



Applied nutritional investigation

## Hyperphagia in short bowel patients: Fat-free mass is a strong predictor



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## ABSTRACT

**Objectives:** Some patients with short bowel syndrome (SBS) develop hyperphagic behavior. Such an increase in food intake stimulates intestinal adaptation and limits dependence on parenteral nutrition (PN). The aim of this study was to determine the factors modulating food consumption in patients with SBS.

**Methods:** The associations between oral energy intake (OEI) and anthropometric, metabolic, nutritional, and intestinal absorption–related characteristics were determined in a monocentric cohort of patients with SBS on PN with a stable nutritional status. Body composition was assessed by dual x-ray absorptiometry. Data were retrospectively collected from clinical records.

**Results:** After screening, 38 adult patients with a SBS on PN were included in this study. OEI ranged from 577 to 4054 kcal/d. OEI correlated positively with weight, fat-free mass, handgrip strength, and resting energy expenditure (REE) and negatively with free triiodothyronine and C-reactive protein using Spearman correlation. Fat-free mass and thyroid-stimulating hormone remained positively correlated with OEI independently of all other parameters in a multilinear regression model.

**Conclusions:** Fat-free mass is a strong predictor of OEI in patients with SBS on PN and without debilitating gastrointestinal symptoms. Increasing fat-free mass could be a way to stimulate OEI in these patients. Further studies are needed to assess this assumption.

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### Introduction

In adults, short bowel syndrome (SBS) is secondary to intestinal resection for gastrointestinal conditions including mesenteric ischemia, inflammatory bowel diseases, occlusive syndromes, or bowel cancers. SBS is defined by a remnant bowel length inferior to 150 to 200 cm. Massive small intestine resection induces

temporary or permanent intestinal failure owing to malabsorption related to a reduced intestinal surface [1].

The development of parenteral nutrition (PN) over the last decades has changed the prognosis for patients with SBS. However, long-term PN induces serious complications (e.g., central venous catheter–related bloodstream infections and intestinal failure–associated liver disease) [2,3]. Moreover, home parenteral nutrition (HPN) is an expensive treatment associated with a poor quality of life [4,5]. Thus, one of the main objectives of care for patients with SBS is to promote intestinal adaptation and to reduce dependence on PN. Some patients with SBS present adaptive hyperphagia, which is critical for intestinal adaptation [6,7]. Stimulating food consumption could therefore be a safe and inexpensive way to reduce dependence on PN [8].

Few studies have assessed the factors that modulate oral energy intake (OEI) in patients with SBS. These studies focused on the links between hyperphagia and certain hormones—namely leptin, dipeptidyl peptidase-4, peptide YY, and ghrelin—with inconclusive results [9–11]. Because fat-free mass (FFM) correlates with OEI in

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individuals who are of healthy normal weight or obese, we hypothesized that body composition could at least partly determine OEI in patients with SBS [12–14]. The aim of the present study was to determine the factors associated with OEI in patients with SBS on HPN and stable nutritional status.

## Materials and methods

### Study population

This study was based on observational, routinely collected data from one HPN referral center in Lyon, France. Health data were recorded in electronic patient records during clinical practice. In our center, every patient who is on HPN for an extended period is routinely hospitalized for nutritional assessment. All patients with SBS who were hospitalized for this assessment from January 2007 to October 2016 were screened. Clinically stable patients with an SBS for  $\geq 1$  y and on HPN were included. SBS was defined as a remnant short bowel length inferior to 200 cm with or without colon resection [1]. Owing to the eating difficulties of adults with a pediatric SBS, these patients were excluded from the study [15]. Patients with intestinal transplantation and those with an OEI  $< 500$  kcal or frequent nausea or vomiting were also excluded.

### Nutritional assessment

All included patients received a standardized nutritional assessment during a hospital stay of a few days. If a patient received several nutritional assessments, only the data from the most recent hospitalization were collected. These nutritional assessments are routinely performed in the HPN referral center of Lyon. The purpose was to ensure that the long-term HPN was appropriate. Nutritional assessment includes body composition analysis and anthropometry, a 3-d food diary, indirect calorimetry, and blood and stool tests.

