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Title: Theoretical Explanation for Reduced Body Mass Index and Obesity Rates in *Cannabis* Users

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Abstract:

Obesity is treatment-resistant, and is linked with a number of serious, chronic diseases. Adult obesity rates in the United States have tripled since the early 1960s. Recent reviews show that an increased ratio of omega-6 to omega-3 fatty acids contributes to obesity rates by increasing levels of the endocannabinoid signals AEA and 2-AG, overstimulating CB_1R and leading to increased caloric intake, reduced metabolic rates, and weight gain. *Cannabis*, or THC, also stimulates CB_1R and increases caloric intake during acute exposures. The present meta-analysis reveals significantly reduced body mass index and rates of obesity in *Cannabis* users, in conjunction with increased caloric intake. We provide for the first time a causative explanation for this paradox, in which rapid and long-lasting downregulation of CB_1R following acute *Cannabis* consumption reduces energy intake and storage and increases metabolic rates, thus reversing the impact on body mass index of elevated dietary omega-6/omega-3 ratios.

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Introduction:

Diet is the main cause of premature death and disability in the United States. The modern Western diet is pro-inflammatory and obesogenic (Murray et al., 2013, Cordain et al., 2005). Diseases associated with inflammation and obesity include cancer, cardiovascular disease, diabetes mellitus, Alzheimer's disease, mood disorders, autoimmune disorders, liver and kidney disease, and musculoskeletal disabilities (Esser et al., 2014, Giugliano et al., 2006, Manzel et al., 2014, Bosma-den Boer et al., 2012, Lontchi-Yimagou et al., 2013, Murray et al., 2013, Farooqui et al., 2012, Kaur, 2014, Khan et al., 2014b, Jourdan et al., 2016, Galland, 2010). A significant dietary factor contributing to these health problems is an increased ratio of omega-6 (linoleic acid, LA) to omega-3 (α-linolenic acid, ALA) fatty acids (Wall et al., 2010, Cordain et al., 2005, Aguilar et al., 2015, Brown et al., 2013, Blasbalg et al., 2011, Jing et al., 2013, Simopoulos, 2002, Simopoulos, 2016, Kelly et al., 2013, Khan et al., 2014b, Kim et al., 2013), especially in the context of a high glycemic load and reduced physical activity.

Recent reviews show that dysregulation of the endocannabinoid system plays a major role in development of obesity and metabolic disorders, and strongly implicate the elevated omega-6/omega-3 ratio as a primary cause of this dysregulation (Freitas et al., 2017, Mazier et al., 2015, Matias and Di Marzo, 2007, Simopoulos, 2016, Bisogno and Maccarrone, 2014, De Petrocellis and Di Marzo, 2009, Matias et al., 2008, DiPatrizio and Piomelli, 2012, Engeli, 2008, Brown et al., 2013, Simopoulos, 2002). Omega-6 fatty acids are precursors of the endocannabinoids AEA and 2-AG. These endocannabinoid signals act via receptors including CB_1R and CB_2R, and CB_1R plays a primary role in energy homeostasis. An elevated dietary omega-6/omega-3 ratio therefore leads to elevated levels of AEA and 2-AG, overstimulation of CB_1R, and dysregulation of energy homeostasis leading to weight gain (Freitas et al., 2017, Mazier et al., 2015, Kim et al., 2013, Engeli, 2008, Engeli et al., 2005, Cota et al., 2003a, Cota et al., 2003b, Bisogno and Maccarrone, 2014).

Metabolic consequences of the modern Western diet.

Among the defining features of the modern Western diet are a superabundance of calories from sugars and refined starches leading to increased glycemic load, and a strongly elevated ratio of omega-6 to omega-3 polyunsaturated fatty acids. The dietary omega-6/omega-3 ratio in hunter-gatherers is estimated to be around 1:1 to 3:1, whereas the ratio in the modern Western diet is as high as 20:1 or more (Blasbalg et al., 2011, Cordain et al., 2005, Wall et al., 2010, Simopoulos, 2002, Simopoulos, 2016). This shift in dietary fatty acids increased sharply as more vegetable oils (especially soybean oil) and grains were incorporated into the diet. Corresponding with these changes in diet, rates of obesity and metabolic syndrome are increasing rapidly (Aguilar et al., 2015). Obesity is a major health concern, strongly associated with systemic

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inflammation and metabolic syndrome, and with increased risk of diabetes mellitus, a variety of cancer types, cardiovascular disease, autoimmune disorders, anxiety, depression, Alzheimer's disease, and other serious medical conditions (O'Neill and O'Driscoll, 2015, Simopoulos, 2002, Vidot et al., 2014, Haan, 2006, Farooqui et al., 2012, Esser et al., 2014, Bisogno and Di Marzo, 2008, Jourdan et al., 2016, Lontchi-Yimagou et al., 2013). Dietary dysregulation of the endocannabinoid system is emerging as a primary cause of these conditions, suggesting that therapeutic interventions targeting this system should be investigated as a primary way to reduce or eliminate many of the most serious chronic diseases characteristic of modern Western societies.

Overview of the eCB system

The endocannabinoid (eCB) system is a signaling system with a prominent role in homeostasis, and is reviewed extensively elsewhere (Di Marzo et al., 1998, Bisogno and Maccarrone, 2014, De Petrocellis and Di Marzo, 2009, Brown et al., 2013, Freitas et al., 2017, Mazier et al., 2015, DiPatrizio and Piomelli, 2012). This signaling system occurs within the central nervous system and in multiple peripheral organs. The eCB system involves signals and receptors. There are both strong and weak signals. The strong signals are N-arachidonoylethanolamide (AEA, or anandamide), and 2-arachidonoylglycerol (2-AG). These are formed from dietary omega-6 fatty acids (FAs) via arachidonic acid. Weaker endocannabinoids include DHEA and EPEA, derived from the omega-3 FAs.

AEA and 2-AG act through multiple receptors. Best-known are CB_1R and CB_2R, G-protein coupled receptors that are located in the CNS and peripherally, on a variety of organs and tissues including the gut, liver, bones, skeletal muscle, and adipose tissues (Di Marzo et al., 1998, Bisogno and Maccarrone, 2014, De Petrocellis and Di Marzo, 2009, Brown et al., 2013, Freitas et al., 2017, Mazier et al., 2015, Bab et al., 2008, Bab et al., 2009, Purohit et al., 2010, Cardinal et al., 2012).

Impact of the dietary omega-6/omega-3 ratio on the endocannabinoid system.

