.0 to 48.1)	.103	N/A		
Time with plasma glucose < 3.5 mmol/L, %	34.4 (12.2 to 56.7)	68.1 (45.3 to 90.8)	77.5 (55.0 to 100.1)	< .001	.002	.001	.531

Note: Results obtained from linear mixed-effects models (participant as random effect and adjusted for visit number) and estimated marginal means. Overall *P* values represent main treatment effects obtained from the ANOVA table. *P* values for pairwise marginal means were adjusted using the Tukey method. Pairwise comparisons are only reported for significant overall *P* values.
Abbreviations: ANOVA, analysis of variance; G15, hypoglycaemia correction with 15 g of glucose; G5, hypoglycaemia correction with 5 g of glucose; P10, hypoglycaemia correction with protein bar (10 g of protein).

speech. This visit was excluded from the analysis of affected outcomes (all outcomes based on plasma glucose values during the 40 minutes after the initial hypoglycaemia correction). Another adverse event occurred during the same visit, consisting of symptomatic postprandial hypotension during rapidly decreasing glucose levels (plasma glucose was ~9.4 mmol/L and decreasing by ~1.4 mmol/L per 5 minutes). The patient recovered fully after positioning measures were taken.

4 | DISCUSSION

In this randomized crossover clinical trial, we compared different nutritional strategies for correcting meal-induced postprandial hypoglycaemia in patients with PBH after RYGB. Although the postcorrection time in euglycaemia did not significantly differ between the ingestion of 15 g of glucose, 5 g of glucose, or a protein bar (10 g of protein), correction with 15 g of glucose led to a shorter time to reach euglycaemia and a shorter time in hypoglycaemia. However, 15 g of glucose also resulted in a longer time with glucose levels above 5.5 mmol/L, higher insulin exposure and rebound hypoglycaemia in three cases (38%). No difference in the time spent in the assessed glycaemic ranges was observed between the protein bar and 5 g of glucose. At 40 minutes postcorrection, plasma levels remained below 3.0 mmol/L in two and three participants following intake of 5 g of glucose and 10 g of protein, respectively. Nevertheless, plasma glucose was higher than that at the time of correction, and none of the participants were symptomatic. Higher glucagon levels were observed following correction with the protein bar, without any

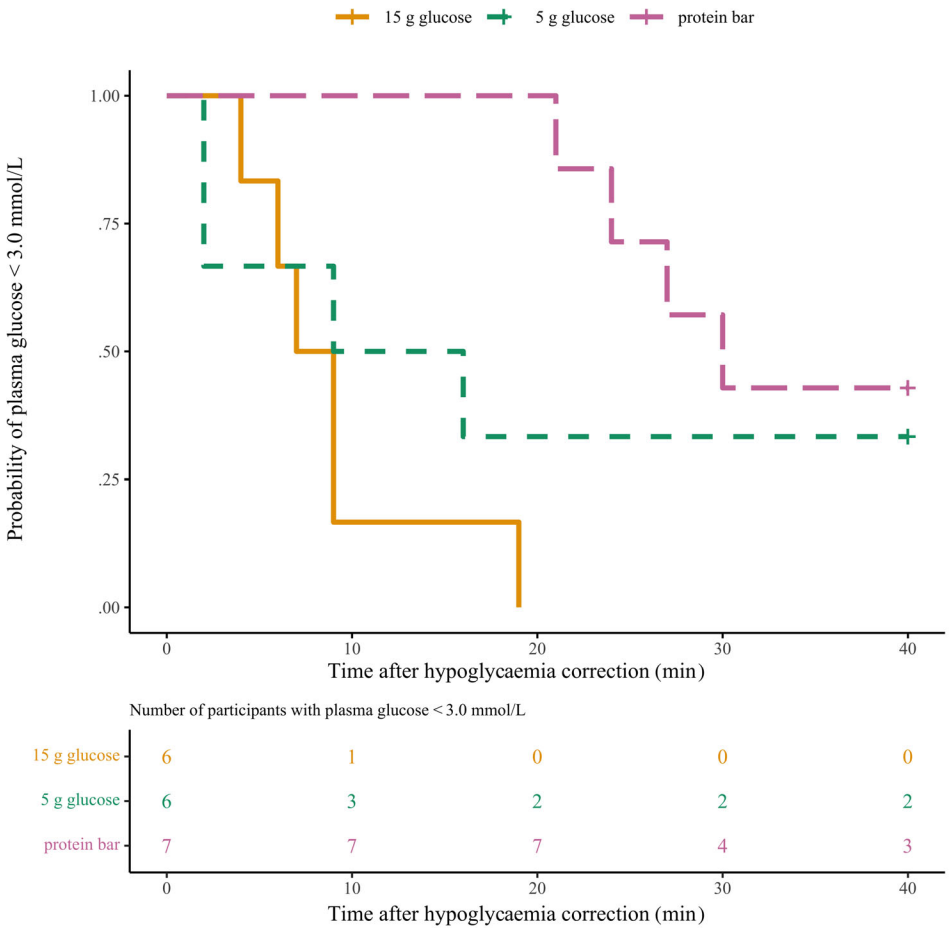


FIGURE 2 Kaplan–Meier curves of treatment failure (plasma glucose < 3.0 mmol/L). One visit with correction of 5 g of glucose was excluded because of repeated (rescue) hypoglycaemia correction, two visits with correction of 15 g glucose were excluded because plasma glucose values were just above the threshold value (3.12 and 3.07 mmol/L) by the time the hypoglycaemia correction was administered, and two visits (one with correction of 5 g of glucose and one with a protein bar) were excluded because the patient did not develop hypoglycaemia < 3.0 mmol/L during the visit.

TABLE 3 Hormonal responses to hypoglycaemia correction

	Estimated mean (95% CI)			*P* value			
Outcome	G15	G5	P10	Overall	G15 versus G5	G15 versus P10	G5 versus P10
Baseline insulin, mU/L	5.7 (3.8 to 7.7)	5.5 (3.6 to 7.5)	5.7 (3.7 to 7.7)	.918	N/A		
Insulin at hypoglycaemia, mU/L	30.1 (7.9 to 52.4)	30.4 (8.2 to 52.5)	28.0 (5.3 to 50.7)	.963	N/A		
Insulin 15 minutes after hypoglycaemia correction, mU/L	63.9 (49.7 to 78.1)	25.0 (10.8 to 39.1)	25.2 (10.7 to 39.7)	< .001	< .001	< .001	.999
Change in insulin between 0 and 15 minutes after hypoglycaemia correction, mU/L	33.8 (17.0 to 50.5)	−5.4 (−22.0 to 11.1)	−2.8 (−20.4 to 14.8)	< .001	.003	.011	.964
Baseline glucagon, pmol/L	6.4 (4.3 to 8.5)	7.7 (5.6 to 9.8)	6.9 (4.8 to 9.0)	.219	N/A		
Glucagon at hypoglycaemia, pmol/L	8.5 (3.7 to 13.2)	8.8 (3.6 to 14)	11.2 (6.2 to 16.2)	.651	N/A		
Glucagon 15 minutes after hypoglycaemia correction, pmol/L	7.4 (3.3 to 11.6)	8.0 (3.9 to 12.1)	18.5 (14.2 to 22.9)	< .001	.966	.002	.003
Change in glucagon between 0 and 15 minutes after hypoglycaemia correction, pmol/L	−1.0 (−4.1 to 2.1)	−0.8 (−4.2 to 2.6)	7.3 (4.0 to 10.7)	< .001	.995	.010	.014

Note: Results obtained from linear mixed-effects models (participant ID as random effect and adjusted for visit number) and estimated marginal means. Overall *P* values represent main treatment effects obtained from the ANOVA table. *P* values for pairwise marginal means were adjusted using the Tukey method. Pairwise comparisons are only reported for significant overall *P* values.

Abbreviations: ANOVA, analysis of variance; G15, hypoglycaemia correction with 15 g of glucose; G5, hypoglycaemia correction with 5 g of glucose; P10, hypoglycaemia correction with protein bar (10 g of protein).

increase in the two glucose-only treatments. The protein bar was the preferred treatment for seven out of eight participants.

Various pathophysiological concepts support a gradual correction of hypoglycaemia in patients with PBH. First, rapid increases in plasma glucose, as observed after correction with 15 g of glucose, may predispose to rebound hypoglycaemia, which occurred in three cases in the present study. Besides the glucose-stimulated insulin response, the vulnerability to rebound hypoglycaemia is further supported by the attenuation of counter-regulatory hormones after antecedent hypoglycaemia.[22,23] In this context, the higher glucagon exposure following the intake of 10 g of protein observed in our study may be particularly beneficial and support the notion of combining carbohydrates with proteins for hypoglycaemia correction. Additionally, proteins may serve as a source for gluconeogenesis. Second, higher insulin exposure because of an inadequately high glucose intake and rebound hypoglycaemia may predispose patients to weight regain. Associations between recurrent hypoglycaemia exposure and weight gain have not only been observed in patients with diabetes,[24] but has also been suggested as a predisposing factor for weight regain after bariatric surgery.[25] Third, the rapid correction of hypoglycaemia resulting in supraphysiological glucose levels is an important contributor to glucose variability. Glucose variability, particularly acute intraday glucose fluctuations, has been shown to trigger oxidative stress and endothelial dysfunction in previous studies.[26–28] Increased glycaemic variability because of inadequate hypoglycaemia correction may therefore negatively impact the cardiovascular risk profile of patients with PBH.

Of note, current recommendations for hypoglycaemia correction in patients with PBH suggest to correct glucose levels below 3.9 mmol/L with 15 g of glucose and to repeat the same treatment if they are not above 4.4 mmol/L after 15 minutes.[9] Our findings and the above-mentioned considerations, however, suggest the possibility of a more gradual hypoglycaemia correction strategy, with lower amounts of rapidly available carbohydrates potentially combined with proteins to stabilize glucose dynamics. Our data did not clearly indicate a superior treatment, but the three treatments exhibited marked differences in several aspects. As such, appropriate treatment may vary depending on the patient's glucose-insulin phenotype (e.g. glucose absorption kinetics, insulin sensitivity, magnitude of insulin exposure, counter-regulation to hypoglycaemia) and situative factors (e.g. activity level). Therefore, the selection of a hypoglycaemic treatment strategy may require individual consideration, underscoring the need for personalization.

Because none of the tested strategies was unequivocally superior to the others, the most appropriate method may not have been captured by the study. Our findings lead us thus to speculate that 10 g of glucose or 10 g of protein combined with 5 g of glucose would lead to a lower proportion of participants experiencing treatment failures at 40 minutes post-correction while avoiding rebound hypoglycaemia. Alternatively, glucose may be combined with other carbohydrates, such as fructose (e.g. in the form of sucrose), which has a slower and more sustained effect on glycaemia.[29,30] Such strategies are in line with the common practice of combining carbohydrates with high and low glycaemic indices.

In addition, the threshold to apply corrective actions should be reconsidered in PBH patients, as bariatric surgery alters glucose and insulin kinetics and, consequently, postprandial nadir glucose values.[31,32] In our study, we implemented a threshold of less than 3.0 mmol/L as this level does not occur under physiological conditions in individuals without diabetes and is currently recognized as defining clinically significant hypoglycaemia.[12] As glucose levels continued to rise 15 minutes after correction, we recommend waiting for at least 20 minutes before further action is considered. Symptoms may not be reliable indicators of repeated corrections. Instead, trend arrows in continuous glucose monitoring systems accompanied by capillary glucose testing may provide important decision support to avoid both persistent hypoglycaemia and overshoot hyperglycaemia.

The strengths of the present study include the randomized crossover design and experimental procedures resulting in standardized solid meal-induced hypoglycaemia, which is representative of postprandial hypoglycaemia experienced under real-life conditions. The treatment strategies were chosen based on current recommendations,[9] feasibility in daily life and underlying hypotheses. However, this study had several limitations. The sample size was small and predominantly female, the follow-up period was short, and there was intra-individual variability in meal-induced glucose dynamics despite identical stimuli, as reported in other investigations.[33]

In conclusion, recommendations to correct hypoglycaemia with 15 g of glucose should be reconsidered for patients with PBH after RYGB. Instead, a lower dose of glucose appears to be sufficient to increase glucose levels outside the critical range in most cases. Although preferred by patients, protein bars as a hypoglycaemia treatment method seem to require added low amounts of rapidly available carbohydrates for sufficient hypoglycaemia correction. Although our study may provide a rationale for using lower amounts of rapid-acting carbohydrates for hypoglycaemia correction in patients with PBH after RYGB, the clinical heterogeneity of PBH requires tailoring such strategies to individual needs. Additional larger studies are required to further elucidate the personalized approach for PBH.

AUTHOR CONTRIBUTIONS

Conceptualization: KAS, DH and LB. Data curation: KAS. Formal analysis: KAS, CTN and DH. Funding acquisition: SM and LB. Investigation: KAS, AFe, CS and JG. Methodology: KAS, CTN, DH and LB. Project administration: KAS and AFe. Resources: LB. Supervision: SM, ZS, AFa, DH and LB. Validation: KAS and CS. Visualization: KAS. Writing – original draft: KAS and LB. Writing – review and editing: AFe, CS, FP, JG, CTN, SM, ZS, AFa and DH.

ACKNOWLEDGEMENTS

The authors thank all the participants for their time and effort. We would like to thank Noah Näf for his assistance with study visits. We thank the Study Nurse Team of the Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, for their assistance in patient care and data collection. We also thank Laura Goetschi and Nina Schorno for providing administrative support and operational oversight. This work

was supported by the Swiss National Science Foundation (grant number PCEGP3_186978) and the Division of Clinical Pharmacy and Epidemiology, University of Basel (third-party grant number FO119900). This work was partially supported by the DVTDSS project funded by the Department of Information Engineering (University of Padova, Italy) under the initiative 'SID-Networking Project 2021'. The funding sources had no involvement in the study design, collection, analysis and interpretation of data, writing of the report, or decision to submit the article for publication. Open access funding provided by Inselspital, Bern University Hospital.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

ORCID

Katja A. Schönenberger https://orcid.org/0000-0002-2122-4746
Francesco Prendin https://orcid.org/0000-0002-8055-8199
Joanna Gawinecka https://orcid.org/0000-0003-3859-0934
Christos T. Nakas https://orcid.org/0000-0003-4155-722X
Stefan Mühlebach https://orcid.org/0000-0002-8471-7513
Zeno Stanga https://orcid.org/0000-0002-8630-2477
Andrea Facchinetti https://orcid.org/0000-0001-8041-2280
David Herzig https://orcid.org/0000-0003-1028-9445
Lia Bally https://orcid.org/0000-0003-1993-7672

REFERENCES

1. Salehi M, Vella A, McLaughlin T, Patti ME. Hypoglycemia after gastric bypass surgery: current concepts and controversies. *J Clin Endocrinol Metab*. 2018;103(8):2815-2826. doi:10.1210/jc.2018-00528
2. Ilesanmi I, Tharakan G, Alexiadou K, et al. Roux-en-Y gastric bypass increases glycemic variability and time in hypoglycemia in patients with obesity and prediabetes or type 2 diabetes: a prospective cohort study. *Diabetes Care*. 2021;44(2):614-617. doi:10.2337/dc20-1609
3. Ohrstrom CC, Worm D, Hansen DL. Postprandial hyperinsulinemic hypoglycemia after Roux-en-Y gastric bypass: an update. *Surg Obes Relat Dis*. 2017;13(2):345-351. doi:10.1016/j.soard.2016.09.025
4. Salehi M, Gastaldelli A, D'Alessio DA. Blockade of glucagon-like peptide 1 receptor corrects postprandial hypoglycemia after gastric bypass. *Gastroenterology*. 2014;146(3):669-680.e2. doi:10.1053/j.gastro.2013.11.044
5. Patience N, Sheehan A, Cummings C, Patti ME. Medical nutrition therapy and other approaches to management of post-bariatric hypoglycemia: a team-based approach. *Curr Obes Rep*. 2022;11:277-286. doi:10.1007/s13679-022-00482-0
6. Scarpellini E, Arts J, Karamanolis G, et al. International consensus on the diagnosis and management of dumping syndrome. *Nat Rev Endocrinol*. 2020;16(8):448-466. doi:10.1038/s41574-020-0357-5
7. Diabetes Canada Clinical Practice Guidelines Expert Committee, Yale JF, Paty B, Senior PA. Hypoglycemia. *Can J Diabetes*. 2018;42-(Suppl 1):S104-S108. doi:10.1016/j.jcjd.2017.10.010
8. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes-2021. *Diabetes Care*. 2021;44(Suppl 1):S73-S84. doi:10.2337/dc21-S006
9. Suhl E, Anderson-Haynes SE, Mulla C, Patti ME. Medical nutrition therapy for post-bariatric hypoglycemia: practical insights. *Surg Obes Relat Dis*. 2017;13(5):888-896. doi:10.1016/j.soard.2017.01.025
10. Kandel D, Bojsen-Moller KN, Svane MS, et al. Mechanisms of action of a carbohydrate-reduced, high-protein diet in reducing the risk of postprandial hypoglycemia after Roux-en-Y gastric bypass surgery. *Am J Clin Nutr*. 2019;110(2):296-304. doi:10.1093/ajcn/nqy310
11. Claessens M, Saris WH, van Baak MA. Glucagon and insulin responses after ingestion of different amounts of intact and hydrolysed proteins. *Br J Nutr*. 2008;100(1):61-69. doi:10.1017/S0007114507886314
12. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2017;40(1):155-157. doi:10.2337/dc16-2215
13. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing; 2022. https://www.R-project.org/
14. Wickham H, Averick M, Bryan J, et al. Welcome to the Tidyverse. *J Open Source Softw*. 2019;4(43):1-6. doi:10.21105/joss.01686
15. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. 2015;67(1):1-48. doi:10.18637/jss.v067.i01
16. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest package: tests in linear mixed effects models. *J Stat Softw*. 2017;82(13):1-26. doi:10.18637/jss.v082.i13
17. *A Package for Survival Analysis in R*. Version 3.4-0. 2022. https://CRAN.R-project.org/package=survival
18. Therneau TM, Grambsch PM. *Modeling survival data: extending the cox model*. Springer; 2000.
19. coxme: Mixed Effects Cox Models. Version 2.2-18.1. 2022 https://CRAN.R-project.org/package=coxme
20. Fox J, Weisberg S. *An R companion to applied regression*. 3rd ed. Sage; 2019.
21. emmeans: estimated marginal means, aka least-squares means. Version 1.8.2. 2022 https://CRAN.R-project.org/package=emmeans
22. Davis SN, Shavers C, Mosqueda-Garcia R, Costa F. Effects of differing antecedent hypoglycemia on subsequent counterregulation in normal humans. *Diabetes*. 1997;46(8):1328-1335. doi:10.2337/diab.46.8.1328
23. Abrahamsson N, Borjesson JL, Sundbom M, Wiklund U, Karlsson FA, Eriksson JW. Gastric bypass reduces symptoms and hormonal responses in hypoglycemia. *Diabetes*. 2016;65(9):2667-2675. doi:10.2337/db16-0341
24. Bumbu A, Moutairou A, Matar O, et al. Non-severe hypoglycaemia is associated with weight gain in patients with type 1 diabetes: results from the diabetes control and complication trial. *Diabetes Obes Metab*. 2018;20(5):1289-1292. doi:10.1111/dom.13197
25. Varma S, Clark JM, Schweitzer M, Magnuson T, Brown TT, Lee CJ. Weight regain in patients with symptoms of post-bariatric surgery hypoglycemia. *Surg Obes Relat Dis*. 2017;13(10):1728-1734. doi:10.1016/j.soard.2017.06.004
26. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*. 2006;295(14):1681-1687. doi:10.1001/jama.295.14.1681
27. Nosso G, Lupoli R, Saldalamacchia G, et al. Diabetes remission after bariatric surgery is characterized by high glycemic variability and high oxidative stress. *Nutr Metab Cardiovasc Dis*. 2017;27(11):949-955. doi:10.1016/j.numecd.2017.07.004
28. Ceriello A, Novials A, Ortega E, et al. Evidence that hyperglycemia after recovery from hypoglycemia worsens endothelial function and increases oxidative stress and inflammation in healthy control subjects and subjects with type 1 diabetes. *Diabetes*. 2012;61(11):2993-2997. doi:10.2337/db12-0224

29. Bantle AE, Wang Q, Bantle JP. Post-gastric bypass hyperinsulinemic hypoglycemia: fructose is a carbohydrate which can be safely consumed. *J Clin Endocrinol Metab*. 2015;100(8):3097-3102. doi:10.1210/jc.2015-1283
30. Gabriely I, Hawkins M, Vilcu C, Rossetti L, Shamoon H. Fructose amplifies counterregulatory responses to hypoglycemia in humans. *Diabetes*. 2002;51(4):893-900. doi:10.2337/diabetes.51.4.893
31. Sandoval DA, Patti ME. Glucose metabolism after bariatric surgery: implications for T2DM remission and hypoglycaemia. *Nat Rev Endocrinol*. 2022;19:164-176. doi:10.1038/s41574-022-00757-5
32. Jacobsen SH, Bojsen-Moller KN, Dirksen C, et al. Effects of gastric bypass surgery on glucose absorption and metabolism during a mixed meal in glucose-tolerant individuals. *Diabetologia*. 2013;56(10):2250-2254. doi:10.1007/s00125-013-3003-0
33. Vega-Lopez S, Ausman LM, Griffith JL, Lichtenstein AH. Interindividual variability and intra-individual reproducibility of glycemic index values for commercial white bread. *Diabetes Care*. 2007;30(6):1412-1417. doi:10.2337/dc06-1598

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Schönenberger KA, Ferreira A, Stebler C, et al. Nutritional strategies for correcting low glucose values in patients with postbariatric hypoglycaemia: A randomized controlled three-arm crossover trial. *Diabetes Obes Metab*. 2023;25(10):2853-2861. doi:10.1111/dom.15175

Paper 4

Attitudes and Expectations of Patients on Home Parenteral Nutrition Towards eHealth: A Multicenter Survey

Katja A. Schönenberger [1,2], Emilie Reber [1], Duy-Tan Vu [1,2], Claudia Krieger-Grübel [3], Philipp A. Gerber [4], Raphaela Muri [1], Valentina V. Huwiler [1,2], Stefan Mühlebach [2], Michèle Leuenberger [5], Zeno Stanga [1]

[1] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Bern, Switzerland

[2] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3] Department of Gastroenterology and Hepatology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

[4] Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Zurich (USZ) and University of Zurich (UZH), Zurich, Switzerland

[5] Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Clinical Nutrition ESPEN. 2022;52:445-449. doi: 10.1016/j.clnesp.2022.09.026

Clinical Nutrition ESPEN 52 (2022) 445–449

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Attitudes and expectations of patients on home parenteral nutrition towards eHealth: A multicenter survey

Katja A. Schönenberger [a, b, *], Emilie Reber [a], Duy-Tan Vu [a, b], Claudia Krieger-Grübel [c], Philipp A. Gerber [d], Raphaela Muri [a], Valentina V. Huwiler [a, b], Stefan Mühlebach [b], Michèle Leuenberger [e], Zeno Stanga [a]

[a] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[b] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland
[c] Department of Gastroenterology and Hepatology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland
[d] Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Zurich (USZ) and University of Zurich (UZH), Zurich, Switzerland
[e] Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

ARTICLE INFO

Article history:
Received 29 April 2022
Accepted 25 September 2022

Keywords:
eHealth
Home parenteral nutrition
mHealth
Mobile health
Telehealth
Telemedicine

SUMMARY

Background & aims: Advances in technology enable patients on home parenteral nutrition (HPN) to manage their treatment more independently and safely. eHealth is a promising application of electronic means in healthcare, aimed at improving and simplifying processes and connecting the different parties involved. A thorough understanding of the attitudes and expectations of patients on HPN towards eHealth is a prerequisite for a successful implementation. However, to the best of our knowledge, such a survey preceding the implementation of HPN specific eHealth care has never been conducted. The objective of this preliminary survey is the acquisition of insights on the attitudes and expectations of patients on HPN towards eHealth. Resulting findings then serve as the basis for the design of an eHealth platform to facilitate communication among those involved in HPN care, improve the HPN management, and safeguard and monitor the treatment.

Methods: We conducted a survey on the attitudes and expectations of patients towards an envisioned eHealth platform for HPN. Patients were recruited from large Swiss hospitals by their treating physician or directly by the research team. The surveys were conducted between September 2020 and October 2021 by structured personal interviews based on a questionnaire.

Results: We included 35 patients on HPN (21 [60%] females) treated in ambulant care of 4 hospitals. They had a median (interquartile range) age of 55 (18) years and a median (interquartile range) duration of parenteral nutrition of 1.3 (3.1) years. Most patients (n = 30, 86%) were equipped with a smartphone, tablet, or computer and 22 (63%) used apps and rated themselves as proficient with the corresponding digital device. A majority of patients rated the following aspects and features of the platform as important: Data collection and storage (n = 29, 83%), checklists for PN, catheter, and infusion pump handling (n = 28, 80%), video instructions (n = 27, 77%), and videoconferencing with physicians (n = 25, 71%). Most patients (n = 26, 74%) were willing to enter data into the platform themselves. The type of data to be entered should be defined on an individual basis.

Conclusions: Patients on HPN are open to videoconference consultations and using an eHealth platform. Two-thirds have the necessary technical skills including suitable digital devices for an eHealth care. We identified key features of an eHealth platform to improve HPN management.

1. Introduction

For patients unable to meet their dietary requirements via oral and enteral routes, parenteral nutrition (PN) is a life-saving therapy and, if PN is required for long-term care, can be provided outside

Abbreviation: HCP, healthcare professional; HPN, home parenteral nutrition; IQR, interquartile range; NST, nutrition support team; PN, parenteral nutrition.

* Corresponding author. Inselspital, Bern University Hospital, Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Freiburgstrasse 15, 3010 Bern, Switzerland.
E-mail address: katja.schoenenberger@extern.insel.ch (K.A. Schönenberger).

https://doi.org/10.1016/j.clnesp.2022.09.026

hospital settings as home PN (HPN) [1,2]. Few patients require HPN and the prevalence varies widely between countries, ranging from about 5 to 50 cases/million/year, with increasing tendency [3–6].

HPN is a challenging treatment for patients, their relatives and healthcare professionals (HCPs), requiring a multiprofessional and multidisciplinary approach [3,7]. The aseptic preparation and administration of PN through a central venous catheter at home is a difficult and critical task that needs to be rigorously trained, as non-compliance can have severe consequences, such as catheter-related, infectious, and metabolic complications [8]. Moreover, long-term monitoring and close collaboration between patients, their relatives and caregivers, and a multiprofessional nutrition support team (NST) is required [7–9]. An eHealth approach for HPN presents a novel and promising opportunity for keeping all parties involved up to date and for improving patient outcome.

eHealth is an umbrella term covering all electronic health services that employ electronic means to improve processes in the healthcare system and to connect the involved persons [10]. The World Health Organization defines eHealth as the "[…] use of information and communications technologies in support of health and health-related fields, including health-care services, health surveillance, health literature, and health education, knowledge and research" [11].

Among the applications of eHealth is telemedicine, i.e. the delivery of health care services where patients and providers are separated by distance, such as through a telephone or videoconference consultation [12]. Videoconference consultations can deliver more frequent and timely health care to patients with chronic conditions at a distance, thus improving access to healthcare [13]. A second application is remote patient monitoring to detect clinical or technical complications at an early stage. Electronic data processing and analysis may automatically alert healthcare providers to out-of-range values, avoiding delays in interventions [13]. Finally, eHealth may improve patient education and digital HPN peer-support groups can be beneficial for quality of life, depression scores and prevention of catheter-related infections [14].

It is well known that the effectiveness of eHealth depends on several factors, including those related to the study population, e.g. disease severity and progression, the healthcare provider and the healthcare system [13]. However, attitudes and expectations of HPN patients not yet familiar with an eHealth intervention are poorly explored. Their unique health situation likely has a substantial influence on their attitudes and expectations in comparison with the population average.

We aimed to explore patients' attitudes and expectations towards eHealth before designing a national eHealth platform for HPN patients.

2. Materials and methods

We developed a questionnaire for the survey on the attitudes and expectations of HPN patients towards an eHealth platform. Nutritional scientists, physicians, and pharmacists specialized and experienced in (H)PN were involved in the creation of the questionnaire. We tested the questionnaire with one HPN patient. After minor adaptations, the final questionnaire consisted of 18 questions. Following a short section on basic demographic characteristics and the PN regimen, the remainder was concerned with acquiring information on the use of electronic media and obtaining ratings on suggested features for an envisioned eHealth platform for HPN patients. The questionnaire is included in the supplementary materials.

We recruited HPN patients from four large hospitals (University Hospitals Bern and Zurich; Cantonal Hospitals St. Gallen and Lucerne). The investigators conducted the interviews in person or via telephone between 14 September 2020 and 22 October 2021.

Statistical analysis was performed using R (R Core Team, 2021) [15], version 4.1.2. We used medians and interquartile ranges (IQR) or sizes of a subsample (n) and percentages. To test for subgroup differences of categorical variables we used the Person's Chi-squared test. A p-value $\leq$.05 was considered statistically significant. No data were excluded and missing data were not imputed.

The employment of an anonymous questionnaire (i.e., without patients' names or dates of birth), renders any backtracing of responses to patients impossible. The Ethics Commission of the Canton of Bern confirmed that an ethical approval was not required, as it is not in the scope of the Human Research Act, Art. 2, para. 1 (BASEC-Nr: Req-2021-00090).

Table 1
Baseline characteristics.

Patients, N	35
Patients per hospital, n (%)	
Inselspital, Bern University Hospital	24 (69)
University Hospital Zurich	5 (14)
Cantonal Hospital St. Gallen	5 (14)
Cantonal Hospital Lucerne	1 (3)
Females, n (%)	21 (60)
Age in years, median (IQR)	55 (18)
PN regimen, median (IQR)	
PN duration in years	1.3 (3.1)
Cyclic PN frequency in nights per week	7 (2.5)
Responsible staff involved in HPN care, n (%)	
Hospital physician	34 (97)
General practitioner	5 (14)
Home care nurse	22 (63)

Abbreviations: HPN, home parenteral nutrition; IQR, interquartile range.

3. Results

We conducted the survey with 35 patients from 4 hospitals treated by 5 different specialists in nutritional medicine. Table 1 shows the baseline characteristics.

Table 2 shows the number of patients meeting given prerequisites for the use of an eHealth platform. Patients below the age of 60 rated themselves significantly more proficient with digital devices than patients aged 60 years or older (the ratings were: 17 [81%] very/rather proficient, 2 [10%] neutral, and 2 [10%] rather not/not at all proficient in the age group <60 years vs. 5 [36%], 1 [7%], and 8 [57%] in the age group $\geq$60 years, respectively, $p = .009$).

A total of 15 patients (43%) found it burdensome to go to the hospital for consultations regarding HPN, while 17 (49%) did not.

Table 2
Prerequisites for eHealth.

	n (%)
Owning digital devices	
Smartphone	27 (77)
Computer	23 (66)
Tablet	16 (46)
Cell phone without internet capability	8 (23)
Using apps	22 (63)
Self-rated skills in the use of digital devices	
Very/rather proficient	22 (63)
Neutral	3 (9)
Rather not/not at all proficient	10 (29)
Restrictions to using digital devices	
No impairments	32 (91)
Visual impairments	1 (3)
Hearing impairments	1 (3)
Lack of motor/coordination skills	1 (3)

Table 3
Differences in selected survey responses according to duration of parenteral nutrition and age.

	PN duration	Age
	<6 vs. ≥6 months	<60 vs. ≥60 years
Found it burdensome to go to the hospital for HPN consultations	36% vs. 46%	43% vs. 43%
Found in-person contact with the treating physician important	100% vs. 75%	71% vs. 100%
Rated the following eHealth platform features as important:		
Data collection and storage	91% vs. 79%	86% vs. 79%
Checklists for PN, catheter and pump handling	82% vs. 79%	86% vs. 71%
Video instructions	82% vs. 75%	86% vs. 64%
Videoconferencing with physicians	64% vs. 75%	67% vs. 79%

Abbreviation: (H)PN, (home) parenteral nutrition.

The majority of patients (n = 25, 71%) would attend videoconference consultations, with in-person contact with the treating physician nevertheless being important to 29 patients (83%). Table 3 shows differences according to PN duration and age.

Figure 1 shows how many of the patients considered the suggested eHealth platform features important and the ratings of the four most important features according PN duration and age are shown in Table 3.

Data security was important to 27 patients (77%) and ease of use to 26 (74%). For the data collection and storage, a majority (n = 26, 74%) would enter data into the platform themselves, 5 (14%) would prefer someone else to enter data, and 4 (11%) would not enter data at all. Figure 2 shows to whom the patients would give data access.

Figure 3 shows the patients' rating of the importance of the suggested data entries. When asked what they were missing from our suggested features and data entries, 3 patients (8.6%) independently stated that they would welcome functionality for tracking mental health and quality of life. One-fourth of patients (n = 9, 26%) reported interest in connecting with other patients.

4. Discussion

The most important suggested feature of the envisioned eHealth platform was data collection and storage. Digital data entry for remote monitoring is well structured, simple and regularly backed-up. Centrally stored data are accessible to the patient, involved caregivers and the NST, which facilitates communication and allows for rapid information exchange to keep everyone up to date. All HCPs in the NST should have access to the platform; however, access to specific data must be regulated on an individual basis and limited to the minimum necessary. Patients considered almost all the suggested data entries to be important, given that the treating NST requires them for treatment monitoring. This demonstrates the importance of customizability of the eHealth platform, e.g. through selective feature activation and data entry relevant for the treatment of a specific patient.

A recent study suggests the need for improvement in patient education and training, highlighting their importance for aseptic handling, as patients who self-administer PN are at higher risk for infection than patients cared for by home nurses [3]. Patients in our survey also recognize an opportunity for the application of eHealth in patient education and thus rated checklists for PN, catheter and pump handling, as well as video instructions as important.

Another feature central to an eHealth platform was videoconferencing. Videoconference consultations facilitate access to PN specialists for some patients at a distance. In Switzerland, HPN programs are not implemented in all hospitals and the management of patients varies widely [3]. As a result, not all patients have

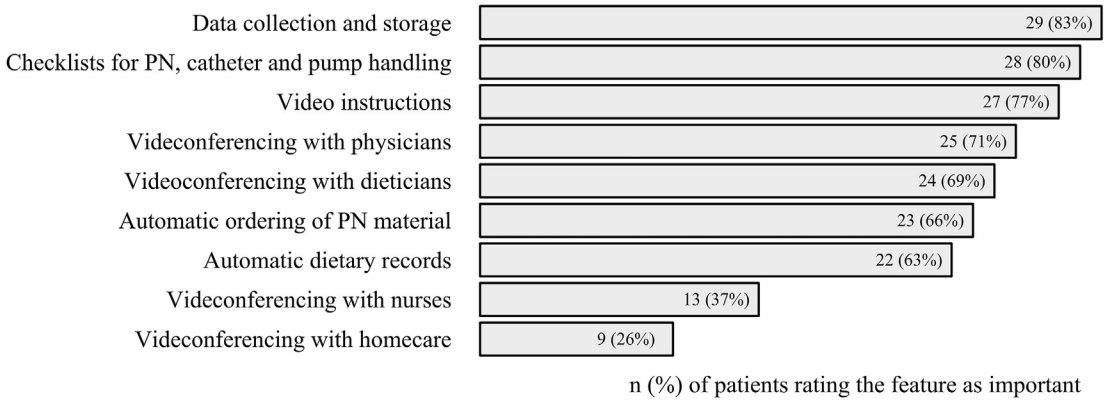


Fig. 1. Patients' rating of the importance of suggested features of the eHealth platform. Abbreviation: PN, parenteral nutrition.

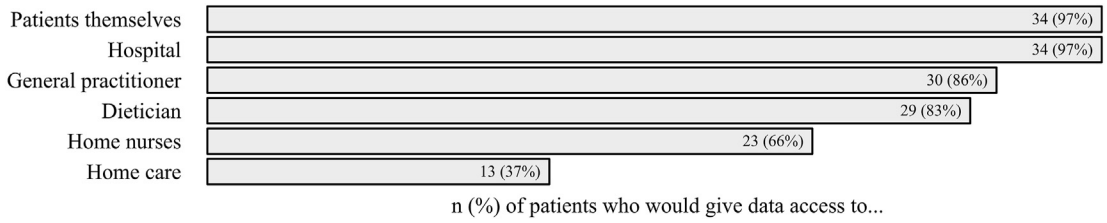


Fig. 2. Number (percentage) of patients who would give data access to those involved in HPN care.

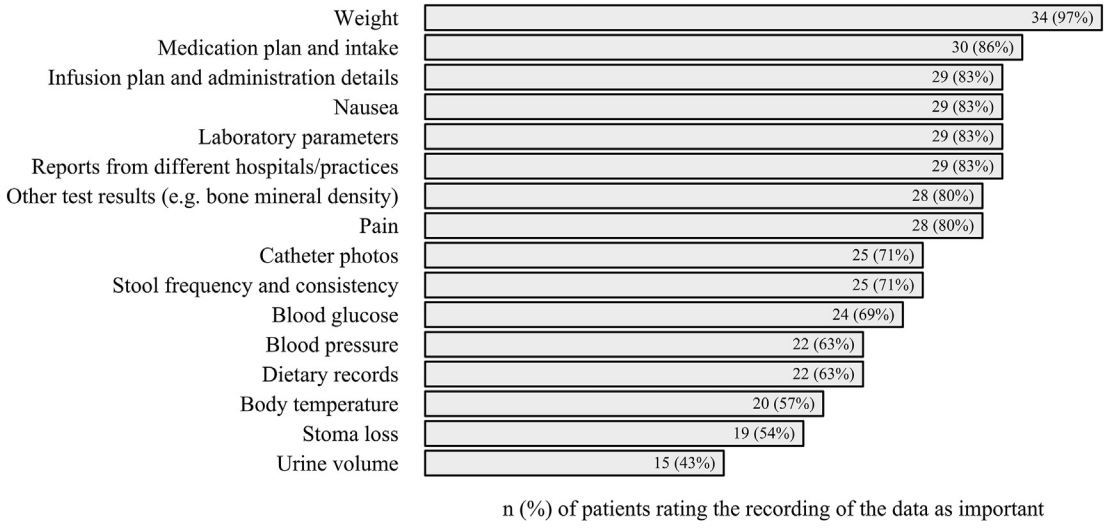


Fig. 3. Patients' rating of the importance of suggested data to be recorded in the eHealth platform.

access to a specialized hospital in their proximity and HPN patients have unequal access to short-term care and prompt diagnosis. Due to the lower barriers of videoconference consultations, more frequent contact between patients and PN specialists is possible, which has the potential to prevent complications in general and increase the treatment quality and safety. Furthermore, high-risk patients do not need to go to the hospital as often, which, besides saving time, money and travel, also reduces the risk for nosocomial infections. Most importantly, appropriate treatment can be provided more quickly due to the time saved.

A number of patients suggested mental health tracking as an additional feature. HPN monitoring does indeed include mental health tracking, as depression and anxiety are prevalent issues reported by patients receiving HPN [16]. We therefore intend to include functionality for the tracking of mental health in the envisioned eHealth platform. For instance, the implementation of questionnaires on quality of life [17] and general mental health (e.g. Optum® SF-36v2® Health Survey) would facilitate monitoring patients' emotional well-being and allow HCPs to act promptly upon any significant changes. Regular videoconferences would provide HCPs with the opportunity to discuss changes in the well-being of their patients in a timely manner.

Smith and colleagues provided HPN patients affected by benign short bowel disorders with tablets [18]. After two videoconference appointments over a median interval of two months, patients, family members, and HCPs evaluated the appointments and reported which tasks the tablets were used for. The majority found the videoconference appointments convenient and of comparable quality of care to an in-person meeting. Patients reported sending photos of their catheter and 24-h urine collection containers to their physicians. Patients also used the tablet to track their medication, laboratory values, medical supplies, and fluid intake and output [18]. Similarly, the patients in our survey considered it important to access the medication list, track medication intake and PN administration as well as laboratory values, among other data. Smith and colleagues also delivered synchronous group videoconferencing sessions via tablets and uploaded additional material (written information, forms, illustrations and graphics) to mobile devices [19]. Patients highly valued the group videoconferencing sessions [19], while only a minority of the patients in our survey reported interest in group sessions.

Almost two-thirds of patients, and 81% of patients below the age of 60, had proficient digital skills, but a third did not use apps on smartphones or tablets. Nevertheless, HPN patients valued in-person contact with their physician and about half of patients find going to the hospital for follow-up visits not burdensome. Patients who had already had PN for more than 6 months tended to find it more burdensome to go to the hospital for consultations and in-person contact with their physician was less important to them. Consequently, they rated the feature video conferencing with physicians more important. Patients over the age of 60 considered in-person contact to be highly important. The use of an eHealth platform among this age group is thus likely to be limited to other features. These results confirm the appeal of a hybrid solution of in-person contact and videoconference consultations to most patients while the data entry could be used both for in-person and online consultations. Data collection was important for all patients, but seems to be even more important for patients who have PN for less than 6 months. Which services of eHealth care are beneficial for a patient must therefore be decided on the basis of individual needs and factors, which in turn shows the importance of customizability of a platform.

Our survey population had a similar age and gender distribution as a previous study investigating a representative Swiss adult HPN cohort [3]. Although the absolute sample size of our survey was rather small, it corresponds to about 15% of the Swiss HPN population (241 HPN patient cases in 2015 [6]). Therefore, we conclude that our results are well generalizable to the Swiss HPN population.

While our survey focused on the prerequisites for eHealth from the patients' perspective, Zachrison, et al. recently identified physician characteristics associated with the transition to eHealth care [20]. They found that female (odds ratio [OR], 1.23; 95%CI, 1.06–1.44), behavioral health (OR, 2.92; 95%CI, 2.11–4.04), and primary care (OR, 1.69; 95%CI, 1.36–2.09) physicians had greater odds of being early adopters of eHealth, while patient characteristics were less strongly associated with physicians' adoption of eHealth.

To the best of our knowledge, this is the first survey on the attitudes and expectations of HPN patients towards eHealth in a more holistic approach and as a tool to better define a subsequent eHealth platform design. However, previous studies conducted videoconference appointments with HPN patients and retrospectively assessed the satisfaction and use of digital tools provided to the patients. Patients were generally satisfied with videoconference sessions for consultations and education [18,19,21,22]. This is in line with the expectations of patients in our survey, in which checklists

and video instructions were rated as even more important than videoconferencing with HCPs.

