WINNING BY LOSING?

Nutritional consequences of bariatric surgery

Laura Heusschen

Propositions

1. Specialized multivitamin supplements for bariatric patients are more effective in preventing micronutrient deficiencies than standard, over-the-counter supplementation.
   (this thesis)

2. Improving patient adherence to daily intake of multivitamin supplementation is essential in achieving optimal nutritional status after bariatric surgery.
   (this thesis)

3. Research collaborations with industrial partners are essential for the continuous implementation of science-based knowledge.

4. Completing a PhD often feels like turning pirouettes in ballet, you have to keep focusing or you will tumble.

5. Gender bias in medicine and medical research is putting women's health at risk.

6. Social media influencers should use their reach to promote a healthy lifestyle.

Propositions belonging to the thesis, entitled
Winning by losing? Nutritional consequences of bariatric surgery

Laura Heusschen
Wageningen, 31 May 2023

Winning by losing? Nutritional consequences of bariatric surgery

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This research was conducted under the auspices of the VLAG Graduate School (Biobased, Biomolecular, Chemical, Food and Nutrition Sciences)

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Thesis

submitted in fulfilment of the requirements for the degree of doctor
at Wageningen University
by the authority of the Rector Magnificus,
Prof. Dr A. P. J. Mol,
in the presence of the
Thesis Committee appointed by the Academic Board
to be defended in public
on Wednesday 31 May 2023
at 11 a.m. in the Omnia Auditorium.

Laura Heusschen
Winning by losing? Nutritional consequences of bariatric surgery.
258 pages.

PhD thesis, Wageningen University, Wageningen, The Netherlands (2023).
With references, with summaries in English and Dutch.

ISBN: 978-94-6447-601-9
DOI: https://doi.org/10.18174/588217

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CHAPTER 1

General introduction

Obesity is a complex multifactorial disease defined by excessive adiposity that poses a major risk to health [1-3]. In recent decades, obesity has reached epidemic proportions with at least 2.8 million people dying each year as a result of being overweight or obese [3]. In the Netherlands, about 15 percent of the adults were living with obesity in 2022, and about 35% of the population was moderately overweight and thus at risk of entering the obese state [4].

Body mass index (BMI) is the most commonly used index to classify overweight and obesity in adults. The World Health Organization defines obesity as a BMI greater than or equal to 30 [2]. Subsequently, obesity is frequently subdivided into the following categories [5]:

- Class I: BMI of 30 to <35
- Class II: BMI of 35 to <40
- Class III: BMI of 40 or higher, sometimes referred to as 'severe obesity'.

Obesity is associated with a significant increase in mortality and an increased risk of many noncommunicable diseases including cardiovascular diseases, type 2 diabetes mellitus, chronic respiratory diseases and certain types of cancer [1-3]. In terms of mental health, obesity is closely linked to mental illness such as depression and anxiety [6-8].

The wide-spread impact of obesity and its complications does not only affect a person's health, wellbeing and quality of life on the individual level but also imposes a large economic burden on society and the health care system [9-11]. According to recent research, average societal costs of people living with obesity in the Netherlands are about €15,000 per year, with its impact going well beyond the healthcare sector alone [12].

Treatment of obesity – Bariatric and metabolic surgery

Obesity has a multifactorial etiology that includes complex interactions between genetic, behavioral, environmental, physiological, social, and cultural factors that lead to an imbalance between energy intake and expenditure during a prolonged period of time [13]. Although prevention of obesity should be the cornerstone in this public health issue, prevention alone cannot reverse the current obesity epidemic. Treatment options for obesity include lifestyle interventions (dietary changes and increased physical activity), pharmacotherapy, and in some cases, surgical treatment. Unfortunately, lifestyle intervention programs often result in insufficient weight loss, and maintenance of weight loss is usually inadequate in individuals with severe obesity [14-17]. Pharmacotherapy in general leads to a 2-11% weight loss and should only be considered in conjunction with lifestyle changes [18, 19].

For individuals with severe obesity who are unable to lose weight by lifestyle modifications or pharmacotherapy, metabolic or bariatric surgery (coming from the Greek words 'baros' meaning 'weight' and 'iatrikos' meaning 'medicine') can be considered. Bariatric surgery is currently the only effective treatment for severe obesity that results in long-term weight loss, reduction of obesity-related comorbidities and overall mortality, and improvement in quality of life [20-24]. Between 2015 and 2020, more than 60,000 bariatric procedures were performed in the Netherlands, increasing up to about 12,000 procedures yearly [25]. The American Society for Metabolic and Bariatric Surgery (ASMBS) and The International Federation for the Surgery of Obesity and Metabolic disorders (IFSO) have recently revised the indications for bariatric and metabolic surgery [26]. The ASMBS/IFSO guidelines now recommend bariatric and metabolic surgery for individuals with a BMI of 35 or more, regardless of presence, absence or severity of obesity-related comorbidities [26]. Furthermore, bariatric and metabolic surgery should be considered for individuals with a BMI of 30-34.9 and metabolic disease [26]. Currently, the Roux-en-Y gastric bypass and sleeve gastrectomy are the most commonly performed procedures worldwide, accounting for respectively 24% and 67% of all primary procedures [27] (**Figure 1**).

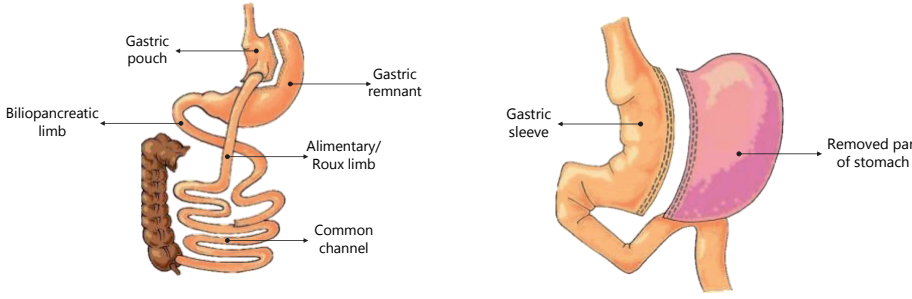

Figure 1. Anatomy of the Roux-en-Y gastric bypass (left) and sleeve gastrectomy (right)

During a Roux-en-Y gastric bypass procedure, the stomach is first divided into a smaller pouch which is about the size of an egg (±30 ml). The larger part of the stomach is bypassed and no longer stores or digests food. The pouch is then directly connected to a part of the small intestine, called the Roux limb or alimentary limb (length of ±100 cm). As a result, food will go into the small pouch and then directly into the alimentary limb, thereby bypassing the distal part of the stomach, duodenum and the proximal jejunum. Secretion fluids from the gastric remnant, liver and pancreas go through the biliopancreatic limb (length of ±150 cm) and only come in contact with the ingested

foods in the common channel, which is the point where the alimentary limb and the biliopancreatic limb come together.

The sleeve gastrectomy is performed by removing approximately 75-80% of the stomach. The pyloric valve at the bottom of the stomach is preserved such that the stomach function and digestion remain unaltered.

The underlying mechanisms of weight loss after bariatric surgery are complex and include reduced food intake and malabsorption induced by modifications in the gastrointestinal tract, as well as changes in neural and gut hormonal signals that regulate hunger and satiety, gut microbiota, bile acids, food preferences, and possibly energy expenditure [28-30]. The percentage total body weight loss after 5 years is approximately 25.5% (95% CI: 25.1-25.9%) after Roux-en-Y gastric bypass and 18.8% (95% CI: 18.0-19.6%) after sleeve gastrectomy [31].

Nutritional status after bariatric surgery

Despite their effectiveness on weight reduction and improved health-outcomes, all bariatric procedures alter the anatomy and physiology of the gastrointestinal tract, thereby influencing intake, digestion and absorption of nutrients, which in turn may impact nutritional status [32, 33]. Nutritional status has been defined as "a physiological state of an individual, which results from the relationship between nutrient intake and requirements, and from the body's ability to digest, absorb and use these nutrients" [34]. Optimizing post-operative nutritional status starts pre-operatively. Despite the high-caloric intake, poor diet quality and low nutrient intake are consistently reported in individuals with (severe) obesity, including those undergoing bariatric surgery [35, 36]. As a result, most individuals with obesity already present with a number of micronutrient deficiencies prior to surgery [37-39]. Next to poor diet quality and low nutrient intake, reduced bioavailability of specific nutrients such as vitamin D, inflammatory effects, use of certain medication and small intestinal bacterial overgrowth may also play a role in the development of nutritional deficiencies [37-39]. Most common pre-operative deficiencies are reported for vitamin D (up to 99%), folic acid (0-63%), vitamin B12 (0-34%) and iron (0-47%) [38, 40].

Post-operatively, nutritional deficiencies are dependent on the type of the bariatric procedure affecting nutrient intake, digestion and absorption as well as on post-surgical complications (e.g. nausea, vomiting), compliance to dietary and supplement recommendations, food intolerances and changes in taste and eating patterns [37]. Major areas for nutrient absorption could be bypassed, resulting in reduced absorption of these nutrients (**Figure 2**). Furthermore, digestion and absorption of nutrients could

be impaired by the reduced gastric capacity that is needed for initiating protein digestion, releasing protein-bound vitamin B12, digesting lipids, optimizing calcium and iron solubility, and reducing iron into its absorbable ferrous form [32]. Inadequate secretion of intrinsic factor from parietal cells may limit vitamin B12 absorption, and digestion of proteins, carbohydrates and lipids is postponed until the ingested food reaches the pancreatic enzymes and biliary secretions in the common channel [32].
Depending on the type of procedure, supplementation strategies, reference ranges and time after surgery, most frequent micronutrient deficiencies are reported for iron (0-42%), vitamin B12 (0-26%), folic acid (0-22%) and vitamin D (up to 73%) [39, 41-45].

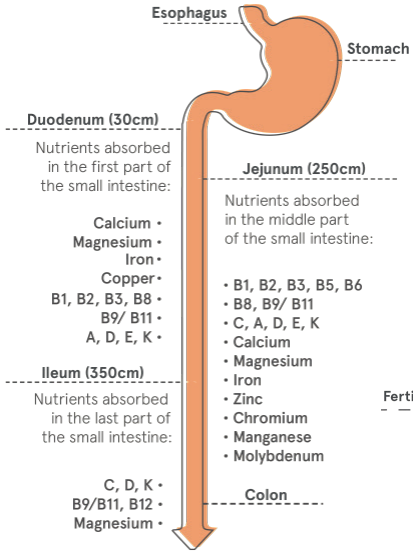

Figure 2. Absorption of nutrients in the intestinal tract

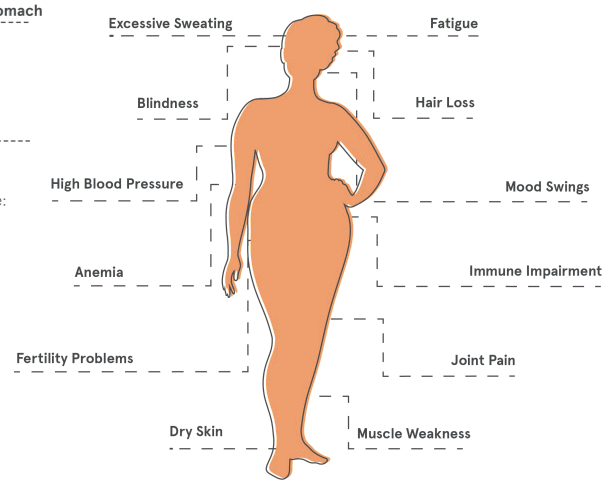

Figure 3. Consequences of deficiencies (source: FitForMe)

Nutritional deficiencies can present with a wide range of clinical manifestations, depending on the specific nutrient, the severity, and the duration of the deficiency (**Figure 3**). Thus, nutritional surveillance is essential in the management of bariatric patients. Optimal nutritional surveillance includes regular monitoring of micronutrient status and dietary intake; prior to surgery as well as long-term after surgery. In this way, the detection of potential nutritional deficiencies can be facilitated and patients' adherence to dietary and supplementation guidelines can be increased, ultimately contributing to improved nutritional status.

Dietary intake and diet quality after bariatric surgery

Dietary counselling aimed at optimizing dietary intake and diet quality is crucial for improving long-term health and maintaining weight loss after bariatric surgery [46-50]. General dietary recommendations include prioritizing protein intake, minimizing high-sugar and high-fat foods, eliminating sugar-sweetened beverages and alcohol, and increasing the consumption of fiber-rich foods [51, 52]. In the Netherlands, individuals who undergo bariatric surgery are advised to use an energy-restricted diet based on the general Dutch food-based dietary guidelines published in 2015 by the Health Council of the Netherlands [53].

Overall, a substantial decrease in energy intake is widely reported following bariatric surgery [48, 54-56]. However, it is unclear whether these changes are accompanied with changes in nutrient composition of the diet [57]. Furthermore, the decrease in energy intake may not only be a consequence of simply eating smaller portions of the same food items but also from a change in intake towards healthier, less energy-dense foods [58]. A qualitative improvement in the diet could compensate for the absolute decrease in food intake and malabsorption of nutrients. However, this goal seems difficult to achieve as poor diet quality is frequently reported in this population [46, 47, 50]. Accurate measures of dietary intake and diet quality are needed to gain more insight into changes in food intake following bariatric surgery in order to optimize dietary counselling of bariatric patients. However, validated dietary assessment tools in this specific population are currently lacking [59].

Nutritional supplementation after bariatric surgery

After bariatric surgery, micronutrient intake from food alone is not sufficient to meet the required nutritional needs for preventing nutrient deficiencies. Therefore, lifelong daily use of multivitamin supplementation (MVS) containing vitamin A, vitamin B1, folic acid, vitamin B12, vitamin D, vitamin E, vitamin K, calcium, iron, zinc and copper is advised [40, 60]. In most bariatric centers in the Netherlands, specialized 'weight loss surgery' supplements that are specifically developed for bariatric patients are recommended. The formulation of these supplements is often tailored to the type of bariatric procedure and varies between brands, but they generally contain high doses of folic acid, vitamins B12 and D, elementary iron and zinc. Yet, their efficacy in preventing nutritional deficiencies as well as their superiority compared to standard over-the-counter MVS is largely unknown. Furthermore, adherence to lifelong MVS use appears to be a challenge within this patient population. As with the general adherence to medical follow-up visits after bariatric surgery, compliance with post-operative supplementation protocols tends to

decrease with time from surgery with (self-reported) compliance rates ranging between 37-93% up to five years post-surgery [56, 61-65]. This could play an important role in the development of nutritional deficiencies after bariatric surgery [56, 66]. Insight into contributing factors is necessary in order to improve patient adherence to daily MVS use and to prevent poor nutritional status.

Nutritional consequences during pregnancy after bariatric surgery

After bariatric surgery, certain circumstances or life events may pose an exceptional risk on nutritional status. An example of such a life event is pregnancy. More than half of all women undergoing bariatric surgery in the Netherlands are of reproductive age [67]. For about a quarter of the women, future pregnancy even is the underlying motivation for undergoing surgery [68].

Weight loss following bariatric surgery not only improves fertility [69], it also reduces the risk of gestational diabetes, hypertensive disorders and large-for-gestational age neonates [70, 71]. However, pregnancy after bariatric surgery is not entirely without risk. The decreased intake and absorption of nutrients after surgery in combination with the increased demand for nutrients during pregnancy may lead to more pronounced nutritional deficiencies [33, 72]. Furthermore, pregnancy symptoms such as morning sickness or hyperemesis and abdominal complaints may worsen nutritional status over time [72, 73]. These risks may be most pronounced in pregnancies within the first 12 months following surgery as this period carries the highest risk of malnutrition [71]. Maternal caloric restriction and subsequent weight loss during this catabolic period may also limit gestational weight gain. As a result, nutritional supply to the growing fetus may be decreased. Overall, low maternal concentrations of vitamins A, B12 and D, folic acid, iron, calcium and zinc are frequently reported during pregnancy after bariatric surgery [74-76]. Potential neonatal adverse effects that are associated with maternal deficiencies during pregnancy include preterm birth, fetal growth restriction, congenital malformations, and neurological and developmental impairment [72, 73, 75, 77].

Consensus-based recommendations on pregnancy following bariatric surgery have been proposed [60, 78-80], but evidence-based guidelines regarding optimal timing of conception, gestational weight gain, nutritional monitoring and supplementation regimes are lacking. Regular or prenatal supplements are likely not sufficient to cover the needs of pregnant women who have undergone bariatric surgery, but research on the use of specialized supplementation during pregnancy is scarce [72, 81].

Aim and outline of this thesis

As outlined above, nutritional status after bariatric surgery may be compromised by reduced intake, digestion and absorption of nutrients. Adequate dietary intake and supplementation can play a vital role in achieving optimal nutritional status post-surgery. However, accurate measures of dietary intake and diet quality as well as validated dietary assessment tools for this specific patient population are limited. Furthermore, evidence-based guidelines for micronutrient supplementation after bariatric surgery are lacking and the efficacy of specialized MVS is largely unknown, particularly after sleeve gastrectomy and during pregnancy. Besides, understanding the determinants of poor adherence to lifelong, daily supplement intake in this patient population is urgently needed.

The main aim of this thesis was to gain more insight into factors affecting nutritional status after bariatric surgery, including dietary intake and nutritional supplementation. Furthermore, we have studied a specific window that may pose an exceptional risk on nutritional status of women who underwent bariatric surgery.

The central question of this thesis is:

How can we optimize nutritional status after bariatric surgery?

Part A of this thesis focuses on dietary intake and diet quality after bariatric surgery. In **Chapter 2**, short-term changes in macro- and micronutrient composition and diet quality in the first six months following bariatric surgery are assessed. In **Chapter 3**, the relative validity and reproducibility of the Eetscore FFQ as a screener for diet quality in individuals undergoing bariatric surgery are evaluated.

Part B of this thesis focuses on nutritional supplementation after bariatric surgery, particularly after sleeve gastrectomy. In **Chapter 4, 5 and 6**, a specialized MVS for sleeve gastrectomy patients was designed and optimized. In **Chapter 7**, underlying factors as well as potential facilitators and barriers for daily MVS use are described. The final part of this thesis (**Part C**) is dedicated to pregnancy after bariatric surgery. In **Chapter 8**, pregnancy and neonatal outcomes are evaluated by surgery-to-conception interval and by gestational weight gain. In **Chapter 9**, differences in nutritional status between users of specialized supplementation and standard supplementation among pregnant women with a history of Roux-en-Y gastric bypass or sleeve gastrectomy are described.

References

1. World Health Organization, *WHO European Regional Obesity Report 2022*. 2022, World Health Organization: Copenhagen.
2. World Health Organization. *Obesity and overweight*. 2021. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
3. World Health Organization. *Obesity*. 2021. https://www.who.int/news-room/facts-in-pictures/detail/6-facts-on-obesity.
4. Centraal Bureau voor de Statistiek. *Leefstijl; persoonskenmerken*. 2023. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/85457ned/table?ts=1680780220202.
5. World Health Organization. *A healthy lifestyle - WHO recommendations*. 2010. https://www.who.int/-europe/news-room/fact-sheets/item/a-healthy-lifestyle---who-recommendations.
6. Abiri, B, Hosseinpanah, F, Banihashem, S, et al., *Mental health and quality of life in different obesity phenotypes: a systematic review.* Health Qual Life Outcomes, 2022. **20**(1): p. 63.
7. Luppino, FS, de Wit, LM, Bouvy, PF, et al., *Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies.* Arch Gen Psychiatry, 2010. **67**(3): p. 220-229.
8. Rajan, TM and Menon, V, *Psychiatric disorders and obesity: A review of association studies.* J Postgrad Med, 2017. **63**(3): p. 182-190.
9. Kim, DD and Basu, A, *Estimating the Medical Care Costs of Obesity in the United States: Systematic Review, Meta-Analysis, and Empirical Analysis.* Value Health, 2016. **19**(5): p. 602-613.
10. Lette, M, Bemelmans, WJ, Breda, J, et al., *Health care costs attributable to overweight calculated in a standardized way for three European countries.* Eur J Health Econ, 2016. **17**(1): p. 61-69.
11. Tremmel, M, Gerdtham, UG, Nilsson, PM, et al., *Economic Burden of Obesity: A Systematic Literature Review.* Int J Environ Res Public Health, 2017. **14**(4).
12. Hecker, J, Freijer, K, Hiligsmann, M, et al., *Burden of disease study of overweight and obesity; the societal impact in terms of cost-of-illness and health-related quality of life.* BMC Public Health, 2022. **22**(1): p.46.
13. Bray, GA, Frühbeck, G, Ryan, DH, et al., *Management of obesity.* The Lancet, 2016. **387**(10031): p. 1947-1956.
14. Brauw, LMd, *De gecombineerde leefstijlinterventie.* Ned Tijdschr Geneesk, 2021. **165**.
15. Curioni, CC and Lourenco, PM, *Long-term weight loss after diet and exercise: a systematic review.* Int J Obes (Lond), 2005. **29**(10): p. 1168-1174.
16. Franz, MJ, Boucher, JL, Rutten-Ramos, S, et al., *Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials.* J Acad Nutr Diet, 2015. **115**(9): p. 1447-1463.
17. Ge, L, Sadeghirad, B, Ball, GDC, et al., *Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials.* BMJ, 2020. **369**: p. m696.
18. Shi, Q, Wang, Y, Hao, Q, et al., *Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials.* The Lancet, 2022. **399**(10321): p. 259-269.
19. Tak, YJ and Lee, SY, *Long-Term Efficacy and Safety of Anti-Obesity Treatment: Where Do We Stand?* Current obesity reports, 2021. **10**(1): p. 14-30.
20. Gloy, VL, Briel, M, Bhatt, DL, et al., *Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials.* BMJ, 2013. **347**: p. f5934.
21. O'Brien, PE, Hindle, A, Brennan, L, et al., *Long-Term Outcomes After Bariatric Surgery: a Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding.* Obes Surg, 2019. **29**(1): p. 3-14.

22. Sjostrom, L, *Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery.* J Intern Med, 2013. **273**(3): p. 219-234.
23. Sjostrom, L, Peltonen, M, Jacobson, P, et al., *Bariatric surgery and long-term cardiovascular events.* JAMA, 2012. **307**(1): p. 56-65.
24. Syn, NL, Cummings, DE, Wang, LZ, et al., *Association of metabolic–bariatric surgery with long-term survival in adults with and without diabetes: a one-stage meta-analysis of matched cohort and prospective controlled studies with 174 772 participants.* The Lancet, 2021. **397**(10287): p. 1830-1841.
25. DICA, *DATO Bariatrische chirurgie - Jaarrapportage 2020*. https://dica.nl/jaarrapportage-2018/dato
26. Eisenberg, D, Shikora, SA, Aarts, E, et al., *2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): Indications for Metabolic and Bariatric Surgery.* Surg Obes Relat Dis, 2022. **18**(12): p. 1345-1356.
27. Brown, WA, Shikora, S, Liem, R, et al., *Seventh IFSO Global Registry Report*, in *The IFSO Global Registry*, The International Federation for the Surgery of Obesity and Metabolic Disorders, Editor. 2022.
28. Akalestou, E, Miras, AD, Rutter, GA, et al., *Mechanisms of Weight Loss After Obesity Surgery.* Endocr Rev, 2022. **43**(1): p. 19-34.
29. Mulla, CM, Middelbeek, RJW and Patti, ME, *Mechanisms of weight loss and improved metabolism following bariatric surgery.* Ann N Y Acad Sci, 2018. **1411**(1): p. 53-64.
30. Pucci, A and Batterham, RL, *Mechanisms underlying the weight loss effects of RYGB and SG: similar, yet different.* J Endocrinol Invest, 2019. **42**(2): p. 117-128.
31. Arterburn, D, Wellman, R, Emiliano, A, et al., *Comparative Effectiveness and Safety of Bariatric Procedures for Weight Loss: A PCORnet Cohort Study.* Ann Intern Med, 2018. **169**(11): p. 741-750.
32. Steenackers, N, Vanuytsel, T, Augustijns, P, et al., *Adaptations in gastrointestinal physiology after sleeve gastrectomy and Roux-en-Y gastric bypass.* Lancet Gastroenterol Hepatol, 2021. **6**(3): p. 225-237.
33. Lupoli, R, Lembo, E, Saldalamacchia, G, et al., *Bariatric surgery and long-term nutritional issues.* World J Diabetes, 2017. **8**(11): p. 464-474.
34. FAO, I, UNICEF, WFP and WHO, *The State of Food Security and Nutrition in the World 2018. Building climate resilience for food security and nutrition.* 2018, FAO: Rome.
35. Harbury, C, Collins, CE and Callister, R, *Diet quality is lower among adults with a BMI >/=40kgm(-2) or a history of weight loss surgery.* Obes Res Clin Pract, 2019. **13**(2): p. 197-204.
36. Harbury, CM, Verbruggen, EE, Callister, R, et al., *What do individuals with morbid obesity report as a usual dietary intake? A narrative review of available evidence.* Clin Nutr ESPEN, 2016. **13**: p. e15-e22.
37. Argyrakopoulou, G, Konstantinidou, SK, Dalamaga, M, et al., *Nutritional Deficiencies Before and After Bariatric Surgery: Prevention and Treatment.* Curr Nutr Rep, 2022. **11**(2): p. 95-101.
38. Ciobarca, DM, Catoi, AF, Copaescu, C, et al., *Nutritional status prior to bariatric surgery for severe obesity: a review.* Med Pharm Rep, 2022. **95**(1): p. 24-30.
39. Gasmi, A, Bjorklund, G, Mujawdiya, PK, et al., *Micronutrients deficiences in patients after bariatric surgery.* Eur J Nutr, 2022. **61**(1): p. 55-67.
40. O'Kane, M, Parretti, HM, Pinkney, J, et al., *British Obesity and Metabolic Surgery Society Guidelines on perioperative and postoperative biochemical monitoring and micronutrient replacement for patients undergoing bariatric surgery-2020 update.* Obes Rev, 2020. **21**(11): p. e13087.
41. Dix, CF, Bauer, JD and Wright, OR, *A Systematic Review: Vitamin D Status and Sleeve Gastrectomy.* Obes Surg, 2017. **27**(1): p. 215-225.
42. Gao, Z, Liang, Y, Zheng, C, et al., *Prevalence and associated factors of secondary hyperparathyroidism after Roux-en-Y gastric bypass: A meta-analysis.* Obes Rev, 2022. **23**(10): p. e13488.
43. Lewis, CA, de Jersey, S, Hopkins, G, et al., *Does Bariatric Surgery Cause Vitamin A, B1, C or E Deficiency? A Systematic Review.* Obes Surg, 2018. **28**(11): p. 3640-3657.

44. Patel, JJ, Mundi, MS, Hurt, RT, et al., *Micronutrient Deficiencies After Bariatric Surgery: An Emphasis on Vitamins and Trace Minerals.* Nutr Clin Pract, 2017. **32**(4): p. 471-480.
45. Weng, TC, Chang, CH, Dong, YH, et al., *Anaemia and related nutrient deficiencies after Roux-en-Y gastric bypass surgery: a systematic review and meta-analysis.* BMJ open, 2015. **5**(7): p. e006964.
46. da Silva, FB, Gomes, DL and de Carvalho, KM, *Poor diet quality and postoperative time are independent risk factors for weight regain after Roux-en-Y gastric bypass.* Nutrition, 2016. **32**(11-12): p. 1250-1253.
47. Freire, RH, Borges, MC, Alvarez-Leite, JI, et al., *Food quality, physical activity, and nutritional follow-up as determinant of weight regain after Roux-en-Y gastric bypass.* Nutrition, 2012. **28**(1): p. 53-58.
48. Kanerva, N, Larsson, I, Peltonen, M, et al., *Changes in total energy intake and macronutrient composition after bariatric surgery predict long-term weight outcome: findings from the Swedish Obese Subjects (SOS) study.* Am J Clin Nutr, 2017. **106**(1): p. 136-145.
49. Nymo, S, Lundanes, J, Aukan, M, et al., *Diet and physical activity are associated with suboptimal weight loss and weight regain 10-15 years after Roux-en-Y gastric bypass: A cross-sectional study.* Obes Res Clin Pract, 2022. **16**(2): p. 163-169.
50. Zarshenas, N, Tapsell, LC, Neale, EP, et al., *The Relationship Between Bariatric Surgery and Diet Quality: a Systematic Review.* Obes Surg, 2020. **30**(5): p. 1768-1792.
51. Moize, VL, Pi-Sunyer, X, Mochari, H, et al., *Nutritional pyramid for post-gastric bypass patients.* Obes Surg, 2010. **20**(8): p. 1133-1141.
52. Sherf Dagan, S, Goldenshluger, A, Globus, I, et al., *Nutritional Recommendations for Adult Bariatric Surgery Patients: Clinical Practice.* Adv Nutr, 2017. **8**(2): p. 382-394.
53. Kromhout, D, Spaaij, CJ, de Goede, J, et al., *The 2015 Dutch food-based dietary guidelines.* Eur J Clin Nutr, 2016. **70**(8): p. 869-878.
54. Farias, G, Silva, RMO, da Silva, PPP, et al., *Impact of dietary patterns according to NOVA food groups: 2 y after Roux-en-Y gastric bypass surgery.* Nutrition, 2020. **74**: p. 110746.
55. Raatz, SK, Johnson, LK, Caliquary, A, et al., *Reported nutrient intake over 7 years after Roux-en-Y gastric bypass in the Longitudinal Assessment of Bariatric Surgery-3 (LABS-3) psychosocial study.* Surg Obes Relat Dis, 2020. **16**(8): p. 1022-1029.
56. Sherf Dagan, S, Keidar, A, Raziel, A, et al., *Do Bariatric Patients Follow Dietary and Lifestyle Recommendations during the First Postoperative Year?* Obes Surg, 2017. **27**(9): p. 2258-2271.
57. Redpath, TL, Livingstone, MBE, Dunne, AA, et al., *Methodological issues in assessing change in dietary intake and appetite following gastric bypass surgery: A systematic review.* Obes Rev, 2021. **22**(6): p. e13202.
58. Nielsen, MS, Christensen, BJ, Ritz, C, et al., *Factors Associated with Favorable Changes in Food Preferences After Bariatric Surgery.* Obes Surg, 2021. **31**(8): p. 3514-3524.
59. Legault, M, Leblanc, V, Marchand, GB, et al., *Evaluation of Dietary Assessment Tools Used in Bariatric Population.* Nutrients, 2021. **13**(7).
60. Mechanick, JI, Apovian, C, Brethauer, S, et al., *Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update.* Surg Obes Relat Dis, 2020. **16**(2): p. 175-247.
61. Ben-Porat, T, Elazary, R, Goldenshluger, A, et al., *Nutritional deficiencies four years after laparoscopic sleeve gastrectomy-are supplements required for a lifetime?* Surg Obes Relat Dis, 2017. **13**(7): p. 1138-1144.
62. James, H, Lorentz, P and Collazo-Clavell, ML, *Patient-Reported Adherence to Empiric Vitamin/Mineral Supplementation and Related Nutrient Deficiencies After Roux-en-Y Gastric Bypass.* Obes Surg, 2016. **26**(11): p. 2661-2666.

63. Lier, HO, Biringer, E, Stubhaug, B, et al., *The impact of preoperative counseling on postoperative treatment adherence in bariatric surgery patients: a randomized controlled trial.* Patient Educ Couns, 2012. **87**(3): p. 336-342.
64. Mahawar, KK, Clare, K, O'Kane, M, et al., *Patient Perspectives on Adherence with Micronutrient Supplementation After Bariatric Surgery.* Obes Surg, 2019. **29**(5): p. 1551-1556.
65. Zarshenas, N, Nacher, M, Loi, KW, et al., *Investigating Nutritional Deficiencies in a Group of Patients 3 Years Post Laparoscopic Sleeve Gastrectomy.* Obes Surg, 2016. **26**(12): p. 2936-2943.
66. Henfridsson, P, Laurenius, A, Wallengren, O, et al., *Micronutrient intake and biochemistry in adolescents adherent or nonadherent to supplements 5 years after Roux-en-Y gastric bypass surgery.* Surg Obes Relat Dis, 2019. **15**(9): p. 1494-1502.
67. Brown, WA, Kow, L, Shikora, S, et al., *Sixth IFSO Global Registry Report*, in *The IFSO Global Registry*, The International Federation for the Surgery of Obesity and Metabolic Disorders, Editor. 2021.
68. Goldenshluger, A, Elazary, R, Ben Porat, T, et al., *Knowledge, attitudes, and behaviors of women during pregnancy after bariatric surgery.* Surg Obes Relat Dis, 2020. **16**(7): p. 925-930.
69. Edison, E, Whyte, M, van Vlymen, J, et al., *Bariatric Surgery in Obese Women of Reproductive Age Improves Conditions That Underlie Fertility and Pregnancy Outcomes: Retrospective Cohort Study of UK National Bariatric Surgery Registry (NBSR).* Obes Surg, 2016. **26**(12): p. 2837-2842.
70. Johansson, K, Cnattingius, S, Naslund, I, et al., *Outcomes of pregnancy after bariatric surgery.* N Engl J Med, 2015. **372**(9): p. 814-824.
71. Kwong, W, Tomlinson, G and Feig, DS, *Maternal and neonatal outcomes after bariatric surgery; a systematic review and meta-analysis: do the benefits outweigh the risks?* Am J Obstet Gynecol, 2018. **218**(6): p. 573-580.
72. Vanheule, G, Ceulemans, D, Vynckier, AK, et al., *Micronutrient supplementation in pregnancies following bariatric surgery: a practical review for clinicians.* Obes Surg, 2021. **31**(10): p. 4542-4554.
73. Slater, C, Morris, L, Ellison, J, et al., *Nutrition in Pregnancy Following Bariatric Surgery.* Nutrients, 2017. **9**(12).
74. Chapmon, K, Stoklossa, CJ, Benson-Davies, S, et al., *Nutrition for pregnancy after metabolic and bariatric surgery: literature review and practical guide.* Surg Obes Relat Dis, 2022. **18**(6): p. 820-830.
75. Jans, G, Matthys, C, Bogaerts, A, et al., *Maternal micronutrient deficiencies and related adverse neonatal outcomes after bariatric surgery: a systematic review.* Adv Nutr, 2015. **6**(4): p. 420-429.
76. Rottenstreich, A, Elazary, R, Goldenshluger, A, et al., *Maternal nutritional status and related pregnancy outcomes following bariatric surgery: A systematic review.* Surg Obes Relat Dis, 2019. **15**(2): p. 324-332.
77. Milman, N, Paszkowski, T, Cetin, I, et al., *Supplementation during pregnancy: beliefs and science.* Gynecol Endocrinol, 2016. **32**(7): p. 509-516.
78. American College of, O and Gynecologists, *ACOG practice bulletin no. 105: bariatric surgery and pregnancy.* Obstet Gynecol, 2009. **113**(6): p. 1405-1413.
79. Ciangura, C, Coupaye, M, Deruelle, P, et al., *Clinical Practice Guidelines for Childbearing Female Candidates for Bariatric Surgery, Pregnancy, and Post-partum Management After Bariatric Surgery.* Obes Surg, 2019. **29**(11): p. 3722-3734.
80. Shawe, J, Ceulemans, D, Akhter, Z, et al., *Pregnancy after bariatric surgery: Consensus recommendations for periconception, antenatal and postnatal care.* Obes Rev, 2019. **20**(11): p. 1507-1522.
81. Snoek, K, van de Woestijne, N, Willemsen, S, et al., *The Impact of Preconception Gastric Bypass Surgery on Maternal Micronutrient Status before and during Pregnancy: A Retrospective Cohort Study in the Netherlands between 2009 and 2019.* Nutrients, 2022. **14**(4).

PART A

Dietary intake and diet quality
after bariatric surgery

CHAPTER 2

Changes in nutrient composition and diet quality in the first six months following bariatric surgery

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Submitted

Abstract

Background: Bariatric surgery (BS) may result in inadequate nutrient intake and poor diet quality, which can lead to nutritional complications. The present study aimed to evaluate changes in macro- and micronutrient composition and diet quality in the first six months following BS.

Methods: A total of 107 participants undergoing BS (RYGB: n=87, SG: n=20) completed 3-day food records directly before and six months after surgery. Changes in macronutrient (energy, carbohydrates, protein, fat and dietary fiber) and micronutrient (folate, vitamin B12, vitamin D, calcium and iron) intake were evaluated. Diet quality was assessed by adherence to the Dutch food-based dietary guidelines.

Results: Eighty percent of the population was female with a median age of 50.0 [39.0, 56.0] years and a median BMI of 41.3 [38.9, 45.2] kg/m^2 before surgery.
After BS, a 27% decrease in energy intake was accompanied by a significant decrease in absolute intake of total carbohydrates, protein, fat and fiber as well as of folate, vitamin B12, vitamin D and iron. Overall, nutrient composition slightly changed with an increase in the relative intake of total protein and mono- and disaccharides after BS. Consumption of vegetables, wholegrain products, liquid fats, red and processed meat, sodium and unhealthy food choices significantly decreased post-surgery.

Conclusion: Our results demonstrate both favorable and unfavorable changes in macro- and micronutrient composition and diet quality in the first six months following BS. Insight into these changes can improve dietary counselling in this population. Future research into long-term changes is needed as dietary intake and eating behavior may change over time.

Introduction

Bariatric surgery (BS) is currently the most effective treatment for severe obesity resulting in sustained weight loss, resolution of obesity-related comorbidities and improvement of quality of life [1-3]. Worldwide, the Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most commonly performed bariatric procedures [4]. Despite their effectiveness on weight reduction and improved health-outcomes, all bariatric procedures alter the anatomy and physiology of the gastrointestinal tract, thereby influencing intake, digestion and absorption of nutrients [5, 6]. Reduced gastric capacity, gastrointestinal complaints such as reflux or vomiting, food intolerances and changes in appetite, taste and smell post-surgery may result in inadequate dietary intake and eventually lead to nutritional complications such as anemia, osteoporosis and malnutrition [5, 7]. Overall, nutritional deficiencies are frequently reported in this population, particularly for iron, folate, vitamin B12, vitamin D and calcium [8]. Next to lifelong multivitamin supplementation, dietary counselling aimed at optimizing dietary intake and diet quality is crucial for improving nutritional status and long-term health after BS [9].

General dietary recommendations include prioritizing protein intake, minimizing high-sugar and high-fat foods, eliminating sugar-sweetened beverages and alcohol, and increasing the consumption of fiber-rich foods [10, 11]. Within the Netherlands, BS patients are advised to use an energy-restricted diet based on the general Dutch food-based dietary guidelines issued in 2015 by the Health Council of the Netherlands [12, 13]. Overall, reductions in energy intake of about 45-60% are reported at six months post-surgery [14-17]. However, it is unclear whether these changes are accompanied with changes in nutrient composition of the diet [18]. Furthermore, the decrease in energy intake may not only be a consequence of simply eating smaller portions of the same food items but also from a change of intake towards healthier, less energy-dense foods [19]. In addition to quantifying energy and nutrient intake, analysis of food intake from a qualitative point of view has therefore gained interest. A qualitative improvement in the diet could compensate for the absolute decrease in food intake and malabsorption of nutrients. However, this goal seems difficult to achieve as poor diet quality is frequently reported in this population [9, 20-24]. While most studies generally report a low consumption of protein, fiber, fruit and vegetables, and a high consumption of carbohydrates, sugar, and fat [21, 25-28], others did observe beneficial changes in dietary intake after BS, characterized by an increased intake of protein-rich foods and vegetables [29] and a reduced consumption of sugar-containing snacks and beverages [29, 30]. However, findings are inconsistent across different time points after surgery and studies

are mostly limited to small sample sizes. The present study aimed to evaluate short-term changes in macro- and micronutrient composition and diet quality in the first six months following BS.

Methods

Study design and participants

This study was conducted as part of the Eetscore study, a prospective cohort study on dietary intake and dietary assessment methods before and after BS [31].

Recruitment took place at Vitalys Obesity Clinic (Arnhem, the Netherlands) between October 2018 and September 2019. Participants were included approximately six weeks pre-surgery and followed up until six months post-surgery. Exclusion criteria for the study were a non-Dutch eating pattern, suffering from an eating disorder, inability to fill in questionnaires or food records and having a previous bariatric procedure other than an adjustable gastric band in medical history. Participants with a missing or incomplete (<2 days) food record at baseline and/or six months of follow-up were excluded from data analysis. Of the 200 participants who signed the informed consent and were included in the study, 107 participants completed the 3-day food record before and after surgery.

This study was approved by the Local Ethical Committee of Rijnstate Hospital and conducted according to the guidelines laid down in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Data collection

Demographic information

Socio-demographic (age, sex, educational level) and health-related information (type of surgery, smoking status, comorbidities, anthropometrics) were obtained from electronic patient records.

Educational level was defined as low (primary education and prevocational secondary education), medium (senior general secondary education, pre-university education and secondary vocational education) or high (higher vocational education and university).

Anthropometric measurements were performed during standard visits at the hospital. Body weight was measured to the nearest 0.1 kg with a digital weighing scale (Tanita BC-420MA), after removal of heavy clothing and shoes. Height was measured in standing position with a wall-mounted stadiometer (Seca 206). BMI was calculated as body weight (kg) divided by squared height (m^2). Total body weight loss (TWL) at 6 months was calculated as weight loss divided by body weight before surgery, multiplied by 100%.

Dietary assessment

Dietary intake was assessed by means of estimated 3-day food records. At both time points, recorded days were randomly selected and consisted of two weekdays (Monday-Thursday) and one weekend day (Friday-Sunday). To remind participants to record all foods and drinks consumed, a preformatted food record was used including six meal occasions (breakfast, morning, lunch, afternoon, dinner, evening). All participants received verbal instructions and were provided with a written example. They were asked to record all consumptions over the three days in as much detail as possible, to report cooking methods and to include the recipes for any mixed dishes. Portion sizes were reported in household measures or measured in grams or milliliters.

Completed food records were reviewed for completeness with regards to portion sizes, cooking methods and description of foods. Telephone interviews with the participants were conducted in case of any uncertainties.

Dietary intake data were entered in Compl-eat™, a computer-based nutrition calculation program that is linked to the Dutch Food Composition Database (NEVO-online, version 2016) [32] according to standardized coding procedures. All consumed foods and meals were coded into as much detail as possible. Mixed dishes such as pasta or rice dishes were broken down into individual ingredients, including corresponding portion sizes, and coded as individual foods. In case of missing recipes for mixed dishes, standard recipes of the Dutch Food Composition Database were used [32].

Evaluation of nutrient composition and diet quality

Macronutrient composition of the diet was evaluated by intake of total energy, total carbohydrates and mono- and disaccharides, total protein, plant-based and animal-based protein, total fat, saturated fat, monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA, including ALA, EPA, DHA), and dietary fiber. Furthermore, dietary intake of the following micronutrients was assessed: folate, vitamin B12, vitamin D, calcium and iron. Use of vitamin and mineral supplementation was not included in this study as our aim was to determine the nutritional value of reported food intake only.

Diet quality was assessed using the cut-off criteria of the Dutch Healthy Diet index 2015 (DHD2015-index). The development of the DHD2015-index has been previously described [33] and consists of 15 components representing the Dutch food-based dietary guidelines of 2015 [13]: vegetables, fruit, wholegrain products, legumes, nuts, dairy, fish, tea, fats and oils, coffee, red meat, processed meat, sugar-sweetened beverages, alcohol, and sodium [33].

As information on the type of coffee was not available from the food records, this component was not included in the analyses. The intake of cheese was included in total dairy intake but limited to a maximum of 40 grams per day (as set by the Netherlands Nutrition Centre) to account for differences in portion sizes between milk and cheese, and to ensure that recommended intake for dairy could only be obtained when milk or yoghurt products were consumed [33]. For fish, the recommendation to consume one portion (100 grams) of fish weekly was translated into a cut-off value of 15 grams of fish per day. As the recommendation favors intake of oily fish, a maximum of 4 grams per day for lean fish was included. This maximum was derived from the ratio of three times oily fish to one time lean fish (per month) as set by the Netherlands Nutrition Centre [33]. With regards to the sodium component, the recommended consumption of ≤2.4 grams of sodium daily was adjusted by 20% to compensate for the lack of data on the amount of added salt.

In addition to these 15 components, the component 'unhealthy food choices' was added based on the guideline of the Netherlands Nutrition Centre to limit the consumption of high-sugar and high-fat foods [34]. Food items that contributed most to total energy, saturated fat and mono- and disaccharide intake according to the Dutch National Food Consumption Survey of 2007-2010 were included in this component, such as sweet spreads, pastries, chocolate, savory snacks, sauces and use of sugar in coffee or tea. Consumption of unhealthy food choices was assessed as the number of servings per week and cut-off criteria were based on the work of de Rijk et al. [35].

Statistical analysis

General characteristics of the study population are reported as median [Q1, Q3] for continuous data and as frequency (percentage) for categorical data.

Dietary intake data assessed by the 3-day food records were averaged over the number of completed days. Daily dietary intake is reported as mean ± standard deviation for normally distributed data and as median [Q1, Q3] for non-normally distributed. Changes in dietary intake from baseline to six months after surgery were tested with a paired t-test (normally distributed variables) or a Wilcoxon Signed Rank test (non-normally distributed variables).

All statistical analyses were performed using IBM SPSS Statistics software version 25 (IBM Corp., Armonk USA). A two-sided *P*-value below 0.05 was considered statistically significant.

Results

Participant characteristics

The total study population consisted of 107 participants with a median age of 50.0 [39.0, 56.0] years (**Table 1**). The majority was female (79.4%), had a medium educational level (65.3%) and never smoked (57.9%). Half of the study population had no comorbidities before surgery (50.5%). All participants underwent either RYGB (81.3%) or SG (18.7%). Median BMI decreased from 41.3 [38.9, 45.2] kg/m^2 before surgery to 30.8 [28.5, 34.0] kg/m^2 six months after surgery, resulting in a median TWL of 25.9 [21.1, 29.4] percent.

Table 1. General characteristics of the total study population.

	Total study population (n=107)	
Age (years)	50.0	[39.0, 56.0]
Sex (female)	85	(79.4)
Educational level[1]		
Low	17	(17.3)
Medium	64	(65.3)
High	17	(17.3)
Smoking status		
Never	62	(57.9)
Former	39	(36.4)
Current	6	(5.6)
Comorbidity		
None	54	(50.5)
Diabetes Mellitus type 2	18	(16.8)
Dyslipidemia	21	(19.6)
Hypertension	35	(32.7)
OSAS	19	(17.8)
Adjustable gastric band in history	16	(15.0)
Type of surgery		
RYGB	87	(81.3)
SG	20	(18.7)
BMI before surgery (kg/m²)	41.3	[38.9, 45.2]
BMI after surgery (kg/m²)	30.8	[28.5, 34.0]
Waist circumference before surgery (cm)[2]	127.0	[117.0, 134.8]
Waist circumference after surgery (cm)[3]	101.0	[92.3, 110.0]
TWL since surgery (%)	25.9	[21.1, 29.4]

Data are presented as median [Q1, Q3] and frequency (valid percentage).

OSAS, obstructive sleep apnea syndrome; *RYGB*, Roux-en-Y gastric bypass; *SG*, sleeve gastrectomy; *BMI*, body mass index; *TWL*, total body weight loss.

[1] Low education = primary education and prevocational secondary education; medium education = senior general secondary education, pre-university education and secondary vocational education; high education = higher vocational education and university. Missing for n=9.

[2] Missing for n=11.

[3] Missing for n=27.

Changes in nutrient composition

Energy intake at baseline was 1877 ± 470 kcal and decreased by 27% (-512 ± 433 kcal, $P<0.001$; **Table 2**). Similarly, intake of total carbohydrates, protein, fat and fiber in grams significantly decreased at six months post-surgery ($P<0.01$). Overall, nutrient composition of the diet slightly changed with an increase in the relative intake of total protein (+1.1 ± 4.3 en%, $P=0.01$) and mono- and disaccharides (+4.2 ± 6.4 en%, $P<0.001$) after BS. Relative intake of total carbohydrates and fat remained similar between the two time points (respectively +0.2 ± 7.7 en% and -0.8 ± 7.4 en%). Micronutrient intake of folate, vitamin B12, vitamin D and iron significantly decreased ($P<0.01$), whereas the intake of calcium remained stable at six months post-surgery.

Changes in diet quality

Overall, consumption of vegetables, wholegrain products, liquid fats, red and processed meat, sodium and unhealthy food choices decreased whereas the consumption of dairy tended to increase after BS (**Table 3**). Consumption of fruit, legumes, fish, tea, sugar-sweetened beverages and alcohol remained similar from baseline to six months post-surgery. Daily consumption of vegetables and wholegrain products markedly decreased with 50 [-120, 6] grams and 38 [-81, -8] grams, respectively ($P<0.001$). Similarly, the percentage of participants with a consumption according to the recommendation decreased from 28% to 13% for vegetables and from 58% to 19% for wholegrain products ($P<0.01$; **Figure 1**). Daily consumption of liquid fats significantly decreased, while the consumption of solid fats remained similar (-5 [-13, 2] grams vs 0 [-2, 3] grams, respectively). As a result, the percentage of participants adhering to the recommendation decreased from 62% to 47% ($P=0.03$). Intake of red meat, processed meat and sodium also significantly decreased post-surgery ($P<0.01$ for all), which resulted in an increased adherence to the recommendations for sodium (35% to 73%, $P<0.001$) and red meat (77% to 87%, $P=0.051$) but not for processed meat (3% to 4%, $P=0.99$). Consumption of unhealthy food choices decreased from 5.9 [3.1, 9.7] to 3.5 [1.5, 5.7] servings per week ($P<0.001$), increasing the adherence to the recommendation from 24% to 41% after BS ($P=0.009$). Dairy was the only food group that showed a notable increase in daily consumption (+25 [-121, 231] grams; $P=0.052$). The percentage of participants with a consumption within the recommended range of 300-450 grams remained similar (25% to 22%), but more participants consumed over 450 grams of dairy per day post-surgery (29% to 45%, $P=0.051$). Although we also observed a slight increase in the consumption of nuts, median intake at six months was still extremely low and compliance with the recommendation did not change after BS (11% to 20%, $P=0.09$).

Table 2. Daily dietary intake of energy and macro- and micronutrients before and six months after BS in 107 participants.

		Intake			*P*-value
		Baseline	6 months	Change	
Total Energy (kcal)		1877 ± 470	1365 ± 376	-512 ± 433	**<0.001**
Carbohydrates	Total carbohydrates (en%)	41.0 ± 5.9	41.2 ± 6.4	+0.2 ± 7.7	0.77
	Total carbohydrates (g)	191.0 ± 52.3	139.3 ± 40.0	-51.7 ± 50.0	**<0.001**
	Mono- and disaccharides (en%)	16.9 ± 5.2	21.0 ± 5.4	+4.2 ± 6.4	**<0.001**
	Mono- and disaccharides (g)	78.2 ± 30.0	71.3 ± 24.0	-6.9 ± 33.1	**0.03**
Protein	Total protein (en%)	18.2 ± 3.9	19.3 ± 3.5	+1.1 ± 4.3	**0.01**
	Total protein (g)	84.1 ± 23.5	65.5 ± 20.7	-18.6 ± 24.3	**<0.001**
	Plant-based protein (g)	29.3 ± 9.1	18.5 ± 6.2	-10.9 ± 8.7	**<0.001**
	Animal-based protein (g)	54.2 ± 19.0	46.1 ± 17.8	-8.1 ± 21.9	**<0.001**
	Total protein (g/kg)[1]	1.1 ± 0.3	0.9 ± 0.3	-0.2 ± 0.3	**<0.001**
Total fat	Total fat (en%)	37.3 ± 6.6	36.4 ± 6.3	-0.8 ± 7.4	0.25
	Total fat (g)	79.1 ± 28.0	55.9 ± 19.9	-23.2 ± 26.7	**<0.001**
	Saturated fat (en%)	13.3 ± 3.2	13.4 ± 3.3	+0.1 ± 4.1	0.89
	Saturated fat (g)	28.4 ± 11.2	20.6 ± 8.1	-7.8 ± 11.0	**<0.001**
	MUFA (g)	27.6 ± 11.1	19.4 ± 8.0	-8.2 ± 11.5	**<0.001**
	PUFA (g)	15.7 ± 6.3	10.4 ± 4.7	-5.2 ± 6.4	**<0.001**
	ALA (g)	1.5 [1.2, 2.0]	1.0 [0.7, 1.3]	-0.5 [-0.8, -0.1]	**<0.001**
	EPA (g)	0.03 [0.01, 0.06]	0.02 [0.01, 0.06]	0.00 [-0.03, 0.02]	0.36
	DHA (g)	0.02 [0.01, 0.07]	0.02 [0.00, 0.07]	0.00 [-0.05, 0.02]	0.20
Fiber	Total fiber (g)	21.0 ± 5.9	14.6 ± 5.2	-6.4 ± 6.1	**<0.001**
Micronutrients	Folate (µg)[2]	245.9 [206.9, 293.1]	184.2 [148.3, 217.7]	-57.0 [-110.2, -12.8]	**<0.001**
	Vitamin B12 (µg)	4.3 [3.2, 5.5]	3.7 [2.6, 4.6]	-0.7 [-2.1, 0.7]	**0.002**
	Vitamin D (µg)	2.9 [1.9, 4.0]	1.9 [1.4, 2.8]	-0.7 [-2.1, 0.1]	**<0.001**
	Calcium (mg)	982.1 ± 321.7	943.1 ± 346.7	-39.0 ± 404.6	0.32
	Iron (mg)	10.0 ± 2.7	7.1 ± 2.3	-2.9 ± 2.8	**<0.001**

Data are presented as mean ± SD or median [Q1, Q3].

[1] Based on ideal body weight at BMI 25. [2] Dietary folate equivalents (DFE). 1 DFE = 1 µg food folate = 0.6 µg of folic acid from fortified food.

Table 3. Consumption of food groups according to the Dutch food-based dietary guidelines before and six months after BS in 107 participants.

	Recommendation	Intake			*P*-value
		Baseline	6 months	Change	
Vegetables (g/d)	≥200 g	146 [94, 208]	87 [52, 140]	-50 [-120, 6]	**<0.001**
Fruit (g/d)	≥200 g	187 [113, 255]	168 [111, 255]	-8 [-77, 51]	0.34
Wholegrain products (g/d)	≥90 g	99 [58, 136]	47 [26, 73]	-38 [-81, -8]	**<0.001**
Legumes (g/d)	≥10 g	0 [0, 0]	0 [0, 0]	0 [0, 0]	0.89
Nuts (g/d)	≥15 g	0 [0, 3]	0 [0, 8]	0 [0, 8]	**0.02**
Dairy (g/d)[1]	300-450 g	337 [222, 507]	418 [242, 534]	+25 [-121, 231]	0.05
Fish (g/d)[2]	≥15 g	0 [0, 4]	0 [0, 4]	0 [-3, 4]	0.78
Tea (g/d)	≥ 450 g	200 [0, 507]	133 [0, 517]	0 [-200, 105]	0.37
Fats and oils (g/d)					
Liquid fats (g/d)	Only consumption of liquid fats or	13 [5, 24]	7 [3, 12]	-5 [-13, 2]	**<0.001**
Solid fats (g/d)	Ratio of liquid fats to solid fats ≥13	0 [0, 6]	1 [0, 6]	0 [-2, 3]	0.57
Red meat (g/d)	≤45 g	27 [0, 45]	6 [0, 30]	-3 [-30, 4]	**0.003**
Processed meat (g/d)	0 g	67 [33, 103]	43 [20, 65]	-32 [-55, 13]	**<0.001**
Sugar-sweetened beverages (g/d)	0 g	58 [0, 150]	50 [0, 183]	0 [-67, 75]	0.89
Alcohol (g/d)	≤10 g of ethanol	0 [0, 0]	0 [0, 0]	0 [0, 0]	0.12
Sodium (g/d)[3]	≤ 1.9 g	2.2 [1.7, 2.9]	1.6 [1.2, 2.0]	-0.7 [-1.1, -0.2]	**<0.001**
Unhealthy choices (serv/wk)	≤ 3 servings per week	5.9 [3.1, 9.7]	3.5 [1.5, 5.7]	-2.4 [-5.0, 0.6]	**<0.001**

Data are presented as median [Q1, Q3]. Cut-offs are based on the DHD2015-index [33, 35].

[1] Maximum of 40 g cheese included.

[2] Maximum of 4 g lean fish included.

[3] The recommendation of <6 g of table salt corresponding to ≤2.4 g of sodium was adjusted by 20% to compensate for missing data on added salt.

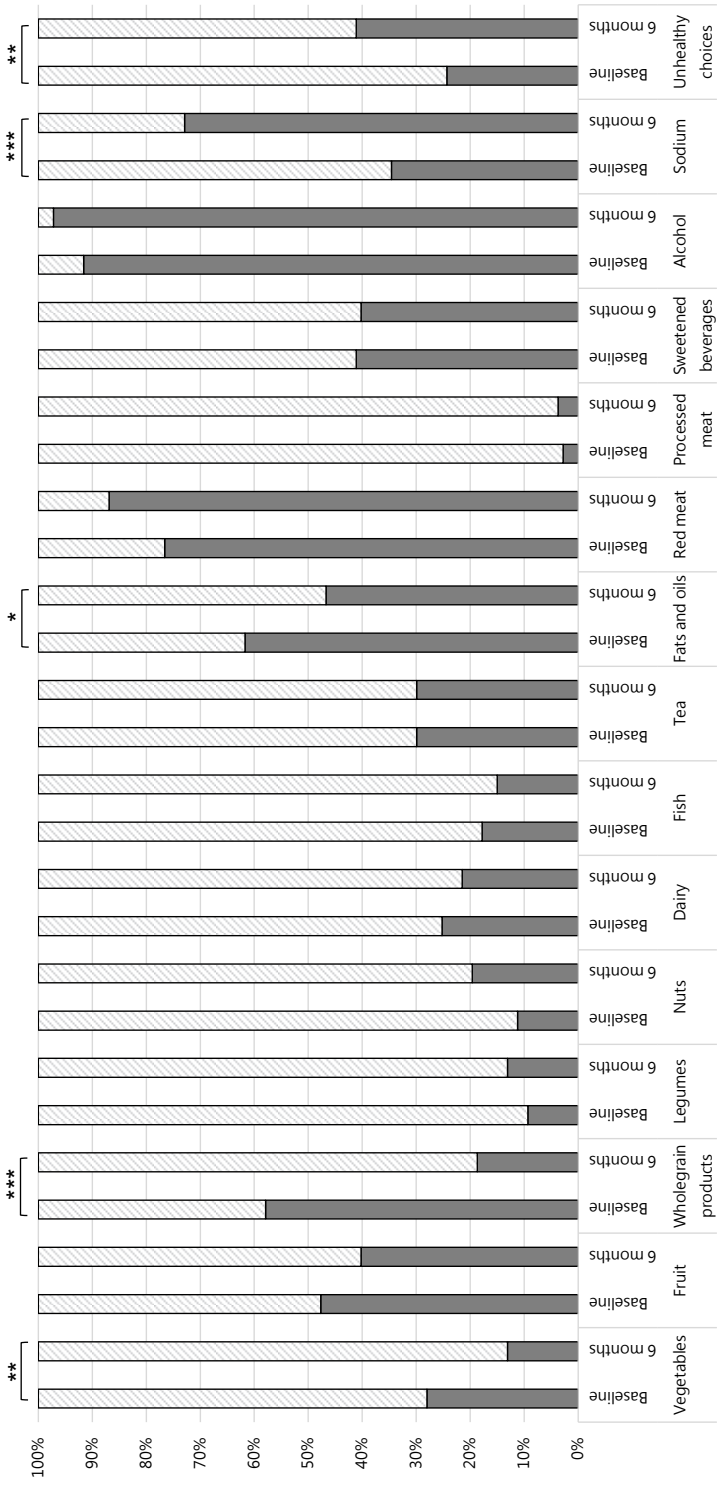

Figure 1. Adherence to the Dutch food-based dietary guidelines before and six months after BS in 107 participants. Significant difference between time points: * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

Discussion

The present study aimed to evaluate short-term changes in macro- and micronutrient composition and diet quality in the first six months following BS. Favorable changes included a decrease in the consumption of unhealthy food choices, red and processed meat and sodium, and an increase in dairy consumption as well as in relative protein intake after BS. However, unfavorable changes including reduced consumption of vegetables and wholegrain products along with a decreased fiber and micronutrient intake, and an increase in the intake of mono- and disaccharides were also observed six months post-surgery.

Overall, we found that macronutrient composition of the diet slightly changed with an increase in the relative intake of total protein, whereas the relative intake of total carbohydrates and fat remained similar after surgery. Still, only 59% of the participants had an adequate protein intake according to the recommended goal of ≥60 grams per day after BS [10, 36], which is in line with previous research [14, 16, 17, 37, 38]. Adequate protein intake is needed to prevent the loss of fat-free mass, hair loss, poor wound healing and edema [38], and may increase satiety and therefore be an important factor in maintaining weight loss after surgery [15]. The relative increase in protein intake post-surgery might be explained by the slight increase in dairy as this was the only food group that showed a notable increase in daily consumption whereas consumption of most other food groups decreased after BS. This might also explain the fairly stable intake of calcium while the intake of all other micronutrients decreased post-surgery. The relative increase in total protein intake was accompanied by a slightly increased intake of animal-based protein compared to plant-based protein at six months. This might also be due to the increase in dairy consumption as the consumption of red and processed meat as well as the consumption of lean meat (data not shown) decreased, which can be explained by a lower tolerance for meat observed after BS [9, 39, 40].

As only a minority of the participants reported to consume plant-based protein sources such as legumes (14%) and nuts (41%), many bariatric patients may benefit from increasing their consumption of plant-based protein sources. In addition to the intake of protein-rich foods, protein supplementation could also contribute to achieving the recommended goal of 60 grams per day in patients who fail to consume adequate amounts of protein. In the present study, additional protein supplementation was not routinely advised and only a few participants reported the use of artificial sources of protein (e.g. protein bars, powders and shakes).

The poor consumption of vegetables and wholegrain products observed in this study is in line with the findings of Schiavo et al., who also found an inadequate intake of vegetables and complex carbohydrates in a cohort of patients ≥4 years after SG [26]. Vegetable consumption in the present study was already low at baseline (146 grams) and further decreased at six months after surgery (87 grams), with only 13% reaching the recommended amount of 200 grams per day. Poor vegetable consumption is common within the general Dutch population with a mean consumption of 131 grams per day [41]. As 85% of the vegetables in the Dutch diet are consumed during dinner [42], including vegetables at other eating occasions during the day could improve vegetable consumption, particularly in the bariatric population because of their higher meal frequency.

The reduced intake of wholegrain products may be explained by food intolerances to bread, cereals, pasta and rice [9, 39, 40, 43] as well as prioritizing protein intake over the consumption of grains to limit overall energy intake, as generally advised after BS. Together with the large decrease in the consumption of vegetables and wholegrains, dietary fiber intake in the present study decreased to 14.6 ± 5.2 grams per day with only 10% reaching the recommended intake of 14 g/1000 kcal [10] at six months post-surgery, which is in accordance with low fiber intakes reported in previous research in the bariatric population [14, 28, 43-46]. Next to the general health benefits of dietary fiber, poor fiber intake in this population has also been linked to constipation, which is a common problem after BS [43, 44]. Besides increasing the consumption of vegetables and wholegrains, consumption of other fiber-rich foods such as (low sugar) fruits, legumes and nuts could also contribute to a higher fiber intake.

The number of unhealthy food choices such as sweet and savory snacks significantly decreased from 5.9 to 3.5 servings per week. Next to a positive impact of dietary counselling, changes in taste could offer an explanation for this finding. After BS, taste sensitivity to sweet and fatty stimuli appears to increase, along with a reduced hedonic response to these stimuli [47]. However, consumption of sugar-sweetened beverages did not decrease in the present study, despite beneficial changes observed in previous research [30, 48]. At the same time, a relative increase in the intake of mono- and disaccharides was observed (16.9 ± 5.2 en% to 21.0 ± 5.4 en%), implying that high-sugar foods and drinks comprised a relatively larger part of the diet after surgery compared to before. In the study of Kapoor et al., deselection of high-fat and/or high-sugar foods at an ad libitum buffet was prevalent but not universal [49], suggesting that food preferences may not change favorably in all patients after BS [19, 49]. This may also

explain the large variation in the intake of sugar-sweetened beverages post-surgery (0-183 grams per day).
Reducing the intake of unhealthy food choices is not only needed for improved weight loss outcomes [50], consumption of high-sugar foods and drinks could also lead to common post-surgical gastrointestinal symptoms such as dumping syndrome [10, 11, 27]. Identifying potential contributing factors to the variation in food preferences post-surgery could be useful to help identify patients that need additional support in making the desired dietary changes [19].

Overall, dietary counselling remains a key component in the bariatric surgery program, especially during the first months post-surgery as short term changes in dietary intake have been related to longer term weight outcomes. For instance, short-term reductions in energy intake at six months post-surgery were associated with greater weight loss over ten years in the Swedish Obese Subjects study [15]. This association is consistent with the research from Ostad et al. [45] and Nymo et al. [50], who also reported better weight loss outcomes when intake of energy was lower. Additionally, attention should be paid to the qualitative aspects of the diet in order to optimize weight outcomes. Masood and colleagues suggested that weight regain after BS might be less due to excessive consumption of food and more to a poor selection of healthy foods [51]. Indeed, multiple other studies found poor diet quality to be associated with weight regain in the late postoperative period [9, 20, 21, 50]. Overall, poor diet quality is commonly reported in this population [9, 20-24]. Two studies showed that diet quality of individuals who had previously undergone bariatric surgery was lower compared to individuals with normal weight [22, 24]. This highlights the importance of improving dietary habits in the first months following surgery and not solely relying on the initial benefits of the bariatric procedure.

Poor diet quality can also result in low micronutrient intake and thereby contribute to the development of nutritional deficiencies. Overall, nutritional deficiencies are frequently reported in this population, particularly for iron, folate, vitamin B12, vitamin D and calcium [8]. In the present study, the significant reduction in energy intake was accompanied with a reduced intake of folate, vitamin B12, vitamin D and iron. In general, reported dietary micronutrient intake was already low before surgery and worsened post-surgery, which is in accordance with previous research [16, 25]. Nonetheless, micronutrient intake from food is highly unlikely to provide the required levels needed to prevent micronutrient deficiencies after BS. To illustrate, intake of iron at six months

post-surgery was 7.1 ± 2.3 mg, whereas daily iron requirements are estimated to be 45-60 mg after BS [36]. For vitamin B12, the disagreement between intake and requirement is even more pronounced with a median intake of 3.7 [2.6-4.6] ug versus a requirement of 350-1000 ug vitamin B12 per day [36]. This was also demonstrated in the study of Gesquiere et al., who showed that dietary intake of iron and vitamin B12 comprised only a small part of total micronutrient intake when intake from supplements was included (25% and 5%, respectively) at 12 months after RYGB [52]. For these reasons, adequate daily vitamin and mineral supplementation is also essential to prevent nutritional deficiencies after BS.

