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Micronutrient status in bariatric surgery patients receiving postoperative supplementation per guidelines: Insights from a systematic review and meta-analysis of longitudinal studies

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Summary

The micronutrient status and optimal monitoring schedule after bariatric surgery have not been sufficiently assessed. This systematic review and meta-analysis investigated the longitudinal changes in micronutrient status after bariatric surgery. PubMed, EMBASE, and Cochrane Library were searched for articles that measured preoperative and postoperative serum micronutrient levels in patients undergoing Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG). Among guideline-adherent studies, the longitudinal changes in micronutrient status were investigated using weighted mean difference (WMD) using a random-effects model. Among the 82 included studies, the guideline adherence rates for micronutrient supplementation after bariatric surgery did not exceed 20%. In patients supplemented per guidelines, vitamin A significantly decreased after RYGB by −7.54 (95% confidence interval [CI], −10.16 to −4.92) μg/dl at 12–23 months, vitamin E decreased after RYGB by −2.35 (95% CI, −3.65 to −1.05) μg/dl at ≥24 months, and ferritin by −54.93 (95% CI, −77.19 to −32.67] μg/L at ≥24 months after SG, compared with baseline, with moderate level of evidence. Significant decreases in micronutrient levels at certain follow-up intervals in studies with supplementation per guidelines need to be considered to establish a post-bariatric micronutrient monitoring schedule for timely detection and management of micronutrient deficiencies.

KEYWORDS
bariatric surgery, micronutrients, nutritional supplementation, vitamin

1 | INTRODUCTION

Bariatric surgery is an established treatment that results in sustained weight loss and improvements in obesity-related comorbidities.[1,2] Postoperative nutritional health, especially preventing micronutrient deficiencies, is also a significant concern in bariatric surgery because patients experience reduced dietary intake and malabsorption in the postoperative period.[3,4] Micronutrients, including vitamins and minerals, are essential dietary factors and micronutrient deficiencies after bariatric surgery can have severe consequences, including neurological disorders and anemia.[5]

Prevention and monitoring of micronutrient deficiencies after bariatric surgery are imperative, as postoperative micronutrient deficiencies are prevalent,[6] and worsen over time[7,8]; however, it can be prevented by adequate supplementation.[9] Although clinical

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guidelines provide comprehensive strategies for preventing postoperative micronutrient deficiencies,[10–13] such recommendations are difficult to adhere to in clinical settings and are based on insufficient evidence. Guidelines and bariatric reviews recommend taking 1–2 multivitamin tablets twice daily and additional supplements of certain micronutrients, including calcium, iron, vitamin B_{12}, and fat-soluble vitamins.[9–13] As various commercial products exhibit inconsistent micronutrient composition, the recommended number of tablets usually leads to nonadherence to supplementation guidelines after bariatric surgery.[14]

Additionally, evidence supporting the timeframes of postoperative micronutrient monitoring is scarce. Although monitoring every 3–6 months postoperatively for the first year and every 6–12 months thereafter is recommended,[10,11,13] these recommendations are largely based on clinical experience, and few studies have investigated these monitoring intervals with respect to the characteristic changes in micronutrients occurring after bariatric surgery. Investigating the micronutrient trajectory in patients adhering to nutritional guidelines is imperative to establish an evidence-based reference monitoring schedule to enable healthcare professionals to personalize the schedule of patients with various nutritional statuses (e.g., shortening the time intervals of patients with increased deficiency risk).

Therefore, this systematic review and meta-analysis aimed to estimate the adherence of longitudinal studies to micronutrient supplementation recommendations and to investigate the longitudinal changes and identify significant decreases in micronutrient levels occurring after bariatric surgery despite supplementation per guidelines, according to the surgical procedure and postoperative time, which can be referred to when establishing a micronutrient monitoring schedule.

2 | METHODS

This study was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement,[15] and its protocol was registered in the International Prospective Register for Systematic Reviews (PROSPERO registration number: CRD42020199190). This study was approved by the Institutional Review Board of Korea University Anam Hospital (registration number: 2020AN0483).

2.1 | Literature search

We conducted a literature search for relevant studies published before May 9, 2020, in PubMed, EMBASE, and Cochrane Library with support from a trained librarian. The main keywords used for the search were "bariatric surgery," "metabolic surgery," "Roux-en-Y gastric bypass," "sleeve gastrectomy," "micronutrients," "minerals," "vitamins," and "nutritional deficiency" (Table S1).

2.2 | Eligibility criteria and study selection

The inclusion criteria were as follows: (1) studies including participants who underwent Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG), (2) measurement of at least one serum micronutrient (among vitamins B_1, B_{12}, A, E, D, and K, folate, ferritin, calcium, zinc, and copper) ≥ 2 times longitudinally including both preoperatively and postoperatively, and (3) disclosure of a postoperative micronutrient supplemental strategy (name of supplement product or micronutrient included in the supplement). The exclusion criteria were as follows: (1) abstracts, case reports, reviews, and editorials, (2) studies of pediatric or pregnant populations, (3) articles written in languages other than English, (4) non-extractable outcomes or lack of precision measures (e.g., standard deviations), and (5) lack of a classified analysis of outcomes by surgical methods (RYGB or SG).

Two authors (J. H. and Y. K.) independently assessed the eligibility of all studies identified in the electronic search based on title and abstract reviews. The full texts were then reviewed. Disagreements were resolved through discussions among the study panel.

2.3 | Data extraction and risk-of-bias assessment

Two authors (J. H. and Y. K.) independently extracted data including the first author's name, publication year, study location, design, and groups, surgical methods, demographic data of the study population, serum micronutrient concentrations measured in each follow-up, follow-up duration after bariatric surgery, and postoperative nutritional strategy, including dose of each micronutrient. For studies without specified doses of micronutrient supplementation, a detailed strategy was obtained from the authors. Serum micronutrient concentration units were converted into predominantly reported measurement units for each micronutrient, so that they had unified measurement units. The quality assessment tool for before-after (pre-post) studies with no control group from the National Heart, Lung, and Blood Institute was adapted to evaluate the quality of the included studies.[16] We excluded two criteria with little relevance to the study's quality considering the design of this meta-analysis (investigator blinding and consideration of group-level intervention). We added three criteria of particular importance in this study (reporting of patients' adherence to the supplementation protocol, test methodology, and consideration of inflammation).

2.4 | Data and statistical analyses

We investigated the proportion of studies that adhered to micronutrient supplementation per guidelines. Among the nutritional guidelines relevant to bariatric surgery,[10–13] the "Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures"[10] and "British Obesity and Metabolic Surgery Society Guidelines on perioperative and postoperative biochemical monitoring and micronutrient replacement for patients undergoing bariatric surgery,"[13] which were recently updated, were used to assess sufficiency of micronutrient supplementation. When the two guidelines were inconsistent, the former guideline was used. The recommended doses of postoperative micronutrient supplements are summarized in Table S2.

The differences in preoperative and postoperative micronutrient serum levels were presented as estimates transformed into weighted mean differences (WMDs) using the inverse variance-weighted average method, according to the following postoperative time intervals: <6, 6–11, 12–23, and ≥24 months. For studies with ≥2 measurements in the same postoperative time interval, the measurement closest to the median postoperative time interval was selected. WMDs were coded so that positive values represented increased postoperative micronutrient levels compared with preoperative levels. We estimated the pooled WMDs and 95% confidence intervals (CIs) using a random-effects (DerSimonian and Laird) model. Two-tailed *p*-values of <0.05 were considered statistically significant. Heterogeneity was assessed using the Mantel–Haenszel model and I^2 values. Absolute values of preoperative and postoperative micronutrient concentrations were pooled using a random-effects model to determine the micronutrient status at each time interval. We assessed publication bias based on funnel plot asymmetry using the Begg's and Egger's tests at $p < 0.1$. Stata 13 (StataCorp., College Station, TX, USA) was used for the statistical analyses.

2.5 | Quality of evidence

We used the criteria developed by the Grading of Recommendations Assessment, Development, and Evaluation Working Group[17] to assess the quality of evidence for each finding. The design, risk of bias, inconsistency, indirectness, imprecision, and publication bias of the studies were considered, and the quality was classified as high, moderate, low, or very low.

3 | RESULTS

3.1 | Studies included in the meta-analysis

The systematic literature search retrieved 5453 studies. Altogether, 843 duplicates were removed, and the remaining 4610 studies were subjected to title and abstract review. Full-text review of 355 studies resulted in the exclusion of 273 studies (Figure 1). Among the 82 included studies, 15 were of vitamin B_1,[18–32] 28 of folate,[18–45] 42 of vitamin B_{12},[18–59] 13 of vitamin A,[18,19,23,25,26,28–30,36,39,55,60,61] 11 of vitamin E,[18,19,23,25,26,28,29,61–64] 57 of vitamin D,[18,19,21–33,37–39,41,42,45,47,51,52,55,59,61,65–94] 42 of calcium,[19,22–27,30–33,37–41,43–45,47,55,61,65,68,70,72,74–76,79,81,82,84,86,88,89,91,95–98] 39 of ferritin,[19,21,22,24–27,29–35,37,39–43,45,46,48,50,51,57,59,61,95,99–105] and 17 of zinc.[27,29–31,33,40,41,44,58,61,98,99,101,106–109] Vitamin K and copper were not analyzed because <3 studies met our inclusion criteria. The characteristics of the included studies are summarized in Table 1.

3.2 | Quality assessment of included studies

Table 2 summarizes the quality of the individual studies. The study question, population, intervention, and measurements were appropriate and clearly described in most studies. Forty-two studies (51.2%) stated that they included all eligible participants, and follow-up rates were high (>80%) in 40 studies (48.8%). Only 14 studies (17.1%) presented participants' compliance with the postoperative supplementation protocol at each follow-up point. Fifty-five studies (67.1%) clearly described the test methodology, including the equipment or coefficient of variation, and 22 studies (26.8%) considered the impact of inflammation and measured inflammatory markers, such as C-reactive protein.

3.3 | Adherence to micronutrient supplementation per guidelines after bariatric surgery

Less than 25% of the included studies administered vitamin B_1, B_{12}, and D, and calcium supplementations after RYGB and SG per guidelines (Figure 2); folate, vitamin A, and iron supplementations were administered per guidelines in approximately 50% of studies, whereas zinc and vitamin E supplementations were administered per guidelines in 58.8% and 72.7% of studies, respectively. Studies performing RYGB showed a higher proportion of patients adhering to the postoperative micronutrient supplementation guidelines, compared with those performing SG, except for vitamin D.

3.4 | Longitudinal micronutrient level changes after bariatric surgery with supplementation per guidelines

WMDs of preoperative and postoperative micronutrient levels and pooled micronutrient levels at each follow-up interval estimated by synthesis of studies with supplementation per guidelines are presented in Table S3. Table 3 illustrates the level of evidence for each micronutrient at each follow-up interval, and the longitudinal trajectory of pooled micronutrient levels before and at each follow-up interval is presented in Figure 3. Table 4 summarizes the significant micronutrient level changes after surgery and presents micronutrients and follow-up intervals investigated by ≥2 studies administering sufficient supplementation.

3.4.1 | Water-soluble vitamins (vitamin B_1, folate, vitamin B_{12})

Two studies evaluated the postoperative changes in vitamin B_1 levels with sufficient supplementation per guidelines,[18,20] and reported that the vitamin B_1 levels did not significantly change after RYGB (<6 and 6–11 months) and SG (<6 months) (Table 3). No studies have assessed the vitamin B_1 level at other postoperative time intervals.