### Body composition and anthropometry

All anthropometric measurements were performed by medical practitioners. Weight, height, brachial circumference at the center of the upper limb, and triceps skinfold at the same site using an anthropometric calliper were determined. The device used for determination of handgrip strength (HGS) changed in 2012. Thus, only HGS measured with a Jamar dynamometer data after 2012 was considered. FFM and fat mass were estimated by dual x-ray absorptiometry (DXA). Indirect calorimetry (Quark RMR – Cosmed, France) was performed for 30 min in fasting individuals after discontinuation of PN for  $\geq 6$  h.

### Determination of food intake and definition of hyperphagia

OEI was assessed by a trained dietitian using a 3-d food diary filled out at home before hospitalization.

Some authors have attempted to define hyperphagia in SBS; however, no clear definition has yet to emerge. Based on a review of the literature, two principal definitions have been retained in this study to classify the participants as hyperphagic or non-hyperphagic. We defined participants as hyperphagic if they had a daily OEI  $> 40$  kcal/kg [9] or 1.5 times their REE [6].

### Blood and stool tests

Blood tests, including determination of albuminemia, C-reactive protein (CRP) level, thyroid function, and plasma amino acids to measure plasma citrulline concentration, were performed. Intestinal carbohydrate absorption was determined using a blood D-xylose test. Fasting individuals were given 5 g of D-xylose dissolved in 200 mL water and D-xylose blood concentration was measured after 1 h. Stools were collected by the participants for 3 d at home before hospitalization to determine average daily stool weight.

### Ethics statement

According to current French law, patients were individually informed that their data could be used for research and did not object. Data were collected during routine medical examination. Patients did not undergo any treatment or examination specifically devised to collect data for this study.

### Statistical analysis

Statistical analysis was performed using RStudio Version 1.0.136 with occasional reliance on “prettyR,” “RVAideMemoire,” “ggplot2,” “car,” and “zoo” [16]. Owing to the small number of patients, non-parametric statistics were used. Data are presented as medians and 95% confidence intervals.  $P < 0.05$  was considered significant.

The relationship between OEI and the following 24 variables were examined: age, sex, SBS causes, bowel anatomy, remnant small bowel length, duration of SBS, REE, body weight, FFM, fat mass, brachial circumference, skinfold, HGS, plasma albumin, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), CRP, parenteral energy intake, number of parenteral infusions per week, volume of parenteral infusion stool weight, 1-h D-xylose blood concentration, and citrullinemia. To determine the predictive factors of OEI, a univariate analysis was first completed using Spearman's correlations and Wilcoxon Mann–Whitney test or Kruskal–Wallis test for categorical variables with more than two factors. For the Spearman's correlation determination, the results were expressed as  $\rho$  and 95% confidence interval (CI). CIs were determined using a bootstrap with 1000 replicates.

Subsequently, a multiple regression analysis was performed to determine the factors significantly and independently associated with OEI. Variables with  $P < 0.1$  in univariate analyses as well as age and sex were entered. HGS was excluded because too many values were missing. Owing to the collinearity between weight and FFM, assessed by variance influence factor, weight was replaced by fat mass. Variance influence factor was  $< 5$  for each factor after this adjustment. The residual of multiple linear regression was normally distributed using the Shapiro–Wilk test [17].

## Results

### Patient inclusion

We screened all patients ( $N = 119$ ) on HPN and hospitalized for a nutritional assessment between January 2007 and October 2016 (Fig. 1). Of these 119 patients, 38 were included in the study.