The main strength of this study was the focus on both nutrient composition as well as diet quality assessed by consumption of different food groups. This approach aligns with the trend to comprehensively represent the totality of the diet by focusing on foods and beverages rather than individual nutrients.
Nevertheless, our results should also be interpreted in light of certain limitations. First, loss to follow-up was relatively high with only half of the study population completing the 3-day food records at both time points, which may limit the generalizability of our findings. Nevertheless, the study population was still found representative of the general Dutch bariatric patient population [53], indicating a minor risk of selection bias. Second, reporting dietary intake on only three days may not have been representative of usual dietary intake as this is likely not sufficient to capture the daily variation in food intake. This could have resulted in an underestimation of foods that are not consumed on a daily basis. Third, underreporting of energy intake is a common bias in nutrition research, particularly among participants with overweight or obesity [18, 54, 55]. In a previous study using data of the same cohort, we estimated that 57% of the 140 participants potentially underreported their energy intake at baseline [31]. However, the degree of underreporting after BS could not be identified as most techniques largely rely on the condition of weight stability. Therefore, the magnitude and direction of underreporting as well as potential consequences for data interpretation in the present study remain unknown. Last, the use of a preformatted food record prevented us from gaining insight into other relevant aspects of eating behavior such as meal frequency and separation of liquid and solid foods.

Conclusion

Our results demonstrate both favorable and unfavorable changes in macro- and micronutrient composition and diet quality during the first six months after BS.

Insight into these changes may help dietitians and other healthcare practitioners to understand potential pitfalls in order to improve dietary counselling of their patients. Based on the findings of this study, increasing the consumption of plant-based protein sources such as legumes and nuts could improve absolute protein intake, while the consumption of vegetables and wholegrain products should be targeted to improve fiber intake. Although the consumption of unhealthy food choices decreased after surgery, more attention is needed to also limit the consumption of sugar-sweetened beverages in order to reduce sugar intake. Moreover, an overall improvement in diet quality could also improve micronutrient intake, although additional supplementation will always be necessary in order to meet the required levels for preventing micronutrient deficiencies after BS.

Future research into long-term changes in dietary intake of bariatric patients is needed as dietary intake and eating behavior is likely to change over time.

References

1. Gloy, VL, Briel, M, Bhatt, DL, et al., *Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials.* BMJ, 2013. **347**: p. f5934.
2. O'Brien, PE, Hindle, A, Brennan, L, et al., *Long-Term Outcomes After Bariatric Surgery: a Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding.* Obes Surg, 2019. **29**(1): p. 3-14.
3. Sjostrom, L, Peltonen, M, Jacobson, P, et al., *Bariatric surgery and long-term cardiovascular events.* JAMA, 2012. **307**(1): p. 56-65.
4. Angrisani, L, Santonicola, A, Iovino, P, et al., *IFSO Worldwide Survey 2016: Primary, Endoluminal, and Revisional Procedures.* Obes Surg, 2018. **28**(12): p. 3783-3794.
5. Lupoli, R, Lembo, E, Saldalamacchia, G, et al., *Bariatric surgery and long-term nutritional issues.* World J Diabetes, 2017. **8**(11): p. 464-474.
6. Steenackers, N, Vanuytsel, T, Augustijns, P, et al., *Adaptations in gastrointestinal physiology after sleeve gastrectomy and Roux-en-Y gastric bypass.* The Lancet Gastroenterology & Hepatology, 2021. **6**(3): p. 225-237.
7. Osland, E, Powlesland, H, Guthrie, T, et al., *Micronutrient management following bariatric surgery: the role of the dietitian in the postoperative period.* Ann Transl Med, 2020. **8**(Suppl 1): p. S9.
8. Gasmi, A, Bjorklund, G, Mujawdiya, PK, et al., *Micronutrients deficiences in patients after bariatric surgery.* Eur J Nutr, 2022. **61**(1): p. 55-67.
9. Zarshenas, N, Tapsell, LC, Neale, EP, et al., *The Relationship Between Bariatric Surgery and Diet Quality: a Systematic Review.* Obes Surg, 2020. **30**(5): p. 1768-1792.
10. Moize, VL, Pi-Sunyer, X, Mochari, H, et al., *Nutritional pyramid for post-gastric bypass patients.* Obes Surg, 2010. **20**(8): p. 1133-1141.
11. Sherf Dagan, S, Goldenshluger, A, Globus, I, et al., *Nutritional Recommendations for Adult Bariatric Surgery Patients: Clinical Practice.* Adv Nutr, 2017. **8**(2): p. 382-394.
12. Janssen-Burg, W, van der Kaaden, I, den Otter, J, et al., *Dieetbehandelingsrichtlijn Bariatrische chirurgie bij obesitas II en III.* 2017.
13. Kromhout, D, Spaaij, CJ, de Goede, J, et al., *The 2015 Dutch food-based dietary guidelines.* Eur J Clin Nutr, 2016. **70**(8): p. 869-878.
14. Farias, G, Silva, RMO, da Silva, PPP, et al., *Impact of dietary patterns according to NOVA food groups: 2 y after Roux-en-Y gastric bypass surgery.* Nutrition, 2020. **74**: p. 110746.
15. Kanerva, N, Larsson, I, Peltonen, M, et al., *Changes in total energy intake and macronutrient composition after bariatric surgery predict long-term weight outcome: findings from the Swedish Obese Subjects (SOS) study.* Am J Clin Nutr, 2017. **106**(1): p. 136-145.
16. Raatz, SK, Johnson, LK, Caliquary, A, et al., *Reported nutrient intake over 7 years after Roux-en-Y gastric bypass in the Longitudinal Assessment of Bariatric Surgery-3 (LABS-3) psychosocial study.* Surg Obes Relat Dis, 2020. **16**(8): p. 1022-1029.
17. Sherf Dagan, S, Keidar, A, Raziel, A, et al., *Do Bariatric Patients Follow Dietary and Lifestyle Recommendations during the First Postoperative Year?* Obes Surg, 2017. **27**(9): p. 2258-2271.
18. Redpath, TL, Livingstone, MBE, Dunne, AA, et al., *Methodological issues in assessing change in dietary intake and appetite following gastric bypass surgery: A systematic review.* Obes Rev, 2021. **22**(6): p. e13202.
19. Nielsen, MS, Christensen, BJ, Ritz, C, et al., *Factors Associated with Favorable Changes in Food Preferences After Bariatric Surgery.* Obes Surg, 2021. **31**(8): p. 3514-3524.
20. Da Silva, FB, Gomes, DL and De Carvalho, KM, *Poor diet quality and postoperative time are independent risk factors for weight regain after Roux-en-Y gastric bypass.* Nutrition, 2016. **32**(11-12): p. 1250-1253.

21. Freire, RH, Borges, MC, Alvarez-Leite, JI, et al., *Food quality, physical activity, and nutritional follow-up as determinant of weight regain after Roux-en-Y gastric bypass.* Nutrition, 2012. **28**(1): p. 53-58.
22. Harbury, C, Collins, CE and Callister, R, *Diet quality is lower among adults with a BMI >/=40kgm(-2) or a history of weight loss surgery.* Obes Res Clin Pract, 2019. **13**(2): p. 197-204.
23. Harbury, CM, Verbruggen, EE, Callister, R, et al., *What do individuals with morbid obesity report as a usual dietary intake? A narrative review of available evidence.* Clin Nutr ESPEN, 2016. **13**: p. e15-e22.
24. Hong, YR, Yadav, S, Suk, R, et al., *Assessment of Physical Activity and Healthy Eating Behaviors Among US Adults Receiving Bariatric Surgery.* JAMA Netw Open, 2022. **5**(6): p. e2217380.
25. Marques da Silva, M, Waitzberg, DL, Dipppolito, RMS, et al., *Nutritional guidance, monitoring, and supplementation before and after bariatric surgery - Are we doing this correctly?* Nutr Hosp, 2021. **38**(3): p. 478-487.
26. Schiavo, L, Di Rosa, M, Tramontano, S, et al., *Long-Term Results of the Mediterranean Diet After Sleeve Gastrectomy.* Obes Surg, 2020. **30**(10): p. 3792-3802.
27. Soares, FL, Bissoni de Sousa, L, Corradi-Perini, C, et al., *Food quality in the late postoperative period of bariatric surgery: an evaluation using the bariatric food pyramid.* Obes Surg, 2014. **24**(9): p. 1481-1486.
28. Ziadlou, M, Hosseini-Esfahani, F, Mozaffari Khosravi, H, et al., *Dietary macro- and micro-nutrients intake adequacy at 6th and 12th month post-bariatric surgery.* BMC Surg, 2020. **20**(1): p. 232.
29. Ullrich, J, Ernst, B, Wilms, B, et al., *Roux-en Y gastric bypass surgery reduces hedonic hunger and improves dietary habits in severely obese subjects.* Obes Surg, 2013. **23**(1): p. 50-55.
30. Miller, GD, Norris, A and Fernandez, A, *Changes in nutrients and food groups intake following laparoscopic Roux-en-Y gastric bypass (RYGB).* Obes Surg, 2014. **24**(11): p. 1926-1932.
31. Heusschen, L, Berendsen, AAM, Balvers, MGJ, et al., *Relative validity of a short screener to assess diet quality in patients with severe obesity before and after bariatric surgery.* Public Health Nutr, 2022. **25**(10): p1-11.
32. *NEVO-online versie 2016/5.0*.
33. Looman, M, Feskens, EJ, de Rijk, M, et al., *Development and evaluation of the Dutch Healthy Diet index 2015.* Public Health Nutr, 2017. **20**(13): p. 2289-2299.
34. Brink, E, van Rossum, C, Postma-Smeets, A, et al., *Development of healthy and sustainable food-based dietary guidelines for the Netherlands.* Public Health Nutr, 2019. **22**(13): p. 2419-2435.
35. de Rijk, MG, Slotegraaf, AI, Brouwer-Brolsma, EM, et al., *Development and evaluation of a diet quality screener to assess adherence to the Dutch food-based dietary guidelines.* Br J Nutr, 2021: p. 1-28.
36. Mechanick, JI, Apovian, C, Brethauer, S, et al., *Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists.* Surg Obes Relat Dis, 2020. **16**(2): p. 175-247.
37. Ito, MK, Goncalves, VSS, Faria, S, et al., *Effect of Protein Intake on the Protein Status and Lean Mass of Post-Bariatric Surgery Patients: a Systematic Review.* Obes Surg, 2017. **27**(2): p. 502-512.
38. Steenackers, N, Gesquiere, I and Matthys, C, *The relevance of dietary protein after bariatric surgery: what do we know?* Curr Opin Clin Nutr Metab Care, 2018. **21**(1): p. 58-63.
39. Boerlage, TC, van de Laar, AW, Westerlaken, S, et al., *Gastrointestinal symptoms and food intolerance 2 years after laparoscopic Roux-en-Y gastric bypass for morbid obesity.* Br J Surg, 2017. **104**(4): p. 393-400.
40. Freeman, RA, Overs, SE, Zarshenas, N, et al., *Food tolerance and diet quality following adjustable gastric banding, sleeve gastrectomy and Roux-en-Y gastric bypass.* Obes Res Clin Pract, 2014. **8**(2): p. e115-200.

41. Van Rossum, CTM, Buurma-Rethans, EJM, Dinnissen, CS, et al., *The diet of the Dutch. Results of the Dutch National Food Consumption Survey 2012-2016.* 2020, National Institute for Public Health and the Environment.: Bilthoven.
42. van der Krieken, SE, van Dooren, C, Mensink, F, et al., *Vegetables. Fact sheet.* 2018, Netherlands Nutrition Centre.
43. Grosse, CS and Cope, VC, *Dietary Fibre Intake and Bowel Habits After Bariatric Surgery: a Structured Literature Review.* Obes Surg, 2019. **29**(7): p. 2247-2254.
44. Afshar, S, Kelly, SB, Seymour, K, et al., *The Effects of Bariatric Procedures on Bowel Habit.* Obes Surg, 2016. **26**(10): p. 2348-2354.
45. Ostad, AN, Barghchi, H, Jangjoo, A, et al., *Macro- and Micro-nutrient Intake Adequacy in Gastric Bypass Patients after 24 Months: a Cross-sectional Study.* Clin Nutr Res, 2021. **10**(4): p. 341-352.
46. Reichmann, MTF, Todeschini, S, Setter, N, et al., *Comparison of the dietary intake amongst women in the late postoperative period after Roux-en-Y gastric bypass with the bariatric food pyramid.* Nutr Hosp, 2019. **36**(3): p. 599-603.
47. Ahmed, K, Penney, N, Darzi, A, et al., *Taste Changes after Bariatric Surgery: a Systematic Review.* Obes Surg, 2018. **28**(10): p. 3321-3332.
48. Molin Netto, BD, Earthman, CP, Farias, G, et al., *Eating patterns and food choice as determinant of weight loss and improvement of metabolic profile after RYGB.* Nutrition, 2017. **33**: p. 125-131.
49. Kapoor, N, Al Najim, W, Menezes, C, et al., *A Comparison of Total Food Intake at a Personalised Buffet in People with Obesity, before and 24 Months after Roux-en-Y-Gastric Bypass Surgery.* Nutrients, 2021. **13**(11).
50. Nymo, S, Lundanes, J, Aukan, M, et al., *Diet and physical activity are associated with suboptimal weight loss and weight regain 10-15 years after Roux-en-Y gastric bypass: A cross-sectional study.* Obes Res Clin Pract, 2022.**16**(2): p. 163-169.
51. Masood, A, Alsheddi, L, Alfayadh, L, et al., *Dietary and Lifestyle Factors Serve as Predictors of Successful Weight Loss Maintenance Postbariatric Surgery.* J Obes, 2019. **2019**: p. 7295978.
52. Gesquiere, I, Foulon, V, Augustijns, P, et al., *Micronutrient intake, from diet and supplements, and association with status markers in pre- and post-RYGB patients.* Clin Nutr, 2017. **36**(4): p. 1175-1181.
53. DICA, *DATO Bariatrische chirurgie - Jaarrapportage 2018*. 2018. https://dica.nl/jaarrapportage-2018/dato
54. Poslusna, K, Ruprich, J, de Vries, JH, et al., *Misreporting of energy and micronutrient intake estimated by food records and 24 hour recalls, control and adjustment methods in practice.* Br J Nutr, 2009. **101 Suppl 2**: p. S73-85.
55. Trijsburg, L, Geelen, A, Hollman, PC, et al., *BMI was found to be a consistent determinant related to misreporting of energy, protein and potassium intake using self-report and duplicate portion methods.* Public Health Nutr, 2017. **20**(4): p. 598-607.

CHAPTER 3

Relative validity of a short screener to assess diet quality in patients with severe obesity before and after bariatric surgery

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Public Health Nutrition, 2022; 25(10): 2731-2741

Abstract

Objective: To determine the relative validity and reproducibility of the Eetscore FFQ, a short screener for assessing diet quality, in patients with (severe) obesity before and after bariatric surgery (BS).

Methods: 140 participants with obesity who were scheduled for BS participated in this study. The Eetscore FFQ was evaluated against 3-day food records before (T0) and six months after BS (T6) by comparing index scores of the Dutch Healthy Diet index 2015 (DHD2015-index). Relative validity was assessed using paired t-tests, Kendall's tau-b correlation coefficients (τb), cross-classification by tertiles, weighted kappa values (k_w) and Bland-Altman plots. Reproducibility of the Eetscore FFQ was assessed using intraclass correlation coefficients (ICC).

Results: At T0, mean total DHD2015-index score derived from the Eetscore FFQ was 10.2 points higher than the food record-derived score (P<0.001) and showed an acceptable correlation (τb=0.42, 95% CI: 0.27-0.55). There was a fair agreement with a correct classification of 50% (k_w=0.37, 95% CI: 0.25-0.49). Correlation coefficients of the individual DHD components varied from 0.01-0.54. Similar results were observed at T6 (τb=0.31, 95% CI: 0.12-0.48, correct classification of 43.7%; k_w=0.25, 95% CI: 0.11-0.40). Reproducibility of the Eetscore FFQ was considered good (ICC=0.78, 95% CI: 0.69-0.84).

Conclusion: The Eetscore FFQ showed to be acceptably correlated with the DHD2015-index derived from 3-day food records, but absolute agreement between the methods was poor. Considering the need for dietary assessment methods that reduce the burden for patients, healthcare practitioners and researchers, the Eetscore FFQ can be used for ranking according to diet quality and for monitoring changes over time.

Introduction

Obesity is reaching epidemic proportions and bariatric surgery (BS) is proven to be one of the most effective treatments, resulting in substantial and long-term weight loss and improvement of obesity-related comorbidities [1-3]. BS is performed in individuals with a Body Mass Index (BMI) above 40 kg/m^2, or a BMI above ≥35 kg/m^2 with obesity-related comorbidities such as diabetes mellitus type 2, hypertension, obstructive sleep apnea and dyslipidemia [4]. Worldwide, the Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most commonly performed bariatric procedures [5].

After BS, the amount of food that can be ingested is significantly reduced, resulting in a lower energy intake [6]. Additionally, food intolerances after surgery may lead to avoidance of food groups which in turn may impact diet quality [7]. Poor diet quality is consistently reported in patients with (severe) obesity, including those presenting for bariatric surgery [8-10]. This could impact their risk of developing nutritional deficiencies as well as the success of their weight loss after surgery [10-12]. Therefore, monitoring diet quality is an important component in the bariatric surgery program.

Diet quality can be assessed with the Dutch Healthy Diet index 2015 (DHD2015-index) [13]. The DHD2015-index measures adherence to the Dutch food-based dietary guidelines published in 2015 by the Health Council of the Netherlands [14]. The DHD2015-index can be calculated using data from multiple food records, 24-hour dietary recalls or a single food frequency questionnaire (FFQ). Unfortunately, these methods are time consuming and burdensome, and therefore less likely to be used in everyday clinical practice. For this reason, a short screener, the Eetscore FFQ, was developed to estimate the DHD2015-index in time-limited situations. The Eetscore FFQ showed to be acceptably correlated with the DHD2015-index derived from a full-length FFQ in a normal-weight adult population [15]. However, the Eetscore FFQ has not been evaluated in patients with (severe) obesity before or after undergoing BS. Accurate measures of diet quality are needed to optimize nutritional care provided to these patients during the bariatric surgery program, but validated dietary assessment tools in this specific population are lacking [16].

Therefore, this study aimed to evaluate the relative validity and reproducibility of the Eetscore FFQ as a screener for diet quality in patients with (severe) obesity before and six months after BS.

Methods

Study design and participants

Between October 2018 and September 2019, patients with obesity who were eligible and scheduled for BS at Vitalys Obesity Clinic, part of Rijnstate hospital (Arnhem, the Netherlands) were asked to participate in this prospective cohort study.

Participants were included approximately six weeks pre-surgery (T0) and followed up until six months post-surgery (T6). Exclusion criteria were a non-Dutch eating pattern, suffering from an eating disorder, inability to fill in questionnaires or food records and a previous bariatric procedure other than an adjustable gastric band in medical history.

In total, 200 participants signed the informed consent and were included in the study. Both before and after BS, we evaluated the Eetscore FFQ against 3-day food records (3d-FR) as reference method by comparing index scores of the DHD2015-index derived from both methods. At both timepoints, demographic information was collected and participants were asked to complete the Eetscore FFQ, followed by the 3d-FR. At T0, the Eetscore FFQ was completed twice (Eetscore FFQ1, Eetscore FFQ2) with an interval of approximately five weeks in order to analyze reproducibility.

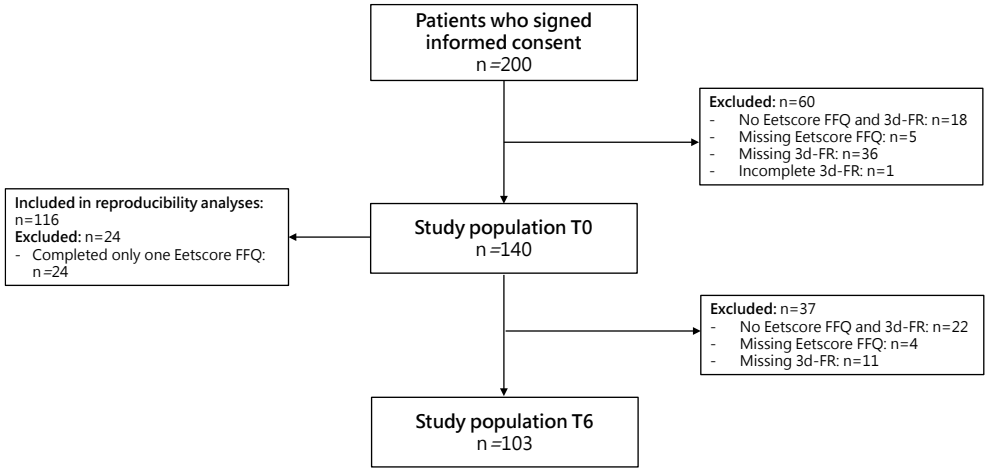


Figure 1. Flowchart of the study population at T0 and T6.

From the total study sample of 200 participants, we excluded 60 participants with no Eetscore FFQ and 3d-FR (n=18), a missing Eetscore FFQ (n=5) or a missing or incomplete 3d-FR (n=37) at T0. The final study sample for data analysis at T0 consisted of 140 participants, of whom 116 completed both Eetscore FFQ1 and Eetscore FFQ2 (**Figure 1**).

For the study sample at T6, we additionally excluded 37 participants with no Eetscore FFQ and 3d-FR (n=22), a missing Eetscore FFQ (n=4) or a missing 3d-FR (n=11) at T6, resulting in a final study sample of 103 participants for data analysis at T6 (**Figure 1**).
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 Local Ethical Committee of Rijnstate Hospital. Written informed consent was obtained from all participants.

Data collection

Demographic information

Socio-demographic (age, sex, educational level) and health-related information (anthropometrics, type of surgery, comorbidities, smoking status) were obtained from electronic patient records.
Educational level was defined as low (primary education and prevocational secondary education), medium (senior general secondary education, pre-university education and secondary vocational education) or high (higher vocational education and university).
Anthropometric measurements were performed during standard visits at the hospital. Body weight was measured to the nearest 0.1 kg with a digital weighing scale (Tanita BC-420MA), after removal of heavy clothing and shoes. Height was measured in standing position with a wall-mounted stadiometer (Seca 206). BMI was calculated as weight (kg) divided by squared height (m^2). Total body weight loss (TWL) at six months was calculated as weight loss divided by body weight before surgery, multiplied by 100%.
Physical activity at T0 was assessed with the validated Baecke Questionnaire [17] that evaluates a person's habitual physical activity and separates it into three domains: work index, sports index and leisure index. Each domain could receive a score from 1-5 points, resulting in a total score ranging from 3-15. A score of 15 indicates being physically active at a high intensity.

DHD2015-index

The development of the DHD2015-index has been previously described [13]. The DHD2015-index consists of 15 components representing the Dutch food-based dietary guidelines of 2015 [14]: vegetables, fruit, wholegrain products, legumes, nuts, dairy, fish, tea, fats and oils, coffee, red meat, processed meat, sweetened beverages, alcohol, and sodium. Additionally, the component 'unhealthy food choices' was added based on the guideline of the Netherlands Nutrition Centre [18].

Food items that contributed most to total energy, saturated fat and mono- and disaccharide intake according to the Dutch National Food Consumption Survey (DNFCS) 2007-2010 were included in this component, such as sweet spreads, pastries, chocolate, savory snacks, sauces and use of sugar in coffee or tea.

A complete overview of the 16 components and their cut-off and threshold values is presented in **Table 1**. For every component, the score ranges from 0 (no adherence) to 10 points (complete adherence), resulting in a total score between 0 and 160 points.
A graphic presentation of the scoring of the different types of components can be seen in **Supplementary Figure 1**. For adequacy components (vegetables, fruit, legumes, nuts, fish and tea), no intake is awarded with 0 points and intakes between the cut-off and threshold value are scored proportionally. For moderation components (red meat, processed meat, sweetened beverages, alcohol, sodium and unhealthy food choices), intakes between the cut-off and threshold value are also scored proportionally but no intake is awarded with 10 points. Optimum components (dairy) have an optimal range of intake and ratio components (fat and oils) reflect replacement of less preferred foods (e.g. solid fats) by more preferred foods (e.g. liquid fats and oils). The wholegrain products component is scored based on two sub-components: an adequacy component for wholegrain consumption and a ratio component to reflect replacement of refined grain products by wholegrain products. The coffee component is a qualitative component, based on the type of coffee (filtered vs unfiltered). As information on the type of coffee used was not available from the food records, this component could not be included in the validity analyses. For this reason, total score ranged between 0 and 150 for that part of the study.

Table 1. Cut-off and threshold values for the DHD2015-index components and the component 'Unhealthy food choices'. *Adapted from De Rijk et al.* [15].

	Component	Type	Dutch food-based dietary guidelines 2015	Minimum score (= 0 points)	Maximum score (= 10 points)
1	**Vegetables**	A	Eat at least 200 g of vegetables daily	0 g/day	≥ 200 g/day
2	**Fruit**	A	Eat at least 200 g of fruit daily	0 g/day	≥ 200 g/day
3	**Wholegrain products**	A	Eat at least 90 g of wholegrain products daily	0 g/day	≥ 90 g/day
		R	Replace refined cereal products by wholegrain products	No consumption of wholegrain products or ratio of whole grains to refined grains ≤0.7	No consumption of refined products or ratio of whole grains to refined grains ≥11
4	**Legumes**	A	Eat legumes weekly	0 g/day	≥ 10 g/day
5	**Nuts**	A	Eat at least 15 g of unsalted nuts daily	0 g/day	≥ 15 g/day
6	**Dairy**[1]	O	Eat a few portions of dairy products daily, including milk or yogurt	0 g/day or ≥ 750 g/day	300-450 g/day
7	**Fish**[2]	A	Eat one serving of fish weekly, preferably oily fish	0 g/day	≥ 15 g/day
8	**Tea**	A	Drink three cups of black or green tea daily	0 g/day	≥ 450 mL/day
9	**Fats and oils**	R	Replace butter, hard margarines and cooking fats by soft margarines, liquid cooking fats and vegetable oils	No consumption of soft margarines, liquid cooking fats and vegetable oils or ratio of liquid fats to solid fats ≤0.6	No consumption of butter, hard margarines and cooking fats or ratio of liquid fats to solid fats ≥13
10	**Coffee**	Q	Replace unfiltered coffee by filtered coffee	Any consumption of unfiltered coffee	Consumption of only filtered coffee or no coffee consumption
11	**Red meat**	M	Limit consumption of red meat	≥ 100 g/day	≤ 45 g/day
12	**Processed meat**	M	Limit consumption of processed meat	≥ 50 g/day	0 g/day
13	**Sweetened beverages**	M	Limit consumption of sweetened beverages and fruit juices	≥ 250 g/day	0 g/day
14	**Alcohol**	M	If alcohol is consumed at all, intake should be limited to one unit (10 g ethanol) daily	Women: ≥ 20 g ethanol/day Men: ≥ 30 g ethanol/day	Women: ≤ 10 g ethanol/day Men: ≤ 10 g ethanol/day
15	**Sodium**	M	Limit consumption of table salt to 6 g daily	≥ 3.8 g Na/day	≤ 1.9 g Na/day
16	**Unhealthy food choices**	M	Limit consumption of unhealthy food choices	≥ 7 week choices/week	≤ 3 week choices/week

A, adequacy component (consume an adequate amount); R, ratio component (replace less healthy products by more healthy alternatives); O, optimum component (optimal consumption range); Q, qualitative component (choose healthier option); M, moderation component (limit consumption). [1] maximum of 40 g/d cheese could be included. [2] maximum of 4 g/d lean fish could be included.

The Eetscore FFQ

The development of the Eetscore FFQ has been described in detail elsewhere [15]. Briefly, the Eetscore FFQ was developed to assess the DHD2015-index as a measure of adherence to the Dutch food-based dietary guidelines. The Eetscore FFQ assesses dietary intake over the previous month, based on 55 food items that account for 85% of energy intake from the adult population of the DNFCS 2007-2010 [19]. The six answer categories for questions on frequency of consumption range from 'never' to 'every day' for regularly consumed foods and from 'not this month' to 'more than once a week' for episodically consumed foods. Portion sizes are assessed in standard portions and commonly used household measures. Average daily intakes of food items are calculated by multiplying frequency of consumption by portion size in grams. The Eetscore FFQ directly reports index scores for all components of the DHD2015-index.

Three-day food records

A 3-day estimated food record was used as reference method. This method is considered acceptable for the assessment of usual dietary intake and is commonly used in dietary validation studies [20]. We used structured, open-ended food records containing predefined food groups (including the option 'others') at six food occasions (breakfast, lunch, dinner + three eating occasions between main meals). All participants received verbal instructions and were provided with a written example. They were asked to record all foods and beverages consumed over the three days in as much detail as possible, to describe the amounts consumed in units, household measures or provide weights when known, to report cooking methods and to include the recipes for any mixed dishes. At both timepoints, recorded days were randomly selected and consisted of two weekdays (Monday-Thursday) and one weekend day (Friday-Sunday) within a one-week period. Completed food records were reviewed for completeness with regards to portion sizes, cooking methods and description of foods. Telephone interviews with the participants were conducted in case of any uncertainties. Dietary intake data were entered in Compl-eat™, a computer-based nutrition calculation program that is linked to the Dutch Food Composition Database (NEVO-online, version 2016) [21]. All foods and beverages from the food records were categorized into one of the 15 DHD components (excluding coffee) to calculate the scores of the DHD2015-index. In case of missing recipes for mixed meals such as pasta or rice dishes, standard recipes of the Dutch Food Composition Database (NEVO-online, version 2016) were used [21]. Food items that did not fall into one of the DHD components (e.g. potatoes, soups) were not included.

Total dietary intake of the 15 DHD components in grams were averaged over the number of completed days before calculating corresponding index scores.

Statistical analysis

General characteristics of the study population are reported as median [Q1-Q3] for continuous data and as frequency (percentage) for categorical data. Total DHD2015-index scores and individual component scores calculated from the Eetscore FFQ and the 3d-FR are presented as means and standard deviations. Relative validity of the Eetscore FFQ compared to the 3d-FR was assessed by calculating Kendall's tau-b (τb) as well as Spearman's rho (ρ) correlation coefficients between the DHD index scores derived from both methods. At T0, we used data of the Eetscore FFQ that was completed in the same month as the 3d-FR. Confidence intervals for the correlations were obtained using Fisher's z-transformation. Correlation coefficients less than 0.20 were classified as poor, 0.20–0.49 as acceptable and ≥0.50 as good [22]. Additionally, total DHD2015-index scores derived from the Eetscore FFQ and the 3d-FR were categorized into tertiles. If ≥50% of the participants were classified into the same tertile and/or ≤10% into the opposite tertile, this was considered a good outcome [22]. Weighted kappa coefficients (k_w) were calculated to further evaluate the relative level of agreement: k_w coefficients less than 0.20 indicated a poor level of agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 good agreement and greater than 0.80 a very good level of agreement [23]. Paired t-tests were used to test the mean differences in the DHD index scores between the two methods. Bland-Altman plots with 95% limits of agreement were used to visualize the differences in the total DHD2015-index score.

We additionally explored the degree of potential misreporting of dietary intake by comparing reported energy intake calculated from the food records at T0 with energy requirements as identified by the revised Goldberg cut-off method [24]. Basal metabolic rate (BMR) was estimated using the Mifflin St-Jeor Equation [25] as this method provides the best estimation in individuals with (severe) obesity [26-28]. We used a physical activity level (PAL) of 1.55, reflecting a moderate active lifestyle that was in line with the median physical activity score resulting from the Baecke questionnaire.

Reproducibility of the Eetscore FFQ was examined by calculating single measures intraclass correlation coefficients (ICC) of absolute agreement between the DHD index scores of both FFQs at T0, using a two-way mixed model. ICCs less than 0.50 indicated poor reproducibility, 0.50-0.75 moderate, 0.75-0.90 good, and greater than 0.90 excellent reproducibility [29].

All statistical analyses were performed using IBM SPSS Statistics 25 for Windows (IBM).

Results

Participant characteristics

The study population at T0 consisted of 140 participants. The majority was female (79.3%), never smoked (55.0%), had a medium educational level (62.8%) and no comorbidities (51.4%) (**Table 2**). Median age was 49.0 [36.5-55.0] years and median BMI was 41.2 [39.0-45.6] kg/m^2. Median physical activity score of the Baecke questionnaire was 8.4 [7.1-9.1].

Baseline characteristics of the study population at T6 (n=103) were similar to those of the study population at T0 (**Supplementary Table 1**). The majority had undergone a RYGB (80.7%) and median BMI six months after surgery was 30.9 [28.5-34.3] kg/m^2, resulting in a median TWL of 25.8 [21.1-29.3] percent.

Table 2. Baseline characteristics of the study population at T0.

	Study population at T0 (n=140)	
Sex (female)	111	(79.3)
Age (years)	49.0	[36.5-55.0]
BMI (kg/m²)	41.2	[39.0-45.6]
Smoking status		
Never	77	(55.0)
Former	53	(37.9)
Current	10	(7.1)
Educational level[1]		
Low	24	(18.6)
Medium	81	(62.8)
High	24	(18.6)
Comorbidity		
None	72	(51.4)
Diabetes Mellitus type 2	23	(16.4)
Dyslipidemia	25	(17.9)
Hypertension	43	(30.7)
OSAS	29	(20.7)
Physical activity[2]	8.4	[7.1-9.1]
Adjustable gastric band in history	18	(12.9)

Data are presented as median [Q1-Q3] and frequency (valid percentage).

BMI, body mass index; *OSAS*, obstructive sleep apnea syndrome.

[1] Low education = primary education and prevocational secondary education; medium education = senior general secondary education, pre-university education and secondary vocational education; high education = higher vocational education and university. Missing for n=11.

[2] Based on the Baecke questionnaire: total score ranging from 3-15. Missing for n=27.

Relative validity of the Eetscore FFQ compared to 3-day food records

Average time difference between completing the Eetscore FFQ and the 3d-FR at T0 was 5.8 ± 7.2 days. Mean total DHD2015-index score derived from the Eetscore FFQ was 10.2 points higher than the score derived from the 3d-FR (91.8 ± 18.6 vs 81.5 ± 17.7 points, $P<0.001$; **Table 3a**). Visual inspection of the Bland-Altman plot additionally showed relatively wide limits of agreement (-21.1 and 41.5 points, **Figure 2a)**.

Index scores for the individual DHD components were significantly different for vegetables, fruit, wholegrain products, legumes, nuts, dairy, fish, tea, processed meat and sodium ($P<0.05$ for all).

Correlation of the total DHD2015-index score was acceptable (τb=0.42, 95% CI: 0.27-0.55) and there was a fair level of agreement between the two methods (k_w=0.37, 95% CI: 0.25-0.49). The Eetscore FFQ correctly classified 50.0% of the participants into the same tertile as the 3d-FR, and 5.7% was misclassified into the opposite tertile. For the individual DHD components, a good correlation (≥0.50) was observed for alcohol (τb=0.54, 95% CI: 0.40-0.65). Poor correlations (<0.20) were observed for red meat (τb=0.01, 95% CI: -0.16-0.18) and legumes (τb=0.04, 95% CI: -0.13-0.20). Correlation coefficients of all other components ranged between 0.20 and 0.49.

At T6, average time difference between completing the Eetscore FFQ and the 3d-FR was 8.5 ± 7.4 days. Similar to T0, mean total DHD2015-index score derived from the Eetscore FFQ was higher than from the 3d-FR (mean difference of 17.4 points, $P<0.001$; **Table 3b**) with relatively wide limits of agreement (-14.6 and 49.4 points, **Figure 2b**).

Index scores for the individual DHD components were significantly different for vegetables, fruit, wholegrain products, legumes, nuts, fish, fats and oils, processed meat, sweetened beverages and unhealthy food choices ($P<0.05$ for all).

Correlation of the total DHD2015-index score was acceptable (τb=0.31, 95% CI: 0.12-0.48) and there was a fair level of agreement between the two methods (k_w=0.25, 95% CI: 0.11-0.40). The Eetscore FFQ correctly classified 43.7% of the participants into the same tertile as the 3d-FR, and 9.7% was misclassified into the opposite tertile. For the individual DHD components, a good correlation (≥0.50) was observed for tea (τb=0.53, 95% CI: 0.36-0.66). Poor correlations (<0.20) were observed for processed meat (τb=0.06, 95% CI: -0.14-0.25), legumes (τb=0.07, 95% CI:-0.13-0.26), sodium (τb=0.15, 95% CI: -0.05-0.33), red meat (τb=0.16, 95% CI: -0.04-0.34) and fats and oils (τb=0.17, 95% CI: -0.03-0.35). Correlations coefficients of all other components ranged between 0.20 and 0.49.

Table 3a. Mean DHD2015-index scores derived from the 3d-FR and the Eetscore FFQ and corresponding validity statistics in 140 participants *before* BS (T0).

		3d-FR		Eetscore FFQ		Difference						
		Mean	SD	Mean	SD	Mean	SD	*P*-value	τb	95% CI	ρ	95% CI
1.	Vegetables	6.7	2.9	5.4	2.8	-1.3	3.3	**<0.001**	0.23	0.06, 0.38	0.34	0.18, 0.48
2.	Fruit	7.5	3.4	5.9	3.5	-1.5	3.1	**<0.001**	0.41	0.26, 0.54	0.52	0.38, 0.64
3.	Wholegrain products	5.4	2.9	7.1	2.9	+1.7	3.1	**<0.001**	0.32	0.16, 0.46	0.42	0.27, 0.55
4.	Legumes	0.8	2.6	5.7	4.5	+4.9	5.1	**<0.001**	0.04	-0.13, 0.20	0.05	-0.12, 0.21
5.	Nuts	1.8	3.5	4.0	3.6	+2.2	3.5	**<0.001**	0.42	0.27, 0.55	0.50	0.36, 0.62
6.	Dairy	6.9	3.0	6.1	3.3	-0.8	3.8	**0.02**	0.21	0.04, 0.36	0.28	0.12, 0.43
7.	Fish	2.3	3.8	5.5	3.4	+3.2	4.1	**<0.001**	0.31	0.15, 0.46	0.38	0.22, 0.52
8.	Tea	5.0	4.3	4.1	4.3	-0.9	3.9	**0.01**	0.48	0.33, 0.60	0.57	0.44, 0.68
9.	Fat and oils	6.4	4.5	6.9	4.3	+0.5	5.2	0.26	0.26	0.10, 0.41	0.30	0.14, 0.45
10.	Coffee[1]	*NA*	*NA*	7.5	2.7	-	-	-	-	-	-	-
11.	Red meat	8.9	2.7	8.7	2.7	-0.2	3.7	0.59	0.01	-0.16, 0.18	0.01	-0.16, 0.18
12.	Processed meat	2.2	3.4	3.3	3.1	+1.2	3.5	**<0.001**	0.34	0.18, 0.48	0.43	0.28, 0.56
13.	Sweetened beverages	6.6	3.8	7.0	3.8	+0.4	4.0	0.20	0.37	0.21, 0.51	0.47	0.32, 0.60
14.	Alcohol	9.4	2.2	9.3	2.2	-0.1	2.0	0.56	0.54	0.40, 0.65	0.55	0.41, 0.66
15.	Sodium	7.1	3.2	7.8	2.5	+0.7	3.2	**0.01**	0.29	0.13, 0.44	0.39	0.23, 0.53
16.	Unhealthy food choices	4.6	4.4	4.8	4.4	+0.2	4.7	0.57	0.34	0.18, 0.48	0.44	0.29, 0.57
DHD2015-index score[2]		81.5	17.7	91.8	18.6	+10.2	16.0	**<0.001**	0.42	0.27, 0.55	0.60	0.47, 0.70

3d-FR, three day food records.

[1]The component coffee was not assessed in the 3d-FR.

[2]The total score ranges between 0 and 150 points (excluding coffee component).

Table 3b. Mean DHD2015-index scores derived from the 3d-FR and the Eetscore FFQ and corresponding validity statistics in 103 participants *after* BS (T6).

		3d-FR		Eetscore FFQ		Difference						
		Mean	SD	Mean	SD	Mean	SD	*P*-value	τb	95% CI	ρ	95% CI
1.	Vegetables	4.9	3.0	4.0	2.4	-1.0	3.0	**<0.01**	0.27	0.08, 0.44	0.39	0.21, 0.55
2.	Fruit	7.3	3.2	6.4	3.4	-0.9	2.8	**<0.01**	0.48	0.31, 0.62	0.60	0.45, 0.72
3.	Wholegrain products	4.4	3.0	6.9	3.0	+2.4	3.5	**<0.001**	0.24	0.05, 0.42	0.33	0.14, 0.50
4.	Legumes	1.4	3.5	5.5	4.2	+4.1	5.4	**<0.001**	0.07	-0.13, 0.26	0.08	-0.12, 0.27
5.	Nuts	3.0	4.0	4.9	3.5	+2.0	4.1	**<0.001**	0.32	0.13, 0.49	0.39	0.21, 0.55
6.	Dairy	6.2	3.7	6.7	3.5	+0.6	4.2	0.17	0.21	0.02, 0.39	0.27	0.08, 0.44
7.	Fish	2.3	3.7	5.9	3.5	+3.7	4.0	**<0.001**	0.30	0.11, 0.47	0.36	0.17, 0.52
8.	Tea	4.7	4.4	4.0	4.1	-0.7	3.5	0.06	0.53	0.36, 0.66	0.65	0.51, 0.76
9.	Fat and oils	4.9	4.6	6.2	4.4	+1.3	5.7	**0.02**	0.17	-0.03, 0.35	0.21	0.02, 0.39
10.	Coffee[1]	*NA*	*NA*	7.2	2.7	-	-	-	-	-	-	-
11.	Red meat	9.2	2.3	9.5	1.8	+0.2	2.6	0.34	0.16	-0.04, 0.34	0.17	-0.03, 0.35
12.	Processed meat	2.9	3.3	5.2	3.0	+2.3	4.0	**<0.001**	0.06	-0.14, 0.25	0.09	-0.11, 0.28
13.	Sweetened beverages	6.5	4.0	8.3	2.7	+1.9	4.0	**<0.001**	0.25	0.06, 0.43	0.31	0.12, 0.48
14.	Alcohol	9.9	1.0	9.6	1.7	-0.3	1.9	0.18	0.20	0.00, 0.38	0.20	0.00, 0.38
15.	Sodium	9.1	1.8	9.2	0.5	0.0	1.8	0.90	0.15	-0.05, 0.33	0.17	-0.03, 0.35
16.	Unhealthy food choices	6.6	4.0	8.3	3.0	+1.7	4.5	**<0.001**	0.33	0.14, 0.50	0.42	0.24, 0.57
DHD2015-index score[2]		83.4	17.2	100.8	14.2	+17.4	16.3	**<0.001**	0.31	0.12, 0.48	0.44	0.26, 0.59

3d-FR, three day food records.

[1]The component coffee was not assessed in the 3d-FR.

[2]The total score ranges between 0 and 150 points (excluding coffee component).

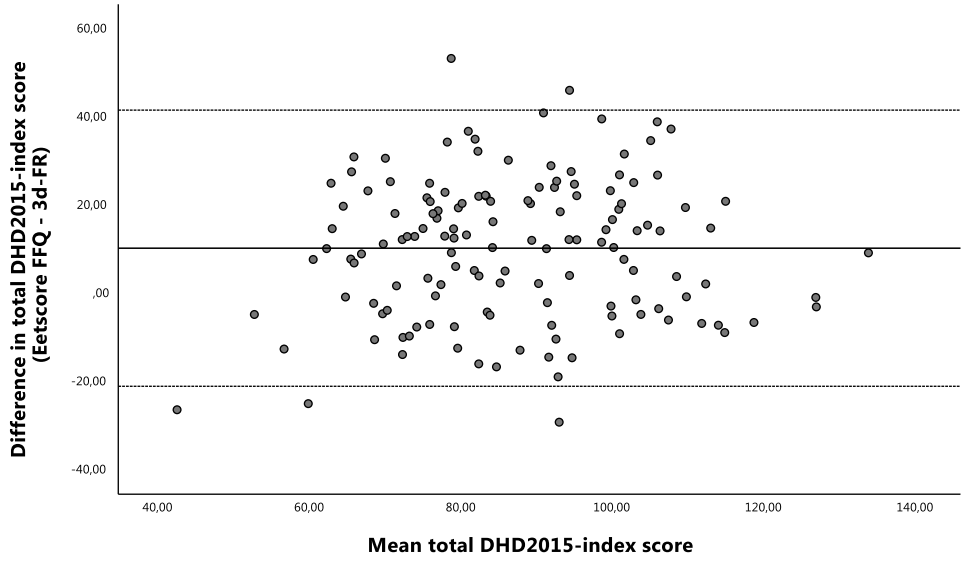


Figure 2a. Bland-Altman plot of the total DHD2015-index score derived from the Eetscore FFQ and 3d-FR at T0 (n=140). Middle line indicates the mean difference; upper and lower lines indicate limits of agreement based on mean difference ± 1.96×SD (10.2 ± 31.3).

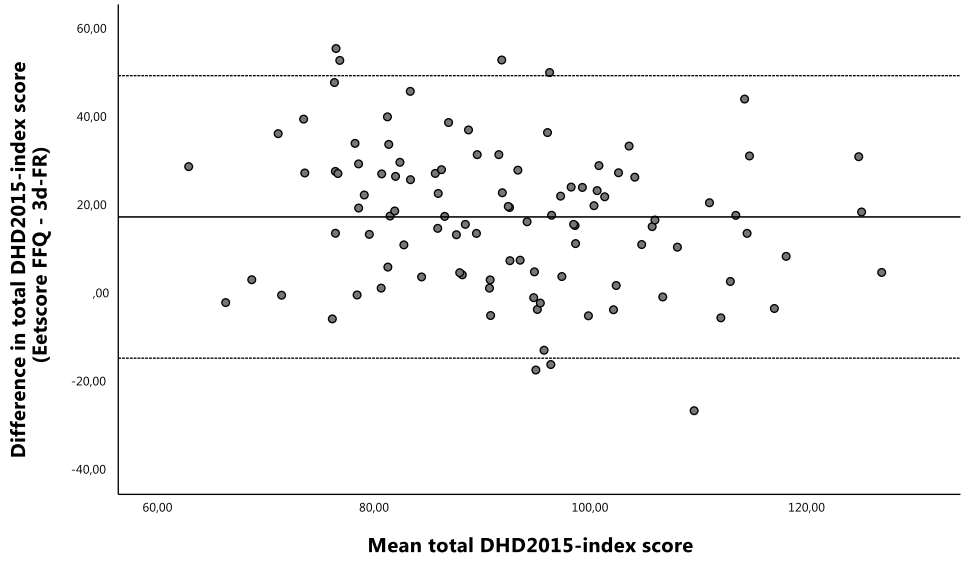


Figure 2b. Bland-Altman plot of the total DHD2015-index score derived from the Eetscore FFQ and 3d-FR at T6 (n=103). Middle line indicates the mean difference; upper and lower lines indicate limits of agreement based on mean difference ± 1.96×SD (17.4 ± 32.0).

Misreporting

According to the revised Goldberg cut-off method, 57.1% of the participants were classified as potential underreporters of energy intake at T0, and 58.3% of the participants at T6. We did not identify potential overreporters of energy intake. Excluding potential misreporters did not markedly affect our results regarding the relative validity of the Eetscore FFQ at both timepoints (**Supplementary Tables 2a, 2b)**.

Reproducibility of the Eetscore FFQ

Average time difference between completing the first and second Eetscore FFQ at T0 was 4.8 ± 2.3 weeks. Mean total DHD2015-index score was 100.4 ± 19.1 points for Eetscore FFQ1 and 103.3 ± 18.3 points for Eetscore FFQ2 (**Table 4**) with an ICC of 0.78 (95% CI: 0.69-0.84).

Index scores of the individual DHD components were fairly similar for most components, with ICCs ranging from 0.26-0.78. Good reproducibility (ICC 0.75-0.90) was observed for fruit (ICC=0.76, 95% CI: 0.67-0.83), fish (ICC=0.76, 95% CI: 0.68-0.83) and coffee (ICC=0.78, 95% CI: 0.70-0.84). Poor reproducibility (ICC <0.50) was observed for dairy (ICC=0.26, 95% CI: 0.08-0.42), red meat (ICC=0.29, 95% CI: 0.11-0.44), processed meat (ICC=0.43, 95% CI: 0.27-0.57), fats and oils (ICC=0.46, 95% CI: 0.30-0.59) and sweetened beverages (ICC=0.46, 95% CI: 0.30-0.59). ICCs of all other components ranged between 0.50 and 0.75 (**Table 4**).

Table 4. Mean DHD2015-index scores derived from the first and second Eetscore FFQ and corresponding intraclass correlation coefficients (ICC) in 116 participants *before* BS (T0).

		Eetscore FFQ1		Eetscore FFQ2			
		Mean	SD	Mean	SD	ICC	95% CI
1.	Vegetables	5.7	2.8	5.1	2.8	0.54	0.40, 0.66
2.	Fruit	6.0	3.5	6.5	3.3	0.76	0.67, 0.83
3.	Wholegrain products	7.2	2.8	7.6	2.7	0.70	0.59, 0.78
4.	Legumes	5.7	4.6	6.2	4.4	0.62	0.49, 0.72
5.	Nuts	4.3	3.7	4.1	3.5	0.71	0.61, 0.79
6.	Dairy	6.2	3.3	6.4	3.4	0.26	0.08, 0.42
7.	Fish	5.3	3.4	5.4	3.5	0.76	0.68, 0.83
8.	Tea	4.0	4.2	3.4	3.9	0.68	0.56, 0.76
9.	Fat and oils	7.2	4.2	6.5	4.4	0.46	0.30, 0.59
10.	Coffee	7.4	2.8	7.5	2.7	0.78	0.70, 0.84
11.	Red meat	8.8	2.5	9.0	2.4	0.29	0.11, 0.44
12.	Processed meat	3.3	3.1	3.7	3.3	0.43	0.27, 0.57
13.	Sweetened beverages	7.2	3.7	7.9	3.1	0.46	0.30, 0.59
14.	Alcohol	9.3	2.6	9.4	2.3	0.74	0.65, 0.82
15.	Sodium	8.0	2.4	8.5	1.9	0.55	0.41, 0.67
16.	Unhealthy food choices	4.9	4.3	6.2	4.2	0.60	0.45, 0.72
	DHD2015-index score[1]	100.4	19.1	103.3	18.3	0.78	0.69, 0.84

[1]The total score ranges between 0 and 160 points.

Discussion

In this study, we determined the relative validity and reproducibility of the Eetscore FFQ as a screener for diet quality in patients with (severe) obesity before and after BS by comparing index scores of the DHD2015-index derived from the Eetscore FFQ to the scores derived from 3d-FR (reference method). We demonstrated an overall reasonable relative agreement between the two methods, although the Eetscore FFQ showed higher index scores in comparison with the 3-FR and absolute agreement between the two methods was poor. Correlation coefficients for the DHD component scores varied widely with best coefficients observed for fruit and tea, and worst for legumes and red meat. Reproducibility of the Eetscore FFQ was considered good.

We observed lower correlations for the total DHD2015-index score based on 15 components (excluding coffee) between the Eetscore FFQ and 3d-FR than reported in the study of de Rijk et al., who compared the Eetscore FFQ to a full-length FFQ [15]. They reported a Kendall's tau-b coefficient of 0.51 (95% CI: 0.47-0.55) for the total DHD2015-index score based on 13 DHD components (excluding fish, fats and oils, and coffee). This could be explained by a difference in the number of DHD components included in the total score as well as by a difference in reference method. The Eetscore FFQ is an FFQ; therefore more correlated errors might be expected with a full-length FFQ, resulting in higher correlations. Yet, a full-length FFQ might capture habitual dietary intake more accurately than 3d-FR. Although all days of the week were equally represented across all records, foods that are not consumed on a daily basis, e.g. fish or legumes, could have been underestimated when recording only three days. This is also reflected in relative large absolute differences for these components. It has been suggested that when dietary methods assessing habitual dietary intake, such as the Eetscore FFQ, are validated against food records, a certain degree of disagreement can be expected due to the greater within-subject variations that occur over the shorter reference period of a food record [20]. In a study of Papadaki et al., a Pearson's correlation coefficient of 0.52 was observed comparing the English version of the 'Mediterranean Diet Adherence Screener' to 3d-FR in patients with high cardiovascular risk in the UK [30]. Schröder et al. found a Pearson's correlation coefficient of 0.61 when they compared the 'Diet Quality Index' derived from the 'Short Diet Quality Screener' to ten 24-h dietary recalls in a Spanish population [31]. In the same study, they also observed a correlation of 0.40 for the 'Modified Mediterranean Diet Score' derived from the 'Brief Mediterranean Diet Screener' compared with the score derived from ten 24-h dietary recalls [31]. These

values are comparable to the Spearman's Rho correlations observed in the current study (ρ=0.60, 95% CI: 0.47-0.70 at T0 and ρ=0.44, 95% CI: 0.26-0.59 at T6).
In contrast to the findings on relative agreement, absolute agreement between the Eetscore FFQ and the 3d-FR was poor. According to the Bland-Altman plots, the Eetscore FFQ systematically overestimated the total DHD2015-index score compared to the 3d-FR at both time points with relatively wide limits of agreement. However, no significant proportional bias was observed. This is in line with other studies that also found higher mean index scores derived from a diet screener in comparison with food records [15, 30-32]. As most FFQ's, the Eetscore FFQ can be considered more appropriate for ranking patients according to their diet quality or monitoring relative differences over time, rather than assessing absolute individual scores. It is however important to note that a food record is also no golden reference method and has its own limitations with regard to assessing dietary intake. Furthermore, we evaluated the intake of food groups instead of nutrients which is more difficult because of the high day-to-day variation. This may have impacted our findings with respect to the poor absolute agreement between the two methods.

With regard to the individual DHD components, correlations varied widely with highest values found for fruit and tea, and lowest values for legumes and red meat.
For legumes, we observed many participants with an extreme difference of 10 points between the index score derived from the Eetscore FFQ compared to the food record-derived score, meaning that these participants had a score of 10 for legumes according to the Eetscore FFQ, whereas their score was 0 based on the food records. This resulted in large mean differences for this component (4.9 ± 5.1 points at T0 and 4.1 ± 5.4 points at T6, $P<0.001$). This could be due to the fact that food records might not accurately capture habitual dietary intake, especially for foods that are not consumed on a daily basis such as legumes, as mentioned earlier. This is in accordance with an Australian study (age ≥ 70) validating a six-item dietary screener against three 24-h dietary recalls, that also observed a poor agreement for legume intake (k_w=0.12) [33].
For red meat, we observed poor correlations of <0.20 at both timepoints, whereas mean index scores for this component were fairly similar between the two methods (8.7 vs 8.9 points at T0 and 9.5 vs 9.2 points at T6, $P>0.05$). This might be explained by a low variation in the index scores for red meat. Over half of the participants scored 10 points based on the Eetscore FFQ as well as the 3-day food records. As a result, the few observations with (relatively) large differences in index score could have biased the correlation towards zero.

We also aimed to define participants who substantially under- or overreported their dietary intake by using the revised Goldberg cut-off method in which energy intake is compared with (estimated) energy expenditure. However, adequately estimating energy expenditure in subjects with (severe) obesity is challenging. In a study of Cancello et al. [26], predictive equations for resting energy expenditure were compared to indirect calorimetry in 4,247 subjects with obesity (69% women, mean age 48 ± 19 years, mean BMI 44 ± 7 kg/m^2). The authors found that the Mifflin-St Jeor equation had the highest performance for both accuracy and bias but emphasize that the accuracy was still far from ideal [26]. Furthermore, the revised Goldberg cut-off method cannot be applied after BS as the condition of weight stability is violated, resulting in an invalid ratio between reported energy intake and energy requirement. We therefore assumed that participants who were identified as potential misreporters of dietary intake at T0, also misreported their intake at T6. At both time points, the percentage of potential misreporters was relatively high with 57.1% of the study population potentially underreporting their dietary intake at T0, and 58.3% at T6. According to a review of Poslusna et al., the percentage of underreporters in studies using estimated food records ranged from 12 to 44% [34], which is lower than the observed percentages in the present study. This is in line with previous research showing that a higher BMI is associated with underreporting of dietary intake [35].
Overall, excluding potential misreporters did not markedly affect our results although caution is needed in this interpretation because of the aforementioned limitations in the use of the Goldberg cut-off method within this population.

Reproducibility of the Eetscore FFQ before surgery was considered good. Yet, the observed ICC of 0.78 was slightly lower than reported in previous research by de Rijk et al., who found an ICC of 0.91 for the total DHD2015-index score [15]. This could be due to a difference in study population as well as to the multidisciplinary lifestyle program that all participants started before undergoing BS. During this program, patients received general information on healthy eating behavior and dietary counseling. For most participants, the first Eetscore FFQ was administered before entering the multidisciplinary program while they completed the second Eetscore FFQ during the program. It is therefore plausible that participants already implemented beneficial changes with respect to their diet. This might explain the slightly higher DHD2015-index score resulting from the second Eetscore FFQ. Future studies are needed to confirm our findings while limiting the influence of such external factors.

For the individual DHD components, most correlation coefficients ranged between 0.5 and 0.7 which are common in reproducibility studies of FFQs [20].

Dietary assessment is an important component in the bariatric surgery program. Currently, dietary intake of patients undergoing BS is often assessed by a dietitian with the use of food records. This assessment method is very time-consuming, might be prone to reactivity and recall bias and only reflects the intake of the past days. The Eetscore FFQ is a short, web-based tool that can be used to assess general aspects of a healthy nutrient-dense diet such as the consumption of fruits and vegetables, wholegrains and dairy. However, the Eetscore FFQ does not include additional information on patients' eating behavior including the distribution of food intake (e.g. few large meals or frequent smaller feedings) and the separation of food and beverages. Also, other factors affecting dietary intake may be missed by the Eetscore FFQ, such as food preparation methods and non-included food items (e.g. plant-based dairy, meat substitutes and fast-food). The Eetscore FFQ can therefore be used as an additional dietary assessment tool in the bariatric surgery program rather than as a replacement for the current methodology.
Considering the need for dietary assessment methods that reduce the burden for patients, healthcare practitioners and researchers, the Eetscore FFQ can be used for ranking patients according to diet quality and for monitoring relative changes in intake over time in order to indicate an improvement or a deterioration in diet quality. This can be relevant before undergoing surgery, during annual follow-up in the late post-operative phase or in case of weight regain. Dietary assessment methods assessing actual intake may be preferred in the early post-operative phase when patients are still adapting to the new eating habits and in case of food-related complaints such as dumping syndrome or hypoglycemia.

The main strength of this study is the validation of an existing dietary assessment tool in patients with (severe) obesity before and after BS as there is a clear lack of validated, easy to use tools within this patient population. Another strength is the use of multiple statistical tests to provide a comprehensive insight into various facets of validity. As Kendall's tau-b correlation coefficients tend to be smaller, we also reported Spearman's Rho correlations to allow for comparison with other research. Furthermore, by choosing 3-day food records as reference method, we minimized the risk of correlated measurement errors between the two methods [20].

We aimed to determine relative validity of the Eetscore FFQ both before and after BS but 37 participants dropped out between T0 and T6, resulting in two different study populations. We are aware that the study population at T0 and T6 are therefore not mutually exclusive and direct comparisons between the populations cannot be made. Nonetheless, both populations as well as the drop-outs were similar with respect to sex, age, BMI, smoking status, education, physical activity, prevalence of comorbidities and type of surgery. Moreover, both the study population at T0 and T6 were found representative of the general Dutch bariatric patient population [36], indicating a minor risk of selection bias.

Another limitation is the lack of a golden standard reference method for dietary intake. To reduce participant burden, we chose for 3-day food records using household measures, which are prone to report bias and are not ideal for foods that are not consumed daily. For future research, we suggest to evaluate the Eetscore FFQ against dietary biomarkers that are suitable for patients after bariatric surgery to provide an objective measure of dietary intake.

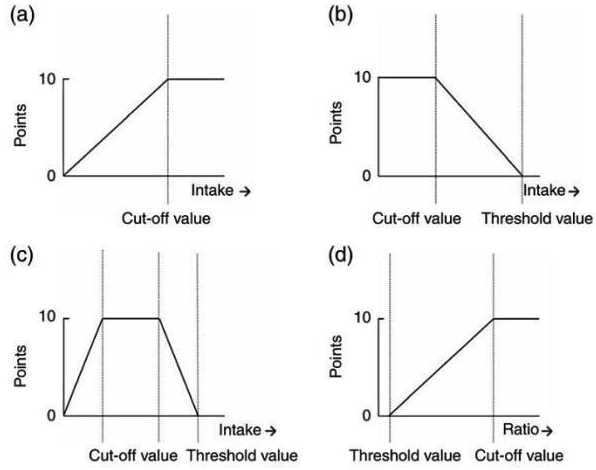
Conclusion

The Eetscore FFQ is a short screener for diet quality that assesses adherence to the Dutch food-based dietary guidelines. Based on our findings, the Eetscore FFQ was considered an acceptable screener for ranking individuals according to their diet quality and showed good reproducibility to monitor relative changes in diet quality over time. However, the tool showed poor absolute agreement and is not suitable for assessing diet quality on the individual level. Future research is needed to improve the use of the Eetscore FFQ for this purpose.

References

1. Gloy, VL, Briel, M, Bhatt, DL, et al., *Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials.* BMJ, 2013. **347**: p. f5934.
2. O'Brien, PE, Hindle, A, Brennan, L, et al., *Long-Term Outcomes After Bariatric Surgery: a Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding.* Obes Surg, 2019. **29**(1): p. 3-14.
3. Sjostrom, L, Peltonen, M, Jacobson, P, et al., *Bariatric surgery and long-term cardiovascular events.* JAMA, 2012. **307**(1): p. 56-65.
4. Fried, M, Yumuk, V, Oppert, JM, et al., *Interdisciplinary European guidelines on metabolic and bariatric surgery.* Obes Surg, 2014. **24**(1): p. 42-55.
5. Angrisani, L, Santonicola, A, Iovino, P, et al., *IFSO Worldwide Survey 2016: Primary, Endoluminal, and Revisional Procedures.* Obes Surg, 2018. **28**(12): p. 3783-3794.
6. Al-Najim, W, Docherty, NG and le Roux, CW, *Food Intake and Eating Behavior After Bariatric Surgery.* Physiol Rev, 2018. **98**(3): p. 1113-1141.
7. Freeman, RA, Overs, SE, Zarshenas, N, et al., *Food tolerance and diet quality following adjustable gastric banding, sleeve gastrectomy and Roux-en-Y gastric bypass.* Obes Res Clin Pract, 2014. **8**(2): p. e115-200.
8. Harbury, C, Collins, CE and Callister, R, *Diet quality is lower among adults with a BMI >/=40kgm(-2) or a history of weight loss surgery.* Obes Res Clin Pract, 2019. **13**(2): p. 197-204.
9. Harbury, CM, Verbruggen, EE, Callister, R, et al., *What do individuals with morbid obesity report as a usual dietary intake? A narrative review of available evidence.* Clin Nutr ESPEN, 2016. **13**: p. e15-e22.
10. Zarshenas, N, Tapsell, LC, Neale, EP, et al., *The Relationship Between Bariatric Surgery and Diet Quality: a Systematic Review.* Obes Surg, 2020. **30**(5): p. 1768-1792.
11. Freire, RH, Borges, MC, Alvarez-Leite, JI, et al., *Food quality, physical activity, and nutritional follow-up as determinant of weight regain after Roux-en-Y gastric bypass.* Nutrition, 2012. **28**(1): p. 53-58.
12. Lupoli, R, Lembo, E, Saldalamacchia, G, et al., *Bariatric surgery and long-term nutritional issues.* World J Diabetes, 2017. **8**(11): p. 464-474.
13. Looman, M, Feskens, EJ, de Rijk, M, et al., *Development and evaluation of the Dutch Healthy Diet index 2015.* Public Health Nutr, 2017. **20**(13): p. 2289-2299.
14. Kromhout, D, Spaaij, CJ, de Goede, J, et al., *The 2015 Dutch food-based dietary guidelines.* Eur J Clin Nutr, 2016. **70**(8): p. 869-878.
15. de Rijk, MG, Slotegraaf, AI, Brouwer-Brolsma, EM, et al., *Development and evaluation of a diet quality screener to assess adherence to the Dutch food-based dietary guidelines.* Br J Nutr, 2021: p. 1-28.
16. Legault, M, Leblanc, V, Marchand, GB, et al., *Evaluation of Dietary Assessment Tools Used in Bariatric Population.* Nutrients, 2021. **13**(7).
17. Baecke, JA, Burema, J and Frijters, JE, *A short questionnaire for the measurement of habitual physical activity in epidemiological studies.* Am J Clin Nutr, 1982. **36**(5): p. 936-942.
18. Brink, E, van Rossum, C, Postma-Smeets, A, et al., *Development of healthy and sustainable food-based dietary guidelines for the Netherlands.* Public Health Nutr, 2019. **22**(13): p. 2419-2435.
19. Van Rossum, CTM, Fransen, HP, Verkaik-Kloosterman, JV, et al., *Dutch National Food Consumption Survey 2007-2010. Diet of children and adults aged 7 to 69 years.* 2011, National Institute for Public Health and the Environment. Bilthoven.
20. Cade, J, Thompson, R, Burley, V, et al., *Development, validation and utilisation of food-frequency questionnaires - a review.* Public Health Nutr, 2002. **5**(4): p. 567-587.
21. *NEVO-online versie 2016/5.0*.

22. Lombard, MJ, Steyn, NP, Charlton, KE, et al., *Application and interpretation of multiple statistical tests to evaluate validity of dietary intake assessment methods.* Nutrition journal, 2015. **14**: p. 40.
23. Masson, LF, McNeill, G, Tomany, JO, et al., *Statistical approaches for assessing the relative validity of a food-frequency questionnaire: use of correlation coefficients and the kappa statistic.* Public Health Nutr, 2003. **6**(3): p. 313-321.
24. Black, AE, *Critical evaluation of energy intake using the Goldberg cut-off for energy intake:basal metabolic rate. A practical guide to its calculation, use and limitations.* Int J Obes Relat Metab Disord, 2000. **24**(9): p. 1119-1130.
25. Mifflin, MD, St Jeor, ST, Hill, LA, et al., *A new predictive equation for resting energy expenditure in healthy individuals.* Am J Clin Nutr, 1990. **51**(2): p. 241-247.
26. Cancello, R, Soranna, D, Brunani, A, et al., *Analysis of Predictive Equations for Estimating Resting Energy Expenditure in a Large Cohort of Morbidly Obese Patients.* Front Endocrinol (Lausanne), 2018. **9**: p. 367.
27. Frankenfield, D, Roth-Yousey, L and Compher, C, *Comparison of predictive equations for resting metabolic rate in healthy nonobese and obese adults: a systematic review.* J Am Diet Assoc, 2005. **105**(5): p. 775-789.
28. Madden, AM, Mulrooney, HM and Shah, S, *Estimation of energy expenditure using prediction equations in overweight and obese adults: a systematic review.* J Hum Nutr Diet, 2016. **29**(4): p. 458-476.
29. Koo, TK and Li, MY, *A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research.* J Chiropr Med, 2016. **15**(2): p. 155-163.
30. Papadaki, A, Johnson, L, Toumpakari, Z, et al., *Validation of the English Version of the 14-Item Mediterranean Diet Adherence Screener of the PREDIMED Study, in People at High Cardiovascular Risk in the UK.* Nutrients, 2018. **10**(2).
31. Schroder, H, Benitez Arciniega, A, Soler, C, et al., *Validity of two short screeners for diet quality in time-limited settings.* Public Health Nutr, 2012. **15**(4): p. 618-626.
32. Radd-Vagenas, S, Fiatarone Singh, MA, Inskip, M, et al., *Reliability and validity of a Mediterranean diet and culinary index (MediCul) tool in an older population with mild cognitive impairment.* Br J Nutr, 2018. **120**(10): p. 1189-1200.
33. Gadowski, AM, McCaffrey, TA, Heritier, S, et al., *Development, Relative Validity and Reproducibility of the Aus-SDS (Australian Short Dietary Screener) in Adults Aged 70 Years and Above.* Nutrients, 2020. **12**(5).
34. Poslusna, K, Ruprich, J, de Vries, JH, et al., *Misreporting of energy and micronutrient intake estimated by food records and 24 hour recalls, control and adjustment methods in practice.* Br J Nutr, 2009. **101 Suppl 2**: p. S73-85.
35. Trijsburg, L, Geelen, A, Hollman, PC, et al., *BMI was found to be a consistent determinant related to misreporting of energy, protein and potassium intake using self-report and duplicate portion methods.* Public Health Nutr, 2017. **20**(4): p. 598-607.
36. DICA, *DATO Bariatrische chirurgie - Jaarrapportage 2018*. 2018. https://dica.nl/jaarrapportage-2018/dato



Supplementary Figure 1. Graphic presentation of the scoring system for the different types of components: adequacy component (A), moderation component (B), optimum component (C) and ratio component. *Adapted from Looman et al.* [13].

