Dietary lipids with potential to affect satiety: Mechanisms and evidence.

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Abstract

Dietary fat has been implicated in the rise of obesity due to its energy density, palatability and weak effects on satiety. As fat is a major contributor to overall energy intake, incorporating fat with satiating properties could potentially reduce energy intake. This review outlines the potential mechanisms, as far as we know, by which Medium-Chain Triglycerides (MCT), Conjugated Linoleic Acid (CLA), Short-Chain Fatty Acids (SCFA), Diacylglycerol (DAG), *n*-3 PUFA, and Small Particle Lipids, exerts their satiating effects. The evidence suggests that the lipid with the most potential to enhance satiety is MCT. SCFA can also promote satiety, but oral administration has been linked to poor tolerability rather than satiety. Data on the appetite effects of CLA is limited but does suggest potential. Research comparing these lipids to each other is also lacking and should be explored to elucidate which of these 'functional lipids' is the most beneficial in enhancing satiety.

Introduction

The continual growth of global obesity is well documented (WHO 2000), as is the concomitant rise of comorbidities such as type 2 diabetes, various cancers and cardiovascular disease (Guh et al. 2009). The main driver of weight gain is a positive energy balance, where an individual consumes more energy than they expend, for a prolonged period. The current obesogenic environment we live in can promote obesity due to the large volume of time spent sedentary (Deforche et al. 2015; Dong, Block, and Mandel 2004) as well as increases in the energy density (Stelmach-Mardas et al. 2016), portion size (Ello-Martin, Ledikwe, and Rolls 2005) and relative cost (Drewnowski and Darmon 2005) of food, all promoting overconsumption. Dietary fat has also been implicated in the rise of obesity due to its energy density, palatability and weak effects on satiety (Blundell et al. 1993; Blundell and MacDiarmid 1997).

Appetite is the internal driving force for the search, choice and ingestion of food (De Graaf et al. 2004). Humans eat in episodes consisting of either meals or snacks (Gibney and Wolever 1997). The way in which food intake is controlled is described within the satiety cascade (Blundell, Rogers, and Hill 1987). Satiation occurs during the course of eating and eventually brings the period of eating to an end. Satiety occurs after the end of an eating episode and is the situation in which initiation of further eating is inhibited (Blundell et al. 2010). Calorie restriction is a common method employed by individuals trying to achieve weight loss (Das et al. 2007). The lack of success of many of these calorie-restricted diets lies in the individual's failure to adhere to the diet (Heymsfield et al. 2007), due to feelings of intense hunger, constant thoughts of food, and emotional changes; all of which can culminate in temptations to break the diet (Franklin et al. 1948). Foods or ingredients with the potential to enhance satiety could be beneficial in augmenting the success of calorie restricted diets, by decreasing the adverse effects associated with low energy intake and prolonging the feeling of fullness (Chambers, McCrickerd, and Yeomans 2015). Indeed,

results have shown that consumers are willing to try satiety-promoting foods and that many would also prefer a greater amount of foods with this functional element (Hetherington et al. 2013).

Although dietary fat can lead to passive overconsumption (Green et al. 2000), there is a growing body of research which suggests that some fats may elicit stronger satiety responses than others. These fats may not be able to match the satiating properties of protein or carbohydrate on an isocaloric basis (Blundell and MacDiarmid 1997); however given that fat should make up to 35% of energy intake (Department of Health 1984) and some obese individuals have reported intakes exceeding 40% (Dreon et al. 1988), incorporating lipids with satiating properties has the potential to reduce overall energy intake. Data investigating lipids with satiating properties is still inconclusive.

The purpose of this review is to highlight fat with the potential to promote satiety in humans, the mechanisms by which they work and to evaluate which has the greatest potential to be utilised in weight management strategies. We discuss the potential role and mechanisms of medium chain triglycerides, conjugated linoleic acid, short-chain fatty acids, diacylglycerol, omega-3 polyunsaturated fatty acids, and small particle lipids on satiety, satiation and perceptions of these. Acute research refers to studies which examine the transient effect of dietary lipids, usually a single bolus, whereas chronic adaptation refers to the study of a dietary lipid administered over two or more days. Studies were included that focused on satiety, satiation, perceived satiety or satiation (i.e visual analogue scales) or included elements that allowed for speculation into the effects of satiety (i.e. energy intake). This allowed for discussion into the potential role of a lipid where limited research is currently available. Due to the production of SCFA in the gut, both ‘direct’ and ‘indirect’ studies are included; the direct administration of SCFA in a vehicle, or indirectly via insoluble fibre which is fermented in the gut. Where possible, human studies are included, but where mechanistic data in human studies are missing, animal studies are discussed.

Medium-Chain Triglycerides

Medium-Chain Triglycerides (MCT) are triglycerides (esters derived from glycerol and three fatty acids) with fatty acid chain lengths of 6-12 carbon atoms. These include: capronic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0) and lauric acid (C12:0). Along with synthetically produced oils, MCTs are found naturally in coconut oil, palm kernel oil, and a small amount in dairy fat (Marten, Pfeuffer, and Schrezenmeir 2006). According to the 2014 report on nutrient intake in the U.S, approximately 1.8% of all fat is MCFA (Agriculture 2014). However, due to a growing global popularity for coconut oil, this is likely to have increased.

Mechanisms of Satiety

MCT have been proposed to affect satiety by a number of mechanisms which may be cumulative. Outlined below are some of the possible mechanisms.

Absorption

In 1951, Bloom, Chaikoff, and Reinhardt (1951) tested absorption rates of different ^{14}C labelled acids and found that lauric acid and capric acid (both medium chain fatty acids) are transported via the portal venous system, unlike long-chain triglycerides (LCT) which are transported by the lymphatic system. This method of absorption is faster and more efficient than triglycerides with a longer chain. Further, the esterification of MCT is limited, resulting in high levels of oxidation to the point of MCT behaving more like glucose than fat (Marten, Pfeuffer, and Schrezenmeir 2006). The results of Van Wymelbeke and colleagues (Van Wymelbeke, Louis-Sylvestre, and Fantino 2001) and Rolls *et al.* (Rolls et al. 1988) indicate pre-absorptive mechanisms pertaining to the rapid rate of absorption of MCT. Where LCT result in two ‘peaks’ of absorption; that being at the initial point of ingestion and a second delayed peak at the beginning of the next meal (Fielding et al. 1996; Evans et al. 1988; Cohn et al. 1988), MCT are fully absorbed at the point of ingestion. Therefore, MCT may contribute to satiation by this ‘full absorption’ mechanism.

Substrate Oxidation

Fatty acid oxidation has been linked with increased satiety (Langhans and Scharrer 1987; Friedman et al. 1999). MCT may have an anorexigenic effect through the concomitant production of ketones that is a result of increased acetyl-CoA influx (Tsuji et al. 2001). Ingestion of MCT has been shown to lead to increased concentrations of the ketone body β-hydroxybutyrate (Page et al. 2009), which is thought to suppress appetite (Laeger, Metges, and Kuhla 2010; Scharrer 1999). The increase in ketone bodies provides a substrate for energy, thereby sparing glucose (Zhang et al. 2013) and decreasing food intake (Mayer 1953).

Satiety Hormones

Few papers have examined the response of these satiety hormones to MCT consumption (Maas et al. 1998; Barbera et al. 2000; M-P St-Onge et al. 2014). Cholecystokinin (CCK) was the first gut hormone found to influence satiety (Gibbs, Young, and Smith 1973). Lipid ingestion is linked to the secretion of CCK, however this is dependent on the fatty acid chain length. The majority of MCT do not lead to increased CCK levels (McLaughlin et al. 1999; Beglinger et al. 2010). However, in a study by McLaughlin and colleagues (McLaughlin et al. 1999) CCK was released after either emulsions of capric (C10) or lauric (C12) acid were infused into the gut of healthy volunteers. The control lipid in that study was Tween 80 mixed with a phosphate-buffered saline, which also increased CCK secretion above baseline, meaning that the increase observed by C10 was not significant. Feltrin and colleagues (Feltrin et al. 2004) aimed to address this limitation by using an appropriate control and found that both C12 and C10 lead to increased CCK release, although the magnitude of this increase was greater with C12. Further, C12 significantly decreased perceptions of hunger, desire to eat, and prospective food consumption as well as energy intake at an *ad libitum* buffet meal, whereas C10 did not. This suggests that even though some fatty acids with chain lengths below 12 cause secretion of CCK, this is unlikely to affect appetite sensation. Multiple

156 studies confirm that fatty acids with chain lengths of 12 and above are able to stimulate CCK,
157 whereas chain lengths of 10 and below are not as effective (D Matzinger et al. 2000; J. T.
158 McLaughlin et al. 1998; Feltrin et al. 2007, 2006; Feinle et al. 2001; Lal et al. 2004; French et al.
159 2000). Furthermore, despite initial findings suggesting otherwise (Hildebrand et al. 1990), CCK
160 receptor antagonist studies indicate no role of CCK in fat induced satiety (Drewe et al. 1992).
161 Despite the controversial role of CCK, it is still widely reported that CCK is a mediator of fat-
162 related satiety, through a delaying of gastric emptying (Liddle et al. 1986; Daniel Matzinger et al.
163 1999) by modulation of antropyloroduodenal motility (Feltrin et al. 2004), and a reduction of the
164 capacity that can be tolerated in the upper gastrointestinal (GI) tract (Lal et al. 2004); processes
165 which rely on the digestion of triglycerides into free fatty acids (Feinle et al. 2001; D Matzinger et
166 al. 2000; Feinle et al. 2003; Pilichiewicz et al. 2003). Therefore as MCT do not require bile salts,
167 secreted by CCK, for emulsification (McLaughlin et al. 1999), this could explain the lack of CCK
168 response by shorter chain fatty acids. Despite this, MCT do seem to have appetite-suppressing
169 effects, which are independent of CCK.
170
171 PYY is a 36 amino acid peptide belonging to the pancreatic polypeptide family, and its secretion is
172 initiated by the sensing of nutrients, primarily protein (Batterham et al. 2006) and fat (Aponte et al.
173 1985; Pironi et al. 1993), in the GI lumen. Its anorectic effect has been demonstrated via peripheral
174 administration of $PYY_{3-36,}$ which increases c-fos expression in the arcuate nucleus (ARC); and
175 direct injection into the ARC inhibits food intake in rats and mice (Batterham et al. 2002; Riediger
176 et al. 2004). After administering intraduodenal infusions of LCFA (corn oil) or MCT (56% octanoic
177 acid and 43% decanoic acid), Maas *et al.* (Maas et al. 1998) found that MCT did result in PYY
178 secretion, but not to the same extent as LCT. However, the caloric load of each infusion differed;
179 11.6 kJ·min from MCT and 22.7 kJ·min from LCFA which may have affected the potential for
180 PYY release. C10 has also been shown to stimulate PYY secretion in a dose-dependent manner

(Feltrin et al. 2007). It must be noted that CCK is a potent stimulator of PYY secretion (Marie-Pierre St-Onge and Jones 2002), which could explain the weaker release of PYY by MCT. To date no study has investigated MCT alongside PYY receptor antagonists, which could provide conclusive information as to the effects of MCT on PYY release (St-Onge et al. 2014).

A more recent pilot study in overweight men investigated MCT ingested orally (as opposed to these aforementioned studies which utilised duodenal infusions) on a variety of gut peptide hormones, and found that, compared to LCT, MCT did not affect total ghrelin or GLP-1; but leptin and PYY concentrations remained higher after the MCT meal (St-Onge et al. 2014). However, correlations between these results and food intake at the *ad libitum* meal provided were opposite to the expected direction, suggesting that the MCT suppression of food intake is not mediated by gut peptide hormones. While these results do not appear to show a link between gut peptides and MCT driven satiety, there is clearly more work to be done to confirm this.

