The Influence of Bariatric (Metabolic) Surgery on Blood Polyunsaturated Fatty Acids: A Systematic Review

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Abbreviations used: AA, arachidonic acid; ALA, alpha-linolenic acid; BMI, body mass index; BPD/DS, biliopancreatic diversion/duodenal switch; CE, cholesteryl ester; DHA, docosahexaenoic acid; DJBL, duodenal-jejunal bypass liner; EFA, essential fatty acid; EPA, eicosapentaenoic acid; FA, fatty acid; LA, linoleic acid; LAGB, laparoscopic adjustable gastric banding; LSG, long sleeve gastrectomy; OAGB, one anastomosis gastric bypass; PL, phospholipid; PUFA, polyunsaturated fatty acid; RYGB, Roux-en-Y gastric bypass; TG, triglyceride.

Abstract

Background and Aims: Bariatric, also termed metabolic, surgery is an increasingly common treatment for severe and complex obesity. It decreases macronutrient intake, influences nutrient absorption and modifies gastrointestinal physiology with the aim of reducing adiposity, improving metabolism and reducing disease risk. Bariatric surgery has been shown to result in micronutrient deficiencies. Whether it results in deficiencies of essential fatty acids (EFAs) and their bioactive polyunsaturated fatty acid (PUFA) derivatives is not clear. The aim of this systematic review is to identify whether there are effects of bariatric surgery on the blood levels of EFAs and other PUFAs.

Methods: A database search was conducted up to November 2020 using Medline, Embase and Cinahl databases, using relevant search terms identified by a PICO protocol. Only human studies reporting on PUFAs in a blood pool, published in the English language and available in full text were included. The Cochrane tool for assessing risk of bias was used and data were extracted.

Results: Fifteen papers from fourteen studies with relevant data were identified for inclusion. Studies differed according to surgical intervention, duration, measured timepoints, sample size and PUFAs reported. Both increases and decreases in selected PUFAs were reported in different studies. For the EFAs linoleic acid and α-linolenic acid and for the longer-chain omega-3 PUFA eicosapentaenoic acid, bariatric surgery is associated with a transient decline in status (to about 6 months post-surgery) with a later return to pre-surgery levels. All studies had some risk of bias and most studies were of small size.

Conclusion: There is a decrease in blood levels of both EFAs and of eicosapentaenoic acid in the months following bariatric surgery. This may partly counter the desired effects of the surgery on blood lipids, insulin sensitivity and inflammation. Nutritional strategies (e.g. use of modified formulas or of supplements) may be able to correct the decrease in those PUFAs. Nevertheless, the observed decrease in PUFAs is transient.

Key words: Bariatric surgery; Essential fatty acid; Polyunsaturated fatty acid; Obesity

Introduction

The prevalence of obesity, including severe obesity, is increasing in many countries [1,2]. Obesity increases risk of chronic conditions such as type 2 diabetes, cardiovascular disease, fatty liver disease and some cancers [3] and has adverse psychological, and social impacts [4,5]. Treating existing obesity, especially severe and complex obesity is critical for improving prognosis and quality of life. Bariatric surgery is currently the most effective treatment for severe and complex obesity [6]. The original intentions of bariatric surgery were to reduce intake of food through physically restricting stomach volume and/or to reduce digestive and absorptive capacity to limit the availability of macronutrients (fat, carbohydrate, protein and alcohol) from the diet, thus inducing weight loss [7-9]. These approaches are referred to as being restrictive and malabsorptive, respectively. However, beyond these physical impacts there is a strong physiological impact of bariatric surgery. For example, restriction of stomach size alters secretion of gastrointestinal hormones, while malabsorptive procedures alter aspects of gastrointestinal physiology including release of incretins affecting appetite, satiety, gut motility and metabolism; bile acid signalling; and the gut microbiota [10-14]. As a result of the combination of effects on macronutrient availability and gastrointestinal physiology, bariatric surgery is able to reduce adiposity, with accompanied weight loss, and to increase insulin sensitivity, with accompanied metabolic improvements. Together, these result in decreased risk of several conditions including diabetes, cardiovascular diseases, obstructive sleep apnoea, infertility, and some types of cancer, and in decreased use of medications [15-18]. In recognition that bariatric surgery is more than being simply restrictive and malabsorptive and goes beyond weight loss, it has been termed metabolic surgery [19]. Bariatric surgery has become a common procedure: the International Federation for the Surgery of Obesity and Metabolic Disorders Worldwide Survey of 2018 reported 634,897 bariatric operations were performed globally in 2016 [20].

Types of bariatric surgery procedures include laparoscopic adjustable gastric banding (LAGB), Roux-en-Y gastric bypass (RYGB), one anastomosis gastric bypass (OAGB) and

duodenal switch (DS) which is involved in biliopancreatic diversion (BPD/DS); these are further described elsewhere [19,21]. RYGB has long been considered the gold standard for surgical treatment of morbid obesity [22] and has been the most common form of bariatric surgery in Western Europe and the Americas. However, LSG has become more prevalent over the last 10 years globally and is now the most commonly performed procedure worldwide [23]. An alternative non-surgical endoscopic approach to reduce macronutrient absorption and induce similar gastrointestinal and systemic physiological changes as other foregut exclusion procedures, is the use of a duodenal-jejunal bypass liner (DJBL or Endobarrier™), an implanted sleeve that forms a barrier between the proximal 60 cm of the small intestinal lumen and wall; DJBL mimics some of the effects of RYGB.

Unsurprisingly, bariatric surgery has effects on nutrient status. For example, protein deficiency can be a common and sometimes severe complication associated with bariatric surgery, especially malabsorptive procedures [24,25]. It usually occurs in the first months after these procedures and is the result of the combination of the reduced intake [26] and digestion/absorption [27,28] of protein and the acquisition of intolerance to protein-rich foods after surgery [29]. Hence, protein requirements are increased, especially after malabsorptive surgery [24,25]. Micronutrient deficiencies (e.g. calcium, iron, and vitamins B12 and D) are also common after bariatric surgery (see [24,25] for references), particularly malabsorptive procedures [30]. Hence, micronutrient supplements are advised post-bariatric surgery [31]. Reduced fat intake and fat malabsorption are aims of bariatric surgery, and certainly occur [32]. However, the 2013 American guidelines for support of the bariatric surgery patient state that there is insufficient evidence to support routine screening for essential fatty acid (EFA) deficiencies [31].

There are two EFAs: linoleic acid (LA), an omega-6 polyunsaturated FA (PUFA), and alpha-linolenic acid (ALA), an omega-3 PUFA. LA lowers blood total and LDL-cholesterol concentrations [33] and higher blood LA has been associated with lower incidence of type-2 diabetes [34] and lower coronary heart disease mortality [35]. ALA is also cholesterol lowering [36] and a recent meta-analysis reports that higher blood levels of ALA are associated with

lower risk of mortality from coronary heart disease [37]. In addition to health benefit roles in their own right, LA and ALA are precursors for synthesis of other bioactive PUFAs. LA is converted to arachidonic acid (AA), which has structural roles in the brain and supports cognition [38] and via its eicosanoid derivatives (prostaglandins, thromboxanes and leukotrienes) regulates inflammation, the immune system, bone turnover and platelet aggregation [39,40]. ALA is converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have multiple physiological roles resulting in significant health benefits [41-44]. These have been most clearly demonstrated through multiple cohort trials linking higher blood plasma/serum, blood cell and tissue status of EPA and DHA to lower risk of coronary heart disease mortality [45-47]. EPA and DHA are also anti-inflammatory [48] and give rise to lipid mediators involved in resolution of inflammation [49]. EPA and DHA also appear to reduce skeletal muscle protein breakdown, perhaps through reducing inflammation, and to promote protein synthesis as reviewed elsewhere [50]. Low levels of these various PUFAs in the blood for prolonged periods would limit supply to cells and tissues and this could oppose some of the desired actions of the surgery, for example on blood lipids, inflammation and risk of diabetes and cardiovascular disease. A lack of EFAs in the diet results in the synthesis of mead acid starting with oleic acid as the substrate a pathway that uses the enzymes that would otherwise be metabolising LA and ALA; therefore, the appearance of mead acid is used as an indicator of EFA deficiency.

As well as being synthesised from their precursor EFAs, AA, EPA and DHA can be obtained directly from diet. Bariatric surgery could reduce availability of LA, ALA, AA, EPA and DHA from the diet due to altered intake or decreased absorption after surgery, in part as a result of an energy (and fat)-restricted diet. This decreased availability could result in reduced body status of these important FAs. This could be an adverse consequence of bariatric surgery, akin to the recognised effects on micronutrients and protein (see earlier), that might act to counter some of the intended benefits of the surgery. However, whether bariatric surgery does adversely influence blood levels of PUFAs is not clear, as mentioned in the 2013 American guidelines [32]. The aim of this systematic review is to identify whether bariatric surgery alters blood levels of EFAs and their PUFA derivatives.

Methods

Literature Search

The literature search was conducted using Ovid MEDLINE without Revisions (1996 to 2020), Ovid EMBASE CLASSIC + EMBASE (1947 to 2020) and Ebsco CINAHL (Plus with Free Text). A first search was conducted on 26 September 2020 and this was repeated on 13 November 2020.

Search Methodology

The PICO (Patient or population, Intervention, Comparison and Outcome) protocol was utilised to identify search terms. The patient group was those with obesity/overweight; the intervention was bariatric surgery; the comparison was either between groups receiving different treatments (e.g. different types of bariatric surgery or bariatric surgery vs no surgery) or between prior to and following bariatric surgery; the outcome measure was one or more PUFAs measured in a blood pool. Synonyms for each category were then generated, which included alternative weight loss surgeries such as Roux-en-Y, gastric sleeve and bypass; alternate words for PUFAs included omega-3, omega-6, essential FA, alpha-linolenic and linoleic acid and their derivatives. Mead acid was also included in the search terms. Abbreviations and acronyms were also searched for, with consideration to UK and US spelling differences. The search incorporated both free text and controlled vocabulary subject headings, known as MeSH terms. Extending results to find those with significant mention of MeSH terms allowed sourcing of greater content while increasing search sensitivity. In addition, proximity commands and truncation were utilised, such as ‘gastric band*’ to account for suffix variations. Individual searches were combined simultaneously using Boolean AND/OR coupling. Limits of Full Text, Human and English Language were applied after the final combined search to complete the database searching. Final search methodologies for the two platforms are included as Supplementary material.

Article Selection

Studies were selected on the basis of the following inclusion criteria: conducted in humans, published in the English language, full text available, and reporting of one or more FAs of interest in a blood pool. No parameter of age of participants nor years since publication was set in order to identify all relevant studies. Exclusion criteria were defined as animal studies, studies solely reporting on short chain FAs, and any types of literature other than empirical scholarly articles, such as conference abstracts and case study reports. Articles that were identified to be relevant for the purposes of the review but not having an accessible full text were excluded. Identified articles underwent manual screening of title, abstract and full text (where necessary), to ensure suitability before exporting into an EndNote library, at which point duplicates were removed. A-LM was responsible for filtering articles for inclusion; A-LM and PCC worked together in the final selection of articles suitable for inclusion.

Data Extraction

Descriptive and analytical data were extracted from articles that fully met the prespecified criteria. A-LM was responsible for data extraction, which was done in discussion with PCC. Descriptive data encompassed study characteristics (both design and methods) and participants' characteristics. Information on study characteristics included: study design, inclusion and exclusion criteria, type of bariatric surgery intervention or comparator (where there was more than one surgical group or control), number of participants, type of FA measured and from which blood pool, timepoints of FA sampling and completeness of follow up. Information on participants' characteristics included: age, sex, comorbidity and dietary information. Analytical data summarised key numerical findings from study results, including blood PUFA levels and method used for expressing these and all statistically significant differences.

Bias and Quality Assessment

Minimisation of selection bias within the review itself was achieved by using a comprehensive search strategy across multiple electronic databases. Identified articles were assessed for bias

in parallel to the data extraction phase. The bias assessment strategy was adapted from the revised Cochrane risk of bias tool for randomised trials template [51]. Some aspects of this tool were not applicable in this context due to the non-randomised nature of many of the studies in this review; focus was honed toward representativeness of participants to the greater patient population and complete, or otherwise justified, follow-up of participants. Originality, clarity of study design, and statistical aspects of methodologic quality were also considered [52]. A-LM conducted the bias and quality assessments in discussion with PCC. This systematic review was not registered as it was performed for educational purposes and a formal protocol was not prepared.

Results

Article Identification and selection

The database search yielded a total of 1515 articles (Figure 1); 254 articles were discarded after applying exclusion criteria and limits, resulting in 1261 articles. A further 375 articles were removed by EndNote deduplication. The remaining 886 articles were manually screened for their suitability for inclusion this review, resulting in twenty-three articles (Figure 1) [53-75]. Out of these twenty-three articles, ten were identified to be relevant but did not report the data required (i.e. the authors mentioned fatty acid measurements, but the article did not show the data) [53-62]. Authors of these ten articles were contacted by email and data were provided for two of them [61,62]. Other authors did not reply or could not provide the data required and so these eight articles were excluded at this stage [53-60]. Thus, fifteen articles, relevant and fitting all criteria, were included in the systematic review (Figure 1). Of these, two articles [61,74] report data from the same study; these were FA data at different time points after surgery. Thus, the fifteen included articles represent fourteen studies.

Characteristics of included articles

Study Design

All studies were prospective cohort and observational (see Table 1). One study was part of a larger cohort study [71], another was a sub-study of a multicentre, non-blinded randomised controlled trial [75] and another reported on patients primarily involved in another randomised controlled trial [72].

Data frequency & intervals

All except two articles [65,68] reported FA levels with a pre-surgery baseline, which is specified in each case, between 4 weeks [73] to 1 day [64] prior to surgery; this timepoint varied among studies (see Table 2). Of the two articles omitting pre-surgery data, one reported only a generalised decrease in all PUFAs based on metabolite profiling using gas chromatography coupled to mass spectrometry [65] and one lacked pre-surgery data for the 3 month post-LSG surgery group, which served as a comparator for an investigational arm of the study [68]. As well as reporting immediate pre-surgery baseline data, one article additionally reported data at 3 months prior to surgery [67].

Length of observation (i.e. follow-up) varied among studies, ranging from 2 days (1 day pre- and 1 day post-surgery) [64] to an 18 month follow-up [73]. Seven articles reported data from two timepoints; five articles give three timepoints; two articles give four or more timepoints; one gives data solely at three months post-surgery [68]. The most commonly reported timepoints aside from pre-surgery were at six months (five articles) and twelve months (seven articles) post-surgery.

Surgical Intervention

A variety of bariatric surgeries were studied. These were BPD/DS, RYGB, LAGB, LSG and OAGB; in addition, one study of DJBL was included (see Table 2). Overall, the most commonly studied surgery was RYGB (seven articles), followed by LSG (five articles) and LAGB (two articles); OAGB, DJBL and BPD/DS were each studied once. Three articles compared the effect of two bariatric surgery procedures [66,68,73].

Participants' characteristics

Study size ranged from 10 [64,65] to 100 [72] patients (see Table 2). Enrolled participants were mainly female (Table 3), reflecting the greater proportion of females in the study populations; sex was not specified in 2 articles [65,67],. Most studied patients of a comparable age, with mean age ranging 36.6-51.6 years for surgery groups (Table 3), albeit with variable standard deviations. Two articles did not give the age of participants [65,67] and one documented ≥18 years [73].

Study bias & quality

Findings from the bias and quality assessment analysis are summarised in Table 4. The traffic light system indicates good (green), acceptable (amber) and poor (red) quality, respectively, which was determined based on the published information available in each article. Overall, the articles demonstrate ranging bias and methodologic quality. All articles except two had no element of randomisation; only one was a randomised controlled trial (RCT) [75], comparing DJBL with best medical therapy. Participant characteristics were mostly well described and reflective of the wider obese population, apart from two studies excluding participants based on endocrine, cardiovascular or pulmonary disease [63,64], two with mental health-related exclusion criteria [67,68] and two excluding those in relation to diabetes [72,73].

Performance and detection bias were common in all studies. Attrition and reporting bias was low generally, although in several articles full explanation for loss of follow-up [67,68,72,73,75] or of particular PUFA data [62,64,65,71-73] was omitted. Studies all had a novel contribution and methods were clearly described, except for one where time point of sampling was not stated [64] and this impeded its full use in this review. Four studies were of acceptable cohort size [61,69,72,75], although most were of small size and none referred to using a power calculation with respect to PUFA outcomes.

PUFAs

FAs reported & their units

Twelve articles reported on LA; eleven on ALA; all fifteen on AA; thirteen on EPA and DHA; three on total n-3 and n-6 PUFAs; and one on total PUFAs (see Table 5 for data on all PUFAs). Eight articles reported FA absolute concentrations (e.g. mg/L). Five articles reported FAs as percentages of total fatty acids (e.g. mol% or weight%). Out of these, one article presented both mol% and mg/L values [69]. One article reported relative concentrations from a metabolomic analysis [62] and one article did not publish any values but stated decreasing levels of all PUFAs [65].

FA pools & fractions studies

Eight of the articles reported serum FAs [61,62,67-69,72-74], while seven reported plasma FAs [63-66,70,71,75]. Ten articles reported FAs in whole plasma or serum, while four reported FAs in individual lipid fractions like phospholipids (PLs) [63,66,69,71], cholesteryl esters (CEs) and triglycerides (TGs) [69]; the latter article additionally reported FAs in adipose tissue, although this was not considered relevant to the current systematic review. All articles reported blood pool values in samples where the patients were fasted on collection, apart from one article that did not specify this [62].

Individual FAs

i) Linoleic Acid

Six articles reported LA in absolute concentration [62,67-69,73,75] and five reported LA as percentage of total FAs [61,63,69,70,74]. One article reported a significant increase of LA at 12 mo following LAGB [63]. In contrast, several articles reported a statistically significant decrease of LA following surgery, for example 2 wk or 6-9 mo following OAGB [61,74], 6 or 18 mo following RYGB [73], 12 mo following BPD/DS [67] and 3 mo following LSG [68]. Another article reported that LA was decreased 12 mo following RYGB, but the data were not reported [65]. Some articles report LA at different time points following surgery. The decrease in LA following both RYGB and LAGB was reported to be significantly greater at 1 mo than 6 mo [66]. Likewise, the decrease was significantly greater 6 mo after RYGB than after 18 mo [73]. In contrast, the

decrease in LA was significantly greater at 12 mo following BPD/DS than at 3 d or 30 d [67]. One study reported LA in different serum lipid fractions (TGs, CEs, PLs) and as both absolute concentration and percentage [69]: the absolute concentration of LA significantly decreased in TGs 12 mo following RYGB, but did not change in CEs or PLs. Where different types of surgery have been compared within a study, LA showed a significantly greater decrease after RYGB than after LSG [73], and after BPD/DS than after LSG [67] and tended to show a greater decrease after RYGB than after LAGB [66]. The study of DJBL reported that LA was significantly lower after 6 mo compared to both pre-surgery baseline and compared to a control group receiving best practice care but without DJBL [75]. DJBL also significantly lowered LA at 10 d and 12 mo compared with baseline but the values were not different from the control group [75]. Taken together, these data strongly suggest that plasma/serum LA decreases following bariatric surgery and similar malabsorptive interventions, possibly with a greater effect within the first months following intervention, and with a subsequent return towards pre-intervention values. Nevertheless, LA was reported not to change from pre-surgery levels 3 and 6 mo after RYGB [62], 12 mo after RYGB [70] or 3 and 12 mo after LSG [67].

In order to integrate these data, percentage changes from pre-surgery value (data expressed either as absolute concentration or % contribution to FAs) were calculated for each reported timepoint in every article (except those that did not report numerical pre-surgery data [65,68]); percentage change from all available LA data is summarised in Figure 2a. This figure indicates that a decrease in LA from pre-surgery value is common in the first 6 mo.

ii) Alpha-Linolenic Acid

Five articles reported ALA in absolute concentration [66-69,75] while six reported ALA as percentage [61,63,69-71,74]. Several articles reported a statistically significant decrease of ALA following surgery, for example 2 wk following OAGB [61], 3 mo following LSG [68] and 3 mo following RYGB [71]. Another article reported that ALA was decreased 12 mo following RYGB, but the data were not reported [65]. The decrease in ALA following RYGB at 3 mo was reversed

by 12 mo [71]. One study reported LA in different serum lipid fractions (TGs, CEs, PLs) and as both absolute concentration and percentage [69]: the absolute concentration of ALA significantly decreased in TGs 12 mo following RYGB, but it significantly increased in CEs and PLs. The study of DJBL reported that ALA was significantly lower at 10 d, 6 mo and 11.5 mo compared with pre-surgery baseline, with the latter two timepoints also being significantly different from the control group receiving best practice care but without DJBL [75]. Taken together, these data strongly suggest that plasma/serum ALA decreases following bariatric surgery and similar malabsorptive interventions, possibly with a greater effect within the first months following intervention, with a subsequent return towards pre-intervention values. Nevertheless, ALA was reported not to change from pre-surgery levels 12 mo after LAGB [63], 1 or 6 mo after RYGB or LAGB [66] or 12 mo after RYGB or BPD/DS [70]. Percentage change for all available ALA data is summarised in Figure 2b. This figure indicates that a decrease in ALA from pre-surgery value is common in the first 3-6 mo.

iii) Arachidonic Acid

Eight articles reported AA in absolute concentration [64,66-69,72,73,75], while six reported AA as percentage [61,63,69-71,74]. The data present an inconsistent picture. Several articles report a significant increase in AA 3 and 12 mo following RYGB [71], 12 mo following LAGB [63] and 2 wk following OAGB [61]. In contrast, several articles report significantly decreased AA, for example 12 mo following BPD/DS [67] and 12 mo following LSG [72]. Another article reported that AA was decreased 12 mo following RYGB, but the data were not reported [65]. The significant decrease in AA following RYGB at 1 mo was reversed by 6 mo [68]. One study reported AA in different serum lipid fractions (TGs, CEs, PLs) and as both absolute concentration and percentage [69]: the absolute concentration of AA significantly decreased in TGs and CEs 12 mo following RYGB. The study of DJBL reported that AA was significantly lower after 6 and 11.5 mo compared to both pre-surgery baseline and compared to a control group receiving best practice care but without DJBL [75]. DJBL also significantly lowered AA at 10 d compared with baseline but the values were not different from the control group [75]. AA

was reported not to change from pre-surgery levels in several articles [62,66,68]. Percentage change for all available AA data is summarised in Figure 3a. No clear conclusion can be dawn.

iv) EPA

Six articles reported EPA in absolute concentration [64,66-69,75], while six reported as a percentage [61,63,69-71,74]. Several articles reported a significant decrease of EPA, for example 2 wk or 6-9 mo following OAGB [61,74], 3 or 12 mo following RYGB [71], 12 mo following BPD/DS [67] and 3 mo following LSG [68]. Another article reported that EPA was decreased 12 mo following RYGB, but the data were not reported [65]. One study reported EPA in different serum lipid fractions (TGs, CEs, PLs) and as both absolute concentration and percentage [69]: the absolute concentration of EPA significantly decreased in TGs 12 mo following RYGB, but did not change in CEs or PLs. The study of DJBL reported that EPA was significantly lower after 6 and 11.5 mo compared to both pre-surgery baseline and compared to a control group receiving best practice care but without DJBL [75]. DJBL also significantly lowered EPA at 10 d compared with baseline but the values were not different from the control group [75]. Taken together, these data strongly suggest that plasma/serum EPA decreases following bariatric surgery and similar malabsorptive interventions, possibly with a greater effect within the first months following intervention, with a subsequent return towards pre-intervention values. Nevertheless, EPA was reported not to change from pre-surgery levels 3 and 6 mo after RYGB [62], 12 mo after RYGB [70] or 12 mo after LAGB [63]. Percentage change for all available EPA data is summarised in Figure 3b. This figure indicates that a decrease in EPA from pre-surgery value is common in the first 3-6 mo.

v) DHA

Six articles reported DHA in absolute concentration [64,66-69,75] and six articles reported DHA as a percentage [61,63,69-71,74]. Some articles reported a significant decrease of DHA, for example 12 mo following BPD/DS [67], and 6-9 mo following OAGB [61]. Another article reported that DHA was decreased 12 mo following RYGB, but the data were not reported [65].

The study of DJBL reported that DHA was significantly lower after 6 and 11.5 mo compared to both pre-surgery baseline and compared to a control group receiving best practice care but without DJBL [75]. DJBL also significantly lowered DHA at 10 d compared with baseline but the values were not different from the control group [75]. One study reported DHA in different serum lipid fractions (TGs, CEs, PLs) and as both absolute concentration and percentage [69]: the absolute concentration of DHA significantly decreased in TGs, CEs and PLs 12 mo following RYGB. In contrast some articles report a significant increase in DHA 1 mo, but not 6 mo, following RYGB [66], 12 mo following RYGB [70] and 3 mo following RYGB [71]. Other artices report no change in DHA following LAGB [63], LSG [67], and RYGB [62]. Percentage change for all available DHA data is summarised in Figure 3c. This figure indicates that no clear conclusion can be drawn with regard to the change in DHA.

vi) Total n-3, n-6 & PUFAs

Each of the three articles reporting total n-3 and n-6 PUFAs [63,69,74] do so as percentage of total fatty acids; one of these also reports on total PUFAs and additionally absolute values for all [69]. One article shows significantly lower n-3 and n-6 PUFA levels after OAGB compared to non-surgical controls [74] and additionally reports significantly decreased n-6 PUFAs compared to pre-surgery baseline values. In contrast, one article reports significantly increased total n-6 PUFAs 12 mo following LAGB [63]. The absolute concentrations of n-3, n-6 and total PUFAs in serum TGs significantly decreased 12 mo following RYGB, while the percentages increased [69]. The percentages of n-6 and total PUFAs significantly decreased in serum CEs and PLs, while n-3 PUFAs did not change [69]. Absolute concentrations of n-6, n-3 and total PUFAs in serum CE and PL did not change [69].

vii) Mead acid

One study [66] reported no change from pre-surgery for mead acid, an indicator of EFA deficiency, in plasma PLs 1 and 6 mo after either RYGB or LAGB.

Discussion

This systematic review identified that blood levels of the two essential PUFAs, LA and ALA, and of the bioactive n-3 PUFA, EPA, significantly decrease in the period following bariatric surgery or other malabsorptive interventions and remain low for perhaps 6 months or more, before (possibly) returning to (or towards) pre-surgery levels at around 12 months. Effects on DHA and AA are unclear with significant inconsistency in the literature reviewed, although there are also reports from some of the studies reviewed that DHA and AA are decreased following bariatric surgery. The one study that reported on mead acid, an indicator of EFA deficiency saw no effect of two different surgical procedures [66].

All included studies had risk of bias and most studies were of small size. However, it would not be possible to improve some aspects of bias, such as surgical treatment allocation, which is usually based on clinical grounds. Nevertheless, some studies have compared different types of surgery [66,67,73] and one study compared DJBL with lifestyle modification over 11.5 mo in a randomised design [75]. One study did not report numerical data for PUFAs [65] and eight studies were excluded [53-60] because data were not available either in the publication or from the authors. Studies included in this systematic review reported PUFAs in total serum or plasma or in different serum or plasma lipid fractions (TGs, PLs, CEs) and these data were reported in absolute concentrations (e.g. mg/L) or as % weight or molar contribution to the total FAs present. Our analysis reports on blood PUFAs before and at least one time-point after surgery, although those time points differed among studies. We did not consider any relationship of blood PUFAs post-surgery with degree of weight loss, gain in insulin sensitivity or change in blood lipid concentrations. Nor did we consider medications or change in medications. Most studies did not report on dietary changes post-surgery so those could not be considered in the interpretation of the PUFA data.

Studies assessed various bariatric surgical interventions; a small number of studies compared two surgical interventions [66,67,73]. Plasma LA (mg/L) decreased 6 and 12 mo after RYGB but increased after LSG [73]. Plasma EPA (mmol/L) decreased 1 and 6 mo after RYGB

but did not change (a small but non-significant increase) after LAGB [66]. Plasma LA, AA, EPA and DHA decreased 12 mo after BPD/DS but did not change after LSG [67]. Both RYGB and BPD/DS are malabsorptive surgeries, whereas LAGB and LSG are restrictive; thus it appears that malabsorptive interventions have a larger impact on blood PUFA levels than restrictive interventions.

Most studies reported PUFAs in total plasma or serum. PUFAs are carried in the bloodstream mostly in complex lipids (TGs, PLs, CEs) within lipoproteins, although some non-esterified PUFAs also circulate. Thus, any measurement of PUFAs in total plasma or serum will assess the FAs across these different complex lipids, which have different FA compositions from one another. Only one study compared effects of bariatric surgery on PUFAs in different complex lipid fractions [69]. Greater effects of RYGB were seen in serum TGs than in PLs or CEs, at least when PUFAs were expressed in absolute concentration (mg/L serum): RYGB decreased all five PUFAs under study in serum TGs and decreased ALA, AA and DHA in serum CEs and DHA in serum PLs (all at 12 mo post-surgery). The greater effect on PUFA concentrations within TGs than within PLs or CEs may relate to the substrate preferences of the enzymes that synthesise and metabolise the different complex lipids. The same study [69] is the only to report PUFAs in both absolute concentration and as a percentage of total fatty acids within the lipid fraction. It is evident that the precise finding is influenced by how the data are expressed. For example, although the absolute concentration of all five PUFAs decreased in serum TGs after RYBG, the percentages of LA, AA and EPA increased while the percentages of ALA and DHA did not change. One explanation for this may be that the effect of bariatric surgery is to decrease plasma/serum TG concentration and as a result the concentration of individual PUFAs within TGs is also decreased although their contribution to all fatty acids within TGs (i.e their %) is little changed. This effect of the way of expressing data on PUFA concentrations may contribute to some of the inconsistencies in the findings of different studies. There is no clear consensus on the preferred way of expressing FA composition data. Brenna et al [76] discuss this matter and do not favour one way over the other, making a recommendation that “the rationale for primary reporting of fatty acid profile or absolute fatty acid concentration

should be reported with respect to the hypotheses". Such a rationale was not offered by any of the studies included in the current systematic review.

Except for one study, which did not specify when blood was collected, all studies included in this systematic review measured FAs in blood measured in the fasting state. This is important because, in the absence of any dietary or physiological change, PUFAs in blood remain stable over a long period of time. For example, data from the placebo group in a RCT of omega-3 PUFAs reported by Browning et al. [77] reveal that EPA and DHA in PLs, TGs, CEs and NEFAs in fasting plasma, as well as in red blood cells, mononuclear cells, platelets, buccal cavity cells and adipose tissue, do not change over 12 months. Likewise, data from the placebo group of the RCT of Katan et al. [78] showed that EPA and DHA in fasting plasma CEs and in red blood cells and adipose tissue did not change over 18 months. Both these studies reported the FAs as % of total FAs. In contrast, the FA composition of blood changes with some changes in physiological state, most obviously in the hours after eating a meal [79]. Hence, collection of blood in the fasting state is important to remove any acute effect of diet. There may be small diurnal effects in blood FAs, most likely related to rhythms in hormones and in metabolism. One study recently reported a modest, but significant, rhythm in plasma PUFAs (expressed as μg/mL) in healthy, young to middle-aged adults [80], with the lowest concentration being seen in the morning and the highest in the late afternoon-early evening.

There are no accepted normal values for PUFAs in plasma or serum. Hodson et al. [81] gathered data from the literature for different FAs reported as mol % in different lipid fractions in healthy adult male and female humans and used these to identify typical average values. Stark et al. [82] collate data for different FAs expressed as weight % in total plasma and plasma PLs, revealing considerable heterogeneity in findings, in part likely to be related to dietary differences among individuals in the different studies which came from different global locations. Only one study included in the current systematic review reported PUFAs as mol % [69]. Hodson et al. [81] report average values of 15.0, 52.0 and 21.9 mol % for LA in plasma TGs, CEs and PLs, respectively. LA values for serum TGs, CEs and PLs reported pre-surgery by Walle et al. [69] were 11.9, 45.2 and 17.3 mol %, respectively. These indicate a lower LA status in the patients

studied by Walle et al. [69] compared to those individuals whose data were used by Hodson et al. [81]. In Walle et al. [69] patients were put on to a very low calorie diet (600-800 kcal/d) for 4 wk pre-surgery; details of this diet are not provided but clearly it would have contained limited fat which perhaps explains this low serum LA status. At 12 mo post-surgery LA status remained lower than reported in Hodson et al., with values of 12.4, 45.4 and 17.9 mol % in serum TGs, CEs and Pls, respectively [69]. Conversely however, the pre-surgery mol % ALA in serum TGs and AA, EPA and DHA in serum TGs, CEs and PLs reported by Walle et al. [69] was higher than seen in the data presented by Hodson et al. [81]. It is not clear why this is.

It is anticipated that any effect of bariatric surgery on blood PUFAs would be due to altered availability either through decreased intake (through restriction, reduced appetite or increased satiety) or decreased digestion and absorption. However, there could be other effects of bariatric surgery that might influence blood PUFAs, for example improved insulin sensitivity [83,84] which would alter whole body lipid homeostasis influencing processes such as clearance and release of PUFAs by insulin sensitive tissues and long chain PUFA synthesis from EFA substrates. A brief period (3 wk) of lifestyle intervention lowered plasma concentrations of LA, ALA and EPA [67], which were also lowered 3 mo after LSG in the same study. This suggests that a major influence on blood PUFA concentrations is supply from the diet, although an effect of both lifestyle intervention and bariatric surgery on insulin sensitivity and the systemic handling of PUFAs cannot be ruled out. The study of DJBL over 11.5 mo made a direct comparison with lifestyle modification, with both groups subject to an initial 20 d period of caloric restriction (7 days before and 13 days after the intervention) [75]. Both groups showed decreases in all five PUFAs (expressed in absolute concentration in plasma) at 10 d, 6 mo and 11.5 mo; however the effect of DJBL was greater at 6 and 11.5 mo. There was no difference in hepatic insulin sensitivity between the groups, although DJBL resulted in a superior improvement in peripheral insulin sensitivity compared with lifestyle modification (M. Glaysher personal communication). Whatever the exact mechanism involved, this study shows that an intervention that reduces nutrient absorption lowers blood PUFA concentrations to a greater extent than lifestyle modification but that the effect is

transient with a return towards baseline PUFA concentrations by 11.5 mo post-DJBL implantation. The return of blood PUFA concentrations towards pre-surgery values after about 12 mo may reflect changes in dietary habits - food intake is likely to be more markedly reduced in the period immediately after surgery (indeed patients are often supported with low energy, low fat formulas following surgery [25,31]) - and/or an alteration in carbohydrate, fatty acid and lipid metabolism. This might be related to weight loss and/or altered insulin sensitivity.

It is recognised that bariatric surgery adversely impacts protein and micronutrient status [24,25] and recommendations for the nutritional support of patients following bariatric surgery include increasing protein intake and providing micronutrient supplements [24,25,31]. This systematic review indicates that bariatric surgery and other malabsorptive approaches are likely to cause a significant decrease in EFA (LA and ALA) and other PUFA (especially EPA) status in the first months. Since these FAs have physiological effects that align with the aims of the surgical interventions, such a decrease in status may partly mitigate the desired effects of the surgery, for example on blood lipids, insulin sensitivity and inflammation. Nutritional strategies (e.g. use of modified formulas or of supplements) may be able to correct the decrease in those PUFAs. Nevertheless, the observed decrease in PUFAs is transient and for most surgery types, PUFAs return towards starting (i.e. pre-surgery) levels by 12 months. The physiological impact of lowered PUFA status in the weeks and months following malabsorptive interventions in particular, should be investigated and whether exogenous supply of these PUFAs improves the metabolic effects of the interventions should be explored.