Supplementary Table 1. Baseline characteristics of the study population at T6.

	Study population at T6 (n=103)	
Sex (female)	81	(78.6)
Age (years)	50.0	[41.0-56.0]
BMI (kg/m²)	41.6	[39.3-45.0]
Smoking status		
Never	61	(59.2)
Former	37	(35.9)
Current	5	(4.9)
Educational level[1]		
Low	16	(17.0)
Medium	61	(64.9)
High	17	(18.1)
Comorbidity		
None	52	(50.5)
Diabetes Mellitus type 2	18	(17.5)
Dyslipidemia	21	(20.4)
Hypertension	33	(32.0)
OSAS	18	(17.5)
Physical activity[2]	8.4	[7.1-8.9]
Adjustable gastric band in history	15	(14.6)

Data are presented as median [Q1-Q3] and frequency (valid percentage).

BMI, body mass index; *OSAS*, obstructive sleep apnea syndrome.

[1] Low education = primary education and prevocational secondary education; medium education = senior general secondary education, pre-university education and secondary vocational education; high education = higher vocational education and university. Missing for n=9.

[2] Based on Baecke questionnaire; total score ranging from 3-15. Missing for n=21.

Supplementary Table 2a. Mean DHD2015-index scores derived from the 3d-FR and the Eetscore FFQ and corresponding validity statistics in 60 participants before BS (T0). Potential underreporters of energy intake are excluded (n=80).

		3d-FR		Eetscore FFQ		Difference						
		Mean	SD	Mean	SD	Mean	SD	*P*-value	τb	95% CI	ρ	95% CI
1.	Vegetables	7.0	2.9	5.3	2.6	-1.7	3.4	**<0.001**	0.14	-0.12, 0.38	0.20	-0.06, 0.43
2.	Fruit	7.6	3.4	5.8	3.6	-1.9	3.2	**<0.001**	0.41	0.16, 0.61	0.51	0.28, 0.69
3.	Wholegrain products	5.4	2.9	6.8	2.9	+1.4	3.1	**<0.001**	0.35	0.10, 0.56	0.45	0.21, 0.64
4.	Legumes	0.7	2.5	5.5	4.5	+4.9	5.3	**<0.001**	-0.07	-0.32, 0.19	-0.08	-0.33, 0.18
5.	Nuts	2.1	3.7	4.2	3.6	+2.0	3.8	**<0.001**	0.39	0.14, 0.59	0.46	0.22, 0.65
6.	Dairy	6.5	3.3	6.2	3.3	-0.4	3.4	0.37	0.32	0.07, 0.54	0.43	0.19, 0.62
7.	Fish	1.9	3.6	5.3	3.2	+3.5	4.0	**<0.001**	0.29	0.03, 0.51	0.36	0.11, 0.57
8.	Tea	5.1	4.3	4.0	4.3	-1.0	3.9	**0.04**	0.52	0.29, 0.69	0.61	0.40, 0.76
9.	Fat and oils	6.0	4.5	6.5	4.4	+0.5	5.1	0.43	0.28	0.02, 0.50	0.34	0.09, 0.55
10.	Coffee[1]	*NA*	*NA*	7.4	2.8	-	-	-	-	-	-	-
11.	Red meat	8.6	3.0	8.4	3.3	-0.2	4.5	0.75	-0.04	-0.29, 0.22	-0.05	-0.30, 0.21
12.	Processed meat	1.4	2.9	3.0	2.9	+1.5	3.2	**<0.001**	0.32	0.07, 0.54	0.39	0.14, 0.59
13.	Sweetened beverages	5.9	4.2	7.1	3.8	+1.2	3.9	**0.02**	0.41	0.16, 0.61	0.50	0.27, 0.68
14.	Alcohol	9.1	2.7	9.1	2.4	0.0	2.2	0.90	0.58	0.36, 0.74	0.60	0.39, 0.75
15.	Sodium	5.9	3.3	7.2	3.0	+1.4	3.8	**0.01**	0.26	0.00, 0.49	0.33	0.08, 0.54
16.	Unhealthy food choices	3.3	4.2	3.4	4.3	+0.1	4.7	0.91	0.36	0.11, 0.57	0.44	0.20, 0.63
DHD2015-index score[2]		76.5	16.9	87.8	17.0	+11.3	15.8	**<0.001**	0.39	0.14, 0.59	0.57	0.35, 0.73

3d-FR, three day food records.

[1]The component coffee was not assessed in the 3d-FR.

[2]The total score ranges between 0 and 150 points (excluding coffee component).

Supplementary Table 2b. Mean DHD2015-index scores derived from the 3d-FR and the Eetscore FFQ and corresponding validity statistics in 43 participants after surgery (T6). Potential underreporters of energy intake are excluded (n=60).

		3d-FR		Eetscore FFQ		Difference						
		Mean	SD	Mean	SD	Mean	SD	*P*-value	τb	95% CI	ρ	95% CI
1.	Vegetables	5.0	3.1	4.0	2.4	-1.0	3.1	0.05	0.27	-0.04, 0.53	0.37	0.07, 0.61
2.	Fruit	7.7	2.8	6.8	3.3	-0.9	2.3	**0.01**	0.52	0.24, 0.72	0.64	0.40, 0.80
3.	Wholegrain products	4.6	2.9	7.3	3.3	+2.7	3.4	**<0.001**	0.28	-0.03, 0.54	0.39	0.09, 0.63
4.	Legumes	1.2	3.2	5.2	4.1	+4.1	5.2	**<0.001**	0.02	-0.28, 0.32	0.02	-0.28, 0.32
5.	Nuts	2.7	3.7	4.6	3.8	+1.8	4.4	**0.01**	0.23	-0.08, 0.50	0.28	-0.03, 0.54
6.	Dairy	6.6	3.5	6.9	3.2	+0.4	4.5	0.61	0.18	-0.13, 0.46	0.24	-0.07, 0.51
7.	Fish	2.7	3.9	5.8	3.3	+3.2	3.8	**<0.001**	0.37	0.07, 0.61	0.43	0.14, 0.65
8.	Tea	4.8	4.6	4.4	4.3	-0.4	2.8	0.32	0.65	0.41, 0.81	0.76	0.57, 0.87
9.	Fat and oils	4.8	4.5	6.0	4.4	+1.2	6.0	0.18	0.13	-0.18, 0.42	0.30	-0.01, 0.56
10.	Coffee[1]	*NA*	*NA*	7.3	2.5	-	-	-	-	-	-	-
11.	Red meat	9.2	2.5	9.7	1.3	+0.5	2.3	0.17	0.17	-0.14, 0.45	0.26	-0.05, 0.52
12.	Processed meat	2.4	3.3	4.8	2.6	+2.5	3.2	**<0.001**	0.22	-0.09, 0.49	0.31	0.00, 0.56
13.	Sweetened beverages	6.5	4.0	8.3	2.6	+1.7	4.1	**0.01**	0.26	-0.05, 0.52	0.29	-0.02, 0.55
14.	Alcohol	9.8	1.5	9.7	1.6	-0.1	2.2	0.75	-0.06	-0.35, 0.25	-0.06	-0.35, 0.25
15.	Sodium	8.6	2.3	9.2	0.5	+0.6	2.2	0.10	0.09	-0.22, 0.38	0.11	-0.20, 0.40
16.	Unhealthy food choices	4.8	4.2	8.1	2.9	+3.3	4.9	**<0.001**	0.22	-0.09, 0.49	0.29	-0.02, 0.55
DHD2015-index score[2]		81.2	17.6	100.8	13.6	+19.6	16.5	**<0.001**	0.28	-0.03, 0.54	0.40	0.10, 0.63

3d-FR, three day food records.

[1]The component coffee was not assessed in the 3d-FR.

[2]The total score ranges between 0 and 150 points (excluding coffee component).

PART B

Nutritional supplementation
after bariatric surgery

CHAPTER 4

The true story on deficiencies after sleeve gastrectomy: Results of a double-blind RCT

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Obesity Surgery, 2020; 30(4): 1280-1290

Abstract

Background: Since a few years, the laparoscopic sleeve gastrectomy (SG) has become the most performed bariatric operation worldwide. However, as with all bariatric procedures, SG also leads to vitamin and mineral deficiencies post-operatively and standard multivitamin supplements are probably not sufficient. The present study evaluates the effectiveness of a specialized multivitamin supplement for SG patients (WLS Optimum 1.0, FitForMe), compared to a standard multivitamin supplement (sMVS).

Methods: A double-blind randomized controlled trial was performed. For 12 months, patients in the intervention group received WLS Optimum, containing elevated doses of multiple vitamins and minerals. Patients in the control group were provided with sMVS, containing 100% of the recommended dietary allowance.

Results: In total, 139 patients were available for analysis (WLS Optimum; n=69, sMVS; n=70). Intention-to-treat analysis revealed more folic acid deficiencies and higher serum vitamin B1 levels in the WLS Optimum group. Per protocol analysis showed that in patients using WLS Optimum, serum folic acid and vitamin B1 levels were higher, serum PTH levels were lower, and only one patient (2.6%) was anemic compared to eleven patients (17.5%) using a sMVS ($P<0.05$ for all). No differences were found in prevalence of deficiencies for iron, vitamin B12, vitamin D and other micronutrients.

Conclusion: This optimized multivitamin supplement only affected serum levels of folic acid, PTH and vitamin B1, and anemia rates compared to a sMVS. There is a clear need to further optimize multivitamin supplementation for SG patients. Besides, non-compliance with multivitamin supplements remains an important issue that should be dealt with.

Introduction

Originally designed as the first step of a biliopancreatic diversion with duodenal switch, the sleeve gastrectomy (SG) was technically improved and implemented as a standalone procedure [1]. Since a few years, the laparoscopic SG has become the most performed bariatric operation worldwide [2]. It is considered to be an easy, quick and safe procedure [3] that provides significant weight loss and improvement of obesity-related comorbidities by reducing dietary intake and hormonal changes [3, 4].

Perhaps one of the reasons why the Roux-en-Y gastric bypass (RYGB) is no longer the preferred procedure for many surgeons, is because it is associated with vitamin and mineral deficiencies and lifelong use of supplements [5, 6]. Since the anatomy of the intestinal tract remains unaltered when performing a SG, the risk of developing deficiencies is theoretically considered lower [7]. Some authors even state that a SG has minimal impact on micronutrient status [3] and taking multivitamin supplements (MVS) for more than three months postoperatively is unnecessary [8]. However, short and midterm studies found that in SG patients, deficiencies are as common as in RYGB patients [9-12]. Especially deficiencies for iron, folic acid, vitamin B12 and vitamin D are frequently reported [7, 13-17]. Standard MVS are probably not sufficient to prevent nutritional deficiencies after SG. However, specific MVS that contain higher doses of vitamins and minerals were not available at the time of this study. Based on literature and studies performed in our hospital, a customized MVS for SG patients was developed (WLS Optimum 1.0, FitForMe, Rotterdam, the Netherlands). The present study evaluates the effectiveness of this SG-specific MVS compared to a standard MVS in a double-blind randomized controlled trial.

Methods

Study design

The present study was a double-blind randomized controlled trial. All patients who underwent a primary laparoscopic SG operation at Rijnstate Hospital Arnhem (RHA; >1200 bariatric procedures per year) between November 2011 and October 2014 were eligible for the study. Exclusion criteria were a secondary SG, creatinine >150 µmol/L, liver enzymes >2 times the upper limit, concomitant diseases (e.g. gastrointestinal diseases), psychiatric illness, use of drugs that affect bone metabolism and known pregnancy. The study was approved by the Medical Ethics Review Committee of the Radboud University Medical Centre and the Local Ethical Committee of RHA, and was conducted in concordance with the principles of the Declaration of Helsinki.

The study protocol was registered at the clinical trials registry of the National Institutes of Health (ClinicalTrials.gov; identifier NCT01609387). Included patients were randomized into two groups: the intervention group received the customized MVS for SG patients (WLS Optimum) and the control group received a standard MVS (sMVS).

Surgical procedure

A standardized operating technique was performed by three experienced bariatric surgeons (>500 procedures each). First, the greater omentum was dissected from the greater curvature of the stomach using Enseal® (Ethicon, Somerville USA). Then, the stomach and angle of His were mobilized, using a posterior approach. This was completed by dissection of the anterior part of the angle of His and small gastric vessels. Next, transection of the stomach was performed using lengthwise stapling along a 40 French calibration bougie positioned along the lesser curvature, starting four cm proximal of the pylorus until the cardia (Echelon FlexTM Powered Plus Stapler, Ethicon, Somerville USA). A bougie size of 40 Fr is associated with a significant lower leak rate and similar weight loss results compared to smaller bougie sizes [18, 19]. The remnant of the stomach was retrieved through an enlarged port incision in the left flank. This port was closed with Vicryl (Ethicon, Somerville USA) using a suture retriever. Finally, the skin was closed with staples.

Intervention and Control

WLS Optimum version 1.0 is a customized MVS for SG patients and contains high doses of multiple vitamins and minerals (**Table 1**). A sMVS, similar to a regular, over-the-counter MVS, served as a control and contained most micronutrients in a dose equivalent to 100% of the RDA. To prevent bias, both supplements had the exact same raw base compounds and cherry flavor, and were similar in color and size (**Figure 1**). Both supplements were dosed as one capsule per day.

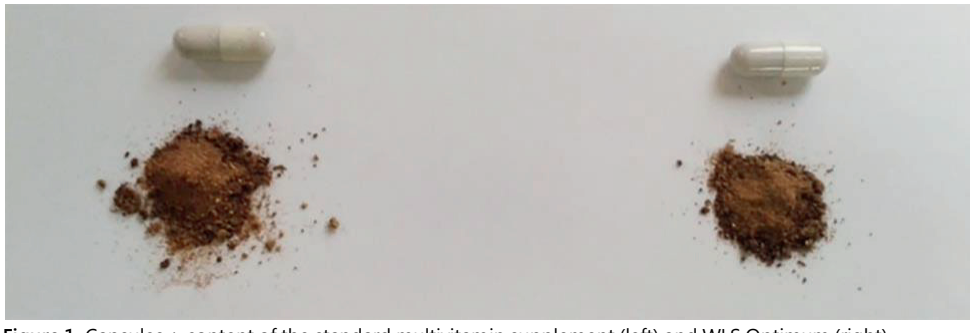

Figure 1. Capsules + content of the standard multivitamin supplement (left) and WLS Optimum (right).

Additional medication

All patients received fraxiparin (nadroparin, 0.6 mg/5700 IU daily) for six weeks and proton-pump inhibitors (omeprazole, 20 mg daily) for six months, as part of the standard postoperative protocol. All patients were additionally prescribed calcium/cholecalciferol (500 mg/800 IE) supplementation two times a day.

Table 1. Composition of the intervention and control supplement.

	sMVS		WLS Optimum	
Micronutrients	**Dose**	**RDA (%)**	**Dose**	**RDA (%)**
Vitamins				
Vitamin A, mg	0.60	75.0	1.00	125.0
Vitamin B1, mg	1.10	99.7	2.00	182.0
Vitamin B2, mg	1.40	100.0	2.00	143.0
Vitamin B3, mg	16.00	100.0	25.00	156.0
Vitamin B5, mg	6.00	100.0	9.00	150.0
Vitamin B6, mg	1.40	100.2	2.00	143.0
Biotin, µg	25.00	50.0	150.00	300.0
Folic acid, µg	200.00	100.0	300.00	150.0
Vitamin B12, µg	2.50	100.0	10.00	400.0
Vitamin C, mg	80.00	100.0	100.00	125.0
Vitamin D, µg	4.00	80.0	7.50	150.0
Vitamin E, mg	10.00	83.4	12.00	100.0
Vitamin K1, µg	25.00	33.3	90.00	120.0
Minerals				
Chrome, µg	40.00	100.0	40.00	100.0
Iron, mg	14.00	100.0	21.00	150.0
Iodine, µg	153.70	102.5	150.00	100.0
Copper, mg	1.00	100.0	1.00	100.0
Chloride, mg	0.14	0.0	0.00	0.0
Magnesium, mg	30.00	8.0	30.00	8.0
Calcium, mg	91.43	11.4	0.00	0.0
Manganese, mg	2.00	100.1	3.00	150.0
Molybdenum, µg	50.00	100.0	50.00	100.0
Selenium, µg	55.00	100.0	55.00	100.0
Zinc, mg	10.00	100.0	15.00	150.0

sMVS, standard multivitamin supplement; *RDA*, recommended daily allowance.

Randomization and blinding

The allocation sequence was computer generated, using a variable block schedule. Besides an independent pharmacist, no one had access to the randomization list to ensure allocation concealment. All supplements were packaged in nonmarked blisters with the same expiration date, each containing twelve capsules. The blisters were packaged in a nonmarked sealed box, and numbered according to the randomization list. After the last visit of the last study patient, the unblinded randomization list was available to the research team. No earlier unblinding occurred.

Data collection, follow-up and outcome

Standard laboratory blood tests were performed at baseline (T0), and six (T6) and twelve months (T12) after surgery. These included: hemoglobin, mean corpuscular volume (MCV), iron, ferritin, folic acid, vitamin B12, vitamin D, parathyroid hormone (PTH), calcium, magnesium, phosphate, albumin, vitamin B1 and B6, and zinc. Calcium levels were corrected for albumin using the following equation: Ca_{corr} = total calcium - (0.025 x albumin) + 1. Iron deficiency was the primary outcome measure. Secondary outcome measures included vitamin D and vitamin B12 deficiencies developed during the first twelve months after SG (reference values in tables).

Excess body weight loss (EWL) was calculated as [weight loss/excess weight based on ideal body weight at BMI 25 kg/m^2 x 100%]. Total body weight loss (TWL) was calculated as [weight loss/initial weight x 100%].

Correction of deficiencies

Preoperative vitamin B12 and vitamin D deficiencies were treated with predefined medication. If a deficiency occurred after surgery, it was recorded for the purpose of this study where after the deficiency was treated according to local protocol. After additional supplementation, subsequent data of the corresponding micronutrient were excluded to prevent biased estimates. Moreover, follow up measurements of patients who were pregnant at T6 and/or T12 were excluded from the analyses.

Sample size calculation and statistical analysis

Sample size calculation was performed using Openepi.com [20]. To detect a 25% reduction of iron deficiency at twelve months after surgery, with 95% sensitivity and a power of 90%, a minimum of 56 patients per group was required. Taking into account a 10% dropout rate and 15% of cases excluded because of iron deficiency diagnosed and treated at six months, this resulted in 75 patients per group.

An intention-to-treat analysis was used as the primary analysis. Additionally, a per protocol analysis was performed. Differences between groups at baseline, T6 and T12 were calculated using independent samples t-tests for continuous data and Chi-Square tests for categorical data (or Fisher's Exact test when >20% of expected counts were <5). Linear Mixed Models were used to assess if serum levels changed differently over time between the groups. Log transformations were performed to normalize the following data: serum levels of ferritin, PTH, vitamin B1 and vitamin B6.

All statistical analyses were performed using IBM SPSS Statistics 25 for Windows (IBM Corp., Armonk USA).

Results

Eleven patients were excluded from analysis because they underwent a RYGB (n=1), were pregnant during follow-up (n=1) or did not complete any of the follow-up measurements (n=9).

In total, 139 patients were available for analysis: 69 patients receiving WLS Optimum and 70 patients receiving sMVS. Both groups were similar at baseline with respect to age, gender, weight and BMI (**Table 2)**. The groups differed on the prevalence of dyslipidemia, which was three times higher in the sMVS group compared to the WLS Optimum group (14.3% vs 4.3%, *P*=0.047). In six patients (three in each group), a gastric band had to be removed before conversion to SG.

Table 2. Baseline characteristics of the study population.

	WLS Optimum (n=69)		**sMVS** (n=70)	
Age (years)	38.2	± 12.4	39.7	± 10.8
Gender (female)	51	(79.9)	54	(77.1)
Body weight before surgery (kg)	141.3	± 26.1	140.4	± 31.2
BMI before surgery (kg/m^2)	47.6	± 9.0	48.4	± 9.9
Adjustable gastric band in history	3	(4.3)	3	(4.3)
Comorbidities				
T2DM	9	(13.0)	7	(10.0)
Hypertension	15	(21.7)	19	(27.1)
Dyslipidemia	3	(4.3)	10	(14.3)*
OSAS	7	(10.1)	7	(10.0)

Data are presented as mean ± standard deviation and frequency (percentage).

sMVS, standard multivitamin supplement; *BMI*, body mass index; *T2DM*, type 2 diabetes mellitus; *OSAS*, obstructive sleep apnea syndrome.

* *P*<0.05.

Weight loss

The degree of weight loss after twelve months was similar in both groups. Mean BMI at T12 was 32.7 kg/m^2 in the WLS Optimum group and 33.8 kg/m^2 in the sMVS group. Furthermore, patients using WLS Optimum showed 70.5 ± 22.7 %EWL and 31.3 ± 8.6 %TWL compared to 68.5 ± 23.2 %EWL and 30.5 ± 8.4 %TWL for patients using sMVS (*P*> 0.05 for all).

Pre-operative deficiencies

The number of pre-operative deficiencies as well as mean serum levels at baseline were comparable between the groups (**Table 3, 4 and 5)**. Pre-operative deficiencies for vitamin D (76.1%), phosphate (34.1%) and albumin (12.2%) were most prevalent.

Post-operative deficiencies

Mean serum levels and prevalence of deficiencies regarding hemoglobin metabolism, calcium and vitamin D metabolism, and vitamin B1, B6 and zinc can be found in **Table 3, 4 and 5.**

At T6, mean serum vitamin B1 concentrations were significantly higher in patients using WLS Optimum compared to sMVS users (148.0 ± 27.6 nmol/L vs 134.8 ± 24.8 nmol/L, P=0.01). Mean serum concentrations of all other parameters were comparable between the groups at T6 and T12.

During the study, significantly more patients in the WLS Optimum group were deficient for folic acid compared to the sMVS group (10 patients, 14.5% versus 2 patients, 2.9%; P=0.02). No differences were found in the prevalence of anemia, and deficiencies for iron, vitamin B12, vitamin D and other micronutrients.

Elevated serum vitamin B1 and B6 levels were found in 11 (18.0%) and 20 patients (32.8%) using WLS Optimum, and 5 (7.9%) and 13 patients (20.6%) using sMVS (P>0.05). For PTH, elevated serum levels tended to be more frequent in the sMVS group (11 patients, 15.7%) compared to the WLS Optimum group (4 patients, 5.8%), but this difference was not statistically significant (P=0.06).

Compliance

Of the 69 patients in the intervention group, only 44 patients (63.8%) reported to use the WLS Optimum supplement after six months. This number decreased to 38 patients (55.1%) after 12 months. The main reported reason for discontinuation was nausea. Most patients switched to an over-the-counter MVS. Others did not tolerate any MVS and therefore stopped using multivitamin supplementation. Based on self-reported compliance, the total group of patients was re-divided into WLS Optimum users and sMVS-users. Results are shown in **Table 6.**

At T6 and T12, mean serum folic acid concentrations were significantly higher in patients using WLS Optimum compared to patients using a sMVS (T6: 24.1 ± 8.7 mmol/L vs 20.2 ± 7.0 mmol/L, T12: 24.4 ± 10.3 mmol/L vs 19.6 ± 6.6 mmol/L, P<0.05 for both). Mean serum vitamin B1 concentrations were still higher at T6 for WLS Optimum users than sMVS users (150.2 ± 27.6 nmol/L vs 137.9 ± 23.3, P=0.03). At 12 months, mean serum PTH levels were significantly lower in the group using WLS Optimum compared to the group using a sMVS (3.2 ± 1.7 pmol/L vs 4.0 ± 2.1 pmol/L, P=0.03).

During the study, only one patient (2.6%) using WLS Optimum was anemic compared to eleven of the patients (17.5%) using a sMVS (P=0.03). No significant differences were found for other micronutrients.

Table 3. Mean serum concentrations and prevalence of anemia, and deficiencies for iron, folic acid and vitamin B12.

Serum variables (reference values)	Type MVS	Serum levels				Deficiencies		
		T0	T6	T12	Δ (T12-T0)	T0	T6	T12
Hemoglobin	**WLS Optimum**	8.7 ± 0.8	8.6 ± 0.8	8.4 ± 0.7	-0.2 ± 0.6	4 (5.8)	3 (4.5)	7 (10.6)
(M: 8.4-10.8 mmol/L	(n=69/67/66)							
F: 7.4-9.9 mmol/L)	**sMVS**	8.8 ± 0.7	8.7 ± 0.8	8.5 ± 0.7	-0.3 ± 0.5	4 (5.8)	6 (9.0)	7 (10.9)
	(n=69/67/64)							
MCV	**WLS Optimum**	88.7 ± 4.1	90.5 ± 3.3	91.8 ± 4.4	+3.2 ± 4.2	1 (1.5)	0 (0.0)	0 (0.0)
(80-100 fL)	(n=68/67/66)							
	sMVS	88.9 ± 4.7	90.6 ± 4.8	91.7 ± 4.7	+2.7 ± 2.9	2 (2.9)	1 (1.5)	1 (1.6)
	(n=68/67/64)							
Iron	**WLS Optimum**	10.8 ± 4.4	13.7 ± 4.2	15.1 ± 5.3	+4.6 ± 5.6	18 (29.5)	7 (14.6)	7 (12.7)
(9-31 µmol/L)	(n=61/48/55)							
	sMVS	11.0 ± 4.7	14.1 ± 5.2	16.1 ± 7.0	+4.9 ± 6.2	24 (35.8)	8 (14.0)	3 (5.9)
	(n=67/57/51)							
Ferritin	**WLS Optimum**	127.6 ± 96.4	149.0 ± 114.0	139.4 ± 104.7	+8.1 ± 55.4	2 (2.9)	0 (0.0)	2 (3.1)
(20-300 ng/mL)	(n=69/53/65)							
	sMVS	128.8 ± 97.7	133.1 ± 73.6	129.1 ± 74.5	-3.0 ± 78.6	3 (4.3)	4 (6.8)	3 (4.7)
	(n=70/59/64)							
Folic acid	**WLS Optimum**	16.6 ± 6.7	22.3 ± 9.5	21.8 ± 10.0	+5.1 ± 9.2	2 (2.9)	5 (7.6)	5 (7.6)
(9.1-36 nmol/L)	(n=68/66/66)							
	sMVS	16.7 ± 6.0	19.8 ± 6.9	19.2 ± 6.7	+2.7 ± 7.3	4 (5.8)	0 (0.0)	2 (3.1)
	(n=69/66/65)							
Vitamin B12	**WLS Optimum**	289.8 ± 96.4	276.1 ± 84.6	267.3 ± 80.0	-32.9 ± 76.2	1 (1.5)	11 (21.2)	15 (25.4)
(200-570 pmol/L)[1]	(n=67/52/59)							
	sMVS	315.9 ± 110.1	291.7 ± 92.3	284.4 ± 85.7	-34.2 ± 91.1	0 (0.0)	11 (18.3)	14 (22.2)
	(n=70/60/63)							

Data are presented as mean ± standard deviation and frequency (percentage).

MVS, multivitamin supplement; s*MVS,* standard multivitamin supplement; *MCV,* mean corpuscular volume.

[1] Reference range before surgery (T0) was 145-570 pmol/L.

P>0.05 for all outcomes.

Table 4. Mean serum concentrations and prevalence of deficiencies for vitamin D, calcium, magnesium and phosphate.

Serum variables (reference values)	Type MVS	Serum levels				Deficiencies		
		T0	T6	T12	Δ (T12-T0)	T0	T6	T12
Vitamin D	**WLS Optimum**	36.6 ± 21.8	86.7 ± 27.6	84.5 ± 32.3	+48.8 ± 29.0	51 (73.9)	5 (7.6)	7 (10.9)
(>50 nmol/L)	(n=69/66/64)							
	sMVS	34.0 ± 16.7	93.8 ± 36.8	89.7 ± 28.8	+55.6 ± 28.9	54 (77.1)	4 (6.0)	4 (6.2)
	(n=70/67/65)							
PTH	**WLS Optimum**	3.7 ± 2.0	3.4 ± 1.6	3.5 ± 1.9	-0.3 ± 2.1	1 (1.4)	2 (3.0)	2 (3.1)
(1.3-6.8 pmol/L)	(n=69/66/65)							
	sMVS	4.0 ± 2.5	3.8 ± 1.9	4.0 ± 2.3	-0.1 ± 2.6	4 (5.7)	5 (7.4)	0 (0.0)
	(n=70/68/65)							
Calcium[1]	**WLS Optimum**	2.35 ± 0.11	2.40 ± 0.08	2.40 ± 0.08	+0.05 ± 0.11	1 (1.6)	0 (0.0)	0 (0.0)
(2.10-2.55 mmol/L)	(n=62/65/65)							
	sMVS	2.35 ± 0.09	2.39 ± 0.08	2.38 ± 0.07	+0.03 ± 0.10	0 (0.0)	0 (0.0)	0 (0.0)
	(n=68/68/65)							
Magnesium	**WLS Optimum**	0.80 ± 0.07	0.82 ± 0.05	0.83 ± 0.06	+0.03 ± 0.07	3 (4.8)	1 (2.5)	1 (2.3)
(0.70-1.10 mmol/L)	(n=63/40/43)							
	sMVS	0.80 ± 0.06	0.83 ± 0.05	0.83 ± 0.04	+0.03 ± 0.06	3 (4.5)	0 (0.0)	0 (0.0)
	(n=67/45/43)							
Phosphate	**WLS Optimum**	0.95 ± 0.18	1.01 ± 0.15	1.02 ± 0.20	+0.07 ± 0.20	22 (35.5)	10 (20.4)	10 (18.2)
(0.87-1.45 mmol/L)	(n=62/49/55)							
	sMVS	0.93 ± 0.16	0.95 ± 0.15	1.02 ± 0.15	+0.07 ± 0.23	22 (32.8)	14 (24.6)	7 (13.7)
	(n=67/57/51)							
Albumin	**WLS Optimum**	37.8 ± 3.8	38.8 ± 3.4	38.5 ± 3.2	+1.0 ± 3.5	9 (14.3)	6 (9.2)	8 (12.3)
(35-50 g/L)	(n=63/65/65)							
	sMVS	37.8 ± 2.6	39.0 ± 3.0	38.8 ± 2.7	+1.0 ± 3.0	7 (10.3)	5 (7.4)	3 (4.6)
	(n=68/68/65)							

Data are presented as mean ± standard deviation and frequency (percentage).

MVS, multivitamin supplement; s*MVS,* standard multivitamin supplement; *PTH,* parathyroid hormone.

[1] Corrected for albumin levels (total calcium – (0.025 x albumin) + 1).

P>0.05 for all outcomes.

Table 5. Mean serum concentrations and prevalence of deficiencies for vitamin B1 and B6, and zinc.

Serum variables (reference values)	Type MVS	Serum levels				Deficiencies		
		T0	T6	T12	Δ (T12-T0)	T0	T6	T12
Vitamin B1	**WLS Optimum**	167.8 ± 29.5	148.0 ± 27.6*	145.4 ± 29.8	-19.3 ± 40.6	0 (0.0)	1 (2.0)	2 (3.7)
(95-175 nmol/L)	(n=61/49/54)							
	sMVS	162.3 ± 31.1	134.8 ± 24.8	144.1 ± 44.1	-17.2 ± 45.1	1 (1.5)	4 (7.3)	2 (3.8)
	(n=67/55/52)							
Vitamin B6	**WLS Optimum**	79.3 ± 24.0	91.7 ± 36.1	82.9 ± 27.3	+3.1 ± 26.6	0 (0.0)	0 (0.0)	0 (0.0)
(25-100 nmol/L)	(n=61/49/54)							
	sMVS	75.3 ± 29.5	88.1 ± 63.0	78.2 ± 25.9	+5.9 ± 30.8	0 (0.0)	0 (0.0)	0 (0.0)
	(n=66/55/51)							
Zinc	**WLS Optimum**	12.2 ± 1.6	11.7 ± 1.6	11.7 ± 1.9	-0.4 ± 2.2	1 (1.6)	3 (6.3)	2 (3.8)
(9.2-18.4 µmol/L)	(n=61/48/53)							
	sMVS	12.2 ± 2.0	12.1 ± 1.9	11.8 ± 1.7	-0.8 ± 2.2	4 (6.1)	2 (3.5)	4 (8.2)
	(n=66/57/49)							

Data are presented as mean ± standard deviation and frequency (percentage).

MVS, multivitamin supplement; s*MVS,* standard multivitamin supplement.

*$P<0.05$ for WLS Optimum vs sMVS.

Table 6. Results of the per protocol analysis.

Serum variables (reference values)	Type MVS	Serum levels			Deficiencies	
		T6	T12	Δ (T12-T0)	T6	T12
Hemoglobin (M: 8.4-10.8, F: 7.4-9.9 mmol/L)	**WLS Optimum** (n=44/38)	8.7 ± 0.7	8.5 ± 0.6	-0.3 ± 0.7	0 (0.0)	1 (2.6)
	sMVS (n=66/62)	8.7 ± 0.8	8.5 ± 0.7	-0.2 ± 0.5	5 (8.2)	8 (12.9)
Ferritin (20-300 ng/mL)	**WLS Optimum** (n=37/37)	148.3 ± 116.4	150.0 ± 116.5	+2.7 ± 60.3	0 (0.0)	1 (2.7)
	sMVS (n=56/62)	136.3 ± 74.2	130.5 ± 75.9	-3.6 ± 80.1	2 (3.6)	2 (3.2)
Folic acid (9.1-36 nmol/L)	**WLS Optimum** (n=44/38	24.1 ± 8.7*	24.4 ± 10.3*	+6.8 ± 9.7*	0 (0.0)	1 (2.6)
	sMVS (n=65/63)	20.2 ± 7.0	19.6 ± 6.6	+2.4 ± 7.1	0 (0.0)	3 (4.8)
Vitamin B12 (200-570 pmol/L)	**WLS Optimum** (n=36/33)	278.9 ± 90.0	277.5 ± 77.8	-25.3 ± 83.2	8 (22.2)	7 (21.2)
	sMVS (n=57/61)	300.0 ± 88.8	286.0 ± 87.6	-29.3 ± 83.7	8 (14.0)	14 (23.0)
Vitamin D (>50 nmol/L)	**WLS Optimum** (n=44/37)	87.4 ± 25.2	88.0 ± 28.4	+48.2 ± 28.2	1 (2.3)	2 (5.4)
	sMVS (n=66/62)	91.6 ± 32.8	86.9 ± 27.7	+53.8 ± 25.5	4 (6.1)	5 (8.1)
PTH (1.3-6.8 pmol/L)	**WLS Optimum** (n=44/37)	3.1 ± 1.4	3.2 ± 1.7*	-0.3 ± 1.9	2 (4.5)	1 (2.7)
	sMVS (n=67/63)	3.7 ± 1.7	4.0 ± 2.1	-0.1 ± 2.7	4 (6.0)	0 (0.0)
Vitamin B1 (95-175 nmol/L)	**WLS Optimum** (n=36/33)	150.2 ± 27.6*	146.9 ± 33.2	-21.0 ± 46.6	0 (0.0)	2 (6.1)
	sMVS (n=50/49)	137.9 ± 23.3	146.2 ± 44.4	-14.0 ± 43.9	2 (4.0)	1 (2.0)

Table 6. Results of the per protocol analysis. *(continued).*

Serum variables (reference values)	Type MVS	Serum levels			Deficiencies	
		T6	T12	Δ (T12-T0)	T6	T12
Zinc (9.2-18.4 µmol/L)	**WLS Optimum** (n=35/33)	11.9 ± 1.7	11.8 ± 2.0	-0.2 ± 2.2	2 (5.7)	0 (0.0)
	sMVS (n=52/46)	12.1 ± 1.8	11.7 ± 1.5	-0.7 ± 2.3	1 (1.9)	2 (4.3)

Data are presented as mean ± standard deviation and frequency (percentage).

MVS, multivitamin supplement; s*MVS,* standard multivitamin supplement; *PTH,* parathyroid hormone.

Information about compliance was missing for 17 patients at T6 and 23 patients at T12. These patients were excluded from analysis for that time point. Non-users of multivitamin supplements were also excluded.

*$P<0.05$ for WLS Optimum vs sMVS.

Discussion

The present study demonstrated that the specialized multivitamin supplement WLS Optimum 1.0 had no clear advantages over standard multivitamin supplementation as it was not associated with fewer micronutrient deficiencies after SG. Therefore, the content of this first version of WLS Optimum should be further optimized. More importantly, the present study illustrates that nutritional deficiencies are highly prevalent after SG, despite the anatomy of the intestinal tract remaining unaltered. There are several factors that put patients at risk for developing nutritional deficiencies after SG, including reduced food intake, decreased hydrochloric acid and intrinsic factor secretion, vomiting, poor food choices and food intolerances [7, 21]. Yet, some believe that SG has minimal impact on nutrient status [3] and that maintenance of MVS more than three months postoperatively seems to be of no benefit [8]. According to Ruiz-Tovar et al., once a patient is able to eat all kinds of food, additional vitamin and mineral supplementation can be discontinued [8]. In the present study, about three-quarters of the patients showed at least one micronutrient deficiency during the first year after SG, despite the use of multivitamin supplements. In view of our findings, a specialized multivitamin supplement for SG patients should at least contain higher doses of elementary iron, vitamin B12, vitamin D, vitamin B1 and zinc to prevent nutritional deficiencies post-operatively.

In total, 17 patients (12%) were anemic during the study. Additionally, three patients (2%) had iron deficiency anemia. This is in line with the prospective cohort study of Hakeam et al., who also found a low prevalence of iron deficiency anemia (1.6%) one year after SG [22]. In contrast, Abdulrahman and colleagues reported that 36% of their patients developed iron deficiency anemia [23]. However, this study likely used serum iron concentrations to define iron deficiency anemia as they did not report on ferritin levels. Post-bariatric anemia is in most cases due to iron deficiency, along with vitamin B12 deficiency as a secondary cause [5]. We observed iron deficiency, expressed as low serum ferritin levels, in seven patients (5%). After surgery, reduced secretion of HCl, use of proton-pump inhibitors (PPI) and faster gastric emptying may limit absorption [13, 14, 21, 24]. Besides low absorption, reduced oral intake and intolerances to iron rich foods such as red meat might also be a cause of iron deficiency post-SG [14, 21]. The dose of 21 mg elementary iron in WLS Optimum should be increased to prevent iron deficiencies after SG. Yet, considering the low number of deficiencies observed in the present study, the recommendation of 45-60 mg for supplementation according to the guidelines of The American Society for Metabolic & Bariatric Surgery (ASMBS) [25] is probably overestimated and increasing the dose of iron to 28 mg might already be sufficient.

Occurrence of vitamin B12 deficiency after SG is mainly due to the reduction of HCl and intrinsic factor as a consequence of the surgical procedure, which is even more pronounced with PPI intake [14, 26]. In the present study, a marked decrease in mean serum vitamin B12 concentrations over the first year post-operatively was found in both groups, indicating that the dose of 10 µg vitamin B12 in the WLS Optimum supplement was insufficient. In the study of Al-Mutawa and colleagues, patients were prescribed additional B-complex tablets for 1-3 months, including 200 µg vitamin B12 (next to 100 mg vitamin B1 and 200 mg vitamin B6) [14]. This high dose of vitamin B12 (8400% RDA) significantly improved serum vitamin B12 concentrations during the early post-operative period in comparison to baseline. Thereafter, patients continued with a daily multivitamin supplement that provided only 1 µg (42% RDA) of vitamin B12, which was insufficient to prevent deficiencies [14]. These findings indicate that SG-specific MVS do not need to contain more than 200 µg of vitamin B12 to prevent deficiencies. This is not in line with the ASMBS recommendation of 350-500 µg per day [25]. This is probably because they do not make a distinction between the different types of procedures.

Vitamin D deficiency was the most prevalent micronutrient deficiency at baseline (76%). During the study, 10% of the patients was deficient. This is not in line with other studies, reporting between 16-89% of patients being deficient [7, 27, 28]. Next to supplementation and monitoring post-surgery, the improvement in vitamin D status is probably due to our preoperative supplementation protocol. According to the systematic review of Dix et al., only three of the seventeen included studies used additional supplementation to improve vitamin D status before SG [27]. Prevalence rates of post-operative vitamin D deficiencies in studies using a preoperative treatment protocol ranged from 14% to 36% [9, 15, 17, 29], being closer to our observation.
Calcium and magnesium deficiencies were rare during the first year post-SG, but low levels of phosphate were found more frequently. Hypophosphatemia is usually due to vitamin D deficiency [30]. However, because of the low prevalence of vitamin D deficiencies, we could not confirm this in the present study. Nevertheless, the dose of vitamin D in a SG-specific supplement should be increased to the levels advised for RYGB patients by the ASMBS (75 µg per day) to improve post-operative phosphate levels [25].

Vitamin B1 deficiencies are not commonly reported after SG, probably because they are not routinely measured. We found lowered vitamin B1 levels in nine patients (7%) throughout the study period, but none showed clinical symptoms. This is completely different compared to RYGB patients in whom such deficiencies hardly occur [7, 8].

Theoretically, this could be explained by the higher risk of minimized intake and vomiting after SG compared to RYGB. When thiamin levels are below the adequate level, this can result in serious cardiovascular and neurologic consequences such as Wernicke's encephalopathy (WE) and beriberi [31, 32]. Risk factors known to cause post-bariatric WE include alcohol consumption, vomiting and rapid weight loss, but poor compliance with vitamin supplementation is also an important predisposing factor [28, 32, 33]. For non-vomiting patients, the dose of thiamin required to prevent deficiencies after SG should be increased from 2 mg to ±3 mg. In our opinion, the recommendation of 12 mg per day by the ASMBS [25] is thus highly overestimated.

As with thiamin, only a few studies have evaluated zinc status after bariatric surgery, mainly focusing on one type of surgery (RYGB). In the present study, prevalence of zinc deficiency was 13%, which is quite low compared to the wide range of 5–39% described in the available literature [12, 17, 34-36]. It is suggested that initially, zinc deficiency may be caused by malabsorption and protein malnutrition [35]. In our study, the only marker for protein status was albumin. About half of the patients that were deficient for zinc also had low albumin levels, and at twelve months serum zinc levels were significantly correlated with serum albumin levels ($r=0.496$). Other factors associated with zinc deficiency include a reduction of gastric HCl limiting zinc absorption, and inadequate intake of dietary zinc because of intolerance to foods rich in zinc such as red meat [35, 37]. The dose of 15 mg zinc in WLS Optimum was not sufficient to prevent deficiencies. However, this dose was already higher than the recommendation of 8-11 mg per day according to the ASMBS [25]. For SG patients, recommendations should be increased to at least the levels advised for RYGB patients (8-11 mg/day to 16-22 mg/day).

Some patients showed elevated serum levels of vitamin B1 (13%) and vitamin B6 (27%) throughout the study period. For both vitamins, excess cases were more prevalent than deficient ones. Complications of high doses of vitamin B1 are rare as the body can excrete excess amounts of thiamin in the urine [13, 31]. However, elevated serum levels of vitamin B6 can cause neuropathic symptoms [38]. Despite the higher dose of vitamin B6 in WLS Optimum (143% RDA) compared to the sMVS (100% RDA), no difference in prevalence of elevated levels was found between the two groups. In three patients, extremely high serum levels (>200 nmol/L) of vitamin B6 were found. Clinical manifestations of vitamin toxicity have not been actively investigated in the present study. Consequently, it is difficult to ascertain whether the observed elevated levels are clinically relevant. High serum vitamin B6 levels can also occur due to over-use of vitamin

supplements. As serum folic acid concentrations rapidly increase after intake [39], these concentrations can be used as a marker for compliance of MVS intake in countries where it is not a food additive. In our study, serum vitamin B6 levels were significantly correlated with serum folic acid levels at 12 months (r=0.494).

The present study has some limitations, especially the relatively high number of incompliant patients which most likely led to underpowering. Even when provided free of charge, about one third of the patients were not compliant to the assigned supplement protocol. With respect to product optimization, this finding is very important as it indicates that this version of WLS Optimum was probably not well tolerated. In addition, information on compliance was subjective (collected via questionnaires and medical files) and incomplete which might have led to an overestimation of compliant patients. Yet, comparing self-reported intake to blister counting in a previous study showed that the majority of the patients are honest in their self-reports. Besides, presuming that serum folic acid levels can serve as a marker for compliance, the absence of folic acid deficiencies in the per protocol analysis implies that these patients were indeed compliant. Furthermore, only preoperative deficiencies for vitamin B12 and vitamin D were treated. Not correcting for all preoperative deficiencies could have affected our findings regarding the efficacy of both multivitamin supplements in relation to the observed nutritional status. Despite these limitations, we believe that we can draw important conclusions about nutritional status of the investigated micronutrients after SG and the need for long-term nutritional follow-up and maintenance of routine multivitamin supplementation.

Conclusion

This randomized controlled study showed that nutritional deficiencies are prevalent after sleeve gastrectomy. Despite the fact that the specialized multivitamin supplement contained higher doses of multiple vitamins and minerals, it only significantly affected serum levels of folic acid, PTH and vitamin B1, and anemia rates compared to a standard MVS. This indicates that there is a clear need to further optimize multivitamin supplementation for SG patients. These supplements should contain higher doses of elementary iron, folic acid, vitamin B12, vitamin D, vitamin B1 and zinc to prevent deficiencies post-operatively. However, caution is needed to prevent over supplementation as we found that most of the recommended doses for supplementation according to the ASMBS guidelines might be overestimated. Besides, non-compliance with multivitamin supplementation was frequently encountered. More

research is needed to identify which factors affect (non-)compliance and how this can be improved.

References

1. Nguyen, NT, Nguyen, B, Gebhart, A, et al., *Changes in the makeup of bariatric surgery: a national increase in use of laparoscopic sleeve gastrectomy.* J Am Coll Surg, 2013. **216**(2): p. 252-257.
2. Higa, K, Himpens, J, Welbourn, R, et al., *Third IFSO Global Registry Report*, in *IFSO Global Registry*, The International Federation for the Surgery of Obesity and Metabolic Disorders, Editor. 2017: Oxfordshire, United Kingdom. p. 74.
3. Kehagias, I, Zygomalas, A, Karavias, D, et al., *Sleeve gastrectomy: have we finally found the holy grail of bariatric surgery? A review of the literature.* Eur Rev Med Pharmacol Sci, 2016. **20**(23): p. 4930-4942.
4. Juodeikis, Z and Brimas, G, *Long-term results after sleeve gastrectomy: A systematic review.* Surg Obes Relat Dis, 2017. **13**(4): p. 693-699.
5. Lupoli, R, Lembo, E, Saldalamacchia, G, et al., *Bariatric surgery and long-term nutritional issues.* World J Diabetes, 2017. **8**(11): p. 464-474.
6. Weng, TC, Chang, CH, Dong, YH, et al., *Anaemia and related nutrient deficiencies after Roux-en-Y gastric bypass surgery: a systematic review and meta-analysis.* BMJ Open, 2015. **5**(7): p. e006964.
7. Ben-Porat, T, Elazary, R, Goldenshluger, A, et al., *Nutritional deficiencies four years after laparoscopic sleeve gastrectomy-are supplements required for a lifetime?* Surg Obes Relat Dis, 2017. **13**(7): p. 1138-1
8. Ruiz-Tovar, J, Llavero, C, Zubiaga, L, et al., *Maintenance of Multivitamin Supplements After Sleeve Gastrectomy.* Obes Surg, 2016. **26**(10): p. 2324-2330.
9. Coupaye, M, Riviere, P, Breuil, MC, et al., *Comparison of nutritional status during the first year after sleeve gastrectomy and Roux-en-Y gastric bypass.* Obes Surg, 2014. **24**(2): p. 276-283.
10. Guan, B, Yang, J, Chen, Y, et al., *Nutritional Deficiencies in Chinese Patients Undergoing Gastric Bypass and Sleeve Gastrectomy: Prevalence and Predictors.* Obes Surg, 2018. **28**(9): p.2727-2736.
11. Kwon, Y, Kim, HJ, Lo Menzo, E, et al., *Anemia, iron and vitamin B12 deficiencies after sleeve gastrectomy compared to Roux-en-Y gastric bypass: a meta-analysis.* Surg Obes Relat Dis, 2014. **10**(4): p. 589-597.
12. Moize, V, Andreu, A, Flores, L, et al., *Long-term dietary intake and nutritional deficiencies following sleeve gastrectomy or Roux-En-Y gastric bypass in a mediterranean population.* J Acad Nutr Diet, 2013. **113**(3): p. 400-410.
13. Aarts, EO, Janssen, IM and Berends, FJ, *The gastric sleeve: losing weight as fast as micronutrients?* Obes Surg, 2011. **21**(2): p. 207-211.
14. Al-Mutawa, A, Al-Sabah, S, Anderson, AK, et al., *Evaluation of Nutritional Status Post Laparoscopic Sleeve Gastrectomy—5-Year Outcomes.* Obes Surg, 2017. **28**(6): p. 1473-1483.
15. Caron, M, Hould, FS, Lescelleur, O, et al., *Long-term nutritional impact of sleeve gastrectomy.* Surg Obes Relat Dis, 2017. **13**(10): p. 1664-1673.
16. Kikkas, EM, Sillakivi, T, Suumann, J, et al., *Five-Year Outcome of Laparoscopic Sleeve Gastrectomy, Resolution of Comorbidities, and Risk for Cumulative Nutritional Deficiencies.* Scand J Surg, 2019. **108**(1): p. 10-16
17. van Rutte, PW, Aarts, EO, Smulders, JF, et al., *Nutrient deficiencies before and after sleeve gastrectomy.* Obes Surg, 2014. **24**(10): p. 1639-1646.
18. Parikh, M, Issa, R, McCrillis, A, et al., *Surgical strategies that may decrease leak after laparoscopic sleeve gastrectomy: a systematic review and meta-analysis of 9991 cases.* Ann Surg, 2013. **257**(2): p. 231-237.

19. Yuval, JB, Mintz, Y, Cohen, MJ, et al., *The effects of bougie caliber on leaks and excess weight loss following laparoscopic sleeve gastrectomy. Is there an ideal bougie size?* Obes Surg, 2013. **23**(10): p. 1685-1691.
20. Dean, A, G., Sullivan, KM and Soe, MM. *OpenEpi Version 3.0.1: Open Source Epidemiologic Statistics for Public Health*. Apr 6, 2013; Available from: www.OpenEpi.com.
21. Steenackers, N, Van der Schueren, B, Mertens, A, et al., *Iron deficiency after bariatric surgery: what is the real problem?* Proc Nutr Soc, 2018. **77**(4): p. 445-455.
22. Hakeam, HA, O'Regan, PJ, Salem, AM, et al., *Impact of laparoscopic sleeve gastrectomy on iron indices: 1 year follow-up.* Obes Surg, 2009. **19**(11): p. 1491-1496.
23. Al-Mulhim, AS, *Laparoscopic Sleeve Gastrectomy and Nutrient Deficiencies: A Prospective Study.* Surg Laparosc Endosc Percutan Tech, 2016. **26**(3): p. 208-211.
24. Sioka, E, Tzovaras, G, Perivoliotis, K, et al., *Impact of Laparoscopic Sleeve Gastrectomy on Gastrointestinal Motility.* Gastroenterol Res Pract, 2018. **2018**: p. 4135813.
25. Parrott, J, Frank, L, Rabena, R, et al., *American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients.* Surg Obes Relat Dis, 2017. **13**(5): p. 727-741.
26. Lam, JR, Schneider, JL, Zhao, W, et al., *Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency.* JAMA, 2013. **310**(22): p. 2435-2442.
27. Dix, CF, Bauer, JD and Wright, OR, *A Systematic Review: Vitamin D Status and Sleeve Gastrectomy.* Obes Surg, 2017. **27**(1): p. 215-225.
28. Pellitero, S, Martinez, E, Puig, R, et al., *Evaluation of Vitamin and Trace Element Requirements after Sleeve Gastrectomy at Long Term.* Obes Surg, 2017. **27**(7): p. 1674-1682.
29. Zarshenas, N, Nacher, M, Loi, KW, et al., *Investigating Nutritional Deficiencies in a Group of Patients 3 Years Post Laparoscopic Sleeve Gastrectomy.* Obes Surg, 2016. **26**(12): p. 2936-2943.
30. Mechanick, JI, Youdim, A, Jones, DB, et al., *Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery.* Obesity, 2013. **21 Suppl 1**: p. S1-27.
31. Kerns, JC and Gutierrez, JL, *Thiamin.* Adv Nutr, 2017. **8**(2): p. 395-397.
32. Schimpke, S and Guerron, AD, *Prevalence and predictors of postoperative thiamine deficiency after vertical sleeve gastrectomy.* Surg Obes Relat Dis, 2018. **14**(7): p. 950-951.
33. Milone, M, Velotti, N and Musella, M, *Wernicke Encephalopathy Following Laparoscopic Sleeve Gastrectomy-a Call to Evaluate Thiamine Deficiencies After Restrictive Bariatric Procedures.* Obes Surg, 2018. **28**(3): p. 852-853.
34. Gehrer, S, Kern, B, Peters, T, et al., *Fewer nutrient deficiencies after laparoscopic sleeve gastrectomy (LSG) than after laparoscopic Roux-Y-gastric bypass (LRYGB)-a prospective study.* Obes Surg, 2010. **20**(4): p. 447-453.
35. Salle, A, Demarsy, D, Poirier, AL, et al., *Zinc deficiency: a frequent and underestimated complication after bariatric surgery.* Obes Surg, 2010. **20**(12): p. 1660-1670.
36. Saif, T, Strain, GW, Dakin, G, et al., *Evaluation of nutrient status after laparoscopic sleeve gastrectomy 1, 3, and 5 years after surgery.* Surg Obes Relat Dis, 2012. **8**(5): p. 542-547.
37. Livingstone,C. *Zinc: physiology, deficiency and parenteral nutrition.*Nutr Clin Pract,2015.**30**(3):p.371-82
38. Alsabah, A, Al Sabah, S, Al-Sabah, S, et al., *Investigating Factors Involved in Post Laparoscopic Sleeve Gastrectomy (LSG) Neuropathy.* Obes Surg, 2017. **27**(5): p. 1271-1276.
39. Navarro, M and Wood, RJ, *Plasma Changes in Micronutrients Following a Multivitamin and Mineral Supplement in Healthy Adults.* J Am Coll Nutr, 2003. **22**(2): p. 124-132.

CHAPTER 5

Optimizing multivitamin supplementation for sleeve gastrectomy patients

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Obesity Surgery, 2021; 31(6): 2520-2528

Abstract

Background: Micronutrient deficiencies are frequently reported after sleeve gastrectomy (SG), and therefore lifelong daily multivitamin supplementation is highly recommended. Based on literature and the results of a previous randomized controlled trial, a specialized multivitamin supplement for SG patients was further optimized (WLS Optimum 2.0, FitForMe). The present study reports on its short-term effectiveness.

Methods: An open-label study was performed in which 76 patients were included to receive WLS Optimum 2.0 for 12 months (Opt 2.0 group). This group was compared to a group of 75 patients that had received WLS Optimum 1.0 for 12 months during a previous study (Opt 1.0 group).

Results: Intention-to-treat analysis (Opt 1.0, n=69 vs Opt 2.0, n=75) showed higher serum levels of vitamin B12, vitamin B6 and zinc, and a lower prevalence of deficiencies for vitamin B12 and phosphate in the Opt 2.0 group. MCV and serum folic acid levels were higher in the Opt 1.0 group. Over the 12-month study period, mean increase in serum levels of phosphate, vitamin B6 and zinc was higher in the Opt 2.0 group, and MCV and serum vitamin D levels increased more in the Opt 1.0 group.

Conclusion: The present study showed that the use of a specialized multivitamin supplement for SG patients is effective at preventing deficiencies for many vitamins and minerals, specifically in compliant patients. However, a strict follow-up regime remains necessary to monitor nutritional status and to improve patient compliance.

Introduction

The laparoscopic sleeve gastrectomy (SG) is currently the most commonly performed bariatric procedure worldwide [1]. Whereas the impact of more malabsorptive procedures such as the Roux-en-Y gastric bypass (RYGB) on nutritional status is well known, the occurrence of nutritional deficiencies after SG is often underestimated [2-4]. After SG, there are several factors that put patients at risk for developing nutritional deficiencies, including reduced dietary intake, decreased hydrochloric acid and intrinsic factor secretion, poor food choices and food intolerances [5, 6]. Although prevalence estimates vary widely, micronutrient deficiencies including vitamin D (5-89%), vitamin B12 (9-26%) and iron (12-43%), and elevated parathyroid hormone levels (PTH; 14-39%) have been frequently reported in the first year post-SG [7-11]. To prevent patients from developing these micronutrient deficiencies, lifelong daily multivitamin supplementation is highly recommended [12].

A customized multivitamin supplement with elevated doses of vitamins and minerals, specifically designed for SG patients was introduced (WLS Optimum 1.0; FitForMe, Rotterdam, the Netherlands). In a double-blind randomized controlled trial (RCT) [13], WLS Optimum 1.0 has shown to be effective in reducing the prevalence of anemia and improving serum levels of folic acid, PTH and vitamin B1 in comparison to a standard, over-the-counter multivitamin supplement [13]. No differences were found for the prevalence of deficiencies for iron, vitamin B12, vitamin D and other micronutrients. Based on these findings, the composition of WLS Optimum 1.0 was further optimized by elevating the levels of elementary iron, folic acid, vitamin B12, vitamin B1, copper and zinc. The present study reports on the short-term effectiveness (≤ 12 months) of WLS Optimum 2.0 in comparison to its previous version, WLS Optimum 1.0.

Methods

Study design

The present study combines data of two prospective studies, i.e. the VITAAL I study and the VITAAL II study. The VITAAL I study was a double-blind RCT, in which included patients received either WLS Optimum 1.0 (intervention group) or a standard, over-the-counter multivitamin supplement (sMVS, control group) for 12 months [13]. All 75 patients who received WLS Optimum 1.0 were included in this study (Opt 1.0 group). During the VITAAL II study, 76 new patients were recruited to receive WLS Optimum 2.0 for 12 months (Opt 2.0 group). Exclusion criteria were creatinine >150 µmol/L, systemic diseases that affect the gastrointestinal tract, psychiatric illness, use of drugs that affect

bone metabolism and known pregnancy during the study period. All SG procedures were performed by experienced bariatric surgeons, using the standardized operating technique as described earlier [13]. Both study protocols were approved by the Medical Ethics Review Committee of Radboud University Medical Centre and the Local Ethical Committee of Rijnstate Hospital Arnhem, and were conducted in concordance with the principles of the Declaration of Helsinki. The initial RCT was registered at the clinical trials registry of the National Institutes of Health (ClinicalTrials.gov; NCT01609387).

WLS Optimum

WLS Optimum is a customized MVS for SG and contains elevated doses of multiple vitamins and minerals. The contents of WLS Optimum 1.0 and 2.0 are shown in **Table 1**. Both supplements were similar in color and size. They had the exact same raw base compounds and cherry flavored capsule. In comparison to its previous version, WLS Optimum 2.0 contained higher levels of elementary iron, folic acid, vitamin B12, vitamin B1, copper and zinc, and a lower level of vitamin A. For both supplements, patients were instructed to take one capsule per day, starting from the day of surgery. Instructions on intake were given before surgery and at all medical checkups postoperatively.

Table 1. Composition of WLS Optimum 1.0 and WLS Optimum 2.0.

	WLS Optimum 1.0		WLS Optimum 2.0	
Micronutrients	**Dose**	**RDA (%)**	**Dose**	**RDA (%)**
Vitamins				
Vitamin A, mg	1.00	125.0	0.80	100.0
Vitamin B1, mg	2.00	182.0	2.75	250.0
Vitamin B2, mg	2.00	143.0	2.00	143.0
Vitamin B3, mg	25.00	156.0	25.00	156.0
Vitamin B5, mg	9.00	150.0	9.00	150.0
Vitamin B6, mg	2.00	143.0	2.00	143.0
Biotin, µg	150.00	300.0	150.00	300.0
Folic acid, µg	300.00	150.0	500.00	250.0
Vitamin B12, µg	10.00	400.0	100.00	4000.0
Vitamin C, mg	100.00	125.0	100.00	125.0
Vitamin D, µg	7.50	150.0	7.50	150.0
Vitamin E, mg	12.00	100.0	12.00	100.0
Vitamin K1, µg	90.00	120.0		
Minerals				
Chrome, µg	40.00	100.0	40.00	100.0
Iron, mg	21.00	150.0	28.00	200.0
Iodine, µg	150.00	100.0	150.00	100.0
Copper, mg	1.00	100.0	1.90	190.0
Magnesium, mg	30.00	8.0		
Manganese, mg	3.00	150.0	3.00	150.0
Molybdenum, µg	50.00	100.0	50.00	100.0
Selenium, µg	55.00	100.0	55.00	100.0
Zinc, mg	15.00	150.0	28.00	280.0

RDA, recommended daily allowance.

In addition, patients were instructed to take calcium/cholecalciferol (500 mg/800 IE) supplementation two times a day as part of the standard post-SG treatment protocol.

Data collection

All patients visited the hospital for standard laboratory blood tests and anthropometric measurements during regular visits before surgery (T0) and at 6 months (T6) and 12 months (T12) after surgery. Blood was collected by venipuncture. The following blood parameters were measured on random access analyzers: hemoglobin, mean corpuscular volume (MCV; XN-10 Sysmex); ferritin, folic acid, vitamin B12, 25-OH vitamin D and PTH (Modular E170, Roche) and calcium, magnesium, phosphate and albumin (Modular P800, Roche). Calcium levels were corrected for albumin using the following equation: Ca_{corr} = total calcium – (0.025 x albumin) + 1. Vitamin B1 and vitamin B6 were analyzed on a high-performance liquid chromatography with fluorescence detector (Shimadzu). Zinc was analyzed by inductively coupled plasma mass spectrometry (Shimadzu).

A deficiency was defined as a serum level below the local reference value (reference values in tables). Serum ferritin levels were used for the diagnosis of iron deficiency. Preoperative vitamin B12 and vitamin D deficiencies were treated with predefined medication. In case of a deficiency after surgery, treatment was performed according to local protocol as described earlier [14]. Subsequent data of the corresponding parameter were excluded. Weight loss was expressed as excess body weight loss (EWL) and total body weight loss (TWL). EWL was calculated as [weight loss/excess weight based on ideal body weight at BMI 25 kg/m^2 x 100%]. TWL was calculated as [weight loss/initial weight x 100%].

Statistical analysis

General characteristics of the Opt 1.0 and Opt 2.0 group were compared using independent samples t-tests for continuous data and Chi-Square tests for categorical data (or Fisher's Exact test when >20% of expected counts were <5).

Serum levels of ferritin, folic acid, PTH, vitamin B1 and vitamin B6 were transformed to natural logarithms before analysis. Differences in mean serum levels at T6 and T12 were tested using one-way analysis of covariance (ANCOVA) with baseline serum level as covariate. Analyses of vitamin B12 and vitamin D were not corrected by baseline serum level as baseline deficiencies were treated before surgery. Linear Mixed Models were used to assess if serum levels changed differently over time between the groups.

The number of deficiencies between the groups at T6 and T12 were compared using Chi-Square tests (or Fisher's Exact test when >20% of expected counts were <5).

Follow up measurements of patients who became pregnant or underwent revisional surgery were excluded from analysis. Intention-to-treat (ITT) analysis was performed as the primary analysis. Additionally, a per-protocol (PP) analysis was performed, excluding all patients who reported to not use the assigned supplement.
All statistical analyses were performed using IBM SPSS Statistics 25 for Windows (IBM Corp., Armonk USA).

Results

The total study population consisted of 151 patients. Seven patients were excluded because they did not complete any of the follow-up measurements during the 12-month study period. In total, 144 patients were available for the ITT analysis: 69 patients receiving Optimum 1.0 (Opt 1.0 group) and 75 patients receiving Optimum 2.0 (Opt 2.0 group). For the PP analysis, 44 patients (63.8%) reported to use Optimum 1.0 and 50 patients reported to use Optimum 2.0 (66.7%) at T6. At T12, these numbers decreased to 38 (55.1%) and 41 patients (54.7%), respectively. General characteristics of patients in the Opt 1.0 and Opt 2.0 group are shown in **Table 2**.

Table 2. General characteristics of the study population.

	Optimum 1.0 (n=69)		**Optimum 2 .0** (n=75)	
Age (years)	38.2	± 12.4	38.1	± 12.9
Gender (female)	51	(73.9)	58	(77.3)
Body weight before surgery (kg)	141.3	± 26.1	140.5	± 28.2
BMI before surgery (kg/m^2)	47.6	± 9.0	47.1	± 7.9
Adjustable gastric band in history	3	(4.3)	6	(8.0)
Comorbidities				
T2DM	9	(13.0)	9	(12.0)
Hypertension	15	(21.7)	22	(29.3)
Dyslipidemia	3	(4.3)	8	(10.7)
OSAS	7	(10.1)	8	(10.7)
BMI at 12 months after surgery (kg/m^2)	32.7	± 7.2	31.9	± 6.3
EWL at 12 months after surgery (%)	70.5	± 22.7	72.2	± 20.6
TWL at 12 months after surgery (%)	31.3	± 8.6	32.1	± 8.7

Data are presented as mean ± standard deviation and frequency (percentage).
BMI, body mass index; *T2DM*, type 2 diabetes mellitus; *OSAS*, obstructive sleep apnea syndrome; *EWL*, excess body weight loss; *TWL*, total body weight loss.
P>0.05 for all outcomes.

Both groups were similar with respect to age (38.2 ± 12.4 years vs 38.1 ± 12.9 years), gender (73.9% vs 77.3% female), preoperative body weight (141.3 ± 26.1 kg vs 140.5 ± 28.2 kg) and BMI (47.6 ± 9.0 kg/m^2 vs 47.1 ± 7.9 kg/m^2), and comorbidities (*P*>0.05 for all). In nine patients, a gastric band was removed before conversion to SG (4.3% vs 8.0%).

The degree of body weight loss after twelve months was similar for patients in the Opt 1.0 group and the Opt 2.0 group with a mean BMI of 32.7 ± 7.2 kg/m^2 vs 31.9 ± 6.3 kg/m^2, EWL of 70.5 ± 22.7% vs 72.2 ± 20.6% and TWL of 31.3 ± 8.6% vs 32.1 ± 8.7%, respectively (P>0.05 for all). The use of medication known to cause drug-nutrient interactions at T12 (e.g. proton-pump inhibitors, metformin) was also comparable between the groups (28.8% vs 34.4%).

Hemoglobin Metabolism

Mean serum concentrations and prevalence of anemia, and deficiencies for iron, folic acid and vitamin B12 can be found in **Table 3**. At baseline, mean serum concentrations and prevalence of pre-operative deficiencies were similar between the groups.

MCV increased over time in the Opt 1.0 group but not in the Opt 2.0 group (+3.2 ± 4.2 fL vs +0.9 ± 3.4 fL, P=0.002), resulting in a significantly lower MCV in the Opt 2.0 group at T12 (89.8 ± 4.0 fL vs 91.8 ± 4.4 fL, P<0.001).

At T6, mean serum folic acid concentration was also lower in the Opt 2.0 group than in the Opt 1.0 group (18.3 ± 10.1 nmol/L vs 22.3 ± 9.5 nmol/L, P=0.047). This difference was no longer present at T12 (19.7 ± 13.4 nmol/L vs 21.8 ± 10.0 nmol/L, P=0.15). The prevalence of folic acid deficiencies did not differ between the groups during the study period.

Mean serum vitamin B12 concentrations were higher in the Opt 2.0 group compared to the Opt 1.0 group at both T6 (310.8 ± 94.6 pmol/L vs 276.1 ± 84.6 pmol/L, P=0.04), and T12 (302.4 ± 93.2 pmol/L vs 267.3 ± 80.0 pmol/L, P=0.03). At T12, the prevalence of vitamin B12 deficiencies was also lower in the Opt 2.0 group (10.5% vs 25.4%, P=0.04). Over time, serum vitamin B12 levels increased in the Opt 2.0 group while they decreased in the Opt 1.0 group, but this difference was not statistically significant (+5.5 ± 103.7 pmol/L vs -32.9 ± 76.2 pmol/L, P=0.18).

No significant differences were observed between the groups for hemoglobin and ferritin. In the PP analysis, only the observed differences for MCV and serum vitamin B12 level at T12 were statistically significant (**Supplementary Table 1**).

Calcium and Vitamin D Metabolism

Mean serum concentrations and prevalence of deficiencies for vitamin D, calcium, magnesium and phosphate can be found in **Table 4**.

At baseline, mean serum vitamin D level was higher in the Opt 2.0 group than in the Opt 1.0 group (55.8 ± 24.7 nmol/L vs 36.6 ± 21.8 nmol/L, P<0.001), and the prevalence of vitamin D deficiencies was also lower in this group (respectively 38.7% vs 73.9%,

P<0.001). Over time, mean increase in serum vitamin D level was lower in Opt 2.0 group than in the Opt 1.0 group (+28.6 ± 23.4 nmol/L vs +48.8 ± 29.0 nmol/L, *P*<0.001), and the differences in vitamin D serum levels and deficiencies were no longer present at T6 and T12.

Although mean serum phosphate level was lower in the Opt 2.0 group compared to the Opt 1.0 group at baseline (0.85 ± 0.16 mmol/L vs 0.95 ±0.18 mmol/L, *P*=0.002), the prevalence of phosphate deficiencies at T6 was lower in the Opt 2.0 group (4.8% vs 20.4%, *P*=0.03). At T12, this prevalence was 3.7% vs 18.2% (*P*=0.09). Over time, mean increase in phosphate level was higher in the Opt 2.0 group than in the Opt 1.0 group (+0.17 ± 0.25 mmol/L vs +0.07 ± 0.20 mmol/L, *P*=0.003).

The ITT analysis demonstrated no differences for PTH, calcium, magnesium and albumin between both groups. In contrast, the PP analysis showed significantly different changes in serum levels of PTH, calcium and albumin between the two groups over the study period (**Supplementary Table 2**). Mean increase in serum level was higher in the Opt 2.0 group than in the Opt 1.0 group for PTH (+0.5 ± 1.4 pmol/L vs -0.3 ± 1.9 pmol/L, *P*=0.01) and calcium (+0.06 ± 0.09 mmol/L vs +0.05 ± 0.11 mmol/L, *P*=0.04) but lower for albumin (-0.03 ± 2.6 g/L vs +1.3 ± 3.0 g/L, *P*=0.02).

Vitamin B1, vitamin B6 and zinc

Mean serum levels and prevalence of deficiencies regarding vitamin B1, vitamin B6 and zinc can be found in **Table 5**.

Mean change in serum vitamin B6 level was greater in the Opt 2.0 group than in the Opt 1.0 group (+25.7 ± 29.7 nmol/L vs +3.1 ± 26.6 nmol/L, *P*=0.01), resulting in a significantly higher mean serum vitamin B6 level in the first group at T12 (99.8 ± 31.7 nmol/L vs 82.9 ± 27.3 nmol/L, *P*=0.01).

Mean baseline serum zinc level was lower in the Opt 2.0 group compared to the Opt 1.0 group (11.2 ± 2.3 µmol/L vs 12.2 ± 1.6 µmol/L, *P*=0.003), and the prevalence of zinc deficiencies at baseline was also higher in this group (respectively 17.1% vs 1.6%, *P*=0.003). In spite of the lower level at baseline, at T6 mean serum zinc level was higher in the Opt 2.0 group than in the Opt 1.0 group (12.9 ± 2.2 µmol/L vs 11.7 ± 1.6 µmol/L, *P*=0.003).). Over time, zinc levels increased in the Opt 2.0 group but decreased in the Opt 1.0 group (+1.3 ± 3.9 µmol/L vs -0.4 ± 2.2 µmol/L, *P*<0.001). The prevalence of zinc deficiencies at T6 and T12 did not differ between the groups.

No significant differences were observed for vitamin B1. Results of the PP analysis were similar to the results of the ITT analysis (**Supplementary Table 3**).

Table 3 . Mean serum concentrations and prevalence of anemia, and deficiencies for iron, folic acid and vitamin B12.

Serum variables (reference values)	Type MVS	Serum levels				Deficiencies		
		T0	T6	T12	Δ (T12-T0)	T0	T6	T12
Hemoglobin	**Optimum 1.0**	8.7 ± 0.8	8.6 ± 0.8	8.4 ± 0.7	-0.2 ± 0.6	4 (5.8)	3 (4.5)	7 (10.6)
(M: 8.4-10.8 mmol/L	(n=69/67/66)							
F: 7.4-9.9 mmol/L)	**Optimum 2.0**	8.8 ± 0.8	8.5 ± 0.7	8.4 ± 0.8	-0.3 ± 0.6	3 (4.0)	6 (8.6)	6 (9.4)
	(n=75/70/64)							
MCV	**Optimum 1.0**	88.7 ± 4.1	90.5 ± 3.3	91.8 ± 4.4	+3.2 ± 4.2	1 (1.5)	0 (0.0)	0 (0.0)
(80-100 fL)	(n=68/67/66)							
	Optimum 2.0	88.8 ± 3.8	89.7 ± 3.6	89.8 ± 4.0***	+0.9 ± 3.4**	1 (1.3)	0 (0.0)	1 (1.6)
	(n=75/68/64)							
Ferritin	**Optimum 1.0**	127.6 ± 96.4	149.0 ± 114.0	139.4 ± 104.7	+8.1 ± 55.4	2 (2.9)	0 (0.0)	2 (3.1)
(20-300 ng/mL)	(n=69/53/65)							
	Optimum 2.0	119.8 ± 99.3	146.8 ± 109.7	124.1 ± 101.8	+3.5 ± 54.0	1 (1.3)	1 (1.5)	7 (11.1)
	(n=75/67/63)							
Folic acid	**Optimum 1.0**	16.6 ± 6.7	22.3 ± 9.5	21.8 ± 10.0	+5.1 ± 9.2	2 (2.9)	5 (7.6)	5 (7.6)
(9.1-36 nmol/L)[1]	(n=68/66/66)							
	Optimum 2.0	14.9 ± 6.2	18.3 ± 10.1*	19.7 ± 13.4	+4.8 ± 13.5	0 (0.0)	3 (4.4)	5 (7.9)
	(n=75/68/63)							
Vitamin B12	**Optimum 1.0**	289.8 ± 96.4	276.1 ± 84.6	267.3 ± 80.0	-32.9 ± 76.2	1 (1.5)	11 (21.2)	15 (25.4)
(200-570 pmol/L)[2]	(n=67/52/59)							
	Optimum 2.0	299.7 ± 95.6	310.8 ± 94.6*	302.4 ± 93.2*	+5.5 ± 103.7	1 (1.4)	7 (10.8)	6 (10.5)*
	(n=71/65/57)							

Data are presented as mean ± standard deviation and frequencies (percentages).

MVS, multivitamin supplement; *MCV*, mean corpuscular volume.

[1] Reference range for the assay in the VITAAL II study (Optimum 2.0) was 6-28 nmol/L.

[2] Reference range before surgery (T0) was 145-570 pmol/L.

*P<0.05, **P<0.01, ***P<0.001 for Optimum 1.0 vs. Optimum 2.0.

Table 4. Mean serum concentrations and prevalence of deficiencies for vitamin D, calcium, magnesium and phosphate.

Serum variables (reference values)	Type MVS	Serum levels				Deficiencies		
		T0	T6	T12	Δ (T12-T0)	T0	T6	T12
Vitamin D	**Optimum 1.0**	36.6 ± 21.8	86.7 ± 27.6	84.5 ± 32.3	+48.8 ± 29.0	51 (73.9)	5 (7.6)	7 (10.9)
(>50 nmol/L)	(n=69/66/64)							
	Optimum 2.0	55.8 ± 24.7***	92.5 ± 24.1	86.2 ± 22.5	+28.6 ± 23.4***	29 (38.7)***	1 (1.5)	3 (4.8)
	(n=75/68/63)							
PTH	**Optimum 1.0**	3.7 ± 2.0	3.4 ± 1.6	3.5 ± 1.9	-0.3 ± 2.1	7 (10.1)[1]	1 (1.5)[1]	4 (6.2)[1]
(1.3-6.8 pmol/L)	(n=69/66/65)							
	Optimum 2.0	3.3 ± 2.0	3.1 ± 1.7	3.5 ± 2.0	+0.4 ± 1.6	2 (2.7)[1]	1 (1.5)[1]	4 (6.6)[1]
	(n=75/68/61)							
Calcium[2]	**Optimum 1.0**	2.35 ± 0.11	2.40 ± 0.08	2.40 ± 0.08	+0.05 ± 0.11	1 (1.6)	0 (0.0)	0 (0.0)
(2.10-2.55 mmol/L)[3]	(n=62/65/65)							
	Optimum 2.0	2.34 ± 0.10	2.42 ± 0.08	2.39 ± 0.09	+0.05 ± 0.09	6 (9.1)	0 (0.0)	1 (1.6)
	(n=66/70/61)							
Magnesium	**Optimum 1.0**	0.80 ± 0.07	0.82 ± 0.05	0.83 ± 0.06	+0.03 ± 0.07	3 (4.8)	1 (2.5)	1 (2.3)
(0.70-1.10 mmol/L)	(n=63/40/43)							
	Optimum 2.0	0.80 ± 0.06	0.82 ± 0.05	0.81 ± 0.06	+0.01 ± 0.06	4 (6.3)	1 (2.7)	1 (5.0)
	(n=64/37/20)							
Phosphate	**Optimum 1.0**	0.95 ± 0.18	1.01 ± 0.15	1.02 ± 0.20	+0.07 ± 0.20	22 (35.5)	10 (20.4)	10 (18.2)
(0.87-1.45 mmol/L)[4]	(n=62/49/55)							
	Optimum 2.0	0.85 ± 0.16**	1.02 ± 0.15	1.05 ± 0.20	+0.17 ± 0.25**	17 (27.0)	2 (4.8)*	1 (3.7)
	(n=63/42/27)							
Albumin	**Optimum 1.0**	37.8 ± 3.8	38.8 ± 3.4	38.5 ± 3.2	+1.0 ± 3.5	9 (14.3)	6 (9.2)	8 (12.3)
(35-50 g/L)	(n=63/65/65)							
	Optimum 2.0	38.2 ± 2.9	38.2 ± 2.9	38.2 ± 2.9	-0.02 ± 2.6	5 (7.6)	5 (7.1)	6 (9.7)
	(n=66/70/62)							

Data are presented as mean ± standard deviation and frequency (percentage).

MVS, multivitamin supplement; *PTH,* parathyroid hormone.

[1] Elevated PTH levels.

[2] Corrected for albumin levels (total calcium – (0.025 x albumin) + 1).

[3] Reference range for the assay in the VITAAL II study (Optimum 2.0) was 2.20-2.65 mmol/L.

[4] Reference range for the assay in the VITAAL II study (Optimum 2.0) was 0.80-1.40 mmol/L.

*P<0.05, **P<0.01, ***P<0.001 for Optimum 1.0 vs. Optimum 2.0.

Table 5. Mean serum concentrations and prevalence of deficiencies for vitamin B1 and B6, and zinc.

Serum variables (reference values)	Type MVS	Serum levels				Deficiencies		
		T0	T6	T12	Δ (T12-T0)	T0	T6	T12
Vitamin B1 (95-175 nmol/L)	**Optimum 1.0** (n=61/49/54)	167.8 ± 29.5	148.0 ± 27.6	145.4 ± 29.8	-19.3 ± 40.6	0 (0.0)	1 (2.0)	2 (3.7)
	Optimum 2.0 (n=70/39/22)	171.4 ± 28.2	144.8 ± 29.2	153.9 ± 36.5	-14.6 ± 37.5	0 (0.0)	1 (2.6)	0 (0.0)
Vitamin B6 (25-100 nmol/L)	**Optimum 1.0** (n=61/49/54)	79.3 ± 24.0	91.7 ± 36.1	82.9 ± 27.3	+3.1 ± 26.6	0 (0.0)	0 (0.0)	0 (0.0)
	Optimum 2.0 (n=70/39/21)	75.0 ± 23.0	87.1 ± 31.3	99.8 ± 31.7*	+25.7 ± 29.7**	0 (0.0)	0 (0.0)	0 (0.0)
Zinc (9.2-18.4 µmol/L)	**Optimum 1.0** (n=61/48/53)	12.2 ± 1.6	11.7 ± 1.6	11.7 ± 1.9	-0.4 ± 2.2	1 (1.6)	3 (6.3)	2 (3.8)
	Optimum 2.0 (n=70/38/21)	11.2 ± 2.3**	12.9 ± 2.2**	12.6 ± 2.1	+1.3 ± 3.9***	12 (17.1)**	2 (5.3)	1 (4.8)

Data are presented as mean ± standard deviation and frequency (percentage).

MVS, multivitamin supplement.

*P<0.05, **P<0.01, ***P<0.001 for Optimum 1.0 vs. Optimum 2.0.

Hypervitaminosis

The prevalence of elevated serum levels was similar between the two groups. Overall, serum levels above the reference values were observed for ferritin (11.2%), folic acid (20.8%), vitamin B1 (19.2%) and vitamin B6 (39.4%) throughout the study period. Serum levels above the reference values for all other micronutrients were rare (<3%).

For vitamin B1, about one third of the patients (35%) already presented with elevated serum levels at baseline, whereas elevated serum levels for vitamin B6 developed de novo after surgery in more than three quarters of the patients (79%). Extremely high serum vitamin B6 levels (>200 nmol/L) were found in only one patient.

Discussion

The present study evaluated the short-term effectiveness of the optimized WLS Optimum 2.0 supplement on preventing micronutrient deficiencies after SG in comparison to its previous version, WLS Optimum 1.0. WLS Optimum 2.0 contained higher levels of elementary iron, folic acid, vitamin B12, vitamin B1, copper and zinc, and a lower level of vitamin A than WLS Optimum 1.0.

We found higher serum concentrations of vitamin B12, vitamin B6 and zinc, and a lower prevalence of deficiencies for vitamin B12 and phosphate in the Opt 2.0 group. MCV and serum folic acid concentrations were higher in the Opt 1.0 group. Over the 12-month study period, mean increase in serum levels of phosphate, vitamin B6 and zinc was higher in the Opt 2.0 group, and MCV and serum vitamin D concentrations increased more in the Opt 1.0 group. According to the PP analysis, we additionally found that mean increase in PTH and serum calcium concentrations were higher in the Opt 2.0 group whereas the mean increase in serum albumin levels was lower in this group.

The level of elementary iron was increased from 21 mg to 28 mg. Although we found that serum ferritin levels equally increased in both groups, 11% of the patients in the Opt 2.0 group was iron deficient during the study period compared to 3% in the Opt 1.0 group. In the PP analysis, only 3% of the patients in the Opt 2.0 group were iron deficient. This indicates that most of the iron deficiencies occurred in non-compliant patients. In the Opt 1.0 group, the prevalence of iron deficiency did not change in the PP analysis. Our findings therefore suggest that a level of 28 mg of elementary iron is sufficient to prevent deficiencies at 12 months post-surgery. According to the nutritional guidelines of the American Society for Metabolic and Bariatric Surgery (ASMBS), patients who have undergone RYGB or SG should take at least 45-60 mg of elemental iron daily [15]. Based

on our findings, this recommendation should be revised for SG patients as high doses of elementary iron may increase the risk of adverse gastrointestinal side effects [16, 17].

The level of folic acid was increased from 300 µg to 500 µg. Mean increase in serum folic acid concentration and the prevalence of folic acid deficiencies were similar between the groups according to the ITT analysis. However, mean increase in serum folic acid concentration was twice as high in the Opt 2.0 group compared to the Opt 1.0 group in the PP analysis (+11.2 nmol/L vs +6.8 nmol/L, P=0.11). Our results indicate that 500 µg of folic acid is sufficient, which is in line with the ASMBS recommendation of 400-800 µg per day [15].

The 10-fold increase in vitamin B12 (10 µg to 100 µg) was clearly reflected in significantly higher serum levels and less vitamin B12 deficiencies in the Opt 2.0 group compared to the Opt 1.0 group. The ASMBS recommendation for vitamin B12 is 350-500 µg oral supplementation per day for all bariatric patients, irrespective of the type of weight loss surgery [15]. Based on our results, it would better to distinguish between the different types of surgery as our data indicate that a lower vitamin B12 level of 100 µg is sufficient to maintain adequate serum vitamin B12 concentrations in SG patients. Our findings for vitamin B12 might also explain why we found a higher mean increase in MCV in the Opt 1.0 group than in the Opt 2.0 group (+3.2 ± 4.2 fL vs. +0.9 ± 3.4 fL, P=0.002). Mean corpuscular volume (MCV) is a laboratory value that measures the average size and volume of a red blood cell [18]. MCV below the lower limit of 80 fL can indicate iron deficiency anemia while MCV above the upper limit of 100 fL is associated with vitamin B12 deficiency [18]. In the present study, the increase in MCV in the Opt 1.0 group was indeed accompanied by a decrease in serum vitamin B12 concentration in this group. Moreover, the change in MCV was significantly correlated with the change in serum vitamin B12 level (r = -0.32, P<0.001).

The level of vitamin B1 was increased from 2.00 mg to 2.75 mg in Optimum 2.0. Although mean serum vitamin B1 concentrations decreased in both groups, deficiencies were rare. In fact, elevated vitamin B1 levels were more prevalent than vitamin B1 deficiency in the present study (19% vs 4%, respectively). Despite the fact that complications of high doses of vitamin B1 are rare as the body can excrete excess amounts of thiamin in the urine [19], the ASMBS recommendation of at least 12 mg vitamin B1 per day seems highly overestimated and should be revised [15]. Since mean serum vitamin B1 decreased less in the Opt 2.0 group, the dose of 2.75 mg is preferred over the dose of 2.00 mg.

The level of zinc was nearly doubled from 15 mg to 28 mg. This resulted in a larger increase in mean serum zinc concentration in the Opt 2.0 group than in the Opt 1.0 group. The ASMBS recommendation for zinc is 8–11 mg per day for SG patients [15]. This seems highly underestimated as we found that mean serum zinc concentrations decreased in patients using Optimum 1.0, which contained 15 mg of zinc. Despite the high level of zinc in Optimum 2.0, only one patient in the Opt 2.0 group slightly exceeded the upper limit of the reference range (level of 19.6 µmol/L). Acute adverse effects of excess zinc include epigastric pain, nausea, vomiting, loss of appetite, abdominal cramps, diarrhea and headaches [20]. On the long term, excessive absorption of zinc can suppress copper and iron absorption [20]. The Tolerable Upper Intake Level for zinc is 40 mg per day [20]. Basfi-Fer et al. found that dietary intake of zinc varied between 6.3-8.4 mg per day in the first two years post-SG [21]. It would hence appear safe to recommend 28 mg zinc for these patients without any significant risk of zinc toxicity. The level of copper in WLS Optimum 2.0 was also increased from 1.0 mg to 1.9 mg to maintain the recommended ratio of 15 mg of zinc to 1 mg of copper [22].

Whereas no vitamin B6 deficiencies were observed, elevated serum levels for vitamin B6 were highly prevalent in both groups (39%). This is in line with previous research reporting a low prevalence of vitamin B6 deficiency (0-0.5%) but elevated serum vitamin B6 levels in up to 50% of the patients [7, 8, 14, 23]. Elevated serum levels of vitamin B6 can cause neuropathic symptoms [24], but the toxicity of vitamin B6 may depend on which form of vitamin B6 is used in a supplement. Vrolijk et al. found that the neuropathy observed after taking a relatively high dose of vitamin B6 supplements is due to pyridoxine [25]. They suggested to replace pyridoxine by pyridoxal or pyridoxal-phosphate in vitamin B6 supplements to reduce the risk of toxicity [25]. Therefore, the form of vitamin B6 was changed from pyridoxine in Optimum 1.0 to pyridoxal-phosphate in Optimum 2.0. This could also explain why we found a higher increase in serum vitamin B6 levels in the Opt 2.0 group compared to the Opt 1.0 group. Unlike pyridoxine, pyridoxal-phosphate is the active coenzyme form of vitamin B6 which can be directly utilized by the body without conversion [25]. In order to decrease the risk of adverse effects from elevated serum vitamin B6 levels, the level of vitamin B6 in WLS Optimum should be decreased to 1.5 mg pyridoxal-phosphate.

The prevalence of phosphate deficiencies was significantly higher in the Opt 1.0 group than in the Opt 2.0 group at T6 (20.4% vs 4.8%). This difference might be explained by a change in the reference value for phosphate halfway during the VITAAL I study. The

reference value for phosphate was changed from 0.87-1.45 mmol/L to 0.80-1.40 mmol/L due to a new assay. However, all patients in the VITAAL I study were analyzed by using the old reference value. When using the correct reference value for each individual patient in the VITAAL I study, prevalence of phosphate deficiency was 21% at T0, 8.2% at T6 and 10.9% at T12 in the Opt 1.0 group. These rates were no longer significantly different from those observed in the Opt 2.0 group.

Overall, we found that observed differences in serum concentrations and prevalence of deficiencies between the two groups were most pronounced in the PP analysis. However, most of these results did not reach statistical significance, which might be because of a reduced power due to the small sample of compliant patients. Unfortunately, lifelong compliance with a daily multivitamin supplement is difficult to achieve in this patient population [26]. In the present study, compliance decreased to 55% at 12 months in both groups. The main reported reason for discontinuation of the assigned MVS was nausea. Most patients switched to a regular, over-the-counter MVS, but others did not tolerate any MVS and therefore stopped using multivitamin supplementation. More research is needed to explore the underlying factors in order to increase patient compliance with MVS intake.

Although all study participants received the supplements free-of-charge, the costs of treatment with specialized MVS have also been considered a major barrier to adequate lifelong adherence [26]. Compared to the price of other commercially available bariatric multivitamin formulations, WLS Optimum is in the mid-range with a price of €0.29 per capsule. Whereas the use of such supplements initially seems more expensive, Homan et al. showed that the use of a specialized multivitamin resulted in less overall costs compared to using sMVS [27].

Because of the large variety in composition of bariatric multivitamin formulations, this study can contribute towards the achievement of the most optimal form and content of bariatric MVS. However, it is important to note that although our data can give an indication about the doses needed to prevent deficiencies and hypervitaminosis, longer term follow-up studies are necessary to confirm our findings. In that respect, it would also be very useful if data of other MVS formulations become available.

One of the strengths of the present study was the performance of both an ITT analysis and PP analysis based on self-reported compliance. In this way, we could establish the efficacy in a real life setting as well as in an ideal setting in which all patients adhere to

the assigned supplement protocol. Furthermore, we were able to minimize the risk of bias related to a difference in supplements as they were produced by the same manufacturer.

Limitations include the absence of information on nutritional intake and the lack of a (randomized) control group in the current study. The VITAAL II study was a single-arm open label study and we compared this group to the intervention group of the VITAAL I RCT. Although these studies were performed in different time periods, the operative technique, surgeons, researchers and hospital were the same in both studies. Moreover, both study populations were similar with respect to age, gender, preoperative body weight and BMI, and comorbidities. Another limitation is that according to clinical practice, only preoperative deficiencies for vitamin B12 and vitamin D were treated. Not correcting for all preoperative deficiencies could have affected our findings regarding the efficacy of both multivitamin supplements. We therefore corrected for baseline serum levels in the statistical analysis. Moreover, we excluded serum level data of patients who used additional supplementation to prevent biased estimates. However, information on the intake of additional supplementation was subjective (collected via self-report and medical files) and probably, despite an extensive check, not complete which could also have influenced our results.

Conclusion

The present study showed that the use of a specialized multivitamin supplement for SG patients (WLS Optimum 2.0) is effective at preventing deficiencies for many vitamins and minerals, particularly in compliant patients. The level of vitamin B6 should be lowered from 2 mg to 1.5 mg pyridoxal-phosphate to decrease the risk of vitamin B6 toxicity. A strict follow-up regime remains necessary to be able to diagnose nutritional deficiencies as well as hypervitaminosis in an early stage, and to improve patients' compliance with a daily multivitamin supplement. More research is needed to identify which factors affect compliance and how this can be improved.

References

1. Ramos, A, Kow, L, Brown, W, et al., *Fifth IFSO Global Registry Report*, in *The IFSO Global Registry*, The International Federation for the Surgery of Obesity and Metabolic Disorders, Editor. 2019. p. 74.
2. Coupaye, M, Sami, O, Calabrese, D, et al., *Prevalence and Determinants of Nutritional Deficiencies at Mid-Term After Sleeve Gastrectomy.* Obes Surg, 2020. **30**(6):2165-2172
3. Ruiz-Tovar, J, Llavero, C, Zubiaga, L, et al., *Maintenance of Multivitamin Supplements After Sleeve Gastrectomy.* Obes Surg, 2016. **26**(10): p. 2324-2330.
4. Kehagias, I, Zygomalas, A, Karavias, D, et al., *Sleeve gastrectomy: have we finally found the holy grail of bariatric surgery? A review of the literature.* Eur Rev Med Pharmacol Sci, 2016. **20**(23): p. 4930-4942.
5. Lupoli, R, Lembo, E, Saldalamacchia, G, et al., *Bariatric surgery and long-term nutritional issues.* World J Diabetes, 2017. **8**(11): p. 464-474.
6. Sawaya, RA, Jaffe, J, Friedenberg, L, et al., *Vitamin, mineral, and drug absorption following bariatric surgery.* Curr Drug Metab, 2012. **13**(9): p. 1345-1355.
7. Aarts, EO, Janssen, IM and Berends, FJ, *The gastric sleeve: losing weight as fast as micronutrients?* Obes Surg, 2011. **21**(2): p. 207-211.
8. Al-Mutawa, A, Al-Sabah, S, Anderson, AK, et al., *Evaluation of Nutritional Status Post Laparoscopic Sleeve Gastrectomy—5-Year Outcomes.* Obes Surg, 2017. **28**(6): p. 1473-1483.
9. Ben-Porat, T, Elazary, R, Goldenshluger, A, et al., *Nutritional deficiencies four years after laparoscopic sleeve gastrectomy-are supplements required for a lifetime?* Surg Obes Relat Dis, 2017. **13**(7): p. 1138-1144.
10. Caron, M, Hould, FS, Lescelleur, O, et al., *Long-term nutritional impact of sleeve gastrectomy.* Surg Obes Relat Dis, 2017. **13**(10): p. 1664-1673.
11. Gillon, S, Jeanes, YM, Andersen, JR, et al., *Micronutrient Status in Morbidly Obese Patients Prior to Laparoscopic Sleeve Gastrectomy and Micronutrient Changes 5 years Post-surgery.* Obes Surg, 2017. **27**(3): p. 606-612.
12. Mechanick, JI, Apovian, C, Brethauer, S, et al., *Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists.* Surg Obes Relat Dis, 2019. **16**(2):175-247
13. Heusschen, L, Schijns, W, Ploeger, N, et al., *The True Story on Deficiencies After Sleeve Gastrectomy: Results of a Double-Blind RCT.* Obes Surg, 2019. **30**(4):1280-1290
14. van Rutte, PW, Aarts, EO, Smulders, JF, et al., *Nutrient deficiencies before and after sleeve gastrectomy.* Obes Surg, 2014. **24**(10): p. 1639-1646.
15. Parrott, J, Frank, L, Rabena, R, et al., *American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients.* Surg Obes Relat Dis, 2017. **13**(5): p. 727-741.
16. Cancelo-Hidalgo, MJ, Castelo-Branco, C, Palacios, S, et al., *Tolerability of different oral iron supplements: a systematic review.* Curr Med Res Opin, 2013. **29**(4): p. 291-303.
17. Tolkien, Z, Stecher, L, Mander, AP, et al., *Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis.* PLoS One, 2015. **10**(2): p. e0117383.
18. Maner, BS and Moosavi, L, *Mean Corpuscular Volume (MCV)*, in *StatPearls*. 2020.
19. Kerns, JC and Gutierrez, JL, *Thiamin.* Adv Nutr, 2017. **8**(2): p. 395-397.

20. Trumbo, P, Yates, AA, Schlicker, S, et al., *Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* J Am Diet Assoc, 2001. **101**(3): p. 294-301.
21. Basfi-Fer, K, Rojas, P, Carrasco, F, et al., *[Evolution of the intake and nutritional status of zinc, iron and copper in women undergoing bariatric surgery until the second year after surgery].* Nutr Hosp, 2012. **27**(5): p. 1527-1535.
22. Osredkar, J and Sustar, N, *Copper and zinc, biological role and significance of copper/zinc imbalance.* J Clin Toxicol, 2011. **3001**: p. 3-001.
23. Smelt, HJM, van Loon, S, Pouwels, S, et al., *Do Specialized Bariatric Multivitamins Lower Deficiencies After Sleeve Gastrectomy?* Obes Surg, 2020. **30**(2): p. 427-438.
24. Alsabah, A, Al Sabah, S, Al-Sabah, S, et al., *Investigating Factors Involved in Post Laparoscopic Sleeve Gastrectomy (LSG) Neuropathy.* Obes Surg, 2017. **27**(5): p. 1271-1276.
25. Vrolijk, MF, Opperhuizen, A, Jansen, E, et al., *The vitamin B6 paradox: Supplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function.* Toxicol In Vitro, 2017. **44**: p. 206-212.
26. Smelt, HJM, Pouwels, S, Smulders, JF, et al., *Patient adherence to multivitamin supplementation after bariatric surgery: a narrative review.* J Nutr Sci, 2020. **9**.
27. Homan, J, Schijns, W, Janssen, IMC, et al., *Adequate Multivitamin Supplementation after Roux-En-Y Gastric Bypass Results in a Decrease of National Health Care Costs: a Cost-Effectiveness Analysis.* Obes Surg, 2019. **29**(5): p. 1638-1643.

Supplementary Table 1. Per-protocol results for hemoglobin metabolism.

Serum variables (reference values)	Type MVS	Serum levels			Deficiencies	
		T6	T12	Δ (T12-T0)	T6	T12
Hemoglobin (M: 8.4 – 10.8 mmol/L F: 7.4 – 9.9 mmol/L)	**Optimum 1.0** (n=44/38)	8.7 ± 0.7	8.5 ± 0.6	-0.3 ± 0.7	0 (0.0)	1 (2.6)
	Optimum 2.0 (n=46/35)	8.7 ± 0.7	8.7 ± 0.8	-0.3 ± 0.6	3 (6.5)	2 (5.7)
MCV (80-100 fL)	**Optimum 1.0** (n=44/38)	90.2 ± 3.1	91.7 ± 3.9	+2.1 ± 2.9	0 (0.0)	0 (0.0)
	Optimum 2.0 (n=44/35)	89.6 ± 3.5	89.6 ± 3.7*	+0.8 ± 3.1	0 (0.0)	0 (0.0)
Ferritin (20-300 ng/mL)	**Optimum 1.0** (n=37/37)	148.3 ± 116.4	150.0 ± 116.5	+2.6 ± 60.3	0 (0.0)	1 (2.7)
	Optimum 2.0 (n=45/34)	151.5 ± 105.3	151.0 ± 112.6	+2.4 ± 55.6	1 (2.2)	1 (2.9)
Folic acid (6-28 nmol/L)[1]	**Optimum 1.0** (n=44/38)	24.1 ± 8.7	24.4 ± 10.3	+6.8 ± 9.7	0 (0.0)	1 (2.6)
	Optimum 2.0 (n=45/34)	21.5 ± 10.1	26.6 ± 14.1	+11.2 ± 13.8	1 (2.2)	1 (2.9)
Vitamin B12 (200-570 pmol/L)	**Optimum 1.0** (n=36/33)	278.9 ± 90.0	277.5 ± 77.8	-25.3 ± 83.2	8 (22.2)	7 (21.2)
	Optimum 2.0 (n=43/29)	312.6 ± 105.1	322.2 ± 98.4*	+19.3 ± 100.6	6 (14.0)	1 (3.4)

Data are presented as mean ± standard deviation and frequency (percentage).

MVS, multivitamin supplement; *MCV* mean corpuscular volume.

[1] Reference range for the used assay in the VITAAL II study (Optimum 2.0) was 6-28 ng/mL.

* $P<0.05$ for Optimum 1.0 vs. Optimum 2.0.

Supplementary Table 2. Per-protocol results for vitamin D and calcium metabolism.

Serum variables (reference values)	Type MVS	Serum levels			Deficiencies	
		T6	T12	Δ (T12-T0)	T6	T12
Vitamin D	**Optimum 1.0**	87.4 ± 25.2	88.0 ± 28.4	+48.2 ± 28.2	1 (2.3)	2 (5.4)
(>50 nmol/L)	(n=44/37)					
	Optimum 2.0	93.9 ± 24.8	88.5 ± 20.6	+30.8 ± 23.0*	0 (0.0)	1 (2.9)
	(n=44/35)					
PTH	**Optimum 1.0**	3.1 ± 1.4	3.2 ± 1.7	-0.3 ± 1.9	0 (0.0)[1]	2 (5.4)[1]
(1.3-6.8 pmol/L)	(n=44/37)					
	Optimum 2.0	3.1 ± 1.8	3.9 ± 2.2	+0.5 ± 1.4*	1 (2.2)[1]	3 (8.8)[1]
	(n=45/34)					
Calcium[2]	**Optimum 1.0**	2.39 ± 0.08	2.41 ± 0.09	+0.05 ± 0.11	0 (0.0)	0 (0.0)
(2.10-2.55 mmol/L)[3]	(n=43/37)					
	Optimum 2.0	2.42 ± 0.08	2.39 ± 0.09	+0.06 ± 0.09*	0 (0.0)	1 (2.9)
	(n=46/34)					
Magnesium	**Optimum 1.0**	0.82 ± 0.04	0.82 ± 0.05	+0.02 ± 0.07	0 (0.0)	0 (0.0)
(0.70-1.10 mmol/L)	(n=29/27)					
	Optimum 2.0	0.82 ± 0.06	0.81 ± 0.06	+0.03 ± 0.05	1 (3.7)	0 (0.0)
	(n=27/14)					
Phosphate	**Optimum 1.0**	1.01 ± 0.16	1.03 ± 0.22	+0.08 ± 0.20	7 (19.4)	7 (21.2)
(0.87-1.45 mmol/L)[4]	(n=36/33)					
	Optimum 2.0	1.04 ± 0.14	1.08 ± 0.21	+0.22 ± 0.19**	1 (3.3)	1 (5.3)
	(n=30/19)					
Albumin	**Optimum 1.0**	38.8 ± 3.2	38.6 ± 2.6	+1.3 ± 3.0	4 (9.3)	2 (5.4)
(35-50 g/L)	(n=43/37)					
	Optimum 2.0	38.2 ± 3.0	38.5 ± 3.1	-0.03 ± 2.6*	4 (8.7)	4 (11.8)
	(n=46/34)					

Data are presented as mean ± standard deviation and frequency (percentage).

MVS, multivitamin supplement; *PTH,* parathyroid hormone.

[1] Elevated PTH levels.

[2] Corrected for albumin levels (total calcium – (0.025 x albumin) + 1).

[3] Reference range for the used assay in the VITAAL II study (Optimum 2.0) was 2.20-2.65 mmol/L.

[4] Reference range for the used assay in the VITAAL II study (Optimum 2.0) was 0.80-1.40 mmol/L.

*P<0.05, **P<0.01 for Optimum 1.0 vs. Optimum 2.0.

Supplementary Table 3. Per-protocol results for vitamin B1 and B6, and zinc.

Serum variables (reference values)	Type MVS	Serum levels			Deficiencies	
		T6	T12	Δ (T12-T0)	T6	T12
Vitamin B1 (95-175 nmol/L)	**Optimum 1.0** (n=36/33)	150.2 ± 27.6	146.9 ± 33.2	-21.0 ± 46.6	0 (0.0)	2 (6.1)
	Optimum 2.0 (n=28/16)	149.9 ± 26.6	156.1 ± 29.8	-8.6 ± 41.8	0 (0.0)	0 (0.0)
Vitamin B6 (25-100 nmol/L)	**Optimum 1.0** (n=36/33)	93.8 ± 39.0	84.9 ± 29.4	+7.1 ± 26.6	0 (0.0)	0 (0.0)
	Optimum 2.0 (n=28/15)	90.4 ± 25.9	105.7 ± 27.8*	+33.7 ± 28.2*	0 (0.0)	0 (0.0)
Zinc (9.2-18.4 µmol/L)	**Optimum 1.0** (n=35/33)	11.9 ± 1.7	11.8 ± 2.0	-0.2 ± 2.2	2 (5.7)	0 (0.0)
	Optimum 2.0 (n=28/15)	13.5 ± 2.1***	12.9 ± 2.2	+2.0 ± 4.1***	0 (0.0)	1 (6.7)

Data are presented as mean ± standard deviation and frequency (percentage).

MVS, multivitamin supplement.

*P<0.05, ***P<0.001 for Optimum 1.0 vs. Optimum 2.0.

CHAPTER 6

Nutritional deficiencies 3 years after sleeve gastrectomy can be limited by a specialized multivitamin supplement

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Obesity Surgery, 2022; 32(11): 3561-3570

Abstract

Background: Lifelong daily multivitamin supplementation is highly recommended after sleeve gastrectomy (SG). Based on previous research, a specialized multivitamin supplement (MVS) for SG patients was developed and optimized (WLS Optimum 1.0 and 2.0). This study presents its mid-term effectiveness and compares micronutrient status of SG patients using this specialized MVS to users of standard MVS (sMVS) and non-users of multivitamin supplementation during the first three years post-surgery.

Methods: Of the 226 participants that were included at baseline, yearly follow-up blood tests were completed by 193 participants (85%) at 12 months, 176 participants (78%) at 24 months and 140 participants (62%) at 36 months of follow-up. At each time point, participants were divided into four groups: (1) Optimum 1.0, (2) Optimum 2.0, (3) sMVS and (4) non-users.
Serum concentrations (linear mixed-effects models) and the prevalence of micronutrient deficiencies (chi-square tests) during follow-up were compared between the groups.

Results: Users of specialized MVS (Optimum 1.0 and 2.0) had higher serum concentrations of hemoglobin, folic acid and vitamin D compared to sMVS users and non-users during follow-up. Serum concentrations of vitamin B12 and (corrected) calcium were higher in specialized MVS users than in non-users. Overall, fewer deficiencies for folic acid and vitamin D were observed in the Optimum groups.

Conclusion: Although the perfect multivitamin supplement for all SG patients does not exist, WLS Optimum was more effective in sustaining normal serum concentrations than standard, over-the-counter supplementation. Non-users of MVS presented with most micronutrient deficiencies and will evidently develop poor nutritional status on the longer term.

Introduction

During the past decade, the laparoscopic sleeve gastrectomy (SG) has become the most performed metabolic procedure worldwide, accounting for about 50% of all registered procedures [1]. While SG is primarily considered a restrictive procedure, the reduction in gastric acid production and intrinsic factor secretion due to removal of a large part of the stomach may also affect absorption of micronutrients [2]. Contrary to initial belief, similar rates of long-term nutritional deficiencies are found in SG patients when compared to patients that have undergone Roux-en-Y gastric bypass, even though the intestinal surface area remains intact following SG [3-6]. Micronutrient deficiencies for vitamin D, vitamin B12 and iron as well as elevated parathyroid hormone (PTH) levels have been reported up to five years after SG [7-10].

For that reason, a specialized multivitamin supplement specifically targeted to the needs of SG patients was developed (WLS Optimum; FitForMe, Rotterdam, the Netherlands). The composition of WLS Optimum was previously evaluated in a randomized controlled trial and optimized afterwards [11, 12]. The first version of WLS Optimum (1.0) was effective in reducing the prevalence of anemia and improving serum levels of folic acid, PTH, and vitamin B1 one year after SG in comparison to a standard, over-the-counter multivitamin supplement (sMVS) [11]. The optimized version of WLS Optimum (2.0) additionally improved serum levels of vitamin B12, vitamin B6, and zinc and resulted in less deficiencies for vitamin B12 and phosphate during the first year after SG, in comparison to WLS Optimum 1.0 [12]. However, the effectiveness of such specialized MVS on the longer term after SG is still unknown. In addition, compliance to supplementation regimes appears to be poor after bariatric surgery and a part of the patients discontinue the use of (specialized) MVS several years after surgery [13-16]. Research reporting on nutritional status of non-users of MVS following SG is limited. Therefore, the aim of this study was to evaluate micronutrient status of SG patients using specialized MVS (WLS Optimum 1.0, WLS Optimum 2.0) compared to sMVS and non-users during the first three years after surgery.

Methods

Study design and participants

The present study uses follow-up data of two former studies investigating the specialized multivitamin supplement WLS Optimum; the VITAAL I and VITAAL II study [11, 12].

VITAAL I was a randomized controlled trial aimed to evaluate the effectiveness of the first version of WLS Optimum (Optimum 1.0) [11]. Included patients received Optimum 1.0

(intervention group) or a standard, over-the-counter multivitamin supplement (sMVS; control group) for 12 months. After the intervention period, the blinded component of the study was terminated. During follow-up, standard blood tests were performed yearly up to three years post-SG. VITAAL II was designed to evaluate the effectiveness of the improved version of the WLS Optimum supplement (Optimum 2.0). In contrast to the initial RCT, there was no control group in this study [12]. All participants received Optimum 2.0 and were instructed to use this supplement on a daily basis for 12 months. Similarly, all patients were invited to complete their yearly follow-up blood tests up to three years post-SG.

Both study protocols were approved by the Medical Ethics Review Committee of Radboud University Medical Centre and the Local Ethical Committee of Rijnstate Hospital Arnhem, and were conducted in concordance with the principles of the Declaration of Helsinki. The VITAAL I study was registered at the clinical trials registry of the National Institutes of Health (ClinicalTrials.gov; identifier NCT01609387).

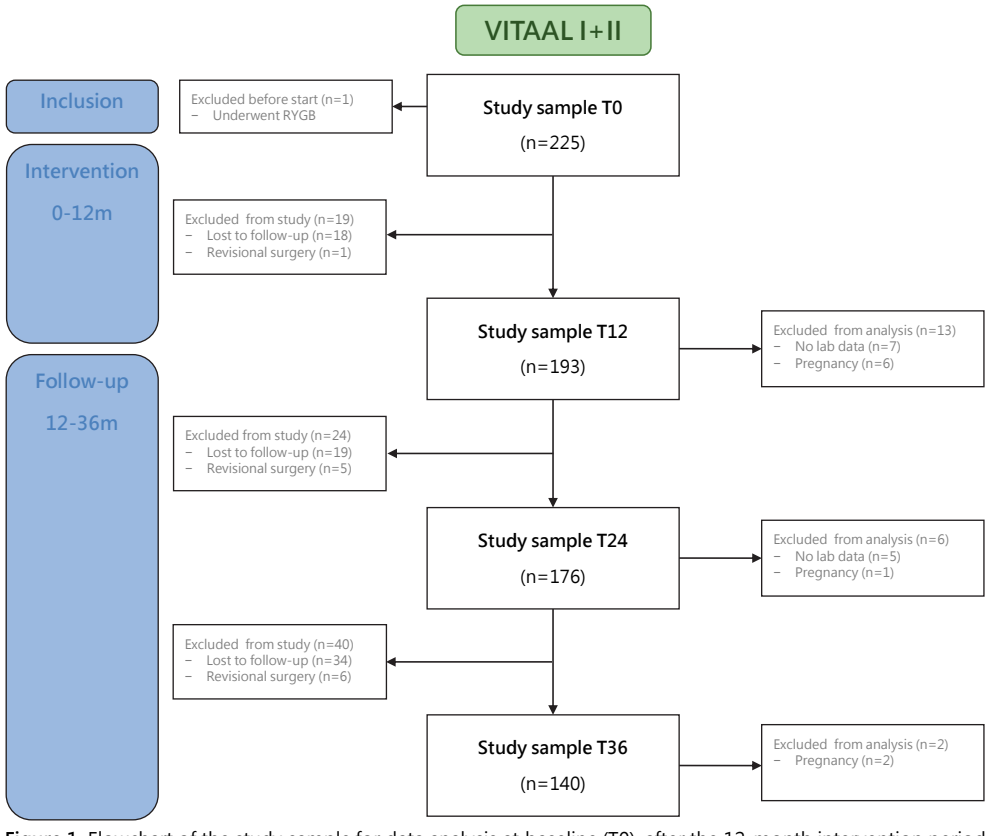


Figure 1. Flowchart of the study sample for data analysis at baseline (T0), after the 12-month intervention period (T12), and at 24 and 36 months of follow-up (T24, T36).

A total of 226 participants were included in the VITAAL I (n=150) and VITAAL II study (n=76). During the follow-up period (12-36 months), 53 participants were lost to follow-up and 11 underwent revisional surgery. Additionally, participants with missing laboratory data (n=12) or known pregnancy (n=9) at the time of follow-up were excluded from the analyses (**Figure 1**). A detailed flowchart of the individual studies can be found in **Supplementary Figure 1**. For the present study, the final study sample for data analysis consisted of 193 participants (85%) at 12 months, 176 participants (78%) at 24 months and 140 participants (62%) at 36 months of follow-up.

Data collection

Demographic information

Socio-demographic and health-related information were collected during standard follow-up visits at the hospital. Body weight was measured to the nearest 0.1 kg with a digital weighing scale (Tanita BC-420MA), after removal of heavy clothing and shoes. Height was measured in standing position with a wall-mounted stadiometer (Seca 206). BMI was calculated as weight (kg) divided by squared height (m^2). Total body weight loss (TWL) was calculated as weight loss divided by weight before surgery, multiplied by 100%. Excess body weight loss (EWL) was calculated as weight loss divided by excess weight before surgery (based on ideal body weight at BMI 25 kg/m^2), multiplied by 100%.

Supplementation use

Self-reported information on the use of multivitamin supplementation (type, content and compliance) at each follow-up visit were obtained via medical chart review and participants were divided into four different treatment modalities: (1) Optimum 1.0 (2), Optimum 2.0 (3), sMVS and (4) non-users. The composition of WLS Optimum 1.0 and Optimum 2.0 is shown in **Table 1**. Compared to the first version, Optimum 2.0 contained higher doses of elementary iron, folic acid, vitamin B12, vitamin B1, copper and zinc, and a lower dose of vitamin A. Moreover, it is important to note that after the 12-month study period of the VITAAL II study, the dose of vitamin D in Optimum 2.0 was increased from 7.5 µg (150% RDA) to 75 µg (1500% RDA). During follow-up, all participants received the supplement with this higher dose of vitamin D. Both supplements were dosed as one capsule per day.

sMVS were defined as standard, over-the-counter supplements that usually contain nutrients in amounts of 100% of the RDA. In addition, participants were advised to take calcium/vitamin D3 (500 mg/800 IE) supplementation two times a day as part of the standard treatment post-SG.

Furthermore, data on the use of additional supplementation (e.g. vitamin B12 injections) were also retrieved from the medical records. When additional supplementation was used, data of subsequent serum concentrations for that micronutrient were removed from the analysis to prevent biased estimates.

Table 1. Composition of WLS Optimum 1.0 and WLS Optimum 2.0

	WLS Optimum 1.0		WLS Optimum 2.0	
Micronutrients	**Dose**	**RDA (%)**	**Dose**	**RDA (%)**
Vitamins				
Vitamin A, mg	1.00	125.0	0.80	100.0
Vitamin B1, mg	2.00	182.0	2.75	250.0
Vitamin B2, mg	2.00	143.0	2.00	143.0
Vitamin B3, mg	25.00	156.0	25.00	156.0
Vitamin B5, mg	9.00	150.0	9.00	150.0
Vitamin B6, mg	2.00	143.0	2.00	143.0
Biotin, µg	150.00	300.0	150.00	300.0
Folic acid, µg	300.00	150.0	500.00	250.0
Vitamin B12, µg	10.00	400.0	100.00	4000.0
Vitamin C, mg	100.00	125.0	100.00	125.0
Vitamin D, µg	7.50	150.0	75.00[1]	1500.0[1]
Vitamin E, mg	12.00	100.0	12.00	100.0
Vitamin K1, µg	90.00	120.0	-	-
Minerals				
Chrome, µg	40.00	100.0	40.00	100.0
Iron, mg	21.00	150.0	28.00	200.0
Iodine, µg	150.00	100.0	150.00	100.0
Copper, mg	1.00	100.0	1.90	190.0
Magnesium, mg	30.00	8.0	-	-
Manganese, mg	3.00	150.0	3.00	150.0
Molybdenum, µg	50.00	100.0	50.00	100.0
Selenium, µg	55.00	100.0	55.00	100.0
Zinc, mg	15.00	150.0	28.00	280.0

RDA, recommended daily allowance.

[1] After the 12-month study period, the dose was increased from 7.5 µg (150% RDA) to 75 µg (1500% RDA).

Table 2. Reference ranges of the evaluated micronutrients

Micronutrients	**Reference range**
Hemoglobin	Male: 8.4-10.8 mmol/L, Female: 7.4-9.9 mmol/L
MCV	80-100 fL
Ferritin	20-300 ng/mL
Folic acid[1]	6-28 nmol/L
Vitamin B12	200-570 pmol/L
Vitamin D	>50 nmol/L
PTH[2]	1.3-6.8 pmol/L
Calcium[3]	2.10-2.55 mmol/L
Albumin	35-50 g/L

MCV, mean corpuscular volume, *PTH,* parathyroid hormone.

[1] Reference range for the assay in the VITAAL II study: 5-35 nmol/L at T24 and >12.2 nmol/L at T36.

[2] Reference range for the assay in the VITAAL II study: 1.96-9.33 pmol/L at T36.

[3] Reference range for the assay in the VITAAL II study: 2.20-2.55 mmol/L at T24 and 2.08-2.65 mmol/L at T36.

Laboratory blood tests

Standard laboratory blood tests were performed at baseline (T0, pre-surgery), after the 12-month intervention period (T12), and at 24 months (T24) and 36 months (T36) of follow-up. Blood serum and plasma were collected by venipuncture at all timepoints. The following blood parameters were measured on random access analyzers: hemoglobin, mean corpuscular volume (MCV; XN-10 Sysmex); ferritin, folic acid, vitamin B12, 25-OH vitamin D, PTH (Modular E170, Roche); and calcium, albumin (Modular P800, Roche). Calcium levels were corrected for albumin (Ca_{corr}=total calcium-(0.025*albumin) + 1).
A deficiency was defined as a serum level below the local reference value at the time of blood collection (**Table 2**).

Statistical analysis

General characteristics of the study population are reported as median and interquartile range [Q1-Q3] for continuous data and as frequency (percentage) for categorical data. Differences in pre-operative characteristics between the study population at baseline and during follow-up were analyzed using the Kruskal-Wallis test for continuous data and Chi-Square tests for categorical data (or Fisher's Exact test when >20% of expected counts were <5).
Serum concentrations during follow-up were analyzed using a mixed-effects model accounting for the fixed effects of MVS (Optimum 1.0; Optimum 2.0; sMVS; non-users) and Time (T12; T24; T36), and their interaction term, plus the random effect of the participants. Time entered the model as a repeated measure using a first-order autoregressive structure with heterogeneous variances. BMI was used as a covariate, entering the model as a fixed effect. Results are presented as estimated marginal mean ± standard error. Means and standard deviations of the original serum data at the different time points can be found in **Supplementary table 1**.
The prevalence of deficiencies at each time point was analyzed using Chi-Square tests (or Fisher's Exact test when >20% of expected counts were <5). In case of a significant main effect, post-hoc pairwise comparisons were performed. *P*-values of post-hoc tests were adjusted using the Bonferroni correction.
All statistical analyses were performed using IBM SPSS Statistics 25 for Windows (IBM Corp., Armonk USA). A two-sided *P*-value below 0.05 was considered statistically significant.

Results

Preoperative characteristics of the study population at baseline (n=225) were comparable to those of the study population at T12 (n=193), T24 (n=176) and T36 (n=140) with respect to sex, age, BMI and comorbidities (**Table 3**). At baseline, 76% of the participants were female, with a median age of 38.4 [29.0-47.5] years and a median BMI of 45.5 [40.6-54.1] kg/m^2. During follow-up, median BMI declined to 30.8 [26.7-36.6] kg/m^2 at T24 and 30.3 [27.2-35.8] kg/m^2 at T36, with a median TWL of 32.1 [24.1-38.8] percent and 30.0 [22.1-35.5] percent, respectively. After the intervention period (T12), 23% of the study population used Optimum 1.0, 18% used Optimum 2.0, 46% used a sMVS and 12% of the participants were non-users. During follow-up, Optimum 1.0 was used by 37% at T24 and 33% at T36, Optimum 2.0 by 18% and 16%, and sMVS by 27% and 28%. The group of non-users increased from 18% at T24 to 24% at T36.

Micronutrient serum concentrations

Changes in serum concentrations over time for the four groups are shown in **Figure 2.** Significant main effects of MVS were found for folic acid, vitamin B12 and corrected calcium. Serum folic acid concentrations were highest in Optimum 2.0 users (26.2 ± 1.2 nmol/L) followed by Optimum 1.0 users (21.9 ± 0.9 nmol/L) and sMVS users (17.6 ± 0.8 nmol/L), and lowest in the non-users (13.8 ± 1.0 nmol/L), $P<0.05$ for all. Serum vitamin B12 concentrations were also lowest in non-users (253.9 ± 11.3 pmol/L) compared to all other groups ($P<0.01$ for all). Corrected calcium concentrations were higher in Optimum 1.0 users (2.37 ± 0.01 mmol/L) than in non-users (2.33 ±0.01 mmol/L), $P=0.02$.

For hemoglobin and vitamin D, there was a significant interaction between MVS and time, indicating that serum hemoglobin and vitamin D concentrations differed significantly over time between the four groups. Serum hemoglobin concentrations were comparable between all groups at T12 and T24 but higher in Optimum 1.0 users (8.7 ± 0.08 mmol/L) compared to sMVS users (8.3 ± 0.08 mmol/L, $P<0.01$) and non-users (8.4 ± 0.09 mmol/L, $P=0.04$) at T36. For vitamin D, serum concentrations were similar for all groups at T12 and higher in Optimum 1.0 users (90.9 ± 2.9 nmol/L) and Optimum 2.0 users (91.4 ± 4.2 nmol/L) than in non-users (75.4 ± 3.5 nmol/L, $P<0.01$ for both) at T24. At T36, serum vitamin D concentrations were also higher in the Optimum 1.0 group (90.0 ± 3.7 nmol/L) compared to the group of non-users (64.7 ± 4.1 nmol/L, $P<0.001$) as well as the sMVS group (66.5 ± 3.9 nmol/L, $P<0.001$). Serum vitamin D concentrations of the Optimum 2.0 group (74.6 ± 5.5 nmol/L) were no longer different from the other groups at T36. No differences between the groups were observed for MCV, ferritin, PTH and albumin.

Table 3. General characteristics of the study sample at baseline (T0) and at 12, 24 and 36 months of follow-up (T12, T24, T36).

	T0 (n=225)		T12 (n=193)		T24 (n=176)		T36 (n=140)	
Age before surgery (years)	38.4	[29.0-47.5]	39.2	[29.5-47.8]	39.3	[30.0-47.9]	40.9	[30.1-49.0]
Sex (female)	171	(76.0)	145	(75.1)	136	(77.3)	105	(75.0)
Body weight before surgery (kg)	135.7	[119.9-162.4]	135.7	[120.7-164.7]	135.2	[119.8-162.5]	131.0	[117.0-154.8]
BMI before surgery (kg/m^2)	45.5	[40.6-54.1]	44.2	[40.6-54.9]	44.9	[40.6-54.5]	42.4	[40.1-52.8]
Adjustable gastric band in history	12	(5.3)	11	(5.7)	9	(5.1)	8	(5.7)
Comorbidities before surgery								
Diabetes Mellitus type 2	25	(11.1)	23	(11.9)	21	(11.9)	19	(13.6)
Hypertension	57	(25.3)	50	(25.9)	46	(26.1)	39	(27.9)
Dyslipidemia	21	(9.3)	19	(9.8)	17	(9.7)	18	(12.9)
OSAS	22	(9.8)	21	(10.9)	22	(12.5)	18	(12.9)
BMI after surgery (kg/m^2)[1]	-		30.5	[26.9-37.5]	30.8	[26.7-36.6]	30.3	[27.2-35.8]
EWL after surgery (%)[1]	-		69.2	[54.1-88.0]	70.5	[55.4-91.7]	67.2	[53.5-87.7]
TWL after surgery (%)[1]	-		30.9	[25.6-37.6]	32.1	[24.1-38.8]	30.0	[22.1-35.5]

Data are presented as median [Q1-Q3] and frequency (percentage).

BMI, body mass index; *OSAS,* obstructive sleep apnea syndrome; *EWL,* excess body weight loss; *TWL,* total body weight loss.

[1]Missing for n=2 at T12, n=2 at T24 and n=5 at T36.

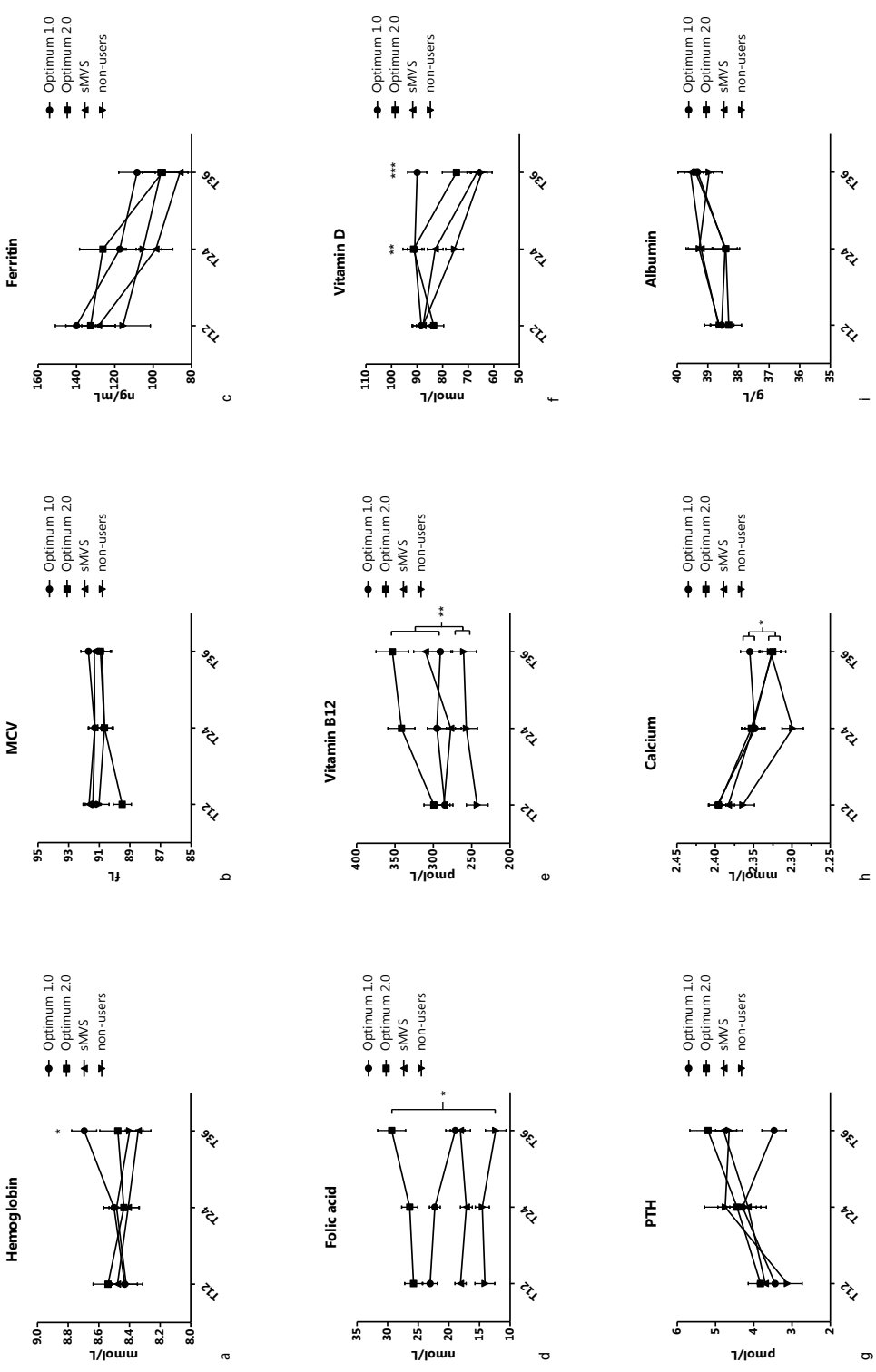

Hemoglobin
mmol/L
Optimum 1.0
Optimum 2.0
sMVS
non-users
T12
T24
T36
a
MCV
fL
b
Ferritin
ng/mL
c
Folic acid
nmol/L
d
Vitamin B12
pmol/L
e
Vitamin D
nmol/L
f
PTH
pmol/L
g
Calcium
mmol/L
h
Albumin
g/L
i

Figure 2. Serum concentrations after the 12-month intervention period (T12), and at 24 and 36 months of follow-up (T24, T36). Lines depict estimated marginal means ± standard errors (error bars).

a. Hemoglobin.

* Significantly higher serum levels for Optimum 1.0 vs sMVS and non-users at T36 ($P<0.05$).

b. MCV.

c. Ferritin.

d. Folic acid.

* Significantly different serum levels between all groups ($P<0.05$).

e. Vitamin B12.

** Significantly lower serum levels for non-users vs all other groups ($P<0.01$).

f. Vitamin D.

** Significantly higher serum levels for Optimum 1.0 and Optimum 2.0 vs non-users at T24 ($P<0.01$).

*** Significantly higher serum levels for Optimum 1.0 vs non-users and sMVS at T36 ($P<0.001$).

g. PTH.

h. (Corrected) calcium.

* Significantly higher serum levels for Optimum 1.0 vs non-users ($P=0.02$).

i. Albumin

Micronutrient deficiencies

During follow-up, the number of deficiencies for folic acid (T24, T36) and vitamin D (T36) were significantly different between the four groups ($P<0.01$ for all, **Table 4**). For folic acid, the number of deficiencies was lower in the Optimum 1.0 group compared to the group of non-users at both T24 (1.6% vs 21.9%, $P=0.01$) and T36 (0% vs 24.2%, $P<0.01$). The number of vitamin D deficiencies at T36 was also lowest in the Optimum 1.0 group (2.2%), compared to all other groups (respectively 26.3%, 35.1% and 32.3% for Optimum 2.0, sMVS and non-users, $P<0.05$ for all). At T36, the prevalence of vitamin B12 deficiency tended to be lower in the Optimum 2.0 group with no deficiencies observed in this group, compared to 12.1% in the Optimum 1.0 group, 9.4% in the sMVS group and 20.8% in the group of non-users ($P>0.05$).

Overall, the number of participants with one or more micronutrient deficiencies during follow-up was markedly lower in the Optimum 1.0 (32.4%) and Optimum 2.0 (28.3%) group, than in the sMVS group (49.4%) and the group of non-users (66.2%), $P<0.001$. For the Optimum users, anemia and deficiencies for vitamin B12 (Optimum 1.0) and vitamin D (Optimum 2.0) were most prevalent whereas in the group of sMVS and non-users, deficiencies for folic acid, vitamin B12 and vitamin D were most common.

Elevated serum levels

Elevated serum levels during follow-up were more prevalent in Optimum users than in sMVS and non-users. At T24, serum ferritin levels above the normal range (>300 ng/mL) were observed in 6.6% and 21.4% of the Optimum 1.0 and 2.0 users vs 0% and 3.1% of the sMVS-users and non-users ($P<0.01$). At T36, the prevalence of elevated serum ferritin levels was no longer significantly different between the groups as it decreased to 5.0% in the Optimum 2.0 group. Serum vitamin B12 levels above the normal range (>600 pmol/L) were mostly observed in the Optimum 2.0 group at both timepoints (12.0%, 15.8%), followed by the Optimum 1.0 users (2.0%, 0%) and sMVS users (0%, 3.1%) ($P<0.05$ for both). There were no elevated serum levels for vitamin B12 observed in the non-users group.

Table 4. Prevalence of deficiencies at baseline (T0), after the 12-month intervention period (T12), and at 24 and 36 months of follow-up (T24, T36) for the four supplement groups.

