NUTRITION AND HEALTH-RELATED QUALITY OF LIFE: IS IT AN IGNORED OUTCOME?

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NUTRITION AND HEALTH-RELATED QUALITY OF LIFE: IS IT AN IGNORED OUTCOME?

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Table of Contents

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EDITORIAL
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Editorial: Nutrition and Health-Related Quality of Life: Is It an Ignored Outcome?

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Editorial on the Research Topic

Nutrition and Health-Related Quality of Life: Is It an Ignored Outcome?

The concept of quality of life (QoL) represents the well-being of people living in a certain society, broadly including physical health, family, education, employment, wealth, religious beliefs, finance and the environment (1). In the last three decades, a new dimension of QoL has increased in interest and has become known as the "health-related quality of life" (HRQoL) (2), which assesses how the individual's well-being may be affected over time, either as a result of a disease, disability or disorder. In fact, the research which focused on HRQoL is extremely important, since its assessment helps monitor progress in terms of achieving the nation's health objectives (3), through its influence on current and future treatments, and health protocols across a wide spectrum of diseases (4).

On the other hand, nutrition is a vital process through which human beings retrieve energy needed for reproduction, growth and development, as well as health maintenance (5). In fact, over- and malnutrition are both associated with medical diseases (6) and psychological disorders (7). It must be remembered that the management of many of these conditions is the result of adequate nutrition (8–10). However, and despite this fact, there is a lack of knowledge relating to the link between nutrition and HRQoL (6), consequently, our Research Topic is entitled: "*Nutrition and Health-Related Quality of Life: Is it an Ignored Outcome?*" so as to attract investigators from different backgrounds, interested in both areas, namely, human nutrition and HRQoL, in order to clarify the link between the two and the nature of their interaction.

We received 17 submissions; six of these were declined following an initial editorial assessment. Eleven papers were accepted after one or more rounds of peer revision as follows: 1 clinical trial, 7 original research documents, 1 systematic review, 1 data report and 1 commentary, sourced from 11 different countries.

Di Iorio et al. reported on the beneficial effect of 30-min monthly sessions over 12 months in patients with type 2 diabetes mellitus, using an "Individualized Nutritional Therapy," based on counting carbohydrates, which improved the patients' state of health, preventing cardiovascular risk and exponentially impacting their QoL.

Yue et al., in a pilot study, tested the feasibility and impact of a nutritional support strategy on the clinical outcomes of severe and critical patients with SARS-CoV-2 pneumonia, based on underfeeding, which restricted non-protein calories but preserved protein intake. Following the same theme, De Pipaòn et al. argued in a commentary that consumer reports of "Keto Flu" were associated with a ketogenic diet.

Liu et al. conducted a large, multicentre, prospective study, composed of 9,996 participants, aged 65 years and older. Their nutritional status and HRQoL were measured using the Mini Nutritional

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Assessment—Short Form (MNA-SF) and the EuroQoL, respectively. The authors found that higher MNA-SF scores were related to an improved HRQoL.

Chen et al. identified an inflammatory-nutritional marker in a study composed of patients with acute kidney injury (AKI), that could predict mortality in this population; a higher PCT to Albumin ratio was strongly associated with higher mortality in sepsis-induced AKI patients.

Gathercole et al. compared the impact of the two dietary interventions modification of dietary protein intake over a period of 10 weeks on the host fecal proteome in elderly males, who either met the minimum dietary protein recommendations (RDA) or consumed twice the recommended dietary allowance (2RDA).

Lachaud et al. examined the housing trajectories of homeless people with mental illness over a follow-up period of 6 years, and the association of these trajectories with food security. Authors in this study reported that individuals with substance use disorder, who never moved into stable accommodation, had the lowest food security status.

Wu et al. investigated the associations of diet quality, physical activity (PA), sedentary behaviors (SB) and HRQoL among children with mental health disorders. They found that health promotion programs, which focused on promoting a high-quality diet, increased PA, a better HRQoL and reduced SB among children, could contribute to improving mental health.

Gao et al. evaluated the effect of home enteral nutrition on nutritional status, body composition (BC), HRQoL and other clinical outcomes in malnourished patients with intestinal failure. It was found that home enteral nutrition improves nutritional status, BC and HRQoL.

Wang et al. conducted a systematic review of controlled trials (RCTs) to explore the efficacy of a low-FODMAP diet (LFD) with regard to alleviating the symptoms of irritable bowel syndrome (IBS). They found that an LFD is effective in reducing the global symptoms and improving the bowel habits of adult patients with IBS.

Leão et al. explored the association between nutritional status and functional status among older adults receiving assistance from the in-home nursing care service. The primary finding of this study was that better functional status is directly associated with good nutritional status.

All the studies included in this Research Topic either directly or indirectly explored the link between nutrition and HRQoL, based upon which we can identify two types of interaction: (1) bi-direction interaction: in other words, a good nutritional status leads to a better HRQoL and vice-versa or (2) synchronic interaction: the two interact with one other to impact another outcome, i.e., an adequate nutritional status plus adoption of a good QoL may improve a medical disease or a psychological disorder. Clearly, future research is still needed to replicate these findings and to consolidate them.

In conclusion, we are grateful to "Frontiers in Nutrition" for giving us the opportunity to serve as editors for this Research Topic; it has been such a challenging and motivating experience from which we have learned a great deal and which we intend to continue. Secondly, we would like to thank our valuable authors for sharing their research in this collection, which we believe will have relevance for the readership in their clinical practice. Last but not least, we wish to thank our reviewers for their time and input, which undoubtedly improved the quality of our studies.

AUTHOR CONTRIBUTIONS

All authors claim authorship, and have approved and made substantial contributions to the conception, drafting and final version of the paper.

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GENERAL COMMENTARY
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Commentary: Consumer Reports of "Keto Flu" Associated With the Ketogenic Diet

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Keywords: ketogenic diet, blogs, adverse effects, scientific method, online forum

A Commentary on

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INTRODUCTION

In recent years, interest in patient centered care has increased with the aim of improving patient experiences. An enormous amount of data describing health care experiences has been generated on social media including blogs, which are public forums were private experiences are described. Although there are advantages to using online forums to decrease research costs and catch a wider geographic or social area in research, it is important that they are not the single source of data used in an investigation.

Personal blogs and the opinions they contain offer insights into living experiences, including those connected with different illnesses. It has been suggested that patient experience of a disease can be inferred on a larger scale through automated textual analysis of health-related forums (1). However, using only this information, relevant clinical data could be missing with a selective publication and inadequate dissemination. If the data differs systematically from other published research that is based on scientific method, the results will be biased by an inaccurate assessment of the intervention effect. In publications based on non-professional blog information, no quality assessment tool exists. When patients access and share their experiences on online forums, they express a perception of their disease in a way that might be noticeably different from quality of life assessments with a more rigorous method of evaluation.

There is currently a lack of primary research on the limitations of social media in health communications among patients. There are some systematic reviews or meta-analysis that identify the uses, benefits, and limitations of social media in health communications (2, 3). The main recurring discussions in this literature outline the limitations of social media, examining quality concerns and the unreliable nature of this information. Importantly, automatic analysis cannot be conducted without a detailed knowledge of the subject area, advocating the need for more interdisciplinary research. Although some case samples of meta-analyses, not including gray literature or unpublished data, clearly overestimate treatment effects, quantifying this effect by considering all metaepidemiological studies implies minimal effects. In most health studies, the

effects of excluding unpublished data are minimal, and the results are unaffected in the results. To have a real impact on science, more effective and reliable ways of locating and retrieving unpublished data and gray literature need to be developed, including the use of peer review and a lower risk of bias.

DISCUSSION

We read with interest the recent article on "Consumer Reports of "Keto Flu" Associated With the Ketogenic Diet" published in Frontiers in Nutrition (4), but would like to add some considerations. The article caused an immediate reaction in the media, with journalists discussing "flu" and its effects. However, these symptoms are based on information posted by people on social networks and this method and its conclusions are not reliable. This information was obtained from global internet forums that discussed keto flu, but which did not use or design a more objective validated method (i.e., questionnaire) to corroborate these opinions. It is interesting to consider, as the authors commented, that these discussion forums on health issues are a practical source for gathering information on patient experiences. However, the article's analysis and conclusion, that content from online forums provides new insights into the side effects of the Ketogenic Diet (KD), did not adhere to the criteria of a quantitative or qualitative scientific method. Gathering many people's experience of these symptoms does add information, but these sources do not provide evidence nor confirm the side effects of this treatment.

As the article commented, "the experiences of online forum users may not be representative of the larger group of people who follow the KD. However, the symptom patterns produced may indicate key lines of questioning for future survey-based approaches." It is therefore necessary to work on these key lines of questioning before publishing, as the forums are unreliable. This information has not adjusted for factors such as the origin of the blog, the level of education, the type of KD diet, or if the information is manipulated, and therefore is not a complementary source in gathering clinical observations. It would be convenient to know more about the different people who participate in the forums, why they use a KD and if there were medical controls on their use diet.

The KD diet presents very precise indications for severe pathologies, with great side effects. Bostock et al. (4) indicate in their paper that the KD is often self-administered by patients, and that this could also be the situation for the users of online forums. There is limited evidence of its efficacy for conditions including weight loss, cognitive and memory enhancement, type II diabetes, cancer, neurological and psychiatric disorders. Keto flu may cluster a set of symptoms that appear when the body goes into ketosis with an electrolyte imbalance. The KD should be started with close monitoring by specialized medical professionals who can track hydration and the slow incorporation of adequate food to generate ketosis. When monitored, these effects can be avoided and are not interpreted as symptoms of the KD *per se*.

It is impossible to characterize the pattern, severity and time course of keto flu if it has not been previously described in scientific journals. Bostock et al. (4) did not include any specific references to literature about it. After reviewing the evidence from randomized controlled trials including 778 patients, this "flu" is not reported as being associated with KD (5). It is known that there are frequently side effects, as gastrointestinal, clearly related at starting the KD. At follow up appointments (between 2 and 16 months) some patients have reported infections (6–9). Even during childhood, the KD is an efficient and safe treatment and side effects such as nausea or constipation are early onset and not frequent (10). Moreover, "Flu KD" is neither a MeSh term nor a keyword related with this area of research. Symptoms of keto-induction were reported two decades ago (11), referred to in mainstream and gray literature as "keto-flu," but these were not well-described in scientific literature (12). In recent years, other than the article by Bostock et al., there have been no publications.

AUTHOR CONTRIBUTIONS

All authors contributed to the search for scientific literature in this general commentary. This commentary advocates research that uses appropriate scientific methods, in this case related to the side effects of the ketogenic diet, and discusses opinions and experiences described in blogs, outlining that they do not contribute reliable scientific evidence.

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ORIGINAL RESEARCH
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Associations Between Nutritional Status, Sociodemographic Characteristics, and Health-Related Variables and Health-Related Quality of Life Among Chinese Elderly Patients: A Multicenter Prospective Study

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Background: Studies that explore the nutritional status, sociodemographic factors, mental health variables, and physical health variables that affect the health-related quality of life (HRQoL) of elderly patients are scarce in China.

Objective: This study aimed to examine the association between health-related quality of life (HRQoL) and nutritional status, sociodemographic characteristics, and health-related variables among Chinese elderly patients.

Materials and Methods: Participants were recruited from six tertiary-level hospitals in six provinces or municipalities/cities throughout China from October 2018 to February 2019: a total of 9,996 participants aged 65 years and older were enrolled. The nutritional status and HRQoL were measured using the Mini Nutritional Assessment—Short Form (MNA-SF) and the EuroQoL Five-Dimension Visual Analog Scale, respectively. BMI was taken using standard measurement protocols. Sociodemographic characteristics included age, sex, education, marital status, ethnicity, smoking, alcohol drinking, and current residence. Mental and physical health variables such as frailty and depression were assessed using validated tested instruments. Multiple linear regression analysis was used to analyze whether the nutritional status, sociodemographic characteristics, and health-related variables were associated with HRQoL.

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Results: According to the MNA-SF scores at the 30- and 90-day follow-up, 9.7% and 9.1% of participants were malnourished, respectively. Higher MNA-SF scores were related to higher HRQoL scores in older patients (regression coefficient; 95% confidence interval) both at the 30-day (0.660; 0.499–0.821) and 90-day (0.622; 0.434–0.809) follow-up. However, there were no significant associations between the body mass index values and HRQoL. Sociodemographic characteristics (such as age, smoking, and current residence), physical health variables (frailty, urinary function, defecation function, sleeping condition, and falling accidents in the past 12 months), and mental health variables (depression) were the main factors influencing HRQoL in this group.

Conclusion: There are several factors associated with HRQoL among the population derived from this investigation of a representative sample of the Chinese hospitalized elderly population in tertiary hospitals. These findings could have major importance for the planning of "active aging" policies and programs.

Trial Registration: Chinese Clinical Trial Registry, ChiCTR1800017682, registered August 9, 2018.

Keywords: aging, malnutrition, depression, frailty, health-related quality of life, China

INTRODUCTION

The aging population is growing rapidly worldwide and looks set to continue to increase even further in the future (1, 2). For example, by 2050, one-fifth of the world's population will be aged 60 years or older, and the proportion of the older population is expected to double from about 11% in 2000 to 22% in 2050 (3). In 2018, the number of Chinese older adults approached 241 million, accounting for 17.2% of the total population, and this figure is expected to approach 480 million by 2050 (1, 4).

Aging in humans may be accompanied by physiological and pathological changes relevant to nutrition, social, psychological, and physical factors, such as weight loss, impaired appetite, depression, and functional disability (5–9). There is growing evidence that malnutrition is a common health problem among older adults in hospital, community, and nursing home settings (5, 10, 11). The burden of malnutrition among the Chinese elderly is serious, and in 2017, for example, malnutrition increased hospital costs by RMB 214 (14% increase) per older adult (12). Also, poor mental health and physical functioning contributes to a progressive decline in health, hindering recovery from illness and leading to increased utilization of health care services and premature institutionalization (6, 13, 14).

Health-related quality of life (HRQoL) is a subjective, multidimensional measure reflecting functional status and emotional and social well-being as well as general health (8, 15). HRQoL has become a main goal in the promotion and development of health among older adults (8, 16, 17). Deterioration of physical functioning can result in difficulties with daily activities including cooking and eating, which may affect nutritional status (2, 4). Malnutrition and declining functional status are two critical factors related to loss of independence with aging (18). Therefore, low HRQoL in older adults can reflect potential health problems contributing to functional disability and dependence as well as a risk of malnutrition (19, 20).

Previous studies have shown a direct association between poor nutritional status and worse HRQoL in some groups, such as adults aged 80 years and older (16). Most previous studies have used differing nutritional screening tools, such as the Mini Nutritional Assessment (MNA) and Malnutrition Universal Screening Tool (MUST) (8, 17), as well as estimated nutritional status and HRQoL in older adults using data from only a single hospital or a smaller sample size (8, 16, 17, 21). Studies conducted in China have explored frailty, depression, and the association between HRQoL and functional abilities among the elderly (22–25), but only a few studies have focused on the association between nutrition and HRQoL among elderly patients. Therefore, studies that explore the sociodemographic factors, nutritional status, mental health variables, and physical health variables that affect the HRQoL of the elderly are scarce in China. To address this issue, we conducted a study designed to examine the association between nutritional status, sociodemographic characteristics, health-related variables, and HRQoL in Chinese elderly patients aged 65 years and above based on a large-scale prospective national survey.

MATERIALS AND METHODS

Study Design and Participants

The participants were derived from a large-scale cohort study in a representative sample of the Chinese hospitalized elderly population in tertiary hospitals, which is an ongoing survey of the physiological and psychological conditions in elderly

Abbreviations: MNA-SF, Mini Nutritional Assessment—Short Form; BMI, body mass index; ICU, intensive care unit; CI, confidence interval; EQ5DVAS, EuroQoL five-dimension visual analog scale; HRQoL, health-related quality of life.

patients nationwide (Chinese Clinical Trial Registry number ChiCTR1800017682). The baseline data collected from the period from October 2018 to February 2019 represent the baseline survey data used in this study.

The target population is all older inpatients in tertiary hospitals. Eligible participants were recruited using a two-stage cluster sampling method to ensure the representativeness of the study sample. In the first stage, five provinces and one municipality/city in China (southwest: Sichuan Province; northeast: Heilongjiang Province; south central: Hubei Province; northern: Beijing municipality/city; northwest: Qinghai Province; eastern: Zhejiang Province) were selected. A simple random sampling method was used in this stage. In the second stage, one tertiary hospital was selected in each province or municipality/city: The Peking Union Medical College Hospital (PUMCH), where the author works, as a form of convenience sampling. In addition to this hospital, five other hospitals were selected through simple random sampling. All eligible elderly patients from the surgical, internal medicine, neurology, and orthopedics departments and the intensive care unit (ICU) of the selected hospitals were continuously enrolled.

A sample size of 7,299 can produce a two-sided 95% confidence interval with a tolerance error equal to 0.005 when the predicted prevalence rate is 5% (26). Considering the potential non-response and loss to follow, 10,000 participants will be recruited in this study. The inclusion criteria were as follows: aged 65 years and older; signed the consent form; understood the aims of the study; and with sufficient mental ability to answer the interview questionnaire.

Measurement Instruments

The Mini Nutritional Assessment—Short Form (MNA-SF) is a six-item scale that assesses nutritional risk. Assessment is a validated test with sensitivity and specificity for the diagnosis of malnutrition, especially for the elderly (5). Responses yield a score from 0 to 14 points. The participants were then categorized into normal nutritional status (12–14 points), at risk for malnutrition (8–11 points), or malnourished (0–7 points) (6). The MNA-SF has been validated in the Chinese population and has excellent test characteristics (27).

Weight (in kilograms), height (in centimeters), and body mass index (BMI) were recorded. The participants were weighed in light clothing with the footwear removed. The weight of the participants was measured to the nearest 0.1 kg using digital electronic chair scales and the height to the nearest 1 mm using a portable stadiometer. BMI was calculated by dividing the body weight by the height squared (in kilograms per square meter) (28) and was used to classify participants into groups of emaciation ($<$18.5 kg/m^2), normal (18.5–23.9 kg/m^2), overweight (24–27.9 kg/m^2), and obesity ($\geq$28 kg/m^2) according to the Chinese guidelines for the prevention and control of adult overweight and obesity (29) and the Chinese criteria by the Working Group on Obesity in China (WGOC) (30).

HRQoL was measured using the EuroQoL Five-Dimension Visual Analog Scale (EQ5DVAS), in which the participants were asked to rate their overall health status. Possible scores range from 0 to 100, in which 0 represents the worst imaginable health state and 100 the best imaginable health state (8, 13, 16, 31). This scale has been validated among the Chinese population (32, 33).

TABLE 1 | Demographic characteristics of the participants (N = 9,996).

Variables	Values
Department (*n*, 100%)	
Surgical	3,296 (32.97)
Medicine	4,694 (46.96)
Neurology	970 (9.70)
Orthopedics	719 (7.19)
ICU	317 (3.17)
Province or municipality/city (*n*, 100%)	
Sichuan Province	1,808 (18.09)
Heilongjiang Province	1,742 (17.43)
Hubei Province	1,824 (18.25)
Beijing municipality/city	1,401 (14.02)
Qinghai Province	1,417 (14.18)
Zhejiang Province	1,804 (18.05)
Length of stay	9.79 ± 7.56
Age	72.47 ± 5.77

ICU, intensive care unit.

Data Collection and Quality Control

The data on nutritional status, sociodemographic characteristics, and health-related variables were collected by 589 well-trained and certified registered nurses who conducted face-to-face questionnaire interviews, health assessment, and physical examinations and reviewed clinical records. To ensure data quality, firstly, the research group developed the project survey manual, operation manual, and training manual. Secondly, a database was built using an electronic data collection (EDC) system to guarantee the accuracy and integrity of the data. Also, to ensure accurate data collection, all nurses received systematic training on completing the case report form (CRF) before they recorded the patients' information daily on the web-based online CRF; they were proficient in the investigation process, the method of using the EDC system, and the application of the depression assessment, frailty assessment, and other health assessment scales. Data on HRQoL were collected at both 30 and 90 days in a telephone follow-up.

Definition of Covariates

We developed a multiple linear regression model including factors potentially associated with HRQoL: age, sex, education, marital status, ethnicity, smoking, alcohol consumption, falling accidents in the past 12 months, sleeping condition, urinary function, defecation function, frailty, depression, and current residence. Sleeping condition, urinary function, and defecation function were dichotomized as normal function or dysfunction. Frailty was assessed using the Frailty Scale (34), with a higher total score indicating a more severely frail condition, which represents frail (3–5), pre-frail (1, 2), and robust (0). The FRAIL scale has been validated for use in older Chinese population (22).

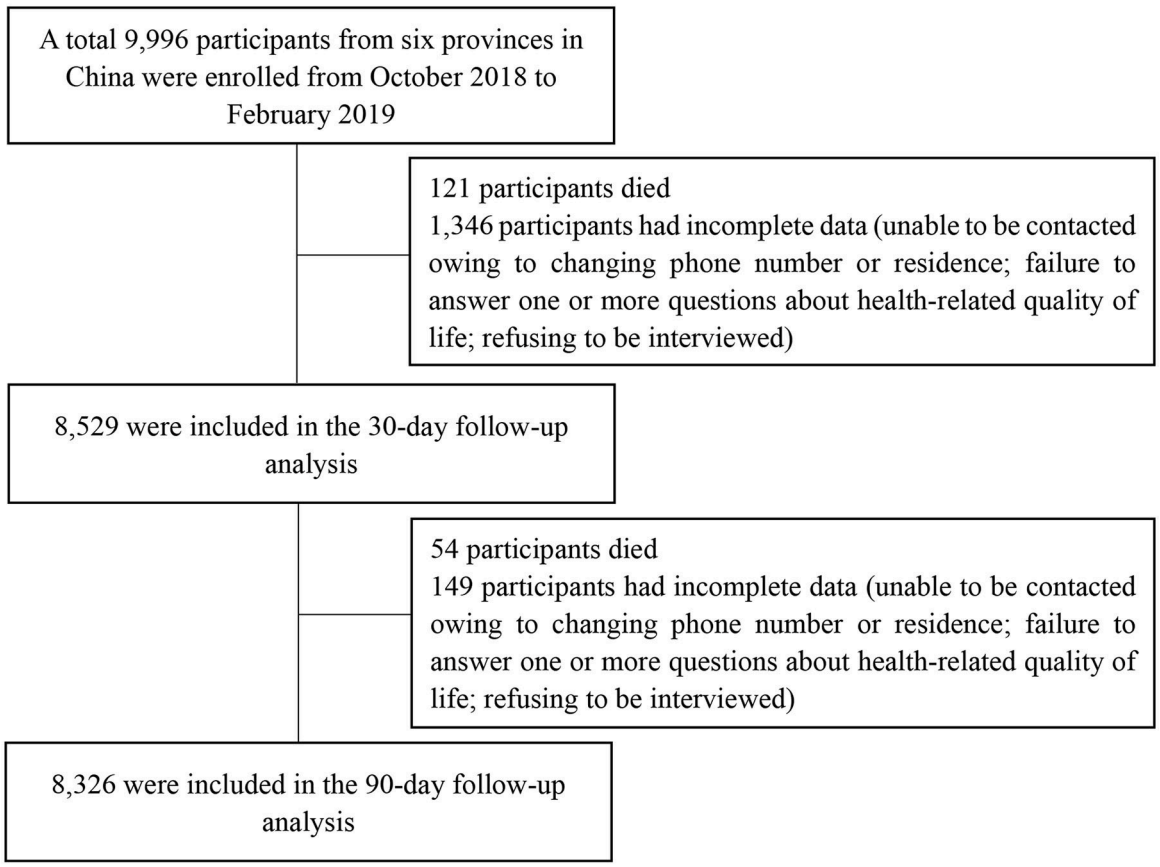

FIGURE 1 | Recruitment and follow-up of participants.

Depression assessment was based on the 15-item Geriatric Depression Scale 15 (GDS-15) (35). The total GDS score was the sum of the responses of the 15 depression questions (range, 0–15). If the total GDS score is above 5, the patient was considered as depressed, with a larger GDS-15 score denoting more severe depression. The GDS-15 has been validated for use in Chinese elderly (36).

Statistical Analysis

A descriptive analysis of the participants' characteristics was performed using proportions and measures of central tendency and dispersion, in accordance with the nature of the variables. Normality probability plots showed that the EQ5DVAS scores were normally distributed. Multiple linear regression analysis was used to predict EQ5DVAS scores according to the sociodemographic characteristics, health-related variables, and nutritional status. Variables that were not multicollinear were entered into the multiple linear regression model. Regression coefficients and 95% confidence intervals (CIs) were used to assess the strength of the relationships. All statistical analyses were conducted using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Statistical significance was accepted at the level of 0.05.

Ethics

This study received approval from the ethics committee of the Peking Union Medical College Hospital (S-K540). All participants signed a form consenting to participate in this study, which adhered to the principles of the Declaration of Helsinki. The participants and their families were provided detailed information about the aim of the study, the terms of participation in the study, the rights of the participants, and questions to be asked. The interview language used is standard Mandarin/Putonghua. If the participants had specific conditions, such as cognitive decline, the nurse interviewed a legal guardian or representative who took care of him to provide consent to participate in this study. Participants were excluded if they had persistent unconsciousness or were unable to provide ethical consent for their participation and if their caregivers were unable to provide effective information.

RESULTS

A total of 9,996 elder patients from 314 wards of six hospitals were enrolled in this study. Descriptive statistics and the frequencies of demographics are shown in **Table 1**. The mean age of this population was 72.47 ± 5.77 years. The average length of stay in the hospital was 9.79 ± 7.56 days. The study flowchart

is presented in **Figure 1**. At the 30-day follow-up, 8,529 (85.3%) participants remained in the study, 121 (1.2%) participants died, and 1,346 (13.5%) had incomplete data (changing phone number or residence permanently, failure to respond to one or more questions about HRQoL, and refusal to be interviewed). At the 90-day follow-up, 8,326 (83.3%) completed the study, 54 (0.5%) participants died, and 149 (1.5%) had incomplete data. At the 30- and 90-day follow-up, the baseline characteristics of those who dropped out of the study (age, sex, frailty, depression, current residence, and nutritional status) did not differ significantly from those who completed it.

The general characteristics and nutritional status of the participants completing the study at 30-day follow-up are shown in **Table 2**. A total 56.7% of the participants were aged 70 years and 57.7% were men; 94.1% of the participants were of Han ethnicity. A total 66.1 and 76.2% of the participants were non-smokers and non-drinkers, respectively. A total 14.3% of the participants had a falling accident in the past 12 months, 42.3% had sleeping difficulties, 12.8% had urinary dysfunction, and 11.3% had defecation dysfunction. The prevalence rates of frailty and depression were 16.4 and 15.4%, respectively. The proportion of participants living in the community was 96.0%. According to the MNA-SF scores, 9.7% of the participants were found to be malnourished; only 6.6% were emaciated, according to the BMI values.

The descriptive characteristics and nutritional status of the participants completing the study at the 90-day follow-up are presented in **Table 3**. A total 56.9 and 57.5% of the participants were aged 70 years and are males, respectively. In total, 94.0% of the participants were of Han ethnicity; 66.1 and 76.1% were non-smokers and non-drinkers, respectively. Of the participants, 14.0% had a falling accident in the past 12 months. The proportion of participants with sleeping difficulties was 42.2%, those with urinary dysfunction was 12.9%, and the proportion with defecation dysfunction was 11.1%. The prevalence rates of frailty and depression were 15.9 and 15.1%, respectively. The percentage of participants living in the community was 98.4%. In total, 9.1% of the participants were found to be malnourished, according to the MNA-SF scores; only 6.4% were emaciated, according to the BMI values.

At the 30-day follow-up, male sex (regression coefficient, 1.351; 95% CI, 0.567–2.135), normal sleeping (1.335; 0.685–1.985), normal urinary function (1.104; 0.133–2.075), normal defecation function (3.598; 2.575–4.622), and a higher MNA-SF score (0.660; 0.499–0.821) were associated with higher EQ5DVAS scores in the multiple linear regression model. In contrast, age (−0.156; −0.213 to −0.099), former smoker (−1.152; −2.055 to −0.249), falling accidents in the past 12 months (−1.005; −1.906 to −0.104), frailty (−4.587; −5.515 to −3.658), depression (−3.455; −4.429 to −2.481), and living in a hospital or nursing home setting (−13.163; −14.753 to −11.572) were associated with lower EQ5DVAS scores. Contrary to the results of the univariate analysis, the association with BMI values was not significant in the multivariate model (**Table 4**).

At the 90-day follow-up, current drinker (regression coefficient, 1.623; 95% CI, 0.407–2.838), normal sleeping (1.145;

TABLE 2 | General characteristics of the participants at the 30-day follow-up (N = 8,529).

Features			*N*	%
Sociodemographic characteristics	Age group (years)	65–69	3,691	43.3
		70–74	2,352	27.6
		75–79	1,490	17.5
		80–84	740	8.7
		85 and above	256	3.00
	Sex	Male	4,922	57.7
		Female	3,607	42.3
	Education	University	1,277	15.0
		Middle school	3,475	40.7
		Primary school	2,423	28.4
		Illiterate	1,354	15.9
	Marital status	Divorced or widowed	930	10.9
		Married	7,599	89.1
	Ethnicity	Han	8,028	94.1
		Others	501	5.9
	Smoking	Non-smoker	5,638	66.1
		Current smoker	943	11.1
		Former smoker	1,948	22.8
	Alcohol drinking	Non-drinker	6,498	76.2
		Current drinker	997	11.7
		Former drinker	1,034	12.1
	Falling accidents in the past 12 months	Yes	1,219	14.3
		No	7,310	85.7
	Sleeping	Normal	4,925	57.7
		Dysfunction	3,604	42.3
	Urinary function	Normal	7,435	87.2
		Dysfunction	1,094	12.8
	Defecation function	Normal	7,569	88.7
		Dysfunction	960	11.3
	Frail	Yes	1,395	16.4
		No	7,134	83.6
	Depression	Yes	1,309	15.4
		No	7,220	84.7
	Current residence	Community	8,187	96.0
		Hospital or nursing home	342	4.0
Nutritional status	MNA-SF	Malnourished (0–7)	823	9.7
		Malnutrition risk (8–11)	2,940	34.5
		Normal (12–14)	4,766	55.9
	BMI (kg/m^2)	Emaciation (<18.5)	562	6.6
		Normal (18.5–23.9)	4,142	48.6
		Overweight (24–27.9)	2,953	34.6
		Obesity (≥28)	872	10.2

MNA-SF, Mini Nutritional Assessment—Short Form; BMI, body mass index.

TABLE 3 | General characteristics of the participants at the 90-day follow-up (N = 8,326).

Features			*N*	%
Sociodemographic characteristics	Age group (years)	65–69	3,589	43.1
		70–74	2,333	28.0
		75–79	1,453	17.5
		80–84	703	8.4
		85 and above	248	3.0
	Sex	Male	4,786	57.5
		Female	3,540	42.5
	Education	University	1,221	14.7
		Middle school	3,393	40.8
		Primary school	2,400	28.8
		Illiterate	1,312	15.8
	Marital status	Divorced or widowed	933	11.2
		Married	7,393	88.8
	Ethnicity	Han	7,825	94.0
		Others	501	6.0
	Smoking	Non-smoker	5,499	66.1
		Current smoker	929	11.2
		Former smoker	1,898	22.8
	Alcohol drinking	Non-drinker	6,338	76.1
		Current drinker	986	11.8
		Former drinker	1,002	12.0
	Falling accidents in the past 12 months	Yes	1,168	14.0
		No	7,158	86.0
	Sleeping	Normal	4,810	57.8
		Dysfunction	3,516	42.2
	Urinary function	Normal	7,251	87.1
		Dysfunction	1,075	12.9
	Defecation function	Normal	7,406	89.0
		Dysfunction	920	11.1
	Frail	Yes	1,322	15.9
		No	7,004	84.1
	Depression	Yes	1,254	15.1
		No	7,072	84.9
	Current residence	Community	8,193	98.4
		Hospital or nursing home	133	1.6
Nutritional status	MNA-SF	Malnourished (0–7)	757	9.1
		Malnutrition risk (8–11)	2,831	34.0
		Normal (12–14)	4,738	56.9
	BMI (kg/m^2)	Emaciation (<18.5)	534	6.4
		Normal (18.5–23.9)	4,037	48.5
		Overweight (24–27.9)	2,909	34.9
		Obesity (≥28)	846	10.2

MNA-SF, Mini Nutritional Assessment—Short Form; BMI, body mass index.

0.403–1.888), normal urinary function (2.147; 1.045–3.249), normal defecation function (3.581; 2.404–4.758), and a higher MNA-SF score (0.622; 0.434–0.809) were associated with higher EQ5DVAS scores in the multiple linear regression model. Age (−0.144; −0.210 to −0.078), Han ethnicity (−1.569; −3.104 to −0.035), former smoker (−1.291; −2.325 to −0.256), falling accidents in the past 12 months (−1.270; −2.306 to −0.233), frailty (−4.187; −5.264 to −3.111), depression (−3.448; −4.571 to −2.326), and living in hospital or a nursing home (−16.029; −18.874 to −13.185) were associated with lower EQ5DVAS scores. Contrary to the results of the univariate analysis, the association with BMI values was not significant in the multivariate model (**Table 5**).

DISCUSSION

To our knowledge, this is the first study to examine the associations between nutritional status, sociodemographic characteristics, and health-related variables and HRQoL among a nationally representative sample of Chinese hospitalized elderly population in tertiary hospitals. The main finding was that higher MNA-SF scores were related to higher HRQoL scores in elderly patients, both at the 30- and 90-day follow-up. However, we found no significant associations between the BMI values and HRQoL. Sociodemographic characteristics (such as age, smoking, and current residence), physical health variables (frailty, urinary function, defecation function, sleeping condition, and falling accidents in the past 12 months), and mental health variables (depression) were the main factors influencing HRQoL in this group.

The MNA-SF scores showed significant associations with the HRQoL scores, suggesting that nutritional status may have an important influence on the HRQoL among the elderly. This finding is consistent with previous studies reporting that the HRQoL scores decrease with the decline of the MNA-SF scores (6, 8, 13). Poor nutrition leads to ill health and ill health to poor nutrition, so identifying priorities for management is a key issue as well as a challenge. One study from Turkey reported that a 12-week intervention with oral nutritional supplementation plus physical exercise improved the nutritional status and HRQoL in older adults (13). Therefore, developing targeted nutritional supplementation plans to help older people to improve their HRQoL is fundamental to the management of healthy aging among older individuals in China. In addition, despite growing evidence that nutritional support improves HRQoL in older people, more data are urgently needed regarding the effects of nutritional support on HRQoL in the elderly.

In this study, MNA-SF and BMI were assessed at the time of admission to the hospital, and HRQoL was recorded at 30 and 90 days after admission via follow-up regardless of whether the participant is hospitalized or discharged. Generally, MNA-SF may reflect the nutritional status in the past 3 months; thus, the MNA-SF is more representative of the long-term nutritional status of participants than does BMI. Accordingly, the potential association between MNA-SF and HRQoL is more convincing in reflecting the relationship between nutritional status and

TABLE 4 | Variables that can affect the EQ5DVAS score from the regression model (30-day follow-up).

Characteristics	Univariate		Multivariate	
	Regression coefficient	95% CI	Regression coefficient	95% CI
Age	−0.243	−0.300 to −0.185	−0.156	−0.213 to −0.099
Sex				
Male	1.145	0.478–1.811	1.351	0.567–2.135
Female (ref.)	–	–	–	–
Education				
University	0.698	−0.489 to 1.886	−0.727	−1.892 to 0.437
Middle school	0.880	−0.095 to 1.855	−0.621	−1.578 to 0.335
Primary school	0.607	−0.426 to 1.639	−0.472	−1.469 to 0.525
Illiterate (ref.)	–	–	–	–
Marital status				
Married	1.213	0.155–2.270	−0.327	−1.363 to 0.709
Divorced or widowed (ref.)	–	–	–	–
Ethnicity				
Han	1.074	−0.327 to 2.476	0.054	−1.305 to 1.413
Others (ref.)	–	–	–	–
Smoking				
Current smoker	0.817	−0.254 to 1.887	−0.522	−1.641 to 0.597
Former smoker	−0.434	−1.234 to 0.366	−1.152	−2.055 to −0.249
Non-smoker (ref.)	–	–	–	–
Alcohol drinking				
Current drinker	1.736	0.702–2.771	0.205	−0.866 to 1.275
Former drinker	−0.273	−1.292 to 0.745	−0.201	−1.284 to 0.882
Non-drinker (ref.)	–	–	–	–
Falling accidents in the past 12 months				
Yes	−2.533	−3.474 to −1.593	−1.005	−1.906 to −0.104
No (ref.)	–	–	–	–
Sleeping				
Normal	3.155	2.491–3.819	1.335	0.685–1.985
Dysfunction (ref.)	–	–	–	–
Urinary function				
Normal	3.402	2.419, 4.385	1.104	0.133, 2.075
Dysfunction (ref.)	–	–	–	–
Defecation function				
Normal	6.466	5.432, 7.500	3.598	2.575, 4.622
Dysfunction (ref.)	–	–	–	–
Frail				
Yes	−8.584	−9.456 to −7.712	−4.587	−5.515 to −3.658
No (ref.)	–	–	–	–
Depression				
Yes	−7.558	−8.458 to −6.657	−3.455	−4.429 to −2.481
No (ref.)	–	–	–	–
Current residence				
Hospital or nursing home	−14.502	−16.154 to −12.850	−13.163	−14.753 to −11.572
Community (ref.)	–	–	–	–
MNA-SF	1.300	1.174–1.42	0.660	0.499–0.821
BMI	0.363	0.269, 0.457	−0.001	−0.104 to 0.102

All models were adjusted for age, sex, education, marital status, ethnicity, smoking, alcohol drinking, falling accidents in the past 12 months, sleeping, urinary function, defecation function, frailty, depression, and current residence.

MNA-SF, Mini Nutritional Assessment—Short Form; EQ5DVAS, EuroQoL Five-Dimension Visual Analog Scale; BMI, body mass index; CI, confidence interval.

TABLE 5 | Variables that can affect the EQ5DVAS score from the regression model (90-day follow-up).

Characteristics	Univariate		Multivariate	
	Regression coefficient	95% CI	Regression coefficient	95% CI
Age	−0.239	−0.304 to −0.174	−0.144	−0.210 to −0.078
Sex				
Male	0.009	−0.758 to 0.739	−0.335	−1.242 to 0.572
Female (ref.)	–	–	–	–
Education				
University	1.848	0.506–3.189	1.122	−0.218 to 2.463
Middle school	0.052	−1.045 to 1.149	−0.773	−1.870 to 0.323
Primary school	0.456	−0.723 to 1.594	−0.118	−1.257 to 1.021
Illiterate (ref.)	–	–	–	–
Marital status				
Married	1.540	0.367–2.712	0.364	−0.811 to 1.538
Divorced or widowed (ref.)	–	–	–	–
Ethnicity				
Han	−0.286	−1.841 to 1.270	−1.569	−3.104 to −0.035
Others (ref.)	–	–	–	–
Smoking				
Current smoker	0.687	−0.509 to 1.884	−0.178	−1.453 to 1.098
Former smoker	−1.059	−1.957 to −0.160	−1.291	−2.325 to −0.256
Non-smoker (ref.)	–	–	–	–
Alcohol drinking				
Current drinker	2.395	1.240, 3.549	1.623	0.407, 2.838
Former drinker	−0.537	−1.684 to 0.609	0.386	−0.853 to 1.625
Non-drinker (ref.)	–	–	–	–
Falling accidents in the past 12 months				
Yes	−2.604	−3.668 to −1.540	−1.270	−2.306 to −0.233
No (ref.)	–	–	–	–
Sleeping				
Normal	2.928	2.182, 3.675	1.145	0.403, 1.888
Dysfunction (ref.)	–	–	–	–
Urinary function				
Normal	4.302	3.202–5.401	2.147	1.045–3.249
Dysfunction (ref.)	–	–	–	–
Defecation function				
Normal	6.413	5.241–7.558	3.581	2.404–4.758
Dysfunction (ref.)	–	–	–	–
Frail				
Yes	−8.144	−9.141 to −7.147	−4.187	−5.264 to −3.111
No (ref.)	–	–	–	–
Depression				
Yes	−7.448	−8.471 to −6.426	−3.448	−4.571 to −2.326
No (ref.)	–	–	–	–
Current residence				
Hospital or nursing home	−18.510	−21.434 to −15.587	−16.029	−18.874 to −13.185
Community (ref.)	–	–	–	–
MNA-SF	1.267	1.121–1.412	0.622	0.434–0.809
BMI	0.363	0.256–0.470	0.017	−0.102 to 0.136

All models were adjusted for age, sex, education, marital status, ethnicity, smoking, alcohol drinking, falling accidents in the past 12 months, sleeping, urinary function, defecation function, frailty, depression, and current residence.

MNA-SF, Mini Nutritional Assessment—Short Form; EQ5DVAS, EuroQoL Five-Dimension Visual Analog Scale; BMI, body mass index; CI, confidence interval.

clinical outcomes. BMI is prone to changes owing to weight gain or loss during hospitalization, which could explain the statistically non-significant results between BMI and HRQoL (8). Still, we believe that controlling BMI is essential to improving the clinical outcomes, as many researchers have shown that BMI is closely related to patients' inflammation and oxidation levels. Further research is required to confirm the relationships between nutritional status and clinical outcomes in this regard.

Similar to the present results, some studies have shown that HRQoL indicators decrease with aging in older adults (25, 37–39). In addition, our results suggest that the HRQoL scores among the participants in the hospital or nursing home settings were lower compared to the participants living in the community. This is perhaps because the community-dwelling elderly can receive support from family, friends, and neighbors and assistance with activities of daily living, such as the sourcing and preparation of meals and help with eating, when necessary (40), which means that such individuals have a better quality of life. Therefore, investing in adequate geriatric care sources, developing a home care-dominated system, supported by community care, and supplemented with institutional care aimed at helping the elderly to self-manage their daily activities and improving their HRQoL are warranted.

Apart from age and residence, former smokers had lower HRQoL scores than non-smokers. Previous studies have also demonstrated a negative relationship between smoking and HRQoL and that smoking cessation significantly improves HRQoL (41).

With regard to the health-related variables, our results suggest that physical and mental health variables including frailty, depression, and falling accidents in the past 12 months can bring about a series of negative effects on HRQoL; other research support these findings. In a study conducted among older adults, frail participants had leaner body mass, lower HRQoL scores, greater depression, and greater vulnerability to falls than the non-frail participants (9). Schoene et al. (42) demonstrated that a history of falling accidents might greatly affect HRQoL in older people. Other studies have reported that depression has a major influence on HRQoL, which can affect general appetite, and the HRQoL scores decrease with decreased general appetite (8, 39, 43). Besides, HRQoL was positively correlated with urinary function, defecation function, and sleeping condition in the present study. Regarding these factors, early assessment, identification, and prevention are important. More advanced risk factor assessment scales, standardized nursing care measures, and nutrition and physical activity interventions may be useful in improving the HRQoL among elderly patients in the future.

Compared with women, the men in our study had a lower risk of poor HRQoL at the 30-day follow-up; in addition, HRQoL was poorer in women than in men, as reported in other studies (44–46). This is perhaps because men generally have better muscle storage than women, and that may affect physical conditions (such as frailty), appetite, and other factors linked to HRQoL (47–49). At the 90-day follow-up, Han ethnicity was associated with lower HRQoL scores than did other ethnicities, which might be owing to differences in the ethnic distribution of our participants. In addition, current drinkers had higher HRQoL scores than non-drinkers; this can be ascribed to the fact that older adults who consume small to moderate amounts of alcohol are more likely to maintain physical functioning than non-drinkers, as moderate alcohol consumption has been associated with a decreased risk of cardiovascular disease (19). However, detailed assessments based on the amount and frequency of alcohol consumption are needed.

This study has some limitations that should be considered when interpreting the results. First, because of convenience sampling, the patients enrolled in our study were selected from tertiary hospitals and from only one hospital in each province or municipality/city, which limited the generalizability of this study. Second, there were a considerable number of potential participants who were unable to be contacted, most of whom were in distant provinces or were migrant workers; this may have led to selection bias. Thirdly, although nutritional status and HRQoL can be assessed using several different assessment scales, our use of a limited number of measurement tools restricted the comparison of our results with those of other studies. Fourth, the participants enrolled in this study were relatively young—nearly half of the participants were 65–69 years old—which limited the generalizability of this study. Fifth, the reason for the admission might be a major factor influencing HRQoL. The target population in this study involved multiple wards or departments; we did not analyze the reason for the admission, nor did we analyze the application of medical and nursing care in older patients. Finally, chronic diseases (such as cancer, diabetes, and cardiovascular diseases) could be associated with poor HRQoL among elderly patients. The participants in this study covered many departments, and we did not analyze the impact of chronic diseases in this paper. Prospective studies with more sophisticated evaluations are required in the future.

CONCLUSION

This study suggests that higher MNA-SF scores were associated with higher HRQoL scores in Chinese elderly patients, whereas there were no significant associations between BMI and HRQoL. Sociodemographic characteristics and physical and mental health variables were the main factors influencing HRQoL in this group. Investing in adequate geriatric care sources, developing a home care-dominated system, supported by community care, and supplemented with institutional care aimed at improving HRQoL are warranted. In light of the factors associated with HRQoL, attention should be paid to risk assessment, preventive measures, nutrition, and physical activity intervention. These findings could have major importance in the planning of "active aging" policies and programs.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Peking Union Medical College Hospital (S-K540). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XWu conceived and designed this study. HL prepared and edited the manuscript and drafted the tables. JJia and TX performed the statistical analyses and reviewed the manuscript. CZ, MZ, XWe, JJin, HW, DL, and SZ recruited participants, collected data, and edited the manuscript. All authors read and approved the final manuscript.

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Nutritional Support and Clinical Outcome of Severe and Critical Patients With COVID-19 Pneumonia

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Background: In 2020, a novel coronavirus has spread throughout the world. More than four hundred thousand people have died of SARS-CoV-2 pneumonia, most of which were severe and critical patients. No effective antiviral treatment has been verified thus far. Nutrition support has become one of the important treatments for severe and critical patients.

Methods: In this retrospective study, 26 severe patients and 22 critical patients with laboratory confirmed COVID-19 were enrolled. We recorded the diet and nutritional treatments in severe and critical patients. Baseline characteristics and clinical outcomes of severe and critical patients were also collected.

Results: Average calorie intake of severe patients (19.3 kcal/kg/d) was higher than critical patients (15.3 kcal/kg/d) ($P = 0.04$). Protein intake was similar in the two groups (0.65 and 0.62 g/kg per day, respectively; $P = 0.29$). There was no significant difference in the median duration of viral shedding between the severe and critical patients ($P = 0.354$).

Conclusions: A permissive underfeeding strategy that restricts non-protein calories but preserves protein intake is feasible for critical patients with SARS-CoV-2 pneumonia. Viral shedding duration of critical patients was the same as severe patients who received standard feeding. Nevertheless, evidence of the conclusion is not sufficient because of small sample size. To show the real clinical benefit of permissive low-calorie and adequate protein intake in critical SARS-CoV-2 pneumonia patients, a large and pragmatic randomized controlled trial is needed.

Keywords: nutrition support, protein, severe and critical patients, 2019-nCoV pneumonia, permissive low calorie intake

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INTRODUCTION

In December, 2019, a series of cases of pneumonia associated with a novel coronavirus, SARS-CoV-2, emerged in China. The novel coronavirus pneumonia was declared as a global pandemic by World Health Organization (WHO) director general, Tak Desai, in March 11, 2020. So far, over 9 million people have been infected, and four hundred thousand people have died of COVID-19 (1). According to diagnosis and treatment of novel coronavirus pneumonia (trial version seventh), SARS-CoV-2 pneumonia can be classified as light, general, severe, and critical types (2). Most patients have mild symptoms and good prognosis while some severe and

critical cases may appear as acute respiratory distress syndrome or septic shock, even death (3). A large number of medical resources were invested in the treatment of severe and critical cases. Compared with that of severe patients, the progress of critical patients was rapid and difficult to control. At present, no effective antiviral drug is available against this pathogen. Life support is the main treatment for severe and critical patients with SARS-CoV-2 pneumonia (4).

Respiratory support and clinical nutritional support are important parts of supportive therapy for severe and critical patients. It is well-known that a nutrition risk score (NRS2002) ≥3 would result in poor prognosis (5). Up to now, studies on SARS-CoV-2 pneumonia have mainly focused on the clinical characteristics and treatment process of patients (6, 7). Previous studies have reported that high risk factors for death in patients with SARS-CoV-2 pneumonia are older age, high SOFA score, and d-dimer >1 μg/L (8). So far, no study has discussed the relationship between nutritional support and clinical outcomes in severe and critical patients infected COVID-19.

In this paper, we described baseline characteristics, nutritional support, and clinical outcomes of severe and critical patients. We hope our study results can provide some valuable suggestions on nutritional support of severe and critical patients with SARS-CoV-2 pneumonia.

METHODS AND MATERIALS

Study Design and Participants

Forty-eight patients were recruited from January 29 to March 6, 2020 at a designated hospital for SARS-CoV-2 pneumonia. All patients were diagnosed as having SARS-CoV-2 pneumonia according to WHO interim guidance. Among the 48 patients included, 26 were categorized as severe type, and 22 were critical type. We calculated the nutritional intake of severe and critical patients and analyzed the relationship between the nutrition supply and clinical outcomes. The assigned time was 7 days from admission into the intensive care unit (ICU) and discharge. If the ICU stay time is <7 days, assigned time is from the first day in ICU until discharge. The primary outcome was the time of COVID-19 viral clearance. This study was approved by the research project ethics committee in our hospital (2020-KY-115).

Data Collection

The data of treatments and outcomes were extracted from electronic medical records using a standard data collection statistical analysis form (modified case record form for severe acute respiratory infection clinical characterization shared by the International Severe Acute Respiratory and Emerging Infection Consortium). We directly contacted doctors or nurses to obtain the missing data. All data were checked by two physicians (YXF and LM), and a third researcher (WY) adjudicated any difference in interpretation between the two primary reviewers.

Definitions

Critical patients met one of the following conditions (2): respiratory failure and need for mechanical ventilation or shock combined with other organ failure and need for ICU monitoring and treatment.

Severe patients meet one of the following conditions (2): respiratory distress or respiratory frequency ≥30 times/min, The oxygen saturation is ≤93%, PaO_2/FiO_2 × [atmospheric pressure (mmHg)/760] should be corrected according to the following formula in the area with PaO_2/FiO_2 ≤300 mmHg (1 mmhg = 0.133 kpa) (altitude over 1,000 m). In addition, if pulmonary imaging shows that the lesions have progressed more than 50% within 24–48 h, the patient can also be classified as severe.

Statistical Analysis

Continuous variables were presented as mean (SD) if they are normally distributed or median (IQR) if they are not. Categorical variables were expressed as number (%). Mann-Whitney *U*-test, independent sample *t*-test, χ^2-test, or Fisher's exact test was used to compare differences between severe and critical patients where appropriate. Boxplots were drawn to describe calorie intake and protein intake. Statistical analyses were done using SPSS software (version 21.0).

Role of the Funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Baseline Characteristics

All of the 48 patients involved in this study were identified as laboratory-confirmed SARS-CoV-2 infection. They were admitted to ICU because of uncorrectable hypoxemia. There was no difference in age ($P = 0.197$), sex ($P = 0.514$), weight ($P = 0.25$), and body mass index (BMI) ($P = 0.379$) between severe and critical patients at the time of admission. All patients had nutrition risk (NRS2002 score ≥3). The NRS2002 scores of critical patients mainly were 5–7 (21[95.5%]), while the severe patients were 3–4 (20 [76.9%]). The NRS2002 scores of critical patients were higher than those of severe patients ($P < 0.0001$) (**Table 1**).

The median time from illness onset to ICU admission was 16.5 days (10.0–20.8), and there was no difference between critical and severe patients ($P = 0.259$) (**Table 1**). Comorbidities were not present in only 10 patients. Hypertension was the most common chronic disease (16[33.3%]), followed by diabetes, coronary heart disease, chronic obstructive pulmonary disease (COPD), cancer and immune system diseases, and chronic renal failure. Twelve patients required invasive mechanical ventilation, and one patient needed hemodialysis before admission to the ICU (**Table 1**).

Life and Nutrition Support

Twenty-three patients (47.9%) received invasive mechanical ventilation, 15 patients (31.3%) received extracorporeal membrane oxygenation (ECMO) support, and 11 patients

TABLE 1 | Baseline characteristics of patients included*.

Variable	Total (48)	Severe ($n = 26$)	Critical ($n = 22$)	*P*-value
Age: years	61.9 ± 15.8	59 ± 15.4	65 ± 15.8	0.16
Sex: number (%)				0.312
Male	29 (60.4)	15 (57.7)	13 (59.1)	
Female	19 (39.6)	11 (42.7)	9 (40.9)	
Weight: kg	68.1 ± 8.1	68.1 ± 9.1	68.2 ± 7.1	0.501
Body mass index†	24.6 ± 2.3	24.7 ± 2.6	24.5 ± 2.0	0.682
NRS2002 score				<0.0001
5–7	27 (56.3)	6 (23.1)	21 (95.5)	
3–4	21 (43.8)	20 (76.9)	1 (4.5)	
Admission to ICU from illness onset: days (IQR)‡	16.5 (10.0–20.8)	18.5 (10.8–23.0)	14.5 (10.0–18.3)	0.259
Invasive mechanical ventilation: number (%)	12 (24)	0	12(54.5)	<0.0001
Hemodialysis: number (%)	1 (4.8)	0	1(4.5)	0.458
Complications: number (%)				
Hypertension	16 (33.3)	10 (38.5)	6 (27.3)	0.413
Diabetes	11 (22.9)	4 (15.4)	7 (31.8)	0.177
Coronary heart disease	8 (16.7)	4 (15.4)	4 (18.2)	1
COPD	3 (6.2)	1 (3.8)	2 (9.1)	0.587
Cancer and immune diseases	4 (8.3)	3 (11.5)	1 (4.5)	0.614
Chronic renal failure	2 (4.2)	1 (3.8)	1 (4.5)	1

Plus–minus values are means ± SD.
† The body–mass index is the weight in kilograms divided by the square of the height in meters.
‡ IQR means interquartile range.

TABLE 2 | The included patients' nutrition and life support for a duration of 7 days*.

Variable	Total ($n = 48$)	Severe ($n = 26$)	Critical ($n = 22$)	*P*-value
Daily calorie intake: kcal/d	1202.2 ± 365.1	1306.6 ± 329.6	1082.1 ± 374.8	0.04
Average calorie intake: kcal/kg/d	17.4 ± 5.6	19.3 ± 5.4	15.3 ± 5.1	0.018
Daily protein intake: g/d	43.2 ± 17.6	39.0 ± 12.7	47.7 ± 21.1	0.106
Average protein intake: g/kg/d	0.64 ± 0.25	0.65 ± 0.21	0.62 ± 0.29	0.076
Invasive mechanical ventilation: number (%)	23 (47.9)	6 (23.1)	17 (77.3)	<0.0001
ECMO: number (%)†	15 (31.3)	4 (15.4)	11 (50)	0.01
Hemodialysis: number(%)	11 (22.9)	1 (3.8)	10 (45.5)	0.001
Gastrointestinal complications: number (%)				
Diarrhea: number (%)‡	13 (27.1)	6 (23.1)	7 (31.8)	0.497
Feeding intolerance: number (%)§	5 (10.4)	0	5 (22.7)	0.015

Plus–minus values are mean ± SD.
† ECMO is extracorporeal membrane oxygenation.
‡ Diarrhea was defined as three or more loose or liquid stools per day for 2 consecutive days.
§ Feeding intolerance was defined as vomiting, abdominal distention, or a gastric residual volume of more than 200 ml.

(22.9%) received hemodialysis until discharged from ICU. The percentage of critical patients who needed life support was markedly higher than critical patients (**Table 2**).

The average calorie intake of severe and critical patients was 19.3 kcal/kg/d (5.4) and 15.3 kcal/kg/d (5.2), respectively. There was a significant difference between the two types of patients ($P =$ 0.018). The average protein intake of severe and critical patients was 0.65 g/kg/d (0.21) and 0.62 g/kg/d (0.29), respectively. A significant difference was not observed between the two types of patients ($P = 0.076$). The calorie intake per day of severe patients was 1306.6 kcal (329.6), which was higher than that of critical patients (1082.1 kcal [374.8], $P = 0.04$). The protein intake per day of severe patients was 39.0 g (12.7), which was lower than that of critical patients (47.7 g [21.1]). A significant difference was also not observed ($P = 0.106$) (**Table 2**). The 7-day calorie and protein intake in severe and critical patients are shown in **Figure 1**.

Compared with that of the severe patients, oral intake for critical patients was more affected: 11 severe patients (42.3%) and 15 critical patients (68.2%) received enteral nutrition support. The incidence of gastric retention was higher in critically patients

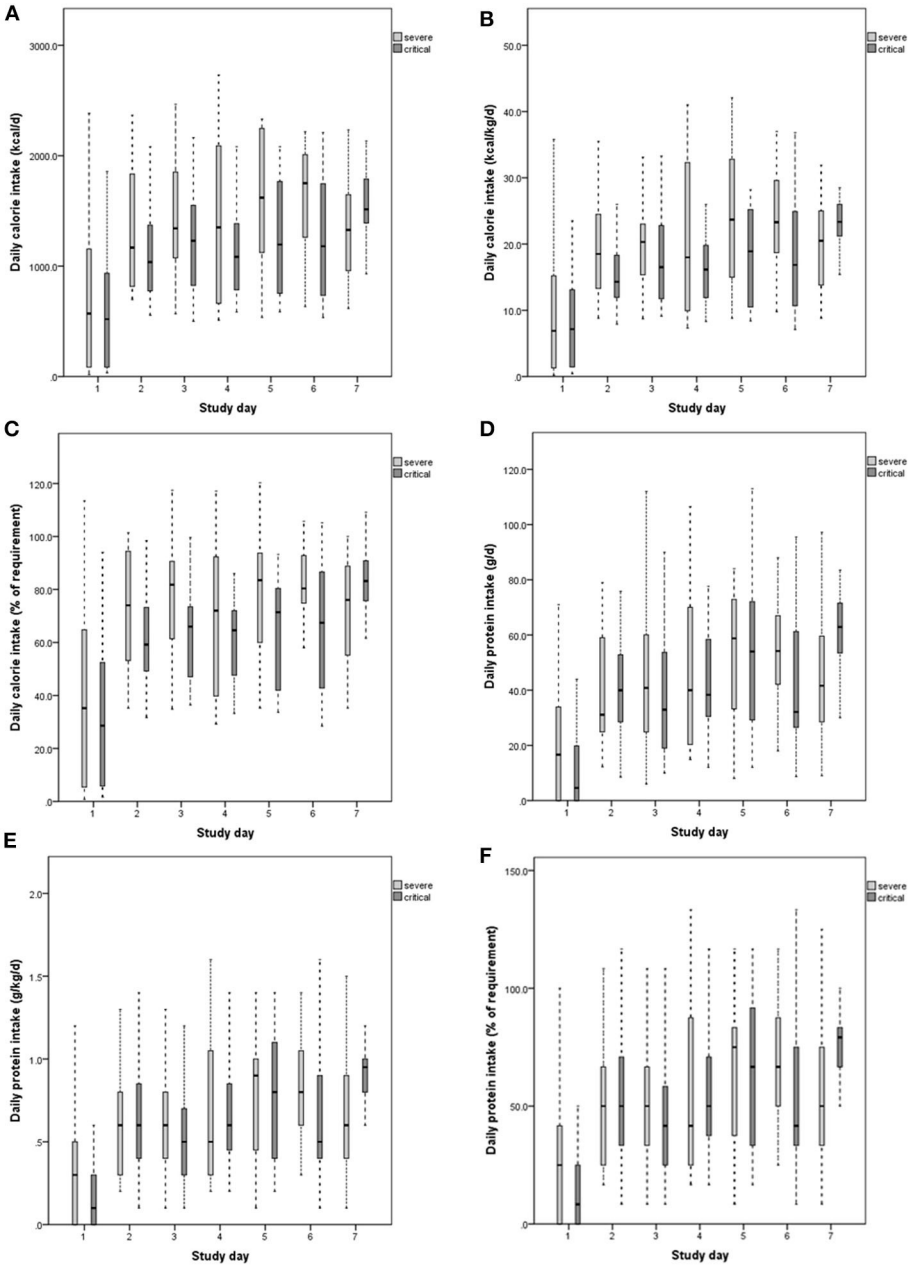

FIGURE 1 | Daily calorie intake **(A–C)**, protein intake **(D–F)** of severe and critical patients 7 days after admission to ICU (from day 0 to day 7). The calorie intake requirement is 25 kcal/kg/d. The protein intake requirement is 1.2 g/kg/d. The top panels show the amount of calories administered daily over 7 days after admission to ICU, expressed in kcal/d **(A)** and kcal/kg/d **(B)**. **(C)** Shows percentages of calorie intake compared with the required level. Protein intake was expressed in g/d **(D)** and d/kg/d **(E)**. **(F)** Shows percentages of protein intake compared with the required level.

($P = 0.015$). There was no difference in the incidence of diarrhea between the two types of patients (**Table 2**).

Clinical Outcomes and Clinical Indicators

The nucleic acid test was negative in 45 patients (93.8%) while 3 critical patients (6.2%) died before the viral clearance until ICU discharge. The nucleic acid test was negative in 20 (90.9%) critical patients and 25 (96.2%) severe patients ($P = 0.587$). The median duration of viral shedding in severe patients was 21.0 days (IQR 16.0–25.0) from illness onset and 24.0 days (IQR 10.0–20.8) in critical patients. The median time of viral clearance of the critical and severe patients had no significant difference ($P = 0.354$) (**Table 3**).

Certain clinical indicators reflect the nutrition status of patients, such as blood phosphorus, uric acid, cholinesterase (**Table 3**). There was no significant difference in blood

TABLE 3 | Clinical outcome and clinical indicators of severe and critical patients*.

Variable	Total ($n = 48$)	Severe ($n = 26$)	Critical ($n = 22$)	*P*-value
Ratio of viral shedding–: number (%)	45 (93.8)	25 (96.2)	20 (90.9)	0.587
Median duration of viral shedding: –days (IQR)†	21.0 (16.0–27.0)	21.0 (16.0–25.0)	24.0 (10.0–20.8)	0.354
Clinical indicators				
Serum phosphorus: –mmol/L	0.90 ± 0.19	0.88 ± 0.20	0.92 ± 0.18	0.51
Uric acid: –μmol/L	188.4 ± 90.6	215.5 ± 103.0	158.4 ± 64.6	0.047
Cholinesterase: –KU/L	4.72 ± 1.91	5.41 ± 1.82	3.92 ± 1.75	0.016
Lactic dehydrogenase: –U/L	438.8 ± 254.4	326.8 ± 108.9	563.2 ± 310.6	0.001
Lymphocyte absolute value: -10^9/L	0.57 ± 0.25	0.64 ± 0.22	0.49 ± 0.26	0.06

*Plus–minus values are means ± SD.
†IQR means interquartile range.

phosphorus ($P = 0.51$) between the severe (0.88 [0.20]) and critical patients (0.92 [0.18]). The uric acid (215.5 [103.0]) in severe patients was higher ($P = 0.047$) than that of critical patients (158.4 [64.6]). Cholinesterase (5.41 [1.82]) in severe patients was significantly higher ($P = 0.016$) than that of critical patients (3.92 [1.75]). Laboratory markers were recorded from entering the ICU. Compared with that of the severe group (326.8 [108.9]), lactate dehydrogenase (LDH) in the critical group (563.2 [310.6]) was significantly higher ($P = 0.001$). There was no significant difference in the absolute value of lymphocytes between the severe patients and the critical patients ($P = 0.06$) (**Table 3**).

DISCUSSION

The risk factors of poor prognosis and high mortality in patients with SARS-CoV-2 pneumonia infection are old age and multiple basic diseases (8). Therefore, we used the NRS2002 (inpatient) screening tool to measure nutrition risk. Both severe and critical patients with SARS-CoV-2 pneumonia had nutrition risk (NRS2002 score ≥3). Moreover, recent studies have shown that patients with high FM have poor prognosis (9). It should be noted that BMI leaves a portion of the obese population unrecognized when using the NRS2002 (inpatient) screening tool. Acute respiratory distress syndrome (ARDS) was one of the common serious complications of COVID-19 infected critical patients, which required invasive mechanical ventilation. However, invasive mechanical ventilation will consume a lot of calories and further increase the incidence of malnutrition. Special life supports, such as continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO), may also result in nutrition loss (10, 11). SARS-CoV-2 pneumonia patients often suffered from fever. The increase in body temperature could lead to increased calorie consumption. The albumin level of patients with severe infection was significantly lower than patients without severe infection. Hypoalbuminemia also could lead to edema of the intestinal mucosa, resulting in decreased intake capacity of nutrients. In the early stage of stress, a large number of visceral proteins and skeletal muscles were decomposed to compensate for the lack of calories in the body. The loss of skeletal muscle volume and function would increase the risk of death (12). Malnutrition in ICU patients is correlated with the incidence of infection complications and mortality rate (13).

Therefore, nutritional support has become one of the important treatments for ICU patients. Nutritional support could reduce the loss of endogenous protein caused by stress (14). The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for nutrition diagnosis and treatment of critically ill patients suggest that early nutritional intervention should be initiated within 24 h after admission to the ICU for patients with nutrition risk (15). The calorie supply target (25–30 kcal/kg/d) and protein supply target (1.2–2.0 g/kg/d) should be achieved within 3–7 days if hemodynamics are stable (15).

However, it was difficult to achieve the target supply for severe and critical patients with COVID-19. The reasons were as follows. Because of their high-stress state, the critical SARS-CoV-2 pneumonia patients were more likely to suffer from intolerance of enteral nutrition (EN), with conditions such as diarrhea, abdominal distention, constipation, and gastric retention (16). Although reducing the speed of infusion EN can alleviate gastrointestinal intolerance symptoms (20 ∼30 mL/h), but the daily supply of EN was decreased. Second, in the early stages of the disease outbreak, conditions in the isolation ward did not allow the implementation of jejunal tube placement and jejunal stoma. Therefore, it was impossible for the patients with gastric retention to implement jejunal feeding. Supplementary parenteral nutrition (SPN) shall be administrated when the nutrition supply cannot be met by EN (<60% of caloric requirements) for more than seven days (17). However, the brain natriuretic peptides (BNP) of critical SARS-CoV-2 pneumonia patients were generally increased, which led to a higher incidence of heart failure. The total amount of daily liquid intake was limited to reduced cardiac load. Therapeutic drugs took up too much liquid, which restricted the amount of parenteral nutrition. Adoption of ECMO limited the use of fat emulsion, making it more difficult to achieve the sufficient calorie supply through SPN. In addition, due to their stress, infection, hypoxia, and use of glucocorticoids, most severe patients with SARS-CoV-2 pneumonia had different degrees of hyperglycemia. Hyperglycemia could increase the incidence of infection-related complications and finally increased mortality (18). Therefore, enteral nutrition preparations for diabetes of low calorie and protein nutrient density (0.9 kcal ml-1 and 0.038 g

kcal-1, respectively) were first used by clinicians, which could not meet the feeding target (25 kcal/kg/d) for patients with SARS-CoV-2 pneumonia.

As nutritional pharmacists, we attempted many methods to solve the aforementioned difficulties during nutritional support. First, a tumor-specific enteral nutritional preparation was applied instead of diabetes preparation, which provided far more calories (1.3 kcal ml^{-1}) and protein (0.045 g $kcal^{-1}$). It also had a light impact on blood glucose due to its high dietary fiber and fat content, and low carbohydrate content. Secondly, SPN was started immediately if EN supply was <60% of the caloric target. Meanwhile, the amino acid proportion (≥20% total calories) was higher than normal PN formulation, especially for patients who had received ECMO and CRRT. This was the reason why protein intake was higher in critical patients than severe patients (although no significant difference was observed). Third, we reformed the treatment liquid. Amino acid was infused alone, electrolyte and vitamin were added into 5%glucose. If electrolytes are added to amino acid, the patient's infusion volume will be reduced. To our experience, liquid reforming was very important to critical patients with SARS-CoV-2 pneumonia; it could reduce unnecessary liquid intake and increase liquid for nutritional supply. As a result, the calorie intake of severe and critical patients with SARS-CoV-2 pneumonia reached more than 60% of the recommended amounts for all 7 days except for the first day. The average calorie intake of severe and critical patients was 77.2 and 61.2% of the feeding targets, respectively.

As shown in **Table 3**, no difference existed in the viral shedding duration and the absolute value of lymph between critical and severe patients. This result was similar to previously reported (8). This may be attributed to a similar protein intake. In 2015, Arabi et al. examined the effect of "permissive low calorie" (40–60% of target calories) and "standard calorie" (70–100% of target calories) on the prognosis of ICU patients with the same amount of protein. The results of this multicenter prospective randomized clinical trial (RCT) studies showed that there was no difference in short- or longterm mortality, sequential organ failure score (SOFA), length of stay, mechanical ventilation time between the two groups (19). Meanwhile, a number of RCT studies showed that the mortality was negatively correlated with protein supply (20). At present, there is no effective treatment for SARS-CoV-2 pneumonia patients. Elimination of the virus mainly depended on the autoimmune system of patients. A recent study reported SARS-CoV-2 pneumonia patients with high lymphocyte levels, excluding B cells, and with low Interleukin-6 (IL-6) or Interleukin-10 (IL-10) levels, had a better survival rate (21). Early nutritional intervention could enhance the therapeutic effect of severe pneumonia patients with ARDS and reduce systemic inflammatory response (22, 23). Its mechanism may be directly related to optimizing nutrition status and improving cellular immune function (24). Protein is the material basis of immune function. When protein intake is insufficient, the structure and function of immune organs could be impaired (25). Permissive low-calorie feeding could reduce the occurrence of metabolic complications. At the same time, sufficient protein intake could promote protein synthesis to make up for the loss of immunoprotein and accelerate the elimination of the virus by the immune system.

CONCLUSION

To the best of our knowledge, this is the first retrospective study to report clinical nutrition and life support among severe and critical patients with SARS-CoV-2 pneumonia. This study involved 26 severe patients and 22 critical patients. This paper discusses the status of nutrition support in severe and critical patients with SARS-CoV-2 pneumonia. The differences in calorie intake, protein intake, negative viral infection status, and clinical indexes between severe and critical patients were compared. On the premise of ensuring the metabolic stability of critical patients, adequate nutritional support should be provided to critical patients. Sufficient protein is beneficial for maintaining the amount of lymphocytes, thus promoting virus clearance. Therefore, if adequate calorie intake cannot be achieved, permissive low calorie intake with adequate protein intake is appropriate for critical patients with SARS-CoV-2 pneumonia.

This study has some limitations. The sample size was small, and patients came from one hospital. That there is a real clinical benefit of permissive low-calorie intake and sufficient protein supply in severe SARS-CoV-2 pneumonia patients needs to be further verified by large and pragmatic randomized controlled trials.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the research project ethics committee of The First Affiliated Hospital of Zhengzhou University (2020-KY-115). The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

XY, ML, and SD equally contributed to the conception and design of the research. YW and JZ contributed to the design of the research. LK and XW contributed to the acquisition and analysis of the data. XW contributed to the analysis of the data. XZ contributed to the acquisition, analysis, and interpretation of the data. All authors drafted the manuscript and approved the final manuscript.

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Analysis of Human Faecal Host Proteins: Responsiveness to 10-Week Dietary Intervention Modifying Dietary Protein Intake in Elderly Males

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Faecal proteomics targeting biomarkers of immunity and inflammation have demonstrated clinical application for the identification of changes in gastrointestinal function. However, there are limited comprehensive analyses of the host faecal proteome and how it may be influenced by dietary factors. To examine this, the *Homo sapiens* post-diet proteome of older males was analysed at the completion of a 10-week dietary intervention, either meeting the minimum dietary protein recommendations (RDA; $n = 9$) or twice the recommended dietary allowance (2RDA, $n = 10$). The host faecal proteome differed markedly between individuals, with only a small subset of proteins present in $\geq$ 60% of subjects (14 and 44 proteins, RDA and 2RDA, respectively, with only 7 common to both groups). No differences were observed between the diet groups on the profiles of host faecal proteins. Faecal proteins were detected from a wide range of protein classes, with high inter-individual variation and absence of obvious impact in response to diets with markedly different protein intake. This suggests that well-matched whole food diets with two-fold variation in protein intake maintained for 10 weeks have minimal impact on human faecal host proteins.

Keywords: faeces, dietary protein, host proteins, gastrointestinal health, proteomics

INTRODUCTION

The gastrointestinal tract (GIT) coordinates the complex tasks of digestion and nutrient absorption (1, 2). Beyond these functions, it is increasingly understood that the GIT interacts symbiotically with the resident microbiome population (3). Given the inherent complexity of both nutrient digestion and sustaining the symbiotic gut microbiome, the GIT requires

the coordinated functioning of a large network of immune, secretory and neural cells and systems that exhibit specialisation and coordinated functionality along its length (4). This entire GIT system achieves the coordination required to digest and/or eliminate a staggering diversity of ingested compounds, including potentially pathogenic microorganisms. For the majority of individuals this occurs in the absence of discomfort or illness, yet estimates suggest that up to 35% of people over 65 years old suffer from a chronic gastrointestinal disease in the USA and 25% of women in the Zurich Cohort study (5). This includes a diverse array of functional gastrointestinal disorders (FGIDs), including functional dyspepsia (FD) and irritable bowel syndrome (IBS), that are characterised on the basis of differing combinations of chronic or acute gastrointestinal symptoms. Functional gastrointestinal disorders are defined by their lack of explanatory GIT structural or biochemical abnormalities that account for this symptomology. Therefore, there is an ongoing requirement to gain insight into GIT function in healthy individuals and the mechanisms which may underpin FGID development.

To date, high throughput methods to comprehensively profile the genes and proteins from the microbiota have been applied to the analysis of the biological functioning of the human GIT. These techniques have been used to comprehensively describe the taxonomy and functional attributes of the microbiome population (6, 7). Fewer studies have addressed the inherent expression and abundance of self-derived genetic material or proteins. This is important, as host-derived inflammatory and heightened immune response are a hallmark feature of GIT diseases and in situations of intestinal dysbiosis. This is evident in the analysis of biomarkers, including calprotectin and lactoferrin (8) in faecal matter. Experimental studies have identified a widening list of possible protein candidate for disease associations, including calprotectin, pyruvate kinase, myeloperoxidase and matrix metalloproteinase protein family members (8–10). Yet whilst these markers have potential as disease biomarkers (8), these discrete proteins provide little insight into the complexity of the disturbances in the GIT, providing very limited understanding into the altered functioning of the complex cellular systems underpin the disease aetiology and pathobiology.

Current proteomic techniques are capable of measuring thousands of proteins. However, significant challenges remain for proteomic application in human faecal samples. The faecal proteome is inherently complex because it contains various groupings of proteins that are, respectively, derived from either the host, the microbiome and proteome remnants from the ingested food (9, 11, 12). Further, data dependent analysis of peptides in mass spectrometry is frequently limited to the most abundant peptides. Dynamic exclusion is then used to prevent the same peptide being analysed twice over the chromatographic peak (13, 14). A more complete proteome can be obtained using fractionation prior to LC, which reduces the complexity of each LC separation and allows for more peptides to be fragmented and thus identified when comparing to analysing the whole sample in one run (15). These fractions can be combined prior to searching to identify all compounds at once. This strategy is applied in many proteomic analysis (e.g., shotgun proteomics which separated peptides by their ionic strength followed by their hydrophobicity prior to MS/MS analysis) (16). Different extraction, preparation and fractionation procedures for faecal proteomics have been used which are more beneficial to different parts of the proteome. For the current study SDS extraction was used to improve protein extractability from the samples (17).

Of particular interest in the regulation of the GIT host proteome is the impact of dietary protein. High protein diets are the subject of considerable interest, given the proposed benefits for appetite regulation, cardiovascular health, glucose homeostasis, body condition and weight loss (18). Studies on elderly people suggest a potential requirement for a greater daily protein or amino acid intake to aid in sustaining skeletal muscle mass and function (19, 20). Yet, protein digestion is likely to have significant impact on the GIT. Experimental rodent studies demonstrate that alteration in protein diet affected small intestinal jejunal and goblet cell function, with altered protein expression and mucus secretions (21–24). Similarly, clinical analysis of the impact of isocaloric substitution of maltodextrin for protein (casein or soy protein) identifies marked changes in the mucosal gene transcriptome obtained from rectal biopsies (25). The current study used an untargeted discovery proteomics which allows for all proteins in humans to be identified instead of a sub-set of proteins in animals which were done in previous studies. This process was used to identify the faecal host proteome classes in a cohort of older males who were fed on either the RDA diet (0.8 g/kg/day), which included the recommended dietary allowance for 10 weeks or 2RDA, containing double the recommended dietary allowance (1.6 g/kg/day), as previously described (26). We understood that the faecal host proteome would include proteins secreted into the gastrointestinal tract, including enzymes, mucus proteins, secretory, immune proteins and shredded cells (4). We further hypothesised the diet can affect the presence of human (self) proteins after the 10-week diet. Although food and microbiota protein fragments were observed the discussion on these is part of other work.

EXPERIMENTAL

Diet and Sample Collection

Nineteen healthy older men aged 70 years and above with BMI (kg/m^2) between 18 and 35 were recruited from the local community to participate in the study. The RDA group had an average age of 75.2 $\pm$ 4.5 s.d. years and an average BMI of 27.3 $\pm$ 4.7 s.d. kg/m^2. The 2RDA group had an average age of 73.8 $\pm$ 3.5 s.d. years and an average BMI of 28.3 $\pm$ 3.3 s.d. kg/m^2. All were non-smokers and not consuming dietary supplements for at least 1 month prior to participating in this trial. Potential participants were excluded if they adhered to restricted diet practises, including vegetarians or those with self-reported food allergies or intolerances (e.g., nuts, fish, dairy). Further exclusion was applied to those with a prior history of digestive or cardio-metabolic disease.

Experimental Design

The design of this trial has been previously described (26). Participants were randomised into two groups, where 9 participants received a controlled diet of 0.8 g protein/kg/d (RDA) and 10 participants received a controlled diet of 1.6 g protein/kg/d (2RDA) for 10 weeks. Protein equal to twice the recommended dietary allowance was chosen because evidence showed that protein at this level is absorbed well before the large intestine (26). All meals consumed by the participants were provided by the investigators. The percentage of energy derived from fat was 28–31%, from proteins it was 11.7% for RDA and 20.6% for 2RDA. The remaining energy was made up from carbohydrates. All diets adhered to Eating and Activity Guidelines for New Zealand and met recommendations for intake of fruit and vegetables (27). All participants completed dietary records to ensure all food provided was consumed, and food selection was adjusted according to participants' preferences to maintain high compliance. Any non-study food consumed was also recorded. The energy content of the intervention diet was individually calculated to match participants' estimated energy needs based on the Harris-Benedict equation and adjusted for physical activity, which was assessed by wrist-worn accelerometers (Fitbit Charge HR). The estimated energy needs were calculated before the intervention and adjusted fortnightly based on participant satiety and weight maintenance to ensure participants consumed adequate protein relative to energy intake. During the intervention participants were instructed to maintain their normal lifestyle, and prepared meals were delivered to their homes. All testing was conducted at the University of Auckland Nutrition and Mobility Clinic.

Sample Collection and Storage

Faecal samples were collected during the 10th week of the study, post-intervention. Briefly, participants were provided with a sample collection kit and instructions for collection at home. Once collected, samples were couriered to the Liggins Institute (Auckland, New Zealand) on ice within 3 h and stored immediately at −80°C. For proteomic analysis, 1–2 g was aliquoted from the frozen sample and shipped on ice for proteomic analysis. The faeces were separated into particulate matter and supernatant based on previously published protocols (17, 28). Guanidine hydrochloride was added to denature proteins and limit the activity of bacterial proteins.

Preparation for Proteomics

A schematic showing the preparation and analysis of samples for proteomics is shown in **Figure 1**. The pellet and supernatant (see section Sample Collection and Storage) were combined 1:1. Methanol—chloroform was used to extract proteins and remove guanidine hydrochloride as described previously (29). The precipitated protein was resuspended in two extraction buffers—lysis buffer and urea-tris buffer. For the lysis buffer, the precipitate was resuspended in buffer containing (4% w/v sodium deoxycholate, 50 mM tris(hydroxymethyl)aminomethane, pH 8.0 using hydrochloric acid). This homogenate was heated to 95°C for 10 min, followed by homogenising in a ground glass tube for 1 min with an electric hand drill (Firebreak 50 Hz P/N 0–2,809 RPM). For the urea buffer, the precipitated peptides were resuspended in urea- tris buffer [8 M urea, 100 mM NaCl and 25 mM tris(hydroxymethyl)aminomethane]. The mixture was pipetted up and down and then vortexed at room temperature overnight. All extracts from both methods were then centrifuged at 14 100 × *g* for 10 min, followed by the collection of the clear supernatants. Methanol—chloroform extraction was done on urea- tris buffer extraction samples to remove urea and isolate the proteins as described in Gathercole et al. (30).

For each sample, the supernatants from both extracts was combined and then dried down using a speed vacuum concentrator. The proteins were resuspended in 50 mM ammonium bicarbonate, pH 8. The proteins were reduced by addition of 1 mmol of tris(2-carboxyethyl)phosphine heated at 56°C for 45 min followed by alkylation with 3 mmol of iodoacetamide, incubated at room temperature in the dark. The proteins were digested overnight at 37°C after the addition of trypsin (∼1 μg of trypsin to 133 μg of protein) and final concentration of 10% v/v acetonitrile. To cease the digestion and precipitate sodium deoxycholate, formic acid was added to a concentration of 1% v/v. After centrifugation, the clear supernatant was split in two, dried and purified using Empore C18 disks in both acidic and basic conditions. For acidic conditions, the peptides were resuspended in 0.1% v/v formic acid (pH 4.5). For basic (pH 10) conditions, the peptides were resuspended in 10 mM ammonium formate (pH 10). Three conditioned Empore discs were incubated in these solutions for 3 h. The Empore discs were eluted with vortexing with 75% v/v acetonitrile for 1 h. After removal of the discs, the peptide solutions were dried in a speed vacuum concentrator. The dried peptides were resuspended in 100 μl of 0.1% v/v formic acid. The two C18 elutions were combined 1:1 for each sample prior to LC-MS/MS analysis.

LC-MS-MS Analysis

The combined C18 elutions for each sample were run in random order with two different separation methods and the mgf (spectra) files were combined prior to protein searching. Samples were injected (5 μl) onto a ProntoSIL C18AQ Nano trap column (5 μm, 200Å) at a flow rate of 5 μl/min. The trap column was then switched in-line with the ProntoSIL C18AQ (100 μm ID × 150 mm, 3 μm, 200 Å) analytical column on a NanoAdvance LC (Bruker Daltonics) in nanoflow mode. After separation the analytes were injected in to the CaptiveSpray followed by an ion trap mass spectrometer (Amazon, Bruker Daltonics). A Nanobooster (Bruker Daltonics) was attached to insert acetonitrile into the captive spray to improve sensitivity. Separation method one was run at 50°C and involved starting with 98% solvent A (0.1% formic acid in water), increasing to 5% B (0.1% formic acid in acetonitrile) at 5 min followed by increasing to 25% B at 65 min then 35% B at 75 min. The column was then cleaned by increasing to 95% B at 80 min, holding for 5 min and then re-equilibrating at 2% B until the end of the 90 min run. The flow rate was set to 800 nL/min. Separation method two was run with a column temperature of 60°C and involved starting with 98% solvent A (0.1% formic acid in water), and 2% solvent B (0.1% formic acid in acetonitrile), increasing

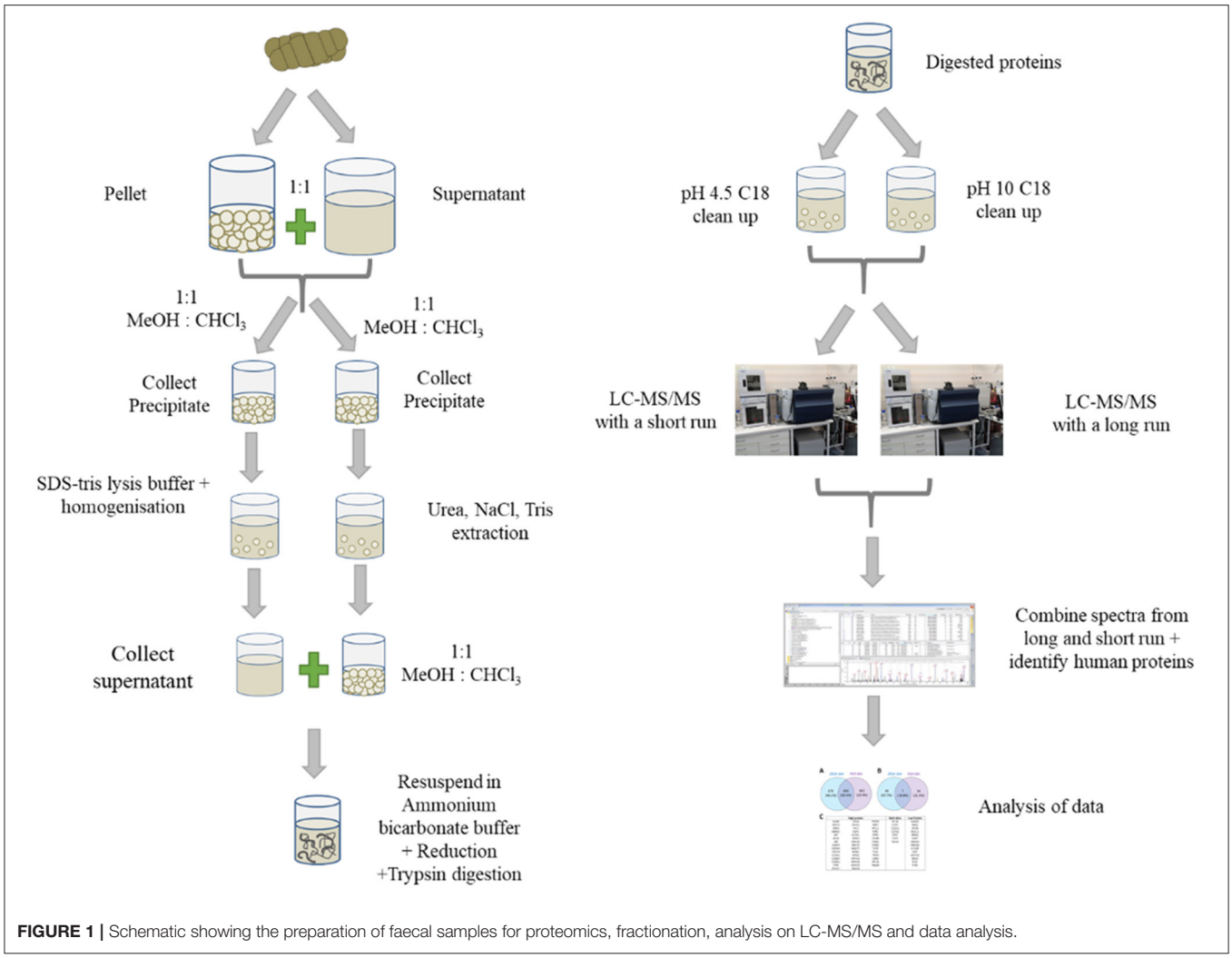

FIGURE 1 | Schematic showing the preparation of faecal samples for proteomics, fractionation, analysis on LC-MS/MS and data analysis.

to 45% B at 60 min. The column was then cleaned by increasing to 95% B at 62 min, holding for 3 min and then re-equilibrating at 2% B until the end of the 70 min run. The flow rate was set to 400 nl/min. For both separation methods, the MS mode was run with CID positive mode looking for compounds between 350 and 1,200 m/z. MS/MS was done on 10 precursors at a time. Compounds analysed by MS/MS were excluded after 1 spectra for 0.20 min unless the intensity increased by at least 5-fold.

The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium via the PRIDE (31) partner repository with the dataset identifier PXD021424.

Protein Identification

The MS data was exported to ProteinScape (Version 3.1.0 348; Bruker Daltonics). The file for both separation methods was combined into one for each sample. Protein searches were conducted using Mascot Server v 2.5.1 (Matrix Science, UK). Spectra were searched against the Swissprot *Homo sapiens* database. Semitrypsin was selected as the enzyme specificity allowing up to two missed cleavages. The MS error tolerance was set to 0.3 Da and the MS/MS error tolerance was set to 0.8 Da. Peptide and protein Mascot threshold scores were set to 20 and 80, respectively. Instrument specificity was set to ESI-TRAP. The modifications included were carbamidomethyl (C) as fixed and oxidation (M), ammonia loss (N-term-C), sodium (DE) and deamidation (NQ) as variable modifications. Protein identifications required at least one unique peptide identification from the list of identified peptides for that protein.

Protein Group Identification

To identify protein classes and function, protein identifications were converted from the UNIPROT accessions to gene names using the UNIPROT identification conversion API available at (https://www.uniprot.org/help/api_idmapping). The resulting UNIPROT identifications were then used to query the Human Gene Nomenclature Committee (HUGO) database for additional annotations, including the PANTHER gene annotations (http://www.pantherdb.org version 14.0). PANTHER terms were associated with the related accessions using the R-package PANTHER.db.

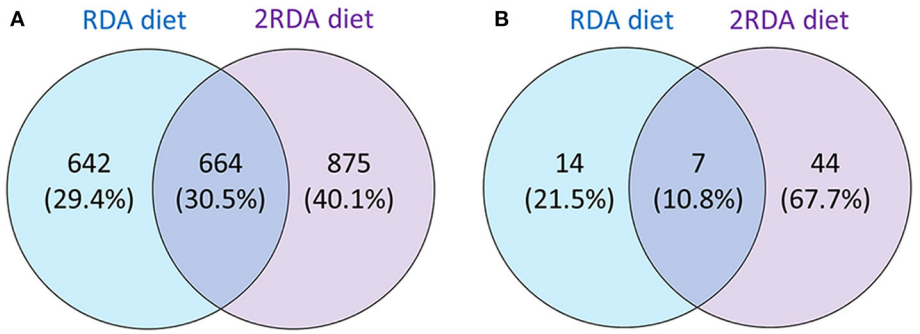

FIGURE 2 | Showing the number of all identified proteins unique to each diet or common to each diet **(A)**; and proteins present in at least 60% of one diet group (n = 6 for both diet groups) observed in either one or both diet groups **(B)**.

RESULTS AND DISCUSSION

The human or host proteome isolated from faecal samples may be an insightful strategy to profile the adaptive regulation of the complex physiological processes associated with nutrient digestion and gut microbiome homeostasis. We hypothesised that the faecal host proteome would include proteins secreted into the gastrointestinal tract, including enzymes, mucus proteins, secretory immune proteins and potentially proteins from epithelial cells dislodged along the GIT (4). We further hypothesised that significantly different diets would change the faecal self-proteome. In the current study LC-MS analysis was undertaken on stool samples isolated after healthy elderly male volunteers had consumed one of two diets differing in total protein content (26). The RDA diet satisfied the minimum WHO dietary protein guidelines and the 2RDA diet provided double this protein amount, with compensatory changes in carbohydrate intake, to maintain energy-balance.

Although in this manuscript we looked into the self-proteome, the samples also included proteins from the microbiome and fragments of dietary proteins. As mass spectrometry cannot select only the human peptides in the LC-MS/MS run, fractionation was performed on the samples prior to LC separation to increase peptide and thus protein identification. Fractionation allows for more peptides to be fragmented when using data-dependent analysis with MS. To limit the peptide identifications to humans, spectra were compared to human peptides in the Swissprot database and a unique peptide was required for each protein identification. Although proteins from food and the microbiota would be present, the searches were restricted to the human proteome database in accordance with the aim of this work. A list of the proteins identified for each sample can be found in the **Supplementary Material**.

While investigating differences between the two diets, the proteins identified in each group were examined for differences using a Venn diagram (see **Figure 2**). The first Venn diagram (**Figure 2A**) showed the complete list of proteins identified in the 19 samples. Unique proteins were found in the RDA and the 2RDA diets but 30.5% of the proteins (664) were found in both diets. A higher number of host human proteins were identified from the 2RDA diet samples. An average of 233 ± 11 s.d. proteins and 575 ± 28 s.d. peptides were identified in the RDA protein diet samples and 266 ± 14 proteins and 637 ± 38 peptides were identified in each of the 2RDA diet samples. There was no significant difference in the number of identifications between the two diets ($p = 0.07$ for proteins and $p = 0.21$ for peptides). There were, however, large differences observed between individuals. Overall fragments from 2181 different host-proteins were identified in the 19 samples and 76% of these proteins were identified in only two or fewer samples. Thus, there was very limited overlap between individuals for the majority of identified proteins. The protein identified most consistently across all samples was chymotrypsin-like elastase family member 3A (Uniprot ID CEL3A). CEL3A was present in all of the 2RDA diet samples and absent in just 1 sample from the RDA protein group. CEL3A, also known as Elastase 3A, is a serine protease that is secreted by the pancreas (32).

To observe differences in proteins that are more consistently specific to each diet, the second Venn diagram (**Figure 2B**) showed the proteins found in at least 60% of the samples with the same diet (proteins listed in **Table 1**). In the RDA diet, 14 proteins were unique to the proteins found in ≥ 60% of the samples and 44 proteins were found only in the 2RDA diet. Only 7 proteins were found in 60% of the samples for both diets). None of the proteins were observed in all of the 19 samples. To see if any of these common proteins were unique to either diet, we checked the proteins against the full list for the other diet. All of the 51 proteins in the 2RDA diet were found in at least one sample in the RDA diet.

A diverse number of self-proteins were identified pertaining to a wide array of functions. Many of the proteins had more than one protein function class. In both diets, ∼40% of all the identified protein classes were part of a protein class made up of <1% of the total protein. Approximately 20% of the proteins had no class identification according to Panther (see **Figure 3**). In both diets, the top four classes all had < 10% of the total proteins and in descending order were nucleic acid binding, enzyme modulators, cytoskeletal proteins and transcription factors which suggest the presence of shed cells and/or signs of proliferation (nucleic acid binding, cytoskeletal proteins and transcription factors) in faeces. Overall there were limited differences observed in the protein classes between each diet.

TABLE 1 | Frequency of host proteins found in at least 60% ($n = 6$) of at least one of the diet groups and corresponds to the Venn diagram in **Figure 2B**.

Accession	Protein name	RDA	2RDA
Found in ≥ 60% of RDA and 2RDA samples			
CEL3A	Chymotrypsin-like elastase family member 3A	8	10
CO7A1	Collagen alpha-1(VII) chain	6	9
CLIP1	CAP-Gly domain-containing linker protein 1	7	8
FAT3	Protocadherin Fat 3	6	7
TACC2	Transforming acidic coiled-coil-containing protein 2	6	7
CO2A1	Collagen alpha-1(II) chain	6	6
DYST	Dystonin	6	6
Found in ≥ 60% of RDA and ≤ 60% of 2RDA samples			
BD1L1	Biorientation of chromosomes in cell division protein 1-like 1	7	5
BIRC6	Baculoviral IAP repeat-containing protein 6	7	5
KMT2D	Histone-lysine N-methyltransferase 2D	7	5
K1109	Uncharacterized protein KIAA1109	7	4
APOB	Apolipoprotein B-100	6	5
HMCN1	Hemicentin-1	6	5
TLN2	Talin-2	6	5
ANK2	Ankyrin-2	6	4
HMCN2	Hemicentin-2	6	4
NAV2	Neuron navigator 2	6	4
KI67	Antigen KI-67	6	3
PLEC	Plectin	6	3
CHD7	Chromodomain-helicase-DNA-binding protein 7	6	2
Found in ≥ 60% of 2RDA and ≤ 60% of RDA samples			
FSIP2	Fibrous sheath-interacting protein 2	5	9
AHNK	Neuroblast differentiation-associated protein AHNAK	4	9
VP13C	Vacuolar protein sorting-associated protein 13C	3	9
CTRC	Chymotrypsin-C	2	9
RYR1	Ryanodine receptor 1	2	9
BCL9	B-cell CLL/lymphoma 9 protein	4	8
MACF1	Microtubule-actin cross-linking factor 1, isoforms 1/2/3/5	3	8
DYHC1	Cytoplasmic dynein 1 heavy chain 1	1	8
HERC2	E3 ubiquitin-protein ligase HERC2	5	7
KMT2A	Histone-lysine N-methyltransferase 2A	5	7
MDN1	Midasin	5	7
RYR3	Ryanodine receptor 3	4	7
SYNE2	Nesprin-2	4	7
TLN1	Talin-1	4	7
UBR4	E3 ubiquitin-protein ligase UBR4	4	7
ZN469	Zinc finger protein 469	4	7
CNTLN	Centlein	3	7
OBSCN	Obscurin	3	7
STAR9	StAR-related lipid transfer protein 9	3	7
DYH8	Dynein heavy chain 8, axonemal	2	7
SYNE1	Nesprin-1	2	7
ANK3	Ankyrin-3	5	6
CO3A1	Collagen alpha-1(III) chain	5	6
APC	Adenomatous polyposis coli protein	4	6
CBP	CREB-binding protein	4	6
COOA1	Collagen alpha-1(XXIV) chain	4	6
MYH13	Myosin-13	4	6
RBP2	E3 SUMO-protein ligase RanBP2	4	6
RP1L1	Retinitis pigmentosa 1-like 1 protein	4	6
ANKH1	Ankyrin repeat and KH domain-containing protein 1	3	6
CMYA5	Cardiomyopathy-associated protein 5	3	6
CO6A5	Collagen alpha-5(VI) chain	3	6
GCN1L	Translational activator GCN1	3	6
KMT2C	Histone-lysine N-methyltransferase 2C	3	6
MPDZ	Multiple PDZ domain protein	3	6
PDZD2	PDZ domain-containing protein 2	3	6
TCOF	Treacle protein	3	6
AKP13	A-kinase anchor protein 13	2	6
CKAP5	Cytoskeleton-associated protein 5	2	6
FAT1	Protocadherin Fat 1	2	6
MYH14	Myosin-14	2	6
MYO15	Unconventional myosin-XV	2	6
TRIPB	Thyroid receptor-interacting protein 11	2	6
DYH17	Dynein heavy chain 17, axonemal	1	6

The identified self-proteins included those that would be expected to be present in the faeces, including; enzymes (e.g., chymotrypsin), zinc fingers, collagen, myosin proteins, and mucin proteins. In this study, four mucins were identified: MUC4, associated with membranes, in one sample for the RDA diet group; MUC16 (also known as CA125) was found in samples from the RDA diet; MUC5A, a secreted mucin, found in one sample from the 2RDA diet group and MUC19, a secreted protein, which was found in three RDA samples and four 2RDA samples (33, 34). MUC19 helps to maintain the permeability of the intestinal epithelial layer and regulation of immune responses. The presence of this protein may suggest the presence of inflammation or other intestinal disease as the protein has not been previously reported in healthy human intestines (35). All of the participants in this study were healthy but further work could be used to determine if it is a marker for asymptomatic inflammation.

One protein, K167 (Antigen KI-67), was unique to the samples from the RDA diet. K167 is used as a sign of proliferation in research studies including cancer prognosis. It has been found to act as a surfactant that helps to keep mitotic chromosomes apart after release into the cytoplasm (36) which suggests that it may have been a sign of cell proliferation occurring in the RDA diet. Evidence is shown on the Protein Atlas website that this protein is expressed in the gastrointestinal tract including the glandular cells of the colon in a number of individuals of different ages and gender (37, 38).

Protein classes were determined using Panther (39) for all of the identified proteins from each diet. From the proteins found in at least 60% of one of the diets (listed in **Figure 2C**), 39 of the proteins were classified according to their functions in Panther. The most common function identified were cytoskeletal proteins.

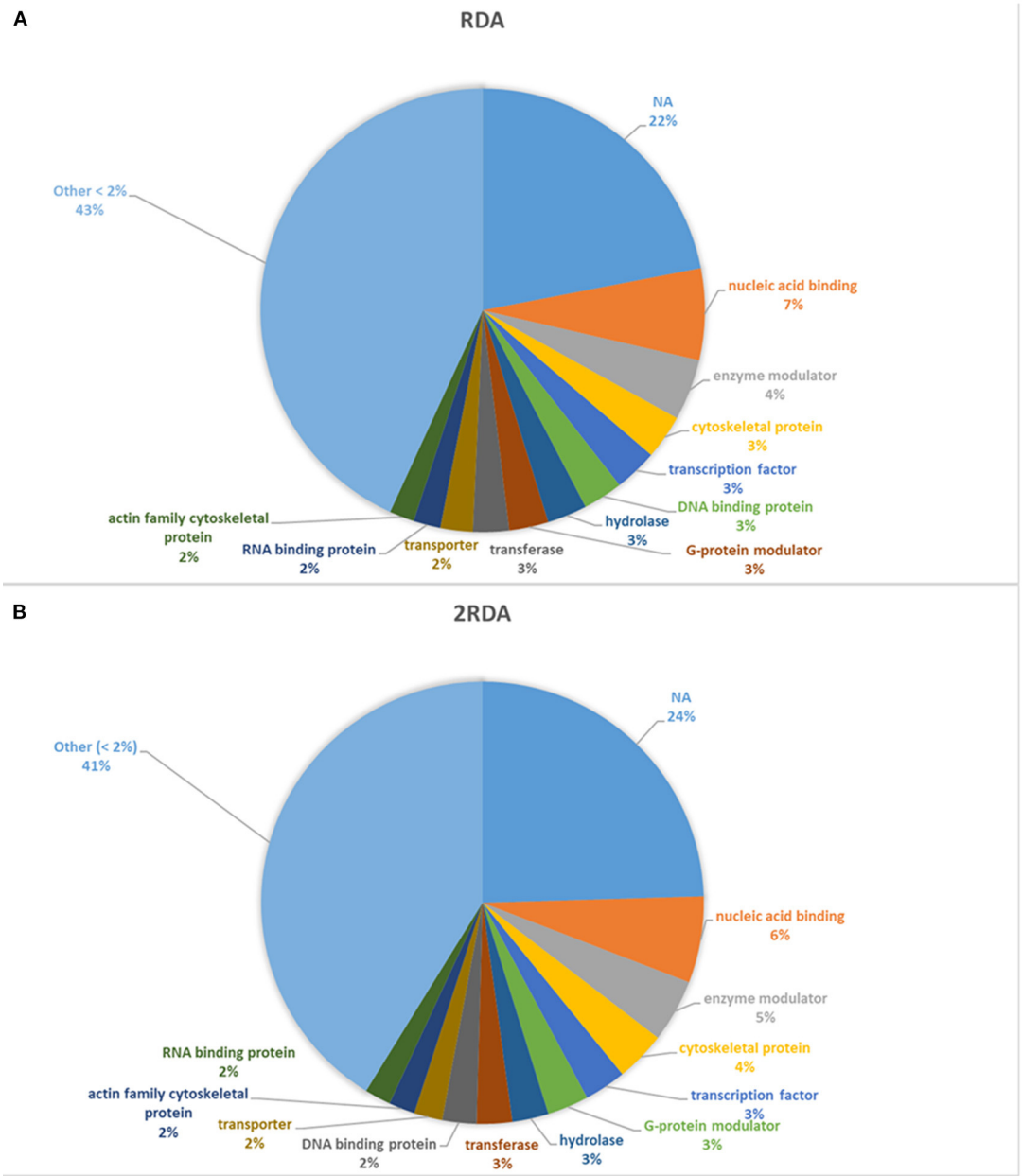

FIGURE 3 | Distribution of protein classes present >2% of reads. NA refers to unassigned proteins. **(A)** includes the 9 participants on the RDA diet and **(B)** refers to the results from the 10 participants in the 2RDA diet.

Nine out of the 10 proteins were observed in at least 60% of the samples from the 2RDA diet group [including cytoskeleton-associated protein 5 (CKAP5) and talin 1 (TLN1)]. Five of the function groups were related to DNA and included the proteins CREB binding protein (CBP), lysine methyltransferase 2A (KMT2A) and methyltransferase 2C (KMT2C). Both cytoskeletal proteins and DNA related proteins are involved in cell proliferation (40, 41) and suggest that increasing protein intake increases cell proliferation. This plausible effect is supported by similar findings in rat colons (42) but is not supported by the presence of K167, a sign of proliferation, only being found in the RDA group. The lack of K167 suggests that these proteins may be involved in proliferation not identified by the K167 antigen or the increase of cytoskeletal and DNA related proteins did not affect the cell proliferation in this study. Work conducted with a cohort of men which included the cohort in this study showed that some microRNAs were altered in the 2RDA diet and that the 2RDA diet also increased the immune systems post-transcriptional regulation (43). The intestine contains many transporter proteins, and proteins with these functions were also observed in this list of proteins, for example, ryanodine receptor 1 (RYR1) and ryanodine receptor 3 (RYR3).

To give an overview of the number of samples in which each of the proteins were found in the two diets, the top 26 proteins observed in the 2RDA diet (according to frequency observed) are listed in **Table 1**. Twenty of these proteins are found in the intestinal region according to Protein Atlas (38). These proteins had functions related to digestive enzymes, molecular motors, signalling, and cytoskeleton including placement of organelles. Literature searches resulted in 4 proteins that were newly discovered faecal/intestinal proteins. These were Collagen alpha-1(VII) chain (Uniprot ID CO7A1), Protocadherin Fat 3 (Uniprot ID FAT3), Zinc finger protein 469 (Uniprot ID ZN496), and Dynein heavy chain 8, axonemal (Uniprot ID DYH8). The presence of these proteins also supported our hypothesis that proteins are exfoliated from cells found along the intestinal wall are present in faecal matter. This has been observed previously in colorectal cancer screening although it was less common in the healthy subjects (44).

CO7A1 is a fibril that joins the external epithelia to underling stroma (45). This protein has been shown to be upregulated after addition of TNF-α in cultured fibroblasts (46), which suggests that fibroblasts can produce CO7A1. A layer of fibroblast cells are found under the epithelium in the intestine (47). CO7A1 was observed in the majority of samples, in 6 of the RDA samples and 9 of the 2RDA samples, 90 and 67%, respectively. This suggests that peptides of this protein are commonly found in faecal matter. This may be because the protein is observed close to the external layer of the intestine and may be broken off during normal wear and tear as we hypothesised would happen.

FAT3, in humans, is one of four FAT proteins which are members of the cadherin protein family (48, 49). FAT3 is involved in the interactions with the actin cytoskeleton. There is evidence of FAT3 upregulating β-catenin and proteins downstream of the Wnt signalling pathway (50). This is interesting as two other common proteins BCL9 and MACF1 that were both found 8 times in the 2RDA participants are also part of the Wnt signalling pathway and have previously been observed in the intestinal system (38). Proteins in the Wnt pathway are involved in the development of foetuses and in homeostasis in adults. The process eliminates the degradation pathway leading to an increase of β-catenin both in the cytoplasm and nucleus of cells and increasing transcription and thus protein expression, cell growth and are potentially involved in cell to cell adhesion. In some situations, this function can lead to tumour growth (51) and possibly could be part of the reason that a mutation in FAT3 has been shown to result in pancreatic tumours (50). Since FAT3 is part of the Wnt signalling pathway and other members of this pathway were observed in the samples, it is possible that this pathway was active in the intestinal system which led to fragments of these proteins being found in the faecal samples.

Little is known of the function of ZN469 except that it is a transcription factor like other zinc finger proteins (34). Some research has shown that a peptide from ZN486 is present over twice as much in serous ovarian cancer tissue compared to healthy ovarian epithelium tissue (52). It had been hypothesised that ZN486 polymorphisms could cause keratoconus and reduces vision abilities, but studies from Poland and Saudi Arabia have found that it does not (53, 54). Further research would need to be conducted to theorise and determine the exact function of ZN486 and why it could be present in faecal matter.

DYH8 is an axonemal heavy chain dynein. These heavy chain proteins form a major part of the dynein molecular motors along with minor chain dynein proteins (55, 56). Dynein complexes transport biomolecules along microtubules within cells (56). In staining studies, DYH8 showed a strong presence in testis (38). DYH8 was found in 70% of the 2RDA participants but only 22% of the RDA participants. We suspect that because of the role this protein has in transportation within cells, this could have entered the intestinal system via breakdown of cells.

An additional two proteins that have not been noted from faecal/intestinal proteins, but are found in muscle, were ryanodine receptor 1 (Uniprot ID RYR1) and ryanodine receptor 3 (Uniprot ID RYR3). Ryanodine receptors are part of calcium channels and trigger muscle contraction. There are three of these receptors that are each dominant in different types of muscle. RYR1 is dominant in skeletal muscle whereas RYR3 is dominant in smooth muscle which is found in the intestine. Antibody assays have shown the presence of RYR3 in the intestine (38, 57–59).

Prior to analysis the proteins were digested with trypsin. The cleavage sites of the peptides were examined to see if there were non-tryptic cleavages suggesting breakage of the proteins *in situ*. A peptide was considered to be tryptic if it was the start or end of the protein or a breakage after lysine or arginine. An average of 0.4% of peptides in each sample contained no tryptic cleavages; 8.3% had tryptic cleavages at both ends; and 91% had a tryptic cleavage at one end of the peptide. Overall the average lysine and arginine cleavage sites were 31 and 27%, respectively, in both diets. This suggests that the trypsin digestion accounted for the majority of cleavages but it should be noted that trypsin is used to digest proteins in the small intestine (1) so some of the cleavages may have occurred during this phase of digestion rather than during sample preparation. This work involved extractions optimal to proteins rather than peptides from the faecal samples which suggests the presence of intact host-proteins in the faecal samples that are not completely digested in the small intestine's digestive system.

The participants were older men and hence may not be reflective of the population variation that might exist in women, younger populations or if variation is impacted by age. What was shown is that despite markedly different diets and adherence to a prescribed diet, in this case a high protein diet, there was little or no evidence of increasing uniformity of the proteome in healthy participants. Nor was there a discernible effect of the diet itself.

Thus, analysis and comparison between a healthy and defined unhealthy population in which aspects of GIT function are compromised would be beneficial. Any studies in this area need to be scaled appropriately to take account of the large degree of individual variation in faecal protein composition. The addition of pre-diet samples would help to understand variability prior to the study and add to understanding what self-proteins change with twice the recommended protein allowance. This work was done using a qualitative approach which allows all proteins identified to be studied rather than just those with appropriate quantitative information (60). Further studies using label-free

quantitative mass spectrometry could add to the information we have on human proteins by determining differences in the concentration of faecal proteins between the two diets.

CONCLUSIONS

In this study we identified human proteins present in the faeces of elderly men after 10 weeks on a healthy diet consisting of either the RDA or twice the RDA of protein. We used a qualitative approach and found no significant differences between these two healthy diets which suggests that the protein increase used in the 2RDA diet of this study does not affect the shedding of cells and secretion of digestive enzymes into the faecal matter. We did observe that the human host faecal proteome is variable in a set of individuals matched to age and sex. Limited differences in the proteins identified and protein classes was observed between the diets. But there is evidence of proteins relating to cell proliferation more often in the 2RDA than the RDA diet. Higher protein or longer-term diet studies may show further differences not observed in this work. During this process we have been able to show the host-proteome of human faeces from these men. There is no dominant class of proteins, but nucleic acid binding and enzyme modulators are more dominant in the human faeces of these men than other Panther protein classes. Four proteins, CO7A1, FAT3, AN469, and DYH8, previously unidentified in faecal matter were present in at least 70% of the 2RDA diet samples. Since limited differences were observed in the two diets, we now have a foundation to compare to for future human faeces studies. An extension of this foundation that looks at a larger number of participants and especially takes into consideration the inter-individual variation would be beneficial. This extended baseline could be compared to further understand intestinal biopathways or looking for markers of disease. It would be advantageous for future studies to use more extreme variations in dietary habits (omnivore vs. vegan) or from longer intervention studies to see if protein effects are observed when comparing extremes or over extended time frames. Such studies are warranted as GIT dysfunction is a major cause of ill-health, with many people experiencing syndromes for which symptoms are varied and frequently overlapping.

DATA AVAILABILITY STATEMENT

The datasets generated in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: PRIDE with identifier PXD021424, http://proteomecentral.proteomexchange.org/cgi/GetDataset?ID=PXD021424.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Southern Health and Disability Ethics Committee (New Zealand; 15/STH/236). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DC-S, CM, JG, and AG: conceptualisation. DC-S, CM, and AM: dietary methodology. EL, AT, JG, and AG: faecal analysis. CM, AM, SM, NZ, FR, and PS: investigation. JG: data curation and writing—original draught preparation. AM, CM, NZ, FR, PS, SK, NR, AS, K-HW, DC-S, and AG: writing—review and editing. DC-S, NR, SK, AS, and K-HW: funding acquisition. All authors approved the final version of the manuscript for submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2020.595905/full#supplementary-material

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The Adaptation of the Carbohydrate Counting Method Affects HbA1c and Improves Anthropometric Indicators in Patients With Diabetes Mellitus 2

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INTRODUCTION

The worldwide growth of diabetes mellitus (DM) has, in recent years, generated an exponential increase in associated comorbidities such as high blood pressure, cholesterol, and cardiovascular risk (CVR), with an increase in mortality in the population (1). At the same time, the global DM pandemic increased by 75% in recent decades, with a large proportion of affected individuals spanning all age groups from 1988 to 2010 (2). In the Americas, its prevalence has increased from 5 to 8.3% in recent years, particularly in Honduras, where 6% of individuals over 20 years of age have DM (3). As such, DM increases health care costs in low- and middle-income nations (4).

Diagnosing diabetes mellitus type 2 (DM2) has changed since the inclusion of glycosylated hemoglobin (HbA1-c), as it is ≥6.5% in DM2. The criterion for fasting glucose is ≥126 mg/dL, whereas glucose at 2 h is ≥200 mg/dL (5). A hyperglycemic state can lead to an underlying prothrombotic environment, an overactivation of the coagulation cascade, fatal thromboembolic complications, and, eventually, increased mortality in DM patients (6). Medical treatment focuses on three pillars: drugs, nutrition, and education (7). The use of metformin acts as a standard pharmacological insulin used by patients to avoid weight gain (8). Nutritional medical therapy (NMT) prioritizes glycemic control and reduces comorbidities (7, 9). The diet promotion program is based on dietary guidelines, with group physical activity proving effective for predicting DM2 sowing but ineffective for long term benefits due to the lack of adherence (10). To this effect, the American Diabetes Association emphasized the need for individualized medical nutritional therapy (IMNT) (11).

Carbohydrate counting (CCHO) has been shown to be effective for glycemic control in diabetes mellitus type 1 patients when being intensively treated with insulin (12, 13). Carbohydrate counting considers the actual content of food consumed based on the individual's usual intake and coordinates insulin-glucose utilization so that both curves act as a single exponentially flattened growth curve (14). The resulting weight gain is a consequence of decreased urine sugar loss (15). Few studies have used carbohydrate counting in DM2 in the primary care setting, and although it showed improvements in HbA1c, compression of carbohydrate counting was considered difficult for participants (16). Given the paucity of evidence from randomized controlled clinical trials in Latin American for carbohydrate counting DM2 patients, this work aimed to evaluate the effectiveness of this medical nutritional treatment, which minimizes the risk of developing comorbidities and public spending on health care.

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METHODS AND MATERIALS

Study Type

The present work was a double-blind randomized controlled clinical trial. The allocation of the University School Hospital of Honduras was random. The study design was submitted and approved by the Biomedical Research Ethics Committee (IRB N°419-CGPGFCM/UNAH/2017) of the National Autonomous University of Honduras, on June 9, 2017. The doctors and nutritionists assigned to this study took an online ethics course titled "Human Subjects Research, IRB, Behavioral and Educational Focus" via the Collaborative Institutional Training program. As such, they were in compliance with the CONSORT checklist (17), which states the information to be included when reporting a randomized clinical trial. The study was carried out at the National Autonomous University of Honduras. The University School Hospital of Honduras has a specialized unit for the comprehensive care of DM patients and has recently created facilities conducive to the interdisciplinary medical-nutritional approach named "Model Center for Training and Comprehensive Care in Diabetes." It has become the most prominent medical center in Honduras.

The working group was made up of the clinical epidemiology unit and the endocrinology unit belonging to the University School Hospital of Honduras. The director of the Model Center for Training and Comprehensive Care in Diabetes selected two doctors to adjust drug treatments and two nutritionists to apply and follow up with the carbohydrate (CCHO) count and current dietary recommendations (RDC). The working groups were trained separately for the application of nutritional medical therapies. The randomization of the participants was carried out by the head of the clinical epidemiology service. using the "random" function in Microsoft Excel.

Sample Description

Inclusion Criteria

Participants with a DM2 diagnosis were selected based on clinical records, glycosylated hemoglobin $\geq$7% (not older than 6 months), aged between 18 and 65 years, insulin use between 1 and 10 years, no use of sulfonylureas, body mass index (BMI) $<$35 kg/m^2, and waist–hip ratio $\geq$0.90 in men and $\geq$0.85 in women.

Exclusion Criteria

Patients excluded were those who had been clinically diagnosed as having cancer, chronic respiratory disease, pregnancy, cognitive impairment (e.g., dementia, amnesia, delirium), macroangiopathy (e.g., ischemic heart disease, stroke, peripheral vascular disease), microangiopathy (e.g., proliferative retinopathy or maculopathy, kidney failure grade IIb, III, or IV), amputations, temporary staff of the institution, and those with insulin use over 10 years.

Sample Size

In 2016, the diabetic population of the University School Hospital of Honduras was 4,247 patients. In this study, 400 eligible patients in the endocrinology unit were selected. A mean value of 8.33% glycosylated hemoglobin was considered a regular value (11). For the sample size, we assumed risks foreseen in the current dietary recommendations of the control group (10%). The risk value of making an error was the conventional alpha of 5% (bilateral hypothesis) and beta of 20%. Participants ($n = 62$), per medical nutritional treatment, were adjusted for 15% loss and resulted in 71 participants per carbohydrate counting group for the current dietary recommendations.

Figure 1 shows the flow chart of the selection process. The sample chosen was made up of participants registered with the endocrinology unit. In total, 400 participants were eligible, 258 participants did not meet the inclusion criteria, 142 participants were randomized, and only women decided to participate. During allocation, ten patients with glycosylated hemoglobin values $\leq$7% at the start did not receive allocated intervention. This left a total of 132 patients who met our inclusion criteria. During the 6-month follow-up, three participants were excluded because they had been diagnosed with cancer, chronic renal failure, and Zika, respectively. A total of 9.2% ($n = 13$) participants were excluded from the analysis. In total, 48.1% ($n = 62$) of participants remained on the carbohydrate counting diet, whereas 51.9% ($n = 67$) of participants followed their current dietary recommendations.

Nutritional Medical Therapy Allocation

Nutritional Medical Therapy With Carbohydrate Counting

Participants adjusted to the insulin dose prescribed in the drug treatments (13, 14). The calorie requirements based on total energy expenditure were obtained (18). A reduction of 250 kcal/day to allow for adherence to treatment was applied. The nutritional medical therapy was delivered with a list of foods that contained the weight of carbohydrates and insulin (UI) dose, which was adapted to local culinary habits (forms of preparation and ways in which the food was cooked). Moreover, the nutritional medical therapy was adapted to the Central American food pattern (19).

Nutritional Medical Therapy With Current Dietary Recommendations

Participants were issued a brochure by the Honduran Ministry of Health to help better manage their diabetes mellitus type 2 (20). The brochure details glycemic index, fat content, and food preparation style but does not estimate caloric requirements nor provide food caloric adjustments.

Study Follow-Up

Participants in both nutritional medical therapy groups (i.e., carbohydrate counting and current dietary recommendations) took part in 30-min sessions in which they observed photographs that showed food portions, food fiber, types, and cooking techniques. Biochemical glucose, glycosylated hemoglobin, and anthropometric (i.e., weight, height, body mass index, waist circumference, hip circumference, and blood pressure) parameters were evaluated at 6 and 12 months of individualized nutritional therapy. Glucose, however, was evaluated monthly. At each visit, doubts were cleared up, and concepts were reinforced for each nutritional medical therapy.

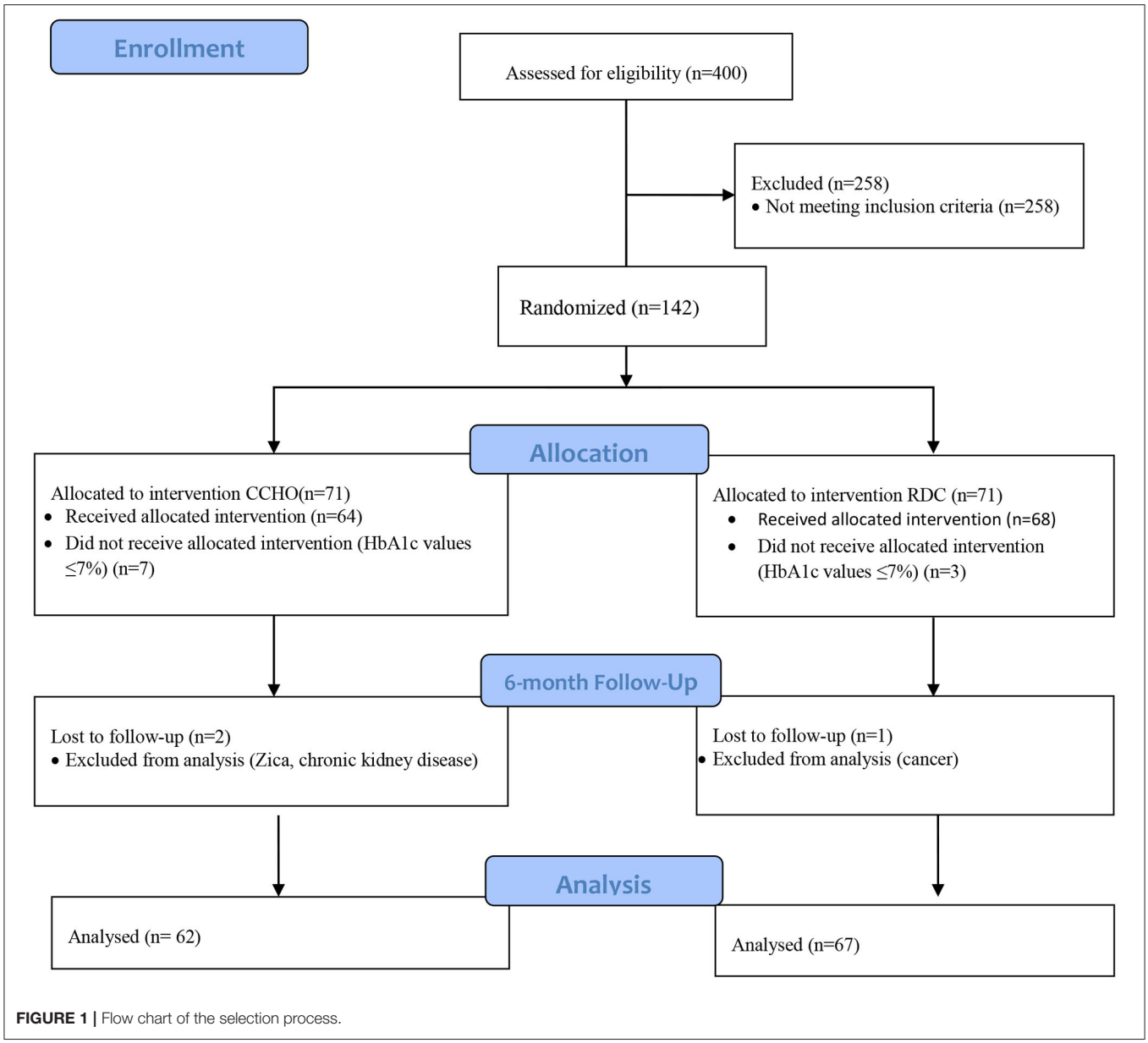

FIGURE 1 | Flow chart of the selection process.

Data Collection

Biochemical Parameters

For both nutritional medical therapies the glucose (mg/dL) and glycosylated hemoglobin (%) blood parameters were collected the day of the appointment and analyzed at the University School Hospital of Honduras's clinical laboratory. Participants attended these sessions on an empty stomach and without having previously smoked for 8 h. The 3-mL blood samples obtained using venipuncture were stored in anti-clotting tubes labeled with the code of each participant. They were centrifuged with a Z-29 digital macro-centrifuge kit at a speed of 2,500–3,000 rpm for 5 to 10 min to separate the serum from the clot. They were incubated at 65–85°F ± 5°F (17–30°C ± 2.8°C) per h. Glucose and HbA1c values were analyzed using Siemens Dimension RxLMax equipment (Siemens Healthcare Germany 2010). HbA1c determination was performed using the ascendant/enzymatic endpoint method, with FlexR reagent cartridge reagents.

Anthropometric Measurements

On the same day of the biochemical measurements, we recorded the weight, height, waist–hip size, and blood pressure of participants in accordance with recommendations (21). They were weighed (kg) with precision class I equipment (seca 803). Height (recorded in cm) was measured using a stadiometer (seca 213). Body mass index was calculated in accordance with the standard formula (kg/m^2) (22). Blood pressure (mmHg) was measured three times at an interval of 1 min between each

measurement (23) using a digital automatic blood pressure monitor (OMRON M6 (HEM-7001-E (V); precision ± 3 mmHg). Therefore, we obtained the values with the means of the second and third measurements of systolic (SBP, mmHg) and diastolic blood pressure (DBP, mmHg).

Definition of Central Obesity

Waists and hips (cm) were measured with a flexible tape measurer (SECA 201). Pressure was avoided on the tissues. Central obesity, waist circumference (≥80 cm), and waist–hip ratio (≥0.85) were defined in accordance with World Health Organization (WHO) criteria (24).

Statistical Analysis

The results of each dietary treatment were expressed as mean ± standard error of the mean. The normality of the data was verified using the Kolmogorov-Smirnov test. The uniformity and variance were verified using the Bartlett test. An unpaired Student *t*-test was performed. Pearson correlations were analyzed to verify the association between HbA1c and anthropometric indicators. The data to compare experimental stages were processed using the Friedman test. Over time, we adjusted the mixed linear multivariate model for HbA1c, taking into account the possible effect of the explanatory variables. A stepwise variable selection process was carried out based on the AIC (Akaike Information Criterion), until the optimal model was reached. The optimal model is shown, with the coefficients, standard error, degrees of freedom, and the *t*-value and *p*-value associated with each coefficient of the fixed effects. The standard deviation and the correlation of the random effects (time) are also shown. We used SPSS software version 22 (IBM (International Business Machine), New York, USA) and the nlme package. The R statistical program was used for mixed models.

RESULTS

Table 1 shows the effect of carbohydrate counting and current dietary recommendations on anthropometric and biochemical values at 0, 6, and 12 months of treatment. Significant differences were observed between treatment for diastolic blood pressure, body mass index, waist, glycosylated hemoglobin, insulin units, and metformin doses. Diastolic blood pressure was reduced in CCHO from 82.73 to 77.05 mmHg ($p = 0.001$), while RDC did not obtain a reduction ($p = 0.747$). Changes in diastolic blood pressure values were observed between groups from 6 months of nutritional medical therapy with statistical significance at 12 months (77.03 mmHg CCHO vs. 80.87 mmHg RDC $p = 0.019$). Body mass index varied over time, with its highest efficacy at 12 months of CCHO (30.74 to 29.74 in CCHO vs. 31.21 to 32.06 in RDC $p < 0.001$).

Participants' waists achieved reductions of 1.143 cm at 6 months for CCHO and RDC ($p = 0.02$); however, at 12 months, waists began showing a marked trend, with a reduction of 1.23 cm in CCHO ($p < 0.01$). As a biochemical indicator, glycosylated hemoglobin showed an intergroup reduction at 6 and 12 months ($p = 0.05$). The intergroup ($p < 0.01$) compared with the RDC showed an increase in its values at 6 and 12 months (0.69%).

TABLE 1 | Effect of medical nutritional treatment vis-à-vis anthropometric and biochemical markers.

	Nutritional medical treatments			
	CCHO	**RDC**	**SEM ±**	***p*-value[1]**
Diastolic pressure (mmHg)				
Initial	82.73[a]	80.60	1.106	0.179
6 months	81.63[a]	79.79	1.151	0.264
12 months	77.03[b]	80.87	1.144	0.019
p-value[2]	(80.46) 0.001	(80.42) 0.747		
Body mass index (Kg/m^2)				
Initial	30.74	31.21	0.377	0.384
6 months	30.41	31.63	0.390	0.028
12 months	29.74	32.06	0.409	< 0.001
p-value[2]	(30.28) 0.173	(31.63) 0.311		
Waist (cm)				
Initial	96.24[a]	99.16	1.130	0.069
6 months	94.98[b]	100.16	1.143	0.002
12 months	92.16[c]	101.21	1.237	<0.001
p-value[2]	(94.46) 0.026	(100.17) 0.533		
Hip (cm)				
Initial	102.60	104.16	1.148	0.336
6 months	101.79	105.21	1.199	0.045
12 months	100.32	105.2	1.189	0.002
p-value[2]	(101.57) 0.309	(104.85) 0.694		
Glucose (mg/dL)				
Initial	175.16	173.53[b]	9.089	0.977
6 months	173.53	188.41[b]	7.594	0.190
12 months	166.44	205.76[a]	6.662	< 0.001
p-value[2]	(171.71) 0.257	(189.23) 0.007		
HbA1c (%)				
Initial	9.54[a]	9.29[b]	0.175	0.262
6 months	8.97[ab]	9.93[a]	0.175	< 0.001
12 months	8.20[b]	9.97[a]	0.161	< 0.001
p-value[2]	(8.90) 0.050	(9.73) 0.004		
Insulin (UI)				
Initial	49.81	52.00	2.614	0.552
12 months	42.95	55.41	2.6154	0.001
p-value[2]	(46.38) 0.079	(53.7) 0.477		
Metformin (mg)				
Initial	1762.74	1882.11	87.659	0.343
12 months	1407.95	2103.33	70.359	<0.001
p-value[2]	(1585.34) 0.003	(1992.72) 0.048		

[a,b]Means with different letters in the same column differ at p < 0.05.
p-value[1]: Unpaired Student t-test.
p-value[2]: Friedman test.
CCHO: carbohydrate counting.
RDC: current dietary recommendations.
SEM: standard error of the mean.

The insulin and metformin values for the CCHO behaved with a reduction of administered units for the pharmacologic insulin intergroup (6.85, $p < 0.001$). Moreover, there was a decrease of 354.79 mg metformin at 12 months of nutritional medical therapy with a $p < 0.001$ difference between groups.

TABLE 2 | Linear mixed multivariate model of intercept and two random slopes.

Fixed effects	β_i	Std. Error	DF	*t*-value	*p*-value
(Intercept)	6.3366	0.4928	241	12.86	<0.001
Time factor (2)*	−0.1288	0.0933	241	−1.38	0.169
Time factor (3)*	−0.4568	0.1003	241	−4.55	<0.001
Group: CCHO	−0.5036	0.1688	124	−2.98	0.003
Educational level Complete high school or higher	0.5470	0.2293	124	2.39	0.019
SBP (mmHg)	0.0144	0.0056	241	2.56	0.011
Glucose (mg/dL)	0.0079	0.0008	241	10.00	<0.001
Calories (cal)	0.0002	0.0001	241	1.95	0.052
Carbohydrates (g)	0.0017	0.0007	241	2.31	0.022
Cholesterol (mg)	0.0008	0.0003	241	2.86	0.005

**Time factor (2): 6 months of treatment; time factor (3); 12 months of treatment.*
DF: degree of freedom.
CCHO: carbohydrate counting.
SBP: systolic blood pressure.

Table 2 shows a linear regression between HbA1c, BMI, waist, hip, glucose, insulin, and metformin. The β_i coefficient associated with each variable shows the average change in HbA1c by a one-unit increase in the model variable. In this way, in the RDC group, hemoglobin decreased by 0.12 (β of time factor 2) and 0.45 units (β of time factor 3) when passing from the basal level at 6 and 12 months, respectively. In the CCHO group, the average decrease was 0.62 (0.12 + 0.50) and 0.95 (0.45 + 0.50) units at 6 and 12 months, respectively. The significant reduction occurred at 12 months (p-value < 0.001), not at 6 months (p-value 0.169). The model presented a good fit. There was no lack of normality or homoscedasticity.

DISCUSSION

DM2 patients who counted carbohydrates showed effective gains regarding the main anthropometric and biochemical indicators during 30-min monthly sessions for 12 months. **Table 1** shows that this individualized nutritional therapy presents beneficial effects to improve the state of health to prevent cardiovascular risk, which exponentially impacts quality of life. This potential decrease in cardiovascular risk is measured by a significant reduction of diastolic blood pressure (5.5 mmHg) at 6 and 12 months of treatment. The DASH sodium trial showed positive effects in blood pressure after 4 weeks of nutritional medical therapy with sodium reduction from 12 to 6 g, and a decrease of 10 mmHg in 5 weeks (25). Intra-abdominal fat produces certain proteins and hormones such as adipocin, angiotensinogen, and cortisol, all of which cause inflammatory processes that lead to high blood pressure (26). However, for this reduction to be effective, it is necessary for declines to coexist in other indicators, such as body mass index and waist. As suggested by the American Diabetes Association, no studies have demonstrated the efficacy of DM2 patients counting carbohydrates in an individualized medical nutritional treatment.

The present work reduced body mass index in participants, who transitioned from obese to overweight. These reductions depended on the time between groups, i.e., 6 and 12 months ($p = 0.028$) and ($p < 0.001$), waist (4.08 cm) ($p = 0.026$), and hip (2.23 cm) at 12 months. As such, cardiovascular risk (26, 27) decreased. Our study corroborated what has been mentioned by other authors on the relationship between weight gain at the expense of visceral adipose tissue. Further, we noticed an increase in systolic blood pressure (25–27), where a reduction in these indicators had an impact on the reduction cardiovascular risk (28–30). Carbohydrate counting at 12 months had the potential to normalize and improve these indicators, as well as reduce cardiovascular risk by improving the life expectancy for individuals.

Another important point to highlight in the evolution of this disease and its impact on quality of life are the biochemical indicators of glucose and glycosylated hemoglobin. In this study, it is shown that carbohydrate counting at 12 months achieved comprehension and adherence (31, 32), as well as a reduction in both indicators. A prospective study showed that severe visceral, parenchymal, and generalized adiposity are accompanied by inflammatory, neurohormonal, vascular, and metabolic responses that converge in cardiac and renal damage. Hypertension and diabetes mellitus are pathologies that amplify and perpetuate cardiovascular risk (33). Fasting glucose decreased by 8.72 mg / dL. Yet without statistical differences over time, glycosylated hemoglobin reflected a marked reduction of 1.34% over time ($p < 0.001$). Associated with these indicators, decreases in 12-month insulin and metformin doses of 6.86 IU and 354.79 mg ($p = 0.003$). Further, we found that $p = 0.001$ for insulin and p <0.001 for metformin between groups.

These results demonstrate that carbohydrate counting affected not only the aforementioned benefits but also health expenses at the individual level. From a public health perspective, metformin reduced body weight by 2.1 kg compared to individuals who only receive drug treatment with insulin (8). However, this result was inconsistent with the data of the present study, as the current dietary recommendations did not improve any of the previously mentioned indicators.

Likewise, in accordance with the American Diabetes Association, which considers carbohydrate counting the standard goal when managing diabetes mellitus type 1, we emphasized individualized nutritional therapy for stability and improvement of glycemic control in the prevention of vascular complications with HbA1c values <8% (5, 11). The present work achieved a glycosylated hemoglobin value of 8.20%, where it was clearly demonstrated that carbohydrate counting was effective for DM2 patients at 12 months. Moreover, it improved all indicators associated with cardiovascular risk.

Insulin is necessary to metabolize carbohydrates, proteins, fats, and maintain a certain euglycemia after meals. The main goal of insulin treatment is to mimic the physiological pattern of insulin secretion for better glycemic control (34). To maintain basal metabolism and limit liver glucose production between meals, 0.5–1 unit/h of insulin is needed. One unit of insulin is released for every 10 g of carbohydrate in the postprandial phase of insulin secretion (the meal-stimulated phase), which causes the diffusion of ingested nutrients (mainly glucose) to the periphery (35). A healthy patient's insulin secretion normally takes place 5 min after food intake. However, for DM2 patients, the first phase of insulin secretion is completely absent. The second phase, which in healthy patients lasts 1 to 2 h until blood glucose is normalized, is reduced by 50% in DM2 (33). In accordance with the data found in this paper, there is an association between the variable HbA1c and the values of insulin. Therefore, this indicator can be said to reduce the pharmacological dose and have a beneficial effect on individual health, given that cardiovascular risk is the main cause of death.

Intervention programs for physical lifestyle changes, such as weight loss, are proven to be ineffective (10). Therefore, individualized medical nutritional treatment and drug treatments could be key to preventing and reducing mortality rates for DM2 patients (11, 36). Past studies have shown the negative effects of weight gain with respect to indicators of arterial pressure and cardiovascular risk, among other effects (37). Herein, we observed anthropometric indicators for current dietary recommendations in accordance with similar studies where the increase in pressure was positively impacted by weight, central fat, body mass index, and basal metabolic rate (38). Another study that examined women in middle age correlated diastolic pressure positively with weight, visceral adipose tissue, and other indicators (26, 39). These results coincided with the data found in current dietary recommendations, which clearly shows that these factors negatively impact cardiovascular risk.

CONCLUSION

For DM patients, individualized medical nutritional treatment, i.e., carbohydrate counting, improved patients' reduction of their cardiovascular risk measured via anthropometric indicators: body mass index ($p < 0.001$) diastolic pressure ($p = 0.019$), waist ($p < 0.001$), biochemical/glycosylated hemoglobin ($p < 0.001$), and glucose ($p < 0.001$). A decrease in the pharmacological dose of insulin ($p = 0.001$) and metformin ($p = 0.001$) was demonstrated.

Study Strengths and Limitations

Our findings should be considered in light of the benefits of metabolic enhancement and its cardiovascular implications. The nutritional education received at each 30-min meeting allowed individuals to understand the method. The portion graphs and equivalent food measurements, as well as the adaptation of the method to the Central American diet, allowed participants to attend monthly scheduled appointments. From a social and health perspective, implementing the model for DM2 patients will not only impact the quality of life (i.e., less expenditure on drugs such as insulin and metformin), but it will also create a lower rate of long-term complications. The non-digitization of medical records and low educational levels of participants prevented a deeper understanding of the study's purpose, delaying the start of sampling. There were no methodological limitations during the development of this study.

Future Directions

Future studies should replicate the present work at a local multicenter level and regional level and assess the similarities of data with the present work. Future studies should also insist on the importance of the nutritionist's role in primary health care centers in order to make possible the use of the method in the most needed regions.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study design was submitted and approved by the Biomedical Research Ethics Committee (CEIB), (IRB 419-CGPGFCM/UNAH/2017) of the National Autonomous University of Honduras (UNAH). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Health Behavior, Health-Related Quality of Life, and Mental Health Among Canadian Children: A Population-Based Cohort Study

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Objective: Studies that have reported the associations of diet quality, physical activity (PA), sedentary behavior (SB), and health-related quality of life (HRQoL) with mental health among children and adolescents are predominantly cross-sectional in design. Very few studies have examined the longitudinal relationship of mental health with health behavior and HRQoL among children. This study aimed to investigate the associations of diet quality, PA, SB, and HRQoL among children with mental health disorders throughout childhood.

Methods: We linked data from grade five students aged primarily 10 and 11 years who participated in the Raising Healthy Eating and Active Living (REAL) Kids Alberta survey in 2012 in the Canadian province of Alberta with their administrative health care data from birth to 2012. Mental health outcomes included internalizing disorder and attention deficit and hyperactivity disorder (ADHD) defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or Tenth Revision, Canadian version (ICD-10-CA). The HRQoL was measured by the EQ-5D-Y, a five-dimensional descriptive system for children and youth. We applied negative binomial regressions to examine the associations between health behaviors, HRQoL, and mental health.

Results: Of the 1,352 participating students, 12.31 and 8.32% had a diagnosis of internalizing disorders and ADHDs, respectively, during childhood from birth to the ages of 10–11 years. Students in the highest tertile for diet quality, relative to the lowest tertile, were 56% less likely to have diagnoses of internalizing disorders (incidence rate ratio, IRR = 0.44, 95% CI = 0.23–0.85). Students engaged in less PA (*vs.* more PA) were more likely to be diagnosed for internalizing disorders (IRR = 1.98, 95% CI = 1.19–3.30). Poorer diet quality, low PA, excessive use of computers/video games, and watching TV were significantly associated with more diagnoses of ADHDs. Children who experienced some or a lot of problems in "feeling worried, sad, or unhappy" and "having pain or discomfort" were more likely to receive diagnoses of internalizing disorders and ADHDs, respectively.

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Conclusions: These observed associations suggest that health promotion programs targeting promoting diet quality, PA, and HRQoL and reducing SB among children may contribute to improving mental health.

Keywords: health behavior, diet quality, physical activity, sedentary behavior, health-related quality of life, internalizing disorder, attention-deficit and hyperactivity disorder, children

INTRODUCTION

Childhood and adolescent mental health disorders are a significant global public health issue and constitute a considerable burden for public health and medical care systems (1). Approximately half of all lifetime mental health disorders begin in early childhood and adolescence before the age of 14 years (2). Poor mental health in children and adolescents is associated with lower health-related quality of life (3, 4), poor educational achievements (5), and increased risk of engaging in risky behaviors like substance use, self-harm, suicide attempts, and suicide (6). The mental health problems in childhood and adolescence often remain stable and persist into adulthood (7–9), and thus exacerbating the global burden of diseases with substantial disability-adjusted life years lost (10). Therefore, identification of modifiable risk factors for poor mental health in childhood is a high priority in order to develop health promotion initiatives among children.

Previous studies have documented the associations of health-related behaviors, including physical activity (PA) (11, 12), diet quality (13, 14), and sedentary behavior (SB) (15, 16), with mental health among children and adolescents. The evidence-based findings suggest that low levels of PA and high SB are associated with poor mental health, including depression, anxiety, emotional disorders, and other internalizing problems (11, 12, 16), and poor diet quality is associated with decreased mental health (13, 14) among children, and adolescents. However, the existing findings are predominantly based on cross-sectional investigations, and very few longitudinal studies have examined the importance of these health-related behaviors for mental health among children and adolescents (11, 13, 16). The health benefits of PA for mental health have been more described by researchers than the health benefits of SB and diets for mental health among children and youth (11–13, 16). Less research has been conducted to examine the effects of diet quality and SB on mental health among children and adolescents (11, 13). The existing findings for the relationship of SB and diet quality with mental health problems among children and youth appear considerably variable. Some studies found a significant association between SB or diet quality and mental health (17, 18), and others did not observe an adverse effect of elevated SB or poor diet quality on mental health (19, 20). Moreover, studies that investigated the importance of health behaviors for mental health in young people have mostly been carried out among adolescents, and considerably less research has been conducted among children and preadolescents (11, 13). Particularly, of the studies that have used a longitudinal design to examine the relationship of diet quality with mental health among children and adolescents, the majority of the studies had a short follow-up period (e.g., < 5 years) (17, 21) and have investigated the influence of diet quality on mental health among adolescents rather than children (13, 14). As healthy behaviors, like active lifestyles, healthy diet habits, and low SB are often established during childhood and persist into later in life (22, 23), it is essential to examine the relationships of PA, SB, and diet quality with mental health disorders among children to inform health intervention initiatives in childhood in order to enhance their mental health. In addition, most of the previous studies have examined mental health outcomes by utilizing self-reported measures of mental health indicators. Very few studies have used physician diagnosis of a mental health disorder indicating a clinically significant mental health problem (e.g., mental illness) (15).

The associations of mental health problems with health-related quality of life (HRQoL) have been mostly examined among adults (24) or among children and adolescents with chronic diseases (e.g., type 1 diabetes) or are overweight (25, 26). Very few population-based studies have analyzed the relationship between HRQoL and mental health among children and adolescents (3, 4, 27), and studies based on longitudinal data are scarce. HRQoL is a multidimensional construct that comprises the physical, psychological, and social functioning of an individual (28). It is important to examine which specific dimension or subscale of HRQoL (e.g., physical or psychosocial functioning) is related to mental health problems and in what manner (e.g., negative or positive association and strength of the association). More population-based studies among children are needed to better understand the relationships of mental health and HRQoL with multiple health behaviors and socioeconomic confounders being considered.

The purpose of this study was to examine the associations between diet quality, PA, SB, and HRQoL in children aged primarily 10–11 years and mental health disorders throughout childhood.

METHODS

The Survey

The 2012 Raising Healthy Eating and Active Living Kids in Alberta (REAL Kids Alberta) survey was a population-based survey among grade five students aged primarily 10 and 11 years and their parents in the province of Alberta, Canada (29). The 2012 REAL Kids Alberta survey aimed to evaluate a comprehensive initiative by Alberta Health and Wellness to promote healthy behaviors and health among school children. The survey employed a one-stage stratified random sampling design with a sampling frame that included all elementary schools

in the province. Schools were stratified according to residential regions (metropolitan, city, or rural town) to ensure proportional representation of schools in each geographic region (29). Of the 170 selected schools, 143 (84%) agreed to participate. A total of 2,673 students from the participating schools had home surveys returned, among which 2,427 (91%) provided parental consent for their child's participation, and 2,308 (95%) of these students completed the survey.

The REAL Kids Alberta survey included a home survey completed by parents and a student survey that was completed by students in the schools. The survey was administered to students during classroom time by trained assistants who also measured the standing height and body weight of the students. The student survey included the validated Harvard Youth/Adolescent Food Frequency Questionnaire (YAQ) (30, 31) adapted version for Canadian children and youth, questions on physical activities, sedentary behaviors (watching TV and playing computers or video games), and the EQ-5D-Y descriptive system (32). The home survey collected information on children's socio-demographic characteristics, including gender, place of residency, household income, and highest level of parental education. Parents were also asked to provide Alberta health insurance number for their child and consent for their child's survey information to be linked with the child's administrative health care records.

The Administrative Health Data

The administrative health care data in Alberta included the Canadian Institute for Health Information Discharge Abstract Database (DAD), the physician services and claims database, and the ambulatory care database. The physician claims database includes physicians' services and billing information for these services. The DAD contains comprehensive administrative records for each inpatient admission to a hospital facility in Alberta. The Alberta ambulatory care database includes emergency department visits and outpatient day procedures. All of these databases contain individual patient-level information including patient demographic characteristics, diagnoses of diseases and procedures received, and services and treatments received. The health care data of the children used in this study were from 2000 (child's birth) to the end of March 2012 (before the survey began in April 2012).

Of the 2,308 students who completed the REAL Kids Alberta survey, 1,352 (59%) students with valid health care card numbers provided by their parents were successfully linked with the disease diagnosis records in the administrative health data.

Mental Health Disorder Outcomes

The outcomes included the total number of physician visits, emergency department visits, and hospitalizations for internalizing disorders and attention deficit and hyperactivity disorders (ADHDs) throughout childhood. Mental health disorder was defined as a mental disorder by a physician's diagnosis using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or Tenth Revision, Canadian version (ICD-10-CA). The ICD-9-CM and ICD-10-CA codes for the mental health internalizing disorders included "296, 296.2–296.3, 296.6–296.9, 300, 308, 309, 311, 313, F32–F34, F38–F43, F48, F92, and F93" (20, 21). These codes cover the diagnostic groups of depressive episode and recurrent depressive disorders, mood disorders (excluding bipolar), neurotic disorders, general anxiety disorders, reaction to stress, adjustment reaction, and emotional disorders. For the ADHDs, participants were considered to have an ADHD if they received one or more diagnoses of attention deficit disorder, hyperactivity disorder, hyperkinetic syndrome, or hyperkinetic conduct disorder according to the ICD-9/ICD-10 codes. The diagnosis of ADHDs in this study includes the ICD-9-CM codes "314.xx" and the ICD-10-CA codes "F90.xx" (33). All the primary diagnoses of internalizing disorders and ADHDs between 2000 (children's birth) and 2012 (children's age 10–11 years) were considered.

Assessments of Health Behaviors

Health behaviors included diet quality, physical activity, and sedentary behavior of children aged 10–11 years. The YAQ presented detailed information on the frequency of various kinds of foods that children consume, including fruits and vegetables, grain products, meat products, and milk and alternatives (30). The YAQ also contained both macro- and micronutrients like sugar, fats, amino acids, and multivitamins and minerals (29). On the basis of the nutrient intake and dietary information of the students from the YAQ and the Canadian nutrient files (34), we calculated the intake of nutrients and the daily energy intake. We then calculated the Diet Quality Index (DQI) based on the DQI—International (DQI-I) measure (35). The DQI-I constitutes four components: variety, adequacy, moderation, and overall balance of the diet. The total DQI-I score ranges between 0 and 100, with a higher score indicating better diet quality (35). We divided the total DQI-I scores into tertiles in the analysis.

Physical activity was measured by the questions asking students and their parent/guardian(s) about: (a) travel to and from school; (b) time spent to get to and from school; (c) frequency of child's activities outside school hours; (d) activities at morning and lunch recess in the past 7 days; and (e) frequency in sports and physical activities in the 7 days. These questions, consisting of 29 items, were largely adopted from the Physical Activity Questionnaire for Children (PAQ-C) (30), which has been demonstrated to be valid and have high reliability (31). A composite score ranging from 1 to 6 was computed based on the score on each of the 29 items. For the purpose of our analysis, the PAQ-C score was dichotomized into "physically active" if a student had a score of 3 or greater and "physically inactive" if a student had a score < 3.

Sedentary behavior was measured by students' self-reported questions on the number of hours daily spent on playing computers or video games and on watching TV, with four response categories: $<$ 1 h a day, 1–2 h a day, 3–4 h a day, and 5 h or more a day. Few students responded to the level of 5 h or more a day; hence, we categorized the SB variables into three levels: $<$ 1 h/day, 1–2 h/day, and $\geq$3 h/day.

Assessments of Health-Related Quality of Life

HRQoL was assessed by the EQ-5D-Y (youth) that was developed by the EuroQol group (https://euroqol.org/) and is suitable for use among children and youth between the ages of 8 and 18 years (32). The instrument consists of a five-dimensional descriptive system asking children whether they have (a) no problems, (b) some problems, or (c) a lot of problems on each of the following items: (i) walking; (ii) looking after myself; (iii) doing usual activities; (iv) having pain or discomfort; and (v) feeling worried, sad, or unhappy (32). The EQ-5D-Y has been previously validated and showed high reliability, and construct and discriminant validity (36). The variable for each question was dichotomized into two levels: "some problems or a lot of problems" and "no problems."

Assessments of Covariates

The socio-demographic characteristics of the students included child's gender, household income, highest parental educational level, and residential area. Household income was categorized into four levels: $0–$50,000, $50,001–$75,000, $75,001–$100,000, and >$100,000. Parental educational attainment was categorized into three levels: secondary school or less, college, and university or above. The residential area was classified as urban and rural based on the school location (metropolitan, city, or rural town). For body weight status, we adopted the age- and gender-specific body mass index (BMI) cutoff points for children established by the International Obesity Task Force (37) and classified body weight into normal weight, overweight, and obese. In the analysis, body weight was dichotomized as obese and non-obese (normal weight and overweight).

Statistical Analysis

Descriptive analysis was conducted to describe the frequency distribution of students by health behaviors, the EQ-5D-Y dimensions, body weight, and socio-demographic variables. The percentage of students receiving a diagnosis of internalizing disorders and ADHDs was calculated for each group of the described variables.

To examine the associations between diet quality, PA, SB, HRQoL, and mental health disorder, we employed univariate (unadjusted) and multivariable (adjusted) negative binomial regression models (NBMs). The NBM is an appropriate method to analyze over-dispersed counts data, like the number of a diagnosis of mental health disorders by health care providers, where the variance (7.54 for internalizing disorder and 12.21 for ADHD) is greater than its mean (0.46 for internalizing disorder and 0.71 for ADHD) under the Poisson distribution. The multivariable NBM adjusted for the confounding influence of students' gender, household income, parental education, place of residency, and body weight status. The incidence rate ratio (IRR) and 95% confidence interval (CI) were reported for the regression result.

Missing values for household income (23.8%), parental education (3.1%), weight status (3.1%), and sedentary behavior (0.4% for computers/video games) were entered as separate covariate categories in the regression models, and their estimates

TABLE 1 | Socio-demographic characteristics, health behaviors, HRQoL, and body weight status of the grade five students participating in the 2012 REAL Kids survey, Alberta, Canada, and percentage of receiving a diagnosis of internalizing disorders and ADHDs from 2000 to 2012.

Variables	% of Students (n = 1,352)	% of internalizing disorders	% of ADHDs
Total sample	–	12.31 (n = 154)	8.32 (n = 113)
DQI			
Lowest tertile	–	12.72	9.71
Middle tertile	–	12.65	8.54
Highest tertile	–	11.57	6.76
Physical activity			
Inactive (PAQ-C score <3.0)	29.7	13.93	13.01
Active (PAQ-C score ≥3.0)	70.3	11.62	6.33
Computers/video games			
<1 h/day	40.8	12.43	4.80
1–2 h/day	31.5	13.32	7.04
≥3 h/day	27.4	11.13	14.92
Missing	0.4	–	–
TV viewing			
<1 h/day	27.4	12.78	7.87
1–2 h/day	45.7	11.88	7.07
≥3 h/day	26.9	12.68	10.98
HRQoL: the EQ-5D-Y dimensions			
Walking			
No problems	91.7	11.74	8.14
Some or a lot of problems	8.3	18.70	10.41
Looking after self			
No problems	96.4	12.37	8.09
Some or a lot of problems	3.6	11.20	14.75
Doing usual activities			
No problems	89.6	11.98	8.07
Some or a lot of problems	10.4	14.92	10.58
Having pain or discomfort			
No problems	59.0	11.35	7.66
Some or a lot of problems	41.0	13.71	9.29
Feeling worried, sad, or unhappy			
No problems	69.9	10.72	7.79
Some or a lot of problems	30.1	16.02	9.56
Obese status			
Normal weight/overweight	90.1	11.89	8.06
Obese	6.8	13.41	8.43
Missing	3.1	–	–
Gender			
Girls	52.0	10.60	4.55
Boys	48.0	13.83	12.23
Residence			
Urban	65.2	13.32	9.25
Rural	34.8	10.40	6.57
Parental education			
Secondary school or less	23.9	14.92	10.48
College	36.3	14.83	8.60
University or above	36.7	9.04	6.69
Missing	3.1	–	–

(Continued)

TABLE 1 | Continued

Variables	% of Students (n = 1,352)	% of internalizing disorders	% of ADHDs
Household income (Can$)			
≤50,000	19.3	14.91	8.44
50,001–75,000	12.4	10.00	6.91
75,001–100,000	13.4	8.95	7.18
>100,000	31.0	13.19	7.31
Do not know/not to answer/missing	23.8	–	–

Weighted percentages of students are presented.
HRQoL, health-related quality of life; ADHD, attention deficit and hyperactivity disorder; DQI, diet quality index.

were not presented. All analyses were weighted such that the estimates represent the population of grade five students in the province of Alberta. The STATA/IC 15 software (StataCorp. 2017 Stata Statistical Software: Release 15, StataCorp LLC, College Station, TX) was used for the statistical analysis.

Research Ethics

The 2012 REAL Kids Alberta survey, including the parental informed consent forms, was approved by the Human Research Ethics Boards of the University of Alberta. The data linkage of the 2012 REAL Kids Alberta survey with the administrative health data was approved by the Human Research Ethics Boards of the University of Alberta and by Alberta Health and Wellness (reference no. REQ-01555).

RESULTS

Table 1 shows the descriptive results for the socio-demographic characteristics, health behaviors, HRQoL, and body weight status of the grade five students participating in the 2012 Alberta REAL Kids survey and the percentage of receiving a diagnosis of internalizing disorders and ADHDs from 2000 to 2012. Of the 1,352 participating students, 12.31% (n = 154) were diagnosed with an internalizing disorder and 8.32% (n = 113) were diagnosed with an ADHD during the time between birth (2000–2011) and the beginning of the survey in April in 2012 (children at age 10 or 11 years). Students who had a poorer diet quality and engaged in an inactive lifestyle received more physicians' diagnoses of internalizing disorders and ADHDs throughout childhood. Students who spent more time using a computer or playing video games (e.g., ≥3 h/day relative to < 1 h/day) had more health care provider contacts for an ADHD. The prevalence of diagnosis for an internalizing disorder was higher among students who reported having some or a lot of problems in "feeling worried, sad or unhappy" of the EQ-5D-Y, and the prevalence of diagnosis for an ADHD was greater among students who had some or a lot of problems in "having pain or discomfort." The number of students who received a diagnosis of internalizing disorder and ADHD was higher among boys than girls.

Table 2 presents the negative binomial regression results for the associations between health behaviors, and internalizing disorder and ADHD, respectively. Students in the highest tertile for diet quality had significantly lower number of diagnoses of internalizing disorder (IRR = 0.44, 95% CI = 0.23–0.85) and ADHD (IRR = 0.43, 95% CI = 0.20–0.91), respectively, relative to students in the lowest tertile for diet quality after adjusting for the effects of socio-demographic variables (adjusted model 1, **Table 2**). Students who were physically inactive had significantly more diagnoses of internalizing disorder (IRR = 1.98, 95% CI = 1.19–3.30) and ADHD (IRR = 4.17, 95% CI = 2.25–7.72) relative to their peers who were physically active (adjusted model 1). Children who played computers or video games more than 3 h daily had more health care contacts for ADHD than their peers who played computers or video games < 1 h daily (IRR = 2.96, 95% CI = 1.37, 6.41; adjusted model 1). TV viewing was not significantly associated with increased diagnoses of internalizing disorder. Excessive TV viewing (>3 *vs.* <1 h/day) was significantly associated with increased diagnoses of ADHD in the unadjusted model (IRR = 2.43, 95% CI = 1.14–5.16), but the association was attenuated to be insignificant in the adjusted models. The adjusted associations between health behaviors and mental health disorders were similar after additional adjustment for obese status (adjusted model 2, **Table 2**).

Boys were more likely than girls to receive health care contacts for both internalizing disorder and ADHD. Obese children were less likely to be diagnosed with ADHD than normal weight children. Students with the highest level of parental education (university or above *vs.* secondary or less) experienced lower number of diagnoses of internalizing disorder (IRR = 0.43, 95% CI = 0.22–0.86), while students in a household with the highest parental education as college level (*vs.* secondary or less) had more diagnoses of ADHD (IRR = 2.03, 95% CI = 1.02–4.04) (adjusted model 1, **Table 2**). Children with an annual household income of $50,001–$75,000 were less likely to be diagnosed with an internalizing disorder compared to those children with the lowest annual household income (< $50,001) (**Table 2**).

Table 3 shows the negative binomial regression results for the association between HRQoL measured by the EQ-5D-Y and mental health disorders. Children who reported having some or a lot of problems relative to no problems in "feeling worried, sad or unhappy" had more health care provider visits for internalizing disorders (unadjusted IRR = 2.38, 95% CI = 1.07–5.29; adjusted model 1: IRR = 1.91, 95% CI = 1.05–3.47; adjusted model 2: IRR = 1.81, 95% CI = 1.06–3.07). Children who reported having some or a lot of problems in "having pain or discomfort" received more diagnoses of ADHDs based on the univariate regression result (unadjusted IRR = 1.80, 95% CI = 1.00–3.23).

DISCUSSION

In this study, we observed that poor diet quality and low physical activity among grade five students were associated with increased diagnoses of both internalizing disorders and ADHDs during childhood. Excessive use of computer and video games and watching TV were associated with increased health care services

TABLE 2 | IRRs and 95% CIs for diagnoses of internalizing disorder and ADHD by health behaviors among grade five students participating in the 2012 REAL Kids survey, Alberta, Canada (n = 1,352).

Variables	Internalizing disorder: IRR (95% CI)			ADHD: IRR (95% CI)		
	Unadjusted model	Adjusted model 1	Adjusted model 2	Unadjusted model	Adjusted model 1	Adjusted model 2
DQI (ref.: Lowest tertile)						
Middle tertile	0.55 (0.24–1.25)	0.80 (0.43–1.51)	0.82 (0.43–1.55)	0.71 (0.34–1.48)	**0.35 (0.16–0.76)**	**0.41 (0.19–0.90)**
Highest tertile	**0.29 (0.13–0.65)**	**0.44 (0.23–0.85)**	**0.46 (0.24–0.87)**	0.57 (0.29–1.13)	**0.43 (0.20–0.91)**	**0.45 (0.21–0.97)**
Physical activity (ref.: Active)						
Inactive (PAQ-C score<3.0)	**2.31 (1.03–5.17)**	**1.98 (1.19–3.30)**	**2.01 (1.21–3.35)**	**2.43 (1.34–4.41)**	**4.17 (2.25–7.72)**	**4.36 (2.30–8.28)**
Computers/video games (ref.: <1 h/day)						
1–2 h/day	0.79 (0.39–1.60)	0.87 (0.49–1.53)	0.86 (0.49–1.52)	1.35 (0.60–3.05)	0.81 (0.39–1.68)	0.82 (0.40–1.68)
≥3 h/day	1.08 (0.35–3.32)	0.69 (0.35–1.37)	0.70 (0.36–1.39)	**3.25 (1.53–6.91)**	**2.96 (1.37–6.41)**	**3.34 (1.59–6.99)**
TV viewing (ref.: <1 h/day)						
1–2 h/day	1.33 (0.66–2.67)	1.05 (0.60–1.84)	1.03 (0.59–1.79)	1.12 (0.54–2.32)	0.92 (0.46–1.85)	0.88 (0.44–1.76)
≥3 h/day	1.65 (0.59–4.64)	1.06 (0.56–1.99)	1.05 (0.56–1.97)	**2.43 (1.14–5.16)**	1.41 (0.64–3.08)	1.31 (0.60–2.82)
Gender (ref.: Girls)						
Boys	1.10 (0.49–2.47)	**1.77 (1.04–3.00)**	**1.81 (1.07–3.05)**	**3.57 (1.76–7.21)**	**8.19 (4.56–14.72)**	**7.92 (4.41–14.22)**
Residential area (ref.: Urban)						
Rural	**0.51 (0.26–1.00)**	0.63 (0.38–1.05)	0.64 (0.39–1.06)	0.65 (0.36–1.19)	0.70 (0.40–1.24)	0.75 (0.43–1.32)
Parental education (ref.: Secondary or less)						
College	0.44 (0.18–1.08)	0.60 (0.30–1.18)	0.58 (0.29–1.15)	0.83 (0.43–1.61)	**2.03 (1.02–4.04)**	**2.03 (1.01–4.08)**
University or above	0.43 (0.16–1.15)	**0.43 (0.22–0.86)**	**0.43 (0.21–0.86)**	0.45 (0.20–1.05)	0.77 (0.38–1.56)	0.77 (0.38–1.56)
Household income (ref.: ≤$50,000)						
$50,001–$75,000	**0.19 (0.07–0.57)**	**0.30 (0.12–0.73)**	**0.30 (0.12–0.73)**	0.74 (0.21–2.57)	1.52 (0.42–5.52)	1.48 (0.42–5.23)
$75,001–$100,000	0.52 (0.17–1.63)	0.52 (0.21–1.29)	0.53 (0.22–1.29)	0.78 (0.33–1.82)	0.53 (0.23–1.23)	0.56 (0.24–1.30)
>$100,000	0.52 (0.18–1.47)	0.78 (0.37–1.61)	0.78 (0.38–1.61)	1.00 (0.45–2.21)	1.09 (0.46–2.59)	1.11 (0.47–2.62)
Obese (yes vs. no)	0.64 (0.27–1.53)		0.87 (0.37–2.05)	**0.24 (0.09–0.62)**		**0.21 (0.08–0.53)**

Adjusted model 1, adjusted for the demographic variables; adjusted model 2, inclusion of obese status from adjusted model 1. The adjusted models also adjusted for energy intake. All estimates were weighted to represent population estimates.

IRRs, incidence rate ratios; CIs, confidence intervals; ADHD, attention deficit and hyperactivity disorder; ref., reference group; DQI, diet quality index. Bold values indicate statistical significance ($p < 0.05$).

for ADHDs throughout childhood. Students with some or a lot of problems in the EQ-5D-Y dimensions of "feeling worried, sad or unhappy" and "having pain or discomfort" had greater health care contacts with health care providers for internalizing disorders and ADHDs, respectively.