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References

1. World Health Organisation. *Obesity and overweight.* Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight [Accessed 20th February 2021].
2. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet* 2016;387:1377-1396.
3. Pi-Sunyer X. The medical risks of obesity. *Postgraduate Medical Journal* 2009;121:21-33.
4. Collins J, Meng C, Eng A. Psychological impact of severe obesity. *Current Obesity Reports* 2016;5:435-440.
5. Duarte C, Matos M, Stubbs RJ, Gale C, Morris L, Gouveia JP, Gilbert P. The impact of shame, self-criticism and social rank on eating behaviours in overweight and obese women participating in a weight management programme. *PLoS One* 2017;12:e0167571.
6. Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. *Cochrane Database of Systematic Reviews* 2014;8:CD003641.
7. Hopkins J, Howes N, Chalmers K, Whale K, Savovic J, Coulman K, Nicholson A, Byrne J, Whistance R, Welbourn R, Andrews R, Blazeby J, By-Band Trial Management Group. What are important outcomes of bariatric surgery? An in-depth analysis to inform the development of a core outcome set and a comparison between the views of surgeons and other health professionals (the BARIACT study). *Lancet* 2015;385(suppl 1):S43.
8. Wilkinson LH, Peloso OA. Gastric (reservoir) reduction for morbid obesity. *Archives of Surgery* 1981;116:602-605.
9. Mason EE, Ito C. Gastric bypass in obesity. *Obesity Research* 1996;4:316-319.
10. Sinclair P, Brennan DJ, le Roux CW. Gut adaptation after metabolic surgery and its influences on the brain, liver and cancer. *Nature Reviews Gastroenterology and Hepatology* 2018;15:606-624.
11. Ionut V, Burch M, Youdim A, Bergman RN. Gastrointestinal hormones and bariatric surgery-induced weight loss. *Obesity (Silver Spring)* 2013;21:1093-1103.
12. Meek CL, Lewis HB, Reimann F, Gribble FM, Park AJ. The effect of bariatric surgery on gastrointestinal and pancreatic peptide hormones. *Peptides* 2016;77:28-37.
13. Ochner CN, Gibson C, Shanik M, Goel V, Geliebter A. Changes in neurohormonal gut peptides following bariatric surgery. *International Journal of Obesity* 2011;35:153-166.
14. Vella A. Enteroendocrine secretion after Roux-en-Y gastric bypass: is it important? *Neurogastroenterology and Motility* 2013;25:1-3.
15. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. *JAMA Surgery* 2014;149:275-287.

16. Wiggins T, Antonowicz SS, Markar SR. Cancer risk following bariatric surgery - systematic review and meta-analysis of national population-based cohort studies. *Obesity Surgery* 2019;29:1031-1039.
17. Maggard MA, Yermilov I, Li Z, Maglione M, Newberry S, Suttorp M, Hilton L, Santry HP, Morton JM, Livingston EH, Shekelle PG. Pregnancy and fertility following bariatric surgery: a systematic review. *JAMA* 2008;300:2286-2296.
18. Cardoso L, Rodrigues D, Gomes L, Carrilho F. Short- and long-term mortality after bariatric surgery: a systematic review and metaanalysis. *Diabetes Obesity and Metabolism* 2017;19:1223-1932.
19. Wilson R, Aminian A, Tahrani AA. Metabolic surgery: A clinical update. *Diabetes Obesity and Metabolism* 2021;23 Suppl 1:63-83.
20. Welbourn R, Hollyman M, Kinsman R, Dixon J, Liem R, Ottosson J, Ramos A, Våge V, Al-Sabah S, Brown W, Cohen R, Walton P, Himpens J. Bariatric surgery worldwide: baseline demographic description and one-year outcomes from the Fourth IFSO Global Registry Report 2018. *Obesity Surgery* 2019;29:782-795.
21. Steenackers N, Vanuytsel T, Augustijns P, Tack J, Mertens A, Lannoo M, Van der Schueren B, Matthys C.Adaptations in gastrointestinal physiology after sleeve gastrectomy and Roux-en-Y gastric bypass. *Lancet Gastroenterology and Hepatology* 2021;6:225-237.
22. Leeman M, Gadiot RPM, Wijnand JMA, Birnie E, Apers JA, Biter LU, Dunkelgrun M Effects of standard v. very long Roux limb Roux-en-Y gastric bypass on nutrient status: a 1-year follow-up report from the Dutch Common Channel Trial (DUCATI) Study. *British Journal of Nutrition* 2020;123:1434-1440.
23. The UK National Bariatric Surgery Registry. *Third Registry Report 2020*. Reading: Dendrite Clinical Systems; 2020. Available from: https://e-dendrite.com/Publishing/Reports/Bariatric/NBSR2020.pdf [Accessed 3 May 2021].
24. Sherf Dagan S, Goldenshluger A, Globus I, Schweiger C, Kessler Y, Kowen Sandbank G, Ben-Porat T, Sinai T. Nutritional recommendations for adult bariatric surgery patients: clinical practice. *Advances in Nutrition* 2017;8:382-394.
25. Busetto L, Dicker D, Azran C, Batterham RL, Farpour-Lambert N, Fried M, Hjelmesæth J, Kinzl J, Leitner DR, Makaronidis JM, Schindler K, Toplak H, Yumuk V. Practical recommendations of the Obesity Management Task Force of the European Association for the Study of Obesity for the post-bariatric surgery medical management. *Obesity Facts* 2017;10:597-632.
26. Bavaresco M, Paganini S, Pereira Lima T, Salgado W Jr, Ceneviva R, Dos Santos JE, Nonino-Borges CB. Nutritional course of patients submitted to bariatric surgery. *Obesity Surgery* 2010;20:716-721.
27. Brolin RE, LaMarca LB, Kenler HA, Cody RP: Malabsorptive gastric bypass in patients with superobesity. *Journal of Gastrointestinal Surgery* 2002;6:195-203.
28. Faintuch J, Matsuda M, Cruz ME, Silva MM, Teivelis MP, Garrido AB Jr, Gama-Rodrigues JJ. Severe protein calorie malnutrition after bariatric procedures. *Obesity Surgery* 2004;14:175-181.
29. Mechanick JI, Kushner RF, Sugerman HJ, Gonzalez-Campoy JM, Collazo-Clavell ML, Guven S, Spitz AF, Apovian CM, Livingston EH, Brolin R, Sarwer DB, Anderson WA, Dixon J, American Association of Clinical Endocrinologists, The Obesity Society, American Society for Metabolic & Bariatric Surgery: Medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. *Endocrine Practice* 2008;14(suppl 1):1-83.

30. Handzlik-Orlik G, Holecki M, Orlik B, Wylezol M, Dulawa J. Nutrition management of the post-bariatric surgery patient. *Nutrition in Clinical Practice* 2015;30:383-392.
31. Mechanick JI, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM, Heinberg LJ, Kushner R, Adams TD, Shikora S, Dixon JB, Brethauer S, American Association of Clinical Endocrinologists, Obesity Society, American Society for Metabolic & Bariatric Surgery. 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. *Endocrine Practice* 2013;19:337-372.
32. Kumar R, Lieske JC, Collazo-Clavell ML, Sarr MG, Olson ER, Vrtiska TJ, Bergstralh EJ, Li X. Fat malabsorption and increased oxalate absorption are common after roux-en-Y gastric bypass surgery. *Surgery* 2011;149:654-661.
33. Katan MB, Zock PL, Mensink RP.Effects of fats and fatty acids on blood lipids in humans: an overview. *American Journal of Clinical Nutrition* 1994;60(6 Suppl):1017S-1022S.
34. Forouhi NG, Imamura F, Sharp SJ, Koulman A, Schulze MB, Zheng J, Ye Z, Sluijs I, Guevara M, Huerta JM, Kröger J, Wang LY, Summerhill K, Griffin JL, Feskens EJ, Affret A, Amiano P, Boeing H, Dow C, Fagherazzi G, Franks PW, Gonzalez C, Kaaks R, Key TJ, Khaw KT, Kühn T, Mortensen LM, Nilsson PM, Overvad K, Pala V, Palli D, Panico S, Quirós JR, Rodriguez-Barranco M, Rolandsson O, Sacerdote C, Scalbert A, Slimani N, Spijkerman AM, Tjonneland A, Tormo MJ, Tumino R, van der A DL, van der Schouw YT, Langenberg C, Riboli E, Wareham NJ. Association of plasma phospholipid n-3 and n-6 polyunsaturated fatty acids with type 2 diabetes: The EPIC-InterAct Case-Cohort Study. *PLoS Medicine* 2016;13:e1002094.
35. de Goede J, Verschuren WM, Boer JM, Verberne LD, Kromhout D, Geleijnse JM. N-6 and N-3 fatty acid cholesteryl esters in relation to fatal CHD in a Dutch adult population: a nested case-control study and meta-analysis. *PLoS One* 2013;8:e59408.
36. Baker EJ, Miles EA, Burdge GC, Yaqoob P, Calder PC. Metabolism and functional effects of plant-derived omega-3 fatty acids in humans. *Progress in Lipid Research* 2016;64:30-56.
37. Naghshi S, Aune D, Beyene J, Mobarak S, Asadi M, Sadeghi O. Dietary intake and biomarkers of alpha linolenic acid and risk of all cause, cardiovascular, and cancer mortality: systematic review and dose-response meta-analysis of cohort studies. *BMJ* 2021;375:n2213.
38. Tallima H, El Ridi R. Arachidonic acid: physiological roles and potential health benefits - A review. *Journal of Advanced Research* 2017;11:33-41.
39. Christie WW, Harwood JL. Oxidation of polyunsaturated fatty acids to produce lipid mediators. *Essays in Biochemistry* 2020;64:401-421.
40. Calder, PC. Eicosanoids. *Essays in Biochemistry* 2020;64:423-441.
41. Calder, PC. Very long-chain n-3 fatty acids and human health: fact, fiction and the future. *Proceedings of the Nutrition Society* 2018;77:52-72.
42. Innes JK, Calder PC. The differential effects of eicosapentaenoic acid and docosahexaenoic acid on cardiometabolic risk factors: a systematic review. *International Journal of Molecular Sciences* 2018;19:532.
43. Troesch B, Eggersdorfer M, Laviano A, Rolland Y, Smith AD, Warnke I, Weimann A, Calder PC. Expert opinion on benefits of long-chain omega-3 fatty acids (DHA and EPA) in aging and clinical nutrition. *Nutrients* 2020;12:2555.

44. Djuricic I, Calder PC. Beneficial outcomes of omega-6 and omega-3 polyunsaturated fatty acids on human health: an update for 2021. *Nutrients* 2021;13:2421.
45. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, Franco OH, Butterworth AS, Forouhi NG, Thompson SG, Khaw KT, Mozaffarian D, Danesh J, Di Angelantonio E. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. *Annals of Intern Medicine* 2014;160:398-406.
46. Del Gobbo LC, Imamura F, Aslibekyan S, Marklund M, Virtanen JK, Wennberg M, Yakoob MY, Chiuve SE, Dela Cruz L, Frazier-Wood AC, Fretts AM, Guallar E, Matsumoto C, Prem K, Tanaka T, Wu JH, Zhou X, Helmer C, Ingelsson E, Yuan JM, Barberger-Gateau P, Campos H, Chaves PH, Djoussé L, Giles GG, Gómez-Aracena J, Hodge AM, Hu FB, Jansson JH, Johansson I, Khaw KT, Koh WP, Lemaitre RN, Lind L, Luben RN, Rimm EB, Risérus U, Samieri C, Franks PW, Siscovick DS, Stampfer M, Steffen LM, Steffen BT, Tsai MY, van Dam RM, Voutilainen S, Willett WC, Woodward M, Mozaffarian D; Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Fatty Acids and Outcomes Research Consortium (FORCe). Omega-3 polyunsaturated fatty acid biomarkers and coronary heart disease: pooling project of 19 cohort studies. *JAMA Internal Medicine* 2016;176:1155-1166.
47. Harris WS, Tintle NL, Imamura F, Qian F, Korat AVA, Marklund M, Djoussé L, Bassett JK, Carmichael PH, Chen YY, Hirakawa Y, Küpers LK, Laguzzi F, Lankinen M, Murphy RA, Samieri C, Senn MK, Shi P, Virtanen JK, Brouwer IA, Chien KL, Eiriksdottir G, Forouhi NG, Geleijnse JM, Giles GG, Gudnason V, Helmer C, Hodge A, Jackson R, Khaw KT, Laakso M, Lai H, Laurin D, Leander K, Lindsay J, Micha R, Mursu J, Ninomiya T, Post W, Psaty BM, Risérus U, Robinson JG, Shadyab AH, Snetselaar L, Sala-Vila A, Sun Y, Steffen LM, Tsai MY, Wareham NJ, Wood AC, Wu JHY, Hu F, Sun Q, Siscovick DS, Lemaitre RN, Mozaffarian D; Fatty Acids and Outcomes Research Consortium (FORCE). Blood n-3 fatty acid levels and total and cause-specific mortality from 17 prospective studies. *Nature Communications* 2021;12:2329.
48. Calder PC. N-3 PUFA and inflammation: from membrane to nucleus and from bench to bedside*. Proceedings of the Nutrition Society* 2020;79:404-416.
49. Chiang N, Serhan CN. Specialized pro-resolving mediator network: an update on production and actions*. Essays in Biochemistry* 2020;64:443-462.
50. McGlory C, Calder PC, Nunes EA. The influence of omega-3 fatty acids on skeletal muscle protein turnover in health, disuse, and disease. *Frontiers in Nutrition* 2019;6:144.
51. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I. RoB 2: a revised tool for assessing risk of bias in randomised trials. *British Medical Journal* 2019;366:l4898.
52. Greenhalgh T. How to Read a Paper: The Basics of Evidence-Based Medicine and Healthcare. *How To Series*. 6th ed. Newark: John Wiley & Sons; 2019.
53. Chalut-Carpentier A, Pataky Z, Golay A, Bobbioni-Harsch E. Involvement of dietary fatty acids in multiple biological and psychological functions, in morbidly obese subjects. *Obesity Surgery* 2015;25:1031–1038.
54. Thomas F, Smith GC, Lu J, Barbor R, Booth M, Beban G, Chase JG, Murphy R. Differential acute impacts of sleeve gastrectomy, Roux-en-Y gastric bypass surgery and matched caloric restriction diet on insulin secretion, insulin effectiveness and

non-esterified fatty acid levels among patients with type 2 diabetes. *Obesity Surgery* 2016;26:1924-1931.
55. Nemati R, Lu J, Tura A, Smith G, Murphy R. Acute changes in non-esterified fatty acids in patients with type 2 diabetes receiving bariatric surgery. *Obesity Surgery* 2017;27:649-656.
56. Zhao L, Ni Y, Yu H, Zhang P, Zhao A, Bao Y, Liu J, Chen T, Xie G, Panee J, Chen W, Rajani C, Wei R, Su M, Jia W, Jia W. Serum stearic acid/palmitic acid ratio as a potential predictor of diabetes remission after Roux-en-Y gastric bypass in obesity. *FASEB Journal* 2017;31:1449-1460.
57. Palau-Rodriguez M, Tulipani S, Marco-Ramell A, Miñarro A, Jauregui O, Gonzalez-Dominguez R. Characterization of metabolomic profile associated with metabolic improvement after bariatric surgery in subjects with morbid obesity. *Journal of Proteome Research* 2018;17:2704-2714.
58. Samczuk P, Hady HR, Adamska-Patruno E, Citko A, Dadan J, Barbas C, Kretowski A, Ciborowski M. In-and-out molecular changes linked to the type 2 diabetes remission after bariatric surgery: an influence of gut microbes on mitochondria metabolism. *International Journal of Molecular Sciences* 2018;19:3744.
59. Wijayatunga NN, Sams VG, Dawson JA, Mancini ML, Mancini GJ, Moustaid-Moussa N. Roux-en-Y gastric bypass surgery alters serum metabolites and fatty acids in patients with morbid obesity. *Diabetes Metabolism Research and Reviews* 2018;34:e3035.
60. Mendonça Machado N, Torrinhas RS, Sala P, Ishida RK, Guarda IFMS, Moura EGH, Sakai P, Santo MA, Linetzky Waitzberg D. Type 2 diabetes metabolic improvement after Roux-en-Y gastric bypass may include a compensatory mechanism that balances fatty acid β and ω oxidation. *Journal of Parenteral and Enteral Nutrition* 2020;44:1417-1427.
61. Pakiet A, Wilczynski M, Rostkowska O, Korczynska J, Jabłonska P, Kaska L, Proczko-Stepaniak M, Sobczak E, Stepnowski P, Magkos F, Sledzinski T, Mika A. The effect of one anastomosis gastric bypass on branched-chain fatty acid and branched-chain amino acid metabolism in subjects with morbid obesity. *Obesity Surgery* 2020;30:304-312.
62. Mutch DM, Fuhrmann JC, Rein D, Wiemer JC, Bouillot JL, Poitou C, Clerment K. Metabolite profiling identifies candidate markers reflecting the clinical adaptations associated with Roux-en-Y gastric bypass surgery. *PLoS One* 2009;4:e7905.
63. Zambon S, Romanato G, Sartore G, Marin R, Busetto L, Zanoni S, Favretti F, Sergi G, Fioretto P, Manzato E. Bariatric surgery improves atherogenic LDL profile by triglyceride reduction. *Obesity Surgery* 2009;19:190-195.
64. Aslan M, Aslan I, Özcan F, Eryılmaz R, Ensari CO, Bilecik T. A pilot study investigating early postoperative changes of plasma polyunsaturated fatty acids after laparoscopic sleeve gastrectomy. *Lipids in Health and Disease* 2014;13:62.
65. Lopes TI, Geloneze B, Pareja JC, Calixto AR, Ferreira MM, Marsaioli AJ. Blood metabolome changes before and after bariatric surgery: a (1)H NMR-based clinical investigation. *OMICS* 2015;19:318-327.
66. Forbes R, Gasevic D, Watson EM, Ziegler TR, Lin E, Burgess JR, Gletsu-Miller N. Essential fatty acid plasma profiles following gastric bypass and adjusted gastric banding bariatric surgeries. *Obesity Surgery* 2016;26:1237-1246.
67. Lin C, Våge V, Mjøs SA, Kvalheim OM. Changes in serum fatty acid levels during the first year after bariatric surgery. *Obesity Surgery* 2016;26:1735-1742.

68. Lin C, Andersen JR, Våge V, Rajalahti T, Mjøs SA, Kvalheim OM. Intensive lifestyle intervention provides rapid reduction of serum fatty acid levels in women with severe obesity without lowering omega-3 to unhealthy levels. *Clinical Obesity* 2016;6:59-267.
69. Walle P, Takkunen M, Männistö V, Vaittinen M, Käkelä P, Ågren J, Schwab U, Lindström J, Tuomilehto J, Uusitupa M, Pihlajamäki J. Alterations in fatty acid metabolism in response to obesity surgery combined with dietary counseling. *Nutrition and Diabetes* 2017;7:e285.
70. Hovland A, Nestvold T, Bohov P, Trøseid M, Aukrust P, Berge RK, Waage-Nielsen E, Retterstøl K, Lappegård KT. Bariatric surgery reduces fasting total fatty acids and increases n-3 polyunsaturated fatty acids in morbidly obese individuals. *Scandinavian Journal of Clinical and Laboratory Investigation* 2017;77:628-633.
71. Garla P, Sala P, Torrinhas RSM, Machado NM, Fonseca DC, da Silva MM, Ravacci GR, Belarmino G, Ishida RK, Guarda IFMS, de Moura EGH, Sakai P, Santo MA, da Silva IDCG, Pereira CCA, Heymsfield S, Corrêa-Giannella MLC, Calder PC, Waitzberg DL. Reduced intestinal FADS1 gene expression and plasma omega-3 fatty acids following Roux-en-Y gastric bypass. *Clinical Nutrition* 2019;38:1280-1288.
72. Azar S, Sherf-Dagan S, Nemirovski A, Webb M, Raziel A, Keidar A, Goitein D, Sakran N, Shibolet O, Tam J, Zelber-Sagi S. Circulating endocannabinoids are reduced following bariatric surgery and associated with improved metabolic homeostasis in humans. *Obesity Surgery* 2019;29:268-276.
73. Sarkar S, Anokye-Danso F, Tronieri JS, Millar JS, Alamuddin N, Wadden TA, Ahima RS. Differential effects of Roux-en-Y gastric bypass surgery and laparoscopic sleeve gastrectomy on fatty acid levels. *Obesity Surgery* 2019;29:3941-3947.
74. Mika A, Wilczynski M, Pakiet A, Kaska L, Proczko-Stepaniak M, Stankiewicz M, Stepnowski P, Sledzinski T. Short-term effect of one-anastomosis gastric bypass on essential fatty acids in the serum of obese patients. *Nutrients* 2020;12:187.
75. Glaysher MA, Ward J, Aldhwayan M, Ruban A, Prechtl CG, Fisk HL, Chhina N, Al-Najim W, Smith C, Klimowska-Nassar N, Johnson N, Falaschetti E, Goldstone AP, Miras AD, Byrne JP, Calder PC, Teare JP. The effect of a duodenal-jejunal bypass liner on lipid profile and blood concentrations of long chain polyunsaturated fatty acids. *Clinical Nutrition* 2021;40:2343-2354.
76. Brenna JT, Plourde M, Stark KD, Jones PJ, Lin YH. Best practices for the design, laboratory analysis, and reporting of trials involving fatty acids. American Journal of Clinical Nutrition 2018;108:211-227.
77. Browning LM, Walker CG, Mander AP, West AL, Madden J, Gambell JM, Young S, Wang L, Jebb SA, Calder PC. Incorporation of eicosapentaenoic and docosahexaenoic acids into lipid pools when given as supplements providing doses equivalent to typical intakes of oily fish. *American Journal of Clinical Nutrition* 2012;96:748-758.
78. Katan MB, Deslypere JP, van Birgelen AP, Penders M, Zegwaard M. Kinetics of the incorporation of dietary fatty acids into serum cholesteryl esters, erythrocyte membranes, and adipose tissue: an 18-month controlled study. *Journal of Lipid Research* 1997;38:2012-2022.
79. Kagan ML, West AL, Zante C, Calder PC. Acute appearance of fatty acids in human plasma--a comparative study between polar-lipid rich oil from the microalgae Nannochloropsis oculata and krill oil in healthy young males. *Lipids in Health and Disease* 2013;12:102.

80. Jackson PA, Husberg C, Hustvedt SO, Calder PC, Khan J, Avery H, Forster J, Kennedy DO. Diurnal rhythm of plasma EPA and DHA in healthy adults. *Prostaglandins Leukotrienes and Essential Fatty Acids* 2020;154:102054.
81. Hodson L, Skeaff CM, Fielding BA. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. *Progress in Lipid Research* 2008;47:348-380.
82. Stark KD, Van Elswyk ME, Higgins MR, Weatherford CA, Salem N Jr. Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults. *Progress in Lipid Research* 2016;63:132-152.
83. Gumbs AA, Modlin IM, Ballantyne GH. Changes in insulin resistance following bariatric surgery: role of caloric restriction and weight loss. *Obesity Surgery* 2005;15:462-473.
84. Ferrannini E, Mingrone G. Impact of different bariatric surgical procedures on insulin action and beta-cell function in type 2 diabetes. *Diabetes Care* 2009;32:514-520.

Figure captions

Figure 1. Overview of article selection process.

Figure 2. Calculated percentage change in a) linoleic acid (LA) and b) alpha-linolenic acid (ALA) from pre-surgery value at different time points post-surgery. Closed cicles indicate where original data were expressed as % of total fatty acids; open circles indicate where original data were data expressed as absolute concentration; closed diamonds indicate where original data were expressed as arbitrary values.

Figure 3. Calculated percentage change in a) arachidonic acid (AA), b) eicosapentaenoic acid (EPA) and c) docosahexaenoic acid (DHA) from pre-surgery value at different time points post-surgery. Closed cicles indicate where original data were expressed as % of total fatty acids; open circles indicate where original data were data expressed as absolute concentration; closed diamonds indicate where originnal data were expressed as arbitrary values.