Recent reviews suggest that disruption of the eCB system by an elevated omega-6/omega-3 ratio contributes strongly to the metabolic dysregulation associated with the modern Western diet (Freitas et al., 2017, Mazier et al., 2015, Brown et al., 2013, Matias and Di Marzo, 2007, Matias et al., 2008, Bisogno and Maccarrone, 2014, De Petrocellis and Di Marzo, 2009, Engeli, 2008, DiPatrizio and Piomelli, 2012, Engeli et al., 2005, Simopoulos, 2002, Simopoulos, 2016, Alvheim et al., 2014). Elevated production of the endocannabinoids AEA and 2-AG is central to the health problems associated with the elevated omega-6/omega-3 ratio. Omega-6 FAs are converted to the strong eCB signals AEA and 2-AG, and omega-3 FAs are converted to the weaker signals DHEA and EPEA, by the same enzymes (elongases and Δ-desaturases), which

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are limiting. Therefore, the elevated omega-6/omega-3 ratio results in increased synthesis of AEA and 2-AG, resulting in overstimulation of CB_1R (Fig. 1). Elevated CB_1R activity in turn directly causes excess intake, storage, and conservation of energy leading to disruption of body mass and adipose tissue homeostasis (Engeli, 2008, Simopoulos, 2002, Simopoulos, 2016, DiPatrizio and Piomelli, 2012, Freitas et al., 2017, Mazier et al., 2015, Bisogno and Maccarrone, 2014, Alvheim et al., 2014, Khan et al., 2014b, Cardinal et al., 2012, Cota et al., 2003a, Cota et al., 2003b, Engeli et al., 2005). Omega-3 fatty acids are receiving considerable attention as dietary supplements due to their apparent ability to reduce obesity, inflammation and associated chronic diseases. Their actions, at least in part, stem from their competition with omega-6 fatty acids for shared enzymes, leading to reduced AEA and 2-AG levels and CB_1R activity (Brown et al., 2013, Bigford and Del Rossi, 2014, Galland, 2010, Giugliano et al., 2006, Rhee et al., 2017, Jing et al., 2013, Kelly et al., 2013, Khan et al., 2014b, Berge et al., 2013, Hu et al., 2002, Kim et al., 2013, Freitas et al., 2017, Simopoulos, 2002, Simopoulos, 2016).

Role of eCB and CB_1R in obesity and metabolic disorders.

CB_1R is a primary mediator of energy uptake, storage, and conservation. It acts to maximize energy uptake and conservation through multiple mechanisms. Stimulation of CB_1R modulates taste and smell pathways to increase the palatability of food. It stimulates the appetite centers of the brain, leading to hyperphagia and favoring fat accumulation in adipose tissue. At the same time, CB_1R activation reduces energy expenditures (Simopoulos, 2002, DiPatrizio and Piomelli, 2012, Freitas et al., 2017, Mazier et al., 2015, Engeli, 2008, Bisogno and Maccarrone, 2014, Alvheim et al., 2014, Khan et al., 2014a, Cota et al., 2003a, Cota et al., 2003b, Farrimond et al., 2011). These actions contribute to homeostasis in the context of a hunter-gatherer diet of plants, plant-feeding animals, and fish. However, the modern industrial Western diet, characterized by an elevated omega-6/omega-3 ratio (Blasbalg et al., 2011), leads to chronic overstimulation of CB_1R (Freitas et al., 2017, Mazier et al., 2015, Simopoulos, 2016). When combined with the elevated glycemic load of the modern Western diet, this contributes strongly to increased rates of obesity, unfavorable lipid profiles, insulin resistance, exacerbation of inflammation in the liver and kidneys, and increased cardiometabolic risk (Gertsch, 2017, Engeli, 2008, Ginsberg and Woods, 2009, Alvheim et al., 2014).

The critical role of CB_1R in accumulation of energy reserves and BMI homeostasis is revealed in studies using the CB_1R antagonist rimonabant. In laboratory and clinical trials, this drug was successful at reducing weight, but severe psychiatric side effects including dizziness, anxiety, depression, and nausea caused discontinuation of clinical trials (Ginsberg and Woods, 2009, Van Gaal et al., 2005). Peripherally restricted CB_1R antagonists would not act upon centrally mediated

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processes such as appetite, limiting their therapeutic potential (Quarta et al., 2010, Cluny et al., 2012, Ginsberg and Woods, 2009). However, these trials highlight the importance of the endocannabinoid system as a target of interest in weight control strategies (Ginsberg and Woods, 2009, Van Gaal et al., 2005). A therapeutic approach that acts both peripherally and centrally on the endocannabinoid system but does not cause severe psychiatric side effects would be of great interest.

The present study summarizes the data on *Cannabis* use, caloric intake, and body mass index (BMI), establishing conclusively that *Cannabis* use is associated with reduced BMI and obesity rates despite increased caloric intake. It then provides a theoretical, causative explanation for this paradox. This theory encompasses the causative role in obesity of dietary disruption of the endocannabinoid system by an elevated omega-6/omega-3 fatty acid ratio. *Cannabis* (or THC) results in downregulation of CB_1R, leading to reduced sensitivity to AEA and 2-AG, leading to significant health benefits in the context of this diet.

Methods:

Data on the BMI of *Cannabis* users and non-users, or studies reporting adjusted odds ratios (AOR) for *Cannabis* users being obese or overweight, were obtained from the literature. Studies addressing the health impact of *Cannabis* use were identified using database searches and citation lists. Studies addressing the impact of therapeutic Cannabis use by cancer or AIDS patients, etc., as a means to increase appetite and caloric intake, were eliminated. Studies in which *Cannabis* was provided to non-users over a several day period were rejected because short term weight gain can be caused by water retention from increased sodium intake rather than accumulation of tissue mass. One study (Ceccarini et al., 2015) focused on imaging of CB_1R and was rejected due to low sample size (N = 10 users and N = 10 non-users). The remaining data were compiled into a spreadsheet. Paired t-tests were used for comparing BMI of users and non-users. When different usage rates were reported, data from the highest dosage group were used. The mean across all usage groups, relative to non-users, is also reported. For caloric intake, data from short term experimental studies are eliminated to ensure that subjects had reached a steady state.

Results:

BMI data:

Nine studies were included that reported BMI of users and non-users and met selection criteria (Table 1), and an additional two studies were identified that reported lower BMI in *Cannabis* users but did not provide numerical data. Of these studies, only one reported lower BMI values in users relative to non-users that did not reach statistical significance. A second study did not report statistical analysis of the BMI data.

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Of those studies reporting significant negative correlations, two reported that longer duration of *Cannabis* use was associated with reduced BMI (Meier et al., 2016, Rajavashisth et al., 2012).

Across all studies reporting BMI, the overall mean BMI of non-users was 27.5 kg/m^2, while that of users (including data for each usage group) was 26.0 kg/m^2 (Table 1). Limiting the analysis to the data from the highest dosage or duration of use reported in each study resulted in a mean BMI of users of 25.5 kg/m^2, a difference of 2 kg/m^2 and significantly lower than the BMI of non-users ($P < 0.001$, paired t-test, $T = 6.00$, Fig. 2, Table 2). Thus, on average, non-users in these studies are overweight, whereas *Cannabis* users are significantly leaner and are near the healthy BMI range (18.5 – 25 kg/m^2). Further support for reduced BMI in *Cannabis* users comes from the study by Warren et al. (Warren et al., 2005). Although Warren et al. (Warren et al., 2005) did not report BMI values, they grouped obese patients by BMI. The percent of each group that consumed *Cannabis* was negatively and linearly related to the BMI of the group ($R^2 = 0.96$). Danielsson et al. (Danielsson et al., 2016) also reported decreased rates of overweight (BMI > 24.9) in *Cannabis* users but did not provide numerical data for BMI of the two groups. Thus, of eleven studies reporting data on the relationship between *Cannabis* use and BMI, nine showed a significant negative relationship between *Cannabis* use and BMI while the remaining two either reported lower BMI values in *Cannabis* users than non-users that did not reach statistical significance, or failed to provide statistical analyses (Table 1).

Of course, decreased BMI in *Cannabis* users could result from activities correlated with *Cannabis* use, rather than *Cannabis* use itself. Two of the BMI studies adjusted for potential confounders, and significant differences remained following adjustment (Table 1). An additional six studies were identified that reported adjusted odds ratios (AOR) of *Cannabis* users being obese or overweight (Table 2). Hayatbakhsh et al. (Hayatbakhsh et al., 2010) followed a cohort of patients from birth until age 21, and found that subjects who used *Cannabis* showed a strongly reduced incidence of being overweight or obese relative to non-users. A fully adjusted model that included BMI at age 14 yielded an AOR of 0.2 for daily users being overweight (95% CI = 0.1 - 0.4). BMI was inversely correlated with the frequency of *Cannabis* use, lending support for causation (Hayatbakhsh et al., 2010). Waterreus et al. (Waterreus et al., 2016) found that a significantly lower percentage of users than non-users were obese (53.7% of non-users, 36.7% of occasional users, and 28.7% of frequent users were obese ($P < 0.001$). Huang et al. (Huang et al., 2013) studied three categories of adolescent *Cannabis* users; high users, sporadic users, and increasing users. Sporadic and high usage groups showed far lower obesity rates than low users (AOR for sporadic use = 0.2, for high use = 0.1). In contrast, the subjects on the increasing usage trajectory showed increased obesity rates relative to low users (AOR = 1.6). This was the only report identified in the literature of an AOR for obesity greater than one. The

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mean AOR across data points from these studies was 0.68 (95% CI = 0.53 – 0.84), further supporting reduced BMI in users (Table 2).

A recent review cited Mittleman (Mittleman et al., 2001) as reporting increased obesity rates in *Cannabis* users (Vidot et al., 2014), but this appears to be a misinterpretation of the data presented in that study. Mittleman et al. (Mittleman et al., 2001) showed that, of patients who had suffered an MI, those who used *Cannabis* were more likely to be obese. This is quite different from finding that *Cannabis* users were more likely to be obese. These data could be interpreted instead as evidence for protection of non-obese *Cannabis* users from MI. These data were therefore not included in the analysis.

Overall, 17 studies have presented data from 19 data sets on the relationship between *Cannabis* use and body mass or rates of obesity. These studies provided a total of thirty six individual data points for BMI or AOR, and thirty five of these show BMI or obesity values for *Cannabis* users that are less than values for non-users. Both the BMI data and the AOR data show significantly lower BMI or rates of overweight or obesity in *Cannabis* users (BMI: paired t-test $P < 0.001$; OR 95% CI = 0.53 – 0.84) (tables 1 and 2). Further evidence comes from the recent observation that legalization of medical *Cannabis* at the state level is associated with a rapid decrease in statewide obesity rates (Sabia et al., 2017), and that obese rats exposed to *Cannabis* extract show reduced rates of weight gain (Levendal et al., 2012). Indeed, the inverse relationship between obesity and *Cannabis* use led Le Foll et al. (Le Foll et al., 2013) to propose *Cannabis* as a possible therapeutic option for weight loss, and evidence accumulated since then has only strengthened the association.

Caloric intake data:

Interestingly, frequent *Cannabis* users appear to have increased caloric intake relative to non-users, despite lower BMI. Rodondi et al. (Rodondi et al., 2006) found that users who had consumed *Cannabis* for more than 1,800 days over 15 years consumed on average 619 more calories/day than non-users, yet showed no difference in BMI (Table 1). Smit and Crespo (Smit and Crespo, 2001) reported lower BMI in users (24.7 ± 0.3) than non-users (26.6 ± 0.1), despite users consuming 564 additional calories relative to non-users ($P < 0.0001$). Ngueta et al. (Ngueta et al., 2015) also observed higher values for caloric intake in *Cannabis* users relative to non-users; although this was not statistically significant (2375 vs 2210 kcal/day; $P = 0.07$). Despite this, the users had lower BMI ($P < 0.001$). Foltin et al. (Foltin et al., 1988) found *Cannabis* users to have a substantial increase (1095 kcal/day) in daily caloric intake, although this was a short-term experimental study rather than a comparison between free-range *Cannabis* users and non-users. Across these studies, on average, *Cannabis* users consumed an additional 834 kcal/day relative to non-users. As BMI of *Cannabis* users is lower than non-users, this suggests that *Cannabis* users must have increased metabolic rates.

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Previous explanations proposed for lower BMI in Cannabis users

Any theory explaining mechanistically how *Cannabis* use causes reduced BMI must consider the paradoxical increase in caloric intake of users. To date, such a theory is lacking (Vidot et al., 2014, Gertsch, 2017). Proposed explanations for reduced BMI in *Cannabis* users include substitution of *Cannabis* for food in brain reward pathways (Warren et al., 2005). Pagotta et al. (Pagotto et al., 2006) suggested that the sedative effects of high doses of *Cannabis* could reduce food consumption, but Rajavashiseth et al. (Rajavashisth et al., 2012) observed detectable effects on BMI at usage rates of four times or less per month (25% of non-users were obese, whereas 16% of people who used *Cannabis* 1 – 4 times/month were obese, $P < 0.001$). Sabia et al. (Sabia et al., 2017) suggested that reduced alcohol use by younger users, and increased physical activity of older users upon initiating medical marijuana use, may be responsible for the observed decrease in BMI. These explanations obviously do not account for increased caloric intake in *Cannabis* users. Le Foll et al. (Le Foll et al., 2013) suggested that THC may act as a functional antagonist in high endocannabinoid tone, as occurs in obesity, reducing BMI in *Cannabis* users (Le Foll et al., 2013). This is essentially what we are proposing, but does not address the mechanism involved. While all of these may contribute, reduced BMI in conjunction with increased caloric intake strongly suggests that the mechanisms causing the observed decreases in BMI or obesity rates of *Cannabis* users must include differences in metabolism, not changes in caloric intake or activity-related energy expenditures alone.

Theoretical explanation for the decreased BMI of Cannabis users

There are currently no proposed mechanisms explaining reduced BMI in *Cannabis* users that account for their increased caloric intake. The central role of CB_1R in appetite, energy intake, energy conservation, and diet-induced obesity (Freitas et al., 2017, Mazier et al., 2015, Alvheim et al., 2014, Engeli et al., 2005, Engeli, 2008, Cota et al., 2003a, Cota et al., 2003b, Cardinal et al., 2012, DiPatrizio and Piomelli, 2012, Matias and Di Marzo, 2007, Matias et al., 2008, Pagotto et al., 2006), and the hyperphagia and hypothermia resulting from acute stimulation of CB_1R by THC (Farrimond et al., 2011, Borgen et al., 1973), makes CB_1R a prime suspect for a causative role in the effects of *Cannabis* use on BMI.

A novel theory for the impact of *Cannabis* use on BMI involving changes in CB_1R expression is proposed here (Fig. 3). This multipart theory includes the following components:

1. A diet characterized by an elevated ratio of omega-6/omega-3 fatty acids, typical of processed foods high in grains and soybean oil, and animals reared on these foods, results in elevated levels of the endocannabinoid signals AEA and 2-AG.

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The evidence is well established (Freitas et al., 2017, Mazier et al., 2015, DiPatrizio and Piomelli, 2012, Bisogno and Maccarrone, 2014, Berge et al., 2013, Simopoulos, 2016).

2. Elevated AEA and 2-AG act to overstimulate the endocannabinoid receptor CB_1R, resulting in increased appetite and palatability of food, increased rates of energy uptake and storage, and decreased resting metabolic rates. These result in dysregulation of glucose and lipid metabolism, metabolic syndrome, and obesity.

The evidence is well established, and is summarized in multiple recent reviews, see for example (Simopoulos, 2016, Mazier et al., 2015, Freitas et al., 2017).

3. Decreased CB_1R activity reduces obesity and metabolic disruption.

Strong evidence in support of this statement is provided in lab experiments and clinical trials using the CB_1R antagonist rimonabant. Rimonabant causes weight loss, improved lipid profiles, improved glucose sensitivity, and reduced atherosclerosis in animals and human subjects (Ginsberg and Woods, 2009, Dol-Gleizes et al., 2009). Unfortunately, it also caused severe psychiatric side effects in clinical trials, including depressive disorders, dizziness, nausea, and anxiety, and trials were therefore terminated (Ginsberg and Woods, 2009, Dol-Gleizes et al., 2009, Van Gaal et al., 2005).

4. *Cannabis* use causes downregulation of CB_1R, reducing the impact of enhanced AEA and 2-AG production arising from an elevated dietary omega-6/omega-3 ratio.

Multiple studies show that CB_1R is downregulated during *Cannabis* tolerance, and the receptor remains downregulated for about 3-4 weeks after cessation of use (D'Souza et al., 2016, Hirvonen et al., 2012, Ginsberg and Woods, 2009, Ceccarini et al., 2015, Dudok et al., 2015, Bonnet and Preuss, 2017).

Observations supporting this theory:

There is abundant evidence that rates of obesity and metabolic syndrome are increasing with changes in diet (Fryar C.D., 2016, Murray et al., 2013, Blasbalg et al., 2011, Aguilar et al., 2015, O'Neill and O'Driscoll, 2015, Cordain et al., 2005, Esser et al., 2014, Bosma-den Boer et al., 2012, Giugliano et al., 2006, Wall et al., 2010).

There is abundant evidence that these dietary changes include a shift to a high omega-6/omega-3 ratio (Blasbalg et al., 2011, Aguilar et al., 2015, Wall et al., 2010, Brown et al., 2013, Jing et al., 2013, Simopoulos, 2002, Simopoulos, 2016, Mazier et al., 2015, Freitas et al., 2017).

There is abundant evidence that an elevated omega 6/omega 3 ratio increases endocannabinoid tone by increasing AEA and 2-AG levels, overstimulating CB_1R.

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(Muller et al., 2017, Matias et al., 2008, Freitas et al., 2017, Ginsberg and Woods, 2009, Mazier et al., 2015).

There is abundant evidence that overstimulation of CB_1R increases adiposity and leads to metabolic syndrome, contributing to chronic diseases (Muller et al., 2017, Matias et al., 2008, Freitas et al., 2017, Ginsberg and Woods, 2009, Mazier et al., 2015, Gertsch, 2017, Engeli et al., 2005, Engeli, 2008, Alvheim et al., 2014).

There is abundant evidence that reduced CB_1R activity results in weight loss. The CB_1R antagonist rimonabant increases O_2 consumption and resting energy expenditures in both rats and in humans. In rats, it increases O_2 consumption by 18% at a dosage of 3 mg/kg, and 49% at 10 mg/kg, after 3 hours of exposure. In humans, it increases resting energy expenditures of overweight or obese subjects (Ginsberg and Woods, 2009, Van Gaal et al., 2005, Dol-Gleizes et al., 2009).

There is abundant evidence that exposure to *Cannabis* and/or THC results in downregulation of CB_1R. Because CB_1R plays a major role in assimilation, storage, and conservation of energy, this downregulation results in decreased endocannabinoid tone. According to this hypothesis, acute exposure results in the “munchies”, stimulating appetite and energy consumption, and causes hypothermia as metabolic rates decrease. Regular *Cannabis* use is associated with desensitization and downregulation of CB_1R, and CB_1R levels remain depressed for 3-4 weeks following cessation of use (Bonnet and Preuss, 2017, D’Souza et al., 2016, Dudok et al., 2015, Ceccarini et al., 2015). Rapid downregulation of CB_1R more than offsets the short-term increase in energy stores that follow acute exposures.

There is abundant evidence that *Cannabis* use, and/or exposure to THC, results in reduced BMI (Table 1,2, Figure 2).

Predictions arising from theory.

Prediction 1. *Cannabis* users lose additional weight during abstinence.

BMI is reduced in *Cannabis* users, and should decrease even more when users stop using *Cannabis* because CB_1R remains downregulated for several weeks following chronic *Cannabis* consumption (Bonnet and Preuss, 2017, D’Souza et al., 2016, Ceccarini et al., 2015, Dudok et al., 2015, Hirvonen et al., 2012). Recently abstinent users would show reduced appetite and increased metabolic rates during this time. However, they will no longer experience short-term stimulation of appetite, energy intake and storage, and reduced metabolic rates during each episode of acute *Cannabis* consumption. Therefore, weight loss will increase as energy intake and storage remain depressed, and metabolism stimulated, until CB_1R returns to pre-*Cannabis* use levels.

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This prediction is supported, as weight loss during withdrawal from *Cannabis* is one of the seven symptoms of *Cannabis* withdrawal listed in DSM-V (Katz et al., 2014, Association, 2013).

Prediction 2: Moderate *Cannabis* use reduces the incidence of disorders associated with obesity and metabolic syndrome.

Because *Cannabis* use is associated with reduced rates of obesity, it should also reduce rates of obesity-related diseases in users. There is some evidence for this, but results are inconsistent. Multiple studies have reported in *Cannabis* users reduced rates of diabetes mellitus, insulin insensitivity, or metabolic syndrome in fully adjusted models including age (Rajavashisth et al., 2012, Ngueta et al., 2015, Alshaarawy and Anthony, 2015, Penner et al., 2013, Thompson and Hay, 2015, Waterreus et al., 2016). Yankey et al. (Yankey et al., 2016) also reported decreased DM rates (AOR 0.42) that did not reach statistical significance (95% CI = 0.13 – 1.36). In contrast, analysis of data from the CARDIA data set failed to detect this relationship (Bancks et al., 2015). Daniellson et al. (Danielsson et al., 2016) found decreased rates of DM in *Cannabis* users in a dataset of Swedish conscripts (OR 0.74), but unlike the studies from the NHANES data set this effect was no longer significant after adjustment for age (AOR 0.74 prior to adjustment, 0.94 after adjustment).