Other Considerations

MCFA are considered unpalatable, and if initially digested in the mouth MCT may play a role in sensory specific satiation (Clegg 2010). As well as their unpalatability, MCT have been shown to cause GI distress, including vomiting and cramping (Jeukendrup et al. 1998; Goedecke et al. 2005). This has been shown at high dosages of up to 85g, which are not typically used in appetite research; more so sports performance (Jeukendrup et al. 1998). Infusion studies have reported greater nausea after LCT than MCT (Barbera et al. 2000; Feinle et al. 2001), which is not supported by more recent findings that nausea was greatest after a breakfast containing MCT (Coleman, Quinn, and Clegg 2016). Regardless, this must be considered to ensure that any effects on satiety are not a result of GI distress.

Effect of acute intake of medium chain triglycerides on satiety

Acute studies examining the effect of MCT on satiety and energy balance appear to have equivocal findings. Some studies have found reductions at *ad libitum* meals following intake of MCT (Rolls et al. 1988; Van Wymelbeke, Louis-Sylvestre, and Fantino 2001; Van Wymelbeke et al. 1998); whereas others have reported no effect (Barbera et al. 2000; Poppitt et al. 2010). There are limitations in several studies reporting no effect of MCT on satiety which suggests there is potential for MCT to increase satiety. In the first study to investigate the effect of MCT on satiety in humans, Rolls *et al.* (1988) administered three doses of either MCT or LCT (100, 200 and 300 kcal) in beverage form and examined the effect on food intake at an *ad libitum* meal in dieters and non-dieters. In dieters, they found no consistent change in intake. However, in non-dieters there was an overall decrease of ~14% in energy intake after MCT, and this was dose-dependent. Similarly, Van Wymelbeke *et al.* (1998) found that MCT led to decreased intake at lunch when it was added to a carbohydrate breakfast. Furthermore, in a later study by the same research group, there was decreased intake at dinner after an MCT lunch when compared to a lunch with either LCT, carbohydrate or a fat substitute (Van Wymelbeke, Louis-Sylvestre, and Fantino 2001). However, Poppit *et al.* (2010) report no influence of MCT on perceived satiety after 18 healthy men consumed high-fat breakfasts containing short-chain triglycerides, MCT or LCT. This could be explained by the small dose of MCT in that study (10g), whereas previous studies have observed significant results with doses of 20 g or more (St-Onge et al. 2014; Rolls et al. 1988; Van Wymelbeke, Louis-Sylvestre, and Fantino 2001; Van Wymelbeke et al. 1998).

As aforementioned, adverse effects related to MCT ingestion may confound any purported satiety effects. Therefore, this must be either considered when analysing results or, preferably, when designing the vehicle for the lipids. The studies of Poppit and colleagues (2010) and Van Wymelbeke and colleagues (1998) both administered visual analogue scales to examine if there were any subjective sensory differences between the meals provided and found that there was no

231 difference, concluding that any effects were not related to palatability. A later study by Van
232 Wymelbeke's group (Van Wymelbeke, Louis-Sylvestre, and Fantino 2001) along with the study by
233 Rolls' research group (Rolls et al. 1988) included a pre-test where palatability of the test meals were
234 assessed; participants who registered low palatability scores were excluded in Rolls' study, whereas
235 the preliminary screening indicated participants were unable to distinguish between the breakfasts
236 in the study by Van Wymelbeke.
237
238 ***Effects on satiety of chronic consumption of medium chain triglycerides***
239 There are few long-term studies reporting the effects of MCT on satiety, though many have studied
240 weight loss effects primarily through diet-induced thermogenesis. However, this is outside the
241 scope of this review. Krotkiewski (2001) examined extreme hypocaloric diets combined with either
242 MCT or LCT in overweight women. Weight loss was accelerated in the MCT group for the first two
243 weeks; however this decreased in weeks 3 and 4. This pattern was also observed in perceived
244 appetite and satiety, as after the first two weeks perceived appetite was lower at all time points and
245 perceived postprandial satiety was higher. The difference between the groups diminished by week
246 4, perhaps indicating an adaptation to chronic MCT intake. However, it must be noted that the
247 amounts of each fat provided in this study were very low (9.9g of MCT and 8.8g of LCT).
248 Therefore if MCT has an effect at such low doses there is a rationale to increase the dose after the
249 initial adaptation has taken place. The results of this study (Krotkiewski 2001) show some exciting
250 potential as the decreased feelings of hunger may aid weight loss program adherence by reducing
251 dropout rates.

252 **Conjugated linoleic acid**

253 Conjugated linoleic acid (CLA) is the name of a family of stereo and positional isomers of
254 octadecadienoic acid (linoleic acid), meaning isomers with the same formula and constitution but
255 different structures. 'Conjugated' refers to the conjugated double bonds, in that they are only
256 separated by one single bond. Of the 24 isomers of CLA (Kreider et al. 2010), the most commonly
257 examined in research are the cis-9, trans-11 CLA isomer, and the trans-10, cis-12 CLA isomer
258 (Campbell and Kreider 2008). The richest sources of these isomers are meat and dairy derived from
259 ruminants, of which approximately 90% is the cis-9, trans-11 isomer and the remaining 10% is the
260 trans-10, cis-12 isomer (Mushtaq, Heather Mangiapane, and Hunter 2010; Kennedy et al. 2010).
261 Commercially available CLA typically contain approximately equal amounts of the cis-9, trans-11
262 and the trans-10, cis-12 isomers (Hargrave et al. 2002; Norris et al. 2009).

263

264 ***Mechanisms of Satiety***

265 CLA effects on body weight and body composition have been widely reported (Blankson et al.
266 2000; Belury, Mahon, and Banni 2003; Gaullier et al. 2007, 2005). CLA is thought to reduce the
267 size of adipocytes through stimulation of pro-inflammatory cytokines such as TNFα (tumour
268 necrosis factor α) and by the inhibition of PPARγ (peroxisome proliferator-activated receptors)
269 receptors by inhibiting adipocyte differentiation (Salas-Salvadó, Márquez-Sandoval, and Bulló
270 2006; Cawthorn and Sethi 2008). The *trans*-10, *cis*-12 isomer is reported to exert the most anti-
271 adipogenic effects through decreased expression of genes which regulate triglyceride storage and
272 transport of fatty acids (Brown and McIntosh 2003).

273

274 Although CLA has received little attention to date in relation to satiety, it does also have the
275 potential to reduce energy intake. Despite many not human studies specifically examining food
276 intake following CLA consumption, various animal studies have shown a decrease in intake after

277 administration of CLA (Cao et al. 2007; Hargrave et al. 2002; Miner et al. 2001; Santora,
278 Palmquist, and Roehrig 2000; Yeonhwa Park et al. 1997; R Dugan et al. 1997), although some
279 studies found no effect (Tsuboyama-Kasaoka et al. 2000; DeLany et al. 1999; Wong et al. 1997).
280 Furthermore, even when decreased food intake was observed, the reductions do not completely
281 explain decreases in body fat (Shelton et al. 2012; Hargrave et al. 2002; Y. Park et al. 2007; Miner
282 et al. 2001), suggesting favourable changes in body composition are independent of appetite
283 control.

284 Substrate Oxidation

285 Despite a lack of studies specifically examining CLA and satiety, it is possible to discuss the
286 potential link between the two. The glucostatic theory of appetite, developed by Mayer in the 1950s
287 (Mayer 1953), proposed the presence of glucose receptors in the brain which respond to a
288 fluctuation in glucose levels. Therefore, a drop in blood glucose level promotes an increase in
289 hunger, and an increase in blood glucose (after exogenous carbohydrate ingestion) promotes the
290 onset of satiation, due to the fact that glucose is the primary fuel for the central nervous system, and
291 so it is tightly regulated in order to prevent hypoglycaemia (De Graaf et al. 2004; Campfield et al.
292 1996). CLA has been shown to increase lipolytic activity (Yeonhwa Park et al. 1997, 1999; Choi et
293 al. 2000; Pariza, Park, and Cook 2001), which potentially may spare glucose oxidation and act as a
294 satiety signal (Kamphuis et al. 2003; J. M. Brown and McIntosh 2003); however, this is speculative.

295 *Leptin*

296 Leptin is a satiety-promoting hormone which is released by white adipose tissue (Perry and Wang
297 2012). Leptin has been shown to inhibit orexigenic neuropeptide Y (NPY) and agouti-related
298 peptide (AgRP) co-expressing neurons (Sahu 2003), meaning that the centre of the hypothalamus
299 which promotes hunger is inhibited. Increased body fat is associated with increased leptin
300 circulation (Myers, Cowley, and Unzberg 2008), whereas reduced sensitivity to leptin has been

shown to play a role in obesity, and can potentially be a strong driver of metabolic syndrome (Paz-Filho et al. 2009; J. M. Friedman and Halaas 1998). Medina *et al.* (Medina 2000) observed a decrease in leptin that was significant at 7 weeks of CLA supplementation but returned to normal in the final 2 weeks. There was no effect on energy intake or body mass index (BMI) between baseline and at the end of the study, suggesting CLA decreased leptin levels independently of body fat levels. Gaullier *et al.* (2005) also observed decreases in circulating leptin and energy intake after 24 months of supplementation with both triglyceride and free fatty acids forms of CLA. These findings suggest that, in the absence of leptin resistance, increased levels of leptin decreases energy intake (Klok, Jakobsdottir, and Drent 2007), indicating a potential mechanism for CLA-mediated satiety.

Conversely, Iwata *et al.* (2007) reported an increase in leptin concentrations after CLA but no concurrent decrease in energy intake. However, leptin concentrations also increased in the placebo group, again with no change in energy intake indicating the changes in leptin are likely to be unrelated to CLA intake. Increased leptin concentrations was also reported after intracerebroventricular administration of CLA in rats, which decreased expression of NPY and AgRP and consequently feed intake (Cao et al. 2007). However, another study rejected the idea that CLA affects neuropeptide expression in the hypothalamus, as no CLA isomers were identified in the brain (Shelton et al. 2012). CLA did significantly decrease feed intake, but the authors suggest CLA may have altered serum hormone levels as opposed to a central mechanism.

Acute intake of conjugated linoleic acid on satiety

To date, there is only one study which has examined the effect of CLA on food intake (Coleman, Quinn, and Clegg 2016). In that study, participants consumed a smoothie drink containing either vegetable oil (as the control) CLA or MCT after which they consumed an *ad libitum* sandwich lunch, which was provided upon request. Both test fats elicited non-significant decreases at the *ad libitum* lunch, and intake throughout the rest of the day (and therefore overall energy intake) was

significantly lower following CLA and MCT compared to the control. CLA resulted in the longest time-to-meal request. More research is required to examine further the effectiveness of CLA as a method of reducing food intake and enhancing satiety.

Effects on satiety of chronic consumption of conjugated linoleic acid

Where few studies have examined CLA in the short term, there are many studies examining its effects as a long-term dietary intervention for improving body composition and reducing body weight. An excellent meta-analysis of this topic was conducted by Onakpoya and colleagues (Onakpoya et al. 2012). We have included papers which allowed for speculation as to the satiety effects of CLA.

The majority of studies have not shown any significant impact of CLA on energy intake, indicating that there are satiating effects associated with CLA consumption (Cornish et al. 2009; Gaullier et al. 2005; Iwata et al. 2007; E. V Lambert et al. 2007; Medina et al. 2000; Norris et al. 2009; Wanders et al. 2010). Cornish *et al.* (2009) investigated the combination of mixed isomer CLA, creatine and whey protein versus creatine plus placebo oil, and the placebo oil alone. Whereas there were significant increases in lean mass and strength with all three supplements combined, there was no difference in dietary intake between groups during the intervention period. The findings of Pinkoski *et al.* (2006) corroborate this, as lean mass was increased to a greater extent after 7 weeks of mixed isomer CLA supplementation alongside resistance exercise compared to a placebo. However, there was no change in self-assessed energy intake between baseline and 7 weeks between the two groups. Norris *et al.* (2009) reported reductions in BMI, in overweight postmenopausal women with type 2 diabetes after 36 weeks of supplementation with 6.4g/d of mixed isomer CLA. Interestingly, the decline in BMI had not yet reached a plateau, and there may have been further decreases had the study period been longer. This study also showed no difference in energy intake over the study period, which was assessed via 3-day diet diary 4 times over the intervention period. These studies

indicate that CLA may be beneficial for improving body composition and promoting weight loss; however these changes are achieved independently of satiety. Nonetheless, this is an inference based on self-reported diet diary data and satiety was not the primary measure of the aforementioned studies, and so more work is required to confirm this.

In contrast, Kamphuis *et al.* (2003) found mixed isomer CLA dose-dependently increased feelings of fullness and decreased feelings of hunger after 13 weeks of supplementation with a low (1.8g) and high (3.6g) dose. This did not affect energy intake at breakfast, although as this was the only meal analysed it is possible that intake may have been affected during the rest of the day. Watras *et al.* (2007) reported that mixed isomer CLA led to decreased weight gain over a 6 month period compared to a placebo. This was especially true during the winter holiday period, when the placebo trial subjects increased their energy intake yet there was no change in energy intake in the CLA group indicating that the CLA may have suppressed food intake.

CLA does appear to be promising in the management of obesity and as a supplement to improve body composition (Blankson et al. 2000; Belury, Mahon, and Banni 2003; Gaullier et al. 2007, 2005); however, this appears to be achieved without increasing satiety. Further work is required before conclusions can be drawn, especially studies focusing on satiety and not body composition. It is also noteworthy to mention that there have been some deleterious effects reported with CLA ingestion, particularly insulin resistance (Risérus, Berglund, and Vessby 2001; Medina et al. 2000; Smedman and Vessby 2001), which seems intuitive given the key role of leptin in glucose homeostasis (Denroche, Huynh, and Kieffer 2012) and the aforementioned reported decrease of leptin by CLA. An early review by Wahle and colleagues (Wahle, Heys, and Rotondo 2004) suggested that more research is warranted in order to conclude whether CLA is truly beneficial or detrimental to health.

Short-chain fatty acids

Short-chain fatty acids (SCFA) are carboxylic acids which are aliphatic, ranging from two carbons to four carbons in length. SCFA are made in the colon through bacterial fermentation when non-digestible carbohydrates pass through the upper GI tract and reach the large intestine (Byrne et al. 2015). The three main SCFA created are acetate (C2), propionate (C3) and butyrate (C4) in a ratio of approximately 60:20:20. There are also some dietary sources of SCFA such as sourdough bread, vinegar and vinegar-based products such as pickles, and finally some cheeses and other dairy products (Darzi, Frost, and Robertson 2011).

Mechanisms of Satiety

Central control of appetite

There are a number of potential mechanisms by which SCFA may influence satiety. These involve an increase in circulating anorexigenic hormones (Cani et al. 2006; E. S. Chambers et al. 2015; Nilsson et al. 2013) and a decrease in circulating ghrelin (Parnell and Reimer 2009). Acetate has also been shown to cross the blood-brain barrier and be taken up by the brain, specifically by the hypothalamus in both mice (Chambers et al. 2015) and humans. Appetite may be suppressed by SCFA via this mechanism, as the anorectic signal in the ARC produces increased expression of proopiomelanocortin (POMC) and reduced expression of AgRP (Frost et al. 2014). AgRP, along with NPY, is a potent stimulator of food intake, whereas POMC, along with cocaine- and amphetamine-regulated transcript (CART) provides a tonic anorexigenic signal to suppress appetite and food intake (Cone 2005; Wynne et al. 2005; Morton and Schwartz 2006; Millington 2007). SCFA may also be involved in a similar central control of feeding via intestinal gluconeogenesis (IGN). It has been shown that both butyrate and propionate stimulate IGN (Bienenstock, Kunze, and Forsythe 2015a; De Vadder et al. 2014). This is sensed by sodium-glucose cotransporters (possibly SGLT3) in the portal vein which send an afferent nervous signal to decrease food intake

(Delaere et al. 2013). Butyrate has been shown to increase directly expression of phosphoenolpyruvate carboxykinase 1 (*PCK1*) and glucose-6-phosphatase catalytic subunit (*G6PC*) – genes involved in the regulation of IGN – 2 to 3-fold. In contrast, propionate does not directly stimulate IGN genes, but binds to FFA3, which sends signals to the parabrachial and paraventricular nuclei in the brain; driving a reflex arc to induce IGN in the gut (De Vadder et al. 2014).

Satiety Hormones and Gastric Emptying

The SCFA receptors FFA2 and FFA3 have been shown to be co-expressed in L-cells which release glucagon-like peptide-1 (GLP-1) and PYY (Byrne et al. 2015). Indeed, it has been shown that propionate stimulates the release of GLP-1 and PYY via FFA2 (Psichas et al. 2014). These findings are corroborated by animal models which show that GLP-1 concentrations are decreased in FFA2 knockout mice (Tolhurst et al. 2012) and likewise with PYY in FFA3 knockout mice (Samuel et al. 2008). The satiating effects of PYY have already been mentioned, and GLP-1 similarly enhances satiety via a delay in gastric emptying (Flint et al. 1998; Shah and Vella 2014). GLP-1 receptors appear in areas in the central nervous system which are involved in feeding control, such as the paraventricular nucleus (PVN), the ARC and on POMC neurons (Dailey and Moran 2013; De Silva and Bloom 2012).

The satiating properties of propionate have also been attributed to gastric emptying (Liljeberg and Björck 1996). Colonic contractile activity has been shown to be reduced in rats after SCFA infusion to the colon (Squires et al. 1992), but a more recent study showed no effect of colonic infusion on contractile activity in human volunteers (Jouët et al. 2013). Liljeberg and Björck (1996) found greater perceived satiety linked to slower gastric emptying after SCFA ingestion.

Other considerations

Darzi and colleagues (Darzi, Frost, and Robertson 2012) attribute the satiating effects of SCFA to the hedonic unpleasantness of propionate rather than post-absorptive mechanisms. They found no effect of bread containing a small amount of propionate, which was more acceptable and did not cause nausea, lending credence to this hypothesis. They concluded that any effects seen may be due to the palatability of orally administered SCFA, and do not support a role in appetite regulation (Darzi, Frost, and Robertson 2011). Future studies need to mask these unpleasant characteristics of the SCFA.

This review aims to discuss dietary lipids and satiety. However it must be briefly mentioned that studies in mice and rats have shown that fermentable carbohydrates (such as inulin and fructooligosaccharides [FOS]) lead to production of SCFA in the large intestine (Ten Bruggencate et al. 2005; Arora et al. 2012), and this may also affect satiety. Long-term ingestion of soluble fibre may also lead to increased satiety due to increased proliferation of GLP-1 producing L-cells (Kaji et al. 2011; Kuwahara 2014). Kuwahara (2014) explains how this can only occur after long-term ingestion of FOS, as fermentation can take a number of days to occur and only then can this affect GLP-1 production. This may not manifest in changes in short-term satiety, but possibly in long-term energy homeostasis.

Acute intake of short-chain fatty acids on satiety

As outlined above studies examine SCFA via two methods: direct administration (such as through the use of vinegar (Kondo et al. 2009; Ostman et al. 2005)) or indirectly (through the use of fibre (Nilsson et al. 2013) and fermented dairy beverages (Ruijschop, Boelrijk, and te Giffel 2008)). Ruijschop *et al.* (2008) examined the use of a dairy beverage fermented with *Lactobacillus acidophilus* and *Propionibacterium freudenreichii* on satiety and food intake, and found greater feelings of satiety when compared to a placebo although there was no corresponding change in food intake. This is the only study to date, to our knowledge, which has investigated cultured propionic

449 acid bacteria in a dairy beverage on satiety. Despite the fact there was no effect on energy intake, it
450 would be apposite to conduct more studies to fully elucidate its potential.

451 A dose-response study investigating different amounts of acetate in the form of vinegar added to a
452 bread meal found that there is a linear relationship between subjective satiety and acetate ingestion
453 (Ostman et al. 2005). Similarly, Hlebowicz *et al.* investigated different breads soaked in acetic acid
454 (white, wholemeal or wholegrain) and compared them to an un-soaked white bread control
455 (Hlebowicz et al. 2008). While the wholegrain/acetate combination led to the greatest subjective
456 satiety, these results must be treated with caution as there was no wholegrain control (i.e. not
457 soaked with the acetate). Hence it is difficult to ascertain whether the wholegrain bread or the
458 acetate influenced satiety in that study. Conversely, some studies have failed to link SCFA to
459 satiety. Mettler *et al.* found no significant effect of adding either acetate, cinnamon, both, or neither
460 to a rice pudding meal on subjective satiety (Mettler, Schwarz, and Colombani 2009). Poppit *et al.*
461 (2010) also found no effect of short-chain triglycerides from soft fraction milk fat on subjective
462 feelings of hunger or energy intake.

463 In the review by Darzi and colleagues discussing the role of SCFA in appetite regulation (Darzi,
464 Frost, and Robertson 2011), the authors discuss unpublished data on which they conducted pooled
465 correlations. According to the authors, these findings suggest that acetate-containing vinegar may
466 influence satiety through palatability effects rather than any mechanistic/physiological effects of
467 SCFA. More recently, the same group conducted a series of experiments investigating the satiety
468 effects of vinegar alongside a study investigating the orosensory properties of a vinegar containing
469 beverage (Darzi et al. 2014). These studies showed that tolerability of vinegar, as opposed to
470 palatability per se, is the cause of nausea after ingestion. This is due to the significant increase in
471 perceived nausea after consuming the test drink but no difference when the drink was sham fed (i.e.
472 held in the mouth and then expectorated). These findings discredit the use of vinegar as a satiety-

enhancing product, as poor tolerability and nausea are possibly the main causes of reduced intake, rather than the physiological effect of activating FFA2 and FFA3.

Despite systematic reviews examining both acute and chronic randomised control trials concluding that fibre only yields small satiety effects (Wanders et al. 2011) and the majority of studies failing to find significant effects (Clark and Slavin 2013), fibre may promote satiety by delaying gastric emptying and leading to a greater release of satiety hormones (Chambers, McCrickerd, and Yeomans 2015). Nilsson *et al.* (2013) reported that feeding healthy participants an evening meal consisting of brown beans – which contain large amounts of indigestible carbohydrates – increases circulating PYY and decreases circulating ghrelin after a standard breakfast meal. This was attributed to propionate, as concentrations were significantly increased after the brown bean meal compared to the control. However, the results of this study could also be due to other characteristics of fibre and not SCFA exclusively. Tarini and Wolever (2010) found concentrations of plasma GLP-1 were increased and serum ghrelin were decreased after 24g of inulin was added to a test drink; effects attributed to increased colonic SCFA production. Considering that the daily reference value for fibre is 30g·day, this is a large bolus of fibre to consume in a single sitting; but it does demonstrate the potential for fermentable fibre to mediate satiety, possibly through increased SCFA levels in the gut.