### Patient characteristics

The study population was made up of 24 men (63%) and 14 women with a median age of 63 y (range, 37–77). Patients underwent intestinal resection owing to mesenteric ischemia ( $n = 24$ , 63%), small bowel obstruction ( $n = 5$ , 13%), intestinal tumor ( $n = 3$ , 8%), radiation enteritis ( $n = 3$ , 8%), or other causes ( $n = 3$ , 8%). The median remnant small bowel length was 70 cm (range, 8–164). Among the 18 patients with a stoma, 16 had an end-jejunostomy and 2 had a colostomy with a jejuno-colic anastomosis. Among the 20 patients without a stoma, 17 had a jejuno-colic anastomosis and 3 a jejuno-ileal anastomosis. The median period between nutritional assessment and bowel resection was 52 mo (range, 16–214). Table 1 shows the demographic, anthropometric, metabolic, nutritional, and intestinal absorption-related characteristics.

### Oral and parenteral energy intake

Patients were assigned either to the hyperphagic or the non-hyperphagic group according to the two retained hyperphagia definitions, namely an oral daily energy intake  $> 40$  kcal/kg (Fig. 2A) or 1.5 times their REE (Fig. 2B). Patients with hyperphagia accounted for 26% ( $n = 10$ ) using the first definition (Fig. 2A) and 43% ( $n = 16$ ) using the second definition (Fig. 2B). As illustrated in Figures 2A and B, OEI had a Gaussian distribution, which did not make it possible to clearly distinguish the group of hyperphagic patients from the group of non-hyperphagic patients. Whatever the definition of hyperphagia, the hyperphagic patients were only those with the greatest energy intake (on the right of the curve). Given this and for further analyses, the population was analyzed as a whole. Oral and parenteral energy intake and REE for each patient are provided in Figure 2C. In the vast majority of cases, OEI provided more than resting energy needs.

### Relationship between OEI and characteristics of the population and parenteral intake

Significant univariate analyses are illustrated in Figure 3. OEI was correlated with weight ( $\rho = 0.418$ ; 95% CI, 0.095–0.684;