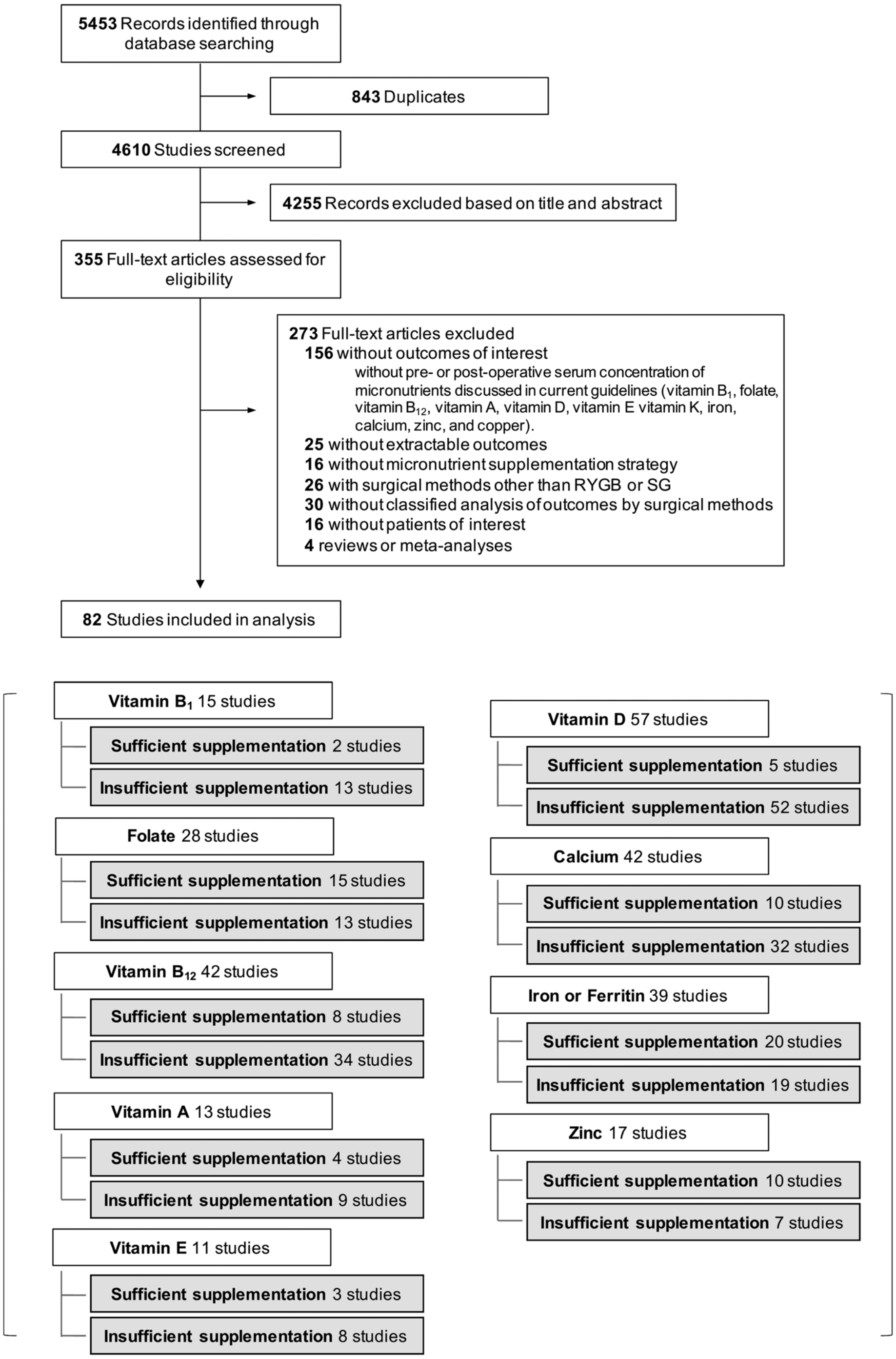

FIGURE 1 Flow diagram for literature selection process. RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy

Fifteen studies[18–20,23,25–27,34–37,39,40,42,44] reported folate levels after bariatric surgery with sufficient supplementation per guidelines. Folate levels significantly increased by 2.21 (95% CI, 1.90–2.51) to 4.19 (95% CI, 1.43–6.95) ng/ml after RYGB with sufficient supplementation in every follow-up interval (Table 3). After SG, folate levels significantly increased by 1.42 (95% CI, 0.87–1.96) and 2.78 (95% CI, 0.22–5.33) ng/ml at <6 and 6–11 months, respectively, and did not significantly change at 12–23 and ≥24 months.

Eight studies[18,20,22,27,34,35,38,58] (19.0% of included studies) administered vitamin B_{12} supplementation per guidelines and reported that the vitamin B_{12} level significantly increased by 272.19 (95% CI, 246.33–298.05) to 336.46 (95% CI, 185.18–487.73) pg/ml after RYGB with sufficient supplementation (Table 3). Only four studies[20,22,38,58] on vitamin B_{12} levels after SG with sufficient supplementation reported that the vitamin B_{12} level significantly increased by 128.36 [95% CI, 89.36–167.37] pg/ml at <6 months postoperatively and did not significantly change from baseline at 12–23 months. Less than two studies reported level changes at 6–11 and ≥24 months after SG.

The quality of evidence was moderate for the increase in folate level at ≥24 months after RYGB and at <6 and 6–11 months after SG, and for the increase in vitamin B_{12} level at 12–23 and ≥24 months

TABLE 1 Characteristics of analyzed studies

	Study population					Outcomes	
First author (year, location)	No. of participants, *n*	Age, mean (SD), years	Proportion of women, %	Baseline BMI, mean (SD), kg/m^2	Surgical methods	Outcomes included in the meta-analysis (nutritional supplement strategy if indicated)[a]	Assessment time after surgery, months
Carlin (2006, USA)	108	46 (9)	93	47 (5)	RYGB	Calcium (1500 mg/day), vitamin D (800 IU/day)	12
Cominetti (2006, Brazil)	24	37 (10)	83.3	43.6 (3.7)	RYGB	Zinc (NR)	2
Jin (2007, USA)	140	44.7 (0.8)	90	49.2 (0.7)	RYGB	Calcium (1000 mg/day), vitamin D (400–800 IU/day)	12
DiGiorgi (2008, USA)	403	41 (16–67)[b]	84	49.5 (8.7)	RYGB	Calcium (1200 mg/day), vitamin D (800–1200 IU/day)	3, 6, 12, 24
Vargas-Ruiz (2008, Mexico)	30	41 (21–56)[b]	83.4	44 (6)	RYGB	Iron (18 mg/day), folic acid (400 μg/day), vitamin B_{12} (6 μg/day)	6, 12, 24, 36
Goldner (2009, USA)	41	46.9 (10.1)	NR	56.4 (12.3)	RYGB	Calcium (2000 mg/day), vitamin D (800/2000/5000 IU/day depending on group)	3, 6, 9, 12, 18, 24
Hakeam (2009, Saudi Arabia)	67	NR	49.1	47.5 (9.6)	SG	Iron (0 mg/day), ferritin, vitamin B_{12} (12 μg/day)	6, 12
Dalcanale (2009, Brazil)	75	49.3 (10.6)	89.3	56.5 (8.1)	RYGB	Iron (60 mg/day), ferritin, calcium (250 mg/day), folic acid (1000 μg/day), magnesium (25 mg/day), phosphorus (NR), vitamin B_{12} (12 μg/day), zinc (25 mg/day)	24, 83.4
Coupaye (2009, France)	49	43 (10)	91.8	49 (8)	RYGB	Iron (60 mg/day), ferritin, calcium (125 mg/day), folic acid (800 μg/day), magnesium (100 mg/day), vitamin A (4000 IU/day), vitamin B_1 (1.6 mg/day), vitamin B_{12} (4 μg/day), vitamin D (500 IU/day), vitamin E (15 mg/day)	12

(Continues)

TABLE 1 (Continued)

	Study population					Outcomes	
First author (year, location)	No. of participants, *n*	Age, mean (SD), years	Proportion of women, %	Baseline BMI, mean (SD), kg/m^2	Surgical methods	Outcomes included in the meta-analysis (nutritional supplement strategy if indicated)[a]	Assessment time after surgery, months
Jin (2009, USA)	145	44 (10)	86	49.5 (36.4–74.6)[b]	RYGB	Calcium (1000 mg/day), vitamin D (400–800 IU/day)	3, 6, 12
Bavaresco (2010, Brazil)	48	41.9 (8.8)	85	51.9 (7.8)	RYGB	Iron, calcium (multivitamin contents are NR)	3, 6, 12
Flores (2010, Spain)	222	44.1 (10.2)	74	46.4 (4.9)	RYGB	Calcium (1200 mg/day), vitamin D (800 IU/day)[c]	12
Signori (2010, USA)	123	46.6 (10.4)	79	49.9 (8.0)	RYGB	Vitamin D (1200–2000 IU/day)	12
Boesing (2010, Brazil)	20	37.8 (11.1)	85	48.1 (8.7)	RYGB	Vitamin A (3000 μg/day), zinc (NR)	3, 6
Sallé (2010, France)	RYGB, 266; SG, 33	RYGB, 43 (10); SG, 53 (12)	RYGB, 83.8; SG, 78.8	RYGB, 45 (6); SG, 51 (10)	RYGB, SG	Zinc (15 mg/day)	RYGB, (6, 12, 24); SG, (6, 12)
Rosa (2011, Brazil)	9	41 (12)	100	51 (9)	RYGB	Iron (NR), ferritin, zinc (NR)	3
Drygalski (2011, USA)	1125	42 (20.5)	88.8	50.1 (17.1)	RYGB	Iron (18 mg/day), ferritin, folic acid (400 μg/day), vitamin B_{12} (1 mg/day)	36[d]
Lin (2011, USA)	20	33.8 (1.7)	100	48.0 (0.9)	RYGB	Vitamin D (NR)	1, 6, 24
Rojas (2011, Chile)	63	36.9 (9.2)	100	43.8 (4.3)	RYGB	Standard supplement group, iron (0 mg/day), zinc (7.5 mg/day) Improved supplement group, iron (18 mg/day), zinc (15 mg/day) Extra iron/zinc group, iron (60 mg/day), zinc (25 mg/day)	6
Aarts (2011, Netherlands)	14	37.0 (2.1)	100	44.9 (1.7)	RYGB	Calcium (1500 mg/day), vitamin D (1200 IU/day)	1

TABLE 1 (Continued)

	Study population					Outcomes	
First author (year, location)	No. of participants, *n*	Age, mean (SD), years	Proportion of women, %	Baseline BMI, mean (SD), kg/m²	Surgical methods	Outcomes included in the meta-analysis (nutritional supplement strategy if indicated)[a]	Assessment time after surgery, months
Ruz (2011, Chile)	67	36.9 (9.8)	100	45.2 (4.7)	RYGB	Zinc (7.5/15 mg/day depending on group)	6, 12, 18
Thurnheer (2012, Switzerland)	355	41.4 (10.8)	72.4	48.5 (11.5)	RYGB	Ferritin (iron 100 mg/day or ferric carboxymaltose 500 mg IV every 6–8 months), calcium (1500 mg/day), folic acid (multivitamin contents are NR), vitamin B_{12} (multivitamin and vitamin B complex contents are NR, 1000 μg IM every 3 months), vitamin D (1500 IU/day), zinc (multivitamin contents are NR)	12, 24, 36, 48, 60
Saif (2012, USA)	82	46.4 (13.9)	67	55.7 (13.7)	SG	Calcium (1200 mg/day), iron, ferritin, vitamin B_1, vitamin D (multivitamin contents are NR)	12, 36, 60
Ruz (2012, Chile)	RYGB, 32; SG, 26	35.9 (9.1)	100	RYGB, 42.0 (4.2); SG, 37.3 (3.2)	RYGB, SG	Ferritin (iron 60 mg/day after RYGB and 36 mg/day after SG)	6, 12
Capoccia (2012, Italy)	138	43.9 (10.9)	79.7	44.4 (6.5)	SG	Iron (5 mg/day during first 6 months), calcium (162 mg/day during first 6 months), folic acid (200 μg/day during first 6 months, and then 5 mg/day for 10 days a month), vitamin B_{12} (2.5 μg during first 6 months)	12
Blume (2012, Brazil)	170	39.5 (10.8)	80	48.8 (9.0)	RYGB	Iron, ferritin, folic acid, vitamin B_{12} (multivitamin contents are NR)	1, 6, 12, 24, 36