Effects on satiety of chronic consumption of short-chain fatty acids

Current knowledge on SCFA is limited as the majority of studies conducted to date are in animal models, with more studies in human participants required to elucidate the effects and mechanisms of SCFA on energy expenditure, intake, and balance. Kondo *et al.* (2009) conducted the first study to investigate the effect of SCFA (in the form of acetic acid present in vinegar) on body composition. This double-blind parallel study administered beverages with either no vinegar (control) or a low or high dose (15 and 30 ml, respectively) of cider vinegar for 12 weeks. They

found that body composition was improved in a dose-dependent manner, showing that acetic acid, in the form of vinegar, can beneficially alter body composition, fat mass, and body weight. However, there were no differences between any of the groups during the supplementation period for energy intake, macronutrient composition of foods eaten or physical activity. From this, we may infer that the beneficial effects of orally ingested acetate, the most abundant of the SCFA, are not linked to satiety. Conversely, in a study by Cani *et al.* (2006) two 8g portions of oligofructose were taken at breakfast and dinner for two weeks. Subjective satiety after an *ad libitum* breakfast was significantly higher than baseline after the supplementation and intake was lower at the meal. Intake was also lower at the *ad libitum* lunch provided, but not at dinner, corresponding to a significant decrease in energy intake throughout the whole day of approximately 5% after oligofructose intake. Despite discussing the fermentation of fibres at length and commenting on SCFA production, this paper, unfortunately, did not measure SCFA production, which would have allowed for a link between satiety and SCFA. SCFA concentrations, however, were reportedly increased after 6 weeks of oligofructose supplementation in another study, which corresponded to decreased energy intake and reported hunger, as well as increased PYY (Daud et al. 2014). Similarly, Chambers *et al.* measured the release of GLP-1 and PYY from L cells *in vitro* and found that SCFA led to significant increases in hormone release above basal levels (Chambers et al. 2015). That group produced a novel ester which bound propionate to inulin by an ester bond. This allowed delivery of propionate to the gut as inulin which was fermented by colonic fermentation, thereby releasing the propionate. In a 24-week follow-up supplementation study in 49 volunteers, 10g of propionate per day led to significant reductions in energy intake of 14% compared to the control group. This decrease was attributed to the increased stimulation of GLP-1 and PYY that the authors found in the *in vitro* part of the study. Similarly, Freeland *et al.* (2010) reported increased plasma butyrate and increased GLP-1 release after chronic intake of fibre. This may outline the mechanisms behind

SCFA and satiety, although these results were only observed after 9 months of intake (20g of fibre·day over baseline intake).

Clearly, the literature surrounding SCFA is far from unequivocal, although it is possible that the specific SCFA may exert different effects on satiation and body composition. This is an avenue for future work.

Diacylglycerol

Diacylglycerol (DAG) is a glyceride which consists of two fatty acids on a glycerol backbone and naturally occurs in small amounts in cooking oils; from 0.8% in rapeseed oil to 5.5% in olive oil and 9.5% in cottonseed oil (Rudkowska et al. 2005; Flickinger and Matsuo 2003; D'Alonzo, Kozarek, and Wade 1982). In 1999, the Kao Corporation in Japan introduced DAG oil which contained over 80% DAG and sold over 70 million bottles between then and 2003 (Flickinger and Matsuo 2003).

Mechanisms of Satiety

Substrate Oxidation

Chronic studies examining the effects of DAG on weight loss have attributed the decrease in adipose tissue to greater levels of β-oxidation (Maki et al. 2002; Nagao et al. 2000), although to the authors' knowledge only one study has directly measured this (Kamphuis, Mela, and Westerterp-Plantenga 2003). Scharrer and Langhans (1986) first established that inhibited fatty acid oxidation stimulates feeding, and since then hepatic fatty acid oxidation has been linked with hunger (Kahler, Zimmermann, and Langhans 1999). Therefore the decrease in appetite shown in the study by Kamphuis *et al.* (2003) could be attributed to the lipoprivic control of eating.

Gastric Motility

The transport and absorption of DAG are similar to medium-chain triglycerides, despite the fact it is mainly comprised of long-chain fatty acids. Long-chain fatty acids (≥12 carbon atoms) slow gastric emptying – the rate of food leaving the stomach and entering the duodenum (Clegg and Shafat 2009) – to a greater extent than shorter chain fatty acids (Hunt and Knox 1968). It has been shown that gastric emptying is correlated with satiety, and therefore the longer food remains in the stomach the greater is the satiating effect (Bergmann et al. 1992; Geliebter 1988). Therefore it is possible

551 that DAG may influence satiety through delayed gastric emptying, although this is only speculation
552 as there are currently no studies which have investigated this.
553
554 *Satiety Hormones*
555 Stoeckel *et al.* (2008) compared the effect of a high-fat beverage consisting mainly of DAG to a
556 very low-calorie beverage on PYY release. Participants were divided into either high PYY release
557 or low PYY release groups. In the high PYY group, the response was significantly higher after the
558 DAG drink compared to the low-calorie drink, which also corresponded to decreased ratings of
559 hunger. No other study to the authors' knowledge has reported PYY 'non-responders' and it is not
560 currently known why this study found this. It is tempting to speculate an effect of DAG on PYY
561 release; however without a control oil to compare it to it is impossible to say whether this response
562 is similar to other long-chain oils.
563
564 ***Acute intake of diacylglycerol on satiety***
565 As aforementioned, Kamphuis, Mela and Westerterp-Plantenga (2003) examined the effect of
566 energy-balance diets for 4.5 days on substrate oxidation, energy expenditure, and subjective
567 appetite when 40% of the fat provided was either DAG or TAG oil. On the fourth day, DAG oil
568 intake was 33.0 ± 2.3 g which provided 26.4 ± 1.9 g of DAG, and on the fifth day, DAG oil intake
569 was 22.2 ± 1.4 g which provided 17.8 ± 1.1 g of DAG. DAG oil led to decreased subjective hunger
570 and increased subjective satiety, which was attributed to higher rates of β-oxidation. Participants
571 were fed a prescribed amount in order to achieve energy balance, and so whether these subjective
572 feelings would lead to changes in *ad libitum* intake is unknown. Given that the inhibition of fatty
573 acid oxidation stimulates hunger (Langhans et al. 2011; Leonhardt and Langhans 2004), it is
574 possible that this increase in β-oxidation will have the opposing effect and prevent hunger, although
575 this requires further study. To the authors' knowledge, this is the only study to date which has

576 investigated the role of DAG on appetite. Taking into account the potential for cumulative
577 mechanisms which could lead to enhanced satiety, this is an exciting avenue for further research.
578
579 ***Effects on satiety of chronic consumption of diacylglycerol***
580 It has been repeatedly shown that chronic intake of DAG can lead to decreased body weight and
581 reduced accumulation of adipose tissue (Kawashima et al. 2008; Li et al. 2008; Yasunaga et al.
582 2004; Maki et al. 2002; Yamamoto et al. 2001; Taguchi et al. 2001). There are clearly some long-
583 term benefits associated with the intake of DAG, although this is outside the scope of the current
584 review; however, readers are directed to the meta-analysis of Xu *et al.* (2008). To the authors'
585 knowledge, no study to date has investigated chronic DAG intake on satiety specifically. Self-
586 reported diet diary data suggests that DAG has no long-term effect on satiety (Yamamoto et al.
587 2001) or can decrease energy intake but no more than a triacylglycerol control oil (Kawashima et al.
588 2008). Li *et al.* (2008) found that carbohydrate intake was decreased after 120 days of DAG
589 supplementation, but the decrease in total energy intake only approached significance ($P = 0.08$). It
590 is noteworthy to mention that the study by Kawashima and colleagues (2008) administered DAG oil
591 in an *ad libitum* protocol where participants merely swapped their normal cooking oil with DAG
592 oil. This is of particular importance as most studies administer lipids by adding extra lipid to food,
593 such as yoghurt (Kamphuis, Mela, and Westerterp-Plantenga 2003) or a beverage (Stoeckel et al.
594 2008), and so this *ad libitum* protocol has been shown to yield significantly positive effects without
595 administering set doses. This study also reported no differences in fasting ketone bodies after the
596 treatment period, which suggests the increase in hepatic fatty acid oxidation is transient. It would be
597 pertinent to investigate if there is increased postprandial β-oxidation after chronic DAG
598 supplementation to elucidate whether there is an added benefit to short-term intake. However, the
599 current evidence suggests that DAG supplementation does not increase satiety.

Omega-3 Polyunsaturated Fatty Acids

Omega-3 (*n*-3) polyunsaturated fatty acids (PUFA) are essential fatty acids as they cannot be synthesized *de novo* (Lorente-Cebrián et al. 2013). The main *n*-3 PUFA are eicosapentaenoic acid (EPA, 20:5*n*-3) and docosahexaenoic acid (DHA, 22:6*n*-3) which are found in large quantities in certain fish, such as mackerel, salmon, and sardines; therefore these are considered to be 'fish oils' (Ackman 2008). Whereas *n*-6 PUFA possesses inflammatory properties by leading to the secretion of the proinflammatory cytokine interleukin-1 and the leukotriene LTB_4, *n*-3 PUFA are anti-inflammatory and may help protect against inflammatory and autoimmune diseases (Simopoulos 2002). Research has shown positive effects of fish oil on cardiovascular diseases (Chowdhury et al. 2012; Ebrahimi et al. 2009), dyslipidaemia (Paniagua et al. 2011; Jiménez-Gómez et al. 2010) and body composition (Bender et al. 2014), however few studies to date have investigated the effect of *n*-3 PUFA on satiety and food intake.

Mechanisms of Satiety

Central control of appetite

The endocannabinoid system is a complex system with various physiological roles, one of which is the regulation of food intake (Pagotto et al. 2006). Lipids have diverse roles in the control of appetite through this system, such as the orexigenic anandamide (*N*-arachidonoylethanolamine, AEA) and the opposing anorexigenic oleoylethanolamide (OEA) (Lambert and Muccioli 2007; Petersen et al. 2006). Levels of gut OEA are low during prolonged fasting and rise postprandially, and OEA has been shown to suppress food intake in rats through peroxisome proliferator-activated receptor α (PPARα) (de Fonseca et al. 2001; Fu J. et al. 2003). In contrast, anandamide has been shown to increase appetite to the point of inducing over-consumption (Williams and Kirkham 1999). Wood *et al*. (2010) noted that DHA-enhanced mouse-chow led to decreased plasma concentrations of both OEA and AEA, which may suggest a homeostatic mechanism in order to

maintain energy balance. However, given that OEA can exerts its anorexigenic effects when accumulating locally in the intestine without affecting plasma levels (Borrelli and Izzo 2009), this requires further research for confirmation.

As briefly mentioned previously, the hypothalamus is the main centre of the brain for regulating energy intake. In recent years, there has been emerging evidence that other areas of the brain are involved with energy intake, such as mesolimbic dopamine system (Volkow, Wang, and Baler 2011). The controversial idea of categorising appetite as an addiction and obesity as a neurobehavioral disorder has been proposed in recent years (Dagher 2009), and in this context, obesity may be a result of the excess energy intake from the consumption of energy dense foods due to their potent reward. Chalon (2006) found that the mesolimbic dopaminergic pathway was overactive in rats with *n*-3 PUFA deficiency, and this could possibly manifest in changes in eating behaviour due to its role in reward-seeking behaviours, such as the consumption of palatable foods. Indeed, Cordeira *et al.* (2010) found that depleted brain-derived neurotrophic factor (BDNF) led to increased intake of chow in mice due to modulation of the mesolimbic dopamine system. Further research is required to investigate the link between *n*-3 PUFA and the mesolimbic system, but if supplementation can suppress reward-seeking behaviour, it could be a useful tool for decreasing energy intake.