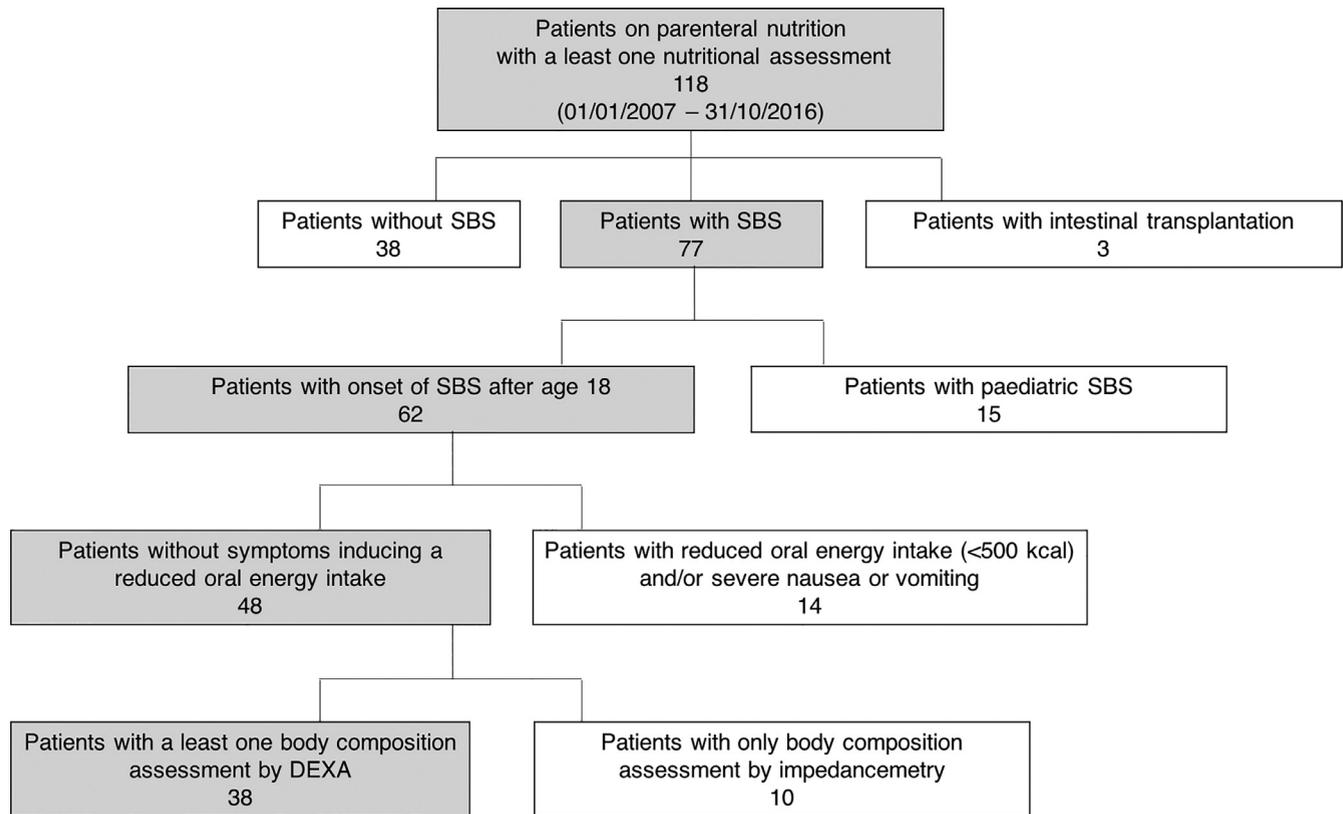


Fig. 1. Patient inclusion flowchart. DXA, dual-energy x-ray absorptiometry; SBS, short bowel syndrome.

Table 1

Anthropometric, metabolic, nutritional, and intestinal absorption–related characteristics of the population

| Parameters   | Median (95% CI)  |
|--|------------------|
| Age, y (range)*  | 63 (37–77)       |
| Sex, % (M/F)   | 63 (24/14)       |
| Anthropometric characteristics                             |                  |
| Body weight, kg  | 63 (48.9–80)     |
| BMI, kg/m <sup>2</sup>                                     | 22 (17.3–26.8)   |
| FFM, kg  | 42.9 (34.9–58.2) |
| FFMI, kg/m <sup>2</sup>                                    | 15.5 (13.4–9.5)  |
| FM, kg   | 16.5 (7.9–28.3)  |
| FMI, kg/m <sup>2</sup>                                     | 6.2 (2.7–11)     |
| Brachial circumference, cm, n = 35                         | 27 (23–34)       |
| Skinfold, mm, n = 35                                       | 14 (5–33)        |
| Handgrip strength, kg, n = 14                              | 32 (17–43)       |
| Metabolic characteristics                                  |                  |
| REE, kcal, n = 37  | 1394 (1053–1685) |
| TSH, mIU/L, n = 36   | 1.29 (0.48–3.07) |
| FT3, pmol/L, n = 35  | 4.1 (3.3–5.2)    |
| FT4, pmol/L, n = 35  | 12.8 (10.1–17.3) |
| CRP, mg/L  | 3.3 (0.9–15.7)   |
| Albumin, g/L   | 37.3 (28.1–44)   |
| Nutritional characteristics                                |                  |
| Oral energy intake, kcal/d                                 | 2087 (1293–3586) |
| Parenteral energy intake, kcal/d                           | 840 (286–1682)   |
| Number of parenteral infusions, per week                   | 4 (2–7)          |
| Volume of parenteral infusion, L, per bag                  | 1142 (286–3038)  |
| Amino acid content of parenteral infusion, g/kg/d, per bag | 0.62 (0.24–1.22) |
| Intestinal absorption–related characteristics              |                  |
| Stool weight, g/d, n = 35                                  | 1165 (186–2939)  |
| 1-h D-xylose blood concentration, mmol/L, n = 31           | 0.60 (0.24–1.51) |
| Citrullinemia, mmol/L                                      | 20 (7–43)        |

BMI, body mass index; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; REE, resting energy expenditure; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; CRP, C-reactive protein.