Table 1. Summary of the Characteristics of Included Studies: Design and Outcomes

Ref no.	Author, year	Study design	Where conducted	Inclusion criteria	Exclusion criteria	Primary outcome(s)	Secondary outcome(s)
[62]	Mutch et al. (2009)	Cohort	France	BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with at least two co-morbidities (hypertension, type-II diabetes, dyslipidemia or obstructive sleep apnea syndrome); stable weight (i.e. variation of less than 62 kg) for at least 3 months prior to operation	Acute or chronic inflammatory disease; infectious diseases; viral infection; cancer and/or known alcohol consumption (>20 g per day)	Metabolite profiling of serum metabolites	To identify metabolites associated with surrogates of steady-state insulin sensitivity in diabetic and non-diabetic groups
[63]	Zambon et al. (2009)	Cohort	Italy	BMI > 40 kg/m^2.	Endocrine diseases and acute or chronic systemic diseases. Taking medications known to affect body weight or plasma lipids.	LDL size and density in relation to weight reduction, plasma lipid, lipoprotein and apoprotein levels, and plasma phospholipid fatty acid composition	n/a
[64]	Aslan et al. (2014)	Pilot short-term cohort	Turkey	n/a	Apparent history of stroke, coronary heart disease, arrhythmia, peripheral artery disease, severe kidney dysfunction, liver disease, thyroid	Plasma levels of PUFAs	Serum PGE_2, glucose and insulin levels and insulin resistance

					dysfunction, infectious disease		
[65]	Lopes et al. (2015)	Cohort	Brazil	Volunteered	n/a	Metabolomics data for metabolic and lipoprotein profiles; plasma fatty acid profile	n/a
[66]	Forbes et al. (2016)	Cohort	USA	Female; T2DM	Age < 18 yr or > 65 yr; BMI < 35 kg/m^2.	Plasma phospholipid FAs	Body fat composition, anthropometric measures and dietary intake
[67]	Lin et al. (2016)	Cohort	Norway	BMI > 40 kg/m^2, or BMI > 35 kg/m^2 and the presence of obesity-related disease T2DM for BPD/DS Control group: from the same region in Norway with BMI 24.5 ± 2.8 kg/m^2 who were not taking omega-3 fatty acid supplements or lipid-lowering agents	Alcohol or drug abuse; active psychosis; using omega-3 fatty acid supplements	Serum levels of 16 FAs including EPA/AA ratio	n/a
[68]	Lin et al. (2016)	Cohort	Norway	Age 18–60 yr, BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 and the	Pregnancy, heart disease, drug or alcohol abuse, previous bariatric surgery,	Serum FAs	Comparing total FA level between the obese cohort during

				presence of obesity-related disease Control group: Inclusion criteria were age 18–60 yr and BMI in the range 18.5–30 kg/m^2	mental disorder or physical impairment Control group: pregnancy, smoking, drug abuse, use of lipid-lowering drugs and established CVD, type 2 diabetes and cancer. LSG controls: alcohol or drug abuse and active psychosis		lifestyle treatment, matching cohorts of healthy subjects and patients subjected to bariatric surgery
[69]	Walle et al. (2017)	Cohort	Finland	n/a		FAs in serum triglycerides, cholesteryl esters and phospholipids, and subcutaneous adipose tissue triglycerides	Changes in the subcutaneous adipose tissue mRNA expression of selected genes involved in FA metabolism
[70]	Hovland et al. (2017)	Cohort	Norway	n/a	Patients in the intervention group who did not achieve 10% preoperative weight loss through lifestyle changes were excluded from the study	Plasma FAs	n/a
[71]	Garla et al. (2019)	Interventional trial part of a larger cohort study with 2 yr follow up	Brazil	Female; BMI ≥35 kg/m^2; age of 18-60 yr; proven diagnosis of T2DM (fasting plasma glucose ≥ 126 mg/dL and haemoglobin A1c > 6.5%) and/or use of	Use of insulin, diagnosis of thyroid or hepatic diseases, subjects undertaking alternative bariatric surgery, refusal to participate in the study, current or recent participation in another interventional study	Dietary ingestion and plasma concentrations of PUFAs; intestinal expression of genes involved in PUFA biosynthesis	n/a

				oral antidiabetic medication, and absence of *Helicobacter pylori* infection			
[72]	Azar et al. (2019)	Cohort: Patients involved in RCT (6 m), data for treatment groups combined	Israel 2014-15	Age between 18 and 65 yr; BMI > 40 kg/m^2 or > 35 kg/m^2 with co-morbidities, approval to undergo BS, and ultrasound-diagnosed NAFLD	Infection with hepatotrophic viruses (hep B and C), fatty liver suspected to be secondary to hepatotoxic drugs, excessive alcohol consumption, use of antibiotics or probiotics in the past 3 months or use of antibiotics for > 10 days during the study, previous BS; Diabetic patients with antidiabetic medications, other than exclusive treatment with metformin at a stable dose for at least 6 months	Circulating endocannabinoids (eCBs) and related molecules	Examination of the association between eCBs and numerous clinical/metabolic features pre- and post-operatively
[73]	Sarkar et al. (2019)	Cohort	USA	Age ≥ 18 years, with a BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with significant comorbid conditions	Pregnancy, lactation, or history of diabetes; recent substance abuse; weight loss medication use; unstable psychiatric disease	Serum FAs	BMI, fasting serum glucose and insulin
[61]	Pakiet et al. (2020) – data provided by authors	Cohort	n/a	OAGB patients: International Federation for the Surgery of Obesity and with European	Absence of a period of identifiable medical management. Inability to participate in prolonged medical follow-up. Non-	Serum levels of bio-active fatty acids, including branched chain fatty acids and odd chain fatty acids	Expression of genes involved in branched chain amino acids catabolism in adipose tissue

	through email correspondence			Chapter and European Association for the Study of Obesity criteria Control group: indications for surgical treatment in planned mode for non-cancerous reasons	stabilized psychotic disorders, severe depression, personality, and eating disorders unless specifically advised by a psychiatrist experienced in obesity. Alcohol abuse or drug dependencies. Diseases threatening life in the short term. Inability to self-care and lack of long-term family or social support Control: obesity, diabetes, metabolic syndrome, steroid therapy, chronic use of NSAIDs or acute inflammation		
[74]	Mika et al. (2020)	Cohort	n/a	n/a	n/a	Selected serum FAs.	n/a
[75]	Glaysher et al. (2021)	Sub-study of a multicentre randomised controlled, non-blinded trial	UK	Confirmed T2DM diagnosis for at least 1 y, inadequate glycaemic control, on oral anti-hyperglycaemic medications	n/a	Blood concentrations of EFAs and bioactive PUFAs	n/a

Table 2. Summary of Characteristics of Included Studies: Intervention, Sample Size and Methods

Ref no.	Surgical intervention (and comparator if appropriate)	Starting number of participants	Completeness of follow up and accountability for dropouts	Which pool were FAs measured in? (+indicates fasted blood sample)	Timepoints measured
[62]	RYGB	14 (11 Caucasian, 2 Caribbean, and 1 African)	n/a	Serum	Pre-surgery, 3 mo and 6 mo after surgery
[63]	LAGB	15	n/a	Plasma+ phospholipid	Pre-surgery and 12 mo after surgery
[64]	LSG vs controls	10 obese + 11 controls	n/a	Plasma+	1 d pre-surgery, 1 d after surgery, and after post-op oral feeding (time not specified)
[65]	RYGB	10	n/a	Plasma+	Pre-surgery and 12 mo after surgery
[66]	RYGB vs LAGB	18 (13 RYGB, 5 LAGB)	n/a	Plasma+ phospholipid	Pre-surgery, 1 mo and 6 mo after surgery
[67]	BPD/DS vs LSG	36 (12 BPD/DS and 24 LSG) + 136 healthy non-obese men and women controls	2 BPD/DS and 1 LSG patient were excluded because the FA analyses revealed that they used EPA supplements = 10 BPD/DS patients and 23 LSG patients remain No. of patients that did not provide samples: BPD/DS:	Serum+	3 mo and 1 d pre-surgery; 3 d, 3 mo, and 12 mo after surgery

			3 at 3 mo after surgery 1 at 12 mo after surgery LSG: 1 at 1 d before 3 at 3 mo after surgery 5 at 12 mo after surgery		
[68]	Intensive lifestyle intervention (primary aim) compared with 2 control groups: healthy women and 3 mo post LSG surgery patients	31 lifestyle intervention patients. 45 healthy women. 18 post LSG patients	5 lifestyle change patients excluded (3 due to use of lipid-lowering drugs, 2 because of type 2 diabetes). Patients' blood samples that were missing: 2 blood samples at baseline; 1 blood sample after intervention Lifestyle change patients at baseline = 24 Lifestyle change patients to compare with controls n = 25 At 3 mo 1 LSG surgery subject was on lipid-lowering drugs and was excluded; LSG n = 17	Serum^{+}	Lifestyle intervention: Pre-intervention, 3 wk and 6 wk into treatment LSG group: pre-surgery and 3 mo after surgery.
[69]	RYGB	122	n/a	Serum^{+} triglycerides, cholesteryl esters and phospholipids, and adipose tissue triglycerides	Pre-surgery and 12 mo after surgery
[70]	RYGB for BMI < 50 kg/m^2 or duodenal	34 surgical + 17 controls	n/a	Plasma^{+}	At admission, after 3 mo for lifestyle intervention and 12 mo after surgery

	switch for BMI > 50 kg/m^2 vs control				
[71]	RYGB	20	3 patients did not present adequate venous access at any time point studied to enable blood collection for plasma fatty acid analysis; n = 17	Plasma$^+$ phospholipid	Pre-surgery, 3 mo and 12 mo after surgery
[72]	LSG	100	77 attended the 12 mo visit. A total of 65 patients who completed this 12 mo follow-up were included in the analysis	Serum$^+$	Pre-surgery and 12 mo after surgery
[73]	RYGB vs LSG vs weight-matched controls incentivised to maintain weight	38 surgical patients (21 RYGB, 17 LSG) + 19 controls	57 at baseline 56 at 6 mo 41 at 18 mo	Serum$^+$	Pre-surgery (within 4 wk), 6 mo and 18 mo after surgery
[61, 74]	OAGB	50 obese + 32 lean controls 38 patients + 30 lean controls	n/a	Serum$^+$	Pre-surgery, 2 wk and 6-9 mo (data provided by authors) after surgery
[75]	DJBL vs best medical therapy, diet and exercise (control)	170 eligible randomised as 85 DJBL + 85 controls	DJBL: At -2 wk, n = 70 At 10 d, n = 70 At 6 mo, n = 61 At 11.5 mo, n = 52 Control: At -2 wk, n = 70 At 10 d, n = 70 At 6 mo, n = 62 At 11.5 mo, n = 59	Plasma$^+$	2 wk before intervention, 10 d, 6 mo and 11.5 mo after intervention

Table 3. Summary of Study Participants' Characteristics

Ref no.	Age (in years, mean ± SD)	Sex (% female)	Mental/physical health diagnoses or comorbidities	Dietary information
[62]	45.4 ± 3.6	100	35.7% T2DM (4 Caucasians and 1 Caribbean from French Antilles) of 7.4±1.0 years duration	Multivitamins and iron supplements were provided to avoid deficiencies
[63]	43.9 ± 12.9	73.3	n/a	After surgery, patients 'followed a diet'
[64]	SG: 38 ± 11 Control: 41 ± 18	SG: 70 Control: 64	n/a	SG patients were on preoperative diet for 2 weeks. This diet contained liquid protein supplements and sugar-free, non-carbonated, low calorie fluids and required a minimum of 2 litres of fluid intake daily. Female and male patients were aimed to receive 65 and 80 g protein daily, respectively
[65]	n/a	n/a	100% diabetic	n/a
[66]	36.6 ± 2.3	100	44% diabetic (7 RYGB, 1 AGB)	n/a
[67]	n/a	n/a	100% of BPD/DS group diabetic	Advised to increase physical activity and change to a less carbohydrate-rich and more protein-rich diet
[68]	Lifestyle patients: 43.1 ± 11.3 Healthy controls: 40.4 ± 10.6 LSG: 43.1 ± 12.4	Lifestyle patients: 100 LSG: 82.4	n/a	LSG patients were recommended a diet of small protein-rich meals, to avoid sugar and sugar-containing products, to use a multivitamin supplement and 1 g of calcium on daily basis during the first year after surgery
[69]	47.2 ± 8.7	67.2	100% T2DM	Preoperative very low-calorie diet (600–800 kcal) for an average of 4 weeks. After operation, the subjects were instructed to consume 3 teaspoons of rapeseed oil and 6 teaspoons of mainly rapeseed oil based spreads daily, for at least 1–2 years after the obesity surgery. They were also instructed to consume fish 2–3 times a week