Cannabinoids have potent anti-cancer properties (Brown et al., 2013, Velasco et al., 2012), and a recent review concluded that *Cannabis* users have lower rates of cancer than non-users (Clark, 2017). Multiple laboratory studies have shown that THC slows or reverses the progression of Alzheimer's disease, although clinical trials are lacking (Eubanks et al., 2006, Cao et al., 2014, Currais et al., 2016, Ramírez et al., 2005, Bedse et al., 2015). In contrast, evidence available to date does not support reduced rates of cardiovascular disease in *Cannabis* users (Reis et al., 2017), although more studies are clearly warranted on this topic.

Prediction 3. The occurrence and magnitude of metabolic benefits from *Cannabis* use depend on the dietary omega-6/omega-3 ratio.

The impact of diet on the eCB system is predicted to differ among populations because different populations have different diets, consuming different proportions of green vegetables, industrially produced animals, oceanic fishes, and processed foods. According to the theory established in the current paper, populations with diets characterized by a high omega-6/omega-3 ratio will see significantly larger health improvements from *Cannabis* use than those eating diets with more moderate ratios of omega-6/omega-3 FAs. This may explain some of the inconsistencies in the data on the metabolic impact of *Cannabis* use; for example, *Cannabis* use by Swedish populations (Danielsson et al., 2016, Cerdá et al., 2016) may not have the same health impacts as *Cannabis* use by Americans due to the different dietary backgrounds and obesity rates of these populations. *Cannabis* use in the United States appears to provide significant

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public health benefits due to partial or complete reversal of the metabolic dysregulation caused by the strongly elevated omega-6/omega-3 ratio of the American diet.

Prediction 4: *Cannabis* use and omega-3 supplements have similar impacts on health.

Both omega-3 FAs and *Cannabis* reduce endocannabinoid tone, through distinct mechanisms. Omega-3 FAs compete with omega-6 FAs for the enzymes synthesizing AEA and 2-AG from omega-6 FAs, and omega-3 supplements thereby reduce the synthesis of AEA and 2-AG and reduce stimulation of CB_1R (Bisogno and Maccarrone, 2014, Freitas et al., 2017, Berge et al., 2013, Kim et al., 2013, Wall et al., 2010). *Cannabis* causes downregulation of CB_1R (Bonnet and Preuss, 2017, D'Souza et al., 2016, Dudok et al., 2015, Ceccarini et al., 2015), reducing the sensitivity to elevated AEA and 2-AG. Thus, the theory predicts that omega-3 FA supplements and *Cannabis* use should have similar positive health impacts in the context of metabolic dysregulation from a diet with an elevated omega-6/omega-3 ratio. However, it is likely that the overlap is not complete as the precursor of AEA and 2-AG, arachidonic acid (Freitas et al., 2017), also gives rise to proinflammatory leukotrienes and prostaglandins (Meng et al., 2015), an effect that would not be impacted by decreased CB_1R tone.

Prediction 5: The combination of omega-3 supplements and *Cannabis* or cannabinoids could be a particularly potent treatment or preventative for obesity, metabolic syndrome, cancer, etc.

Reducing AEA and 2-AG synthesis with omega-3 supplements, and at the same time reducing CB_1R density with *Cannabis* use, should reduce BMI and cardiometabolic risk factors more than either option alone (Fig. 4). Note that, because CB_1R remains downregulated for some time following use, weekly *Cannabis* use may be sufficient to observe significant weight loss and metabolic benefits.

Conclusions/summary

Obesity and elevated BMI are strongly associated with disease states, and there are significant financial and public health incentives to develop effective interventions to help people achieve a healthy body mass. Pharmacological weight loss therapy is recommended when BMI is greater than or equal to 27 in the presence of obesity-related risk factors, and greater than 30 in the absence of such risk factors (Ginsberg and Woods, 2009). However, the development of pharmacological weight loss methods has been problematic. Rimonabant, a CB_1R antagonist, showed promise in lab studies, but clinical trials were discontinued due to serious psychiatric side effects (Ginsberg and Woods, 2009). Surgical methods such as the lap band or bariatric surgeries are frequently used when dietary or pharmaceutical interventions do not work, and any

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surgical procedure entails risk and recovery. Surgical procedures are also expensive. Therefore, relatively safe and inexpensive methods to reduce obesity and prevent or reduce some of the most deadly and costly chronic diseases characterizing Western societies merit serious consideration. For many patients, *Cannabis* may be a better option for weight loss than surgery or pharmaceuticals. However, patients with preexisting cardiovascular conditions or prior myocardial infarctions should avoid cannabinoids or use them with caution (Clark, 2017, Mittleman et al., 2001, Franz and Frishman, 2016).

A number of states, and the federal government, have legalized *Cannabis* products containing CBD but continue to ban legal access to products containing THC. Evidence available at this time suggests that it is ingestion of THC that is responsible for downregulation of CB_1R, and therefore, for reduced obesity rates of *Cannabis* users. Our theory suggests that the "high" that occurs upon CB_1R stimulation with THC may be a necessary accompaniment to weight loss, because downregulation of CB1R is required for reduced BMI and it is not yet clear whether microdosing will cause downregulation. However, weekly or biweekly *Cannabis* use may be sufficient as significant decreases in BMI are observed at weekly usage rates (Rajavashisth et al., 2012).

Medical marijuana use is increasing, leading to decreased use of multiple classes of pharmaceuticals. Patients cite improved symptom management, fewer adverse side effects, and milder withdrawal symptoms as reasons for switching from pharmaceuticals to medical *Cannabis* (Boehnke et al., 2016, Bradford and Bradford, 2016, Bradford et al., 2018, Haroutounian et al., 2016, Bachhuber et al., 2014, Lucas and Walsh, 2017, Lucas et al., 2013, Wen and Hockenberry, 2018). Once patients become aware that the side effects of medical *Cannabis* may include weight loss and reduced risk of obesity-associated medical conditions, this shift toward medical *Cannabis* is likely to accelerate. Available data suggests that this will save many lives, not only from reduced rates of obesity-related chronic illnesses, but also from reduced deaths from pharmaceutical overdose (Jones et al., 2013, Clark, 2017, Bachhuber et al., 2014).

This study provides a theoretical platform to inform future studies on the correlations between *Cannabis* use and cardiometabolic risk factors. This theory may explain inconsistencies among studies on the impact of *Cannabis* use on metabolic dysregulation, as different populations have different diets. For example, epidemiological studies of the impact of *Cannabis* use by cohorts of Swedish conscripts may reveal different results than epidemiological studies in the United States, due to different levels of obesity in the two countries. Cerdá et al. (Cerdá et al., 2016) found that early, heavy *Cannabis* use among Swedish conscripts is associated with increased mortality later in life. In contrast, Clark (Clark, 2017) concluded that *Cannabis* use is

associated with a substantial decrease in the premature death rate in the United States, as it is associated with reduced rates of cancer, diabetes mellitus, pharmaceutical use, deaths from brain trauma, and may slow the progression of Alzheimer's and other neurodegenerative diseases. The strong evidence for interactions between the dietary omega-6/omega-3 ratio, obesity, and *Cannabis* use suggests that the balance between positive and negative health impacts of *Cannabis* use will differ in Swedish and United States populations. In the U.S., many people may actually achieve health benefits from moderate *Cannabis* use due to reduced risk of obesity and associated diseases.

This theory raises a number of important questions. How many other conditions respond in opposite directions during acute and long-term exposures to *Cannabis*? How does this paradox impact therapeutic uses of *Cannabis*? Do the long term effects of *Cannabis* use arising from downregulation of CB_1R exacerbate the underlying condition that drove patients to therapeutic use of *Cannabis* in the first place? For example, if a patient uses *Cannabis* for anxiety, will the resulting downregulation of CB_1R result in increased anxiety between therapeutic doses? How does dosage influence this relationship? Is CB_2R also downregulated during *Cannabis* use, and if so, what are the implications for treatment of CB_2R-related conditions with *Cannabis*?

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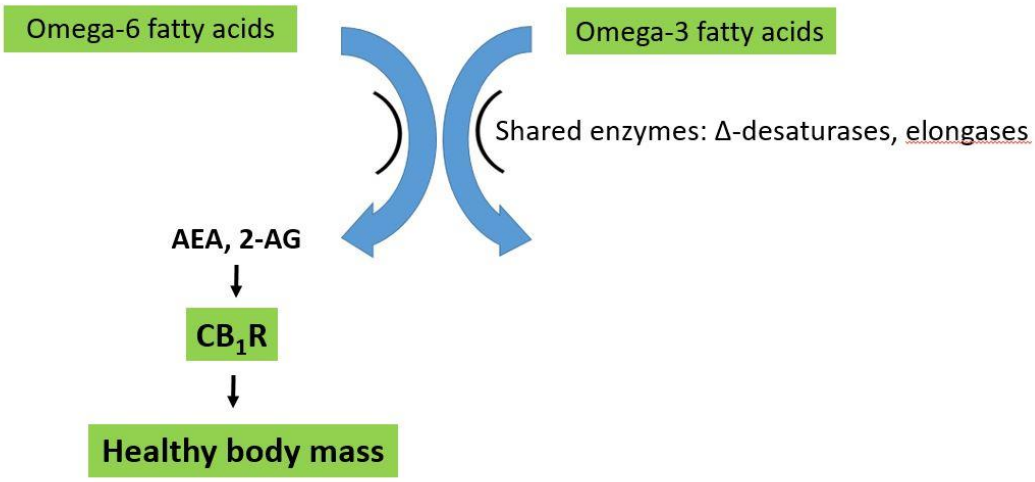
A.



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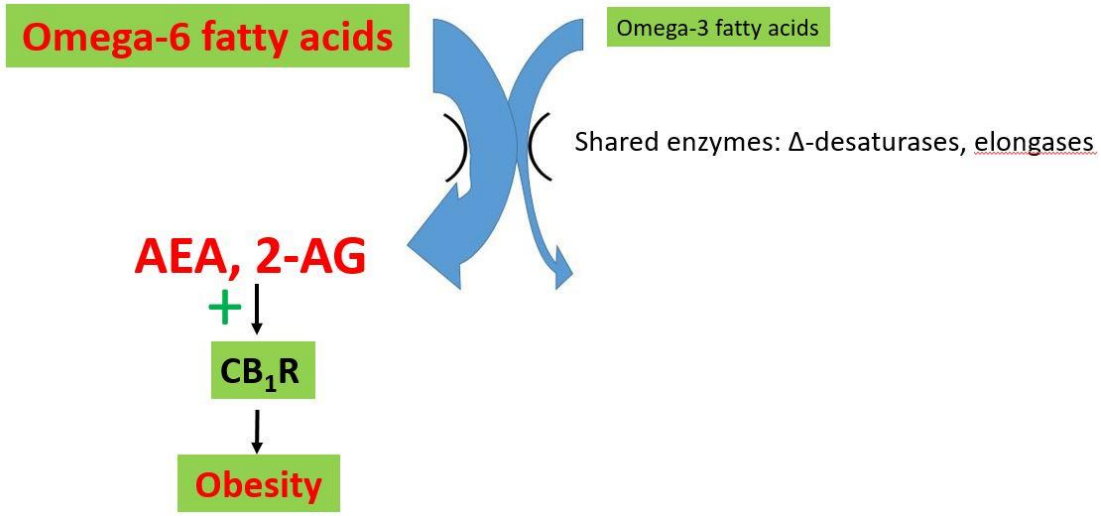

Figure 1: The impact of the modern Western diet on the endocannabinoid system. A. In the presence of a natural omega-6/omega-3 ratio, production of the endocannabinoid signals AEA and 2-AG and resulting stimulation of CB1R are compatible with a healthy BMI. B. The modern western diet, with its elevated omega-6/omega-3 ratio, leads to excess production of AEA and 2-AG. This overstimulates CB_1R, leading to weight gain and metabolic dysregulation. Modified from Frietas et al. (Freitas et al., 2017).

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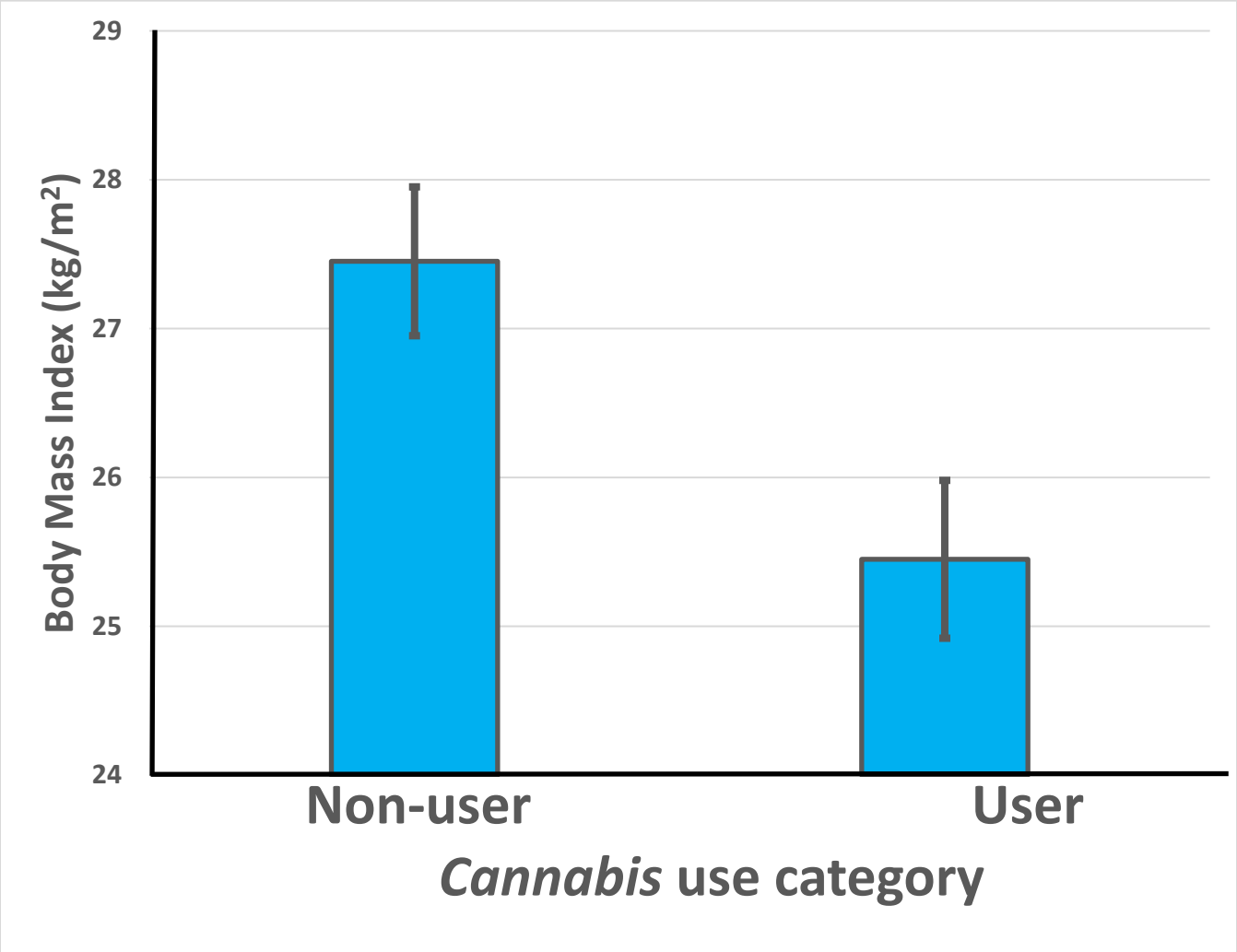

Figure 2: A comparison of body mass index (kg/m^2) of *Cannabis* users and non-users. Data from current user, highest dosage presented in Table 1. Available data show that non-users are overweight on average, whereas the mean BMI of users is not different from the upper limit of the healthy weight range. Data are expressed as mean ± SEM (N = 12 data points from 11 studies). $P < 0.001$.

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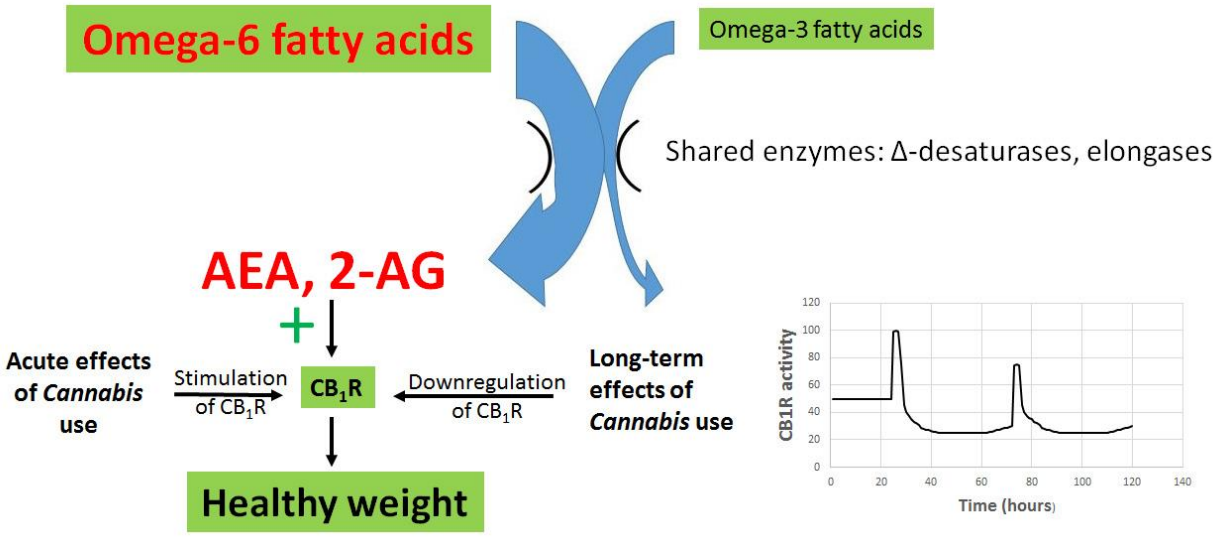

Figure 3: The impact of *Cannabis* use on the endocannabinoid system of people consuming a diet characterized by an elevated omega-6/omega-3 ratio. Acute effects of *Cannabis* and/or THC consumption include hypothermia and hyperphagia, leading to increased energy intake and storage. However, *Cannabis* use also causes long-term downregulation of CB_1R, leading to decreased CB_1R activity, as shown in the insert on the lower right. Decreased CB_1R activity results in a decrease in energy assimilation and an increase in metabolic rates, resulting in a decline in body mass despite stimulation of CB_1R during acute exposure.

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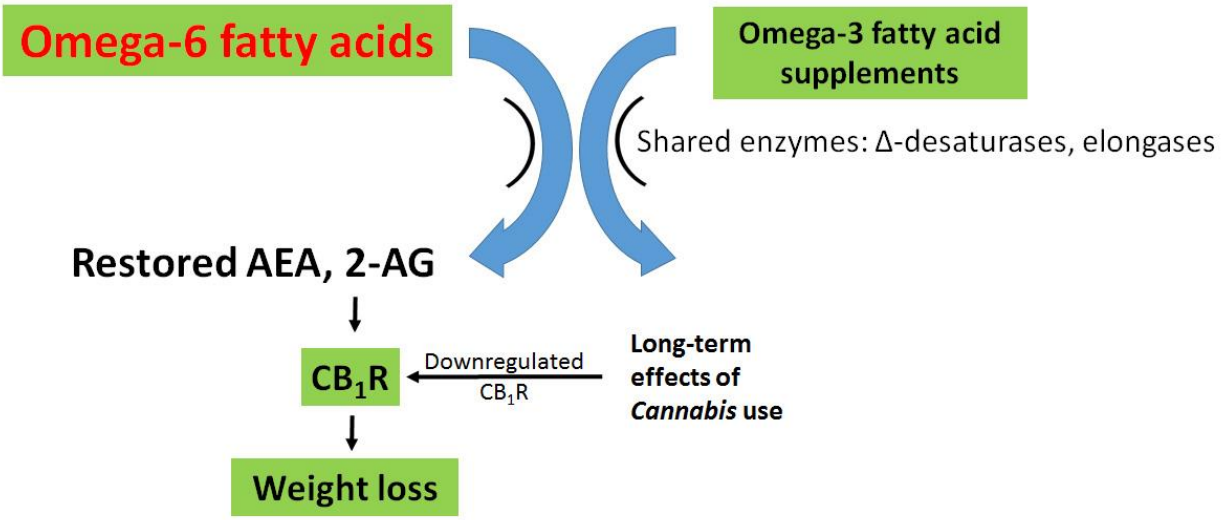

Figure 4: Proposed weight loss therapy based on theory. Daily omega-3 fatty acid supplements (especially with decreased dietary omega-6 fatty acids) will reduce levels of AEA and 2-AG, reducing stimulation of CB_1R, while weekly *Cannabis* use will cause downregulation of CB_1R. Thus, this approach will act to both reduce levels of the endocannabinoid signals and reduce the sensitivity of target cells to those signals. The net effect is predicted to be a more potent weight loss strategy than diet alone.