Increasing appetite

It is important to remember that not all individuals need to reduce their energy intake. Patients with cancer can suffer from cancer anorexia-cachexia, the muscle wastage that occurs as a result of the disease (Dodson et al. 2011). One of the complications of this condition is poor appetite, possibly due to cytokine-inhibition of neuropeptide Y (Donohoe, Ryan, and Reynolds 2011). Supplementation with *n*-3 PUFA can reduce the production of interleukin-1 and interleukin-6

650 cytokines (Barber, Ross, and Fearon 1998). Therefore, supplementation with EPA may help combat
651 the loss of appetite associated with this condition. This suggests that there may be a role for *n*-3
652 PUFA in overall energy intake regulation, managing both over- and under-consumption.
653
654 ***Acute intake of omega-3 PUFA on satiety***
655 To the authors' knowledge, there are no studies to date which have investigated the acute effect of
656 *n*-3 PUFA intake on satiety. *n*-3 PUFA appears to mediate its effects by increasing the phospholipid
657 content of the cell membrane of EPA and DHA (Calder 2010), which occurs in a dose-dependent
658 manner after supplementation (Rees et al. 2006). Therefore, there may be no benefit to satiety when
659 *n*-3 PUFA are taken acutely. Some studies have found that *n*-3 PUFA ingestion can lead to mild
660 side-effects, such as nausea (Bruera et al. 2003), and have an unpleasant taste (Damsbo-Svendsen,
661 Rønsholdt, and Lauritzen 2013). These are factors which must be taken into consideration when
662 studies assessing acute intake of *n*-3 PUFA on satiety are designed, as they may confound the
663 results.
664
665 ***Effects on satiety of chronic consumption of omega-3 PUFA***
666 Studies have measured the effect of *n*-3 PUFA in various chronic diseases, whereas the role of *n*-3
667 PUFA in satiety has received little attention. The current evidence is equivocal. Parra *et al.* (2008)
668 examined the use of seafood diets and fish oil capsules on appetite in overweight and obese
669 participants who were already undergoing caloric restriction, and found that participants in the high
670 *n*-3 PUFA groups reported increased fullness and decreased hunger and desire to eat after a test
671 meal, assessed by visual analogue scale after the evening meal, which was consumed in habitual
672 conditions. However, it is difficult to conclude whether these effects are chronic effects from the
673 supplementation and diet manipulation or acute effects from the test meals, as the test dinners
674 differed between groups (cod in the low *n*-3 group, salmon in the high *n*-3 group). This does

675 indicate that the long-term intake is associated with appetite suppression, but more research is
676 needed to confirm this. Furthermore, this study did not measure pre-meal appetite sensations and
677 therefore the results must be interpreted with caution, as differences from baseline may have
678 affected the results. Damsbo-Svendsen *et al.* (2013) found that fish oil tablets were not as effective
679 as soybean tablets for increasing satiety, as they reported that postprandial fullness was increased
680 and desire to eat decreased after soybean supplementation for 3 weeks. However, the washout
681 period in this study was one week long, and this may not be enough to completely remove any
682 effects from the previous supplementation (Brown, Pang, and Roberts 1991; Hansen et al. 1998).

683 Interestingly, Bruera *et al.* (2003) found that appetite decreased in both an intervention group and a
684 control group. The aim of that study was to investigate whether *n*-3 PUFA can aid patients with
685 cachexia, which can manifest in symptoms such as weight loss and a reduction in appetite.
686 Unexpectedly, results from this study showed that appetite decreased in patients with cancer
687 cachexia, although it has been previously shown that supplementation with EPA can improve
688 appetite in these patients (Barber et al. 1999). Jatoi *et al.* (2004) examined the use of supplementing
689 1.09 g of EPA and 0.46 g of DHA versus the appetite stimulating progesterone megestrol acetate,
690 and found no differences between the two (or a combination) in terms of appetite, as appetite
691 ratings increased in all three arms. Where this showed no benefit of EPA compared to megestrol, it
692 does show the ability of EPA to increase appetite in cachexia. Similar results have been found in
693 Yehuda *et al.* (2005) who reported that a mixture of *n*-3 and *n*-6 fatty acids led to increased
694 subjective appetite in those who suffered test anxiety compared to a placebo mineral oil. It was
695 again further corroborated by Zaid *et al.* (2012), who found that there was an increase in subjective
696 appetite ratings in children with leukaemia after 8 weeks of supplementation with 360 mg EPA and
697 240 mg DHA daily. These results also indicate that *n*-3 may be useful in appetite control, but for
698 those who need to increase appetite and not for those undertaking a weight loss intervetion.

699 Clearly, more research is needed in healthy volunteers and in a cohort attempting to lose weight.
700 Some of these studies have shown that *n*-3 PUFA supplementation can increase appetite in
701 inflammatory diseases (such as cancer cachexia), but, counterintuitively, they have also been shown
702 to be beneficial in weight loss as well. More research is needed to strengthen our understanding of
703 the role of *n*-3 PUFA in the modulation of appetite.

704 **Small Particle Lipids**

705 Research into lipid droplets is a relatively new field, as it was believed until the early 1990s that
706 they were inert deposits (Suzuki et al. 2011). Lipids droplets consist of a core of lipids surrounded
707 by a phospholipid monolayer (Tauchi-Sato et al. 2002; Fujimoto and Parton 2011) and range in size
708 from 0.3 μm to 20 μm in various milks and infant formulas (Favé, Coste, and Armand 2004). Small
709 particle lipids (SPL) are created via fractionation.

710

711 ***Mechanisms of Satiety***

712 *Digestion*

713 Smaller lipid droplets lead to increased emulsion surface area, meaning that fat hydrolysis will
714 increase, as lipase is active on the surface (Maljaars et al. 2012). Armand (Armand 2007) states that
715 as lipase is abundant, therefore a larger lipid/surface inter-surface area allows for extra binding.
716 Also, human pancreatic lipase is inhibited by large amounts of free fatty acids which accumulate at
717 the surface of lipid droplets; a greater surface area delays this inhibition, thereby increasing the
718 amount of hydrolysis (Armand et al. 1999; Patrick Borel et al. 1994). Increased rates of hydrolysis
719 may increase satiety by increasing fatty acid sensing in the small intestine (Maljaars et al. 2012).
720 Borel *et al.* (1994) conducted the first *in vivo* (in rats) study examining lipid droplet size and
721 digestion, and found that finer emulsions led to greater hydrolysis than coarser emulsions. These
722 findings were confirmed in healthy humans a few years later when emulsions were administered
723 intragastrically (Armand et al. 1999). Furthermore, CCK was more potently released with
724 emulsified LCT – with reduced droplet size – than non-emulsified LCT (Ledeboer et al. 1999).

725 *Gastric Motility*

726 The concept of the 'ileal brake' was first established in the mid-1980s and was shown to both
727 reduce jejunal motility (Spiller et al. 1984) and delay gastric emptying (Read et al. 1984). The ileal
728 brake has been shown to delay gastric emptying to a greater extent than the duodenal brake (Welch,

729 Saunders, and Read 1985; Maljaars et al. 2012). This was confirmed in later studies by the
730 University Hospital Maastricht research group who showed that smaller lipid droplets led to
731 increased peptide secretion and satiety scores over larger droplets, but only when infused into the
732 ileum and not the duodenum (Maljaars et al. 2012). It must be noted that droplet size does also
733 appear to have an effect when administered to the duodenum, as Seimon *et al.* (2009) found that
734 infusion of lipids with a droplet size of 0.26 μm led to greater stimulation of CCK, PYY and hunger
735 suppression, leading to decreased energy intake. However, it was also found in another study that
736 this was only apparent when fat is infused as compared to oral consumption of the same load
737 (Maljaars et al. 2011). However, intragastric infusions are not a feasible method of decreasing
738 energy intake.
739
740 ***Acute intake of small particle lipids on satiety***
741 Fabuless^{TM} (previously Olibra^{TM}) is an emulsion comprised of palm oil and oat oil, produced by
742 DSM (Delft, the Netherlands). GI transit time has been shown to be delayed when Fabuless^{TM} was
743 delivered intra-gastrically (Knutson et al. 2010). Early studies conducted at the University of Ulster
744 showed that this product decreased energy intake by an impressive 22-27% when compared to a
745 control fat in lean, overweight and obese subjects (Burns et al. 2002, 2001, 2000). These results
746 have, unfortunately, not been replicated (Smit et al. 2011; Smit et al. 2012; Chan et al. 2012), even
747 by the same research group (Logan et al. 2006). Smit and colleagues investigated the possible role
748 in the processing of the emulsion, and even with minimal processing (i.e. no shear and a maximum
749 temperature of 42°C), there were effects on subjective appetite or energy intake (H. J. Smit et al.
750 2012). This may explain why the early studies from Burns' group found positive effects, whereas
751 later studies did not; as processing may have rendered the active ingredient in the test drinks
752 inactive. In reality, this study concludes there is no efficacy of Fabuless^{TM} in improving satiety.

753 Fractionated oat oil (LOO) has a smaller particle size than milk globules (100 nm vs 1000 nm) and
754 may remain partially undigested when entering the ileum. It has been shown to result in increased
755 circulation of PYY, GLP-1, and CCK, but no changes in energy intake (Ohlsson et al. 2014). The
756 authors claim that the concentration of polar lipid in the oil investigated is considerably higher than
757 those in Fabuless^{TM}, and the resulting liposomes are stable enough to pass through the stomach
758 without structural changes. This may explain the larger effect seen in postprandial concentrations of
759 CCK, PYY, and GLP-1 with LOO compared to Fabuless^{TM}, but further study is required to confirm
760 this.

761 Peters *et al.* (2014) reported no effect of droplet size when administered in a meal-replacement
762 drink, and they discuss the potential for the background effect of the drink (which contained 10g of
763 protein in the 606 kJ drink) which may have decreased sensitivity to the lipids added. This is in
764 spite of the fact that lipolysis was significantly higher in the smaller droplet (0.1 μm) compared to
765 the larger droplet (3 μm). Marciani *et al.* (2009) showed that acid-unstable emulsions were broken
766 down in the stomach before entering the small intestine, whereas acid stable emulsions were not and
767 led to slower gastric emptying and greater satiety scores. A more recent study also found no
768 increase in subjective satiety or a decrease of energy intake when comparing Fabuless^{TM} soft lipid
769 emulsions or hard emulsions (dairy and palm oil, respectively) which were matched for particle size
770 (Chan et al. 2017). The aforementioned findings regarding site delivery and acid stability may
771 explain the lack of significant difference between the droplet sizes in the study by Peters and
772 colleagues. Hussein *et al.* (2015) added locust bean gum to lipids of 6 μm or 0.4 μm and found that
773 these were more stable than a control coarse lipid of 6 μm with no locust bean gum. This stability
774 allowed for delivery of the lipids to the duodenum, and resulted in slower gastric emptying and
775 decreased food intake, without altering subjective sensations of appetite. This shows that the
776 development of novel foods containing small lipid droplets which remain unchanged in the stomach
777 until breakdown in the duodenum could be a promising avenue to increase satiety.

778

779 ***Effects on satiety of chronic consumption of small particle lipids***

780 To the authors' knowledge, only three studies to date have investigated SPL chronically, and these
781 investigated Fabuless™. Logan *et al.* (2006) found no significant suppressive effects of the novel
782 lipid emulsion on either satiety or food intake. There are some methodological limitations which
783 may have affected the results, such as the *ad libitum* trials being conducted in social environments
784 instead of a secluded booth. However, despite errors in design, this study does not support the
785 previous findings of Fabuless™ as a long term mediator of satiety. Diepvens *et al.* (2007) found that
786 hunger was significantly decreased, and weight re-gain was significant in the placebo group but not
787 in the emulsion group, indicating Fabuless™ may be useful in weight maintenance. However, Heer
788 (2012) discussed that the 1.2 kg difference in body mass between groups may not be clinically
789 significant or even attributed to the emulsion, as this can be achieved with a negative energy
790 balance of 100 kcal·day over the 18 week period. A more recent study investigated the concurrent
791 application of a low-calorie diet (1500 kcal·day), an exercise program, and supplementation of 4.2 g
792 of Olibra or 3.9 g milk fat for a 12 week period (Rebello et al. 2012). They concluded no significant
793 effect of supplementation with the emulsion on energy intake, subjective feelings of fullness or
794 body weight/composition. Thus, there appears to be little evidence that Fabuless™ can be useful in
795 promoting satiety and decreasing energy intake.

796 More studies are required, examining different small lipid droplet emulsions and satiety, to confirm
797 whether there is a long-term effect. It would be beneficial to develop a novel lipid or food product –
798 such as capsules – which could release smaller lipid droplets directly into the ileum. Once this has
799 been developed and shown to decrease satiety when administered acutely, then chronic strategies to
800 enhance satiety can be examined.

Discussion and future directions

There is some evidence to suggest that the lipids included in this review do provide satiating effects; however, the side effects of taking these, particularly in high doses, must be taken into consideration. The evidence presented here suggests that the lipids with the most potential to enhance satiety are MCTs. SCFA can also promote satiety, but oral administration is more likely linked to poor tolerability rather than a satiety effect. MCT have been shown to enhance satiety when administered in beverage form (Rolls et al. 1988), when added to pasta (Van Wymelbeke et al. 1998), and non-significant trends have been seen when incorporated into a fried breakfast (Clegg, Golsorkhi, and Henry 2013). As aforementioned, MCT exert their appetite-suppressing effects through an increase in ketone body production and not by an increase in appetite-suppressing hormones. Therefore it is possible that combining MCT alongside other nutrients that are potent stimulators of hormone release, such as protein (van der Klaauw et al. 2013) or indeed other fats (Huda, Wilding, and Pinkney 2006; McLaughlin et al. 1999), would lead to an even greater satiety response, although this is speculative.

Only one study to date has investigated CLA, and CLA led to reduced energy intake compared to a control, but with no significant difference to MCT (Coleman, Quinn, and Clegg 2016). There was no difference in self-reported hunger, fullness, desire to eat or prospective food consumption between any of the three oils. Further studies should aim to analyse this further, in different modes of delivery (i.e. liquid vs solid food).

SCFA do appear promising in the promotion of satiety, although this is difficult to quantify due to the background effect of fibre utilised in many studies (Nilsson et al. 2013; Johansson et al. 2013; Hlebowicz et al. 2008). Earlier studies investigating oral administration of SCFA initially seemed promising, with reported increases in satiety (Ostman et al. 2005; Hlebowicz et al. 2008; Kondo et al. 2009). A recent paper by Darzi and colleagues concluded that the apparent satiety effect is

actually poor tolerability (Darzi et al. 2014). Whilst this indicates that oral administration of these SCFA (acetate and propionate) is not recommended, no study to date has investigated oral administration of butyrate. It is likely that the same result will be seen, and so studies investigating this should consider nausea as a possible explanation for any apparent satiety effect.

DAG may influence satiety through a variety of mechanisms. The major limitation of DAG is its availability. The product used in some of the studies mentioned in this review (Maki et al. 2002; Yamamoto et al. 2001; Kamphuis, Mela, and Westerterp-Plantenga 2003) has since been withdrawn from production, due to the presence of the carcinogenic glycidol fatty acid ester. DAG oil has been verified as safe, with no adverse effects reported during 12 weeks of supplementation with a high dosage of 0.5 g·kg·d (Yasunaga et al. 2004), although the DAG in this study was created by the research group and not purchased commercially. Until a safe version of DAG is available which can be purchased commercially, this does not appear to be a feasible avenue for the promotion of satiety.

The evidence in support of fish oil and SPL is equivocal at best, with a majority of the research indicating no benefit of SPL (Y. K. Chan et al. 2017; Peters et al. 2014), despite earlier studies suggesting otherwise (Burns et al. 2001, 2000, 2002). In one study, fractionated oat oil was shown to increase satiety and the circulating concentration of satiety hormones (Ohlsson et al. 2014), and so more data is required to support these initial positive findings. *n*-3 PUFA can possibly be utilised in increasing appetite in scenarios where this is necessary, such as in cancer patients (Jatoi et al. 2004; Zaid et al. 2012). There is a lack of studies investigating *n*-3 PUFA and satiety, and some of the current evidence did not measure satiety or appetite specifically.

A recurring limitation of the use of functional lipids in the enhancement of satiety is the adverse side effects commonly reported (Table 1). Both CLA and fish oil supplementation have been reported to result in adverse side-effects in small doses of 6.8 g·d with CLA (Blankson et al. 2000)

and 5 ml·d with *n*-3 PUFA (Damsbo-Svendsen, Rønsholdt, and Lauritzen 2013). Intakes of 85 g have been reported with MCT (Jeukendrup et al. 1998). Where this high amount did result in GI distress, it does show the potential for larger increases in satiety compared to some other lipids.

In conclusion, future work should examine the combination of these lipids with other macronutrients (including fat) and other methods of promoting a negative energy balance in order to assess the cumulative effects. As there is currently no study directly comparing the effects of these lipids, it would be pertinent for this to be investigated. Finally, only one of the studies discussed in this review has employed a design by which the participants swapped their daily oil for the test oil (Kawashima et al. 2008). Considering that adding lipids to foods is counter-intuitive to an individual attempting to decrease energy intake, this protocol should be examined in more studies for ecological validity.

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Table 1. Studies on the effect of medium chain triglycerides (MCT) on satiety

Study	Study Design	Fat used	Major Results
Barbera *et al*. (2000)	Infusion study	0.9% Saline, 20% LCT or 22% MCT emulsions	↑ gastric volume and satiation after LCT ↑ gastric volume after MCT but not enough to induce the same satiation ↑ CCK, GIP, neurotensin and PP after LCT
Feltrin *et al*. (2004)	Infusion study	Lauric acid (C12), Decanoic acid (C10), and control infused at a rate of 0.375 kcal min^{-1}	Both C12 and C10 elicited CCK release, ↑ in C12 ↓ subjective sensations of hunger and EI after C12
Krotkiewski *et al*. (2001)	4 week very low-calorie diet in peri-menopausal women	9 g MCT, 8.8 g LCT or low-fat control (3 g fat)	MCT ↓ hunger and ↑ satiety ↑ ketones in MCT MCT ↑ BW loss after 2 weeks, but no difference by week 4
Maas *et al*. (1998)	Infusion study	LCT (corn oil) or MCT (octanoic and decanoic acid) infused at a caloric load of 22.7 kJ min^{-1} and 11.6 kJ min^{-1} respectively	↑ PYY secretion after LCT PYY was released after MCT, to a lesser extent
McLaughlin *et al.* (1999)	Infusion study	Various fatty acids of different chain lengths from butyric acid (C4) to octadecanoic acid (C18)	Fatty acids with chain length $\leq^{11}$C: ↔ CCK secretion Fatty acids with chain length $\geq^{12}$C: ↑ CCK secretion
Poppit *et al*. (2010)	High-fat breakfast in healthy men	SCT (milk fat), MCT (coconut oil) or LCT (tallow). *Ad libitum* meal 210 min after breakfast	↔ *ad libitum* EI ↔ subjective sensations between trials
Rizzo *et al*. (2016)	Preload study in 36 healthy women	Ice cream containing different ratios of coconut oil (CO) and sunflower oil (SO)	↓ fat intake after High CO Inverse trend of CO and EI at dinner, but

		High CO: 75%CO:25%SO Equal: 50:50 High SO: 75%SO:25%CO	non-significant ↔ EI between trials
Rolls *et al*. (1988)	Preload study in 24 women, 12 dieters, and 12 non-dieters	30% fat liquid preload of which all 30% LCT or 24% MCT and 6% LCT 3 doses of each providing 100, 200 or 300kcal	↓ *ad libitum* EI after MCT Larger doses led to ↓ EI ↔ subjective sensations No consistent pattern emerged in dieters
St-Onge *et al*. (2014)	2 studies: one breakfast study and one preload study.	Both studies: breakfast containing 20g of either MCT or LCT (corn oil) Preload study: 3h after breakfast participants consumed a preload yoghurt containing an extra 10g of either oil.	↓ intake at *ad lib* lunch after MCT ↑ PYY and leptin after MCT ↔ total ghrelin and GLP-1 ↑ suppression after preload as opposed to the breakfast
Van Wymelbeke *et al.* (1998)	High carbohydrate breakfast in 12 healthy volunteers	4 high CHO breakfast with either 70 kJ fat substitute, or 1460 kJ from different fats: saturated LCT (from 42 g lard), monounsaturated LCT (from 40 g olive oil) or MCT (from 43 g of Ceres MCT oil).	↓hunger after MCT ↔ in time to request lunch other than ↓ in fat substitute ↔ in time to request dinner
Van Wymelbeke, Louis-Sylvester and Fantino (2001)	Preload lunch in 10 men	4 lunches: 2310 kJ meal containing 40 kJ fat substitute (Sub), 32 g LCT, 35 g MCT or 53 g CHO and 8 g LCT (CHO)	↑ delay in meal request in CHO ↑ delay in MCT over LCT and Sub, but not as long as CHO ↓ EI in MCT

MCT: Medium-chain triglycerides; LCT: Long-chain triglycerides; EI: Energy Intake; CCK: Cholecystokinin; GIP: Gastric Inhibitory Peptide; PP: Pancreatic Polypeptide; BW: Body Weight; CHO: Carbohydrate. ↑ shows increased or greater ↓ shows decreased or lesser ↔ shows no change or difference.

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Table 2. Studies on the effect of conjugated linoleic acids on satiety

Study	Study Design	Fat used	Major Results
Blankson *et al*. (2000)	12 weeks supplementation study	CLA capsules: 75% CLA, equal parts c9,t11 and t10,c12 isomers Placebo capsules: olive oil Varying dosages: Placebo: 9g olive oil. CLA doses of 1.7g, 3.4g, 5.1g or 6.8g	↓ Appetite after 12 week period in 3.4g and 7.8g CLA groups ↑ Lean mass after all CLA doses.
Coleman, Quinn and Clegg (2016)	Preload breakfast in 19 men	22g vegetable oil (control) 5 g CLA and 16g vegetable oil (CLA) 25 g MCT oil (MCT)	↓ (non-sig) EI at *ad libitum* lunch in both CLA and MCT ↓ Overall EI in MCT ↑ Time to meal request in CLA
Cornish *et al*. (2009)	5-week strength training, 69 participants	3 groups: 6 g·day CLA (36.1% c9,t11 and 36.3% t10,c12 isomers), 36 g·day whey and 9 g·d creatine (CPP) 36 g·day whey, 9 g·d creatine and placebo oil (CP) Placebo oil (P)	↔ EI in all groups from baseline to 12 weeks and between groups from self-reported diet diary data
Gaullier *et al*. (2005)	2 year CLA supplementation study	4.5 g·d olive oil (Placebo) 4.5 g·d Triglyceride CLA (CLA-TG) providing 3.4 g active isomers 4.5 g·d Free fatty acid CLA (CLA-FA) providing 3.6 g active isomers	↓ EI by 1289kJ·day in CLA-TG ↓ EI by 870kJ·day in CLA-FFA ↓ Leptin both CLA-TG and CLA-FFA
Iwata et al. (2007)	12 weeks supplementation in 60 healthy volunteers	5.4 g CLA-triacylglycerol (3.4 g as CLA isomers) 10.8 g CLA- triacylglycerol (6.8 g as CLA	↔ In energy intake after treatment: no effect of CLA on satiety ↑ Leptin in all groups (including placebo)