Serum variables	Type of MVS	*n*	T0		*n*	T12		*n*	T24		*n*	T36	
Hemoglobin	Optimum 1.0	*69*	4	(5.8)	*45*	2	(4.4)	*65*	6	(9.2)	*46*	3	(6.5)
	Optimum 2.0	*75*	3	(4.0)	*35*	2	(5.7)	*31*	4	(12.9)	*22*	4	(18.2)
	sMVS	*69*	4	(5.8)	*88*	13	(14.8)	*48*	3	(6.3)	*39*	4	(10.3)
	Non-users	-			*24*	2	(8.3)	*31*	1	(3.2)	*32*	1	(3.1)
MCV	Optimum 1.0	*68*	1	(1.5)	*45*	0	(0.0)	*65*	2	(3.1)	*46*	0	(0.0)
	Optimum 2.0	*75*	1	(1.3)	*35*	0	(0.0)	*31*	0	(0.0)	*22*	1	(4.5)
	sMVS	*68*	2	(2.9)	*88*	2	(2.3)	*48*	0	(0.0)	*39*	0	(0.0)
	Non-users	-			*24*	0	(0.0)	*31*	0	(0.0)	*32*	0	(0.0)
Ferritin	Optimum 1.0	*69*	2	(2.9)	*44*	1	(2.3)	*61*	6	(9.8)	*42*	5	(11.9)
	Optimum 2.0	*75*	1	(1.3)	*34*	1	(2.9)	*28*	2	(7.1)	*20*	2	(10.0)
	sMVS	*70*	3	(4.3)	*88*	5	(5.7)	*47*	6	(12.8)	*38*	5	(13.2)
	Non-users	-			*24*	4	(16.7)	*32*	5	(15.6)	*31*	4	(12.9)
Folic acid	Optimum 1.0	*68*	2	(2.9)	*45*	1	(2.2)	*63*	1	(1.6)[a]	*43*	0	(0)[a]
	Optimum 2.0	*75*	0	(0.0)	*34*	1	(2.9)	*29*	1	(3.4)[a,b]	*19*	1	(5.3)[a,b]
	sMVS	*69*	4	(5.8)	*89*	6	(6.7)	*48*	5	(10.4)[a,b]	*37*	5	(13.5)[a,b]
	Non-users	-			*24*	4	(16.7)	*32*	7	(21.9)[b]	*33*	8	(24.2)[b]
Vitamin B12	Optimum 1.0	*67*	1	(1.5)	*40*	8	(20.0)[a,b]	*51*	9	(17.6)	*33*	4	(12.1)
	Optimum 2.0	*71*	1	(1.4)	*29*	1	(3.4)[a]	*25*	3	(12.0)	*19*	0	(0.0)
	sMVS	*70*	0	(0.0)	*86*	16	(18.6)[a,b]	*34*	6	(17.6)	*32*	3	(9.4)
	Non-users	-			*22*	10	(45.5)[b]	*28*	9	(32.1)	*24*	5	(20.8)
Vitamin D	Optimum 1.0	*69*	51	(73.9)[a]	*44*	3	(6.8)	*63*	4	(6.3)	*45*	1	(2.2)[a]
	Optimum 2.0	*75*	29	(38.7)[b]	*35*	1	(2.9)	*31*	1	(3.2)	*19*	5	(26.3)[b]
	sMVS	*70*	54	(77.1)[a]	*87*	9	(10.3)	*47*	6	(12.8)	*37*	13	(35.1)[b]
	Non-users	-			*24*	1	(4.2)	*32*	7	(21.9)	*31*	10	(32.3)[b]

Table 4. Prevalence of deficiencies at baseline (T0), after the 12-month intervention period (T12), and at 24 and 36 months of follow-up (T24, T36) for the four supplement groups. *(continued).*

Serum variables	Type of MVS	*n*	T0		*n*	T12		*n*	T24		*n*	T36	
PTH[1]	Optimum 1.0	*69*	7	(10.1)[a,b]	*44*	3	(6.8)	*33*	2	(6.1)	*44*	1	(2.3)
	Optimum 2.0	*75*	2	(2.7)[b]	*34*	3	(8.8)	*30*	2	(6.7)	*19*	0	(0.0)
	sMVS	*70*	10	(14.3)[a]	*88*	7	(8.0)	*33*	2	(6.1)	*37*	2	(5.4)
	Non-users	-			*23*	1	(4.3)	*25*	3	(12.0)	*33*	3	(9.1)
Calcium[2]	Optimum 1.0	*62*	1	(1.6)[a,b]	*44*	0	(0.0)	*31*	0	(0.0)	*34*	1	(2.9)
	Optimum 2.0	*66*	6	(9.1)[b]	*34*	1	(2.9)	*31*	0	(0.0)	*20*	0	(0.0)
	sMVS	*68*	0	(0.0)[a]	*88*	0	(0.0)	*28*	1	(3.6)	*35*	2	(5.7)
	Non-users	-			*23*	0	(0.0)	*26*	3	(11.5)	*32*	1	(3.1)
Albumin	Optimum 1.0	*63*	9	(14.3)	*44*	4	(9.1)	*31*	5	(16.1)	*34*	2	(5.9)
	Optimum 2.0	*66*	5	(7.6)	*34*	4	(11.8)	*31*	0	(0.0)	*20*	0	(0.0)
	sMVS	*68*	7	(10.3)	*89*	9	(10.1)	*28*	2	(7.1)	*35*	0	(0.0)
	Non-users	-			*23*	0	(0.0)	*26*	2	(7.7)	*32*	2	(9.4)

Data are presented as frequency (percentage).

MVS, multivitamin supplement; *sMVS,* standard multivitamin supplement; *MCV,* mean corpuscular volume; *PTH,* parathyroid hormone.

[1] Elevated PTH levels.

[2] Corrected for albumin levels (total calcium – (0.025 x albumin) + 1).

Different letters denote significant differences between groups ($P<0.05$).

Discussion

Despite previous research and multiple guidelines, no multivitamin supplement has been able to consistently sustain normal serum concentrations for all micronutrients. The present study found that users of specialized MVS (WLS Optimum 1.0 and 2.0) had higher serum concentrations of hemoglobin, folic acid, vitamin B12, vitamin D and corrected calcium compared to sMVS users and non-users three years after SG. Similar trends were found for ferritin, although not statistically significant. Overall, least micronutrient deficiencies were also found for users of specialized MVS, followed by sMVS users. Non-users presented with the most deficiencies as well as the lowest serum concentrations for almost all micronutrients.

Over time, supplement use varied and adherence to MVS declined with less than half of the participants consistently using the same MVS throughout follow-up and the percentage of non-users increasing up to 24% at three years after SG. This is in line with previous research on adherence to supplementation regimes after bariatric surgery with (self-reported) compliance rates ranging between 37-93% up to five years post-surgery [7, 14, 15, 17-20]. Besides commonly reported barriers as gastrointestinal side effects, and poor taste, smell, size and high costs of MVS [13, 15, 19], some patients believe that their diet provides sufficient nutrients and therefore do not feel the need to use MVS [15, 19]. This is concerning as we found that about 66% of the non-users in this study presented with one or more nutrient deficiencies during follow-up, whereas this was only about 30% in the groups that used a specialized MVS. Moreover, serum concentrations of almost all evaluated micronutrients were lowest in the group of non-users throughout follow-up. This in line with a study of Dagan et al. including 77 SG patients, that showed that adherence to multivitamin supplementation at 12 months was significantly associated with higher serum levels of hemoglobin, iron, folic acid, and vitamins B12 and D [14]. As with the general adherence to medical follow-up visits after bariatric surgery, compliance with post-surgery supplementation protocols tends to decrease with time from surgery [7, 13-16]. As a result, nutritional status may worsen over time. This reinforces the need for long-term nutritional follow-up and counseling while taking patients' barriers related to supplementation use into account.

The increase in the level of folic acid (300 ug to 500 ug) and vitamin B12 (10 ug to 100 ug) between the first and second version of WLS Optimum was clearly reflected in higher serum concentrations for these micronutrients in the Optimum 2.0 group. For vitamin B12, this also resulted in fewer vitamin B12 deficiencies in the Optimum 2.0 group compared to the Optimum 1.0 group, although these findings did not reach statistical

significance. In contrast, the 10-fold increase in vitamin D (7.5 to 75 µg) did not consistently result in higher serum vitamin D concentrations in the Optimum 2.0 group throughout follow-up. At T24, Optimum 2.0 users showed higher serum vitamin D concentrations and fewer vitamin D deficiencies than Optimum 1.0 users, whereas the opposite was observed at T36 with 26% of the Optimum 2.0 users being vitamin D deficient compared to 2% of the Optimum 1.0 users. This could have been caused by seasonal differences in the timing of follow-up measurements as vitamin D levels are highly influenced by the amount of sun exposure [21]. The number of patients completing their follow-up measurements between November and April, which is the period of low sun exposure in the northern latitudes [22], was indeed markedly higher in the Optimum 2.0 group compared to the Optimum 1.0 group, especially at three years of follow up (77% vs 50%). Furthermore, a difference in compliance to the standard postoperative calcium/vitamin D3 supplementation regimen could have also impacted our findings with regard to vitamin D status.

The level of elementary iron in WLS Optimum was increased from 21 mg in Optimum 1.0 to 28 mg in Optimum 2.0, but this did not result in fewer iron deficiencies (expressed as low ferritin levels) in the latter group. In fact, the number of iron deficiencies was comparable between all groups, ranging from 7-16% at two years and from 10-13% at three years of follow-up, which is lower than reported in previous literature (17-59% at 2-4 years after SG) [8, 9, 20, 23-25]. Although serum ferritin concentrations were highest in Optimum 2.0 users at each specific time point, we still observed a decrease in serum levels over time in this group. In a recent systematic review and meta-analysis including 82 studies on longitudinal changes in micronutrient status after bariatric surgery, ferritin levels also decreased at 24 months after SG despite supplementation per guidelines [26]. The observed decrease in serum ferritin concentration might have been secondary to depletion of the body's iron reserves after bariatric surgery as the prevalence of anemia in the Optimum 2.0 group also increased from 13% at T24 to 18% at T36, suggesting that the body's iron stores were not sufficient to prevent patients from developing iron-deficiency anemia. This could indicate that 28 mg elementary iron is not sufficient to keep serum ferritin concentrations stable on the longer term, particularly in patients who are at higher risk such as premenopausal women. Alternate day dosing of iron could be an alternative solution as it significantly increases iron absorption and results in a lower incidence of gastrointestinal side effects compared with dosing iron every day [27, 28]. On the other hand, elevated serum ferritin levels were most frequently observed in the Optimum 2.0 group, showing the complexity of micronutrient supplementation.

Overall, elevated serum levels during follow-up were more prevalent in Optimum users compared to sMVS-users and non-users. Yet, it is important to note that certain nutrients such as folic acid are highly sensitive to recent intake [29, 30]. Healthcare practitioners may therefore suggest fasting from MVS intake up to 12-24 hours prior to a blood test. Regarding folic acid, the upper assay limit of 45 nmol/L also hindered to assess whether plasma levels were extremely elevated. However, this was the case in only 15 patients.
Clinical manifestations of toxicity have not been actively investigated in the present study, but no adverse events due to hypervitaminosis were reported. Yet, toxicity on the long term is largely unknown. For example, high plasma concentrations of vitamin B12 have been associated with increased risks of certain types of cancer [31, 32] and all-cause mortality [33]. Observational data that evaluate the long-term consequences of supplementing such high doses in this patient population are needed.

The main strength of this study is that it is one of the first that evaluates mid-term micronutrient status after SG, while discriminating between different types of MVS. By using mixed-effects models analysis, we approximated the longitudinal effect of MVS use as much as possible, but we could not prevent potential cross-over effects resulting from switching between different MVS formulations in-between time points. As only a small number of participants consistently used the same MVS throughout the follow-up period, we were not able to determine the efficacy of supplementation within these subgroups and to take compliance into account. Other limitations include the changes in composition of WLS Optimum over time and the high number of participants who were lost to follow-up, which resulted in a lack of statistical power, particularly for the analyses on micronutrient deficiencies.

Conclusion

Evidently, there is no one-size-fits-all formulation when it comes to multivitamin supplementation after sleeve gastrectomy. Even specialized supplementation that is specifically targeted to the needs of this patient population could not completely prevent micronutrient deficiencies from occurring. Nevertheless, daily use of specialized MVS is markedly more effective in sustaining normal serum concentrations than standard, over-the-counter supplementation. Non-users of MVS presented with most micronutrient deficiencies and will evidently develop poor nutritional status on the longer term, reinforcing the need of long-term nutritional follow-up and counseling while taking patients' barriers related to supplementation use into account.

References

1. Brown, WA, Kow, L, Shikora, S, et al., Sixth IFSO Global Registry Report, in *The IFSO Global Registry, The International Federation for the Surgery of Obesity and Metabolic Disorders*, Editor. 2021.
2. Lupoli, R, Lembo, E, Saldalamacchia, G, et al., *Bariatric surgery and long-term nutritional issues.* World J Diabetes, 2017. **8**(11): p. 464-474.
3. Ferraz, AAB, Carvalho, MRC, Siqueira, LT, et al., *Micronutrient deficiencies following bariatric surgery: a comparative analysis between sleeve gastrectomy and Roux-en-Y gastric bypass.* Rev Col Bras Cir, 2018. **45**(6): p. e2016.
4. Kwon, Y, Ha, J, Lee, YH, et al., *Comparative risk of anemia and related micronutrient deficiencies after Roux-en-Y gastric bypass and sleeve gastrectomy in patients with obesity: An updated meta-analysis of randomized controlled trials.* Obes Rev, 2022. **23**(4): p. e13419.
5. Nunes, R, Santos-Sousa, H, Vieira, S, et al., *Vitamin B Complex Deficiency After Roux-en-Y Gastric Bypass and Sleeve Gastrectomy-a Systematic Review and Meta-Analysis.* Obes Surg, 2022. **32**(3): p. 873-891.
6. Via, MA and Mechanick, JI, *Nutritional and Micronutrient Care of Bariatric Surgery Patients: Current Evidence Update.* Curr Obes Rep, 2017. **6**(3): p. 286-296.
7. Ben-Porat, T, Elazary, R, Goldenshluger, A, et al., *Nutritional deficiencies four years after laparoscopic sleeve gastrectomy-are supplements required for a lifetime?* Surg Obes Relat Dis, 2017. **13**(7): p. 1138-1144.
8. Caron, M, Hould, FS, Lescelleur, O, et al., *Long-term nutritional impact of sleeve gastrectomy.* Surg Obes Relat Dis, 2017. **13**(10): p. 1664-1673.
9. Gillon, S, Jeanes, YM, Andersen, JR, et al., *Micronutrient Status in Morbidly Obese Patients Prior to Laparoscopic Sleeve Gastrectomy and Micronutrient Changes 5 years Post-surgery.* Obes Surg, 2017. **27**(3): p. 606-612.
10. Kikkas, EM, Sillakivi, T, Suumann, J, et al., *Five-Year Outcome of Laparoscopic Sleeve Gastrectomy, Resolution of Comorbidities, and Risk for Cumulative Nutritional Deficiencies.* Scand J Surg, 2018: p. 1457496918783723.
11. Heusschen, L, Schijns, W, Ploeger, N, et al., *The True Story on Deficiencies After Sleeve Gastrectomy: Results of a Double-Blind RCT.* Obes Surg, 2019. **30**(4):1280-1290
12. Heusschen, L, Berendsen, AAM, Cooiman, MI, et al., *Optimizing Multivitamin Supplementation for Sleeve Gastrectomy Patients.* Obes Surg, 2021. **31**(6): p. 2520-2528.
13. Santonicola, A, Cersosimo, G, Angrisani, L, et al., *Nonadherence to Micronutrient Supplementation After Bariatric Surgery: Results from an Italian Internet-Based Survey.* J Am Coll Nutr, 2021: p. 1-9.
14. Sherf Dagan, S, Keidar, A, Raziel, A, et al., *Do Bariatric Patients Follow Dietary and Lifestyle Recommendations during the First Postoperative Year?* Obes Surg, 2017. **27**(9): p. 2258-2271.
15. Smelt, HJM, Heusschen, L, Theel, W, et al., *Factors Affecting Patient Adherence to Multivitamin Intake After Bariatric Surgery: a Multicentre Survey Study from the Patient's Perspective.* Obes Surg, 2021. **31**(10): p. 4316-4326.
16. Zarshenas, N, Tapsell, LC, Neale, EP, et al., *The Relationship Between Bariatric Surgery and Diet Quality: a Systematic Review.* Obes Surg, 2020. **30**(5): p. 1768-1792.
17. James, H, Lorentz, P and Collazo-Clavell, ML, *Patient-Reported Adherence to Empiric Vitamin/Mineral Supplementation and Related Nutrient Deficiencies After Roux-en-Y Gastric Bypass.* Obes Surg, 2016. **26**(11): p. 2661-2666.
18. Lier, HO, Biringer, E, Stubhaug, B, et al., *The impact of preoperative counseling on postoperative treatment adherence in bariatric surgery patients: a randomized controlled trial.* Patient Educ Couns, 2012. **87**(3): p. 336-342.

19. Mahawar, KK, Clare, K, O'Kane, M, et al., *Patient Perspectives on Adherence with Micronutrient Supplementation After Bariatric Surgery.* Obes Surg, 2019. **29**(5): p. 1551-1556.
20. Zarshenas, N, Nacher, M, Loi, KW, et al., *Investigating Nutritional Deficiencies in a Group of Patients 3 Years Post Laparoscopic Sleeve Gastrectomy.* Obes Surg, 2016. **26**(12): p. 2936-2943.
21. Klingberg, E, Olerod, G, Konar, J, et al., *Seasonal variations in serum 25-hydroxy vitamin D levels in a Swedish cohort.* Endocrine, 2015. **49**(3): p. 800-808.
22. Snellman, G, Melhus, H, Gedeborg, R, et al., *Seasonal genetic influence on serum 25-hydroxyvitamin D levels: a twin study.* PLoS One, 2009. **4**(11): p. e7747.
23. Al-Mutawa, A, Al-Sabah, S, Anderson, AK, et al., *Evaluation of Nutritional Status Post Laparoscopic Sleeve Gastrectomy—5-Year Outcomes.* Obes Surg, 2017. **28**(6): p. 1473-1483.
24. Mulita, F, Lampropoulos, C, Kehagias, D, et al., *Long-term nutritional deficiencies following sleeve gastrectomy: a 6-year single-centre retrospective study.* Prz Menopauzalny, 2021. **20**(4): p. 170-176.
25. Pellitero, S, Martinez, E, Puig, R, et al., *Evaluation of Vitamin and Trace Element Requirements after Sleeve Gastrectomy at Long Term.* Obes Surg, 2017. **27**(7): p. 1674-1682.
26. Ha, J, Kwon, Y, Kwon, JW, et al., *Micronutrient status in bariatric surgery patients receiving postoperative supplementation per guidelines: Insights from a systematic review and meta-analysis of longitudinal studies.* Obes Rev, 2021. **22**(7): p. e13249.
27. Stoffel, NU, Cercamondi, CI, Brittenham, G, et al., *Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials.* Lancet Haematol, 2017. **4**(11): p. e524-e533.
28. Stoffel, NU, Zeder, C, Brittenham, GM, et al., *Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women.* Haematologica, 2020. **105**(5): p. 1232-1239.
29. Bailey, LB, Stover, PJ, McNulty, H, et al., *Biomarkers of Nutrition for Development-Folate Review.* J Nutr, 2015. **145**(7): p. 1636S-1680S.
30. Navarro, M and Wood, RJ, *Plasma Changes in Micronutrients Following a Multivitamin and Mineral Supplement in Healthy Adults.* J Am Coll Nutr, 2003. **22**(2): p. 124-132.
31. Arendt, JFH, Sorensen, HT, Horsfall, LJ, et al., *Elevated Vitamin B12 Levels and Cancer Risk in UK Primary Care: A THIN Database Cohort Study.* Cancer Epidemiol Biomarkers Prev, 2019. **28**(4): p. 814-821.
32. Lacombe, V, Chabrun, F, Lacout, C, et al., *Persistent elevation of plasma vitamin B12 is strongly associated with solid cancer.* Sci Rep, 2021. **11**(1): p. 13361.
33. Flores-Guerrero, JL, Minovic, I, Groothof, D, et al., *Association of Plasma Concentration of Vitamin B12 With All-Cause Mortality in the General Population in the Netherlands.* JAMA Netw Open, 2020. **3**(1): p. e1919274.

Supplementary Table 1. Serum concentrations at baseline (T0), after the 12-month intervention period (T12), and at 24 and 36 months of follow-up (T24, T36) for the four supplement groups.

Serum variables	Type of MVS	*n*	T0		*n*	T12		*n*	T24		*n*	T36	
Hemoglobin	Optimum 1.0	*69*	8.7	±0.8	*45*	8.6	±0.7	*65*	8.5	±0.7	*46*	8.6	±0.7
(mmol/L)	Optimum 2.0	*75*	8.8	±0.8	*35*	8.7	±0.8	*31*	8.4	±0.7	*22*	8.6	±0.9
	sMVS	*69*	8.8	±0.7	*88*	8.4	±0.7	*48*	8.3	±0.7	*39*	8.4	±0.7
	Non-users	-			*24*	8.4	±0.7	*31*	8.6	±0.5	*32*	8.5	±0.6
MCV	Optimum 1.0	*68*	88.7	±4.1	*45*	91.6	±3.8	*65*	91.5	±4.5	*46*	91.6	±4.9
(fL)	Optimum 2.0	*75*	88.8	±3.8	*35*	89.6	±3.7	*31*	90.8	±3.2	*22*	90.1	±4.1
	sMVS	*68*	88.9	±4.7	*88*	91.7	±4.7	*48*	91.5	±3.8	*39*	91.4	±4.4
	Non-users	-			*24*	91.5	±4.7	*31*	90.1	±3.7	*32*	90.9	±3.8
Ferritin	Optimum 1.0	*69*	127.6	±96.4	*44*	144.9	±111.6	*61*	123.6	±96.8	*42*	100.8	±86.5
(ng/mL)	Optimum 2.0	*75*	119.8	±99.3	*34*	151.0	±112.6	*28*	152.8	±134.0	*20*	127.6	±111.6
	sMVS	*70*	128.8	±97.7	*88*	128.0	±78.2	*47*	91.5	±68.4	*38*	94.6	±88.1
	Non-users	-			*24*	97.5	±77.3	*32*	99.6	±80.0	*31*	94.9	±93.2
Folic acid	Optimum 1.0	*68*	16.6	±6.7	*45*	24.6	±9.9	*63*	23.5	±9.3	*43*	21.9	±9.1
(nmol/L)	Optimum 2.0	*75*	14.9	±6.2	*34*	26.6	±14.1	*29*	28.3	±13.1	*19*	30.8	±14.4
	sMVS	*69*	16.7	±6.0	*89*	17.9	±7.0	*48*	16.4	±7.9	*37*	18.3	±10.6
	Non-users	-			*24*	11.8	±6.1	*32*	12.3	±4.8	*33*	10.9	±4.7
Vitamin B12	Optimum 1.0	*67*	289.8	±96.4	*40*	279.4	±76.0	*51*	298.8	±101.3	*33*	310.8	±102.6
(pmol/L)	Optimum 2.0	*71*	299.7	±95.6	*29*	322.2	±98.4	*26*	382.1	±176.7	*19*	403.3	±151.3
	sMVS	*70*	315.9	±110.1	*86*	286.3	±83.9	*34*	297.0	±89.7	*32*	331.7	±120.2
	Non-users	-			*22*	233.3	±84.4	*28*	232.1	±64.7	*24*	263.7	±72.0
Vitamin D	Optimum 1.0	*69*	36.6	±21.8	*44*	91.0	±30.4	*63*	92.4	±27.6	*45*	92.2	±26.7
(nmol/L)	Optimum 2.0	*75*	55.8	±24.7	*35*	88.5	±20.6	*31*	100.6	±31.8	*19*	84.7	±41.1
	sMVS	*70*	34.0	±16.7	*87*	86.4	±29.6	*47*	84.0	±31.9	*37*	67.8	±32.9
	Non-users	-			*24*	80.2	±27.8	*32*	69.6	±24.0	*31*	65.3	±29.1

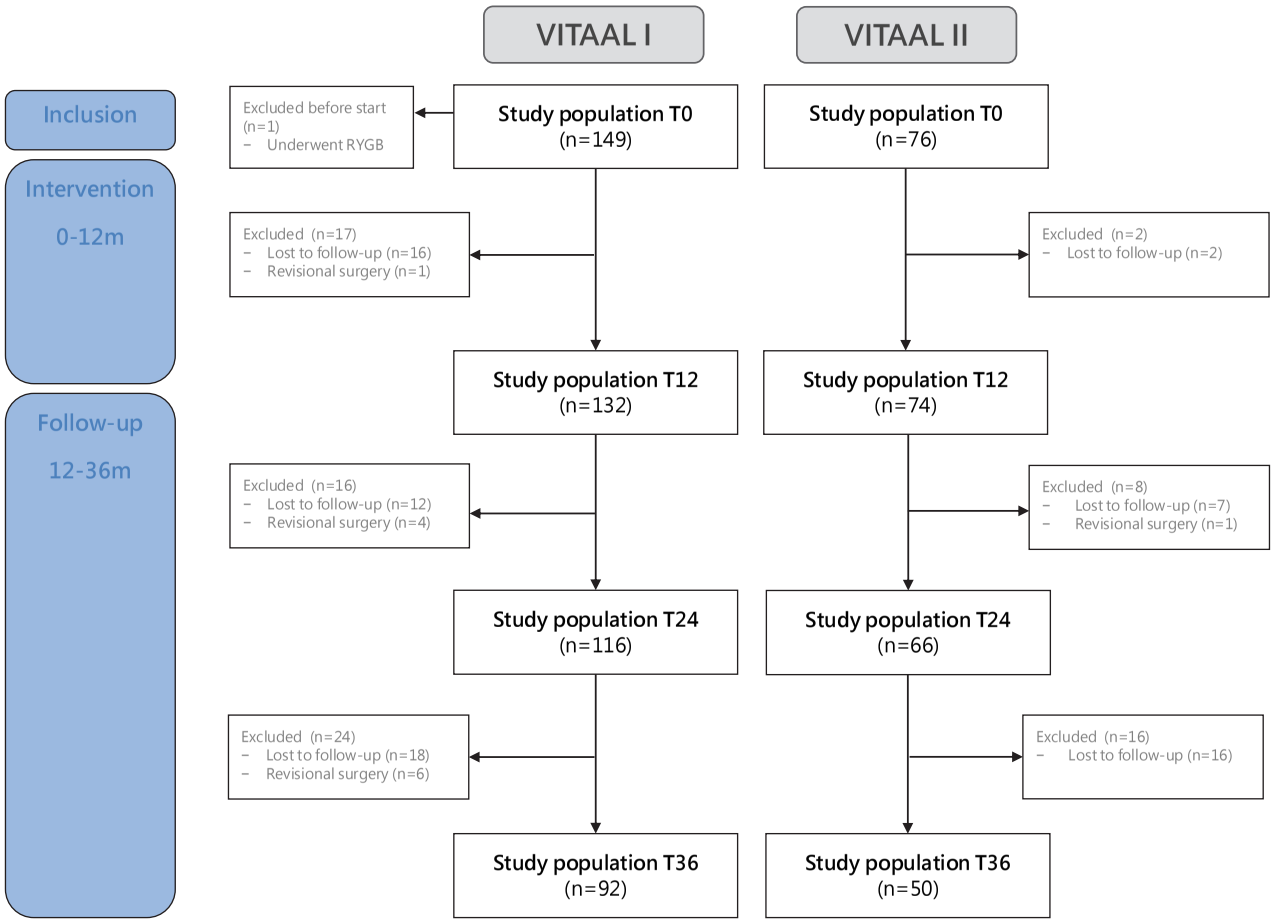
Supplementary Table 1. Serum concentrations at baseline (T0), after the 12-month intervention period (T12), and at 24 and 36 months of follow-up (T24, T36) for the four supplement groups. *(continued).*

Serum variables	Type of MVS	*n*	T0		*n*	T12		*n*	T24		*n*	T36	
PTH	Optimum 1.0	*69*	3.7	±2.0	*44*	3.3	±2.1	*33*	4.5	±4.2	*44*	3.6	±1.6
(pmol/L)	Optimum 2.0	*75*	3.3	±2.0	*34*	3.9	±2.2	*30*	4.5	±2.0	*19*	5.0	±1.2
	sMVS	*70*	4.0	±2.5	*88*	3.8	±2.0	*33*	3.9	±1.7	*37*	4.7	±2.1
	Non-users	-			*23*	3.2	±1.8	*25*	4.9	±2.5	*33*	4.6	±2.9
Calcium[1]	Optimum 1.0	*62*	2.35	±0.11	*44*	2.40	±0.09	*31*	2.36	±0.09	*34*	2.36	±0.09
mmol/L	Optimum 2.0	*66*	2.34	±0.10	*34*	2.39	±0.09	*31*	2.35	±0.07	*20*	2.32	±0.07
	sMVS	*68*	2.35	±0.09	*88*	2.39	±0.08	*28*	2.35	±0.07	*35*	2.34	±0.09
	Non-users	-			*23*	2.36	±0.06	*26*	2.29	±0.09	*32*	2.33	±0.09
Albumin	Optimum 1.0	*63*	37.8	±3.8	*44*	38.7	±3.1	*31*	38.1	±2.8	*34*	38.6	±3.1
(g/L)	Optimum 2.0	*66*	38.2	±2.9	*34*	38.5	±3.1	*31*	38.6	±2.4	*20*	40.1	±3.4
	sMVS	*68*	37.8	±2.6	*89*	38.3	±2.9	*28*	39.2	±3.1	*35*	39.7	±3.1
	Non-users	-			*23*	38.8	±2.7	*26*	39.8	±3.3	*32*	38.8	±3.1

Data are presented as mean ± standard deviation.

MCV, mean corpuscular volume; *sMVS,* standard multivitamin supplementation.

[1]Corrected for albumin levels (total calcium – (0.025 x albumin) + 1).



Supplementary Figure 1. Flowchart of the study population of the VITAAL I and VITAAL II study at baseline (T0), after the 12-month intervention period (T12), and at 24 and 36 months of follow-up (T24, T36).

CHAPTER 7

Factors affecting patient adherence to multivitamin intake after bariatric surgery: A multicentre survey study from the patient's perspective

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Obesity Surgery, 2021; 31(10): 4316-4326

Abstract

Background: Lifelong multivitamin supplementation (MVS) after bariatric surgery is recommended to prevent nutritional deficiencies. Despite this advice, deficiencies are common which may be due to poor adherence to MVS intake. The aim of this study was to identify which factors affect patient adherence to MVS intake after bariatric surgery.

Methods: A 42-item questionnaire was sent to 15,424 patients from four bariatric centers in the Netherlands. In total, 4614 patients were included in the study, and MVS users (n=4274, 92.6%) were compared to non-users (n=340, 7.4%). Most patients underwent Roux-en-Y gastric bypass (64.3%) or sleeve gastrectomy (32.3%).

Results: Overall, 710 patients (15.4%) reported inconsistent MVS use and 340 patients (7.4%) did not use any MVS. For inconsistent MVS users, most reported reasons included forgetting daily intake (68.3%), gastrointestinal side effects of MVS (25.6%) and unpleasant smell or taste of MVS (22.7%), whereas for non-users general gastrointestinal side effects (58.5%), high costs of MVS (13.5%) and the absence of deficiencies (20.9%) were most frequently reported. Overall, 28.5% of the patients were dissatisfied about instructions on MVS use, attention paid to MVS use during medical consultations and the extent to which personal preferences were taken into account.

Conclusion: The attitude of bariatric patients towards MVS use is predominantly negative. It is important to provide accurate information on different options of MVS and collect information about patient's personal preferences when prescribing supplements. Improving adherence to MVS intake is challenging and requires implementation of a shared decision-making process, further optimization of MVS formulations and exploring options for reimbursement.

Introduction

Worldwide, severe obesity is a fast-growing problem for which bariatric surgery is an effective treatment to lose weight and improve obesity-related comorbidities, including hypertension, dyslipidemia, type 2 diabetes mellitus and obstructive sleep apnea syndrome [1]. In spite of multiple clinical benefits, all bariatric procedures alter the anatomy and physiology of the gastrointestinal tract to variable degrees. As a result, patients are more susceptible to developing nutritional deficiencies. Therefore, lifelong use of multivitamin supplementation (MVS) is recommended [2-4]. However, therapeutic non-adherence to MVS intake after bariatric surgery is frequently encountered in both clinical practice and research, and is therefore a major topic of discussion [5, 6]. Despite proven safety and effectiveness, a large number of bariatric patients stop taking MVS or become less consistent with MVS intake over time. Potential barriers and facilitators of non-adherence have recently been described in a narrative review by our group [7], but research in the population of bariatric patients is lacking. The aim of this study is to identify which factors affect patient adherence to MVS intake after bariatric surgery from the patient's perspective.

Methods

We conducted a cross-sectional, non-validated 42-item survey among bariatric patients from four high-volume bariatric centers in the Netherlands: Catharina Hospital Eindhoven (CZE), Rijnstate Hospital Arnhem (RHA), Franciscus Gasthuis & Vlietland (FGV) and Onze Lieve Vrouwe Gasthuis (OLVG). All questions were multiple-choice and divided into four topics: patient-related factors, MVS-related factors, psychosocial and economic-related factors and healthcare-related factors. The format of these topics was established based on the study by Jin et al. [8]. A previous review on potential influential factors for adherence to MVS intake by our research group was used as input for the questionnaire [7].

We included patients who underwent bariatric surgery from 2010 to 2020, including Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), one-anastomosis gastric bypass, single anastomosis duodenal-ileal bypass and duodenal switch. Patients who underwent revisional and/or secondary surgery were also included. Exclusion criteria were incomplete questionnaires and reversal of the bariatric procedure ('undo surgery'). In total, 15,424 patients were recruited between October and December 2020 (**Figure 1**). All data were anonymously collected in Data Management (Research Manager, Deventer, The Netherlands). Digital informed consent was obtained from all participants.

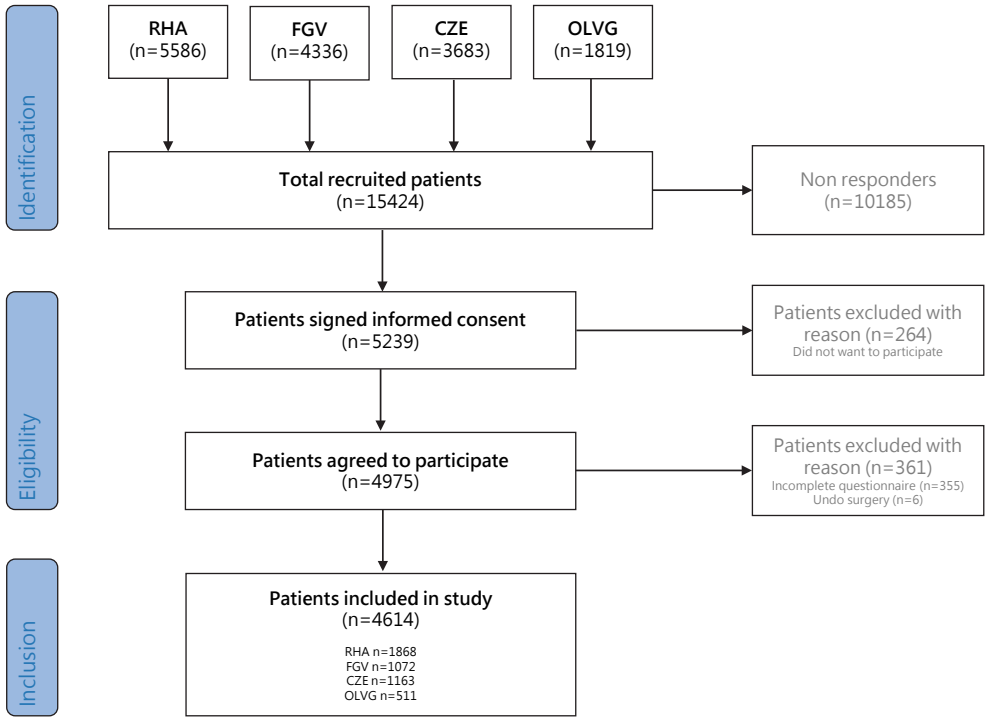

Figure 1. Flowchart of patient inclusion.
RHA, Rijnstate Hospital Arnhem; *FGV*, Franciscus Gasthuis & Vlietland; *CZE*, Catharina Hospital Eindhoven; *OLVG*, Onze Lieve Vrouwe Gasthuis.

Statistical analysis

Continuous data are presented as mean ± standard deviation for normally distributed data and as median [Q1-Q3] for non-normally distributed data. Categorical variables are presented as frequencies and percentages.

Differences in outcomes between MVS users and non-users were compared using independent t-tests and Mann-Whitney U tests for normally distributed and non-normally distributed continuous variables, respectively. Chi-square tests were used for comparing categorical variables.

All statistical analyses were performed using IBM SPSS Statistics 25 for Windows (IBM Corp., Armonk USA). A two-sided *P*-value below 0.05 was considered statistically significant.

Results

Patient-related factors

In total, 5239 patients (34%) signed the informed consent of which 4614 patients were available for analysis (**Figure 1**). The study population was divided into two groups: MVS users (n=4274, 92.6%) and non-users (n=340, 7.4%) (**Table 1**). Both groups were similar with respect to gender, educational level, body weight and BMI. In comparison with MVS users, non-users were younger (51.0 [43.0-57.0] years vs 43.0 [33.0–53.0] years) and differed in marital status, type of surgery and time since surgery (*P*<0.01 for all).

Table 1. General characteristics of the total study population, MVS users and non-users.

	Total group (n=4614)	**MVS users** (n=4274)	**Non-users** (n=340)	***P*-value**
Age (years)	51.0 [43.0-57.0]	51.0 [43.0-57.0]	43.0 [33.0-53.0]	**<0.001**
Gender (male)	930 (20.2)	871 (20.4)	59 (17.4)	0.18
Marital status				**0.001**
Single	772 (16.7)	694 (16.2)	78 (22.9)	
Living with partner	606 (13.1)	547 (12.8)	59 (17.4)	
Married or registered	2900 (62.9)	2721 (63.7)	179 (52.6)	
Divorced or separated	251 (5.4)	233 (5.5)	18 (5.3)	
Widowed	85 (1.8)	79 (1.8)	6 (1.8)	
Education level[1]				0.62
Low	1165 (25.2)	1085 (25.4)	80 (23.5)	
Medium	2062 (44.7)	1902 (44.5)	160 (47.1)	
High	1387 (30.1)	1287 (30.1)	100 (29.4)	
Body weight (kg)	84.0 [73.6-97.0]	84.0 [73.5-97.0]	85.0 [74.1-98.8]	0.26
BMI (kg/m^2)	28.7 [25.7-32.4]	28.7 [25.7-32.4]	28.7 [25.9-33.2]	0.47
Type of surgery				**<0.001**
RYGB	2966 (64.3)	2819 (66.0)	147 (43.2)	
SG	1490 (32.3)	1305 (30.5)	185 (54.4)	
OAGB	108 (2.3)	105 (2.5)	3 (0.9)	
Other	43 (0.9)	39 (0.9)	4 (1.2)	
Unknown	7 (0.2)	6 (0.1)	1 (0.3)	
Time since surgery				**<0.001**
0-1 years	680 (14.7)	658 (15.4)	22 (6.5)	
1-2 years	1071 (23.2)	1024 (24.0)	47 (13.8)	
2-3 years	1096 (23.8)	1011 (23.7)	85 (25.0)	
3-4 years	866 (18.8)	771 (18.0)	95 (27.9)	
4-5 years	570 (12.4)	521 (12.2)	49 (14.4)	
>5 years	331 (7.2)	289 (6.8)	42 (12.4)	

Data are presented as median [Q1-Q3] and frequency (percentage).

MVS, multivitamin supplementation; *BMI*, body mass index; *RYGB*, Roux-en-Y gastric bypass; *SG*, sleeve gastrectomy; *OAGB*, one-anastomosis gastric bypass.

[1] Low education = primary education and prevocational secondary education; medium education = senior general secondary education, pre-university education and secondary vocational education; high education = higher vocational education and university.

MVS-related factors

In total, 4274 patients (92.6%) used a MVS after bariatric surgery. The majority of the MVS users (85.2%) used specifically designed 'weight loss surgery' (WLS) MVS, of which most used the formulations of 'FitForMe' (69.5%). Other reported WLS formulations were 'Vitamine op recept' (8.5%), 'Flindall' (3.9%) and 'Elan' (3.0%). A small part of the MVS users (12.7%) used regular over-the-counter MVS.

Of all MVS users, 15.4% did not take their MVS consistently, for which most frequently reported reasons were 'forgetting daily intake' (68.3%), 'gastrointestinal side effects' (e.g. dyspepsia, difficulty with swallowing; 25.6%) and 'unpleasant smell or taste' (22.7%) (**Figure 2**). Moreover, 17.0% reported that scheduling their daily intake is difficult because of interactions with the calcium/vitamin D supplement or other medication. They believed that their MVS intake would improve if they could take all tablets at the same time. The majority of the non-users stopped taking MVS more than one year after surgery (52.7%). Compared to MVS users with inconsistent MVS intake, non-users reported different reasons for non-compliance with daily MVS intake (**Figure 2**). For non-users, gastrointestinal side effects of MVS were also a major factor (58.5%), as well as high costs of MVS (13.5%). A large part of the non-users also believed that they do not require any MVS as their laboratory results are good and they feel physically fit (20.9%). In both groups, a small part of the patients reduced or stopped MVS intake on advice of their physician due to elevated serum levels.

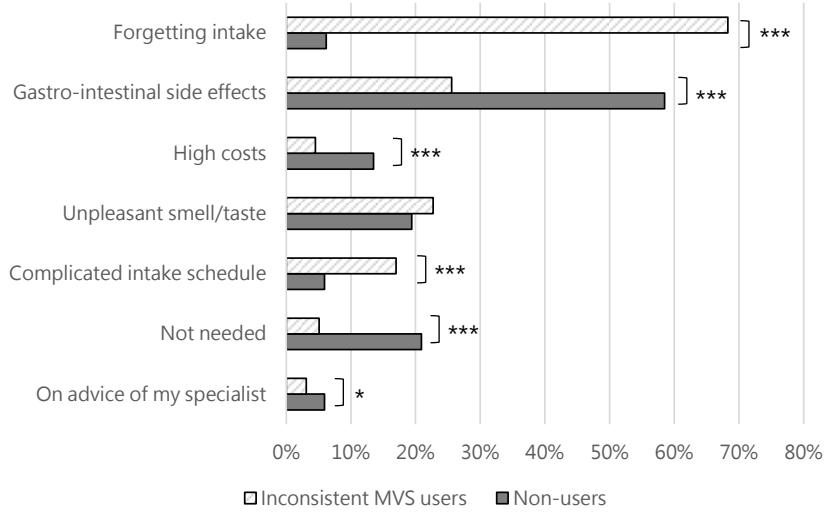

Figure 2. Reported reasons for non-compliance with MVS for inconsistent MVS users and non-users.
* $P<0.05$, *** $P<0.001$.

Gastrointestinal complaints

In this paragraph, a distinction is made between post-operative gastrointestinal complaints in general (independent of MVS intake) and gastrointestinal side effects that are directly related to MVS intake.

General post-operative gastrointestinal complaints occurred more often in non-users than in MVS users (37.4% vs 26.3%, $P<0.001$). Most reported complaints included nausea, vomiting, difficulty with swallowing, abdominal bloating, (abdominal) pain or stomach cramps and dumping (**Figure 3a**). Less frequent reported complaints were diarrhea, gastro-esophageal reflux disease (GERD), belching and hiccups. The frequency of complaints was significantly different between both groups (**Figure 3b**). Most non-users experienced these complaints daily while this was a few days per week or month for most MVS users. Gastrointestinal complaints that were directly related to MVS intake were reported by 58.5% of the non-users. Most frequently reported complaints were nausea (85.4%), excessive belching and hiccups (43.7%), vomiting (42.7%), difficulty with swallowing (40.2%), bloated feeling (21.1%) and reflux (18.1%). These complaints occurred immediately after ingestion (29.4%), 5-10 minutes after ingestion (43.8%), 15-30 minutes after ingestion (18.6%) or more than one hour after ingestion (5.2%). For the majority, these complaints have arisen directly after starting MVS use (72.7%). After discontinuation of MVS use, 61.9% was free of complaints, while complaints reduced in 12.9% and worsened in 4.1%. In 17.0%, no differences were observed.

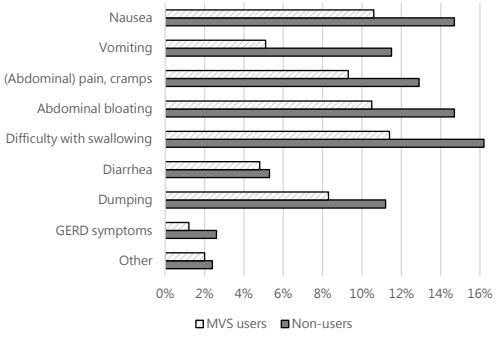

Figure 3a. Reported gastrointestinal complaints for MVS users and non-users.
Multiple answers were possible.

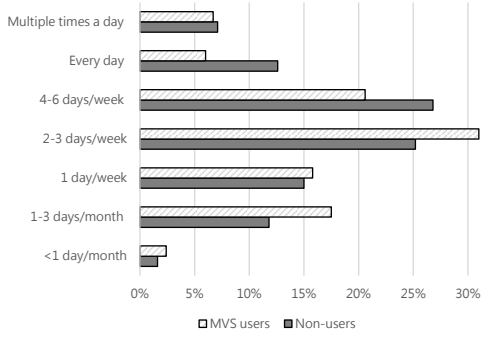

Figure 3b. Frequency of reported gastrointestinal complaints for MVS users and non-users.

Psychosocial and economic-related factors

Differences in psychosocial-related factors are described in **Table 2**. Of the MVS users, 10.6% was not motivated for daily MVS intake compared to 69.1% of the non-users ($P<0.001$). For the total study population, most reported reasons for poor motivation were absence of deficiencies (15.9%), absence of complaints (20.8%) or a combination of both (32.4%). Other reported factors included experiencing gastrointestinal side effects directly after MVS intake (10.4%) and the unpleasant smell, taste and/or size of MVS (2.9%). Some patients reported to only take their MVS because the healthcare professional tells them they have to take them. Moreover, some patients believed that they receive plenty of nutrients from their diet and therefore do not need to use MVS. A quarter of the non-users believed that the risk of nutrient deficiencies cannot be reduced by using MVS, compared to 9.1% of the MVS-users ($P<0.001$). The lifelong aspect of daily MVS intake is also a barrier for many patients (38.0% vs 60.6% for MVS-users vs non-users, $P<0.001$). The majority of these patients think that their adherence would be better if the treatment period was shorter (40.3% vs 64.6% for MVS-users vs non-users, $P<0.001$).

Strikingly, 72.3% of the MVS users reported no disadvantages of MVS use compared to 39.1% of the non-users ($P<0.001$). Similar to the reported reasons for demotivation, expected disadvantages from MVS use also include the high costs (17.0%), unpleasant side effects (12.2%), and risk of elevated serum levels (7.9%). Most of the MVS users though that the price of MVS is acceptable (60.6%), whereas most non-users found the price too high (61.2%). Many patients indicated that reimbursement of supplements would improve their adherence to MVS intake (38.1% vs. 43.5% for MVS-users vs non-users, $P=0.049$).

Overall, non-users were more often dissatisfied about the achieved postoperative weight loss compared to MVS-users (32.9% vs 21.0%, $P<0.001$) and 14.7% believed that MVS use has influenced their postoperative weight loss (15.2% vs 7.4% for MVS users vs non-users, $P<0.001$). Similarly, more non-users reported to receive no emotional support for lifestyle changes after bariatric surgery compared to MVS-users (30.9% vs. 18.3%, $P<0.001$). However, the majority of all patients (79.0%) reported that their MVS intake is not better because of this emotional support (78.0% vs 92.8% for MVS-users vs non-users, $P<0.001$).

Table 2. Differences in psychosocial-related factors between MVS users and non-users.

	MVS users (n=4274)	Non-users (n=340)	*P*-value
Are you motivated to use MVS lifelong?			**<0.001**
Yes	3819 (89.4)	105 (30.9)	
No	455 (10.6)	235 (69.1)	
Why are you not motivated?			
Good blood tests	72 (15.8)	38 (16.2)	
No complaints	104 (22.8)	40 (17.0)	
Good blood tests and no complaints	136 (29.8)	88 (37.4)	
Gastrointestinal side effects after MVS intake	47 (10.3)	25 (10.6)	
Unpleasant smell/taste/size	11 (2.4)	9 (3.8)	
Other	86 (18.9)	35 (14.9)	
Do you know why it is important to use MVS lifelong?[1]			-
To prevent nutrient deficiencies	4058 (94.9)	300 (88.2)	
To feel fit and energetic	1894 (44.3)	159 (46.8)	
To strengthen the immune system	1821 (42.6)	131 (38.5)	
To lose more weight	34 (0.8)	8 (2.4)	
Because the physician tells me to take them	200 (4.7)	38 (11.2)	
I don't know	41 (1.0)	16 (4.7)	
What disadvantages do you expect from MVS use? [1]			-
None	3088 (72.3)	133 (39.1)	
Unpleasant side effects	443 (10.4)	120 (35.3)	
The (high) costs of MVS	719 (16.8)	66 (19.4)	
The risk of elevated serum levels	331 (7.7)	32 (9.4)	
Having no effect on serum levels	138 (3.2)	44 (12.9)	
The physician having shares in MVS	66 (1.5)	9 (2.6)	
Lower weight loss	58 (1.4)	4 (1.2)	
Other	50 (1.2)	8 (2.4)	
Do you receive emotional support for lifestyle changes after surgery?[1]			-
No	782 (18.3)	105 (30.9)	
Yes, from my partner	2463 (57.6)	171 (50.3)	
Yes, from family	2247 (52.6)	161 (47.4)	
Yes, from friends	1618 (37.9)	98 (28.8)	
Yes, from healthcare professionals	1333 (31.2)	58 (17.1)	
Is your MVS intake better because of this emotional support?			**<0.001**
Yes	767 (22.0)	17 (7.2)	
No	2725 (78.0)	218 (92.8)	

Data are presented as frequency (percentage).

MVS, multivitamin supplementation.

[1] multiple answers were possible.

Healthcare-related factors

Compared to MVS users, non-users were more often dissatisfied with the instructions provided on the importance of MVS use, attention paid to MVS use during medical consultations and the extent to which personal preferences of MVS use were taken into account (*P*<0.001 for all, **Figure 4**). Most frequently reported reasons for scoring poor or inadequate on one of these subscales (n=1315, 28.5%) were 'information is too general' (57.1%), 'personal preferences are not taken into account' (51.0%) and 'there is not enough time for adequate information about MVS during medical consultations' (36.5%). Other reasons were that patients needed to actively ask for information by themselves (28.9%) and that the consultation time was too short (23.5%). Less frequently reported reasons were that the patient was only told what he or she was doing wrong (9.4%), healthcare professionals only advised one type of MVS formulation and did not provide alternatives (6.5%), the patient did not feel understood (5.1%) and other reasons (Covid-19, topic of MVS was not discussed and misunderstanding the physician).

Topics that were reported to be unclear or missing were information about side effects (17.8%), disadvantages (12.2%) and benefits (4.9%) of MVS use. Moreover, patients reported that they do not know when (6.8%) or how (4.1%) to take their MVS. Some experienced a lack of information about alternative MVS options and what to do in case of complaints (3.0%). Half of all patients reported that their healthcare professional did not ask about MVS-related complaints (50.6% vs 42.4% for MVS users and non-users, *P*<0.001).

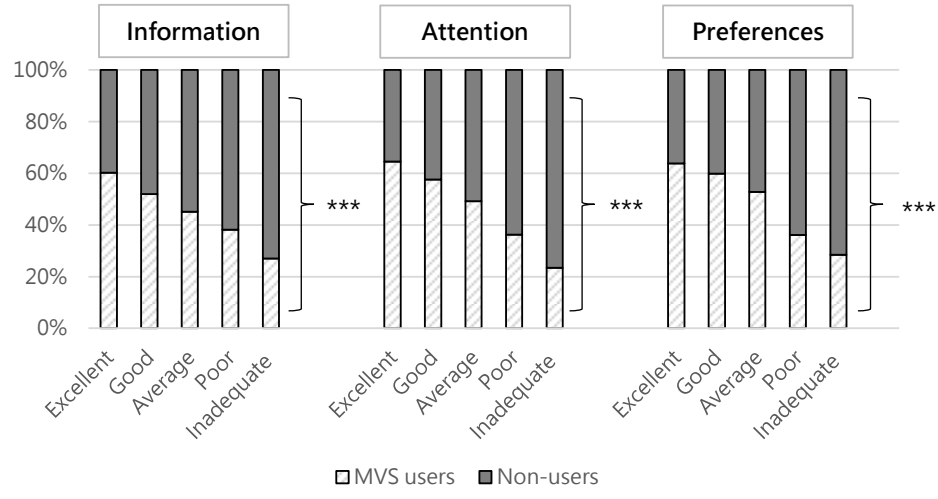

Figure 4. Rating scores of healthcare-related factors for MVS users and non-users.
***P<0.001.

Discussion

Overall, adherence to MVS intake was poor in 22.8% of all included patients, of which one third did not use any MVS. This non-adherence rate is in line with the review of Zarshenas et al. (20-32%) [9, 10]. An important difference between the MVS users and non-users in this study was the time since surgery, which was shorter for MVS users. In the study of Ben-Porat et al., 92.6% of the patients took MVS during the first postoperative year, whereas only 37.0% took MVS at 4 years post-surgery [11]. It is plausible that adherence to MVS intake is better in the first postoperative year due to an intensive follow-up compared to multiple years after surgery when most patients are often no longer supervised. The number of compliant MVS users in our study could therefore be overestimated. However, irrespective of adherence to MVS intake, the attitude of many bariatric patients towards MVS use was predominantly negative.

Barriers influencing adherence to MVS intake

Most frequently reported reasons to stop taking MVS (consistently) are gastrointestinal complaints, high costs and an unpleasant smell, taste or size of MVS. About one third of the patients suffered from gastrointestinal complaints and half of the patients indicated that healthcare professionals did not discuss these complaints during medical consultations, letting this problem underexposed.

A large part of the non-users believed that they do not need to take any MVS because their laboratory results are good and they feel fit. The majority of all patients understand that MVS is necessary, but not everyone seems convinced of the advantages of specialized WLS MVS. Patients often believe that the costs of WLS MVS do not outweigh the benefits, which can lead to lower adherence. However, it has been shown by Homan et al. that adequate supplementation results in less deficiencies and reduces overall healthcare costs [12]. Total costs per patient for prevention and treatment of vitamin deficiencies were €306 (regular MVS users) vs €216 (WLS MVS users) every three months, with a risk of developing a vitamin deficiency of 30% (regular MVS) vs 14% (WLS MVS) [12].

Dissatisfaction with medical consultations is another striking topic of this survey study. A third of the patients in our study was dissatisfied with the explanation about, and awareness for MVS use. Many patients indicated that the information on MVS use is too general and limited and that their personal preferences are not taken into account. Healthcare professionals often recommend one type of MVS supplement and patients therefore cannot choose which supplement suits their preferences. All of these issues may consequently contribute to poor motivation for adequate MVS intake.

The study by Osterberg et al. described that healthcare professionals contribute to patients' poor adherence by prescribing complex medication regimens, failing to explain side effects and benefits, not giving consideration to patients' lifestyle or the attributed costs of MVS, which may lead to a poor relationship with their patients [13]. In addition, the overall ability of healthcare professionals to recognize patients' non-adherence is poor [13]. These findings are confirmed by our study as many patients indicated to have received a lack of proper information. These healthcare-related findings are quite similar to those found in long-term adherence studies in other chronic diseases [7].

Challenges to improve adherence to MVS intake

There are three different parties that can improve patient adherence to MVS intake after bariatric surgery.

First, the healthcare professionals play a large part in improving satisfaction and patient adherence to MVS intake. They need to provide better education on MVS use and implement better shared-decision making with patients after bariatric surgery. Explanation about the necessity of MVS after bariatric surgery is an essential point, but MVS advices by healthcare professionals are often not in line with patients' personal preferences. There are several options for using MVS, all with pros and cons, which therefore should always be discussed during consultations to increase patient satisfaction. In addition, gastrointestinal complaints, in general or related to MVS intake, should also be part of the medical consultation in order to improve patient adherence to MVS intake. Assessment, prevention and management of gastrointestinal complaints are important parts of postoperative bariatric care, which is also described in the study by Zarshenas et al. [10]. Besides that, there should be more focus on improving the relationship between patient and healthcare professional. Having knowledge of patients' perceptions, beliefs and their personal circumstances is crucial for a decision-making process. It needs to be taken into account that the preferences of bariatric patients may differ considerably from those of the healthcare professional. Thus, the solution lies in shared decision-making (SDM) [14]. SDM describes the process where the patient must be well-informed, and patient preferences must become a more important part during medical consultations. The emphasis is not on the final decision but on the process that works towards this decision. Several studies show that SDM has a positive effect on the interaction between patient and healthcare professional. It increases the patient's level of knowledge, which leads to more accurate risk assessment of treatment options and increases patient assertiveness during SDM [15-20]. Application of SDM in MVS use after bariatric surgery could therefore be a breakthrough in improving the adherence.

Second, MVS manufactures can increase MVS adherence by further optimizing their supplements. MVS formulations should be scrutinized due to the high percentage of gastrointestinal side effects and an unpleasant taste and smell, which is indicated as an important barrier by many patients in our study. A significant decrease in intensity of taste and aversion to certain food types after bariatric surgery could be a contributing factor [21]. For this reason, many patients switch from WLS MVS to regular MVS. Many regular MVS have an enteric coating, which may reduce the unpleasant aftertaste that many patients suffer from. However, this type of coating is not desirable as the ability to absorb MVS is compromised after bariatric surgery [22]. A proper formula of supplements is necessary to ensure adequate absorption, which requires considerations of all drug substances and pharmaceutical ingredients [23]. An ideal combination of taste, appearance and color in supplements will contribute to its acceptance [24]. MVS manufacturers must investigate how these aspects can be improved while simultaneously ensuring adequate absorption.

Third, insurance companies could contribute to the improvement of patient adherence to MVS intake by reimbursing supplements. Costs are a frequently reported reason for patients to stop using specialized WLS MVS. Reimbursement of supplements with proven effectiveness could improve the therapy adherence, which is indicated by many patients in our study. Therefore, healthcare authorities involved in the reimbursement of bariatric procedures should consider integrating costs of WLS MVS with post-operative follow-up. We believe that only reimbursing WLS MVS with proven effectiveness, based on extensive scientific research should be considered. This reimbursement will motivate many patients to switch to WLS MVS.

Strengths and limitations

A strength of this study is that all patients between 2010 and 2020 were recruited to avoid selection bias. Participation was anonymous, no information from the electronic patient file was retrieved. There was no risk or personal benefit, which reduced the risk of giving socially desirable answers. To provide accurate assessment of MVS intake, the questions were designed with a free text field option to avoid that answers possibilities were too limited. Since patients from four hospitals were included, the external validity of this study is high and results can be used by many (inter)national obesity centers.

An important limitation is that 10,810 patients (70.1%) did not participate in this study. It is unclear whether these patients used a MVS. Long-term follow-up after bariatric surgery is poor despite clear international guidelines [25]. Furthermore, no validated questionnaire was used as such a questionnaire does not exist. However, our survey

study was intended to get a first impression of factors influencing adherence to MVS intake and to get insight into various topics for advice in daily practice. A validated questionnaire was therefore not required. Moreover, our questionnaire only contained self-reported patient data and provided subjective information that could not be verified due to the anonymous character, which could have caused both underestimation or overestimation of our findings.

Future perspectives

These results can be used for further hypothesis-generating research such as research into the influence of different bariatric procedures (primary vs revisional surgery) and time after surgery on patient adherence to MVS intake. It is important to analyze which patient groups are at higher risk for poor adherence to MVS intake and whether the percentage of deficiencies is higher in patients who do not use any MVS. The relationship between patient and healthcare professional and discrepancies between experiences from both perspectives are also important topics that need further clarification. Last, the development of tools supporting SDM in MVS use is important as well.

Conclusion

The attitude of many bariatric patients towards MVS use is predominantly negative. A large proportion of patients is dissatisfied with the advices on MVS intake during medical consultations and patients' personal preferences are often not taken into account. High costs, no reimbursement and gastrointestinal complaints lead to poor motivation for MVS intake. Gastrointestinal side effects, good laboratory results and an unpleasant taste and smell are the most frequently reported reasons for the discontinuation of MVS intake. It is important to take patients' preferences into account and to provide more extensive information about the different possibilities in MVS use.

Challenges lie in improving patient adherence by implementing SDM in MVS use, further optimization of WLS MVS formulations and exploring options for reimbursement, which could be major contributing factors in reducing nutritional deficiencies following bariatric surgery.

References

1. Genser, L and Barrat, C, *[Long term outcomes after bariatric and metabolic surgery].* Presse Med, 2018. **47**(5): p. 471-479.
2. Heber, D, Greenway, FL, Kaplan, LM, et al., *Endocrine and nutritional management of the post-bariatric surgery patient: an Endocrine Society Clinical Practice Guideline.* J Clin Endocrinol Metab, 2010. **95**(11): p. 4823-4843.
3. Mechanick, JI, Youdim, A, Jones, DB, et al., *Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient-2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery.* Surg Obes Relat Dis, 2013. **9**(2): p. 159-191.
4. Aills, L, Blankenship, J, Buffington, C, et al., *ASMBS Allied Health Nutritional Guidelines for the Surgical Weight Loss Patient.* Surg Obes Relat Dis, 2008. **4**(5 Suppl): p. S73-108.
5. Schijns, W, Schuurman, LT, Melse-Boonstra, A, et al., *Do specialized bariatric multivitamins lower deficiencies after RYGB?* Surg Obes Relat Dis, 2018. **14**(7): p. 1005-1012.
6. Heusschen, L, Schijns, W, Ploeger, N, et al., *The True Story on Deficiencies After Sleeve Gastrectomy: Results of a Double-Blind RCT.* Obes Surg, 2020. **30**(4): p. 1280-1290.
7. Smelt, HJM, Pouwels, S, Smulders, JF, et al., *Patient adherence to multivitamin supplementation after bariatric surgery: a narrative review.* J Nutr Sci, 2020. **9**.
8. Jin, J, Sklar, GE, Min Sen Oh, V, et al., *Factors affecting therapeutic compliance: A review from the patient's perspective.* Ther Clin Risk Manag, 2008. **4**(1): p. 269-286.
9. James, H, Lorentz, P and Collazo-Clavell, ML, *Patient-Reported Adherence to Empiric Vitamin/Mineral Supplementation and Related Nutrient Deficiencies After Roux-en-Y Gastric Bypass.* Obes Surg, 2016. **26**(11): p. 2661-2666.
10. Zarshenas, N, Tapsell, LC, Neale, EP, et al., *The Relationship Between Bariatric Surgery and Diet Quality: a Systematic Review.* Obes Surg, 2020. **30**(5): p. 1768-1792.
11. Ben-Porat, T, Elazary, R, Goldenshluger, A, et al., *Nutritional deficiencies four years after laparoscopic sleeve gastrectomy-are supplements required for a lifetime?* Surg Obes Relat Dis, 2017. **13**(7): p. 1138-1144.
12. Homan, J, Schijns, W, Janssen, IMC, et al., *Adequate Multivitamin Supplementation after Roux-En-Y Gastric Bypass Results in a Decrease of National Health Care Costs: a Cost-Effectiveness Analysis.* Obes Surg, 2019. **29**(5): p. 1638-1643.
13. Osterberg, L and Blaschke, T, *Adherence to medication.* N Engl J Med, 2005. **353**(5): p. 487-497.
14. Donovan, JL and Blake, DR, *Patient non-compliance: deviance or reasoned decision-making?* Soc Sci Med, 1992. **34**(5): p. 507-513.
15. Zorginstituut Nederland. *Toetsingskader kwaliteitsstandaarden, informatiestandaarden en meetinstrumenten 2015.* 2015. https://wetten.overheid.nl/BWBR0036641/2019-01-01
16. Joosten, EA, DeFuentes-Merillas, L, de Weert, GH, et al., *Systematic review of the effects of shared decision-making on patient satisfaction, treatment adherence and health status.* Psychother Psychosom, 2008. **77**(4): p. 219-226.
17. Legare, F, Adekpedjou, R, Stacey, D, et al., *Interventions for increasing the use of shared decision making by healthcare professionals.* Cochrane Database Syst Rev, 2018. **7**(7): p. CD006732.
18. Legare, F, Ratte, S, Gravel, K, et al., *Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions.* Patient Educ Couns, 2008. **73**(3): p. 526-535.
19. Stacey, D, Legare, F, Lewis, K, et al., *Decision aids for people facing health treatment or screening decisions.* Cochrane Database Syst Rev, 2017. **4**(4): p. CD001431.

20. Knops, AM, Legemate, DA, Goossens, A, et al., *Decision aids for patients facing a surgical treatment decision: a systematic review and meta-analysis.* Ann Surg, 2013. **257**(5): p. 860-866.
21. Tichansky, DS, Boughter, JD, Jr. and Madan, AK, *Taste change after laparoscopic Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding.* Surg Obes Relat Dis, 2006. **2**(4): p. 440-444.
22. Roth, DE, Pezzack, B, Al Mahmud, A, et al., *Bioavailability of enteric-coated microencapsulated calcium during pregnancy: a randomized crossover trial in Bangladesh.* Am J Clin Nutr, 2014. **100**(6): p. 1587-1595.
23. Lizer, MH, Papageorgeon, H and Glembot, TM, *Nutritional and pharmacologic challenges in the bariatric surgery patient.* Obes Surg, 2010. **20**(12): p. 1654-1659.
24. Allen, LV, Jr., *Dosage form design and development.* Clin Ther, 2008. **30**(11): p. 2102-2111.
25. Thereaux, J, Lesuffleur, T, Paita, M, et al., *Long-term follow-up after bariatric surgery in a national cohort.* Br J Surg, 2017. **104**(10): p. 1362-1371.

PART C

Pregnancy after bariatric surgery

CHAPTER 8

A matter of timing: Pregnancy after bariatric surgery

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Obesity Surgery, 2021; 31(5): 2072-2079

Abstract

Background: Current guidelines recommend to avoid pregnancy for 12-24 months after bariatric surgery because of active weight loss and an increased risk of nutritional deficiencies. However, high quality evidence is lacking and only a few studies included data on gestational weight gain. We therefore evaluated pregnancy and neonatal outcomes by both surgery-to-conception interval and gestational weight gain.

Methods: Multi-center retrospective analysis of 196 singleton pregnancies following Roux-en-Y gastric bypass, sleeve gastrectomy and one-anastomosis gastric bypass. Pregnancies were divided into the early group (≤12 months), the middle group (12-24 months) and the late group (>24 months) according to surgery-to-conception interval. Gestational weight gain was classified as inadequate, adequate or excessive according to the National Academy of Medicine recommendations.

Results: Pregnancy in the early group (23.5%) was associated with lower gestational age at delivery (267.1 ± 19.9 days vs 272.7 ± 9.2, and 273.1 ± 13.5 days, P=0.03), lower gestational weight gain (-0.9 ± 11.0 kg vs +10.2 ± 5.6, and +10.0 ± 6.4 kg, P<0.001) and lower neonatal birth weight (2979 ± 470 grams vs 3161 ± 481 and 3211 ± 465 grams, P=0.01) than pregnancy in the middle and late group. Inadequate gestational weight gain (40.6%) was also associated with lower gestational age at delivery (266.5 ± 20.2 days vs 273.8 ± 8.4 days, P=0.002) and lower neonatal birth weight (3061 ± 511 grams vs 3217 ± 479 grams, P=0.053) compared to adequate weight gain. Additionally, preterm births were more frequently observed in this group (15.9% vs 6.0%, P=0.04).

Conclusion: Our findings support the recommendation to avoid pregnancy for 12 months after bariatric surgery. Specific attention is needed on achieving adequate gestational weight gain.

Introduction

More than half of all female patients undergoing bariatric surgery are of reproductive age. Weight loss after bariatric surgery not only improves fertility [1], it also reduces the risk of gestational diabetes (GDM), hypertensive disorders and large-for-gestational age (LGA) neonates [2, 3]. On the other hand, infants born after maternal bariatric surgery may be at risk for preterm birth, admission to the neonatal intensive care unit and being small-for-gestational-age (SGA) [3-5]. These risks may be most pronounced in pregnancies within the first 12 months after surgery as this period theoretically carries the highest risk of malnutrition due to a markedly reduced caloric intake and rapid weight loss [6]. As a result, nutritional supply to the growing fetus may be decreased. Moreover, maternal caloric restriction and subsequent weight loss during this catabolic period may limit gestational weight gain. In 2009, the National Academy of Medicine (NAM; formerly known as the Institute of Medicine) presented recommendations on gestational weight gain according to the women's pregestational BMI [7]. In overweight and obese women, gestational weight gain below the lower limit of 5 kg is associated with an increased risk of SGA neonates and decreased neonatal birth weight, fat mass, lean mass, birth length and head circumference [8, 9].