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Reference	**Non-user**	**Usage pattern**	**Current User**	**Current user, highest dosage**	**P value or 95% CI**
(Ngueta et al., 2015)[a]	28.6 (335)		26.8	**26.8 (451)**	**< 0.001**
(Gerberich et al., 2003)	24.4 (23,705)	(women)	23	**23 (6,504)**	**< 0.05**
	25.4 (14,324)	(men)	24.3	**24.3 (7,474)**	**< 0.05**
(Meier et al., 2016)	28.22 (265)				**< 0.05 (joint years)**
		< 5 years	26.8 (552)		
		5-10 years	27.1 (42)		**< 0.009 (dependence)**
		10-15 years	26.6 (44)		
		15+ years	25.5 (37	**25.5 (37)**	
(Rajavashisth et al., 2012)	28 (6,667)				
		1-4 x/month	24.8 (557)		**< 0.001**
		> 5x/month	24.1 (326)	**24.1 (326)**	**< 0.001**
(Penner et al., 2013)	29.1 (2,103)		27.2 (579)	**27.2 (579)**	**< 0.0001**
(Rodondi et al., 2006)	28.1 (2,252)				Not significantly different
		< 180 days	28.5 (610)		
		180 - 1799 days	28.7 (601)		
		> 1800 days	28.0 (154)	28 (154)	
(Smit and Crespo, 2001)[b]	26.6 (9,771)				
		1-4x/month	25 (541)		
		5-10x/month	26.1 (135)		
		11x+/month	24.7 (176)	24.7 (176)	**P < 0.0001**
(Hirvonen et al., 2012)	27 (28)		24 (30)	**24 (30)**	**< 0.05**
(Thompson and Hay, 2015)	29.1 (2,861)		**26.9 (831)**	**26.9 (831)**	**< 0.0001**
(Danielsson et al., 2016)	**Numerical data not provided; user BMI < non-user**				**Not provided**
(Warren et al., 2005)	**Numerical data not provided; lower BMI groups contain more *Cannabis* users, $R^2 = 0.96$**				**< 0.02**

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Mean	**27.5 (60,059)**		**26.0**	**25.5 (18,272)**	**< 0.0005**

Table 1. Published values of BMI for *Cannabis* users and non-users. Statistically significant differences between *Cannabis* users and non-users are indicated with bold font.

a. adjusted for age (continuous), gender, small communities (yes/no), more than or equal to secondary school (yes/no), income level (<$20,000, _$20,000, do not know/refuse to answer), marital status (single, married/common law, separated/divorced/widowed), _3.5 hours/week of leisure physical activity (yes/no), smoking status (never/former/current smoker with 1-14 cig./day, 15-24 cig./day, _25 cig./day), ever drink alcohol (yes/no/do not know or refuse to answer), total energy intake (kcal/day).

b. effect remained after adjustment for age, gender, education, cigarette smoking, and caloric intake (P = 0.003)

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Reference	Usage category	OR users	95% CI	P values
(Le Strat and Le Foll, 2011)[a]				
NESARC, N = 41,633	1+ x/yr, < 1x/month	0.70	0.63 – 1.05	**< 0.001**
	1x/month – 2x/week	0.84	0.62 – 1.01	
	daily	**0.61**	**0.46 – 0.82**	
NCS-R, N = 9,103	1+ x/yr, < 1x/month	0.7	0.44 – 1.11	**< 0.001**
	1x/month – 2x/week	0.84	0.54 – 1.31	
	daily	0.73	0.43 – 1.23	
(Ngueta et al., 2015)[b]	Past year	**0.56**	**0.37 – 0.84**	**< 0.05**
(Hayatbakhsh et al., 2010)[c]	1x in last month	0.8	0.5 – 1.2	
N = 2,566	Every few days	**0.5**	**0.3 – 0.8**	**< 0.01**
	daily	**0.2**	**0.1 – 0.4**	**< 0.001**
(Yankey et al., 2016)[d]		0.42	0.13 – 1.36	
(Huang et al., 2013)[e]	high vs low use	**0.2**		**< 0.01**
N = 5,141	Sporadic vs. low use	**0.1**		**< 0.01**
	increasing vs low	**1.6**		**< 0.05**
(Barry and Petry, 2009)[f]	**Male, past year**			
N = 40,364	overweight	0.88	0.67 – 1.16	
	obese	0.84	0.6 – 1.16	
	Female, past year			
	overweight	0.88	0.53 – 1.45	
	obese	0.81	0.48 – 1.38	
Mean and summary CI		**0.68**	**0.53 – 0.84**	**< 0.05**

Table 2. Published values for adjusted odds ratios for *Cannabis* users being obese and/or overweight. Statistically significant differences between *Cannabis* users and non-users are indicated with bold font. Only one data point shows AOR > 1.

a. Data from two databases, NESARC = National Epidemiologic Survey on Alcohol and Related Conditions (2001–2002), NCS-R = National Comorbidity Survey–Replication (2001–2003). Adjusted for sex, age, race/ethnicity, educational level, marital status, region, and tobacco smoking status. Prevalence of obesity significantly lower in Cannabis users in both data sets ($P < 0.001$).

b. Age-standardized.

c. Odds ratio for BMI ≥ 25. Adjusted for participant's gender and age, mother's age and education, participant's cigarette smoking, alcohol consumption, anxiety/depression and aggression/delinquency, participants BMI at 14 years.

d. Regular user, OR for abdominal obesity. Adjusted for age, gender, education, participation in at least moderate physical activity, weekly alcohol use, income to poverty ratio, having health insurance, marital status, other illicit drug use and having had rehabilitation.

e. Controlled for adolescent obesity status, gender, ethnicity, and average family income.

f. Controlled for age, level of education, race/ethnicity, income, marital status, region of country, urban vs. rural residence, and lifetime and pastyear DSM-IV diagnoses of any mood disorder, any anxiety disorder, any personality disorder, any alcohol use disorder, and nicotine dependence.

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Abbreviations

AEA: anandamide; N-arachidonoylethanolamide
2-AG: 2-arachidonoylglycerol
CB_1R: Cannabinoid receptor 1
CB_2R: Cannabinoid receptor 2
BMI: body mass index
THC: Δ^9-tetrahydrocannabinol
eCB: endocannabinoid
DHEA: N-docosahexaenoylethanolamine
EPEA: N-eicosapentaenoyl-ethanolamine
CNS: central nervous system
AOR: adjusted odds ratio
MI: myocardial infarction
DM: Diabetes mellitus
CBD: cannabidiol
LA: linoleic acid
ALA: α-linolenic acid

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