		isomers) Placebo (10.8 g safflower oil) CLA comprised ~50:50 c9,t11 and t10,c12 isomers	
Kamphuis *et al*. (2003).	3 weeks of very low-calorie diet in 54 healthy volunteers before 13 weeks of supplementation	High or low doses High doses: 3.6 g·day of CLA or Placebo Low dose: 1.8 g·day of CLA or Placebo	↔ EI at standardized breakfast ↑ Fullness and satiety in CLA ↓ Hunger in CLA ↔ Weight regain
Lambert *et al*. (2007)	12 weeks supplementation in 64 healthy volunteers	3.9 g CLA capsule (65.9% CLA: 29.7% c9,t11; 30.9% t10,c12; 2.9% other isomers) 3.9 g high-oleic acid sunflower oil (placebo)	↔ Subjective sensations (fullness, appetite, satiety)
Medina *et al*. (2000)	64 days supplementation in 17 healthy women	3.9 g CLA (65% CLA: 22.6% t10,c12; 23.6% c11,t13; 17.6% c9,t1; and 36.2% other isomers) 3 g placebo (72.6% linoleic acid)	Leptin initially ↓ but then returned to baseline in CLA ↔ appetite, despite ↓ leptin
Norris *et al*. (2009)	36-week supplementation study in 55 obese postmenopausal women with T2D	CLA: 8.0 g·day oil providing 6.4 g·day CLA (41.6% c9,t11 and 40.4% t10,c12 isomers) and 1.6 g oleic/palmitic acids Placebo: 8.0 g·day oil providing 8.0 g·day safflower oil	↓ BMI ↔ EI (from self-reported diet diary data) ↔ Leptin
Pinkoski *et al*. (2006)	7 weeks resistance training with supplementation in 76 healthy men and women	Placebo: 7 g·day sunflower oil CLA: Tablets containing ~66% CLA (of which 36.1% c9,t11 and 36.3% t10,c12 isomers) providing 5 g·day	↑ Lean tissue mass after CLA for 7 weeks ↔ Self-assessed energy intake after the intervention period
Wanders *et al*. (2007)	3-week supplementation	Fed diet containing 14.6 g c9,t11 CLA and	↔ Self-assessed energy intake during the

	study in 20 healthy subjects	3.3 g t10,c12 CLA, and 1.4 g other CLA isomers	supplementation period
Watras *et al*. (2007)	6-month supplementation study	Placebo: 4 g·day safflower oil CLA: 4 g·day of oil providing 3.2 g·day CLA (39.2% c9,t11 and 38.5% t10,c12)	↓ Weight gain over the 6 month period in CLA ↔ EI during EI, whilst EI ↑ in placebo

CLA: Conjugated Linoleic Acid; EI: Energy Intake; CCK: Cholecystokinin; GIP: Gastric Inhibitory Peptide; PP: Pancreatic Polypeptide; BW: Body Weight. ↑ shows increased or greater ↓ shows decreased or lesser ↔ shows no change or difference.

Table 3. Studies on the effect of short-chain fatty acids on satiety

Study	Study Design	Fat used	Major Results
Cani *et al*. (2006)	2 x 2-week crossover with 10 healthy subjects	16 g·day oligofructose (OF) 16 g·day placebo (PLA) Two-week washout between each.	↑ satiety after breakfast with OF intake ↓ intake at breakfast and lunch after 2 weeks of OF ↓ overall EI in OF
Chambers *et al*. (2015)	24 weeks parallel in 60 subjects	10 g·day inulin-propionate (IP) 10 g·day of inulin-control (CON)	↑ PYY and GLP-1 release after IP ↓EI after IP by 14% ↔ Subjective sensations
Darwiche *et al.* (2001).	Breakfast study in 9 healthy volunteers	Control bread made with basic recipe, or same bread with the addition of sodium propionate	↓ GE after bread containing propionate
Darzi, Frost and Robertson (2012)	Breakfast study in 20 healthy unrestrained eaters	Sandwiches made with a propionate rich sourdough to yield 4.8 mmol propionate per 100 g of bread or a control equivalent	↔ EI at *ad lib* lunch between trials ↔ 24 h EI between trials ↔ Appetite ratings
Darzi *et al.* (2014)	2 studies investigating the oral properties of SCFA	Study 1: Control drink: 75g in 275g water across two drinks Unpalatable drink: 25g vinegar and 25g squash in 100g water followed by 50g squash in 100g water Palatable drink: 25g vinegar and 75g squash in 250g water across two drinks Study 2:	Study 1: ↑ Nausea after unpalatable drink ↓ *ad lib* and 24 h EI after vinegar treatments Study 2: ↓ Pleasantness after vinegar drink ↔ Nausea ratings

		Modified sham feeding of a control drink (180g water) or a vinegar drink (230g white wine vinegar in 150g water)	↔ Appetite ratings ↔ EI at *ad lib* meal
Daud *et al*. (2014)	6 weeks parallel in 22 subjects	30 g·day oligofructose (OF) 30 g·day cellulose (CON)	↑ acetate concentrations after OF ↑ fasting serum propionate and butyrate after OF ↑ PYY AUC after OF ↑ GLP-1 AUC after CON ↓ EI and hunger after OF
Freeland *et al*. (2010)	One year dietary modification to alter fibre intakes in 28 hyperinsulinaemic volunteers	Two groups: High-wheat fibre cereal (All Bran) Low-fibre cereal (Rice Krispies)	↑ plasma butyrate and GLP-1 secretion after 9-12 months of high fibre intake
Frost *et al*. (2014)	Series of tests in mice	^{11}C Acetate injections	↓ EI ↓ agouti-related peptide expression ↑ proopiomelacocortin expression
Hlebowicz *et al*. (2015)	Crossover trial with 15 healthy subjects	28 mmol acetate soaked in different breads: White (W), Wholemeal (WM) Whole-kernel wheat (WK) Unsoaked white bread (CON)	↑ satiety in WK ↔ GE
Jouët *et al*. (2013)	Perfusion study in 20 healthy	SCFA mixture: 66% acetic acid, 24%	↔ colonic motility

	volunteers	propionic acid, and 10% butyric acid	
Kondo *et al*. (2009)	12 week parallel supplementation study in 155 obese individuals	0 mg/100 ml acetate (PLA) 15 mg/100 ml acetate (LOW) 30 mg/100 ml acetate (HIGH)	↔ EI, macronutrient breakdown or EE
Liljeberg and Björck (1998)	Breakfast study with 12 healthy volunteers	Different breads baked to include lactic acid, sodium propionate or basic whole meal (as a control).	↓ GE after bread containing propionate ↑ satiety after bread containing propionate
Mettler, Schwarz and Colombani (2009)	Repeated measures study in 27 subjects	Milk rice meal with either: No additive (CON) 4 g cinnamon (CIN) 28 mmol acetate (ACE) Cinnamon and acetate (C&A)	↔ satiety AUC ↓ satiety 15-30 min post ingestion in C&A
Nilsson *et al*. (2013)	Crossover trial in 16 healthy adults	Evening meal of Swedish brown beans (SBB) or white bread (WB), in portions to provide 35g of starch, given the night before a standardised breakfast.	↑ PYY (51%) and oxyntomodulin after SBB ↓ ghrelin after SBB (by 14%) ↔ subjective sensations
Ostman *et al*. (2005)	Crossover trial with 12 healthy subjects	White bread (CON) With 18 mmol acetate (LOW) With 23 mmol acetate (MED) With 28 mmol acetate (HIGH)	↑ satiety in HIGH: dose-response relationship
Parnell and Reimer (2009)	12-week supplementation in 48 overweight/obese individuals	21 g·day oligofructose (OF) 21 g·day maltodextrin (PLA)	↓ ghrelin after OF ↑ PYY after OF ↔ GIP and GLP-1 ↓EI after OF

Ruijschop *et al*. (2008)	Preload study in 43 healthy women	Non-fermented dairy beverage (placebo) Fermented dairy beverage Non-fermented beverage with the addition of 0.6% calcium propionate	↑ fullness after fermented and non-fermented beverage with addition of calcium propionate ↔ *Ad lib* EI between all conditions
Tarini and Wolver (2010)	Acute feeding study in 12 healthy participants	Three test drinks: 80g high fructose corn syrup 56g high fructose corn syrup and 24g inulin 56g high fructose corn syrup	↑ serum SCFA concentrations after inulin ingestion ↓ ghrelin after inulin ↔ GIP and GLP-1 between inulin and 80g high fructose corn syrup drinks

GE: Gastric emptying; EI: Energy Intake; EE: Energy Expenditure; BW: Body Weight; PYY: Peptide YY; GLP-1: Glucagon-Like Peptide 1; GIP: Gastric Inhibitory Peptide. ↑ shows increased or greater ↓ shows decreased or lesser ↔ shows no change or difference.

Table 4. Studies on the effect of diacylglycerol on satiety

Study	Study Design	Fat used	Major Results
Kamphuis *et al*. (2003)	Crossover trial with 12 healthy women	36h stay in respiration chamber where 40% of fat came from DAG or TAG oil after 3 days of energy maintenance	↑ satiety after DAG ↑ β-oxidation
Kawashima *et al*. (2008)	1 year parallel trial in overweight or obese individuals	Participants were given DAG or TAG oil to replace normal cooking oil.	↓ EI in both groups
Li *et al*. (2008)	120 day parallel in 127 individuals with T2D	25 g·day diacylglycerol (DAG) 25 g·day triacylglycerol (TAG)	↓ CHO intake after DAG ↓ EI (non-sig) after DAG ↑ leptin after TAG
Stoeckel *et al*. (2008)	Acute study in 12 normal-weight humans	Control beverage: 21 kcal lipid free beverage Lipid beverage: made from 16 g ethyl oleate and 28g Enova oil which contains 80% diglycerides and 20% triglycerides	Participants stratified into high and low PYY responders. ↑ Plasma PYY after lipid drink In high PYY responders, lipid beverage ↑ satiety No effect in low PYY group
Yamamoto *et al*. (2001)	12 week parallel trial in 16 diabetic patients	10 g·day diacylglycerol (DAG) 10 g·day triacylglycerol (TAG) – normal cooking oil	↔ EI (*from self-reported diet diary data)*

DAG: Diacylglycerol; TAG: Triacylglycerol; GE: Gastric emptying; EI: Energy Intake; EE: Energy Expenditure; BW: Body Weight; PYY: Peptide YY; GLP-1: Glucagon-Like Peptide 1; GIP: Gastric Inhibitory Peptide; CHO: carbohydrate. ↑ shows increased or greater ↓ shows decreased or lesser ↔ shows no change or difference.

Table 5. Studies on the effect of omega-3 polyunsaturated acids on satiety

Study	Study Design	Fat used	Major Results
Bruera *et al*. (2003)	2-week high-dose supplementation study in patients with cancer cachexia	Control: 1000 mg·day olive oil Intervention: 1000 mg·day fish oil (providing 180 mg EPA and 120 mg DHA)	↔ change in appetite after 2 weeks supplementation
Damnsbo-Svendsen, Rønsholdt and Lauritzen (2013)	3 weeks supplementation in healthy individuals	Control: 10 soybean tablets a day providing a total of 5.2 g soybean oil Intervention: 10 fish oil tablets a day providing a total of 3.5 g n-3 PUFA, of which 1.9g was EPA and 1.1g was DHA	↑ appetite and ↓ postprandial fullness after fish oil supplementation
Jatoi *et al*. (2004)	An international clinical trial involving supplementation in 421 patients with cancer. Median study involvement of volunteers was "slightly more than 3 months"	Supplementation was as follows: 1.09 g of EPA and 0.46 g of DHA a day 600 mg·day megestrol acetate Or a combination of the two	↔ appetite improvement in all three groups
Parra *et al*. (2008)	Supplementation of during the last phase of a weight loss program in overweight and obese individuals	4 diets Control: no seafood, 6 placebo capsules a day Lean fish: 150 g cod 3 times a week Fatty fish: 150 g salmon 3 times a week Fish oil supplementation: 6 capsules a day The two low *n*-3 PUFA provided > 260 mg·day *n*-3 fatty acids. The two high *n*-3 PUFA provided > 1300	↑ fullness in high *n*-3 groups ↓hunger and desire to eat in high *n*-3 groups

		mg·day *n*-3 fatty acids.	
Yehunda, Rabinovitz and Mostofsky (2005)	3-week supplementation study in students	33 students in control group received a placebo "mineral oil" 88 students took Awake (TransCulture, Japan tables containing *n*-3 and *n*-6 in a ratio of 1:4	↑ appetite after supplementation with the mixture of lipids
Zaid *et al*. (2012)	8-week supplementation study in 51 children with leukaemia	2 groups: Control group that received individualised dietary advice Trial group that received individualised dietary advice alongside fish oil supplementation: 1 x 1200 mg capsule per day containing 360 mg EPA and 240 mg DHA	↑ appetite in children with leukaemia ↑ energy intake over control group

EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; PUFA: polyunsaturated fatty acids. ↑ shows increased or greater ↓ shows decreased or lesser ↔ shows no change or difference.