(Continues)

TABLE 1 (Continued)

	Study population					Outcomes	
First author (year, location)	No. of participants, *n*	Age, mean (SD), years	Proportion of women, %	Baseline BMI, mean (SD), kg/m^2	Surgical methods	Outcomes included in the meta-analysis (nutritional supplement strategy if indicated)[a]	Assessment time after surgery, months
Dadalt (2012, Brazil)	35	39.5 (1.5)	85.7	47.1 (1.5)	RYGB	Vitamin A (5000 IU/day), vitamin E (30 mg/day)	6, 12, 24
Damms-Machado (2012, Germany)	54	44 (9.9)	72	51.0 (7.8)	SG	Iron, calcium, folic acid, vitamin A, vitamin B_{12}, vitamin D, vitamin E (multivitamin contents are NR)	1, 3, 6, 12
Da Silva (2012, Brazil)	36	39.6 (9.2)	86.1	47.6 (9.1)	RYGB	Vitamin A (60 mg/day), vitamin E (30 mg/day)	3, 6, 12
Vilarrasa (2013, Spain)	RYGB, 33; SG, 33	RYGB, 49.7 (8.4); SG, 45.8 (12)	100	RYGB, 46.9 (4.8); SG, 49.1 (7.2)	RYGB, SG	Calcium (RYGB, 1050 mg/day; SG, 50 mg/day), vitamin D (RYGB, 1600 IU/day; SG, 800 IU/day)	12
Gesquiere (2013, Belgium)	164	43.1 (12.0)	60.4	42.0 (4.9)	RYGB	Ferritin, vitamin B_{12}, vitamin D (NR)	6, 12, 24, 36, 48, 60
Ledoux (2013, France)	144	42.9 (9.9)	90.3	48.2 (15.4)	RYGB	Calcium (125 mg/day), folic acid (200 μg/day), vitamin A (4000 IU/day), vitamin B_1 (1.6 mg/day), vitamin B_{12} (4000 μg/day), vitamin D (500 IU/day), vitamin E (10 mg/day)	12, 36
Beckman (2013, USA)	29	48 (2)	100	48 (1)	RYGB	Vitamin D (dietary/supplemental vitamin D intake was obtained at each visit, 129–602 IU/day)	0.5, 1.5, 6.5, 13
Coupaye (2013, France)	202	40.5 (10.3)	89.1	45.9 (6.5)	RYGB, SG	Calcium (125 mg/day), vitamin D (500 IU/day)	6
Ruiz-Tovar (2013, Spain)	42	43.6 (10.1)	92.9	51.2 (6.7)	SG	Calcium (NR), vitamin D (0 IU/day)	12, 24

TABLE 1 (Continued)

	Study population					Outcomes	
First author (year, location)	No. of participants, *n*	Age, mean (SD), years	Proportion of women, %	Baseline BMI, mean (SD), kg/m^2	Surgical methods	Outcomes included in the meta-analysis (nutritional supplement strategy if indicated)[a]	Assessment time after surgery, months
Carrasco (2014, Chile)	RYGB, 23; SG, 20	RYGB, 37.3 (8.1); SG, 34.2 (10.2)	100	RYGB, 42.0 (4.2); SG, 37.3 (3.2)	RYGB	Vitamin D (400 IU/day)	12
Lancha (2014, Spain)	RYGB, 40; SG, 11	RYGB, 38.7 (13.5); SG, 44.3 (10.5)	RYGB, 80; SG, 63.6	RYGB, 45.2 (7.9); SG, 40.4 (6.1)	RYGB, SG	Calcium, vitamin D (supplement contents are NR)	15
Coupaye (2014, France)	RYGB, 43; SG, 43	RYGB, 44 (9); SG, 45 (11)	RYGB, 72.1; SG, 72.1	RYGB, 48.6 (7.8); SG, 48.5 (9.6)	RYGB, SG	Iron (60 mg/day), ferritin, calcium (125 mg/day), folic acid (800 μg/day), vitamin A (4000 IU/day), vitamin B_1 (1.6 mg/day), vitamin B_{12} (4 μg/day), vitamin D (500 IU/day), vitamin E (15 mg/day)	6, 12
Moore (2014, USA)	RYGB, 11; SG, 11	RYGB, 45 (13); SG, 37 (11)	100	RYGB, 46.2 (6.9); SG, 46.2 (9.3)	RYGB, SG	Folic acid (800 μg/day), vitamin B_1 (12 mg/day), vitamin B_{12} (350 μg/day)	3
Kim (2014, Korea)	33	45.8 (9.9)	69.7	32.9 (4.3)	RYGB	Iron (3.5 mg/day), calcium (500 mg/day), vitamin B_{12} (3 μg/day), vitamin D (1000 IU/day)	12, 24
Vix (2014, France)	RYGB, 45; SG, 55	RYGB, 35.2 (9.4); SG, 35.1 (9.7)	RYGB, 86.7; SG, 78.1	RYGB, 47.1 (5.6); SG, 45.6 (4.8)	RYGB, SG	Vitamin D (0 IU/day)	1, 3, 6, 12
Dogan (2014, Netherlands)	sMVS, 74; WLS forte, 74	sMVS, 43.4 (10.0); WLS Forte, 45.3 (10.2)	sMVS, 68; WLS Forte, 71	sMVS, 44.8 (4.8); WLS Forte, 44.8 (6.4)	RYGB	Iron (sMVS, 14 mg/day; WLS Forte, 70 mg/day), ferritin, calcium (sMVS, 1591 mg/day; WLS Forte, 1500 mg/day), folic acid (sMVS, 200 μg/day; WLS Forte, 600 μg/day), vitamin B_1 (sMVS, 1.1 mg/day; WLS Forte, 2.75 mg/day), vitamin B_{12} (sMVS, 12.5 μg/day; WLS Forte, 350 μg/day), vitamin D (sMVS, 1360 IU/day; WLS Forte, 1700 IU/day), zinc (sMVS, 10 mg/day; WLS Forte, 22.5 mg/day)	6, 12

(Continues)

TABLE 1 (Continued)

First author (year, location)	Study population: No. of participants, *n*	Age, mean (SD), years	Proportion of women, %	Baseline BMI, mean (SD), kg/m^2	Surgical methods	Outcomes: Outcomes included in the meta-analysis (nutritional supplement strategy if indicated)[a]	Assessment time after surgery, months
Moore (2014, USA)	RYGB, 12; SG, 11	RYGB, 38 (10); SG, 43 (13)	100	RYGB, 44.8 (9.4); SG, 47.6 (6.8)	RYGB, SG	Vitamin D (2000 IU/day)	3
Biagioni (2014, Brazil)	22	30.3 (8.9)	100	50.6 (11.6)	RYGB	Calcium (250 mg/day), vitamin D (400–800 IU/day)	3, 6
Worm (2015, Denmark)	835	43.3	70.9	47.2 (1.0)	RYGB	Iron (9 mg/day), ferritin, folic acid (400 μg/day), vitamin B_{12} (200 μg/day and additional 1 mg subcutaneous injection every 3 months	6, 12, 24
Lanzarini (2015, Spain)	RYGB, 68; SG, 96	RYGB, 42.5 (8.5); SG, 45.7 (8.9)	76.8	RYGB, 44.9 (2.8); SG, 43.0 (5.5)	RYGB, SG	Vitamin D (400 IU/day)	12, 24
Schafer (2015, USA)	33	45.4 (12.8)	76	44.7 (7.4)	RYGB	Vitamin D (2636 [SD, 822] IU/day in average)	6
Ben-Porat (2015, Israel)	192	36.5 (11.1)	69.3	42.9 (4.2)	SG	Iron, ferritin, folic acid, vitamin B_{12} (multivitamin containing iron, folic acid, vitamin B_{12}, and vitamin D in concentrations between 100% and 200% of the recommended daily intake), vitamin D (800 IU/day)	12
Aaseth (2015, Norway)	441	41.5	75.1	44.9 (6.9)	RYGB	Folic acid (200 μg/day), vitamin A (1600 IU/day), vitamin B_1 (1.4 mg/day), vitamin B_{12} (1 mg IM every 3 months), vitamin D (800 IU/day), vitamin E (10 mg/day)	12, 24, 60
Zarshenas (2016, Austrailia)	91	51.9 (11.4)	69.2	42.8 (6.1)	SG	Iron (18 mg/day), ferritin, calcium (1200 mg/day), folic acid (500 μg/day), vitamin B_{12} (100 μg/day), vitamin D (1000 IU/day)	6, 12, 24, 36

TABLE 1 (Continued)

	Study population					Outcomes	
First author (year, location)	No. of participants, *n*	Age, mean (SD), years	Proportion of women, %	Baseline BMI, mean (SD), kg/m^2	Surgical methods	Outcomes included in the meta-analysis (nutritional supplement strategy if indicated)[a]	Assessment time after surgery, months
Obeid (2016, USA)	328	41.4 (9.8)	83	47.5 (7.1)	RYGB	Iron, calcium, folic acid, vitamin B_{12}, vitamin D, zinc[e] (Patients were instructed to take multivitamin, iron, and calcium supplements indefinitely)	12, 24, 36, 48, 60, 72, 84, 96, 108, 120
Ruiz-Tovar (2016, Spain)	Group 1, 40; group 2, 40[f]	Group 1, 42.6 (7.1); group 2, 43.6 (7.4)	75	Group 1, 46.9 (7.5); group 2, 48.7 (7.6)	SG	Iron (5 mg/day), ferritin, calcium (162 mg/day), folic acid (200 μg/day), vitamin B_{12} (2.5 μg/day), vitamin D (200 IU/day), zinc (5 mg/day)	3, 6, 12
Verger (2016, France)	RYGB, 30; SG, 22	RYGB, 43.5 (38.0–51.0); SG, 41.0 (36.0–49.0)[g]	RYGB, 68,2; SG, 66.7	RYGB, 45.5 (41.6–49.1); SG, 43.2 (39.0–47.7) [g]	RYGB, SG	Iron (168 mg/day), ferritin, calcium (1000 mg/day), folic acid (200 μg/day), vitamin B_1 (1.4 mg/day), vitamin B_{12} (1 μg/day), vitamin D (1000 IU/day)	3 [h], 6, 12
Aron-Wisnewsky (2016, France)	14	40.5 (31.0–45.0)[g]	100	41.2 (38.9–43.7)[g]	RYGB	Iron (168 mg/day), ferritin, calcium (1000 mg/day)	1, 3
Wolf (2016, Germany)	Vitamin D group, 47; placebo group, 47	Vitamin D group, 43 (11); placebo group, 43 (10)	Vitamin D group, 66; placebo group, 61.7	Vitamin D group, 46.7 (44.6–57.4); placebo group, 50.0 (46.3–58.8)[g]	SG	Calcium (NR), vitamin D (vitamin D group, 3200 IU/day; placebo group, 0 IU/day)	1, 3
Cepeda-Lopez (2016, Mexico)	38	34 (8)	84.2	34.3 (3.5)	SG	Ferritin (multivitamin contents are NR)	6
Pellitero (2017, Spain)	176	49.3 (9.1)	69.9	46.7 (7.4)	SG	Ferritin (iron, 14 mg/day), calcium (1120 mg/day), folic acid (200 μg/day), vitamin B_1 (1.1 mg/day), vitamin B_{12} (2.5 μg/day), vitamin D (800 IU/day)	12, 24, 60

(Continues)

TABLE 1 (Continued)

	Study population					Outcomes	
First author (year, location)	No. of participants, *n*	Age, mean (SD), years	Proportion of women, %	Baseline BMI, mean (SD), kg/m^2	Surgical methods	Outcomes included in the meta-analysis (nutritional supplement strategy if indicated)[a]	Assessment time after surgery, months
Wei (2017, Taiwan)	RYGB, 322; SG, 360	RYGB, 35.8 (10.5); SG, 34.8 (9.9)	RYGB, 72.7; SG, 69.7	RYGB, 38.9 (7.5); SG, 38.5 (7.4)	RYGB, SG	Calcium, vitamin D (twice daily multivitamin supplementation and calcium/vitamin D3 supplementation after RYGB and single multivitamin supplementation after SG were recommended)	12
Silva (2017, Brazil)	64	16.9 (1.5)	65.6	45.8 (7.2)	RYGB	Vitamin A (5000 IU/day)	1, 6, 12
Caron (2017, Canada)	537	48.0 (11.3)	63.5	48.1 (8.7)	SG	Iron (10 mg/day), ferritin, calcium (200 mg/day), folic acid (400 μg/day), vitamin A (1000 IU/day), vitamin B_{12} (20 μg/day), vitamin D (600 IU/day)	3, 6, 12, 18, 24, 36, 48, 60
Perin (2018, USA)	Standard arm, 21; investigational arm, 26	Standard arm, 43.0 (12.1); investigational arm, 43.2 (9.8)	Standard arm, 90.5; investigational arm, 69.2	Standard arm, 46.2 (7.8); investigational arm, 46.2 (6.8)	RYGB	Iron (standard, 72 mg/day; investigational, 72 mg/day), folic acid (standard, 1600 μg/day; investigational, 800 μg/day), vitamin A (standard, 12,000 IU/day; investigational, 20,000 IU/day), vitamin B_1 (standard, 6 mg/day; investigational, 12.5 mg/day), vitamin B_{12} (standard, 1020 μg/day; investigational, 1500 μg/day), vitamin D (standard, 1600–2200 IU/day; investigational, 3000–3600 IU/day), vitamin E (standard, 108 mg/day; investigational, 270 mg/day)	3, 6

TABLE 1 (Continued)

	Study population					Outcomes	
First author (year, location)	No. of participants, *n*	Age, mean (SD), years	Proportion of women, %	Baseline BMI, mean (SD), kg/m^2	Surgical methods	Outcomes included in the meta-analysis (nutritional supplement strategy if indicated)[a]	Assessment time after surgery, months
Schijns (2018, Netherlands)	Fe-fumarate, 12; Fe-gluconate, 12[h]	Fe-fumarate, 47.2 (2.5); Fe-gluconate, 48.8 (2.0)	100	Fe-fumarate, 43.5 (1.2); Fe-gluconate, 45.3 (2.2)	RYGB	Ferritin (iron, 70 mg/day)	1
Al-Mutawa (2018, Kuwait)	1330	35.0 (11.2)	74	46.1 (8.0)	SG	Iron (10 mg/day), ferritin, folic acid (195 μg/day), vitamin B_1 (1.4 mg/day), vitamin B_{12} (1 μg/day), vitamin D (200 IU/day)	6, 12, 36, 60
Madhok (2018, UK)	200	45.0 (11.0)	69.5	48.0 (6.7)	RYGB	Iron (100 mg/day), ferritin, folic acid (multivitamin contents are NR), vitamin B_{12} (multivitamin and 1 mg IM every 3 months)	6, 12, 18, 24
Guan (2018, China)	RYGB, 120; SG, 149	RYGB, 33.5 (9.9); SG, 30.2 (10.7)	RYGB, 42.5; SG, 73.8	RYGB, 43.8 (11.0); SG, 37.2 (7.1)	RYGB, SG	Iron (18 mg/day), ferritin, calcium (762 mg/day), folic acid (400 μg/day), vitamin A (5000 IU/day), vitamin B_1 (1.5 mg/day), vitamin B_{12} (6 μg/day), vitamin D (525 IU/day), vitamin E (13.5 mg/day)	6, 12
Carrasco (2018, Chile)	RYGB, 26; SG, 32	RYGB, 36.9 (8.4); SG, 33.6 (8.8)	100	RYGB, 42.0 (4.2); SG, 37.3 (3.2)	RYGB, SG	Calcium (RYGB, 750 mg/day; SG, 662 mg/day), vitamin D (RYGB, 800 IU/day; SG, 600 IU/day)	12, 24
Ferraz (2018, Brazil)	RYGB, 238; SG, 338	RYGB, 41.9 (11.1); SG, 37.1 (11)	RYGB, 67.6; SG, 85.8	RYGB, 42.7 (5.9); SG, 39.4 (2.6)	RYGB, SG	Iron (100 mg/day), vitamin B_{12} (6 μg/day, 5000 μg IM injection at 1 month after surgery), zinc (15 mg/day)	3, 6, 12, 24
Antoniewicz (2019, Poland)	RYGB, 47; SG, 51	RYGB, 44.3 (9.0); SG, 43.9 (11.0)	RYGB, 70.2; SG, 66.0	RYGB, 49.8 (46.3–55.6); SG, 44.1 (41.3–49.1)[g]	RYGB, SG	Iron (100 mg/day), ferritin, calcium (162 mg/day), folic acid (200 μg/day), vitamin B_{12} (2.5 μg/day)	1, 12
DiSilvestro (2019, USA)	Standard product, 13; new product, 13	Standard product, 44 (2); new product, 41 (3)	100	Standard product, 50 (3); new product, 47 (2)	RYGB	Vitamin D (standard product, 200 IU/day; new product, 0 IU/day)	1.5

(Continues)

TABLE 1 (Continued)

	Study population					Outcomes	
First author (year, location)	No. of participants, *n*	Age, mean (SD), years	Proportion of women, %	Baseline BMI, mean (SD), kg/m^2	Surgical methods	Outcomes included in the meta-analysis (nutritional supplement strategy if indicated)[a]	Assessment time after surgery, months
Duran (2019, Turkey)	RYGB, 11; SG, 62	41.5 (9.6)	80.8	RYGB, 58.9 (3.6); SG, 46.1 (1.2)	RYGB, SG	Calcium (500 mg/day), vitamin D (800 IU/day)	12
Kikkas (2019, Estonia)	86	52.1 (10.1)	73.7	46.5 (7.7)	SG	Ferritin (iron, 14 mg/day), vitamin B_{12} (1 μg/day), vitamin D (NR)	12, 60
Santos (2019, Brazil)	60	39.4 (5.5)	68.3	43.5 (4.4)	RYGB	Calcium (250 mg/day), vitamin D (800 IU/day), zinc (NR)	6, 12
Vinolas (2019, France)	RYGB, 28; SG, 29	RYGB, 42.9 (11); SG, 45.2 (9.2)	NR	RYGB, 46.8 (6.9); SG, 44.1 (9.4)	RYGB, SG	Iron (14 mg/day), ferritin, folic acid (200 μg/day), vitamin A (1000 IU/day), vitamin B_1 (2.5 mg/day), vitamin B_{12} (3 μg/day), vitamin D (400 IU/day), vitamin E (18 mg/day), zinc (12 mg/day)	1, 3, 6, 12
Cadart (2020, France)	RYGB, 47; SG, 48	RYGB, 44.4 (10.6); SG, 47.3 (11.5)	RYGB, 68; SG, 79	RYGB, 46.1 (7.4); SG, 45.4 (10.1)	RYGB, SG	Calcium (NR), vitamin D (100,000 IU every 15 days for 1 or 2 months and then every 3 months depending on serum level)	12, 48
Coupaye (2020, France)	Not taking postop. MV, 108; taking postop. MV, 39	Not taking postop. MV, 42.8 (9.8); taking postop. MV, 45.6 (11.8)	Not taking postop. MV, 87; taking postop. MV, 90	Not taking postop. MV, 44.4 (7.5); taking postop. MV, 44.8 (6.9)	SG	Iron (8 mg/day), ferritin, calcium (120 mg/day), folic acid (200 μg/day), vitamin A (2700 IU/day), vitamin B_1 (1.4 mg/day), vitamin B_{12} (1 μg/day), vitamin D (200 IU/day), zinc (15 mg/day)	Not taking postop. MV, 44.8; taking postop. MV, 42.1
	WLS Optimum, 69; sMVS, 70	WLS Optimum, 38.2 (12.4); sMVS, 39.7 (10.8)	WLS Optimum, 73.9; sMVS, 68.8	WLS Optimum, 47.6 (9.0); sMVS, 48.4 (9.9)	SG	Iron (WLS Optimum, 21 mg/day; sMVS,	6, 12

TABLE 1 (Continued)

	Study population					Outcomes	
First author (year, location)	No. of participants, *n*	Age, mean (SD), years	Proportion of women, %	Baseline BMI, mean (SD), kg/m^2	Surgical methods	Outcomes included in the meta-analysis (nutritional supplement strategy if indicated)[a]	Assessment time after surgery, months
Heusschen (2020, Netherlands)						14 mg/day), ferritin, calcium (WLS Optimum, 0 mg/day; sMVS, 91.43 mg/day), folic acid (WLS Optimum, 300 μg/day; sMVS, 200 μg/day), vitamin B_1 (WLS Optimum, 2 mg/day; sMVS, 1.4 mg/day;), vitamin B_{12} (WLS Optimum, 10 μg/day; sMVS, 2.5 μg/day), vitamin D (WLS Optimum, 300 IU/day; sMVS, 160 IU/day), zinc (WLS Optimum, 15 mg/day; sMVS, 10 mg/day)	
Hosseini-Esfahani (2020, Iran)	RYGB, 58; SG, 122	RYGB, 41.4 (10); SG, 39.2 (12)	RYGB, 89.7; SG, 72.1	RYGB, 45.2 (6); SG, 45.2 (7)	RYGB, SG	Iron (10 mg/day), ferritin, calcium (400 mg/day), vitamin B_{12} (1 μg/day), vitamin D (200 IU/day), zinc (4 mg/day)	12
Hung (2020, Taiwan)	129	38.1 (10.8)	59.7	39.1 (5.1)	SG	Calcium (208 mg/day), folate (400 μg/day), vitamin B_{12} (200 μg/day), zinc (15 mg/day)	12
Ministrini (2020, Italy)	152	43.5 (11.6)	64.5	45.5 (6.7)	SG	Calcium (NR), vitamin D (50,000 IU/month)	12
Paredes (2020, Portugal)	330	41.9 (10.4)	86	43.9 (6.2)	SG	Iron (5 mg/day), ferritin, calcium 162 mg/day), folate (200 μg/day), vitamin B_{12} (2.5 μg/day), vitamin D (20,010 IU/week and 200 IU/day)	12
Sandvik (2020, Norway)	644	39.8 (9.7)	75	43.9 (5.1)	RYGB	Ferritin (iron, 15 mg/day recommended only for iron-deficient patients)	12, 24, 36, 48, 60

(Continues)

TABLE 1 (Continued)

	Study population					Outcomes	
First author (year, location)	No. of participants, *n*	Age, mean (SD), years	Proportion of women, %	Baseline BMI, mean (SD), kg/m^2	Surgical methods	Outcomes included in the meta-analysis (nutritional supplement strategy if indicated)[a]	Assessment time after surgery, months
Smelt (2020, Netherlands)	Non-MV user, 679; MV user, 291	Non-MV user, 43 (11); MV user, 46 (10)	Non-MV user, 75; MV user, 67	Non-MV user, 44 (6); MV user, 43 (5)	SG	Iron (MV user, 21 mg/day), ferritin, calcium (1000 mg/day), folic acid, (MV user, 300 μg/day), vitamin B_1 (MV user, 2 mg/day), vitamin B_{12} (MV user, 10 μg/day), vitamin D (non-MV user, 800 IU/day; MV user, 1100 IU/day)	6, 12, 24, 36, 48

Abbreviations: BMI, body mass index; DM, diabetes mellitus; IM, intramuscular injection; IV, intravenous injection; MV, multivitamin at the time of the postoperative evaluation; NR, not reported; RYGB, Roux-en-Y gastric bypass; SD, standard deviation; SG, sleeve gastrectomy; sMVS, standard multivitamin supplement.