This study contributes to the existing research by investigating the associations between health behavior and HRQoL among children and their mental health disorders during childhood. Particularly, we observed that higher diet quality among children aged 10–11 years was related to less clinical diagnoses of both internalizing disorders and ADHDs during childhood. Studies among adults suggest that poor diet quality is associated with a higher risk of depression over time (38). The evidence for the relationship between overall diet quality and mental health in children and youth is inconclusive due to variabilities in the measure of diets, mental health, and the study design (13, 14). Especially, longitudinal studies that investigate the association between diet quality and mental health among children < 12 years old are still lacking (13). For example, in a systematic review that synthesized the relationship between diet and mental health in children and adolescents, there were only three prospective studies among the total of 12 included studies (17, 21, 39), and only one of the three prospective studies has analyzed the association between diet and mental health in children (39). More studies using longitudinal design in childhood are needed to reinforce the evidence. The finding in this study aligns with few prior longitudinal studies showing that poor diet quality is associated with worse internalizing mental health among adolescents (17, 40). Concerning the relationship between diet quality and externalizing problems like ADHD, the observation for the effect of diet quality on ADHD in childhood in this study is consistent with our previous research (33) and other studies showing that healthy diets are associated with less ADHDs (41, 42). Notably, the present study adds to the existing findings in the literature by presenting data on diet quality and mental disorders among a school-based cohort of preadolescent children. In this study, we used the composite measure of diet quality that was based on the DQI-I (35). One major advantage of the DQI-I is that it constitutes four relevant components, including variety, adequacy, moderation, and overall balance of the diet, and it can be used for the comparison of diet quality across countries. Previous studies have also evaluated the effect of essential nutrients on mental health, such as the association of omega-3 and omega-6 fatty acids and their balance with mental health (43). Given that food items and nutrients are usually consumed in combinations that may produce a synergistic effect

TABLE 3 | IRRs and 95% CIs for diagnoses of internalizing disorder and ADHD by the EQ-5D-Y dimensions among grade five students participating in the 2012 REAL Kids survey, Alberta, Canada.

Variables	Internalizing disorder: IRR (95% CI)			ADHD: IRR (95% CI)		
	Unadjusted model (n = 1,352)	Adjusted model 1 (n = 1,346)	Adjusted model 2 (n = 1,346)	Unadjusted model (n = 1,352)	Adjusted model 1 (n = 1,346)	Adjusted model 2 (n = 1,346)
The EQ-5D-Y dimensions (ref.: No problems)						
Walking Some or a lot of problems	1.25 (0.59–2.62)	1.25 (0.57–2.77)	0.96 (0.48–1.91)	1.89 (0.78–4.62)	**3.58 (1.00–12.79)**	3.01 (0.87–10.37)
Looking after self						
Some or a lot of problems	0.82 (0.24–2.79)	0.72 (0.24–2.23)	1.06 (0.35–3.26)	1.21 (0.43–3.42)	1.43 (0.45–4.52)	0.92 (0.29–2.91)
Doing usual activities						
Some or a lot of problems	0.99 (0.42–2.33)	1.45 (0.57–3.67)	1.30 (0.59–2.86)	1.11 (0.39–3.18)	0.77 (0.33–1.79)	0.67 (0.28–1.57)
Having pain or discomfort						
Some or a lot of problems	1.75 (0.79–3.85)	1.27 (0.75–2.13)	1.43 (0.87–2.34)	**1.80 (1.00–3.23)**	1.56 (0.82–2.99)	1.30 (0.67–2.52)
Feeling worried, sad, or unhappy						
Some or a lot of problems	**2.38 (1.07–5.29)**	**1.91 (1.05–3.47)**	**1.81 (1.06–3.07)**	1.46 (0.78–2.73)	1.22 (0.65–2.27)	1.34 (0.70–2.56)

Adjusted model 1, adjusted for the variables in the table and the following demographic variables: gender, residency, parental education, and household income; adjusted model 2, additionally adjusted for health behaviors (diet quality, physical activity, use of computers/video games, and TV viewing) from the adjusted model 1. The adjusted models also adjusted for energy intake. All estimates were weighted to represent population estimates.

IRRs, incidence rate ratios; CIs, confidence intervals; ADHD, attention deficit and hyperactivity disorder; ref., reference group; DQI, diet quality index. Bold values indicate statistical significance ($p < 0.05$).

on mental health, more in-depth research in the future will help to better elucidate the relationship between various forms of fatty acids and mental health disorders while accounting for the effect of other relevant nutrients (e.g., essential minerals and vitamins) (21, 44).

The health benefits of PA on mental health have been well-demonstrated in cross-sectional studies in children and adolescents (11, 12). Findings from prospective studies are less consistent (18, 45–47). We found that low PA among grade five students (relative to high PA) is related to increased diagnoses of internalizing disorders in childhood, which is in line with some longitudinal studies observing that insufficient PA is associated with more internalizing problems in children and adolescents (18, 47). We observed a significant association between higher levels of PA and fewer diagnoses of ADHD among children. This finding is in line with our previous finding in adolescents (33) and some other prospective studies revealing the health benefits of PA for ADHD (48). The findings suggest that PA may present a protective effect for ADHD.

We observed that children who engaged in excessive use of computers and video games (≥3 *vs.* <1 h/day) had significantly more diagnoses of ADHDs, which is consistent with previous studies reporting that playing computers and video games was associated with increased attention problems and ADHD among children and adolescents (33, 49, 50). While some studies observed that increased time spent on playing computers and video games was related to more internalizing disorder problems such as depression and anxiety among youth (20, 51), we did not find a significant association between the use of computers and video games and internalizing disorder in children. This observation is in line with other studies reporting that playing computers or video games was not related to poor mental health (52, 53).

The effect of TV viewing on mental health among children and adolescents is inconclusive. Some studies found a significant association between increased TV viewing and lower mental health (51, 54), and other studies did not observe a significant association (19, 55). We found that watching TV was not significantly associated with diagnoses of internalizing disorder. One possible explanation for the inconsistent findings across studies is that the association of TV viewing with mental health may be related to both the time of exposure and the content of TV viewing. Watching educational TV programs may have beneficial effects for mental health (55, 56), whereas exposure to some stress- or anxiety-stimulating contents of TV programs such as violent shows or games may exacerbate children' emotional stress and anxiety (57). Studies on the relationship between SB and mental health among children and preadolescents are still lacking as the majority of the prior relevant studies in young people have examined the relationship among adolescents and youth. More research is needed to examine the relationship between different types of sedentary behaviors and mental health among children.

To the best of our knowledge, this is the first study that examined the correlations between HRQoL and mental health among a population-based sample of children using the EQ-5D-Y. Previous studies that used the EQ-5D-Y have mostly investigated the psychometric properties (e.g., validity and reliability) of the measure or applied the measure among children and youth with chronic diseases (36, 58). In this study, we found that "feeling more worried, sad or unhappy" is associated with a higher rate of internalizing disorder diagnosis and that "having more pain or discomfort" is related to a higher rate of ADHD diagnosis, which are in agreement with several other studies presenting that a lower HRQoL (both the physical and mental dimensions) is associated with both more internalizing and externalizing problems among children and adolescents

(4, 27, 59). We observed in this study that 41% of children reported having "some or a lot of problems" in the EQ-5D-Y dimension "pain or discomfort" (**Table 1**). This finding is consistent with our previous studies that showed a similar pattern in the prevalence of health problems in the EQ-5D-Y dimensions (60).

In this study, we performed retrospective data analysis and focused on the association between health behaviors and HRQoL (exposures), respectively, among grade five students and mental health disorder outcomes throughout childhood (as lifetime diagnoses of internalizing disorder and ADHD). Prior research has shown that health behaviors and dietary habits are usually established during childhood and remain later on in adolescence or adulthood (22, 23). Our findings emphasize the importance of interventions targeting promoting healthy lifestyle behaviors to improve mental health in childhood and preadolescence. It is worth mentioning that bidirectional or reverse associations between health behaviors or HRQoL and mental health may exist. For example, health-related behaviors or HRQoL and mental health may have reciprocal associations over time (61). Longitudinal data with mental health, health behaviors, and HRQoL data available over time would warrant better elucidation of the longitudinal reciprocal associations between these variables. In this study, while the mental health disorder data were available from children's birth to the time when they were 10 or 11 years old, as students' health behaviors and HRQoL were collected at the ages of 10–11 years, and no earlier data on these variables were available, the study is limited to testing whether mental health disorders were influenced by earlier health behaviors or HRQoL among children before the ages of 10–11 years.

The observation that boys were more likely than girls to seek health care for internalizing disorder and ADHD is consistent with our previous studies in cohorts of adolescents (15, 20, 33). While some previous studies have shown that adolescent girls had more internalizing disorder problems than adolescent boys, this study observed that boys appeared more vulnerable to internalizing disorders occurring in childhood than girls. The difference may be explained by differences in the developmental trajectories of mental health problems by gender and age of children. Previous research showed that internalizing disorders such as depression, emotional problems, and anxiety increase markedly in the adolescent period, and the increase tends to be greater among girls than boys after 10–11 years (2, 62). During childhood, boys may be more subject to mental health problems than girls (62, 63). More research among children would warrant confirming the observation of gender differences in internalizing disorder problems. The findings of the present study suggest that programs targeting preventions of internalizing disorders and ADHD in childhood should be gender-focused and emphasize health promotion efforts to meet the needs among boys in order to reduce the burden of mental health disorders.

This study has several strengths. The analysis was based on a large sample of grade five students in the Canadian province of Alberta with their lifetime administrative health records linked to the population health survey data. The availability of the lifetime longitudinal administrative health data for children provided a unique opportunity for us to examine the relationship between the health behaviors and HRQoL of children and the clinical diagnoses of both internalizing disorders and ADHDs throughout childhood. The use of physician-diagnosed internalizing disorders and ADHD yielded a more accurate and clinically meaningful assessment of mental health relative to self-reported mental health measures among children. The regression analysis for the associations of mental health disorder with health behaviors and HRQoL adjusted for the confounding influence of socio-demographic variables and childhood obesity among children; thus, the findings provide more valid and robust inferences to the target population.

Limitations of this study should also be acknowledged. Assessments of diet quality, SB, and PA were based on self-report and therefore may be subject to recall bias or error. Due to the observational nature of this study, the study findings preclude causal inferences, although retrospective medical care data are better than cross-sectional studies to elucidate directionality between the predictor variables and disease outcomes. In addition, ∼41% of the students who completed the REAL Kids Alberta survey were not included in the analysis because their parents did not provide valid health care card numbers for their children. However, there was not a significant difference between the participating and the non-participating students with respect to the demographic characteristics and the exposure variables, except that the prevalence of "having pain or discomfort" in the HRQoL was slightly lower in the study sample (41.22%) than in the excluded sample (45.68%, $p = 0.032$).

CONCLUSIONS

This study revealed that low diet quality, physical inactivity, high sedentary behavior, and poor HRQoL among children were associated with more diagnoses of mental health disorders throughout childhood. Taking into consideration the growing body of literature suggesting a role of health behaviors in the causation of mental health, our findings suggest that effective health promotion programs targeting promoting healthy diet quality and physical activity, reducing sedentary behavior, and improving HRQoL among children may contribute to reducing the burden of mental health.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available due to privacy and ethical restrictions. Details of the administrative health data access process are available from: https://www.alberta.ca/health-research.aspx. Requests to access the datasets should be directed to PV, paulus.veugelers@ualberta.ca.

ETHICS STATEMENT

The 2012 RealKids Alberta survey data collection, including parental informed consent forms, were approved by the Human Research Ethics Boards of the University of Alberta. The data linkage of the 2012 RealKids Alberta survey with the administrative health data was approved by the Human Research Ethics Boards of the University of Alberta and by Alberta Health and Wellness (Reference number: REQ-01555). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

PV and AO conceived and designed the study. XW analyzed the data. PV, AO, and XW wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Severe Psychopathology and Substance Use Disorder Modify the Association Between Housing Trajectories and Food Security Among Homeless Adults

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Purpose: We examined the housing trajectories of homeless people with mental illness over a follow-up period of 6 years and the association of these trajectories with food security. We then examined the modifying role of psychopathology and alcohol and substance use disorders in this association.

Materials and Methods: We followed 487 homeless adults with mental illness at the Toronto site of the At Home/Chez-Soi project—a randomized trial of Housing First. Food security data were collected seven times during the follow-up period. Psychopathology (Colorado Symptom Index score) and alcohol and substance use disorders were assessed at baseline. Housing trajectories were identified using group-based trajectory modeling. Logistic regression was used to estimate the association between housing trajectory groups and food security.

Results: Three housing trajectory groups were identified: rapid move to consistent stable housing (34.7%), slow and inconsistent housing (52.1%), and never moved to stable housing (13.2%). Individuals included in the rapid move to consistent housing trajectory group had higher odds of remaining food secure compared with those in the never moved to stable housing trajectory group over the follow-up period [AOR 2.9, 95% CI: 1.3–6.6, *P*-value: 0.009]. However, when interactions were considered, this association was significant among those with moderate psychopathology but not severe psychopathology. Individuals with substance use disorder and in the never moved to stable housing group had the lowest food security status.

Discussion: Severe psychopathology and substance use disorders modified the association between housing trajectories and food security.
International Standard Randomized Control Trial Number Register (ISRCTN42520374).

Keywords: psychopathology, substance use disorder, housing trajectories, food security, homeless adults

INTRODUCTION

Homelessness (living without stable, safe, permanent, appropriate housing or the immediate prospect, means and ability of acquiring it (1) is detrimental for almost every life dimension of affected individuals. Being homeless is a crucial stress factor for well-being as it reflects severe material deprivation and, in addition, erodes mental, cognitive, and physical health (2–8); exposes individuals to risky conditions and behaviors [e.g., violence, bad meteorological conditions, discrimination; (9, 10)]; and precludes access to such basic services as sanitation, healthcare, water, or food (11–13).

Access to food is a consistent unmet need of homeless populations. Compared with the general population, homeless individuals have lower food security (14), lower nutrient intake, and diet insufficiency (15, 16). Homeless individuals typically cannot access kitchens to prepare meals and preserve perishable foods (17, 18), forcing them to depend on fast food, shelter or community meals, and even food waste to meet their needs or to remain hungry (19–21). The intertwinement of homelessness with mental illness and substance use worsens access to food because it generates competing needs for purchasing medications and substances (22–25).

Housing First (HF) interventions—generally including rent supplements and mental health support services—have been implemented internationally to facilitate exit from homelessness to stable housing while also providing social and health services to support housing stability and enhance health and well-being (26, 27). Studies in Canada and the United States demonstrate the effectiveness of HF interventions in promoting rapid exit from homelessness (28–30). However, two main concerns have been raised about these interventions. First, exiting homelessness remains a complex and non-linear process (31–33). Although some individuals who participate in HF interventions move rapidly and remain stably housed, others are either less successful in remaining stably housed or are never able to become stably housed (31, 32). These different housing trajectories affect and reflect other aspects of the lives of homeless adults. A study by Kerman et al. finds that housing trajectories shape patterns of social services use, independent of whether individuals are in the intervention or standard treatment arms (34). For example, participants who achieved sustained housing stability across both intervention and standard treatment groups have similar patterns of emergency department use, hospitalization, inpatient psychiatric admission, or food bank use. Within the intervention group, social and health services use was largely different among subgroups of individuals with different housing patterns.

Second, as for several mental health outcomes, HF interventions seem to have limited effect on quality of life of homeless individuals, including the satisfaction of some basic needs, such as food security, which is at the physiological level of Maslow's pyramid of needs and well-being (35–37). Previous analysis of HF in five Canadian cities over a 2-year period showed that access to stable housing was not sufficient to improve food security among individuals with mental illness (37). However, the heterogeneity of housing trajectories was not adequately accounted for in that study.

Here, we examine patterns of exiting homelessness to stable housing (housing trajectory groups) among homeless individuals with mental illness participating in the Toronto At Home/Chez Soi Study over a follow-up period of 6 years (38). This long follow-up period provided enough time to observe consistent changes over time, contrary to previous analyses that were limited to 2 years (31, 33, 39). Second, we ask whether these housing trajectory groups were associated with food security of study participants over the study period. Finally, we investigated whether the association between housing trajectory groups and food security differed across the severity of psychopathology and alcohol and substance use disorders. We hypothesized that a rapid move to stable housing was associated with consistent food security over the follow-up period and that this association was weaker among participants with severe psychopathology and alcohol and substance use disorders.

MATERIALS AND METHODS

AH/CS Intervention

This study used data from the Toronto site of the At Home/Chez Soi (AH/CS) study, which was a randomized trial that compared the HF intervention (provision of mental health support services, such as assertive community treatment or intensive case management, plus rent supplement) to treatment as usual (TAU) (access to social, housing, and health services available in the community) (40). Participants were recruited from Toronto community agencies, shelters, clinics, and directly from the street between October 2009 and July 2011. The Toronto AH/CS participants were initially followed for 2 years (Phase I) between October 2009 and July 2013. In 2013, the study received additional funding to extend its follow-up period from January 2014 to March 2017 (Phase II) for a total follow-up period of approximately 6 years. Detailed information on study recruitment, design, population, and measurement instruments is reported elsewhere (41).

Four inclusion criteria were used to select AH/CS study participants: (1) being 18 years of age or older, (2) being absolutely homeless or precariously housed, (3) having a diagnosed severe mental disorder, and (4) not being served by assertive community treatment or an intensive case management program. Prior to randomization, participants were stratified by their level of needs for mental health services as high needs (HN) and moderate needs (MN). The level of need for mental health services was assessed using a combined algorithm that included having a psychotic disorder or bipolar affective disorder with psychotic symptoms [based on the Mini International Neuropsychiatric Interview 6.0 (MINI)], low community functioning [based on the Multnomah Community Ability Scale (MCAS)], presence of a comorbid substance use disorder, and prior history of hospitalizations and incarcerations (40–43). Out of the 575 Toronto participants, 197 participants met criteria to be classified as HN and 378 as MN. Then, according to their level of need, participants were randomly assigned to either the HF treatment or TAU. Participants assigned to the treatment group with HN received HF support services with assertive community treatment (ACT), and those

with MN received HF support services with intensive case management (ICM) treatment. Participants assigned to the TAU group continued to have access to housing and social and health support services locally available in their communities.

Ethical considerations

The Toronto AH/CS study received approval from the St. Michael's Hospital Research Ethics Board (Canada), and all participants gave informed written consent to participate in the AH/CS study. The AH/CS study is also registered with the International Standard Randomized Control Trial Number Register (ISRCTN42520374).

Measures and Operational Definitions

Stable Housing

We captured stable housing through a residential timeline follow-back calendar (RTLFB) questionnaire (31, 44), which was administered every 3 months (Phase I) or 6 months (Phase II) to track the number of days living/sleeping in different types of housing accommodations. An accommodation was defined to be stable housing if the participant had tenancy rights or was expected to remain in the same accommodation for more than 6 months. For each follow-up year, participants were classified as being stably housed if they remained in stable housing for at least 75% of RTLFB-accounted days over a calendar year.

Consistent Food Security

The modified version of the U.S. Adult Food Security Survey Module (US FSSM) [U.S. Department of Agriculture, Economic Service Research (45) U.S. Adult Food Security Survey Module: Three-Stage Design, with Screeners, 2012] was used to assess the food security status of each participant over the 30 days prior to interview time points. Data were gathered every 6 months during phase I and every 12 months during phase II up to seven times across the 6-year follow-up period. This instrument has been validated in previous studies to assess food security for individuals experiencing homelessness (46–48). It contains 10 items related to food access, and the code responses were summed up to compute the food security score. This score ranges from 0 to 10 and classifies food security status into two main groups: food secure [those with high food security (score = 0) and marginal food security (score = 1–2)] and food insecure [those with low food security (score = 3–5), and very low food security (score = 6–10)] (37, 49, 50).

Participants were classified as being consistently food secure over the follow-up time if they were in the "food secure" group for more than 50% of the duration of their follow-up interviews. For example, a participant with four follow-up interviews had to be food secure at least three times (more than 50%) to be classified as consistently food secure. To ensure that participants had a minimum follow-up number of interviews for the analysis, we excluded those who had fewer than three food security interviews ($n = 88$).

Covariates

HF Intervention

Because the present study is embedded within an HF intervention, we considered the indicator of HF treatment (HF vs. TAU) as a covariate to adjust for the housing trajectory groups over the follow-up period.

Other covariates included sociodemographic variables (age at baseline (in years), self-reported gender (classified as male or not male), ethno-racial group membership [ethno-racial and not ethno-racial group), and marital status (single or not)], number of children under 18 years, and lifetime duration of homelessness prior to study enrolment (<3 and ≥ 3 years). No other gender categories were considered because there were fewer than 10 non-binary individuals in our sample. Participants were asked whether they used a food bank in the last 6 months prior to food security interviews, and we counted the number of times over the follow-up period.

Modifier Variables

Severe psychopathology

We used the Colorado Symptom Index score (CSI) at baseline to assess for the effect of psychopathology on food security (40, 51). CSI is a widely used self-report measure of psychiatric symptomatology and includes 14 items. Participants were asked how often they experienced specific psychiatric symptoms, such as "How often have you felt nervous, tense, worried, frustrated, or afraid?" or "How often have your voices, thoughts, or feelings interfered with your doing things?" Their responses were graded using a five-point Likert-items rated from "not at all" (1) to "at least every day" (5). Total scores ranged from 14 to 70, and higher scores indicated more severe psychiatric symptoms. Previous studies show that this index has high internal consistency (Cronbach's alpha = 0.92) (52, 53). CSI was dichotomized using a preestablished clinical threshold 30 or higher to indicate individuals with high (1) or low (0) psychopathology severity (52).

Alcohol and Substance disorders

Alcohol and non-alcohol substance use disorders were identified separately based on DSM-IV criteria using the MINI 6.0 and were evaluated at the time participants were screened for entering the study (40, 54).

Statistical Methods

We used group-based trajectory modeling to identify patterns of exiting homelessness to stable housing over the 6-year follow-up period (55). This modeling technique allows for the identification of clusters of individuals who followed a similar housing trajectory over time (56). Assuming a logistic distribution of housing stability, it uses intercept and time as change parameters to estimate latent trajectory groups. For the shape of trajectory groups, we tested different polynomial growth factors (linear, quadratic, and cubic time factors) and determined the optimal number of trajectory groups through the Bayesian information criterion (BIC). To determine the best-fit trajectory shapes, we used the average posterior probability measure and the weighted odds of correct classification (OCC) (55). Afterward, the model

TABLE 1 | Characteristics of the At Home/Chez Soi participants at baseline ($n = 487$).

Variable	*n*	%
Consistently food secure		
Yes	194	39.8
No	293	60.2
Gender		
Male	333	68.4
Female	154	31.6
Age group		
18–34	172	35.3
35–44	127	26.1
45–74	188	38.6
Education level		
Middle/high school	228	48.1
Completed high school	85	17.9
Graduate/post-graduate	161	34.0
Ethno-racial group membership		
Ethno-racial	282	57.9
not ethno-racial	205	42.1
Marital status		
Not married	327	67.1
Married	160	32.9
Lifetime duration of homelessness		
<3 years	210	44.97
3 years or more	257	55.03
Number of children under 18 [Mean (SD)]	487	1.6 (1.1)
Food bank use [Mean (SD)]	487	1.97 (1.96)
Intervention		
Housing First (HF)	272	55.9
Treatment as usual (TAU)	215	44.1
Severe psychopathology (CSI* ≥30)	378	77.6
Alcohol use disorder	214	43.9
Substance use disorder	231	47.4

**Colorado symptoms index—SD, standard deviation.*

was adjusted for HF intervention group membership. All models were estimated using the module *Traj* in Stata 15 (55).

Next, we used logistic regression models to estimate odds ratios and 95% confidence intervals for the association between housing trajectory groups and consistent food security over the 6-year follow-up period. Then, we adjusted the model including the following covariates: age, self-reported gender, ethno-racial group membership, marital status, number of children under 18 years, lifetime duration of homelessness, food bank use, severe psychopathology, alcohol use disorder, and substance use disorder. To assess the modifying effect of severe psychopathology and alcohol and substance use disorders, we reestimated the model with interaction terms, and the interaction graphs are presented. All statistical analyses were performed with Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.).

RESULTS

Sample characteristics are summarized in **Table 1**. Of 487 participants, 39.8% were consistently food secure (with high or marginal food security status) over the study period. Severe psychopathology was present in 77.6%, and 43.9 and 47.4% had alcohol and substance use disorders, respectively.

Housing Trajectories

Three housing trajectory groups were identified: a rapid move to consistent stable housing trajectory with a quadratic form, a slow and inconsistent housing trajectory with a cubic form, and a never moved to stable housing trajectory (see **Table 2** and **Figure 1**). Of the 487 participants, 34.7% of participants were classified in the rapid move to consistent stable housing group and 52.1% in the slow and inconsistent housing group; 13.2% never moved to stable housing during the study period. The BIC fit statistics confirmed this model as the best fit model (BIC for the two-group model $= -1416.08$; $BIC_3 = -1400.10$, and $BIC_4 = -1455.53$). The average posterior probability (>0.70) and the OCC-weighted posterior portability (>5) also indicate good fit. The adjusted model demonstrates that the HF intervention influences the trajectories, mainly by increasing the probability of having a rapid move to consistent housing and decreasing the probability of never moving or slow compared with the slow and inconsistent housing trajectory. Average posterior probabilities and two of the OCC-weighted posterior probabilities indicate improvement after the adjustment.

Housing Trajectory and Consistent Food Security

Compared with those in the never moved to stable housing trajectory, those in the rapid move to consistent housing stability group were more likely to be consistently food secure, AOR 2.9 [95% CI (1.3–6.6)] (see **Table 3**). Likewise, those with severe psychopathology and a substance use disorder were less likely to be consistently food secure (AOR 0.39 [95% CI (0.24–0.63)]) and 41% (AOR 0.59 [95% CI (0.37–0.95)]), respectively.

Modification Effects of Psychopathology and Substance Use Disorder

As shown in **Figure 2**, among participants with low psychopathology, those who moved to housing (rapid move to consistent housing and slow and inconsistent housing) were 40% more likely to be consistently food secure compared with those who never moved to stable housing. Conversely, among participants with severe psychopathology, no difference is observed between the housing trajectory groups. Likewise, those with no alcohol or substance use disorders and who never moved to stable housing were least likely to be consistently food secure (**Figure 3**). No modification effect was observed for alcohol use disorder.

DISCUSSION

This study examined housing trajectories and their association with food security among homeless adults with mental illness

TABLE 2 | Housing Trajectory Groups adjusted from Group-Based Trajectory modeling.

Parameters	Model I				Model adjusted for intervention group					
	Intercept	Linear	Quadratic	Cubic	Intercept	Linear	Quadratic	Cubic	AH	*P*-value
Rapid to consistent housing	−12.2	16.4	−2.3		−14.9	20.9	−3.0		**2.1**	**0.001**
Slow and inconsistent housing	−3.5	3.2	−0.8	0.1	−3.7	3.4	−0.9	0.1	**Ref.**	
Never moved to stable housing	−3.0				−2.9				**−1.2**	**0.017**
BIC	−1400.1				−1353.6					

Group	*N* (%)	Group APP	OCC weighted	*N* (%)	Group APP	OCC weighted
Membership and posterior probability						
Rapid to consistent housing	206 (38.4)	0.88	11.29	186 (34.7)	0.92	22.64
Slow and inconsistent housing	264 (49.2)	0.86	6.54	279 (52.1)	0.86	5.69
Never moved to stable housing	66 (12.4)	0.83	34.16	71 (13.2)	0.86	39.22

APP, average of the maximum posterior probability of assignments. OCC, Odds of correct classification weighted posterior probability. Bold: significant at a level of 5%.

in a large urban center. Three housing trajectory groups were identified: a rapid move to consistent housing group, a slow and inconsistent housing group, and a never moved to stable housing group. These results corroborate findings from previous studies on the complexity of exiting homelessness. Adair et al., using data from the multisite at Home/Chez Soi study of HF, found different housing trajectories over a 2-year period, including a group of almost no time housed (29%); a group of rapid and sustained housing (33%); and several small groups, such as slow and sustained housing, early housing, and gradually lost, rapid gain, and steep decline (31). Another study among homeless youth in Los Angeles County identified three trajectories over a 2-year period, a consistently sheltered group, a group with a high probability of finding and maintaining shelter over time, and a last group who remained inconsistently sheltered over a long term (33). Contrary to these studies conducted over a period up to 2 years, our study looked at pathways out of homeless to housing over a period of 6 years.

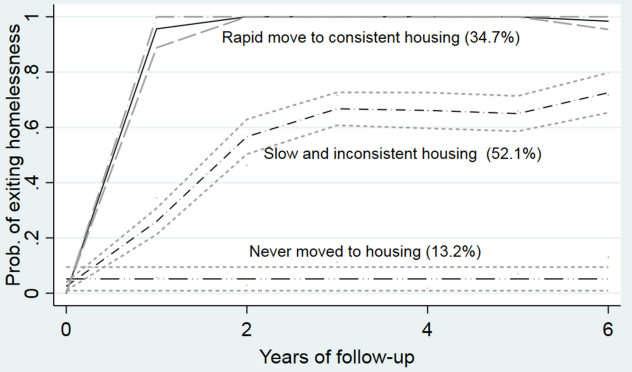

FIGURE 1 | Housing trajectory groups over time points with 95% confidence interval.

Our results indicate that providing housing is only one step toward supporting people experiencing homelessness by helping them leave streets and shelters and entering a residence. However, even after achieving housing, these individuals face several personal, economic, and social challenges and extreme poverty that can impede their achievement of long-term housing stability (32, 57–59). Moving into stable housing is accompanied by additional living costs (e.g., paying for utilities) that compete with other basic needs (e.g., food), rendering individuals vulnerable to eviction and repeated homelessness.

Our results also show that individuals in the rapid move to consistent housing group were more likely to be food secure compared with those in the never moved to stable housing group over the follow-up period. However, this association disappeared for those with severe psychopathology. Furthermore, those with substance use disorders and in the never moved to stable housing group were least likely to be food secure. Our results support findings from a recent study conducted by O'Campo et al. (37) on the role of housing stability as a key determinant of food security. Our findings offer new insight into the complexity of how pathways out of homelessness interact with mental health and substance use disorders to prevent individuals from achieving food security. The combination of a difficult housing trajectory with mental illness might prevent employment, forcing individuals to make trade-offs between food security, stable housing (e.g., rent), and other basic needs (59–61).

There are several study limitations to note. First, food security data may be affected by recall bias, which might influence the accuracy of reported findings. Second, there were not enough follow-up interviews to consistently assess food security over the

TABLE 3 | Multivariable logistic regressions for consistent food security and housing trajectory groups adjusted for baseline characteristics.

Variable	AOR (95% CI)	*P*-value
Housing Trajectory groups		
Never moved to stable housing (ref.)		
Slow and inconsistent housing	2.2 (1.0–4.8)	0.053
Rapid and stable housing	2.9 (1.3–6.6)	**0.009**
Severe psychopathology	0.39 (0.24–0.63)	**0.001**
Alcohol use disorder	1.01 (0.63–1.61)	0.964
Substance use disorder	0.59 (0.37–0.95)	**0.031**
Intercept	1.24 (0.40–3.90)	0.709

AOR, adjusted odd ratios.
The model is adjusted for the following variables: Gender, age, education level, ethno-racial group, marital status, lifetime homelessness, number of children under 18, and food bank use. Bold: significant at a level of 5%.

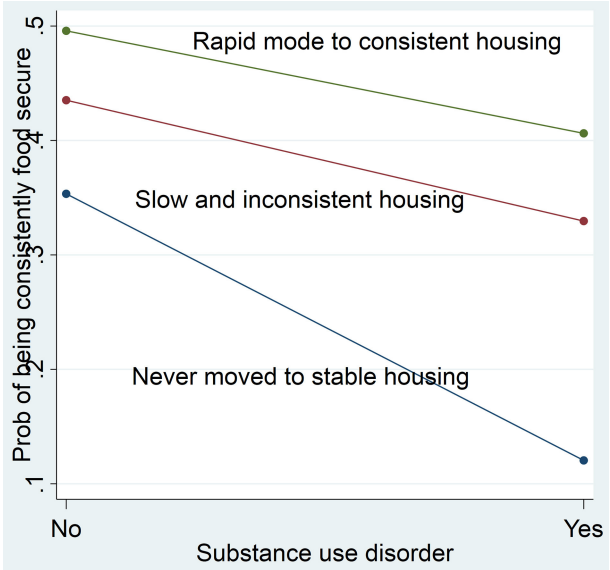

FIGURE 2 | Psychopathology modifies the effect of housing trajectory on food security.

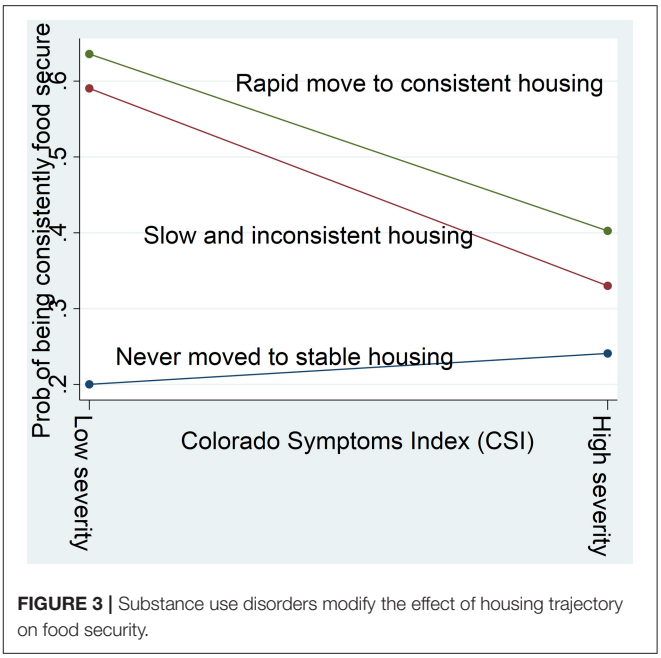

FIGURE 3 | Substance use disorders modify the effect of housing trajectory on food security.

entire study period. More food security interviews over the same follow-up period would have required reducing the time interval between interviews. Finally, this study focuses on homeless adults who have mental illness and is also limited to an only site, Toronto City, and cannot be generalized to all homeless adults.

Notwithstanding these limitations, this study provides a comprehensive view of the complexity of exiting homelessness to stable housing and its influence on food security. The analysis also offers insight into how psychopathology and substance use disorders contribute to poor food security even after homeless people achieve long-term housing stability. This study has two main policy implications. First, housing interventions must focus on achieving housing stability over a long period of time with special attention on factors that increase risk for unsuccessful housing trajectories. Second, it is important to enhance housing interventions with food security programs to better address the food needs of homeless adults with severe psychopathology and substance use disorders.

DATA AVAILABILITY STATEMENT

Data cannot be made publicly available for both ethical and legal reasons. They were collected from randomized trial implemented within a hospital setting, St. Michael's Hospital in Toronto, which conferred the participants the status of patient. Data also contain information related to mental health status of the participants. Data collection, use, and disclosure are governed by the Personal Health Information Protection Act (PHIPA, 2004) and must not be disclosed without their written informed consent, as was stated in the written informed consent form by law. As the study addresses a specific and small subpopulation, any combination of three to four variables can facilitate the identification of some participants. Nonetheless, Home/Chez Soi Toronto Data will be available to investigators for studies that have received approval from research ethics boards. Study proposals and data access requests should be sent to Evie Gogosis at evie.gogosis@unityhealth.to.

ETHICS STATEMENT

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Research Ethics Board of St. Michael's Hospital (Canada). Written informed consent was obtained from all subjects/patients. The At Home/Chez-Soi study is registered with the International Standard Randomized Control Trial

Number Register (ISRCTN42520374). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JL, CM-L, and PO'C conceived and designed the present research study. JL conducted the final statistical analysis, interpreted the data, and wrote the first manuscript draft. CM-L, RW, RN, and ML assisted in the study design, interpretation of the results, and revision of the first manuscript draft. PO'C, VS, and SH were also the principal investigators of the AH/CS study, Toronto site. All the co-authors revised and approved the present final manuscript version. All authors contributed to the interpretation of the results and critical revision and edition of the final manuscript.

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The PCT to Albumin Ratio Predicts Mortality in Patients With Acute Kidney Injury Caused by Abdominal Infection-Evoked Sepsis

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Purpose: Considerable evidence suggests that inflammation and malnutrition are common in patients with acute kidney injury (AKI) and correlated with mortality of various diseases. Despite this, few studies have reported the underlying predictive effects of inflammatory and nutritional markers in combination on the mortality of AKI patients. Herein, we aimed to explore the values of PCT and CRP as well as the ratios of PCT/Alb and CRP/Alb in the poor prognosis of patients with sepsis-induced AKI.

Patients and Methods: A total of 171 patients with AKI, caused by abdominal infection-evoked sepsis, were retrospectively studied and divided into a survival group (107 cases) and a non-survival group (64 cases). Univariate analysis was used to compare the clinical data of the two groups. Multivariate logistic regression analysis was used to analyze the independent risk factors of poor prognosis in patients with sepsis-induced AKI. The ROC curve was used to evaluate the diagnostic value of PCT, CRP, PCT/Alb, and CRP/Alb in the poor prognosis of patients with sepsis-induced AKI.

Results: Univariate analysis revealed that the values of PCT, CRP, CRP/Alb, and PCT/Alb were significantly different between AKI survival and non-survival groups, and further analysis found that PCT and PCT/Alb were independent risk factors for poor prognosis in patients with sepsis-induced AKI after adjusting with age and gender. Of note, the predictive accuracy (0.864 vs. 0.807), specificity (83.2 vs. 69.2), and sensitivity (79.7 vs. 76.6) of PCT/Alb were all higher than that of the simple PCT.

Conclusions: The ratio of PCT to Alb is an independent risk factor possessing a robust and accurate risk assessment for the poor prognosis of patients with sepsis-induced AKI, and it offers the potential to improve the management of this type of disease and a lower resultant mortality.

Keywords: procalcitonin, C-reactive protein, albumin, acute kidney injury, intra-abdominal infection

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INTRODUCTION

Sepsis, a systemic inflammatory response syndrome caused by infection, is mainly characterized by excessive release of inflammatory mediators and cytokines, which subsequently result in life-threatening organ dysfunction, especially in the heart and kidney. Although the implementation of the Surviving Sepsis Campaign (SSC) guidelines for sepsis management

has effectively reduced the incidence of sepsis, sepsis shock still accounts for 62% of overall shock cases, with hospital mortality > 40% (1–3). Of the intensive care unit (ICU) patients, intra-abdominal infection (IAI) is the primary cause of sepsis, with an overall mortality of 10.5% worldwide (4). Notably, in patients with sepsis, the renal microvascular system is sensitive to vasoconstrictor substances, which is often concomitant with blockage of renal blood flow and diminishing glomerular filtration rate, and these kinds of pathological changes in the kidney also contribute to the resultant development of sepsis-induced AKI (SAKI). Indeed, more than 45% of patients with sepsis suffered from AKI, and all displayed poor outcomes (5, 6). Hence, owing to the hazardous effects of kidney sepsis, discovering robust predictive markers of mortality risk for sepsis-induced shock or AKI is imperative and will be beneficial for the management of such complications and future therapeutic intervention.

It has been well-known that inflammation and malnutrition are ubiquity in AKI patients (7), but few studies have suggested that inflammation and malnutrition, individually or in combination, were associated with the prognosis of AKI patients (7, 8). Moreover, so far, there is no research about the combination of inflammation and malnutrition markers to predict mortality in patients with sepsis-induced AKI. The purpose of our study was to assess the correlation among inflammation markers Serum C reactive protein (CRP), procalcitonin (PCT), and nutritional marker albumin (Alb) and 90-day mortality in sepsis-induced AKI and to put more attention on the combined markers (CRP/Alb and PCT/Alb). Considering that previous studies always found the markers in combination outperforming either marker alone in terms of making predictions of patients' prognosis, we speculated CRP/Alb or PCT/Alb might be the valuable marker for predicting mortality in sepsis-induced AKI patients.

PATIENTS AND METHODS

Clinical Definition

IAI was defined as an infection limited to a hollow viscus or extended into a sterile area of the abdomen, such as the peritoneal cavity, mesentery, retroperitoneum, and abdomen wall (9, 10). Sepsis met the clinical criteria for septic shock [The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)] (1). Patients with AKI were enrolled in conformance with the criteria of the Kidney Disease Improving Global Outcomes (KDIGO) classification (11), and this was based on the serum creatinine increasing by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h or the serum creatinine level increasing ≥1.5 times over the baseline level within 7 days or cumulative 6 h urine output ≤0.5 ml/kg/h.

Patients

This observational retrospective study was conducted in the comprehensive ICU of the Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University. From January 1, 2016, to December 31, 2019, a total of 1,285 critically ill patients were admitted to the ICU. Among these admissions, 171 patients who met the criteria of septic shock-induced AKI [The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)] were studied (**Figure 1**). The exclusion criteria were applied and are depicted in **Figure 1**. Based on their prognosis, they were divided into two groups: the survival group (107 cases) and the non-survival group (64 cases). The study was approved by the ethics committee of Huaian No. 1 People's Hospital (date: September 10, 2020; approval number: YX-P-2020-153-01).

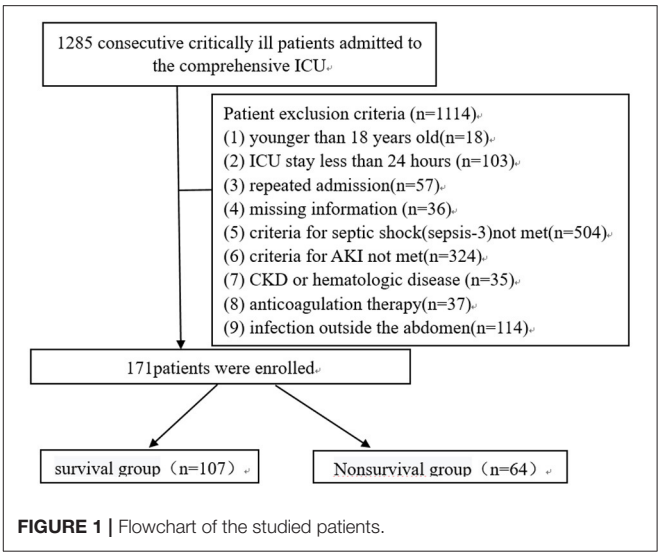

FIGURE 1 | Flowchart of the studied patients.

Data Collection

The data of patients were from electronic and paper medical records and recorded on electronic forms, including the following aspects: (1) demographic data: age, sex, weight, and body mass index (BMI); (2) admission status data: the source of IAI, comorbidities (hypertension and diabetes); and (3) laboratory data within 24 h of admission: serum procalcitonin (PCT), serum creatinine (SCr), serum albumin (Alb), white blood cell (WBC), neutrophil percentage (NEUT%), C-reactive protein (CRP), PCT/Alb ratio, CRP/Alb ratio, use of renal replacement therapy (CRRT), ventilation duration, and length of ICU stay.

STATISTICAL ANALYSIS

Continuous variables were expressed as mean ± SD for normally distributed variables or median with interquartile range for non-normally distributed variables, and categorical variables were expressed as percentages. In univariate analysis, a student *t*-test or Mann-Whitney U-test was performed to compare continuous variables, and a Pearson chi test or Fisher exact test was used to compare the categorical variables. For multivariate logistic regression analysis, PCT and PCT/Alb were served as continuous variables, and we adjusted age (a continuous variable) and gender (a categorical variable), two confounding factors, to remove the influence of confounding factors and to achieve high predictive accuracy of PCT and PCT/Albumin (the two primary indicators) in mortality of sepsis-induced AKI patients. The ROC curve was

applied to analyze and evaluate the diagnostic value of PCT, CRP, CRP/Alb, and PCT/Alb in the poor prognosis of patients (i.e., 90-day mortality) with sepsis-induced AKI. The power analysis (checking the sample size) and statistical analysis were performed using PASS 15.0 and SPSS 22.0 software packages, respectively (IBM, Chicago, Illinois, USA). The power analysis showed that the minimum number for our experimental design was forty-one, and our simple size met this demand. The value of $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics and Etiologies of Abdominal Infection

As presented in **Table 1**, mortality for abdominal abscess (caused by small intestinal necrosis or perforation disease) was significantly higher in patients (32.81%, $P < 0.01$), while mortality for the ileocecal and appendiceal disease was relatively lower (3.12%, $P < 0.05$). However, in respect to other etiologies of intra-abdominal infection, the mortality among patients showed no differences ($P > 0.05$). **Table 1** also displayed the demographic and clinical features, including age, gender, weight, BMI, comorbidities (hypertension and diabetes), length of ICU stay, ventilation duration, and CRRT; however, apart from weight and BMI, the remaining features displayed no differences between the survival group and the non-survival group ($P > 0.05$).

TABLE 1 | Baseline characteristics of patients between survival group and non-survival groups and etiologies of intra-abdominal infection.

	Survival group ($n = 107$)	Non-survival group ($n = 64$)	*P-value*
Age (y) (mean ± SD)	75.40 ± 10.78	73.76 ± 10.69	0.663
Male sex, *n* (%)	55 (51.40)	34 (53.12)	0.718
Weight (kg)	65.49 ± 11.23	60.37 ± 10.56	0.039
BMI (kg/m^2)	23.41 ± 2.76	22.04 ± 2.21	0.016
Hypertension, *n* (%)	64 (59.81)	25 (39.06)	0.120
Diabetes, *n* (%)	32 (29.90)	17 (26.56)	0.202
WBC (g/l) (mean ± SD)	18.18 ± 3.93	23.62 ± 17.22	0.328
NEUT% (mean ± SD)	92.52 ± 5.23	91.80 ± 8.61	0.802
Length of ICU stay (days), median (IQR)	10.5 (5.25–38.5)	7 (4–13)	0.864
Ventilation duration (days), median (IQR)	4.0 (0.75–34.75)	6 (3–11.5)	0.242
CRRT, *n* (%)	67 (62.62)	38 (59.37)	0.993
Gastroduodenal disease, *n* (%)	36 (33.64)	10 (15.62)	0.058
Biliary disease, *n* (%)	20 (18.69)	9 (14.06)	0.590
Colorectal disease, *n* (%)	24 (22.42)	13 (20.31)	0.838
Ileocecal and appendiceal disease, *n* (%)	16 (14.95)	2 (3.12)	0.040
Abdominal abscess, *n* (%)	4 (3.74)	21 (32.81)	0.003
Severe acute pancreatitis, *n* (%)	7 (6.5)	9 (14.06)	0.374

Continuous variables were expressed as mean ± SD or median with interquartile range, and categorical variables were expressed as a percentage.
IQR, range of quartile; WBC, white blood cell; NEUT%, neutrophil percentage; CRRT, renal replacement therapy; ICU, intensive care unit.

Univariate Analysis of Selected Inflammation and Nutritional Indicators in Patients With Sepsis-Induced AKI

Table 2 depicts the inflammation and nutritional indicators obtained from the blood of involved patients within 24 h of admission, including CRP, PCT, and Alb. Compared with the survival group, the concentration of PCT [52.57 (19.16–100.00) mg/l vs. 8.74 (1.07–21.93) mg/l, $P < 0.001$] and CRP [224.38 (188.13–276.77) mg/l vs. 186.33 (136.33–235.85) mg/l, $P = 0.008$] significantly increased in the non-survival group. In contrast, Alb, a marker used to reflect the nutritional status, showed a slight (non-significant) downward trend in the non-survival group when compared to the survival group (22.15 ± 5.48 g/l vs. 24.41 ± 4.72 g/l). Most notably, we found that the ratio of PCT/Alb and CRP/Alb in the non-survival group were both remarkably higher than that of the survival group [for PCT/Alb: 2.43 (2.93) vs. 0.29 (0.49), $P < 0.001$; for CRP/Alb: 10.81 (6.65) vs. 5.84 (5.58.), $P < 0.001$].

TABLE 2 | Univariate analysis of PCT, PCT/Alb, CRP, and CRP/Alb between survival and non-survival groups in patients with sepsis-induced AKI.

	Survival group ($n = 107$)	Non-survival group ($n = 64$)	*P*-value
PCT (ng/ml), median (IQR)	8.74 (1.07–21.93)	52.57 (19.16–100.00)	0.000
CRP (mg/l), median (IQR)	186.33 (136.33–235.85)	224.38 (188.13–276.77)	0.008
Alb(g/l) (mean ± SD)	24.41 ± 4.72	22.15 ± 5.48	0.234
CRP/Alb, median (IQR)	5.84 (5.34–10.92)	10.81 (7.14–13.79)	0.001
PCT/Alb, median (IQR)	0.29 (0.04–0.53)	2.43 (0.85–3.79)	0.000

IQR, range of quartile; Alb, Serum albumin; CRP, C-reactive protein; PCT, procalcitonin; CRP/Alb, the ratio of CRP to Alb; PCT/Alb, the ratio of PCT to Alb.

Multivariate Logistic Regression Analysis of Possible Predictors of Mortality in Sepsis-Induced AKI Patients

As shown in **Table 3**, after adjustment for age and gender, multivariate logistic regression analysis revealed that the odds ratio (OR) of PCT [OR, 1.060; 95% confidence interval (CI), 1.016–1.107] and PCT/Alb [OR, 2.372; 95% confidence interval (CI), 1.154–4.878] were >1 and that the *P*-values were all <0.05 (on the basis of $P < 0.05$, OR > 1 indicated the increase of risk and the higher the PCT and PCT/Alb value, the greater the mortality). Overall, both PCT and PCT/Alb were independent risk factors for poor prognosis in patients with sepsis-induced AKI. To further evaluate the diagnostic value of PCT and PCT/Alb in sepsis-induced AKI patients, the possible predictors were analyzed using the receiver operating characteristic (ROC) curve. As shown in **Table 4** and **Figure 2**, the predictive accuracy (0.864 vs. 0.807), specificity (83.2 vs.

TABLE 3 | Multivariate logistic regression analysis of predictive values of PCT, PCT/Alb, CRP, and CRP/Alb in patients with sepsis-induced AKI.

Variable	Unadjusted					Adjusted				
	β	SE	Wald	OR (95% CI)	*P*-value	β	SE	Wald	OR (95% CI)	*P*-value
PCT	0.059	0.022	7.081	1.060 (1.016–1.107)	0.008	0.065	0.027	5.889	1.067 (1.013–1.125)	0.015
PCT/Alb	0.864	0.368	5.517	2.372 (1.154–4.878)	0.019	0.979	0.459	4.544	2.662 (1.082–6.549)	0.033
CRP	0.014	0.011	1.624	1.014 (0.992–1.037)	0.203	0.023	0.013	3.120	1.023 (0.998–1.049)	0.077
CRP/Alb	0.229	0.183	1.563	1.257 (0.878–1.800)	0.211	0.152	0.202	0.563	1.164 (0.783–1.730)	0.453

Alb, Serum albumin; CRP, C-reactive protein; PCT, procalcitonin; CRP/Alb, the ratio of CRP to Alb; PCT/Alb, the ratio of PCT to Alb.

TABLE 4 | PCT, PCT/Alb, CRP, and CRP/Alb were analyzed by the ROC curve.

Variable	AUC	95% CI	Sensitivity (%)	Specificity (%)	Youden index	Critical value
PCT	0.807	0.740–0.875	76.6	69.2	0.458	18.455
PCT/Alb	0.864	0.807–0.922	79.7	83.2	0.629	0.6827

Alb, Serum albumin; PCT, procalcitonin; PCT/Alb, the ratio of PCT to Alb.

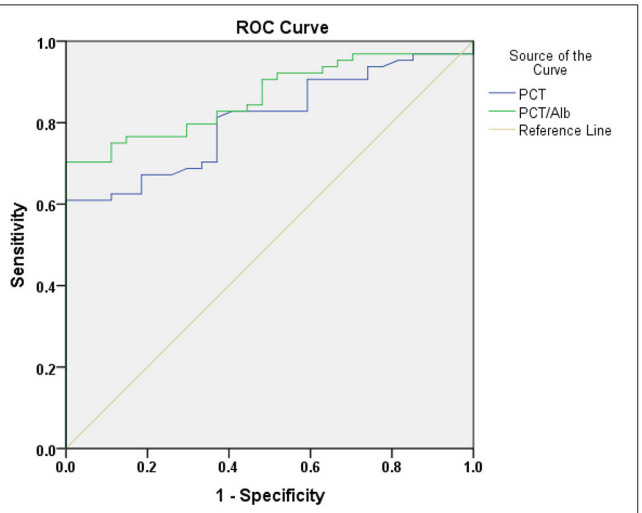

FIGURE 2 | The predictive value of PCT and PCT/Alb in the poor prognosis of sepsis-induced AKI patients.

69.2), and sensitivity (79.7 vs. 76.6) of PCT/Alb were all higher than the simple PCT, indicating that PCT/Alb might be a robust risk assessment marker for the poor prognosis of patients with sepsis-induced AKI.

DISCUSSION

We retrospectively assessed 1,285 patients' clinical data from the ICU of the Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University, from January 1, 2016, to December 31, 2019. Patients who met the sepsis-induced AKI criteria (171 cases) were further analyzed and compared. In the present study, we found that abdominal abscess and ileocecal and appendiceal disease were the etiologies with higher mortality in sepsis-induced AKI patients and that the values of PCT, PCT/Alb, CRP, and CRP/Alb were significantly higher in the non-survival group compared to the survival group. Further analysis discovered that both PCT and PCT/Alb were independent risk factors for poor prognosis in patients with sepsis-induced AKI and that PCT/Alb exhibited a more robust risk assessment value.

Inflammation and malnutrition are highly associated with the pathogenesis of AKI (12–14). CRP, an acute-phase protein synthesized by the liver, and PCT, a marker for detecting infection/inflammation, have been receiving attention in predicting mortality of diseases, including AKI (15–18). CRP was implicated in renal fibrosis and renal ischemia-reperfusion injury, and its increase was significantly related to the occurrence and mortality of AKI (19). Gaini et al. revealed that elevation of serum CRP concentration was closely associated with the mortality of patients in the setting of sepsis and critical illness (16). Additionally, a high level of PCT was a risk predictor for patients with sepsis-induced organ dysfunction (including kidney damage) as well as AKI, and it also negatively correlated with patients' prognosis (20–23). Moreover, serum albumin, prealbumin, and cholesterol are markers recommended by the International Society of Renal Nutrition and Metabolism (ISRNM) to assess the nutritional status of patients (24). Malnutrition (such as lower concentration of prealbumin and cholesterol) was a risk predictor for patients with severe trauma and AKI (25). Accordingly, in the present study, we found higher levels of CRP and PCT and a slight (non-significant) decrease tendency in respect to Alb concentration in the non-survival group when compared to the survival group, suggesting that CRP, PCT, and Alb might also play pivotal roles in sepsis-induced AKI.

In pathological conditions, the interactions between inflammation and malnutrition are intimate and complicated. For example, inflammation could result in malnutrition, while malnutrition, in turn, served as a detrimental factor for the management of inflammation. In this context, a single marker (inflammation or malnutrition) can hardly provide a robust risk prediction for diseases, such as AKI. Indeed, some studies utilized the integration marker to predict the risk of diseases. For instance, Pinilla et al. reported that the value of CRP/prealbumin was correlated to the severity of organ dysfunction in critically ill patients (26). Besides, a high ratio of CRP/Alb indicated higher inflammation superimposed with malnutrition status and was inversely associated with the prognosis of patients with acute myocardial infarction (27, 28). Notably, Xie et al. discovered that

the CRP/prealbumin ratio could predict the risk of mortality in patients with hospital-acquired AKI (29). However, no research about whether CRP/Alb and PCT/Alb can evaluate the prognosis of patients with sepsis-induced AKI has been reported so far. Herein, we found that the values of PCT, PCT/Alb, CRP, and CRP/Alb were significantly higher in the non-survival group and that PCT, PCT/Alb were independent risk factors for poor prognosis in patients with sepsis-induced AKI. As expected, the combination markers (PCT/Alb) exhibited more predictive value than either single marker in sepsis-induced AKI patients. Intriguingly, it seems that the PCT value might contribute to the principal proportion of the predictive value of the PCT/Alb due to its significant change between the survival group and non-survival group, while the Alb value can enhance the predictive power of PCT even though a slight (non-significant) reduction in the non-survival group, implying that the non-significantly changed nutrition markers in sepsis-induced AKI patients also have crucial predictive value, especially when combined with inflammation markers.

Overall, we found a robust predictor (PCT/Alb) of mortality in sepsis-induced AKI patients through a long-time retrospectively study, indicating, at least partly, that when higher levels of PCT/Alb appeared in patients with sepsis-induced AKI, a poorer prognosis and more aggressive diagnostic and therapeutic interventions were needed to avoid mortality. However, some limitations still existed in our study: (i) this was an observational, single-center study with relatively small cohort size; (ii) apart from Alb, other nutritional markers and variables (such as prealbumin, cholesterol, and MUAC) should also be taken into consideration when combined with inflammatory markers; and (iii) the involved population was composed of heterogeneous AKI patients in a tertiary comprehensive hospital and a potential selection bias might influence the result. Hence, a multi-center study with adequate cohort size and a comprehensive assessment of the combined diagnosis value of nutrition and inflammation should be performed in the following study to further confirm the predictive value of PCT/Alb in the poor prognosis of patients with sepsis-induced AKI and to find other potentially valuable combination markers.

CONCLUSIONS

In conclusion, the present study first evaluated the correlation between CRP/Alb and PCT/Alb levels and the mortality of sepsis-induced AKI patients. Higher PCT/Alb level was strongly associated with higher mortality in sepsis-induced AKI patients. Therefore, it was a robust predictor marker of mortality in these patients.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was conducted following the Declaration of Helsinki and was approved by the Ethical Committee of the Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University. All patient data were analyzed in anonymity. Patient consent was waived by the ethics committee, as no individual data were published, nor was any intervention performed on patients.

AUTHOR CONTRIBUTIONS

LC summarized the AKI factors, wrote and edit the manuscript. HZ designed the content, reviewed and edited the manuscript, others summarized the content of the abdominal infection-evoked sepsis. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Malnutrition Is Associated With Impaired Functional Status in Older People Receiving Home Care Nursing Service

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Objective: This study aimed to explore the magnitude and significance of associations among nutritional status, functional status, comorbidities, age, and gender in older adults receiving assistance from the in-home nursing care service.

Method: In this cross-sectional study, 210 home-dwelling persons 65 years or older who received in-home nursing care service were evaluated. Demographic variables, nutritional status, comorbidities, and the dependency levels of activities of daily living were analyzed. To assess the correlation among the factors that influence nutritional status, a theoretical model was developed and adjusted using the path analysis model.

Results: The primary finding is that functional status is directly associated with nutritional status ($\beta = 0.32$; $p < 0.001$) and severity of comorbidities is indirectly associated with nutritional status ($\beta = -0.07$; $p < 0.017$).

Conclusion: The elicited outcomes in this study reinforce the concept that nutritional status is linked with functional status in older adults receiving in-home care nursing service.

Keywords: nutritional status, older adult, nutritional assessment, frailty, comorbididites

INTRODUCTION

According to demographic data, the older adult population has been increasing dramatically in the last 50 years, and it will increase further in the year to come. In 2019, 703 million people were aged 65 years or above in the world. In 2,050, the number is expected to increase to 1.5 billion, meaning that one in every six people worldwide will be aged 65 years or over (1).

Aging is defined as an individual, sequential and cumulative series of physiological changes that occur in an organism over time, resulting in progressive deterioration of functioning, increased vulnerability to disease, and reduced viability (2). Aging is in most people accompanied by multimorbidity and physically debilitating conditions such as sarcopenia, frailty, dementia, and/or malnutrition (3).

Older people may suffer from frailty and malnutrition at the same time. Previous studies have shown a strong association between physical frailty and risk of malnutrition and malnutrition in older adults (4, 5). Thus, a critical agent for healthy aging is an ideal nutritional status. There are several causes for this: reduced appetite and energy expenditure, fluid and electrolyte imbalance, altered levels of cytokines and hormones, delayed gastric emptying, and an impaired sense of smell and taste. Moreover, pathologic changes of aging such as chronic disease, depression, cognitive impairment, multiple morbidities, and polypharmacy play an important role in the complex etiology of malnutrition in older adults (6–8). Hence, studies worldwide have shown the importance of an adequate nutritional status in this critical period of life (9, 10).

Early identification of older adults who are at risk for insufficient caloric intake and nutrient adequacy, termed nutritional risk, or malnutrition, is paramount to maintaining health, independence, quality of life, and longevity (11). The prevalence of malnutrition is reported to be 10–50% in different populations of older people in need of health care services (8, 12). A previous study of older patients receiving domiciliary health care in Norway reported that 41% had dementia and 72% had neuropsychiatric symptoms such as depression, apathy, and anxiety (13). These findings underline that this population is very vulnerable and may consist of older frail people at risk for malnutrition, or even present insufficient caloric intake. Therefore, this study aimed to explore the magnitude and significance of associations among nutritional status, functional status, comorbidities, age, and gender in older adults receiving assistance from the in-home nursing care service in Norway.

METHODS

Study Design and Population

This study is part of the Capturing Acute and Social Care in Dependent Elders (CASCADE), a prospective cross-sectional study on home-dwelling persons 65 years and older who received in-home nursing care service at least once a week in 2016 in a small city (Sandefjord) in the southeast of Norway. Sample size calculation was carried out using information regarding the Norwegian older population receiving home care nursing services (N = 140,000 individuals) (14), the confidence level (95%), confidence interval (5%), and the proportion of potential events (prevalence of malnutrition = average 19%) (15). Data were inserted in the Sample Size Calculator, a tool designed by the Australian Bureau of Statistics (16). The estimated sample was established (n = 237 participants). To be included, the patients must have had in-home nursing care service for 4 weeks or more to ensure the service's knowledge about the patients' function in a stable situation. From the 588 persons aged >65 years receiving home care nursing in this community, the head nurses continuously selected patients by alphabetical order that fulfilled the inclusion criteria. Patients were not included if they suffered from a terminal illness (life expectancy <2 weeks); if they had a diagnosis of Lewy-body dementia (fluctuations of symptoms make the diagnostic of delirium challenging in these patients); if suffering from chronic disease that has led to need of assistance from the in-home nursing care service before the age of 65 years; or if need of in-home nursing care service due to substance abuse or psychiatric disease (not dementia) that arise before the age of 65 years adults. Although the sampling calculation established $n = 237$ participants, due to the exclusion criteria aforementioned, in all, 210 older persons were included, of whom 138 (65.7%) were women. The mean age of the entire sample was 84.5 years (± 8.3), in women it was 85.9 years (± 7.85) and in men, it was 81.4 years (± 8.25). The Regional Committee for Ethics in Medical and Health Research and the Data Protection Officer approved the project (2014/1972).

Assessment

The visits in the participants' own homes for collecting data were performed by trained health professionals. The following information was collected: demographic variables and for nutritional status, the full version of the Mini Nutritional Assessment (MNA) was performed. The MNA comprises 18 items grouped in four sections: anthropometric assessment (weight, height, and weight loss); general assessment (lifestyle, medication use, and mobility); dietary assessment (number of meals, food and fluid intake, and autonomy of feeding); and subjective assessment (self-perception of health and nutrition status). Each response has a numerical value and contributes to the final score, which has a maximum value of 30. A score of 24 or higher indicates satisfactory nutritional status; a score of 17 to 23.5 indicates a risk of malnutrition; a score below 17 indicates protein-energy malnutrition (17, 18). Charlson Comorbidity Index (CCI) was calculated according to the comorbidities reported, and the severity scale of CCI was used to classify the severity of comorbidity. The CCI is primarily based on medical record review so as to assign weights for a number of major comorbid conditions. For each condition, the weight is approximately equal to the one-year relative risk of death for that condition. The index score is the total of assigned weights and represents a measure of the burden of comorbid disease (19). The Barthel Index (BI) was applied to measure the functional status. The BI measures the severity of impairment of tasks, such as toilet use, eating, dressing, and climbing stairs. The maximum score is 20 with higher scores indicating better performance and a higher degree of independence in activities of daily living (20).

Statistical Analyses

Continuous variables were summarized as mean and standard deviation (SD). Chi-square, One-way and Two-way ANOVA were used to compare variables of subgroups. We grouped the participants into two age-groups, <85 and ≥85 years old. The 85-year cutoff point was adopted because people aged 85 years and above are considered to be the "oldest old," and this group presents increased risks of malnutrition, multimorbidity, and disability (21). Categorical variables were described by their frequency distribution and chi-square tests were executed for comparison of categorical variables. The following numerical variables were tested for normality: MNA (sk = 0.82; ku = 0.36); Age (sk = −0.38; ku = −0.71), Years of Education (sk = 1.15; ku = 1.57), BI (sk = −1.37; ku = 1.65 and CCI (sk = 0.99; ku = 1.02). Values of skew (sk) > 3 and/or kurtosis (ku)> 7

were considered indicators of a violation of the assumption of normality (22). According to evidence, the nutritional status in older adults is related to a great range of factors, including gender, age, comorbidities, and functional status (23–26). To assess the correlations among the factors that influence nutritional status in the investigated sample, a theoretical model illustrated in **Figure 1** was developed.

The model was adjusted using the path analysis. Direct and indirect effects were estimated using standardized coefficients, adopting a significance level of 0.05. Standardized coefficients with values 0.10–0.29, 0.30–0.49, and >0.50 were interpreted as small, medium, and large effects, respectively (22).

The Bentler's comparative fit index (CFI), the goodness of fit index (GFI), and the Tucker-Lewis index (TLI) were used to assess the quality of the adjustments of the measurement and structural models. These indexes indicate a good adjustment when values >0.90 are reached. The root mean squared error of approximation (RMSEA) was also used, whose value below 0.10 was considered an indicator of reasonable adjustment. In addition, the absolute index χ^2/df was adopted, since this indicates an acceptable adjustment for a value <3 (22, 27–29). The IBM SPSS 23.0 software was used to perform the descriptive analyzes. The software IBM SPSS AMOS 23.0 and R 3.5.0 were used to adjust the model.

RESULTS

The proportion of females was higher than males. Concerning the comorbidities, 29.5 and 22.4% had dementia and heart failure, respectively. A lower CCI score mean was found among women (2.38 ± 1.86), while men presented a higher score (3.09 ± 2.18; $p = 0.014$). According to the MNA score in this study, 15.3% of men and 16.8% of females were malnourished, and most (59.7% of men and 59.1% of women) of the participants were at risk of malnutrition. **Table 1** shows the descriptive statistics and characteristics of the participants, whereas **Tables 2**, **3** show the patients' functional status, the severity of comorbidities, and prevalence of malnutrition and at risk for malnutrition separated by age groups (<85 years vs. ≥85 years). The highest CCI score (3.05 ± 2.18; $p = 0.002$) was seen in the group <85 years. However, there was no difference in the CCI score according to the nutritional status in both age groups ($p = 0.154$). Among the oldest old men, 40% were malnourished, whereas 60% of women of the same age group were malnourished. Among the oldest-old group, 21.7% of the men, and 78.3% of the women were at risk of malnutrition. No significant difference in nutritional status was found between men and women ($\chi^2 = 0.080$; $p = 0.961$) or among the marital status ($\chi^2 = 1{,}926$; $p = 0.926$).

Figure 2 displays the results of the path analysis, whose adjustment indexes were considered satisfactory: χ^2/df = 2.416; CFI = 0.974; GFI = 0.861; TLI = 0.800; RMSEA = 0.08 (CI90% 0.03–0.13; $p = 0.134$). The variables considered in the adjusted model were Age, CCI and BI. The BI score was the only variable with a medium direct positive and significant effect on the MNA score (β = 0.37; $p < 0.001$). The CCI score had a small negative direct effect on BI score (β = −0.19; $p < 0.005$) and

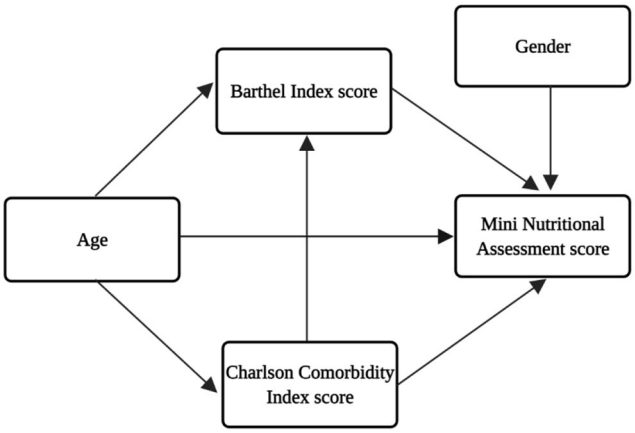

FIGURE 1 | Theoretical model for the interrelationships of the factors that influence nutritional status (MNA score).

TABLE 1 | Sex, years of education, marital status and comorbidities of the participants.

Categorical variables	N	%
Sex		
Male	72	34.3
Female	138	65.7
Years of education		
≤ 10	142	67.6
>10	68	32.4
Age		
<85	101	48.1
≥85	109	51.9
Marital status		
Married/cohabitant	66	31.4
Divorced	31	14.7
Widowed	107	51.0
Single	06	2.9
Comorbidity prevalence		
Myocardial Infarction	38	18.1
Heart failure	47	22.4
Peripheral vascular disease	19	9
Transient ischemic attack	42	20
Dementia	62	29.5
Chronic obstructive pulmonary disease	42	20
Connective tissue disease	33	15.7
Peptic ulcer disease	28	13.3
Mild liver disease	2	1
Diabetes	41	19.5
Diabetes with end-organ damage	9	4.3
Hemiplegia	23	11
Moderate-to-severe renal disease	23	11
Tumor	23	11
Metastatic solid tumor	7	3.3
Leukemia	1	0.5

Values are expressed as n and % for categorical variables.

TABLE 2 | Distribution of participants' characteristics by age groups.

Variables	Age				
	<85 *n* = 101		≥85 *n* = 108		
	Mean	SD	Mean	SD	p
Age (years)	77.29	5.37	91.13	3.57	**<0.001**
Years of education	10	3.43	9.514	3.27	0.325
Barthel Index (score)	15.78	4.03	15.84	3.34	0.906
Charlson Comorbidity Index (score)	3.05	2.18	2.21	1.75	**0.002**
Malnourished	3.84	2.47	2.13	1.59	0.154*
At risk of malnutrition	3.09	2.31	2.30	1.87	
Normal nutritional status	2.44	1.45	2.00	1.57	

*Values are expressed as mean and SD for continuous variables. *P-value of the comparison between the nutritional status groups. P-value results are from ANOVA. Bold values indicate statistical significance.*

TABLE 3 | Participants' nutritional status by age according to sex and marital status.

Nutritional status	Variables	*n*	%	*n*	%	Significance
		<85 *n* = 101		≥85 *n* = 108		
Malnourished	Men	5	26.3	6	40	0.316 $\chi^2 = 0{,}717$
	Women	14	73.7	9	60.0	
	Married/cohabitant	6	31.6	5		0.086 $\chi^2 = 4{,}911$
	Divorced	5	26.3	0	0.0	
	Widowed	8	42.1	10	66.7	
At risk of malnutrition	Men	28	50.9	15	21	**0.001** $\chi^2 = 11{,}496$
	Women	27	49.1	54	78.3	
	Married/cohabitant	24	43.6	16		**0.013** $\chi^2 = 10{,}825$
	Divorced	10	18.2	8	11.6	
	Widowed	18	32.7	43	62.3	
	Single	3	5.5	2	2.9	
Normal	Man	12	44.4	6	25	0.123 $\chi^2 = 2{,}104$
	Women	15	55.6	18	75.0	
	Married/cohabitant	8	29.6	7		0.096 $\chi^2 = 6{,}338$
	Divorced	7	25.9	1	4.2	
	Widowed	11	40.7	16	66.7	
	Single	1	3.7	0	0.0	

Values are expressed as n and % for categorical variables. Significance according to the Chi-square test. Bold font indicates statistical significance.

age had a negative small effect on the CCI score ($\beta = -0.25$; $p < 0.001$). The CCI score also had an indirect effect on the MNA score ($\beta = -0.07$; $p < 0.017$). This indirect effect was calculated by multiplying the β result of the BI and the MNA β. The other trajectories showed in the theoretical model (**Figure 1**) were not statistically significant and were removed from the adjusted model.

DISCUSSION

The current study examined the associations among nutritional status, functional status, comorbidities, age, and gender in older adults receiving assistance from the in-home nursing care service. The primary finding is that functional status is directly associated with nutritional status and comorbidities are indirectly associated with nutritional status.

Malnutrition is an important public problem observed more frequently in older people compared to the general population (30). This study showed that 15.3% of men and 16.8% of females were malnourished, and most of the participants were at risk of malnutrition. Similarly, Yamamoto et al. (31) also evaluated the nutritional status of older patients (mean age of 84 years old) receiving home care in Japan. According to the MNA evaluation, 18.6 and 49.5% of the participants in the Japanese study were

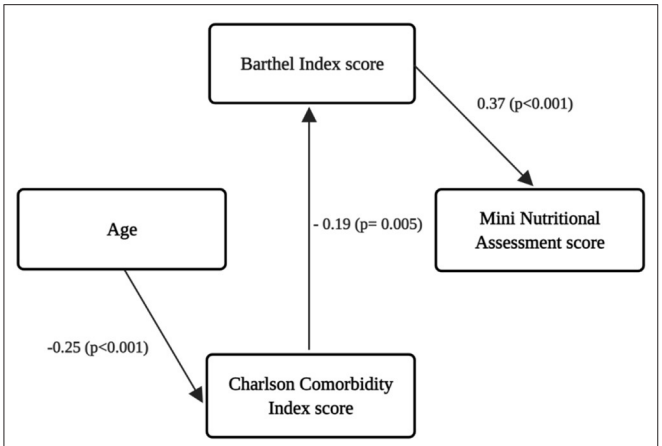

FIGURE 2 | Adjusted model showing the significant associations among variables.

malnourished and at risk of malnutrition, respectively. It has been reported that health, environmental, and social factors or determinants are connected with the risk of malnutrition in older people (32). Especially the widowed older adults are the most malnourished or at the most risk of malnutrition (33). Our study did not find a significant association between marital and nutritional status. However, 62.3% of the widowed oldest-old participants were at risk of malnutrition. According to Besora-Moreno et al. (33), widowhood is related to poor eating habits and less enjoyment of eating.

Although previous research showed a significant correlation between the nutritional status and female gender (34), we did not find any significant relationship between nutritional status and the two age groups of men and women. A similar result was found by Asamane et al. (35) in the United Kingdom. This could be because in general, the women presented fewer comorbidities when compared to men in our study. Moreover, Norway is currently one of the most egalitarian countries in the world according to the Global Gender Gap Index Ranking (36). Thus, it could be assumed that females had fairly equal access to food and therefore eat diets similar to their male counterparts.

Our study also showed an indirect effect of the CCI on the MNA score. The correlation between malnutrition and comorbidities is well-known, and previous studies reported that malnourished older people have higher CCI scores (37, 38). The most prevalent comorbidity found in the participants of the current study was dementia (29.5%). Sanders et al. (39) examined the association of nutritional status and rate of cognitive and functional decline in older adults. The findings showed that malnutrition is associated with more severe symptoms of dementia, and those older people with higher MNA scores would likely experience higher overall cognitive abilities over the course of dementia than those with lower MNA scores.

Furthermore, in this study, age had a direct negative effect on the CCI score. This result diverges from Magdalini et al. (40) study, which shows that there is a significant correlation between older age and increased CCI. However, as our population was receiving in-home nursing services, which is already identified as a very frail group (41), the younger older people presented more severe comorbidities when compared to the oldest old people. Moreover, the other hypothesis is that the oldest old group could be the fittest due to genetic factors and a lifelong favorable lifestyle. However, we did not explore those other factors.

The CCI score had a direct negative effect on functional status, as expected. Mayoral et al. (42) evaluated older adults with osteoporotic hip fracture in order to verify the influence of comorbidities and cognitive impairment on the physical recovery of those patients, during the first year following the fracture. The results demonstrated that CCI clearly influenced the functional status recovery. Low values of CCI indexes resulted in better BI recovery (42).

Malnutrition has been linked with poor functional status as it is an important contributor toward increased vulnerability for developing negative health outcomes, loss of independence, and mortality (18, 43). Meal preparation and eating disabilities seem to be the main cause of malnutrition in older adults with poor functional status (44). Our study showed a positive and significant effect of functional status on the MNA score. Indeed, these findings are in agreement with previous studies. MNA scores and functional status are positively correlated, and it is shown that both nutritional and functional status worsens with age (38, 45, 46). One possible explanation of how nutritional status affects the functional status could be that low energy and especially low protein intake leads to a loss of muscles and strength and consequent loss of daily function (47). Prevention and treatment of age-related disorders can be done through nutritional interventions, which consider both material and human resources required, such as attendance of qualified nutritionists to routinely conduct effective evaluations and interventions required for maintenance of proper health of older adults receiving home care nursing service.

A strength of this study is the availability of information regarding nutrition and health status which was obtained by standardized questionnaires and geriatric assessment tools. This research, however, has some limitations. First, the cross-sectional design, which limits conclusions regarding causal effects or intraindividual changes. Second, the inclusion of patients in alphabetical order may represent a bias for the participants' selection. Third, the comorbidity assessment was based on information from medical records only. Furthermore, the muscle mass index, physical performance, and polypharmacy were not available to all participants, which make insertion as control variables difficult. Finally, dietary intake was not assessed; therefore, the reasons for malnutrition risk could not be identified.

CONCLUSION

In this study, 15.3% of men and 16.8% of women were malnourished and almost 60% of both sexes were at risk of malnutrition. The elicited outcomes reinforce that severity of comorbidities had a direct impact on functional status, and functional status, in turn, had a direct effect on the nutritional status of older adults receiving in-home nursing care service.

DATA AVAILABILITY STATEMENT

The raw data supporting the findings of this study are available from the corresponding author, Maria Krogseth, upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Committee for Ethics in Medical and Health Research and the Data Protection Officer approved the project (2014/1972). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LL and MK: conceptualization/study design, methodology, manuscript preparation, review, editing, supervision, project administration, and funding acquisition. LL and RM-J: statistical analysis, review, and editing. KE and GT: data curation and review. All authors contributed to the article and approved the submitted version.

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Effect of Home Enteral Nutrition on Nutritional Status, Body Composition and Quality of Life in Patients With Malnourished Intestinal Failure

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Background: The ultimate goal of intestinal failure (IF) management is to maintain optimal nutritional status, improve the quality of life (QoL), and promote intestinal adaptation. Enteral nutrition support is safe and effective in patients with IF and plays a central role in the management of patients with IF. The purpose of this study was to evaluate the effect of home enteral nutrition on nutritional status, body composition (BC), QoL and other clinical outcomes in malnourished patients with intestinal failure.

Methods: This prospective observational study included 166 malnourished patients with intestinal failure presented to Jinling Hospital from January 2016 to October 2018. All patients were supported with home enteral nutrition after discharge. We evaluated clinical outcomes, including nutritional status, BC, phase angle (PhA), QoL, mortality, gastrointestinal complications related to enteral feeding, and other clinical outcomes at 1, 3, and 6 months after discharge.

Results: Body weight, BC, and other nutritional parameters were maintained or significantly increased during the period of home enteral nutrition after discharge ($p < 0.01$). Especially, the quality of skeletal muscle mass in body composition was significantly improved ($p < 0.01$). SF-36 quality of life scores was significantly improved (discharged at 6 months: reported health transition 40.7 ± 12.1 vs. 69.3 ± 16.3, $p < 0.01$). There were no differences between hospital and out of hospital with respect to tube-related or gastrointestinal complications. Advanced age, disease type, and poor nutritional status were risk factors for poor clinical outcomes.

Conclusions: Home enteral nutrition support is effective for malnourished patients with intestinal failure. It improves nutritional status, BC, PhA, and QoL.

Clinical Trial Registration: identifier: ChiCTR2000035145.

Keywords: intestinal failure, home enteral nutrition, quality of life, nutritional status, phase angle

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INTRODUCTION

Intestinal failure (IF), a rare type of organ failure, is defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation (IVS) is required to maintain health and/or growth" (1). Based on the onset, metabolic and expected outcome criteria, the functional classification of IF including Type I (acute, short-term, and usually self-limiting condition), Type II (prolonged acute condition), and Type III (chronic condition) (2).

The goal of IF management is to maintain optimal nutritional status, reduce complications, improve quality of life, and promote intestinal adaptation or enteral autonomy (2–4). In the case of patients with intestinal dysmotility or an intestinal mechanical obstruction mainly depend on parenteral nutrition to sustain life, due to insufficient intestinal nutrition. Although, PN is a life-saving therapy for patients with IF (5, 6). Long-term use of PN is associated with many complications (5), including PN-associated liver disease, catheter-related infections, thrombosis and metabolic complications (5–8). At present, it is accepted that enteral nutrition (EN) can enhance the intestinal adaptation in patients with IF (9). Therefore, EN should be started as soon as possible the gut is functional. Compared with parenteral nutrition, enteral nutrition as a preferred option has the advantages of being more economical, more convenient, and safer. Furthermore, enteral feeding conforms to physiological functions, which could protect the gastrointestinal barrier, immune function, and motility (10). Therefore, it is important for IF patients to successfully implement EN feeding to significantly improve the intestinal rehabilitation process and the patient's QoL (5).

Home enteral nutrition (HEN) therapy delivers nutrients and/or fluids to the gastrointestinal tract (GI) through tube or stoma to patients who are medically stable and unable to meet oral nutrition (11). Since its introduction in the 1970's, HEN has been identified as a reliable and effective nutritional intervention (12). Enteral nutrition is started during a hospital stay and continued as a long-term home enteral nutrition therapy (12), which is only minor different from the indication for hospital enteral nutrition.

Nutritional support treatment is usually indicated in patients who are malnourished or at high risk of malnutrition in the hospital. When the patients discharged from the hospital, HEN can be used as a supplementary life-sustaining therapy (12) and can be maintained or even saved the lives patients who unable to meet energy needs via daily oral intake (13, 14). Home enteral nutrition improves prognosis in patients with severe chronic diseases and allows the integration of patients with their families and society (15), thereby improving QoL (12). Moreover, it is associated with improved health outcomes, lower readmission rates, and reduced medical costs (16, 17). EN is safe and effective for patients with IF (18) and plays a central role in the management of patients with intestinal failure (3). For these reasons, as a cost-effective and reliable complementary treatment method, home enteral nutrition is also quite essential for patients with IF who need nutritional support after discharged. HEN combined with home parenteral nutrition can prevent further deterioration of the nutritional status in malnourished patients with IF. However, large sample prospective studies specifically aimed at investigating the effects of home enteral nutrition in malnourished patients with IF are lacking.

Therefore, the main purpose of this study was to determine the effect of HEN on nutritional status, body composition, phase angle (PhA), quality of life, and physiological function in malnourished patients with IF.

MATERIALS AND METHODS

Study Design and Ethics Approval

The protocol for this prospective observational study conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Jinling Hospital. In accordance with the Austrian law and Research Ethics Committee guidelines, all participants or their guardians obtained written informed consent. The trial was registered at Chinese Clinical Trial Registry (ChiCTR2000035145).

Patients and Setting

The data of 166 patients who received HEN treatment in the Clinical Nutrition Treatment Center of Jinling Hospital from January 2016 to October 2018 were analyzed. Patients receive appropriate HEN treatment according to standard protocols from the nutrition support team.

The definition of intestinal failure is as described above, according to ESPEN guidelines (1). Malnutrition is defined according to the 2015 ESPEN Consensus Statement (19). Adult patients with IF were eligible if they met the following inclusion criteria: age $\geq$18 years; inability to meet nutritional requirements orally; estimated duration of enteral nutrition therapy at home for at least 4 weeks; stable clinical status; patient and family acceptance; and appropriate and safe home environment. Exclusion criteria included contraindication for enteral nutrition; life expectancy of fewer than 2 months; pregnancy; severe renal or liver dysfunction; participation in another clinical study; and inability or unwillingness to provide informed consent.

Standardized enteral nutrition was provided according to a nutritional protocol. The energy requirement target was calculated based on actual body weight as 25–30 kcal/kg, and protein requirements ranged from 1.0 to 1.5 g/kg/day. Before being discharged from the hospital, members of the nutrition team will train caregivers who would assist them at home (family members or informal caregivers) to implement HEN therapy (20). The specific training content mainly includes the safe utilization of the infusion pump, proper use and storage of enteral feeding formulas, the management of drugs and water through enteral feeding devices, and the protection of tube position (21). Nutrition support team members followed up on patients once a month. The home visiting staff performed physical examinations and assessments of each patient following standard procedures. During each home visit, assessments included body weight, body composition, blood pressure, blood glucose, and QoL using the SF-36 Health Survey.

In the standard protocol, we define the conditions and cut-off values for the diagnosis of HEN treatment complications. Gastrointestinal complications (GIC) were defined as follows: constipation: despite the use of constipation drugs, no bowel movement for more than 3 days; abdominal distension: abdominal changes during the physical examination with tympany and/or no bowel sounds; diarrhea: loose and watery bowel movements (stools), with more than three stools per day; vomiting: enteral formula ejected through the mouth; and aspiration: diet presence in the airway or respiratory tract (with or without exteriorization) (21, 22). Metabolic complications were defined as follows: hyperglycemia (>11.1 mmol/L) and hypoglycemia (<4.4 mmol/L); hypernatremia (>150 mmol/L); hyponatremia (<136 mmol/L); hyperkalemia (>5.5 mmol/L); hypokalemia (<3.5 mmol/L); high blood urea nitrogen levels (>405 mg/dl); and dehydration based on clinical signs, such as oliguria (<400 mL urine/day) (21). The hospital physician specialized in clinical nutrition undertook the prevention and treatment of GIC and metabolic complications, high blood urea nitrogen levels, and dehydration after notification by the home visiting staff (21).

When tube-related complications occurred, including displacement, occlusion and breakage, infection around the wound exit site, and the presence of granulation tissue, home visiting staff diagnosed them and when possible addressed them directly at the patients' homes (21).

Bioelectrical Impedance Analysis

In Body S10 (InBody Co, Ltd., Seoul, South Korea) was selected to perform BIA measurement to assess body composition. The device has a tetrapolar eight-point contact electrode system that contains six different Frequency (1, 5, 50, 250, 500, and 1,000 kHz) (23). The patient is required to fasting and keep the quiescent condition for 3 h in advance, and then take a supine position during the measurement, with both hands placed on both sides of the body's midline (23). PhA derived from BIA was determined as follows: PhA = arctangent (reactance/resistance)*(180/π). Reactance and resistance were measured at 50 kHz (24).

Laboratory Analysis

Blood samples were drawn in the morning after overnight fasting. Hemoglobin, serum levels of albumin, prealbumin, transferrin, retinol binding protein, fibronectin, insulin-like growth factor 1(IGF-1), liver enzymes and bilirubin, electrolytes, urea nitrogen, and creatinine were measured using routine methods at the Department of Laboratory Medicine, Jinling Hospital or the local hospital laboratory.

Data Collection

All participants of baseline data collection are starting home enteral nutrition treatment, including demographic data (age, gender, primary disease, etc.), information about nutrition therapy, nutritional status, body composition, PhA, and QoL. The implementation of enteral feeding relies on infusion pump or gravity infusion.

Information on the frequencies and types of complications associated with HEN therapy, nutritional status, body composition, PhA, quality of life, and the clinical outcomes of the HEN therapy (death, moving from tube-feeding to oral feeding, and work status) was collected during hospitalization and at 1, 3, and 6 months after discharge.

Data Analyses

Patient characteristics are displayed by descriptive statistics, and then statistical methods are selected according to the data type and distribution status. Continuous variables are expressed as mean ± SD or median and range, and categorical variables are expressed as absolute values and relative frequencies. The incidence rates of complications were compared for inpatients and outpatients using the chi-square test. Nutritional status,

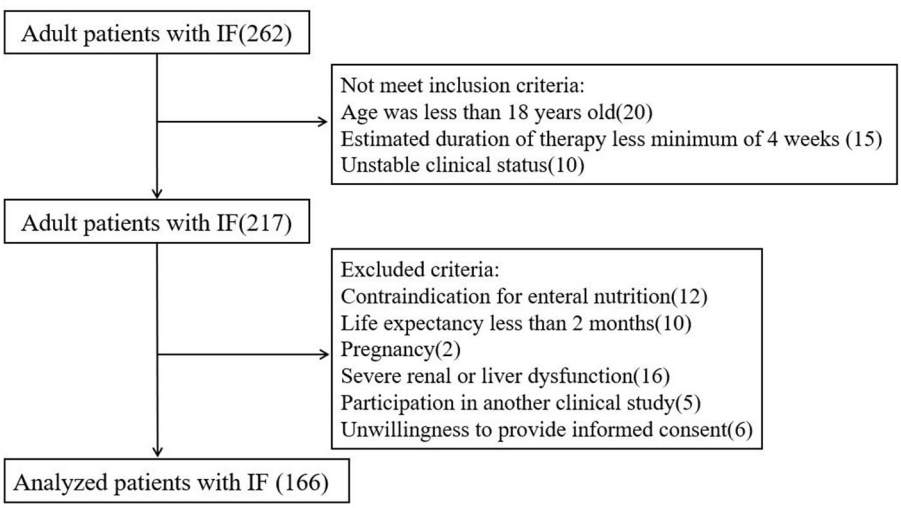

FIGURE 1 | The flow chart of study design and patient selection.

TABLE 1 | Patients and disease characteristics at baseline.

Variable	Range
Total no. of patients	166
Age (years)	46.2 ± 16.5
Male/female	70/96
Height (cm)	165.8 ± 7.8
Weight (kg)	49.4 ± 10.8
BMI kg/m^2	17.9 ± 3.4
Duration after diagnosis of IF (months), median (IQR)	3 (1.5–22)
Functional classification	
Type **II** (prolonged acute)	24 (14.5)
Type **III** (chronic)	142 (85.5)
Pathophysiological classification	
Short bowel syndrome	43 (25.9)
Mesenteric infarction (arterial or venous thrombosis)	20
Crohn's disease	8
Radiation enteritis	6
Surgical complications	5
Intestinal volvulus	2
Abdominal trauma	2
Extensive small bowel mucosal disease	35 (21.1)
Crohn's disease	10
Radiation enteritis	12
Chemotherapy related enteritis	9
Celiac disease	4
Intestinal dysmotility	32 (19.3)
Post-operative	15
Systemic inflammatory	9
Chronic intestinal pseudo-obstruction	8
Mechanical obstruction	25 (15.1)
Obturation (polypoid tumors, feces)	11
Intrinsic bowel lesions (neoplastic, IBD, anastomotic)	8
Extrinsic lesions (abdominal adhesions, neoplasia, volvulus)	6
Intestinal fistula	4 (2.4)
Radiation enteritis	2
Neoplastic	1
Trauma	1
Others	27 (16.3)
Miscellaneous	25
Congenital diseases	2

Data are number of participants (%) or mean (SD) unless otherwise noted.
BMI, body mass index.

TABLE 2 | Techniques used for HEN.

GI tract access	
PEG-J	11 (6.6)
Nasogastric tube	70 (42.2)
Naso-intestinal tube	62 (37.3)
Jejunostomy	7 (4.2)
Oral administration	16 (9.6)
Mean duration of HEN (months) % of patients treated:	
<1 months	23 (13.9)
1–3 months	87 (52.4)
3–6 months	56 (33.7)
Infusion technique (pts, %)	
Bolus technique	16 (9.6)
Gravity set	12 (7.2)
Pump infusion	138 (83.1)
Person responsible for HEN	
Patient him/herself	92 (55.4)
Caregiver	74 (44.6)
Enteral diet used (%):	
Standard	113 (68.1)
Fiber-rich	5 (3.0)
Protein-rich	6 (3.6)
Energy-dense	2 (1.2)
Diabetic	6 (3.6)
Oligopeptide	25 (15.1)
Blenderized diet	9 (5.4)

Data are number of participants (%).

body composition, PhA, and QoL were analyzed using one-way ANOVA. Logistic regression analysis was applied to assess which risk factors were correlated with survival. All statistical analysis was using SPSS 21.0 software (Statistical Program for Social Sciences, SPSS Inc, Chicago, IL, USA) and a value of $P < 0.05$ was considered statistically significant.

RESULTS

A total of 262 patients were admitted to our clinical nutrition center between January 2016 and October 2018. According to the inclusion and exclusion criteria, 166 patients were finally included in the analysis (**Figure 1**).

Patient Population

In total, 166 patients (57.8% female, 42.2% male; mean age 46.2 ± 16.5 years) were enrolled. The main reasons for requiring HEN were short bowel syndrome (SBS) (25.9%), extensive small bowel mucosal disease (21.1%), intestinal dysmotility (19.3%), mechanical obstruction (15.1%), intestinal fistula (2.4%), and others (16.3%). The functional classification of IF was as follow: Type II (14.5%) and Type III (85.5%). Baseline characteristics are displayed in **Table 1**.

The majority of patients were fed by naso-intestinal tube (37.3%), nasogastric tube (42.2%), and percutaneous endoscopic gastrostomy/jejunostomy (PEG-J) (6.6%), and most infusions were pump infusion (83.1%) rather than bolus (9.6%). The mean duration of home enteral feeding (HEF) was within 3 months in 66.3% and 6 months in 33.7%. The main types of enteral nutrition products are standard type (**Table 2**).

Body Weight, Body Composition, and Phase Angle

Compared with the values before admission, the body weights, body composition, and PhA significantly increased during home enteral nutrition, especially within 3 months after discharge ($p < 0.05$) (**Table 3**). BIA analysis was also indicated that the

TABLE 3 | Body weight, body composition, and phase angle change.

Variable	Pre-hospital	First month after hospital discharge	Three months after hospital discharge	Six months after hospital discharge	*p*-value
Weight (kg)	49.4 ± 10.8	55.5 ± 12.6	54.4 ± 12.9	53.8 ± 13.3	<0.001[a,b,c]
ICW (L)	18.26 ± 4.02	20.10 ± 4.51	18.99 ± 4.51	19.09 ± 4.36	0.0020[a,d,e]
ECW (L)	11.77 ± 2.42	12.63 ± 2.77	12.17 ± 2.74	12.51 ± 2.95	0.020[a,c]
TBW (L)	30.03 ± 6.33	32.72 ± 7.19	31.16 ± 7.17	31.61 ± 7.20	0.006[a,c,d]
ECW/TBW (%)	0.39 ± 0.02	0.39 ± 0.02	0.39 ± 0.02	0.40 ± 0.02	<0.001[a,d,e,f]
TBW/FFM (%)	73.18 ± 0.57	73.06 ± 0.63	73.12 ± 0.51	73.26 ± 0.60	0.018[e,f]
Protein (Kg)	7.89 ± 1.74	8.69 ± 1.95	8.20 ± 1.95	8.26 ± 1.90	0.002[a,d,e]
Mineral (Kg)	3.10 ± 0.59	3.38 ± 0.76	3.25 ± 0.72	3.27 ± 0.71	0.004[a,b,c]
FAT (Kg)	8.35 ± 5.38	10.71 ± 6.73	11.82 ± 6.44	10.62 ± 7.81	<0.001[a,b,c]
SLM (Kg)	38.41 ± 8.16	41.95 ± 9.25	39.88 ± 9.22	40.38 ± 9.19	0.004[a,d]
FFM (Kg)	41.01 ± 8.58	44.79 ± 9.83	42.62 ± 9.78	43.13 ± 9.72	0.004[a,b,d]
SMM (Kg)	21.81 ± 5.24	24.21 ± 5.88	22.75 ± 5.88	22.90 ± 5.69	0.002[a,d,e]
PBF (%)	16.34 ± 8.51	18.63 ± 9.66	21.00 ± 8.95	18.42 ± 10.99	<0.001[c]
BCM (Kg)	26.15 ± 5.75	28.79 ± 6.46	27.19 ± 6.45	27.35 ± 6.24	0.002[a,d,e]
BMC (Kg)	2.61 ± 0.50	2.84 ± 0.65	2.73 ± 0.61	2.75 ± 0.60	0.004[a,b,c]
AC (cm)	22.86 ± 3.43	24.94 ± 4.44	24.36 ± 3.50	24.37 ± 4.95	<0.001[a,b,c]
AMC (cm)	19.28 ± 2.79	20.52 ± 3.29	19.97 ± 2.51	20.22 ± 4.09	0.004[a,c]
Waist Cir. (cm)	63.26 ± 7.18	65.41 ± 7.66	66.68 ± 8.68	66.07 ± 9.86	0.001[b,c]
VFA (cm^2)	37.47 ± 22.22	41.02 ± 28.06	49.44 ± 30.92	49.29 ± 38.04	<0.001[b,c]
RA phase angle	4.57 ± 1.83	5.12 ± 2.20	4.59 ± 1.05	4.48 ± 1.39	0.002[a,d,e]
LA phase angle	4.38 ± 1.70	4.90 ± 2.46	4.41 ± 1.07	4.70 ± 3.57	0.137
TR phase angle	5.74 ± 3.36	6.00 ± 2.64	4.73 ± 1.92	5.61 ± 4.27	0.002[b,d]
RL phase angle	4.89 ± 1.86	5.84 ± 2.08	5.21 ± 1.89	4.72 ± 1.74	<0.001[a,d,e,f]
LL phase angle	4.84 ± 1.96	5.83 ± 2.05	5.13 ± 1.80	4.71 ± 1.82	<0.001[a,d,e]
Average phase angle	4.88 ± 1.85	5.54 ± 1.72	4.81 ± 1.39	4.84 ± 2.01	<0.001[a,d,e]

Data are mean (SD) unless otherwise noted. a, b, c, d, e, f indicates pair-wise differences were significant at $p < 0.05$. Where [a]indicates $p < 0.05$ for pre-hospital vs. first month after hospital discharge, [b]indicates $p < 0.05$ for pre-hospital vs. three months after hospital discharge, [c]indicates $p < 0.05$ for pre-hospital vs. 6 months after hospital discharge, [d]indicates $p < 0.05$ for first month after hospital discharge vs. 3 months after hospital discharge, [e]indicates $p < 0.05$ for first month after hospital discharge vs. six months after hospital discharge, and [f]indicates $p < 0.05$ for 3 months vs. 6 months after hospital discharge.

ICW, intracellular water; ECW, extracellular water; TBW, total body water; SLM, soft lean mass; FFM, fat free mass; SMM, skeletal muscle mass; PBF, percent body fat; BCM, body cell mass; BMC, bone mineral content; AC, arm circumference; AMC, arm muscle circumference; Waist Cir., waist circumference; VFA, visceral fat area; RA, right arm; LA, left arm; TR, trunk; RL, right leg; LL, left leg; PhA, phase angle.

skeletal muscle mass, soft lean mass, and fat-free mass of body composition significantly improved (discharged at 6 months: skeletal muscle 21.81 ± 5.24 vs. 22.90 ± 5.69, $p < 0.05$; soft lean mass 38.41 ± 8.16 vs. 40.38 ± 9.19, $p < 0.01$; fat-free mass 41.01 ± 8.58 vs. 43.13 ± 9.72, $p < 0.01$) (**Table 3**).

Other Nutritional Parameters

At 1, 3, and 6 months after discharge, the serum concentrations of biochemical nutritional indicators (albumin, prealbumin, retinol binding protein, transferrin, fibronectin, and IGF-1) were significantly higher in HEN patients, compared with the pre-hospital values ($p < 0.01$) (**Table 4**).

Quality of Life

Overall, the reported health transition scores were improved at all three time points, with respect to baseline values (40.7 ± 12.1 vs. 57.4 ± 15.6 vs. 61.7 ± 17.6 vs. 69.3 ± 16.3, $p < 0.001$). The self-completed questionnaire includes 36 items, divided into eight domains (physical functioning [PF], role-physical [RP], bodily pain [BP], general health [GH], vitality [VT], social functioning [SF], role-emotional [RE], and mental health [MH]) scores, which also significantly improved during home enteral nutrition after discharge ($p < 0.001$) (**Table 5**).

Complications

Compared with the hospital treatment period, there were no significant increases in gastrointestinal, metabolic, or mechanical complications during HEN ($p > 0.05$) (**Table 6**).

Other Clinical Outcomes

The outcomes of the HEN therapy (moving from tube-feeding to oral feeding, received calories and protein from EN and work status) significantly improved at 6 months after discharge (**Supplementary Table 1**). There were 18 deaths in the study population (**Supplementary Table 1**). The results of logistic regression analysis indicate that the risk factors for mortality in malnourished patients with IF who were treated with HEN included advanced age (age >65 years), disease

TABLE 4 | Other nutritional parameters.

Variable	Pre-hospital	First month after hospital discharge	Three months after hospital discharge	Six months after hospital discharge	*p*-value
Albumin (g/L)	36.1 ± 6.6	37.1 ± 5.4	41.2 ± 4.0	39.9 ± 4.6	<0.001[b,c,d,e]
Prealbumin (mg/L)	159.5 ± 73.7	166.1 ± 62.0	182.6 ± 81.4	198.3 ± 71.8	<0.001[c,e]
Retinol binding Protein (mg/L)	31.4 ± 14.7	31.3 ± 14.7	35.1 ± 10.3	39.3 ± 19.3	<0.001[c,e]
Transferrin (g/L)	2.23 ± 0.67	2.43 ± 0.64	2.44 ± 0.78	2.42 ± 0.70	0.0230[a]
Fibronectin (mg/L)	192.3 ± 54.3	210.1 ± 33.0	211.0 ± 59.9	217.2 ± 39.7	0.0010[a,c]
IGF-1 (ug/L)	104.5 ± 86.8	139.6 ± 69.3	191.6 ± 112.9	170.5 ± 127.7	<0.001[a,b,c,d]

Data are mean (SD) unless otherwise noted. a, b, c, d, e, f indicates pair-wise differences were significant at $p < 0.05$. Where [a]indicates $p < 0.05$ for pre-hospital vs. first month after hospital discharge, [b]indicates $p < 0.05$ for pre-hospital vs. 3 months after hospital discharge, [c]indicates $p < 0.05$ for pre-hospital vs. 6 months after hospital discharge, [d]indicates $p < 0.05$ for first month after hospital discharge vs. 3 months after hospital discharge, [e]indicates $p < 0.05$ for first month after hospital discharge vs. 6 months after hospital discharge and [f]indicates $p < 0.05$ for 3 months vs. 6 months after hospital discharge.
IGF-1, insulin-like growth factor-1.

TABLE 5 | HEN quality of life scores.

Variable	Pre-hospital	First month after hospital discharge	Three months after hospital discharge	Six months after hospital discharge	*p*-value
RHT	40.7 ± 12.1	57.4 ± 15.6	61.7 ± 17.6	69.3 ± 16.3	<0.001[a,b,c,e,f]
PF	45.4 ± 12.0	59.2 ± 11.5	60.9 ± 15.0	62.9 ± 16.7	<0.001[a,b,c]
RP	36.4 ± 12.5	55.6 ± 16.6	58.7 ± 19.2	59.0 ± 19.6	<0.001[a,b,c]
BP	56.2 ± 10.3	66.6 ± 10.0	71.9 ± 14.2	70.8 ± 14.3	<0.001[a,b,c,d,e]
5GH	51.7 ± 9.1	64.9 ± 10.5	67.0 ± 12.5	66.1 ± 14.4	<0.001[a,b,c]
VT	50.0 ± 9.0	63.7 ± 10.8	66.7 ± 14.2	66.8 ± 15.2	<0.001[a,b,c]
SF	56.7 ± 6.1	69.4 ± 7.6	72.1 ± 9.9	71.8 ± 10.2	<0.001[a,b,c,d]
RE	46.1 ± 16.2	71.1 ± 21.7	73.4 ± 16.0	70.5 ± 16.2	<0.001[a,b,c]
MH	42.4 ± 5.3	57.7 ± 9.1	63.8 ± 17.5	65.6 ± 18.3	<0.001[a,b,c,d,e]

Data are mean (SD) unless otherwise noted. a, b, c, d, e, f indicates pair-wise differences were significant at $p < 0.05$. Where [a]indicates $p < 0.05$ for pre-hospital vs. first month after hospital discharge, [b]indicates $p < 0.05$ for pre-hospital vs. 3 months after hospital discharge, [c]indicates $p < 0.05$ for pre-hospital vs. 6 months after hospital discharge, [d]indicates $p < 0.05$ for first month after hospital discharge vs. 3 months after hospital discharge, [e]indicates $p < 0.05$ for first month after hospital discharge vs. 6 months after hospital discharge, and [f]indicates $p < 0.05$ for 3 months vs. 6 months after hospital discharge.
RHT, reported health transition; PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; HEN, home enteral nutrition.

type (cancer), and poor nutritional status (BMI < 16.5 kg/m^2) (**Supplementary Table 2**).

DISCUSSION

Weight loss and the accompanying malnutrition are the major issues in patients with IF. This disease could give rise to reduced food intake, malabsorption, and increased metabolism, thereby increasing the risk of deteriorating nutritional status and ultimately negatively affecting clinical outcomes. Previous studies have shown the importance of enteral nutrition in reducing weight loss in patients with IF or intestinal insufficiency (25, 26). However, there is a lack of prospective studies evaluating the effects of long-term use of HEN in these patients.

In the present study, we assessed the effect of HEN on nutritional status, BC, PhA, and QoL in malnourished patients with IF. The results suggested that patients treated with HEN succeeded in maintaining stable body weight and body composition and PhA significantly increased during home enteral nutrition within the 1st month of discharge. Our results found that the serum concentrations of biochemical nutritional indicators (albumin, prealbumin, retinol binding protein, transferrin, fibronectin, and IGF-1) were significantly higher at 1, 3, and 6 months after discharge. Our results show that home enteral nutrition can improve nutritional status in patients with IF. We also identified changes in body composition and PhA in patients with intestinal failure in home enteral nutrition that no previous study has reported.

According to the ASPEN guidelines, BIA is a practical, portable, non-invasive body composition assessment tool (27). PhA can be used as an indicator of cell membrane quality and cell function (24). Low PhA is associated with increased number of readmissions, prolonged length of hospital stays, and deteriorated mortality in patients with intestinal failure (24). PhA may be a predictive factor for acute complications, muscle

TABLE 6 | Complications of HEN.

Variable	In hospital complications	Out of hospital complications	*p*-value
Tube complications			0.985
Reflux of feed/vomiting	4	5	
Tube displacement or migration	3	3	
Inadvertent tube removal	4	6	
Tube fracture	1	1	
Leakage around insertion site	1	2	
Tube occlusion	6	7	
Gastrointestinal complications			0.907
Gas/bloating	10	7	
Nausea/vomiting	5	6	
Diarrhea	6	7	
Constipation	8	6	
Bleeding	0	0	
Other complications			0.648
Fever	6	3	
Pain	5	6	
Aspiration	0	0	
Pneumonia	11	8	

Data are number of participants (%). HEN, home enteral nutrition.

mass, and nutritional status (28). Indeed, we found that the PhA of patients with intestinal failure increased at 1 month and decreased at 3 and 6 months. These findings suggest that further researches are necessary to explore the physiologic and cellular mechanisms associated with PhA. However, due to the variability of body composition estimated within studies and the limited number of studies applying the same equipment, it was difficult to consolidate data by manufacturer to support summary statistics (27). It is urgent in future studies to cross verify the PhA values between devices of different brands or standardize their PhA values through device specific reference values, to enable comparisons of outcomes between studies applying different BIA devices (24, 29).

In the present study, we found that skeletal muscle mass, soft lean mass, and fat-free mass markedly increased with home enteral nutrition. It is well-known that as a highly plastic tissue, skeletal muscle is indispensable in human health and disease (30). Disease-related malnutrition is mainly manifested as decreased muscle mass and function, and this phenotype is related to loss of independence and decreased quality of life (30). Therefore, maintaining the quality of skeletal muscle is essential to achieve a normal nutritional status. The GLIM consensus has regarded skeletal muscle quality as the decisive criterion for diagnosing malnutrition due to its role in responding to trauma and disease (31, 32). This maintenance of body weight, body composition (skeletal muscle mass), PhA, and other nutritional indicators can be attributed to the increased caloric and protein intake from home enteral nutrition. The caloric intake was significantly higher in patients supported with HEN compared with baseline. Our results found a positive effect of home enteral nutrition on the up-regulation of IGF-I concentration. Previous research findings that IGF-1 contributes to enhance muscle function by increasing the production of muscle satellite cells and promoting the synthesis of muscle contractile proteins and mediator of muscle growth and repair (33, 34).

Compared with baseline values, the SF-36 scores, including the reported health transition, was significantly increased at 1, 3, and 6 months after discharge, suggesting that HEN improves QoL in patients with IF. The SF-36 score includes eight domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health), all of which significantly improved. This finding is in line with those of other studies that suggested that HEN improves QoL (12, 35, 36). We speculate that the improvement of the patient's quality of life is mainly related to the improvement of skeletal muscle mass and function and the improvement of nutritional status, although further evidence appears necessary to fully investigate this issue.

We found that there were no significant increases in gastrointestinal, tube, or mechanical complications during HEN compared with the hospital treatment period. This finding suggests that HEN is safe as well as effective in patients with IF, similar to the findings of a previous study (14). Of note, HEN was not associated with any severe adverse effects.

Although guidelines recommend gastrostomy or jejunostomy as the first choice when nutritional support is necessary for more than 2–3 months (37), the nasogastric tube is easier to maintain in the home setting and some patients or caregivers can place the nasogastric tube by themselves. In the present study, the most common mode of administration for enteral nutrition was nasogastric feeding (42.2%). This can probably be explained by its wide use for patients with enteral nutrition of short duration, such as those with malignancies and inflammatory bowel diseases. The gastrostomy was more frequently applied in neuromuscular and gastroesophageal diseases (38). Jejunostomy was an exceptional alternative in our experience, as reported in other studies, this operation is only available to patients with severe and persistent gastroesophageal reflux or gastric dysmotility (38).

Our research results suggest that commercially manufactured standard types of enteral nutrition are the main type of formula used. This is due to commercial enteral nutrition convenience and ease of use that makes them the preferred choice among patients requiring formula. In clinical practice, patients with normal basic gastrointestinal function are recommended to take polymeric enteral feeding. However, some patients with altered GI function may require specialized formulas (i.e., severe hepatic diseases and malabsorption). Another noteworthy finding in our research is the low level of use of special formula enteral nutrition (i.e., fiber-rich, protein-rich, and energy-dense), accounting for only 7.8% of all patients using enteral nutrition. This may be made clear by the fact that standard enteral nutrition is well-tolerated by most patients. There is a lack of data on the benefits of special formula enteral nutrition in IF patients. Gravity feeding was rare in our study. This feeding route is unfit for IF patients because the precise flow cannot be achieved and the delivery target volume cannot be adjusted. Moreover, continuous enteral feeding is largely used in patients for both tolerance and acceptability, and flow regulator pumps were required for most patients receiving HEN (38).

Our study has certain limitations. First, our study had a limited sample size and relative heterogeneity of disease types. Nevertheless, the main focus of our observational, descriptive study was clinical outcomes within 6 months after discharge. Second, we did not have complete collection information on home parenteral nutrition use over the study period, as well as parenteral nutrition use time, amount, and proportion, all of which may have potential impact on prognosis.

In conclusion, the results of our study support the importance of HEN in malnourished patients with IF. HEN helps maintain body weight, body composition, PhA, and nutritional status with minimal safety concerns and has a positive impact on the quality of life.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committee of the Jinling Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XW, XG, and JL equally contributed to the conception and design of the study. LZ and SL contributed to the design of the study. YZ contributed to the acquisition and analysis of the data. HL and DZ contributed to the analysis of the data. LZ contributed to the acquisition, analysis, and interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, read, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.643907/full#supplementary-material

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A Low-FODMAP Diet Improves the Global Symptoms and Bowel Habits of Adult IBS Patients: A Systematic Review and Meta-Analysis

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Background: A low-fermentable oligo-, di-, monosaccharides, and polyols (FODMAP) diet has been reported to be associated with improving the symptoms of irritable bowel syndrome (IBS); however, its efficacy as evaluated by different studies remains controversial.

Objective: A systematic review and meta-analysis of randomized controlled trials (RCTs) were conducted to explore the efficacy of a low-FODMAP diet (LFD) in alleviating the symptoms of IBS.

Methods: A search of the literature for RCTs that assessed the efficacy of an LFD in treating IBS patients was conducted using the electronic databases PubMed, Embase, Cochrane Central Register of Controlled Trials, and Web of Science. The searches in each database were conducted from the inception of the database to February 2021. Two independent reviewers screened citations and a third reviewer resolved disagreements. Two independent reviewers also performed eligibility assessments and data extraction. The RCTs that evaluated LFDs vs. a normal IBS or usual diet and assessed changes of IBS symptoms were included in the search. Data were synthesized as the relative risk of global symptoms improvement, mean difference of IBS Severity Scoring System (IBS-SSS) score, sub-items of IBS-SSS irritable bowel syndrome-related quality of life (IBS-QOL), hospital anxiety and depression scale (HADS), stool consistency/frequency, and body mass index (BMI) using a random effects model. The risk of bias was assessed using Risk of Bias Tool 2 (RoB 2). The bias of publication was assessed based on Egger's regression analysis. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Results: A total of 2,768 citations were identified. After full-text screening, a total of 10 studies were eligible for the systematic review and were subsequently used to compare an LFD with various control interventions in 511 participants. An LFD was associated with the improvement of global symptoms [$n = 420$; Risk Ratio (RR) = 1.54; 95% Confidence Interval (CI) 1.18 to 2; $I^2 = 38\%$], improvement of stool consistency [$n = 434$; Mean difference (MD) = −0.25; 95% CI −0.44 to −0.06; $I^2 = 19\%$), and a reduction trend of stool frequency ($n = 434$; MD = −0.28; 95% CI −0.57 to 0.01; $I^2 = 68\%$) compared

with control interventions. There was no statistically significant change in IBS-QOL (n = 484; MD = 2.77; 95% CI −2 to 7.55; I^2 = 62%), anxiety score (n = 150; MD = −0.45; 95% CI −3.38 to 2.49; I^2 = 86%), depression score (n = 150; MD = −0.05; 95% CI −2.5 to 2.4; I^2 = 88%), and BMI (n = 110; MD = −0.22; 95% CI −1.89 to 1.45; I^2 = 14%). The overall quality of the data was "moderate" for "global improvement of IBS symptom," "stool consistency," "stool consistency for IBS with diarrhea (IBS-D)," and "stool frequency for IBS-D," and "low" or "very low" for other outcomes according to GRADE criteria.

Conclusion: An LFD is effective in reducing the global symptoms and improving the bowel habits of adult IBS patients. The efficacy for IBS-D patients can also be more pronounced.

Systematic Review Registration: CRD42021235843.

Keywords: FODMAP, diet, irritable bowel syndrome, quality of life, meta-analysis, HADS

INTRODUCTION

Irritable bowel syndrome is one of the most prevalent chronic gastrointestinal diseases, with a prevalence of ∼7–21% (1, 2). In some Western countries, the prevalence of irritable bowel syndrome (IBS) is around twice as high in females than in males, which may be higher in Asian countries (1). The diagnosis of IBS is based on the association of recurrent abdominal pain with altered bowel habits, namely, diarrhea and/or constipation, in the absence of organic diseases, such as inflammatory bowel disease or colon cancer (2). IBS is usually categorized into subtypes according to predominant bowel habits: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS (IBS-M), or unsubtyped IBS (IBS-U) (1–3). Irritable bowel syndrome has been conceptualized as a brain–gut disorder (4), which is also associated with poor quality of life, impaired social function (5), and psychological-psychiatric conditions, such as anxiety and depression (6–8). Medications that improve diarrhea (e.g., loperamide, probiotics) or constipation (e.g., fiber supplements, laxatives) are used as the first-line IBS therapies to improve altered bowel habits but offer little benefit for abdominal pain, bloating, and psychosocial problems (1, 2). Up to 70% of IBS patients report that symptom onset or exacerbation are associated with certain food, such as milk and milk products, wheat products, caffeine, cabbage, onion, peas, beans, hot spices, and fried and smoked food (3, 9–11). Some IBS patients tend to avoid certain food items and try gluten-free or lactose-free diets to prevent the onset of their symptoms (12, 13). However, these avoidances of food may make them susceptible to long-term nutritional deficiencies and low body weight (14).

Restricting food with highly fermentable oligo-, di-, monosaccharides, and polyols (FODMAPs), which can trigger and/or exacerbate IBS symptoms, may contribute to managing IBS symptoms according to a growing body of clinical trials (15–19). Examples of FODMAPs include fructose, lactose, sugar alcohols (sorbitol, maltitol, mannitol, xylitol, and isomalt), fructans, and galactans, which are widely presented in a large range of food, such as wheat, rye, vegetables, fruits, and legumes (20).

Fermentable oligo-, di-, monosaccharides, and polyols might exacerbate IBS symptoms through various mechanisms, such as increasing small intestinal water volume, colonic gas production and intestinal motility (21). A series of high-quality randomized controlled trials (RCTs) have been conducted to assess the efficacy of a low-FODMAP diets (LFDs) in IBS (15, 17–19, 21–26). However, these resulted in controversial conclusions.

Five recent meta-analyses (27–31) have been performed on this topic. However, none of them paid enough attention to the efficacy of LFD on stool output and psychological or psychiatric conditions in IBS patients. Therefore, this study was aimed to conduct an updated and more comprehensive meta-analysis of RCTs, evaluate the effects of LFD therapy for IBS patients to improve their symptoms and IBS-QOL, stool consistency and frequency score, anxiety and depression score based on hospital Anxiety and Depression Scale (HADS), and body mass index (BMI).

METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (32) and was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42021235843).

Search Strategy

The search of the literature for RCTs that assessed the efficiency of an LFD in treating with IBS was conducted using the electronic databases PubMed, Embase, Cochrane Central Register of Controlled Trials, and Web of Science. The searches in each database were conducted from the inception of the databases to February 2021. Search terms included "'irritable bowel syndrome' OR 'IBS'" AND "'fermentable oligosaccharides, disaccharides, monosaccharides, and polyols' OR 'fodmap,' OR 'fermentable oligo-, di- and monosaccharides and polyols.'" No language restrictions were used in the search process.

Study Selection

The inclusion criteria were presented as the following: (1) randomized controlled trials (including cross-over trials); (2) participants aged ≥ 18 years, (3) an objective basis for diagnosis (Rome I, II, III, or IV); (4) comparing LFD with a placebo diet or a usual diet; (5) outcomes including global improvement in IBS symptoms, IBS-QOL, HADS, stool consistency/frequency, or BMI; (6) the duration of therapy ≥ 3 weeks. The exclusion criteria were presented as the following: (1) non-randomized controlled trials, cohort studies, retrospective studies, or case reports, (2) participants aged < 18 years, (3) participants suffered from other digestive disorders, such as inflammatory bowel disease, (4) participants in the experimental group received multiple interventions at the same time. Two independent reviewers (Wang JS and Yang PC) performed the screening of the citations and a third reviewer (Zhang L) resolved disagreements.

Outcome Assessment

The primary outcome was assessed according to the global improvement in IBS symptoms. Secondary outcomes included IBS-QOL, stool consistency/frequency, HADS, and BMI.

Data Extraction

Two independent reviewers (WJ and YP) performed the data abstraction for this study. Data extracted included data on the year of publication, country of origin, design of the study, clinically meaningful improvement standard, duration of therapy, IBS criteria, IBS subtype involved, the comparator intervention, and outcomes. Risk ratio of symptom improvement was abstracted as an intention-to-treat analysis, and the dropouts would be treated in the groups to which they had been initially randomized. The mean difference of the IBS Severity Scoring System (IBS-SSS) score, sub-items of IBS-SSS (including "pain intensity," "pain frequency," "abdominal distension," "dissatisfaction of bowel habit," and "interference on life in general"), IBS-QOL score, HADS score, stool consistency and frequency score, and BMI were assessed. Disagreements were resolved by a third reviewer (ZL).

Assessment of Risk of Bias and GRADE Methodology

The risk of bias assessment was performed by two independent reviewers (WJ and YP) using the Cochrane Risk of Bias Tool with Review Manager (RevMan) (Version 5.3, Cochrane Collaboration). Each study was evaluated based on the reporting of randomization, allocation, blinding, and outcome assessment and reporting. Data was analyzed to assess the quality of evidence according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology using the GRADEPro Guideline Development Tool (GDT) (33).

Data Synthesis and Statistical Analysis

Data analysis was performed using RevMan 5 (Version 5.3, Cochrane Collaboration). The risk ratio (RR) was calculated with 95% confidence intervals (CIs) of symptoms improving, mean difference (MD) with 95% confidence intervals of IBS-SSS score, IBS-QOL score, HADS score, stool consistency and frequency score, and BMI in the IBS with LFD group compared with control. Data were pooled with a random effects model. Heterogeneity was evaluated with the I^2 statistic, with >50% considered to be significant heterogeneity. Forest plots were used with RRs or MDs for primary or secondary outcomes. The 153Publication bias was assessed based on Egger's regression analysis (using the Stata 16 software). The reasons for heterogeneity were explored using subgroup analyses based on the definition of clinically meaningful improvement for IBS global symptoms, type of control intervention, duration of treatment, and subtype of IBS.

RESULTS

Search Results and Study Selection

The literature search identified 2,768 citations through electrical databases, and 46 studies underwent full manuscript review. After full-text screening, 36 articles were excluded for different reasons, leaving a total of 10 studies that were eligible for the systematic review, comparing an LFD with control diets (including the traditional IBS diet, high-FODMAP diet, or usual diet) in 511 participants (**Figure 1**). A summary of the trial characteristics is given in **Table 1**.

Global Improvement of Symptoms

Seven studies reported the global improvement of symptoms with different clinically meaningful improvement definitions as dichotomous outcomes (**Figure 2**), where an LFD was associated with an improvement of global symptoms in IBS patients compared with controls (n = 420; RR = 1.54; 95% CI 1.18–2; I^2 = 38%). Five studies assessed global symptom changes using IBS-SSS as continuous variables, showing that an LFD was associated with a reduction in total IBS-SSS score (n = 354; MD = −37.72; 95% CI −53.97 to −21.46; I^2 = 40%) (**Figure 3**), pain intensity (n = 354; MD = −11.27; 95% CI −16.32 to −6.23; I^2 = 47%) (**Supplementary Figure 1**), pain frequency (n = 354; MD = −9.11; 95% CI −16.26 to −1.96; I^2 = 73%) (**Supplementary Figure 2**), interference on life in general (n = 354; MD = −11.58; 95% CI −13.92 to −9.24; I^2 = 0%) (**Supplementary Figure 3**), and dissatisfaction of bowel habit (n = 354; MD = −8.95; 95% CI −12.6 to −5.31; I^2 = 26%) (**Supplementary Figure 4**), but with no statistically significant effect on abdominal distension (n = 354; MD = −4.82; 95% CI −10.75 to 1.11; I^2 = 57%) (**Supplementary Figure 5**).

Stool Output

Six studies reported the improvement of stool output in IBS patients due to an LFD. An LFD also showed significant effects on stool consistency scores (n = 434; MD = –.25; 95% CI −0.44 to −0.06; I^2 = 19%) (**Figure 4**), and a trend of reduced stool frequency per day (n = 434; MD = −0.28; 95% CI −0.57 to 0.01; I^2 = 68%) (**Figure 5**) compared with control interventions. Interestingly, the improvement of stool output in IBS-D patients seemed to be more sensitive to an LFD according to subgroup

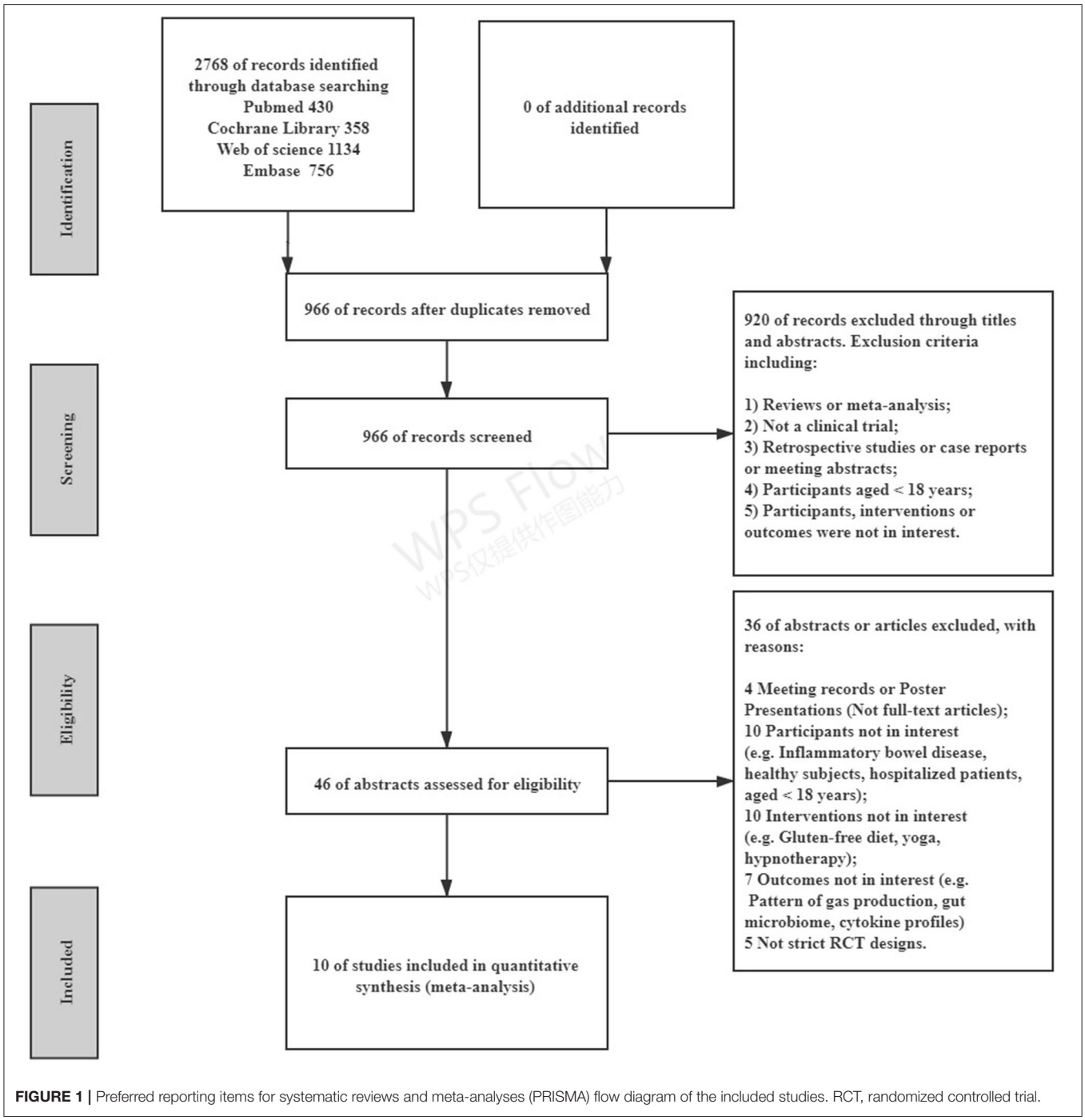

FIGURE 1 | Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the included studies. RCT, randomized controlled trial.

analysis: stool consistency score (n = 183; MD = −0.34; 95% CI −0.55 to −0.14; I^2 = 0%) (**Figure 4**) and stool frequency (n = 183; MD = −0.67; 95% CI −0.96 to −0.38; I^2 = 0%) (**Figure 5**).

IBS-QOL

The irritable bowel syndrome-related quality of life score was analyzed using the synthesis from five studies, showing no significant changes (n = 484; MD = 2.77; 95% CI −2 to 7.55; I^2 = 62%). Subgroup analysis based on IBS subtype showed no statistical difference between subgroups (p = 0.48) (**Figure 6**).

HADS

Two studies reported HADS, however, both showed no difference between low-FODMAP groups and controls: anxiety score (n = 150; MD = −0.45; 95% CI −3.38 to 2.49; I^2 = 86%) (**Figure 7**) and depression score (n =150; MD = −0.05; 95% CI −2.5 to 2.4; I^2 = 88%) (**Figure 8**).

TABLE 1 | Baseline characteristics of the studies included in the meta-analysis.

References	Design	Duration	IBS definition	IBS type	Age range or mean age (SD)/year	Female/ total	Intervention	Participants (LFD/ND)	Drops (LFD/ND)	Clinically meaningful improvement	Symptom assessment
Böhn et al. (22) Sweden	Multi-center parallel single-blind RCT	4 weeks	ROME III	IBS-D IBS-C IBS-M IBS-U	43 (16)	56/67	Traditional IBS diet vs. LFD	33/34	5/3	A reduction in IBS-SSS ≥ 50	IBS-SSS Stool consistency/ frequency BMI HADS
Halmos et al. (21) Australia	Single-blind cross-over RCT	3 weeks	ROME III	IBS-D IBS-C IBS-M IBS-U	23–60	21/30	Typical Australian diet vs. LFD	30/24	5/2	A reduction in VAS ≥ 10 mm	100-mm (VAS)
McIntosh et al. (18) Canada	Single-blind parallel RCT	3 weeks	ROME III	IBS-D IBS-C IBS-M IBS-U	18–52	32/37	High FODMAP diet vs. LFD	18/19	5/2	A reduction in IBS-SSS ≥ 50	IBS-SSS
Staudacher et al. (24) the UK	RCT	4 weeks	ROME III	IBS patients with bloating and/or diarrhea as major IBS symptom	LFD:35.2 (11.4) ND:35.0 (8.7)	23/35	Habitual diet vs. LFD	19/16	1/2	Answer "yes" to "Were your symptoms adequately controlled over the previous week?"	Global symptom question; Stool consistency/ frequency
Staudacher et al. (25) the UK	Multi-center 2 × 2 factorial RCT	4 weeks	ROME III	IBS-D IBS-M IBS-U	LFD:36 (11) ND:33 (12)	70/104	Sham diet vs. LFD	51/53	2/1	Answer "yes" to "Did you have adequate relief of your symptoms over the past 7 days?"	"Adequate symptom relief" question; IBS-SSS; IBS-QOL; Stool consistency/ frequency
Wilson et al. (26) the UK	Double-blind 3-arm RCT	4 weeks	ROME III	IBS-D IBS-C IBS-M IBS-U	LFD:38.9 (10.0) ND:30.3 (9.8)	25/45	Sham diet vs. LFD	21/21	4/3	Answer "yes" to "Over the past 7 days, do you feel that you have had adequate relief of your IBS symptoms?"	"Adequate symptom relief" question; IBS-SSS; IBS-QOL; Stool consistency/ frequency
Zahedi et al. (19) Iran	Single-blind RCT	6 weeks	ROME III	IBS-D	LFD:37.60 (11.9) ND:37.43 (13.27)	51/101	GDA vs. LFD	50/51	2/3	–	IBS-SSS; IBS-QOL; Stool consistency/ frequency; HADS

(Continued)

TABLE 1 | Continued

References	Design	Duration	IBS definition	IBS type	Age range or mean age (SD)/year	Female/total	Intervention	Participants (LFD/ND)	Drops (LFD/ND)	Clinically meaningful improvement	Symptom assessment
Eswaran et al. (23) America	Single-center single-blind RCT	4 weeks	ROME III	IBS-D	LFD:41.6 (14.7) ND:43.8 (15.2)	65/92	mNICE vs. LFD	45/39	8/9	–	IBS-QOL; HADS
Eswaran et al. (15) America	Single-center single-blind RCT	4 weeks	ROME III	IBS-D	LFD:41.6 (14.7) ND:43.8 (15.2)	65/92	mNICE vs. LFD	45/39	8/9	Answer "yes" to "In regard to all your IBS symptoms, as compared with the way you felt before you started the diet, have you, in the past seven days, had adequate relief of your IBS symptoms?"	"Adequate symptom relief" question; Stool consistency/ frequency
Laatikainen et al. (17) Finland	Double blind cross-over RCT	4 weeks	ROME III	IBS-D IBS-M IBS-U	42.9 (21–64)	73/80	Regular rye bread vs. Low-FODMAP rye bread	80/80	4/6	–	IBS-SSS IBS-QOL

RCT, randomized controlled trial; BMI, body mass index; FODMAP, fermentable oligo-di-mono-saccharides and polyols; LFD, low fermentable oligo-di-mono-saccharides and polyols diet; GDA, general dietary advice; IBS-D, irritable bowel syndrome with diarrhea; IBS-M, mixed stool pattern irritable bowel syndrome; IBS-C, constipation predominant irritable bowel syndrome; IBS-U, unclassified irritable bowel syndrome; VAS, visual analog scale; HADS, hospital anxiety and depression scale; IBS-SSS, irritable bowel syndrome-severity symptom scale; IBS-QOL, irritable bowel syndrome related quality of life; mNICE, modified diet recommended by the National Institute for Health and Care Excellence; vs., versus.

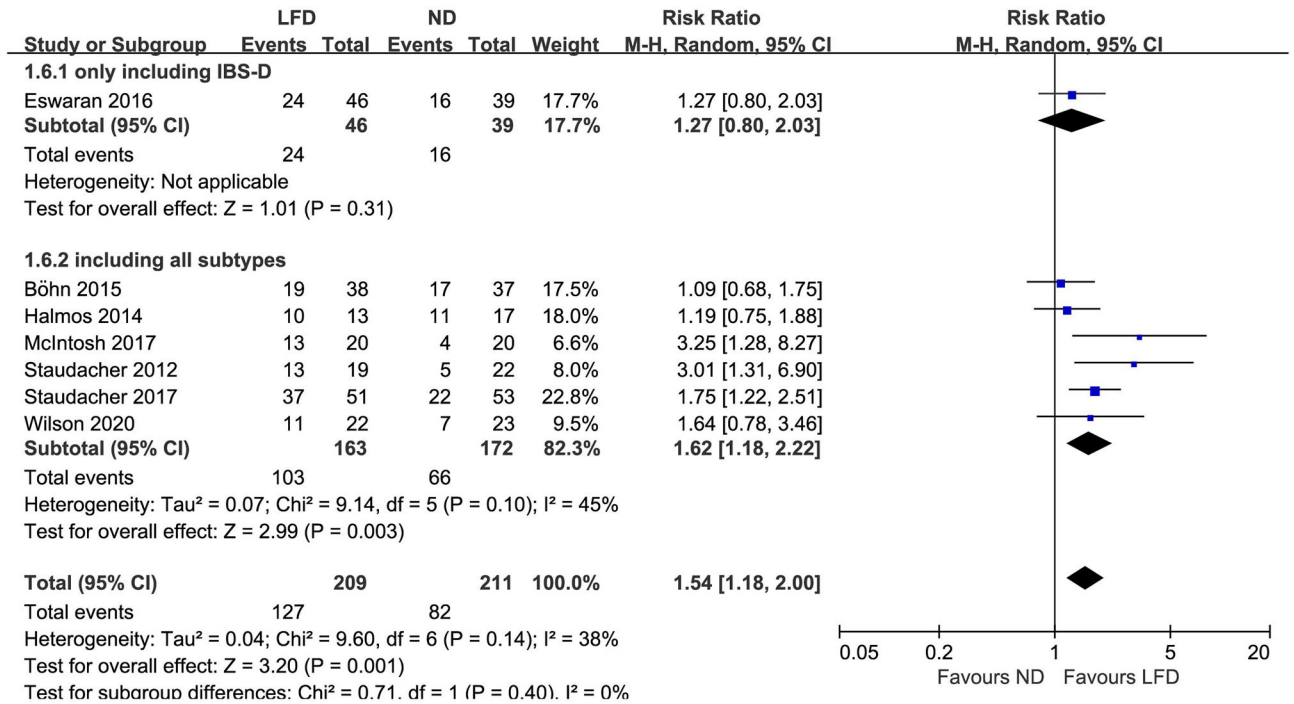

FIGURE 2 | Pooled relative risk for the improvement of irritable bowel syndrome (IBS) global symptoms. LFD, low-FODMAP diet; ND, normal diet.

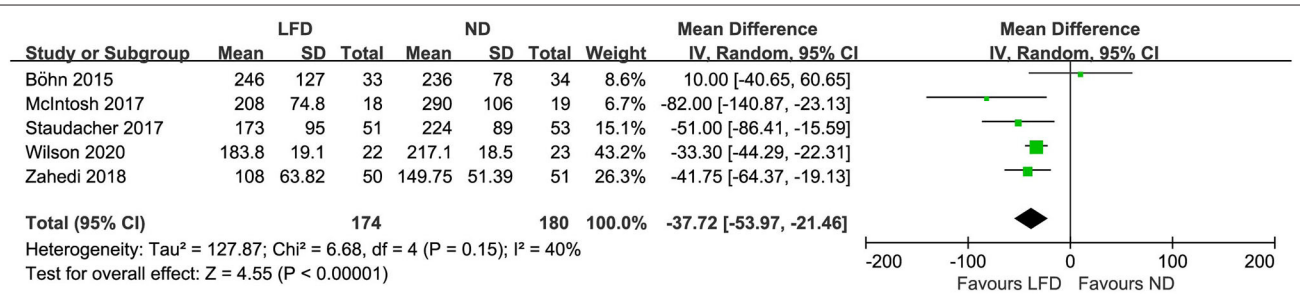

FIGURE 3 | Pooled mean difference for the improvement of IBS global symptoms. LFD, low-FODMAP diet; ND, normal diet.

BMI

Only two studies reported the effect of LFD on BMI changes, but showed no statistical difference ($n = 110$; MD $= -0.22$; 95% CI -1.89 to 1.45; $I^2 = 14\%$) (**Figure 9**).

Risk of Bias and GRADE

The overall risk of bias is relatively low as shown in **Figure 10**. A summary of the quality of evidence according to GRADE for the included RCTs is given in **Table 2**.

Publication Bias

There was no evidence of publication bias based on Egger's regression analysis: global improvement of symptoms ($p = 0.0765$); IBS-SSS ($p = 0.1558$); pain intensity ($p = 0.7638$); pain frequency ($p = 0.7686$); abdominal distension ($p = 0.7689$); dissatisfaction of bowel habit ($p = 0.1871$); interference on life in general ($p = 0.0785$); IBS-QOL ($p = 0.1086$); stool consistency ($p = 0.4353$); stool frequency ($p = 0.9699$).

Subgroup Analysis

Subgroup analysis of the outcomes (except "HADS" and "BMI" because only 2 RCTs were included for each outcome) was conducted based on "treatment duration," "FODMAP level in the control diet," "definition of clinically meaningful improvement," and "IBS subtype." Results are shown in **Supplementary Table 1**.

DISCUSSION

This updating meta-analysis included 10 high-quality RCT studies involving 511 participants according to the above criteria. The study aimed to provide clinicians with evidence-based data proving that an LFD alleviates symptoms in patients with IBS

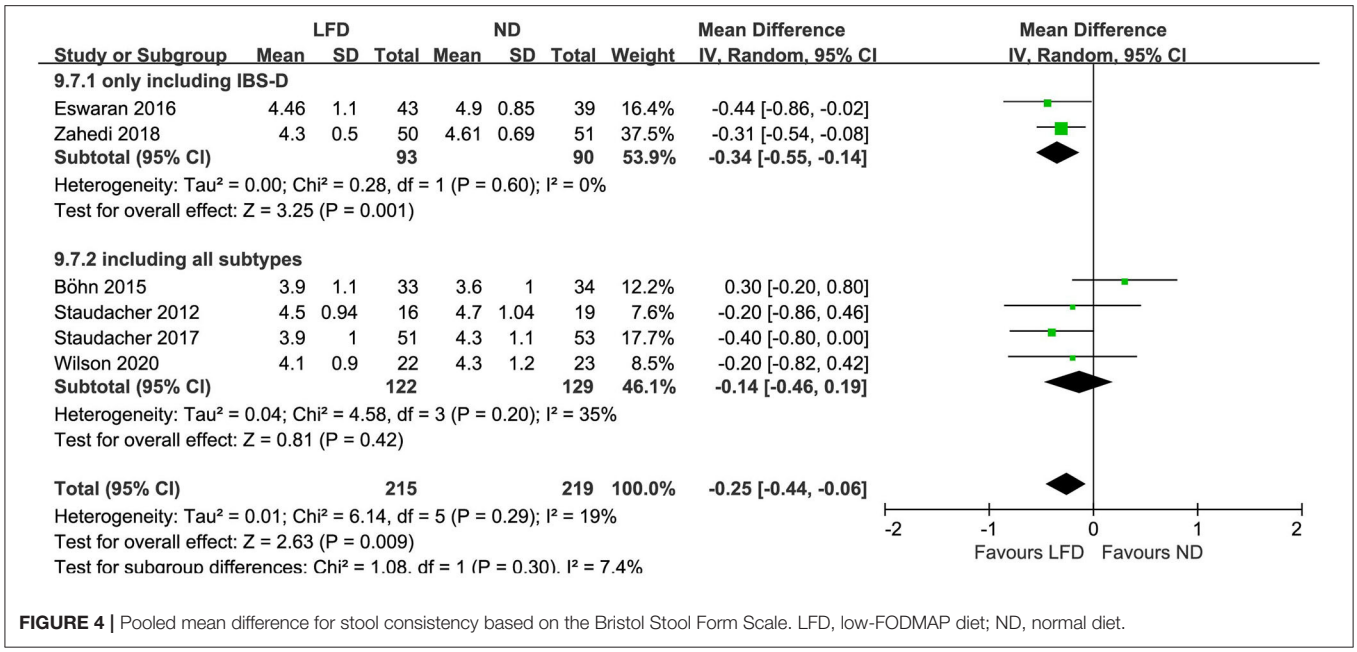

FIGURE 4 | Pooled mean difference for stool consistency based on the Bristol Stool Form Scale. LFD, low-FODMAP diet; ND, normal diet.

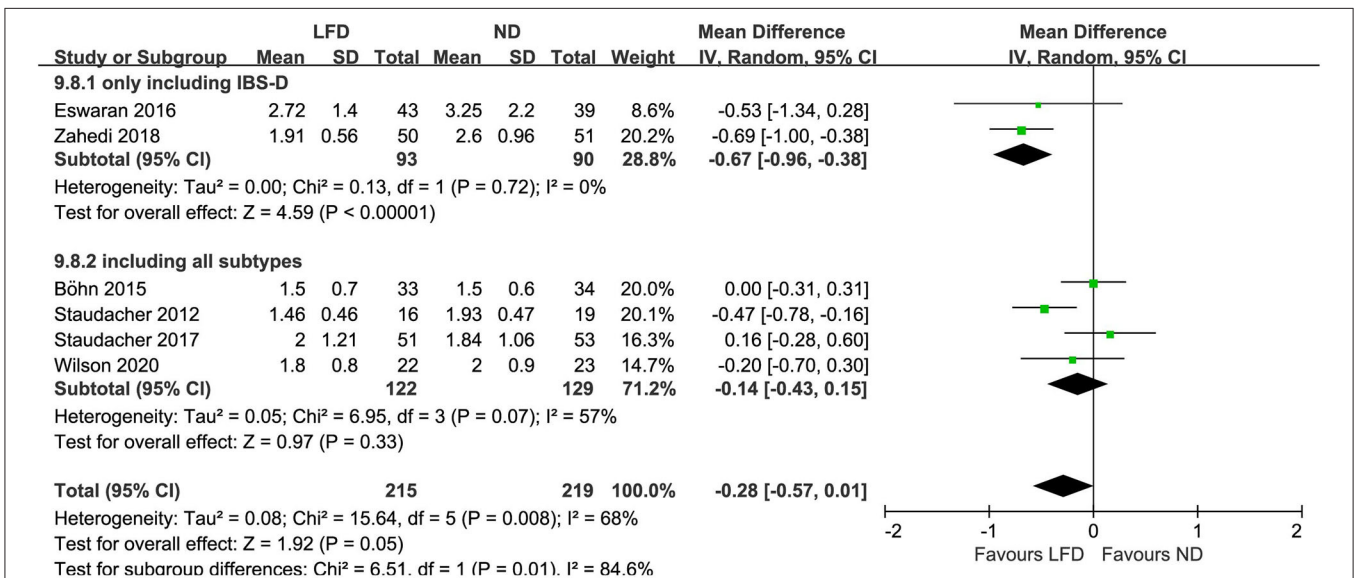

FIGURE 5 | Pooled mean difference for stool frequency (per day). LFD, low-FODMAP diet; ND, normal diet.

effectively. More research data were attempted to be extracted from existing studies to explore the effects of an LFD on the overall symptoms, stool output, IBS-QOL, anxiety and depression, and BMI of IBS patients. The study found that an LFD significantly reduced the global symptoms of patients with IBS and improved their stool output, especially for those with IBS-D, and that the quality of evidence was moderate. However, LFDs had no statistically significant effects on IBS-QOL, anxiety and depression score, and BMI in patients with IBS, while the quality of evidence was low or very low. The reasons for the low level of evidence quality mainly include inappropriate blinding methods, large heterogeneity, and a limited number of studies. Even though some potential limitations and concerns of an LFD have been raised, such as nutritional adequacy, cost, difficulty in teaching, learning, and continuing, most of the limitations (20, 34). In conclusion, based on the evidence presented in this meta-analysis, adult IBS patients, especially those with IBS-D, are recommended to try an LFD with professional advice from health care professionals.

Global symptom improvement was treated as the primary outcome in this systematic review. Seven studies (15, 18, 21, 22, 24–26) evaluated the effectiveness of an LFD in improving

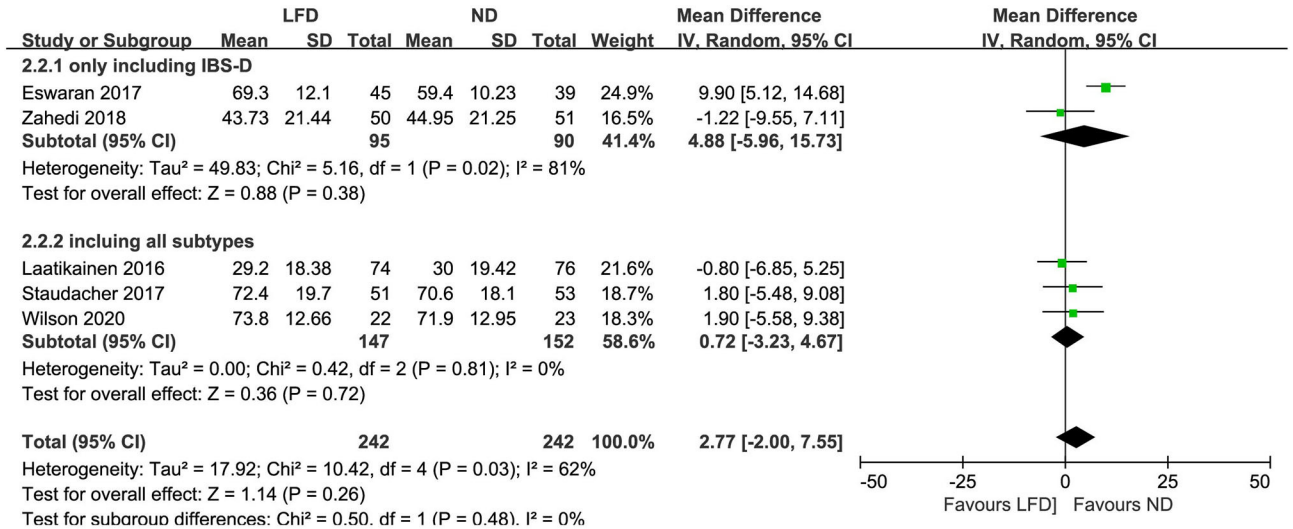

FIGURE 6 | Pooled mean difference for irritable bowel syndrome-related quality of life (IBS-QOL). LFD, low-FODMAP diet; ND, normal diet.

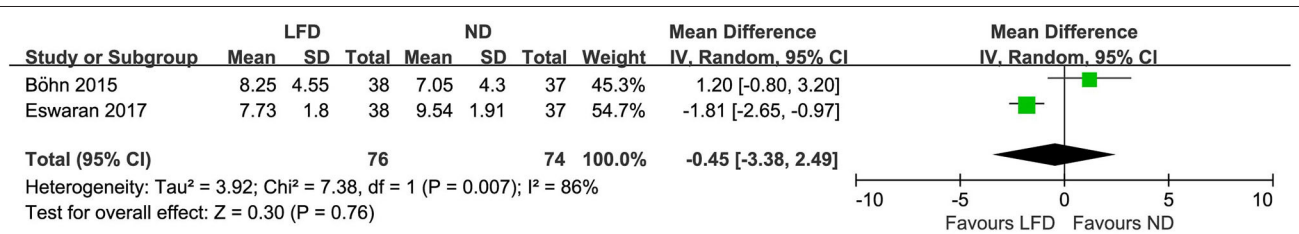

FIGURE 7 | Pooled mean difference for anxiety score based on the hospital anxiety and depression scale. LFD, low-FODMAP diet; ND, normal diet.

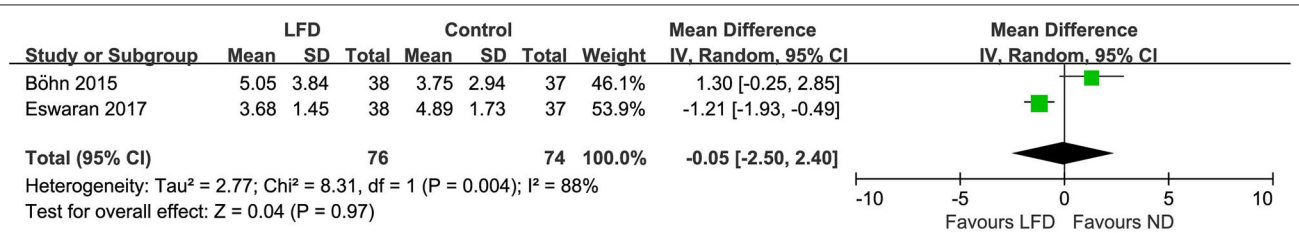

FIGURE 8 | Pooled mean difference for depression score based on the hospital anxiety and depression scale. LFD, low-FODMAP diet; ND, normal diet.

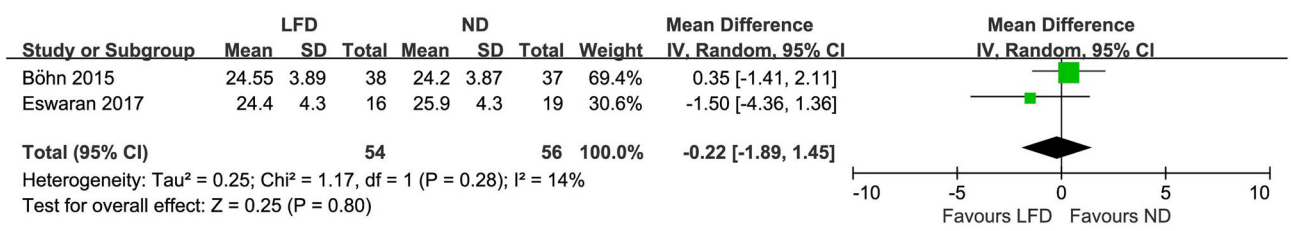

FIGURE 9 | Pooled mean difference for body mass index (BMI). LFD, low-FODMAP diet; ND, normal diet.

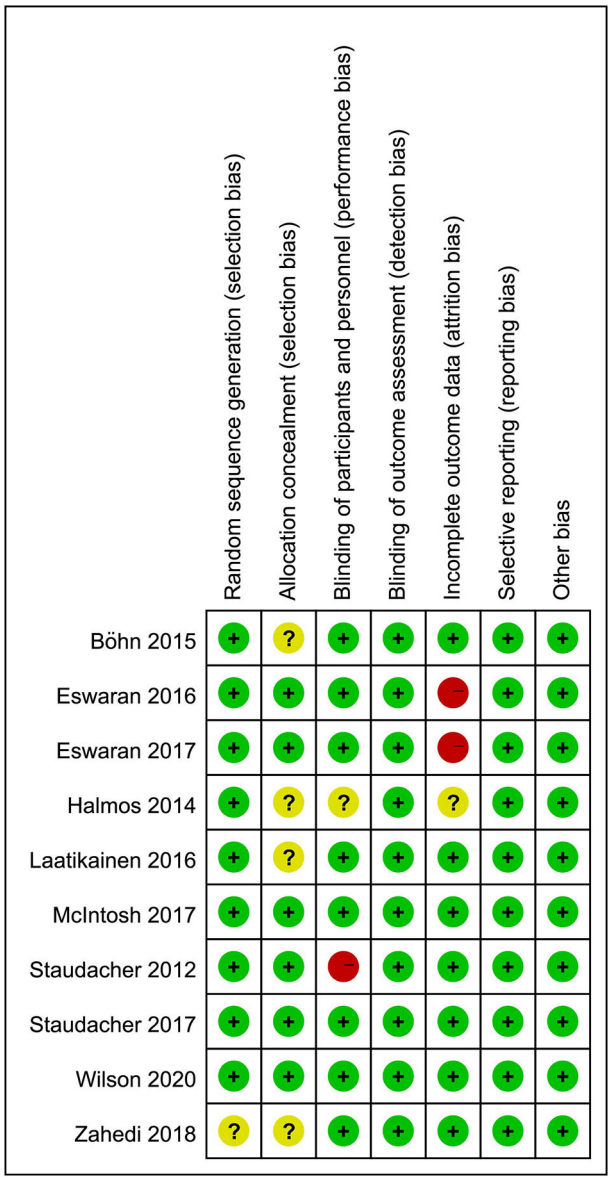

FIGURE 10 | Summary of risk of bias.

the overall symptoms of IBS with dichotomous variables, using different clinically meaningful improvement criteria. Meanwhile, there were 5 RCTs (18, 19, 22, 25, 26) that used IBS-SSS to assess the IBS global symptoms with continuous variables, which also supported this conclusion. According to the results, over 60% (127/209) of IBS patients in the LFD group experienced significant relief, which seems to be an acceptable result; whereas, GRADE (35) would ideally require 300 responders to be classified as robust. More large-sample studies are needed to provide reliable evidence in the future. However, it is a challenge to conduct a high-quality RCT on this subject due to a lack of support from the pharmaceutical industry and funding agencies (27). Three previous meta-analyses used "mean difference" or "standardized mean difference" based on IBS-SSS as their effect sizes (30, 31, 36). These two kinds of effect sizes can only reflect the effect of an LFD on the IBS population, but cannot evaluate individual differences. At the same time, a statistically significant mean difference may not be clinically significant. For example, a 50-point reduction in IBS-SSS is generally considered to reflect a clinically meaningful improvement (22, 37). Thus, risk ratio (RR) was chosen to evaluate the difference between LFD and control diets, trying to make the results more clinically meaningful and easier to understand. In addition, comparing responder rates between trials is difficult because of the different responder definitions that were used (22). A 50-point reduction of IBS-SSS in two trials (18, 22) and a 10-point reduction in the visual analog scale (VAS) in one trial (21) were considered to reflect a clinically meaningful improvement. On the other hand, patients who felt adequate relief of their IBS symptoms were seen as responders in another four papers (15, 24–26). The existing scales for assessing the severity of IBS symptoms are not uniform, and it makes no sense to directly pool these scores together for meta-analysis. If the continuous variables of scores from a scale can be transformed into a dichotomous variable according to an appropriate "responding criteria," the results of these clinical trials can be directly compared despite the different scales. Moreover, dropout is inevitable in clinical research and the reasons should be clarified. For instance, in patients who were intolerant of the intervention: the data of these results should be attributed to treatment failure rather than simple data loss in an intention-to-treat analysis.

According to ROME III (2, 38) and IV (4, 39) criteria, IBS is diagnosed on the basis of recurrent abdominal pain related to defecation or in association with a change in stool frequency or form. Thus, the effect of LFDs on altered bowel habits in IBS patients is an important aspect to evaluate. To our knowledge, this is the first meta-analysis that included stool output as a crucial outcome on this subject, which has not been demonstrated by previous meta-analyses (27–31). Stool consistency generally refers to the rheology or viscosity of the stool, which is largely determined by stool water content (40, 41). Gastrointestinal water absorption is limited by rapid intestinal transit limits, causing loose or liquid stools (42). It can be measured as a finite number of categories by the Bristol Stool Form Scale (BSFS), which is the most widely used criteria (43, 44). According to our study, pooled data from six RCTs showed a moderate improvement in the stool output of IBS patients following an LFD, which was consistent with a previous meta-analysis study (only containing three RCTs for this outcome) (28). Interestingly, patients with IBS-D (however, only 93 IBS-D patients were included) seemed to benefit more from an LFD, probably obtaining a greater improvement in stool output than other IBS subtypes according to the subgroup analysis. The results mentioned above indicate that an LFD may contribute to reduced stool water content, increase stool hardness, and further reduce stool frequency effectively. Nevertheless, according to this theory, constipation in IBS-C patients would not be improved by an LFD and may even be worsened. However, more research is needed in the future to confirm this.

Irritable bowel syndrome affects the quality of life negatively (44–46), to the same degree as organic gastrointestinal disorders

TABLE 2 | Grading of recommended assessment, development and evaluation (GRADE) summary of findings.

Certainty assessment							Summary of findings				
Participants (studies) follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With normal diet	**With LFD**		**Risk with normal diet**	**Risk difference with LFD**
Global improvement of IBS symptom											
420 (7 RCTs)	Serious	Not serious	Not serious	Not serious	None	⨁⨁⨁◯ MODERATE	82/211 (38.9%)	127/209 (60.8%)	RR 1.58 (1.29–1.93)	389 per 1,000	225 more per 1,000 (from 113 more to 361 more)
Stool consistency											
434 (6 RCTs)	Serious	Not serious	Not serious	Not serious	None	⨁⨁⨁◯ MODERATE	219	215	–	The mean stool consistency was 4.41	MD 0.27 lower (0.43 lower to 0.11 lower)
Stool frequency											
434 (6 RCTs)	Serious	Not serious	Not serious	Serious	None	⨁⨁◯◯ LOW	219	215	–	The mean stool frequency was 2.24	MD 0.28 lower (0.57 lower to 0.01 higher)
Stool consistency for IBS-D											
183 (2 RCTs)	Not serious	Not serious	Not serious	Serious	None	⨁⨁⨁◯ MODERATE	90	93	–	The mean stool consistency for IBS-D was 4.74	MD 0.34 lower (0.55 lower to 0.14 lower)
Stool frequency for IBS-D											
183 (2 RCTs)	Not serious	Not serious	Not serious	Serious	None	⨁⨁⨁◯ MODERATE	90	93	–	The mean stool frequency for IBS-D was 2.88	MD 0.67 lower (0.96 lower to 0.38 lower)
IBS related quality of life											
555 (6 RCTs)	Serious	Serious	Not serious	Serious	None	⨁◯◯◯ VERY LOW	279	276	–	The mean IBS related quality of life was 51.59	MD 2.66 higher (1.42 lower to 6.74 higher)
Anxiety score											
150 (2 RCTs)	Serious	Serious	Not serious	Serious	None	⨁◯◯◯ VERY LOW	74	76	–	The mean anxiety score was 8.30	MD 0.45 lower (3.38 lower to 2.49 higher)
Depression score											
150 (2 RCTs)	Serious	Very serious	Not serious	Serious	None	⨁◯◯◯ VERY LOW	74	76	–	The mean depression score was 4.32	MD 0.05 lower (2.5 lower to 2.4 higher)
BMI											
110 (2 RCTs)	Serious	Not serious	Not serious	Serious	None	⨁⨁◯◯ LOW	56	54	–	The mean BMI was 24.78	MD 0.16 lower (1.65 lower to 1.34 higher)

CI, Confidence interval; RR, Risk ratio; MD, Mean difference.

like Crohn's disease (47). This imposes a substantial burden on patients and employers (45, 46), which suggests a significant unmet need for effective therapies to treat the symptoms of IBS and alleviate the considerable societal and patient burden associated with this condition. The IBS-QOL, validated in 1998 by Patrick et al. (48) is utilized as a conceptually valid self-administered questionnaire with highly reproducible results for assessing the perceived quality of life for individuals with IBS (48). Meaningful clinical improvement is seen by a rise in IBS-QOL score > 14 (48). Six RCTs involved the evaluation of the effects of an LFD on this term with relatively high heterogeneity. Sensitivity analysis showed that the greatest heterogeneity among the studies came from Eswaran et al. (23). When this study was excluded, the heterogeneity index I^2 decreased from 62 to 0%. However, the final result was still not statistically significant, suggesting that no clinical improvement in this term occurred after an LFD intervention in IBS patients. Consistent results were observed in the subgroup analysis based on IBS subtype. It is important to note that restrictive diets can sometimes be stressful for patients with chronic diseases. Any effort to eliminate more food or impose further dietary restrictions might hamper the adherence rate, produce opposite results, and have a negative effect on the quality of life in patients with IBS (49). In the LFD group, in particular, available dietary choices were restricted to a great degree, reducing long-term adherence (20, 33). Ooi et al. (50) and Halmos (51) noted that extensive or inappropriate use of the LFD could have a negative impact on the health of patients. On the other hand, the duration of most LFD trials was limited (<8 weeks) and could not ensure long-term efficacy comparable to the drug trials (52). An additional period may be necessary for clinically significant improvement in quality of life for IBS patients to manifest following an LFD.

Major psychosocial problems have been reported to be observed in 50–60% of IBS patients (6). Three pieces of meta-analyses showed that levels of anxiety and depression were significantly higher in IBS patients compared with healthy controls (6–8). Meanwhile, the prevalence rates of anxiety and depression symptoms in IBS patients are near 40 and 30%, respectively (6). It is not difficult to accept that chronic IBS symptoms can have a destabilizing impact on quality of life and be associated with stress, work impairment, and further aggravation of mental disorders. However, there was no significant difference in the anxiety and depression scores between LFD and control groups in the included studies. Eswaran et al. (23) demonstrated that LFDs could alleviate the symptoms of anxiety but not have any effects on depression. The other study conducted by Bohn et al. (22) showed that LFDs had no effect on depression in patients with IBS. At present, a limited number (only two papers included in this study) of studies cannot come to a definite conclusion on this proposition, and further studies are needed to put more focus on the effect of LFDs on improving the anxiety and depression statuses of IBS patients.

Quality assessment of the RCTs yielded high risk in the blinding process of one RCT (24) and in the outcome assessment process of another two RCTs (15, 23), although the overall risk of bias was relatively low. We used the GRADE methodology (53) to evaluate the quality of the evidence, which is the most widely accepted approach. Eventually, it was found that the evidence supporting the significant effects of LFDs on IBS symptoms was relatively reliable. Generally, the blinding of patients to the LFD can be challenging (52). Many IBS patients are aware of the concept of an LFD, and information on this diet is freely available. An IBS patient can easily deduce which diet they have been allocated to if they participate in an RCT. Only one paper (21) that was included had assessed blinding to the diets by asking participants to identify the diet that they had been allocated to prove the success of the blinding process. Therefore, adhering to a diet regime that is considered "healthy" might reduce anxiety and subsequently alleviate IBS symptoms; thus creating a placebo response. Most studies [except the three studies (15, 19, 23) that had only recruited IBS-D patients] did not address differences in responses to dietary interventions in IBS subgroups, making it difficult to demonstrate a difference in the response rates and other outcomes among IBS subtypes. However, according to the subgroup analysis, IBS-D patients seemed to get more benefits from an LFD in improving their bowel habits.

As reported, FODMAPs have important physiological effects: they increase stool bulk, enhance calcium absorption, modulate immune function, and decrease the levels of serum cholesterol, triacylglycerols, and phospholipids (48). Because of the effects mentioned above, many potential limitations and concerns about LFDs have been raised (21, 51) such as nutritional adequacy, cost, and difficulty in teaching, learning, and continuing the diet. Although a relatively short-term (<6 weeks) LFD was generally well-tolerated, with adverse events rarely reported (16, 26), the pooled mean difference of BMI was not statistically significant between LFD and control groups according to our study. The effects, both positive and negative, of a long-term LFD on IBS still need to be assessed by expanding the sample quantity and extending the time of intervention (52). Therefore, a minimum length of 6 months has been recommended to establish long-term efficacy (53).

This research has significant strengths. Firstly, on the basis of the previous meta-analyses (27, 30) on this topic, we have included new high-quality RCTs that were conducted recently after comprehensive retrieval and strict screening, increasing the total population and making the results more credible. Secondly, the risk of bias of every single trial was evaluated strictly according to the standards of Cochrane Risk of Bias Tool, and GRADE was used to evaluate the quality of evidence for each outcome. Although the study focused on the improvement of the overall symptoms of IBS, it also crucially analyzed the effects on stool output, quality of life, and anxiety and depression status. To our knowledge, this is the first meta-analysis to comprehensively evaluate the effects of an LFD on IBS symptoms from a multi-perspective. However, there are limitations to this systematic review as well. Firstly, the sample size of the participants involved is small. Additionally, most studies did not address differences in response to dietary interventions among IBS subgroups, which may exaggerate or minimize the effect of LFDs on specific subtypes of IBS. However, as shown in the pooled data, an LFD may be more effective in patients with IBS-D than those with constipation as a major symptom. Finally, different studies did not use a unified evaluation scale, such as IBS-SSS, to evaluate the overall symptoms of IBS. Different definitions of IBS symptom improvement may limit the reported benefit of LFDs in IBS

patients and lead to a certain degree of heterogeneity among different studies.

In conclusion, this systematic review and meta-analysis provide a moderate quality of evidence for supporting the efficacy of an LFD in the improvement of global symptoms and bowel habits of adult IBS patients. The improvement in bowel habits seems to be more pronounced in IBS-D patients. Recommending adult IBS patients, especially those with IBS-D, to try an LFD with professional advice from health care professionals is worth promoting.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

JW came up with the idea of the study. JW and LZ designed the research. JW, PY, LZ, and XH conducted the research, analyzed the data, and performed the statistical analysis. JW and PY wrote initial version. LZ and XH provided critical input. All authors had equal responsibility for the final content of the paper, read, and agreed to the published version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.683191/full#supplementary-material

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