Table 6. Studies on the effect of small particle lipids on satiety

Study	Study Design	Fat used	Major Results
Burns *et al*. (2000)	Acute feeding study in two groups of 30 volunteers	Control: Yoghurt containing 6 g dairy fat Test: Yoghurt containing 5 g Olibra™ and 1 g dairy fat	↓ Energy intake, food intake, and intake of all macronutrients after test food at 4 h ↔ subjective sensations of appetite and hunger
Burns *et al*. (2001)	Breakfast study in healthy weight, overweight and obese participants	Control: Yoghurt containing 6 g dairy fat Test: Yoghurt containing 5 g Olibra™ and 1 g dairy fat	↓ fat, carbohydrate, protein and total energy intake at both 4 h and 8 h after test infusion across all groups ↔ Obese intake at 4 h ↓ Obese intake at 8 h ↔ subjective sensations of appetite and hunger
Burns *et al*. (2002)	Breakfast study in 50 healthy individuals	Yoghurt with varying doses of Olibra™: 0g (control), 5 g, 10 g, or 15 g. 5 and 10 g amounts also had 10 and 5 g of milk fat, respectively, whereas the control was 15 g of milk fat.	↑ suppression with food intake as dose of Olibra™ increased ↔ subjective sensations of appetite and hunger
Chan *et al*. (2012)	Acute crossover feeding study	4.2 g lipids from a control or 15 g of Fabuless™ provided in (or alongside) liquid form, semi-solid form and solid form, with a control for each state: Liquid emulsion (LE) Liquid control (LC) Semi-solid emulsion (LE + Yoghurt) Semi-solid control (LC + Yoghurt) Solid emulsion (LE + Muffin)	↑ fullness after LE + Yoghurt, no effect of Fabuless™ in liquid or solid form ↔ EI across all conditions

		Solid control (LC + Muffin)	
Chan *et al*. (2017)	Acute crossover feeding study	6 conditions, 4 lipids and 2 controls: Fabuless™ emulsion Dairy emulsion with dairy emulsifier Dairy emulsion with soy lecithin emulsifier Dairy control (non-emulsified) Palmolein emulsion with dairy emulsifier Palmolein control (non-emulsified)	↔ satiety ratings between lipids and respective controls ↔ EI between lipids and respective controls
Diepvens *et al*. (2007)	18-week weight maintenance and dietary manipulation in 50 overweight women	Control: 500 g of yoghurt containing 10 g milk fat, split into 2 doses Test: 500 g of yoghurt containing 6 g milk fat and 4 g vegetable fat from Olibra™, split into 2 doses	↓ hunger after test product ↑ CCK, GLP-1, and βHB after test product ↓ weight regain after test product
Hussein *et al*. (2014)	Crossover feeding study in 11 healthy people	3 emulsions: Control: Coarse emulsion (6 μm droplets) Coarse+LBG: Coarse emulsion (6 μm droplets) + 0.5% locust bean gum Fine+LBG: Fine emulsion (0.4 μm droplets) + 0.5% locust bean gum	↓ GE after LBG, of which Fine+LBG ↓ the most ↑ CCK after both LBG trials, no diff between Coarse+LBG and Fine+LBG ↓ EI after both LBG trials, greater ↓ after Fine+LBG compared to Coarse+LBG ↔ VAS
Knutson *et al*. (2010)	Intragastric perfusion study	Control: 300 g of yoghurt containing 8.5 g dairy fat Test: 300g of yoghurt containing 8.5 g of Fabuless™ emulsion	↑ Lipids remaining in the jejunum after test perfusion ↓ GE after test perfusion
Ledeboer *et al*.	Randomised crossover study involving intraduodenal	Control: Saline with emulsifier	↑ CCK release and gallbladder contraction

(1999)	infusion study in 6 healthy men	Emulsion trial: Emulsified soybean oil Non-emulsion trial: Non-emulsified soybean oil	after emulsified LCT ↔ Emulsifier in saline and non-emulsified LCT
Logan *et al*. (2006)	Crossover dietary manipulation study	Control: 5 g milk fat Test: 12.5 Olibra™ providing 5 g fat	↔ EI across trials ↔ on subjective sensations across trials
Marciani *et al*. (2009)	Acute feeding study with specially designed lipid emulsions	Emulsions made from [^{13}C]palmitate-enriched olive oil, providing 50 g of fat in 3.6 μm droplets. Two conditions were 'acid-stable' and 'acid-unstable' emulsions	↑ GE in acid-unstable emulsion ↓ ratings of hunger and appetite after acid-stable emulsion
Ohlsson *et al.* (2014)	Two acute feeding studies	Three doses of lipids from yoghurt (control) or fractionated oat oil (LOO): 1.8 g, 14 g, and 35 g	↑ satiety after LOO in women but not men ↑ GLP-1, PYY and CCK after 14 g and 35 g of LOO ↔ EI across trials
Peters *et al*. (2014)	Acute feeding study	Fat-free drink with: 5g fat in 3 μm droplets 9g fat in 3 μm droplets 5g fat in 0.1 μm droplets 9g fat in 0.1 μm droplets	↔ EI across all trials ↑ CCK release in smaller droplet trial, but only in 9 g fat load
Rebello *et al*. (2012)	12-week dietary supplementation study	Control group: yoghurt providing 1.95 g milk fat twice daily Test group: yoghurt providing 2.1 g Olibra™ twice daily	↓ hunger after Olibra™ supplementation ↔ EI and ratings of appetite and satiety between trials
Seimon *et al*. (2009)	Randomised crossover study involving intraduodenal infusion study in 10 healthy men	Control: Saline 0.26 μm droplet infusion: Intralipid (Fresenius Medical Care	↑ CCK and PYY release after 0.26 μm droplet infusion ↓ hunger after 0.26 μm droplet infusion

		Australia) 30 μm: Tween 80, water and canola oil 170 μm: Tween 80, water and canola oil	
Smit *et al*. (2011)	Breakfast study in 24 healthy volunteers	Test drinks with 5 g milk/corn fat added ('Control') or 12.5 g of Fabuless^{TM} (containing 5 g of fat) added: During the manufacturing process ('Processed') After the manufacturing process ('Unprocessed')	↔ In EI at *ad lib* lunch ↓ In EI at *ad lib* dinner after Unprocessed ↔ on subjective sensations across trials
Smit *et al.* (2012)	Breakfast and preload study comprising of 2 separate studies	100 g test drinks comprising of: 2.0g added milk fat 2.0g added fat from 5 g Fabuless^{TM} 3.2 g added milk fat 3.2 g added fat from 8 g Fabuless^{TM}	↔ energy intake and subjective sensations of satiety when comparing each dose to the control ↑ hunger at one timepoint after the Fabuless^{TM} drink, no other differences ↑ EI at one timepoint after the Fabuless^{TM} drink, no other differences

EI: Energy Intake; GE: Gastric Emptying; VAS: Visual Analogue Scale; CCK: Cholecystokinin, GLP-1: Glucagon-Like Peptide 1; βHB: β-Hydroxybutyrate. ↑ shows increased or greater ↓ shows decreased or lesser ↔ shows no change or difference.

Table 7. Summary of the advantages and disadvantages of the functional lipids discussed within this review.

Advantages	Disadvantages
Medium chain triglycerides	
• Strong potential to mediate satiety(Coleman, Quinn, and Clegg 2016; Rolls et al. 1988; Van Wymelbeke et al. 1998; Van Wymelbeke, Louis-Sylvestre, and Fantino 2001). • Safe for consumption. • Possible for effects to be additive with other satiating foods due to hormone-independent effects(Miriam E Clegg 2010). • Can beneficially alter body composition without altering appetite or satiety(Krotkiewski 2001).	• Repulsive taste, ecological validity possibly questionable(Miriam E Clegg 2010). • Can cause nausea when ingested in high amounts(Jeukendrup et al. 1998; Goedecke et al. 2005).
Conjugated Linoleic Acid	
• Only one study investigating the acute use of CLA on satiety found it suppressed hunger compared to a control oil, even in small amounts(Coleman, Quinn, and Clegg 2016). • Satiety-independent effects on weight loss(Blankson et al. 2000; Belury, Mahon, and Banni 2003; Gaullier et al. 2007).	• Chronic studies indicate no effect on satiety(Blankson et al. 2000; Belury, Mahon, and Banni 2003; Gaullier et al. 2007). • Lack of short-term data investigating effects regarding appetite, more studies needed to draw conclusions. • Possible deleterious effects related to insulin resistance(Medina et al. 2000; Ulf Risérus et al. 2002; Smedman and Vessby 2001).
Short Chain Fatty Acids	

• Various mechanisms by which SCFA can regulate satiety, including stimulation of satiety hormones(Psichas et al. 2014; Tolhurst et al. 2012; Samuel et al. 2008), intestinal gluconeogenesis(Bienenstock, Kunze, and Forsythe 2015b; De Vadder et al. 2014) and gastric emptying. Could possibly be additive with other functional lipids or foods with satiating properties(Liljeberg and Björck 1996; Darwiche et al. 2001).	• Mode of delivery varies between studies, so the determination of the effects of each different mode is difficult. • Many confounding factors, effects reported previously possibly not due to SCFA(J Darzi, Frost, and Robertson 2012; J Darzi et al. 2014). • Low tolerability and palatability of acetate means effects are not necessarily related to satiety(J Darzi et al. 2014). • No study to date has investigated the oral delivery of butyrate, no data on its effects.
Diacylglycerol	
• Potentially cumulative mechanisms which, in theory, could result in a strong satiety signal. • Shown to be effective when replacing other fats in the diet in an *ad libitum* protocol. Beneficial as DAG does not require set doses to elicit its effects(Kawashima et al. 2008).	• DAG used in previous studies no longer in production, and to the knowledge of the author, there is currently no other available source. Until another DAG is produced, this, unfortunately, does not seem a feasible avenue of research. • No chronic adaptation; must be used repeatedly for repeated acute effects(Yamamoto et al. 2001).
***n*-3 PUFA**	

• Possibly as good as a steroidal treatment in increasing cancer patients' energy intakes in an attempt to reverse cachexia(Bruera et al. 2003; M D Barber et al. 1999; Jatoi et al. 2004). • Widely available.	• Possibly needs supplementation to induce effects, no acute effect. • Various fish oil supplements commercially, with various concentrations and ratios of EPA:DHA, and some may be more beneficial than others.
Small particle lipid emulsions	
• Possible decrease in hunger when supplementing with Fabuless^{TM}(Burns et al. 2001, 2000, 2002), but most studies do not corroborate this(H. J. Smit et al. 2012; Y.-K. Chan et al. 2012). • Strong evidence that droplet size can be linked to the ileal brake(Knutson et al. 2010; Hussein et al. 2015; Seimon et al. 2009).	• The only commercially available SPL has little evidence of its efficaciousness(H. J. Smit et al. 2012; Y.-K. Chan et al. 2012), other SPL are manufactured specifically for studies. • A suitable emulsion still needs developing. • Evidence supporting droplet size and the ileal brake focuses mainly on the intragastric administration of the SPL which are not feasible methods of increasing satiety.