[a]Nutritional supplement was administrated orally unless otherwise indicated. Iron supplementation strategy was iron or ferritin.

[b]Mean (range).

[c]Calcium and vitamin D supplementation after bariatric surgery was only recommended to patients with parathyroid hormone level >70 pg/ml (63% of participants).

[d]The authors collected data with a follow-up duration of 3, 6, 12, 18, or 24–48 months, but numeral data are available for only 24–48 months.

[e]This study was not weighted when pooling changes in zinc concentrations because it included only one preoperative zinc concentration measurement.

[f]Group 1 maintained the multivitamin supplement for 3 months, whereas group 2 maintained supplementation for 12 months.

[g]Median (interquartile range).

[h]Patients were divided into two groups: the Fe-fumarate group received a single 600-mg dose of ferrous fumarate, whereas the Fe-gluconate group received a single 1390-mg dose of ferrous gluconate before surgery.

[i]Measurements at 3 months were available for iron, ferritin, and calcium.

TABLE 2 Quality rating of analyzed studies

First author (year, country)	Sample size	Q1[a]	Q2[a]	Q3[a]	Q4[a]	Q5[a]	Q6[a]	Q7[a,b]	Q8[a]	Q9[a]	Q10[c]	Q11[d]	Q12[e]
Carlin (2006, USA)	108	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Cominetti (2006, Brazil)	24	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Jin (2007, USA)	140	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	No
DiGiorgi (2008, USA)	403	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No
Vargas-Ruiz (2008, Mexico)	30	Yes	Yes	Yes	Yes	Yes	Yes	NA[e]	No	Yes	No	No	No
Goldner (2009, USA)	41	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
Hakeam (2009, Saudi Arabia)	67	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Dalcanale (2009, Brazil)	75	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Coupaye (2009, France)	49	Yes	Yes	Yes	Yes	Yes	Yes	NA[e]	Yes	Yes	No	Yes	Yes
Jin (2009, USA)	145	Yes	Yes	Yes	Yes	Yes	Yes	NA[e]	Yes	Yes	No	Yes	No
Bavaresco (2010, Brazil)	48	Yes	No	Yes	CD	Yes	Yes	Yes	Yes	Yes	No	No	No
Flores (2010, Spain)	222	Yes	Yes	Yes	NR	Yes	Yes	NA[e]	Yes	Yes	No	Yes	No
Signori (2010, USA)	123	Yes	Yes	Yes	NR	Yes	Yes	NA[e]	Yes	Yes	No	No	No
Boesing (2010, Brazil)	20	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Sallé (2010, France)	299	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Rosa (2011, Brazil)	9	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Drygalski (2011, USA)	1125	Yes	Yes	Yes	CD	Yes	Yes	No	Yes	Yes	No	No	Yes
Lin (2011, USA)	20	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	Yes	No	Yes	No
Rojas (2011, Chile)	63	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes[f]	Yes	No	Yes	Yes
Aarts (2011, Netherlands)	14	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Ruz (2011, Chile)	67	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Thurnheer (2012, Switzerland)	355	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No
Saif (2012, USA)	82	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No
Ruz (2012, Chile)	58	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Capoccia (2012, Italy)	138	Yes	Yes	Yes	NR	Yes	Yes	NR	No	Yes	No	No	No
Blume (2012, Brazil)	170	Yes	Yes	Yes	Yes	Yes	Yes	NA[e]	Yes	Yes	No	Yes	No
Dadalt (2012, Brazil)	35	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Damms-Machado (2012, Germany)	54	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Da Silva (2012, Brazil)	36	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Vilarrasa (2013, Spain)	66	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No
Gesquiere (2013, Belgium)	164	Yes	Yes	Yes	NR	Yes	Yes	No	No	Yes	No	No	No
Ledoux (2013, France)	144	Yes	Yes	Yes	Yes	Yes	Yes	NA[e]	Yes	Yes	Yes	Yes	Yes
Beckman (2013, USA)	29	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Coupaye (2013, France)	202	Yes	Yes	Yes	NR	Yes	Yes	NA[e]	Yes	Yes	No	Yes	Yes
Ruiz-Tovar (2013, Spain)	42	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Carrasco (2014, Chile)	43	Yes	No	Yes	CD	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Lancha (2014, Spain)	51	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Coupaye (2014, France)	86	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Moore (2014, USA)	22	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Kim (2014, Korea)	33	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Vix (2014, France)	100	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Dogan (2014, Netherlands)	148	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	No	No
Moore (2014, USA)	23	Yes	Yes	Yes	Yes	Yes	Yes	NA[e]	Yes	Yes	No	Yes	No
Biagioni (2014, Brazil)	22	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Worm (2015, Denmark)	835	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Lanzarini (2015, Spain)	164	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No

(Continues)

TABLE 2 (Continued)

First author (year, country)	Sample size	Q1[a]	Q2[a]	Q3[a]	Q4[a]	Q5[a]	Q6[a]	Q7[a,b]	Q8[a]	Q9[a]	Q10[c]	Q11[d]	Q12[e]
Schafer (2015, USA)	33	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Ben-Porat (2015, Israel)	192	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	Yes	No	Yes	No
Aaseth (2015, Norway)	441	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Zarshenas (2016, Australia)	91	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Obeid (2016, USA)	328	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No
Ruiz-Tovar (2016, Spain)	80	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Yes	No	No	No
Verger (2016, France)	52	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Aron-Wisnewsky (2016, France)	14	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wolf (2016, Germany)	94	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cepeda-Lopez (2016, Mexico)	38	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Pellitero (2017, Spain)	176	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Wei (2017, Taiwan)	682	Yes	Yes	Yes	Yes	Yes	Yes	NA[e]	Yes	Yes	No	Yes	Yes
Silva (2017, Brazil)	64	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Caron (2017, Canada)	537	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No
Perin (2018, USA)	47	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No
Schijns (2018, Netherlands)	24	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Al-Mutawa (2018, Kuwait)	1330	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	Yes	No	No	No
Madhok (2018, UK)	200	Yes	Yes	Yes	CD	Yes	Yes	No	Yes	Yes	No	No	No
Guan (2018, China)	269	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	Yes	No	Yes	No
Carrasco (2018, Chile)	58	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
Ferraz (2018, Brazil)	576	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No
Antoniewicz (2019, Poland)	98	Yes	Yes	Yes	Yes	Yes	Yes	NA[e]	Yes	Yes	No	No	No
DiSilvestro (2019, USA)	26	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Duran (2019, Turkey)	73	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Kikkas (2019, Estonia)	86	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Santos (2019, Brazil)	60	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Vinolas (2019, France)	47	Yes	Yes	Yes	Yes	Yes	Yes	NA[e]	Yes	Yes	No	No	No
Cadart (2020, France)	95	Yes	Yes	Yes	CD	Yes	Yes	NA[e]	Yes	Yes	No	Yes	Yes
Coupaye (2020, France)	147	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Heusschen (2020, Netherlands)	139	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Hosseini-Esfahani (2020, Iran)	180	Yes	Yes	Yes	Yes	Yes	Yes	NA[e]	Yes	Yes	No	Yes	No
Hung (2020, Taiwan)	129	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No
Ministrini (2020, Italy)	152	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
Paredes (2020, Portugal)	330	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No
Sandvik (2020, Norway)	644	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Smelt (2020, Netherlands)	970	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes

Abbreviations: CD, cannot determine; NA, not applicable; NR, not reported.

[a]Quality assessment tool for before-after (pre-post) studies with no control group developed by the National Heart, Lung, and Blood Institute consists of the following 12 questions: Q1. Was the study question or objective clearly stated? Q2. Were the eligibility criteria for the study population prespecified and clearly described? Q3. Were the participants in the study representative of those who would be eligible for the intervention in the general or clinical population of interest? Q4. Were all eligible participants who met the prespecified entry criteria enrolled? Q5. Was the intervention clearly described and delivered consistently across the study population? Q6. Were the outcome measured prespecified, clearly defined, and assessed consistently across all study participants? Q7. Was the loss to follow-up after baseline 20% or less? Q8. Did the statistical methods examine changes in outcome measures from before to after the intervention? Q9. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention?

[b]"Yes" if follow-up rate was ≥80% until at least 12 months after surgery (until the end of the study if the follow-up duration was <12 months).

[c]Q10. Did the authors report patients' adherence to supplementation protocol?

[d]Q11. Did the authors present test methodology, including testing method coefficient of variation?

[e]Q12. Did the authors consider the impact of inflammation on micronutrient status? Follow-up rate was not applicable because the study design was retrospective and included patients for whom both preoperative and postoperative measurements were available.

[f]The statistical analysis was performed of all participants, not within groups.

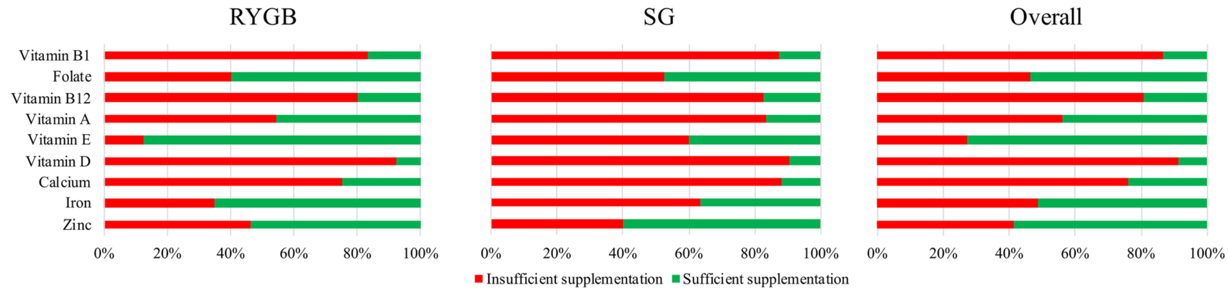

FIGURE 2 Adherence of included studies to postoperative micronutrient supplementation recommendations of the current guidelines. Among the included studies reporting micronutrient status, the proportion of studies adhering to the current guidelines and supplied the recommended amount of micronutrients postoperatively (as illustrated in Table S2) is shown using bar graphs. RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy

after RYGB and at <6 months after SG (Table 3). The quality of evidence was low or very low for the longitudinal changes in all water-soluble vitamins after bariatric surgery at other follow-up intervals due to risk of bias, imprecision, inconsistency, or publication bias.

3.4.2 | Fat-soluble vitamins (vitamins A, E, and D)

Four studies[18,26,36,60] reported changes in vitamin A levels after supplementation per guidelines. Vitamin A level significantly decreased at <6 (WMD, −7.87 μg/dl; 95% CI, −12.05 to −3.68), 6–11 (WMD, −9.91 μg/dl; −15.61 to −4.21), and 12–23 months (WMD, −7.54 μg/dl; 95% CI, −10.16 to −4.92) after RYGB (Table 3) when vitamin A supplementation was administered per guidelines. Only one study[26] reported vitamin A level after SG with sufficient supplementation.

Vitamin E status after bariatric surgery with supplementation per guidelines was assessed by data synthesis of eight studies.[18,19,23,25,29,62–64] Vitamin E level significantly at <6 (WMD, −0.77 μg/ml; 95%CI, −1.15 to −0.39), 11–23 (WMD, −2.41 μg/ml; 95% CI, −2.84 to −1.98), and ≥24 months (WMD, −2.35 μg/ml; 95% CI, −2.84 to −1.98) after RYGB (Table 3). No significant vitamin E level change was observed at 6–11 and 12–23 months after SG with sufficient supplementation in the synthesis of two studies.[19,29] Less than two studies reported vitamin E status at <6 and ≥24 months after SG.

Only five studies[18,45,75,82,93] (12.5% and 7.3% of the included studies performing RYGB and SG, respectively) administered vitamin D supplementation per guidelines postoperatively. Vitamin D levels significantly increased at 6–11 months after RYGB (WMD, 22.71 ng/ml; 95% CI, 15.87–29.56) and 12–23 months after SG (WMD, 6.03 ng/ml; 95% CI, 4.18–7.89) (Table 3). The levels did not significantly change at 12–23 and ≥24 months after RYGB, and <2 studies reported vitamin D levels at other follow-up intervals.

The quality of evidence was moderate for decreases in vitamin A and E levels at 12–23 and ≥24 months, respectively, after RYGB (Table 3). The quality of evidence was low or very low for longitudinal changes of fat-soluble vitamin levels after bariatric surgery at other time intervals due to risk of bias, inconsistency, or imprecision.

3.4.3 | Minerals (calcium, iron, and zinc)

The analysis of 10 studies[27,30,33,37,72,74–76,81,86] with postoperative calcium supplementation per guidelines demonstrated no significant change in calcium levels after RYGB (Table 3). The calcium level increased at 12–23 months after SG with supplementation per guidelines (WMD, 0.17 mg/dl; 95% CI, 0.07–0.28) and did not significantly change at ≥24 months. Less than two studies reported calcium status at <6 and 6–11 months after SG.

Twenty studies[19,24–27,31–34,37,40,42,43,46,48,57,95,101,103,104] presenting post-bariatric changes in ferritin levels with iron supplementation per guidelines reported that the ferritin levels significantly decreased by 16.42 μg/ml (95% CI, −18.29 to −14.56) at 6–11 months (Table 3). The ferritin levels also decreased at ≥24 months after SG despite supplementation per guidelines (WMD, −54.93 μg/ml; 95% CI, −77.19 to −32.67). No significant changes in ferritin levels were observed at other follow-up intervals.

Ten studies[27,29,30,40,44,58,101,107,108] on postoperative zinc supplementation per guidelines reported that the zinc levels significantly decreased at <6 (WMD, −6.92 μg/dl; 95% CI, −11.53 to −2.32) and ≥24 months (WMD, −8.81 μg/dl; 95% CI, −12.61 to −5.00) after RYGB and 6–11 months after SG (WMD, −3.61 μg/dl; 95% CI, −6.89 to −0.33) (Table 3). Zinc levels did not significantly change at the other follow-up intervals.

The quality of evidence was moderate for a decrease in ferritin level at ≥24 months after SG and low or very low for the longitudinal changes of mineral levels after bariatric surgery at other time intervals due to risk of bias, inconsistency, or imprecision.

4 | DISCUSSION

Although current clinical guidelines for bariatric surgery specify nutritional supplementation and monitoring of each micronutrient after bariatric surgery, they recommend a collective monitoring schedule (e.g., every 3–6 months for the first year and 6–12 months thereafter); the rationale of which is mainly derived from the cross-sectional data of postoperative micronutrient deficiency.[11,13,110] A longitudinal

TABLE 3 Changes in micronutrient levels after bariatric surgery with micronutrient supplementation per guidelines and their quality of evidence

Micronutrient	Postoperative time	Study design	No. of studies	No. of patients	Risk of bias	Inconsistency
Roux-en-Y gastric bypass						
Vitamin B_1 (thiamin)	<6 months	Observational	2	57	Serious	No serious inconsistency
Folate	<6 months	Observational	3	163	Serious	No serious inconsistency
	6–11 months	Observational	6	915	Serious	No serious inconsistency
	12–23 months	Observational	7	1014	No serious risk of bias	No serious inconsistency
	≥24 months	Observational	4	1537	No serious risk of bias	No serious inconsistency
Vitamin B_{12} (cobalamin)	<6 months	Observational	3	343	Serious	No serious inconsistency
	6–11 months	Observational	3	965	Serious	No serious inconsistency
	12–23 months	Observational	2	871	No serious risk of bias	No serious inconsistency
	≥24 months	Observational	2	1761	No serious risk of bias	No serious inconsistency
Vitamin A	<6 months	Observational	3	216	Serious	No serious inconsistency
	6–11 months	Observational	4	286	Serious	No serious inconsistency
	12–23 months	Observational	3	192	No serious risk of bias	No serious inconsistency
Vitamin E	<6 months	Observational	4	178	No serious risk of bias	No serious inconsistency
	6–11 months	Observational	6	256	No serious risk of bias	Serious
	12–23 months	Observational	6	335	No serious risk of bias	Serious
	≥24 months	Observational	2	179	No serious risk of bias	No serious inconsistency
Vitamin D	6–11 months	Observational	2	62	No serious risk of bias	No serious inconsistency
	12–23 months	Observational	2	62	No serious risk of bias	No serious inconsistency
	≥24 months	Observational	2	62	No serious risk of bias	No serious inconsistency
Calcium	<6 months	Observational	2	224	No serious risk of bias	Serious
	6–11 months	Observational	3	399	No serious risk of bias	No serious inconsistency
	12–23 months	Observational	6	1184	No serious risk of bias	Serious
	≥24 months	Observational	3	606	No serious risk of bias	Serious
Ferritin	<6 months	Observational	4	111	No serious risk of bias	Serious
	6–11 months	Observational	8	559	Serious	No serious inconsistency
	12–23 months	Observational	11	1396	Serious	Serious
	≥24 months	Observational	6	1114	Serious	Serious

TABLE 3 (Continued)

Micronutrient	Postoperative time	Study design	No. of studies	No. of patients	Risk of bias	Inconsistency
Zinc	<6 months	Observational	2	266	Serious	No serious inconsistency
	6–11 months	Observational	6	751	Serious	Serious
	12–23 months	Observational	5	711	Serious	Serious
	≥24 months	Observational	3	579	Serious	No serious inconsistency
Sleeve gastrectomy						
Folate	<6 months	Observational	2	461	No serious risk of bias	No serious inconsistency
	6–11 months	Observational	4	583	No serious risk of bias	No serious inconsistency
	12–23 months	Observational	6	482	No serious risk of bias	Serious
	≥24 months	Observational	2	583	No serious risk of bias	Serious
Vitamin B_{12} (Cobalamin)	<6 months	Observational	2	348	No serious risk of bias	No serious inconsistency
	12–23 months	Observational	2	314	Serious	Serious
Vitamin E	6–11 months	Observational	2	72	No serious risk of bias	Serious
	12–23 months	Observational	2	72	No serious risk of bias	Serious
Vitamin D	12–23 months	Observational	2	118	No serious risk of bias	No serious inconsistency
Calcium	12–23 months	Observational	2	167	No serious risk of bias	No serious inconsistency
	≥24 months	Observational	3	206	No serious risk of bias	No serious inconsistency
Ferritin	<6 months	Observational	2	117	No serious risk of bias	Serious
	6–11 months	Observational	7	543	No serious risk of bias	No serious inconsistency
	12–23 months	Observational	9	545	No serious risk of bias	Serious
	≥24 months	Observational	2	374	No serious risk of bias	No serious inconsistency
Zinc	<6 months	Observational	2	367	Serious	No serious inconsistency
	6–11 months	Observational	4	457	Serious	Serious
	12–23 months	Observational	6	656	Serious	No serious inconsistency
	≥24 months	Observational	2	377	Serious	No serious inconsistency

Abbreviations: NA, not applicable; WMD, weighted mean difference.

TABLE 3 Continued

Micronutrient	Indirectness	Imprecision	Publication bias	Quality of evidence (grade)	WMD (95% CI), I^2, *p*-value	Findings
Roux-en-Y gastric bypass						
Vitamin B_1 (thiamin)	No serious indirectness	Serious	Undetected	Very low due to risk of bias and imprecision	10.57 (−5.55, 26.69) nmol/L, 0%, 0.199	Insignificant change in postoperative vitamin B_1 level.
Folate	No serious indirectness	Serious	Undetected	Very low due to risk of bias and imprecision	4.19 (1.43, 6.95) ng/ml, 83.7%, 0.003	Folate level increased postoperatively in all but 1 study.
	No serious indirectness	No serious imprecision	Undetected	Low due to risk of bias	2.21 (1.90, 2.51) ng/ml, 92.8%, <0.001	Folate level increased postoperatively in all studies.
	No serious indirectness	No serious imprecision	Suspicious	Low due to publication bias	4.02 (3.54, 4.51) ng/ml, 96.9%, <0.001	Folate level increased postoperatively in all studies.
	No serious indirectness	No serious imprecision	Undetected	Moderate	3.28 (2.50, 4.05) ng/ml, 99.4%, <0.001	Folate level increased postoperatively in all studies.
Vitamin B_{12} (cobalamin)	No serious indirectness	No serious imprecision	Suspicious	Very low due to risk of bias and publication bias	277.43 (154.33, 400.53) pg/ml, 68.4%, <0.001	Vitamin B_{12} level increased postoperatively in all studies.
	No serious indirectness	No serious imprecision	Undetected	Low due to risk of bias	272.19 (246.33, 298.05) pg/ml, 96.9%, <0.001	Vitamin B_{12} level increased postoperatively in all studies.
	No serious indirectness	No serious imprecision	Undetected	Moderate	303.82 (258.70, 348.93) pg/ml, 99.3%, <0.001	Vitamin B_{12} level increased postoperatively in all studies.
	No serious indirectness	No serious imprecision	Undetected	Moderate	336.46 (185.18, 487.73) pg/ml, 99.9%, <0.001	Vitamin B_{12} level increased postoperatively in all studies.
Vitamin A	No serious indirectness	No serious imprecision	Undetected	Low due to risk of bias	−7.87 (−12.05, −3.68) μg/dl, 32.2%, <0.001	Vitamin A level decreased postoperatively in all but 1 study.
	No serious indirectness	No serious imprecision	Undetected	Low due to risk of bias	−9.91 (−15.61, −4.21) μg/dl, 77.8%, 0.001	Vitamin A level decreased postoperatively in all but 1 study.
	No serious indirectness	No serious imprecision	Undetected	Moderate	−7.54 (−10.16, −4.92) μg/dl, 0%, <0.001	Vitamin A level decreased postoperatively in all studies.
Vitamin E	No serious indirectness	Serious	Undetected	Low due to imprecision	−0.77 (−1.15, −0.39) μg/ml, 25.9%, <0.001	Vitamin E level decreased postoperatively in all but 1 study.
	No serious indirectness	Serious	Undetected	Very low due to inconsistency and imprecision	−0.21 (−0.91, 0.50) μg/ml, 85.9%, 0.569	Insignificant change in postoperative vitamin E level.
	No serious indirectness	No serious imprecision	Undetected	Low due to inconsistency	−2.41 (−2.84, −1.98) μg/ml, 75.3%, <0.001	Vitamin E level decreased postoperatively, but two studies found an increase.
	No serious indirectness	No serious imprecision	Undetected	Moderate	−2.35 (−3.65, −1.05) μg/ml, 91.3%, <0.001	Vitamin E level decreased postoperatively in all studies.