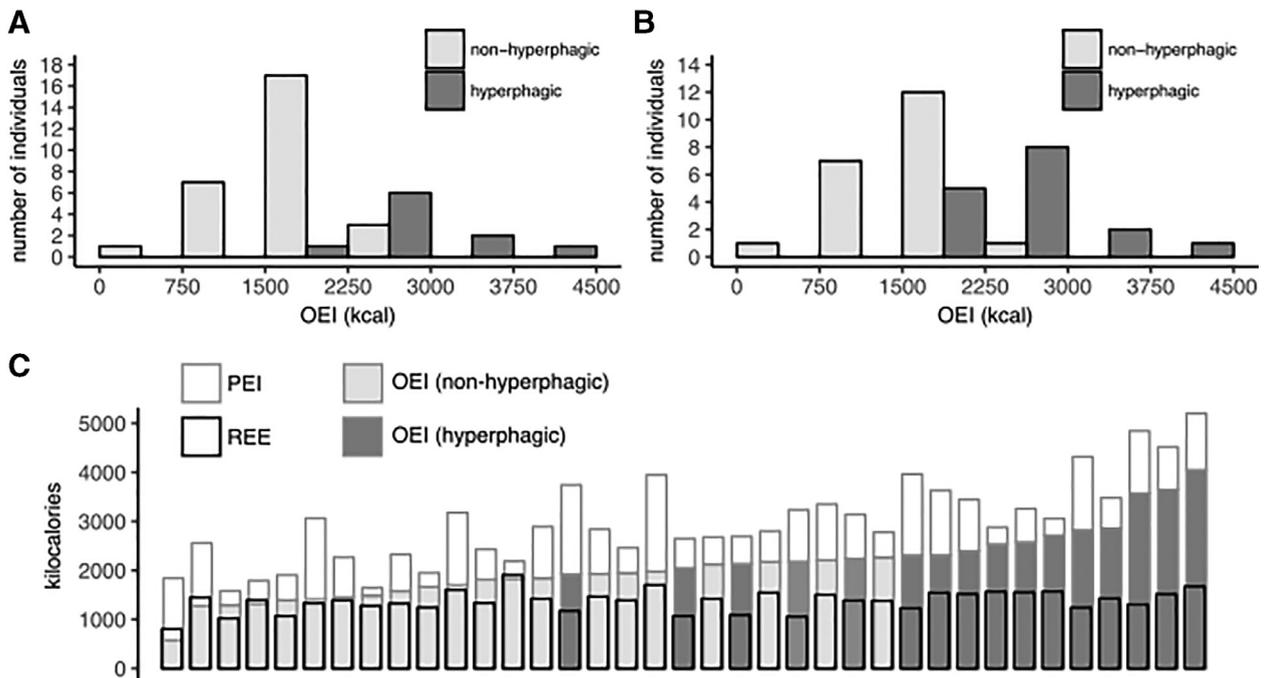
\*All n = 38, except where noted.

$P = 0.009$ ), FFM ( $\rho = 0.474$ ; 95% CI, 0.158–0.699;  $P = 0.003$ ) but not with fat mass ( $\rho = 0.021$ ; 95% CI,  $-0.313$  to 0.337;  $P = 0.90$ ). Despite the low numbers of participants with a measure of HGS ( $n = 14$ ), OEI was significantly correlated with HGS ( $\rho = 0.585$ ; 95% CI, 0.053–0.869). OEI was also positively correlated with REE ( $\rho = 0.365$ ; 95% CI, 0.042–0.628;  $P = 0.03$ ) and negatively correlated with FT3 ( $\rho = -0.346$ ; 95% CI,  $-0.622$  to  $-0.031$ ;  $P = 0.04$ ) and CRP ( $\rho = -0.360$ ; 95% CI,  $-0.625$  to  $-0.027$ ; Fig. 3). OEI was not correlated with any other parameters including age, mean remnant small bowel length, duration of SBS, parameters related to PN, and intestinal functions (Table 2). The OEI in subgroups of patients categorized by sex, SBS syndrome causes, and bowel anatomy was not significantly different ( $P = 0.11$ ,  $P = 0.97$ ,  $P = 0.88$ , respectively). Using multiple linear regression analysis with OEI as the dependent variable, and with age, sex, FFM, REE, TSH, FT3, and CRP as independent variables, OEI positively correlated with FFM ( $P < 0.05$ ) and TSH ( $P < 0.01$ ) independently of all other parameters (Table 3).

## Discussion

In patients with SBS, luminal nutrients are essential for intestinal adaptation and hyperphagia can reduce dependence on PN in some patients. Despite much interest in this area, previous studies have failed to determine the factors that explain the increase in food consumption in some patients with SBS.

In this observational study, we reported the correlations between OEI and the factors potentially involved in OEI in these patients. The most striking result is that OEI strongly correlated with FFM, both in linear and multiple linear regression models. We hypothesize that FFM drives OEI in patients with SBS. However, one may argue that in these patients, greater OEI induces a better



**Fig. 2.** OEI, PEI, and REE in the cohort of 38 patients with short bowel syndrome. (A) Distribution of the OEI in patients designated either non-hyperphagic (OEI/weight  $< 40 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ,  $n=28$ , 73.7%) or hyperphagic patients (OEI/weight  $\geq 40 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ,  $n=10$ , 26.3%). (B) Distribution of the OEI in patients designated either non-hyperphagic (OEI  $< 1.5 \cdot \text{REE}$ ,  $n=21$ , 56.8%) or hyperphagic patients (OEI  $\geq 1.5 \cdot \text{REE}$ ,  $n=16$ , 43.2%). (C) Individual variations of PEI, OEI, and REE. Participants were ranked according to their OEI. OEI is marked in dark gray if patients are hyperphagic with either of the two definitions. One participant was not represented in Fig. 2B and C because the REE was missing. OEI, oral energy intake; PEI, parenteral energy intake; REE, resting energy expenditure.

nutritional status leading to greater FFM. This hypothesis is unlikely because the correlation between FFM and OEI is shared across many different populations (i.e., healthy normal weight, overweight, or obese adults and adolescents who are not expected to be malnourished) [12–14,18–20]. Furthermore, all of the patients in the present cohort were thoroughly monitored before their nutritional assessment, and the PN was periodically adjusted to maintain a satisfactory nutritional status. A difference in nutritional status within the cohort was therefore not expected. We also found a positive correlation between TSH and OEI in the multivariate model. One possible explanation for this result is that the participants with the highest OEI tend to be overfed. Indeed, an increase in TSH was previously demonstrated in response to experimental overfeeding [21].

To understand the drivers of OEI, one important and controversial issue was to know if PN inhibits oral intake. In the present study, OEI was not correlated with any parameter related to PN, namely energy and number and volume of infusions in good agreement with other observational studies [6,22]. It is also reinforced by experimental studies showing the lack of acute effect of PN on hunger and satiety both in patients with SBS [23] and healthy individuals [24], even if some other studies suggest an effect of PN on subsequent OEI [25,26]. The present results also showed that the duration of SBS was not associated with OEI, at least in the included patients who were on PN for  $\geq 1$  y.

The main limitation of the present study was its retrospective design. This limitation is related to the difficulty of collecting prospective data in patients with SBS because of the low population size. To limit the bias of recruitment and to ensure consecutive recruitment during the study period, we used a nutritional assessment to screen all patients in our unit. We analyzed only FFM data assessed by DXA to ensure the homogeneity of the results. OEI determination was based on a 3-d diary and one concern is

therefore possible misreporting of OEI. Nevertheless, good agreement between objective and subjective assessment of OEI in the population with SBS has been previously shown [7]. Finally, we excluded patients with limited OEI or frequent nausea/vomiting. In our retrospective study, these gastrointestinal symptoms were not precisely quantified. Thus, we were not able to include them in statistical analyses and to determine in which measure they affect OEI.