A limitation is that the survey was conducted through an interview, risking interviewer bias and acquiescence bias. However, topic complexity prevented some patients from completing the survey without the assistance of an interviewer. A further limitation is that the questionnaire was tested on one patient only.

Through this preliminary survey of a representative sample of Swiss HPN patients, we better understand HPN patients' attitudes and expectations towards eHealth. Patients are open to videoconference consultations and eHealth care, which hold the potential to facilitate communication and improve efficiency and flexibility in contact with HCPs. Overall, two-thirds, and especially patients under the age of 60, have good technical skills and possess appropriate digital devices. To optimally target the benefits for patients receiving critical long-term care such as HPN, centralized data collection and storage, checklists and video instructions, and videoconferencing with HPN specialists are key features of an eHealth platform. Furthermore, additional functionality for mental health tracking was requested.

Funding sources

This work was supported by a third-party grant of the Division of Clinical Pharmacy and Epidemiology, University of Basel [grant number FO119900]; and the Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Inselspital, Bern University Hospital [research fund number WFE-002].

Statement of authorship

Katja A. Schönenberger: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing - original draft. **Emilie Reber:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Duy-Tan Vu:** Investigation, Writing - review & editing. **Claudia Krieger:** Resources, Writing - review & editing. **Philipp A. Gerber:** Resources, Writing - review & editing. **Raphaela Muri:** Writing - review & editing. **Valentina V. Huwiler:** Writing - review & editing. **Stefan Mühlebach:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing - review & editing. **Michèle Leuenberger:** Conceptualization, Methodology, Resources, Writing - review & editing. **Zeno Stanga:** Conceptualization, Methodology, Funding acquisition, Resources, Supervision, Writing - review & editing.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2022.09.026.

References

[1] Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr 2017;36(1):49–64. https://doi.org/10.1016/j.clnu.2016.09.004.
[2] Reber E, Messerli M, Stanga Z, Mühlebach S. Pharmaceutical aspects of artificial nutrition. J Clin Med 2019;8(11). https://doi.org/10.3390/jcm8112017.
[3] Reber E, Staub K, Schönenberger KA, Stanga A, Leuenberger M, Pichard C, et al. Management of home parenteral nutrition: complications and survival. Ann Nutr Metabol 2021:1–10. https://doi.org/10.1159/000515057.
[4] Pironi L. Development of home artificial nutrition in Italy over a seven year period: 2005–2012. BMC Nutr 2017;3(1). https://doi.org/10.1186/s40795-016-0118-y.
[5] Folwarski M, Klek S, Szlagatys-Sidorkiewicz A, Wyszomirski A, Brzezinski M, Skotnicka M. Trend observations in home parenteral nutrition. Prevalence, hospitalizations and costs: results from a nationwide analysis of health care provider data. Nutrients 2021;13(10). https://doi.org/10.3390/nu13103465.
[6] Storck LJ, Ruehlin M, Wagener N, Moeltgen C, Genton L, Ballmer PE. Results from an epidemiological follow-up survey on home artificial nutrition in Switzerland from 2010 to 2015. Ann Nutr Metabol 2020;76(5):345–53. https://doi.org/10.1159/000510796.
[7] Reber E, Strahm R, Bally L, Schuetz P, Stanga Z. Efficacy and efficiency of nutritional support teams. J Clin Med 2019;8(9). https://doi.org/10.3390/jcm8091281.
[8] Pironi L, Boeykens K, Bozzetti F, Joly F, Klek S, Lal S, et al. ESPEN guideline on home parenteral nutrition. Clin Nutr 2020;39(6):1645–66. https://doi.org/10.1016/j.clnu.2020.03.005.
[9] Dibb M, Lal S. Monitoring long-term parenteral nutrition. Curr Opin Gastroenterol 2019;35(2):119–25. https://doi.org/10.1097/MOG.0000000000000504.
[10] eHealth Suisse Kompetenz- und Koordinationsstelle von Bund und Kantonen. Bern 2017 [updated 12. Apr 2021; cited 06. Jun 2021]. Available from: www.e-health-suisse.ch.
[11] World Health Assembly. WHA58.28 eHealth. Fifty-eighth world health assembly, geneva, 16-25 may 2005: resolutions and decisions: annex. Geneva: World Health Organization; 2005. p. 108–10.
[12] Third Global Survey on eHealth 2015: the use of eHealth in support of universal health coverage. Geneva: World Health Organization; 2015.
[13] Flodgren G, Rachas A, Farmer AJ, Inzitari M, Shepperd S. Interactive telemedicine: effects on professional practice and health care outcomes. Cochrane Database Syst Rev 2015;(9):CD002098. https://doi.org/10.1002/14651858.CD002098.pub2.
[14] Smith CE, Curtas S, Werkowitch M, Kleinbeck SV, Howard L. Home parenteral nutrition: does affiliation with a national support and educational organization improve patient outcomes? JPEN – J Parenter Enter Nutr 2002;26(3):159–63. https://doi.org/10.1177/0148607102026003159.
[15] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2021. URL, https://www.R-project.org/.
[16] Huisman-de Waal G, Schoonhoven L, Jansen J, Wanten G, van Achterberg T. The impact of home parenteral nutrition on daily life-a review. Clin Nutr 2007;26(3):275–88. https://doi.org/10.1016/j.clnu.2006.10.002.
[17] Miller TL, Greene GW, Lofgren I, Greaney ML, Winkler MF. Content validation of a home parenteral nutrition-patient-reported outcome questionnaire. Nutr Clin Pract 2017;32(6):806–13. https://doi.org/10.1177/0884533617725041.
[18] Smith CE, Spaulding R, Piamjariyakul U, Werkowitch M, Yadrich DM, Hooper D, et al. mHealth clinic appointment PC tablet: implementation, challenges and solutions. J Mobile Technol Med 2015;4(2):21–32. https://doi.org/10.7309/jmtm.4.2.4.
[19] Smith CE, Piamjariyakul U, Werkowitch M, Yadrich DM, Thompson N, Hooper D, et al. A clinical trial of translation of evidence based interventions to mobile tablets and illness specific internet sites. Int J Sens Netw Data Commun 2016;5(1):138. https://doi.org/10.4172/2090-4886.1000138.
[20] Zachrison KS, Yan Z, Samuels-Kalow ME, Licurse A, Zuccotti G, Schwamm LH. Association of physician characteristics with early adoption of virtual health care. JAMA Netw Open 2021;4(12):e2141625. https://doi.org/10.1001/jamanetworkopen.2021.41625.
[21] Saqui O, Chang A, McGonigle S, Purdy B, Fairholm L, Baun M, et al. Telehealth videoconferencing: improving home parenteral nutrition patient care to rural areas of Ontario, Canada. JPEN - J Parenter Enter Nutr 2007;31(3):234–9. https://doi.org/10.1177/0148607107031003234.
[22] Smith CE, Curtas S, Kleinbeck SV, Werkowitch M, Mosier M, Seidner DL, et al. Clinical trial of interactive and videotaped educational interventions reduce infection, reactive depression, and rehospitalizations for sepsis in patients on home parenteral nutrition. JPEN - J Parenter Enter Nutr 2003;27(2):137–45. https://doi.org/10.1177/0148607103027002137.

Paper 5

Aluminum and Other Chemical Elements in Parenteral Nutrition Components and All-in-One Admixtures

Katja A. Schönenberger [1,2,3,*], Christoph Saxer [1,*], Peter J. Neyer [1], Valentina V. Huwiler [1,2,3], Emilie Reber [3], Angelika Hammerer-Lercher [1], Zeno Stanga [3], Stefan Mühlebach [2]

[1] Institute of Laboratory Medicine, Cantonal Hospital Aarau, Aarau, Switzerland

[2] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Bern, Switzerland

*Joint first authors

Clinical Nutrition. 2023;42(12):2475-2483. doi: 10.1016/j.clnu.2023.10.012

Clinical Nutrition 42 (2023) 2475–2483

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Aluminum and other chemical elements in parenteral nutrition components and all-in-one admixtures

Katja A. Schönenberger [a, b, c, 1, *], Christoph Saxer [a, 1], Peter J. Neyer [a], Valentina V. Huwiler [a, b, c], Emilie Reber [c], Angelika Hammerer-Lercher [a], Zeno Stanga [c], Stefan Mühlebach [b]

[a] Institute of Laboratory Medicine, Cantonal Hospital Aarau, Tellstrasse 25, 5001 Aarau, Switzerland
[b] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Spitalstrasse 26, 4056 Basel, Switzerland
[c] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 15, 3010 Bern, Switzerland

ARTICLE INFO

Article history:
Received 26 April 2023
Accepted 12 October 2023

Keywords:
Parenteral nutrition
Aluminum
Trace elements
Inductively coupled plasma mass spectrometry (ICP-MS)
Safety
Toxicity

SUMMARY

Background & aims: Parenteral nutrition (PN) can lead to high or even toxic exposure to aluminum (Al). We aimed to quantify concentrations of Al and other chemical elements of all-in-one (AIO) PN admixtures for adults prepared from commercial multichamber bags (Olimel® 5.7%, Omegaflex® special, SmofKabiven®, all with and without electrolytes) and vitamin and trace element additives over a 48-h period. Secondly, we determined the level of Al contamination resulting from admixing and infusion set use.

Methods: We used dynamic reaction cell and kinetic energy discrimination inductively coupled plasma mass spectrometry (ICP-MS) to quantify Al, arsenic (As), cadmium (Cd), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo), nickel (Ni), antimony (Sb), selenium (Se), tin (Sn), vanadium (V), and zinc (Zn) in AIO PN admixtures. We extracted samples for analysis via the bag injection ports and infusion sets over a 48-h period after admixing. We compared the measured Al concentrations of AIO PN admixtures with calculated values based on the measured concentrations of individual chamber contents and additives.

Results: Mean (standard deviation) baseline Al concentrations in AIO PN admixtures ranged from 10.5 (0.5) to 59.3 (11.4) μg/L and decreased slightly over the 48 h (estimate [standard error] -0.09 [0.02] μg/L/hour, p <0.001). Thus, certain products exceeded the widely accepted limit of 25 μg/L. There was no significant difference in Al concentrations between samples extracted via the bag injection ports or infusion sets ($p = 0.33$), nor between measured and calculated Al concentrations of AIO PN admixtures ($p = 0.91$).

Conclusion: Because certain commercially available PN admixtures for adults proved to contain excessively high levels of Al in our study, regulations and corresponding quality requirements at the authority level (e.g., Pharmacopoeia and regulatory authorities) are urgently required. Our results showed that the PN handling process (admixing and supplementing additives) or the materials of the infusion set did not lead to additional Al contamination to any extent. Moreover, calculated Al concentrations of AIO PN admixtures derived from individual chamber contents and additives are valid.

1. Introduction

Aluminum (Al) is ubiquitous in soil, air, water, food, pharmaceuticals, and cosmetic products. Although humans ingest Al through the diet, intestinal absorption is minimal [1]. However, if uptake or elimination of Al is affected, such as upon bypass of the protective gastrointestinal barrier or impaired kidney function, Al

* Corresponding author. Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Freiburgstrasse 15, 3010 Bern, Switzerland.
E-mail address: katja.schoenenberger@extern.insel.ch (K.A. Schönenberger).
[1] Co-first authors.

https://doi.org/10.1016/j.clnu.2023.10.012

Abbreviations

AIO	all-in-one
Al	aluminum
Ar	argon
As	arsenic
Cd	cadmium
Co	cobalt
Cr	chromium
Cu	copper
DRC	dynamic reaction cell
Fe	iron
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP-MS	inductively coupled plasma mass spectrometry
Mg	magnesium
Mn	manganese
Mo	molybdenum
Ni	nickel
PN	parenteral nutrition
Rh	rhodium
RPa	retarding potential analyzer
RPq	retarding potential quadrupole
Sb	antimony
SD	standard deviation
Se	selenium
Sn	tin
U.S. FDA	United States Food and Drug Administration
V	vanadium
Zn	zinc

can accumulate in tissues and exert pro-inflammatory effects as well as oxidative injuries [2,3]. Patients on parenteral nutrition (PN), especially those with prolonged administration or impaired kidney function, as well as neonates, are at significant risk for Al accumulation [3]. In adults, approximately 40% of the Al infused with PN is retained in the body [4]. Systemic Al toxicosis can lead to various pathological conditions, including pulmonary, cardiovascular, inflammatory bowel, neurologic, pancreatic, and hepatorenal diseases, anemia, sclerosis, macrophagic myofasciitis, osteomalacia, oligospermia, infertility, and breast cancer and cysts [2]. With regard to PN, metabolic bone disease, neurologic complications, and PN-associated liver disease are of particular concern [5]. Safe parenteral doses of Al range from 2 to 5 μg/kg body weight/day [6,7].

Calcium, phosphate, potassium, multivitamins, and trace elements are major sources of Al contamination in PN [8]. Raw materials can be naturally contaminated with Al, or contamination may occur during manufacturing and handling. Additionally, Al may leach from containers or contact materials [9]. Historically, substituting natural casein hydrolysate with crystalline amino acids substantially reduced Al contamination [10]. Nowadays, high Al content in PN is mostly due to contamination through calcium gluconate, inorganic phosphates, and cysteine hydrochloride [3,9]. Strategies to reduce Al contamination include substituting glass containers, which contain Al oxide, and rubber closures with plastic packaging, replacing calcium gluconate with calcium chloride, and using organic sources of phosphate [3,9]. The use of calcium chloride is controversial due to the increased risk of precipitation with inorganic phosphate salts [3,11].

Currently, there are no European regulations limiting the quantity of Al in PN and its components. However, in January 2023, the European Pharmacopoeia initiated the Aluminum in Parenteral Solutions Working Party responsible for drafting a new general chapter on Al in PN solutions to limit the risk of exposure to toxic levels of Al [12]. The United States Food and Drug Administration (U.S. FDA) mandates that the Al concentration of large-volume PN products must not exceed 25 μg/L. Additionally, specifications of small-volume parenteral drug products and pharmacy bulk packages used in the preparation of PN admixtures must disclose the maximum level of Al at expiry. Furthermore, Al concentrations must be determined with validated assay methods submitted to the U.S. FDA [7].

Infants are at the greatest risk of developing Al toxicity from PN, and because of this, there is plenty of information on Al exposure resulting from pediatric PN [8,13–28]. In adults, Al concentrations of PN admixtures used for long-term PN are not well studied. Therefore, we aimed to quantify Al in commercial PN components and all-in-one (AIO) admixtures used routinely for long-term PN in adults (Olimel® 5.7%, Omegaflex® special, SmofKabiven®, all with and without electrolytes and corresponding vitamin and trace element additives). In particular, we determined the changes in Al concentrations over a 48-h period and aimed to quantify Al contamination potentially arising from the infusion set or admixing procedures.

2. Materials & methods

2.1. Parenteral nutrition samples and analytical materials

We selected PN admixtures that are commonly used in adults in Switzerland and other European countries (Table 1) and quantified Al, arsenic (As), cadmium (Cd), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo), nickel (Ni), antimony (Sb), selenium (Se), tin (Sn), vanadium (V), and zinc (Zn) in the admixtures and their components. AIO admixtures were prepared from commercial three-chamber bags containing glucose solutions, amino acid solutions, and lipid emulsions, with and without electrolytes, and additives of vitamins and trace elements (specific investigated combinations of three-chamber bags and additives are shown in Fig. 1). For Al analysis, we extracted samples via the bag injection ports with a syringe as well as via the infusion set with a three-way stopcock under normal laboratory conditions at baseline and after 6, 12, 24, and 48 h at room temperature. Figure 1 shows the steps involved in preparing and sampling the AIO admixtures. In addition, we determined Al concentrations of all individual chamber contents (glucose solutions, amino acid solutions, lipid emulsions) and additives (vials) in the baseline (0 h) run. Blanks used as laboratory environment controls were treated in the same way as the test samples and were stored in the measurement cups for at least as long. To ensure quality control, we analyzed serum calibrator samples, ultrapure water blanks, and laboratory environment samples together with all analytical runs. Table 1 provides manufacturer details and lot numbers of products analyzed. Packaging and composition of PN products are detailed in Supplementary Table 1. The infusion set was made of diethylhexyl phthalate-free polyvinyl chloride and the three-way stopcock of microcrystalline polyamide.

2.2. Analytical procedure and inductively coupled plasma mass spectrometry settings

In a 2.5 mL polypropylene disposable sample cup, 200 μL of samples or standards was diluted in 1800 μL of diluent and mixed by repetitive pipetting. The diluent consisted of 500 mL of ultrapure

Table 1
Manufacturer details and lot numbers of used materials.

Product	Supplier	Lot
Parenteral nutrition mutlichamber bags		
Olimel® 5.7% 1000 mL	Baxter AG, Opfikon, Switzerland	21A15N41
Olimel® 5.7% E 1000 mL	Baxter AG, Opfikon, Switzerland	22A10N50
Omegaflex® special 1875 mL	B. Braun Medical AG, Sempach, Switzerland	220428231
Omegaflex® special without electrolytes 1875 mL	B. Braun Medical AG, Sempach, Switzerland	221458231
SmofKabiven® 986 mL	Fresenius Kabi (Schweiz) AG, Kriens, Switzerland	16RC75-1
SmofKabiven® EF 986 mL	Fresenius Kabi (Schweiz) AG, Kriens, Switzerland	16QM76-2
Vitamin additives		
Cernevit®	Baxter AG, Opfikon, Switzerland	LE22V048
Soluvit® N	Fresenius Kabi (Schweiz) AG, Kriens, Switzerland	10QL2748
Vitalipid® N Adult	Fresenius Kabi (Schweiz) AG, Kriens, Switzerland	10QE5654
Viant®	B. Braun Melsungen AG, Melsungen, Germany	39961TB21
Trace element additive		
Addaven®	Fresenius Kabi (Schweiz) AG, Kriens, Switzerland	12PMB99
Nutryelt®	Baxter AG, Opfikon, Switzerland	D0523A04
Tracutil®	B. Braun Medical AG, Sempach, Switzerland	22121050
Infusion set and devices		
Discofix® C three-way stopcock	B. Braun Melsungen AG, Melsungen, Germany	22K22D9040
Volumed® Set AirLock, 235 cm	Acromed AG, Kloten, Switzerland	22PH832
Materials for analysis		
TruQ™ms 1000 µg/mL aluminum in 2% HNO_3	PerkinElmer Inc., Waltham, Massachusetts, USA	CL13-57ALY1
ClinCal® serum calibrator, lyophilized, for trace elements	RECIPE Chemicals + Instruments GmbH, Munich, Germany	1318
ROTIPURAN® Supra 69% nitric acid	Carl Roth GmbH + Co. KG, Karlsruhe, Germany	1119101
2-Propanol, CHROMASOLV™ LC-MS, ≥99.9%	Honeywell Specialty Chemicals Seelze GmbH, Seelze, Germany	L120A
Standard 1000 µg/mL rhodium in 10% HCl	PerkinElmer, Inc., Waltham, Massachusetts, USA	23-142RHY1
BD™ Blunt Fill Needle	Becton Dickinson S.A., Fraga, Spain	1511 29
Injekt® 5 mL syringe	B. Braun Medical Inc., Bethlehem, Pennsylvania, USA	16N12C8
Injekt® 10 mL syringe	B. Braun Medical Inc., Bethlehem, Pennsylvania, USA	21F03C8
Omican® 50 syringe	B. Braun Melsungen AG, Melsungen, Germany	18L29C8

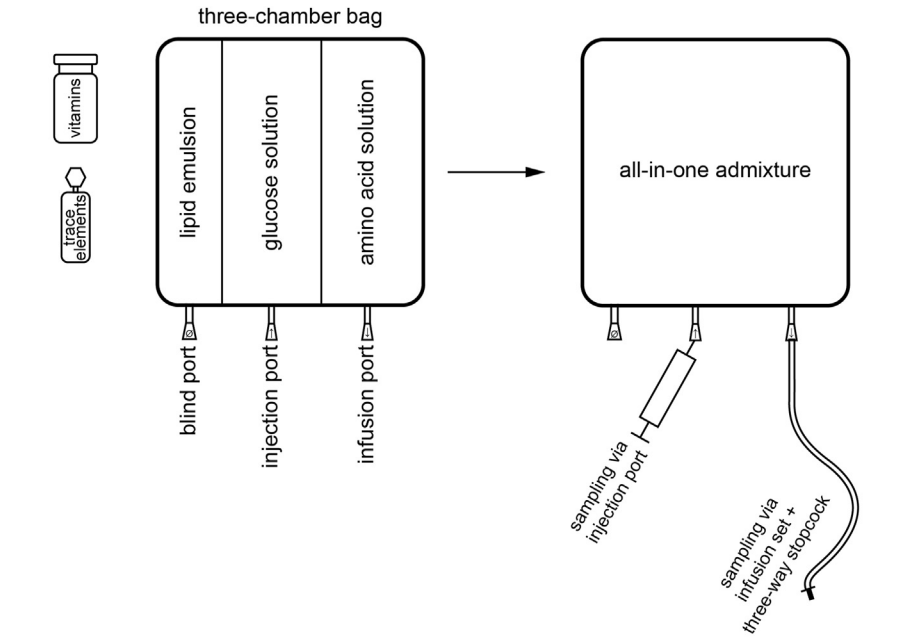


Fig. 1. Admixing of parenteral nutrition from commercial multichamber bags and vitamin and trace element additives, and sampling via the bag injection port and infusion set with a three-way stopcock.

water, 10 µL of rhodium standard, 5 mL of propan-2-ol, and 5 mL of nitric acid. Diluted samples were injected into the inductively coupled plasma mass spectrometry (ICP-MS) instrument (NexION 2000, PerkinElmer, Inc., Waltham, Massachusetts, USA) with an autosampler (Single Cell Micro DX, PerkinElmer, Inc., Waltham, Massachusetts, USA). Table 2 shows the final method specifications,

with method development details provided in the Supplementary Material.

2.2.1. Method verification

Linearity was assessed by measuring dilutions of Al reference material (see Table 1, TruQ™ms 1000 μg/mL Al in 2% HNO_3, traceable to NIST SRM #3101a) to yield the following concentrations 20′000 μg/L, 10′000 μg/L, 1′000 μg/L, 100 μg/L, 10 μg/L, 1 μg/L, 0.1 μg/L, 0.01 μg/L, and 0.001 μg/L in water and AIO PN. Each dilution was then subjected to the same analytical procedure as described above. Signals were corrected for background by subtraction of the signal from a blank sample, plotted against their theoretical concentrations and correlation coefficients were calculated as defined below. Starting from the lowest concentration, samples were sequentially excluded until linearity was reached.

Limit of quantification for Al was determined by recovery experiments with concentrations of 0.75 μg/L, 1 μg/L, 2.5 μg/L, 5 μg/L, 7.5 μg/L, 10 μg/L. All concentrations demonstrated sufficient precision to establish 1 μg/L as the lower limit of detection. The coefficient of variation for net intensities in samples spiked to 0.75 μg/L and 1.00 μg/L, measured in triplicates across three runs ($n = 9$), was 37% and 25%, respectively. Instrument method settings (gas flows, retarding potentials, dwell time) were optimized for maximum signal while specificity was accounted for by including potential multicharge interferences such as ^{54}Fe.

2.2.2. Calibration

We used a 6-point calibration series for the main analyte Al (1, 5, 25, 50, 100, 200 μg/L) and a one-point calibration for all other analytes. We calibrated the counts of the calibration standard samples linearly through zero and calculated the slope and correlation coefficient as $m = \frac{\sum xy}{\sum x^2}$ and $R = \frac{\sum xy}{\sqrt{\sum x^2} \times \sqrt{\sum y^2}}$, respectively, where x denotes the concentrations and y the intensities of the calibration standards.

Table 2
Inductively coupled plasma mass spectrometry settings.

Mass/analyte	^{103}Rh (IS) ^{27}Al ^{51}V ^{52}Cr	^{103}Rh (IS) ^{24}Mg ^{55}Mn ^{59}Co ^{57}Fe ^{60}Ni ^{63}Cu ^{66}Zn ^{75}As ^{78}Se ^{98}Mo ^{111}Cd ^{118}Sn ^{121}Sb
Mode	DRC	KED
Dwell time	50.0 ms	50.0 ms
RPa	0	0
RPq	0.5	0.25
Cell gas (NH_3) flow rate	0.6 mL/min	N/A
He flow rate	N/A	4.75 mL/min
Auxiliary gas (Ar) flow rate	1.2 mL/min	
Nebulizer gas (Ar) flow rate	0.84 mL/min	
Plasma gas (Ar) flow rate	15 L/min	
Sample introduction gas	None	
Replicates	3	
Readings/replicate	1	
Sample uptake rate	0.43 mL/min	
Cones	Nickel	
Scan mode	Peak hopping	
Sweeps/reading	15	
Dilution factor	1:10	

Abbreviations: Al, aluminum; Ar, argon; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; DRC, dynamic reaction cell; Fe, iron; IS, internal standard; KED, kinetic energy discrimination; Mg, magnesium; Mn, manganese; Mo, molybdenum; NH_3, ammonia; Ni, nickel; Rh, rhodium; RPa, retarding potential analyzer; RPq, retarding potential quadrupole; Sb, antimony; Se, selenium; Sn, tin; V, vanadium; Zn, zinc.

2.3. Calculated vs. measured aluminum concentrations of all-in-one admixtures

We compared measured Al concentrations of AIO admixtures with computations based on measured quantities of Al introduced by the individual chamber contents and vitamin and trace element additives. We calculated the concentrations as $\rho_{calculated} = \frac{\sum(\overline{\rho_{component}} \cdot V_{component})}{\sum V_{component}}$ with a standard deviation of $\sigma(\rho_{calculated}) = \frac{\sqrt{\sum(\sigma(\rho_{component}) \cdot V_{component})^2}}{\sum V_{component}}$ and total content as $m_{calculated} = \sum(\overline{\rho_{component}} \cdot V_{component})$ with a standard deviation of $\sigma(m_{calculated}) = \sqrt{\sum(\sigma(\rho_{component}) \cdot V_{component})^2}$, where components were glucose solution, amino acid solution, lipid emulsion, and additives of vitamins and trace elements.

2.4. Statistical analyses

We identified 92 outliers in 1344 triplicates using two-tailed Dixon's Q tests. These outliers (2.3% of all measurements obtained) were considered true outliers attributable to potential contamination or errors during sample workup and measurement. Therefore, we excluded these outliers from all subsequent analyses.

To assess the differences between calculated and measured Al concentrations in samples extracted via the injection port, we employed a linear mixed-effect model. The concentration determination method variable (with values of “calculated” or “measured”) was considered as fixed effect and PN admixture as random effect. To evaluate the effect of time and infusion set, we used another linear mixed-effect model. In this model, time point and sampling method (injection port vs. infusion set) were considered as fixed effects and admixture as random effect.

Statistical significance was considered at p-values <0.05. All statistical analyses were conducted using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) [29] with packages *tidyverse* version 1.3.2 [30], *outliers* version 0.15, *lme4* version 1.1.31 [31], and *lmerTest* version 3.1.3 [32].

3. Results

Figure 2 shows the measured Al concentrations in AIO PN admixtures over time and Al concentrations calculated from measurements of Al levels in the chambers and additives. Our analysis revealed no significant difference between the Al concentrations of AIO admixtures sampled via infusion sets with three-way stopcocks and those obtained via bag injection ports ($p = 0.33$), with similar results obtained when restricting the model to baseline measurements ($p = 0.18$). However, there was a significant decrease in Al concentrations of AIO admixtures over a 48-h period after admixing (estimate [standard error] -0.09 [0.02] μg/L/hour, p <0.001). Moreover, there was no significant difference between measured and calculated Al concentrations ($p = 0.91$). Table 3 presents the Al concentrations and total contents of AIO PN admixtures as calculated from measurements of individual chamber contents and additives and Supplementary Table 2 presents the body weight at which the limits of safe Al exposure are reached. Calibration curves for Al of all analytical runs are shown in Supplementary Fig. 2.

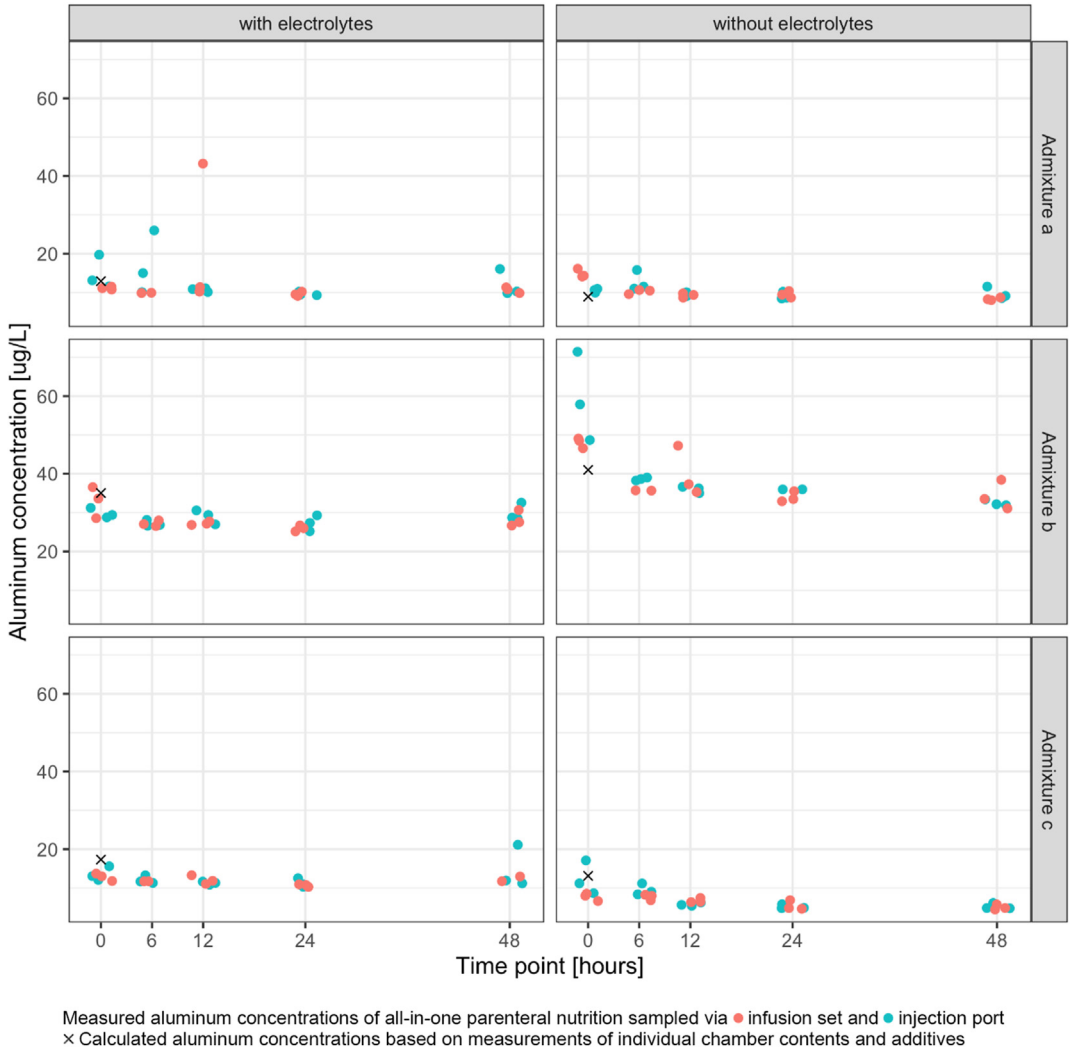


Fig. 2. Measured aluminum concentrations of parenteral nutrition admixtures (triplicates) over time and calculated aluminum concentrations based on measurements of individual chamber contents and additives (Admixture a: Olimel® 5.7% [E] 1000 mL + Cernevit® + Nutryelt®; Admixture b: Omegaflex® special [without electrolytes] 1875 mL + Tracutil®; Admixture c: SmofKabiven® [EF] 986 mL + Soluvit® + Vitalipid® + Addaven®).

Table 4 shows the concentrations of PN components for all analytes (Al, As, Cd, Co, Cr, Cu, Fe, Mg, Mn, Mo, Ni, Sb, Se, Sn, V, Zn). Concentrations of AIO admixtures over time, sampled via the bag injection port and infusion set with a three-way stopcock, are provided in Supplementary Table 1. Removal of outliers is also shown in Table 4 and Supplementary Table 1. Supplementary Table 3 shows differences between measured trace element contents and those declared by the manufacturers.

4. Discussion

The results of this study showed that Al concentrations in commercial PN products were highly variable, some of them excessively high. The Al concentrations calculated from measurements of individual chamber contents and vitamin and trace element additives were similar to the measured Al concentrations in the AIO admixtures. There was a slight decrease in Al concentrations in AIO admixtures over 48 h in the absence of additional contamination from the infusion set with a three-way stopcock. Furthermore, our study demonstrated the suitability of dynamic reaction cell (DRC)-IPC-MS for the analysis of oil-in-water PN emulsions.

None of the glucose solutions exceeded the widely accepted Al limit of 25 μg/L. However, Omegaflex® special amino acid solution without electrolytes and Omegaflex® special lipid emulsion achieved mean (standard deviation) Al concentrations of 24.5 (12.1) μg/L and 28.8 (0.7) μg/L, respectively. All admixtures with electrolytes in our study contained calcium in the form of calcium chloride (either in the glucose or amino acid solution) and phosphate as inorganic sodium salts (sodium glycerophosphate in Olimel® 5.7% and SmofKabiven®, sodium dihydrogen phosphate in Omegaflex® special). The solutions containing sodium glycerophosphate exhibited higher Al concentrations than the corresponding electrolyte-free solutions, while there was no difference between the solution containing dihydrogen phosphate and the corresponding electrolyte-free solution. However, our data do not allow to conclude whether the difference in the amino acid solutions was attributable to sodium glycerophosphate or other electrolytes, such as potassium.

Currently, there is no standard method to quantify Al in oil-in-water PN emulsions. Consequently, the validity of data obtained with variable methods may be questionable, especially if the methods used do not take the unique properties of oil-in-water emulsions into account. Our study highlights the importance of

Table 3
Aluminum concentrations and total content of all-in-one parenteral nutrition admixtures, calculated from measurement of individual chamber contents and additives.

Admixture	Most Al from	Bag size [mL]	Al [μg/L], mean (SD)	Al [μg], mean (SD)
Olimel® 5.7% E + Cernevit® + Nutryelt®	Amino acid solution	1000	12.9 (0.7)	13.2 (0.7)
		1500	12.8 (0.7)	19.5 (1.1)
		2000	12.8 (0.7)	25.9 (1.4)
Olimel® 5.7% + Cernevit® + Nutryelt®	Lipid emulsion	1000	8.9 (0.4)	9.1 (0.4)
		1500	8.8 (0.4)	13.4 (0.6)
		2000	8.8 (0.4)	17.7 (0.8)
Omegaflex® special + Viant® + Tracutil®	Tracutil®	625	75.0 (1.8)	48.4 (1.2)
		1250	45.1 (1.8)	57.3 (2.3)
		1875	34.9 (1.8)	66.1 (3.5)
Omegaflex® special EF + Viant® + Tracutil®	Tracutil®	625	80.8 (4.7)	52.1 (3.0)
		1250	51.0 (4.8)	64.7 (6.1)
		1875	40.8 (4.8)	77.4 (9.1)
SmofKabiven® + Soluvit® + Vitalipid® + Addaven®	Amino acid solution	493	18.5 (1.0)	9.7 (0.5)
		986	17.2 (1.1)	17.4 (1.1)
		1477	16.7 (1.1)	25.1 (1.6)
		1970	16.4 (1.1)	32.9 (2.2)
SmofKabiven® EF + Soluvit® + Vitalipid® + Addaven®	Amino acid solution	986	13.0 (1.0)	13.2 (1.0)
		1477	12.5 (1.0)	18.8 (1.5)

Abbreviations: Al, aluminum; SD, standard deviation.

proper method development and reporting. To the best of our knowledge, there is only one previous paper with a detailed discussion of the analytical method development and the suitability of the method to quantify Al in oil-in-water PN emulsions [33].

While it is challenging to compare our results to published data due to the variability in products, packaging, origin, and analytical methods, our findings for glucose solutions are consistent with previous studies [13,14,17,19,21,22,33–36]. However, published data on amino acid solutions and lipid emulsions vary considerably. Most studies reported Al concentrations <25 μg/L [14,19,21,22,33,34], but others reported higher concentrations [13,17,36]. Aşut et al., who also determined Al concentrations using DRC-ICP-MS, and Menédez et al. reported extremely high Al concentrations in large-volume PN products (up to 2350 μg/L in glucose solutions, 1640 μg/L in amino acid solutions, and 2200 μg/L in lipid emulsions) [15,35]. Of note, Aşut et al. found the highest Al concentrations among lipid emulsions in SMOFlipid® 20%, which is the same lipid emulsion we analyzed as part of the SmofKabiven® EF bag in our study. However, neither our results nor those reported by Lima-Rogel et al. [19] confirmed the high Al concentrations reported by Aşut et al. [15]. Alongside manufacturing and methodological differences that might have contributed to the elevated Al concentrations reported by Aşut et al., the notably high Al concentration in SMOFlipid® 20% observed in their study could be attributable to differing storage containers. Specifically, SMOFlipid® 20% analyzed by Aşut et al. was stored in a glass container (personal communication), whereas in our study, it was stored in a polymeric Biofine® bag.

The Tracutil® trace element additive contained excessively high Al amounts, causing final AIO admixtures to exceed the 25 μg/L limit by approximately 1.5–3 times, depending on the bag size. The three trace element additives analyzed were comparable in terms of the trace elements composition but Tracutil® was the only one with glass packaging investigated. However, all investigated vitamin additives were also stored in glass containers and did not contain particularly high Al concentrations. Aşut et al. reported even higher Al concentrations in Tracutil® [15].

Generally, published data on other multitrace element and multivitamin additives indicate more marked Al contamination than that found in our study [13–15,17,22,35]. Nevertheless, our study supports the criticality of micronutrient addition to the AIO PN admixtures in terms of Al exposure. The variability in Al concentrations stresses the importance of defining quality standards for these medicinal products for parenteral use, as initiated by the European Pharmacopoeia [12].

The comparable Al concentrations in analyzed admixture samples and calculated estimations confirmed the absence of significant Al contamination introduced during aseptic admixing in a laboratory environment. It is important to note that this refers to the mixing of the compartments of multichamber bags in a closed system and adding vitamins and trace elements via the injection port. Prior studies estimating Al concentrations from measurements of components used for pharmaceutical PN compounding found higher Al concentrations if measured rather than estimated. De Oliveira et al. stipulated that 35% of Al contents is contributed by the bag admixing procedure [15,17]. However, calculations based on Al levels of components as reported by manufacturers tend to overestimate total Al contents of admixtures [18,20–22,37]. To enable pharmacists to calculate the total Al content of PN admixtures, manufacturers should state the exact Al concentrations instead of indicating the maximum Al level accepted or making a general statement that the Al concentration of the product is below 25 μg/L.

De Oliveira et al. found that 9% of the total Al content was contributed by the administration set (of unknown material), with most of the Al being released upon the initial flow through the tube [17]. However, we observed no increase in Al concentrations when sampling the liquid through a universally used infusion set (diethylhexyl phthalate-free polyvinyl chloride) with three-way stopcock (microcrystalline polyamide) instead of extracting samples via a syringe inserted into the injection port of the bag. Therefore, estimations of Al exposure from PN admixtures based on calculations from the individual components appear to be valid for these widely used multichamber bags supplemented with vitamin and trace element additives.

Al concentrations decreased slightly over 48 h after admixing, covering the maximally accepted period between the preparation of the AIO admixture and administration to the patient. However, the small decrease of approximately 1 μg Al/L 12 h after admixing is not relevant from a safety perspective.

Assuming a PN dose of one AIO admixture bag per day, adult patients remain within the safe Al exposure of 4–5 μg/kg body weight/day [7], despite the high Al concentrations in some of the tested PN products and AIO admixtures. However, when considering Al infusions of 2 μg/kg body weight/day as safe, as suggested by the American Society for Clinical Nutrition and American Society

Table 4
Mean (SD) concentrations of elements quantified in parenteral nutrition components.

Parenteral nutrition component	Al [μg/L]	As [μg/L]	Cd [μg/L]	Co [μg/L]	Cr [μg/L]	Cu [μg/L]	Fe [mg/L]	Mg [mg/L]	Mn [μg/L]	Mo [μg/L]	Ni [μg/L]	Sb [μg/L]	Se [μg/L]	Sn [μg/L]	V [μg/L]	Zn [mg/L]
Addaven®	17.8 (0.6)	0.2 (0.0)[a]	0.8 (0.1)	0.8 (0.0)	1008.7 (16.1)	42130.6 (1111.3)	112 (4)	<0.1	5377.4 (4.7)[a]	1971.9 (58.3)	5.7 (0.3)	0.1 (0.0)	9252.7 (230.5)	0.2 (0.1)	0.1 (0.0)	666 (17)
Cernevit®	11.2 (0.6)	0.1 (0.1)	<0.1[a]	27.5 (0.3)	2.7 (0.1)	1.0 (0.1)	<1	<0.1	0.4 (0.0)	1.2 (0.0)	0.8 (0.0)	1.1 (0.0)	<2	<0.1	<0.1[a]	<0.1
Nutryelt®	40.7 (19.5)	<0.1	2.6 (0.0)[a]	10.1 (0.2)	965.7 (19.3)	32945.4 (158.8)	103 (1)	<0.1	5263.8 (52.5)	2107.7 (8.3)	9.2 (0.3)	<0.1	7124.9 (107.1)	0.3 (0.1)	4.8 (0.1)	1276 (4)
Olimel® 5.7% amino acid solution	16.5 (1.4)	0.2 (0.0)	<0.1	0.9 (0.0)	3.2 (0.0)	2.7 (0.3)	<1	261.6 (1.1)	3.7 (0.1)	0.7 (0.0)	2.4 (0.1)	4.0 (0.1)	2.2 (0.1)	0.2 (0.1)	0.4 (0.0)	<0.1
Olimel® 5.7% amino acid solution without electrolytes	6.7 (0.4)	<0.1	<0.1	1.2 (0.0)	1.4 (0.1)	1.9 (0.1)	<1	<0.1	0.7 (0.1)	0.2 (0.0)	1.7 (0.0)	<0.1	<2	<0.1	<0.1	<0.1
Olimel® 5.7% glucose solution	5.5 (0.7)	0.6 (0.1)	<0.1	<0.1	0.4 (0.2)	9.2 (10.5)	<1	0.2 (0.0)	1.4 (1.2)	2.6 (2.8)	1.3 (0.0)[a]	<0.1	2.9 (4.6)	<0.1	<0.1	0 (0)
Olimel® 5.7% glucose solution without electrolytes	5.1 (0.0)[a]	0.7 (0.1)	<0.1	<0.1	0.1 (0.0)	0.5 (0.0)	<1	<0.1	0.3 (0.0)	0.2 (0.0)	1.2 (0.1)	<0.1	2.5 (1.4)	<0.1	<0.1	<0.1
Olimel® 5.7% lipid solution	19.2 (1.8)	0.3 (0.1)	<0.1	0.2 (0.0)	0.4 (0.1)	7.3 (0.2)	<1	<0.1	0.2 (0.0)	0.2 (0.1)	0.7 (0.1)	<0.1	<2	<0.1	<0.1	<0.1
Omegaflex® special amino acid solution	11.5 (2.5)	0.1 (0.0)	0.2 (0.1)	0.1 (0.0)	10.8 (0.0)[a]	1.7 (0.1)	<1	269.7 (0.7)	17.1 (0.0)[a]	1.6 (0.1)	5.9 (0.3)	0.1 (0.0)	4.5 (0.7)	0.3 (0.0)	0.4 (0.0)	<0.1
Omegaflex® special amino acid solution without electrolytes	24.5 (12.1)	<0.1	<0.1	<0.1	5.2 (0.2)	1.2 (0.0)	<1	0.2 (0.0)	10.6 (0.0)[a]	0.9 (0.0)	3.3 (0.2)	<0.1	<2	0.5 (0.1)	<0.1	<0.1
Omegaflex® special glucose solution	9.6 (3.9)	1.4 (0.1)	<0.1	<0.1	1.3 (0.1)	7.0 (7.0)	<1	<0.1[a]	0.8 (0.0)[a]	7.1 (6.5)	2.3 (0.1)	0.4 (0.0)	2.8 (2.8)	<0.1	0.1 (0.0)	7 (0)[a]
Omegaflex® special glucose solution without electrolytes	11.5 (0.7)	0.2 (0.0)	<0.1	<0.1	0.5 (0.0)	3.3 (1.2)	<1	<0.1	2.2 (0.6)	0.7 (0.2)	0.9 (0.1)	<0.1	2.1 (0.8)	0.1 (0.0)	<0.1	<0.1
Omegaflex® special lipid solution	28.8 (0.7)	0.4 (0.2)	<0.1	0.5 (0.0)	0.5 (0.0)	4.4 (0.0)	<1	0.2 (0.0)	1.5 (0.1)	0.5 (0.1)	1.0 (0.1)	<0.1	7.9 (0.4)	0.4 (0.2)	1.2 (0.0)	<0.1
SmofKabiven® amino acid solution	21.7 (2.1)	1.2 (1.7)	0.1 (0.1)[a]	<0.1	4.4 (0.1)	1.2 (0.2)	<1	246.3 (5.3)	5.1 (0.3)	1.4 (0.3)	2.0 (0.2)	3.0 (0.5)	<2	0.1 (0.0)[a]	0.3 (0.0)	6 (0)
SmofKabiven® amino acid solution without electrolytes	13.3 (2.0)	<0.1	<0.1	<0.1	1.7 (0.1)	1.2 (0.1)	<1	<0.1	1.4 (0.1)	0.4 (0.1)	1.6 (0.0)[a]	<0.1	<2	<0.1	<0.1	<0.1
SmofKabiven® glucose solution	9.7 (0.6)	1.7 (0.2)	<0.1	<0.1	0.2 (0.0)	0.8 (0.2)	<1	<0.1	0.3 (0.1)	0.1 (0.1)	1.2 (0.1)	<0.1	<2[a]	<0.1	<0.1	<0.1
SmofKabiven® lipid solution	9.1 (0.0)[a]	1.0 (0.2)	<0.1	0.1 (0.0)	0.2 (0.0)	6.3 (0.0)	<1	0.2 (0.0)	0.4 (0.2)	0.4 (0.0)	0.6 (0.1)	0.1 (0.1)	<2	<0.1	<0.1	<0.1
Soluvit®	12.6 (0.5)	0.5 (0.1)	<0.1	21.8 (0.5)	0.9 (0.0)	0.8 (0.0)	<1	<0.1[a]	0.2 (0.1)	0.9 (0.0)[a]	0.6 (0.1)	<0.1	<2	<0.1	<0.1	<0.1
Tracutil®[b]	3940.5 (11.9)	0.3 (0.0)	0.6 (0.1)	0.9 (0.1)	1090.4 (1.4)	87588.3 (353.4)	208 (1)	<0.1	55169.7 (271.7)	1004.6 (10.4)	6.8 (0.2)	<0.1[a]	2314.5 (57.9)	140.7 (1.0)	0.3 (0.0)	434 (3)
Viant®	10.8 (6.2)	0.6 (0.1)	<0.1	19.9 (0.4)	4.4 (0.1)	0.8 (0.1)	<1[a]	<0.1	0.9 (0.5)	0.7 (0.0)	7.9 (0.1)	<0.1[a]	<2	<0.1	0.2 (0.0)[a]	<0.1
Vitalipid®	166.7 (1.7)	0.4 (0.1)	0.1 (0.1)	<0.1[a]	0.9 (0.0)	9.3 (0.1)	<1[a]	0.1 (0.0)	0.4 (0.0)	0.4 (0.0)	2.0 (0.2)	1.0 (0.0)	<2	<0.1	<0.1	<0.1

Abbreviations: Al, aluminum; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; Fe, iron; Mg, magnesium; Mn, manganese; Mo, molybdenum; Ni, nickel; Sb, antimony; SD, standard deviation; Se, selenium; Sn, tin; V, vanadium; Zn, zinc.

[a] One of three samples excluded as outlier.

[b] Repeated measurement in a later analytical run (48-h time point) confirmed Al concentrations with a different Tracutil® vial from the same batch, diluent, and calibration curve. Mean (standard deviation) Al concentration in the repeated measurement was 4204 (63) μg/L.

for Parenteral and Enteral Nutrition [6], patients with a low body weight (<39 kg for Omegaflex® special EF + Viant® + Tracutil®) may exceed the limits of safe Al exposure with some of the tested AIO admixtures.

Considering the safety risks associated with other contaminants of PN, such as small cationic heavy metals, none of the PN admixtures analyzed in this study exhibited concentrations exceeding the maximum daily exposures permitted as defined by the ICH guideline Q3D (R1) on elemental impurities [38] for the secondary analytes As, Cd, Co, Cr, Ni, Sb, Sn, and V. The trace element contents of Addaven® and Nutryelt® declared by the manufacturers were in line with our results, while we measured about 90% less trace elements in Tracutil® than declared by the manufacturer for all investigated trace elements (Cr, Cu, Fe, Mn, Mo, Se, Zn). This difference in measured and declared trace element content of Tracutil® was confirmed by a repeated measurement in a later analytical run with a different vial, diluent, and calibration curve.

To the best of our knowledge, this is the first study determining Al in AIO PN admixtures prepared from widely used multichamber bags for adults. This constitutes a major advance over previous investigations of PN regimens for adults that examined only individual components but not the admixture [34–36]. Harigaya et al. [33] evaluated an admixture that lacked lipids and trace elements, while Speerhans et al. [37] did not report the composition of PN admixtures they analyzed.

4.1. Strengths and limitations

The main strength of our study was the use of a DRC-ICP-MS method which we specifically developed to quantify Al in oil-in-water PN admixtures with a very low limit of detection. Our method featured a 6-point calibration series, and we conducted multiple analytical runs with a new calibration curve for each run. In addition, we measured triplicates of each sample to enable outlier identification and removal from analyses. Moreover, we accounted for environmental influences by analyzing various control samples (i.e. water blank, laboratory environment controls, and serum quality control samples). However, interpretation of our results is limited by the lack of data on lot-to-lot variability of the products tested. Moreover, the tested AIO admixtures may not be fully representative on an international level as we exclusively used combinations that are commonly available in Switzerland.

5. Conclusion

Certain large-volume PN products and admixtures, including those intended for long-term use in adults, exceed the widely accepted limit of 25 μg/L. Therefore, regulations of Al concentrations in PN products are urgently needed on both the European and global level. Moreover, analytical specifications to quantify Al contents of different matrices (aqueous solutions vs. oil-in-water emulsions) such as those presented in this study must be developed. Our results showed that the PN handling process (admixing multichamber bags and supplementing additives) or the materials of the infusion set did not lead to additional Al contamination to any extent. Therefore, labeling of PN components with their actual Al content enables accurate calculations of overall Al exposure from PN.

Funding statement

This work was supported by a third-party grant of the Division of Clinical Pharmacy and Epidemiology, University of Basel [grant number FO119900]. Open access funding was provided by the University of Basel and swissuniversities.

Author contribution

Katja A. Schönenberger: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing - original draft **Christoph Saxer:** Conceptualization, Investigation, Methodology, Project administration, Writing - review & editing **Peter J. Neyer:** Conceptualization, Methodology, Writing - review & editing **Valentina V. Huwiler:** Investigation, Methodology, Writing - review & editing **Emilie Reber:** Conceptualization, Writing - review & editing **Angelika Hammerer-Lercher:** Resources, Supervision, Writing - review & editing **Zeno Stanga:** Supervision, Writing - review & editing **Stefan Mühlebach:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing.

Conflict of interest

There are no conflicts of interest.

Acknowledgments

The authors thank the laboratory staff at the Institute of Laboratory Medicine, Cantonal Hospital Aarau, for their invaluable support and cooperation in conducting the analyses, the Department of Clinical Research of the University of Basel for statistical consulting, and Dr. Silvia Rogers for academic editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.10.012.

References

[1] Safety of aluminium from dietary intake - scientific opinion of the panel on food additives, flavourings, processing aids and food contact materials (AFC). EFSA J 2008;6. https://doi.org/10.2903/j.efsa.2008.754.
[2] Igbokwe IO, Igwenagu E, Igbokwe NA. Aluminium toxicosis: a review of toxic actions and effects. Interdiscipl Toxicol 2019;12:45–70. https://doi.org/10.2478/intox-2019-0007.
[3] Hernandez-Sanchez A, Tejada-Gonzalez P, Arteta-Jimenez M. Aluminium in parenteral nutrition: a systematic review. Eur J Clin Nutr 2013;67:230–8. https://doi.org/10.1038/ejcn.2012.219.
[4] Klein GL, Ott SM, Alfrey AC, Sherrard DJ, Hazlet TK, Miller NL, et al. Aluminum as a factor in the bone disease of long-term parenteral nutrition. Trans Assoc Am Phys 1982;95:155–64.
[5] Gura KM. Aluminum contamination in parenteral products. Curr Opin Clin Nutr Metab Care 2014;17:551–7. https://doi.org/10.1097/MCO.0000000000000091.
[6] ASCN/A.S.P.E.N. Working Group on Standards for Aluminum Content of Parenteral Nutrition Solutions. Parenteral drug products containing aluminum as an ingredient or a contaminant: response to Food and Drug Administration notice of intent and request for information. JPEN - J Parenter Enter Nutr 1991;15:194–8. https://doi.org/10.1177/0148607191015002194.
[7] Code of Federal Regulations § 201.323 Aluminum in large and small volume parenterals used in total parenteral nutrition. Washington, D.C: Food and Drug Administration, Department of Health and Human Services; 2003. at http://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-201/subpart-G/section-201.323. [Accessed 31 May 2023].
[8] Hall AR, Arnold CJ, Miller GG, Zello GA. Infant parenteral nutrition remains a significant source for aluminum toxicity. JPEN - J Parenter Enter Nutr 2017;41:1228–33. https://doi.org/10.1177/0148607116638056.
[9] Bohrer D. Aluminum in subjects receiving parenteral nutrition. In: Rajendram R, Preedy VR, Patel VB, editors. Diet and nutrition in critical care. New York: Springer; 2015. p. 2049–64.
[10] Vargas JH, Klein GL, Ament ME, Ott SM, Sherrard DJ, Horst RL, et al. Metabolic bone disease of total parenteral nutrition: course after changing from casein to amino acids in parenteral solutions with reduced aluminum content. Am J Clin Nutr 1988;48:1070–8. https://doi.org/10.1093/ajcn/48.4.1070.
[11] Gura KM. Aluminum contamination in products used in parenteral nutrition: has anything changed? Nutrition 2010;26:585–94. https://doi.org/10.1016/j.nut.2009.10.015.
[12] European Directorate for the Quality of Medicines & HealthCare. Call for experts – aluminium in parenteral nutrition solutions. Strasbourg, France:

Council of Europe; 2023. https://www.edqm.eu/en/-/call-for-experts-aluminium-in-parenteral-nutrition-solutions. [Accessed 13 February 2023].
[13] Advenier E, Landry C, Colomb V, Cognon C, Pradeau D, Florent M, et al. Aluminum contamination of parenteral nutrition and aluminum loading in children on long-term parenteral nutrition. J Pediatr Gastroenterol Nutr 2003;36:448–53. https://doi.org/10.1097/00005176-200304000-00005.
[14] Alvarez L, Rebollido M, Fernandez-Lorenzo JR, Cocho JA, Fraga JM. Electrothermal atomic absorption spectrometry determination of aluminium in parenteral nutrition and its components. J Trace Elem Med Biol 2007;21(Suppl 1):29–30. https://doi.org/10.1016/j.jtemb.2007.09.009.
[15] Aşut E, Köksal N, Dorum BA, Özkan H. Aluminum exposure in premature babies related to total parenteral nutrition and treatments. Turk J Pediatr 2018;60:385–91. https://doi.org/10.24953/turkjped.2018.04.005.
[16] Courtney-Martin G, Kosar C, Campbell A, Avitzur Y, Wales PW, Steinberg K, et al. Plasma aluminum concentrations in pediatric patients receiving long-term parenteral nutrition. JPEN - J Parenter Enter Nutr 2015;39:578–85. https://doi.org/10.1177/0148607114531046.
[17] de Oliveira SR, Bohrer D, Garcia SC, do Nascimento PC, Noremberg S. Aluminum content in intravenous solutions for administration to neonates: role of product preparation and administration methods. JPEN - J Parenter Enter Nutr 2010;34:322–8. https://doi.org/10.1177/0148607110362531.
[18] Huston RK, Heisel CF, Vermillion BR, Christensen JM, Minc L. Aluminum content of neonatal parenteral nutrition solutions: options for reducing aluminum exposure. Nutr Clin Pract 2017;32:266–70. https://doi.org/10.1177/0884533616668789.
[19] Lima-Rogel V, Romano-Moreno S, de Jesús López-López E, de Jesús Escalante-Padrón F, Hurtado-Torres GF. Aluminum contamination in parenteral nutrition admixtures for low-birth-weight preterm infants in Mexico. JPEN - J Parenter Enter Nutr 2016;40:1014–20. https://doi.org/10.1177/0148607114550001.
[20] Migaki EA, Melhart BJ, Dewar CJ, Huston RK. Calcium chloride and sodium phosphate in neonatal parenteral nutrition containing TrophAmine: precipitation studies and aluminum content. JPEN - J Parenter Enter Nutr 2012;36:470–5. https://doi.org/10.1177/0148607111420154.
[21] Poole RL, Pieroni KP, Gaskari S, Dixon TK, Park K, Kerner Jr JA. Aluminum in pediatric parenteral nutrition products: measured versus labeled content. J Pediatr Pharmacol Therapeut 2011;16:92–7. https://doi.org/10.5863/1551-6776-16.2.92.
[22] Poole RL, Schiff L, Hintz SR, Wong A, Mackenzie N, Kerner Jr JA. Aluminum content of parenteral nutrition in neonates: measured versus calculated levels. J Pediatr Gastroenterol Nutr 2010;50:208–11. https://doi.org/10.1097/MPG.0b013e3181aed70b.
[23] Mouser JF, Wu AH, Herson VC. Aluminum contamination of neonatal parenteral nutrient solutions and additives. Am J Health Syst Pharm 1998;55:1071–2. https://doi.org/10.1093/ajhp/55.10.1071.
[24] Popińska K, Kierkuś J, Lyszkowska M, Socha J, Pietraszek E, Kmiotek W, et al. Aluminum contamination of parenteral nutrition additives, amino acid solutions, and lipid emulsions. Nutrition 1999;15:683–6. https://doi.org/10.1016/s0899-9007(99)00124-0.
[25] Koo WW, Kaplan LA, Bendon R, Succop P, Tsang RC, Horn J, et al. Response to aluminum in parenteral nutrition during infancy. J Pediatr 1986;109:877–83. https://doi.org/10.1016/s0022-3476(86)80718-1.
[26] Koo WW, Kaplan LA, Horn J, Tsang RC, Steichen JJ. Aluminum in parenteral nutrition solution—sources and possible alternatives. JPEN - J Parenter Enter Nutr 1986;10:591–5. https://doi.org/10.1177/0148607186010006591.
[27] Larchet M, Chaumont P, Galliot M, Bourdon R, Goulet O, Ricour C. Aluminium loading in children receiving long-term parenteral nutrition. Clin Nutr 1990;9:79–83. https://doi.org/10.1016/0261-5614(90)90057-y.
[28] Hayes P, Martin TP, Pybus J, Hunt J, Broadbent RS. Reduction of bioavailability of aluminium in neonatal parenteral nutrition solutions by prior complexation in the dosage form. J Parenter Sci Technol 1992;46:169–75.
[29] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2022. URL, https://www.R-project.org.
[30] Wickham H, Averick M, Bryan J, Chang W, McGowan L, François R, et al. Welcome to the tidyverse. J Open Source Softw 2019;4. https://doi.org/10.21105/joss.01686.
[31] Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Software 2015;67. https://doi.org/10.18637/jss.v067.i01.
[32] Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest package: tests in linear mixed effects models. J Stat Software 2017;82. https://doi.org/10.18637/jss.v082.i13.
[33] Harigaya K, Kuwahara Y, Nishi H. Determination of aluminum in large volume parenteral drug products used in total parenteral nutrition therapy by ICP-MS with a dynamic reaction cell. Chem Pharm Bull (Tokyo) 2008;56:475–9. https://doi.org/10.1248/cpb.56.475.
[34] Brown RO, Morgan LM, Bhattacharya SK, Johnson PL, Minard G, Dickerson RN. Potential aluminum exposure from parenteral nutrition in patients with acute kidney injury. Ann Pharmacother 2008;42:1410–5. https://doi.org/10.1345/aph.1L061.
[35] Menendez AM, Farias SS, Servant R, Morisio Y, Misischia Y, Simon S, et al. [Aluminum content in individual components, used to prepare adult total parenteral nutrition mixtures in Argentine, and in comparison with international regulation]. Nutr Hosp 2014;29:1380–7. https://doi.org/10.3305/nh.2014.29.6.7320.
[36] Öztürk E, Yıldırım S, Akyol A. Determination of aluminum concentrations of parenteral nutrition solutions by HPLC. Eur J Clin Nutr 2021;75:567–9. https://doi.org/10.1038/s41430-020-00741-0.
[37] Speerhas RA, Seidner DL. Measured versus estimated aluminum content of parenteral nutrient solutions. Am J Health Syst Pharm 2007;64:740–6. https://doi.org/10.2146/ajhp060468.
[38] European Medicines Agency Committee for Human Medicinal Products. International Council on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) guideline Q3D (R1) on elemental impurities. 2019.

CONCLUSIONS AND OUTLOOK

This dissertation explores various strategies and innovations in medical nutrition, with a focus on anti-inflammatory diets for rheumatoid arthritis and dietary fiber intake in the area of dietetics, management of PBH in the area of obesity, and HPN in the area of nutritional support.

1. Dietetics

Dietetics aims to prevent or treat disease-specific disorders and enhance QOL [2]. In addition to QOL, other patient-reported outcomes are increasingly being employed to evaluate and monitor the effectiveness of nutrition therapy. Our meta-analysis on anti-inflammatory diets in rheumatoid arthritis revealed that although Mediterranean, vegetarian, and vegan diets did not result in significant alterations in objective inflammatory markers (C-reactive protein and erythrocyte sedimentation rate), they significantly improved pain, health assessment questionnaire scores, and swollen joint counts [117]. Consequently, these interventions contribute to perceived improvements in symptoms, disease burden, and QOL, strengthening the evidence for nutrition therapy in rheumatoid arthritis.

In contrast to dietary fiber-rich traditional Mediterranean, vegetarian, and vegan diets, our research demonstrated a widespread dietary fiber deficiency among the Swiss population. This finding is relevant not only for public health interventions, but also renders dietary fiber an important factor to be considered in the area of dietetics, such as the prevention of cardiovascular and coronary heart disease [138, 139], type 2 diabetes [139, 140], and cancer [139, 141-143]. In dietetics, practitioners typically estimate individuals' macronutrient intake using food records and evaluate micronutrient status using biochemical parameters. Dietary fiber intake warrants special attention in this assessment for both disease prevention and treatment. While dietary fiber supplementation may prove advantageous for specific purposes and populations [118], it is generally recommended that individuals meet dietary fiber intake recommendations through the consumption of unprocessed or minimally processed foods [144]. Natural foods provide a favorable combination and a broad spectrum of dietary fibers, and the food matrix plays a crucial role in the effects of dietary fibers. Effects of intrinsic dietary fibers may diminish when isolated dietary fibers or ultra-processed high-fiber ingredients are added to processed foods [145]. Furthermore, unprocessed or minimally processed foods high in dietary fiber offer additional benefits such as reducing a meal's glycemic index and increasing satiety. Data regarding why dietary fiber intake is insufficient are lacking. However, this

understanding is important to develop strategies to increase dietary fiber intake. Thus, we are currently conducting a follow-up analysis of the *menuCH* dataset to examine dietary fiber intake in relation to specific foods and meal pattern and composition.

2. Obesity and Post-Bariatric Hypoglycemia Management

Managing blood glucose in patients with PBH presents major challenges, as blood glucose patterns derived from meal composition are often unreliable, and careful hypoglycemia correction is required to avoid rebound hypoglycemia. The PBH Forecast study indicated that diabetes-inspired guidelines for correcting hypoglycemia with 15 g of glucose are not transferable to patients with PBH. These patients require less glucose, and utilizing a combination of glucose and protein, or a two-step strategy involving high-glycemic index carbohydrates for rapid correction, followed by a low-glycemic index snack to prevent rebound hypoglycemia, appear promising. Moreover, owing to inter-individual variability, distinct approaches might be required for patients based on their metabolic characteristics or medical profiles.

CGM enables real-time blood glucose level monitoring through interstitial glucose measurements every five minutes, allowing tailored blood glucose management in patients with PBH. Understanding past blood glucose patterns and current glucose levels facilitates dietary choices and blood glucose management. Importantly, CGM can enhance patient safety by detecting asymptomatic hypoglycemia, identifying ten times more hypoglycemic events than self-monitoring based on symptoms [41]. Continuous monitoring also aids in decision-making for hypoglycemia correction and helps prevent overcorrection and thus avoid rebound hypoglycemia [26]. However, CGM is currently considered off-label for PBH, necessitating higher-quality evidence for its use in the PBH population and clear criteria for insurance coverage.

Algorithms for predicting glucose trajectories and alerting impending hypoglycemia can be developed using CGM data [146]. Various approaches have been employed, including traditional time-series forecasting, machine learning, and deep learning methods [147-149]. Researchers are also exploring the integration of additional factors, such as food intake, heart rate, and physical activity into these algorithms [150-152]. Timely hypoglycemia warnings can significantly mitigate its consequences, but false alarms may adversely affect user acceptance [153]. Research on hypoglycemia prediction algorithms for patient with PBH is limited, and most CGM-based prediction studies have been conducted in patients with diabetes [154]. A hypoglycemia prediction algorithm developed based on data from the outpatient

observational period of the PBH Forecast study (work package 1) is currently being tested (ClinicalTrials.gov identifier: NCT05216926). Participants undergo a mixed meal test and are randomized to preventive 10 g glucose intake per the algorithm or corrective 10 g glucose intake when plasma glucose decreases below 3.0 mmol/L. The primary outcomes is nadir plasma glucose within 180 minutes after mixed meal consumption, while secondary outcomes assessed within the same timeframe include post-prandial time in specific plasma glucose ranges (< 3.0 mmol/L, < 3.9 mmol/L, ≥ 10.0 mmol/L), proportion of participants developing hypoglycemia, and mean and peak plasma glucose.

Challenges in CGM use for PBH patients include the lag in interstitial blood glucose levels, which may not keep pace with rapid postprandial blood glucose changes in PBH patients [155]. Furthermore, CGM accuracy decreases during hypoglycemia, necessitating capillary measurements upon CGM-detected hypoglycemia [156]. Current CGM devices are not designed for rapid glucose changes typical in PBH patients, leading to data visualization gaps and inflexible hypoglycemia thresholds that are set higher than the clinical PBH thresholds [26]. Making these devices on-label for patients with PBH may present opportunities for improvement specifically for this population.

In addition to CGM, innovative strategies involve image-based macronutrient estimation of meals [157, 158], digital receipt-based grocery selection support [159], and comprehensive platforms that combine multiple data sources with advanced analytical techniques to refine prediction algorithms and decision-making systems [26]. Digital technologies supporting the nutritional management of PBH show considerable potential, and research and development in this area has only recently begun [26].

3. Nutritional Support

Optimizing individualized nutrition therapy to prevent and treat malnutrition is a complex research area. Given the substantial long-term health risks faced by malnourished patients [127], studying post-hospital discharge nutrition therapy is crucial. Patients with varying malnutrition etiologies require tailored nutritional approaches based on underlying conditions and inflammation levels [58, 160]. Large-scale interventional trials with comprehensive participant phenotyping are required to identify predictors for personalized treatment decisions and to advance the field [58].

The landmark EFFORT trial, which did not continue nutritional support after hospital discharge, found no effect six months post-discharge [161]. However, nutritional risk has been identified as a predictor of long-term mortality [127]. A systematic review and meta-analysis of 14 RCTs revealed that post-discharge nutritional support improved long-term mortality in malnourished adult medical patients, but the included trials were of moderate quality [162]. The ongoing Effect of Continued Nutritional Support at Hospital Discharge on Mortality, Frailty, Functional Outcomes and Recovery Trial (EFFORT II, ClinicalTrials.gov identifier: NCT04926597) aims to address this research gap. The data generated will enhance the understanding of the pathophysiological aspects of malnutrition and establish a more robust, evidence-based foundation for new strategies in outpatient nutritional management. This may help derive initial treatment guidelines for disease-related malnutrition outside the hospital. Additionally, analyzing subgroups in the outpatient sector will help classify patients based on their response to nutrition therapy, enabling more personalized interventions [163].

Post-discharge nutritional support also encompasses HPN, the prevalence of which is increasing [87]. The SwissHPN-II study [85, 113] and the survey on HPN patients' attitudes and expectations regarding eHealth [133] demonstrated the need for specialized centers providing improved care for HPN patients. However, some patients face significant travel to access such centers. Moreover, prevention of complications through timely and expert care is crucial. eHealth innovations could close this gap in HPN patient care. Initial attempts to implement videoconference consultations in HPN patient care have been successful, but they are not yet routine [164-168]. Studies have reported that HPN patients and physicians are generally satisfied with telephone or videoconference consultations [164-167], which could potentially address preventable causes of HPN complications, such as catheter exit site infections [165]. Infection rates tend to be lower [165-167], but the results on non-elective rehospitalizations are inconclusive [165, 166, 168]. Professionals highly rate their ability to obtain a medical history and visually inspect patients through videoconferences, with primary and secondary viewer ratings of the clinical accuracy of visual inspections similar to in-person assessments [164].

eHealth presents promising potential for monitoring patients with HPN, offering easier contact and adherence to the ESPEN recommendations for regular HPN team contact, QOL and quality of care measurements, and encouraging patient participation in HPN education and support groups [81]. These measures may benefit patients with HPN in terms of QOL, depression severity, and catheter-related infections [81]. Consequently, we developed the eSwissHPN app and dashboard, a

minimum viable product, based on the most important functionalities identified through the survey. The first version of the eSwissHPN app includes the functionalities listed in Table 4. Figure 8 and Figure 9 depict screenshots of the eSwissHPN app (for patients) and the dashboard (for HCPs), respectively.

Table 4: Features of the first version of the eSwissHPN app

Section	**Functionality**	**Specifications**
Settings	App languages	German, French, Italian
Patient journal	Body weight (morning after going to the toilet, before breakfast)	Entry in kilograms
	Body temperature (morning)	Entry in °C
	Daytime urine color	Selection on Armstrong urine color chart [169]
	Stool frequency (number of bowel movements per day/per week)	Free text entry
	Stool consistency	Selection of Bristol stool scale [170]
	Stoma loss (number of stoma bag changes per day; average mL in stoma bag)	Slider entry
	Other symptoms	Free text entry
	Catheter exit site	Upload of a picture
	Food record	Free text entry fields for breakfast, lunch, dinner, snacks, beverages
	PN and intravenous fluids (if no infusion plan is available, or deviations from the infusion plan: PN, added micronutrients, electrolytes, and medications, additional intravenous fluid)	Free text entry
Communication	Videoconference consultations	Patients enter videoconference via the eSwissHPN app, HCPs via the dashboard
Red flag situations	If any of the following occurs, report immediately to the physician responsible for PN.	– Fever (body temperature above 38.0 °C) – Chills when flushing the catheter – Redness, swelling, secretion or bleeding at the catheter exit site – Pain, swelling, or numbness in the arm or neck on the side of the catheter
History	Visualization of weight course	
	Access to past journal entries	

HCP, health care professional; PN, parenteral nutrition

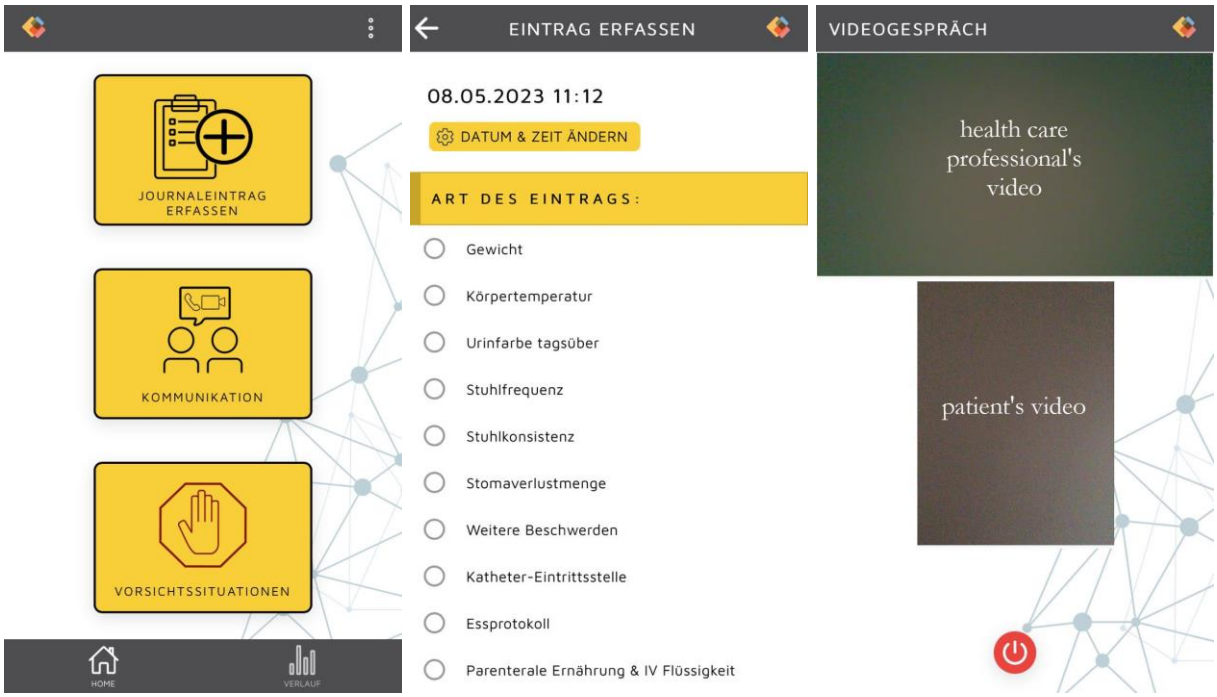


Figure 8: German user interface of the eSwissHPN app (first version) left: home screen; middle: patient journal entries; right: videoconference

We are currently conducting a nationwide multicenter project in which patients transition from usual care (inpatient visits without additional monitoring) to eHealth care (more frequent yet shorter interactions with the treating physician and monitoring via the eSwissHPN dashboard). Our objective is to provide optimal services and efficient medical care for patients with HPN. The goal of the ongoing project is to evaluate the quality and effectiveness of eHealth care for patients with HPN. To this end, eHealth care is delivered as part of routine clinical practice through videoconference consultations. eHealth care is conducted using the eSwissHPN app, which additionally enables HCPs to remotely monitor clinical parameters via the eSwissHPN dashboard. We assess patient satisfaction using the 8-item Client Satisfaction Questionnaire© [171, 172] and the Telehealth Usability Questionnaire [173]. Moreover, we measure QOL using version 2 of the 36-Item Short Form Health Survey (SF-36v2®) and complication rates (catheter-related infections and occlusions, and involuntary hospitalizations due to PN complications). Patients are asked to complete these questionnaires at the start and after four months of eHealth care, and treating physicians document the occurrence of HPN-related complications. Treating physicians also complete the 8-item Client Satisfaction Questionnaire© and the Telehealth Usability Questionnaire.

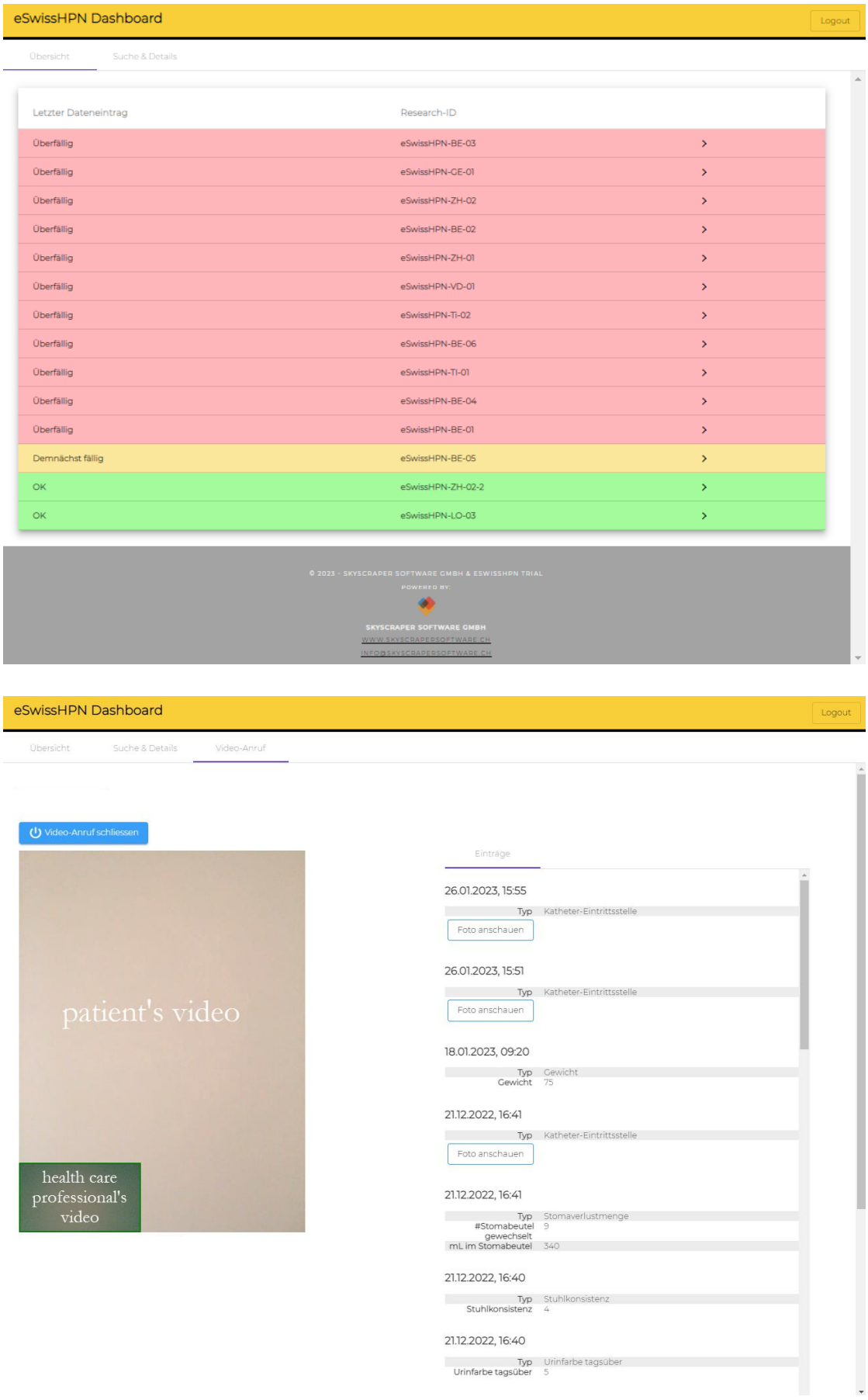


Figure 9: eSwissHPN dashboard for health care professionals
top: home screen with patient overview; bottom: videoconference with a patient and the patient's data entries

While the project is ongoing, the initial feedback indicates that patients need to be carefully selected and digitally proficient. However, patients interested in and capable of using the eSwissHPN app, along with treating physicians, provided positive feedback and appreciated the opportunities offered by the eSwissHPN app. For instance, one patient in the project exhibited signs of a potential catheter infection (redness and tenderness at the catheter exit site). With the eSwissHPN app, the patient could upload daily pictures of the catheter exit site, allowing the treating physician to closely monitor its progress. Ultimately, a potential catheter infection was safely prevented through early and easily accessible physician care. This patient had a significant travel distance to the specialized center, making close monitoring unfeasible through inpatient visits. Unpublished data from the SwissHPN II study shows that the mean (SD) distance to travel in case of PN-related problems in Switzerland is 36 (51) km. This underlines the importance to facilitate remote care for patients with HPN via eHealth. For the app's further improvement and development beyond the minimum viable product, customization of data entries in terms of type and frequency is crucial. Eg, a functionality to hide data entries related to the stoma for patients without a stoma will reduce the patient burden with journal entries and likely increase compliance. In addition, the current version requires patients and HCPs to enter the videoconference room at a specified time for consultation. However, it is becoming apparent that proactive contact from both sides, such as through a chat function, is essential for HPN management.

As the life expectancy of patients on HPN has increased, leading to longer application of PN over decades, the toxicological safety profiles of commercial PN products has become increasingly relevant. Among the patients included in the eSwissHPN project, one patient has received HPN for over 40 years. The doctoral research presented in this dissertation reveals that contamination with aluminum but not other heavy metals is a concern in commercial PN admixtures prepared from multichamber bags for adults with vitamin and trace element additives. The European Pharmacopoeia (Ph. Eur.), responsible for defining quality standards of medicinal products, has recently established the Aluminium in Parenteral Solutions Working Party to draft a new general chapter on aluminum in PN solutions, aiming to limit the risk of exposure to toxic levels of aluminum and provide guidance on PN preparation and administration [174]. It is plausible that they will align with the widely accepted limit of 25 μg/L for large volume PN solutions, such as AIO admixtures, as utilized by the United States Food and Drug Administration and other countries [21 CFR 201.323]. Ensuring that aluminum is determined by methods validated for aqueous solutions and oil-in-water emulsions is crucial. We demonstrated one such possibility using inductively coupled plasma mass

spectrometry. Additionally, presenting aluminum content in a manner that allows the calculation of total exposure is an important aspect that should be addressed in the new chapter of the European Pharmacopoeia.

4. Overall Conclusions

In the area of dietetics, the doctoral research found that the dietary fiber consumption within the Swiss population is insufficient and inversely associated with ultra-processed food consumption. Moreover, anti-inflammatory diets were shown to improve pain in rheumatoid arthritis patients. Within obesity management, the increasingly recognized issue of PBH was addressed. The PBH Forecast project explored the role of nutritional strategies and predictive algorithms in managing this condition. Lastly, in the nutritional support area, the doctoral research led to the development of an eHealth platform for patients with HPN. Additionally, it revealed concerning levels of aluminum in commercial PN admixtures.

In conclusion, the evolving landscape of medical nutrition is increasingly emphasizing the importance of patient-reported outcomes and QOL. As such, QOL is becoming a crucial therapeutic outcome and an indicator of quality of care. New strategies and innovations in medical nutrition are moving towards customized digital solutions and eHealth to guide and support dietary decision making, nutrition therapy, and patient monitoring. However, several challenges must be addressed in the development and implementation of such digital solutions. For users, minimizing the burden of use, such as the effort required for manual data entry and device management, is essential for technology adoption. In addition, developers must adhere to data security and privacy regulations, such as the European Union's General Data Protection Regulation, to ensure patient safety and trust. Moreover, it is important to recognize that some digital tools may be classified as medical devices, subjecting them to regulatory requirements (eg, European Medical Device Regulation) [26]. Navigating these regulations can be challenging, but they ultimately contribute to patient safety and quality of care. Consequently, the successful development and implementation of eHealth and digital solutions for medical nutrition necessitate interprofessional collaboration and research among HCPs, engineers, and legal experts, as well as involvement of patients/users. Patient involvement and monitoring could increase adherence to nutrition therapy and improve cost-effectiveness to be demonstrated in future scientific investigation. To maximize the potential of eHealth and digital solutions in medical nutrition, future efforts should focus on refining and personalizing these technologies, ensuring their ease of use, and fostering a multidisciplinary approach. By doing so, we can advance the field of medical nutrition and improve nutrition therapy and support.

BIBLIOGRAPHY

1. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr. 2017;36(1):49-64. doi: 10.1016/j.clnu.2016.09.004
2. Valentini L, Volkert D, Schütz T, Ockenga J, Pirlich M, Druml W, et al. Leitlinie der Deutschen Gesellschaft für Ernährungsmedizin (DGEM): DGEM-Terminologie in der Klinischen Ernährung. Aktuelle Ernährungsmedizin. 2013;38(02):97-111. doi: 10.1055/s-0032-1332980
3. Valentini L, Volkert D, Schütz T, Ockenga J, Pirlich M, Druml W, et al. Suggestions for terminology in clinical nutrition. e-SPEN Journal. 2014;9(2):e97-e108. doi: 10.1016/j.clnme.2013.12.004
4. Valentini, L. DGEM-Terminologie in der Klinischen Ernährung. Ludwigsburg: Ernährung 2014; 26.-28. June 2014. Available from: www.dgem.de/sites/default/files/PDFs/Veranstaltungen/Ernaehrung2014/Valentini_DGEM-TerminologieInDerKlinischenErnaehrung.pdf [accessed 14. Mar 2023].
5. Flodgren G, Rachas A, Farmer AJ, Inzitari M, Shepperd S. Interactive telemedicine: effects on professional practice and health care outcomes. Cochrane Database Syst Rev. 2015(9):CD002098. doi: 10.1002/14651858.CD002098.pub2
6. eHealth Suisse Kompetenz- und Koordinationsstelle von Bund und Kantonen. Bern, 2017 [updated 26. Sep 2019]. Available from: www.e-health-suisse.ch/header/glossar.html [accessed 24. Apr 2023].
7. 58. World Health Assembly. WHA58.28 eHealth. In: Fifty-eighth World Health Assembly, Geneva, 16-25 May 2005: resolutions and decisions: annex. Geneva: World Health Organization; 2005. p. 108-10.
8. Global diffusion of eHealth: making universal health coverage achievable. Report of the third global survey on eHealth. Geneva: World Health Organization; 2016.
9. Third Global Survey on eHealth 2015: The use of eHealth in support of universal health coverage. Geneva: World Health Organization; 2015.
10. Svačina Š, Haluzík M, Chourdakis M, Matos L, Chernesh I, Bischoff S. Overnutrition - functional and clinical consequences. In: Sobotka L, Allison SP, Forbes A, Meier RF, Schneider SM, Soeters PB, et al., editors. Basics in Clinical Nutrition. 5 ed. Prague: Galén; 2019. p. 31-9.
11. de van der Schueren MAE, Soeters PB, Reijven PLM, Allison SP, Kondrup J. Diagnosis of malnutrition - Screening and Assessment. In: Sobotka L, Allison SP, Forbes A, Meier RF, Schneider SM, Soeters PB, et al., editors. Basics in Clinical Nutrition. 5 ed. Prague: Galén; 2019. p. 18-27.
12. Welbourn R, Hollyman M, Kinsman R, Dixon J, Liem R, Ottosson J, et al. Bariatric Surgery Worldwide: Baseline Demographic Description and One-Year Outcomes from the Fourth IFSO Global Registry Report 2018. Obes Surg. 2019;29(3):782-95. doi: 10.1007/s11695-018-3593-1

13. Bauknecht F. Bariatrische Operationen in der Schweiz 2001-2020. 2021. Available from: www.smob.ch/de/component/jdownloads/?task=download.send&id=113&catid=2&m=0&Itemid=101 [accessed 23. Apr 2023].
14. Steenackers N, Vanuytsel T, Augustijns P, Tack J, Mertens A, Lannoo M, et al. Adaptations in gastrointestinal physiology after sleeve gastrectomy and Roux-en-Y gastric bypass. Lancet Gastroenterol Hepatol. 2021;6(3):225-37. doi: 10.1016/S2468-1253(20)30302-2
15. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. JAMA Surg. 2014;149(3):275-87. doi: 10.1001/jamasurg.2013.3654
16. Wiggins T, Antonowicz SS, Markar SR. Cancer Risk Following Bariatric Surgery-Systematic Review and Meta-analysis of National Population-Based Cohort Studies. Obes Surg. 2019;29(3):1031-9. doi: 10.1007/s11695-018-3501-8
17. Syn NL, Cummings DE, Wang LZ, Lin DJ, Zhao JJ, Loh M, et al. Association of metabolic-bariatric surgery with long-term survival in adults with and without diabetes: a one-stage meta-analysis of matched cohort and prospective controlled studies with 174 772 participants. Lancet. 2021;397(10287):1830-41. doi: 10.1016/S0140-6736(21)00591-2
18. Cardoso L, Rodrigues D, Gomes L, Carrilho F. Short- and long-term mortality after bariatric surgery: A systematic review and meta-analysis. Diabetes Obes Metab. 2017;19(9):1223-32. doi: 10.1111/dom.12922
19. Decker GA, Swain JM, Crowell MD, Scolapio JS. Gastrointestinal and nutritional complications after bariatric surgery. Am J Gastroenterol. 2007;102(11):2571-80. doi: 10.1111/j.1572-0241.2007.01421.x
20. Scarpellini E, Arts J, Karamanolis G, Laurenius A, Siquini W, Suzuki H, et al. International consensus on the diagnosis and management of dumping syndrome. Nat Rev Endocrinol. 2020;16(8):448-66. doi: 10.1038/s41574-020-0357-5
21. Kefurt R, Langer FB, Schindler K, Shakeri-Leidenmuhler S, Ludvik B, Prager G. Hypoglycemia after Roux-En-Y gastric bypass: detection rates of continuous glucose monitoring (CGM) versus mixed meal test. Surg Obes Relat Dis. 2015;11(3):564-9. doi: 10.1016/j.soard.2014.11.003
22. Capristo E, Panunzi S, De Gaetano A, Spuntarelli V, Bellantone R, Giustacchini P, et al. Incidence of Hypoglycemia After Gastric Bypass vs Sleeve Gastrectomy: A Randomized Trial. J Clin Endocrinol Metab. 2018;103(6):2136-46. doi: 10.1210/jc.2017-01695
23. Abrahamsson N, Eden Engstrom B, Sundbom M, Karlsson FA. Hypoglycemia in everyday life after gastric bypass and duodenal switch. Eur J Endocrinol. 2015;173(1):91-100. doi: 10.1530/EJE-14-0821
24. Emous M, van den Broek M, Wijma RB, de Heide LJM, van Dijk G, Laskewitz A, et al. Prevalence of hypoglycaemia in a random population after Roux-en-Y

gastric bypass after a meal test. Endocr Connect. 2019;8(7):969-78. doi: 10.1530/EC-19-0268
25. Halperin F, Patti ME, Skow M, Bajwa M, Goldfine AB. Continuous glucose monitoring for evaluation of glycemic excursions after gastric bypass. J Obes. 2011;2011:869536. doi: 10.1155/2011/869536
26. Schönenberger KA, Cossu L, Prendin F, Cappon G, Wu J, Fuchs KL, et al. Digital Solutions to Diagnose and Manage Postbariatric Hypoglycemia. Front Nutr. 2022;9:855223. doi: 10.3389/fnut.2022.855223
27. Lehmann V, Tripyla A, Herzig D, Meier J, Banholzer N, Maritsch M, et al. The impact of postbariatric hypoglycaemia on driving performance: A randomized, single-blind, two-period, crossover study in a driving simulator. Diabetes Obes Metab. 2021;23(9):2189-93. doi: 10.1111/dom.14456
28. Svane MS, Bojsen-Moller KN, Martinussen C, Dirksen C, Madsen JL, Reitelseder S, et al. Postprandial Nutrient Handling and Gastrointestinal Hormone Secretion After Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy. Gastroenterology. 2019;156(6):1627-41 e1. doi: 10.1053/j.gastro.2019.01.262
29. Camastra S, Muscelli E, Gastaldelli A, Holst JJ, Astiarraga B, Baldi S, et al. Long-term effects of bariatric surgery on meal disposal and beta-cell function in diabetic and nondiabetic patients. Diabetes. 2013;62(11):3709-17. doi: 10.2337/db13-0321
30. Cavin JB, Couvelard A, Lebtahi R, Ducroc R, Arapis K, Voitellier E, et al. Differences in Alimentary Glucose Absorption and Intestinal Disposal of Blood Glucose After Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy. Gastroenterology. 2016;150(2):454-64 e9. doi: 10.1053/j.gastro.2015.10.009
31. Craig CM, Liu LF, Deacon CF, Holst JJ, McLaughlin TL. Critical role for GLP-1 in symptomatic post-bariatric hypoglycaemia. Diabetologia. 2017;60(3):531-40. doi: 10.1007/s00125-016-4179-x
32. Salehi M, Gastaldelli A, D'Alessio DA. Blockade of glucagon-like peptide 1 receptor corrects postprandial hypoglycemia after gastric bypass. Gastroenterology. 2014;146(3):669-80 e2. doi: 10.1053/j.gastro.2013.11.044
33. Toft-Nielsen M, Madsbad S, Holst JJ. Exaggerated secretion of glucagon-like peptide-1 (GLP-1) could cause reactive hypoglycaemia. Diabetologia. 1998;41(10):1180-6. doi: 10.1007/s001250051049
34. McLaughlin T, Peck M, Holst J, Deacon C. Reversible hyperinsulinemic hypoglycemia after gastric bypass: a consequence of altered nutrient delivery. J Clin Endocrinol Metab. 2010;95(4):1851-5. doi: 10.1210/jc.2009-1628
35. Tripyla A, Herzig D, Reverter-Branchat G, Pavan J, Schiavon M, Eugster PJ, et al. Counter-regulatory responses to postprandial hypoglycaemia in patients with post-bariatric hypoglycaemia vs surgical and non-surgical control individuals. Diabetologia. 2023;66(4):741-53. doi: 10.1007/s00125-022-05861-9
36. Abrahamsson N, Borjesson JL, Sundbom M, Wiklund U, Karlsson FA, Eriksson JW. Gastric Bypass Reduces Symptoms and Hormonal Responses in Hypoglycemia. Diabetes. 2016;65(9):2667-75. doi: 10.2337/db16-0341

37. Honka H, Salehi M. Postprandial hypoglycemia after gastric bypass surgery: from pathogenesis to diagnosis and treatment. Curr Opin Clin Nutr Metab Care. 2019;22(4):295-302. doi: 10.1097/MCO.0000000000000574
38. Ohrstrom CC, Hansen DL, Kielgast UL, Bergmann ML, Veedfald S, Holst JJ, et al. Counterregulatory responses to postprandial hypoglycemia after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2021;17(1):55-63. doi: 10.1016/j.soard.2020.08.037
39. Eisenberg D, Azagury DE, Ghiassi S, Grover BT, Kim JJ. ASMBS Position Statement on Postprandial Hyperinsulinemic Hypoglycemia after Bariatric Surgery. Surg Obes Relat Dis. 2017;13(3):371-8. doi: 10.1016/j.soard.2016.12.005
40. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2017;40(1):155-7. doi: 10.2337/dc16-2215
41. Craig CM, McLaughlin TL. Defining clinically important hypoglycemia in patients with postbariatric hypoglycemia. Surg Obes Relat Dis. 2021;17(11):1865-72. doi: 10.1016/j.soard.2021.06.013
42. Kim SH, Liu TC, Abbasi F, Lamendola C, Morton JM, Reaven GM, et al. Plasma glucose and insulin regulation is abnormal following gastric bypass surgery with or without neuroglycopenia. Obes Surg. 2009;19(11):1550-6. doi: 10.1007/s11695-009-9893-8
43. Roslin M, Damani T, Oren J, Andrews R, Yatco E, Shah P. Abnormal glucose tolerance testing following gastric bypass demonstrates reactive hypoglycemia. Surg Endosc. 2011;25(6):1926-32. doi: 10.1007/s00464-010-1489-9
44. Botros N, Rijnaarts I, Brandts H, Bleumink G, Janssen I, de Boer H. Effect of carbohydrate restriction in patients with hyperinsulinemic hypoglycemia after Roux-en-Y gastric bypass. Obes Surg. 2014;24(11):1850-5. doi: 10.1007/s11695-014-1319-6
45. Kandel D, Bojsen-Moller KN, Svane MS, Samkani A, Astrup A, Holst JJ, et al. Mechanisms of action of a carbohydrate-reduced, high-protein diet in reducing the risk of postprandial hypoglycemia after Roux-en-Y gastric bypass surgery. Am J Clin Nutr. 2019;110(2):296-304. doi: 10.1093/ajcn/nqy310
46. Hirabara SM, Silveira LR, Abdulkader F, Carvalho CR, Procopio J, Curi R. Time-dependent effects of fatty acids on skeletal muscle metabolism. J Cell Physiol. 2007;210(1):7-15. doi: 10.1002/jcp.20811
47. Kneepkens CM, Fernandes J, Vonk RJ. Dumping syndrome in children. Diagnosis and effect of glucomannan on glucose tolerance and absorption. Acta Paediatr Scand. 1988;77(2):279-86. doi: 10.1111/j.1651-2227.1988.tb10643.x
48. Speth PA, Jansen JB, Lamers CB. Effect of acarbose, pectin, a combination of acarbose with pectin, and placebo on postprandial reactive hypoglycaemia after gastric surgery. Gut. 1983;24(9):798-802. doi: 10.1136/gut.24.9.798

49. Jenkins DJ, Gassull MA, Leeds AR, Metz G, Dilawari JB, Slavin B, et al. Effect of dietary fiber on complications of gastric surgery: prevention of postprandial hypoglycemia by pectin. Gastroenterology. 1977;73(2):215-7
50. Salehi M, Vella A, McLaughlin T, Patti ME. Hypoglycemia After Gastric Bypass Surgery: Current Concepts and Controversies. J Clin Endocrinol Metab. 2018;103(8):2815-26. doi: 10.1210/jc.2018-00528
51. Sheehan A, Patti ME. Hypoglycemia After Upper Gastrointestinal Surgery: Clinical Approach to Assessment, Diagnosis, and Treatment. Diabetes Metab Syndr Obes. 2020;13:4469-82. doi: 10.2147/DMSO.S233078
52. Suhl E, Anderson-Haynes SE, Mulla C, Patti ME. Medical nutrition therapy for post-bariatric hypoglycemia: practical insights. Surg Obes Relat Dis. 2017;13(5):888-96. doi: 10.1016/j.soard.2017.01.025
53. Sloun BV, Goossens GH, Erdos B, Lenz M, Riel NV, Arts ICW. The Impact of Amino Acids on Postprandial Glucose and Insulin Kinetics in Humans: A Quantitative Overview. Nutrients. 2020;12(10). doi: 10.3390/nu12103211
54. Richardson T, Thomas P, Ryder J, Kerr D. Influence of caffeine on frequency of hypoglycemia detected by continuous interstitial glucose monitoring system in patients with long-standing type 1 diabetes. Diabetes Care. 2005;28(6):1316-20. doi: 10.2337/diacare.28.6.1316
55. Zaharieva DP, Miadovnik LA, Rowan CP, Gumieniak RJ, Jamnik VK, Riddell MC. Effects of acute caffeine supplementation on reducing exercise-associated hypoglycaemia in individuals with Type 1 diabetes mellitus. Diabet Med. 2016;33(4):488-96. doi: 10.1111/dme.12857
56. Reber E, Strahm R, Bally L, Schuetz P, Stanga Z. Efficacy and Efficiency of Nutritional Support Teams. J Clin Med. 2019;8(9). doi: 10.3390/jcm8091281
57. Soeters PB, Reijven PL, van Bokhorst-de van der Schueren MA, Schols JM, Halfens RJ, Meijers JM, et al. A rational approach to nutritional assessment. Clin Nutr. 2008;27(5):706-16. doi: 10.1016/j.clnu.2008.07.009
58. Schuetz P, Seres D, Lobo DN, Gomes F, Kaegi-Braun N, Stanga Z. Management of disease-related malnutrition for patients being treated in hospital. Lancet. 2021;398(10314):1927-38. doi: 10.1016/S0140-6736(21) 01451-3
59. Leij-Halfwerk S, Verwijs MH, van Houdt S, Borkent JW, Guaitoli PR, Pelgrim T, et al. Prevalence of protein-energy malnutrition risk in European older adults in community, residential and hospital settings, according to 22 malnutrition screening tools validated for use in adults ≥65 years: A systematic review and meta-analysis. Maturitas. 2019;126:80-9. doi: 10.1016/j.maturitas.2019.05.006
60. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22(3):321-36. doi: 10.1016/ s0261-5614(02)00214-5
61. Weekes CE, Elia M, Emery PW. The development, validation and reliability of a nutrition screening tool based on the recommendations of the British

Association for Parenteral and Enteral Nutrition (BAPEN). Clin Nutr. 2004;23(5):1104-12. doi: 10.1016/j.clnu.2004.02.003
62. Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). J Gerontol A Biol Sci Med Sci. 2001;56(6):M366-72. doi: 10.1093/gerona/56.6.m366
63. Ferguson M, Capra S, Bauer J, Banks M. Development of a valid and reliable malnutrition screening tool for adult acute hospital patients. Nutrition. 1999;15(6):458-64. doi: 10.1016/s0899-9007(99)00084-2
64. Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst-de van der Schueren MA. Development and validation of a hospital screening tool for malnutrition: the short nutritional assessment questionnaire (SNAQ). Clin Nutr. 2005;24(1):75-82. doi: 10.1016/j.clnu.2004.07.015
65. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr. 1987;11(1):8-13. doi: 10.1177/014860718701100108
66. Leuenberger MS, Joray ML, Kurmann S, Stanga Z. [How to assess the nutritional status of my patient]. Praxis (Bern 1994). 2012;101(5):307-15. doi: 10.1024/1661-8157/a000857
67. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN Guidelines for Nutrition Screening 2002. Clin Nutr. 2003;22(4):415-21. doi: 10.1016/s0261-5614(03)00098-0
68. Harris JA, Benedict FG. A Biometric Study of Human Basal Metabolism. Proc Natl Acad Sci U S A. 1918;4(12):370-3. doi: 10.1073/pnas.4.12.370
69. Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr. 2014;33(6):929-36. doi: 10.1016/j.clnu.2014.04.007
70. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. Clin Nutr. 2019;38(1):1-9. doi: 10.1016/j.clnu.2018.08.002
71. Müller NA, Wimmer R, Wunderle C, Tribolet P, Schütz P, Kägi-Braun N. GLIM-Kriterien in der ärztlichen Praxis - Was bringen die neuen Diagnosekriterien der Mangelernährung im Alltag. Schweizer Zeitschrift für Ernährungsmedizin. 2023;2:14-8
72. Elia M, Austin P, Stratton RJ. Indications for nutritional support. In: Sobotka L, Allison SP, Forbes A, Meier RF, Schneider SM, Soeters PB, et al., editors. Basics in Clinical Nutrition. 5 ed. Prague: Galén; 2019. p. 205-11.
73. Gomes F, Baumgartner A, Bounoure L, Bally M, Deutz NE, Greenwald JL, et al. Association of Nutritional Support With Clinical Outcomes Among Medical Inpatients Who Are Malnourished or at Nutritional Risk: An Updated Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(11):e1915138. doi: 10.1001/jamanetworkopen.2019.15138

74. Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. Lancet. 2019;393(10188):2312-21. doi: 10.1016/S0140-6736(18)32776-4
75. Deutz NE, Matheson EM, Matarese LE, Luo M, Baggs GE, Nelson JL, et al. Readmission and mortality in malnourished, older, hospitalized adults treated with a specialized oral nutritional supplement: A randomized clinical trial. Clin Nutr. 2016;35(1):18-26. doi: 10.1016/j.clnu.2015.12.010
76. Kaegi-Braun N, Tribolet P, Baumgartner A, Fehr R, Baechli V, Geiser M, et al. Value of handgrip strength to predict clinical outcomes and therapeutic response in malnourished medical inpatients: Secondary analysis of a randomized controlled trial. Am J Clin Nutr. 2021;114(2):731-40. doi: 10.1093/ajcn/nqab042
77. Keller U. Nutritional Laboratory Markers in Malnutrition. J Clin Med. 2019;8(6). doi: 10.3390/jcm8060775
78. Bretschera C, Boesiger F, Kaegi-Braun N, Hersberger L, Lobo DN, Evans DC, et al. Admission serum albumin concentrations and response to nutritional therapy in hospitalised patients at malnutrition risk: Secondary analysis of a randomised clinical trial. EClinicalMedicine. 2022;45:101301. doi: 10.1016/j.eclinm.2022.101301
79. Zhang Z, Pereira SL, Luo M, Matheson EM. Evaluation of Blood Biomarkers Associated with Risk of Malnutrition in Older Adults: A Systematic Review and Meta-Analysis. Nutrients. 2017;9(8). doi: 10.3390/nu9080829
80. Evans DC, Corkins MR, Malone A, Miller S, Mogensen KM, Guenter P, et al. The Use of Visceral Proteins as Nutrition Markers: An ASPEN Position Paper. Nutr Clin Pract. 2021;36(1):22-8. doi: 10.1002/ncp.10588
81. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35(2):247-307. doi: 10.1016/j.clnu.2016.01.020
82. Dreesen M, Foulon V, Hiele M, Vanhaecht K, De Pourcq L, Pironi L, et al. Quality of care for cancer patients on home parenteral nutrition: development of key interventions and outcome indicators using a two-round Delphi approach. Support Care Cancer. 2013;21(5):1373-81. doi: 10.1007/s00520-012-1679-1
83. Dreesen M, Foulon V, Vanhaecht K, Hiele M, De Pourcq L, Pironi L, et al. Development of quality of care interventions for adult patients on home parenteral nutrition (HPN) with a benign underlying disease using a two-round Delphi approach. Clin Nutr. 2013;32(1):59-64. doi: 10.1016/j.clnu.2012.05.006
84. Pironi L. Development of home artificial nutrition in Italy over a seven year period: 2005–2012. BMC Nutrition. 2017;3(1). doi: 10.1186/s40795-016-0118-y
85. Reber E, Staub K, Schönenberger KA, Stanga A, Leuenberger M, Pichard C, et al. Management of Home Parenteral Nutrition: Complications and Survival. Ann Nutr Metab. 2021;77(1):46-55. doi: 10.1159/000515057

86. Folwarski M, Klek S, Szlagatys-Sidorkiewicz A, Wyszomirski A, Brzezinski M, Skotnicka M. Trend Observations in Home Parenteral Nutrition. Prevalence, Hospitalizations and Costs: Results from a Nationwide Analysis of Health Care Provider Data. Nutrients. 2021;13(10). doi: 10.3390/nu13103465
87. Storck LJ, Ruehlin M, Wagener N, Moeltgen C, Genton L, Ballmer PE. Results from an Epidemiological Follow-Up Survey on Home Artificial Nutrition in Switzerland from 2010 to 2015. Ann Nutr Metab. 2020;76(5):345-53. doi: 10.1159/000510796
88. Naghibi M, Toskas A, Willsmore J, Smith T, Hughes SJ, Gabe S, et al. United Kingdom artificial nutrition database: The changing landscape of adult home parenteral support. JPEN J Parenter Enteral Nutr. 2023;47(5):635-45. doi: 10.1002/jpen.2504
89. Mundi MS, Pattinson A, McMahon MT, Davidson J, Hurt RT. Prevalence of Home Parenteral and Enteral Nutrition in the United States. Nutr Clin Pract. 2017;32(6):799-805. doi: 10.1177/0884533617718472
90. Pironi L, Arends J, Baxter J, Bozzetti F, Pelaez RB, Cuerda C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34(2):171-80. doi: 10.1016/j.clnu.2014.08.017
91. Cuerda C, Pironi L, Arends J, Bozzetti F, Gillanders L, Jeppesen PB, et al. ESPEN practical guideline: Clinical nutrition in chronic intestinal failure. Clin Nutr. 2021;40(9):5196-220. doi: 10.1016/j.clnu.2021.07.002
92. Pironi L, Boeykens K, Bozzetti F, Joly F, Klek S, Lal S, et al. ESPEN guideline on home parenteral nutrition. Clin Nutr. 2020;39(6):1645-66. doi: 10.1016/j.clnu.2020.03.005
93. Mühlebach S. Diets and Diet Therapy: Parenteral Nutrition. In: Ferranti P, Berry EM, Anderson JR, editors. Encyclopedia of Food Security and Sustainability. vol 2. 1 ed: Elsevier; 2019. p. 131-42.
94. Solassol C, Joyeux H, Etco L, Pujol H, Romieu C. New techniques for long-term intravenous feeding: an artificial gut in 75 patients. Ann Surg. 1974;179(4):519-22. doi: 10.1097/00000658-197404000-00025
95. Mühlebach S. Practical aspects of multichamber bags for total parenteral nutrition. Curr Opin Clin Nutr Metab Care. 2005;8(3):291-5. doi: 10.1097/01.mco.0000165008.47073.ba
96. Sobocki J, Dudrick SJ. Different systems for parenteral nutrition (AIO vs. MB). In: Sobotka L, Allison SP, Forbes A, Meier RF, Schneider SM, Soeters PB, et al., editors. Basics in Clinical Nutrition. 5 ed. Prague: Galén; 2019. p. 342-4.
97. Pertkiewicz M, Dudrick SJ. Basics in clinical nutrition: Systems for parenteral nutrition, different systems for parenteral nutrition (AIO vs. MB). e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism. 2009;4(3):e123-e4. doi: 10.1016/j.eclnm.2009.01.005
98. Mühlebach S, Franken C, Stanga Z, Working group for developing the guidelines for parenteral nutrition of the German Association for Nutritional Medicine. Practical handling of AIO admixtures - Guidelines on Parenteral Nutrition, Chapter 10. Ger Med Sci. 2009;7:Doc18. doi: 10.3205/000077

99. Boullata JI, Gilbert K, Sacks G, Labossiere RJ, Crill C, Goday P, et al. A.S.P.E.N. clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing. JPEN J Parenter Enteral Nutr. 2014;38(3):334-77. doi: 10.1177/0148607114521833
100. Reber E, Messerli M, Stanga Z, Mühlebach S. Pharmaceutical Aspects of Artificial Nutrition. J Clin Med. 2019;8(11). doi: 10.3390/jcm8112017
101. Mühlebach S, Discroll DF, Aeberhard C, Stanga Z. Stability and compatibility of parenteral nutrition (PN) admixtures. In: Sobotka L, Allison SP, Forbes A, Meier RF, Schneider SM, Soeters PB, et al., editors. Basics in Clinical Nutrition. 5 ed. Prague: Galén; 2019. p. 354-62.
102. Dudrick SJ, Sobocki J, Klek S. Peripheral parenteral nutrition (PPN). In: Sobotka L, Allison SP, Forbes A, Meier RF, Schneider SM, Soeters PB, et al., editors. Basics in Clinical Nutrition. 5 ed. Prague: Galén; 2019. p. 324-7.
103. Sobocki J, Dudrick SJ, Klek S. Central parenteral nutrition. In: Sobotka L, Allison SP, Forbes A, Meier RF, Schneider SM, Soeters PB, et al., editors. Basics in Clinical Nutrition. 5 ed. Prague: Galén; 2019. p. 328-36.
104. Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M, Espen. ESPEN Guidelines on Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of complications). Clin Nutr. 2009;28(4):365-77. doi: 10.1016/j.clnu.2009.03.015
105. Weimann A, Braga M, Carli F, Higashiguchi T, Hubner M, Klek S, et al. ESPEN guideline: Clinical nutrition in surgery. Clin Nutr. 2017;36(3):623-50. doi: 10.1016/j.clnu.2017.02.013
106. Wouters Y, Causevic E, Klek S, Groenewoud H, Wanten GJA. Use of Catheter Lock Solutions in Patients Receiving Home Parenteral Nutrition: A Systematic Review and Individual-Patient Data Meta-Analysis. JPEN J Parenter Enteral Nutr. 2020;44(7):1198-209. doi: 10.1002/jpen.1761
107. Lopez-Briz E, Ruiz Garcia V, Cabello JB, Bort-Marti S, Carbonell Sanchis R. Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults. Cochrane Database Syst Rev. 2022(7):CD008462. doi: 10.1002/14651858.CD008462.pub4
108. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1-45. doi: 10.1086/599376
109. Sobotka L, Wanten G, Camilo ME, Van Gossum A. Metabolic complications of parenteral nutrition. In: Sobotka L, Allison SP, Forbes A, Meier RF, Schneider SM, Soeters PB, et al., editors. Basics in Clinical Nutrition. 5 ed. Prague: Galén; 2019. p. 371-6.
110. Schönenberger KA, Reber E, Dürig C, Baumgartner A, Efthymiou A, Huwiler VV, et al. Management of Hyperglycemia in Hospitalized Patients Receiving Parenteral Nutrition. Front Clin Diabetes Healthc. 2022;3:829412. doi: 10.3389/fcdhc.2022.829412

111. Sobotka L, Camilo ME. Basics in clinical nutrition: Metabolic complications of parenteral nutrition. e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism. 2009;4(3):e120-e2. doi: 10.1016/j.eclnm.2009.01.001
112. Aeberhard C, Leuenberger M, Joray M, Ballmer PE, Mühlebach S, Stanga Z. Management of Home Parenteral Nutrition: A Prospective Multicenter Observational Study. Ann Nutr Metab. 2015;67(4):210-7. doi: 10.1159/000440683
113. Schönenberger KA, Reber E, Huwiler VV, Durig C, Muri R, Leuenberger M, et al. Quality of Life in the Management of Home Parenteral Nutrition. Ann Nutr Metab. 2023;79(3):326-33. doi: 10.1159/000530082
114. HPN Patient Testimonials. 2022. Available from: www.fresucare.ch/sites/default/files/2022-02/Bettina-story.mp4 and www.fresucare.ch/sites/default/files/2022-04/Herr-L.mp4 [accessed 28. Apr 2023].
115. Schönenberger KA, Huwiler VV, Reber E, Mühlebach S, Stanga Z, Pestoni G, et al. Dietary fibre intake and its association with ultraprocessed food consumption in the general population of Switzerland: analysis of a population-based, cross-sectional national nutrition survey. BMJ Nutrition, Prevention & Health. 2024. doi: 10.1136/bmjnph-2023-000727
116. Karavasiloglou N, Pestoni G, Pannen ST, Schönenberger KA, Kuhn T, Rohrmann S. How prevalent is a cancer-protective lifestyle? Adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research cancer prevention recommendations in Switzerland. Br J Nutr. 2023;130(5):904-10. doi: 10.1017/S0007114522003968
117. Schönenberger KA, Schüpfer A-C, Gloy VL, Hasler P, Stanga Z, Kaegi-Braun N, et al. Effect of Anti-Inflammatory Diets on Pain in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Nutrients. 2021;13(12):4221. doi: 10.3390/nu13124221
118. Huwiler VV, Schönenberger KA, Segesser von Brunegg A, Reber E, Mühlebach S, Stanga Z, et al. Prolonged Isolated Soluble Dietary Fibre Supplementation in Overweight and Obese Patients: A Systematic Review with Meta-Analysis of Randomised Controlled Trials. Nutrients. 2022;14(13). doi: 10.3390/nu14132627
119. Stocker R, Ceyhan M, Schönenberger KA, Stanga Z, Reber E. Nutrient and fluid requirements in post-bariatric patients performing physical activity: A systematic review. Nutrition. 2022;97:111577. doi: 10.1016/j.nut.2021.111577
120. Tripyla A, Ferreira A, Schönenberger KA, Näf NH, Inderbitzin LE, Prendin F, et al. Relationship Between Symptom Perception and Postprandial Glycemic Profiles in Patients With Postbariatric Hypoglycemia After Roux-en-Y Gastric Bypass Surgery. Diabetes Care. 2023;46(10):1792-8. doi: 10.2337/dc23-0454
121. Schönenberger KA, Ferreira A, Stebler C, Prendin F, Gawinecka J, Nakas CT, et al. Nutritional strategies for correcting low glucose values in patients with postbariatric hypoglycaemia: A randomized controlled three-arm crossover trial. Diabetes Obes Metab. 2023;25(10):2853-61. doi: 10.1111/dom.15175

122. Ferreira A, Schönenberger KA, Potoczna N, Vogt A, Gerber PA, Zehetner J, et al. Randomized, Double-Blind, Placebo-Controlled Crossover Trial of Once Daily Empagliflozin 25 mg for the Treatment of Postprandial Hypoglycemia After Roux-en-Y Gastric Bypass. Diabetes Technol Ther. 2023;25(7):467-75. doi: 10.1089/dia.2023.0036
123. Reber E, Schönenberger KA, Huwiler V, Stanga Z. Mangelernährung: Ein Leichtgewicht mit Schwergewicht. Hausarzt Praxis. 2021;16(4):11-7
124. Reber E, Schönenberger KA, Vasiloglou MF, Stanga Z. Nutritional Risk Screening in Cancer Patients: The First Step Toward Better Clinical Outcome. Front Nutr. 2021;8:603936. doi: 10.3389/fnut.2021.603936
125. Schönenberger KA, Dürig C, Huwiler VV, Reber E, Stanga Z. Ernährungsscreening in der Onkologie: Der erste Schritt zu einem besseren Outcome. Schweizer Zeitschrift für Ernährungsmedizin. 2022;2022(1):6-9
126. Schönenberger KA, Dürig C, Huwiler VV, Reber E, Stanga Z. Ernährungsscreening in der Onkologie: Der erste Schritt zu einem besseren Outcome. Schweizer Zeitschrift für Onkologie. 2022;2022:34-9
127. Efthymiou A, Hersberger L, Reber E, Schönenberger KA, Kägi-Braun N, Tribolet P, et al. Nutritional risk is a predictor for long-term mortality: 5-Year follow-up of the EFFORT trial. Clin Nutr. 2021;40(4):1546-54. doi: 10.1016/j.clnu.2021.02.032
128. Schönenberger KA, Reber E, Bally L, Geiser T, Lin D, Stanga Z. Nutritional assessment in adults with cystic fibrosis. Nutrition. 2019;67-68:110518. doi: 10.1016/j.nut.2019.05.010
129. Kurmann S, Reber E, Schönenberger KA, Schuetz P, Uhlmann K, Vasiloglou MF, et al. MEDPass versus conventional administration of oral nutritional supplements - A randomized controlled trial comparing coverage of energy and protein requirements. Clin Nutr. 2023;42(2):108-15. doi: 10.1016/j.clnu.2022.11.015
130. Schläppi K, Reber E, Schönenberger KA, Stanga Z, Kurmann S. The influence of patients' nutritional risk, nutritional status, and energy density in MEDPass versus conventional administration of oral nutritional supplements - A secondary analysis of a randomized controlled trial. J Nutr Health Aging. 2024;28(3):100170. doi: 10.1016/j.jnha.2024.100170
131. Uhlmann K, Reber E, Schönenberger KA, Stanga Z, Kurmann S. Should handgrip strength be considered when choosing the administration mode of oral nutritional supplements in geriatric patients? A secondary analysis of the MEDPass Trial. Nutrition. 2024;124. doi: 10.1016/j.nut.2024.112429
132. Huwiler VV, Scalise M, Schönenberger KA, Mühlebach S, Stanga Z, Balmer ML. The Role of Dietary Fibre in Enteral Nutrition in Sepsis Prevention and Therapy: A Narrative Review. Nutrients. 2023;15(11). doi: 10.3390/nu15112489
133. Schönenberger KA, Reber E, Vu DT, Krieger-Grubel C, Gerber PA, Muri R, et al. Attitudes and expectations of patients on home parenteral nutrition

towards eHealth: A multicenter survey. Clin Nutr ESPEN. 2022;52:445-9. doi: 10.1016/j.clnesp.2022.09.026
134. Schönenberger KA, Saxer C, Neyer PJ, Huwiler VV, Reber E, Hammerer-Lercher A, et al. Aluminum and other chemical elements in parenteral nutrition components and all-in-one admixtures. Clin Nutr. 2023;42(12):2475-83. doi: 10.1016/j.clnu.2023.10.012
135. Reber E, Neyer P, Schönenberger KA, Saxer C, Bernasconi L, Stanga Z, et al. Physicochemical Stability and Compatibility Testing of Voriconazole in All-in-One Parenteral Nutrition Admixtures. Pharmaceutics. 2021;13(9). doi: 10.3390/pharmaceutics13091447
136. Schönenberger KA, Dürig C, Huwiler VV, Reber E, Stanga Z. [Refeeding Syndrome: Where Do We Stand in 2022?]. Praxis (Bern 1994). 2022;111(7):381-7. doi: 10.1024/1661-8157/a003863
137. Schönenberger KA, Reber E, Schläppi K, Baumgartner A, Stanga Z, Kollar A. Determinants of Treatment Toxicity in Patients with Soft Tissue Sarcomas. Nutr Cancer. 2023;75(8):1638-45. doi: 10.1080/01635581.2023.2227405
138. Threapleton DE, Greenwood DC, Evans CE, Cleghorn CL, Nykjaer C, Woodhead C, et al. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. BMJ. 2013;347:f6879. doi: 10.1136/bmj.f6879
139. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet. 2019;393(10170):434-45. doi: 10.1016/S0140-6736(18)31809-9
140. The InterAct Consortium. Dietary fibre and incidence of type 2 diabetes in eight European countries: the EPIC-InterAct Study and a meta-analysis of prospective studies. Diabetologia. 2015;58(7):1394-408. doi: 10.1007/s00125-015-3585-9
141. O'Keefe SJ. The association between dietary fibre deficiency and high-income lifestyle-associated diseases: Burkitt's hypothesis revisited. Lancet Gastroenterol Hepatol. 2019;4(12):984-96. doi: 10.1016/S2468-1253(19)30257-2
142. Murphy N, Norat T, Ferrari P, Jenab M, Bueno-de-Mesquita B, Skeie G, et al. Dietary fibre intake and risks of cancers of the colon and rectum in the European prospective investigation into cancer and nutrition (EPIC). PLoS One. 2012;7(6):e39361. doi: 10.1371/journal.pone.0039361
143. Aune D, Chan DS, Greenwood DC, Vieira AR, Rosenblatt DA, Vieira R, et al. Dietary fiber and breast cancer risk: a systematic review and meta-analysis of prospective studies. Ann Oncol. 2012;23(6):1394-402. doi: 10.1093/annonc/mdr589
144. McKeown NM, Fahey GC, Jr., Slavin J, van der Kamp JW. Fibre intake for optimal health: how can healthcare professionals support people to reach dietary recommendations? BMJ. 2022;378:e054370. doi: 10.1136/bmj-2020-054370

145. Puhlmann ML, de Vos WM. Intrinsic dietary fibers and the gut microbiome: Rediscovering the benefits of the plant cell matrix for human health. Front Immunol. 2022;13:954845. doi: 10.3389/fimmu.2022.954845
146. Prendin F, Cappon G, Tripyla A, Herzig D, Bally L, Facchinetti A. Forecasting postbariatric hypoglycaemia in patients after Roux-en-Y gastric bypass using model-based algorithms fed by continuous glucose monitoring data: A proof-of-concept study. Diabetes Obes Metab. 2022;24(10):2061-5. doi: 10.1111/dom.14783
147. Prendin F, Del Favero S, Vettoretti M, Sparacino G, Facchinetti A. Forecasting of Glucose Levels and Hypoglycemic Events: Head-to-Head Comparison of Linear and Nonlinear Data-Driven Algorithms Based on Continuous Glucose Monitoring Data Only. Sensors (Basel). 2021;21(5). doi: 10.3390/s21051647
148. Oviedo S, Vehi J, Calm R, Armengol J. A review of personalized blood glucose prediction strategies for T1DM patients. Int J Numer Method Biomed Eng. 2017;33(6). doi: 10.1002/cnm.2833
149. Gadaleta M, Facchinetti A, Grisan E, Rossi M. Prediction of Adverse Glycemic Events From Continuous Glucose Monitoring Signal. IEEE J Biomed Health Inform. 2019;23(2):650-9. doi: 10.1109/JBHI.2018.2823763
150. Zecchin C, Facchinetti A, Sparacino G, De Nicolao G, Cobelli C. Neural network incorporating meal information improves accuracy of short-time prediction of glucose concentration. IEEE Trans Biomed Eng. 2012;59(6):1550-60. doi: 10.1109/TBME.2012.2188893
151. Georga EI, Principe JC, Fotiadis DI. Short-term prediction of glucose in type 1 diabetes using kernel adaptive filters. Med Biol Eng Comput. 2019;57(1):27-46. doi: 10.1007/s11517-018-1859-3
152. Dave D, DeSalvo DJ, Haridas B, McKay S, Shenoy A, Koh CJ, et al. Feature-Based Machine Learning Model for Real-Time Hypoglycemia Prediction. J Diabetes Sci Technol. 2021;15(4):842-55. doi: 10.1177/1932296820922622
153. Shivers JP, Mackowiak L, Anhalt H, Zisser H. "Turn it off!": diabetes device alarm fatigue considerations for the present and the future. J Diabetes Sci Technol. 2013;7(3):789-94. doi: 10.1177/193229681300700324
154. Laguna Sanz AJ, Mulla CM, Fowler KM, Cloutier E, Goldfine AB, Newswanger B, et al. Design and Clinical Evaluation of a Novel Low-Glucose Prediction Algorithm with Mini-Dose Stable Glucagon Delivery in Post-Bariatric Hypoglycemia. Diabetes Technol Ther. 2018;20(2):127-39. doi: 10.1089/dia.2017.0298
155. Pleus S, Schoemaker M, Morgenstern K, Schmelzeisen-Redeker G, Haug C, Link M, et al. Rate-of-Change Dependence of the Performance of Two CGM Systems During Induced Glucose Swings. J Diabetes Sci Technol. 2015;9(4):801-7. doi: 10.1177/1932296815578716
156. Rayannavar A, Elci OU, Mitteer L, De Leon DD. Continuous Glucose Monitoring Systems: Are They Useful for Evaluating Glycemic Control in Children with Hyperinsulinism? Horm Res Paediatr. 2019;92(5):319-27. doi: 10.1159/000506230

157. Herzig D, Nakas CT, Stalder J, Kosinski C, Laesser C, Dehais J, et al. Volumetric Food Quantification Using Computer Vision on a Depth-Sensing Smartphone: Preclinical Study. JMIR Mhealth Uhealth. 2020;8(3):e15294. doi: 10.2196/15294
158. Vasiloglou MF, Mougiakakou S, Aubry E, Bokelmann A, Fricker R, Gomes F, et al. A Comparative Study on Carbohydrate Estimation: GoCARB vs. Dietitians. Nutrients. 2018;10(6). doi: 10.3390/nu10060741
159. Wu J, Fuchs K, Lian J, Haldimann ML, Schneider T, Mayer S, et al. Estimating Dietary Intake from Grocery Shopping Data-A Comparative Validation of Relevant Indicators in Switzerland. Nutrients. 2021;14(1). doi: 10.3390/nu14010159
160. Merker M, Felder M, Gueissaz L, Bolliger R, Tribolet P, Kägi-Braun N, et al. Association of Baseline Inflammation With Effectiveness of Nutritional Support Among Patients With Disease-Related Malnutrition: A Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open. 2020;3(3):e200663. doi: 10.1001/jamanetworkopen.2020.0663
161. Kaegi-Braun N, Tribolet P, Gomes F, Fehr R, Baechli V, Geiser M, et al. Six-month outcomes after individualized nutritional support during the hospital stay in medical patients at nutritional risk: Secondary analysis of a prospective randomized trial. Clin Nutr. 2021;40(3):812-9. doi: 10.1016/j.clnu.2020.08.019
162. Kaegi-Braun N, Kilchoer F, Dragusha S, Gressies C, Faessli M, Gomes F, et al. Nutritional support after hospital discharge improves long-term mortality in malnourished adult medical patients: Systematic review and meta-analysis. Clin Nutr. 2022;41(11):2431-41. doi: 10.1016/j.clnu.2022.09.011
163. Wunderle C, Kägi-Braun N, Tribolet P, Reber E, Stanga Z, Schütz P. EFFORT-II-Studie – erster Einblick – Was bringt die ambulante Ernährungstherapie nach Spitalentlassung. Schweizer Zeitschrift für Ernährungsmedizin. 2023;2:10-4
164. Smith CE, Spaulding R, Piamjariyakul U, Werkowitch M, Yadrich DM, Hooper D, et al. mHealth Clinic Appointment PC Tablet: Implementation, Challenges and Solutions. J Mob Technol Med. 2015;4(2):21-32. doi: 10.7309/jmtm.4.2.4
165. Raphael BP, Schumann C, Garrity-Gentille S, McClelland J, Rosa C, Tascione C, et al. Virtual Telemedicine Visits in Pediatric Home Parenteral Nutrition Patients: A Quality Improvement Initiative. Telemed J E Health. 2019;25(1):60-5. doi: 10.1089/tmj.2017.0298
166. Cloutier A, Bond A, Taylor MI, Ablett J, Teubner A, Farrer K, et al. Successful implementation of remote video consultations for patients receiving home parenteral nutrition in a national UK Centre. Frontline Gastroenterol. 2020;11(4):280-4. doi: 10.1136/flgastro-2019-101257
167. Saqui O, Chang A, McGonigle S, Purdy B, Fairholm L, Baun M, et al. Telehealth videoconferencing: improving home parenteral nutrition patient care to rural areas of Ontario, Canada. JPEN J Parenter Enteral Nutr. 2007;31(3):234-9. doi: 10.1177/0148607107031003234

168. Chambers A, Hennessy E, Powell-Tuck J. Longitudinal trends in quality of life after starting home parenteral nutrition: a randomised controlled study of telemedicine. Clin Nutr. 2006;25(3):505-14. doi: 10.1016/j.clnu.2006.01.001
169. Armstrong LE, Maresh CM, Castellani JW, Bergeron MF, Kenefick RW, LaGasse KE, et al. Urinary indices of hydration status. Int J Sport Nutr. 1994;4(3):265-79. doi: 10.1123/ijsn.4.3.265
170. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32(9):920-4. doi: 10.3109/00365529709011203
171. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: development of a general scale. Eval Program Plann. 1979;2(3):197-207. doi: 10.1016/0149-7189(79)90094-6
172. Attkisson CC, Zwick R. The client satisfaction questionnaire. Psychometric properties and correlations with service utilization and psychotherapy outcome. Eval Program Plann. 1982;5(3):233-7. doi: 10.1016/0149-7189(82)90074-x
173. Parmanto B, Lewis AN, Jr., Graham KM, Bertolet MH. Development of the Telehealth Usability Questionnaire (TUQ). Int J Telerehabil. 2016;8(1):3-10. doi: 10.5195/ijt.2016.6196
174. European Directorate for the Quality of Medicines & HealthCare. Call for experts – Aluminium in parenteral nutrition solutions Strasbourg, France: Council of Europe; 2023. Available from: www.edqm.eu/en/-/call-for-experts-aluminium-in-parenteral-nutrition-solutions [accessed 13. Feb 2023].

APPENDIX A: SUPPLEMENTARY MATERIALS

Supplementary Materials Paper 1

Dietary Fibre Intake and its Association with Ultraprocessed Food Consumption in the General Population of Switzerland: Analysis of a Population-Based, Cross-Sectional National Nutrition Survey

Katja A. Schönenberger [1,2], Valentina V. Huwiler [1,2], Emilie Reber [1], Stefan Mühlebach [2], Zeno Stanga [1], Giulia Pestoni [3,4,*], David Faeh [4,5,*]

[1] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Bern, Switzerland

[2] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3] Nutrition Group, Health Department, Swiss Distance University of Applied Sciences (FFHS) / University of Applied Sciences and Arts of Southern Switzerland (SUPSI), Zurich, Switzerland

[4] Division of Chronic Disease Epidemiology, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland

[5] Health Department, Bern University of Applied Sciences, Bern, Switzerland

*Joint senior authors

BMJ Nutrition, Prevention & Health. 2024;e000727. doi: 10.1136/bmjnph-2023-000727

Supplementary material

Dietary fibre intake and its association with ultra-processed food consumption in the general population of Switzerland: Analysis of a population-based, cross-sectional national nutrition survey

Katja A. Schönenberger[1,2], Valentina V. Huwiler[1,2], Emilie Reber[1], Stefan Mühlebach[2], Zeno Stanga[1], Giulia Pestoni[3,4,*], David Faeh[4,5,*]

[1] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Bern, Switzerland

[2] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3] Nutrition Group, Health Department, Swiss Distance University of Applied Sciences, Zurich, Switzerland

[4] Division of Chronic Disease Epidemiology, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland

[5] Health Department, Bern University of Applied Sciences, Bern, Switzerland

*Joint senior authors: Giulia Pestoni, PhD & Prof. Dr. med. David Faeh

Corresponding author: Prof. Dr. med. David Faeh, david.faeh@bfh.ch

Supplementary Table 1 Additional sociodemographic, socioeconomic, and anthropometric characteristics of the *menuCH* population, overall and by absolute and relative dietary fibre intake groups

	menuCH	**Absolute dietary fibre intake**			**Relative dietary fibre intake**		
	(*n* = 2057)	**<15 g/day (*n* = 527)**	**15-30 g/day (*n* = 1268)**	**≥30 g/day (*n* = 262)**	**<10 g/1000 kcal/day (*n* = 1193)**	**10-14 g/1000 kcal/day (*n* = 624)**	**≥14 g/1000 kcal/day (*n* = 240)**
Civil status							
Single	634 (31)	163 (29)	396 (32)	75 (30)	408 (34)	157 (26)	69 (29)
Married	1125 (52)	276 (51)	694 (51)	155 (59)	628 (50)	368 (56)	129 (53)
Divorced	223 (12)	72 (17)	126 (11)	25 (9.5)	116 (11)	77 (14)	30 (12)
Other	72 (4.4)	16 (3.7)	49 (5.2)	7 (2.1)	39 (4.5)	22 (3.7)	11 (5.9)
NA	3 (0.15)	0 (0)	3 (0.24)	0 (0)	2 (0.21)	0 (0)	1 (0.23)
Household status							
Adult living with parents	158 (7.1)	48 (9.0)	96 (6.5)	14 (6.4)	112 (8.3)	39 (6.3)	7 (3.0)
Living alone	328 (18)	87 (19)	195 (18)	46 (18)	177 (17)	105 (19)	46 (20)
Couple without children	689 (32)	166 (29)	426 (33)	97 (33)	367 (29)	224 (34)	98 (39)
Couple with children	678 (33)	171 (31)	421 (33)	86 (35)	405 (34)	207 (33)	66 (28)
One-parent family with children	92 (4.4)	36 (6.9)	49 (3.8)	7 (2.6)	62 (5.3)	19 (2.6)	11 (4.7)
Others	109 (5.7)	19 (4.6)	78 (6.4)	12 (5.1)	68 (6.4)	30 (4.8)	11 (4.9)
NA	3 (0.15)	0 (0)	3 (0.24)	0 (0)	2 (0.21)	0 (0)	1 (0.23)
Household income							
CHF <6000	346 (18)	95 (20)	210 (17)	41 (16)	201 (18)	107 (17)	38 (15)
CHF 6000-13000	841 (40)	186 (35)	542 (41)	113 (41)	485 (40)	254 (40)	102 (40)
CHF >13000	285 (15)	79 (16)	170 (14)	36 (15)	170 (15)	86 (14)	29 (16)
NA	585 (28)	167 (29)	346 (27)	72 (28)	337 (27)	177 (28)	71 (29)
Self-rated health status							
Bad-Medium	272 (13)	98 (17)	147 (11)	27 (10)	180 (14)	68 (11)	24 (10)
Good	1781 (87)	429 (83)	1117 (88)	235 (90)	1010 (86)	556 (89)	215 (90)
NA	4 (0.22)	0 (0)	4 (0.35)	0 (0)	3 (0.32)	0 (0)	1 (0.23)
Waist group							
No increased risk (≤94 cm [M], ≤80 cm [F])	1320 (66)	303 (59)	825 (67)	192 (74)	740 (64)	416 (68)	164 (71)
Increased risk (94.1-101.9 cm [M], 80.1-87.9 cm [F])	354 (16)	106 (20)	213 (16)	35 (12)	216 (17)	104 (16)	34 (13)
Substantially increased risk (≥102 cm [M], ≥88 cm [F])	349 (16)	109 (19)	209 (16)	31 (12)	217 (18)	95 (15)	37 (14)
NA	34 (1.7)	9 (1.9)	21 (1.6)	4 (1.4)	20 (1.8)	9 (1.3)	5 (1.8)

CHF, Swiss Francs; NA, not available

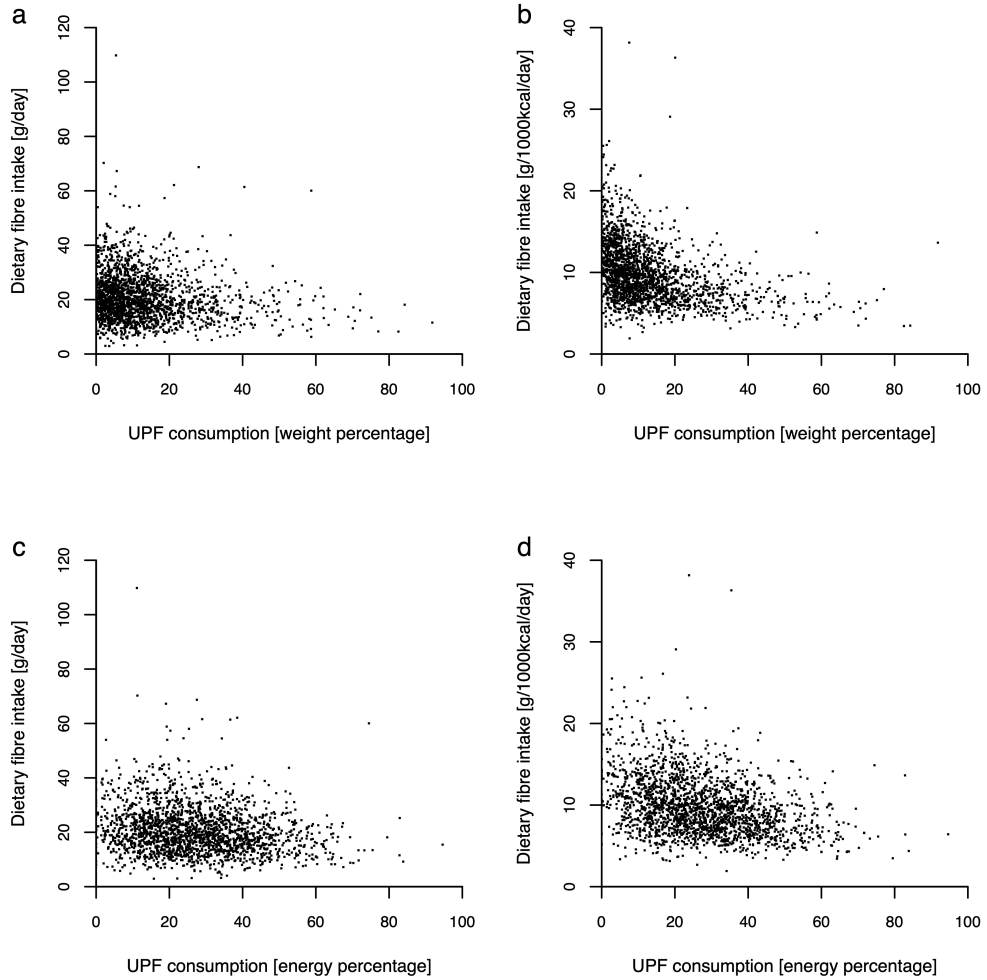
Results are given as *n* (weighted percentage). *n* are unweighted, percentages are weighted for age group, sex, marital status, major region of Switzerland, nationality and household size according to the *menuCH* weighting strategy [1]. If the percentages do not add up exactly to 100%, this is due to rounding differences.

Supplementary Table 2 Additional dietary intakes of the *menuCH* population, overall and by absolute and relative dietary fibre intake groups

	menuCH	**Absolute dietary fibre intake**			**Relative dietary fibre intake**		
		<15 g/day	**15-30 g/day**	**≥30 g/day**	**<10 g/1000 kcal/day**	**10-14 g/1000 kcal/day**	**≥14 g/1000 kcal/day**
	(*n* = 2057)	**(*n* = 527)**	**(*n* = 1268)**	**(*n* = 262)**	**(*n* = 1193)**	**(*n* = 624)**	**(*n* = 240)**
Carbohydrate [g/day]	218 (172-283)	166 (131-208)	227 (186-284)	298 (242-369)	223 (175-296)	207 (166-262)	213 (166-273)
Fat [g/day]	84 (64-108)	66 (50-85)	87 (69-110)	107 (84-136)	91 (70-116)	78 (62-100)	67 (48-88)
UPF [g/day]	314 (157-584)	331 (154-583)	314 (163-593)	279 (139-512)	415 (217-769)	217 (111-409)	154 (67-237)
UPF [kcal/day]	539 (309-831)	472 (286-738)	567 (316-857)	524 (327-859)	659 (410-1005)	437 (238-617)	304 (144-495)
Non-alcoholic beverages [g/day]	1949 (1454-2495)	1827 (1275-2421)	1943 (1472-2488)	2161 (1679-2901)	1910 (1438-2445)	1956 (1426-2511)	2091 (1579-2711)
Alcoholic beverages [g/day]	79 (0.0-265)	62 (0.0-290)	97 (0.0-259)	46 (0.0-248)	149 (0.0-349)	49 (0.0-190)	0.0 (0.0-80)
Cakes [g/day]	16 (0.0-55)	8.6 (0.0-43)	18 (0.0-58)	23 (0.0-63)	20.0 (0.0-61)	13 (0.0-47)	7.5 (0.0-47)
Miscellaneous [g/day]	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Eggs [g/day]	0.0 (0.0-6.2)	0.0 (0.0-23)	0.0 (0.0-0.0)	0.0 (0.0-23)	0.0 (0.0-13)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Fats [g/day]	13 (5.1-23)	8.3 (2.2-16)	15 (6.1-25)	17 (8.7-29)	13 (5.0-22)	15 (5.7-25)	9.8 (5.1-18)
Fish [g/day]	0.0 (0.0-16)	0.0 (0.0-3.9)	0.0 (0.0-14)	0.0 (0.0-44)	0.0 (0.0-6.5)	0.0 (0.0-25)	0.0 (0.0-35)
Meat [g/day]	73 (24-134)	87 (41-145)	73 (23-134)	48 (0.0-101)	92 (45-163)	56 (7.9-100)	35 (0.0-72)
Legumes [g/day]	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0.0 (0.0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Starchy foods [g/day]	0.0 (0.0-70)	0.0 (0.0-47)	0.0 (0.0-73)	0.0 (0.0-95)	0.0 (0.0-71)	0.0 (0.0-70)	0.0 (0.0-50)
Milk [g/day]	189 (90-311)	152 (61-269)	195 (91-314)	217 (126-384)	196 (88-339)	180 (99-286)	164 (90-266)
Savoury snacks [g/day]	0.0 (0.0-3.9)	0.0 (0.0-3.2)	0.0 (0.0-4.5)	0.0 (0.0-1.3)	0.0 (0.0-8.6)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Soups [g/day]	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-104)	0.0 (0.0-0.0)	0.0 (0.0-2.9)	0.0 (0.0-99)
Seasoning [g/day]	28 (10-64)	25 (8.6-48)	28 (9.9-67)	39 (14-86)	29 (11-67)	26 (8.1-62)	23 (7.5-55)
Chocolate [g/day]	26 (10-50)	17 (5.7-36)	29 (12-54)	35 (13-63)	30 (12-55)	25 (9.8-46)	18 (7.8-37)

UPF, ultra-processed food

Results are given as median (interquartile range) weighted for age group, sex, marital status, major region of Switzerland, nationality, household size, season and weekday according to the *menuCH* weighting strategy [1].



Supplementary Fig. 1 Scatter plots of dietary fibre intake and ultra-processed food (UPF) consumption

References

1. Pasquier J, Chatelan A, Bochud M. Weighting strategy. Lausanne, Switzerland: Institute of Social and Preventive Medicine (IUMSP) 2017.

Supplementary Materials Paper 2

Effect of Anti-Inflammatory Diets on Pain in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

Katja A. Schönenberger [1,2] , Anne-Catherine Schüpfer [1], Viktoria L. Gloy [3], Paul Hasler [4], Zeno Stanga [1], Nina Kaegi-Braun [5], Emilie Reber [1]

[1] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Bern, Switzerland

[2] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3] Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland

[4] Division of Rheumatology, Medical University Department, University of Basel Medical Faculty, Kantonsspital Aarau, Aarau, Switzerland

[5] Division of General Internal and Emergency Medicine, Medical University Department, University of Basel, Medical Faculty, Kantonsspital Aarau, Aarau, Switzerland

Nutrients. 2021;13(12):4221. doi: 10.3390/nu13124221

Supplementary Materials

Systematic Review

Effect of Anti-Inflammatory Diets on Pain in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

Katja A. Schönenberger [1, 2,*], Anne-Catherine Schüpfer [1], Viktoria L. Gloy [3], Paul Hasler [4], Zeno Stanga [1], Nina Kaegi-Braun [5], Emilie Reber [1]

[1] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland; anne-catherine.schuepfer@students.unibe.ch (A.-C.S.); zeno.stanga@insel.ch (Z.S.); emilie.reber@insel.ch (E.R.)
[2] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, 4031 Basel, Switzerland
[3] Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, 4031 Basel, Switzerland; viktoria.gloy@usb.ch
[4] Division of Rheumatology, Medical University Department, University of Basel Medical Faculty, Kantonsspital Aarau, 5001 Aarau, Switzerland; paul.hasler@ksa.ch
[5] Division of General Internal and Emergency Medicine, Medical University Department, University of Basel Medical Faculty, Kantonsspital Aarau, 5001 Aarau, Switzerland; nina.kaegi@ksa.ch
* Correspondence: katja.schoenenberger@extern.insel.ch; Tel.: +41-31-664-21-05

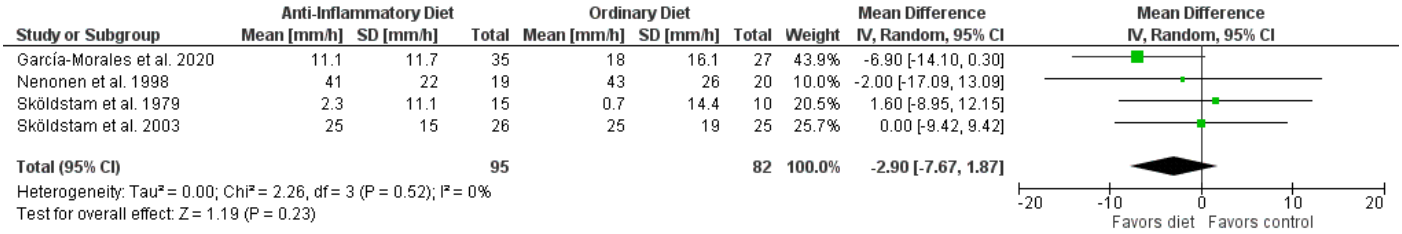


Figure S1. Forest plot summarizing the effect of anti-inflammatory diets on erythrocyte sedimentation rate

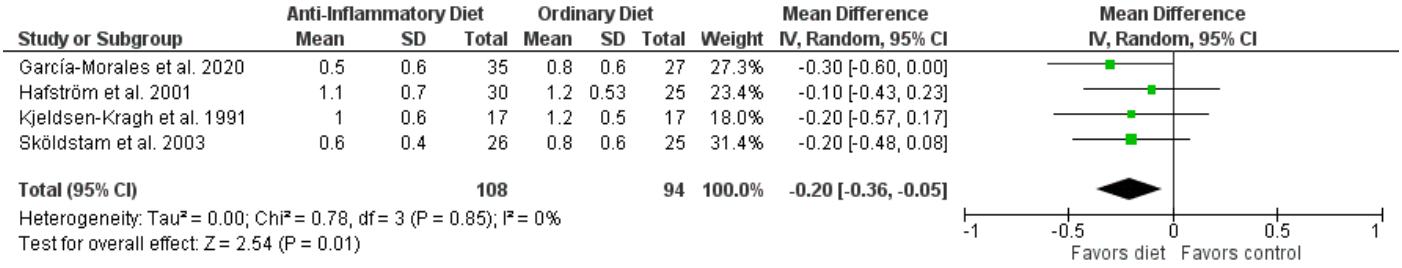


Figure S2. Forest plot summarizing the effect of anti-inflammatory diets on health assessment questionnaire score

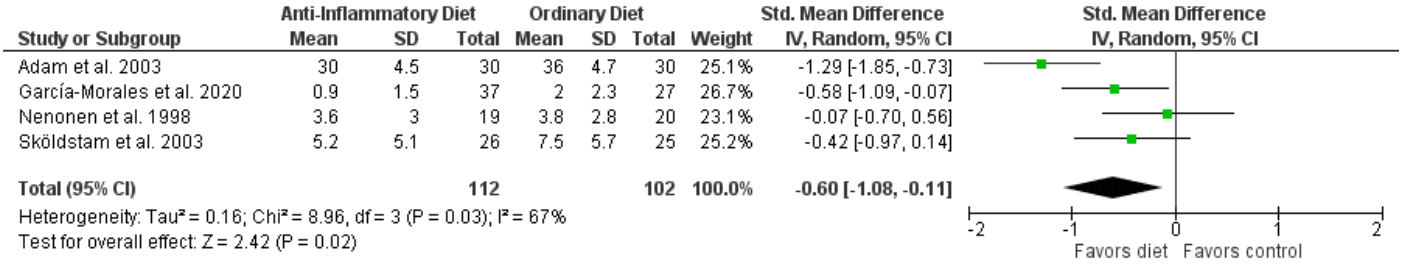


Figure S3. Forest plot summarizing the effect of anti-inflammatory diets on swollen joint count

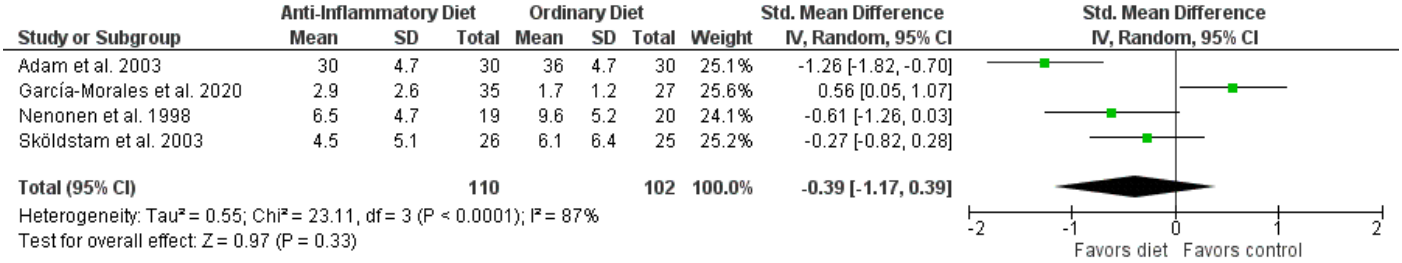


Figure S4. Forest plot summarizing the effect of anti-inflammatory diets on tender joint count

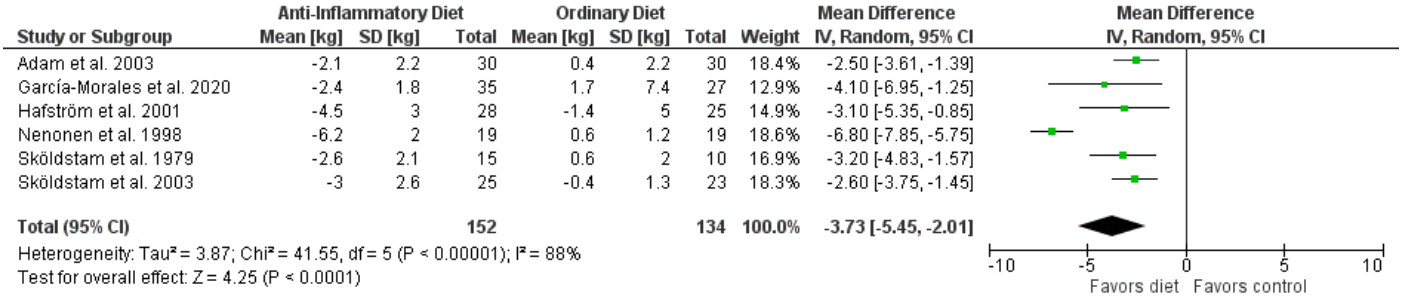


Figure S5. Forest plot summarizing the effect of anti-inflammatory diets on weight loss
SD for Adam et al. 2003, García-Morales et al. 2020, Hafström et al. 2001, and Sköldstam et al. 2003 imputed from Nenonen et al. 1998 [1-3].

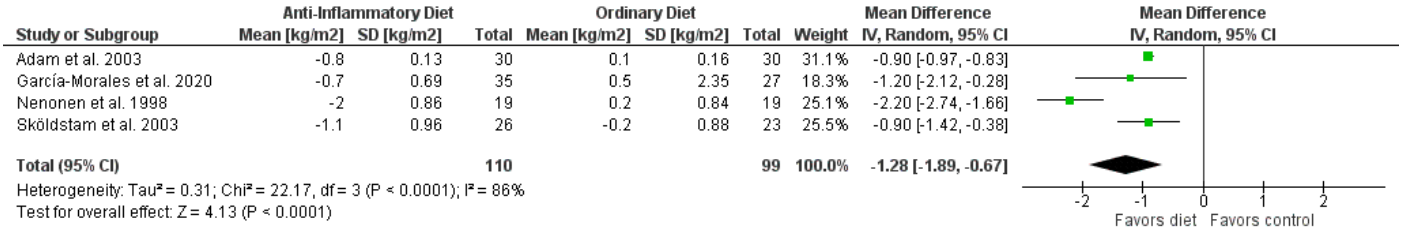


Figure S6. Forest plot summarizing the effect of anti-inflammatory diets on body mass index decrease
SD for Adam et al. 2003, García-Morales et al. 2020, and Sköldstam et al. 2003 imputed from Nenonen et al. 1998 [1-3].

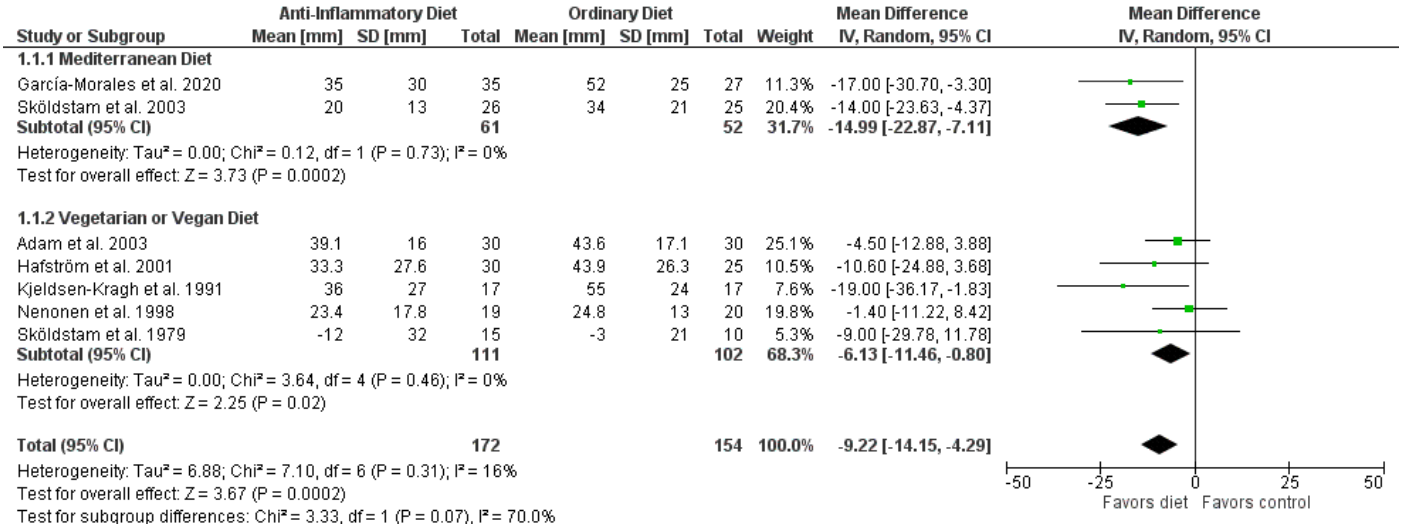


Figure S7. Forest plot summarizing the subgroup analysis on the effect of Mediterranean vs. vegetarian or vegan diets on pain

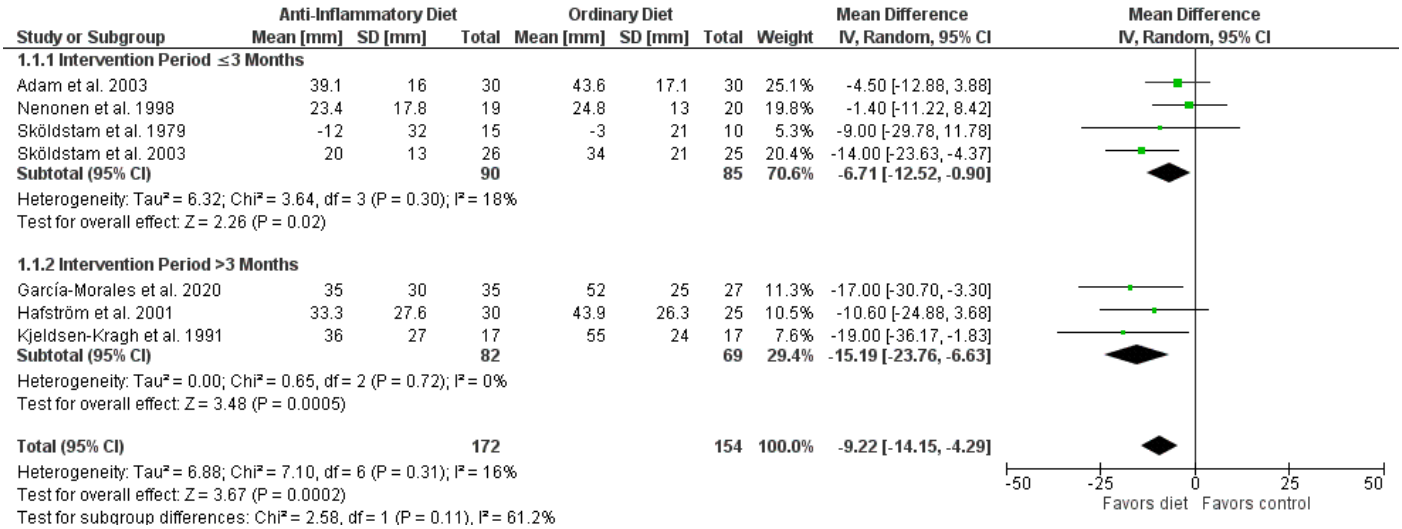


Figure S8. Forest plot summarizing the subgroup analysis on the effect of intervention duration on pain

References

1. Follmann, D.; Elliott, P.; Suh, I.; Cutler, J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol* **1992**, *45*, 769-773, doi:10.1016/0895-4356(92)90054-q.
2. Abrams, K.R.; Gillies, C.L.; Lambert, P.C. Meta-analysis of heterogeneously reported trials assessing change from baseline. *Stat Med* **2005**, *24*, 3823-3844, doi:10.1002/sim.2423.
3. Chapter 6: Choosing effect measures and computing estimates of effect. Higgins, J.P.T.; Li, T.; Deeks, J.J.; Eds. In: *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Higgins, J.P.T.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.J.; Welch, V.A.; Eds. Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Supplementary Materials Paper 3

Nutritional Strategies for Correcting Low Glucose Values in Patients with Postbariatric Hypoglycaemia: A Randomized Controlled Three-Arm Crossover Trial

Katja A. Schönenberger [1,2], Antonio Ferreira [1], Céline Stebler [1], Francesco Prendin [3], Joanna Gawinecka [4], Christos T. Nakas [5,6], Stefan Mühlebach [2], Zeno Stanga [1], Andrea Facchinetti [3], David Herzig [1], Lia Bally [1]

[1] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Bern, Switzerland

[2] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3] Department of Information Engineering, University of Padova, Padova, Italy

[4] Institute of Clinical Chemistry, University Hospital Zurich, University of Zurich, Zurich, Switzerland

[5] Laboratory of Biometry, Department of Agriculture Crop Production and Rural Environment, School of Agriculture, University of Thessaly, Volos, Greece

[6] University Institute of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Diabetes, Obesity and Metabolism. 2023;25(10)2853-2861. doi: 10.1111/dom.15175

Nutritional strategies for correcting low glucose values in patients with postbariatric hypoglycaemia – A randomized controlled three-arm crossover trial

Supporting information

Katja A. Schönenberger [1,2], Antonio Ferreira [1], Céline Stebler [1], Francesco Prendin [3], Joanna Gawinecka [4], Christos T. Nakas [5,6], Stefan Mühlebach [2], Zeno Stanga [1], Andrea Facchinetti [3], David Herzig [1], Lia Bally [1]

[1] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[2] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3] Department of Information Engineering, University of Padova, Padova, Italy

[4] Institute of Clinical Chemistry, University Hospital Zurich, University of Zurich, Zurich, Switzerland

[5] Laboratory of Biometry, Department of Agriculture Crop Production and Rural Environment, School of Agriculture, University of Thessaly, Volos, Greece

[6] University Institute of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Corresponding author:

Prof Lia Bally, MD PhD

Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, University of Bern

Freiburgstrasse 15, 3010 Bern, Switzerland

Tel: +41 31 632 40 70

E-Mail: lia.bally@insel.ch

Contents

Premier Protein High Protein Bar Double Chocolate Cookie:

Ingredients and nutrition information

Ingredients: Milk chocolate couverture with sweetener (18%) [sweetener (maltitols), cocoa butter, milk powder, cocoa mass, emulsifier [lecithins (soy)], flavoring], calcium caseinate (milk) (16%), humectant (glycerol), hydrolyzed collagen (15%), soy protein (11%), water, whey protein (milk) (7%), soy crispies (4%) (soy protein, fat reduced cocoa powder, starch), flavorings, fat reduced cocoa powder, sweetener (sucralose), emulsifier [lecithins (soy)].

Table S1 Nutrition information of the protein bar

Nutrient	**per bar (40 g)**	**per half bar (20 g)**
Energy	136 kcal	68 kcal
Fat	3.0 g	1.5 g
of which saturates	1.8 g	0.9 g
Carbohydrate	10 g	5 g
of which sugars	0.7 g	0.35 g
of which polyols	9.8 g	4.9 g
Protein	20 g	10 g
Salt	0.15 g	0.075 g

Study flow diagram

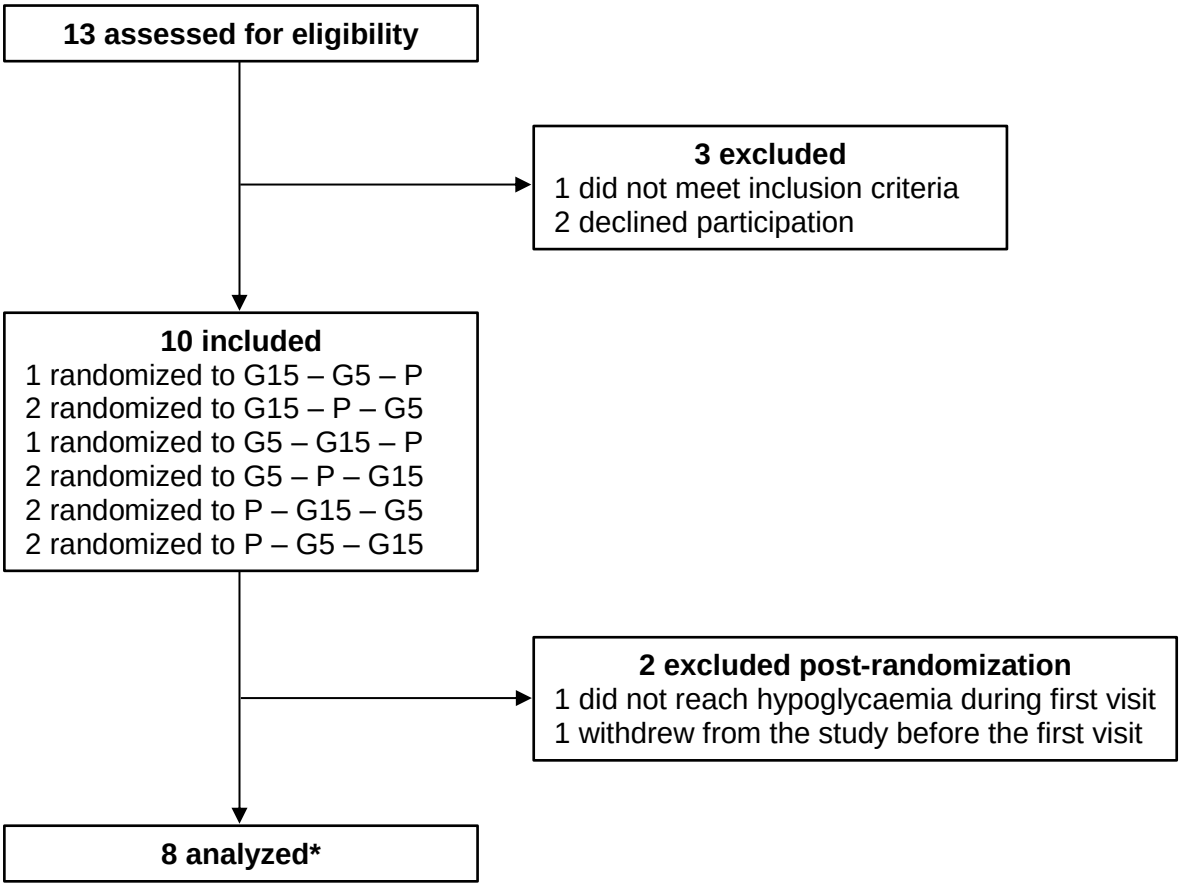


Fig. S1 Flow diagram
* One visit of one patient was excluded from the analysis of outcomes affected by an additional rescue correction 25 minutes after the initial correction (all outcomes based on plasma glucose values during 40 minutes after initial hypoglycaemia correction).

Plasma glucose outcomes

Table S2 Plasma glucose outcomes during 40 minutes posthypoglycaemia correction. Results from models adjusted for plasma glucose at hypoglycaemia correction.

Outcome	Estimated mean (95% CI)			*p*-value			
	G15	G5	P10	Overall	G15 vs. G5	G15 vs. P10	G5 vs. P10
Time with plasma glucose 3.9-5.5 mmol/L, %	25.6 (12.5 to 38.7)	20.0 (5.6 to 34.3)	12.9 (-1.2 to 27.0)	.384		N/A	
Time with plasma glucose < 3.0 mmol/L, %	26.3 (4.3 to 48.2)	52.4 (28.8 to 75.9)	55.8 (32.7 to 78.9)	.035	.131	.116	.967
Time with plasma glucose < 3.9 mmol/L, %	52.6 (35.4 to 69.7)	76.4 (57.7 to 95.1)	93.1 (74.7 to 111.6)	.002	.117	.016	.400
Time with plasma glucose > 5.5 mmol/L, %	21.8 (13.9 to 29.6)	3.5 (-5.0 to 12.0)	-6.0 (-14.4 to 2.4)	< .001	.007	.001	.235
Peak plasma glucose, mmol/L	5.5 (4.8 to 6.2)	3.8 (3.1 to 4.6)	3.3 (2.6 to 4.1)	< .001	.002	.001	.470
Time with plasma glucose 3.5-5.5 mmol/L, %	42.5 (26.6 to 58.3)	29.7 (12.9 to 46.6)	30.4 (13.9 to 47.0)	.207		N/A	
Time with plasma glucose < 3.5 mmol/L, %	35.5 (16.5 to 54.6)	67.1 (47.4 to 86.7)	75.8 (56.4 to 95.2)	< .001	.004	.001	.554

Results obtained from linear mixed-effects models (participant ID as random effect and adjusted for visit number and plasma glucose at hypoglycaemia correction) and estimated marginal means. Overall *p*-values represent main treatment effects obtained from the ANOVA table. *P*-values for pairwise marginal means were adjusted using the Tukey method. Pairwise comparisons are only reported for significant overall *p*-values.
Abbreviations: G15, hypoglycaemia correction with 15 g of glucose; G5, hypoglycaemia correction with 5 g of glucose; P10, hypoglycaemia correction with protein bar (10 g of protein)

Supplementary Materials Paper 4

Attitudes and Expectations of Patients on Home Parenteral Nutrition Towards eHealth: A Multicenter Survey

Katja A. Schönenberger [1,2], Emilie Reber [1], Duy-Tan Vu [1,2], Claudia Krieger-Grübel [3], Philipp A. Gerber [4], Raphaela Muri [1], Valentina V. Huwiler [1,2], Stefan Mühlebach [2], Michèle Leuenberger [5], Zeno Stanga [1]

[1] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Bern, Switzerland

[2] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3] Department of Gastroenterology and Hepatology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

[4] Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Zurich (USZ) and University of Zurich (UZH), Zurich, Switzerland

[5] Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Clinical Nutrition ESPEN. 2022;52:445-449. doi: 10.1016/j.clnesp.2022.09.026

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE
Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin und Metabolismus

Klinikdirektor und Chefarzt
Prof. Dr. med. Christoph Stettler

Leitender Arzt Ernährungsmedizin
Prof. Dr. med. Zeno Stanga

Patientinnen und Patienten mit parenteraler Ernährung zu Hause: Fragebogen zur Einstellung und Erwartungshaltung bezüglich elektronischen Medien

--- Bitte schreiben Sie weder Ihren Namen noch Ihr Geburtsdatum auf diesen Fragebogen ---

Alter: ..... Jahre Geschlecht: ☐ weiblich ☐ männlich

1.	Seit wann bekommen Sie parenterale Ernährung?	DD.MM.JJJJ.....
2.	Wer ist an der Betreuung Ihrer parenteralen Ernährung beteiligt? (mehrere Antworten möglich)	☐ Ernährungsmediziner/in im Spital ☐ Hausarzt/Hausärztin ☐ Spitex
3.	Wie oft pro Woche erhalten Sie parenterale Ernährung?	☐ 1x ☐ 2x ☐ 3x ☐ 4x ☐ 5x ☐ 6x ☐ 7x
4.	Was für digitale Geräte benutzen Sie? (mehrere Antworten möglich)	☐ Handy (kein Smartphone) ☐ Smartphone ☐ Tablet ☐ Laptop/Computer ☐ Keine digitalen Geräte
5.	Nutzen Sie Apps?	☐ Ja ☐ Nein

6.	Wie schätzen Sie Ihre Fähigkeiten im Umgang mit Smartphone/Tablet ein?	sehr geübt ++ ☐	eher geübt + ☐	neutral +/- ☐	eher ungeübt - ☐	gar nicht geübt -- ☐
7.	Haben Sie körperliche Einschränkungen, die den Umgang mit Smartphone/Tablet beeinträchtigen? (mehrere Antworten möglich)	☐ Beeinträchtigung des Sehens ☐ Beeinträchtigung des Hörens ☐ Bewegungseinschränkung ☐ Keine Einschränkungen ☐ Keine Angabe				
8.	Ist es für Sie aufwändig, für die Verlaufskontrollen der parenteralen Ernährung ins Spital zu gehen?	ja ++ ☐	eher ja + ☐	neutral +/- ☐	eher nein - ☐	nein -- ☐
9.	Würden Sie einen Teil der Verlaufskontrollen für die parenterale Ernährung über Videotelefonie durchführen?	ja ++ ☐	eher ja + ☐	neutral +/- ☐	eher nein - ☐	nein -- ☐
10.	Wie wichtig ist Ihnen der persönliche Kontakt (nicht über Videotelefonie) mit dem Arzt/der Ärztin bezüglich der parenteraler Ernährung?	sehr wichtig ++ ☐	eher wichtig + ☐	neutral +/- ☐	eher unwichtig - ☐	gar nicht wichtig -- ☐
11.	Wie oft möchten Sie einen kurzen Kontakt (max. 15 min) mit dem Spitalarzt/der Spitalärztin bezüglich parenteraler Ernährung haben?	☐ Alle 2 Wochen ☐ Einmal pro Monat ☐ Alle 3 Monate ☐ Alle 4-6 Monate				
12.	Wo würden Sie Ihre Laborwerte am liebsten kontrollieren lassen? (mehrere Antworten möglich)	☐ Zu Hause: Selber/durch Familienmitglied (Fingerpicks) ☐ Zu Hause: Durch Spitex/Hausarzt/Hausärztin ☐ Beim Hausarzt/bei der Hausärztin ☐ Im Spital ☐ Keine Präferenz				

13. Würden Sie gewisse Informationen (z. B. Gewicht, Temperatur) in einem einfachen digitalen System (z. B. App) erfassen?
☐ Ja
☐ Ja, aber nicht selber (z. B. Spitex, Familienmitglied)
☐ Nein

14. Wenn es ein einfaches digitales System für die Verlaufskontrollen Ihrer parenteralen Ernährung gäbe, welche Kriterien wären für Sie wichtig?

	sehr wichtig ++	eher wichtig +	neutral +/-	eher unwichtig -	gar nicht wichtig --
Kontakt per Videotelefonie zum Arzt/zur Ärztin	☐	☐	☐	☐	☐
Kontakt per Videotelefonie zur Ernährungsberatung	☐	☐	☐	☐	☐
Kontakt per Videotelefonie zur Home Care	☐	☐	☐	☐	☐
Kontakt per Videotelefonie zur Pflege wenn nötig	☐	☐	☐	☐	☐
Checklisten zur Handhabung der parenteralen Ernährung, Katheter und Pumpe	☐	☐	☐	☐	☐
Videos zur Handhabung der parenteralen Ernährung, Katheter und Pumpe	☐	☐	☐	☐	☐
Automatische Aufzeichnung von Essprotokollen	☐	☐	☐	☐	☐
Automatische Nachbestellung von Material	☐	☐	☐	☐	☐
Erfassung und Speicherung relevanter Ereignisse (z.B. Infekt, Spitalaufenthalt)	☐	☐	☐	☐	☐
Einfache Anwendung	☐	☐	☐	☐	☐
Gewährleistung der Datensicherheit	☐	☐	☐	☐	☐
Erfassung und Speicherung folgender Informationen:					
Gewicht	☐	☐	☐	☐	☐
Körpertemperatur	☐	☐	☐	☐	☐
Blutdruck	☐	☐	☐	☐	☐
Essprotokoll	☐	☐	☐	☐	☐
Fotos vom Katheter	☐	☐	☐	☐	☐
Laborwerte	☐	☐	☐	☐	☐
Blutzucker	☐	☐	☐	☐	☐
Stomaverlustmenge	☐	☐	☐	☐	☐
Stuhlfrequenz und -konsistenz	☐	☐	☐	☐	☐
Urinmenge	☐	☐	☐	☐	☐
Medikamentenliste und -Einnahmen	☐	☐	☐	☐	☐
Infusionsplan und Verabreichung	☐	☐	☐	☐	☐
Schmerzen	☐	☐	☐	☐	☐
Übelkeit	☐	☐	☐	☐	☐
Andere Untersuchungen (z.B. Knochendichte)	☐	☐	☐	☐	☐
Speicherung von Berichten aus verschiedenen Spitälern/Praxen	☐	☐	☐	☐	☐
Sonstiges:	☐	☐	☐	☐	☐

15. Wer soll diese Informationen einsehen dürfen? (mehrere Antworten möglich)
☐ Spitalarzt/-ärztin
☐ Hausarzt/-ärztin
☐ Spitex
☐ Home Care
☐ Ernährungsberatung
☐ Sie selber (Patient/in)

16. Wären Sie interessiert mit anderen Personen mit parenteraler Ernährung in Kontakt zu treten?

ja ++	eher ja +	neutral +/-	eher nein -	nein --
☐	☐	☐	☐	☐

17. Was spricht Ihrer Meinung nach *für* ein solches digitales System?
.....
.....

18. Was spricht Ihrer Meinung nach *gegen* ein solches digitales System?
.....
.....

Kommentar:.....

Herzlichen Dank für Ihre wertvolle Teilnahme!

Freiburgstrasse 15, 3010 Bern, katja.schoenenberger@extern.insel.ch, +41 31 632 40 70

Supplementary Materials Paper 5

Aluminum and Other Chemical Elements in Parenteral Nutrition Components and All-in-One Admixtures

Katja A. Schönenberger [1,2,3,*], Christoph Saxer [1,*], Peter J. Neyer [1], Valentina V. Huwiler [1,2,3], Emilie Reber [3], Angelika Hammerer-Lercher [1], Zeno Stanga [3], Stefan Mühlebach [2]

[1] Institute of Laboratory Medicine, Cantonal Hospital Aarau, Aarau, Switzerland

[2] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[3] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Bern, Switzerland

*Joint first authors

Clinical Nutrition. 2023;42(12):2475-2483. doi: 10.1016/j.clnu.2023.10.012

Supplementary Material

Aluminum and Other Chemical Elements in Parenteral Nutrition Components and All-in-One Admixtures

Katja A. Schönenberger[a,b,c,*], Christoph Saxer[a,*], Peter J. Neyer[a], Valentina V. Huwiler[a,b,c], Emilie Reber[c], Angelika Hammerer-Lercher[a], Zeno Stanga[c], Stefan Mühlebach[b]

[a] Institute of Laboratory Medicine, Cantonal Hospital Aarau, Tellstrasse 25, 5001 Aarau, Switzerland

[b] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Spitalstrasse 26, 4056 Basel, Switzerland

[c] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 15, 3010 Bern, Switzerland

* Co-first authors

Corresponding author:
Katja A. Schönenberger
Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM)
Inselspital, Bern University Hospital
Freiburgstrasse 15
3010 Bern
Switzerland
katja.schoenenberger@extern.insel.ch
+41 31 664 21 05

Contents

Packaging and Composition of Parenteral Nutrition Products

Supplementary Table 1: Packaging and composition of parenteral nutrition products

Product	Packaging	Components[1]
Olimel® 5.7% (E) 1000 mL	3-chamber multilayer plastic bag, the inner (contact) layer of the bag material consists of a mixture of different polyolefin copolymers, other layers consist of polyethylene vinyl acetate and a copolyester	**Chamber I (400 mL):** 110 g glucosum (glucosum monohydricum), *0.98 g calcii chloridum anhydricum (calcii chloridum dihydricum),* acidum hydrochloridum, aqua ad iniectabile **Chamber II (400 mL):** 8.24 g alaninum, 5.58 g argininum, 1.65 g acidum asparticum, 2.84 g acidum glutamicum, 3.95 g glycinum, 3.40 g histidinum, 2.84 g isoleucinum, 3.95 g leucinum, 4.48 g lysinum anhydricum (lysini acetas), 2.84 g methioninum, 3.95 g phenylalaninum, 3.40 g prolinum, 2.25 g serinum, 2.84 g threoninum, 0.95 g tryptophanum, 0.15 g tyrosinum, 3.64 g valinum, *0.90 g natrii acetas (natrii acetas trihydricus), 2.24 g kalii chloridum, 0.38 g magnesii chloridum anhydricum (magnesii chloridum hexahydricum), 2.59 g natrii glycerophosphas (natrii glycerophosphas pentahydricus),* acidum aceticum, aqua ad iniectabile **Chamber III (200 mL):** 40 g olivae oleum raffinatum (~80%) + sojae oleum raffinatum (~20%), phosphatidum ovi depuratum, glycerolum, natrii oleas, natrii hydroxidum, aqua ad iniectabile, 4.53 mg natrium
Omegaflex® special (without electrolytes) 1875 mL	3-chamber multilayer polyolefin bag	**Chamber I (750 mL):** 270 g glucosum (glucosum monohydricum), *4.68 g natrii dihydrogenophosphas dihydricus, 13.17 mg zinci acetas dihydricus,* acidum citricum monohydricum, aqua ad iniectabile **Chamber II (750 mL):** 6.15 g isoleucinum, 8.22 g leucinum, 5.97 g lysinum anhydricum[2], 5.13 g methioninum, 9.22 g phenylalaninum, 4.76 g threoninum, 1.5 g tryptophanum, 6.76 g valinum, 7.09 g argininum, 3.29 g histidinum, 12.73 g alaninum, 3.94 g acidum asparticum, 9.20 g acidum glutamicum, 4.34 g glycinum, 8.93 g prolinum, 7.88 g serinum, *2.20 g natrii hydroxidum, 710 mg natrii chloridum, 470 mg natrii acetas trihydricus, 6.92 g kalii acetas, 1.71 g magnesii acetas tetrahydricus, 1.17 g calcii chloridum dihydricum,* acidum citricum monohydricum, aqua ad iniectabile **Chamber III (375 mL):** 30 g sojae oleum, 37.5 g triglycerida media, 7.5 g omega-3 acidorum triglycerida, glycerolum, lecithinum ex ovo, natrii oleas, natrii hydroxidum, 100 mg E 307, aqua ad iniectabile
SmofKabiven® (EF) 986 mL	3-chamber Biofine® poly-(propylene-co-ethylene), synthetic rubber poly[styrene-block-(butylene-co-etyrene)] and synthetic rubber poly-(styrene-block-isoprene) bag. Infusion and injection ports made of polypropylene and synthetic rubber poly[styrene-block-(butylene-co-etyrene)] with a synthetic polyisoprene stopper (latex-free). Blind port made of polypropylene with a synthetic polyisoprene stopper (latex-free).	**Chamber I (298 mL):** 125 g glucosum (glucosum monohydricum), acidum hydrochloridum, aqua ad iniectabile **Chamber II (500 mL):** 7 g alaninum, 6 g argininum, 5.5 g glycinum, 1.5 g histidinum, 2.5 g isoleucinum, 3.7 g leucinum, 3.3 g lysinum anhydricum (lysini acetas), 2.2 g methioninum, 2.6 g phenylalaninum, 5.6 g prolinum, 3.2 g serinum, 500 mg taurinum, 2.2 g threoninum, 1 g tryptophanum, 200 mg tyrosinum, 3.1 g valinum, *280 mg calcii chloridum anhydricum (calcii chloridum dihydricum), 2.1 g natrii glycerophosphas, 600 mg magnesii sulfas anhydricus (magnesii sulfas heptahydricus), 2.2 g kalii chloridum, 1.7 g natrii acetas (natrii acetas trihydricus), 6.5 mg zinci sulfas anhydricus (zinci sulfas heptahydricus), acidum aceticum glaciale,* aqua ad iniectabile **Chamber III (188 mL):** 11.3 g sojae oleum raffinatum, 11.3 g triglycerida media, 9.4 g olivae oleum raffinatum, 5.6 g piscis oleum, int-rac-alpha-tocopherolum, phospholipida purificata ex ovo, glycerolum, natrii oleas, natrii hydroxidum, aqua ad iniectabile
Addaven®	10 mL polypropylene ampoule	2 µmol ferrum (ferri chloridum hexahydricum), 7.7 µmol zincum (zinci chloridum), 0.10 µmol manganum (mangani chloridum tetrahydricum), 0.60 µmol cuprum (cupri chloridum dihydricum), 0.10 µmol selenium (natrii selenis), 20 nmol molybdenum (natrii molybdas dihydricus), 0.1 µmol iodidum (kalii iodidum), 0.020 µmol chromium (chromii(III) chloridum hexahydricum), 5 µmol fluoridum (natrii fluoridum), xylitolum, acidum hydrochloridum, aqua ad iniectabile, 0.12 mg natrium, 3.9 µg kalium

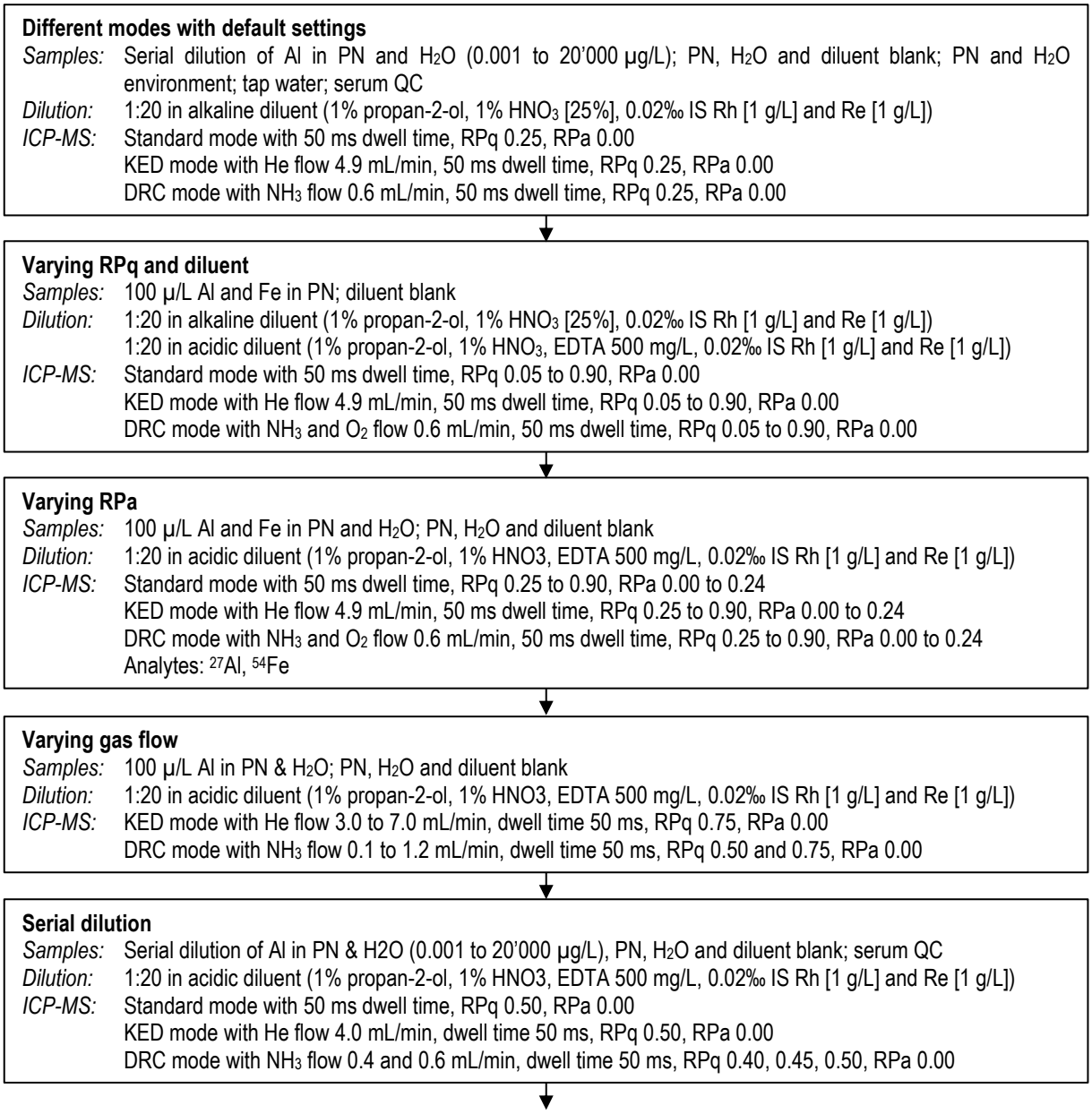
Nutryelt®	10 mL polypropylene ampoule	15.3 µmol zincum (zinci gluconas), 470 nmol cuprum (cupri(II) d-gluconas), 100 nmol manganum (mangani(II) d-gluconas), 5 µmol fluoridum (natrii fluoridum), 100 nmol iodidum (kalii iodidum), 90 nmol selenium (natrii selenis), 21 nmol molybdenum (natrii molybdas dihydricus), 19 nmol chromium (chromii(III) chloridum hexahydricum), 1.8 µmol ferrum (ferrosi gluconas), acidum hydrochloridum concentratum, aqua ad iniectabile
Tracutil®	10 mL clear glass ampoule	35 µmol ferrum (ferrosi chloridum tetrahydricum), 50 µmol zincum (zinci chloridum), 10 µmol manganum (mangani chloridum tetrahydricum), 12 µmol cuprum (cupri chloridum dihydricum), 0.2 µmol chromium (chromii(III) chloridum hexahydricum), 0.3 µmol selenium (natrii selenis pentahydricus), 0.1 µmol molybdenum (natrii molybdas dihydricus), 1 µmol iodidum (kalii iodidum), 30 µmol fluoridum (natrii fluoridum), 30.8 µmol natrium (natrii selenis pentahydricus, natrii molybdas dihydricus, natrii fluoridum), 1 µmol kalium (kalii iodidum), 336 µmol chloridum (ferrosi chloridum tetrahydricum, zinci chloridum, mangani chloridum tetrahydricum, cupri chloridum dihydricum, chromii(III) chloridum hexahydricum), acidum hydrochloridum concentratum, aqua ad iniectabile
Cernevit®	Lyophilisate in brown glass vials with rubber stopper	3500 U.I. retinoli palmitas, 220 U.I. cholecalciferolum, 10.2 mg int-rac-alpha-tocopherolum, 5.8 mg cocarboxylasum tetrahydricum, 5.67 mg riboflavini natrii phosphas, 5.5 mg pyridoxini hydrochloridum, 6 µg cyanocobalaminum, 46 mg nicotinamidum, 0.414 mg acidum folicum, 16.15 mg dexpanthenolum, 69 µg biotinum, 125 mg acidum ascorbicum, acidum glycocholicum, lecithinum, glycinum
Soluvit® N	Lyophilisate in clear glass vials with rubber stopper	2.5 mg thiaminum, 3.1 mg thiamini nitras, 3.6 mg riboflavinum, 4.9 mg riboflavini natrii phosphas, 40 mg nicotinamidum, 4.0 mg pyridoxinum, 15 mg acidum pantothenicum, 4.9 mg pyridoxini hydrochloridum, 15.0 mg acidum pantothenicum, 16.5 mg natrii pantothenas, 100 mg acidum ascorbicum, 100 mg acidum ascorbicum, 113 mg natrii ascorbas, 60 µg biotinum, 0.4 mg acidum folicum, 5.0 µg cyanocobalaminum, glycinum, dinatrii edetas, 0.5 mg E 218, 15 mg natrium
Vitalipid® N Adult	10 mL clear glass ampoule	330 U.I. retinoli palmitas, 20 U.I. ergocalciferolum, 0.91 mg int-rac-alpha-tocopherolum, 15 µg phytomenadionum, sojae oleum fractionatum, lecithinum fractionatum ex vitello ovi, glycerolum, aqua ad iniectabile
Viant®	Lyophilisate in brown glass vials with rubber stopper	3300 U.I. retinoli palmitas, 200 U.I. cholecalciferolum, 9.11 mg all-rac-α-tocopherolum, 0.15 mg all-rac-phytomenadionum, 200 mg acidum ascorbicum, 6.00 mg thiaminum (thiamini hydrochloridum), 3.60 mg riboflavinum (riboflavini natrii phosphas), 6.00 mg pyridoxinum (pyridoxini hydrochloridum), 0.005 mg cyanocobalaminum, 0.60 mg acidum folicum, 15.0 mg acidum pantotheticum (dexpanthenolum), 0.06 mg biotinum, 40.0 mg nicotinamidum, glycinum, acidum hydrochloricum, natrium glycocholicum, lecithinum sojae, natrium hydroxidum

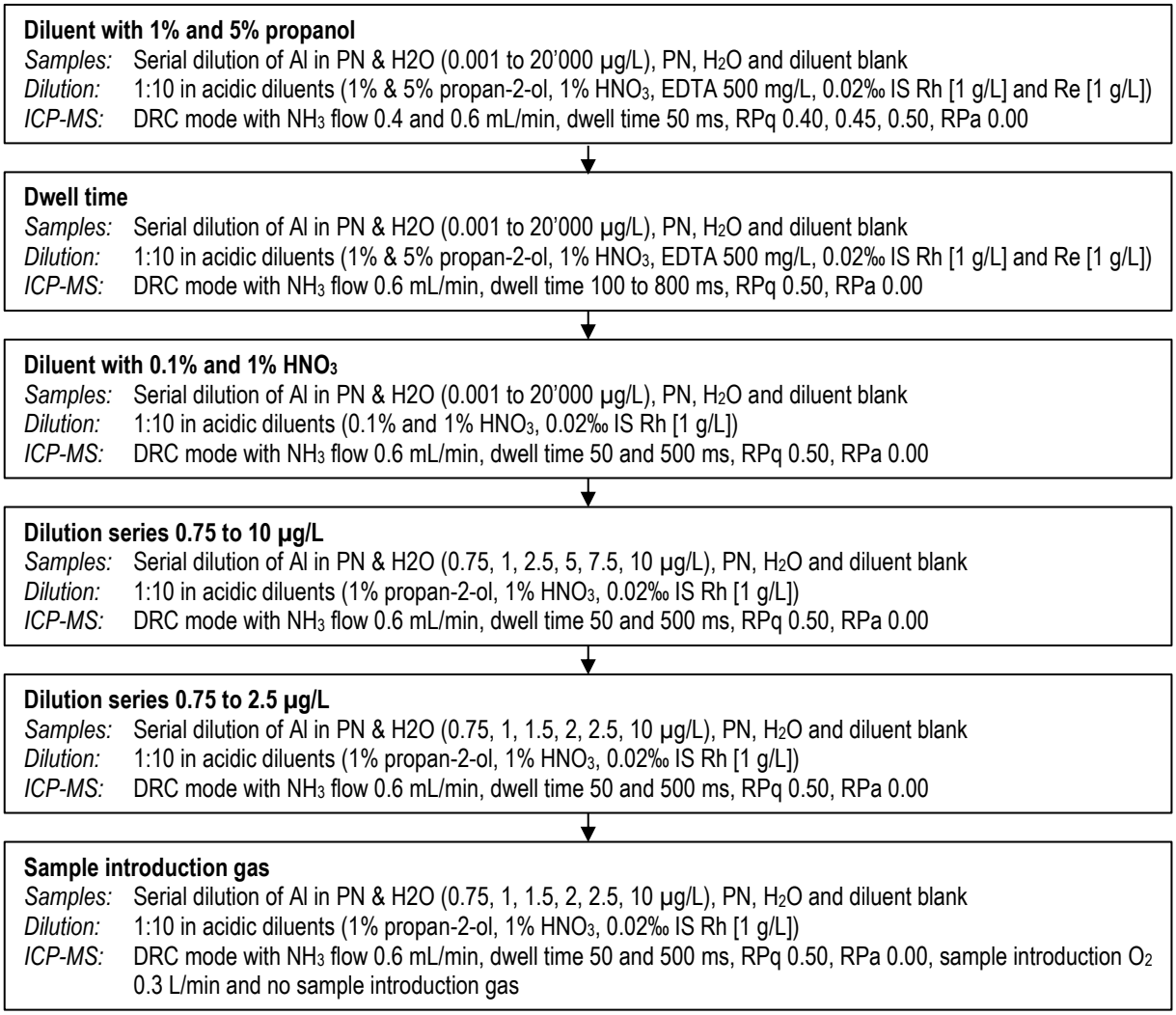
[1] Source: swissmedicinfo.ch [accessed 16. March 2023] and supplier information
Ingredients in *italics* are only contained in the product version with electrolytes

[2] Lysini hydrochloridum in Omegaflex® special with electrolytes, lysini monohydricum in Omegaflex® special without electrolytes

Method Development

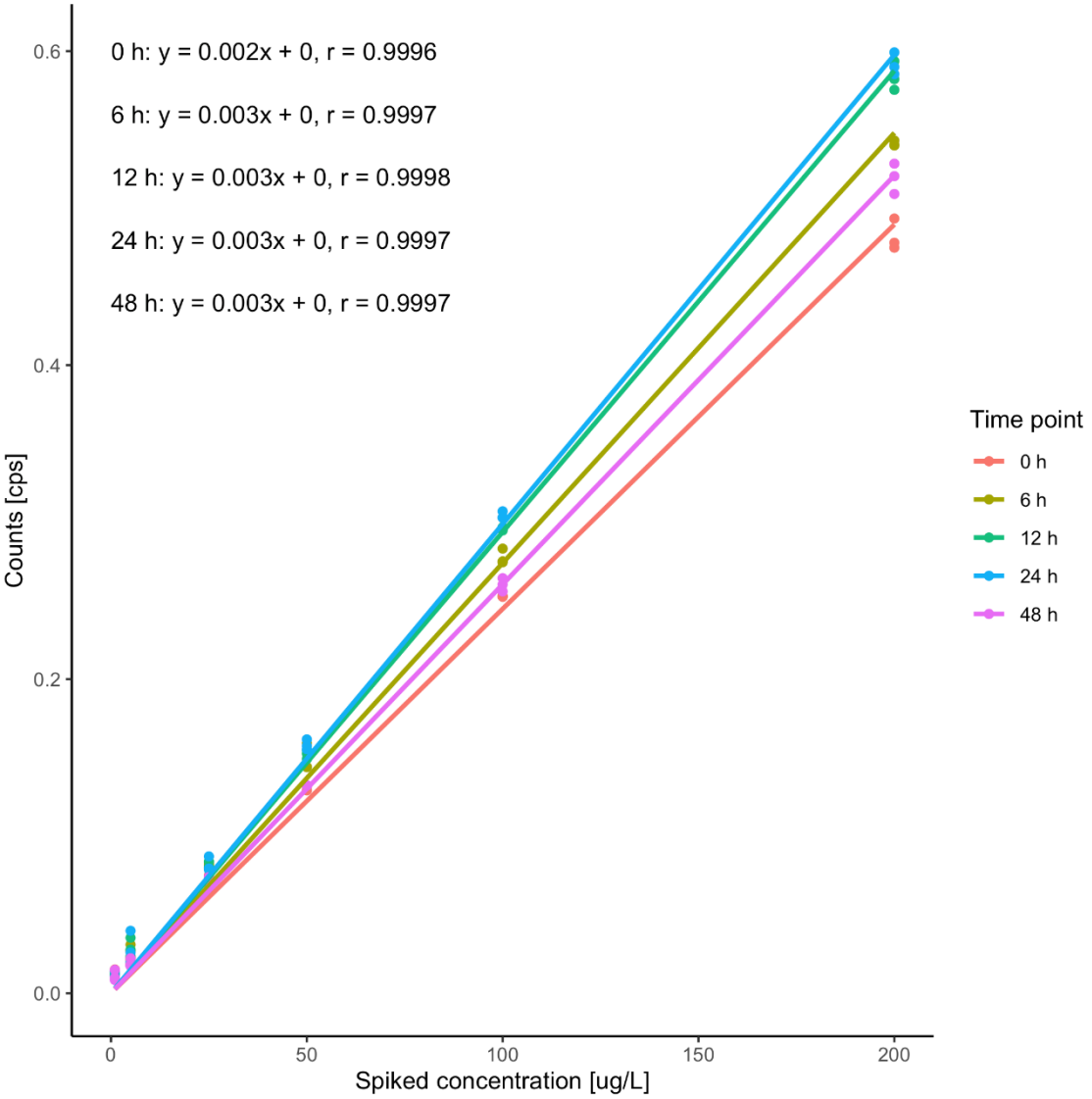
We have developed an inductively coupled plasma mass spectrometry (ICP-MS) method to quantify aluminum (Al) in oil-in-water parenteral nutrition (PN) emulsions consisting of glucose, amino acids, lipids, and electrolytes. The development was a multistep process, including experiments with various Al concentrations, matrices, diluents, and ICP-MS settings. To assess potential polyatomic interference of the iron isotope at mass 54 (^{54}Fe) with ^{27}Al, we additionally measured ^{54}Fe during the method development experiments. We assessed the results of all experiments and based decisions for further experiments on the following criteria: Distinguishable absolute Al counts for spiked samples, favorable Al:blank and Al:^{54}Fe ratios, and steadiness of absolute Al counts. Details and the order of experiments conducted as part of the method development are presented in Supplementary Figure 1.





Supplementary Figure 1: Experiments conducted during ICP-MS method development for the quantification of aluminum in parenteral nutrition. Abbreviations: Al, aluminum; DRC, dynamic reaction cell; EDTA, ethylenediaminetetraacetic acid; Fe, iron; H_2O, water; He, helium HNO_3, nitric acid; ICP-MS, inductively coupled plasma mass spectrometry; IS, internal standard; KED, kinetic energy discrimination; NH_3, ammonia; O_2, oxygen; PN, parenteral nutrition; Re, rhenium; Rh, rhodium; RPa, retarding potential analyzer; RPq, retarding potential quadrupole.

Supplementary Results



Supplementary Figure 2: Calibration curves for aluminum quantification, individual chamber contents and vitamin and trace element additives were measured in the baseline (0 h) run

Supplementary Table 1: Mean (SD) concentrations of elements quantified in all-in-one parenteral nutrition admixtures taken through the bags' injection port and through an infusion set over time

Admixture	Sampling place	Time-point [h]	Al [µg/L]	As [µg/L]	Cd [µg/L]	Co [µg/L]	Cr [µg/L]	Cu [µg/L]	Fe [mg/L]	Mg [mg/L]	Mn [µg/L]	Mo [µg/L]	Ni [µg/L]	Sb [µg/L]	Se [µg/L]	Sn [µg/L]	V [µg/L]	Zn [mg/L]
Olimel® 5.7% E 1000 mL + Cernevit®+ Nutryelt®	Injection port	0	14.8 (4.3)	0.7 (0.1)	<0.1*	0.8 (0.0)*	11.2 (0.0)*	330 (1)	1.08 (0.01)	100 (0)	58 (0)	21.1 (0.5)	1.9 (0.1)	1.7 (0.1)	82 (3)	0.1 (0.1)	0.2 (0.0)	12.3 (0.1)
		6	17.0 (8.1)	0.4 (0.2)	<0.1	1.0 (0.0)	11.7 (0.1)	376 (2)	1.22 (0.00)	115 (1)	67 (0)	23.9 (0.2)	3.5 (0.2)	1.8 (0.1)	96 (9)	0.2 (0.2)	0.2 (0.0)	13.5 (0.0)*
		12	10.7 (0.5)	0.3 (0.0)	<0.1	0.9 (0.0)	11.2 (0.1)	365 (2)	1.22 (0.02)	111 (0)	66 (0)	23.6 (0.1)	2.2 (0.1)	1.7 (0.1)	95 (4)	0.1 (0.2)	0.2 (0.0)	13.2 (0.0)
		24	9.7 (0.5)	0.4 (0.0)	<0.1	0.9 (0.0)	10.9 (0.1)	356 (1)	1.19 (0.02)	110 (1)	64 (0)	22.7 (0.2)	2.0 (0.1)	1.7 (0.0)	104 (4)	0.2 (0.1)	0.2 (0.0)	13.0 (0.0)
		48	12.1 (3.5)	0.4 (0.0)	<0.1	0.7 (0.0)	10.1 (0.1)	300 (1)	<1	96 (0)	55 (1)	19.5 (0.3)	1.6 (0.1)	1.5 (0.0)	96 (2)	<0.1	0.2 (0.0)	10.9 (0.0)
	Infusion set	0	11.1 (0.4)	0.6 (0.1)	<0.1	0.8 (0.1)	11.1 (0.1)	325 (2)	1.05 (0.01)	100 (0)	56 (1)	20.9 (0.3)	1.8 (0.1)	1.6 (0.1)	82 (1)	0.4 (0.2)	0.2 (0.0)	12.1 (0.0)
		6	9.9 (0.0)*	0.3 (0.1)	<0.1	0.9 (0.1)	11.6 (0.1)	374 (4)	1.20 (0.01)	114 (1)	66 (1)	24.1 (0.2)	1.9 (0.0)	1.7 (0.1)	95 (7)	0.2 (0.1)	0.2 (0.0)	13.5 (0.1)
		12	21.6 (18.7)	0.4 (0.0)	0.1 (0.0)	0.9 (0.1)	11.0 (0.2)	362 (1)	1.18 (0.01)	110 (1)	64 (1)	23.3 (0.1)	1.9 (0.1)	1.7 (0.1)	98 (0)*	0.1 (0.1)	0.2 (0.0)	13.0 (0.0)*
		24	9.6 (0.5)	0.4 (0.1)	<0.1	0.9 (0.0)	10.7 (0.1)	356 (0)*	1.15 (0.02)	109 (1)	64 (1)	22.7 (0.0)*	1.8 (0.0)	1.7 (0.1)	99 (1)	0.1 (0.0)*	0.2 (0.0)	12.9 (0.1)
		48	10.7 (0.7)	0.3 (0.1)	<0.1	0.7 (0.0)	9.9 (0.1)	300 (0)*	<1	95 (0)	54 (1)	19.5 (0.1)	1.4 (0.1)	1.4 (0.0)	98 (5)	<0.1	0.2 (0.0)	10.8 (0.0)
Olimel® 5.7% 1000 mL + Cernevit® + Nutryelt®	Injection port	0	10.5 (0.5)	0.5 (0.1)	<0.1	0.9 (0.0)	11.6 (0.0)	342 (7)	1.04 (0.02)	<0.1	55 (1)	19.9 (0.3)	1.5 (0.1)	<0.1	82 (3)	0.2 (0.1)	<0.1	13.2 (0.2)
		6	12.8 (2.6)	0.3 (0.0)	<0.1	1.1 (0.0)	11.8 (0.3)	387 (2)	1.17 (0.00)	<0.1	63 (1)	22.3 (0.2)	1.8 (0.1)	<0.1	93 (2)	<0.1	<0.1	14.4 (0.1)
		12	9.7 (0.5)	0.4 (0.0)*	<0.1	0.9 (0.0)	10.2 (0.3)	371 (1)	1.14 (0.03)	<0.1	61 (0)	21.8 (0.1)	1.7 (0.1)	<0.1	89 (2)	<0.1	<0.1	14.0 (0.1)
		24	9.1 (1.0)	0.3 (0.0)	<0.1	0.9 (0.0)	9.4 (0.2)	364 (1)	1.09 (0.01)	<0.1	60 (0)	20.5 (0.1)	1.6 (0.1)	<0.1	95 (6)	<0.1	<0.1	13.7 (0.0)
		48	9.7 (1.6)	0.2 (0.0)	<0.1	0.8 (0.0)	8.0 (0.1)	308 (0)	<1	<0.1	51 (0)	17.9 (0.1)	1.4 (0.0)	<0.1*	88 (0)	<0.1	<0.1	11.3 (0.1)
	Infusion set	0	14.9 (1.1)	0.5 (0.1)	<0.1	0.9 (0.0)	10.9 (0.1)	337 (7)	1.02 (0.01)	<0.1	55 (1)	19.6 (0.2)	1.4 (0.1)	0.1 (0.1)	84 (6)	0.1 (0.1)	<0.1	13.1 (0.3)
		6	10.2 (0.6)	0.3 (0.0)	<0.1*	1.0 (0.0)	10.8 (0.2)	386 (1)	1.15 (0.00)	<0.1	62 (1)	22.6 (0.3)	1.5 (0.1)	<0.1	92 (2)	0.2 (0.0)	<0.1	14.8 (0.1)
		12	9.3 (0.6)	0.3 (0.1)	<0.1	1.0 (0.0)	9.6 (0.1)	373 (2)	1.13 (0.02)	<0.1	61 (1)	21.6 (0.1)	1.4 (0.1)	<0.1	92 (4)	<0.1	<0.1	14.1 (0.1)
		24	9.5 (0.8)	0.3 (0.1)	<0.1	1.0 (0.0)	8.9 (0.1)	367 (3)	1.10 (0.00)*	<0.1	60 (1)	21.1 (0.2)	1.4 (0.1)	<0.1	96 (5)	0.2 (0.2)	<0.1	13.9 (0.1)
		48	8.3 (0.3)	0.2 (0.0)	<0.1*	0.8 (0.0)	7.7 (0.1)	303 (3)	<1	<0.1	50 (0)	17.9 (0.0)*	1.1 (0.0)	<0.1	88 (3)	<0.1	<0.1	11.2 (0.1)
Omegaflex® special 1875 mL + Tracutil®	Injection port	0	29.8 (1.3)	0.9 (0.2)	<0.1	0.2 (0.0)	11.0 (0.1)	451 (5)	1.12 (0.01)	111 (1)	308 (4)	6.8 (0.3)	4.0 (0.1)	0.2 (0.0)*	16 (2)	0.9 (0.0)	0.6 (0.0)	4.8 (0.1)
		6	27.2 (0.8)	0.8 (0.1)	<0.1*	0.2 (0.0)	11.3 (0.0)	514 (5)	1.27 (0.00)*	127 (1)	356 (6)	7.4 (0.3)	4.6 (0.1)	0.2 (0.0)	20 (2)	1.2 (0.0)*	0.6 (0.0)	5.3 (0.0)
		12	29.0 (1.8)	0.7 (0.0)	<0.1	0.2 (0.0)	11.3 (0.1)	502 (4)	1.25 (0.01)	123 (1)	351 (2)	7.5 (0.3)	4.3 (0.1)	0.2 (0.0)	17 (1)	0.9 (0.2)	0.6 (0.0)	5.2 (0.0)
		24	27.3 (2.0)	0.7 (0.1)	<0.1	0.2 (0.0)	10.9 (0.1)	486 (2)	1.22 (0.01)	120 (0)	342 (2)	7.0 (0.2)	4.2 (0.0)	0.2 (0.1)	22 (4)	1.6 (1.2)	0.6 (0.0)	5.1 (0.0)
		48	29.9 (2.3)	0.6 (0.1)	<0.1*	0.2 (0.0)	10.2 (0.1)	414 (2)	1.04 (0.01)	106 (0)	295 (1)	6.1 (0.2)	3.5 (0.0)	0.2 (0.0)*	20 (2)	0.7 (0.0)	0.5 (0.0)	4.3 (0.0)
	Infusion set	0	32.9 (4.0)	0.9 (0.0)	<0.1	0.2 (0.0)	10.9 (0.1)	453 (2)	1.13 (0.01)	112 (1)	310 (3)	6.5 (0.1)	3.8 (0.2)	0.2 (0.0)	19 (2)	1.0 (0.1)	0.6 (0.0)	4.9 (0.0)
		6	27.2 (0.7)	0.7 (0.1)	<0.1*	0.2 (0.0)	11.5 (0.2)	523 (3)	1.32 (0.01)	129 (1)	361 (5)	7.3 (0.2)	4.0 (0.0)	0.3 (0.1)	19 (0)	1.3 (0.3)	0.6 (0.0)	5.6 (0.0)
		12	27.2 (0.4)	0.8 (0.0)*	0.1 (0.0)	0.2 (0.0)	11.2 (0.1)	508 (7)	1.25 (0.02)	124 (1)	354 (3)	7.4 (0.1)	4.1 (0.2)	0.2 (0.0)	19 (1)	1.0 (0.1)	0.6 (0.0)	5.3 (0.1)
		24	26.0 (0.8)	0.7 (0.1)	<0.1	0.2 (0.0)	10.8 (0.2)	485 (11)	1.20 (0.01)	120 (3)	341 (7)	6.8 (0.1)	3.9 (0.0)	0.2 (0.0)*	20 (0)	0.9 (0.0)	0.6 (0.0)	5.1 (0.1)
		48	28.3 (2.1)	0.6 (0.1)	<0.1	0.2 (0.0)	9.7 (0.2)	409 (0)*	1.02 (0.01)	105 (0)	293 (2)	5.9 (0.1)	3.3 (0.0)	0.2 (0.0)	18 (1)	0.7 (0.0)	0.5 (0.0)	4.3 (0.0)
Omegaflex® special without electrolytes 1875 mL + Tracutil®	Injection port	0	59.3 (11.4)	0.3 (0.0)	<0.1	0.2 (0.0)	9.2 (0.1)	464 (3)	1.07 (0.00)	0 (0)	294 (1)	5.2 (0.1)	2.3 (0.1)	<0.1	15 (0)	1.0 (0.2)	<0.1	2.4 (0.0)
		6	38.6 (0.4)	0.2 (0.1)	<0.1	0.2 (0.1)	8.9 (0.2)	520 (2)	1.18 (0.02)	0 (0)	332 (2)	5.9 (0.1)	2.6 (0.1)	<0.1	16 (1)	1.1 (0.1)	<0.1	2.6 (0.0)
		12	36.0 (0.8)	0.2 (0.0)	<0.1	0.2 (0.0)	8.0 (0.1)	510 (1)	1.15 (0.03)	0 (0)	323 (1)	5.8 (0.1)	2.6 (0.1)	<0.1	16 (0)	1.0 (0.0)	<0.1	2.6 (0.0)
		24	36.0 (0.0)*	0.2 (0.0)	<0.1	0.2 (0.0)*	7.4 (0.7)	494 (3)	1.12 (0.00)	0 (0)	319 (0)*	5.7 (0.1)	2.2 (0.1)	<0.1	16 (2)	1.3 (0.6)	<0.1	2.5 (0.0)
		48	32.5 (0.8)	0.2 (0.0)	<0.1	0.1 (0.0)	6.0 (0.1)	415 (1)	<1	<0.1*	266 (0)	4.8 (0.1)	1.7 (0.0)	<0.1	16 (1)	0.8 (0.1)	<0.1	2.0 (0.0)
	Infusion set	0	48.0 (1.3)	0.3 (0.0)	<0.1	0.1 (0.0)	8.9 (0.3)	468 (14)	1.07 (0.03)	0 (0)	293 (4)	5.2 (0.0)*	2.2 (0.1)	<0.1	15 (1)	1.4 (0.5)	<0.1	2.5 (0.1)
		6	35.7 (0.0)*	0.1 (0.0)	<0.1	0.2 (0.0)	8.1 (0.2)	523 (0)*	1.19 (0.01)	0 (0)	334 (1)	5.9 (0.1)	2.2 (0.0)	<0.1	18 (1)	1.2 (0.1)	<0.1	2.6 (0.0)
		12	39.9 (6.4)	0.2 (0.0)	<0.1	0.2 (0.0)	7.5 (0.1)	511 (0)*	1.14 (0.01)	0 (0)	327 (0)*	5.8 (0.1)	2.2 (0.1)	<0.1	15 (1)	1.0 (0.1)	<0.1	2.6 (0.0)
		24	34.0 (1.4)	0.1 (0.1)	<0.1	0.2 (0.0)	6.8 (0.2)	488 (6)	1.09 (0.03)	<0.1	312 (3)	5.6 (0.1)	2.0 (0.1)	<0.1	18 (1)	1.3 (0.2)	<0.1	2.7 (0.4)
		48	34.3 (3.8)	0.1 (0.0)	<0.1*	0.2 (0.0)	5.7 (0.1)	411 (2)	<1	<0.1	264 (2)	4.7 (0.1)	1.7 (0.0)	<0.1	16 (0)	0.8 (0.0)	<0.1*	2.0 (0.0)

Omegaflex® special without electrolytes 1875 mL + Viant® + Tracutil®	Injection port	0	30.9 (1.2)	0.1 (0.0)	<0.1*	0.2 (0.0)	5.7 (0.1)	391 (10)	<1	<0.1	247 (4)	7.1 (2.8)	1.6 (0.1)	<0.1*	17 (2)	1.2 (0.3)	<0.1	1.8 (0.0)
	Infusion set	0	29.9 (1.3)	0.2 (0.0)	<0.1	0.2 (0.0)	5.5 (0.1)	381 (3)	<1*	<0.1	244 (1)	4.7 (0.1)	1.6 (0.0)	<0.1	15 (1)	1.1 (0.3)	<0.1	1.8 (0.0)
SmofKabiven® 986 mL + Soluvit® + Vitalipid® + Addaven®	Injection port	0	13.6 (1.8)	4.9 (1.5)	<0.1	0.3 (0.0)	12.2 (0.0)*	420 (4)	1.16 (0.00)	125 (1)	59 (0)*	20.6 (0.6)	1.4 (0.1)	1.5 (0.1)	96 (3)	0.1 (0.0)	0.1 (0.0)	9.2 (0.0)*
		6	12.1 (1.0)	0.8 (0.2)	<0.1	0.4 (0.0)	13.9 (0.3)	485 (3)	1.35 (0.03)	145 (1)	68 (1)	23.7 (0.0)*	1.6 (0.1)	1.6 (0.1)	114 (4)	0.2 (0.1)	0.2 (0.0)	10.6 (0.1)
		12	11.3 (0.4)	0.7 (0.0)	<0.1	0.3 (0.0)	12.8 (0.2)	465 (3)	1.32 (0.03)	139 (1)	66 (0)	22.6 (0.8)	1.9 (0.1)	1.6 (0.1)	112 (2)	0.1 (0.0)	0.2 (0.0)	10.1 (0.1)
		24	11.3 (1.1)	0.6 (0.1)	<0.1	0.3 (0.0)	12.7 (0.3)	452 (4)	1.27 (0.02)	135 (1)	63 (0)	21.6 (0.8)	1.7 (0.1)	1.5 (0.2)	114 (6)	0.2 (0.2)	0.2 (0.0)	10.0 (0.1)
		48	14.8 (5.5)	0.5 (0.0)*	<0.1	0.3 (0.0)	11.9 (0.1)	392 (2)	1.11 (0.03)	123 (1)	56 (2)	19.1 (0.2)	1.5 (0.1)	1.4 (0.0)	103 (2)	0.1 (0.0)	0.1 (0.0)	8.7 (0.1)
	Infusion set	0	12.8 (1.0)	1.9 (0.2)	<0.1	0.3 (0.0)	13.0 (1.3)	418 (6)	1.16 (0.01)	125 (2)	58 (1)	20.6 (0.3)	1.3 (0.1)	1.5 (0.1)	98 (2)	0.2 (0.1)	0.1 (0.0)	9.3 (0.1)
		6	11.7 (0.0)*	0.9 (0.0)	<0.1*	0.4 (0.0)	13.8 (0.1)	488 (3)	1.34 (0.01)	146 (1)	68 (0)*	24.1 (0.3)	1.6 (0.1)	1.6 (0.1)	119 (4)	0.4 (0.2)	0.2 (0.0)	11.0 (0.1)
		12	12.1 (1.1)	0.6 (0.0)	<0.1	0.3 (0.0)	12.9 (0.3)	465 (8)	1.30 (0.02)	139 (3)	65 (3)	23.2 (0.3)	1.5 (0.1)	1.7 (0.0)	111 (5)	0.1 (0.0)	0.2 (0.0)	10.2 (0.2)
		24	10.7 (0.3)	0.7 (0.1)	<0.1	0.3 (0.0)	12.8 (0.1)	462 (0)	1.30 (0.02)	139 (0)	65 (1)	22.3 (0.3)	1.6 (0.0)*	1.6 (0.0)	122 (0)*	0.3 (0.2)	0.2 (0.0)	10.1 (0.1)
		48	12.4 (0.9)*	0.6 (0.1)	<0.1	0.3 (0.0)	11.6 (0.2)	393 (3)	1.10 (0.01)	123 (1)	58 (3)	19.5 (0.2)	1.3 (0.1)	1.3 (0.1)	109 (2)	0.2 (0.1)	0.1 (0.0)*	8.6 (0.1)
SmofKabiven® EF 986 mL + Soluvit® + Vitalipid® + Addaven®	Injection port	0	12.3 (4.3)	1.0 (0.2)	<0.1	0.3 (0.0)	12.1 (0.1)	438 (4)	1.08 (0.01)	<0.1	55 (1)	19.0 (0.0)*	1.6 (0.1)	<0.1	91 (2)	<0.1	<0.1	6.6 (0.0)
		6	9.5 (1.5)	0.3 (0.1)	<0.1	0.3 (0.0)	12.5 (0.1)	511 (4)	1.24 (0.02)	<0.1*	65 (1)	21.7 (0.3)	1.7 (0.1)	<0.1	112 (3)	<0.1	<0.1	7.5 (0.1)
		12	5.8 (0.4)	0.3 (0.0)	<0.1	0.3 (0.0)	10.8 (0.3)	496 (3)	1.14 (0.01)	<0.1	63 (0)	21.4 (0.0)*	1.7 (0.1)	<0.1	108 (3)	<0.1	<0.1	7.3 (0.0)
		24	5.2 (0.6)	0.3 (0.0)*	<0.1	0.3 (0.0)	9.9 (0.1)	479 (3)	1.11 (0.02)	<0.1	61 (0)*	20.0 (0.2)	1.7 (0.0)	<0.1	104 (5)	<0.1	<0.1	7.1 (0.1)
		48	5.3 (0.8)	0.2 (0.0)	<0.1	0.2 (0.0)	8.8 (0.2)	404 (3)	<1	<0.1	52 (0)	17.1 (0.3)	1.5 (0.1)	<0.1	92 (2)	<0.1	<0.1	5.8 (0.1)
	Infusion set	0	7.7 (1.0)	0.8 (0.2)	<0.1	0.2 (0.0)*	11.8 (0.4)	436 (13)	1.07 (0.04)	<0.1	55 (2)	18.9 (0.7)	1.6 (0.0)	<0.1	90 (0)*	0.2 (0.0)	<0.1	6.6 (0.0)*
		6	7.7 (0.7)	0.2 (0.1)	<0.1	0.4 (0.0)	12.1 (0.2)	510 (2)	1.24 (0.01)	<0.1	64 (0)*	22.0 (0.4)	1.6 (0.0)	<0.1	110 (3)	0.2 (0.0)	<0.1	7.6 (0.0)
		12	6.8 (0.6)	0.3 (0.0)*	<0.1	0.3 (0.0)	10.3 (0.1)	486 (9)	1.12 (0.02)	<0.1	62 (1)	21.0 (0.6)	1.6 (0.1)	<0.1	98 (4)	<0.1	<0.1	7.2 (0.1)
		24	5.5 (1.2)	0.2 (0.0)	<0.1	0.3 (0.0)	9.7 (0.0)	471 (5)	1.11 (0.02)	<0.1	61 (1)	20.1 (0.0)*	1.5 (0.1)	<0.1	105 (4)	<0.1	<0.1	7.0 (0.1)
		48	5.0 (0.7)	0.2 (0.0)	<0.1	0.2 (0.0)	8.3 (0.1)	397 (3)	<1	<0.1	51 (1)	17.0 (0.1)	1.2 (0.1)	<0.1	89 (2)	<0.1	<0.1	5.8 (0.0)

* One of three samples excluded as outlier.

Abbreviations: Al, aluminum; Ar, argon; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; Fe, iron; Mg, magnesium; Mn, manganese; Mo, molybdenum; Ni, nickel; Rh, rhodium; Sb, antimony; SD, standard deviation; Se, selenium; Sn, tin; V, vanadium; Zn, zinc

Supplementary Table 2: Body weight at which the limits of safe aluminum exposure are reached

Admixture	Bag size [mL]	Al [µg] mean (SD)	Body weight [kg] mean (SD)	
			4 µg/kg/day	2 µg/kg/day
Olimel® 5.7% E + Cernevit® + Nutryelt®	1000	13.2 (0.7)	3.3 (0.2)	6.6 (0.4)
	1500	19.5 (1.1)	4.9 (0.3)	9.8 (0.5)
	2000	25.9 (1.4)	6.5 (0.4)	12.9 (0.7)
Olimel® 5.7% + Cernevit® + Nutryelt®	1000	9.1 (0.4)	2.3 (0.1)	4.6 (0.2)
	1500	13.4 (0.6)	3.3 (0.2)	6.7 (0.3)
	2000	17.7 (0.8)	4.4 (0.2)	8.8 (0.4)
Omegaflex® special + Viant® + Tracutil®	625	48.4 (1.2)	12.1 (0.3)	24.2 (0.6)
	1250	57.3 (2.3)	14.3 (0.6)	28.6 (1.2)
	1875	66.1 (3.5)	16.5 (0.9)	33.1 (1.7)
Omegaflex® special EF + Viant® + Tracutil®	625	52.1 (3.0)	13.0 (0.8)	26.1 (1.5)
	1250	64.7 (6.1)	16.2 (1.5)	32.4 (3.0)
	1875	77.4 (9.1)	19.3 (2.3)	38.7 (4.6)
SmofKabiven® + Soluvit® + Vitalipid® + Addaven®	493	9.7 (0.5)	2.4 (0.1)	4.9 (0.3)
	986	17.4 (1.1)	4.4 (0.3)	8.7 (0.5)
	1477	25.1 (1.6)	6.3 (0.4)	12.6 (0.8)
	1970	32.9 (2.2)	8.2 (0.5)	16.4 (1.1)
SmofKabiven® EF + Soluvit® + Vitalipid® + Addaven®	986	13.2 (1.0)	3.3 (0.3)	6.6 (0.5)
	1477	18.8 (1.5)	4.7 (0.4)	9.4 (0.8)

Abbreviations: Al, aluminum; SD, standard deviation

Supplementary Table 3: Measured and declared contents of elements in trace element additives

		Cr	Cu	Fe	Mn	Mo	Se	Zn
Addaven®	measured concentration	1008.7 µg/L	42130.6 µg/L	112 mg/L	5377.4 µg/L	1971.9	9252.7 µg/L	666 mg/L
	measured content	$1.01 \cdot 10^{-06}$ g	$4.21 \cdot 10^{-05}$ g	$1.12 \cdot 10^{-04}$ g	$5.38 \cdot 10^{-06}$ g	$1.97 \cdot 10^{-06}$ g	$9.25 \cdot 10^{-06}$ g	$6.66 \cdot 10^{-04}$ g
	declared content	0.02 µmol	0.60 µmol	2 µmol	0.1 µmol	20 nmol	0.1 µmol	7.7 µmol
		$1.04 \cdot 10^{-06}$ g	$3.81 \cdot 10^{-05}$ g	$1.12 \cdot 10^{-04}$ g	$5.49 \cdot 10^{-06}$ g	$1.92 \cdot 10^{-06}$ g	$7.9 \cdot 10^{-06}$ g	$5.03 \cdot 10^{-04}$ g
	difference measured – declared content	-3%	10%	0%	-2%	3%	17%	32%
Nutryelt®	measured concentration	965.7 µg/L	32945.4 µg/L	103 mg/L	5263.8 µg/L	2107.7 µg/L	7124.9 µg/L	1276 mg/L
	measured content	$9.66 \cdot 10^{-07}$ g	$3.29 \cdot 10^{-05}$ g	$1.03 \cdot 10^{-04}$ g	$5.26 \cdot 10^{-06}$ g	$2.11 \cdot 10^{-06}$ g	$7.12 \cdot 10^{-06}$ g	$1.28 \cdot 10^{-03}$ g
	declared content	19 nmol	470 nmol	1.8 µmol	100 nmol	21 nmol	90 nmol	15.3 µmol
		$9.88 \cdot 10^{-07}$ g	$2.99 \cdot 10^{-05}$ g	$1.01 \cdot 10^{-04}$ g	$5.49 \cdot 10^{-06}$ g	$2.01 \cdot 10^{-06}$ g	$7.11 \cdot 10^{-06}$ g	$1.00 \cdot 10^{-03}$ g
	difference measured – declared content	-2%	10%	2%	-4%	5%	0%	28%
Tracutil®†	measured concentration	1090.4 µg/L	87588.3 µg/L	208 mg/L	55169.7 µg/L	1004.6 µg/L	2314.5 µg/L	434 mg/L
	measured content	$1.09 \cdot 10^{-06}$ g	$8.76 \cdot 10^{-05}$ g	$2.08 \cdot 10^{-04}$ g	$5.52 \cdot 10^{-05}$ g	$1.00 \cdot 10^{-06}$ g	$2.31 \cdot 10^{-06}$ g	$4.34 \cdot 10^{-04}$ g
	declared content	0.2 µmol	12 µmol	35 µmol	10 µmol	0.1 µmol	0.3 µmol	50 µmol
		$1.04 \cdot 10^{-05}$ g	$7.63 \cdot 10^{-04}$ g	$1.95 \cdot 10^{-03}$ g	$5.49 \cdot 10^{-04}$ g	$9.6 \cdot 10^{-06}$ g	$2.37 \cdot 10^{-05}$ g	$3.27 \cdot 10^{-03}$ g
	difference measured – declared content	-90%	-89%	-89%	-90%	-90%	-90%	-87%

† Repeated measurement in a later analytical run (48-hour time point) with a different Tracutil® vial from the same batch, diluent, and calibration curve confirmed differences between measured and declared trace element contents (Cr = -90%, Cu = -89%, Fe = -90%, Mn = -91%, Mo = -91%, Se = -92%, Zn = -88%).

Abbreviations: Cr, chromium; Cu, copper; Fe, iron; Mn, manganese; Mo, molybdenum; Se, selenium; Zn, zinc

APPENDIX B: LIST OF PUBLICATIONS WITH ABSTRACTS

ORCID iD: 0000-0002-2122-4746

Schönenberger KA, Huwiler VV, Reber E, Mühlebach S, Stanga Z, Pestoni G, Faeh D. Dietary fibre intake and its association with ultraprocessed food consumption in the general population of Switzerland: analysis of a population- based, cross-sectional national nutrition survey. BMJ Nutr Prev Health 2024;e000727. doi: 10.1136/bmjnph-2023-000727

Objectives: The objective of this study was to describe the compliance to dietary fibre recommendations of the Swiss population and to investigate the association between dietary fibre intake and ultraprocessed food (UPF) consumption. **Methods:** Data were obtained from the cross-sectional Swiss National Nutrition Survey *menuCH*. We summarised the sociodemographic, lifestyle and anthropometric parameters as well as dietary data collected with two 24-hour dietary recalls for the whole population and subgroups according to absolute and relative dietary fibre intake. We analysed the associations between dietary fibre intake and UPF consumption by fitting multinomial logistic regression models. Data were weighted according to the *menuCH* weighting strategy to achieve a representation of the Swiss population. **Results:** Data obtained from 2057 adults were included in the analysis, of which 87% had a dietary fibre intake of < 30 g/day. Participants with high UPF consumption had lower odds of being in the medium or high dietary fibre intake groups than participants with low UPF consumption. The odds of being in the medium or high dietary fibre intake groups decreased linearly across quartiles of UPF consumption (p for trend ≤ 0.004). **Conclusions:** Dietary fibre intake is insufficient in all population groups in Switzerland. UPF consumption is inversely and dose dependently associated with dietary fibre intake. To increase dietary fibre intake, public health measures should discourage UPF consumption and increase dietary fibre intake via unprocessed or minimally processed foods.

Schönenberger KA, Saxer C, Neyer PJ, Huwiler VV, Reber E, Hammerer-Lercher A, Stanga Z, Mühlebach S. Aluminum and other chemical elements in parenteral nutrition components and all-in-one admixtures. Clin Nutr 2023;42(12):2475-83. doi: 10.1016/j.clnu.2023.10.012

Background & aims: Parenteral nutrition (PN) can lead to high or even toxic exposure to aluminum (Al). We aimed to quantify concentrations of Al and other chemical elements of all-in-one (AIO) PN admix- tures for adults prepared from commercial multichamber bags (Olimel® 5.7%, Omegaflex® special, SmofKabiven®, all with and without electrolytes) and vitamin and trace element additives over a 48-h period. Secondly, we determined the level of Al contamination resulting from admixing and infusion set use. **Methods:** We used dynamic reaction cell and kinetic energy discrimination inductively coupled plasma mass spectrometry (ICP-MS) to quantify Al, arsenic (As), cadmium (Cd), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo), nickel (Ni), antimony (Sb), selenium (Se), tin (Sn), vanadium (V), and zinc (Zn) in AIO PN admixtures. We extracted samples for analysis via the bag injection ports and infusion sets over a 48-h period after admixing. We compared the measured Al concentrations of AIO PN admixtures with calculated values based on the measured concentrations of individual chamber contents and additives. **Results:** Mean (standard deviation) baseline Al concentrations in AIO PN admixtures ranged from 10.5 (0.5) to 59.3 (11.4) mg/L and decreased slightly over the 48 h (estimate [standard error] -0.09 [0.02] mg/L/ hour, $p < 0.001$). Thus, certain products exceeded the widely accepted limit of 25 mg/L. There was no significant difference in Al concentrations between samples extracted via the bag injection ports or infusion sets ($p = 0.33$), nor between measured and calculated Al concentrations of AIO PN admixtures ($p = 0.91$). **Conclusion:** Because certain commercially available PN admixtures for adults proved to contain excessively high levels of Al in our study, regulations and corresponding quality requirements at the authority level (e.g., Pharmacopoeia and regulatory authorities) are urgently required. Our results showed that the PN handling process (admixing and supplementing additives) or the materials of the infusion set did not lead to additional Al contamination to any extent. Moreover, calculated Al concentrations of AIO PN admixtures derived from individual chamber contents and additives are valid.

Schönenberger KA, Reber E, Schläppi K, Baumgartner A, Stanga Z, Kollar A. Determinants of Treatment Toxicity in Patients with Soft Tissue Sarcomas. Nutr Cancer 2023;75(8):1638-45. doi: 10.1080/01635581.2023.2227405

Soft tissue sarcomas are rare malignant tumors. Traditionally, treatment is guided by patient and tumor characteristics. Data on the influence of patient characteristics, particularly nutritional status, on clinical outcomes are scarce. Body composition and its changes during treatment play an essential role in predicting toxicity, clinical outcomes, and mortality. This analysis aimed to investigate the relationship between treatment toxicity and body composition. Patients diagnosed with sarcoma who underwent first-line palliative chemotherapy between October 2017 and January 2020 were included. Baseline and follow-up computed tomographic scans at the third lumbar vertebra, available from diagnostic purposes, were analyzed using SliceOmatic software. Treatment toxicity was defined as a composite score of the Common Terminology Criteria for Adverse Events. Nutritional Risk Screening (NRS) 2002 score, psoas muscle thickness to height ratio, and comorbidity showed a significant association with overall toxicity, while skeletal muscle index and age showed a strong trend. In summary, the NRS 2002 tool must be routinely implemented in inpatient and outpatient settings for cancer patients, and nutritional therapy needs to become a fixed component of multimodal cancer treatment. Furthermore, validated standardized procedures for the quantification of muscle mass are needed to individualize and optimize cancer treatment.

Schönenberger KA, Ferreira A, Stebler C, Prendin F, Gawinecka J, Nakas CT, Mühlebach S, Stanga Z, Facchinetti A, Herzig D, Bally L. Nutritional strategies for correcting low glucose values in patients with postbariatric hypoglycaemia: A randomized controlled three-arm crossover trial. Diabetes Obes Metab 2023;25(10):2853-61. doi: 10.1111/dom.15175

Aim: To evaluate the efficacy of nutritional hypoglycaemia correction strategies in postbariatric hypoglycaemia (PBH) after Roux-en-Y gastric bypass (RYGB). **Materials and methods:** In a randomized, controlled, three-arm crossover trial, eight post- RYGB adults (mean [SD] 7.0 [1.4] years since surgery) with PBH ingested a solid mixed meal (584 kcal, 85 g carbohydrates, 21 g fat, 12 g protein) to induce hypoglycaemia on three separate days. Upon reaching plasma glucose of less than 3.0 mmol/L, hypoglycaemia was corrected with 15 g of glucose (G15), 5 g of glucose (G5) or a protein bar (P10, 10 g of protein) in random order. The primary outcome was percentage of time spent in the target plasma glucose range (3.9-5.5 mmol/L) during 40 minutes after correction. **Results:** Postcorrection time spent in the target glucose range did not differ significantly between the interventions ($P = .161$). However, postcorrection time with glucose less than 3.9 mmol/L was lower after G15 than P10 ($P = .007$), whereas time spent with glucose more than 5.5 mmol/L, peak glucose and insulin 15 minutes post- correction were higher after G15 than G5 and P10 ($P < .001$). Glucagon 15 minutes postcorrection was higher after P10 than after G15 and G5 ($P = .002$ and $P = .003$, respectively). G15 resulted in rebound hypoglycaemia (< 3.0 mmol/L) in three of eight cases (38%), while no rebound hypoglycaemia occurred with G5 and P10. **Conclusions:** Correcting hypoglycaemia with 15 g of glucose should be reconsidered in post-RYGB PBH. A lower dose appears to sufficiently increase glucose levels out- side the critical range in most cases, and complementary nutrients (e.g. proteins) may provide glycaemia-stabilizing benefits.

Schönenberger KA, Reber E, Huwiler VV, Dürig C, Muri R, Leuenberger M, Mühlebach S, Stanga Z. Quality of Life in the Management of Home Parenteral Nutrition. Ann Nutr Metab 2023;79(3):326-33. doi: 10.1159/000530082

Introduction: Home parenteral nutrition (HPN) is a rare but challenging therapy and care for patients with mostly severe underlying diseases. We aimed to investigate patient-reported health-related quality of life (QOL) of patients receiving HPN and its development over time in particular. **Methods:** We assessed QOL of HPN patients in a prospective multicenter observational study (SWISSHPN II study). We designed a questionnaire to record symptoms and negative impacts of HPN and completed the validated Optum® SF-36v2® Health Survey with the patients. **Results:** 70 patients (50% women) on HPN were included. PN commonly affected feelings of dependency (*n* = 49, 70%), traveling/leaving home (*n* = 37, 53%), attending cultural and social events (*n* = 25, 36%), and sleep (*n* = 22, 31%). Most frequently reported symptoms were diarrhea (*n* = 30, 43%), polyuria (*n* = 28, 40%), nausea/emesis (*n* = 27, 39%), dysgeusia (*n* = 23, 33%), and cramps (*n* = 20, 29%). At baseline, mean (SD) SF-36v2® physical and mental health component summary scores (PCS and MCS) were 45 (20) and 57 (19), respectively, and there was a trend towards improvement in PCS over the study period while MCS remained stable. Satisfaction with HCP involved in HPN care was high. **Conclusion:** QOL is a crucial and decisive aspect of HPN patient care. Symptoms related to the underlying disease and PN are frequent. Impaired social life and an ambivalent attitude towards the life-saving therapy are major concerns for these patients and should be addressed in their care.

Schönenberger KA, Reber E, Vu DT, Krieger-Grübel C, Gerber PA, Muri R, Huwiler VV, Mühlebach S, Leuenberger M, Stanga Z. Attitudes and expectations of patients on home parenteral nutrition towards eHealth: A multicenter survey. Clin Nutr ESPEN 2022;52:445-9. doi: 10.1016/j.clnesp.2022.09.026

Background & aims: Advances in technology enable patients on home parenteral nutrition (HPN) to manage their treatment more independently and safely. eHealth is a promising application of electronic means in health care, aimed at improving and simplifying processes and connecting the different parties involved. A thorough understanding of the attitudes and expectations of patients on HPN towards eHealth is a prerequisite for a successful implementation. However, to the best of our knowledge, such a survey preceding the implementation of HPN specific eHealth care has never been conducted. The objective of this preliminary survey is the acquisition of insights on the attitudes and expectations of patients on HPN towards eHealth. Resulting findings then serve as the basis for the design of an eHealth platform to facilitate communication among those involved in HPN care, improve the HPN management, and safeguard and monitor the treatment. **Methods:** We conducted a survey on the attitudes and expectations of patients towards an envisioned eHealth platform for HPN. Patients were recruited from large Swiss hospitals by their treating physician or directly by the research team. The surveys were conducted between September 2020 and October 2021 by structured personal interviews based on a questionnaire. **Results:** We included 35 patients on HPN (21 [60%] females) treated in ambulant care of 4 hospitals. They had a median (interquartile range) age of 55 (18) years and a median (interquartile range) duration of parenteral nutrition of 1.3 (3.1) years. Most patients (n = 30, 86%) were equipped with a smartphone, tablet, or computer and 22 (63%) used apps and rated themselves as proficient with the corresponding digital device. A majority of patients rated the following aspects and features of the platform as important: Data collection and storage (n = 29, 83%), checklists for PN, catheter, and infusion pump handling (n = 28, 80%), video instructions (n = 27, 77%), and videoconferencing with physicians (n = 25, 71%). Most patients (n = 26, 74%) were willing to enter data into the platform themselves. The type of data to be entered should be defined on an individual basis. **Conclusions:** Patients on HPN are open to videoconference consultations and using an eHealth platform. Two-thirds have the necessary technical skills including suitable digital devices for an eHealth care. We identified key features of an eHealth platform to improve HPN management.

Schönenberger KA, Dürig C, Huwiler VV, Reber E, Stanga Z. Refeeding-Syndrom: Wo stehen wir 2022? [Refeeding Syndrome: Where Do We Stand in 2022?]. Praxis 2022;111(7):381-7. doi: 10.1024/1661-8157/a003863

Das Refeeding-Syndrom ist ein potenziell lebensbedrohlicher Zustand, welcher beim Wiederernähren von mangelnährten Patientinnen und Patienten auftreten kann. In den letzten Jahren wurden von den wichtigen Fachgesellschaften für klinische Ernährung ESPEN und ASPEN zwei Konsensusmanuskripte publiziert. Pathophysiologische Aspekte, klinische Manifestationen, Präventionsmassnahmen sowie Kriterien zur Diagnosestellung und zum Management wurden ausführlich beschrieben. Ziel dieser Mini-Review ist es, einen evidenzbasierten Überblick zum Refeeding-Syndrom zu geben. Zu diesem Zweck wurde die systematische Literatursuche von Friedli et al. 2015 aktualisiert. Es besteht die Evidenz, dass das Refeeding-Syndrom mit einem negativen klinischen Outcome assoziiert ist. Viele Fragen zu Managementaspekten bleiben weiterhin offen. Eine robuste, randomisierte kontrollierte Studie ist dringend notwendig, um diese Fragen evidenzbasiert zu beantworten und zuverlässige Hinweise über unabhängige Prädiktoren sowie eine Abschätzung des metabolischen Risikos zu eruieren.

[The refeeding syndrome is a potentially life-threatening condition that can occur when refeeding malnourished patients. In recent years, two consensus manuscripts were published by the major clinical nutrition societies ESPEN and ASPEN. Pathophysiological aspects, clinical manifestations, prevention measures and criteria for diagnosis and management have been described in detail. The aim of this mini-review is to provide an evidence-based overview on the refeeding syndrome. For this purpose, the systematic literature search by Friedli et al. 2015 was updated. Evidence that the refeeding syndrome is associated with a negative clinical outcome exists. Many questions about management aspects remain unanswered. A robust randomized controlled trial is urgently needed to answer all these questions in an evidence-based manner and to elicit reliable evidence about independent predictors and an estimate of metabolic risk.]

Schönenberger KA, Cossu L, Prendin F, Cappon G, Wu J, Fuchs KL, Mayer S, Herzig D, Facchinetti A, Bally L. Digital Solutions to Diagnose and Manage Postbariatric Hypoglycemia. Front Nutr 2022;9:855223. doi: 10.3389/fnut.2022.855223

Postbariatric hypoglycemia (PBH) is an increasingly recognized late metabolic complication of bariatric surgery, characterized by low blood glucose levels 1–3 h after a meal, particularly if the meal contains rapid-acting carbohydrates. PBH can often be effectively managed through appropriate nutritional measures, which remain the cornerstone treatment today. However, their implementation in daily life continues to challenge both patients and health care providers. Emerging digital technologies may allow for more informed and improved decision-making through better access to relevant data to manage glucose levels in PBH. Examples include applications for automated food analysis from meal images, digital receipts of purchased food items or integrated platforms allowing the connection of continuously measured glucose with food and other health-related data. The resulting multi-dimensional data can be processed with artificial intelligence systems to develop prediction algorithms and decision support systems with the aim of improving glucose control, safety, and quality of life of PBH patients. Digital innovations, however, face trade-offs between user burden vs. amount and quality of data. Further challenges to their development are regulatory non-compliance regarding data ownership of the platforms acquiring the required data, as well as user privacy concerns and compliance with regulatory requirements. Through navigating these trade-offs, digital solutions could significantly contribute to improving the management of PBH.

Schönenberger KA, Dürig C, Huwiler VV, Reber E, Stanga Z. Ernährungsscreening in der Onkologie: Der erste Schritt zu einem besseren Outcome. Schweizer Zeitschrift für Ernährungsmedizin 2022;1:6-9. Schweizer Zeitschrift für Onkologie 2022;2:34-8.

Onkologische Patienten sind häufig von einer krankheitsassoziierten Mangelernährung betroffen. Damit verbunden sind negative Folgen wie erhöhte Morbidität und Mortalität, verminderte Therapietoleranz und reduzierte Lebensqualität. Ein Screening des Risikos auf Mangelernährung mit einem validierten Tool hilft, diesen Mangelzustand frühzeitig zu identifizieren und entsprechende ernährungstherapeutische Massnahmen einzuleiten.

Schönenberger KA, Reber E, Dürig C, Baumgartner A, Efthymiou A, Huwiler VV, Laimer M, Bally L, Stanga Z. Management of Hyperglycemia in Hospitalized Patients Receiving Parenteral Nutrition. Front Clin Diabetes Healthc 2022;3:829412. doi: 10.3389/fcdhc.2022.829412

Almost half of inpatients on parenteral nutrition experience hyperglycemia, which increases the risk of complications and mortality. The blood glucose target for hospitalized patients on parenteral nutrition is 7.8 to 10.0 mmol/L (140 to 180 mg/dL). For patients with diabetes, the same parenteral nutrition formulae as for patients without diabetes can be used, as long as blood glucose levels can be adequately controlled using insulin. Insulin can be delivered *via* the subcutaneous or intravenous route or, alternatively, added to parenteral nutrition admixtures. Combining parenteral with enteral and oral nutrition can improve glycemic control in patients with sufficient endogenous insulin stores. Intravenous insulin infusion is the preferred route of insulin delivery in critical care as doses can be rapidly adjusted to altered requirements. For stable patients, insulin can be added directly to the parenteral nutrition bag. If parenteral nutrition is infused continuously over 24 hours, the subcutaneous injection of a long-acting insulin combined with correctional bolus insulin may be adequate. The aim of this review is to give an overview of the management of parenteral nutrition-associated hyperglycemia in inpatients with diabetes.

Schönenberger KA, Schüpfer AC, Gloy VL, Hasler P, Stanga Z, Kaegi-Braun N, Reber E. Effect of Anti-Inflammatory Diets on Pain in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Nutrients 2021;13(12):4221. doi: 10.3390/nu13124221

Various nutritional therapies have been proposed in rheumatoid arthritis, particularly diets rich in ω-3 fatty acids, which may lead to eicosanoid reduction. Our aim was to investigate the effect of potentially anti-inflammatory diets (Mediterranean, vegetarian, vegan, ketogenic) on pain. The primary outcome was pain on a 10 cm visual analogue scale. Secondary outcomes were C-reactive protein levels, erythrocyte sedimentation rate, health assessment questionnaire, disease activity score 28, tender/swollen joint counts, weight, and body mass index. We searched MEDLINE (OVID), Embase (Elsevier), and CINAHL for studies published from database inception to 12 November 2021. Two authors independently assessed studies for inclusion, extracted study data, and assessed the risk of bias. We performed a meta-analysis with all eligible randomized controlled trials using RevMan 5. We used mean differences or standardized mean differences and the inverse variance method of pooling using a random-effects model. The search retrieved 564 unique publications, of which we included 12 in the systematic review and 7 in the meta-analysis. All studies had a high risk of bias and the evidence was very low. The main conclusion is that anti-inflammatory diets resulted in significantly lower pain than ordinary diets (-9.22 mm; 95% CI -14.15 to -4.29; $P = 0.0002$; 7 RCTs, 326 participants).

Schönenberger KA, Reber E, Bally L, Geiser T, Lin D, Stanga Z. Nutritional assessment in adults with cystic fibrosis. Nutrition 2019;67-68:110518. doi: 10.1016/j.nut.2019.05.010

Objectives: Clinical experience with patients with cystic fibrosis (CF) suggests a nutritional risk in this population. In addition to the lung pathology, a main pathophysiologic concern is the viscous mucus blocking pancreatic ducts, leading to reduced production of pancreatic enzymes. Therefore, maldigestion and consequently malabsorption (particularly fat and fat-soluble vitamins) occur, resulting in steatorrhea, vitamin deficiencies, and subsequently manifest malnutrition. The aim of this study was to investigate the nutritional status and determine the prevalence of malnutrition in an adult Swiss CF cohort. **Methods:** This was an observational cohort study in which the nutritional status and dietary habits of patients with CF and healthy controls were compared. Assessment was based on the nutritional risk screening (NRS-2002), dietary habits (7-d dietary record), body composition (bioelectrical impedance analysis), anthropometrics, resting energy expenditure (REE; indirect calorimetry), and physical or mental function (hand-grip strength, Short Form-36 v2). **Results:** Nineteen patients (15 men, mean age 32 y) and 15 controls (8 men, mean age 49 y) were included. Eight patients (42%) were at nutritional risk (NRS-2002 $\geq$ 3). Patients had higher energy intake/body weight ($p = 0.021$) with lower body fat percentage ($p < 0.001$), body mass index ($p = 0.030$), and physical/mental health scores ($p < 0.001$) than controls. Energy intake was higher than REE in patients ($p = 0.003$), but not in controls ($p = 0.373$). **Conclusions:** Prevalence of malnutrition was high in this CF cohort, coinciding with low body fat percentage and low body mass index despite high energy and protein intake. Energy requirements of patients with CF should be estimated as approximately twice the Harris–Benedict REE and 1.7 times indirect calorimetry REE, while ensuring adequate intake of pancreatic enzymes.

Uhlmann K, Reber E, **Schönenberger KA**, Stanga Z, Kurmann S. Should handgrip strength be considered when choosing the administration mode of oral nutritional supplements in geriatric patients? A secondary analysis of the MEDPass Trial. Nutrition 2024;124:112429. doi: 10.1016/j.nut.2024.112429

Objective: It is important to individualize nutrition therapy and to identify whether certain patient groups benefit from a specific intervention such as oral nutritional supplements (ONS). This study investigated whether patients with weak handgrip strength (HGS) benefit better from ONS administration in the Medication Pass Nutritional Supplement Program (MEDPass) mode regarding the individual coverage of energy and protein requirements throughout their hospitalization. **Methods:** A secondary analysis of the intention-to-treat data set of the randomized controlled MEDPass trial was conducted. Weak HGS was defined as <27 kg for men and <16 kg for women. Linear mixed-effect models adjusted for the stratification factors energy density of ONS and nutritional risk screening 2002 score were used to address the aim of the study. **Results:** We included 188 participants. Energy and protein coverage did not differ between the patients with weak or normal HGS depending on ONS administration mode ($P = 0.084$, $P = 0.108$). Patients with weak HGS and MEDPass administration mode tended to have the lowest energy and protein coverage (estimated mean, 77.2%; 95% confidence interval [CI], 69.3%–85% and estimated mean, 95.1%; 95% CI, 85.3%–105%, respectively). Patients with weak HGS and conventional ONS administration had the highest energy and protein coverage (estimated mean, 90%; 95% CI, 82.8%–97.2% and estimated mean, 110.2%; 95% CI, 101.3%–119%, respectively). **Conclusion:** No clear recommendations regarding the mode of ONS administration depending on HGS can be made. In clinical practice, appetite and satiety in patients with weak HGS should be monitored, and the ONS administration mode should be adjusted accordingly.

Schläppi K, Reber E, **Schönenberger KA**, Stanga Z, Kurmann S. The influence of patients' nutritional risk, nutritional status, and energy density in MEDPass versus conventional administration of oral nutritional supplements – A secondary analysis of a randomized controlled trial. J Nutr Health Aging 2024;28(3):100170. doi: 10.1016/j.jnha.2024.100170

Objectives: The clinical influence of nutritional risk, nutritional status, and energy density of oral nutritional supplements (ONS) in MEDPass versus conventional administration of ONS is currently unknown. The aim of this analysis was to examine whether these variables have an impact on clinical outcomes. **Methods:** Secondary analysis of the intention to treat dataset of the randomized controlled MEDPass Trial in geriatric and medical inpatients. Patients in the intervention group received 4 × 50 ml ONS during the medication rounds (MEDPass mode), while those in the control group received ONS in a non-standardized manner. The examined endpoints included energy and protein coverage, ONS intake, handgrip strength (HGS), weight, appetite nausea and 30-day mortality. Three subgroup analyses for NRS 2002 total score (3, 4 or 5−7 points), NRS 2002 impaired nutritional status score (0, 1, 2 or 3 points) and energy density of the ONS (1.5 kcal/mL or 2 kcal/mL) were performed using linear and logistic regression with interaction and mixed effect models. **Results:** The data of 202 patients (103 women and 99 men) at nutritional risk (NRS total 2002 score ≥ 3), mean (SD) age 82.2 (6.5) years were included. There was no significant difference between the groups in the primary endpoint energy coverage in all three subgroup analyses. There were also no significant differences between the groups in the secondary endpoints of protein coverage, ONS intake, HGS, weight, appetite, nausea, and 30-day mortality. **Conclusion:** The MEDPass mode of ONS administration was not superior to the conventional mode of administration in this study. ONS with high energy density (≥ 2 kcal/mL) should be offered since current evidence shows a tendency towards improved appetite, increased ONS and increased energy intake.

