Title: Genetic Polymorphisms of the Endocannabinoid System in Obesity and Diabetes

Short title: Endocannabinoid polymorphisms in obesity and diabetes

Joseph M. Doris[1,2], Sophie A. Millar[1], Iskandar Idris[1] and Saoirse E. O'Sullivan[1]

[1]Division of Graduate Entry Medicine and Medical Sciences, School of Medicine, University of Nottingham, Royal Derby Hospital, DE22 3DT, United Kingdom

[2]Current address: St George's Hospital Medical School, St George's, University of London

Corresponding author: Joseph M. Doris, m1400346@sgul.ac.uk, St George's Hospital Medical School, St George's, University of London

Key words: Polymorphisms, endocannabinoid, diabetes, obesity, cannabinoid

Word count: 1,788

Abbreviations

2-AG: 2-arachidonoyl glycerol

BMI: Body mass index

CB1: Cannabinoid receptor 1

CB2: Cannabinoid receptor 2

CRP: C-reactive protein

DAGL: Diacylglycerol lipase

ECS: Endocannabinoid system

FAAH: Fatty acid amide hydrolase

HDL-C: High density lipoprotein cholesterol

$HOMA_{IR}$: Homeostatic Model Assessment for Insulin Resistance

IL-6: Interleukin-6

LDL-C: Low density lipoprotein cholesterol

NAPE-PLD: N-acyl phosphatidylethanolamine phospholipase D

MAGL: Monoacylglycerol lipase

MetS: Metabolic syndrome

SNP: Single nucleotide polymorphism

TGs: Triglycerides

TNFα: Tumour necrosis factor alpha

T2DM: Type 2 Diabetes Mellitus

WC: Waist circumference

WHR: Waist-to-hip ratio

Abstract

The endocannabinoid system (ECS) is involved in many physiological processes including fertility, pain and energy regulation. The aim of this systematic review was to examine the contribution of single nucleotide polymorphisms (SNPs) of the ECS to adiposity and glucose metabolism. Database searches returned 734 articles, of which 65 were included covering 70 SNPs in genes coding for cannabinoid receptors 1 and 2 (CB_1, CB_2), fatty acid amide hydrolase (FAAH) and N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD). No studies included SNPs relating to monoacylglycerol lipase or diacylglycerol lipase. The CB_1 receptor SNP rs1049353 showed 17 associations with lower body mass index (BMI) and fat mass (5 studies). It also showed 3 associations with lower insulin levels (1 study). Conversely, the CB_1 receptor SNP rs806368 was associated with increased BMI and waist circumference (2 studies). The FAAH SNP rs324420 as associated with increased obesity (3 studies). A haplotype of NAPE-PLD was associated with decreased BMI (1 study). 60 SNPs showed no association with any measured outcome. This review suggests a complex but important role of ECS SNPs in energy and glucose metabolism.

Introduction

The endocannabinoid system (ECS) consists of two G-protein coupled receptors (CB_1 and CB_2) and endogenously produced ligands (or endocannabinoids, such as anandamide and 2-arachidonoyl glycerol) and the enzymes involved in their synthesis or degradation; fatty acid amide hydrolase (FAAH), monoacylglycerol lipase (MAGL), diacylglycerol lipase (DAGL) and N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD). It is well established that CB_1 activation leads to increases in energy storage [1] which occurs via increased motivation to consume food and decreased satiety.

Single nucleotide polymorphisms (SNPs) are naturally occurring variations of a genetic sequence, which often affect protein structure. To date, studies on the effects of endocannabinoid SNPs have focused on central disorders such as Parkinson's disease and Alzheimer's disease [2]. However, there is accumulating evidence for the role of endocannabinoid SNPs in adiposity [3] and glucose metabolism [4]. Therefore, the aim of this systematic review was to systematically collate the evidence relating to SNPs of the ECS in obese or diabetic phenotypes. By studying amino acid sequence alterations and any resultant residue changes, we hoped to identify important genetic changes which alter the normal physiology of adiposity and glucose metabolism.

Materials and Methods

Searches were performed using PubMed, EMBASE and Web of Science by two independent researchers and concluded on 26/1/2018. Additional studies were identified from bibliographies. The search terms used were: Cannabinoid OR endocannabinoid receptor OR CB_1 OR CB_2 OR FAAH OR fatty acid amide hydrolase AND polymorphism AND obesity OR diabetes OR BMI OR monoacylglycerol lipase OR MAGL OR diacylglycerol lipase OR DAGL OR N-acyl phosphatidylethanolamine-specific phospholipase D OR NAPE PLD. A summary of search results and exclusions is given in supplemental Figure S1, and a full reference list is available in the supplementary appendix. The SNP database dbSNP was used to gather information regarding nucleotide and amino acid changes [5].

Articles included were original studies relating to polymorphisms of the ECS affecting energy regulation, glucose homeostasis and adiposity. Demographic and clinical parameters included were: body mass index (BMI); waist circumference (WC); waist-to-hip ratio (WHR); body weight; adiposity; Type II Diabetes Mellitus (T2DM); insulin and glucose levels; Homeostatic Model Assessment for Insulin Resistance ($HOMA_{IR}$); adipokine levels (adiponectin, leptin, and resistin); cardiovascular parameters (blood pressure, heart rate); inflammation (levels of interleukin 6 (IL-6), tumour necrosis factor alpha (TNFα) and C-reactive protein (CRP)); and lipid levels (triglycerides, HDL-C and LDL-C). Records excluded were review articles, articles on the ECS not relating to polymorphisms, studies regarding central disorders, non-human studies and studies in a language other than English.

Included articles were analysed for significant ($p<0.05$) positive or negative associations between SNPs and relevant parameters. A ‘positive’ association refers to there being a higher value of the measured outcome in the presence of the polymorphism, whereas ‘negative’ refers to there being a lower value in the presence of the polymorphism. A lack of significant association

between the measured outcome and the polymorphism is described as a 'neutral' association. Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias [6].

Results

65 studies were identified from 733 full-text articles. Risk of bias of these studies was overall low and is summarised in supplemental Figure S2. In total, 38 CB_1, 18 CB_2, 13 FAAH and 1 NAPE-PLD SNPs were studied. No studies relating to MAGL or DAGL SNPs were found. The most commonly studied SNPs and those which showed the most significant associations were CB_1 SNPs rs1049353 and rs806368, and FAAH SNP rs324420. Their associations with body weight and glucose metabolism parameters are presented in Table 1. All SNPs and their associations with measured outcomes are documented in supplementary Table S1. A summary of all included studies and their relevant findings is shown in supplementary Table S2.

BMI and body weight

CB_1

The rs1049353 mutant allele was associated with lower BMI in six European populations [7,8,9,10,11,12] and decreased fat mass in a Danish population (n=783) [13]. Conversely, homozygosity for the rs1049353 mutant allele was associated with higher WHR and WC in obese men ($p<0.01$, n=1,064) [14], and increased childhood obesity in a European population ($p=0.01$, n=200) [15]. The majority of associations with rs1049353 were neutral (90%) (Table 1). However, negative associations were more common than positive (Figure 1), suggesting this SNP plays a part in a more complex genetic susceptibility to increase adiposity. Male carriers of the rs806368 mutant allele showed greater BMI values in a Japanese cohort ($p=0.001$), and were more likely to be obese ($p=0.01$, n=1,452) [16] (Table S1).

FAAH

FAAH polymorphism rs324420 was positively associated with obesity in four cohorts (n=18,987) [17,18,19,20].

CB2

The mutant allele of CB_2 SNP rs3123554 was associated with lower total body fat in females but not males in a European cohort (p=0.001), with lower BMI in subjects at risk of T2DM (p<0.01) and reduced weight loss (p<0.01, n=2,006) [21].

NAPE-PLD

In a Norwegian cohort, a haplotype of NAPE-PLD showed an association with increased BMI (p<0.05, n=5,011) [22].

Type II Diabetes

CB_1

The mutant allele of CB_1 polymorphism rs1049353 was associated with lower insulin, glucose and $HOMA_{IR}$ levels in Spanish obese women [29] and lower insulin in two other European cohorts (n=983) [23,24]. CB_1 SNP rs806365 was associated with decreased $HOMA_{IR}$ values and incidence of T2DM in a North American cohort (p=<0.05, n=2,411) [25].

CB_2

The mutant allele of CB_2 polymorphism rs3123554 was associated with raised insulin levels and $HOMA_{IR}$ values in an obese population (n=1,027) [26] (Figure 1).

FAAH

The mutant allele of FAAH polymorphism rs324420 was associated with lower insulin levels in two obese populations (p<0.05, n=165) [27, 28]. rs324420 was also associated with lower $HOMA_{IR}$ levels in obese Spanish females (p<0.05, n=143) [28].

Lipids

Overall, 22 positive associations with lipid levels were seen. The mutant allele of CB_1 SNP rs1049353 was associated with higher HDL and lower TGs in three cohorts [29,30,31], as well as lower TGs in two populations (n=808) [9, 29] (Table 1).

FAAH SNPs rs324420 and rs3123554 were associated with higher TG levels in European cohorts ($p<0.05$, n=1,644) [26, 30] (Table 1). FAAH SNP rs324420 was also associated with raised anandamide levels in a Brazilian population ($p<0.05$, n=200). [42]

Discussion

The aim of this study was to collate evidence relating to SNPs of the ECS and obese or diabetic phenotypes to identify important genetic changes which alter metabolism. From the 65 included articles, 70 polymorphisms were studied. CB_1 SNP rs1049353 showed 17 associations with lower BMI and fat mass. It also showed associations with reduced glucose, insulin and $HOMA_{IR}$ values. CB_1 polymorphism rs806368 showed 5 associations with increases in BMI, WC and WHR. The FAAH SNP rs324420 showed 7 associations with increased incidence of obesity. 60 SNPs showed no association with any measured outcome. These findings suggest an important role of selected SNPs of the ECS in adiposity, although the number of studies showing no associations means that their contribution is likely part of complex interactions.

The SNP rs1049353 occurs at nucleotide position 1359, a region of the CB_1 (CNR1) gene coding for the receptor's intracellular domain or C-terminal. One study showed that replacement of the C-terminal resulted in decreased affinity of the CB_1 agonist CP55940 and increased affinity of the CB_1 antagonist SR141716A [33]. This suggests that the C-terminal is important in receptor signalling. Although rs1049353 is a synonymous SNP and does not result in an amino acid residue change (Thr>Thr), altered substrate interaction deriving from synonymous SNPs has been observed elsewhere [34] suggesting this is a legitimate theory.

The literature showed 13 associations between rs1049353 and reductions in parameters of glucose metabolism [9,10,12,14,22,23,24,29,30,39,45,46,48] (Figure 1). This suggests that that this SNP is important in diabetic phenotypes, likely caused by upregulation of gluconeogenic transcription factors due to increased CB_1 receptor activity. It is unclear why many studies (n=14) showed no association with parameters of glucose metabolism.

186 The rs324420 SNP reduces FAAH activity and increases likelihood for the enzyme itself to be
187 degraded [41], leading to cannabinoid overactivity. Subsequent CB_1 activation leads to adipogenesis
188 and reduced expenditure, all of which contribute to obesity-related phenotypes. Our analysis
189 showed that rs324420 was associated with higher anandamide levels [42], increased BMI and
190 obesity [17,18,32], which suggests cannabinoid over-activation and subsequent adiposity and that
191 this SNP therefore reduces FAAH activity (Table 1).
192
193 The potential contribution of CNR2 polymorphisms to human metabolism is less clear. Fewer
194 studies investigated these SNPs, and the two polymorphisms studied (rs3123554 and
195 rs35761398) showed conflicting associations with body weight parameters and glucose
196 metabolism. As CB_2 receptors are found primarily in the central nervous system and on immune
197 cells, it is likely that they are less involved in the regulation of body fat and therefore any
198 alterations in their genetic structure are less relevant here. As no studies were found relating to
199 SNPs of DAGL or MAGL, their contribution to obesity and glucose metabolism remains unclear.
200
201 Increasing age may determine the impact of the polymorphism. For instance, associations
202 between SNPs rs2023239 and rs806381 and increased anthropometric measurements were
203 found only in adult subjects [35,36]. Ageing leads to reductions in ligand binding [37] and coupling
204 between the CB_1 receptor and its G-protein [38], which may account for the delayed onset of
205 increases in body weight parameters in some populations. There may also be an impact of
206 gender in these data. Male carriers of the mutant alleles of CNR1 polymorphisms rs1049353 and
207 rs806368 have an increased likelihood of obesity [14,16]. Similarly, the associations between the
208 CNR2 polymorphism rs3123554 and lower BMI, weight and body fat percentage were reported in
209 female subjects [21]. Gender differences in feeding behaviour have been previously observed in
210 animal models [39]. This may be explained by the action of oestrogen, which uncouples CB
211 receptors from their effector systems in synaptic terminals, reducing the effect of cannabinoids

[40]. Higher oestrogen levels in non-pregnant females may therefore contribute to these gender-specific findings.

In conclusion, associations between the mutant allele of the CB_1 SNP rs1049353 and decreased fat mass, weight and BMI indicate that this SNP is an important contributor to alterations in metabolism. Evidence points to decreased receptor functionality affecting normal pathways of adipogenesis and energy regulation. Its effects also extend to improvements in lipid levels and parameters of glucose metabolism. The mutant allele of FAAH polymorphism rs324420 was associated with increased BMI and triglyceride levels, possibly caused by decreased enzyme activity and overactivation of the ECS. Other SNPs had varying associations but often presented conflicting results. These findings represent therapeutic targets for the management of obesity and hyperlipidaemia, and assessment of patients for these genetic changes would provide an opportunity to give personalised treatment for a proportion of patients. Further studies in populations of varying demographics are needed to investigate the role that other SNPs play in adiposity and glucose metabolism, as well as genetic studies to determine the molecular changes of SNPs responsible for alterations in function.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work was partly supported by the Biotechnology and Biological Sciences Research Council (Grant number BB/I024291/1).

References:

1. O'Keefe L., Simcocks AC., Hryciw DH, Mathai ML, McAinch AJ. The cannabinoid receptor 1 and its role in influencing peripheral metabolism. *Diabetes, Obesity and Metabolism.* 2014;16:294-304.
2. Greenbaum L, Tegeder, I., Barhum, Y., Melamed, E., Roditi, Y. and Djaldetti, R. . Contribution of genetic variants to pain susceptibility in Parkinson disease. *European Journal of Pain.* 2012;16(9):1243-1250.
3. Russo P, Strazzullo, P., Cappuccio, F. P., Tregouet, D. A., Lauria, F., Loguercio, M., Barba, G., Versiero, M. and Siani, A. Genetic variations at the endocannabinoid type 1 receptor gene (CNR1) are associated with obesity phenotypes in men. *Journal of Clinical Endocrinology & Metabolism.* 2007;92(6):2382-2386.
4. Miguel-Yanes J, Manning, A., Shrader, P., McAteer, J., Goel, A., Hamsten, A., Fox, C., Florez, J., Dupuis, J. and Meigs, J. . Variants at the Endocannabinoid receptor CB1 Gene (CNR1) and insulin sensitivity, type 2 diabetes, and coronary heart disease. *Obesity.* 2011;19(10):2031-2037.
5. NCBI. dbSNP. 2018; https://www.ncbi.nlm.nih.gov/projects/SNP/. Accessed 7/2/2018, 2018.
6. Higgins JP AD, Gotzsche PC, Juni P, Moher D, Oxman AD,. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011.
7. Gazzerro P, Caruso, M., Notarnicola, M., Misciagna, G., Guerra, V., Laezza, C. and Bifulco, M. Association between cannabinoid type-1 receptor polymorphism and body mass index in a southern Italian population. . *International journal of obesity.* 2007;31(6):908-912.
8. de Luis D, Ovalle, H., Soto, G., Izaola, O., de la Fuente, B. and Romero, E. . Role of Genetic Variation in the Cannabinoid Receptor Gene (CNR1) (G1359A Polymorphism) on Weight Loss and Cardiovascular Risk Factors After Liraglutide Treatment in Obese Patients With Diabetes Mellitus Type 2. *Journal of Investigative Medicine.* 2014;62(2):324-327.
9. Hu WC, Feng P., G1359A polymorphism in the cannabinoid receptor-1 gene is associated with metabolic syndrome in the Chinese Han population. *Archives of medical research.* 2010;41(5):378-382.
10. Liu R, Zhang Y. G1359A polymorphism in the cannabinoid receptor-1 gene is associated with coronary artery disease in the Chinese Han population. *Clin Lab.* 2011;57(9-10):689-693.
11. Gazzerro P, Caruso, M., Notarnicola, M., Misciagna, G., Guerra, V., Laezza, C. and Bifulco, M. Association between cannabinoid type-1 receptor polymorphism and body mass index in a southern Italian population. *International journal of obesity.* 2007;31(6):908-912.
12. Wang R., Hu W., Qiang L. G1359A polymorphism in the cannabinoid receptor-1 gene is associated with the presence of coronary artery disease in patients with type 2 diabetes. *Journal of Investigative Medicine.* 2012;60(1):44-48.
13. Frost M, Nielsen, T., Wraae, K., Hagen, C., Piters, E., Beckers, S., De Freitas, F., Brixen, K., Van Hul, W. and Andersen, M. . Polymorphisms in the endocannabinoid receptor 1 in relation to fat mass distribution. . *European Journal of Endocrinology.* 2010;163(3):407-412.

14. Peeters A, Beckers, S., Mertens, I., Van Hul, W. and Van Gaal, L. The G1422A variant of the cannabinoid receptor gene (CNR1) is associated with abdominal adiposity in obese men. *Endocrine.* 2007;31(2):138-141.
15. Col Araz N, Nacak, M., Oguzkan Balci, S., Benlier, N., Araz, M., Pehlivan, S., Balat, A. and Aynacioglu, A. Childhood Obesity and the Role of Dopamine D2 Receptor and Cannabinoid Receptor-1 Gene Polymorphisms. *Genetic Testing and Molecular Biomarkers.* 2012;16(12):1408-1412.

For full list of references, please refer to the Appendix section online.

Table 1. Associations found between single nucleotide polymorphisms and metabolic and anthropometric parameters.

Polymorphism	Gene	Nucleotide change	Nucleotide position	Region of gene	Amino acid change	Amino acid position	Associations
rs1049353	CNR1	G>A	1359	Exon	Thr>Thr	453	**Positive**: • Homozygosity for mutant allele associated with increased WHR and WC in obese men only.[14] • Mutant allele associated with higher fat in post-menopausal women.[43] • Mutant allele associated with increased BMI in T2DM subjects.[44] • Wild-type allele associated with higher $HOMA_{IR}$.[45] • Mutant allele group associated with greater weight loss and decrease in BMI. [46] • Mutant allele associated with childhood obesity.[47] **Negative**: • Mutant allele associated with lower glucose.[46] • Mutant allele associated with lower insulin. [22,39,48] • Mutant allele with lower BMI.[10,11,12,14,31] • Mutant allele with lower $HOMA_{IR}$, TGs.[9,10,12,14,23,24,29,30]
rs806368	CNR1	T>C	4895	Intron	-	-	**Positive:** • Mutant allele associated with increased WHR.[47] • Mutant allele associated with increased TGs.[49] • Mutant allele associated with increased BMI, WC and obesity.[16]
rs324420	FAAH	C>A	385	Exon	Pro>Thr	129	**Positive:** • Mutant allele associated with higher insulin and $HOMA_{IR}$ in patients without MetS.[50] • Homozygosity for mutant allele associated with increased BMI.[17] • Mutant allele associated with obesity.[19,20] • Wild-type allele associated with childhood obesity.[51] • Mutant allele associated with increased TGs.[32] **Negative:** • Mutant allele associated with lower TGs, glucose and $HOMA_{IR}$ levels.[28,44] • Mutant allele associated with better percentage weight loss 9 months and 1 year after bariatric surgery, but not after 3 months.[52] • Lower insulin and $HOMA_{IR}$ in mutant-type group. Mutant allele associated with greater decreases in weight and WC than wild-type following hypocaloric diet. Mutant allele also associated with greater decreases in glucose, $HOMA_{IR}$ and TGs.[27] • Wild-type allele associated with lower WC, BMI, $HOMA_{IR}$ and TGs in subjects with MetS.[53] • Mutant allele associated with lower insulin, glucose and $HOMA_{IR}$ values.[54]

Abbreviations: CNR1, cannabinoid receptor gene 1; FAAH, fatty acid amide hydrolase; WC, waist circumference; WHR, waist-to-hip ratio; BMI, body mass index; TGs, triglycerides; $HOMA_{IR}$, homeostatic model assessment of insulin resistance; TNF-α, tumour necrosis factor α; MetS, metabolic syndrome; T2DM, Type 2 Diabetes Mellitus.

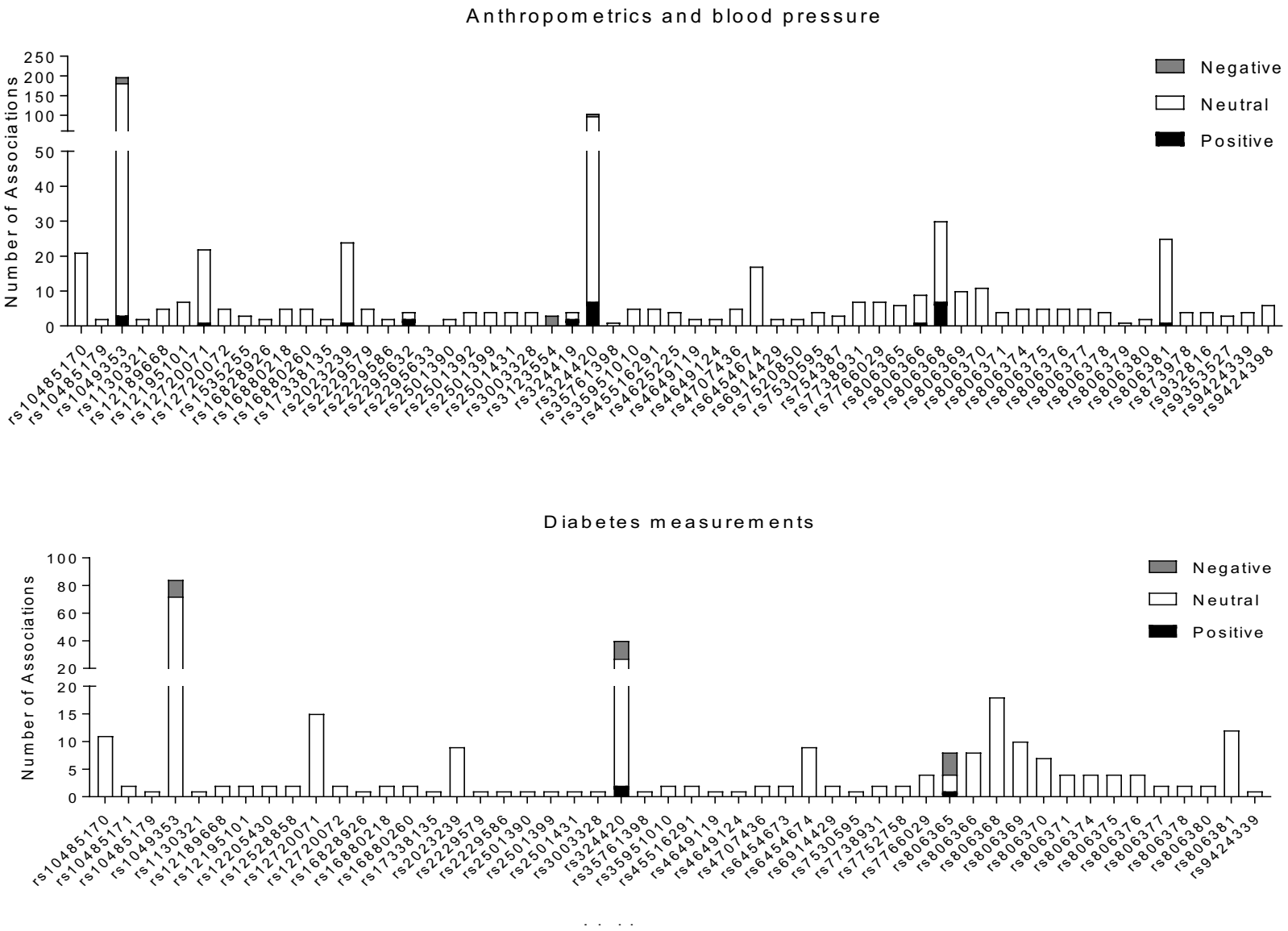

Figure 1. Number of associations found between ECS polymorphisms and anthropometric and diabetic parameters.

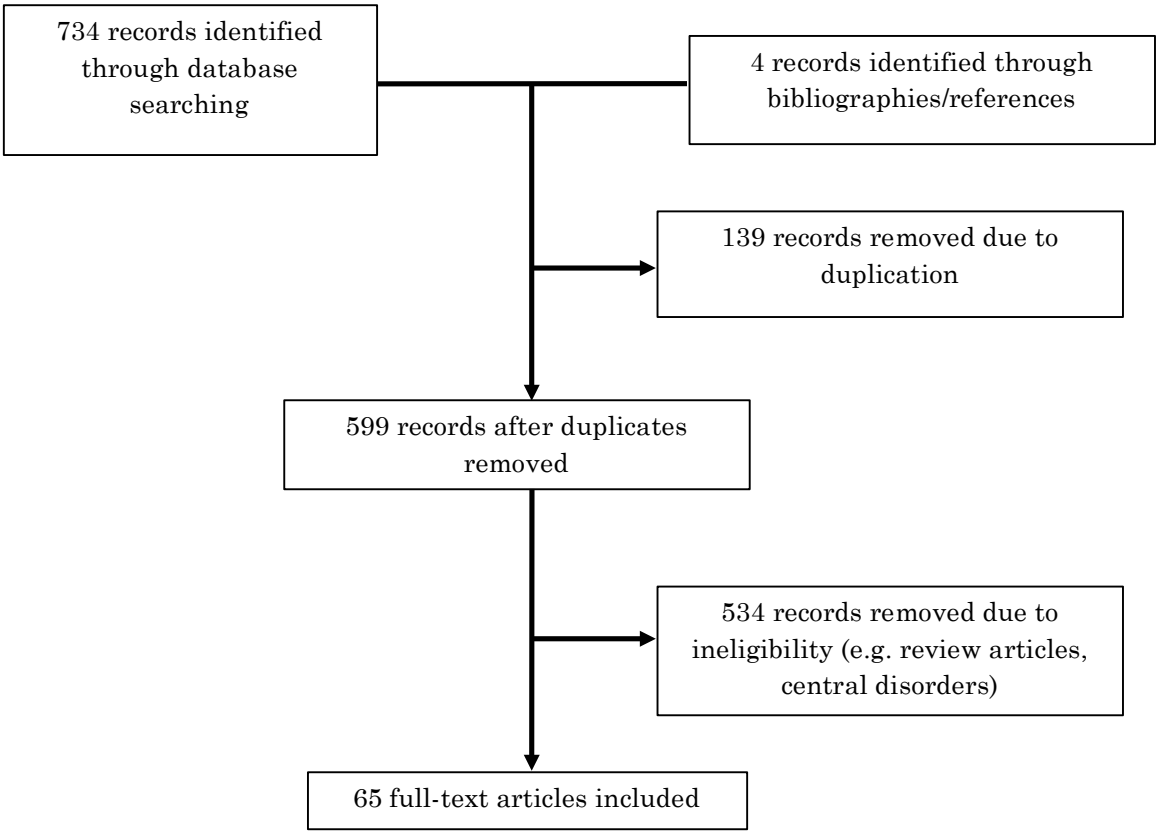

Figure S1: Summary of search results and exclusions

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Aberle J., et al 2008	◦	◦	–	+	+	+	◦
Aberle J., et al 2007	◦	◦	–	+	◦	+	◦
Aller et al. 2012	◦	◦	+	+	◦	+	◦
Baye T., et al 2008	+	◦	+	+	◦	+	◦
Bellini G., et al 2015	+	◦	+	+	◦	+	◦
Benzinou M., et al 2008	+	◦	+	+	+	◦	+
Bordicchia M., et al 2010	◦	◦	+	+	+	+	+
Buraczynska M., et al 2014	◦	◦	+	◦	◦	◦	+
Caruso M., et al 2012	+	◦	+	+	◦	◦	◦
Chmelikova M., et al 2014	+	◦	+	+	+	+	+
Col Araz N., et al 2012	+	◦	+	◦	+	◦	◦
de Luis D., et al 2009	◦	◦	+	◦	+	+	+
de Luis D., et al 2010a	◦	◦	+	+	+	+	+
de Luis D., et al 2010b	+	◦	+	+	+	+	◦
de Luis D., et al 2010c	+	◦	+	+	+	+	+
de Luis D., et al 2010d	+	◦	+	+	+	+	◦
de Luis D., et al 2011a	+	◦	–	–	+	+	+
de Luis D., et al 2011b	◦	◦	+	+	+	+	◦
de Luis D., et al 2011c	+	◦	+	+	+	+	◦
de Luis D., et al 2011d	◦	◦	+	+	+	◦	◦
de Luis D., et al 2011e	◦	◦	–	+	+	◦	◦
de Luis D., et al 2012	+	◦	+	+	+	◦	◦
de Luis D., et al 2013	+	◦	–	–	+	◦	◦
de Luis D., et al 2014	+	◦	+	◦	+	◦	◦
de Luis D., et al 2015a	+	◦	–	–	+	+	◦
de Luis D., et al 2015b	+	◦	+	+	+	◦	◦
de Luis D., et al 2015c	+	◦	+	+	+	◦	◦
de Luis D., et al 2017	+	◦	+	+	+	◦	+
de Miguel-Yanes J., et al 2011	◦	◦	+	◦	+	+	◦
Dinu I., et al 2009	◦	◦	+	+	+	+	◦
Durand E., et al 2008	◦	◦	+	◦	+	+	◦
Feng Q., et al 2010	◦	◦	+	◦	+	+	◦
Feng Q., et al 2013	◦	◦	+	+	+	+	◦
Frost M., et al 2010	+	◦	+	+	+	+	◦
Gazzerro P., et al 2007	◦	◦	+	◦	+	+	◦
Grolmusz VK., et al 2013	+	◦	+	◦	+	+	+
Hu W., et al 2010	+	◦	+	+	+	+	◦
Jaeger JP., et al 2008	+	◦	◦	◦	+	+	◦
Jensen DP., et al 2007	+	◦	+	+	+	+	+
Ketterer C., et al 2014	◦	◦	+	+	+	+	+
Knoll N., et al 2012	+	◦	+	+	+	◦	◦
Laczmanski L., et al 2011	◦	◦	+	◦	+	+	+
Lenarcik-Kabza A., et al 2014	+	◦	+	◦	+	+	+
Lieb W., et al 2009	◦	◦	+	+	+	+	+
Liu R., et al 2011	◦	◦	+	+	◦	◦	+
Martins C., et al 2015	◦	◦	◦	◦	+	+	◦
Milewicz A., et al 2010	◦	◦	+	+	+	+	+
Monteleone P., et al 2008	◦	◦	+	◦	+	+	+
Muller TD., et al 2007	+	◦	+	+	+	+	+
Muller TD., et al 2010	+	◦	◦	+	+	+	◦
Mutombo PB., et al 2011	◦	◦	+	+	+	+	+
Papazoglou D., et al 2008	◦	◦	–	+	+	+	+
Peeters A., et al 2007	◦	◦	+	+	+	◦	◦
Reinhard W., et al 1998	+	◦	+	+	+	+	+
Russo P., et al 2007	◦	◦	◦	◦	+	+	◦
Schleinitz D., et al 2010	◦	◦	+	+	+	+	+
Sipe JC., et al 2005	+	◦	+	+	+	+	+
Suarez-Pinilla P., et al 2015	◦	◦	–	+	◦	◦	+
Tiwari et al., 2010	◦	◦	+	+	◦	◦	+
Vazquez-Roque M., et al 2011	+	◦	+	+	+	◦	+
Wang L., et al 2003	+	◦	+	+	+	+	+
Wang R., et al 2012	+	◦	+	+	+	◦	+
Wangensteen T., et al 2010	◦	◦	◦	+	+	◦	◦
Zhang Y., et al 2009	+	◦	–	+	+	+	◦
Zhuang M., et al 2012	◦	◦	◦	+	+	+	◦

Figure S2: Results of Risk of Bias assessment for included studies

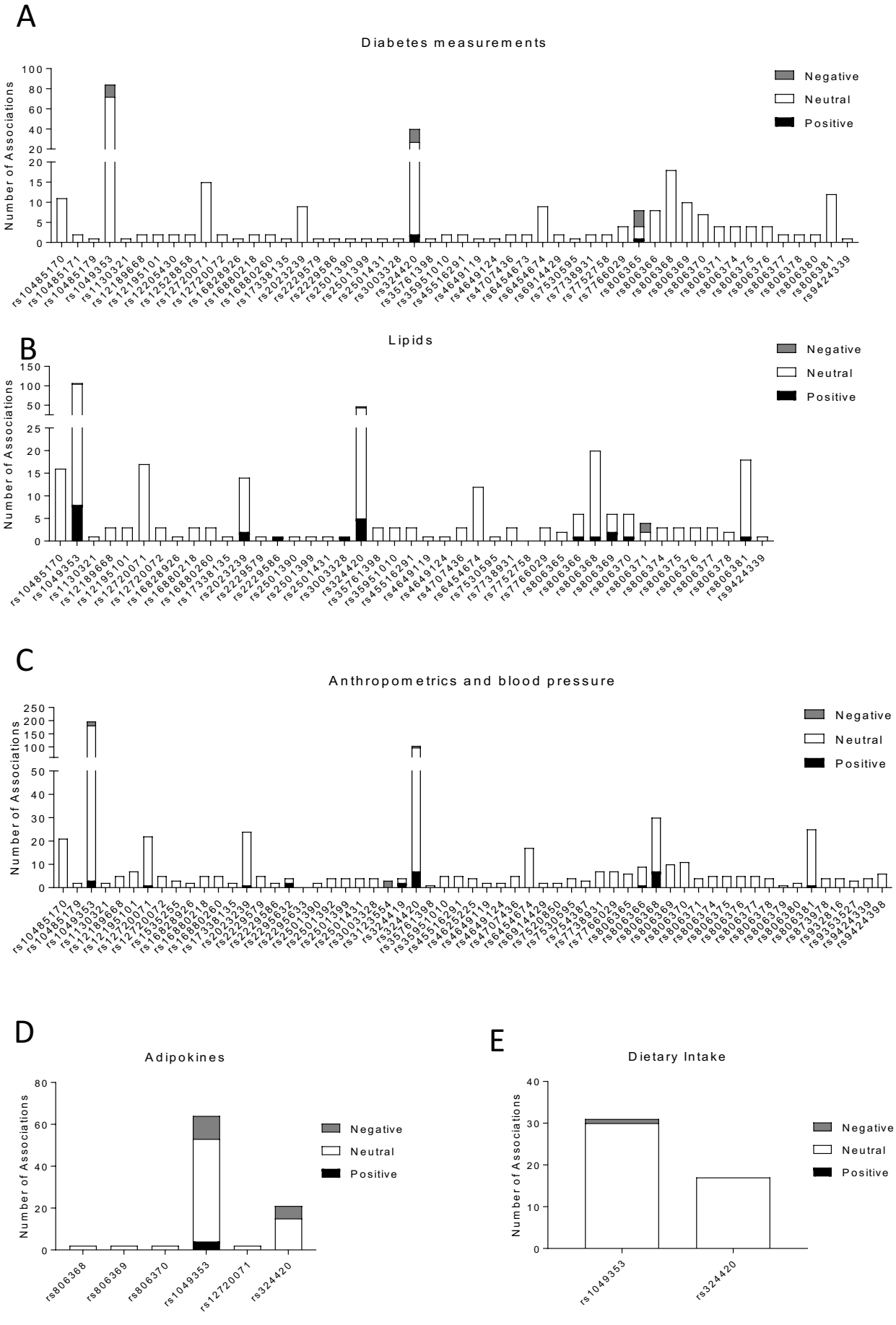
A
Diabetes measurements
Number of Associations
Negative
Neutral
Positive
B
Lipids
C
Anthropometrics and blood pressure
D
Adipokines
E
Dietary Intake

Table S1. Associations found between single nucleotide polymorphisms and metabolic and anthropometric parameters.

Polymorphism	Gene	Nucleotide change	Nucleotide position	Region of gene	Amino acid change	Amino acid position	Associations
rs10485170	CNR1	A>G	-	-	-	-	**Neutral:** • No association with anthropometric measurements (weight, BMI, WC, WHR), biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, HOMAir).[82] • No association with anthropometric measurements (weight, BMI, WC, total fat (g), fat (%), android fat deposit, biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, fasting insulin resistance index) in postmenopausal women.[43,91] • No association with antipsychotic-induced weight gain.[92]
							Positive: • Homozygosity for mutant allele associated with increased WHR and WC in obese men only.[14] • Mutant allele associated with higher android fat deposit and percentage of android fat in post-menopausal women.[43] • Mutant allele associated with increased BMI in T2DM subjects.[74] • Mutant allele associated with higher adiponectin and visfatin levels. Wild-type group had higher HOMAir, TNFa and resistin.[66] • Mutant allele associated with higher adiponectin levels.[75] • After 3 months' diet, mutant allele group associated with greater weight loss, decrease in BMI, and decrease in LDL.[81] • Homozygosity for mutant allele associated with increased cholesterol levels.[80] • Mutant allele associated with childhood obesity.[15] • Mutant allele associated with higher HDL-C.[29,10] • Mutant allele associated with lack of decrease in leptin following hypocaloric diet.[76]
rs1049353	CNR1	G>A	1359	Exon	Thr>Thr	453	**Neutral**: • No association with BMI.[16,35,64,69] • No association with BMI, weight, WC, WHR, glucose, total cholesterol, LDL, HDL, TG, IL-6, or leptin.[66,81] • No association with BMI, cholesterol, LDL-C, HDL-C.[85] • No association with TC, HLD-C, LDL-C.[24] • No association with anthropometric parameters (BMI, weight, fat free mass (kg), fat mass (kg), WC, WHR, SBP, DBP, RMR).[23,30,47,49] • No association with anthropometric parameters (BMI, weight, fat free mass (kg), fat mass (kg), WC, WHR, SBP, DBP, RMR), dietary intake (energy (kcal/day), carbohydrates (g/day), fat (g/day), protein (g/day)) and exercise (hrs/week) or adipocytokines ((IL-6), TNF-a, adiponectin, resistin, leptin).[29,46,68,71,84] • No associations with total body fat mass, BMI, WHR, abdominal and femoral subcutaneous fat mass or any biochemical markers (n=7).[13] • No association with glucose, total cholesterol, LDL-C, HDL-C, TGs, lipoprotein (a), insulin, HOMAir CRP.[8] • No association with BMI, weight, fat mass, WC, WHR, SBP, DBP, glucose, LDL-C, TC, insulin or HOMAir.[31] • No association with T2DM.[74]

							• No association with glucose, TC, LDL-C, HDL-C, TGs, lipoprotein (a), insulin, HOMAir, CRP.[46,68] • No association with glucose, TC, LDL-C, CRP, lipoprotein (a).[29] • No association with glucose, TC, LDL-C, insulin, HOMAir, CRP, dietary intake.[30] • No association with SBP, DBP, TC, HDL-C or LDL-C.[9] • No difference between basal and post-diet anthropometric measurements or cardiovascular risk factors.[76] • No difference in decrease in BMI, weight, fat mass, fat free mass, WC, WHR, SBP, DBP, glucose, HDL-C, TGs or insulin between wild- or mutant-type group following treatment with liraglutide.[8] • No association with carbohydrate, fat, m-fat, p-fat, protein or fibre intake.[31] **Negative**: • Mutant allele associated with lower glucose.[81] • Mutant allele with lower BMI.[10,11] • Mutant allele with lower HOMAir, TGs.[10] • Mutant allele associated with lower weight, BMI, fat mass [8], WC, insulin, HOMAir and CRP.[24] • Mutant allele associated with lower BMI, SBP, HOMAir and CRP and higher HDL-C. [12] Lack of improvement in cholesterol, glucose, insulin, TGs, HOMAir and leptin compared with wild-type group following hypocaloric diet.[84] • Mutant allele with lower TGs, insulin and HOMAir values.[29] • Mutant allele with decreased resistin, leptin and IL-6 following weight loss.[46] • Mutant allele with decreased glucose, insulin, HOMAir and incidence of MetS.[23] • Mutant allele with better improvements in HOMAir following treatment with liraglutide.[8] • Mutant allele with lower TGs and higher HDL-C.[30] • Mutant-type group associated with lower TGs and higher HDL-C, and lower cholesterol and saturated fat intake.[31] • Mutant allele with decreased dietary cholesterol and saturated fats.[93] • Mutant allele associated with lower BMI, WC, HOMAir, TG levels and prevalence of MetS.[9]
rs12720071	CNR1	A>G	3813	3 Prime Untranslated Region (3' UTR)[ˆ]	-	-	Positive: • Mutant allele associated with increased WC and subscapular skinfold thickness.[3] Neutral: • No association with anthropometric (weight, height, BMI, WHR, WC) or biochemical (HDL-C, LDL-C, TGs, glucose) measurements.[47,49] • No association with Anthropometric measurements (weight, BMI, WC, total fat (g), fat (%), android fat deposit, biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, FIRI)[8] • No association with BMI, WC, TC, HDL-C, LDL-C, TGs, glucose, SBP, DBP, MBP.[88] • No association with impaired glucose metabolism.[73] • No association with HOMAir, insulin, glucose.[4] • No associations with BMI, WC or visceral adipose tissue.[64]
rs2023239	CNR1	C>T	5489	Intron	-	-	Positive: • Mutant allele associated with higher BMI.[36] Neutral • No association with obesity.[35,69]

							• No association with anthropometric measurements (weight, BMI, WC, total fat (g), fat (%), android fat deposit, biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, fasting insulin resistance index).[87,91] • No association with anthropometric measurements (BMI, WC, WHR, SBP, DBP) and biochemical (TC, TGs).[94]
rs6454674	CNR1	G>T	-	-	-	-	Neutral • No association with anthropometric measurements (weight, BMI, WC, WHR), biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, HOMAir).[43,82,91]
rs806365	CNR1	C>T	-	-	-	-	Positive: • Mutant allele with increased BMI and TGs.[49] Neutral • No association with glucose.[4] • No association with anthropometric measurements (BMI, obesity, WC, central obesity, SBP, DBP, hypertension) and metabolic variables (HDL-C, LDL-C, TGs, HbA1c, T2DM).[16] • No associations with BMI, waist circumference or visceral adipose tissue.[64] • No association with WC, hip circumference, WHR), insulin responsiveness (insulin, glucose, insulin:glucose, HOMAir), lipids (TC, LDL-C, HDL-C).[49] Negative • Mutant allele with lower HOMAir and insulin levels.[4]
rs806366	CNR1	T>C	-	-	-	-	Positive: • Associated with increased BMI and TGs.[49] Neutral: • No association with HOMAir, glucose or insulin levels.[4] • No association with anthropometric measurements (BMI, obesity, WC, central obesity, SBP, DBP, hypertension) and metabolic variables (HDL-C, LDL-C, TGs, HbA1c, T2DM).[16] • No associations with BMI, waist circumference or visceral adipose tissue.[64]
rs806368	CNR1	T>C	4895	Intron	-	-	Positive: • Mutant allele associated with increased WHR.[47] • Mutant allele associated with increased TGs.[49] • Mutant allele associated with increased BMI, WC, SBP and obesity.[16] Neutral: • No association with weight, height, BMI, WC, HDL-C, LDL-C, TGs, glucose and lifestyle factors (n=3).[47] • No association with BMI [83], WC, subscapular skinfold thickness.[3] • No association with anthropometric measurements (weight, BMI, WC, WHR), biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, HOMAir).[43,82] • No association with HOMAir, glucose, insulin levels.[4] • No associations with BMI, waist circumference or visceral adipose tissue.[64]
rs806369	CNR1	C>T	-	Intron	-	-	Positive: • Mutant allele with increased TGs, TC.[49] Neutral • No association with BMI.[83]

							• No association with BMI, WC, hip circumference, WHR, insulin, glucose, insulin:glucose, HOMAir, LDL-C, HDL-C.[16,49] • No association with association with HOMAir, glucose and insulin levels.[4]
rs806370	CNR1	C>T	-	Intron	-	-	Positive: • Mutant allele with raised HDL-C.[49] Neutral: • No association with BMI.[35,83] • No association with BMI, WC, hip circumference, WHR, insulin, glucose, insulin:glucose, HOMAir, TC, LDL-C, TGs.[16,49]
rs806371	CNR1	G>T	-	Intron	-	-	Neutral: • No association with HOMAir, glucose, insulin levels.[4] • No association with anthropometric measurements (BMI, obesity, WC, central obesity, SBP, DBP, hypertension) and metabolic variables (HDL-C, LDL-C, TGs, HbA1c, T2DM)[16] • No associations with BMI, waist circumference or visceral adipose tissue.[64] Negative: • Mutant allele with lower HDL-C levels.[79]
rs806381	CNR1	A>G	10908	Intron	-	-	Positive: • Mutant allele with higher BMI.[36] Neutral: • No association with anthropometric measurements (weight, BMI, WC, WHR), biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, HOMAir). [13,43,82] • No association with BMI, WC, WHR, SBP, DBP, TC, TGs.[94] • No association with anthropometric measurements (Weight, BMI, WC, fat (%), android fat deposit, gynoid fat deposit, SBP, DBP) and biochemical measurements (TC, HDL-C, LDL-C, TGs, glucose, insulin, FIRI).[91]
rs10485179	CNR1		-	Intron	-	-	• No association with obesity-related or glucose metabolism parameters.[13]
rs35761398	CNR2	A>G	188	Exon	Gln>Arg	63	• No association with BMI, HOMAir, TC, HDL-C or TG levels.[95]
rs3123554	CNR2	G>A	-	-	-	-	Positive: • Mutant-type group had higher BMI, weight, fat mass, WC TGs, insulin and HOMAir than wild-type group.[26] Neutral: • No difference in dietary intake between genotypes.[26] Negative: • Mutant allele associated with lower BMI, weight and body fat in women. Carriers also lost less weight following lifestyle interventions.[21]
rs324419	FAAH	A>G	895	Exon	Ala>Ala	275	Neutral: • No association with obesity.[51] • No association with BMI, waist circumference or visceral adipose tissue.[64]
rs324420	FAAH	C>A	385	Exon	Pro>Thr	129	Positive: • Mutant allele associated with higher insulin and HOMAir in patients without MetS.[50] • Homozygosity for mutant allele associated with increased BMI.[17] • Mutant allele associated with obesity.[19]

	• Wild-type allele associated with childhood obesity.[51] • Wild-type genotype associated with class III adult obesity.[20] • Mutant allele associated with increased HDL-C.[20] • Wild-type allele associated with higher HDL-C levels in subjects with MetS.[53] • Mutant allele associated with increased TGs.[32] Neutral: • No association with BMI.[96] • No differences in cholesterol levels between genotypes.[80] • No association with anthropometric measurements[18,28] or dietary intake.[28,44] • No differences in anthropometric, metabolic parameters or adipocytokines between genotypes ir MetS or non-MetS subjects.[50] • No association with BMI, WC, WHR, glucose, insulin, C-peptide, HOMAir, TGs, TC.[72] • No association with binge-eating disorder.[19] • No association with child obesity or T2DM.[20] • No association with BMI, waist circumference or visceral adipose tissue.[64] • No association with SBP, DBP, TC or LDL-C levels.[53] • No association with BMI, weight, TC, LDL-C, HDL-C, TGs, glucose, insulin, HOMAir, SBP, DBP.[48] Negative: • Mutant allele associated with greater decrease in TGs and total cholesterol following low fat diet.[85] • Mutant allele associated with lower TGs, glucose, HOMAir and IL-6 levels.[44] • Mutant allele associated with lower glucose, insulin, HOMAir and visfatin levels.[28] • Mutant allele associated with better percentage weight loss 9 months and 1 year after bariatric surgery, but not after 3 months.[52] • Lower insulin, HOMAir and CRP in mutant-type group. Mutant allele associated with greater decreases in weight and WC than wild-type following hypocaloric diet. Mutant allele also associated with greater decreases in glucose, TC, LDL-C, HOMAir, CRP and TGs.[27] • Mutant allele associated with lower adiponectin levels and higher AEA levels.[42] • Wild-type allele associated with lower WC, BMI, HOMAir and TGs in subjects with MetS.[53] • Mutant allele associated with lower insulin, glucose and HOMAir values.[54] • Mutant allele associated with reduced levels of HDL-C.[32]

Abbreviations: CNR1, cannabinoid receptor gene 1; CNR2, cannabinoid receptor gene 2; FAAH, fatty acid amide hydrolase; WC, waist circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; RMR, resting metabolic rate; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TGs, triglycerides; $HOMA_{IR}$, homeostatic mode assessment of insulin resistance; FIRI, fasting insulin resistance index; IL-6, interleukin-6; CRP, C-reactive protein; m-fat, monounsaturated fat; p-fat, polyunsaturated fat; MetS, metabolic syndrome; T2DM, Type 2 Diabetes Mellitus.

Supplemental Table S2. All included studies and associations with anthropometric and/or blood measurements of adiposity and glucose metabolism

Study	N	M/F	Population	Endpoint	Polymorphism	Main findings	Association summary
Aller et al. 2012 [66]	71	47/23	NAFLD	Body weight, Insulin resistance, adipokines	rs1049353	No differences for: BMI, weight, WC, WHR, glucose, total cholesterol, LDL, HDL, TG, IL-6, or leptin. Mutant-type group had higher adiponectin and visfatin levels. Wild-type group had higher HOMAir, TNFa and resistin.	Neutral = 11 Positive = 2 Negative = 3
Aberle et al. 2008 [81]	1,721	688/1033	BMI >25 kg/m^2	Body weight parameters, cholesterol, insulin and glucose	rs1049353	At baseline no differences in weight, BMI, TG, total cholesterol, HDL, LDL. Glucose was higher in wild-type. After 3 months' diet, mutant allele group associated with greater weight loss, decrease in BMI, and decrease in LDL. No differences between groups in change in glucose, TGs, cholesterol or HDL.	Neutral = 10 Negative = 4
Chmelikova et al. 2014 [80]	155	Not reported	Chronic heart failure	Cholesterol	rs1049353 rs324420	Homozygosity for mutant allele was associated with increased cholesterol levels No differences in cholesterol levels between groups	Positive = 1 Neutral = 1
Col Araz et al. 2012 [15]	200		Obese children	BMI	rs1049353	Mutant allele associated with childhood obesity	Positive = 1
de Luis et al. 2009 [24]	66	17/49	Morbidly obese	Anthropometric parameters (n=9), cardiovascular risk factors (n=8) and adipocytokines (n=5).	rs1049353	Mutant allele associated with lower weight, BMI, fat mass, WC, insulin, HOMAir and CRP. No differences detected between groups for other parameters (n=10).	Negative = 7 Neutral = 10
de Luis et al. 2010a [68]	60	14/46	Diabetic	Anthropometric parameters (n=9), cardiovascular risk factors (n=9) dietary intake (n=9) and adipocytokines (n=5).	rs1049353	No association with anthropometric parameters (n=9), cardiovascular risk factors (n=9) dietary intake (n=9) or adipocytokines (n=5).	Neutral = 32
de Luis et al. 2011a [84]	249	56/193	BMI>30 kg/m^2	Anthropometric parameters (n=10), cardiovascular risk factors (n=8) and adipocytokines (n=5).	rs1049353	No association with basal or post-treatment anthropometric or biochemical variables in either wild- or mutant-type group (n=46) No difference in effect of either diet on anthropometric variables (n=20) No difference in effect of either diet on glucose, TC, insulin and HOMAir values between mutant- or wild-type group. No improvement of mutant-type group in cholesterol, glucose, insulin, TG, HOMAir and leptin values compared with wild-type group following either diet.	Neutral = 74 Negative = 12
de Luis et al. 2011b [29]	290	0/290	BMI>30 kg/m^2	Anthropometric variables (n=9), cardiovascular risk factors (n=9), dietary intake	rs1049353	No association with anthropometric variables (n=9), dietary intake (n=9) or adipocytokines (n=5) Mutant allele associated with better cardiovascular profile (lower TGs, insulin and HOMAir, higher HDL)	Neutral = 28 Positive = 1 Negative = 3

				(n=9) and adipocytokines (n=5)		No association with glucose, TC, LDL-C, CRP, lipoprotein (a).	
de Luis et al. 2011c [46]	94	24/70	BMI>30 kg/ m^2	Anthropometric variables (n=9), cardiovascular risk factors (n=9), dietary intake (n=5) and adipocytokines (n=5)	rs1049353	No difference in basal and post-treatment anthropometric measurements (n=18), cardiovascular risk factors (n=18), dietary intake (n=5) or cytokines (n=5) between the two genotypes Mutant allele associated with decreased resistin, leptin and IL-6 following weight loss	Neutral = 46 Negative = 3
de Luis et al. 2011d [23]	917	Not reported	BMI>30 kg/ m^2	Anthropometric variables (n=7), biochemical variables (n=7) and adipocytokines (n=3)	rs1049353	Mutant allele associated with lower glucose, insulin and HOMAir values and decreased prevalence of metabolic syndrome	Negative = 4 Neutral = 28
de Luis et al. 2013 [76]	258	64/194	BMI>30 kg/ m^2 subject to one of two hypocaloric diets	Anthropometric variables (n=7), cardiovascular risk factors (n=8) and adipocytokines (n=5)	rs1049353	No difference between basal and post-treatment anthropometric measurements (n=14), cardiovascular risk factors (n=16) or adipocytokines (n=8) Mutant allele associated with lack of decrease in leptin following both diets.	Neutral = 38 Positive = 2
de Luis et al. 2014 [8]	86	44/42	BMI>30 kg/ m^2 with T2DM, given liraglutide	Anthropometric variables (n=8), cardiovascular risk factors (n=8)	rs1049353	BMI, weight, fat mass and WC higher in wild-type group pre- and post-treatment. No difference in biochemical parameters (n=8) pre-treatment No difference in decrease in BMI, weight, fat mass, fat free mass, WC, WHR, SBP, DBP, glucose, HDL-C, TGs or insulin between wild- or mutant-type group following treatment Wild-type allele associated with better improvements in LDL-C and TC Mutant allele associated with better improvements in HOMAir levels following treatment.	Neutral = 17 Positive = 2 Negative = 5
de Luis et al. 2015a [71]	190	57/133	European	BMI, weight, fat mass, WC, WHR, SBP, DBP Glucose. TC. LDL-C, HDL-C, TGs, insulin, HOMAir, CRP. Adiponectin, resistin, leptin. Measured at baseline, 3 months and 9 months following diet.	rs1049353	No association with any measured parameters.	Neutral = 54
de Luis et al. 2015b [30]	341	120/221	BMI>30 kg/ m^2	Anthropometric variables (n=8), cardiovascular risk factors (n=8) and dietary intake (n=9)	rs1049353	No associations with anthropometric variables (n=8) Mutant-type group associated with lower TGs and higher HDL-C No associations with glucose, TC, LDL-C, insulin, HOMAir, CRP or dietary intake measurements (n=9)	Neutral = 24 Positive = 1 Negative = 1

de Luis et al. 2015c [31]	896	0/896	Female, BMI>30 kg/m^2	Anthropometric variables (n=7), cardiovascular risk factors (n=7)	rs1049353	No association with BMI, weight, fat mass, WC, WHR, SBP, DBP, glucose, LDL-C, TC, insulin or HOMAir. No association with energy, carbohydrate, fat, monounsaturated fat, polyunsaturated fat, protein or fibre intake. Mutant-type group associated with lower TGs and higher HDL-C, and lower cholesterol and saturated fat intake.	Neutral = 19 Positive = 1 Negative = 3
Dinu et al. 2011 [75]	305	-	Romanian, 35-75 years	Adiponectin	rs1049353	Mutant allele associated with higher adiponectin levels	Positive = 1
Gazzerro et al. 2007 [11]	419	237/182	Italian, >65 years	BMI	rs1049353	Mutant allele associated with lower BMI	Negative = 1
Hu et al. 2010 [9]	518	209/173	Chinese Han	BMI, WC, SBP, DBP, HOMAir, TGs, TC, HDL-C, LDL-C	rs1049353	Mutant allele associated with lower BMI, WC, HOMAir, TG levels and prevalence of MetS. No association with SBP, DBP, TC, HDL-C or LDL-C	Neutral = 5 Positive = 1 Negative = 4
Muller et al. 2007 [35]	2,595	768/1827	BMI>30 kg/m^2	BMI	rs1049353 rs1535255 rs2023239 rs6454676 rs754387 rs806370 rs806379 rs9353527	No association with obesity for any polymorphism studied	Neutral = 8
Peeters et al. 2007 [14]	1,064	455/568	BMI>30 kg/m^2	WC, WHR, fat mass (kg), fat mass (%)	rs1049353	Homozygosity for mutant allele associated with increased WHR and WC in obese men only. No other associations	Neutral = 6 Positive = 2
Aberle et al. 2007 [85]	451	264/187	BMI>30 kg/m^2	BMI, TGs, cholesterol, LDL-C, HDL-C, VLDL-C, lipoprotein (a), glucose	rs1049353 rs324420	No associations with rs1049353 Mutant allele associated with greater decrease in TGs and total cholesterol following low fat diet	Neutral = 14 Negative = 2
Frost et al. 2010 [13]	783	783/0	Danish, 20-29 years, male	Body weight parameters (n=3) MRI measurements (n=4), biochemical markers (n=7)	rs1049353 rs10485179 rs806381	Wild-type allele associated with visceral and intermuscular fat mass, higher TGs. No associations with total body fat mass, BMI, WHR, abdominal and femoral subcutaneous fat mass or any biochemical markers (n=7) No association with rs10485179 or rs806381 for any endpoint (n=28)	Neutral = 41 Positive = 3
Jaeger et al. 2008 [47]	756	309/447	Caucasian	Anthropometric (weight, height, BMI, WHR, WC), biochemical (HDL-C, LDL-C, TGs, glucose) and lifestyle factors (n=3)	rs1049353 rs12720071 rs806368	No associations No associations rs806368 associated with increased WHR. No other associations.	Neutral = 35 Positive = 1
Reinhard et al. 2008 [97]	1,968	1,072/896	MI patients	Obesity, arterial hypertension, hypercholesterolaemia, T2DM.	rs4649119 rs3003328 rs1130321 rs2229586 rs2229579	rs3003328 and rs2229586 associated with hypercholesterolaemia. No other associations with any SNP and endpoint.	Neutral = 50 Positive = 2

					rs4649124 rs2501431 rs16828926 rs2501390 rs2501399 rs9424339 rs7530595 rs17338135		
Baye et al. 2008 [49]	1,560	Not reported	Obese and non-obese subjects	Anthropometric parameters (BMI, WC, hip circumference, WHR), insulin responsiveness (insulin, glucose, insulin:glucose, HOMAir), lipids (TC, LDL-C, HDL-C, TGs)	rs1049353 rs12730071 rs806366 rs806368 rs806369 rs806370	rs806366 associated with BMI and TGs rs806370 associated with HDL-C rs806369 associated with TGs, TC rs806368 associated with TGs No associations with obesity parameters, insulin responsiveness or lipid levels for rs1049353 or rs12720071 Haplotype H4 associated with higher BMI, insulin and lipids.	Neutral = 56 Positive = 9
Lenarcik-Kabza et al. 2014 [82]	130	0/130	Subjects with PCOS	Anthropometric measurements (weight, BMI, WC, WHR), biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, HOMAir)	rs1049353 rs10485170 rs2023239 rs6454674 rs806381 rs806368	Homozygosity for rs2023239 wild-type allele associated with higher TC and LDL-cholesterol in women with PCOS. No other associations. No association with anthropometric or biochemical measurements for any other polymorphism in study.	Neutral = 64 Positive = 2
Milewicz et al. 2010 [43]	348	0/348	Postmenopausal women	Anthropometric measurements (weight, BMI, WC, total fat (g), fat (%), android fat deposit, biochemical measurements (glucose, TC, HDL-C, LDL-C, TGs, insulin, fasting insulin resistance index)	rs1049353 rs10485170 rs12720071 rs2023239 rs6454674 rs806368 rs806381	rs1049353 associated with higher android fat deposit and percentage of android fat. No other associations. No associations for any other polymorphism.	Neutral = 89 Positive = 2
Bordicchia et al. 2010 [88]	280	Not reported	Obese hypertensive	BMI, WC, TC, HDL-C, LDL-C, TGs, glucose, SBP, DBP, MBP, MetS	rs12720071	Mutant allele associated with lower prevalence of metabolic syndrome. No other associations observed.	Neutral = 10 Negative = 1
Dinu et al. 2010 [73]	191	Not reported	Romanian, 35-75 years	Glucose	rs12720071	No association with impaired glucose metabolism	Neutral = 1
Russo et al. 2007 [3]	1,213	1,213/0	White adult male	BMI, WC, subscapular skinfold thickness	rs12720071 rs806368	Mutant allele associated with increased WC and subscapular skinfold thickness. No association.	Neutral = 4 Positive = 2

Schleinitz et al. 2010 [83]	2,774	Not reported	Two German cohorts	BMI, WHR, fat, glucose, insulin, leptin, adiponectin	rs1049353 rs12720071 rs806368 rs806369 rs806370	No associations observed.	Neutral = 35
Wangensteen et al. 2010 [22]	5,011	1,235/3,776	Norwegian Caucasian	BMI	**CB1**: rs1049353 rs12720071 rs806368 **NAPE-PLD**: rs13232194 rs17605251 rs11487077 rs12540583 rs6465903	Haplotype I (combination of alleles of rs13232194, rs17605251, rs11487077, rs12540583 and 6465903) protective against severe obesity	-
Benzinou et al. 2008 [36]	1,932	Not reported	Caucasian		rs2023239 rs806381	Mutant alleles of both polymorphisms associated with higher BMI	Positive = 2
Zhuang et al. 2012 [94]	2,812	0/2,812	Chinese female, 50-64 years	Anthropometric measurements (BMI, WC, WHR, SBP, DBP) and biochemical (TC, TGs)	rs2023239 rs806381	No association between rs2023239 and any anthropometric or biochemical measurements rs806381 mutant allele associated with increased TGs. No association with this allele and any anthropometric measurements.	Neutral = 13 Positive = 1
Laczmanski et al. 2011 [91]	348	0/348	Polish post-menopausal women	Anthropometric measurements (Weight, BMI, WC, fat (%), android fat deposit, gynoid fat deposit, SBP, DBP) and biochemical measurements (TC, HDL-C, LDL-C, TGs, glucose, insulin, FIRI).	rs10485170 rs2023239 rs6454674 rs806381	No associations with any polymorphism.	Neutral = 60
de Luis et al. 2010b [44]	279	0/279	Obese female	Anthropometric variables (n=9), cardiovascular (n=9) and dietary intake (n=9)	rs324420	No association with anthropometric measurements or dietary intake. Mutant allele associated with lower TGs, glucose, HOMAir and IL-6 levels	Neutral = 23 Negative = 4
de Luis et al. 2010c [28]	143	0/143	Obese female	Anthropometric variables (n=9), metabolic variables (n=9), dietary intake (n=9)	rs324420	No association with anthropometric measurements. Mutant allele associated with lower glucose, insulin, HOMAir and visfatin levels. No association with dietary intake.	Neutral = 23 Negative = 4
de Luis et al. 2010d [52]	67	16/51	BMI >40 kg/m^2, bariatric surgery patients	Anthropometric variables (n=6), metabolic variables (n=5)	rs324420	No differences between genotypes in baseline anthropometric measurements. Mutant allele associated with better percentage weight loss 9 months and 1 year after bariatric surgery, but not after 3 months.	Neutral = 32 Negative = 12

						No association with metabolic variables at baseline, 3 months, 9 months or 12 months.	
de Luis et al. 2011e [27]	122	33/89	BMI >30 kg/m^2	Anthropometric variables (n=9), cardiovascular (n=9) and dietary intake (n=5)	rs324420	Lower insulin, HOMAir and CRP in mutant-type group at baseline. Mutant allele associated with greater decreases in weight and WC than wild-type following hypocaloric diet. Mutant allele also associated with greater decreases in glucose, TC, LDL-C, HOMAir, CRP and TGs. No association with dietary intake measurements at baseline or 3 months.	Neutral = 35 Negative = 11
de Luis et al. 2012 [50]	799	248/551	BMI >30 kg/m^2	Anthropometric variables (n=7), metabolic variables (n=7) and adipocytokines (n=5)	rs324420	Mutant allele associated with higher insulin and HOMAir in patients without MetS. No differences in anthropometric, metabolic parameters or adipocytokines between genotypes in MetS or non-MetS subjects.	Neutral = 36 Positive = 2
de Luis D et al. 2017 [26]	1,027	280/747	BMI >30 kg/m^2	Anthropometric variables (n=5), cardiovascular (n=10) and dietary intake (n=9)	rs3123554	Mutant-type group had higher BMI, weight, fat mass, WC TGs, insulin and HOMAir than wild-type group. No difference in dietary intake between genotypes.	Neutral = 17 Positive = 7
Ketterer et al. 2014 [21]	2,006		Subjects at risk of T2DM	BMI, weight, WHR, total body fat (%)	rs3123554 rs2229579 rs2501392 rs9424398 rs4625225	rs3123554 mutant allele associated with lower BMI, weight and body fat in women. Carriers also lost less weight following lifestyle interventions No associations found with any other polymorphism.	Neutral = 17 Negative = 3
Jensen et al. 2007 [72]	5,738	2,887/2,851	Obesity	BMI, WC, WHR Glucose, insulin, C-peptide, HOMAir, TGs, TC	rs324420	No association with any measured parameters.	Neutral = 9
Martins et al. 2015 [42]	200	100/100	Normal/obese	Anthropometric measurements (n=6), metabolic variables (n=7), adipocytokines/endocannabinoids (n=7)	rs324420	Mutant allele associated with lower adiponectin levels and higher AEA levels. No other associations observed.	Neutral = 18 Negative = 2
Monteleone et al. 2008 [19]	189	0/189	Subjects with binge-eating disorder	Obesity, binge-eating disorder	rs324420	Mutant-allele associated with overweight and obesity, but not binge-eating disorder	Neutral = 1 Positive = 2
Muller et al. 2010 [51]	10,498	5,072/5,426	Obese children and adolescents, siblings and parents.	Obesity (childhood, adult)	rs324419 rs324420 rs2295632 rs873978	rs324420 wild-type allele associated with childhood obesity but not adult obesity.	Neutral = 7 Positive = 1

Sipe et al. 2005 [17]	2,667	Not reported	Caucasian, black and Asian subjects	BMI	rs324420	Homozygosity for mutant allele associated with increased BMI.	Positive = 1
de Miguel-Yanes et al. 2011 [25]	2,411	1,157/1,254	Caucasian	HOMAir, insulin, glucose.	rs10485171 **rs806365** rs7766029 **rs806366** rs806368 rs12720071 rs1049353 **rs806369** rs806371 rs806374 rs806375 rs806376 rs806380 rs7752758 rs12528858 rs12205430 rs6454673 rs6914429	rs806365 wild-type allele associated with higher HOMAir, but not glucose in initial testing. Those in bold underwent meta-analysis for association with HOMAir, glucose and insulin levels, with rs806365 being associated with HOMAir and insulin levels.	Neutral = 42 Negative = 4
Mutombo et al. 2011 [16]	1,452	678/774	Japanese, 25-74 years	Anthropometric measurements (BMI, obesity, WC, central obesity, SBP, DBP, hypertension) and metabolic variables (HDL-C, LDL-C, TGs, HbA1c, T2DM)	rs806368 rs806378 rs806377 rs806376 rs806375 rs12720072 rs12195101 rs806374 rs806371 rs806370 rs806369 rs1049353 rs16880260 rs4707436 rs12720071 rs45516291 rs7738931 rs12189668 rs806366 rs7766029 rs16880218 rs806365	rs806368 mutant allele associated with increased BMI, WC, SBP and obesity. No other associations.	Neutral = 272 Positive = 4

					rs35951010		
Lieb et al. 2009 [64]	2,415	1,143/1,275	Caucasian	BMI, WC, visceral adipose tissue	rs10485171 rs806365 rs7766029 rs806366 rs806368 rs12720071 rs1049353 rs806369 rs806371 rs806374 rs806375 rs806376 rs806380 rs7752758 rs12528858 rs12205430 rs6454673 rs6914429 rs12073998 rs6703669 rs3766246 rs324420 rs324419 rs2295633 rs12029329 rs324425 rs7520850	No associations with BMI, waist circumference or visceral adipose tissue for any polymorphism.	Neutral = 81
Caruso et al. 2012 [93]	118	60/58	Elderly (65-75 years)	BMI, TC, HDL-C, TGs, glucose and dietary variable (n=14)	rs1049354	Mutant allele associated with decreased dietary cholesterol and saturated fats.	Neutral = 17 Negative = 2
Buraczynska et al. 2014 [74]	667	330/337	Polish, T2DM subjects	T2DM, HbA1c, BMI.	rs1049354	No association with T2DM. Mutant allele associated with increased BMI in T2DM subjects	Neutral = 1 Positive = 2
Durand et al. 2008 [20]	5,109	2,274/2,835	French Caucasian	Child obesity, adult obesity, T2DM, BMI, glucose, insulin, WC, HDL-C, TC, TGs.	rs324420	Wild-type genotype associated with class III adult obesity, but not child obesity or T2DM. Mutant allele associated with increased HDL-C	Neutral = 8 Positive = 1 Negative = 1
Liu et al. 2011 [10]	242	-			rs1049353	In patients with coronary artery disease, the mutant allele was associated with lower BMI, HOMAir and TGs, and higher HDL-C	
Zeng et al. 2011 [53]	191	109/82	MetS subjects, healthy controls	BMI, WC, SBP, DBP, HOMAir, TGs, TC, HDL-C, LDL-C	rs324420	Wild-type allele associated with lower WC, BMI, HOMAir and TGs, and higher HDL-C levels in subjects with MetS. No association with SBP, DBP, TC or LDL-C levels.	Neutral = 4 Positive = 4 Negative = 1

Feng et al. 2013 [79]	1,006	497/509	European	HDL-C	rs806371	Mutant allele associated with lower HDL-C levels	Negative = 1
Tiwari et al. 2010 [92]	183	124/59	Schizophrenia/schizoaffective disorder	Antipsychotic-induced weight gain	rs806378 rs806380 rs2180619 rs9450902 rs10485170	rs806378 mutant allele associated with antipsychotic-induced weight gain	Neutral = 4 Positive = 1
Vazquez-Roque et al. 2011 [98]	62	19/43	Overweight/obese	Gastric motor function variables (n=6)	rs324420 rs806378	rs806378 mutant allele associated with increased gastric volume. No associations between rs324420 and gastric motor function.	Neutral = 11 Positive = 1
Wang et al. 2012 [12]	544	263/281	T2DM subjects	BMI, SBP, DBP, glucose, HOMAir, TGs, TC, HDL-C, LDL-C, HbA1c, CRP	rs1049354	Mutant allele associated with lower BMI, SBP, HOMAir and CRP and higher HDL-C. No other associations seen.	Neutral = 6 Negative = 4 Positive = 1
Grolmusz et al. 2013 [54]	130	0/130	Women with PCOS, healthy controls	BMI, WC, glucose, insulin, HOMAir	rs324420	Mutant allele associated with lower insulin, glucose and HOMAir values in healthy controls, but not PCOS subjects.	Neutral = 7 Negative = 3
Zhang et al. 2009 [32]	1,644	Not reported	Subjects of Northern European ancestry	BMI, HDL-C, TGs, insulin sensitivity	rs324420	Mutant allele associated with increased TGs and reduced levels of HDL-C	Neutral = 2 Positive = 1 Negative = 1
Suárez-Pinilla et al. 2015 [69]	65	44/21	Subjects with first episode psychosis	BMI at baseline and 3 years follow-up	rs1049353 rs2023239 rs1535255	No association between any polymorphism and BMI.	Neutral = 6
Bellini et al. 2015 [95]	240	0/240	Female, BMI >30 kg/m^2	BMI, HOMAir, TC, TGs, HDL-C	rs35761398	No association with BMI, HOMAir, TC, HDL-C or triglyceride levels	Neutral = 5
Knoll et al. 2012 [48]	453	Not reported	Overweight/obese children and adults	BMI, weight, TC, LDL-C, HDL-C, TGs, glucose, insulin, HOMAir, SBP, DBP.	rs324420	No association with any measured outcome	Neutral = 11
Papazoglou et al. 2008 [96]	303	153/150	Obesity, obesity and MetS	BMI	rs324420	No association with BMI	
Harismendy et al. 2010 [99]	289	-	BMI >40 kg/m^2	BMI	rs16830415 rs9832418 rs547801 rs520154 rs60963555 rs684358 rs9852837 rs9829319 rs9829320	No association with BMI No association with BMI No association with BMI Associated with high BMI Associated with high BMI Associated with high BMI Associated with high BMI Associated with high BMI No association with BMI	Neutral = 7 Positive = 8

	rs9829321	No association with BMI
	rs9877819	No association with BMI
	rs28753886	No association with BMI
	rs35948688	Associated with high BMI
	rs874546	Associated with high BMI
	rs2011138	Associated with high BMI

Supplemental references:

1. O'Keefe L., Simcocks AC., Hryciw DH, Mathai ML, McAinch AJ. The cannabinoid receptor 1 and its role in influencing peripheral metabolism. *Diabetes, Obesity and Metabolism.* 2014;16:294-304.
2. Greenbaum L., Tegeder, I., Barhum, Y., Melamed, E., Roditi, Y. and Djaldetti, R. Contribution of genetic variants to pain susceptibility in Parkinson disease. *European Journal of Pain.* 2012;16(9):1243-1250.
3. Russo P, Strazzullo, P., Cappuccio, F. P., Tregouet, D. A., Lauria, F., Loguercio, M., Barba, G., Versiero, M. and Siani, A. Genetic variations at the endocannabinoid type 1 receptor gene (CNR1) are associated with obesity phenotypes in men. *Journal of Clinical Endocrinology & Metabolism.* 2007;92(6):2382-2386.
4. Miguel-Yanes J, Manning, A., Shrader, P., McAteer, J., Goel, A., Hamsten, A., Fox, C., Florez, J., Dupuis, J. and Meigs, J. . Variants at the Endocannabinoid receptor CB1 Gene (CNR1) and insulin sensitivity, type 2 diabetes, and coronary heart disease. *Obesity.* 2011;19(10):2031-2037.
5. NCBI. dbSNP. 2018; https://www.ncbi.nlm.nih.gov/projects/SNP/. Accessed 7/2/2018, 2018.
6. Higgins JP, Gotzsche PC, