# Schwanz Nutrition Journal



# Contents

# SMOF Lipid

Lipid emulsions are a standard component of parenteral nutrition regimens, though the ideal composition is debatable. Concerns have been raised about the effects of lipid emulsions that are primarily composed of soybean oil. In ICU patients, there is a concern that receiving excessive linoleic acid from soybean oil may have proinflammatory or immunosuppressive effects, leading to increased rates of infection or poorer outcomes. Another concern is with long-term use of parenteral nutrition, which has been associated with an increased risk of liver disease.

Numerous alternative lipid emulsions have been developed that include different combinations of soybean oil, olive oil, MCT from coconut oil, and fish oil. SMOFlipid is one of the newer emulsions and contains all four of these oils. Many reviews have been published on SMOFlipid previously, but only bits and pieces of the studies completed have been included. This review will focus on the effects of SMOFlipid in an adult population. A total of 12 studies were found and included in this review[1,2,3,4,5,6,7,8,9,10,11,12]. An additional study was found that was completed but it appears that it was never published and the results were not reported (Clinicaltrials.gov ID: NCT00600912). The vast majority of studies were short-term trials in postoperative patients that required TPN for less than one week. Two studies were found that provide information on the risk of liver disease with longer-term use[2,12].

In the short-term studies, the duration of intervention ranged from a single infusion to seven days, sample size in most studies was small to moderate with mostly 30-80 subjects, though one study had 249 subjects[1]. The outcomes included were typically changes in lab values and vital signs, with some studies including length of stay, adverse events, and mortality. All but one of the studies was completed in postoperative patients, with one completed in healthy subjects[4]. Most studies were comparisons of SMOFlipid to soybean oil alone, with a few studies that compared SMOFlipid to a combination of either soybean oil and MCTs or soybean oil and olive oil.

Results of the short-term studies primarily showed that there was no difference or a minimal difference between SMOFlipid and other lipid emulsions. The largest study completed showed no differences in any outcome, which included lab values, vital signs, hospital length of stay, and mortality[1]. Most other studies showed no difference in the majority of outcomes. Occasionally differences were found, typically in favor of the SMOFlipid group. Nine studies evaluated changes in triglycerides, with three showing more favorable changes in the SMOFlipid group[4,7,8] and six showing no difference[1,2,3,5,6,9]. Three studies reported more favorable effects on inflammatory markers in the SMOFlipid group[6,8,10]. Other positive outcomes were not consistently seen and likely random variation. The only negative outcome seen was an increase in headaches with SMOFlipid, though this was a study of a single infusion in healthy subjects[4].

These studies were quite consistent, though there are a few aspects that need to be understood for proper interpretation. Most studies were small and short-term and thus had limited statistical power to detect differences between the groups. It is likely that any large effects from SMOFlipid would have been detected in these studies, but small to moderate effects could likely be missed due to the low statistical power. Also, most studies had an extensive list of exclusion criteria with several common conditions such as diabetes mellitus, obesity, and any history of renal, liver, or heart conditions. This begs the question that if these subjects are excluded from the studies, should they also be excluded from receiving SMOFlipid in clinical practice? At the same time, no studies have shown that soybean oil-based lipid emulsions would be tolerated better in these populations.

Overall, the short-term studies show that SMOFlipid is typically well tolerated and very comparable to other lipid emulsions in postoperative patients. It is unlikely that any large differences in outcomes will be seen with SMOFlipid, but small or moderate differences may exist.

Further studies are needed to establish the effects of SMOFlipid in a more broad patient population.

There were two longer-term studies that focused more on the effects of SMOFlipid on liver function. The first study was completed in 75 subjects that were unable to maintain their nutrition via enteral or oral nutrition, and completed the study intervention for four weeks[2]. Subjects were randomized to either SMOFlipid or soybean oil alone as their lipid emulsion. Results showed minimal differences between the two interventions though subjects in the SMOFlipid group showed lower AST, ALT, and total bilirubin after four weeks, and also had fewer adverse events that were classified as serious. The second trial included 65 subjects with chronic intestinal failure that completed intervention for 12 months[12]. They were randomized to one of four groups: SMOFlipid, soybean oil alone, soybean oil with olive oil, or soybean oil with MCT. Results showed that after 12 months of intervention, no significant differences were found in measures of liver function including bilirubin, alkaline phosphatase, SGPT, SGOT, and GGTP.

Overall, these longer-term studies show similar results to the short-term studies, showing that SMOFlipid is very comparable to other lipid emulsions and might have beneficial effects. There is a lot less data on the long-term effects of SMOFlipid, and the two studies reviewed have conflicting results. However, both showed that SMOFlipid can be well tolerated over longer periods of time.

**Is SMOFlipid Superior?**

The primary question this review seeks to answer is whether SMOFlipid should be recommended over other lipid emulsions. One advantage that older soybean oil emulsions have is the long history of use with relative safety and tolerance. Due to the lack of alternatives, soybean oil-based emulsions were the lipid source for nearly all types of patient populations in the past. These emulsions seem to be tolerated well by most patients and provide needed calories and nutrients. However, there are also well-known complications of TPN, and the cause of these complications has not been definitively proven. It's possible that the lipid emulsions traditionally used have been contributing to these complications, or at least have not been helping to remedy them. Newer lipid emulsions such as SMOFlipid may help prevent these complications or help remedy the problems caused by other TPN components. Fish oil, MCTs, and micronutrients in olive oil all have the potential to provide benefit and possibly help improve outcomes. So does the research that has been done thus far show that these additional lipid components improve outcomes? Not necessarily. The primary takeaway from the studies completed so far is that SMOFlipid seems to be well tolerated and safe to use in the patient populations tested. The studies were really not designed to be a good test of the therapeutic potential of SMOFlipid with small sample sizes and short study durations. Again, the research shows that it is unlikely that SMOFlipid has a large beneficial impact on outcomes, but the studies really did not prove that a small to moderate beneficial impact is not present. It's possible that there are small to moderate negative effects with SMOFlipid too, but since a number of studies showed one or more positive impacts with minimal negative outcomes found, it's more likely that SMOFlipid has beneficial effects. Numerous studies are currently in progress and will hopefully provide more definitive results to base clinical decisions on.

**Overall Conclusions**

SMOFlipid appears to be safe to use and well tolerated in most patient populations. In subjects with diabetes mellitus, obesity, or history of liver, renal, or heart problems, it is more unclear what effects SMOFlipid will have. SMOFlipid will likely not have any major impact on outcomes, but small to moderate effects are possible and should be studied further, especially with longer use.

**References**

1. Mertes, N. et al. Safety and efficacy of a new parenteral lipid emulsion (SMOFlipid) in surgical patients: a randomized, double-blind, multicenter study. Annals of Nutrition and Metabolism 2006. 50:253-259.

**Summary**

This was a randomized, double-blind trial completed at 18 centers in Europe that compared two different lipid emulsions as part of a TPN regimen in surgical patients. A total of 249 subjects with an average age of 60 years were randomized into the trial and received TPN for five days after surgery. One group received a soybean oil-based lipid emulsion and the second group received a mixed lipid emulsion containing soybean oil, MCTs, olive oil, and fish oil. Results showed no major differences in any outcomes including changes in triglyceride levels, cholesterol or phospholipid levels, blood pressure, heart rate, length of hospital stay, or mortality.

**Analysis**

Subjects were enrolled in the immediate postoperative period after having elective abdominal or thoracic surgery, and were included if they were expected to need TPN for at least five days. Exclusion criteria were fasting triglycerides >250 mg/dL, total cholesterol >300 mg/dL, diabetes mellitus, BMI > 30 kg/$m^2$, hepatic or renal insufficiency, acute or chronic heart insufficiency, acute or life-threatening conditions such as myocardial infarction, cerebrovascular accident, or history of drug abuse, among other criteria.

It was estimated that 88 subjects would be needed in each group to provide 85% statistical power to detect a difference of 8 mg/dL/day in area under the curve of serum triglycerides with a P-value of 0.05. A total of 249 subjects were randomized into the trial. An intention to treat analysis as well as a per-protocol analysis that excluded 50 subjects were completed.

Subjects were randomized to one of two groups that differed by the source of lipids provided with the TPN. One group received Lipovenoes 20% (200 g/L soybean oil) and the second group received SMOFlipid 20% (60 g/L soybean oil, 60 g/L MCT, 50 g/L olive oil, and 30 g/L fish oil).

TPN was started on the first postoperative day and was provided as 1.5 grams of fat per kg of bodyweight per day. Lipids were provided over 24 hours along with amino acids and glucose. Subjects were provided a total calorie level of 30-35 kcal/kg bodyweight per day. Oral and enteral nutrition were not allowed during the five days postop except for water and tea. Blood and urine samples were taken before and during the intervention.

Outcomes of the study included measures of metabolic efficacy, product safety, and tolerance. Metabolic efficacy was assessed with serum levels of triglycerides, phospholipids, and total cholesterol. Safety and tolerance were assessed by laboratory values including hematology, chemistry, and coagulation profiles. Other measures included blood pressure, heart rate, body temperature, bodyweight, adverse events, hospital length of stay, and mortality.

Groups were reported to be well-matched at baseline. Results showed no difference in triglyceride levels between the groups, with a gradual increase during the intervention in both groups. There were also no differences found in other outcomes measured including changes in total cholesterol or phospholipid levels, length of stay, mortality, adverse events, heart rate, blood pressure, and bodyweight.

One aspect of the study that needs to be considered is the fact that all subjects received TPN for five days. Typically the length of time a person needs TPN will vary depending on the clinical situation, but it seems that all subjects regardless of the circumstances were provided TPN for five days, with limited information on measures of tolerance or adequacy of intake when TPN was discontinued. However, this will still provide a good comparison of short-term changes in lab values and measures such as heart rate and blood pressure since all subjects received the same length of treatment.

It's concerning that no trial registration was found for this study, given that it was published in 2006, well after clinical trial registers were widely used. Thus, it is uncertain if the primary outcome was chosen before the results were available. Also, the primary outcome was only presented for the per-protocol population, with no details provided for the intention to treat analysis.

**Risk of Bias**

Intention to treat analysis: Included

Blinding: Double-blind

Funding Source: Fresenius Kabi, the manufacturer

Clinical Trial Registration: None found.

Other sources of bias: None noted

Overall risk of bias: High

**Implications**

Short-term provision of SMOFlipid as part of a TPN regimen appears comparable to Lipovenoes (soybean oil) on laboratory and clinical outcomes in patients that underwent elective surgery. Further research is needed to confirm the results due to the high risk of bias; also, further studies should include a wider variety of subjects, as many common medical conditions were exclusion criteria for this study.

2. Klek, S. et al. Four-week parenteral nutrition using a third generation lipid emulsion (SMOFlipid) – a double-blind, randomized, multicenter study in adults. Clinical Nutrition 2013. 32:224-231.

**Summary**

This was a randomized trial completed in seven different countries that compared two different lipid emulsions that were part of a TPN regimen. A total of 75 subjects entered the trial and were randomized to receive either soybean oil (Intralipid) or a mixture of soybean oil, MCT, olive oil, and fish oil (SMOFlipid) for a period of four weeks. Outcomes were mostly based on laboratory values and vital signs, though adverse events were also reported. Results showed minimal differences between the two interventions though subjects in the SMOFlipid group showed lower AST, ALT, and total bilirubin after four weeks, and also had fewer adverse events that were classified as serious.

**Analysis**

Subjects were included in the study if they were between 18 and 85 years of age and needed parenteral nutrition due to an inability to sustain adequate oral or enteral nutrition for at least four weeks. Subjects were excluded if they had a hypersensitivity to any component of the lipid emulsions, hypertriglyceridemia, disorders of lipid metabolism, liver insufficiency, renal insufficiency, acute shock, or chemotherapy during or within four weeks prior to starting the study.

Subjects were randomized to receive either SMOFlipid (soybean oil, MCT, olive oil, fish oil) 20% or Intralipid (soybean oil) 20% as part of 3-in-1 TPN regimens. Subjects received their treatment for four weeks, and fish oil capsules were not allowed during treatment. At baseline, each week during the intervention, and at the end of the trial, measurements were taken that included laboratory values and vital signs.

A total of 75 subjects were randomized into the study; two subjects were not included in the analysis due to not receiving any of the intervention. The most common indication for TPN was short bowel syndrome. At baseline, the groups were well matched except that the soybean oil group was significantly younger than the SMOFlipid group (53.2 vs 45.2 years; P=0.02). Average duration of treatment was 30.2 days in the SMOFlipid group and 29.6 days in the Intralipid group. No differences occurred in the volume of daily TPN infusion or total fat, glucose, or amino acid provision.

A total of 82 adverse events were documented during the intervention, with 51 occurring in 21 patients (53.8%) in the Intralipid group and 31 adverse events in 15 patients (44.1%) in the SMOFlipid group (P=0.11). There were 2 serious adverse events in 2 subjects in the SMOFlipid group and 8 subjects with a total of 10 serious adverse events in the Intralipid group (P=0.03). Biochemical laboratory measurements were no different between the groups except for liver function tests. At the end of the trial alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin decreased in the SMOFlipid group and all showed a slight increase in the Intralipid group. The difference in

these variables between groups was statistically significant at the end of the trial. Triglycerides were stable in both groups during the intervention. Vital signs and hematological values showed no differences between groups.

**Risk of Bias**

Intention to treat analysis: Not included. The authors referred to their analysis as intention to treat, but two randomized subjects were not included because they didn't receive treatment.

Blinding: Double-blind

Funding Source: Fresenius Kabi, the manufacturer of both products tested.

Clinical Trial Registration: Clinicaltrials.gov ID: NCT00451646; no issues found.

Other sources of bias: None noted

Overall risk of bias: Moderate to high

**Implications**

When provided as part of a typical TPN regimen, SMOFlipid appears to show similar efficacy and tolerance to Intralipid in subjects unable to maintain adequate oral or enteral intake, and may be less likely to result in liver issues. These results should be confirmed in larger and longer-term RCTs due to the moderate to high risk of bias, with more focus on long-term clinical outcomes rather than only lab values and vital signs.

3. Ma, C. et al. A double-blind randomized study comparing the efficacy and safety of a composite vs a conventional intravenous fat emulsion in postsurgical gastrointestinal tumor patients. Nutrition in Clinical Practice 2012. 27(3):410-415.

**Summary**

This was a randomized, double-blind trial that compared the safety and tolerance of SMOFlipid to a lipid emulsion of soybean oil and MCT only. A total of 40 subjects that had surgery for gastrointestinal tumors were included in the study and provided the TPN regimen for five days. Outcome measures included numerous laboratory variables, clinical outcomes, hospital length of stay, and adverse events. Results showed the only difference between the groups was a slightly lower LDL-cholesterol level in the SMOFlipid group, showing that both lipid emulsions were very comparable.

**Analysis**

Subjects were included in this study after elective surgery on the digestive tract at Kaohsiung Medical University Hospital in Taiwan. Subjects were excluded if they had a hypersensitivity to any part of the intervention, serum albumin <2.5 g/dL, diabetes mellitus, fasting serum triglyceride >250 mg/dL, BMI >30 kg/$m^2$, renal disease, liver disease, heart failure, or if they had a life-threatening illness, among other criteria. The most common condition leading to surgery was colon cancer.

Parenteral nutrition depended on the subject's clinical situation and followed standard hospital procedures, apart from the lipid emulsions. Subjects were randomized to receive either the SMOFlipid (soybean oil, olive oil, MCT, fish oil) or a lipid emulsion that was 50% soybean oil and 50% MCT. TPN with lipids was provided for five consecutive days following surgery.

Outcomes of the study included numerous laboratory measures (including glucose, triglycerides, albumin, inflammation-related cytokines, C-reactive protein, and liver enzymes, among others), clinical course, adverse events, and hospital length of stay. Groups were well-matched at baseline.

Results showed the only difference between the groups was a lower LDL-cholesterol in the SMOFlipid group. All other measures showed no significant difference between groups.

Perhaps the largest limitation of this study is the small sample size and limited statistical power. No formal statistical power analysis was found; it is unlikely this study would be able to show small differences between the groups. Additionally, it is concerning that no clinical

trial registration was found for this study which was published in 2012, well after clinical trial registers were standard practice. Overall, it shows that there are no major differences between the groups other than LDL-cholesterol, but it's unknown if small differences exist. Additionally, the length of time that parenteral nutrition is needed will vary depending on the clinical situation; in this study it seems that all patients were kept on TPN for five days regardless of the situation.

**Risk of Bias**

Intention to treat analysis: Appears to be intention to treat, though no confirmation was found.

Blinding: Double-blinded

Funding Source: Appears to be independent funding from the Excellence for Cancer Research Center by the Department of Health, Executive Yuan, Taiwan, and the Cancer Center of Kaohsiung Medical University Hospital.

Clinical Trial Registration: None found

Other sources of bias: None noted

Overall risk of bias: Moderate to high

**Implications**

There doesn't appear to be any major difference in the tolerance or safety of SMOFlipid compared to a mixture of soybean oil and MCT alone when provided short-term to post-surgical patients. Larger studies with a longer duration are needed to confirm these results and determine if small to moderate differences exist, and to confirm changes in LDL-cholesterol levels.

4. Schlotzer, E. et al. Elimination and tolerance of a new parenteral lipid emulsion (SMOF) – A double-blind cross-over study in healthy male volunteers. Ann Nutr Metab 2004. 48:263-268.

**Summary**

This was a randomized, double-blind, cross-over study completed in healthy volunteers that compared the tolerance and metabolism of SMOFlipid (soybean oil, MCT, olive oil, and fish oil) to Lipovenoes (soybean oil). A total of 12 healthy male subjects completed the trial and received both infusions. Outcome measures included blood pressure, heart rate, 12-lead electrocardiogram changes, adverse events, and numerous laboratory and urine variables. Results showed no major differences in most outcome measures, with a slightly lower increase in serum triglycerides with SMOFlipid and also slightly more adverse events, mostly headache, with SMOFlipid.

**Analysis**

Subjects included 12 healthy male volunteers with an average age of 26 years and an average weight of 73 kg. Subjects received two different IV lipid emulsions through a peripheral vein for six hours. The treatments were given after an overnight fast, six days apart, and the order in which they were provided was randomized. The two lipid emulsions were SMOFlipid (soybean oil, olive oil, fish oil, and MCT) and Lipovenoes (soybean oil).

Blood and urine samples were taken before, during, and after the lipid infusions to measure triglycerides, cholesterol, hematology variables, liver enzymes, electrolytes, and glucose, among others. Blood pressure, body temperature, heart rate, a 12-lead electrocardiogram, and inspections of the injection site were also completed before, during, and after the infusions. Adverse events were also recorded.

All subjects that entered the trial completed it fully. Results showed that serum triglyceride concentrations increased in both groups, with a steady state being reached after three hours of infusion in the SMOFlipid group and after five hours in the Lipovenoes group. After the infusion, triglyceride levels decreased to baseline levels after two hours in the SMOFlipid group and after three hours in the Lipovenoes group. Serum triglyceride concentrations at the end of the six-hour infusion were significantly lower in the SMOFlipid group (244 vs 331 mg/dL; $P<0.05$). Changes in free fatty acids showed no differences between the groups. Serum levels of free glycerol increased in the SMOFlipid group with only a slight increase in the Lipovenoes group; no report of statistical significance was provided. Other

clinical and laboratory variables showed no differences between the groups. Five subjects reported adverse events with SMOFlipid and one with Lipovenoes, the most common adverse event being headache. No report on the statistical significance or full accounting of adverse events was given, but adverse events were reported to be mild and completely reversible.

This was a preliminary study designed to compare the tolerance and metabolism of the lipid emulsions, rather than their effects on clinical outcomes. Both seem to be metabolized very similarly, with slight differences in triglyceride levels. The report of adverse events, mostly headache, is somewhat concerning given the healthy population and short-term infusion. This should be monitored in further studies.