Tripyla A, Ferreira A, **Schönenberger KA**, Näf NH, Inderbitzin LE, Prendin F, Cossu L, Cappon G, Facchinetti A, Herzig D, Bally L. Relationship Between Symptom Perception and Postprandial Glycemic Profiles in Patients With Postbariatric Hypoglycemia After Roux-en-Y Gastric Bypass Surgery. Diabetes Care 2023;46(10):1792–1798. doi: 10.2337/dc23-0454

Objective: Post-bariatric surgery hypoglycemia (PBH) is a metabolic complication of Roux-en-Y gastric bypass (RYGB). Since symptoms are a key component of the Whipple's triad to diagnose nondiabetic hypoglycemia, we evaluated the relationship between self-reported symptoms and postprandial sensor glucose profiles. **Research Design and Methods:** Thirty patients with PBH after RYGB (age: 50.1 [41.6-60.6] years, 86.7% female, BMI: 26.5 [23.5-31.2] kg/m^2; median [interquartile range]) wore a blinded Dexcom G6 sensor while recording autonomic, neuroglycopenic, and gastrointestinal symptoms over 50 days. Symptoms (overall and each type) were categorized into those occurring in postprandial periods (PPPs) without hypoglycemia, or in the preceding dynamic or hypoglycemic phase of PPPs with hypoglycemia (nadir sensor glucose < 3.9 mmol/L). We further explored the relationship between symptoms and the maximum negative rate of sensor glucose change and nadir sensor glucose levels. **Results:** In 5851 PPPs, 775 symptoms were reported, of which 30.6 (0.0-59.9)% were perceived in PPPs without hypoglycemia, 16.7 (0.0-30.1)% in the preceding dynamic phase and 45.0 (13.7-84.7)% in the hypoglycemic phase of PPPs with hypoglycemia. Per symptom type, 53.6 (23.8-100.0)% of the autonomic, 30.0 (5.6-80.0)% of the neuroglycopenic, and 10.4 (0.0-50.0)% of the gastrointestinal symptoms occurred in the hypoglycemic phase of PPPs with hypoglycemia. Both faster glucose dynamics and lower nadir sensor glucose levels were related with symptom perception. **Conclusions:** The relationship between symptom perception and PBH is complex, challenging clinical judgement and decision-making in this population.

Huwiler VV, Scalise M, **Schönenberger KA**, Mühlebach S, Stanga Z, Balmer ML. The Role of Dietary Fibre in Enteral Nutrition in Sepsis Prevention and Therapy: A Narrative Review. Nutrients 2023;15(11):2489. doi: 10.3390/nu15112489

Objective: This narrative review summarises the current evidence on the role of dietary fibre in enteral nutrition in the prevention and therapy of sepsis, with a focus on critically ill patients. The aim is to discuss the implications for clinical practice and identify future directions for policy and research. **Resources:** We searched MEDLINE and Google Scholar for records on sepsis, critically ill, enteral nutrition, and dietary fibre. We included all types of articles such as meta-analyses, reviews, clinical trials, preclinical studies, and in vitro studies. Data were evaluated for significance and clinical relevance. **Synopsis of Review:** Despite the ongoing debate, enteral nutrition containing dietary fibres showed great potential in attenuating sepsis-related outcomes and preventing the incidence of sepsis in critically ill patients on enteral nutrition. Dietary fibres target different underlying mechanisms such as microbiota, mucosal barrier integrity, local cellular immune response, and systemic inflammation. We discuss the clinical potential and concerns that currently exist with the standard implementation of dietary fibre in enterally fed intensive care patients. Additionally, we identified research gaps that should be addressed to determine effectiveness and the role of dietary fibres in sepsis itself and its associated outcomes.

Ferreira A, **Schönenberger KA**, Potoczna N, Vogt A, Gerber PA, Zehetner J, Giacchino D, Nett P, Gawinecka J, Cossu L, Fuster DG, Dalla Man C, Facchinetti A, Melmer A, Nakas CT, Hepprich M, Donath MY, Herzig D, Bally L. Randomized, double-blind, placebo-controlled crossover trial of once daily empagliflozin 25 mg for the treatment of postprandial hypoglycaemia after Roux-en-Y gastric bypass. Diabetes Technol Ther 2023;25(7):467-75. doi: 10.1089/dia.2023.0036

Aims: To investigate the effect of empagliflozin on glucose dynamics in individuals suffering from postbariatric hypoglycaemia (PBH) after Roux-en-Y gastric bypass (RYGB). **Methods:** Twenty-two adults with PBH after RYGB were randomized to empagliflozin 25 mg or placebo once daily over 20 days in a randomized, double-blind, placebo-controlled, crossover trial. The primary efficacy outcome was the amplitude of plasma glucose excursion (peak to nadir) during a mixed meal tolerance test (MMTT). Outcomes of the outpatient period were assessed using continuous glucose monitoring (CGM) and an event-tracking app. **Results:** The amplitude of glucose excursion during the MMTT was 8.1 ± 2.4 mmol/L with empagliflozin vs 8.1 ± 2.6 mmol/L with placebo (mean ± SD, $p = 0.807$). CGM-based mean amplitude of glucose excursion (MAGE) during the 20 day-period was lower with empagliflozin than placebo (4.8 ± 1.3 vs 5.2 ± 1.6. $p = 0.028$). Empagliflozin reduced the time spent with CGM values > 10.0 mmol/L (3.8 ± 3.5 % vs. 4.7 ± 3.8%, $p = 0.009$), but not the time spent with CGM values < 3.0 mmol/L (1.7 ± 1.6 % vs. 1.5 ± 1.5 %, $p = 0.457$). No significant difference was observed in the quantity and quality of recorded symptoms. Eleven adverse events occurred with empagliflozin (three drug-related) and six with placebo. **Conclusions:** Empagliflozin 25 mg reduces glucose excursions but not hypoglycaemia in individuals with PBH.

Kurmann S, Reber E, **Schönenberger KA**, Schuetz P, Uhlmann K, Vasiloglou MF, Schoenenberger AW, Bertschi D, Sterchi AB, Stanga Z. MEDPass versus conventional administration of oral nutritional supplements – A randomized controlled trial comparing coverage of energy and protein requirements. Clin Nutr 2023;42(2):108-15. doi: 10.1016/j.clnu.2022.11.015

Background & aims: The use of oral nutritional supplements (ONS) in the hospital setting is important to reach individual protein and energy goals in patients at risk for malnutrition. Compliance with ONS can be challenging but may be improved by prescribing ONS in smaller portions with medication rounds (MEDPass). We compared the likelihood of meeting energy and protein requirements in patients receiving ONS with MEDPass versus conventional ONS administration. **Methods:** The MEDPass Trial is a randomized, controlled, open-label superiority trial conducted on medical and geriatric wards in a University Hospital in Switzerland. The MEDPass group was allocated to receive 50 ml of ONS four times per day with the medication rounds. The control group received ONS per conventional care between the meals. The primary outcome was the percentage of energy in relation to the individual requirement. Secondary outcomes included the coverage of protein intake in relation to the individual requirement, the amount of daily consumed ONS, the course of handgrip strength (HGS), body weight appetite and nausea. Furthermore, we compared 30-day mortality and hospital length of stay (LOS) was studied in medical patients. **Results:** From November 22nd, 2018 until November 30th, 2021, 204 patients were included in the trial (MEDPass group $n = 100$, control group $n = 104$). A total of 203 patients at nutritional risk were analyzed in the intention-to-treat analysis (ITT). Regarding the primary endpoint, there was no difference in the coverage of energy requirement between the MEDPass and control group (82 vs. 85% (Δ -3%, 95% CI -11 to 4%), $p = 0.38$). Similarly, no differences were found for the secondary outcomes including coverage of protein requirement (101 vs. 104% (Δ -3%, 95% CI -12 -7%), $p = 0.57$, average daily intake of ONS (170 vs 173 ml (Δ -3 ml, 95% CI -14 to 8 ml), $p = 0.58$) and 30-day mortality (3 vs. 8 patients, OR 0.4 (95% CI 0.1–1.4), $p = 0.15$). The course of HGS, body weight, appetite and nausea did not differ between the groups ($p = 0.29$, $p = 0.14$, $p = 0.65$ and $p = 0.94$, respectively). The per protocol analysis including 178 patients showed similar results. **Conclusion:** Within this controlled trial setting, we found a high compliance for ONS intake and high coverage of protein requirements but no further improvement when ONS was administered using MEDPass compared to conventional care. MEDPass administration may provide an alternative that is easy to integrate into nursing routines, which may lead to lower workload with cost benefits and reduction of food waste.

Karavasiloglou N, Pestoni G, Pannen ST, **Schönenberger KA**, Kuhn T, Rohrmann S. How prevalent is a cancer-protective lifestyle? Adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research cancer prevention recommendations in Switzerland. Br J Nutr 2022;130(5):904-10. doi: 10.1017/S0007114522003968

Population monitoring of lifestyle behaviours that are crucial as risk and protective factors for major chronic diseases is vital for the identification of priority areas for public health. In this study, we aimed to investigate the prevalence of adherence to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) cancer prevention recommendations in Switzerland, overall and by selected sociodemographic and lifestyle characteristics. Data from the population-based, cross-sectional survey menuCH were used. We constructed a score reflecting adherence to the 2018 WCRF/AICR cancer prevention recommendations. Multinomial logistic regression models were fitted to investigate the association of sociodemographic and lifestyle characteristics with the level of adherence to the WCRF/AICR cancer prevention recommendations. The least frequently met cancer prevention recommendations were the ones on fibre intake (met by 13.7%), red and processed meat (25.4%), and ultra-processed food (33.3%) consumption, while the recommendation on physical activity was met by almost 80%. Women and individuals with tertiary education were more likely to have a score of ≥ 5 (as a reflection of adherence to the cancer prevention recommendations), compared with men or those who completed secondary education, respectively. Current smokers were less likely to have a score of ≥ 5, compared with never smokers. A high proportion of the population in Switzerland was found to not adhere closely to the WCRF/AICR cancer prevention recommendations. Differences were detected based on sociodemographic characteristics. Education and policy actions are needed to facilitate the adoption of a cancer-protective lifestyle.

Huwiler VV, **Schönenberger KA**, Segesser von Brunegg A, Reber E, Mühlebach S, Stanga Z, Balmer ML. Prolonged Isolated Soluble Dietary Fibre Supplementation in Overweight and Obese Patients: A Systematic Review with Meta-Analysis of Randomised Controlled Trials. Nutrients 2022;14(13):2627. doi: 10.3390/nu14132627

The prevalence of overweight and obesity is rising rapidly, currently affecting 1.9 billion adults worldwide. Prebiotic dietary fibre supplementation is a promising approach to improve weight loss and reduce metabolic complications in overweight and obese subjects due to modifications of the microbiota composition and function. Previous systematic reviews and meta-analyses addressing similar questions revealed discordant evidence and/or are outdated. We searched MEDLINE, Embase, Google Scholar, and forward and backward citations for randomised controlled trials (RCTs) with isolated soluble dietary fibre supplementation for at least 12 weeks in overweight and obese patients measuring body weight, published through April 2022. We expressed the results as mean differences (MDs) using the random-effects model of the metafor package in R and assessed risk of bias using the Cochrane RoB2 tool. We conducted the study according to the PRISMA guidelines and registered the protocol on PROSPERO (CRD42022295246). The participants with dietary fibre supplementation showed a significantly higher reduction in body weight (MD -1.25 kg, 95% CI -2.24, -0.25; 27 RCTs; 1428 participants) accompanied by a significant decrease in BMI, waist circumference, fasting blood insulin, and HOMA-IR compared to the control group. Certainty of evidence was high, paving the way for the implementation of isolated soluble dietary fibre supplementation into clinical practice.

Stocker R, Ceyhan M, **Schönenberger KA**, Stanga Z, Reber E. Nutrient and fluid requirements in post-bariatric patients performing physical activity: A systematic review. Nutrition 2022;97:111577. doi: 10.1016/j.nut.2021.111577

Objectives: The evidence for the benefits of physical activity in post-bariatric patients is growing. Nevertheless, it remains unclear whether nutritional regimens should be adapted to physical activity levels. The aim of this systematic review was to summarize current evidence regarding nutrient and fluid requirements in physically active post-bariatric patients. **Methods:** We conducted this systematic review according to the PRISMA guidelines. We searched MEDLINE, Embase, and the Cochrane Library for studies assessing nutritional aspects in physically active post-bariatric patients. Data were extracted based on a predefined, standardized form, and assessed for risk of bias. **Results:** Of 582 records, 8 studies were included, mostly implementing general fitness programs (30-60 min/d, 3-4 × /wk). There is no evidence for increased energy requirements in physically active post-bariatric patients. None of the studies determined energy, fat, or carbohydrate requirements. Most studies focused on protein, recommending a minimum intake of 60 g/d to preserve or increase muscle mass (upper limit 1.5 g protein/kg ideal body weight/d). Higher protein intake (108 g/d, thereof 48 g whey protein) combined with physical activity increased muscle strength. The effects of physical activity on micronutrient requirements remain unstudied, whereas fluid requirements appear to be increased. **Conclusion:** The present findings strengthen the importance of adequate protein intake in physically active post-bariatric patients. Nutrient reference values for physically active post-bariatric patients are not definable based on the current evidence. Consequently, clinicians should pay special attention to the monitoring of macro- and micronutrients and fluid balance, especially when post-bariatric patients engage in high levels of physical activity.

Reber E, Neyer P, **Schönenberger KA**, Saxer C, Bernasconi L, Stanga Z, Huber A, Hammerer-Lercher A, Mühlebach S. Physicochemical Stability and Compatibility Testing of Voriconazole in All-in-One Parenteral Nutrition Admixtures. Pharmaceutics 2021;13(9):1447. doi: 10.3390/pharmaceutics13091447

(1) Drug compatibility with all-in-one (AiO) parenteral nutrition (PN) admixtures is a very important pharmaceutical quality issue to be answered based on appropriate laboratory testing. We assessed voriconazole (V), a poorly water-soluble (logP ≈ 1) single-daily dosed antifungal drug monitored in patients and thus candidate for AiO PN admixing for convenient and safe patient care. We evaluated V compatibility and stability in AiO PN admixtures through adapted therapeutic drug monitoring method (drug stability) and visual microscopic emulsion stability by lipid droplets analysis improved by an automated microscopic digital assessment. (2) V was added in concentrations of 0.05/0.25/0.5 mg/mL (143.1/715.7/1431.5 μM), correlating to daily therapeutic dosing, to three commercially available industrial AiO PN admixtures. Three aliquots were stored in the refrigerator (4 °C), at room temperature (24 °C) and under stress conditions in a water bath (37 °C). Samples taken at 0/24/48/72/168 h after admixing were subjected to a stability-indicating one-week analysis. Assessment included visual examination, lipid droplet measurement according to an established and validated method (bright-field microscopy using oil immersion), pH measurement (glass electrode) and V identification/quantification (LC–MS/MS). (3) After one week, all samples at 37 °C showed slight yellow discoloration. The pH values remained stable. All samples met specifications for lipid droplets according to size (upper size ≤ 8 μm, mean size < 4.5 ± 2 μm) and number ($n \leq 9$ lipid droplets > 5 μm). V concentrations were within an acceptable range, calculated for every timepoint as percent of the theoretical concentration spiked into the AiO PN. The median recovery was 98.2% (min-max, 90-112%). (4) At therapeutic doses, commercial V formulations were compatible and stable within specifications over one week in commonly used volumes of commercial AiO PN admixtures at 4-37 °C.

Reber E, **Schönenberger KA**, Huwiler V, Stanga Z. Mangelernährung: Ein Leichtgewicht mit Schwergewicht [Malnutrition: A lightweight with a heavy weight]. Hausarzt Praxis 2021;16(4):11-7

Die Europäische Gesellschaft für klinische Ernährung und Metabolismus (ESPEN) definiert die ME als ein Ernährungszustand, in dem ein Energie-, Protein- und Mikronährstoffdefizit zu einer veränderten Körperzusammensetzung (verringerte Muskelmasse) und zu reduzierter physischer sowie mentaler Funktion führt. In industrialisierten Ländern hat jeder dritte Patient bei Spitaleintritt ein ME-Risiko oder eine manifeste ME. Die ME wird als «einer der wichtigsten versteckten Gründe der Kostensteigerung im Gesundheitswesen» bezeichnet.

Reber E, Staub K, **Schönenberger KA**, Stanga A, Leuenberger M, Pichard C, Schuetz P, Mühlebach S, Stanga Z. Management of Home Parenteral Nutrition: Complications and Survival. Ann Nutr Metab 2021;77(1):46-55. doi: 10.1159/000515057

Background and Aims: Parenteral nutrition (PN) has become an efficient, safe, and convenient treatment over years for patients suffering from intestinal failure. Home PN (HPN) enables the patients to have a high quality of life in their own environment. The therapy management however implies many restrictions and potentially severe lethal complications. Prevention and therapy of the latter are therefore of utmost importance. This study aims to assess and characterize the situation of patients with HPN focusing on prevalence of catheter-related complications and mortality. **Methods:** Swiss multicentre prospective observational study collecting demographic, anthropometric, and catheter-related data by means of questionnaires every sixth month from 2017 to 2019 (24 months), focusing on survival and complications. Data were analysed using descriptive statistics. Logistic regression models were fitted to investigate association between infection and potential co-factors. **Results:** Seventy adult patients (50% women) on HPN were included (≈5 patients/million adult inhabitants/year). The most common underlying diseases were cancer (23%), bariatric surgery (11%), and Crohn's disease (10%). The most prevalent indication was short bowel syndrome (30%). During the study period, 47% of the patients were weaned off PN; mortality rate reached 7% for a median treatment duration of 1.31 years. The rate of catheter-related infection was 0.66/1000 catheter-days (0.28/catheter-year) while the rate of central venous thrombosis was 0.13/1000 catheter-days (0.05/catheter-year). **Conclusion:** This prospective study gives a comprehensive overview of the adult Swiss HPN patient population. The collected data are prerequisite for evaluation, comparison, and improvement of recommendations to ensure best treatment quality and safety.

Reber E, **Schönenberger KA**, Vasiloglou MF, Stanga Z. Nutritional Risk Screening in Cancer Patients: The First Step Toward Better Clinical Outcome. Front Nutr 2021;8:603936. doi: 10.3389/fnut.2021.603936

Disease-related malnutrition is highly prevalent among cancer patients, with 40–80% suffering from it during the course of their disease. Malnutrition is associated with numerous negative outcomes such as: longer hospital stays, increased morbidity and mortality rates, delayed wound healing, as well as decreased muscle function, autonomy and quality of life. In cancer patients, malnutrition negatively affects treatment tolerance (including anti-cancer drugs, surgery, chemo- and radiotherapy), increases side effects, causes adverse reactions, treatment interruptions, postoperative complications and higher readmission rates. Conversely, anti-cancer treatments are also known to affect body composition and impair nutritional status. Tailoring early nutritional therapy to patients' needs has been shown to prevent, treat and limit the negative consequences of malnutrition and is likely to improve overall prognosis. As the optimisation of treatment outcomes is top priority and evidence for nutritional therapy is growing, it is increasingly recognized as a significant intervention and an autonomous component of multimodal cancer care. The proactive implementation of nutritional screening and assessment is essential for patients suffering from cancer – given the interaction of clinical, metabolic, pharmacological factors with systemic inflammation; and suppressed appetite with accelerated muscle protein catabolism. At the same time, a nutritional care plan must be established, and adequate individualized nutritional intervention started rapidly. Screening tools for nutritional risk should be validated, standardized, non-invasive, quick and easy-to-use in daily clinical practice. Such tools must be able to identify patients who are already malnourished, as well as those at risk for malnutrition, in order to prevent or treat malnutrition and reduce negative outcomes. This review investigates the predictive value of commonly used screening tools, as well as the sensitivity and specificity of their individual components for improving clinical outcomes in oncologic populations. Health care professionals' awareness of malnutrition in cancer patients and the pertinence of early nutritional screening must be raised in order to plan the best possible intervention and follow-up during the patients' ordeal with the disease.

Efthymiou A, Hersberger L, Reber E, **Schönenberger KA**, Kägi-Braun N, Tribolet P, Mueller B, Schuetz P, Stanga Z; EFFORT study group. Nutritional risk is a predictor for long-term mortality: 5-Year follow-up of the EFFORT trial. Clin Nutr 2021;40(4):1546-54. doi: 10.1016/j.clnu.2021.02.032

Background and aims: The nutritional risk screening (NRS 2002) is a validated screening tool for malnutrition. This study aims to investigate the prognostic value of the NRS 2002 and its individual components regarding long-term mortality and adverse outcomes in a well-characterized cohort of medical inpatients. **Methods:** We performed a 5-year follow-up investigation of patients included in the investigator-initiated, prospective, randomized controlled multicenter EFFORT trial that evaluated the effects of individualized nutritional intervention vs. standard hospital food. We used multivariable cox regression analyses adjusted for randomisation arm, study centre, comorbidities and main admission diagnosis to investigate associations between NRS 2002 total scores at time of hospital admission and several long-term outcomes. **Results:** We had confirmed mortality data over the mean follow-up time of 3.2 years in 1874 from the initial cohort of 2028 EFFORT patients. Mortality showed a step-wise increase in patients with NRS 3 (289/565 [51.2%]) and NRS 4 (355/717 [49.6%]) to 59.5% (353/593) in patient with NRS $\geq$ 5 corresponding to an adjusted Hazard Ratio (HR) of 1.28 (95%CI 1.15 to 1.42, $p \leq 0.001$) for mortality after one year and 1.13 (95%CI 1.05 to 1.23, $p = 0.002$) for the overall time period. All individual components of NRS including disease severity, food intake, weight loss and BMI provided prognostic information regarding long-term mortality risk. **Conclusion:** Nutritional risk mirrored by a NRS 2002 total score is a strong and independent predictor of long-term mortality and morbidity in polymorbid medical inpatients particularly in patients with high nutritional risk with an NRS $\geq$ 5 points.

Forthcoming manuscripts:

Schönenberger KA, Penitzka SJ, Huwiler VV, Berger MM, Stanga Z, Mühlebach S. Intravenous multivitamin shortage and the management for parenteral nutrition.

Objectives: The objective was to elucidate the current practice and patient impact of managing parenteral nutrition during intravenous multivitamin shortages in Switzerland. **Methods:** We conducted 17 structured interviews with experts involved in parenteral nutrition supply (healthcare professionals, a public servant, and industry representatives) and patients on home parenteral nutrition. **Results:** Awareness and experience with intravenous multivitamin shortages was high among professionals but not in patients. Overall, eight (47%) of the professionals experienced long-lasting shortages (> 90 days). Mentioned reasons for shortages were packaging and transport issues, problems in the procurement of raw materials, lack of personnel due to the COVID-19 pandemic, changed industrial manufacturing prioritizing, e.g. for mRNA vaccines, the 2021 Suez Canal obstruction, low market price, and national authorization withdrawal. **Conclusions:** Managing intravenous multivitamin shortages has become a common task. European guidelines including prioritization of patients relying on intravenous multivitamins and trace elements are warranted.

von Blumenthal F, **Schönenberger KA**, Huwiler VV, Stanga Z, Pestoni G, Faeh D. Dietary Fibre intake in the Adult Swiss Population: A Comprehensive Analysis of Timing and Sources.

Recommended dietary fibre consumption is rarely achieved in high-income countries. Detailed characterization of its consumption is required to identify potential strategies for increasing fibre intake. This study investigated the timing and sources of fibre intake. Data from the cross-sectional Swiss Nutrition Survey menuCH including 2057 individuals were used. We summarized dietary characteristics for the adult population and subgroups stratified by absolute (< 15 g/day, 15-30 g/day, and ≥ 30 g/day) and relative (< 10 g/1000 kcal/day, 10-14 g/1000 kcal/day, and ≥ 14 g/1000 kcal/day) fibre intake. Mean fibre intake of both 24 HDRs for each individual and contribution of food groups and timing (before breakfast, breakfast, during the morning, lunch, during the afternoon, dinner, after dinner/at night) was calculated. Fibre was mainly consumed in three meals: breakfast (4.1 g/day), lunch (6.0 g/day), and dinner (6.4 g/day). At breakfast, intake in the lowest and highest fibre intake groups differed by 6.4 g (absolute intake) and 4.3 g (relative intake). Among low fibre intake groups, skipping breakfast was more frequent (29% for absolute intake and 19% for relative intake) than in the overall study population (15%). The main sources of dietary fibre were grain products (35.6%), followed by vegetables (18.3%) and fruits (18.2%). In the overall study population, 17.5% of the grain products consumed were whole grain. Legumes accounted for 1% of total dietary fibre intake. In order to increase dietary fibre intake, public health measures that encourage regular breakfast eating, the consumption of whole grains and legumes are warranted.

Huwiler VV, Neyer PJ, Saxer C, **Schönenberger KA**, Hammerer-Lercher A, Stanga Z, Mühlebach S. Stability of Nanoparticular Intravenous Iron (Ferinject®) in Commercial All-in-One Parenteral Nutrition: Clinical Potential for Increased Iron Doses.

Background: Iron deficiency and associated iron deficiency anaemia represent a major global health burden. Long-term parenteral nutrition (PN) patients are at increased risk of iron deficiency because of inadequate iron substitution. Currently, iron is added to PN mostly as low-dose ferric chloride in trace element solutions, limited to 1-2 mg in adults, and often absent in paediatric products. This is insufficient for the higher iron requirements often seen in PN patients with gastrointestinal disorders or in neonates. There is insufficient data on the stability of higher doses of modern non-ionic iron formulations in all-in-one (AIO) PN solutions. In contrast to polyvalent cationic iron solution, nanoparticular intravenous iron offers a promising option for adding compatible higher doses of iron to AIO PN. **Aim:** The objective of this study was to evaluate the compatibility and stability of selected widely used nanoparticular iron products in PN over a 48-hour period. Our in vitro study assessed nanoparticle integrity, pH stability, and sedimentation at therapeutic daily iron doses of approximately 200 mg in two widely used commercial AIO PN admixtures. In the absence of a standard for assessing nanoparticle stability, we adapted a novel approach using dialysis tubes with defined molecular size characteristics. **Methods:** Ferric carboxymaltose (Ferinject®) and iron sucrose (Venofer®) were added as nanoparticular intravenous iron to two different commercially available AIO PN admixtures for adults. The iron concentrations used were 100 and 400 mg/L (1.79 and 7.16 mmol/L), corresponding to approximately 200 mg (3.58 mmol) of iron per PN bag. Free and nanoparticular iron were separated using 100 kDa dialysis tubes. Iron sedimentation, free iron, and nanoparticular iron were assessed at 4, 24, and 48 h after admixing. The pH was measured before and 0, 4, 24, and 48 h after admixture. Iron quantification was performed by inductively coupled plasma-mass spectrometry (ICP-MS). **Results:** Over the 48-hour incubation period, we observed no significant changes in nanoparticle iron concentration ($p = 0.449$; 95% CI -0.089, 0.201 per h). The concentration of free iron showed a slight increase over time. Iron recovery ranged from 84.6% to 110.2%. The precision of each replicate ($n = 4$) varied from 3.5% to 18.0%. Neither for iron a significant sedimentation was detected at any time point ($p = 0.130$; 95% CI -1.879, 14.828 per h), nor for calcium, chloride, potassium, sodium, magnesium, phosphorus or zinc. The addition of iron sucrose significantly increased pH ($p = 0.033$; 95% CI 0.031, 0.159), but remained stable thereafter ($p = 0.07$; 95% CI -0.002, 0.042). In contrast, the addition of ferric carboxymaltose did not affect pH ($p = 0.351$; 95% CI -0.05, 0.013). **Conclusion:** Ferric carboxymaltose demonstrated the ability to provide stable intravenous iron admixtures within the PN formulations tested. Further studies should evaluate the stability of lipid emulsions.

Huwiler VV, Tribolet P, Rimensberger C, Roten C, **Schönenberger KA**, Mühlebach S, Schuetz P, Stanga Z. Implementation of Evidence-based Clinical Nutrition: Usability of the New Digital Platform clinicalnutrition.science.

Aim: Malnutrition is a common and complex challenge in inpatient and outpatient settings, associated with increased risk of morbidity and mortality. Its management is often neglected, despite strong evidence of the benefits of an adequate nutritional therapy. We introduced clinicalnutrition.science, a digital platform that provides healthcare professionals with easy online access to evidence and streamlines the nutritional care process. The aim of this study was to assess the usability and validate improvements in the nutritional management when the digital platform is used by healthcare professionals. **Methods:** The usability study, conducted from 28 September to 16 November 2023, involved 56 healthcare professionals from the University Hospital of Bern and the Cantonal Hospital of Aarau. In an adapted crossover study design, participants completed key steps of the nutritional management for a simulated hepatology and oncology case both with and without using the clinicalnutrition.science platform. Usability was assessed using the validated Healthcare Systems Usability Scale (HSUS) questionnaire, supplemented by collection of demographic data. Subgroup analysis was performed for recommended protein and energy intakes by different professional representatives. **Results:** Clinicalnutrition.science achieved a good overall usability score of 71.8%. Use of the platform significantly improved the protein intake recommendation ($p = 0.03$; median 96.5 and 80.0 g/d) and the basal metabolic rate estimate ($p < 0.01$; median 1420.8 and 1755.5 kcal/d) of the simulated oncology case. The variance in protein and energy intake recommendations, basal metabolic rate estimation, and energy deficit estimation was reduced by using the digital platform. These improvements were achieved without increasing the time required to complete key steps in the nutritional management for the two patient cases (median between 10.5 and 15.0 minutes; $p = 0.09$ and 0.67) and without prior training on the platform. There was no effect on malnutrition detection rate, selection of an appropriate nutritional product, or the identification of the most appropriate guideline. **Conclusions:** The use of Clinicalnutrition.science improved evidence-based clinical practice in prescribing personalised nutritional therapy and increased the accuracy of both protein and energy intake recommendations, without increasing the time taken to complete key steps in the nutritional management process.

Castelletti G, Tribolet P, Schütz P, **Schönenberger KA**, Mühlebach S, Stanga Z, Huwiler VV. NutriPro™: A Product-specific E-tool for Healthcare Professionals Guidance in Clinical Nutrition.

Background & aims: Malnutrition is a pressing and increasing global health issue, characterized by inadequate consumption of energy, proteins, and other nutrients. Randomized controlled trials have revealed that individualized nutritional intervention could significantly improve patient outcomes including critical complications and mortality rates. On the Swiss market, there are approximately 600 nutritional products (NPs) from 11 manufacturers that help to meet patients' energy and protein requirements. However, the selection process of a suitable NP is a complex and time-consuming process due to the diverse range of NPs and their different compositions and information presentation. The objective of this project was to develop and launch an independent and interactive digital platform, the NutriPro™ App, to facilitate the selection of suitable NPs by providing compatible, up-to-date, and easily accessible product information. **Methods:** A literature review was conducted to summarize criteria for product information. An online questionnaire was formulated and completed by Swiss healthcare professionals from February to May 2023 to identify key criteria for product information. The collected responses were used to configure our App. A software company assisted in coding and structuring the NutriPro™ app. Fact sheets for each NP were created using official, authority-approved data. **Results:** A total of 92 healthcare professionals completed the online questionnaire. The majority (54%, $n = 49$) were experts in nutrition with over 7 years of experience. The key selection criteria for a NP are its macronutrient composition (79% agreement, $n = 71$), energy content (81% agreement, $n = 73$), protein content (98% agreement, $n = 89$), and the patient's condition (56% agreement, $n = 50$). When compared with the rest of the participants, different sub-groups composed of individual professionals and experts (all professional settings) highlighted additional significant criteria. **Conclusions:** NutriPro™ is a pioneering digital tool created to aid in the selection of NPs by using official, standardized data. Its combination with other medical nutrition support apps (e.g., screening and assessment tools) could enhance the quality of nutritional care, improve health outcomes, and reduce healthcare costs. To evaluate its effectiveness and potential for enhancing clinical nutrition support, efficacy and suitability will be tested with healthcare professionals.

APPENDIX C: CONFERENCE TALKS AND ABSTRACTS

Conference talks

Nahrungsfasern in der Schweizer Bevölkerung. 7. Jahrestagung der Swiss Sports Nutrition Society, 15. June 2023, Ittigen, Switzerland.

Nahrungsfasern in der Schweizer Bevölkerung. 6. Frühjahrskongress SGAIM, 1.-3. June 2022, Lausanne, Switzerland.

See also Elke B. Ziel wird selten erreicht: Nahrungsfasereinnahme in der Schweizer Bevölkerung. Schweizer Zeitschrift für Ernährungsmedizin 2022;4:28-9.

Dietary fiber consumption in the Swiss population. 43th ESPEN 2021 Virtual Congress, 9.-14. September 2021: ESPEN-Event, 12. September 2021, Solothurn, Switzerland.

Management of Home Parenteral Nutrition: Quality of Life, Complications and Survival (SwissHPN II Study). 42th ESPEN 2020 Virtual Congress, 19.-21. September 2020: ESPEN-Event, 20. September 2020, Solothurn, Switzerland.

Nutritional Assessment in Adults with Cystic Fibrosis (NACYFI study). 42nd European Cystic Fibrosis Conference, 5.-8. June 2019, Liverpool, United Kingdom: European Cystic Fibrosis Nutrition Group Meeting, 5. June 2019.

Conference abstracts with oral presentation
(presenting authors underlined)

NutriDays 2023, 24.-25. March 2023, Lausanne, Switzerland:

> Kurmann S, Reber E, Schönenberger KA, Schuetz P, Uhlmann K, Vasiloglou MF, Schoenenberger AW, Bertschi D, Sterchi A-B, Stanga Z. MEDPass versus conventional administration of oral nutritional supplements – a randomized controlled trial comparing coverage of energy and protein requirements.

SGED SSED Annual Meeting 2022, 17.-18. November 2022, Bern, Switzerland:

> Schönenberger KA, Huwiler VV, Reber E, Mühlebach S, Stanga Z, Pestoni G, Faeh D. Dietary Fiber Intake and its Association with Ultra-processed Food Consumption in the General Population of Switzerland.

44th ESPEN Congress 2022, 3.-6. September 2022, Vienna, Austria:

Schönenberger KA, Pestoni G, Huwiler VV, Reber E, Stanga Z, Faeh D. Inverse and Dose-Dependent Association Between Dietary Fiber Intake and Ultra-Processed Food Consumption in the General Population of Switzerland.

Huwiler VV, Schönenberger KA, Segesser von Brunegg A, Reber E, Mühlebach S, Stanga Z, Balmer ML. Isolated Soluble Dietary Fibre Supplementation in Overweight and Obese Patients: Conclusions of an Innovative Systematic Review and Meta-Analyis.

Conference abstracts with poster presentation
(presenting authors underlined)

44th ESPEN Congress 2023, 11.-14. September 2023, Lyon, France:

Schönenberger KA, Saxer C, Neyer PJ, Huwiler VV, Reber E, Hammerer-Lercher A, Stanga Z, Mühlebach S. Aluminum in parenteral nutrition components and all-in-one admixtures.

Huwiler VV, Saxer C, Neyer P, Schönenberger KA, Stanga Z, Hammerer-Lercher A, Mühlebach S. Compatibility of nanoparticulate iv iron with all-in-one parenteral nutrition admixtures tested by ICP-MS.

KSA Innovations- und Forschungstag 2023, 08. June 2023, Aarau, Switzerland:

Schönenberger KA, Saxer C, Neyer PJ, Huwiler VV, Reber E, Hammerer-Lercher A, Stanga Z, Mühlebach S. Aluminum in Parenteral Nutrition Components and All-in-One Admixtures.

Huwiler VV, Schönenberger KA, Neyer PJ , Stanga Z, Saxer C, Hammerer-Lercher A, Mühlebach S. Compatibility of Nanoparticulate Intravenous Iron with All-in-One Parenteral Nutrition Admixtures Tested by ICP-MS.

NUTRITION 2023: " Ernährungstherapie ohne Grenzen" 22. Dreiländertagung der AKE, der DGEM und der GESKES, 01.-03. June 2023, Bregenz, Austria:

Kurmann S, Reber E, Schönenberger KA, Schuetz P, Uhlmann K, Vasiloglou MF, Schoenenberger AW, Bertschi C, Sterchi A-B, Stanga Z. MEDPass versus conventional administration of Oral Nutritional Supplements – a randomized controlled trial comparing coverage of energy and protein requirements.

16th International Conference on Advanced Technologies & Treatments for Diabetes, 22.-25. February 2023, Berlin, Germany:

Tripyla A, Ferreira A, Schönenberger KA, Näf NH, Inderbitzin LE, Cossu L, Cappon G, Facchinetti A, Herzig D, Bally L. Postprandial symptom patterns in patients with post-bariatric hypoglycaemia.

SGED SSED Annual Meeting 2022, 17.-18. November 2022, Bern, Switzerland:

Schönenberger KA, Ferreira A, Stebler C, Näf N, Stanga Z, Herzig D, Bally L. Nutritional correction strategies of low glucose values in patients with postbariatric hypoglycemia – A randomized controlled three-arm crossover trial.

Ferreira A, Vettoretti M, Schönenberger KA, Ovbiye S, Stebler C, Näf N, Potoczna N, Facchinetti A, Herzig D, Bally L. Accuracy of continuous glucose monitoring in patients after gastric bypass surgery during a solid mixed meal tolerance test.

Näf N, Schneider A, Schönenberger KA, Ferreira A, Herzig D, Bally L. Frequency of hypoglycemia and associated symptoms in patients with postbariatric hypoglycemia.

Huwiler VV, Schönenberger KA, Segesser von Brunegg A, Reber E, Mühlebach S, Stanga Z, Balmer ML. Effects of prolonged isolated soluble dietary fibre supplementation in overweight and obese children, adolescents, and adults – Systematic Review with Meta-analysis.

44th ESPEN Congress 2022, 3.-6. September 2022, Vienna, Austria:

Penitzka S, Schönenberger KA, Huwiler VV, Reber E, Stanga Z, Mühlebach S. Impact of Parenteral Multivitamins Shortage in Switzerland.

15th Swiss Pharma Science Day 2022, 19. August 2022, Bern, Switzerland:

Schönenberger KA, Reber E, Huwiler VV, Mühlebach A, Stanga Z, Pestoni G, Faeh D. Dietary fiber intake and its association with ultra-processed food consumption in the general population of Switzerland.

Huwiler VV, Schönenberger KA, Segesser von Brunegg A, Reber E, Mühlebach S, Stanga Z, Balmer ML. Prolonged isolated soluble dietary fibre supplementation in overweight and obese patients: A systematic review with meta-analysis of randomised controlled trials.

Näf N, Schneider A, Schönenberger KA, Lehmann V, Ferreira A, Cossu L, Maritsch M, Herzig D, Facchinetti A, Wortmann F, Stettler C, Bally L. Heart rate variability features in patients with postbariatric hypoglycaemia after Roux-en-Y gastric bypass measured by a wearable device.

SGED SSED Annual Meeting 2021, 11.-12. November 2021, Bern, Switzerland:

Schönenberger KA, Schüpfer A-C, Gloy VL, Stanga Z, Kägi-Braun N, Reber E. Effect of Anti-Inflammatory Diets on Pain in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis.

Schönenberger KA, Reber E, Leuenberger M, Mühlebach S, Stanga Z. Attitudes and Expectations of Patients on Home Parenteral Nutrition Towards eHealth.

43th ESPEN 2021 Virtual Congress, 9.-14. September 2021, online:

Schönenberger KA, Schüpfer A-C, Gloy VL, Stanga Z, Kägi-Braun N, Reber E. The Effect of Anti-Inflammatory Diets on Pain in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis.

Schönenberger KA, Reber E, Leuenberger M, Mühlebach S, Stanga Z. Attitudes and Expectations of Patients on Home Parenteral Nutrition Towards eHealth.

14th Swiss Pharma Science Day 2021, 25. August 2021, online:

Schönenberger KA, Reber E, Leuenberger M, Mühlebach S, Stanga Z. Attitudes and Expectations of Patients on Home Parenteral Nutrition Towards eHealth.

ERNÄHRUNG 2021: "Ernährung: Evidenz gefunden?!" 20. Dreiländertagung der AKE, der DGEM und der GESKES, 24.-26. June 2021, online:

Schönenberger KA, Vu D-T, Reber E, Leuenberger M, Stanga Z. eSwissHPN: eHealth Platform for Patients on Home Parenteral Nutrition.

SGED SSED Annual Meeting 2020, 11.-12. November 2020, online:

Reber E, Staub K, Schönenberger KA, Stanga A, Leuenberger M, Pichard C, Schuetz P, Mühlebach S, Stanga Z. Management of Home Parenteral Nutrition: Complications, Survival and Quality of Life (SwissHPN II study).

42nd European Cystic Fibrosis Conference, 5.-8. June 2019, Liverpool, UK:

Schönenberger KA, Reber E, Bally L, Lin D, Geiser T, Stanga Z. Nutritional Assessment in Patients Affected by Cystic Fibrosis (NACYFI Study).

SGED SSED Annual Meeting 2018, 15.-16. November 2018, Bern, Switzerland:

Schönenberger KA, Reber E, Bally L, Lin D, Geiser T, Stanga Z. Nutritional Assessment in Patients Affected by Cystic Fibrosis (NACYFI Study).

11th Swiss Pharma Science Day 2018, 22. August 2018, Bern, Switzerland:

Schönenberger KA, Reber E, Bally L, Lin D, Geiser T, Stanga Z. Nutritional Assessment in Patients Affected by Cystic Fibrosis (NACYFI Study).

APPENDIX D: TEACHING

Master thesis support:

- Duy-Tan Vu, MSc Pharmacy, University of Basel, spring semester 2021
- Stefanie Penitzka, MSc Pharmacy, University of Bern, spring semester 2022
- Céline Stebler, MSc Pharmacy, University of Bern, spring semester 2022
- Noah Näf, MSc Pharmacy, University of Bern, spring semester 2022

Medical dissertation support:

- Anne-Catherine Schüpfer, Dr. med., University of Bern
- Flurina von Blumenthal, Dr. med., University of Bern

Lectures:

- "Nutritional Assessment in Adults with Cystic Fibrosis", continuing education for the clinical nutrition team, Inselspital, 08. October 2020
- "Evidence-based Practice: Studien suchen, finden und bewerten", report of the clinical nutrition team, Inselspital, 18. May 2021

APPENDIX E: FUNDING ACQUISITION

PhD fellowship funded by a third-party grant of the Division of Clinical Pharmacy and Epidemiology, University of Basel, grant number FO119900 (CHF 166'725.–)

SV Foundation project support for menuCH dietary fiber analysis (CHF 37'000.–)

ESPEN 2022 Travel Grant (EUR 500.–)