Several organizations have proposed recommendations on timing of pregnancy following bariatric surgery, but uniformity and scientific evidence are lacking. According to the American Association of Clinical Endocrinology, the Obesity Society, and the American Society for Metabolic and Bariatric Surgery, pregnancy should be avoided for 12-18 months following bariatric surgery (2013) [10] whereas The American College of Obstetricians and Gynecologists proposes a wider time interval of 12–24 months post-surgery (2009, reconfirmed in 2019) [11]. Since the publication of these guidelines, several studies have evaluated pregnancy course and neonatal outcomes in women who conceived at different time intervals after surgery, but results are often limited by small sample sizes. Furthermore, only a few studies evaluated the impact of gestational weight gain [9, 12, 13].

Therefore, the aim of this retrospective, multi-center study was to evaluate pregnancy and neonatal outcomes by surgery-to-conception interval and by adherence to the recommendations for gestational weight gain of the NAM.

Methods

Study design

Data were extracted from medical records of female patients who previously underwent bariatric surgery and sought obstetric care at three large teaching hospitals in the Netherlands: Rijnstate hospital (Arnhem), Gelderse Vallei hospital (Ede) and Medical Centre Leeuwarden (Leeuwarden). Ethical approval for this study was obtained from all local Institutional Ethics Committees.

All surgeries were performed between 2005 and 2018, and included Roux-en-Y gastric bypass (RYGB), one-anastomosis gastric bypass (OAGB) and sleeve gastrectomy (SG). All deliveries occurred between October 2007 and August 2019. Exclusion criteria were spontaneous abortions, elective termination of pregnancy, multiple births, pre-existing diabetes mellitus and insufficient data about pregnancy.

Pregnancy and neonatal outcomes

All pregnancies were categorized based on (1) surgery-to-conception interval and (2) adherence to the NAM recommendations for gestational weight gain [7].

Time from surgery to conception was defined as the period in months between the date of surgery and the date of conception. Conception date was estimated as 'first day of last menstrual period + 2 weeks' or as 'due date - 40 +2 weeks' when the first day of the last menstrual period was unknown. Based on the surgery-to-conception time interval, patients were categorized into three groups: the early group (≤12 months), the middle group (12-24 months) and the late group (>24 months). Gestational weight gain was calculated as the difference between late pregnancy weight and pre-pregnancy weight in kilograms. Pre-pregnancy weight was reported as weight at the first antenatal visit or self-reported weight before pregnancy. Late pregnancy weight was extracted from medical records four weeks before delivery, at the earliest. Subsequently, weight gain was classified as inadequate, adequate or excessive according to the NAM recommendations (**Table 1**) [7].

Table 1. National Academy of Medicine Weight Gain Recommendations for pregnancy [7].

Pre-pregnancy BMI	Total weight gain (kg)
Underweight (<18.5 kg/m^2)	12.5 – 18.0
Normal weight (18.5-24.9 kg/m^2)	11.5 – 16.0
Overweight (25.0-29.9 kg/m^2)	7.0 – 11.5
Obese (≥30.0 kg/m^2)	5.0 – 9.0

BMI, body mass index.

Primary outcome variables were gestational age at delivery, preterm birth, birthweight and weight-for-age percentile. Preterm birth was defined as <37 weeks of gestation, and very preterm birth as <32 weeks of gestation according to the World Health Organization classification. Weight-for-age percentiles were calculated using the Dutch Perined birthweight charts, stratified for sex and gestational age at delivery in days [14]. Subsequently, LGA neonates (>90th percentile) and SGA neonates (<10th percentile) were identified.

Secondary outcome variables were Apgar score below 7 at 5 minutes, hospitalization of the neonate after birth, congenital defects and perinatal death. Cases of perinatal death were excluded for analyses of other neonatal outcomes.

Additionally, pregnancy-related complications were examined including gestational diabetes mellitus (GDM; new-onset diabetes diagnosed by glucose monitoring), pregnancy-induced hypertension (new-onset hypertension, above 140/90 mmHg at two occasions), preeclampsia (hypertension and proteinuria) and postpartum hemorrhage (postpartum bleeding of ≥1000 ml).

Statistical analysis

Differences in pre-pregnancy characteristics according to surgery-to-conception interval and gestational weight gain were analyzed by using one-way ANOVA for continuous data and Chi-Square tests for categorical data. Pregnancy and neonatal outcomes were analyzed by using multiple linear and logistic regression models while adjusting for maternal age, gravidity, parity, smoking status, pre-pregnancy BMI and type of surgical procedure. The early group and the adequate weight gain group were used as reference groups.

These analyses were performed on individual pregnancies, which made it possible for a woman to contribute more than one pregnancy. Therefore, a sensitivity analysis was performed by the Generalized-Estimating-Equation method with the mother's identification number as a cluster and assuming an exchangeable correlation structure to adjust for the possible dependence between pregnancies from the same mother. In another sensitivity analysis, inclusion was restricted to the first pregnancy per woman (exclusion of 33 pregnancies).

All statistical analyses were performed using IBM SPSS Statistics 25 for Windows (IBM Corp., Armonk USA). A two-sided *P*-value below 0.05 was considered statistically significant. *P*-values of planned pairwise comparisons with the reference groups were corrected by using the Bonferroni method.

Results

Demographic characteristics

A total of 196 singleton pregnancies of 163 women who previously underwent bariatric surgery were included. The majority of the study population had a Caucasian ethnicity (87.8%). The most commonly performed bariatric procedure was RYGB (68.4%), followed by SG (23.5%) and OAGB (8.2%). Mean total body weight loss from surgery to conception was 30.9% and about half of the women still had obesity (BMI ≥30 kg/m^2) at the time of conception. There were a few women with pre-existing hypertension (5.1%).

Pregnancy and neonatal outcomes according to surgery-to-conception interval

Table 2 shows pre-pregnancy characteristics, and pregnancy and neonatal outcomes according to surgery-to-conception interval. All groups were similar on pre-pregnancy characteristics, except for maternal age, pre-pregnancy BMI and type of surgical procedure (P<0.05 for all).

Pregnancy occurred within 12 months after surgery in 23.5% (early group), within 12-24 months in 21.9% (middle group) and after 24 months post-surgery in 54.6% of the pregnancies (late group). Mean time from surgery to conception was 7.6 ± 3 .5 months, 19.8 ± 3.6 months and 48.5 ± 19.7 months, respectively. Mean gestational age was significantly lower in the early group compared to the late group (267.1 ± 19.9 days vs 273.1 ± 13.5 days, P=0.03). There was also a trend towards more preterm births in the early group compared to the middle and late group (15.2% vs 4.7%, and 8.4%, P=0.09), but pairwise comparisons were not statistically significant.

Mean gestational weight gain was significantly lower in the early group compared to the middle and the late group (-0.9 ± 11.0 kg vs 10.2 ± 5.6 kg, and 10.0 ± 6.4 kg, P<0.001 for both). Subsequently, women in the early group had a higher risk of inadequate gestational weight gain compared to women in the middle and late group (75.0% vs 24.4%, and 32.6%, P<0.001), whereas the prevalence of excessive weight gain was lower (5.0% vs 34.1%, and 39.3%, P=0.01).

Mean neonatal birth weight was significantly lower in the early group in comparison to the late group (2979 ± 470 grams vs 3211 ± 465 grams, P=0.01), but there was no significant difference in the prevalence of SGA neonates.

No other differences in pregnancy and neonatal outcomes were found. In both sensitivity analyses, results for gestational age were borderline significant (P<0.10; data not shown).

Table 2. Pre-pregnancy characteristics, and pregnancy and neonatal outcomes according to time from surgery to conception.

Outcomes	Early group (≤12 m, n=46)		Middle group (12-24 m, n=43)		Late group (>24 m, n=107)		*P*-value	Pairwise comparisons
Pre-pregnancy characteristics								
Maternal age (years)	28.9	± 5.0	28.9	± 4.4	31.2	± 4.2	**0.002**	1 vs 3: *P*=0.01
Type of surgical procedure							**0.01**	
RYGB	26	(56.5)	28	(65.1)	80	(74.8)		
OAGB	5	(10.9)	8	(18.6)	3	(2.8)		
SG	15	(32.6)	7	(16.3)	24	(22.4)		
Time from surgery to conception (months)	7.6	± 3.5	19.8	± 3.6	48.5	± 19.7	**<0.001**	*P*<0.001 for both
Pre-pregnancy BMI (kg/m^2)	32.8	± 7.6	29.0	± 4.5	31.1	± 6.8	**0.02**	1 vs 2: *P*=0.02
TWL from surgery to conception (%)	-29.3	± 10.6	-34.2	± 9.0	-30.2	± 11.5	*ns*	
Nulliparous	22	(47.8)	17	(39.5)	45	(42.1)	*ns*	
Smokers	13	(28.3)	7	(16.3)	23	(21.5)	*ns*	
Pre-existent hypertension	4	(8.7)	3	(7.0)	3	(2.8)	*ns*	
Pregnancy outcomes								
Gestational age (days)	267.1	±19.9	272.7	± 9.2	273.1	± 13.5	**0.03**	1 vs 3: *P*=0.03
Preterm birth	7	(15.2)	2	(4.7)	9	(8.4)	*ns*	
Gestational weight gain (kg)[1]	-0.9	± 11.0	+10.2	± 5.6	+10.0	± 6.4	**<0.001**	*P*<0.001 for both
Adherence to the NAM recommendations[1]								
Inadequate	30	(75.0)	10	(24.4)	29	(32.6)	**<0.001**	*P*<0.001 for both
Adequate	8	(20.0)	17	(41.5)	25	(28.1)	*ns*	
Excessive	2	(5.0)	14	(34.1)	35	(39.3)	**0.01**	*P*<0.01 for both
GDM	4	(8.7)	3	(7.0)	9	(8.4)	*ns*	
Pregnancy-induced hypertension	2	(4.3)	3	(7.0)	6	(5.6)	*ns*	
Neonatal outcomes[2]								
Gender (male)	23	(51.1)	27	(64.3)	62	(58.5)	*ns*	
Birth weight (g)	2979	± 470	3161	± 481	3211	± 465	**0.01**	1 vs 3: *P*=0.008
Weight-for-age percentile	31.1	± 25.5	35.5	± 27.0	37.7	± 28.9	*ns*	
LGA (>90th percentile)	1	(2.2)	1	(2.4)	5	(4.7)	*ns*	
SGA (<10th percentile)	14	(31.1)	11	(26.2)	20	(18.9)	*ns*	
Apgar score <7 at 5 min	2	(4.4)	2	(4.9)	1	(0.9)	*ns*	
Admission at neonatology	13	(28.9)	7	(16.7)	22	(20.8)	*ns*	

Data are presented as mean ± SD or frequency (percentage). Reference group in grey.

RYGB, Roux-en-Y gastric bypass; *OAGB*, one-anastomosis gastric bypass; *SG*, sleeve gastrectomy; *BMI*, body mass index; *TWL*, total body weight loss; *NAM*, National Academy of Medicine; *GDM*, gestational diabetes mellitus; *LGA*, large-for-gestational age; *SGA*, small-for-gestational age. [1] missing: n=26. [2] Cases of perinatal death were excluded for analyses of neonatal outcomes (n=3).

Pregnancy and neonatal outcomes according to gestational weight gain

Data on late pregnancy weight was available for 170 pregnancies. **Table 3** shows pre-pregnancy characteristics, and pregnancy and neonatal outcomes according to adherence to the NAM recommendations for gestational weight gain. All groups were similar on pre-pregnancy characteristics, except for pre-pregnancy BMI and type of surgical procedure ($P<0.05$ for both). Gestational weight gain was adequate in only 29.4% of the pregnancies. It was inadequate in 40.6% and excessive in 30.0% of the pregnancies. Mean gestational age at delivery was significantly lower in the inadequate weight gain group compared to the adequate weight gain group (266.5 ± 20.2 days vs 273.8 ± 8.4 days, $P=0.002$). Additionally, there were more preterm births in the inadequate weight gain group (15.9% vs 6.0%, $P=0.04$), among which all three very preterm births. Mean birth weight was also lower in the inadequate weight gain group ($P=0.03$), but pairwise comparisons were not statistically significant and there was no difference in the risk of SGA neonates. When including only the first pregnancy after surgery, results were similar compared to the primary analysis. In the other sensitivity analysis, results for birth weight were not significant (data not shown).

Pregnancy-related complications

The prevalence of pregnancy-related complications was low and not related to surgery-to-conception interval or gestational weight gain. GDM was most prevalent and occurred in 8.2% of the pregnancies (n=16). In most cases, this could be treated by dietary management. Four women needed additional insulin therapy. Eleven women (5.6%) suffered from new-onset hypertension during pregnancy. None of them developed pre-eclampsia. Postpartum hemorrhage occurred in five cases (3.8%). Congenital defects were observed in ten neonates (5.1%) and included congenital talipes equinovarus (clubfoot, n=5), hypospadias (n=2), anal atresia, syndactyly and congenital hydrocephalus. There were three cases of perinatal death, one in each time group. During two of these pregnancies, gestational weight gain was inadequate. One neonate in the early and inadequate weight gain group was admitted to the neonatal intensive care unit because of a very preterm delivery (31+4 weeks). Of the 150 pregnancies following RYGB or OAGB, there were three cases of internal herniations. Two patients underwent successful laparoscopic closure of the internal hernia. The third patient, with a high suspicion of internal hernia at 27 weeks, experienced spontaneous resolution of symptoms and was therefore managed conservatively during pregnancy. Additionally, two women were admitted to the hospital because of gastrointestinal complaints and severe undernutrition, and needed enteral nutrition.

Table 3. Pre-pregnancy characteristics, and pregnancy and neonatal outcomes according to adherence to the NAM recommendations for gestational weight gain.

Outcomes	Inadequate (n=69)		Adequate (n=50)		Excessive (n=51)		*P*-value	Pairwise comparisons
Pre-pregnancy characteristics								
Maternal age (years)	30.3	± 4.5	29.3	± 4.9	30.2	± 4.2	*ns*	
Type of surgical procedure							**0.04**	
RYGB	40	(58.0)	39	(78.0)	37	(72.5)		
OAGB	12	(17.4)	2	(4.0)	2	(3.9)		
SG	17	(24.6)	9	(18.0)	12	(23.5)		
Time from surgery to conception (months)	26.1	± 22.7	30.9	± 20.3	41.1	± 24.3	**0.002**	*ns*
Pre-pregnancy BMI (kg/m^2)	32.7	± 8.7	29.6	± 4.9	29.9	± 4.3	**0.02**	2 vs 1: *P*=0.04
TWL from surgery to conception (%)	-29.8	± 11.9	-33.1	± 9.9	-31.7	± 9.8	*ns*	
Nulliparous	36	(52.2)	20	(40.0)	22	(43.1)	*ns*	
Smokers	18	(26.1)	8	(16.0)	12	(23.5)	*ns*	
Pre-existent hypertension	7	(10.1)	2	(4.0)	1	(2.0)	*ns*	
Pregnancy outcomes								
Gestational age (days)	266.5	± 20.2	273.8	± 8.4	274.6	± 10.1	**<0.001**	2 vs 1: *P*=0.002
Preterm birth	11	(15.9)	3	(6.0)	2	(3.9)	**0.02**	2 vs 1: *P*=0.04
GDM	10	(14.5)	3	(6.0)	1	(2.0)	*ns*	
Pregnancy-induced hypertension	6	(8.7)	1	(2.0)	3	(5.9)	*ns*	
Neonatal outcomes[1]								
Gender (male)	35	(52.2)	31	(63.3)	33	(64.7)	*ns*	
Birth weight (g)	3061	± 511	3217	± 479	3189	± 450	**0.03**	2 vs 1: *P*=0.053
Weight-for-age percentile	37.1	± 29.4	36.2	± 29.3	35.5	± 25.7	*ns*	
LGA (>90th percentile)	4	(6.0)	2	(4.1)	1	(2.0)	*ns*	
SGA (<10th percentile)	17	(25.4)	12	(24.5)	10	(19.6)	*ns*	
Apgar score <7 at 5 min	3	(4.5)	1	(2.0)	1	(2.0)	*ns*	
Admission at neonatology	16	(23.9)	10	(20.4)	11	(21.6)	*ns*	

Data are presented as mean ± SD or frequency (percentage). Reference group in grey.

RYGB, Roux-en-Y gastric bypass; *OAGB, one-anastomosis gastric bypass*; *SG*, sleeve gastrectomy; *BMI*, body mass index; *TWL*, total body weight loss; *GDM*, gestational diabetes mellitus; *LGA*, large-for-gestational age; *SGA*, small-for-gestational age.

[1]Cases of perinatal death were excluded for analyses of neonatal outcomes (n=3).

Discussion

Despite current recommendations, 23.5% of the women in this study cohort conceived within 12 months after bariatric surgery (early group). We found that gestational age at delivery, gestational weight gain and neonatal birth weight were lower in this group than in the middle (12-24 months) and the late (>24 months) group.
Overall, gestational weight gain was adequate in only 29.4% of the pregnancies. Inadequate weight gain during pregnancy was also associated with lower gestational age at delivery and lower neonatal birth weight in comparison with adequate gestational weight gain. In addition, (very) preterm births were more frequently observed in this group.

Previous studies found no associations between the time from surgery to conception and adverse pregnancy or neonatal outcomes [4, 15-24]. In fact, most studies confirm that the risk of these outcomes is not increased during the first 12 months after bariatric surgery compared to later pregnancies [4, 16, 17, 19, 22, 25]. Nevertheless, we found that gestational age at delivery and neonatal birth weight were lower in pregnancies within 12 months post-surgery. Although the difference of ±200 grams in neonatal birth weight is probably not clinically relevant, the lower gestational age in the early group might be alarming as we also found a trend towards more preterm births in this group.
We also found that gestational weight gain was lower during the first 12 months after surgery. Weight gain during pregnancy may directly affect the immediate and future health of mother and child. Therefore, the NAM has published recommendations for adequate weight gain during pregnancy based on pre-pregnancy BMI [7]. In the present study, gestational weight gain was below the NAM recommendations in 75% of the women who conceived within 12 months and in 30% of the women who conceived after 12 months. Our results are in accordance with two other studies that also found that gestational weight gain was higher and more adequate when pregnancy occurred more than 12 months after surgery [19, 26].

Very few studies have addressed the risks of inadequate weight gain during pregnancy after bariatric surgery [9, 13]. In the current study, gestational weight gain was adequate in only 29.4% of all pregnancies. We found that inadequate gestational weight gain was associated with a lower gestational age at delivery. Moreover, we observed three times as many preterm births in this group, including all three very preterm births (<32 weeks). In a large retrospective study including 337 pregnancies after RYGB, SG and laparoscopic adjustable gastric banding, insufficient weight gain was a risk factor for preterm delivery

when compared to excessive weight gain (adjusted OR: 6.40, 95% CI: 2.41–17.0) but not when compared to adequate weight gain [13]. Furthermore, inadequate weight gain was associated with a lower birth weight in the present study. No differences were found for SGA or weight-for-age percentile, which is in line with findings from other studies [9, 27]. Yet, half of the women in the inadequate weight gain group even lost weight during pregnancy. In the systematic review and meta-analysis of Kapadia et al. [28], obese women with gestational weight loss had higher odds of SGA <10th percentile (adjusted OR: 1.76, 95% CI: 1.45–2.14) and SGA <3rd percentile (adjusted OR: 1.62, 95% CI: 1.19–2.20) compared to women with adequate weight gain.

We should encourage women who wish to conceive after bariatric surgery to avoid pregnancy until their weight has stabilized to minimize the risk of inadequate gestational weight gain. This is in line with the consensus recommendations of an international panel of experts [29]. Additionally, the psychological impact of (gestational) weight gain in these women should not be underestimated. In daily practice, we encounter many women who are afraid to gain weight during pregnancy after bariatric surgery. Health care professionals should be aware of the underlying factors and encourage these women to have adequate weight gain during pregnancy.

The prevalence of SGA (23%) was at least twice as high than what would be expected based on its definition (<10th percentile), and higher than previously published data. The increased risk of SGA neonates is concerning since fetal growth restriction is associated with a higher risk of neonatal morbidity and mortality, and the development of metabolic syndrome later in life [30, 31]. In order to break the vicious cycle of obesity and its health consequences, it is important that future research and clinical care focus on the prevention of SGA after bariatric surgery. On the other hand, we remarked a low prevalence of LGA as well as GDM and hypertensive disorders. Whereas obesity is a well-known risk factor for these outcomes, multiple studies found a decrease in LGA neonates, GDM and pregnancy-related hypertensive disorders in pregnancy following bariatric surgery [2, 3].

This study is one of the largest series that evaluated pregnancy course and neonatal outcomes by surgery-to-conception interval and gestational weight gain. It should however be noted that the current sample size might have been too small for infrequent outcomes such as GDM and pregnancy-induced hypertension, increasing the risk of a type II statistical error. Another limitation is the retrospective nature of this study as the collected data depended entirely on the available data. Data on gestational weight gain

were not always consistently registered throughout pregnancy and patients' pre-pregnancy weight may have been underestimated since they were predominantly self-reported. Moreover, data on nutritional deficiencies were limited and could not be included in the analyses. We therefore cannot exclude the possibility that these and additional unknown factors could have influenced the observed outcomes. Lastly, we combined data of pregnancies following different types of surgery as previous studies found no differences in pregnancy outcomes [22, 32, 33]. Despite including this factor into the statistical models, observed differences in type of surgery could indicate an interrelationship between type of surgery, timing of pregnancy and gestational weight gain. Larger, prospective studies are needed to confirm this trend.

Conclusion

Our findings support the recommendation to postpone pregnancy for 12 months after bariatric surgery. During pregnancy, specific attention is needed on achieving adequate gestational weight gain. Future research should focus on the effect of inadequate gestational weight gain and maternal undernutrition on duration of pregnancy and fetal growth, aiming to reduce the increased prevalence of SGA neonates following maternal bariatric surgery.

References

1. Edison, E, Whyte, M, van Vlymen, J, et al., *Bariatric Surgery in Obese Women of Reproductive Age Improves Conditions That Underlie Fertility and Pregnancy Outcomes: Retrospective Cohort Study of UK National Bariatric Surgery Registry (NBSR).* Obes Surg, 2016. **26**(12): p. 2837-2842.
2. Johansson, K, Cnattingius, S, Näslund, I, et al., *Outcomes of Pregnancy after Bariatric Surgery.* N Engl J Med, 2015. **372**(9): p. 814-824.
3. Kwong, W, Tomlinson, G and Feig, DS, *Maternal and neonatal outcomes after bariatric surgery; a systematic review and meta-analysis: do the benefits outweigh the risks?* Am J Obstet Gynecol, 2018. **218**(6): p. 573-580.
4. Kjaer, MM and Nilas, L, *Timing of pregnancy after gastric bypass-a national register-based cohort study.* Obes Surg, 2013. **23**(8): p. 1281-1285.
5. Parent, B, Martopullo, I, Weiss, NS, et al., *Bariatric Surgery in Women of Childbearing Age, Timing Between an Operation and Birth, and Associated Perinatal Complications.* JAMA Surg, 2017. **152**(2): p. 1-8.
6. Carreau, AM, Nadeau, M, Marceau, S, et al., *Pregnancy after Bariatric Surgery: Balancing Risks and Benefits.* Can J Diabetes, 2017. **41**(4): p. 432-438.
7. Rasmussen, KM and Yaktine, AL, *Weight gain during pregnancy: Reexaming the guidelines. Institute of Medicine* 2009, National Academies Press: Washington DC.
8. Catalano, PM, Mele, L, Landon, MB, et al., *Inadequate weight gain in overweight and obese pregnant women: what is the effect on fetal growth?* Am J Obstet Gynecol, 2014. **211**(2): p. 137 e131-137.
9. Stentebjerg, LL, Andersen, LLT, Renault, K, et al., *Pregnancy and perinatal outcomes according to surgery to conception interval and gestational weight gain in women with previous gastric bypass.* J Matern Fetal Neonatal Med, 2016. **30**(10): p. 1182-1188.
10. Mechanick, JI, Youdim, A, Jones, DB, et al., *Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery.* Obesity, 2013. **21 Suppl 1**: p. S1-27.
11. American College of, O and Gynecologists, *ACOG practice bulletin no. 105: bariatric surgery and pregnancy.* Obstet Gynecol, 2009. **113**(6): p. 1405-1413.
12. Berglind, D, Willmer, M, Naslund, E, et al., *Differences in gestational weight gain between pregnancies before and after maternal bariatric surgery correlate with differences in birth weight but not with scores on the body mass index in early childhood.* Pediatr Obes, 2014. **9**(6): p. 427-434.
13. Grandfils, S, Demondion, D, Kyheng, M, et al., *Impact of gestational weight gain on perinatal outcomes after a bariatric surgery.* J Gynecol Obstet Hum Reprod, 2019. **48**(6): p. 401-405.
14. Hoftiezer, L, Hof, MHP, Dijs-Elsinga, J, et al., *From population reference to national standard: new and improved birthweight charts.* Am J Obstet Gynecol, 2019. **220**(4): p. 383 e381-383 e317.
15. Basbug, A, Ellibes Kaya, A, Dogan, S, et al., *Does pregnancy interval after laparoscopic sleeve gastrectomy affect maternal and perinatal outcomes?* J Matern Fetal Neonatal Med, 2018: p. 1-7.
16. Ducarme, G, Parisio, L, Santulli, P, et al., *Neonatal outcomes in pregnancies after bariatric surgery: a retrospective multi-centric cohort study in three French referral centers.* J Matern Fetal Neonatal Med, 2013. **26**(3): p. 275-278.
17. Malakauskiene, L, Nadisauskiene, RJ, Ramasauskaite, D, et al., *Is it necessary to postpone pregnancy after bariatric surgery: a national cohort study.* J Obstet Gynaecol, 2019: p. 1-5.
18. Norgaard, LN, Gjerris, AC, Kirkegaard, I, et al., *Fetal growth in pregnancies conceived after gastric bypass surgery in relation to surgery-to-conception interval: a Danish national cohort study.* PLoS One, 2014. **9**(3): p. e90317.

19. Rasteiro, C, Araujo, C, Cunha, S, et al., *Influence of Time Interval from Bariatric Surgery to Conception on Pregnancy and Perinatal Outcomes.* Obes Surg, 2018.**28**(11): p. 3559-3566.
20. Rottenstreich, A, Shufanieh, J, Kleinstern, G, et al., *The long-term effect of pregnancy on weight loss after sleeve gastrectomy.* Surg Obes Relat Dis, 2018. **14**(10): p. 1594-1599.
21. Sancak, S, Celer, O, Cirak, E, et al., *Timing of Gestation After Laparoscopic Sleeve Gastrectomy (LSG): Does it Influence Obstetrical and Neonatal Outcomes of Pregnancies?* Obes Surg, 2019. **29**(8): p. 2629-2630.
22. Sheiner, E, Edri, A, Balaban, E, et al., *Pregnancy outcome of patients who conceive during or after the first year following bariatric surgery.* Am J Obstet Gynecol, 2011. **204**(1): p. 50 e51-56.
23. Wax, JR, Cartin, A, Wolff, R, et al., *Pregnancy Following Gastric Bypass for Morbid Obesity: Effect of Surgery-to-Conception Interval on Maternal and Neonatal Outcomes.* Obes Surg, 2008. **18**(12): p. 1517-1521.
24. Yau, PO, Parikh, M, Saunders, JK, et al., *Pregnancy after bariatric surgery: the effect of time-to-conception on pregnancy outcomes.* Surg Obes Relat Dis, 2017. **13**(11): p. 1899-1905.
25. Dao, T, Kuhn, J, Ehmer, D, et al., *Pregnancy outcomes after gastric-bypass surgery.* Am J Surg, 2006. **192**(6): p. 762-766.
26. Dolin, CD, Chervenak, J, Pivo, S, et al., *Association between time interval from bariatric surgery to pregnancy and maternal weight outcomes.* J Matern Fetal Neonatal Med, 2019: p. 1-7.
27. Rottenstreich, A, Levin, G, Kleinstern, G, et al., *The effect of surgery-to-conception interval on pregnancy outcomes after sleeve gastrectomy.* Surg Obes Relat Dis, 2018. **14**(12): p. 1795-1803.
28. Kapadia, MZ, Park, CK, Beyene, J, et al., *Weight Loss Instead of Weight Gain within the Guidelines in Obese Women during Pregnancy: A Systematic Review and Meta-Analyses of Maternal and Infant Outcomes.* PLoS One, 2015. **10**(7): p. e0132650.
29. Shawe, J, Ceulemans, D, Akhter, Z, et al., *Pregnancy after bariatric surgery: Consensus recommendations for periconception, antenatal and postnatal care.* Obes Rev, 2019. **20**(11): p. 1507-1522.
30. Cosmi, E, Fanelli, T, Visentin, S, et al., *Consequences in infants that were intrauterine growth restricted.* J Pregnancy, 2011. **2011**: p. 364381.
31. Gascoin, G and Flamant, C, *[Long-term outcome in context of intra uterine growth restriction and/or small for gestational age newborns].* J Gynecol Obstet Biol Reprod (Paris), 2013. **42**(8): p. 911-920.
32. Coupaye, M, Legardeur, H, Sami, O, et al., *Impact of Roux-en-Y gastric bypass and sleeve gastrectomy on fetal growth and relationship with maternal nutritional status.* Surg Obes Relat Dis, 2018. **14**(10): p. 1488-1494.
33. Roos, N, Neovius, M, Cnattingius, S, et al., *Perinatal outcomes after bariatric surgery: nationwide population based matched cohort study.* BMJ, 2013. **347**: p. f6460.

CHAPTER 9

Nutritional status and supplement use during pregnancy following bariatric surgery: A multicenter observational cohort study

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Submitted

Abstract

Background: Pregnant women with a history of bariatric surgery (BS) are at high risk of maternal nutrient deficiencies, but prospective data on the efficacy of specialized multivitamin supplementation (WLS MVS) versus standard supplementation (sMVS) in pregnancies after BS are limited.

Methods: Multicenter observational cohort study including 119 pregnant women who had undergone Roux-en-Y gastric bypass (RYGB, n=80) or sleeve gastrectomy (SG, n=39). Routine blood samples including hemoglobin, MCV, ferritin, folic acid, vitamins A, B1, B6, B12 and D, calcium, PTH and albumin were collected during every trimester. Maternal serum micronutrient concentrations as well as prevalence of deficiencies and elevated serum levels were compared between WLS MVS users and sMVS users.

Results: During pregnancy following RYGB, WLS MVS users had higher serum levels of hemoglobin, ferritin and folic acid and lower serum levels of vitamin B6 compared to sMVS users. Iron deficiencies as well as elevated serum vitamin B6 levels were also less prevalent in the WLS MVS group. During pregnancy following SG, WLS MVS users had higher serum levels of vitamin D but lower serum levels of vitamin B1 than sMVS users. The prevalence of deficiencies and elevated serum levels was similar between the groups.

Conclusion: Our study confirmed that depleted maternal concentrations of micronutrients are highly prevalent in pregnant women who underwent RYGB or SG. Overall, the use of specialized WLS MVS is preferred over the use of standard, over-the-counter supplementation. Future research is needed to investigate how supplementation strategies can be optimized individually for this high-risk population.

Introduction

Bariatric surgery (BS) is the most effective treatment for people with severe obesity, resulting in substantial and long-term weight loss and reduction of obesity-related health risks [1-3]. More than half of all bariatric procedures are performed in women of reproductive age [4], and the Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most commonly performed bariatric procedures [5]. Undergoing BS prior to pregnancy significantly reduces the risk of obesity-related complications such as subfertility, gestational diabetes and hypertensive disorders in pregnancy [6-8]. However, decreased intake and absorption of nutrients after surgery in combination with the increased demand for nutrients during pregnancy may lead to more pronounced deficiencies [9, 10]. Furthermore, pregnancy symptoms such as morning sickness or hyperemesis gravidarum and abdominal complaints may worsen nutritional status during pregnancy [10, 11]. Overall, low maternal concentrations of vitamins A, B12 and D, folic acid, iron and zinc are frequently reported during pregnancy after BS [12-14]. Potential neonatal adverse effects that are associated with maternal deficiencies during pregnancy include preterm birth, fetal growth restriction, congenital malformations, and neurological and developmental impairment [10, 11, 13, 15].

Consensus recommendations for prenatal care of these patients have been proposed [16], but evidence-based guidelines regarding optimal nutritional monitoring and supplementation strategies during pregnancy after BS are lacking. Regular, over-the-counter or prenatal multivitamin supplements (MVS) are likely not sufficient to cover the needs of pregnant women who have undergone BS. Fortunately, specialized 'weight loss surgery' supplements (WLS MVS) that are specifically developed for bariatric patients are emerging. The formulation of these supplements is often tailored to the type of bariatric procedure (e.g. RYGB or SG) and varies between brands, but they generally consist of high doses of folic acid, vitamins B12 and D, elementary iron and zinc. Although the superiority of these supplements compared to standard multivitamin supplementation (sMVS) has been demonstrated in the general population after BS [17-21], their efficacy during pregnancy is largely unknown.

Therefore, the aim of this observational cohort study was to explore differences in nutritional status among women either using WLS MVS or sMVS during pregnancy following RYGB or SG.

Methods

Study design and participants

The NEWBIE study (**N**utritional status of pr**E**gnant **W**omen following **B**ariatr**I**c surg**E**ry) is a multicenter observational cohort study that was conducted from November 2018 until October 2022 at three general hospitals in the Netherlands (Rijnstate hospital, Arnhem; RHA, Máxima Medical Center, Veldhoven; MMC, Hospital Gelderse Vallei, Ede; HGV). Within these hospitals, the care of pregnant women with a history of BS follows a specific protocol recommending supplementation with WLS MVS and close monitoring of maternal nutritional status.

All pregnant women older than 18 years with a medical history of BS presenting at the bariatric or antenatal clinic were eligible for recruitment. Exclusion criteria were elective termination of pregnancy, twin pregnancy, bariatric procedures other than RYGB or SG, reversal of the bariatric procedure and malnutrition due to other causes (e.g. cancer, alcoholism). Participants were preferably included before 12 weeks of pregnancy and followed up until two months post-partum. A total of 129 participants were included of which three women were excluded because of twin pregnancies (n=2) or history of another bariatric procedure (n=1). During data analysis, seven participants were excluded because of insufficient data about pregnancy (n=1), unknown MVS use (n=4) or no use of MVS during pregnancy (n=2). The final population for data analysis consisted of 119 participants of which 80 had undergone RYGB (67%) and 39 SG (33%) (**Figure 1**).

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 local ethical committees of the participating hospitals. Written informed consent was obtained from all subjects.

Data collection

Clinical parameters

Maternal characteristics (age, geographic origin, education, smoking status, pre-existing diabetes or hypertension and anthropometrics) and antepartum variables (time to conception, parity, gestational weight gain and pregnancy complications) were collected from the medical records. Educational level was defined as low (primary education and prevocational secondary education), medium (senior general secondary education, pre-university education and secondary vocational education) or high (higher vocational education and university). Smoking status was defined as never, former (stopped before pregnancy) or current (smoked during pregnancy).

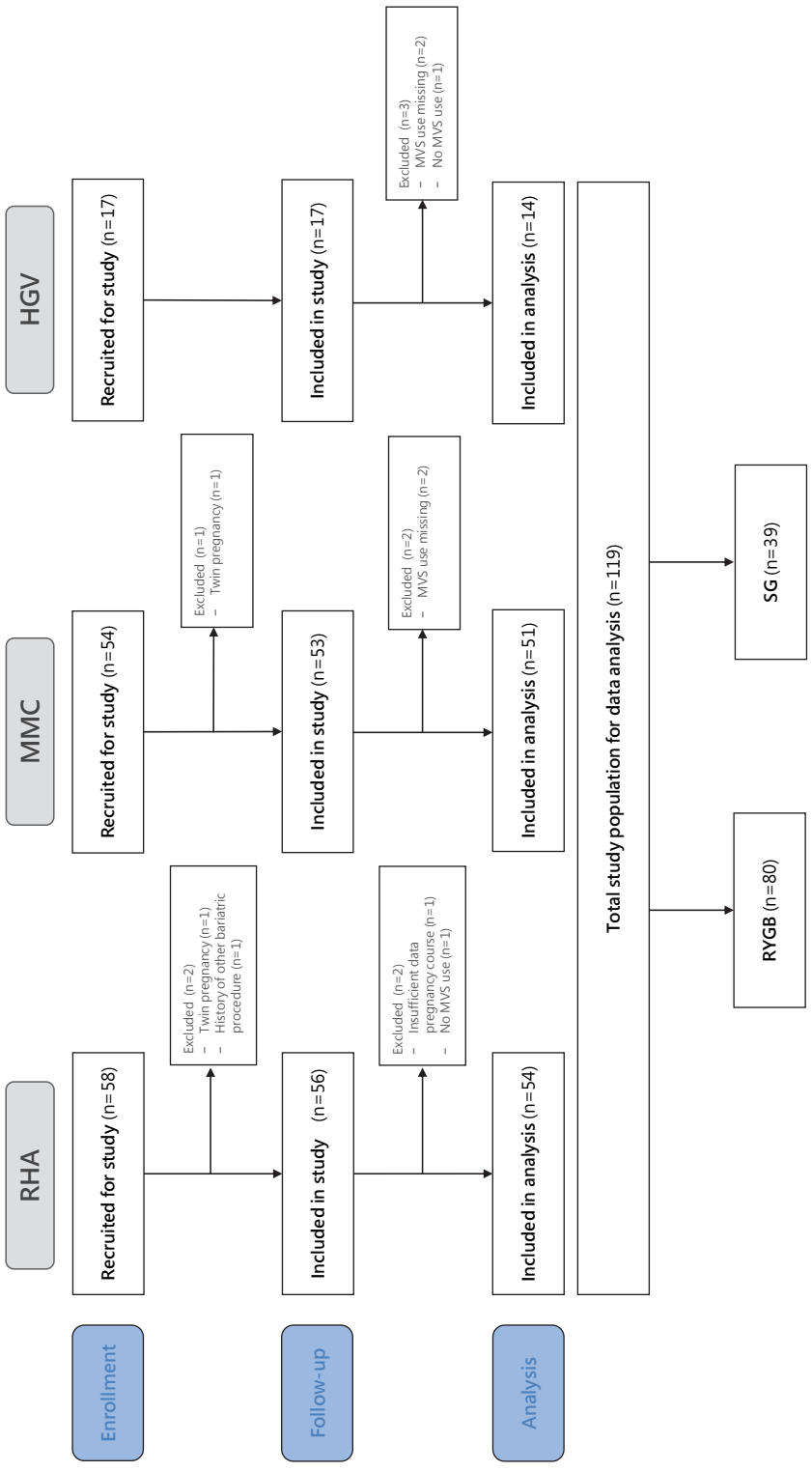


Figure 1. Flowchart of inclusion.
RHA, Rijnstate hospital Arnhem; *MMC,* Maxima Medical Center; *HGV,* Hospital Gelderse Vallei.

Anthropometric measurements including height (m) and body weight (kg) were performed during standard visits. Percent total body weight loss (%TWL) at conception was calculated as body weight loss divided by body weight before surgery, multiplied by 100%.

Conception date was estimated as 'first day of last menstrual period + 2 weeks' or as 'due date - 40 +2 weeks' when the first day of the last menstrual period was unknown. Time from surgery to conception was defined as the period in months between the date of surgery and the date of conception. Gestational weight gain in kilograms was calculated as the difference between late pregnancy weight (weight at the day of delivery or within ≤4 weeks before delivery) and pre-pregnancy weight (weight at the first antenatal visit or self-reported weight before pregnancy). Subsequently, gestational weight gain was classified as inadequate, adequate or excessive based on pre-pregnancy BMI according to the National Academy of Medicine (NAM; formerly known as the Institute of Medicine) recommendations [22]. Evaluated complications during pregnancy included gestational diabetes mellitus (new-onset diabetes diagnosed by glucose monitoring), hypertensive disorders (new-onset hypertension, above 140/90 mm Hg), hyperemesis gravidarum (severe, persistent nausea and vomiting) and internal herniation (small bowel obstruction).

Supplementation use

All women were advised to use daily multivitamin supplementation (MVS), preferably a specialized 'weight loss surgery' supplement (WLS MVS) specifically developed for bariatric patients. Self-reported information on the use of MVS (type, composition, dosage and compliance) was obtained during each trimester and participants were accordingly categorized as either users of WLS MVS or users of standard MVS (sMVS). sMVS were defined as regular over-the-counter MVS or prenatal supplements. The composition of the MVS that were most frequently used can be found in **Supplementary Table 1**. Participants using both WLS MVS and sMVS on a daily basis were assigned to the WLS MVS group, whereas participants who alternately used WLS MVS and sMVS were assigned to the sMVS group. Non-users of MVS were excluded from analysis.

In addition to daily MVS, all participants were advised to use additional calcium/vitamin D3 supplementation as part of the standard treatment after BS. According to general recommendations for pregnancy of the Dutch Health Council [23], supplementation of 400 µg folic acid was also recommended in the preconception period until 8 weeks after conception. In case of observed micronutrient deficiencies during pregnancy, a prescription for the required supplementation was provided according to local protocol.

Laboratory evaluation

Standard routine laboratory blood tests were performed during each trimester (T1: week 1-12, T2: week 13-26. T3: week 27-42). Evaluated laboratory parameters slightly differed between the centers but generally included: hemoglobin, MCV, ferritin, folic acid, vitamin B12, vitamin A, vitamin B1, vitamin B6, 25-OH vitamin D, PTH, calcium and albumin. Although the use of MVS has no direct influence on MCV, PTH and albumin levels, they were added to provide a complete overview of nutritional status during pregnancy after RYGB and SG. Calcium levels were corrected for albumin using the following equation: Ca_{corr} = total calcium + 0.02*(40-albumin). A nutrient deficiency was defined as a serum level below the local reference value at the time of blood collection (**Table 1**) as there were no validated standards available for the required levels of micronutrients during pregnancy, except for hemoglobin [24]. Serum ferritin levels below the reference value were used as a marker for iron deficiency.

Table 1. Reference values of the evaluated micronutrients for each hospital.

Serum variables	Reference values		
	RHA	**MMC**	**HGV**
Hemoglobin[1]	T1: 7.1 mmol/L	T1: 7.1 mmol/L	T1: 7.1 mmol/L
MCV	80-100 fL	80-100 fL	80-100 fL
Ferritin	10-291 µg/L	13-150 µg/L	13-150 µg/L
Folic acid	> 12.2 nmol/L[2]	> 8 nmol/L	7-40 nmol/L
Vitamin B12[3]	>200 pmol/L	>200 pmol/L	>200 pmol/L
Vitamin A	1.05-2.80 µmol/L	*NA*	1.13-2.72 µmol/L
Vitamin B1	95-175 nmol/L	66.5-200 nmol/L	90-200 nmol/L
Vitamin B6	25-100 nmol/L	35-110 nmol/L	51-183 nmol/L
Vitamin D	>50 nmol/L	>50 nmol/L	>50 nmol/L
PTH	2.0-9.3 pmol/L[4]	1.6-6.9 pmol/L	2.0-8.5 pmol/L
Calcium[5]	2.23-2.55 mmol/L	2.15-2.55 mmol/L	2.23-2.55 mmol/L
Albumin	35-50 g/L	35-50 g/L	35-50 g/L

RHA, Rijnstate hospital Arnhem; *MMC,* Maxima Medical Center; *HGV,* Hospital Gelderse Vallei; *MCV,* mean corpuscular volume; *PTH,* parathyroid hormone.

[1] Reference value during pregnancy according to The Royal Dutch Organization of Midwives (2010) [24].

[2] Reference value before 8-1-2019 was 5-35 nmol/L.

[3] Reference value after bariatric surgery according to Parrot (2017) [25].

[4] Reference value before 8-1-2019 was 1,3-6,8 pmol/L.

[5] Corrected for albumin levels.

Statistical analysis

General characteristics are reported as mean ± standard deviation (normal distribution) or as median [Q1-Q3] (non-normal distribution) for continuous variables, and as frequency (percentage) for categorical variables. Differences in serum concentrations across the three trimesters of pregnancy between WLS MVS users and sMVS users were

analyzed using linear mixed-effects models. Serum concentrations of ferritin and vitamin B6 were log-transformed before analysis. The crude model consisted of fixed effects for MVS (WLS MVS; sMVS), trimester (T1; T2; T3), and their interaction term, plus a random effect for participants. Trimester entered the model as a repeated measure using a first-order autoregressive structure. Log-likelihood ratio tests were performed to explore potential confounders including center, smoking status, surgery-to-conception interval, BMI at conception, season of sampling and the use of additional supplementation for iron, folic acid (including preconception supplementation), vitamin B12 and vitamin D during pregnancy. Final models for RYGB included BMI at conception, use of additional supplementation for ferritin and vitamin B12 (yes/no/missing), use of calcium/vitamin D3 supplementation for calcium and vitamin D (yes/no/missing), and season of sampling for vitamin D (in months). Final models for SG included the use of additional supplementation for ferritin (yes/no/missing) and season of sampling for vitamin D (in months). Serum concentrations measured after intravenous iron infusions for ferritin and hydroxocobalamin injections for vitamin B12 were removed from the analyses to prevent biased estimates. Results are presented as estimated (geometric) marginal mean and 95% CI. Means and standard deviations of the original serum data at the different trimesters can be found in **Supplementary Table 2**. The prevalence of nutrient deficiencies and elevated serum levels at each trimester were analyzed using Chi-Square tests or Fisher's Exact test (if >20% of expected counts were less than 5). Results are presented as frequency (percentage). All statistical analyses were performed separately for the RYGB and SG group, using IBM SPSS Statistics 25 for Windows (IBM Corp., Armonk USA). A two-sided *P*-value below 0.05 was considered statistically significant.

Results

General characteristics

General characteristics of the study population according to type of BS are shown in **Table 2**. Mean age at conception was respectively 32.1 ± 4.5 years and 29.7 ± 4.9 years in the RYGB and SG group. The majority of the participants was of West-European origin (RYGB: 95.0%, SG: 87.2%), had a medium educational level (RYGB: 37.5%, SG: 38.5%), and never smoked (RYGB: 56.3%, SG: 71.8%). Median time from surgery to conception was 50.0 [23.4-77.0] months in the RYGB group and 32.2 [16.4-43.8] months in the SG group, and the majority of the participants became pregnant more than 24 months after BS (RYGB: 76.3%, SG: 61.5%). Mean TWL from surgery to conception was 32.0 ± 9.1 percent after RYGB, and 32.5 ± 8.5 percent after SG. The prevalence of pre-existing comorbidities and pregnancy complications was low.

Table 2. General characteristics of the study population according to type of BS.

Characteristic	Study population (n=119)		RYGB (n=80)		SG (n=39)	
Maternal age at conception (years)	31.3	± 4.7	32.1	± 4.5	29.7	± 4.9
Geographic origin						
West European	110	(92.4)	76	(95.0)	34	(87.2)
Other	9	(7.6)	4	(5.0)	5	(12.8)
Highest level of education[1]						
Low	21	(17.6)	16	(20.0)	5	(12.8)
Medium	45	(37.8)	30	(37.5)	15	(38.5)
High	24	(20.2)	15	(18.8)	9	(23.1)
missing	29	(24.4)	19	(23.8)	10	(25.6)
Smoking status						
Never	73	(61.3)	45	(56.3)	28	(71.8)
Former	22	(18.5)	18	(22.5)	4	(10.3)
Current	24	(20.2)	17	(21.3)	7	(17.9)
Pre-existent diabetes mellitus	1	(0.8)	0	(0.0)	1	(2.6)
Pre-existent hypertension	1	(0.8)	1	(1.3)	0	(0.0)
BMI before surgery (kg/m^2)[2]	44.0	± 5.4	43.9	± 5.3	44.2	± 5.5
BMI at conception (kg/m^2)	28.7	[26.0-32.5]	29.0	[25.9-32.0]	27.7	[26.0-33.0]
TWL surgery-conception (%)[2]	32.2	± 8.9	32.0	± 9.1	32.5	± 8.5
Time from surgery to conception	41.0	[18.5-70.0]	50.0	[23.4-77.0]	32.2	[16.4-43.8]
<12 months	11	(9.2)	6	(7.5)	5	(12.8)
12-24 months	23	(19.3)	13	(16.3)	10	(25.6)
>24 months	85	(71.4)	61	(76.3)	24	(61.5)
Primiparity	57	(47.9)	34	(42.5)	23	(59.0)
Gestational weight gain (kg)[3]	10.6	± 7.2	9.9	± 6.9	11.9	± 7.7
Inadequate weight gain	22	(18.5)	16	(20.0)	6	(15.4)
Adequate weight gain	22	(18.5)	15	(18.8)	7	(17.9)
Excessive weight gain	38	(31.9)	25	(31.3)	13	(33.3)
missing	37	(31.1)	24	(30.0)	13	(33.3)
Pregnancy complications						
Gestational diabetes mellitus	6	(5.0)	6	(7.5)	0	(0.0)
Hypertensive disorders	7	(5.9)	3	(3.8)	4	(10.3)
Hyperemesis gravidarum	3	(2.5)	0	(0.0)	3	(7.7)
Internal herniation	3	(2.5)	3	(3.8)	-	

Data are presented as means ± SD, median [Q1-Q3] and frequency (percentage).

RYGB, Roux-en-Y gastric bypass; *SG*, sleeve gastrectomy; *BMI*, body mass index; *TWL*, total body weight loss.

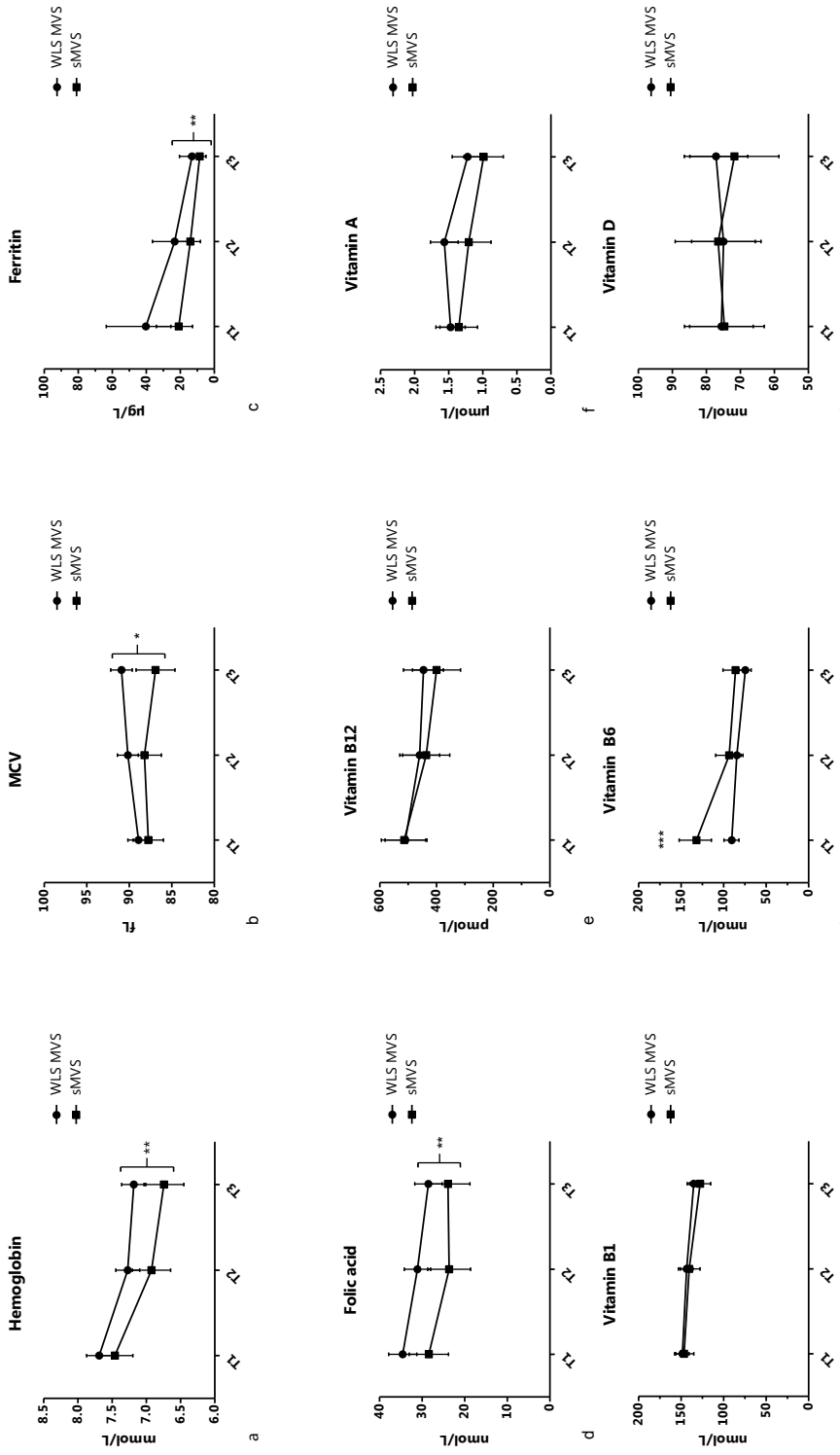
[1] Low education = primary education and prevocational secondary education; medium education = senior general secondary education, pre-university education and secondary vocational education; high education = higher vocational education, university.

[2] Missing for n=5 (RYGB).

[3] According to NAM recommendations [22].

Supplementation use and nutritional status after RYGB

During pregnancy after RYGB, more participants used WLS MVS compared to sMVS (T1: 69.6% vs 30.4%, T2: 75.0% vs 25.0%, T3: 75.3% vs 24.7%). Overall, WLS MVS users had significantly higher serum levels of hemoglobin, ferritin and folic acid during pregnancy than sMVS users (P<0.05 for all; **Figure 2**).


Hemoglobin
mmol/L
WLS MVS
sMVS
**
a
MCV
fL
*
b
Ferritin
µg/L
**
c
Folic acid
nmol/L
**
d
Vitamin B12
pmol/L
e
Vitamin A
µmol/L
f
Vitamin B1
nmol/L
g
Vitamin B6
nmol/L
***
h
Vitamin D
nmol/L
i

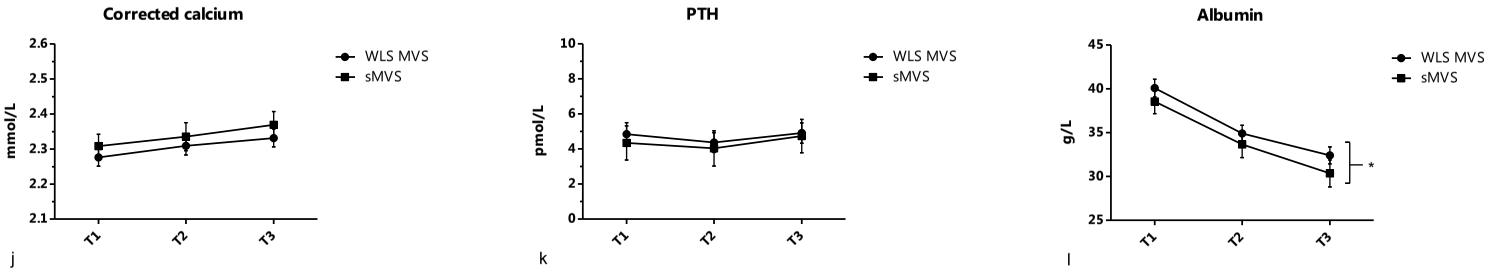


Figure 2. Serum concentrations for WLS MVS users and sMVS users in the RYGB group across the trimesters of pregnancy (T1, T2, T3).

Lines depict estimated marginal means and confidence intervals (error bars).

a. Hemoglobin.

** Significantly higher serum levels for WLS MVS compared to sMVS (P=0.01).

b. MCV.

* Significantly higher serum levels for WLS MVS compared to sMVS (P=0.01).

c. Ferritin.

** Significantly higher serum levels for WLS MVS compared to sMVS (P=0.003).

d. Folic acid. **Significantly higher serum levels for WLS MVS compared to sMVS (P=0.01).

e. Vitamin B12.

f. Vitamin A.

g. Vitamin B1.

h. Vitamin B6

*** Significantly higher serum levels for sMVS compared to WLS MVS at T1 (P<0.001)

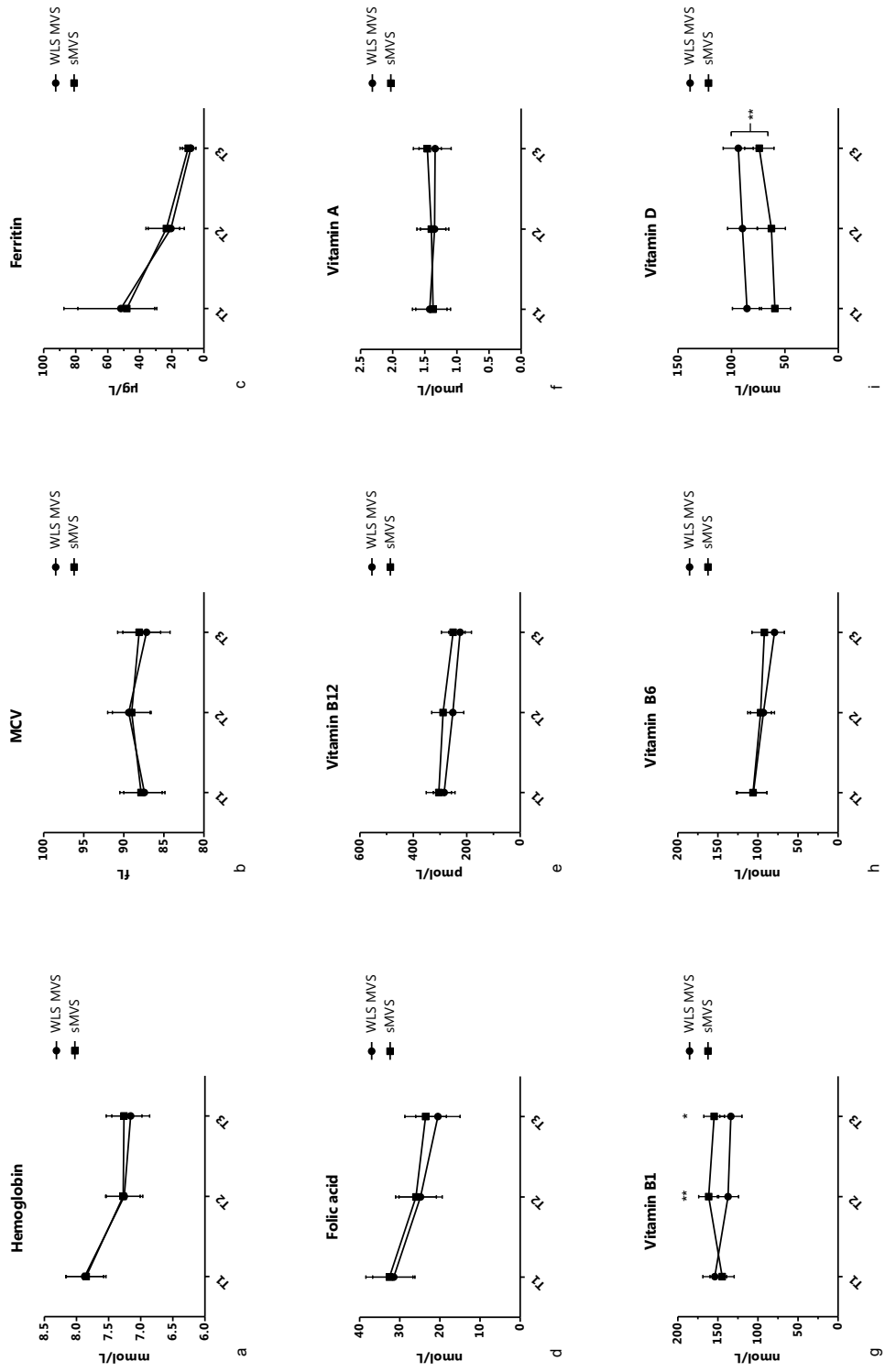
i. Vitamin D

j. Corrected calcium

k. PTH

l. Albumin

* Significantly higher serum levels for WLS MVS compared to sMVS (P=0.02).


Hemoglobin
mmol/L
WLS MVS
sMVS
a
MCV
fL
b
Ferritin
µg/L
c
Folic acid
nmol/L
d
Vitamin B12
pmol/L
e
Vitamin A
µmol/L
f
Vitamin B1
nmol/L
g
Vitamin B6
nmol/L
h
Vitamin D
nmol/L
i
12
24
36

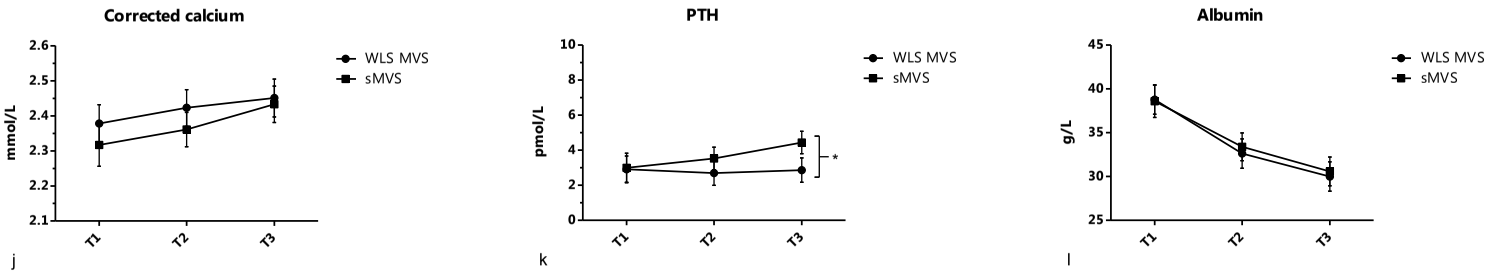


Figure 3. Serum concentrations for WLS MVS users and sMVS users in the SG group across the trimesters of pregnancy (T1, T2, T3). Lines depict estimated marginal means and confidence intervals (error bars).

a. Hemoglobin.

b. MCV.

c. Ferritin.

d. Folic acid.

e. Vitamin B12.

f. Vitamin A.

g. Vitamin B1.

** Significantly higher serum levels for sMVS compared to WLS MVS at T2 (*P*=0.01).

* Significantly higher serum levels for sMVS compared to WLS MVS at T3 (*P*=0.03).

h. Vitamin B6

i. Vitamin D

** Significantly higher serum levels for WLS MVS compared to sMVS (*P*=0.001).

j. Corrected calcium

k. PTH

* Significantly higher serum levels for sMVS compared to WLS MVS (*P*=0.02).

l. Albumin

This also resulted in less iron deficiencies in the WLS MVS group compared to the sMVS group during the second (29.6% vs 55.6%, *P*=0.047) and third trimester (36.5% vs 72.2%, *P*=0.01; **Table 3**). Similarly, anemia tended to be less prevalent in the WLS MVS group, although not statistically significant (11-13% vs 17-33%). The prevalence of folic acid deficiency during pregnancy was low and comparable between the groups (2-12% vs 0-6%). There was also a trend towards higher serum vitamin A concentrations in WLS MVS users compared to sMVS users (1.42 µmol/L, 95% CI: 1.27-1.57 vs 1.18 µmol/L, 95% CI: 0.98-1.39, *P*=0.06). The prevalence of vitamin A deficiency also tended to be lower in the WLS MVS group (14-22% vs 25-46%). Only one participant presented with an elevated serum vitamin A level during pregnancy (WLS MVS, T2: 3.71 µmol/L; **Table 4**). For vitamin B6, there was a significant interaction between MVS and trimester (*P*=0.02; **Figure 2**). Compared to WLS MVS users, sMVS users had higher serum vitamin B6 concentrations in the first trimester, but levels decreased to similar concentrations in the second and third trimester (T1: 90.6 nmol/L, 95% CI: 82.0-99.8 vs 132.1 nmol/L, 95% CI: 114.6-152.4, *P*<0.001). Accordingly, the prevalence of elevated serum vitamin B6 levels was significantly lower in the WLS MVS group compared to the sMVS group during the first and second trimester but not during the third trimester (T1: 32.6% vs 61.9%, *P*=0.02; T2: 13.0% vs 43.8%, *P*=0.01; T3: 12.5% vs 22.2%, *P*=0.44; **Table 4**). We did not find any differences in vitamin B12, vitamin B1, vitamin D and calcium between the two groups.

Supplementation use and nutritional status after SG

During pregnancy after SG, the percentage of participants using WLS MVS was comparable to those using sMVS (T1: 51.7% vs 48.3%, T2: 45.9% vs 54.1%, T3: 50.0% vs 50.0%). Overall, WLS MVS users had significantly higher serum levels of vitamin D during pregnancy than sMVS users (89.7 nmol/L, 95% CI: 77.6-101.8 vs 65.4 nmol/L, 95% CI: 53.3-77.4, *P*=0.001; **Figure 3**). Similarly, vitamin D deficiencies tended to be less prevalent in the WLS MVS group although not statistically significant (13-18% vs 37-39%; **Table 3**). For vitamin B1, there was a significant interaction between MVS and trimester (*P*=0.02; **Figure 3**). Serum vitamin B1 concentrations started similar in the first trimester but slightly decreased over pregnancy in the WLS MVS group, resulting in lower serum vitamin B1 concentrations in this group compared to the sMVS group (T2: 137.4 nmol/L, 95% CI: 124.2-150.6 vs 161.6 nmol/L, 95% CI: 149.0-174.1, *P*=0.01; T3: 133.9 nmol/L, 95% CI: 120.1-147.7 vs 154.7 nmol/L, 95% CI: 141.9-167.5, *P*=0.03). We did not find any differences in hemoglobin, ferritin, folic acid, vitamin B12, vitamin A, vitamin B6 and calcium between the two groups. There were no participants with an elevated serum vitamin A level during pregnancy after SG (**Table 4**).

Table 3. Prevalence of serum levels below the lower reference limit during each trimester (T1, T2, T3) for WLS MVS users vs sMVS users, stratified by type of BS.

Serum variables	Trimester	RYGB (n=80)					SG (n=39)				
		n	WLS MVS	*n*	sMVS	*P*-value	*n*	WLS MVS	*n*	sMVS	*P*-value
Hemoglobin	T1	*48*	6 (12.5)	*21*	7 (33.3)	0.05	*15*	0 (0.0)	*14*	1 (7.1)	0.48
	T2	*57*	7 (12.3)	*19*	4 (21.1)	0.45	*17*	1 (5.9)	*20*	1 (5.0)	0.99
	T3	*55*	6 (10.9)	*18*	3 (16.7)	0.68	*16*	1 (6.3)	*18*	2 (11.1)	0.99
MCV	T1	*46*	2 (4.3)	*20*	2 (10.0)	0.58	*14*	0 (0.0)	*14*	0 (0.0)	-
	T2	*44*	2 (4.5)	*15*	2 (13.3)	0.27	*13*	1 (7.7)	*16*	1 (6.3)	0.99
	T3	*44*	0 (0.0)	*12*	2 (16.7)	**0.04**	*9*	2 (22.2)	*13*	1 (7.7)	0.54
Ferritin	T1	*47*	9 (19.1)	*21*	6 (28.6)	0.53	*14*	0 (0.0)	*11*	1 (9.1)	0.44
	T2	*54*	16 (29.6)	*18*	10 (55.6)	**0.047**	*17*	6 (35.3)	*19*	4 (21.1)	0.46
	T3	*52*	19 (36.5)	*18*	13 (72.2)	**0.01**	*16*	10 (62.5)	*18*	10 (55.6)	0.68
Folic acid	T1	*48*	1 (2.1)	*21*	1 (4.8)	0.52	*14*	0 (0.0)	*11*	0 (0.0)	-
	T2	*54*	3 (5.6)	*16*	0 (0.0)	0.99	*17*	2 (11.8)	*19*	1 (5.3)	0.59
	T3	*51*	6 (11.8)	*18*	1 (5.6)	0.67	*15*	2 (13.3)	*18*	4 (22.2)	0.67
Vitamin B12	T1	*48*	6 (12.5)	*21*	4 (19.0)	0.48	*14*	1 (7.1)	*13*	3 (23.1)	0.33
	T2	*54*	12 (22.2)	*16*	6 (37.5)	0.33	*17*	3 (17.6)	*19*	2 (10.5)	0.65
	T3	*52*	12 (23.1)	*17*	8 (47.1)	0.07	*15*	3 (20.0)	*18*	4 (22.2)	0.99
Vitamin A	T1	*20*	3 (15.0)	*12*	5 (41.7)	0.12	*8*	3 (37.5)	*8*	1 (12.5)	0.57
	T2	*22*	3 (13.6)	*8*	2 (25.0)	0.59	*14*	3 (21.4)	*13*	3 (23.1)	0.99
	T3	*18*	4 (22.2)	*11*	5 (45.5)	0.24	*10*	4 (40.0)	*14*	2 (14.3)	0.19
Vitamin B1	T1	*46*	1 (2.2)	*21*	0 (0.0)	0.99	*12*	0 (0.0)	*12*	0 (0.0)	-
	T2	*53*	0 (0.0)	*16*	0 (0.0)	-	*17*	1 (5.9)	*18*	0 (0.0)	0.49
	T3	*48*	0 (0.0)	*18*	1 (5.6)	0.27	*15*	2 (13.3)	*18*	0 (0.0)	0.20
Vitamin B6	T1	*46*	0 (0.0)	*21*	0 (0.0)	-	*12*	0 (0.0)	*12*	0 (0.0)	-
	T2	*54*	0 (0.0)	*16*	0 (0.0)	-	*17*	0 (0.0)	*18*	0 (0.0)	-
	T3	*48*	1 (2.1)	*18*	1 (5.6)	0.47	*15*	2 (13.3)	*18*	0 (0.0)	0.20
Vitamin D	T1	*48*	12 (25.0)	*21*	9 (42.9)	0.14	*15*	2 (13.3)	*13*	5 (38.5)	0.20
	T2	*54*	12 (22.2)	*17*	5 (29.4)	0.53	*17*	3 (17.6)	*19*	7 (36.8)	0.27
	T3	*51*	12 (23.5)	*18*	6 (33.3)	0.53	*16*	2 (12.5)	*18*	7 (38.9)	0.13
Calcium[1]	T1	*45*	3 (6.7)	*21*	0 (0.0)	0.55	*14*	0 (0.0)	*11*	0 (0.0)	-
	T2	*55*	2 (3.6)	*16*	0 (0.0)	0.99	*17*	0 (0.0)	*19*	0 (0.0)	-
	T3	*50*	0 (0.0)	*17*	1 (5.9)	0.25	*16*	0 (0.0)	*18*	0 (0.0)	-

Table 3. Prevalence of serum levels below the lower reference limit during each trimester (T1, T2, T3) for WLS MVS users vs sMVS users, stratified by type of BS. *(continued).*

Serum variables	Trimester	RYGB (n=80)					SG (n=39)				
		n	WLS MVS	*n*	sMVS	*P*-value	*n*	WLS MVS	*n*	sMVS	*P*-value
PTH	T1	*36*	0 (0.0)	*16*	1 (6.3)	0.31	*12*	1 (8.3)	*10*	1 (10.0)	0.99
	T2	*52*	2 (3.8)	*15*	1 (6.7)	0.54	*15*	5 (33.3)	*18*	0 (0.0)	**0.01**
	T3	*49*	1 (2.0)	*18*	0 (0.0)	0.99	*15*	3 (20.0)	*18*	0 (0.0)	0.08
Albumin	T1	*45*	3 (6.7)	*21*	6 (28.6)	**0.02**	*14*	3 (21.4)	*11*	2 (18.2)	0.99
	T2	*55*	25 (45.5)	*16*	8 (50.0)	0.75	*17*	12 (70.6)	*19*	12 (63.2)	0.64
	T3	*51*	31 (60.8)	*18*	14 (77.8)	0.19	*17*	15 (88.2)	*18*	15 (83.3)	0.99

Data are presented as frequencies (percentages).

RYGB, Roux-en-Y gastric bypass; *SG*, sleeve gastrectomy; *WLS MVS*, 'weight loss surgery' multivitamin supplement; *sMVS*, standard multivitamin supplement (regular or prenatal supplements); *MCV*, mean corpuscular volume; *PTH*, parathyroid hormone.

[1]Corrected for albumin levels.

Table 4. Prevalence of elevated serum levels during each trimester (T1, T2, T3) for WLS MVS users vs sMVS users, stratified by type of BS.

Serum variables	Trimester	RYGB (n=80)					SG (n=39)				
		n	WLS MVS	*n*	sMVS	*P*-value	*n*	WLS MVS	*n*	sMVS	*P*-value
Vitamin A	T1	*20*	0 (0.0)	*12*	0 (0.0)	-	*8*	0 (0.0)	*8*	0 (0.0)	-
	T2	*22*	1 (4.5)	*8*	0 (0.0)	0.99	*14*	0 (0.0)	*13*	0 (0.0)	-
	T3	*18*	0 (0.0)	*11*	0 (0.0)	-	*10*	0 (0.0)	*14*	0 (0.0)	-
Vitamin B6	T1	*46*	15 (32.6)	*21*	13 (61.9)	**0.02**	*12*	8 (66.7)	*12*	5 (41.7)	0.22
	T2	*54*	7 (13.0)	*16*	7 (43.8)	**0.01**	*17*	7 (41.2)	*18*	7 (38.9)	0.89
	T3	*48*	6 (12.5)	*18*	4 (22.2)	0.44	*15*	6 (40.0)	*18*	3 (16.7)	0.24
PTH	T1	*36*	5 (13.9)	*16*	1 (6.3)	0.65	*12*	0 (0.0)	*10*	0 (0.0)	-
	T2	*52*	1 (1.9)	*15*	0 (0.0)	0.99	*15*	0 (0.0)	*18*	0 (0.0)	-
	T3	*49*	2 (4.1)	*18*	1 (5.6)	0.99	*15*	0 (0.0)	*18*	0 (0.0)	-

Data are presented as frequencies (percentages).

RYGB, Roux-en-Y gastric bypass; *SG*, sleeve gastrectomy; *WLS MVS*, 'weight loss surgery' multivitamin supplement; *sMVS*, standard multivitamin supplement (regular or prenatal supplements); *PTH*, parathyroid hormone.

Discussion

This is the first study that compared differences in nutritional status during pregnancy after BS between users of specialized supplementation (WLS MVS) and users of regular or prenatal supplementation (sMVS), while differentiating by the type of surgical procedure.

During pregnancy following RYGB, we found that WLS MVS users (±73% of participants) had higher serum levels of hemoglobin, ferritin and folic acid and lower serum levels of vitamin B6 during pregnancy compared to sMVS users (±27% of participants). Iron deficiencies as well as elevated serum vitamin B6 levels were also less prevalent in the WLS MVS group. During pregnancy following SG, WLS MVS users (±49% of participants) had higher serum levels of vitamin D, but lower serum levels of vitamin B1 than sMVS users (±51% of participants). The prevalence of deficiencies and elevated serum levels was similar between the WLS MVS and sMVS group during pregnancy after SG.

Our results show that using high-dose WLS MVS during pregnancy following BS resulted in higher serum levels and less deficiencies for some but not for all micronutrients. Besides, our findings differed between the two surgery groups. To date, only one other study including 197 singleton pregnancies after RYGB has retrospectively compared serum micronutrient concentrations between users of specialized supplementation and standard supplementation during pregnancy [26]. They also found higher serum levels of hemoglobin and ferritin for WLS MVS users compared to users of prenatal MVS [26]. In contrast to the previous study, we did not find higher serum vitamin D concentrations in RYGB-WLS MVS users, despite their higher dose of vitamin D compared to sMVS (75 µg vs 5-10 µg, respectively). Although we included the use of additional calcium/vitamin D3 supplementation and season of sampling into our statistical models, individual differences in compliance with supplement intake as well as in sun exposure could have impacted our findings with regard to vitamin D status.

To the best of our knowledge, there are no studies available that report on the effect of WLS MVS on the prevalence of nutrient deficiencies and elevated serum levels after RYGB, and research on the efficacy of WLS MVS during pregnancy after SG is also lacking.

Overall, many of our findings are in line with those observed in the general bariatric population. Homan et al. also found higher serum levels of hemoglobin, ferritin and folic acid as well as less anemia and iron deficiencies in WLS MVS users compared to sMVS users three years after RYGB [20]. However, they observed comparable serum vitamin B6 concentrations between the supplement groups [20], whereas we found lower serum

concentrations as well as less elevated levels for vitamin B6 in WLS MVS users compared to sMVS users during pregnancy after RYGB. The prevalence of elevated serum vitamin B6 levels ranged from 13% to 33% in the WLS MVS group compared to 22-62% in the sMVS group, which may be due to the lower dose of vitamin B6 in WLS MVS for RYGB. Most of these supplements contain 0.6-0.98 mg vitamin B6 (43-70% RDA), whereas sMVS usually contain 1.4 mg vitamin B6 (100% RDA). Besides, bariatric patients are sometimes advised to use two standard supplements during pregnancy, which increases the daily dose to 2.8 mg vitamin B6 (200% RDA). Overall, serum vitamin B6 concentrations were near the upper reference limit in all groups. Although exposure to extremely high doses of vitamin B6 (>50 mg/day) did not appear to be associated with an increased risk for major malformations during pregnancy [27], attention on elevated serum vitamin B6 levels is needed as they may cause maternal peripheral neuropathy [28].

The observed higher serum vitamin D concentrations along with the trend towards less vitamin D deficiencies in the WLS MVS group compared to the sMVS group during pregnancy after SG is in accordance with two other studies comparing nutritional status between WLS MVS users and sMVS users in general after SG [18, 21]. Remarkably, serum vitamin B1 concentrations were higher in the WLS MVS group compared to the sMVS group in the previous studies, whereas we found lower vitamin B1 levels in the WLS MVS group during pregnancy [18, 21]. This may be explained by the prevalence of hyperemesis gravidarum, which occurred in three women who all underwent SG and used WLS MVS. Persistent vomiting is a risk factor for thiamine deficiency, which can ultimately result in Wernicke's encephalopathy [29, 30]. Indeed, serum vitamin B1 concentrations were markedly lower in women with versus without hyperemesis gravidarum (110.0 ± 28.9 nmol/L vs 144.0 ±28.4 nmol/L), but excluding these women did not markedly change our results (data not shown). Nevertheless, similar to our findings regarding vitamin B6, serum vitamin B1 concentrations were far above the lower reference limit in all groups and deficiencies during pregnancy were rare.

Overall, differences in nutritional status between WLS MVS users and sMVS users were less pronounced in the SG group, which may be explained by the generally lower doses of iron, folic acid and vitamin B12 in WLS MVS for SG. Furthermore, previous research has indicated that compliance with MVS intake may be lower in patients who underwent SG, both in the general BS population [31] as well as during pregnancy after BS [32], and that poor compliance may in turn result in lower serum concentrations of hemoglobin, iron, folic acid and vitamin B12 [33].

In general, consensus on recommended doses for supplementation during pregnancy after BS has not yet been reached for most micronutrients, evidenced by the lack of evidence-based guidelines as well as the limited consistency across current recommendations [10]. To illustrate, recommendations for vitamin B12 vary from 350-1000 µg orally per day to 1000 µg via intramuscular injection every 1-3 months, and recommendations for iron range from 27 to 80 mg per day during pregnancy after BS [10, 34]. This is concerning as the risk of micronutrient depletion posed by the bariatric procedure may be even higher due to the physiologic changes during pregnancy. Optimal nutritional status during pregnancy is not only vitally important for maternal health but also for fetal health [10, 11, 13, 15].

Next to the well-documented link with congenital abnormalities including neural tube defects [35, 36], inadequate folate status during pregnancy has been associated with pre-eclampsia, spontaneous abortions and low birth weight [10, 37, 38]. In the present study, serum folic acid concentrations significantly decreased during pregnancy but remained far above the lower reference limit and the prevalence of deficiencies was low (± 7%), which is in line with other literature (0-16%) [14]. Yet, it remains uncertain if additional supplementation for folic acid is required when high-dosed WLS MVS are used, and recommendations in clinical practice are inconsistent. Therefore, a critical review of folic acid requirement in pregnancy post-bariatric surgery is needed. Until then, the total dose of supplementation should in any case not exceed 1 mg per day in order to prevent potential negative adverse effects from over-supplementation such as masking of vitamin B12 deficiency [39, 40].

Adequate iron status during pregnancy is also essential for maternal health as well as fetal growth and development. Iron is crucial for red blood cell production and low iron status has been associated with maternal anemia, preterm delivery and low neonatal birth weight [10, 11, 38]. Despite the significant decrease in hemoglobin levels during pregnancy, the prevalence of anemia in the present study was fairly low (± 12%). In contrast, low serum ferritin levels were frequently observed in the present study (± 34%), as well as in previous research [14]. The high prevalence of iron deficiency during pregnancy after BS indicates the need for additional iron supplementation in this population, but oral supplements are often poorly tolerated [41]. Alternate day dosing of iron could provide an alternative solution as it significantly increases iron absorption and results in a lower incidence of gastrointestinal side effects compared with dosing iron every day [42, 43]. Intravenous (IV) iron administration should be considered in pregnant women with iron deficiency anemia who do not respond to or cannot tolerate oral iron supplementation during the second or third trimester [44].

Besides the risk for deficiencies, excess micronutrient supplementation can also have detrimental consequences for both mother and child. The general pregnant population is usually advised to avoid retinol supplementation due to the well-documented risk of teratogenic malformations, especially during the first trimester [45]. Therefore, prenatal supplements often contain beta-carotene, a precursor of vitamin A which appears to have no toxic effects during pregnancy [46]. The presence of retinol in WLS MVS can be a motivation for obstetricians to discontinue the use of these supplements during pregnancy. In the present study, we observed only one case of elevated serum vitamin A when using WLS MVS containing 800 µg retinol (RYGB; 13 weeks: 3.71 µmol/L, reference range: 1.05-2.80 µmol/L). As information on dietary intake was unknown, it is difficult to ascertain whether this elevated level was caused by supplement intake, dietary intake or a combination of both. Overall, most WLS MVS contain about 600-800 µg retinol, which is far below the safe upper level of 3000 µg as indicated by the European Food Safety Authority [47]. Besides, serum vitamin A concentrations significantly decreased within the lower range and deficiencies were prevalent (± 24%) in our study population. Previous research even reports up to 90% of vitamin A deficiencies after BS [14]. Vitamin A deficiency has been shown to cause night blindness and is associated with fetal growth restriction [10, 11, 37]. Based on the results of the present study, continuing the use of WLS MVS during pregnancy after BS is considered safe and may even be preferred over the use of supplements containing beta-carotene because of the low conversion efficiency of beta-carotene [48], increasing the risk of vitamin A deficiency in this population.

Main strengths of the present study include the availability of prospective data on MVS use across the trimesters of pregnancy, including detailed information on supplement composition. In addition to previous research, we also reported data on the prevalence of nutrient deficiencies and elevated serum levels during pregnancy.
However, our results must also be interpreted in light of certain limitations. Most importantly, MVS use differed greatly within and between participants. Because of the relatively small study sample, we were limited to categorizing all MVS as either WLS MVS or sMVS. As a result, the sMVS group consisted of both regular over-the-counter MVS as well as prenatal supplements, respectively accounting for approximately 25% versus 75%. These types of MVS mainly differ in the dose and/or form of folic acid, vitamin D and vitamin A (**Supplementary Table 1**). Furthermore, dosing of sMVS varied from 1-3 supplements per day, which might have impacted the daily administered dose of nutrients. This also applies to women using a combination of different MVS, either both

on a daily basis or alternately. Greater sample sizes are required in order to obtain sufficient statistical power to address these variations in MVS use. Last, we used pregnancy-specific cut-off values for hemoglobin only as uniform, evidence-based pregnancy-specific cut-offs for other nutrients are lacking [49]. During pregnancy, a 25-30% physiological decrease in the levels of hemoglobin, ferritin, folic acid, vitamins A, B12 and D, PTH and calcium is expected as a result of the expanding maternal blood volume by approximately 50% (hemodilution) and increasing demands of the growing fetus [16, 50, 51]. As a result, the number of nutritional deficiencies in the present study may have been overestimated. Nevertheless, this has no impact on the comparisons made between the MVS groups and these standard reference ranges are also used in clinical practice. Ideally, laboratories should provide locally validated reference ranges for pregnant women to recognize changes in normal laboratory values induced by pregnancy. Although some guidelines on laboratory values in healthy pregnant women are available [52, 53], differences in used assays and population groups may limit their transferability to other centers and populations.

Conclusion

Our study confirmed that low maternal concentrations of micronutrients are highly prevalent in pregnant women who underwent RYGB or SG. This leads to greater challenges to reach nutritional requirements in pregnancies after BS, making optimal supplementation essential. Overall, the use of specialized WLS MVS is preferred over the use of standard, over-the-counter supplementation. Future research is needed to investigate how supplementation strategies can be optimized individually for this high-risk population.

Furthermore, as bariatric surgery has become increasingly prevalent among women of reproductive age, understanding the relationship between maternal nutritional status and pregnancy and neonatal outcomes is essential for adequate prenatal care.

References

1. Gloy, VL, Briel, M, Bhatt, DL, et al., *Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials.* BMJ, 2013. **347**: p. f5934.
2. O'Brien, PE, Hindle, A, Brennan, L, et al., *Long-Term Outcomes After Bariatric Surgery: a Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding.* Obes Surg, 2019. **29**(1): p. 3-14.
3. Sjostrom, L, *Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery.* J Intern Med, 2013. **273**(3): p. 219-234.
4. Brown, WA, Kow, L, Shikora, S, et al., *Sixth IFSO Global Registry Report*, in *The IFSO Global Registry*, The International Federation for the Surgery of Obesity and Metabolic Disorders, Editor. 2021.
5. Brown, WA, Shikora, S, Liem, R, et al., *Seventh IFSO Global Registry Report*, in *The IFSO Global Registry*, The International Federation for the Surgery of Obesity and Metabolic Disorders, Editor. 2022.
6. Edison, E, Whyte, M, van Vlymen, J, et al., *Bariatric Surgery in Obese Women of Reproductive Age Improves Conditions That Underlie Fertility and Pregnancy Outcomes: Retrospective Cohort Study of UK National Bariatric Surgery Registry (NBSR).* Obes Surg, 2016. **26**(12): p. 2837-2842.
7. Johansson, K, Cnattingius, S, Näslund, I, et al., *Outcomes of Pregnancy after Bariatric Surgery.* N Engl J Med, 2015. **372**(9): p. 814-824.
8. Kwong, W, Tomlinson, G and Feig, DS, *Maternal and neonatal outcomes after bariatric surgery; a systematic review and meta-analysis: do the benefits outweigh the risks?* Am J Obstet Gynecol, 2018. **218**(6): p. 573-580.
9. Lupoli, R, Lembo, E, Saldalamacchia, G, et al., *Bariatric surgery and long-term nutritional issues.* World J Diabetes, 2017. **8**(11): p. 464-474.
10. Vanheule, G, Ceulemans, D, Vynckier, AK, et al., *Micronutrient supplementation in pregnancies following bariatric surgery: a practical review for clinicians.* Obes Surg, 2021. **31**(10): p. 4542-4554.
11. Slater, C, Morris, L, Ellison, J, et al., *Nutrition in Pregnancy Following Bariatric Surgery.* Nutrients, 2017. **9**(12).
12. Chapmon, K, Stoklossa, CJ, Benson-Davies, S, et al., *Nutrition for pregnancy after metabolic and bariatric surgery: literature review and practical guide.* Surg Obes Relat Dis, 2022. **18**(6): p. 820-830.
13. Jans, G, Matthys, C, Bogaerts, A, et al., *Maternal micronutrient deficiencies and related adverse neonatal outcomes after bariatric surgery: a systematic review.* Adv Nutr, 2015. **6**(4): p. 420-429.
14. Rottenstreich, A, Elazary, R, Goldenshluger, A, et al., *Maternal nutritional status and related pregnancy outcomes following bariatric surgery: A systematic review.* Surg Obes Relat Dis, 2019. **15**(2): p. 324-332.
15. Milman, N, Paszkowski, T, Cetin, I, et al., *Supplementation during pregnancy: beliefs and science.* Gynecol Endocrinol, 2016. **32**(7): p. 509-516.
16. Shawe, J, Ceulemans, D, Akhter, Z, et al., *Pregnancy after bariatric surgery: Consensus recommendations for periconception, antenatal and postnatal care.* Obes Rev, 2019. **20**(11): p. 1507-1522.
17. Dogan, K, Aarts, EO, Koehestanie, P, et al., *Optimization of vitamin suppletion after Roux-en-Y gastric bypass surgery can lower postoperative deficiencies: a randomized controlled trial.* Medicine, 2014. **93**(25): p. e169.
18. Heusschen, L, Berendsen, AAM, Deden, LN, et al., *Nutritional Deficiencies 3 Years After Sleeve Gastrectomy Can Be Limited by a Specialized Multivitamin Supplement.* Obes Surg, 2022. **32**(11): p. 3561-3570.
19. Heusschen, L, Schijns, W, Ploeger, N, et al., *The True Story on Deficiencies After Sleeve Gastrectomy: Results of a Double-Blind RCT.* Obes Surg, 2020. **30**(4): p. 1280-1290.

20. Homan, J, Schijns, W, Aarts, EO, et al., *An optimized multivitamin supplement lowers the number of vitamin and mineral deficiencies three years after Roux-en-Y gastric bypass: a cohort study.* Surg Obes Relat Dis, 2016. **12**(3): p. 659-667.
21. Smelt, HJM, van Loon, S, Pouwels, S, et al., *Do Specialized Bariatric Multivitamins Lower Deficiencies After Sleeve Gastrectomy?* Obes Surg, 2020. **30**(2): p. 427-438.
22. Rasmussen, KM and Yaktine, AL, *Weight gain during pregnancy: Reexaming the guidelines. Institute of Medicine* 2009, National Academies Press: Washington DC.
23. Health Council of the Netherlands, *Towards an optimal use of folic acid*. 2008, Health Council of the Netherlands: The Hague.
24. Jans, S and Beentjes, M, *Anemie in de verloskundige praktijk - Aanbevelingen voor preventie, diagnostiek en behandeling.*, in *KNOV-standaard*, The Royal Dutch Organisation of Midwives, Editor. 2010, The Royal Dutch Organisation of Midwives.
25. Parrott, J, Frank, L, Rabena, R, et al., *American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients.* Surg Obes Relat Dis, 2017. **13**(5): p. 727-741.
26. Snoek, K, van de Woestijne, N, Willemsen, S, et al., *The Impact of Preconception Gastric Bypass Surgery on Maternal Micronutrient Status before and during Pregnancy: A Retrospective Cohort Study in the Netherlands between 2009 and 2019.* Nutrients, 2022. **14**(4).
27. Shrim, A, Boskovic, R, Maltepe, C, et al., *Pregnancy outcome following use of large doses of vitamin B6 in the first trimester.* J Obstet Gynaecol, 2006. **26**(8): p. 749-751.
28. Alsabah, A, Al Sabah, S, Al-Sabah, S, et al., *Investigating Factors Involved in Post Laparoscopic Sleeve Gastrectomy (LSG) Neuropathy.* Obes Surg, 2017. **27**(5): p. 1271-1276.
29. Bahardoust, M, Eghbali, F, Shahmiri, SS, et al., *B1 Vitamin Deficiency After Bariatric Surgery, Prevalence, and Symptoms: a Systematic Review and Meta-analysis.* Obes Surg, 2022. **32**(9): p. 3104-3112.
30. Gasmi, A, Bjorklund, G, Mujawdiya, PK, et al., *Micronutrients deficiences in patients after bariatric surgery.* Eur J Nutr, 2022. **61**(1): p. 55-67.
31. Smelt, HJM, Heusschen, L, Theel, W, et al., *Factors Affecting Patient Adherence to Multivitamin Intake After Bariatric Surgery: a Multicentre Survey Study from the Patient's Perspective.* Obes Surg, 2021. **31**(10): p. 4316-4326.
32. Coupaye, M, Legardeur, H, Sami, O, et al., *Impact of Roux-en-Y gastric bypass and sleeve gastrectomy on fetal growth and relationship with maternal nutritional status.* Surg Obes Relat Dis, 2018. **14**(10):1488-1494.
33. Sherf Dagan, S, Keidar, A, Raziel, A, et al., *Do Bariatric Patients Follow Dietary and Lifestyle Recommendations during the First Postoperative Year?* Obes Surg, 2017. **27**(9): p. 2258-2271.
34. Huang, B, Yo, JH, Gandhi, S, et al., *Micronutrient screening, monitoring, and supplementation in pregnancy after bariatric surgery.* Obstet Med, 2022. **15**(3): p. 151-159.
35. *Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group.* Lancet, 1991. **338**(8760): p. 131-137.
36. Wald, NJ, *Folic acid and neural tube defects: Discovery, debate and the need for policy change.* J Med Screen, 2022. **29**(3): p. 138-146.
37. Bordeleau, M, Fernandez de Cossio, L, Chakravarty, MM, et al., *From Maternal Diet to Neurodevelopmental Disorders: A Story of Neuroinflammation.* Front Cell Neurosci, 2020. **14**: p. 612705.
38. Gernand, AD, Schulze, KJ, Stewart, CP, et al., *Micronutrient deficiencies in pregnancy worldwide: health effects and prevention.* Nat Rev Endocrinol, 2016. **12**(5): p. 274-289.

39. Mechanick, JI, Apovian, C, Brethauer, S, et al., *Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists.* Surg Obes Relat Dis, 2020. **16**(2): p. 175-247.
40. Vynckier, AK, Ceulemans, D, Vanheule, G, et al., *Periconceptional Folate Supplementation in Women after Bariatric Surgery-A Narrative Review.* Nutrients, 2021. **13**(5).
41. Anvari, S, Samarasinghe, Y, Alotaiby, N, et al., *Iron supplementation following bariatric surgery: A systematic review of current strategies.* Obes Rev, 2021. **22**(9): p. e13268.
42. Stoffel, NU, Cercamondi, CI, Brittenham, G, et al., *Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials.* Lancet Haematol, 2017. **4**(11): p. e524-e533.
43. Stoffel, NU, Zeder, C, Brittenham, GM, et al., *Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women.* Haematologica, 2020. **105**(5): p. 1232-1239.
44. Api, O, Breyman, C, Cetiner, M, et al., *Diagnosis and treatment of iron deficiency anemia during pregnancy and the postpartum period: Iron deficiency anemia working group consensus report.* Turk J Obstet Gynecol, 2015. **12**(3): p. 173-181.
45. Bastos Maia, S, Rolland Souza, AS, Costa Caminha, MF, et al., *Vitamin A and Pregnancy: A Narrative Review.* Nutrients, 2019. **11**(3).
46. Dibley, MJ and Jeacocke, DA, *Safety and Toxicity of Vitamin A Supplements in Pregnancy.* Food Nutr Bull, 2001. **22**(3): p. 248-266.
47. EFSA Scientific Committee on Food, *Tolerable Upper Intake Levels for Vitamins and Minerals*. 2006, European Food Safety Authority,.
48. Tang, G, *Bioconversion of dietary provitamin A carotenoids to vitamin A in humans.* Am J Clin Nutr, 2010. **91**(5): p. 1468S-1473S.
49. Lamers, Y, *Approaches to improving micronutrient status assessment at the population level.* Proc Nutr Soc, 2019. **78**(2): p. 170-176.
50. Ciangura, C, Coupaye, M, Deruelle, P, et al., *Clinical Practice Guidelines for Childbearing Female Candidates for Bariatric Surgery, Pregnancy, and Post-partum Management After Bariatric Surgery.* Obes Surg, 2019. **29**(11): p. 3722-3734.
51. Falcone, V, Stopp, T, Feichtinger, M, et al., *Pregnancy after bariatric surgery: a narrative literature review and discussion of impact on pregnancy management and outcome.* BMC Pregnancy Childbirth, 2018. **18**(1): p. 507.
52. Abbassi-Ghanavati, M, Greer, LG and Cunningham, FG, *Pregnancy and laboratory studies: a reference table for clinicians.* Obstet Gynecol, 2009. **114**(6): p. 1326-1331.
53. Larsson, A, Palm, M, Hansson, LO, et al., *Reference values for clinical chemistry tests during normal pregnancy.* BJOG, 2008. **115**(7): p. 874-881.

Supplementary Table 1. Content of the most frequently used WLS MVS and sMVS

	WLS MVS-SG		WLS MVS-RYGB		sMVS-Prenatal		sMVS-Regular A		sMVS-Regular B	
	Dose	*RDA*	*Dose*	*RDA*	*Dose*	*RDA*	*Dose*	*RDA*	*Dose*	*RDA*
Vitamin A	800 µg	100%	600 µg	75%	1200 µg	0%	800 µg	100%	533.4 µg	66%
Vitamin B1	2.75 mg	250%	2.75 mg	250%	1.1 mg	100%	1.1 mg	100%	1.1 mg	100%
Vitamin B2	1.7 mg	121%	2 mg	143%	1.4 mg	100%	1.4 mg	100%	1.4 mg	100%
Vitamin B3	25 mg	156%	32 mg	200%	16 mg	100%	16 mg	100%	16 mg	100%
Vitamin B5	9 mg	150%	18 mg	300%	6 mg	100%	6 mg	100%	6 mg	100%
Vitamin B6	1.5 mg	107%	0.98 mg	70%	1.4 mg	100%	1.4 mg	100%	1.4 mg	100%
Vitamin B8	150 µg	300%	100 µg	200%	50 µg	100%	50 µg	100%	50 µg	100%
Vitamin B11	500 µg	250%	600 µg	300%	400 µg	200%	200 µg	100%	200 µg	100%
Vitamin B12	100 µg	4000%	350 µg	14000%	2.5 µg	100%	2.5 µg	100%	2.5 µg	100%
Vitamin C	100 mg	125%	120 mg	150%	40 mg	50%	80 mg	100%	80 mg	100%
Vitamin D3	75 µg	1500%	75 µg	1500%	10 µg	200%	5 µg	100%	3.4 µg	66%
Vitamin E	15 mg	125%	24 mg	200%	6 mg	50%	12 mg	100%	12 mg	100%
Vitamin K1	-	-	-	-	-	-	75 µg	100%	-	-
Calcium	-	-	-	-	120 mg	15%	160 mg	20%	80 mg	10%
Chrome	40 µg	100%	160 µg	400%	20 µg	50%	25 µg	63%	40 µg	100%
Iodine	150 µg	100%	150 µg	100%	150 µg	100%	150 µg	100%	100 µg	66%
Copper	1.9 mg	190%	3 mg	300%	1 mg	100%	1.5 mg	150%	1 mg	100%
Magnesium	-	-	-	-	56.25 mg	15%	125 mg	33%	37.6 mg	10%
Manganese	3 mg	150%	3 mg	150%	1 mg	50%	1 mg	50%	2 mg	100%
Molybdenum	50 µg	100%	112.4 µg	225%	25 µg	50%	25 µg	50%	50 µg	100%
Selenium	55 µg	100%	105 µg	191%	55 µg	100%	25 µg	45%	55 µg	100%
Iron	28 mg	200%	70 mg	500%	16.1 mg	115%	14 mg	100%	14 mg	100%
Zinc	28 mg	280%	22.5 mg	225%	10 mg	100%	15 mg	150%	6.6 mg	66%

WLS MVS-SG, 'weight loss surgery' multivitamin supplement for sleeve gastrectomy; *WLS MVS-RYGB,* 'weight loss surgery' multivitamin supplement for Roux-en-Y gastric bypass; *sMVS,* standard multivitamin supplement; *RDA,* recommended daily allowance.

Supplementary Table 2. Serum concentrations during each trimester of pregnancy (T1, T2, T3) for WLS users versus sMVS users, stratified by type of BS.

Serum variables	Trimester	RYGB (n=80)				SG (n=39)			
		n	WLS MVS	*n*	sMVS	*n*	WLS MVS	*n*	sMVS
Hemoglobin	T1	*48*	7.7 ± 0.7	*21*	7.4 ± 1.0	*15*	7.9 ± 0.5	*14*	7.9 ± 0.5
(mmol/L)	T2	*57*	7.3 ± 0.7	*19*	7.0 ± 0.8	*17*	7.2 ± 0.6	*20*	7.3 ± 0.5
	T3	*55*	7.2 ± 0.6	*18*	6.8 ± 0.8	*16*	7.1 ± 0.8	*18*	7.3 ± 0.6
MCV	T1	*46*	89.0 ± 4.8	*20*	87.7 ± 8.3	*14*	89.1 ± 4.1	*14*	88.7 ± 3.5
(fL)	T2	*44*	89.9 ± 5.5	*15*	88.3 ± 5.8	*13*	87.6 ± 7.3	*16*	90.6 ± 5.7
	T3	*44*	90.8 ± 4.6	*12*	87.7 ± 6.0	*9*	84.3 ± 8.3	*13*	88.9 ± 5.7
Ferritin	T1	*47*	40.0 [12.0-90.0]	*21*	20.0 [7.5-59.0]	*14*	56.0 [27.8-99.5]	*11*	38.0 [20.0-77.0]
(µg/L)	T2	*54*	20.0 [11.0-48.5]	*18*	12.0 [8.0-30.3	*17*	20.0 [6.5-45.5]	*19*	23.0 [11.0-45.0]
	T3	*52*	16.5 [9.3-32.0]	*18*	8.5 [7.0-14.3]	*16*	9.0 [6.3-13.5]	*18*	9.0 [7.0-15.0]
Folic acid	T1	*48*	34.2 ± 11.6	*21*	27.3 ± 12.2	*14*	33.0 ± 9.8	*11*	31.4 ± 11.6
(nmol/L)	T2	*54*	30.0 ± 11.4	*16*	29.7 ± 10.1	*17*	25.8 ± 13.3	*19*	25.9 ± 12.6
	T3	*51*	28.1 ± 13.6	*18*	28.0 ± 12.5	*15*	21.9 ± 11.8	*18*	23.0 ± 13.5
Vitamin B12	T1	*48*	320.0 [254.5-436.8]	*21*	320.0 [235.0-558.5]	*14*	284.0 [220.3-356.3]	*13*	303.0 [211.0-531.5]
(pmol/L)	T2	*54*	280.0 [207.5-380.0]	*16*	233.0 [167.8-587.8]	*17*	250.0 [229.0-295.0]	*19*	283.0 [223.0-344.0]
	T3	*52*	267.5 [202.5-379.0]	*17*	200.0 [172.0-447.5]	*15*	237.0 [200.0-267.0]	*18*	282.5 [212.5-339.5]
Vitamin A	T1	*20*	1.49 ± 0.43	*12*	1.34 ± 0.47	*8*	1.31 ± 0.38	*8*	1.45 ± 0.29
(µmol/L)	T2	*22*	1.58 ± 0.69	*8*	1.24 ± 0.39	*14*	1.33 ± 0.36	*13*	1.41 ± 0.43
	T3	*18*	1.22 ± 0.31	*11*	1.03 ± 0.38	*10*	1.37 ± 0.45	*14*	1.47 ± 0.48
Vitamin B1	T1	*46*	149.9 ± 28.3	*21*	143.6 ± 24.2	*12*	159.9 ± 21.4	*12*	143.4 ± 24.3
(nmol/L)	T2	*53*	143.6 ± 29.5	*16*	143.3 ± 27.2	*17*	138.1 ± 26.8	*18*	160.2 ± 34.0
	T3	*48*	137.0 ± 26.9	*18*	131.3 ± 29.1	*15*	133.9 ± 31.8	*18*	153.7 ± 26.7
Vitamin B6	T1	*46*	91.5 [73.0-113.0]	*21*	111.0 [90.5-182.5]	*12*	105.0 [93.8-130.5]	*12*	104.0 [76.5-135.3]
(nmol/L)	T2	*54*	81.5 [74.8-95.3]	*16*	97.5 [76.5-122.0]	*17*	96.0 [66.5-125.5]	*18*	100.5 [70.3-108.3]
	T3	*48*	79.0 [57.5-92.8]	*18*	85.5 [71.0-101.5]	*15*	99.0 [77.0-105.0]	*18*	80.0 [63.8-103.8]
Vitamin D	T1	*48*	80.0 ± 37.8	*21*	63.7 ± 33.2	*15*	88.1 ± 31.1	*13*	59.2 ± 30.8
(nmol/L)	T2	*54*	80.1 ± 34.2	*17*	72.8 ± 33.8	*17*	87.9 ± 30.9	*19*	65.1 ± 32.9
	T3	*51*	82.7 ± 36.9	*18*	72.2 ± 34.1	*16*	90.9 ± 32.3	*18*	68.0 ± 37.4
Calcium	T1	*46*	2.27 ± 0.10	*21*	2.31 ± 0.10	*14*	2.32 ± 0.08	*11*	2.31 ± 0.10
(mmol/L)	T2	*55*	2.20 ± 0.09	*16*	2.21 ± 0.11	*17*	2.26 ± 0.08	*19*	2.23 ± 0.10
	T3	*50*	2.18 ± 0.08	*17*	2.18 ± 0.09	*16*	2.24 ± 0.10	*18*	2.25 ± 0.11

Supplementary Table 2. Serum concentrations during each trimester of pregnancy (T1, T2, T3) for WLS users versus sMVS users, stratified by type of BS. *(continued).*

Serum variables	Trimester	**RYGB** (n=80)				**SG** (n=39)			
		n	**WLS MVS**	*n*	**sMVS**	*n*	**WLS MVS**	*n*	**sMVS**
PTH	T1	*36*	4.4 [2.9-6.6]	*16*	3.9 [2.6-5.8]	*12*	2.6 [2.1-3.7]	*10*	3.0 [2.2-3.7]
(pmol/L)	T2	*52*	4.3 [2.9-5.6]	*15*	3.8 [2.6-4.8]	*15*	2.2 [1.8-3.6]	*18*	3.4 [2.7-4.1]
	T3	*49*	4.6 [3.1-6.3]	*18*	3.9 [3.5-5.6]	*15*	2.4 [1.6-4.1]	*18*	4.7 [2.6-5.5]
Albumin	T1	*45*	39.9 ± 3.5	*21*	38.1 ± 4.0	*14*	38.3 ± 4.0	*11*	37.9 ± 3.6
(g/L)	T2	*55*	35.1 ± 3.9	*16*	33.9 ± 3.8	*17*	32.7 ± 3.9	*19*	33.4 ± 3.9
	T3	*51*	32.7 ± 3.6	*18*	30.3 ± 4.2	*17*	30.3 ± 4.0	*18*	30.4 ± 3.6

Data are presented as mean ± sd or median [Q1-Q3].

RYGB, Roux-en-Y gastric bypass; *SG*, sleeve gastrectomy; *WLS MVS*, 'weight loss surgery' multivitamin supplement; *sMVS*, standard multivitamin supplement (regular or prenatal supplements); *MCV*, mean corpuscular volume; *PTH*, parathyroid hormone.

CHAPTER 10

General discussion

The overall aim of this thesis was to gain more insight into factors affecting nutritional status of individuals undergoing bariatric surgery, including dietary intake and nutritional supplementation. Supplementation and nutrition can be seen as two sides of the same coin. Although supplement intake will contribute more to total nutrient intake than dietary intake, both are equally important in achieving optimal nutritional status after bariatric surgery. Supplements are not intended to replace nutrition and simply cannot replicate all of the nutrients and benefits of whole foods, such as fruits and vegetables. However, bariatric surgery limits the intake, digestion and absorption of nutrients, even while following a healthy diet, therefore mandating lifelong use of nutritional supplementation.

This thesis was divided into three parts: **Part A** addressed dietary intake and diet quality following bariatric surgery, **Part B** focused on nutritional supplementation and **Part C** of this thesis was dedicated to pregnancy after bariatric surgery, as this period may pose an additional risk on nutritional status. In this final chapter, the main findings of this thesis are discussed, as well as methodological and conceptual considerations and implications and suggestions for future research.

Main findings

Overall, both favorable and unfavorable changes in nutrient composition and diet quality were observed six months after bariatric surgery. Favorable changes included a decrease in the consumption of unhealthy food choices, red and processed meat and sodium, and an increase in dairy consumption as well as relative protein intake, whereas unfavorable changes included a reduced consumption of vegetables and wholegrain products along with a decreased fiber and micronutrient intake, and an increase in the intake of mono- and disaccharides (**Chapter 2**). A short screener for diet quality (Eetscore FFQ) showed to be acceptably correlated with diet quality index scores derived from 3-day food records, but absolute agreement was poor (**Chapter 3**).

Furthermore, a specialized multivitamin supplement (MVS) for sleeve gastrectomy patients was designed and optimized (**Chapter 4, 5 and 6**). Overall, this supplement was more effective in improving serum levels of hemoglobin, folic acid, vitamin D and vitamin B1 compared to standard over-the-counter supplementation. Non-users of MVS generally presented with the most deficiencies as well as the lowest serum concentrations for most evaluated micronutrients. Factors underlying low adherence to daily MVS use included poor motivation and knowledge, high costs and unpleasant smell and taste of supplements, gastrointestinal side effects after intake, and dissatisfaction with the received healthcare (**Chapter 7**).

Pregnancy within 12 months following bariatric surgery was associated with lower gestational age, gestational weight gain and neonatal birth weight, and inadequate gestational weight gain was in turn also associated with lower gestational age and lower neonatal birth weight in comparison with adequate weight gain during pregnancy (**Chapter 8**). Compared to standard or prenatal supplements, the use of specialized MVS during pregnancy resulted in improved serum levels of hemoglobin, ferritin, folic acid and vitamin B6 after Roux-en-Y gastric bypass, and in improved serum levels of vitamin D after sleeve gastrectomy (**Chapter 9**). However, serum levels of vitamin B1 were lower in specialized MVS users compared to standard MVS users during pregnancy after sleeve gastrectomy.

Nutritional intake after bariatric surgery

In the past decade, scientific interest and evidence on the implications of bariatric surgery on nutritional status has increased considerably. Consequently, several organizations have proposed guidelines for nutritional care of individuals undergoing bariatric surgery. The most commonly used guideline is from the American Society for Metabolic and Bariatric Surgery (ASMBS), who published their first guideline in 2008 [1]. In 2016 and 2019, the guidelines were updated by including more detailed recommendations, amongst others on optimal doses of micronutrients for preventing deficiencies [2, 3]. Yet, the majority of these recommendations were still based on weak (Grade C; 29%) or no conclusive evidence and/or expert opinion (Grade D; 41%) [2]. To illustrate, daily vitamin B1 requirements are estimated to be 12 mg per day, which is based on a single study including a small sample of women undergoing Roux-en-Y gastric bypass (n=11) and sleeve gastrectomy (n=11) that showed stable serum vitamin B1 concentrations after daily supplementation with 12 mg of thiamine for three months post-surgery [4]. In **Chapter 4 and 5**, we observed a deficiency prevalence of less than 5% and mean serum vitamin B1 concentrations near the upper reference limit after daily supplementation with 2.00-2.75 mg of thiamine. Despite the fact that complications of high doses of thiamine are rare as the body can excrete excess amounts of vitamin B1 in the urine [5], the ASMBS recommendation of at least 12 mg vitamin B1 (>1000% RDA) per day seems highly overestimated for bariatric patients who do not experience excessive vomiting.

Overall, evidence-based requirements for the prevention of micronutrient deficiencies after bariatric surgery are still lacking for most nutrients. Besides, consensus on recommended doses for supplementation during pregnancy after bariatric surgery is also urgently needed as there is limited consistency across current recommendations.

For example, recommendations for vitamin B12 vary from 350-1000 µg orally per day to 1000 µg via intramuscular injection every 1-3 months, and iron recommendations range from 27 to 80 mg per day during pregnancy post-bariatric surgery [6, 7].

Uniform evidence-based dietary guidelines for bariatric patients are also lacking. In the Netherlands, individuals who undergo bariatric surgery are advised to use an energy-restricted diet based on the general Dutch food-based dietary guidelines published in 2015 by the Health Council of the Netherlands [8]. Other authors have speculated that it may be inappropriate for bariatric patients to be expected to meet the same dietary recommendations as the general population due to the restrictive nature of the bariatric procedure [9]. General dietary recommendations after bariatric surgery include prioritizing protein intake, minimizing high-sugar and high-fat foods, eliminating sugar-sweetened beverages and alcohol, and increasing the consumption of fiber-rich foods [10, 11]. Moize and colleagues have translated these recommendations into a nutritional pyramid, based on a Mediterranean-style diet [10]. For a 1200-kcal diet with 60 grams of protein, recommended amounts include 2-3 servings of vegetables, 2-3 servings of fruit, 2 servings of (whole)grains and 4-6 servings of protein per day [10]. For comparison, an energy-restricted diet based on the general Dutch food-based dietary guidelines (1500 kcal, 80 grams protein) contains about 2-3 servings of vegetables, 2 servings of fruit, 5-7 servings of (whole)grains and 4-6 servings of protein per day [12, 13]. Both guidelines emphasize to limit the intake of alcohol and high-sugar and high-fat foods and beverages. The main difference between the guidelines is the amount of (whole)grain products that should be consumed on a daily basis. Overall, poor fiber intake is frequently reported in the bariatric population [14-19], which was also demonstrated in **Chapter 2**. Next to the general health benefits of dietary fiber, poor fiber intake in this population has also been linked to constipation, which is a common problem after bariatric surgery [14, 16]. For these reasons, we would recommended the general Dutch dietary guidelines for long-term eating behavior after bariatric surgery in order to achieve a healthy dietary pattern and associated health benefits.

Dietary assessment and misreporting

Accurately assessing dietary intake is challenging as current dietary assessment methods are often limited by reporting inaccuracy, subjective estimation of portion sizes, recall bias and misreporting [20]. It is therefore plausible that dietary intake measured throughout the chapters of this thesis is also prone to some error.

In **Chapter 2 and 3**, dietary intake was assessed with 3-day food records. Limitations of this assessment method include the relatively large respondent burden and reactivity biases such as changing the usual diet to simplify recording or social desirability to overreport foods that are perceived as healthy and underreport less healthy foods [21, 22]. Interviewer bias can also be introduced by insufficient training of the respondents, a non-deep check of the collected food record or mistakes in coding and entering the dietary data [21, 23]. We aimed to increase the reliability of our dietary intake data by providing detailed instructions, randomizing recording days and thoroughly checking completed records. Despite the instructions to weigh all foods and beverages consumed, the majority of the participants used standard units and household measures for the estimation of portion sizes. Weighed food records could have provided more precise estimates of consumed portions. Likewise, increasing the number of reporting days could have minimized random error [21], resulting in a more precise estimation of dietary intake.

In **Chapter 3**, the 3-day food records were used as a reference method for the validation of the Eetscore FFQ, which is a short Food-Frequency Questionnaire (FFQ) that assesses dietary intake over the previous month, based on 55 food items that account for 85% of energy intake from the adult population of the Dutch National Food Consumption Survey of 2007-2010 [24]. FFQs are useful for assessing overall dietary intake or a change in intake over time [21]. An important limitation of this assessment method is recall bias, as accuracy of reporting largely relies on respondent memory [25]. Furthermore, dietary intake data is restricted to items that are listed in the instrument. Especially short FFQs are for that reason not reliable for measuring total energy and nutrient intake [25]. Another challenge is the accurate estimation of portion sizes [26]. Within the Eetscore FFQ, portion sizes are assessed in standard portions and commonly used household measures. Particularly after bariatric surgery, a significant reduction in portion sizes may implicate that methods that rely on predefined portion sizes do not accurately reflect actual intake [27].

Overall, all subjective dietary assessment methods are highly susceptible to misreporting, particularly underreporting, which is a common bias in nutrition research. Various explanations for misreporting have been described, such as misrepresentation of portion sizes, social desirability to overreport foods that are perceived as healthy and underreport less healthy foods, and actual changes in eating behavior when recording food intake [28-30]. Underreporting can be intentional or unintentional and may be influenced by factors such as sex, age and education [28-30]. Body mass index also

appears to be a significant predictor of dietary underreporting, with individuals with obesity underreporting to a greater extent than individuals without obesity [28, 31]. The reasons why individuals with obesity are more likely to underreport are not well understood. They may differ in personal characteristics underlying underreporting such as education [30], but psychological factors including negative social attitudes towards their overweight and guilt about the quantity or type of food consumed may also affect its magnitude [27]. Waterworth and colleagues have recently added another interesting explanation for this observation by stating that the more extensive underreporting seen in this population might simply be a function of larger energy intake values and associated measurement errors [29]. They showed that allometric-scaling of total energy expenditure and energy intake removed the effect of obesity on underreporting, indicating that individuals with obesity do not underreport to a greater extent than normal-weight individuals when the effect of their larger body mass and associated greater energy needs are taken into account [29].
Within studies on dietary intake in the bariatric population, the failure to acknowledge the phenomenon of misreporting is a major concern. In a review including 49 papers on changes in dietary intake and appetite following Roux-en-Y gastric bypass, only three studies evaluated the possibility of misreporting but they differed in the method of calculation and in the interpretation of the outcomes [27].

The most commonly used methods for assessing the accuracy of self-reported dietary intake data are the doubly labelled water (DLW) method [32] and the Goldberg cut-off method [33-35], which are both based on the fundamental principle of energy metabolism. The DLW method has become the gold standard for measuring energy expenditure but is expensive and requires advanced laboratory equipment [36]. Therefore, several studies have used the Goldberg cut-off method to identify potential underreporters of total energy intake. In this method, the ratio of reported energy intake to basal metabolic rate (BMR) is compared against estimated cut-offs based on physical activity level at a confidence level of 95%.
Yet, the applicability of these techniques in the bariatric population is unknown as they largely rely on the condition of weight stability, which is violated post-surgery, resulting in an invalid ratio between reported energy intake and energy requirement. Besides, it is largely unknown if predicting equations for BMR are accurate in this population [37]. In **Chapter 3**, we therefore assumed that participants who were identified as potential underreporters of energy intake before bariatric surgery also underreported their intake after surgery, which is most likely not an accurate representation.

Besides, it is difficult to assess whether underreporting of energy intake is in turn also associated with macronutrient-specific misreporting [27]. Until the efficacy of these methods has been evaluated in the bariatric population, only tentative conclusions should be drawn from subjectively reported dietary intake data [38].

The reliability of dietary intake data is often limited by reporting inaccuracy, subjective estimation of portion sizes, recall bias and misreporting. Improving the accuracy of existing and new dietary assessment tools could result in better evaluation of dietary intake in this population.

Validation of dietary assessment tools

Validation of dietary assessment methods is conducted to determine how accurately self-report instruments measure true dietary intakes [22]. To determine the validity of an instrument, it is often compared with another instrument measuring the same concept and known to be accurate or considered as a gold standard [22]. Ideally, dietary assessment methods need to be validated against objective markers, such as dietary biomarkers. Currently, there are only a few biomarkers for dietary assessment that are well-established, including 24-hour energy expenditure measured by indirect calorimetry for energy, and 24-hour urinary nitrogen for protein [20]. While these biomarkers are accepted as more accurate and useful, they are reflective of dietary nutrient intake rather than consumption of specific foods, highlighting the need for food intake biomarkers [20]. For example, biomarkers as proline betaine for measuring intake of citrus fruit [39] and guanidoacetate for measuring chicken consumption [40] have been identified. Moreover, biomarkers of specific dietary patterns such as the Mediterranean diet are rapidly emerging [41]. However, the use of dietary biomarkers is not without limitations; costs and degree of invasiveness are important factors to take into consideration [42]. For this reason, subjective methods such as food records, as we used for the validation of the Eetscore FFQ in **Chapter 3**, are still most commonly used in dietary validation studies [22, 43]. Efforts to increase the duration of recording in the reference method could have provided a better measure of habitual intake that was generally more similar to the type of information generated by the Eetscore FFQ [43].

Validating dietary assessment tools within the target population is also essential. Currently, there is a clear lack of validated tools that can be used for the bariatric population. According to a recent review documenting dietary assessment tools that are used among patients targeted for bariatric surgery and those who have undergone bariatric surgery, only 25% of the 108 included studies validated their dietary assessment

tool or used a tool that had been previously validated, and only 10% were validated in the bariatric population [22]. Furthermore, none of these studies differentiated the validity of the tool to measure dietary intakes prior to and after surgery [22], as we performed in **Chapter 3**.

Identification of the most relevant dietary assessment tools that are validated prior to and after bariatric surgery would allow to measure dietary intake more accurately.
Additional studies are needed in order to develop valid and robust dietary assessment tools, taking the potential biases in this population into account.

Assessment of supplement use

Collecting accurate information on supplement use including type, composition, dose and compliance is essential in performing research on the efficacy of multivitamin supplementation after bariatric surgery. The high variety in type, composition and dose of available MVS is particularly challenging when comparing nutritional status in a real-life setting (**Chapter 6, 9**), whereas the low compliance with assigned supplement regimes is a major challenge in (controlled) intervention studies (**Chapter 4, 5**). Due to the relatively small sample sizes in **Chapter 6 and 9**, we were limited to categorize all MVS as either specialized MVS or standard MVS. However, the exact composition and dose of nutrients differ between brands, and dosing varied from 1-3 supplements per day which may all have impacted the daily administered dose of micronutrients. Furthermore, many participants stopped taking their assigned supplements or became less consistent with supplement intake over time in **Chapter 4 and 5**, which is in accordance with previous literature [44-49] as well as the findings from **Chapter 7**. In both the intervention and control groups, only about half of the participants still reported to use the assigned supplement at 12 months post-surgery. Additionally, information on compliance was subjective and incomplete which might have led to an overestimation of compliant participants. The large variation in composition and doses of available MVS as well as the level of compliance with the assigned supplement regimen could have played a vital role in the development of nutritional deficiencies and consequently have biased our comparisons between the supplement groups. Strikingly, only 4% of the participants in **Chapter 9** did not use MVS during pregnancy, which implicates that this period offers a window of opportunity to improve compliance with MVS intake.

Next to daily MVS, additional micronutrient supplementation is also frequently used in this patient population. For instance, all bariatric patients are advised to use additional

calcium/vitamin D3 supplementation as part of the standard treatment after surgery. Furthermore, intravenous iron infusions and hydroxocobalamin injections are frequently used and can highly impact subsequent micronutrient serum concentrations. Although we attempted to correct for the use of additional supplementation in **Chapters 4, 5, 6 and 9**, information on the intake of additional supplementation was also subjective and probably incomplete. To some extent, this could have impacted our findings regarding the efficacy of evaluated MVS as well. Overall, we also largely relied on the type of information that was available in the medical records for the assessment of supplement use. The use of questionnaires could have provided more detailed information on supplement intake. Considering the limitations of including questions on supplement intake into general dietary assessment tools [50], validated questionnaires are needed to obtain accurate data on supplement use in this patient population. Moreover, future studies require greater sample sizes in order to obtain sufficient statistical power to address the large variations in real life supplement use.

Evaluating the efficacy of multivitamin supplementation can be limited by the wide variety in available supplements, the level of compliance and the use of additional micronutrient supplementation.
Future research with greater sample sizes should include accurate measures of supplement intake in order to provide more valid comparisons.

Specialized multivitamin supplementation after bariatric surgery

To date, only a few trials are available that study the effect of (specialized) MVS on nutritional status after bariatric surgery. Consequently, the search for the most optimal MVS formulation for bariatric patients is still ongoing. As demonstrated in **Chapters 4, 5 and 6**, the use of specialized MVS containing high doses of several micronutrients including folic acid, vitamins B12 and D, elementary iron and zinc has a positive impact on nutritional status after sleeve gastrectomy by decreasing the risk of developing micronutrient deficiencies. Nevertheless, these conclusions are solely based on our findings with regards to this particular supplement (WLS Optimum; FitForMe, the Netherlands) and are less generalizable to other bariatric MVS formulations. Although comparable findings have been reported after using specialized MVS for Roux-en-Y gastric bypass [51, 52], the supplement under investigation was from the same manufacturer as WLS Optimum (WLS Forte; FitForMe, the Netherlands). Similarly, about 90% of the specialized MVS that were used during pregnancy after bariatric surgery in

Chapter 9 were either WLS Optimum or WLS Forte, and findings were mostly in line with those demonstrated in the general bariatric population (**Box 1**).

Box 1. *Findings with respect to the efficacy of specialized MVS compared to standard MVS in the general vs pregnant population after bariatric surgery.*

	General population	Pregnant population
Roux-en-Y gastric bypass	*Previous research [49, 50]:*	*Chapter 9:*
	↑ serum hemoglobin level	↑ serum hemoglobin level
	↓ anemia	
	↑ serum ferritin level	↑ serum ferritin level
	↓ iron deficiency	↓ iron deficiency
	↑ serum folic acid level	↑ serum folic acid level
	↑ serum vitamin B12 level	
		↓ serum vitamin B6 level
Sleeve Gastrectomy	*Chapter 4, 6:*	*Chapter 9:*
	↑ serum hemoglobin level	
	↑ serum folic acid level	
	↑ serum vitamin D level	↑ serum vitamin D level
	↓ vitamin D deficiency	
	↑ serum vitamin B1 level	↓ serum vitamin B1 level

Considering the large variety in composition of available bariatric MVS, future research into other formulations is urgently needed. Until then, we conclude that despite the efforts to produce different MVS formulations for each type of bariatric procedure, specialized MVS are no one-size-fits-all solution. To illustrate, we observed both low as well as elevated serum ferritin levels in users of specialized MVS after sleeve gastrectomy (**Chapter 6**), pointing out the complexity of micronutrient supplementation. Furthermore, it can be speculated that specific groups are at higher risk of iron deficiency, such as premenopausal and pregnant women. Future dose-response studies in subgroups as well as exploring different methods (i.e. alternate day dosing) or forms (i.e. ferrous fumarate vs ferrous sulphate) of supplementation could provide more insight into the most optimal formulation. Furthermore, new approaches such as nutritional genomics may open the door to implement more personalized recommendations for micronutrient supplementation in the future [53].

The use of specialized 'weight loss surgery' multivitamin supplementation is preferred over the use of standard supplementation after bariatric surgery. Future research should provide more insight into the nutritional needs of different subgroups of bariatric patients.

Nutritional assessment after bariatric surgery

Assessment of the prevalence, causes and consequences of micronutrient deficiencies, along with monitoring and evaluating the impact of interventions is of great importance after bariatric surgery. Micronutrients can be quantitatively measured in various biological matrices such as blood, urine, saliva, cells, hair, and nails [54]. Blood testing is generally the only available tool in clinical settings and research, but this method faces some limitations.

Assessment and interpretation of micronutrient status

The first thing that should be taken into account when interpreting micronutrient status, is that plasma or serum concentrations of specific micronutrients such as folate are only short-term markers of status as they are highly sensitive to recent intake [55-57]. Whole blood and red blood cell measurements generally reflect the longer-term status as they tend not to be affected by recent dietary intake, and are thus considered more reliable indicators of micronutrient status [56]. Furthermore, plasma or serum tests may miss functional deficiencies. Measuring the *mass* (quantity) of a nutrient in a cell is different from measuring its *functionality* (quality); it does not matter how much of the nutrient exists in or out the cell if that cell is incapable of utilizing the nutrient [56]. Functional deficiencies may exist in the presence of apparently normal blood levels because of poor transport of nutrients across the cell membrane, missing cofactors, circadian rhythms and fluctuation of blood levels with recent supplement or food intake [56]. For that reason, the diagnosis of nutritional deficiencies for some micronutrients may be best assessed by functional indicators or a combination of both direct and functional indicators [58]. Direct indicators are circulating concentrations of the micronutrient under investigation [58]. An example of a direct indicator for vitamin B12 status is holotranscobalamin (active B12) [56, 58]. In contrast to direct indicators, functional indicators or biomarkers reflect metabolic or functional consequences of an inadequate micronutrient status and are referred to as indicator of intracellular micronutrient deficiency [58]. In the example of vitamin B12, a functional biomarker is (elevated) methylmalonic acid (MMA). MMA is considered to be the proxy gold standard and the most reliable test for the evaluation of vitamin B12 status as it is unaffected by folate status [56]. Yet, functional biomarkers are not available for many micronutrients and existing biomarkers such as MMA are expensive [59]. As we did not include functional biomarkers of micronutrient status in **Chapters 4, 5, 6 and 9**, we cannot conclude if the observed low nutrient levels in these chapters were true deficiencies. In future studies, it is important to distinguish between low blood levels and true deficiencies, as

emphasized in the latest ESPEN guideline [60]. A deficiency implies a functional or physical effect of impaired status, whereas depletion is impaired status without such effects [60].

Another factor complicating the assessment of poor micronutrient status is inflammation. The acute-phase response to infection can result in significant changes to plasma levels of several micronutrients, independently of dietary supply and of nutritional status [56]. The magnitude of this change varies with the degree of inflammation and is greatest for iron, zinc, selenium, vitamin B6 and vitamin A, resulting in lower circulating levels [56, 61]. C-reactive protein (CRP) can be used as a marker for the intensity of inflammation. Plasma iron, selenium and vitamin B6 are unreliable when CRP is >10 mg/L, and plasma zinc and vitamin A are unreliable when CRP is >20 mg/L [56]. As inflammation can be driven by surgery, any subsequent complications and possibly obesity, it is therefore critical to collect a marker of inflammation when interpreting serum micronutrient status [62]. The presence of inflammation could have led to the misinterpretation of poor micronutrient status in **Chapters 4, 5, 6 and 9**. This particularly affects the reliability of the comparisons between the different MVS groups in these chapters. Including CRP at each blood test could have provided insight into the presence of inflammation, contributing to a more valid interpretation of the results. Nowadays, specific R-packages have even been developed that include inflammation adjustment equations for retinol-binding protein, serum retinol, serum ferritin, soluble transferrin receptor and serum zinc using CRP [63]. Other factors influencing nutrient concentrations include nutrient-nutrient interactions (e.g. folate and vitamin B12), drug–nutrient interactions (e.g. proton-pump inhibitors and metformin) and genetic variants [53, 58].

Lastly, laboratory results may be different based on the used assays which underlines the importance of using locally validated reference ranges [56]. In **Chapter 4, 5, 6 and 9**, used assays and corresponding reference ranges have changed over time and differed between centers. Using the wrong reference range could have led to a false interpretation of status for that nutrient. Ideally, corresponding reference ranges should have been determined on an individual level to provide a more valid interpretation of low blood levels, as was performed in **Chapter 6 and 9**. Additionally, the use of other techniques such as transforming serum data corresponding with different reference values to the same scale could have also been used to provide a more accurate comparison of blood levels resulting from different assays [64].

Adding functional indicators of micronutrient deficiencies, using CRP as a marker for inflammation and applying correct reference ranges in nutritional assessment can largely improve the validity and interpretation of micronutrient status following bariatric surgery.

Assessment and interpretation of micronutrient status during pregnancy

Next to the abovementioned limitations including the lack of biomarkers, the presence of inflammation and the use of different assays and reference ranges, the main challenge in assessing nutritional status in pregnant women is the lack of uniform pregnancy-specific cut-offs for most micronutrients [58]. During pregnancy, a 25-30% physiological decrease in the levels of hemoglobin, ferritin, folic acid, vitamins A, B12 and D, PTH and calcium is expected as a result of the expanding maternal blood volume by approximately 50% (hemodilution) and increasing demands of the growing fetus [65-67]. These physiologic changes likely impact the variability of serum concentrations and thereby the interpretability of available cut-offs [58]. In **Chapter 9**, we only used pregnancy-specific cut-off values for hemoglobin [68] as uniform, evidence-based pregnancy-specific cut-offs for most other micronutrients are lacking. As a result, the number of nutritional deficiencies may have been overestimated. Ideally, laboratories should provide locally validated reference ranges for pregnant women to recognize changes in normal laboratory values induced by pregnancy. Although some guidelines on laboratory values in healthy pregnant women are available [69, 70], differences in used assays and population groups may limit their transferability to other centers and populations. For future research, it would be useful to include control groups of pregnant women with normal weight, overweight and obesity to gain more insight into the course of serum concentrations during general pregnancy in order to establish correct reference ranges for nutritional status during pregnancy following bariatric surgery.

Serum concentrations might naturally decrease during pregnancy. Locally validated reference ranges as well as more insight into nutritional status during regular pregnancy may improve the interpretation of micronutrient status during pregnancy following bariatric surgery.

Long-term consequences of bariatric surgery

As the first bariatric procedure was performed more than five decades ago [71], research on long-term health after bariatric surgery is arising. However, several evidence gaps

including potential long-term adverse effects of using high-dose supplementation and the transgenerational consequences of bariatric surgery still need to be addressed.

Potential adverse effects of high-dose supplementation

Despite the efficacy of specialized MVS on the prevention of nutritional deficiencies after bariatric surgery, a downside of the daily use of high-dose supplementation may be the risk of toxicity or 'hypervitaminosis'. The consequences of hypervitaminosis may be just as important as those resulting from deficiencies; however, clinical symptoms are often rare and difficult to recognize. In the short term, excess serum levels of for example vitamin B6 may cause neuropathic symptoms [72]. In **Chapters 4, 5, 6 and 9**, extremely high serum levels (>200 nmol/L) of vitamin B6 were found in some patients. Clinical manifestations of toxicity have not been actively investigated, but no adverse events due to hypervitaminosis for vitamin B6 were reported. Moreover, toxicity may depend on which form of a nutrient is used in a supplement. Vrolijk et al. [73] found that the neuropathy observed after taking a relatively high dose of vitamin B6 supplements is due to pyridoxine. They suggested to replace pyridoxine by pyridoxal or pyridoxal-phosphate in supplements containing vitamin B6 [73]. More importantly, potential adverse effects resulting from the daily use of high-dose supplementation after bariatric surgery on the long term is largely unknown and observational data is lacking. Research in the general population has indicated several adverse events related to high serum levels of certain nutrients. For instance, high plasma concentrations of vitamin B12 have been associated with increased risks of certain types of cancer [74, 75] and all-cause mortality [76]. Furthermore, a meta-analysis of the dose-response relationship between vitamin E supplementation and all-cause mortality showed that 9 of 11 trials testing a high dose of vitamin E (≥ 400 IU per day) showed an increased risk for all-cause mortality compared to control groups [77]. A dose-response analysis also showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk of doses greater than 150 IU per day [77]. However, it is not known if and how such high doses are being absorbed by individuals who underwent bariatric surgery. More research is needed to confirm the safety of long-term use of high-dose supplementation after bariatric surgery.

Potential toxicity of using high-dose supplementation after bariatric surgery is largely unknown and observational data on the long-term consequences of elevated serum levels in this patient population are urgently needed.