TABLE 3 (Continued)

Micronutrient	Indirectness	Imprecision	Publication bias	Quality of evidence (grade)	WMD (95% CI), I^2, *p*-value	Findings
Vitamin D	No serious indirectness	Serious	Undetected	Low due to imprecision	22.71 (15.87, 29.56) ng/ml, 17.7%, <0.001	Vitamin D level increased postoperatively in all studies.
	No serious indirectness	Serious	Undetected	Low due to imprecision	16.22 (−1.93, 34.36) ng/ml, 88.9%, 0.08	Insignificant change in postoperative vitamin D level.
	No serious indirectness	Serious	Undetected	Low due to imprecision	14.78 (−4.78, 34.34) ng/ml, 92.2%, 0.139	Insignificant change in postoperative vitamin D level.
Calcium	No serious indirectness	Serious	Undetected	Very low due to inconsistency and imprecision	0.01 (−0.34, 0.36) mg/dl, 82.8%, 0.970	Inconsistent (1 study found a decrease in calcium level; 1 study found an increase)
	No serious indirectness	Serious	Suspicious	Very low due to imprecision and publication bias	−0.02 (−0.09, 0.06) mg/dl, 21.4%, 0.695	Insignificant change in postoperative calcium level in all but 1 study.
	No serious indirectness	Serious	Suspicious	Very low due to inconsistency, imprecision, and publication bias	−0.02 (−0.10, 0.06) mg/dl, 82.4%, 0.597	Insignificant change in postoperative calcium level.
	No serious indirectness	Serious	Undetected	Very low due to inconsistency and imprecision	0.02 (−0.13, 0.16) mg/dl, 88.3%, 0.825	Insignificant change in postoperative calcium level.
Ferritin	No serious indirectness	Serious	Undetected	Very low due to inconsistency and imprecision	31.97 (−10.49, 74.43) μg/L, 94.1%, 0.140	Insignificant change in postoperative ferritin level.
	No serious indirectness	No serious imprecision	Undetected	Low due to risk of bias	−16.42 (−18.29, −14.56) μg/L, 0%, <0.001	Ferritin level decreased postoperatively.
	No serious indirectness	Serious	Undetected	Very low due to risk of bias, inconsistency, and imprecision	−14.20 (−32.40, 4.00) μg/L, 88.6%, 0.126	Insignificant change in postoperative ferritin level.
	No serious indirectness	Serious	Undetected	Very low due to risk of bias, inconsistency, and imprecision	−5.64 (−30.88, 19.61) μg/L, 76.4%, 0.662	Insignificant change in postoperative ferritin level.
Zinc	No serious indirectness	Serious	Undetected	Very low due to risk of bias and imprecision	−6.92 (−11.53, −2.32) μg/dl, 0%, 0.003	Zinc level decreased postoperatively.
	No serious indirectness	Serious	Suspicious	Very low due to risk of bias, inconsistency, imprecision, and publication bias	−0.67 (−5.67, 4.34) μg/dl, 86.6%, 0.793	Insignificant change in postoperative zinc level.
	No serious indirectness	Serious	Undetected	Very low due to risk of bias, inconsistency, and imprecision	−3.02 (−10.40, 4.37) μg/dl, 93.0%, 0.423	Insignificant change in postoperative zinc level.
	No serious indirectness	No serious imprecision	Undetected	Low due to risk of bias	−8.81 (−12.61, −5.00) μg/dl, 28.2%, <0.001	Zinc level decreased postoperatively in all but 1 study.

(Continues)

TABLE 3 (Continued)

Micronutrient	Indirectness	Imprecision	Publication bias	Quality of evidence (grade)	WMD (95% CI), I^2, *p*-value	Findings
Sleeve gastrectomy						
Folate	No serious indirectness	No serious imprecision	Undetected	Moderate	1.42 (0.87, 1.96) ng/ml, 0%, <0.001	Folate level increased postoperatively.
	No serious indirectness	No serious imprecision	Undetected	Moderate	2.78 (0.22, 5.33) ng/ml, 89.6%, 0.033	Folate level increased postoperatively in all but 1 study.
	No serious indirectness	Serious	Suspicious	Very low due to inconsistency, imprecision, and publication bias	5.06 (−0.97, 11.10) ng/ml, 98.7%, 0.100	Insignificant change in postoperative folate level.
	No serious indirectness	Serious	Undetected	Very low due to inconsistency and imprecision	2.47 (−0.37, 5.32) ng/ml, 86.3%, 0.088	Insignificant change in postoperative folate level.
Vitamin B_{12} (Cobalamin)	No serious indirectness	No serious imprecision	Undetected	Moderate	128.37 (89.36, 167.37) pg/ml, 0%, <0.001	Vitamin B_{12} level increased postoperatively.
	No serious indirectness	Serious	Undetected	Very low due to risk of bias, inconsistency, and imprecision	61.18 (−67.92, 190.27) pg/ml, 93.0%, 0.353	Insignificant change in postoperative vitamin B_{12} level.
Vitamin E	No serious indirectness	Serious	Undetected	Very low due to inconsistency and imprecision	−0.44 (−1.80, 0.93) μg/ml, 45.9%, 0.531	Insignificant change in postoperative vitamin E level.
	No serious indirectness	Serious	Undetected	Very low due to inconsistency and imprecision	−0.20 (−2.10, 1.71) μg/ml, 65.5%, 0.839	Insignificant change in postoperative vitamin E level.
Vitamin D	No serious indirectness	Serious	Undetected	Low due to imprecision	6.03 (4.18, 7.89) ng/ml, 0.0%, <0.001	Vitamin D level increased postoperatively in all studies.
Calcium	No serious indirectness	Serious	Undetected	Low due to imprecision	0.17 (0.07, 0.28) mg/dl, 0.0%, 0.001	Calcium level increased postoperatively.
	No serious indirectness	Serious	Undetected	Low due to imprecision	0.07 (−0.05, 0.19) mg/dl, 40.7%, 0.256	Insignificant change in postoperative calcium level.
Ferritin	No serious indirectness	Serious	Undetected	Very low due to inconsistency and imprecision	85.48 (−10.21, 181.17) μg/L, 81.7%, 0.080	Insignificant change in postoperative ferritin level.
	No serious indirectness	Serious	Undetected	Low due to imprecision	−1.32 (−3.52, 0.87) μg/L, 0%, 0.238	Insignificant change in postoperative ferritin level in all studies.
	No serious indirectness	Serious	Undetected	Very low due to inconsistency and imprecision	−7.29 (−19.52, 4.94) μg/L, 52.0%, 0.243	Insignificant change in postoperative ferritin level.
	No serious indirectness	No serious imprecision	Undetected	Moderate	−54.93 (−77.19, −32.67) μg/L, 0.0%, <0.001	Ferritin level decreased postoperatively in all studies.

TABLE 3 (Continued)

Micronutrient	Indirectness	Imprecision	Publication bias	Quality of evidence (grade)	WMD (95% CI), I^2, *p*-value	Findings
Zinc	No serious indirectness	Serious	Undetected	Very low due to risk of bias and imprecision	−1.01 (−3.72, 1.70) μg/dl, 0%, 0.465	Insignificant change in postoperative zinc level in all studies.
	No serious indirectness	No serious imprecision	Undetected	Very low due to risk of bias and inconsistency	−3.61 (−6.89, −0.33) μg/dl, 66.9%, 0.031	Zinc level decreased postoperatively, but two studies found no significant change.
	No serious indirectness	Serious	Undetected	Very low due to risk of bias and imprecision	−3.18 (−6.53, 0.17), 63.4%, 0.063	Insignificant change in postoperative zinc level in all but 1 study.
	No serious indirectness	Serious	Undetected	Very low due to risk of bias and imprecision	3.74 (−0.03, 7.51) μg/dl, 0%, 0.052	Insignificant change in postoperative zinc level.

Abbreviations: NA, not applicable; WMD, weighted mean difference.

approach to determining postoperative micronutrient status can identify an optimal timepoint for monitoring when micronutrient levels significantly decrease after bariatric surgery. A significant decrease in micronutrients at each follow-up interval, even on supplementation per guidelines, can be considered to establish a micronutrient monitoring schedule after bariatric surgery.

4.1 | Poor adherence to micronutrient supplementation guidelines

The non-adherence to supplementation of certain micronutrients was considerable (Figure 2). Although daily folate and vitamin E requirements are achieved by common commercial multivitamin supplements, an intensified multivitamin or additional tablet is needed to ensure sufficient micronutrient supplementation of calcium, iron, zinc, vitamin B_{12}, and vitamin D. The development of multivitamin supplements containing sufficient amounts of each micronutrient per guidelines would improve clinician and patient adherence to micronutrient supplementation recommendations.

4.2 | Water-soluble vitamins (vitamin B_1, folate, and vitamin B_{12})

Vitamin B_1 deficiency is associated with central nervous system dysfunction such as Wernicke encephalopathy, which can present with mental status alterations, ataxia, and ocular abnormalities; there have been various reports of early-onset Wernicke encephalopathy after bariatric surgery[111,112] and considerable incidence of post-bariatric vitamin B_1 deficiency.[113,114] Postoperative vitamin B_1 level changes cannot be concluded due to a lack of studies evaluating postoperative vitamin B_1 status with sufficient supplementation (Table 4).

Symptoms of folate deficiency range from weakness and anorexia to macrocytic anemia and increased risk of fetal neural tube defects.[115] Post-bariatric folate deficiency is reportedly related to decreased dietary intake and insufficient supplementation,[113,116] and the effectiveness of its supplementation for preventing deficiency has been previously studied.[20,38,56] These findings are consistent with our observation of increased folate levels after RYGB and SG (Figure 3B, Table 4), implying a low risk of folate deficiency with sufficient supplementation. One possible explanation for the increase in folate level after bariatric surgery, especially RYGB, is small intestine bacterial overgrowth, commonly occurring after bariatric surgery, which is related to bloating and abdominal pain and associated with an increase in folate synthesis by intestinal bacteria.[117–119]

Vitamin B_{12} is responsible for erythropoiesis and neuronal function, and its deficiency can result in pernicious anemia and neurologic complications, including peripheral neuropathy, ataxia, and subacute combined degeneration.[3,120] High-dose oral or intramuscular administration of vitamin B_{12} after bariatric surgery is considered reasonable because the low availability of intrinsic factors