**Risk of Bias**

Intention to treat analysis: Included

Blinding: Double-blind

Funding Source: Not reported, though the lead author was reported to be an employee of Fresenius Kabi, the manufacturer.

Clinical Trial Registration: None found

Other sources of bias: None noted

Overall risk of bias: Moderate to high

**Implications**

SMOFlipid and Lipovenoes appear to be tolerated and metabolized in a similar manner in healthy subjects with a short-term infusion. Larger, longer RCTs should assess the clinical outcomes and monitor for adverse events including headaches.

5. Grimm, H. et al. Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. Eur J Nutr 2006. 45:55-60.

**Summary**

This was a randomized, double-blind trial that compared two different lipid emulsions on changes in lab values and clinical outcomes. A total of 33 patients that had major abdominal surgery were randomized to receive either SMOFlipid (soybean oil, MCT, olive oil, and fish oil) or Lipovenoes (soybean oil) as part of their TPN regimens for five days. Major outcome measures included hospital length of stay, blood pressure, heart rate, adverse events, changes in triglyceride and cholesterol levels, and changes in phospholipid fatty acid concentrations. Results showed that the SMOFlipid group had a shorter hospital length of stay and had several changes in phospholipid fatty acid profile including increased n-3 fatty acids and decreased n-6 fatty acids compared to the Lipovenoes group.

**Analysis**

Subjects were recruited for this study from two hospitals in Germany if they received major abdominal surgery and needed TPN. Subjects were described as well-nourished, though criteria this was based on were not provided. Subjects were excluded if they had diabetes mellitus, hyperlipidemia, BMI > 30 $kg/m^2$, if they had chronic renal, liver, or heart diseases, or if they had acute or life-threatening illnesses, among other criteria.

Subjects were provided with TPN over five days postoperatively with a standard amount of calories and amino acids based on bodyweight. Subjects were randomized to receive one of two different lipid emulsions as a part of their TPN regimen: SMOFlipid or Lipovenoes. Outcomes that were assessed included blood pressure, heart rate, body temperature, body weight, allergic reactions, nausea, blood parameters focusing on lipid metabolism, and length of hospital stay, among other outcomes. Changes in fatty acids in plasma, leukocytes, and platelet phospholipids were also assessed in addition to neutrophil leukotriene profile.

Subjects were well-matched at baseline. The most common surgical sites included the esophagus, stomach, and intestines. Results showed no differences between the groups in adverse events or changes in triglycerides, phospholipids, or cholesterol. Phospholipid-derived fatty acid patterns were

significantly different between the groups: compared to the Lipovenoes group, the SMOFlipid resulted in higher levels of total n-3 fatty acids, EPA, and DHA, and lower levels of total n-6 fatty acids and linoleic acid. Both groups showed a decrease in arachidonic acid, though the Lipovenoes group showed a larger decrease. The authors also reported that the SMOFlipid group showed more beneficial changes in leukotrienes, which they report should help promote the synthesis of anti-inflammatory compounds. Length of hospital stay was found to be significantly shorter in the SMOFlipid group (13.4 vs 20.4 days; P<0.05).

The primary limitations of this study include the short-term duration and focus primarily on changes in laboratory values. The authors believe that the changes seen would be beneficial on outcomes due to the anti-inflammatory effects, which is supported by the shorter hospital length of stay.

**Risk of Bias**

Intention to treat analysis: Appears to be intention to treat, though no confirmation was found.

Blinding: Double-blind

Funding Source: Funded by industry: Fresenius Kabi

Clinical Trial Registration: None found

Other sources of bias: None noted

Overall risk of bias: Moderate to high

**Implications**

In post-surgical patients that need short-term TPN, using a mixed lipid emulsion such as SMOFlipid that includes soybean oil, MCT, olive oil, and fish oil will likely result in higher levels of phospholipid n-3 fatty acids, EPA, and DHA with lower levels of n-6 fatty acids such as linoleic acid compared to a lipid emulsion of soybean oil only. The same lipid emulsion may also decrease hospital length of stay. Further RCTs are needed to confirm these results due to the risk of bias, small sample size, and short study duration.

6. Metry, A. et al. SMOFlipid vs Intralipid in postoperative ICU patients. Enliven: Journal of Anesthesiology and Critical Care Medicine 2014. 1(6):015.

**Summary**

This was a randomized, double-blind trial that compared SMOFlipid to Intralipid in postoperative patients needing TPN. Outcomes assessed included laboratory measures of lipid profile, renal and liver function, coagulation, inflammatory markers, vital signs, and clinical outcomes. A total of 83 subjects completed the trial and received seven days of parenteral nutrition. Results showed no significant differences between the groups for clinical outcomes; decreased interleukin-6 was found in the SMOFlipid group with no other laboratory differences.

**Analysis**

Subjects were recruited from September 2012 to April 2014 in Egypt if they were admitted to a surgical ICU after a major operation. Subjects were excluded if they had an allergy to egg, soybean, or any other component of the interventions or if they had shock, diabetes mellitus with recent DKA, an APACHE II score >25, abnormal renal or liver function, hypertriglyceridemia, or other disorders of lipid metabolism, among other criteria.

Subjects all received parenteral nutrition for at least seven consecutive days after surgery with no difference in the amount of macronutrients provided; both groups were provided with 35 kcal/kg bodyweight. Subjects were randomized to receive one of two different lipid emulsions; group one received Intralipid (soybean oil) and group two received SMOFlipid (soybean oil, MCT, olive oil, fish oil). PN regimens were provided over 12-16 hours per day. Outcomes measured included heart rate, blood pressure, body temperature, laboratory measures of liver and renal function, coagulation profile, lipid profile, interleukin-6, morbidity, mortality, and infectious complications. Blood was drawn for analysis at baseline and after four and seven days of PN use.

Ninety subjects were enrolled into the study; three from the Intralipid group and four from the SMOFlipid group did not complete the study due to early stoppage of the PN or complications. It was not reported if PN was stopped early due to successful advancement of an oral diet or due to deterioration in clinical status. The groups were well-matched at baseline. Results showed no differences in vital signs, lipid profile, markers of renal or liver function, ventilator days, ICU length of stay, hospital length of stay, or mortality. The only difference found between groups was a larger decrease in interleukin-6 (a marker of inflammation) in the SMOFlipid group.

Limited details were provided about certain aspects of this trial. It is unclear if all patients were designated to a seven-day period of PN provision after surgery, or if they were advanced to an oral diet as tolerated prior to seven days if possible. There were a few subjects not included in the analysis due to not completing the seven days of intervention. No statistical power analysis was provided, so it is unclear what effect size this study would be able to detect. It seems to have a sample size large enough to give reasonable power to detect differences in lab values, but likely would only be able to detect a large difference in clinical outcomes.

**Risk of Bias**

Intention to treat analysis: Not included; subjects that received PN for less than seven days were not included in the analysis.

Blinding: Double-blind

Funding Source: No mention of funding source was found

Clinical Trial Registration: None found

Other sources of bias: Given the numerous outcome measures and only one significant difference between the groups, it is certainly possible that random chance alone could account for the difference; no prospectively defined primary outcomes were mentioned.

Overall risk of bias: High

**Implications**

SMOFlipid and Intralipid seem to be very comparable in terms of effects on laboratory parameters in postoperative patients receiving parenteral nutrition for seven days, with the majority of outcome measures showing no difference between the groups. Due to the high risk of bias and limited details provided, further studies are needed to confirm these results and assess if the difference in interleukin-6 is replicable, and if there would be any difference in clinical outcomes with more statistical power.

7. Wu, M. et al. Randomized clinical trial of new intravenous lipid (SMOFlipid 20%) versus medium-chain triglycerides/long-chain triglycerides in adult patients undergoing gastrointestinal surgery. JPEN 2014. 38:800-808.

**Summary**

This was a randomized trial that compared two different lipid emulsions in postoperative patients in Taiwan. A total of 35 subjects completed the trial with at least five days of parenteral nutrition; subjects were randomized to receive either SMOFlipid or Lipovenoes MCT. Outcome measures included laboratory values, vital signs, clinical outcomes, mortality, and length of hospital stay, among others. Results showed no major differences for most outcome measures. Both groups showed increased triglyceride levels during the study, but the increase was smaller in the SMOFlipid group (P=0.029). This study had a high risk of bias and should be interpreted with caution.

**Analysis**

Subjects were recruited for this study between November 2008 and September 2010 if they had gastrointestinal surgery at the National Taiwan University Hospital. Subjects were excluded if they had diabetes mellitus, hyperlipidemia, BMI >30 $kg/m^2$, chronic heart, liver, or renal diseases, acute or life-threatening illnesses, or hypersensitivity to any ingredient of the interventions, among other criteria.

Subjects were started on parenteral nutrition the day after surgery and received it for five days. Subjects were randomized with computer-generated block randomization to receive lipids as either SMOFlipid (soybean oil, MCT, olive oil, fish oil) or Lipovenoes MCT (50% soybean oil, 50% MCT). Macronutrient provision in both groups was equal, with a goal of 30 kcal/kg bodyweight and 1.5 g/kg amino acids per day. Standard procedures were followed for other aspects of the PN regimens which were provided as 3-in-1 solutions. The authors believed they would have enough statistical power to show safety and tolerance of the intervention with 15 subjects in each group, though few details were provided regarding which outcome this was based on and what level of statistical power was desired.

Outcome measures of the study included heart rate, body temperature, blood pressure, bodyweight, medication use, fluid input, blood sugar control, hospital length of stay, and complications. Several laboratory measures were also assessed that included markers of inflammation, oxidative stress, lipids, and a routine biochemistry panel.

A total of 40 subjects were initially enrolled in the study and randomized. Five subjects in the Lipovenoes MCT group did not finish the study due to withdrawal of consent (2), unstable vital signs (2), or allergic reaction (1). Thus, a total of 35 subjects with an average age of 57 years completed the trial. Gastric adenocarcinoma was the most common indication for surgery, and subjects were well-matched at baseline. Results showed no differences occurred in mortality, hospital length of stay, or incision infections. Minimal differences were found in laboratory parameters, though the SMOFlipid group showed a smaller increase in triglycerides (P=0.029). No differences were found in markers of oxidative stress or inflammation including interleukin-6, C-reactive protein, or TNFa, among others.