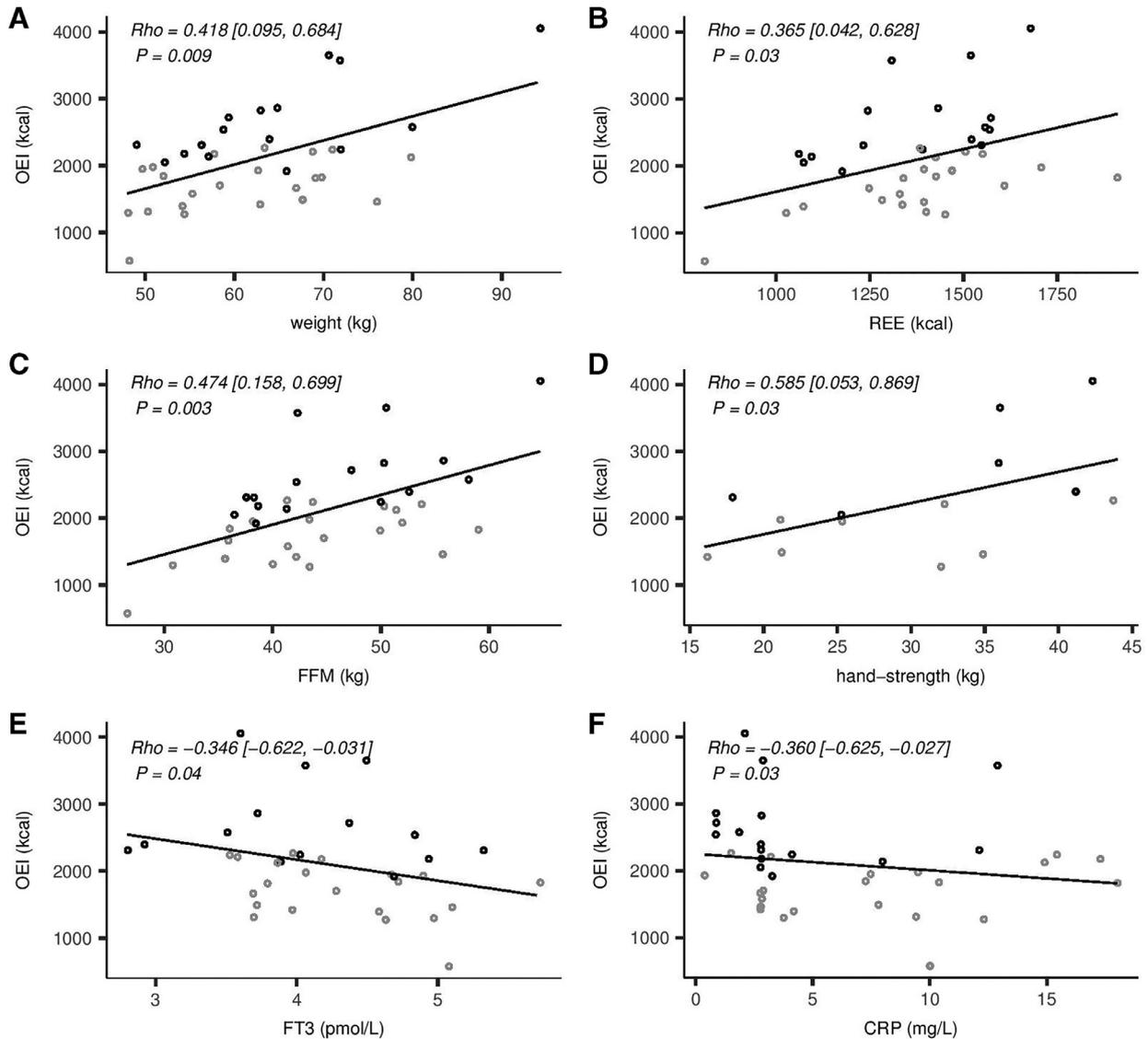
This study revealed that FFM is an important determinant of OEI. One way to increase FFM could be to increase physical activity. Such a strategy was previously assessed with a resistance training program inducing an increase in both FFM and energy intake in nine patients with SBS [27]. This study is promising and should be validated in a larger cohort. Future work should also assess whether increasing FFM limits dependence on PN.