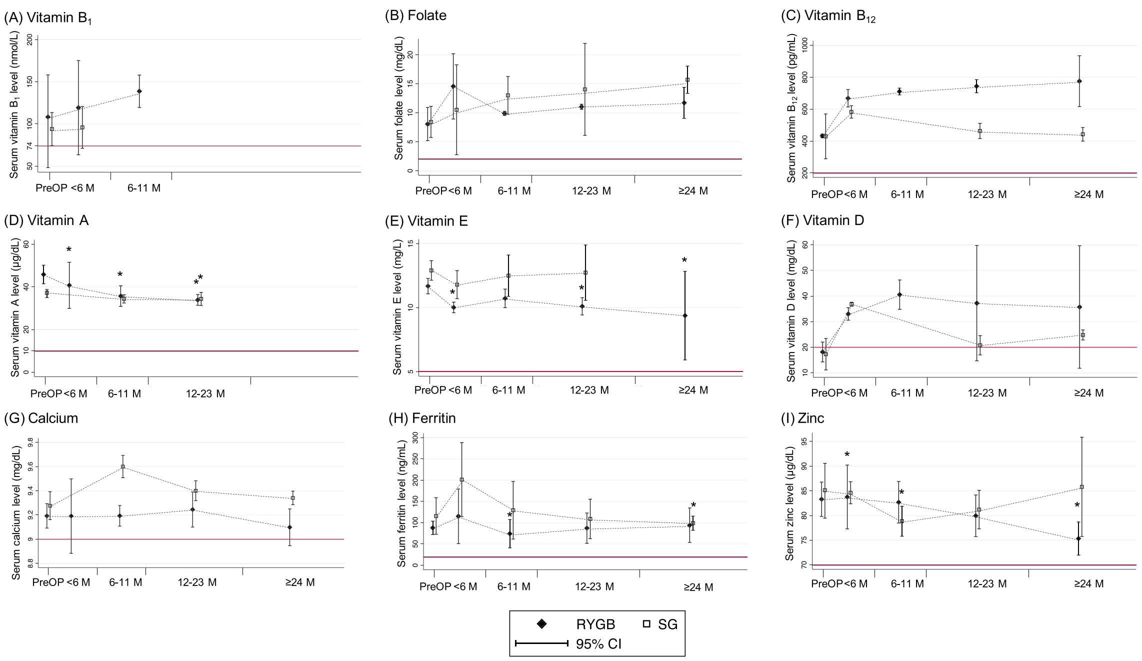

FIGURE 3 Longitudinal changes in pooled serum micronutrient levels after RYGB and SG. Serum micronutrient concentrations at each follow-up interval were pooled using random-effect models according to the surgical method (RYGB or SG) and presented with 95% confidence intervals. The lower limit of the reference range[10] of each micronutrient is presented in the graph. Asterisk (*) indicates a significant decrease in micronutrient level from baseline, based on WMD values (*P* < 0.05). RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; WMD, weighted mean difference

predominantly contributes to its postoperative deficiency, and a small portion of orally administered vitamin B_{12} is independent of intrinsic factor.[121,122] Our findings revealed that vitamin B_{12} levels did not decrease after RYGB in every follow-up interval with supplementation per the guidelines. However, only a few studies (eight out of 42 studies) reporting postoperative vitamin B_{12} levels adhered to the current guidelines, especially after SG (Figure 2); findings from synthesizing these studies yielded very low and low levels of evidence for <6 and 6–11 months after RYGB, respectively, due to the risk of bias (Tables 3 and 4).

4.3 | Fat-soluble vitamins (vitamins A, E, and D)

Vitamin A deficiency is associated with ocular complications, including nyctalopia and xerosis.[123] Post-bariatric deficiencies of fat-soluble vitamins are often explained by alterations in bile acid circulation and delays in fat absorption, especially after RYGB.[115] The British guideline recommends vitamin A level measurement for patients with deficiency-related symptoms,[13] and the US guideline indicates that vitamin A screening every 6–12 months is optional after RYGB.[10] Significant decreases in vitamin A levels at <6, 6–11, and 12–23 months after RYGB (low to moderate level of evidence, Figure 3, Table 4) imply the need to early monitor the vitamin A levels after RYGB. Studies investigating changes in vitamin A levels after RYGB in the long term (≥24 months) and after SG were scarce.

Vitamin E deficiency is associated with neurological symptoms, including hyporeflexia and gait disturbance, and hemolytic anemia. Micronutrient sufficiency of vitamin E following bariatric surgery is rarely discussed,[124] and only three out of 11 studies administered supplementation per guidelines (Figure 2). The current guidelines do not recommend regular monitoring of vitamin E after bariatric surgery.[10,13] However, vitamin E significantly decreased at ≥24 months after RYGB with sufficient supplementation (moderate level of evidence) and at <6 months and 12–23 months (low level of evidence, Figure 3, Table 4). Therefore, evaluation of the risk of vitamin E deficiency (e.g., presence of relevant symptoms or preoperative vitamin E deficiency) and long-term monitoring of vitamin E immediately after RYGB are encouraged. Vitamin E level changes after SG with supplementation per guidelines have not been sufficiently investigated yet.

Vitamin D has attracted the attention of health professionals because of its beneficial role not only in bone health but also in metabolic syndrome, cardiovascular disease, and cancer[125,126]; and a high incidence (up to 90%) of preoperative vitamin D deficiency has been reported[127] in bariatric patients. Pooled mean preoperative vitamin D levels of included studies were 18.14 (95% CI, 14.3–22.0) and 17.3 (95% CI, 11.1–23.4) ng/ml for patients undergoing RYGB and SG, respectively, indicating vitamin D deficiency (Figure 3). Considering the distinctively high prevalence of preoperative vitamin D deficiency, perioperative vitamin D supplementation and monitoring need to be emphasized. However, only six of 52 studies satisfied postoperative

TABLE 4 Summary of micronutrient status after bariatric surgery with supplementation per guidelines

	Roux-en-Y gastric bypass				Sleeve gastrectomy			
	<6 months	6–11 months	12–23 months	≥24 months	<6 months	6–11 months	12–23 months	≥24 months
Vitamin B_1 (thiamin)		X	X	X	X	X	X	X
Folate	Increased[a]	Increased[a]	Increased[a]	Increased[b]	Increased[b]	Increased[b]		
Vitamin B_{12} (cobalamin)	Increased[a]	Increased[a]	Increased[b]	Increased[b]	Increased[b]	X		X
Vitamin A	Decreased[a]	Decreased[a]	Decreased[b]	X	X	X	X	X
Vitamin E	Decreased[a]		Decreased[a]	Decreased[b]	X			X
Vitamin D	X	Increased[a]			X	X	Increased[a]	X
Calcium					X	X	Increased[a]	
Ferritin		Decreased[a]						Decreased[b]
Zinc	Decreased[a]			Decreased[a]		Decreased[a]		

Note: Significant increase or decrease in micronutrient levels at each follow-up interval compared with baseline is indicated in each cell. Follow-up intervals that are investigated in <2 studies are marked with crosses.

Abbreviation: NR, not reported.

[a]Level of evidence is very low to low.

[b]Level of evidence is moderate.

vitamin D supplementation per guidelines, and follow-up intervals with significant vitamin D level changes could not be determined.

4.4 | Minerals (calcium, iron, and zinc)

Calcium absorption is dependent on vitamin D, whereas calcium metabolism is associated with parathyroid hormone and albumin, and its clinical significance lies in bone metabolism. Bariatric surgery is reportedly related to bone loss after bariatric surgery,[128,129] and bone mineral density monitoring is recommended. The relatively consistent serum calcium levels after RYGB observed in this study can be explained as a consequence of compensatory bone loss with secondary hyperparathyroidism for decreased intestinal calcium absorption.[130] This implies that routine calcium monitoring after RYGB is unnecessary, whereas postoperative monitoring of bone mineral density is recommended. The low level of evidence might be due to the high inconsistency among studies due to the inconsistent supplementation dose of vitamin D, which significantly interacts with calcium (Table 3). There is a lack of studies investigating changes in calcium levels at <12 months after SG with supplementation per guidelines (Table 4).

Iron deficiency is associated with metabolic complications, including fatigue, glossitis, and microcytic anemia.[131] The incidence of iron deficiency anemia after RYGB is known to be higher than that after SG,[132] and the guidelines recommend regular iron monitoring after RYGB, although there is inconsistency between guidelines for iron monitoring after SG.[10,13] As ferritin significantly decreased at 6–11 months after RYGB (low level of evidence) and ≥24 months after SG (moderate level of evidence, Figure 3, Table 4) with supplementation per guidelines, postoperative iron monitoring is recommended, especially at follow-up intervals with a significant decrease in ferritin levels observed. Serious inconsistency among the studies might be explained by the different inflammatory states in their enrolled patients, as ferritin is not only a marker of iron storage but also an acute-phase protein that is altered by inflammation.[34]

The body does not store zinc; its deficiency may lead to severe consequences, such as skin eruption, hypoalbuminemia, and glossitis.[115] One retrospective study showed that the incidence of zinc deficiency was 40.7% and 18.8% at 1 year after RYGB and SG, respectively,[108] and postoperative decreases in serum zinc levels have been continuously reported in recent studies.[29,31,98,133] As zinc levels significantly decreased after RYGB (at <6 months, very low level of evidence; at ≥24 months, low level of evidence) and SG (at 6–11 months, very low level of evidence) despite supplementation per guidelines (Figure 3, Table 4), postoperative zinc level monitoring, especially at follow-up intervals with a significant decrease in zinc levels observed, is encouraged. As the quality of evidence was very low to low, mainly due to the risk of bias, high-quality studies need to confirm the zinc level changes after bariatric surgery with sufficient supplementation.

4.5 | Limitations and conclusion

This study had several limitations. First, most of the included studies were observational in nature, which restricts their estimation capability despite thorough quality assessments. Second, the results might provide limited information as a single index; Serum micronutrient levels were used to evaluate the need for postoperative nutritional monitoring for data synthesis. For instance, although comprehensive indices that reflect iron metabolism, such as iron levels, total iron-binding capacity, and transferrin saturation, are needed to diagnose iron deficiency, we only used serum ferritin levels. Similarly, parathyroid hormone, phosphorus, and vitamin D levels need to be considered, in addition to serum calcium levels, when evaluating calcium status. Third, when evaluating the nutritional supplementation in each study, interactions between micronutrients, such as the effects of iron supplementation on zinc concentration and the interplay of vitamin D, calcium, and phosphorus were not considered, as each micronutrient was analyzed separately. Fourth, patients' compliance with the recommended nutritional supplementation and effects of inflammation on micronutrient levels could not be considered, as only a few studies included relevant information. Fifth, the effects of rescue therapy in each study for patients with deficiencies could have influenced the assessed postoperative micronutrient status. Sixth, diet modification after bariatric surgery was not considered because only a few studies provided relevant information, although micronutrient absorption is affected by concomitant food intake (e.g., alteration in fat-soluble vitamin absorption according to fat intake). Seventh, small intestine bacterial overgrowth induced by bariatric surgery[117,118] is a potential confounder when evaluating micronutrient status, as it alters the absorption or synthesis of micronutrients.[119,134,135] However, there is a lack of studies investigating the effects of SIBO on micronutrient status in patients undergoing bariatric surgery by far, and further studies are required. Eighth, there was considerable heterogeneity despite our careful data synthesis. The results require interpretation that involves interindividual variations, including surgical effects, which may affect the micronutrient status.

In conclusion, we presented comprehensive micronutrient status in bariatric surgery patients receiving supplementation per guideline. Significant decreases in micronutrient levels were observed in 11 postoperative time intervals despite supplementation per guidelines, including three postoperative time intervals with moderate level of evidence (vitamin A at 12–23 months and vitamin E at ≥24 months after RYGB and ferritin at ≥24 months after SG). Our findings provide insights into optimal micronutrient monitoring timepoints for bariatric surgery patients receiving supplementation per guidelines. We also examined low adherence to micronutrient supplementation guidelines and identified the paucity of studies on micronutrient status after SG.

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CONFLICT OF INTEREST

No conflict of interest statement' in the first proofs.

AUTHOR CONTRIBUTIONS

J. H. and Y. K. collected the data and wrote the original draft. J.-W. K., D. K., and J. H. conducted the data curation and statistical analyses. S.-H. P. and C. M. L. investigated and critically revised the manuscript. S. P. conceptualized and supervised this study.

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SUPPORTING INFORMATION

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

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