Transgenerational consequences of bariatric surgery

As the number of bariatric procedures in women of childbearing age is still increasing worldwide, there is an urgency to understand the long-term consequences of consequential caloric restriction, micronutrient deficiencies, and lifelong supplementation on the long-term health of mother and child. Maternal nutrition during pregnancy has a pivotal role in the regulation of placental-fetal development and thereby affects the lifelong health of the offspring [78]. Chronic undernutrition and correlated neonatal growth restriction have been linked to health consequences later in life, the so-called 'Barker Hypothesis' [79]. For example, the consequences of lifelong deficiencies and (iatrogenic) undernutrition during the life course have been reported excessively in studies performed in low and middle income countries. More specifically, the transgenerational effects of malnutrition in utero have been investigated in detail in the Dutch Famine Cohort, resulting in an increased risk of cancer and cardiovascular disease later in life [80-82]. A higher prevalence of intrauterine growth restriction and small-for-gestational age has also been observed in infants born after maternal bariatric surgery, compared to infants of non-operated women with obesity [83-87]. Currently, it is not completely understood how maternal bariatric surgery may impact fetal growth and programming, and children's long-term health and development, but these effects are possibly mediated through gestational weight gain, glucose metabolism (e.g. maternal hypoglycemia) and altered absorption of nutrients [88-90]. Araki and colleagues found that personalized nutrition counselling during pregnancy after bariatric surgery improved nutrient intake and may contribute to higher birth weight of the offspring [91]. Data from large prospective cohort studies, starting before pregnancy and continuing after the post-partum period are required to obtain insight in long-term effects and transgenerational consequences of bariatric surgery. This is also in line with the general future research focus which shifts from studying health at one point in time towards studying health over the life course.

In order to break the vicious cycle of obesity and its health consequences, future research should focus on the growth and development of children born after maternal bariatric surgery.
Ultimately, this will contribute to the prevention of obesity in future generations.

Conclusion and future perspectives

Based on the findings of this thesis, the following can be concluded:

A. Both favorable and unfavorable changes in dietary intake and diet quality are observed following bariatric surgery. Insight into these changes may help dietitians and other healthcare practitioners to understand potential pitfalls in order to improve dietary counselling of their patients.

Identification of the most relevant dietary assessment tools that are validated prior to and after bariatric surgery would allow to measure dietary intake more accurately. Moreover, web-based and technology-assisted assessment methods have been emerging and potential benefits and risks associated with these methods need to be evaluated in the bariatric population. Besides, future research is required to establish the magnitude and direction of misreporting within this patient population, and to provide effective methods to account for this bias in nutritional research. Furthermore, additional studies into long-term changes in dietary intake and diet quality are needed as dietary intake and eating behavior are likely to transition over time between the first catabolic phase and the maintenance phase.

B. The high risk of developing poor nutritional status together with the decreased adherence to daily supplement intake over time reinforces the need for long-term nutritional counselling while taking patients' barriers related to supplement use into account. Although they are no one-size-fits-all solution, we carefully conclude that the use of specialized 'weight loss surgery' multivitamin supplementation is preferred over the use of standard over-the-counter supplementation after bariatric surgery.

Future research into other types of specialized supplementation for bariatric patients as well as nutritional needs of different subgroups such as pregnant women is needed to gain more insight into the most optimal formulation. Ideally, nutritional needs of bariatric patients should be assessed on an individual basis but that is currently not feasible. Furthermore, adding functional markers of micronutrient deficiencies, using CRP as a marker for inflammation and applying correct reference ranges can largely improve the validity and interpretation of micronutrient status in future studies. Besides, compliance with daily supplement intake remains an important issue that should be targeted in order to improve nutritional status after bariatric surgery. Next steps towards better compliance with daily supplement intake include optimizing supplements to reduce unpleasant smell, taste and gastrointestinal side effects after intake,

reimbursement of (specialized) supplements to overcome the high costs and improving patient education and patient-tailored decision making.
Meanwhile, observational data on the long-term consequences of using high-dose supplementation in this patient population is urgently needed.

C. During pregnancy after bariatric surgery, specific attention is needed on the optimal timing of conception, achieving adequate gestational weight and providing adequate supplementation to improve nutritional status of this population at risk.
Areas of research that need further robust investigation include gestational weight gain recommendations, nutritional requirements and supplementation strategies, impact of nutritional status on neonatal outcomes and other relevant factors such as adequacy of breast milk after maternal bariatric surgery.
Importantly, future studies should not only include women receiving secondary or tertiary obstetrician-led care, but also women receiving primary midwife-led care to confirm our findings and increase their external validity. Ideally, these studies should be performed by designing transgenerational cohorts that can provide a fundamental basis for the development of evidence-based guidelines for optimal guidance of women of reproductive age with a history of bariatric surgery to ultimately achieve optimal health for mother and child.

Overall, we conclude that:

Regular nutritional assessment and counseling focused on adequate dietary intake and nutritional supplementation are essential in achieving optimal nutritional status, ultimately contributing to improved long-term health after bariatric surgery.

References

1. Allied Health Sciences Section Ad Hoc Nutrition, C, Aills, L, Blankenship, J, et al., *ASMBS Allied Health Nutritional Guidelines for the Surgical Weight Loss Patient.* Surg Obes Relat Dis, 2008. **4**(5 Suppl): p. S73-108.
2. Mechanick, JI, Apovian, C, Brethauer, S, et al., *Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists.* Surg Obes Relat Dis, 2020. **16**(2): p. 175-247.
3. Parrott, J, Frank, L, Rabena, R, et al., *American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients.* Surg Obes Relat Dis, 2017. **13**(5): p. 727-741.
4. Moore, CE and Sherman, V, *Effectiveness of B vitamin supplementation following bariatric surgery: rapid increases of serum vitamin B12.* Obes Surg, 2015. **25**(4): p. 694-699.
5. Kerns, JC and Gutierrez, JL, *Thiamin.* Adv Nutr, 2017. **8**(2): p. 395-397.
6. Huang, B, Yo, JH, Gandhi, S, et al., *Micronutrient screening, monitoring, and supplementation in pregnancy after bariatric surgery.* Obstet Med, 2022. **15**(3): p. 151-159.
7. Vanheule, G, Ceulemans, D, Vynckier, AK, et al., *Micronutrient supplementation in pregnancies following bariatric surgery: a practical review for clinicians.* Obes Surg, 2021. **31**(10): p. 4542-4554.
8. Kromhout, D, Spaaij, CJ, de Goede, J, et al., *The 2015 Dutch food-based dietary guidelines.* Eur J Clin Nutr, 2016. **70**(8): p. 869-878.
9. Zarshenas, N, Tapsell, LC, Neale, EP, et al., *The Relationship Between Bariatric Surgery and Diet Quality: a Systematic Review.* Obes Surg, 2020. **30**(5): p. 1768-1792.
10. Moize, VL, Pi-Sunyer, X, Mochari, H, et al., *Nutritional pyramid for post-gastric bypass patients.* Obes Surg, 2010. **20**(8): p. 1133-1141.
11. Sherf Dagan, S, Goldenshluger, A, Globus, I, et al., *Nutritional Recommendations for Adult Bariatric Surgery Patients: Clinical Practice.* Adv Nutr, 2017. **8**(2): p. 382-394.
12. Brink, E, van Rossum, C, Postma-Smeets, A, et al., *Development of healthy and sustainable food-based dietary guidelines for the Netherlands.* Public Health Nutr, 2019. **22**(13): p. 2419-2435.
13. Brink, EJ, Postma-Smeets, A, Stafleu, A, et al. *The Wheel of Five. Factsheet.* 2017.
14. Afshar, S, Kelly, SB, Seymour, K, et al., *The Effects of Bariatric Procedures on Bowel Habit.* Obes Surg, 2016. **26**(10): p. 2348-2354.
15. Farias, G, Silva, RMO, da Silva, PPP, et al., *Impact of dietary patterns according to NOVA food groups: 2 y after Roux-en-Y gastric bypass surgery.* Nutrition, 2020. **74**: p. 110746.
16. Grosse, CS and Cope, VC, *Dietary Fibre Intake and Bowel Habits After Bariatric Surgery: a Structured Literature Review.* Obes Surg, 2019. **29**(7): p. 2247-2254.
17. Ostad, AN, Barghchi, H, Jangjoo, A, et al., *Macro- and Micro-nutrient Intake Adequacy in Gastric Bypass Patients after 24 Months: a Cross-sectional Study.* Clin Nutr Res, 2021. **10**(4): p. 341-352.
18. Reichmann, MTF, Todeschini, S, Setter, N, et al., *Comparison of the dietary intake amongst women in the late postoperative period after Roux-en-Y gastric bypass with the bariatric food pyramidof dietary intake with reference values among women in late postoperative of y-en-roux gastric bypass.* Nutr Hosp, 2019. **36**(3): p. 599-603.
19. Ziadlou, M, Hosseini-Esfahani, F, Mozaffari Khosravi, H, et al., *Dietary macro- and micro-nutrients intake adequacy at 6th and 12th month post-bariatric surgery.* BMC Surg, 2020. **20**(1): p. 232.
20. McNamara, AE and Brennan, L, *Potential of food intake biomarkers in nutrition research.* Proc Nutr Soc, 2020: p. 1-11.

21. Bailey, RL, *Overview of dietary assessment methods for measuring intakes of foods, beverages, and dietary supplements in research studies.* Curr Opin Biotechnol, 2021. **70**: p. 91-96.
22. Legault, M, Leblanc, V, Marchand, GB, et al., *Evaluation of Dietary Assessment Tools Used in Bariatric Population.* Nutrients, 2021. **13**(7).
23. Ortega, RM, Perez-Rodrigo, C and Lopez-Sobaler, AM, *Dietary assessment methods: dietary records.* Nutr Hosp, 2015. **31 Suppl 3**: p. 38-45.
24. Van Rossum, C, Fransen, HP, Verkaik-Kloosterman, JV, et al., *Dutch National Food Consumption Survey 2007-2010. Diet of children and adults aged 7 to 69 years.* 2011, National Institute for Public Health and the Environment.: Bilthoven.
25. Perez Rodrigo, C, Aranceta, J, Salvador, G, et al., *Food frequency questionnaires.* Nutr Hosp, 2015. **31 Suppl 3**: p. 49-56.
26. Amoutzopoulos, B, Page, P, Roberts, C, et al., *Portion size estimation in dietary assessment: a systematic review of existing tools, their strengths and limitations.* Nutr Rev, 2020. **78**(11): p. 885-900.
27. Redpath, TL, Livingstone, MBE, Dunne, AA, et al., *Methodological issues in assessing change in dietary intake and appetite following gastric bypass surgery: A systematic review.* Obes Rev, 2021. **22**(6): p. e13202.
28. Poslusna, K, Ruprich, J, de Vries, JH, et al., *Misreporting of energy and micronutrient intake estimated by food records and 24 hour recalls, control and adjustment methods in practice.* Br J Nutr, 2009. **101 Suppl 2**: p. S73-85.
29. Waterworth, SP, Kerr, CJ, McManus, CJ, et al., *Obese individuals do not underreport dietary intake to a greater extent than nonobese individuals when data are allometrically-scaled.* Am J Hum Biol, 2022. **34**(7): p. e23743.
30. Wehling, H and Lusher, J, *People with a body mass index ⩾30 under-report their dietary intake: A systematic review.* J Health Psychol, 2019. **24**(14): p. 2042-2059.
31. Trijsburg, L, Geelen, A, Hollman, PC, et al., *BMI was found to be a consistent determinant related to misreporting of energy, protein and potassium intake using self-report and duplicate portion methods.* Public Health Nutr, 2017. **20**(4): p. 598-607.
32. Schoeller, DA and van Santen, E, *Measurement of energy expenditure in humans by doubly labeled water method.* J Appl Physiol Respir Environ Exerc Physiol, 1982. **53**(4): p. 955-959.
33. Black, AE, *Critical evaluation of energy intake using the Goldberg cut-off for energy intake:basal metabolic rate. A practical guide to its calculation, use and limitations.* Int J Obes Relat Metab Disord, 2000. **24**(9): p. 1119-1130.
34. Black, AE, *The sensitivity and specificity of the Goldberg cut-off for EI:BMR for identifying diet reports of poor validity.* Eur J Clin Nutr, 2000. **54**(5): p. 395-404.
35. Goldberg, GR, Black, AE, Jebb, SA, et al., *Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording.* Eur J Clin Nutr, 1991. **45**(12): p. 569-581.
36. Wong, WW, Roberts, SB, Racette, SB, et al., *The doubly labeled water method produces highly reproducible longitudinal results in nutrition studies.* J Nutr, 2014. **144**(5): p. 777-783.
37. Ravelli, MN, Schoeller, DA, Crisp, AH, et al., *Accuracy of total energy expenditure predictive equations after a massive weight loss induced by bariatric surgery.* Clin Nutr ESPEN, 2018. **26**: p. 57-65.
38. Livingstone, MBE, Redpath, T, Naseer, F, et al., *Food intake following gastric bypass surgery: patients eat less but do not eat differently.* J Nutr, 2022. **152**(11): p. 2319-2332.
39. Gibbons, H, Michielsen, CJR, Rundle, M, et al., *Demonstration of the utility of biomarkers for dietary intake assessment; proline betaine as an example.* Mol Nutr Food Res, 2017. **61**(10).

40. Yin, X, Gibbons, H, Rundle, M, et al., *Estimation of Chicken Intake by Adults Using Metabolomics-Derived Markers.* J Nutr, 2017. **147**(10): p. 1850-1857.
41. Liang, S, Nasir, RF, Bell-Anderson, KS, et al., *Biomarkers of dietary patterns: a systematic review of randomized controlled trials.* Nutr Rev, 2022. **80**(8): p. 1856-1895.
42. Hedrick, VE, Dietrich, AM, Estabrooks, PA, et al., *Dietary biomarkers: advances, limitations and future directions.* Nutr J, 2012. **11**: p. 109.
43. Cade, J, Thompson, R, Burley, V, et al., *Development, validation and utilisation of food-frequency questionnaires - a review.* Public Health Nutr, 2002. **5**(4): p. 567-587.
44. Ben-Porat, T, Elazary, R, Goldenshluger, A, et al., *Nutritional deficiencies four years after laparoscopic sleeve gastrectomy-are supplements required for a lifetime?* Surg Obes Relat Dis, 2017. **13**(7): p. 1138-1144.
45. James, H, Lorentz, P and Collazo-Clavell, ML, *Patient-Reported Adherence to Empiric Vitamin/Mineral Supplementation and Related Nutrient Deficiencies After Roux-en-Y Gastric Bypass.* Obes Surg, 2016. **26**(11): p. 2661-2666.
46. Lier, HO, Biringer, E, Stubhaug, B, et al., *The impact of preoperative counseling on postoperative treatment adherence in bariatric surgery patients: a randomized controlled trial.* Patient Educ Couns, 2012. **87**(3): p. 336-342.
47. Mahawar, KK, Clare, K, O'Kane, M, et al., *Patient Perspectives on Adherence with Micronutrient Supplementation After Bariatric Surgery.* Obes Surg, 2019. **29**(5): p. 1551-1556.
48. Sherf Dagan, S, Keidar, A, Raziel, A, et al., *Do Bariatric Patients Follow Dietary and Lifestyle Recommendations during the First Postoperative Year?* Obes Surg, 2017. **27**(9): p. 2258-2271.
49. Zarshenas, N, Nacher, M, Loi, KW, et al., *Investigating Nutritional Deficiencies in a Group of Patients 3 Years Post Laparoscopic Sleeve Gastrectomy.* Obes Surg, 2016. **26**(12): p. 2936-2943.
50. Bailey, RL, Dodd, KW, Gahche, JJ, et al., *Best Practices for Dietary Supplement Assessment and Estimation of Total Usual Nutrient Intakes in Population-Level Research and Monitoring.* J Nutr, 2019. **149**(2): p. 181-197.
51. Dogan, K, Aarts, EO, Koehestanie, P, et al., *Optimization of vitamin suppletion after Roux-en-Y gastric bypass surgery can lower postoperative deficiencies: a randomized controlled trial.* Medicine, 2014. **93**(25): p. e169.
52. Homan, J, Schijns, W, Aarts, EO, et al., *An optimized multivitamin supplement lowers the number of vitamin and mineral deficiencies three years after Roux-en-Y gastric bypass: a cohort study.* Surg Obes Relat Dis, 2016. **12**(3): p. 659-667.
53. Galyean, S, Sawant, D and Shin, AC, *Personalized Nutrition for Management of Micronutrient Deficiency-Literature Review in Non-bariatric Populations and Possible Utility in Bariatric Cohort.* Obes Surg, 2020. **30**(9): p. 3570-3582.
54. Höller, U, Bakker, SJL, Düsterloh, A, et al., *Micronutrient status assessment in humans: Current methods of analysis and future trends.* Trends Analyt Chem, 2018. **102**: p. 110-122.
55. Bailey, LB, Stover, PJ, McNulty, H, et al., *Biomarkers of Nutrition for Development-Folate Review.* J Nutr, 2015. **145**(7): p. 1636S-1680S.
56. Berger, MM, Talwar, D and Shenkin, A, *Pitfalls in the interpretation of blood tests used to assess and monitor micronutrient nutrition status.* Nutr Clin Pract, 2023. **38**(1): p. 56-69.
57. Navarro, M and Wood, RJ, *Plasma changes in micronutrients following a multivitamin and mineral supplement in healthy adults.* J Am Coll Nutr, 2003. **22**(2): p. 124-132.
58. Lamers, Y, *Approaches to improving micronutrient status assessment at the population level.* Proc Nutr Soc, 2019. **78**(2): p. 170-176.

59. Manger, MS, Brown, KH, Osendarp, SJM, et al., *Barriers to and Enablers of the Inclusion of Micronutrient Biomarkers in National Surveys and Surveillance Systems in Low- and Middle-Income Countries.* Nutrients, 2022. **14**(10).
60. Berger, MM, Shenkin, A, Schweinlin, A, et al., *ESPEN micronutrient guideline.* Clin Nutr, 2022. **41**(6): p. 1357-1424.
61. Allen, LH, *Limitations of current indicators of micronutrient status.* Nutr Rev, 2009. **67 Suppl 1**: p. S21-23.
62. Lewis, CA, de Jersey, S, Hopkins, G, et al., *Does Bariatric Surgery Cause Vitamin A, B1, C or E Deficiency? A Systematic Review.* Obes Surg, 2018. **28**(11): p. 3640-3657.
63. Namaste, SM, Aaron, GJ, Varadhan, R, et al., *Methodologic approach for the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project.* Am J Clin Nutr, 2017. **106**(Suppl 1): p. 333S-347S.
64. Meng, F, Jonklaas, J and Leow, MK, *Interconversion of Plasma Free Thyroxine Values from Assay Platforms with Different Reference Intervals Using Linear Transformation Methods.* Biology (Basel), 2021. **10**(1).
65. Ciangura, C, Coupaye, M, Deruelle, P, et al., *Clinical Practice Guidelines for Childbearing Female Candidates for Bariatric Surgery, Pregnancy, and Post-partum Management After Bariatric Surgery.* Obes Surg, 2019. **29**(11): p. 3722-3734.
66. Falcone, V, Stopp, T, Feichtinger, M, et al., *Pregnancy after bariatric surgery: a narrative literature review and discussion of impact on pregnancy management and outcome.* BMC Pregnancy Childbirth, 2018. **18**(1): p. 507.
67. Shawe, J, Ceulemans, D, Akhter, Z, et al., *Pregnancy after bariatric surgery: Consensus recommendations for periconception, antenatal and postnatal care.* Obes Rev, 2019. **20**(11): p. 1507-1522.
68. Jans, S and Beentjes, M, *Anemie in de verloskundige praktijk - Aanbevelingen voor preventie, diagnostiek en behandeling.*, in *KNOV-standaard*, The Royal Dutch Organisation of Midwives, Editor. 2010, The Royal Dutch Organisation of Midwives.
69. Abbassi-Ghanavati, M, Greer, LG and Cunningham, FG, *Pregnancy and laboratory studies: a reference table for clinicians.* Obstet Gynecol, 2009. **114**(6): p. 1326-1331.
70. Larsson, A, Palm, M, Hansson, LO, et al., *Reference values for clinical chemistry tests during normal pregnancy.* BJOG, 2008. **115**(7): p. 874-881.
71. Faria, GR, *A brief history of bariatric surgery.* Porto Biomed J, 2017. **2**(3): p. 90-92.
72. Alsabah, A, Al Sabah, S, Al-Sabah, S, et al., *Investigating Factors Involved in Post Laparoscopic Sleeve Gastrectomy (LSG) Neuropathy.* Obes Surg, 2017. **27**(5): p. 1271-1276.
73. Vrolijk, MF, Opperhuizen, A, Jansen, E, et al., *The vitamin B6 paradox: Supplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function.* Toxicol In Vitro, 2017. **44**: p. 206-212.
74. Arendt, JFH, Sorensen, HT, Horsfall, LJ, et al., *Elevated Vitamin B12 Levels and Cancer Risk in UK Primary Care: A THIN Database Cohort Study.* Cancer Epidemiol Biomarkers Prev, 2019. **28**(4): p. 814-821.
75. Lacombe, V, Chabrun, F, Lacout, C, et al., *Persistent elevation of plasma vitamin B12 is strongly associated with solid cancer.* Sci Rep, 2021. **11**(1): p. 13361.
76. Flores-Guerrero, JL, Minovic, I, Groothof, D, et al., *Association of Plasma Concentration of Vitamin B12 With All-Cause Mortality in the General Population in the Netherlands.* JAMA Netw Open, 2020. **3**(1): p. e1919274.
77. Miller, ER, 3rd, Pastor-Barriuso, R, Dalal, D, et al., *Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality.* Ann Intern Med, 2005. **142**(1): p. 37-46.

78. Belkacemi, L, Nelson, DM, Desai, M, et al., *Maternal undernutrition influences placental-fetal development.* Biol Reprod, 2010. **83**(3): p. 325-331.
79. Barker, DJ, *The fetal and infant origins of adult disease.* BMJ, 1990. **301**(6761): p. 1111.
80. Roseboom, T, de Rooij, S and Painter, R, *The Dutch famine and its long-term consequences for adult health.* Early Hum Dev, 2006. **82**(8): p. 485-491.
81. Stein, Z and Susser, M, *The Dutch famine, 1944-1945, and the reproductive process. II. Interrelations of caloric rations and six indices at birth.* Pediatr Res, 1975. **9**(2): p. 76-83.
82. Stein, Z and Susser, M, *The Dutch famine, 1944-1945, and the reproductive process. I. Effects on six indices at birth.* Pediatr Res, 1975. **9**(2): p. 70-76.
83. Gascoin, G, Gerard, M, Salle, A, et al., *Risk of low birth weight and micronutrient deficiencies in neonates from mothers after gastric bypass: a case control study.* Surg Obes Relat Dis, 2017. **13**(8): p. 1384-1391.
84. Johansson, K, Cnattingius, S, Naslund, I, et al., *Outcomes of pregnancy after bariatric surgery.* N Engl J Med, 2015. **372**(9): p. 814-824.
85. Kjaer, MM, Lauenborg, J, Breum, BM, et al., *The risk of adverse pregnancy outcome after bariatric surgery: a nationwide register-based matched cohort study.* Am J Obstet Gynecol, 2013. **208**(6): p. 464 e461-465.
86. Parent, B, Martopullo, I, Weiss, NS, et al., *Bariatric Surgery in Women of Childbearing Age, Timing Between an Operation and Birth, and Associated Perinatal Complications.* JAMA Surg, 2017. **152**(2): p. 1-8.
87. Rives-Lange, C, Poghosyan, T, Phan, A, et al., *Risk-Benefit Balance Associated With Obstetric, Neonatal, and Child Outcomes After Metabolic and Bariatric Surgery.* JAMA Surg, 2023. **158**(1): p. 36-44.
88. Feichtinger, M, Falcone, V, Schoenleitner, T, et al., *Intrauterine Fetal Growth Delay During Late Pregnancy After Maternal Gastric Bypass Surgery.* Ultraschall Med, 2020. **41**(1): p. 52-59.
89. Gobl, CS, Bozkurt, L, Tura, A, et al., *Assessment of glucose regulation in pregnancy after gastric bypass surgery.* Diabetologia, 2017. **60**(12): p. 2504-2513.
90. Yu, Y and Groth, SW, *Risk factors of lower birth weight, small-for-gestational-age infants, and preterm birth in pregnancies following bariatric surgery: a scoping review.* Arch Gynecol Obstet, 2022.
91. Araki, S, Shani Levi, C, Abutbul Vered, S, et al., *Pregnancy after bariatric surgery: Effects of personalized nutrition counseling on pregnancy outcomes.* Clin Nutr, 2022. **41**(2): p. 288-297.

Appendices

Summary | Samenvatting
Acknowledgements | Dankwoord
About the author

Summary

English summary
Nederlandse samenvatting

To date, bariatric surgery is the only effective strategy to treat severe obesity, resulting in long-term weight loss, reduction of obesity-related comorbidities, overall mortality and improvement in quality of life. Despite these benefits, all bariatric procedures alter the anatomy and physiology of the gastrointestinal tract, thereby influencing intake, digestion and absorption of nutrients. This may in turn impact nutritional status. The overall aim of this thesis was to gain more insight into factors affecting nutritional status after bariatric surgery, including dietary intake and nutritional supplementation. Furthermore, we have studied pregnancy after bariatric surgery as this period may pose an additional risk on nutritional status.

In **part A** of this thesis, we focused on dietary intake and diet quality after bariatric surgery. In **Chapter 2**, short-term changes in macro- and micronutrient composition and diet quality in the first six months following bariatric surgery were evaluated. Diet quality was assessed by adherence to the Dutch food-based dietary guidelines by using the cut-off criteria of the Dutch Healthy Diet index. Favorable changes in dietary intake included a decrease in the consumption of unhealthy food choices (e.g. sweets and snacks), red and processed meat and sodium, and an increase in dairy consumption as well as in relative protein intake after bariatric surgery. However, unfavorable changes including reduced consumption of vegetables and wholegrain products along with a decreased fiber and micronutrient intake, and an increase in the intake of mono- and disaccharides were also observed six months post-surgery.

Collecting accurate measures of dietary intake is essential for optimal nutritional care after bariatric surgery. However, validated dietary assessment tools in this specific population are lacking. In **Chapter 3**, we evaluated the relative validity and reproducibility of the Eetscore FFQ as a short screener for diet quality after bariatric surgery. The Eetscore FFQ showed to be acceptably correlated with the Dutch Healthy Diet index derived from 3-day food records (reference method). Yet, the Eetscore FFQ showed higher index scores than the food records and absolute agreement between the two methods was poor. Considering the need for valid dietary assessment tools that reduce the burden for patients, practitioners and researchers, the Eetscore FFQ can be used for ranking individuals according to diet quality and for monitoring relative changes in diet quality over time.

In **part B** of this thesis, we focused on nutritional supplementation after bariatric surgery. In **Chapters 4, 5 and 6**, a specialized 'weight loss surgery' multivitamin supplement (MVS) for sleeve gastrectomy patients was designed and optimized (WLS Optimum).

In **Chapter** 4, the first version of this supplement was compared to a standard over-the-counter MVS in a randomized controlled trial. Intention-to-treat analysis demonstrated higher serum levels of vitamin B1 and more folic acid deficiencies in the intervention group compared to the control group after 12 months. Based on these results, WLS Optimum was optimized and evaluated in a single-arm open-label trial (**Chapter 5)**. Compared to its previous version, use of WLS Optimum 2.0 resulted in higher serum levels of vitamin B12, vitamin B6 and zinc, but lower serum levels of folic acid during the first year after sleeve gastrectomy. Deficiencies for vitamin B12 and phosphate were also less prevalent in the WLS Optimum 2.0 group. In **Chapter 6**, the three year follow-up results of both studies were presented. We found that users of specialized MVS (WLS Optimum 1.0 + 2.0) had higher serum levels of hemoglobin, folic acid, vitamin B12, vitamin D and calcium compared to standard MVS users and/or non-users of MVS. Deficiencies for folic acid and vitamin D were also least prevalent in the WLS Optimum (1.0) group. Non-users generally presented with the most deficiencies as well as the lowest serum concentrations for most micronutrients.
Low adherence to recommended supplement protocols is a major challenge in both research and clinical practice. In **Chapter 7**, we aimed to gain insight into underlying factors and potential facilitators and barriers for daily MVS intake. Of the 4614 patients that were included in the study, 93% indicated to be MVS user versus 7% non-users. We found that non-users of MVS were younger, more often underwent a sleeve gastrectomy and had a longer time interval since surgery than MVS users. Barriers for daily MVS intake included poor motivation and knowledge, high costs and unpleasant smell and taste of supplements, and gastrointestinal side effects such as nausea after intake. Furthermore, we found that patients were often dissatisfied with the instructions and attention paid to MVS use as well as the extent to which their personal preferences were taken into account during medical consultations.

The final part of this thesis (**Part C**) was dedicated to pregnancy after bariatric surgery, as this period may pose an additional risk on nutritional status. In **Chapter 8**, we evaluated pregnancy and neonatal outcomes by surgery-to-conception interval and by gestational weight gain in pregnant women with a history of bariatric surgery. We found that 24% of the pregnancies occurred within 12 months after bariatric surgery. Gestational age at delivery, gestational weight gain and neonatal birth weight were lower in this group than in pregnancies occurring more than 12 months after surgery. Overall, gestational weight gain was adequate in only 29% of the pregnancies. Inadequate weight gain during pregnancy was also associated with lower gestational age at delivery and lower neonatal

birth weight in comparison with adequate gestational weight gain. In addition, (very) preterm births were more frequently observed in the inadequate weight gain group (16% vs 6%).

In **Chapter 9**, we compared differences in nutritional status between users of specialized MVS and standard MVS (prenatal or regular MVS) among women with a history of Roux-en-Y gastric bypass or sleeve gastrectomy. During pregnancy following Roux-en-Y gastric bypass, we found that users of specialized MVS (± 73% of participants) had higher serum levels of hemoglobin, ferritin and folic acid, and lower serum levels of vitamin B6 during pregnancy compared to standard MVS users (± 27% of participants). Iron deficiencies as well as elevated serum vitamin B6 levels were also less prevalent in the specialized MVS group. During pregnancy following sleeve gastrectomy, specialized MVS users (± 49% of participants) had higher serum levels of vitamin D but lower serum levels of vitamin B1 than standard MVS users (± 51% of participants). The prevalence of deficiencies and elevated serum levels was similar between the groups during pregnancy after sleeve gastrectomy.

In conclusion, the studies described in this thesis contribute to new insights into factors underlying nutritional status after bariatric surgery and paves the way for further research. Insight into changes in dietary intake and diet quality may help dietitians and other healthcare practitioners to understand potential pitfalls in order to improve dietary counselling after bariatric surgery. The high risk of developing poor nutritional status together with the decreased adherence to daily supplement intake over time reinforces the need for long-term nutritional monitoring and counselling while taking patients' barriers related to supplement use into account. Although they are no one-size-fits-all solution, we carefully conclude that the use of specialized 'weight loss surgery' multivitamin supplementation is preferred over the use of standard over-the-counter supplementation after bariatric surgery.

During pregnancy after bariatric surgery, specific attention is needed on the optimal timing of conception and achieving adequate gestational weight gain as well as on adequate supplementation to improve nutritional status of this population at risk.

Overall, we conclude that regular nutritional assessment and counseling focused on adequate dietary intake and nutritional supplementation are essential in achieving optimal nutritional status, ultimately contributing to improved long-term health after bariatric surgery.

Bariatrische chirurgie, ook wel metabole chirurgie genoemd, is momenteel de enige bewezen effectieve behandeling voor langdurig gewichtsverlies bij personen met ernstige obesitas. De meest voorkomende operaties zijn de Roux-en-Y gastric bypass en de gastric sleeve. Bij de gastric bypass wordt de maag verkleind tot het formaat van ongeveer een kiwi en wordt een deel van de dunne darm omgeleid zodat de ingenomen voeding niet volledig wordt opgenomen. Bij de gastric sleeve wordt een groot deel van de maag verwijderd zodat er een kleine, buisvormige maag overblijft. Elke bariatrische ingreep verandert dus in meer of mindere mate iets aan de anatomie en fysiologie van het maagdarmkanaal. Ondanks de voordelen zoals gewichtsverlies en het verminderen of verdwijnen van obesitas-gerelateerde aandoeningen waaronder diabetes en een verhoogde bloeddruk, ontstaat hierdoor ook een hoger risico op voedingstekorten. Dit kan uiteindelijk leiden tot onder andere bloedarmoede, osteoporose (botontkalking) of ondervoeding. Het doel van dit proefschrift was inzicht krijgen in de factoren die van invloed zijn op de voedingsstatus na bariatrische chirurgie, waaronder voedingsinname en het gebruik van supplementen. Voeding en supplementen kunnen worden gezien als twee kanten van dezelfde medaille. Hoewel de inname van supplementen meer bijdraagt aan de totale voedingsstofinname dan de inname via de voeding, zijn beiden even belangrijk voor het bereiken van een optimale voedingsstatus na bariatrische chirurgie. Daarnaast was een deel van dit proefschrift gewijd aan zwangerschap na bariatrische chirurgie, gezien deze periode een extra risico kan vormen voor de voedingstoestand.

In **deel A** van dit proefschrift hebben we ons gericht op de (kwaliteit van) voedingsinname na bariatrische chirurgie. In **hoofdstuk 2** werden veranderingen in de macro- en micronutriënten samenstelling van het eetpatroon en de kwaliteit van de voedingsinname gedurende de eerste zes maanden na bariatrische chirurgie geëvalueerd. De kwaliteit van de voeding werd beoordeeld aan de hand van de Nederlandse voedingsrichtlijnen, waarbij we gebruik hebben gemaakt van de afkapwaarden van de 'Dutch Healthy Diet index'. Gunstige veranderingen in de voedingsinname waren onder meer een afname in de consumptie van ongezonde voedselkeuzes (bijv. snoep en snacks), rood en bewerkt vlees en zout, en een toename in de consumptie van zuivel. Daarnaast zagen we ook een toename in de relatieve eiwitinname na bariatrische chirurgie. Daarentegen werden er zes maanden na de operatie ook ongunstige veranderingen in de voedingsinname waargenomen, waaronder een verminderde consumptie van groenten en volkorenproducten, een verminderde inname van vezels en micronutriënten en een toename van de suikerinname.

Het verkrijgen van nauwkeurige gegevens over de voedingsinname is essentieel voor het kunnen bieden van optimale voedingszorg na bariatrische chirurgie. Er ontbreken echter gevalideerde methoden voor het meten en beoordelen van de (kwaliteit van) voedingsinname in deze specifieke populatie. In **hoofdstuk 3** evalueerden we de relatieve validiteit en reproduceerbaarheid van de Eetscore FFQ als korte screener voor de kwaliteit van voedingsinname na bariatrische chirurgie. We vonden een acceptabele correlatie tussen de 'Dutch Healthy Diet' index scores afkomstig van de Eetscore FFQ en de scores afkomstig van 3-daagse eetdagboeken (referentie methode). Echter resulteerde de Eetscore FFQ over het algemeen in hogere index scores dan de voedingsdagboeken en de absolute overeenkomst tussen de twee methoden was matig. Gezien de grote behoefte aan valide methoden voor het beoordelen van de (kwaliteit van) voedingsinname die minder tijdrovend en belastend zijn voor zowel patiënten, behandelaars als onderzoekers, kan de Eetscore FFQ worden gebruikt om individuen te rangschikken op basis van voedingskwaliteit en om relatieve veranderingen in de kwaliteit van voedingsinname in de loop van de tijd te volgen.

In **deel B** van dit proefschrift hebben we ons gericht op het gebruik van supplementen na bariatrische chirurgie. In **hoofdstukken 4, 5 en 6** werd een gespecialiseerd multivitamine supplement (MVS) dat specifiek was ontworpen voor patiënten met een gastric sleeve geëvalueerd en geoptimaliseerd (WLS Optimum). In **hoofdstuk 4** werd de eerste versie van WLS Optimum vergeleken met een standaard MVS in een gerandomiseerd gecontroleerd onderzoek. Uit de 'intention-to-treat' analyse bleek dat de interventiegroep hogere vitamine B1 serumwaarden had en dat er meer tekorten voor foliumzuur waren in deze groep in vergelijking met de controlegroep. Op basis van deze resultaten werd WLS Optimum geoptimaliseerd en geëvalueerd in een éénarmige, open-label studie (**hoofdstuk 5**). Vergeleken met de vorige versie resulteerde het gebruik van WLS Optimum 2.0 in hogere serumwaarden voor vitamine B12, vitamine B6 en zink, maar in lagere foliumzuur serumwaarden gedurende het eerste jaar na de operatie. Tekorten aan vitamine B12 en fosfaat kwamen minder vaak voor in de WLS Optimum 2.0 groep. In **hoofdstuk 6** werden de follow-up resultaten na drie jaar van beide studies gepresenteerd. Hieruit bleek dat gebruikers van gespecialiseerde MVS (WLS Optimum 1.0 + 2.0) hogere serumwaarden van hemoglobine, foliumzuur, vitamine B12, vitamine D en calcium hadden in vergelijking met standaard MVS-gebruikers en/of niet-gebruikers van MVS. Tekorten aan foliumzuur en vitamine D kwamen ook het minst voor in de WLS Optimum (1.0) groep. Niet-gebruikers vertoonden over het algemeen de meeste voedingstekorten en de laagste serumwaarden voor de meeste micronutriënten.

Therapietrouw aan de dagelijkse inname van MVS is een grote uitdaging in zowel wetenschappelijk onderzoek als de klinische praktijk. In **hoofdstuk 7** probeerden we inzicht te krijgen in de onderliggende factoren en potentiële belemmeringen voor het dagelijks gebruik van MVS. Van de 4614 patiënten die deelnamen aan de studie, gaf 93% aan MVS-gebruiker te zijn versus 7% niet-gebruikers. In vergelijking met MVS gebruikers waren niet-gebruikers van MVS over het algemeen jonger, hadden zij vaker een gastric sleeve ondergaan en was de operatie gemiddeld langer geleden op het moment van de studie. Barrières voor de dagelijkse inname van MVS waren onder meer een slechte motivatie en kennis over het gebruik van MVS, hoge kosten en onaangename geur en smaak van de supplementen, en gastro-intestinale bijwerkingen zoals misselijkheid na inname. Verder vonden we dat patiënten vaak ontevreden waren over de instructies en de hoeveelheid aandacht voor de inname van MVS en de mate waarin rekening werd gehouden met hun persoonlijke voorkeuren tijdens medische consulten.

Het laatste deel van dit proefschrift (**deel C**) was toegewijd aan zwangerschap na bariatrische chirurgie, gezien deze periode een extra risico kan vormen voor de voedingstoestand. In **hoofdstuk 8** werden zwangerschaps- en geboorte uitkomsten op basis van het interval tussen de operatie en conceptie en gewichtstoename tijdens de zwangerschap geëvalueerd in een groep van zwangere vrouwen met een bariatrische ingreep in de voorgeschiedenis. Hieruit bleek dat 24% van de zwangerschappen binnen 12 maanden na de bariatrische ingreep plaatsvond. De zwangerschapsduur, gewichtstoename tijdens de zwangerschap en het geboortegewicht waren lager in deze groep dan bij zwangerschappen die meer dan 12 maanden na de operatie plaatsvonden. Over het algemeen was de gewichtstoename tijdens de zwangerschap voldoende bij slechts 29% van de zwangerschappen. Onvoldoende gewichtstoename werd ook in verband gebracht met een kortere zwangerschapsduur en een lager geboortegewicht in vergelijking met voldoende gewichtstoename tijdens de zwangerschap. Bovendien kwamen (zeer) vroeggeboortes vaker voor in de groep met onvoldoende gewichtstoename (16% versus 6%).

In **hoofdstuk 9** werd de voedingsstatus vergeleken tussen gebruikers van gespecialiseerde MVS en standaard MVS (zwangerschaps- of reguliere MVS) bij zwangere vrouwen die een gastric bypass of gastric sleeve hadden ondergaan. Hieruit bleek dat gebruikers van gespecialiseerde MVS (±73% van de deelnemers) hogere serumwaarden van hemoglobine, ferritine en foliumzuur en lagere serumwaarden van vitamine B6 hadden in vergelijking met gebruikers van standaard MVS (±27% van de deelnemers) tijdens zwangerschap na een gastric bypass. IJzertekorten en verhoogde

vitamine B6-serumspiegels kwamen ook minder vaak voor in de groep van gespecialiseerde MVS-gebruikers. Tijdens zwangerschap na een gastric sleeve hadden gebruikers van gespecialiseerde supplementen (±49% van de deelnemers) hogere serumwaarden van vitamine D, maar lagere serumwaarden van vitamine B1 dan gebruikers van standaard MVS (±51% van de deelnemers). Het aantal voedingstekorten en verhoogde serumwaarden was vergelijkbaar tussen deze twee MVS groepen.

Concluderend dragen de studies beschreven in dit proefschrift bij aan nieuwe inzichten in de factoren die van invloed zijn op de voedingsstatus na bariatrische chirurgie. Inzicht in veranderingen in de (kwaliteit van) voedingsinname kan diëtisten en andere zorgverleners helpen mogelijke valkuilen te begrijpen om zo de voedingszorg voor patiënten na bariatrische chirurgie te verbeteren. Het hoge risico op het ontwikkelen van voedingstekorten in combinatie met een mogelijk verminderde therapietrouw aan de dagelijkse inname van voedingssupplementen versterkt het belang van langdurige monitoring en begeleiding, waarbij rekening moet worden gehouden met mogelijke barrières van patiënten ten aanzien van het dagelijkse gebruik van supplementen. Hoewel ze geen pasklare oplossing zijn, kunnen we voorzichtig concluderen dat het gebruik van gespecialiseerde multivitamine supplementen de voorkeur heeft boven het gebruik van standaard multivitamine suppletie na bariatrische chirurgie.
Tijdens zwangerschap na bariatrische chirurgie is specifieke aandacht nodig voor de optimale timing van conceptie en het bereiken van voldoende gewichtstoename tijdens de zwangerschap, evenals voor adequate suppletie om de voedingsstatus van deze hoog-risico groep te verbeteren.

Over het algemeen concluderen we dat regelmatige monitoring en begeleiding op het gebied van voeding, gericht op adequate voedingsinname en suppletie, essentieel zijn voor het bereiken van een optimale voedingsstatus, wat uiteindelijk bijdraagt aan een verbeterde gezondheid op de lange termijn na bariatrische chirurgie.

Dankwoord

Acknowledgements

It's a wrap! Vijf jaar aan onderzoek zijn eindelijk gebundeld in dit mooie boekje. Ik heb enorm genoten van deze leuke en leerzame, maar soms ook uitdagende periode. Ik wil graag iedereen bedanken die, op welke manier dan ook, heeft bijgedragen aan de realisatie van mijn proefschrift. Een aantal mensen wil ik hier graag in het bijzonder voor bedanken.

Allereerst heel veel dank aan alle **patiënten** die hebben deelgenomen aan mijn studies. Zonder jullie was dit proefschrift er niet geweest!

Daarnaast ook veel dank aan mijn supervisors. Zonder hen was ik nu waarschijnlijk nog steeds bezig met "de laatste aanpassingen"…
Prof. dr. Hazebroek, beste **Eric**, bedankt voor jouw vertrouwen in mij als eerste officiële promovendus binnen jouw chairgroup Nutrition and Obesity Treatment aan de WUR. Ik waardeer het enorm dat jij mij altijd de ruimte en vrijheid gaf om mijn eigen pad te kiezen binnen de onderzoekslijn. Daarnaast waren jouw nuchtere en frisse blik erg fijn om dingen weer even te kunnen relativeren. We gaan gelukkig door met onze samenwerking en daar kijk ik erg naar uit!
Dr. Berendsen, beste **Agnes**, na jouw korte periode in het Rijnstate sloot jij aan als co-promotor. Naast veel kennis en ervaring met voedingsonderzoek, bracht jij daarmee ook structuur in mijn promotietraject. Dankjewel voor jouw kritische blik en de manier waarop je mij stimuleerde om het beste uit mijn onderzoeken te halen. Ik heb erg veel zin om samen verder te gaan werken aan onze enthousiaste plannen voor het opzetten van een toekomstig cohort.

I would like to thank the members of the promotion committee, **prof. dr. Marian de van der Schueren, prof. dr. Catherijne Knibbe, prof. dr. Christophe Matthys and dr. Violeta Moizé**, for taking the time and effort in reading and evaluating my thesis and being present at my defence. Special thanks to **prof. dr. Christophe Matthys** and **dr. Violeta Moizé** for their contribution to our symposium.

Ik wil ook graag al mijn collega's bedanken. Allereerst natuurlijk veel dank aan alle (huidige en voormalige) Barries: **Laura, Mellody, Abel, Sophie, Debby, Adrianne, Yonta, Emma, Sietske, Claudia, Nadia, Tessa en Mitchell.** Een promotietraject kan soms best solistisch zijn, maar gelukkig hadden wij ons Barrie eiland waar we met elkaar brainstormden, successen vierden, frustraties deelden, maar ook veel plezier maakten tijdens onze uitjes en op buitenlandse congressen (waar wij moeiteloos de DJ vermaken

in een lege club!). **Adrianne**, dank voor jouw hulp bij het includeren van deelnemers! Ook een bijzonder bedankje aan mijn paranimfen Laura en Debby. **Laura**, ik vind het enorm knap hoe jij als ware duizendpoot de coördinatie van het onderzoeksteam combineert met je werkzaamheden bij de Radiologie en de afronding van jouw eigen promotie onderzoek. Ik heb de afgelopen jaren veel van je kunnen leren op vele facetten van onderzoek doen en ik ben blij dat we de komende jaren nog meer gaan samenwerken. **Debby**, PhD buddy vanaf het eerste uur! Naast veel lachen en kletsen (en soms misschien een beetje klagen), draaiden wij onze hand ook niet om voor bijvoorbeeld het choreograferen van een flashmob (waar we dankzij de GIF'jes van Sietske voor altijd aan herinnerd zullen worden). Wat was het fijn om de laatste loodjes met jou te kunnen delen! Ik vind het super leuk dat we nu ook elkaars paranimfen zijn en ik kijk erg uit naar de afronding van jouw promotie binnenkort!
Naast de Barries was het dankzij alle andere onderzoekers/onderzoekmedewerkers van de vaatchirurgie en orthopedie ook altijd erg gezellig in de onderzoekskamer. Tijd voor weer een BARIAVAAT uitje!

Daarnaast wil ik graag het hele team van Vitalys bedanken. Dit is in de afgelopen jaren zo enorm gegroeid dat ik onmogelijk iedereen persoonlijk kan bedanken, maar veel dank aan alle chirurgen (**Theo, Bart, Willem, Wouter en Guusje**) voor jullie interesse, input en medewerking bij onze onderzoeken, alle verpleegkundig specialisten en verpleegkundigen (o.a. **Nadine, Annemiek, Linda, Lysbert, Gül, Mirja, Manouk en Laura**) voor jullie betrokkenheid en de gezelligheid op congressen, alle dames van het secretariaat, planning en kwaliteit die ervoor zorgen dat alles op rolletjes loopt, **Brigit** voor de mooie infographics en andere communicatie over onze studies en natuurlijk het management team (**Kristy, Wendy en Claudia**) voor alle ondersteuning. **Kristy,** jij bent de spil binnen de groeiende groep van Vitalys. Bedankt voor jouw support gedurende mijn promotie onderzoek en voor jouw vertrouwen in mij als post-doc onderzoeker terwijl die functie er eigenlijk nog niet was. Ik ben blij dat ik nog even mag blijven hangen :) **Mirja en Arianne,** dank voor jullie hulp bij het includeren van deelnemers en verzamelen van data voor de NEWBIE studie.

Tijdens de eerste helft van mijn promotietraject bracht ik mijn donderdagen vaak door op de WUR. Ik vond het erg leuk om op die manier betrokken te blijven bij al het voedingsonderzoek en ik kijk met veel plezier terug op onder andere de PhD tour naar Canada en de chaos tijdens de befaamde "Dinner game" (met als hoogtepunt de winst voor The Food Hunters!).

Ik wil in het bijzonder al mijn collega's van de chairgroup Nutrition and Disease bedanken voor de interessante discussies en presentaties tijdens de MENU-D meetings, de waardevolle feedback op mijn draft papers bij de NAD-paperclub en natuurlijk de gezellige uitjes. **Ellen Kampman**, bedankt voor jouw vertrouwen bij de start van mijn promotietraject en jouw interesse in ons onderzoek op dit nieuwe vakgebied binnen jouw chairgroup. **Nicole de Roos**, dankjewel voor jouw begeleiding in het begin van mijn promotie onderzoek.
Daarnaast ook veel dank aan **Jeanne de Vries en Michiel Balvers**, jullie waren essentieel bij het uitvoeren, analyseren en beschrijven van de Eetscore studie. Dank voor het vele mee denken!

Ik wil ook graag alle coauteurs bedanken voor hun belangrijke bijdrage aan de publicaties in dit proefschrift. Daarbij in het bijzonder dank aan **Edo** voor het vertrouwen om de VITAAL studies te mogen analyseren en opschrijven. Als expert op het gebied van onderzoek naar micronutriënten was jij een goede mentor waar ik veel van heb kunnen leren. Dankjewel voor de prettig samenwerking! **Marieke**, bedankt voor de fijne samenwerking binnen de compliance studie. We hebben hierdoor veel relevante inzichten opgedaan waar we hopelijk nog veel huidige en toekomstige patiënten mee kunnen helpen. **Wendy Schijns**, dankjewel dat ik het stokje van jou mocht overnemen en verder kon bouwen op jouw studies over deficiënties na metabole chirurgie. **Ineke Krabbendam, Judith van Laar en Sofie van Weelden**, bedankt voor jullie input, ideeën en klinische blik op zwangerschapsonderzoek en voor jullie hulp bij het uitvoeren van de NEWBIE studie in Ziekenhuis Gelderse Vallei en Máxima MC.

Daarnaast wil ik graag nog een aantal andere samenwerkingspartners bedanken. Allereerst veel dank aan **FitForMe**, in het bijzonder aan **Sjoerd, Simon, Ingrid en Peter.** Bedankt voor jullie enthousiasme, support en vertrouwen in mijn onderzoeken met jullie producten. Ik bewonder de manier waarop FitForMe wetenschappelijk onderzoek als belangrijke basis blijft zien. **Ingrid**, dankjewel voor de leuke maandelijkse meetings waarbij we ons vooral verbaasden over hoe snel er weer een maand voorbij was gegaan. Ook veel dank voor de gezelligheid (en dansjes) op congressen!
Daarnaast dank aan **Alliantie Voeding in de Zorg** voor het op de kaart zetten van voedingsonderzoek in de zorg en het bieden van een platform voor het uitdragen van onze studies. Hierbij in het bijzonder dank aan **Menrike Menkveld.** Ook veel dank voor jouw hulp bij de organisatie van het symposium!

Ook bedank ik graag de vele studenten die ik de afgelopen jaren heb mogen begeleiden tijdens hun stage of thesis en die een bijdrage hebben geleverd aan mijn studies: **Demi, Iris, Esther, Laura, Daphne, Veroniek, Ylva, Madeleine, Simone, Florien, Michelle, Sofie, Tessa, Maaike, Robbert en Inge**. **Carla en Steven**, bedankt voor jullie hulp bij de PREBA studie!

Gelukkig was er de afgelopen jaren naast werk ook genoeg tijd voor andere dingen. Dank aan al mijn lieve vriendinnen voor de vele afleiding, steun en gezelligheid.
Emmy, Sanne en Liselotte, onze vriendschap gaat terug tot en met de middelbare school (en voor Lies zelfs tot en met de basisschool!). Inmiddels dus al meer dan 18 jaar vriendinnen, waarin heel veel lief, leed, maar vooral ook veel lol is gedeeld. Bedankt voor de ontelbare gezellige avonden, dagen, weekenden en vakanties! Inmiddels zijn de feestbestemmingen zoals Albufeira en Marmaris ingewisseld voor wat meer culturele plekken, maar dat tripje naar Ibiza moeten we toch echt nog eens plannen!
Pien, Louella, Lisette en Amy, met een gezamenlijke vooropleiding Voeding & Dietetiek was ons lot vanaf dag 1 van de master Nutrition and Health al bezegeld. Als "Meisjes van de HAN" maakten wij Wageningen meer dan twee jaar lang (semi) onveilig. Met twee voeding-gerelateerde opleidingen is het ook niet zo moeilijk om te raden wat het centrale thema van onze avonden en weekendjes weg is... Soms aangevuld met een "inspirerende" docu, een pubquiz of een escape room, maar laten we het er maar op houden dat we die laatste twee met name voor de lol doen. Dankjulliewel voor alle gezelligheid en dat jullie me kunnen laten lachen als een zeehond/dolfijn!

Frans, Lia, Niki, Wiechert, Marit en Jeffrey (en alle kids), wat heb ik het getroffen met jullie als schoonfamilie! Bedankt voor jullie oprechte interesse en betrokkenheid. Naast de gezellige etentjes, weekendjes en wintersportvakanties kunnen we ook altijd op jullie hulp rekenen. Bedankt daarvoor!

En waar zou ik zijn zonder mijn familie... Ook al kom ik tegenwoordig minder vaak naar huis dan vroeger, ik rijd nog steeds met liefde naar Gemert om aan te kunnen schuiven op mijn vaste plek aan tafel, de kast leeg te eten (volgens jullie) en te knuffelen met lieve Tess. **Pap en mam**, bedankt voor alles wat jullie voor mij hebben gedaan en voor jullie onvoorwaardelijke steun en vertrouwen in alles wat ik doe. Ik ben nog (lang) geen professor zoals ik jullie wel eens hoor zeggen, maar de eerste stap is gezet! **Rick**, we lopen elkaar regelmatig mis, maar als ik hulp nodig heb dan kan ik altijd op je rekenen. Nu je bijna uit huis gaat, wordt het toch eens tijd om wat vaker langs te komen samen met Iris.

Eline, volgens mij ben jij de enige van mijn familie en vrienden die daadwerkelijk mijn wetenschappelijke publicaties heeft gelezen. Ik had ook niet anders verwacht, want ondanks het leeftijdsverschil van 8 jaar en onze verschillende karakters zijn we elkaars trouwste supporter!
Daarnaast ook een bijzonder woordje van dank aan mijn lieve oma's die altijd trots op me zijn en bij wie ik veel te weinig langs ga.

Lieve **Ties**, we hebben er vaak grapjes over gemaakt, maar de laatste plek in mijn proefschrift is natuurlijk voor jou. Dankjewel voor jouw humor, liefde, steun, vertrouwen, geduld en nog zo veel meer! Mijn (gebrek aan) planning skills werden regelmatig op de proef gesteld door jou, wat helaas tot meerdere verloren weddenschappen heeft geleid (volgens mij heb je nog steeds een aantal etentjes tegoed…), maar alle artikelen zijn nu dan toch écht klaar! Vandaag sluiten we daarmee niet alleen het hoofdstuk van mijn promotietraject, maar ook ons mooie hoofdstuk in Arnhem af. Ik heb enorm veel zin in ons nieuwe avontuur in de Meern. Eén ding weet ik zeker, met jou is alles leuk!

About the author

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Curriculum Vitae

Laura Heusschen was born on the 13th of September in Helmond, the Netherlands. After completing secondary school at Commanderij College in Gemert, she decided to follow her passion for nutrition and enrolled as a student Nutrition and Dietetics at the Hogeschool van Arnhem en Nijmegen in 2011. During her bachelor, she had a special interest in nutrition and disease. She followed a minor in clinical nutrition and completed her dietetics internship at Elkerliek Hospital in Helmond. Although she really enjoyed the patient contact, Laura was also highly interested in the scientific evidence behind dietary advices. After graduation in 2015, she therefore proceeded to the master Nutrition and Health at Wageningen University during which she specialized in nutritional physiology and health status. She wrote her thesis on the effects of repeated exposure to vegetables during weaning on vegetable consumption of infants aged 12 months. She also performed a research internship on pregnancy after bariatric surgery at Vitalys obesity clinic (part of Rijnstate hospital), for which she won the poster award at the VoedingNL congress in 2018.

After obtaining her MSc degree in 2018, Laura started as a PhD candidate at Vitalys under the supervision of prof. dr. Eric Hazebroek and dr. Agnes Berendsen. Her PhD project was performed in close collaboration with the division of Human Nutrition and Health at Wageningen University & Research. During this period, she performed several studies on factors underlying nutritional status after bariatric surgery. Her research has led to a variety of publications and presentations at national and international congresses, scientific meetings and webinars. Furthermore, she became a member of the Integrated Health committee of the International Federation for the Surgery of Obesity and Metabolic Disorders (European Chapter).

Laura is currently working as a post-doctoral researcher at Vitalys where she will continue her research on nutrition and obesity treatment. Her ambition is to help all bariatric patients achieve optimal nutritional status, ultimately contributing to improved long-term health after bariatric surgery.

List of publications

This thesis

Heusschen, L., Berendsen, A. A. M., Balvers, M. G., Deden, L. N., de Vries, J. H., & Hazebroek, E. J. (2023). Relative validity of a short screener to assess diet quality in patients with severe obesity before and after bariatric surgery. *Submitted to Public Health Nutr.*

Heusschen, L., Berendsen, A. A. M., van Bon, A. C., van Laar, J. O. E. H., Krabbendam, I., & Hazebroek, E.J. (2023). Nutritional Status and Supplement Use during Pregnancy Following Bariatric Surgery: a Multicenter Observational Cohort Study. *Submitted to BJOG.*

Heusschen, L., Berendsen, A. A. M., Deden, L. N., Hazebroek, E. J., & Aarts, E. O. (2022). Nutritional Deficiencies 3 Years After Sleeve Gastrectomy Can Be Limited by a Specialized Multivitamin Supplement. *Obes Surg, 32*(11), 3561-3570.

Heusschen, L., Berendsen, A. A. M., Balvers, M. G., Deden, L. N., de Vries, J. H., & Hazebroek, E. J. (2022). Relative validity of a short screener to assess diet quality in patients with severe obesity before and after bariatric surgery. *Public Health Nutr, 25*(10), 2731-2741.

Smelt, H. J. M., **Heusschen, L.**, Theel, W., van Rutte, P. W. J., Nijboer, T., Pouwels, S., Smulders, J. F., & Hazebroek, E. J. (2021). Factors Affecting Patient Adherence to Multivitamin Intake After Bariatric Surgery: a Multicentre Survey Study from the Patient's Perspective. *Obes Surg, 31*(10), 4316-4326.

Heusschen, L., Berendsen, A. A. M., Cooiman, M. I., Deden, L. N., Hazebroek, E. J., & Aarts, E. O. (2021). Optimizing Multivitamin Supplementation for Sleeve Gastrectomy Patients. *Obes Surg, 31*(6), 2520-2528.

Heusschen, L., Krabbendam, I., & Hazebroek, E. J. (2021). Reply to: Pregnancy After Bariatric Surgery: a Matter of Indications and Procedures? *Obes Surg, 31*(6), 2795-2796.

Heusschen, L., Krabbendam, I., van der Velde, J. M., Deden, L. N., Aarts, E. O., Merien, A. E. R., Emous, M., Bleumink, G. S., Lutgers, H. L., & Hazebroek, E. J. (2021). A Matter of Timing-Pregnancy After Bariatric Surgery. *Obes Surg, 31*(5), 2072-2079.

Heusschen, L., Schijns, W., Ploeger, N., Deden, L. N., Hazebroek, E. J., Berends, F. J., & Aarts, E. O. (2020). The True Story on Deficiencies After Sleeve Gastrectomy: Results of a Double-Blind RCT. *Obes Surg, 30*(4), 1280-1290.

Other publications

Dijkhorst, P. J., Al Nawas, M., **Heusschen, L.**, Hazebroek, E. J., Swank, D. J., Wiezer, R. M. J., & Aarts, E. O. (2021). Single Anastomosis Duodenoileal Bypass or Roux-en-Y Gastric Bypass After Failed Sleeve Gastrectomy: Medium-Term Outcomes. *Obes Surg, 31*(11), 4708-4716.

Publications as part of the GENEVA collaborative

Singhal, R., Omar, I., Madhok, B., et al. (2022). Safety of Bariatric Surgery in ≥ 65-Year-Old Patients During the COVID-19 Pandemic. *Obes Surg, 32*(7), 1-13.

Singhal, R., Omar, I., Madhok, B., et al. (2022). Effect of BMI on safety of bariatric surgery during the COVID-19 pandemic, procedure choice, and safety protocols - An analysis from the GENEVA Study. *Obes Res Clin Pract, 16*(3), 249-253.

Singhal, R., Cardoso, V. R., Wiggins, T., et al. (2021). 30-day morbidity and mortality of sleeve gastrectomy, Roux-en-Y gastric bypass and one anastomosis gastric bypass: a propensity score-matched analysis of the GENEVA data. *Int J Obes (Lond)*.

Singhal, R., Wiggins, T., Super, J., et al. (2021). 30-Day morbidity and mortality of bariatric metabolic surgery in adolescence during the COVID-19 pandemic - The GENEVA study. *Pediatr Obes, 16*(12), e12832.

Singhal, R., Ludwig, C., Rudge, G., et al. (2021). 30-Day Morbidity and Mortality of Bariatric Surgery During the COVID-19 Pandemic: a Multinational Cohort Study of 7704 Patients from 42 Countries. *Obes Surg, 31*(10), 4272-4288.

Overview of completed training activities

Discipline specific activities	Organizer (location)	Year
Courses		
Exposure Assessment in Nutrition Research	VLAG (Wageningen, NL)	2018
Conferences and scientific meetings		
IFSO-EC congress 2018	IFSO (Athens, GR)	2018
STZ-Event 2018	STZ (Utrecht, NL)	2018
NPN Symposium 2018	NPN (Maarssen, NL)	2018
VoedingNL 2019	AVZ, DCN, NAV, NVD, NVVL (Utrecht, NL)	2019
DSMBS 2019	DSMBS (Veenendaal, NL)	2019
IFSO World congress 2019	IFSO (Madrid, ES)	2019
Refeeravond Gynaecologie	Rijnstate (Arnhem, NL)	2019
Pioneering Nutrition Symposium	WUR (Wageningen, NL)	2019
Symposium 'Turning the scale'	WUR, Vitalys (Wageningen, NL)	2019
Food for Thought 2019	AVZ (Ede, NL)	2019
Webinar Preventing Deficiencies after SG	FitForMe (online)	2020
Webinar Obesitas en bariatrie: voeding, microbiota en (mond)gezondheid	Yakult (online)	2020
IFSO-EC congress 2020	IFSO (online)	2020
GGG-themawebinar 'De perfecte subsidieaanvraag (bestaat niet)'	ZonMw (online)	2021
European Congress on Obesity 2021	ECO (online)	2021
Webinar Bone Health after Bariatric surgery	IFSO-EC (online)	2021
Webinar Improving patients' adherence to multivitamin intake after bariatric surgery	FitForMe (online)	2021
IFSO-EC congress 2021	IFSO (Prague, CZ)	2021
DSMBS 2022	DSMBS (Veenendaal, NL)	2022
ECO-ICO/IFSO-EC congress 2022	IFSO/ECO (Maastricht, NL)	2022
Food for Thought 2022	AVZ (Ede, NL)	2022
Frankfurter meeting 2022	DGAV, IFSO (Frankfurt, DE)	2022
Symposium Obesitas	Vitalys (Arnhem, NL)	2022
DSMBS 2023	DSMBS (Veenendaal, NL)	2023
Webinar Pregnancy After Bariatric Surgery: Nutritional Recommendations	FitForMe (online)	2023
Webinar Preventing Deficiencies After Bariatric Surgery	FitForMe (online)	2023
IFSO-EC congress 2023	IFSO (Zurich, CH)	2023

Presentations (oral)		
Pregnancy after bariatric surgery	IFSO (Athens, GR)	2018
Zwangerschap na bariatrische chirurgie	DSMBS (Veenendaal, NL)	2019
Eetscore- Evaluation of a screener to assess diet quality	IFSO (Madrid, ES)	2019
Timing of pregnancy after bariatric surgery	IFSO (Madrid, ES)	2019
Zwangerschap na bariatrische chirurgie	Rijnstate (Arnhem, NL)	2019
Winning by losing? Nutrition and Obesity Treatment	Alliantie Voeding in de Zorg (Ede, NL)	2019
The development of WLS Optimum: Results of the VITAAL studies	FitForMe (online)	2020
Vitamin D-irect: The efficacy of intramuscular cholecalciferol injections	IFSO (online)	2020
Zwangerschap na bariatrische chirurgie	NDBC (online)	2021
Vitamin D and Calcium status after BS	IFSO-EC (online)	2021
Factors affecting patient adherence to multivitamin intake after bariatric surgery	FitForMe (online)	2021
Factors affecting patient adherence to multivitamin intake after bariatric surgery	DGAV, IFSO (online)	2021
Changes in diet quality after BS	IFSO (Prague, CZ)	2021
Efficacy of Specialized MVS for Sleeve Gastrectomy - 3 years follow-up	IFSO (Prague, CZ)	2021
Factors affecting patient adherence to multivitamin intake after bariatric surgery	IFSO (Prague, CZ)	2021
Factors affecting patient adherence to multivitamin intake after bariatric surgery	TUGS (online)	2022
Validiteit en praktische toepasbaarheid van de Eetscore	DSMBS (Veenendaal, NL)	2022
Nutritional status and supplement intake during pregnancy after bariatric surgery	IFSO/ECO (Maastricht, NL)	2022
Bariatric Bites – Lunch symposium	IFSO/ECO (Maastricht, NL)	2022
Pregnancy after bariatric surgery: How effective are FFM multivitamins?	DGAV, IFSO (Frankfurt, DE)	2022
Zwangerschap na bariatrische chirurgie	Vitalys (Arnhem, NL)	2022
Pregnancy after bariatric surgery: Evaluating the effectiveness of specialized MVS	FitForMe (online)	2023
Optimizing multivitamin supplementation for sleeve gastrectomy patients	FitForMe (online)	2023
Adherence to nutritional supplementation pre and post BS: what can we do better?	IFSO (Zürich, CH)	2023

General courses	Organizer (location)	Year
Good Clinical Practice	GCP central (online)	2018
VLAG PhD week	VLAG (Baarn, NL)	2018
Supervising BSc & MSc thesis students	WGS (Wageningen, NL)	2018
Introduction to R	VLAG (Wageningen, NL)	2019
Mixed Linear Models	PE&RC (Wageningen, NL)	2019
Cursus Praktijkbegeleiders van de afstudeerfase	HAN (Nijmegen, NL)	2019
Brain friendly working and writing	WGS (Wageningen, NL)	2019
Reviewing a Scientific Manuscript	WGS (Wageningen, NL)	2019
Scientific Writing	Wageningen into languages (Wageningen, NL)	2020
Project and Time Management	WGS (Wageningen, NL)	2020
Research Data Management	WGS (online)	2021
Writing Propositions for your PhD	WGS (Wageningen, NL)	2021
Last Stretch of the PhD Programme	WGS (Wageningen, NL)	2021
Presentatie training	MVEC (Arnhem, NL)	2022
Career Assessment	WGS (online)	2023

Assisting in teaching and supervision activities	Year
Supervising BSc/MSc students	2018-2023
HNE-27806 General Medicine	2019-2021

Other activities	Organizer	Year
Preparation of research proposal	VLAG	2018
Research meetings Vitalys	Vitalys	2018-2023
Promovendi meetings Rijnstate	Rijnstate	2018-2023
MENU-D meetings NAD	WUR	2018-2022
NAD paper clubs	WUR	2018-2022
PhD study tour to East Canada	HNH, WUR	2019
Reviewing scientific articles	-	2019-2023
Member of the IFSO-EC Integrated Health Committee	IFSO-EC	2021-2023

Colophon

Financial support from Wageningen University, Vitalys, The Dutch Society for Metabolic and Bariatric Surgery, Rijnstate Vriendenfonds and FitForMe for printing this thesis is gratefully acknowledged.

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Printing: ProefschriftMaken | proefschriftmaken.nl