## Conclusion

The present study suggests that FFM is an important determinant of OEI in patients with SBS on PN and without debilitating digestive symptoms. This finding adds to a body of evidence highlighting the correlation of FFM and OEI in other populations. Future studies are therefore required to elucidate the links between OEI, FFM, physical activity, and dependence on PN in patients with SBS. It could help to better follow up these patients to ensure both intestinal adaptation and nutritional adequacy.

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**Fig. 3.** Significant associations between OEI and body weight, REE, FFM, HGS, FT3, and CRP. Univariate associations were assessed using Spearman's correlations. The confidence interval of the Spearman correlation coefficients was determined using a bootstrap with 1000 replicates. Hyperphagic patients with either of the two definitions are marked in dark gray and non-hyperphagic patients are marked in light gray. CRP, C-reactive protein; FT3, free triiodothyronine; FFM, fat-free mass; HGS, handgrip strength; OEI, oral energy intake; REE, resting energy expenditure.

**Table 2**

Correlation between oral energy intake and anthropometric, metabolic, nutritional, and absorption parameters using Spearman's rank correlation

| Parameters                                | $\rho$ | 95% CI*           | P-value |
|---|--------|-------------------|---------|
| Age, y                                    | -0.051 | (-0.385 to 0.288) | 0.76    |
| FM, kg                                    | 0.021  | (-0.313 to 0.337) | 0.90    |
| Brachial circumference, cm                | 0.065  | (-0.322 to 0.401) | 0.71    |
| Skinfold, mm                              | -0.169 | (-0.511 to 0.213) | 0.33    |
| TSH, mIU/L                                | 0.322  | (-0.002 to 0.621) | 0.06    |
| FT4, pmol/L                               | -0.204 | (-0.503 to 0.146) | 0.24    |
| Parenteral energy intake, kcal/d          | 0.154  | (-0.175 to 0.486) | 0.36    |
| Number of parenteral infusions, per week  | 0.098  | (-0.263 to 0.421) | 0.56    |
| Volume of parenteral infusion, L, per bag | 0.129  | (-0.217 to 0.448) | 0.44    |
| Albumin, g/L                              | 0.144  | (-0.213 to 0.475) | 0.39    |
| Duration of the short bowel syndrome, mo  | -0.022 | (-0.367 to 0.317) | 0.90    |
| Remnant small bowel length, cm            | -0.010 | (-0.366 to 0.344) | 0.95    |
| Stool weight, g                           | 0.050  | (-0.340 to 0.395) | 0.77    |
| 1-h blood D-xylose concentration, mmol/L  | 0.112  | (-0.246 to 0.434) | 0.55    |
| Citrullinemia, mmol/L, n = 38             | 0.094  | (-0.220 to 0.408) | 0.57    |

FM, fat mass; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

\*95% CI was determined after bootstrap with 1000 replicates.

**Table 3**

Multivariate model with oral energy intake as the dependent variable and predictor variables as the independent variables

| Predictor variables | $\beta$ (standardized coefficients) | SE   | P-value |
|---------------------|-------------------------------------|------|---------|
| Sex                 | -0.206                              | 0.14 | 0.30    |
| Age                 | 0.103                               | 0.17 | 0.44    |
| FFM                 | 0.660                               | 0.44 | <0.01   |
| FM                  | 0.187                               | 0.11 | 0.18    |
| REE                 | 0.307                               | 0.40 | 0.12    |
| TSH                 | 0.398                               | 0.05 | <0.01   |
| FT3                 | -0.044                              | 0.29 | 0.74    |
| CRP                 | -0.054                              | 0.05 | 0.68    |

FFM, fat-free mass; FM, fat mass; FT3, free triiodothyronine; REE, resting energy expenditure; TSH, thyroid-stimulating hormone.

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