[70]	Surgery group: 43.2 ± 9.0 Control: 48.1 ± 14.9	Surgery: 56 Control: 71	50% of surgical group diabetic	n/a
[71]	46.9 ± 6.2	100	100% T2DM	n/a
[72]	42.78 ± 9.27	55.4	n/a	n/a
[73]	≥ 18	100	n/a	n/a
[61]	OAGB: 48.6 ± 10.5 Control: 52 ± 12	Obese group: 84 Control: 66	50% obese group T2DM	Obese patients were advised a low-calorie diet (high-protein, low-fat, and low-carbohydrate meals) for 2–3 months prior to surgery. Patients were required to restrict their caloric intake, often <500 kcal per day. The diet consisted of low-sugar, low-fat, and high-protein liquids/foods, natural (unsweetened) milk or vegan products (pure protein powder was added to these products); it was instructed that food should be frequently consumed and in small portions. The most important recommendation was that protein intake should be greater than 60 g/day. Vitamin regimens specific for bariatric patients were used from the first postoperative day. Omega-3 FA supplementation was not routinely recommended
[74]	OAGB: 48.09 ± 9.57 Control: 49.97 ± 10.92	OAGB: 84.2 Control: 50	34% obese group T2DM	
[75]	DJBL: 51.6 ± 7.8 Control: 52.3 ± 8.3	DJBL: 45.7 Control: 44.3	100% T2DM	Both groups followed a calorie-restricted liquid diet for the 7 days before and 13 days after intervention. This comprised of 125 mL Fortisip Compact drinks (Nutricia, UK): 5 per day for males, 4 per day for females. Patients were also allowed to consume sugar-free and unsweetened drinks and smooth/clear soup (1 medium bowl per day). Participants were recommended to consume 1200-1500 kcal each day for women and 1500-1800 kcal for men. Advice was given in accordance with standard dietary practice,

	including eating 5 meals per day, to control their portion sizes, to increase their intake of low glycaemic index, high protein foods and vegetables and to reduce their intake of alcohol and of foods high in fat and sugar. Participants were advised to include 150 min per week of moderate intensity and 75 min per week of vigorous intensity aerobic activity and muscle strengthening activities on more than 2 days a week.

Table 4. Bias and Quality Assessment. Format adapted from [51] and [52].

Reference	Generation of allocation and concealment (selection bias)	Representative (recruitment bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias limitations
[62]	Not a RCT: treatment is for medical purposes based on clinical grounds	Cohort is reflective of the obese population	Blinding of patients not possible	Blinding of assessor in not mentioned	Complete follow-up	ALA not reported	
[63]	Not a RCT: treatment is for medical purposes based on clinical grounds	Excludes patients with existing endocrine or systemic disease. Age and sex are comparable to the relevant population (majority female which is fitting to obese demographic)	Blinding of patients not possible	Blinding of assessor is not mentioned	Complete follow-up	All PUFAs of interest reported	

[64]	Not a RCT: treatment is for medical purposes based on clinical grounds	Excludes patients with history of cardiovascular disease kidney/liver/thyroid dysfunction	Blinding of patients not possible	Blinding of assessor in not mentioned	Complete follow-up	LA and ALA not reported.	
[65]	Not a RCT: treatment is for medical purposes based on clinical grounds	Insufficient reporting on participants' characteristics	Blinding of patients not possible	Blinding of assessor in not mentioned	Complete follow-up	Exact values are omitted and only increase or decrease is specified	
[66]	Not a RCT: treatment is for medical purposes based on clinical grounds	Cohort is reflective of the obese population	Blinding of patients not possible	Blinding of assessor in not mentioned	Complete follow-up	All PUFAs of interest reported	
[67]	Not a RCT: treatment is for medical purposes based on clinical grounds	Insufficient reporting on participants' characteristics	Blinding of patients not possible	Blinding of assessor in not mentioned	Although exclusions are justified, it is unclear why some patients did not provide samples at certain timepoints	All PUFAs of interest reported	
[68]	Not a RCT: treatment is for medical purposes based on clinical grounds	Excludes patients with mental disability or physical impairment	Blinding of patients not possible	Blinding of assessor in not mentioned	Although exclusions are justified based on criteria, justification for missing samples is not given	All PUFAs of interest reported	Follow up for the two groups not at the same timepoints so cannot make a comparison
[69]	Not a RCT: treatment is for medical purposes	Cohort is reflective of the obese population	Blinding of patients not possible	Blinding of assessor in not mentioned	Complete follow-up	All PUFAs of interest reported	

	based on clinical grounds						
[70]	Not a RCT: treatment is for medical purposes based on clinical grounds	Cohort is reflective of the obese population.	Blinding of patients not possible	Blinding of assessor in not mentioned	Complete follow-up	All PUFAs of interest reported	Results from two types of bariatric surgery are combined
[71]	Not a RCT: treatment is for medical purposes based on clinical grounds	Cohort is reflective of the obese population	Blinding of patients not possible	Blinding of assessor in not mentioned	Fewer than expected samples but reasons for attrition/exclusions were reported	LA not reported	
[72]	Not a RCT: treatment is for medical purposes based on clinical grounds	Excludes patients having used antibiotics within 3 months prior to study; excludes diabetics taking antidiabetic medication	Blinding of patients not possible	Blinding of assessor in not mentioned	Insufficient reporting of attrition	Only AA reported	
[73]	Not a RCT: treatment is for medical purposes based on clinical grounds	Excludes patients with history of diabetes	Blinding of patients not possible	Blinding of assessor in not mentioned	Insufficient reporting of attrition	Only LA and AA reported	
[61]	Not a RCT: treatment is for medical purposes based on clinical grounds	Excludes patients with eating disorders	Blinding of patients not possible	Blinding of assessor in not mentioned	Complete follow-up	All PUFAs of interest reported, yet total n-3 and n-6 PUFAs were omitted despite reported in [74] within the same study	

[74]	Not a RCT: treatment is for medical purposes based on clinical grounds	Cohort is reflective of the obese population.	Blinding of patients not possible	Blinding of assessor in not mentioned	Complete follow-up	All PUFAs of interest reported
[75]	Randomised, controlled, non-blinded trial. Patients were randomised 1:1 to receive non-surgical best medical therapy or Endobarrier treatment.	Cohort is reflective of the obese population	Blinding of patients not possible	Blinding of assessor in not mentioned	Insufficient reporting of attrition; it is unclear why some samples were missing at certain timepoints although all losses are accounted for	All PUFAs of interest reported

Methodologic Quality	Originality	Clarity study design (specific description, clear outcome measure)	Addressing preliminary statistical questions
[62]	Novel profiling in relation to surgery	Clearly described	No power calculation reported; small cohort (n = 14)
[63]	LDL physical properties novel at time of publication	Clearly described	No power calculation reported; small cohort (n = 15)
[64]	Novel contribution evaluating the effect of LSG on plasma PUFA levels	Post-operation oral feeding timepoint is not stated	No power calculation reported; small cohort (n = 21)
[65]	Novel contribution using NMR analysis	Clearly described	No power calculation reported; small cohort (n = 10)
[66]	Compares surgery types	Clearly described	No power calculation reported; small cohort (n = 18)
[67]	Novel by EPA/AA ratio in relation to type of surgery	Clearly described	No power calculation reported; small surgical cohort (n = 36)
[68]	Compares surgery to lifestyle intervention	Clearly described	No power calculation reported; small LSG group (n = 18)

[69]	Only study to measure FAs in TG, PL, CE serum fractions	Clearly described	No power calculation reported (this was acknowledged by authors); cohort size reasonable (n = 122)
[70]	Only study where cohort had a pre-surgery lifestyle intervention (for 3 mo) and continued to be studied from admission through to 1 y post-surgery following this intervention.	Clearly described	No power calculation reported; small surgical cohort (n = 34)
[71]	Novel contribution on the effect of surgery on intestinal expression of genes	Clearly described	No power calculation reported; small cohort (n = 20)
[72]	Novel contribution of the effect on, and of, circulating endocannabinoids after bariatric surgery	Clearly described	No power calculation reported; cohort size reasonable (n = 100)
[73]	Analyses data from a previously published study	Clearly described	No power calculation reported; small surgical cohort (n = 38)
[61]	Same study as [74] but novel contribution of branched chain fatty acid and amino acid evaluation	Clearly described	No power calculation reported; cohort size reasonable (RYGB surgical group n = 50; lean controls n = 32)
[74]	Same study as [61] but reporting different time points	Clearly described	No power calculation reported; small surgical cohort (n = 38)
[75]	Only study reporting on DJBL	Clearly described	No power calculation reported (secondary outcomes from a randomised controlled trial). The trial was powered according to the primary outcome of a reduction in HbA1c concentration of 20% at 12 months. It was estimated that 15% of patients in the control arm and 35% of the DJBL group would achieve this outcome. 73 patients per group would give 80% power to detect this as a significant effect. Adding 10% loss of follow-up increased the sample size to 80 per group. Cohort size satisfactory (n = 170).

Table 5. Summary of FA Data Reported in Included Studies

Ref no	Measured FA units (all are mean ± SD unless otherwise specified)	PUFAs reported	Blood PUFA levels * = significant change from baseline + = surgical intervention group significantly different from control £ = significantly different between treatment groups			Comments and Limitations
			Before (all pre-surgery baseline unless otherwise specified)	After surgery		
[62]	Mean ± SEM (Arbitrary units based on metabolomics; data provided by the authors)			(3 mo)	(6 mo)	Small cohort (n = 14).
		LA	0.55 ± 0.19	0.50 ± 0.11	0.55 ± 0.12	
		AA	0.60 ± 0.27	0.76 ± 0.25	0.86 ± 0.21	
		EPA	0.35 ± 0.22	0.31 ± 0.34	0.33 ± 0.21	
		DHA	0.51 ± 0.21	0.78 ± 0.33	0.84 ± 0.25	
[63]	Weight %			(12 mo)		Small cohort (n = 15).
		LA	17.14 ± 3.28	22.30 ± 2.52*		
		ALA	0.46 ± 0.22	0.40 ± 0.27		
		AA	7.30 ± 1.61	8.69 ± 1.53*		
		EPA	0.77 ± 0.27	0.86 ± 0.45		
		DHA	2.90 ± 1.13	2.71 ± 0.81		
		n-3 PUFAs	5.16 ± 1.61	4.81 ± 1.39		
		n-6 PUFAs	28.20 ± 4.29	34.47 ± 2.89*		
[64]	mg/L		(-1 d)	(1 d)	(post-op feeding)	No specified day since surgery of post-op feeding
			LSG:			
		AA	143.1 ± 44.5	114.7 ± 30.0	159.7 ± 25.0[l+]	
		EPA	5.6 ± 2.5	4.0 ± 1.2	4.2 ± 1.4	
		DHA	38.3 ± 14.8	33.8 ± 11.8	44.6 ± 10.6	Only a small cohort (n = 21); non-randomised as patients were grouped according to clinical criteria
			Control:			
		AA	124.0 ± 27.8	110.5 ± 22.8	117.5 ± 22.7	
		EPA	9.1 ± 7.7	7.9 ± 9.4	7.2 ± 6.4	
		DHA	50.4 ± 13.6	47.4 ± 13.8	51.1 ± 11.2	

								(! = Significant difference between post operation oral feeding and 1 d post surgery)		
[65]	n/a		n/a		(12 mo)					Findings are stated but numerical data not given
		LA			Decreased					
		ALA			Decreased					Small cohort (n = 10)
		AA			Decreased					
		EPA			Decreased					
		DHA			Decreased					
[66]	Median, [IQR]		RYGB:		(Change at 1 mo)			(Change at 6 mo)		Also reported mead acid, which is an indicator of essential FA deficiency; mead acid did not change significantly
	mmol/L	LA	18.67 [17.44, 24.21]		−3.25 [-5.89, −0.92]			−2.25 [−5.19, 0.95]		
		ALA	0.00 [0.00, 0.13]		0.00 [−0.13, 0.09]			−0.05 [−0.13, 0.00]		
		AA	12.28 [10.44, 13.78]		2.74 [1.09, 3.88]			0.53 [−1.15, 2.89]		
		EPA	0.41 [0.32, 0.55]		−0.29 [−0.55, −0.19]£			−0.29 [−0.48, −0.12]£		
		DHA	2.48 [2.26, 2.83]		1.19 [0.81, 1.49]£			0.46 [−0.05, 1.08]		
			LAGB:							Small cohort (n = 15)
		LA	19.78 [18.33, 20.20]		−1.18 [−5.63, −0.57]			−0.15 [−2.87, 0.62]		
		ALA	0.00 [0.00, 0.10]		0.00 [−0.13, 0.08]			0.00 [−0.13, 0.08]		
		AA	13.23 [12.6, 14.27]		0.52 [−6.74, 2.96]			0.33 [−0.28, 0.34]		
		EPA	0.41 ([0.00, 0.46]		0.00 [−0.15, 0.27]£			0.14 [−0.16, 0.79]£		
		DHA	3.12 [2.31, 4.11]		0.11 [−0.74, 0.55]£			0.04 [−1.06, 0.74]		
[67]	(Mean)		(-3 mo)	(-1 d)	(3 d)		(3 mo)		(12 mo)	Small surgical cohort (n = 36).
	μg/g		BPD/DS:							
		LA	961	959	790		738		648*	
		ALA	21.2	24.4	12.4		13.6		15.4	
		AA	246	268	273		293		212*	
		EPA	47.7	48.5	34.8		32.6		26.8*	
		DHA	97.0	107	109		105		82.1*	
			LSG:							
		LA	1004	920	806		923		1044	
		ALA	24.4	20.5	13.1		15.5		18.2	
		AA	269	273	283		322		276	
		EPA	43.2	39.4	27.3		29.9		33.2	

		DHA	95.4	98.8	98.3	104	96.3	
[68]	μg/g		Lifestyle intervention group:		(3 wk) Lifestyle intervention:		(3 mo) LSG:	Shows LA, ALA and EPA are lower after surgery than after lifestyle intervention. Follow-up for the two groups not at the same timepoints so cannot make a comparison; pre-surgery data were not published; does not state which groups the drop-outs are from. Small LSG group (n = 18)
		LA	1512		1195*		955.2[£]	
		ALA	37.7		25.5*		13.2[£]	
		AA	343.7		320.6		308.3	
		EPA	62.3		51.5*		27.7[£]	
		DHA	121.8		134.8		93.8	
[69]	Mol % and absolute values (mg/L) for TGs, CEs and PLs		mol %	mg/L		(12 mo)		
					mol %		mg/L	
		Serum TGs:						
		LA	11.9 ± 2.3	133.9 ± 59.4	12.4 ± 2.6*		92.5 ± 44.8*	
		ALA	1.3 ± 0.4	14.6 ± 7.9	1.3 ± 0.5		10.2 ± 6.8*	
		AA	1.3 ± 0.5	15.1 ± 5.5	1.5 ± 0.5*		11.6 ± 4.6*	
		EPA	0.5 ± 0.3	5.2 ± 2.9	0.6 ± 0.4*		4.2 ± 2.9*	
		DHA	1.4 ± 0.8	17.8 ± 10.2	1.6 ± 1.1		13.2 ± 8.7*	
		Total PUFAs	17.4 ± 3.3	199.5 ± 82.0	18.6 ± 3.7*		141.9 ± 64.1*	
		Total n-3 PUFAs	3.7 ± 1.4	44.8 ± 20.4	4.2 ± 1.7*		33.4 ± 17.1*	
		Total n-6 PUFAs	13.7 ± 2.4	154.7 ± 65.2	14.4 ± 2.7*		108.5 ± 50.2*	
		Serum CEs:						
		LA	45.2 ± 4.9	368.8 ± 107.4	45.4 ± 5.1		377.2 ± 91.5	
		ALA	0.7 ± 0.2	6.0 ± 2.8	0.9 ± 0.2*		7.5 ± 2.8*	

		AA	8.8 ± 2.7	75.2 ± 23.8	7.5 ± 1.8*	67.7 ± 20.5*	
		EPA	1.8 ± 0.8	16.1 ± 8.8	1.7 ± 0.9	15.4 ± 8.3	
		DHA	1.1 ± 0.3	10.6 ± 3.9	1.0 ± 0.3*	9.5 ± 3.2*	
		Total PUFAs	59.4 ± 3.3	492.1 ± 128.8	58.2 ± 4.0*	491.4 ± 109.0	
		Total n-3 PUFAs	3.7 ± 1.0	32.7 ± 13.5	3.6 ± 1.1	32.4 ± 11.6	
		Total n-6 PUFAs	55.7 ± 3.3	459.4 ± 119.6	54.6 ± 4.2*	458.9 ± 103.6	
		Serum PLs:					
		LA	17.3 ± 2.6	197.0 ± 51.9	17.9 ± 2.9	206.0 ± 43.6	
		ALA	0.2 ± 0.1	2.5 ± 1.3	0.3 ± 0.1*	3.5 ± 1.5*	
		AA	10.6 ± 2.5	128.0 ± 33.5	9.7 ± 1.8*	122.1 ± 30.8	
		EPA	1.7 ± 0.7	21.0 ± 10.4	1.7 ± 0.9	21.3 ± 11.1	
		DHA	6.0 ± 1.4	79.0 ± 23.4	5.5 ± 1.4*	73.9 ± 22.2*	
		Total PUFAs	40.9 ± 1.4	492.7 ± 99.3	39.9 ± 1.7*	490.8 ± 82.1	
		Total n-3 PUFAs	9.1 ± 1.9	118.3 ± 33.6	8.8 ± 2.1	116.7 ± 33.2	
		Total n-6 PUFAS	31.8 ± 1.7	374.4 ± 78.0	31.1 ± 2.1*	374.0 ± 65.0	
[70]	Weight %		(At admission)		(12 wk lifestyle intervention)	(12 mo after surgery)	Results from two types of bariatric surgery are described together
		LA	26.0 ± 4.4[+]		24.3 ± 3.3*	25.5 ± 3.5	
		ALA	0.7 ± 0.2		0.6 ± 0.1*	0.6 ± 0.1	
		AA	6.9 ± 1.4		8.7 ± 1.9*	7.3 ± 1.4^	
		EPA	1.1 ± 0.4		0.8 ± 0.4*	1.3 ± 1.0	
		DHA	2.9 ± 0.7[+]		3.3 ± 0.8*	3.5 ± 1.1*^	
						^ = significant difference from 12 wk	Small surgical cohort (n = 34)
[71]	Median, [IQR].				(3 mo)	(12 mo)	Small cohort (n = 20)
	Weight %	ALA	0.51 [0.43; 0.88]		0.38 [0.32; 0.45]*	0.47 [0.40; 0.59]	
		AA	7.47 [5.97; 10.60]		10.01 [8.35; 10.94]*	9.17 [8.13; 10.11]*	
		EPA	0.40 [0.31; 0.63]		0.22 [0.18; 0.29]*	0.26 [0.22; 0.58]*	
		DHA	1.11 [0.96; 1.32]		1.38 [1.21; 1.64]*	1.31 [1.02; 1.68]	
[72]	pmol/mL				(12 mo)		Reason 12 patients lost, from 12 mo follow up post-surgery is not reported
		AA	5931.76 ± 1326.98		5424.01 ± 1459.97*		

[73]	mg/L			(Change at 6 mo)	(Change at 18 mo)	
		LA	RYGB: 328.4 ± 86.2 LSG: 321.7 ± 97.2 Control: 300.5 ± 84.0	RYGB: −63.9 ± 12.8[£] LSG: +10.0 ± 14.2[+£] Control: −29.7 ± 13.9	RYGB: −18.0 ± 14.4[£] LSG: +47.9 ± 15.3[+£] Control: −39.3 ± 15.3	
		AA	RYGB: 85.3 ± 25.1 LSG: 66.0 ± 37.8 Control: 66.4 ± 28.6	RYGB: −10.7 ± 4.7 LSG: +2.3 ± 5.1 Control: −5.2 ± 5.0.	RYGB: −6.4 ± 5.1 LSG: +7.9 ± 5.4[+] Control: −9.7 ± 5.3	
[61,74]	Weight %	OAGB group:	For 2 wk article:	(2 wk)	(6-9 mo)	Small OAGB cohort (n = 38)
		LA	23.00 ± 3.21[+]	20.63 ± 2.79*[+]		
		ALA	0.24 ± 0.11[+]	0.15 ± 0.10*[+]		
		AA	6.20 ± 2.00	7.85 ± 2.12*[+]		
		EPA	0.76 ± 0.45[+]	0.54 ± 0.18*[+]		
		DHA	1.36 ± 0.54	1.42 ± 0.39[+]		
		n-3 PUFA	2.76 ± 0.95	2.54 ± 0.54[+]		
		n-6 PUFA	30.62 ± 1.93[+]	29.68 ± 3.19*[+]		
			For 6-9 mo article:			
		LA	23.0 ± 3.68[+]		22.5 ± 3.73[+]	
		ALA	0.20 ± 0.09[+]		0.21 ± 0.090[+]	
		AA	6.02 ± 1.72		5.53 ± 1.23*	
		EPA	0.70 ± 0.32[+]		0.63 ± 0.23[+]	
		DHA	1.21 ± 0.38		1.07 ± 0.33*	
		Lean controls:	For 2 wk article:			
		LA	26.24 ± 3.85			
		ALA	0.34 ± 0.11			
		AA	5.61 ± 1.15			
		EPA	1.09 ± 0.72			
		DHA	1.14 ± 0.44			
		n-3 PUFA	2.97 ± 1.14			
		n-6 PUFA	33.32 ± 3.96			
			For 6-9 mo article:			
		LA	27.1 ± 3.59			
		ALA	0.33 ± 0.09			
		AA	5.55 ± 1.16			
			1.11 ± 0.61			

		EPA DHA	1.17 ± 0.45				
[75]	Median [IQR] mg/L	DJBL: LA ALA AA EPA DHA	(-2 wk) 567.9 [432.1; 654.5] 13.8 [11.0; 19.8] 146.8 [113.9; 187.5] 17.3 [11.6; 25.7] 36.3 [26.2; 48.3]	(10 d) 389.1 [295.1; 515.6]* 10.9 [8.0; 13.5]* 131.4 [110.0; 160.5]* 8.1 [5.9; 12.7]* 30.3 [23.2; 38.3]*	(6 m) 429.7 [345.6; 502.6]*+$ 11.1 [9.0; 15.2]*+ 134.9 [104.8; 161.5]*+ 14.2 [9.7; 19.3]*+$ 31.7 [26.2; 44.6]*+ $=compared to 10 d within same group	(11.5 m) 470.4 [354.8; 558.5]*$ 12.4 [8.5; 16.5]*+$ 151.9 [111.7; 174.6]*+$ 14.4 [10.4; 20.4]*+$ 34.1 [26.3; 40.5]*+	Incorrect IQR values shown for 6 mo ALA in DJBL group The trial was powered according to the primary outcome of a reduction in HbA1c concentration of 20% at 12 months. It was estimated that 15% of patients in the control arm and 35% of the DJBL group would achieve this outcome. 73 patients per group would give 80% power to detect this as a significant effect. Adding 10% loss of follow-up increased the sample size to 80 per group.
		Control: LA ALA AA EPA DHA	 500.5 [406.0; 615.6] 14.9 [11.5; 22.0] 149.8 [129.3; 189.8] 17.4 [12.8; 26.0] 40.9 [30.3; 53.0]	 397.5 [303.4; 509.8]* 11.5 [8.0; 15.0]* 136.6 [115.7; 165.0]* 9.3 [6.4; 13.6]* 33.6 [27.4; 41.5]*	 485.1 [407.0; 591.8]+$ 13.1 [9.0; 19.9]*+$ 148.2 [134.6; 188.5]+$ 18.5 [12.6; 24.7]+$ 41.4 [30.4; 49.4]+$	 489.9 [392.1; 603.5]$ 12.5 [10.2; 19.2]+$ 159.9 [128.6; 188.8]+$ 19.1 [12.9; 23.1]+$ 42.6 [31.7; 50.7]+$	