The authors were not very clear with some of the results by not indicating if the intention to treat population was presented or the per protocol population was presented. Either way it will be difficult to have a fair comparison of certain outcomes such as triglyceride levels. Using the intention to treat population will have less risk of bias, but it would include five subjects that did not receive IV lipid emulsion throughout the study to the other group with 100% of subjects receiving IV lipids throughout the study, and thus more likely to have an increase in triglycerides. In the per protocol population, the risk of bias is increased, as subjects with less favorable changes in lab values could be excluded intentionally, but it will provide more of a fair comparison given the equal infusion of lipids. It was also unclear, though it seemed that the subjects were given five days of PN regardless of the clinical situation. This will provide a better comparison of the tolerance and lab changes given the equivalent PN provision, but will be less relevant on the clinical outcomes – if one intervention results in improvement to the extent that the subject could be started on an oral diet, but they are kept on PN because of the study protocol, possible clinical benefits may be masked. Given the short duration of the study, significant impacts on clinical outcomes are unlikely.

**Risk of Bias**

Intention to treat analysis: Included for some outcomes such as the inflammatory markers; for other outcomes including the triglycerides and clinical outcomes it was unclear if the results presented were the intention to treat population or the per protocol population.

Blinding: Unblinded

Funding Source: Industry and independent funding: Fresenius Kabi (manufacturer) and National Taiwan University Hospital

Clinical Trial Registration: Registered at clinicaltrials.gov ID# NCT00885781. The trial was registered after the trial began, but before it was completed. Primary outcome listed was “immunoregulatory effect” of the intervention with no specific parameters provided; in the final publication, the authors stated that “serum triglyceride concentration is the primary measurement for safety”.

Other sources of bias: Mentioned previously

Overall risk of bias: High to very high

**Implications**

SMOFlipid appears to be comparable to Lipovenoes MCT as part of a short-term parenteral nutrition regimen in postoperative patients. Possible advantages to SMOFlipid may be a smaller increase in triglyceride levels. Small to moderate differences in outcomes may be missed by this study due to its statistical power. Confidence in these results is low given the high risk of bias and should be confirmed in further studies.

8. Piper, S. et al. Hepatocellular integrity after parenteral nutrition: comparison of a fish oil-containing lipid emulsion with an olive-soybean oil-based lipid emulsion. European Journal of Anaesthesiology 2009. 26(12):1076-1082.

**Summary**

This was a randomized, double-blind study that compared two different lipid emulsions on their impact on lab values in postsurgical patients. A total of 44 subjects completed the study and received low rate enteral nutrition in addition to parenteral nutrition for at least five days postop. Primary outcome measures included liver enzymes, triglycerides, and markers of inflammation. Results showed that subjects in the SMOFlipid group had significantly lower liver enzymes, triglycerides, and markers of inflammation compared to the ClinOleic group after five days of intervention. This study has a very high risk of bias and should be interpreted with caution.

**Analysis**

Subjects were enrolled in this study after major abdominal surgery or other surgeries if they were expected to need parenteral nutrition for at least five days. Subjects were excluded from the study for renal or hepatic insufficiency, pulmonary edema, decompensated heart failure, hyperlipidemia, insulin-dependent diabetes mellitus, BMI >30 or <18 kg/$m^2$, or hypersensitivity to components of the study intervention, among other criteria.

Subjects all received parenteral nutrition (PN) in addition to low rate enteral nutrition (250 mL/day). Subjects were randomized to receive either SMOFlipid 20% (soybean oil, olive oil, MCT, fish oil) or ClinOleic 20% (soybean oil, olive oil) as a part of their PN regimen. The goal for both groups was to provide 25 kcal/kg/day in nonprotein kcals.

Blood samples were taken before starting PN, on day two, and on day five of PN provision. Vital signs were also taken at the same time points. The authors reported that the primary outcome was α-GST. They estimated that 21 subjects in each group would give 80% statistical power to detect a 125% increase in α-GST at a P-level of 0.05.

Groups were well-matched at baseline. A total of 47 subjects were randomized into the study, with one subject in the SMOFlipid group lost to follow up due to incomplete data collection and two lost in the ClinOleic group due to acute renal failure and reoperation. Results showed no significant differences between groups on vital signs. Results showed significantly lower levels of AST, ALT, α-GST, and triglycerides in the SMOFlipid group on day two and day five. No clinical outcomes were reported on.

Two other publications were found that seem to be based on data from the current study. They were both published in abstract form only and were completed by mostly the same group of authors. The first, “Inflammatory response in patients requiring parenteral nutrition: comparison of a new fish oil-containing emulsion (SMOF®) versus an olive/soybean oil-based formula” focused on inflammatory markers. Outcome measures included IL-6, TNFa, and soluble E-selectin, which were measured at baseline, on day two, and on day five of PN administration. Results showed no significant differences between the groups at baseline or after two days of PN infusion. After five days, subjects receiving SMOFlipid showed significantly lower levels of IL-6, TNFa, and soluble E-selectin. The second publication, “Modulation of lipid utilisation by parenteral administration of a fish-oil-enriched new lipid formula (SMOFlipid®) in surgical ICU patients:

comparison with a lipid emulsion based on olive and soybean oil" focused on triglyceride levels and reported the same results as the primary study as previously reported.

**Risk of Bias**

Intention to treat analysis: Not included

Blinding: Double-blind

Funding Source: Funded by industry: Fresenius Kabi, manufacturer of SMOFlipid

Clinical Trial Registration: None found

Other sources of bias: Two of the authors have ties to Fresenius Kabi. Another author, Joachim Boldt, was the subject of a major investigation of research fraud that led to the retraction of 88 publications in peer-reviewed journals. Some were for falsification of data, most for lying about ethics committee approval. The current study was not retracted, but any study involving this author should be viewed with increased skepticism.

Overall risk of bias: Very high

**Implications**

Due to the very high risk of bias, very limited implications can be drawn from this study. In postsurgical patients receiving low rate enteral nutrition as well as parenteral nutrition, receiving lipids as SMOFlipid may improve lab values such as liver enzymes, triglyceride levels, and inflammatory markers compared to ClinOleic. Further studies should confirm these results and assess clinical outcomes before final conclusions are drawn.

9. Antébi, H. et al. Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: comparison of 2 fat emulsions. JPEN 2004. 28:142-148.

**Summary**

This was a randomized, double-blind study that compared two lipid emulsions on short-term effects in postsurgical patients. A total of 20 subjects completed the trial and were randomized to receive either SMOFlipid or Lipoven as part of a parenteral nutrition regimen for five days. Blood was drawn for analysis at baseline and after five days of intervention; primary outcomes included changes in liver enzymes, markers of inflammation, and lipid profiles. Results showed minimal differences between the groups, though the SMOFlipid group showed higher levels of alpha tocopherol and in vitro LDL oxidation.

**Analysis**

Subjects were included in this study if they were an adult patient in the ICU that was undergoing major surgery and needed parenteral nutrition. Subjects were excluded from the study if they had hypersensitivity to any component of the study interventions, severe hyperlipidemia, severe liver insufficiency, blood coagulation disorders, acute shock, decompensated cardiac insufficiency, diabetes mellitus, severe sepsis, or acute myocardial infarction, among other criteria.

All subjects received parenteral nutrition for at least five days that was isonitrogenous and isocaloric. Subjects were randomized to either SMOFlipid (soybean oil, MCT, olive oil, fish oil) or Lipoven (soybean oil) as their lipid emulsion. Regimens were provided as 3-in-1 solutions and were started on the first postoperative day and were provided continuously. Blood samples were taken at baseline and after five days of parenteral nutrition for analysis. The major outcomes assessed were changes in plasma alanine and aspartate aminotransferases (ALT and AST, Ɣ-glutamyl transferase (Ɣ-GT), alkaline phosphatase (AP), C-reactive protein (CRP), total cholesterol, phospholipids, triglycerides, and plasma antioxidant capacity, among others. LDL oxidation was also compared in vitro by exposing LDL cholesterol to a pro-oxidant.

All subjects that entered into the study completed the intervention with no adverse events reported. Results showed minimal differences between groups after five days of intervention. No differences between groups were reported on liver enzymes, CRP, lipids, or triglycerides. The only significant differences between groups appear to be alpha-tocopherol levels, which

were higher in the SMOFlipid group, and LDL oxidation, also higher in the SMOFlipid group. Other changes were seen from baseline to the end of the intervention in each group, but the differences between groups weren't significant. There were also a few significant differences in absolute values at day six, but not when considering the change from baseline.

The primary limitations of this study are the short-term duration, small number of subjects, and outcomes that focused on lab values. It's possible that the minimal differences in outcomes were due to there being no major differences between the two lipid emulsions, but it is also possible that there are differences that were not detected due to the low statistical power of the study. A formal power analysis was not presented so it is unclear how large of an effect size the study should be able to detect.

**Risk of Bias**

Intention to treat analysis: Appears to be intention to treat, though no confirmation was found.

Blinding: Double-blind

Funding Source: No funding source was found.

Clinical Trial Registration: None found

Other sources of bias: One of the authors is an employee of Fresenius Kabi, the manufacturer of SMOFlipid.

Overall risk of bias: Moderate to high

**Implications**

In postsurgical patients, it appears that short-term provision of SMOFlipid and Lipoven have similar effects on liver enzymes, markers of inflammation, and lipid profile, while alpha tocopherol and in vitro LDL oxidation may be increased with SMOFlipid. Further studies should confirm these results due to the moderate to high risk of bias and limited statistical power. Further studies should also focus on longer-term provision of the lipid emulsions and clinical outcomes.

10. Lin, H. et al. Effect of SMOF fat emulsion on fatty acid profile and inflammatory mediator of in major abdominal surgical patients. Parenter Enteral Nutr 2010. 17:195-198.

[The full text of this study was published in Chinese only; there was an abstract in English which will be summarized.]

**Summary**

This was a randomized, double-blind trial that compared SMOFlipid (soybean oil, MCT, olive oil, fish oil) and Intralipid (soybean oil) on changes in fatty acid profile and inflammatory markers in 48 postoperative patients. After surgery, subjects in both groups received parenteral nutrition for five days that was isocaloric and isonitrogenous. Groups were well-matched at baseline. Results showed that compared to the Intralipid, the SMOFlipid emulsion produced increased EPA and DHA levels while arachidonic acid was decreased. In regards to inflammatory markers, the SMOFlipid resulted in increased LTB5 and TXB3 and decreased LTB4, TXB2, and IL-2 compared to Intralipid. No data on clinical outcomes were included in the abstract.

11. Hallay, J. et al. Hepatobiliary response in postoperative lipid therapy in gastrointestinal surgery. Hepato-Gastroenterology 2010. 57(102-103):1069-1073.

**Summary**

This was a randomized trial that compared two different lipid emulsions as part of a TPN regimen in postsurgical patients in Hungary. A total of 41 subjects completed the trial and were randomized to receive either SMOFlipid or Lipofundin for three days after surgery. Blood was drawn at baseline and daily during the study. Results showed improvement in bilirubin levels in the SMOFlipid group, with no major changes in the Lipofundin group. Other lab values including AST, ALT, lipase, and gamma-glutamyltransferase showed similar changes in both groups, though no direct comparisons between groups were presented.

**Analysis**

Subjects were included in this study if they were undergoing elective gastrointestinal surgery at Debrecen University in Hungary. Subjects were excluded if they had preoperative hepatobiliary dysfunction, severe cardiovascular disease, poor kidney function, prior cholecystectomy, or alcoholism.

In all patients, TPN was provided according to a standard regimen that started the day after surgery without lipids. Starting on the second day of TPN provision, patients received lipids with their TPN as a 3-in-1 mix. Patients received parenteral nutrition for five days, then were transitioned to enteral nutrition and later to an oral diet. Fasting blood samples were taken for analysis as the primary outcome measure.

Subjects were randomized to receive a lipid emulsion of either Lipofundin MCT/LCT 20% (50% soybean oil, 50% MCT) or SMOFlipid (soybean oil, olive oil, MCT, fish oil). All other components of the TPN were equivalent between the groups.

A total of 41 subjects were included in the trial. Average age and BMI were 62 years and 27 $kg/m^2$ in the Lipofundin group and 65 years and 24.5 $kg/m^2$ in the SMOFlipid group. The groups were somewhat unbalanced with 15 subjects in one group and 26 in the other, despite the authors reporting randomization to treatment group. Results were only reported as changes within each group from baseline to the end of the intervention, with no comparison between the groups. Results showed a significant decrease in total bilirubin and conjugated bilirubin during the intervention in the SMOFlipid group with no significant change in the Lipofundin group. Other changes were similar between the groups, with some lab values such as AST, ALT, lipase, and gamma-glutamyltransferase showing an increase in both groups.

This study is very limited by the small sample size, no comparisons between the groups, only three days of lipid provision, and focus on short-term changes in lab values with no clinical outcome data presented. No statistical power analysis was provided, so it's unclear what effect size this study was able to detect. Given the very short-term nature of the intervention and small sample size, the ability of this study to detect any differences between the groups is likely minimal.

**Risk of Bias**

Intention to treat analysis: Appears to be intention to treat, though no confirmation was found.

Blinding: No mention of blinding was found other than the randomization being performed by blinded selection of envelopes.

Funding Source: None identified

Clinical Trial Registration: None found

Other sources of bias: Mentioned previously, unclear reason why one group had almost twice as many subjects if they were randomized to their group.

Overall risk of bias: High

**Implications**

Short-term provision of SMOFlipid as part of a TPN regimen in post-surgical patients may result in more favorable changes in bilirubin levels compared to Lipofundin. Confidence in that conclusion is low and further research is needed to confirm these findings given the short-term intervention, low statistical power, and high risk of bias. Further studies should also include clinical outcomes as study endpoints.

12. Klek, S. et al. Intravenous lipid emulsions and liver function in adult chronic intestinal failure patients: results from a randomized clinical trial. Nutrition 2018. https://doi.org/10.1016/j.nut.2018.03.008.

**Summary**

This was a randomized, controlled trial that compared four different lipid emulsions on liver function in subjects with chronic intestinal failure. A total of 65 subjects completed the trial and were randomized to receive either Intralipid, SMOFlipid, Lipofundin, or ClinOleic as part of a TPN regimen. Subjects received their intervention for 12 months, with assessments

completed at baseline and every three months during intervention. Results showed that after 12 months of intervention, no significant differences were found in measures of liver function including bilirubin, alkaline phosphatase, SGPT, SGOT, and GGTP.

**Analysis**

Subjects were included in this study if they were stable on a home parenteral nutrition regimen for at least three months. The study took place at the Intestinal Failure Center at Stanley Dudrick's Memorial Hospital in Poland between January 2010 and December 2015. A total of 88 patients with chronic intestinal failure and an average age of 54.5 years were included in the study. Subjects were excluded if they had existing liver failure, cancer with anti-cancer treatment in the last five years, severe hyperlipidemia, severe renal insufficiency, or acute thromboembolic events, among other criteria.

Subjects were randomized to a parenteral nutrition regimen that included one of four lipid emulsions: Intralipid (soybean oil), Lipofundin (soybean oil, MCT), ClinOleic (olive oil, soybean oil), or SMOFlipid (soybean oil, MCT, olive oil, fish oil). Subjects continued the intervention for twelve months, with an additional follow up period of four weeks. The intervention was stopped for any subject that had serum triglycerides >262.5 mg/dL, an intolerable or serious adverse event, or for failure of therapeutic safety or tolerability causing an unacceptable risk/benefit ratio (this was not defined). All subjects were allowed to consume food orally, which did not exceed 10% of total calorie or protein intake.

Several assessments were completed that included vital signs, biochemistry, liver enzymes, bilirubin, hematology, coagulation, inflammatory markers, and adverse events. Vital signs and certain lab values were assessed every three months. The authors determined they would have 80% power to detect a 100% change in liver parameters with 15 subjects per group at a P-value of 0.05.

Sixty-five of the 88 randomized subjects completed the trial and were included in the analysis. The authors reported no significant differences between the groups after 12 months of intervention for liver parameters, including the primary outcome which was bilirubin. There were also no serious adverse events noted during the intervention and no signs of fatty acid deficiency. The ClinOleic group did show a significant decrease in bilirubin and GGTP during the intervention compared to baseline levels, though the authors noted that this may partially be regression to the mean, as the ClinOleic group had the highest levels of these labs at baseline.

The authors reported that an intention to treat analysis was not completed as it was thought that subjects with short-term provision of the intervention would not give a meaningful representation of the long-term effect of intervention. This is true, but it would still provide additional information about the short or medium-term effects, especially given that the vast majority of research on SMOFlipid in particular is based on five days of intervention or less.

One difference between the groups was total calorie provision, with the SMOFlipid group receiving 23.1 kcal/kg/day, with 18.2, 20.0, and 20.8 kcal/kg/day provided in the Intralipid, Lipofundin, and ClinOleic groups respectively. This result was of borderline statistical significance (P=0.0627).

**Risk of Bias**

Intention to treat analysis: Not included

Blinding: Double-blind

Funding Source: Independent funding from Stanley Dudrick's Memorial Hospital

Clinical Trial Registration: Clinicaltrials.gov ID: NCT03044639. This study was registered after it was already completed, which is meaningless.

Other sources of bias: Multiple authors had relationships with multiple companies including Baxter, Fresenius Kabi, Nestle, and Nutricia, among others.

Overall risk of bias: High

**Implications**

Intralipid, ClinOleic, Lipofundin, and SMOFlipid appear to have similar long-term effects on measures of liver function and vital signs in subjects with chronic intestinal failure. Further studies should confirm these results given the high risk of bias and limited statistical power to detect differences.

## Artery Clogging Saturated Fat

This is the ninth in a series of articles to critically examine the core research behind the idea that saturated fat is unhealthy. In previous issues, all nine randomized trials in the American Heart Association (AHA) guidelines on saturated fat published as "Omega-6 Fatty Acids and Risk for Cardiovascular Disease" were reviewed. The AHA more recently published a Presidential Advisory that addressed saturated fats "Dietary Fats and Cardiovascular Disease; A Presidential Advisory from the American Heart Association." Additional trials in this publication were also reviewed with minimal if any evidence to support their recommendations. Another major publication on saturated fats comes from the Cochrane Collaboration, which was released in 2015 as "Reduction in saturated fat intake for cardiovascular disease (Review)." Randomized trials in this publication that were not included in the previous reports will now be reviewed.

Chlebowski, R. et al. Dietary fat reduction and breast cancer outcome: Interim efficacy results from the Women's Intervention Nutrition Study. Journal of the National Cancer Institute 2006. 98(24):1767-1776.

**Summary**

This was a multicenter randomized, controlled trial that tested a low-fat diet on breast cancer recurrence in middle-aged women. A total of 2,437 subjects were randomized into the trial which lasted for five years. The intervention group aimed to decrease total fat intake from all sources, while the control group was not asked to make any changes. The primary outcome was recurrence of breast cancer; total mortality was a major secondary outcome. Adherence to the intervention diet was fair, as intervention subjects decreased fat intake significantly more than controls and maintained this difference throughout the trial. Results showed slightly lower rates of recurrence in the intervention group, though this result was of borderline statistical significance (P=0.077). Total mortality showed no major difference between the groups.

**Analysis**

Subjects were included in this study if they had early stage unilateral invasive breast cancer that was histologically confirmed and resected. Subjects were between 48 and 79 years of age and were receiving conventional cancer management. Subjects were enrolled in the study between February 1994 and January 2001. Subjects were excluded if their surgery was more than 365 days ago, if they had inflammatory carcinoma, chest wall or skin involvement, or if the tumor size was less than 1 cm with negative nodes or greater than 5 cm with positive nodes, among other criteria. Breast cancer management was driven by a standard protocol and included surgery, radiotherapy, and medications.

Subjects were randomized to either a control group or an intervention group that aimed to reduce total fat intake to 15% of total calories while maintaining nutritional adequacy. Control subjects met individually with dietitians at baseline and every three months throughout the intervention, and were instructed on general dietary guidelines. Subjects in the intervention group completed eight biweekly individual counseling sessions with dietitians at the beginning of the study, and met once every three months thereafter; they were encouraged to keep a record of their fat intake. Randomization was unbalanced (60% to control group, 40% to intervention) to facilitate increased resources for the intervention group. Unannounced telephone calls were used to assess dietary intake at baseline and annually during the trial.

The primary outcome of the study was relapse-free survival; total mortality was a secondary outcome. The study's funding ended prior to the end of the protocol-defined follow up period. At this point, the WINS External Advisory Committee and the WINS Executive Committee supported stopping the trial. The authors estimated that if 2,502 subjects completed the trial with six years of intervention and three years of follow up after active intervention, they would have 84% power to detect a 7.5% increase in relapse-free survival at a P-level of 0.05.

A total of 2,437 women were included in the study and randomized to a group, with 975 in the intervention group and 1,462 controls. Groups were well-matched at baseline except for the intervention group having more subjects with mastectomy rather than breast-conserving treatment. Adherence to the diets was measured by the phone calls; after the first year, total fat intake decreased slightly in controls (56.3 g/day to 51.3 g/d), but decreased significantly more in the intervention group (57.3 g/day to 33.3 g/day). This difference between groups was maintained throughout the five years of intervention. Similar differences were seen in all different types of fat and percentage of calories from fat. Also, total calorie intake was slightly lower and fiber was slightly higher in the intervention group. Average loss of bodyweight was greater in the intervention group (-6 lbs).

Results showed that breast cancer recurrence was lower in the intervention group (HR 0.76; 277 vs 389 events) and this level was close to statistical significance (P=0.077). The authors primarily focused on a second statistical analysis method that was exploratory in nature (after the data was in, they made adjustments and tested several different models) and produced a P-value of 0.034, meeting the traditional level of statistical significance. This result is much less meaningful as it is most likely cherry-picked, but it is really not that much different than a P-value of 0.077. Total mortality showed no significant difference between the groups though it was slightly lower in the intervention group (HR 0.89; 95% CI: 0.65 – 1.21; P=0.56). The authors completed several subgroup analyses and showed that the intervention diet had a larger effect in women with estrogen receptor-negative cancer than women with estrogen receptor-positive, though the difference was not statistically significant.

Limited details were provided on differences in actual food intake between the groups. In addition to the advice to decrease fat intake, subjects in the intervention group were also encouraged to increase consumption of fruits, vegetables, legumes, and grains. It was unclear how much they implemented this advice. Other publications on this trial did provide some insight to the fruit and vegetable intake, reporting minimal changes, though the authors of one report focusing on flavonoid intake acknowledged that sources of measurement error were several and potentially large[1]. Another publication reported more detail on changes in food intake in the intervention group. It appears that the majority of the decrease in fat intake came from "fats and oils," "beef, pork, and lamb," and "sweet breads" that included pastries, sweet rolls, cookies, and doughnuts. One aspect that was not reported was trans-fat intake. It's likely that trans-fat intake was high during this study at baseline, and it was likely decreased significantly in the intervention group with the significant decrease in high-fat bakery products.

**Risk of Bias**

Intention to treat analysis: Included

Blinding: Outcome assessors were blinded.

Funding Source: Appears to be independent funding from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, the Breast Cancer Research Foundation, and the American Institute for Cancer Research.

Clinical Trial Registration: It was reported that the trial protocol was available as supplementary data online; this seems to be inaccessible.

Other sources of bias: The intervention group had increased contact with health professionals including the dietitians.

Overall risk of bias: Moderate

### Implications

In middle-aged women with a history of invasive breast cancer, reducing fat intake from sources including oils, meats, high-fat bakery products, and dairy may result in lower rates of breast cancer recurrence. Confidence in this conclusion is quite low given the borderline significance of the results. Also, it is unclear if it was the decrease in total fat intake that produced the slightly lower recurrence rates. It's possible that other factors such as decreasing hydrogenated oil intake in bakery products could be responsible for the effects; it's also possible that increasing certain foods such as fruits, vegetables, legumes, or grains could have had an impact. Clearly, further trials are needed to confirm these results and more clearly identify which foods result in harm or benefit.

### Relevance to the Impact of Saturated Fat

It is unclear why this study was included in a review of saturated fat by the Cochrane Collaboration. The outcome used in their review was total mortality, which showed no difference between the groups. It seems that this study was included because the intervention group decreased saturated fat intake; this is true; however, several other changes were made at the same time. Thus, no implications about saturated fat alone can be drawn from this study. If a study was completed with one group taking medications A, B, and C, and a second group taking medications D, E, and F, it would be impossible to determine the effects that medication B had on the results. The same concept applies to studies of foods or nutrients.

### References

1. Dwyer, J. et al. Do flavonoid intakes of postmenopausal women with breast cancer vary on very low-fat diets? Nutrition and Cancer 2008. 60(4):450-460.

2. Winters, B. et al. Dietary patterns in women treated for breast cancer who successfully reduce fat intake: the Women's Intervention Nutrition Study (WINS). J Am Diet Assoc 2004. 104:551-559.

## Maternal Choline Intake and Infant Cognition

Caudill, M. et al. Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study. FASEB J 2018. Epub ahead of print.

### Summary

This was a randomized, double-blind trial completed at Cornell University that compared two different levels of choline supplementation during the third trimester of pregnancy on cognitive function in their infants. Subjects were randomized to a supplement of 100 mg or 550 mg choline per day, in addition to a standard diet that provided 380 mg choline per day. Subjects followed the intervention for 12 weeks or until delivery, and a total of 24 subjects completed the full trial. Results showed improved reaction time in infants from the 550 mg group, with no difference found in the other primary cognitive assessment.

### Analysis

Subjects were recruited if they were entering their third trimester of pregnancy; exclusion criteria were anemia, blood markers of liver or kidney dysfunction, drug use, certain medication use, or if they had cardiovascular disease, cancer, diabetes mellitus, or gastrointestinal disorders, among other conditions. A total of 29 women were recruited into the study, with 26 completing the protocol and 24 giving consent for their child to participate in cognitive assessments.

Subjects were randomized to one of two groups that differed by dosage of choline supplementation. All subjects were expected to eat only foods provided by the research staff, consume at least five meals per week

on site, and consume their supplements under the supervision of study personnel during the week. The study diet provided both groups 380 mg choline per day; both groups took choline supplements of either 100 mg (group 1) or 550 mg (group 2) per day. Supplements were mixed with juice to keep subjects blinded to treatment group.

Compliance was judged to be high due to the close supervision of subjects and provision of foods; additionally, fasting plasma levels of choline were measured and found to be significantly higher in the 550 mg supplement group. Most subjects completed the program for 12 weeks, with some women on the regimen for longer until they delivered their baby.

Infants completed assessments to estimate cognitive performance at 4, 7, 10, and 13 months of age. The primary measure was reaction time when images were shown on a screen and infants changed their focus to the image. Sample size was based on power calculations to provide 80% power to detect a 20% difference in biomarkers of choline metabolism at a P-level of 0.05. The authors also reported the primary measure of infant cognition had >80% power to detect a 10% difference.

Results for the primary outcome of infant cognition showed a significantly faster reaction time in the 550 mg choline supplement group (-22.6 ms; 95% CI: -1.3 to -43.8 ms; P=0.03). The authors also completed analyses that adjusted for variables that may influence the outcomes such as birth weight, maternal age at conception, and complications of labor and delivery. These analyses showed stronger effects than the unadjusted model. The second major test for infant cognitive performance, predictive saccades, showed no difference between the groups.

In the clinical trial register, the primary outcome listed is changes in maternal biomarkers of choline status. The cognitive assessments in the infants were included as a secondary outcome. The timeframe listed for cognitive assessment of infants was 12 months. In the final publication, the outcome was based on the average of scores attained at visits at 4, 7, 10, and 13 months of age. Complex statistical models were used to evaluate the outcomes. Generally, the more simple analyses are, the less risk of bias will exist. The more complex and involved the analysis is, the more opportunity exists to bias the results. Ideally, variables other than the supplement intake should be accounted for by the randomization and shouldn't need to be adjusted for in the analysis. The outcome in the trial register does not match with the outcome presented in the final publication, though the trial register was not very specific. Concerns for risk of bias are increased knowing that the trial included industry funding. Additionally, there was a significant period of time between the trial being completed and the publication of this report. The last pregnant mothers were enrolled in October 2010 and followed the intervention for roughly 12 weeks. Then their infants were followed for assessment until 13 months of age. This means that the last data should have been available around March of 2012. The current article was submitted for review in July of 2017.

Given the previous concerns, it should be noted that nothing concrete was identified that indicates the study was likely manipulated or biased, but many aspects do raise concerns and reduce the confidence in the reliability of the results. The study does have numerous strengths in design that go above and beyond most nutrition studies including the provision of all study foods to ensure dietary intake is equivalent in other nutrients. Additionally, we can be confident in the level of compliance and supplement intake due to the meals and supplements consumed on site in addition to plasma choline levels.

**Risk of Bias**

Intention to treat analysis: Included

Blinding: Double-blind, including outcome assessors

Funding Source: Included industry and independent funding from the Egg Nutrition Center, the Beef Checkoff, and the USDA Cooperative State Research, Education, and Extension Service, among others.

Clinical Trial Registration: www.clinicaltrials.gov ID# NCT01127022

Other sources of bias: Reported previously.

Overall risk of bias: Moderate

**Implications**

For pregnant women, choline supplementation during the third trimester to reach a choline intake of 930 mg per day may improve measures of cognitive function in their kids in the first 13 months of life compared to a choline intake of 480 mg or less per day. Further RCTs should be completed to confirm these results due to the moderate risk of bias. Further studies should also evaluate the efficacy of increasing food sources of choline on outcomes, and also include other measures of cognition and overall health.

# Early Enteral vs Parenteral Nutrition in ICU Patients with Shock

Reignier, J. et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomized, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet 2018. 391:133-143.

**Summary**

This was a randomized, controlled trial that compared enteral and parenteral nutrition therapy when provided to ICU patients that were intubated and using vasoactive medications. A total of 2,410 subjects completed the trial and were randomized to one of the groups. Primary outcome was 28-day mortality, with numerous secondary outcomes also assessed which included 90-day mortality, ICU and hospital mortality, ICU and hospital length of stay, SOFA scores, and infectious complications. Results showed no difference between enteral and parenteral nutrition for the primary outcome and the majority of secondary outcomes. A few gastrointestinal complications were more common in the enteral nutrition group including vomiting, diarrhea, and ischemic bowel.

**Analysis**

This study was completed in 44 different ICUs in France, including 28 in university hospitals. Subjects were included if they were 18 years of age or older and expected to require more than 48 hours of mechanical ventilation, required the use of vasoactive medications for shock, and were going to be started on nutrition support within 24 hours of intubation or ICU admission. Subjects were not eligible for the trial if they had gastrointestinal surgery within the last month, short bowel syndrome, if they had a history of certain major GI surgeries, or if they had certain contraindications to enteral or parenteral nutrition.

Subjects were randomized to either an early enteral nutrition group or early parenteral nutrition group. In the parenteral group, nutrition was provided via a central venous catheter for at least 72 hours. After this time, subjects were assessed daily for hemodynamic stability based on predefined criteria. When these criteria were met, subjects were changed to enteral nutrition. If the patient did not meet criteria for hemodynamic stability, they continued on parenteral nutrition for the first 7 days. On day eight, all patients were changed to enteral nutrition unless there were other contraindications.

In the enteral group, subjects were started on isosmotic, isocaloric, standard formulas for the first week. After this time, the formula could be changed by the attending physician. If subjects could not tolerate enteral nutrition to meet caloric goals, parenteral nutrition could be added, but only after day seven.

In both groups, the caloric goal for the first week was 20-25 kcal/kg actual bodyweight, and 25-30 kcal/kg after day seven.

The primary study outcome was 28-day mortality. A number of secondary outcomes were also assessed which included SOFA scores, amount of calories and protein provided, vomiting, laboratory values, 90-day mortality, ICU mortality, length of stay in the ICU and the hospital, and ICU-acquired infections, among others.

Two interim analyses were planned and data were reviewed by the Data Safety and Monitoring Board. The authors estimated they would need 2,854 subjects to show a 5% reduction in mortality with 80% power at a P-value of 0.049. A total of 2,410 subjects actually completed the trial, as it was stopped after the second interim analysis because the Data Safety and Monitoring Board deemed further enrollment was unlikely to change the results.

Results showed no significant difference in 28-day mortality between the groups (37% enteral group vs 35% parenteral group; P=0.33). There were also no differences found in 90-day mortality, ICU mortality, hospital mortality, ICU or hospital length of stay, ICU-acquired infections, bacteremia, ventilator-associated pneumonia, or other infections. There were some GI complications that were more frequent in the enteral nutrition group which included vomiting (34% vs 24%; P<0.0001), diarrhea (36% vs 33%; P=0.009), and bowel ischemia (2% vs <1%; P=0.007). The parenteral group received a larger amount of calories (17.8 kcal/kg/d vs 19.6 kcal/kg/d; P<0.0001) and protein (0.7 g/kg/d vs 0.8 g/kg/d; P<0.0001).

It is unclear why protein was provided at such a low level to critical care patients. Typically guidelines call for significantly higher doses of protein to improve outcomes. The difference in protein provision between the two groups was small, but if the protein level is insufficient, small additions may have a relatively large impact. The specific enteral formulas used were not identified, so it's unclear whether disease-specific formulas were allowed when indicated. Attending physicians could only change the enteral formula after day seven, limiting potential benefit from adapting the formula to the specific patient and condition. It's unclear if the parenteral nutrition could be adjusted based on lab values or tolerance either. It's interesting to note that infectious complications showed no difference, as previous studies typically show that parenteral nutrition leads to increased infectious complications. The authors believe that this may be due to improved parenteral nutrition management or to the different dose; older studies tended to provide significantly more calories than the current study. The authors noted the possibility of detection bias in gastrointestinal complications. They noted that it is possible that patients on enteral nutrition may have received a more active assessment of GI function.

Overall this was a strong study design comparing early enteral to early parenteral nutrition in ventilated patients with shock. It's possible that different results would be seen with longer-term use of parenteral nutrition, as average length of use was only four days in this study, after which all subjects were converted to enteral nutrition. It's possible that the difference in treatment wasn't large or long enough to produce significant differences in outcomes.

**Risk of Bias**

Intention to treat analysis: Included

Blinding: Not blinded

Funding Source: Independent funding from La Roche-sur-Yon Hospital and the Programme Hospitalier de Recherche Clinique National 2012 of the French Ministry of Health.

Clinical Trial Registration: www.clinicaltrials.gov ID:

NCT01802099

Other sources of bias: mentioned previously

Overall risk of bias: Low to moderate

**Implications**

In ICU patients that are receiving mechanical ventilation and vasoactive medications for shock, early intervention with enteral nutrition appears to produce very similar outcomes as parenteral nutrition. The risk of infectious complications that was once more common with use of parenteral nutrition may now be equal to enteral nutrition due to improvements in the management of parenteral nutrition.

# Low-Fat vs Low-Carbohydrate Diets for Weight Loss (DIETFITS)

Gardner, C. et al. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion. JAMA 2018. 319(7):667-679.

**Summary**

This was a randomized trial that compared a healthy low-fat diet to a healthy low-carbohydrate diet on weight loss after 12 months. A total of 609 subjects were randomized with 481 completing the trial. Intervention was provided as 22 educational classes led by dietitians that encouraged both groups to consume a healthy diet high in vegetables and minimally processed foods that varied by fat and carbohydrate content depending on group assignment. Results showed no differences between the groups on weight loss, with a loss of 5.3-6.0 kg on average. Also, no significant interactions were found between diet and genotype or diet and baseline insulin secretion on weight loss.

**Analysis**

Subjects were recruited from the Stanford and San Francisco Bay area starting in January of 2013 if they were between 18 and 50 years of age and had a BMI of 28 to 40 kg/$m^2$. Exclusion criteria were uncontrolled hypertension or metabolic disease, diabetes mellitus, cancer, heart, renal, or liver disease, pregnant or lactating status, or if subjects were taking antihypertensive, hypoglycemic, or lipid-lowering medications, among others.

A computerized program was used for randomization of subjects to either a healthy low-fat diet or a healthy low-carbohydrate diet. Subjects were unaware of their group assignment until the first class session. The study initially had a 2x2 factorial design to assess interactions between the diet and genotype pattern. This was changed near the study onset after receiving a significant increase in funding, which allowed a much larger sample size, more measurements, and another interaction, diet and insulin secretion, was added.

The study started with a 1-month run-in period during which subjects were told to maintain their usual diet, exercise regimens, and bodyweight. The intervention was provided as group classes that were led by registered dietitians. A total of 22 sessions were held over the 1-year period, with classes being held more frequently at the beginning of the study and gradually getting less frequent throughout the study. The primary goal of the intervention was to produce as large of a difference as possible in the carbohydrate and fat intake between the groups. Foods that were emphasized for reduction in the low-fat group included oils, fatty meats, whole-fat dairy, and nuts; in the low-carbohydrate group, foods discouraged included cereals, rice, grains, starchy vegetables, and legumes. Subjects were encouraged to reduce intake of either fat or carbohydrate to 20 grams per day for the first eight weeks of the study, and gradually increase intake each week until they reached the lowest level of fat or carbohydrate intake they believed they could maintain. Neither group was instructed to focus on calorie intake. Both groups were encouraged to maximize vegetable intake, minimize intake of added sugars, refined flours, and trans-fats, and focus on whole foods that were minimally processed, nutrient dense, and preferably prepared at home.

Study data were collected at baseline and after 3, 6, and 12 months of intervention. Dietary intake was assessed each time by using three unannounced 24-hour recalls. Energy expenditure was assessed with a seven-day physical activity questionnaire. The primary outcome of the study was weight change after 12 months. Genotype pattern and insulin secretion were also assessed to see if there was any impact on the weight loss and if there was any difference between the diets. Subjects were classified by genotype as individuals expected to be more sensitive to fat, more sensitive to carbohydrate, or sensitive to neither. This was based on different combinations of three single-nucleotide polymorphisms thought to be important for fat and carbohydrate metabolism. All subjects completed oral

glucose tolerance tests at baseline and after six and twelve months. Subjects had insulin concentrations measured 30 minutes after glucose ingestion. One hypothesis was that response to a low carbohydrate diet would vary depending on the person's insulin response. Additional anthropometric and laboratory measures were also taken; a few measures such as dual-energy x-ray absorptiometry were not completed on the first subjects to enroll, as the additional funding became available after they completed their baseline assessments.

A total of 481 subjects completed the trial of the 609 that were randomized (79%). Subjects attended an average of 14/22 class sessions in both groups. No baseline differences were found in intake between the groups except for a slightly higher fat intake in the low-carbohydrate group (+5.6 g/day). Calorie intake in both groups decreased by 400-600 kcals/day, which was maintained throughout the study despite slight increases over time. Significant differences in macronutrient intake were present at every time point after baseline. Twelve-month averages for carbohydrate intake were 48% and 30% of kcals for the low-fat and low-carbohydrate groups, respectively; fat intake was 29% and 45% of kcals; and protein was 21% and 23% of kcals.

Results showed no difference in weight loss between the groups after 12 months (-5.3 kg low fat group vs -6.0 kg low carbohydrate group; not significant). Both groups showed a wide range of weight change for individuals that spanned from a 30 kg loss to a 10 kg gain. No interaction was found for genotype and weight loss; individuals with an expected sensitivity to fat or to carbohydrate showed no significant differences in weight loss regardless of the diet they followed. Similar results were found for baseline insulin secretion: it didn't matter which diet they followed, weight loss was similar. Many secondary outcomes improved in both groups including waist circumference, blood pressure, body-fat percentage, insulin, and glucose levels. Cholesterol and triglyceride levels mostly improved but did show some differences between the groups. The low-carbohydrate group increased HDL and LDL-cholesterol levels and significantly decreased triglyceride levels. The low-fat group showed no significant change in HDL-cholesterol but did decrease LDL-cholesterol; triglyceride levels were also decreased, though to a lesser extent than the low-carbohydrate group. A total of 11 adverse events and an additional 7 serious adverse events occurred during the study and were reported to be evenly distributed between groups. Resting energy expenditure was no different between groups.

Major strengths of this study include a large sample size, large differences in fat and carbohydrate intake, and a good range of weight loss outcomes. Another serious strength is the fact that an attempt was made to make sure both diets were healthy and received equal education and intervention. Many studies will have a control group that makes no changes and doesn't interact with study personnel, which can be a confounder. This study did an excellent job of making sure that fat and carbohydrate intake were the only major differences between the groups. This study had good statistical power to detect any differences between the groups if they occurred. This indicates that it is quite unlikely that a real difference between the groups in terms of weight loss was missed. Given the differences in cholesterol and triglycerides between the groups, with each group having some changes that were more favorable, long-term cardiovascular event data would be valuable.

A few limitations to the trial include the self-reported physical activity and dietary intake data, which are well-known to have error and imprecision. Laboratory assessments support the self-reported intake, as cholesterol and triglyceride levels changed as expected based on diet group. Respiratory exchange ratio also supported the results, as a decrease was seen in the low-carbohydrate group and no change in the low-fat group. Another limitation is the change in study protocol after the study began which increases risk of bias. The authors did explain these changes and had a legitimate rationale (significant increase in funding) that allowed 200 additional subjects and more detailed assessments. It should be noted that the lack of

interaction between the genotype and diet reflects the impact of the three SNPs and their combinations that were studied; it's possible that other genes or SNPs could have a different effect.

**Risk of Bias**

Intention to treat analysis: Modified intention to treat analysis that included subjects with missing data

Blinding: Study authors and outcome assessors were blinded.

Funding Source: Independent funding from Stanford University, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Heart, Lung, and Blood Institute. Funding was also provided by the Nutrition Science Initiative, which has fairly strong ties to low-carbohydrate diets.

Clinical Trial Registration: This trial was registered shortly after it began; initially, only Caucasians were included due to the genetic component; the authors reported population level data was established in Caucasians but not other ethnicities. When the study was expanded to 600 subjects, the additional 200 were chosen from non-Caucasian ethnicity to increase generalizability of the results. www.clinicaltrials.gov ID# NCT01826591

Other sources of bias: previously mentioned

Overall risk of bias: Low to moderate

**Implications**

Healthy low-fat and healthy low-carbohydrate diets seem to have a similar efficacy on weight loss after 12 months in overweight subjects. Baseline insulin secretion and genotype based on the three SNPs studied don't seem to impact the weight loss seen on either diet. Longer follow up should be completed to compare cardiovascular endpoints given the differences seen in cholesterol and triglycerides between the groups.

# Plant-Based Diets for Insulin-Resistance and Beta-Cell Function

Kahleova, H. et al. A plant-based dietary intervention improves beta-cell function and insulin resistance in overweight adults: a 16-week randomized clinical trial. Nutrients 2018. 10:189

**Summary**

This was a randomized trial that compared a low-fat vegan diet to a control group that made no changes. A total of 72 men and women with a BMI between 28 and 40 kg/m$^2$ completed the 16-week trial. The primary outcome was weight loss, with several other anthropometric and laboratory measures assessed; insulin resistance was also examined. The authors didn't report on weight loss, and changed their primary outcome to beta-cell function after the study was completed. Overall, the results of this study are mixed, though more in favor of the plant-based diet. Due to a very high risk of bias, this study should be interpreted with caution.

**Analysis**

This trial was conducted between October 2016 and June of 2017 in Washington D.C. Subjects included men and women aged 25 to 75 years of age if their BMI was between 28 and 40 kg/m$^2$. Subjects were excluded for history of diabetes mellitus or for smoking, alcohol or drug abuse, pregnant or lactating status, or if they already followed a vegan diet.

Subjects were randomized to either a low-fat plant-based diet or a control diet for 16 weeks, with assessments completed at baseline and the end of the trial. Subjects following the intervention diet were encouraged to consume mostly vegetables, grains, legumes, and fruits, while limiting all animal products and added fats. Goal fat intake was 20-30 grams per day, and subjects supplemented with vitamin B12. The control group was asked to make no changes to their diet. A 3-day diet record was completed by all subjects

at baseline and after 16 weeks to assess adherence in addition to unannounced phone calls. All subjects were asked to maintain their usual exercise and medication regimens.

Outcomes of the study included anthropometric changes, body composition changes as measured by DXA scans, and laboratory measures. Insulin secretion was assessed after a liquid breakfast of Boost Plus. The primary outcome was reported to be beta-cell function, which was assessed with a mathematical model that considered C-peptide concentrations and estimated body surface area. HOMA-IR was also used to assess insulin resistance.

A total of 75 subjects were randomized into the trial, with three subjects dropping out for reasons unrelated to the diets. Both groups reported significant decreases in calorie intake (350-400 kcals less per day), with no significant difference between groups. Both groups decreased saturated fat intake, with the intervention group further decreasing intake of total fat, polyunsaturated fat, monounsaturated fat, cholesterol, and protein while increasing carbohydrate and fiber.

Results showed BMI, lean mass, fat mass, and visceral fat mass were decreased in the intervention group, with only lean mass decreasing in the control group. The intervention group also showed decreases in total cholesterol, HDL and LDL-cholesterol, and fasting plasma levels of glucose, insulin, and C-peptide. Triglyceride levels were increased in the intervention group, though the difference between groups was not statistically significant. None of these laboratory measures showed changes in the control group.

Measures of beta-cell function and insulin sensitivity were mixed, but more in favor of the intervention group. HOMA-IR, basal insulin secretion, and mean post-prandial glucose levels showed more favorable results in the intervention group, while no difference was found in 3-hour oral glucose insulin sensitivity, total insulin secretion, insulin secretion at a fixed glucose value, mean insulin, glucose sensitivity, or potentiation factor ratio.

Two studies conducted by the Physician's Committee for Responsible Medicine have previously been reviewed for the Schwanz Nutrition Journal, and both of them appeared to be manipulated to influence the results. In the current study, the intervention diet was compared to a control group that made no changes. It will nearly always be a weak study design to find a group of subjects that are overweight, diabetic, have heart disease, or some other health condition that is less than ideal, and ask them to continue living the lifestyle or consuming the diet they developed those conditions on. The control group in this study showed loss of muscle mass with no loss of fat mass, and worse mean glucose levels after completing the study. In addition, the intervention group had weekly classes and support. Contrast this study to the DIETFITS study previously reviewed; in that study, an attempt was made to optimize both diets, with the only major difference being the low-carbohydrate or low-fat nature of the diet. The current study could have held weekly classes for the control group to provide support and encourage them to eat a healthy diet that included a moderate amount of animal products and contained more high-fat foods such as avocados, full-fat dairy, and olive oil. This would have been a high-quality study that compared a low-fat vegan diet to a higher-fat diet with moderate animal products. Instead, the control group received no intervention.

The bias in this study is apparent, though subtle in the final publication; however, it is very clear and unmistakable in the clinical trial register. Typically when studies are completed, subjects are informed of the results so they can make changes in line with the diet that showed the better results. In the current study, it was reported in the trial register that "the control group will be asked to make no changes in diet or exercise for 16 weeks, but will be instructed in the intervention diet at the study's conclusion." To the authors, the results of the study were a foregone conclusion, and they intended to encourage subjects to follow the low-fat vegan diet regardless of what the study showed. The authors reported that the primary outcome of the study was beta-cell function; however, the clinical trial register shows that the primary outcome was actually

weight loss after 16 weeks, which was not even reported in the final publication. Secondary outcomes as reported in the trial register were changes in serum lipids (reported), changes in intramyocellular and/or intrahepatocellular lipid (not reported), glucose tolerance and insulin resistance (reported), resting energy expenditure (not reported), and the dietary recalls. The trial register was updated several times during the study; the outcome of beta-cell function was never mentioned until July 2017, after the study was completed.

This trial was originally intended to assess the mechanism by which a plant-based diet causes weight loss. Variables such as intracellular lipid, insulin sensitivity, and postprandial metabolism were measured to examine their association with weight loss. After the trial was completed, the authors presented it as a trial that intended to focus on the ability of a plant-based diet to improve beta-cell function. The problem with this, even if the results reported are completely legitimate and real effects, is the significantly higher likelihood of false positive results. When a large number of variables are measured, a few significant differences are likely to occur due to random variation alone. It's very concerning when the primary outcome and several secondary outcomes are not reported at all, and other outcomes appear in their place.

**Risk of Bias**

Intention to treat analysis: Reported as intention to treat analysis.

Blinding: None

Funding Source: Physician's Committee for Responsible Medicine – an organization that promotes low-fat vegan diets.

Clinical Trial Registration: www.clinicaltrials.gov ID# NCT02939638. Multiple discrepancies reported previously.

Other sources of bias: Hana Kahleova and Dr. Neal Barnard are the Director of Clinical Research and the President of the Physicians Committee for Responsible Medicine – an organization that advocates for low-fat, vegan diets.

Overall risk of bias: Very High

**Implications**

There is a possibility that a low-fat, plant-based diet can improve beta-cell function and insulin sensitivity compared to an average American diet in an overweight population. This study should be viewed as a weak hypothesis-generating study only due to it's high risk of bias and selective reporting. Further trials are needed that attempt to optimize both groups, provide similar treatment to both groups, and have a lower risk of bias. The study protocol, outcomes, and interventions should be declared prior to beginning the study, and any changes should be reported along with the rationale for the changes.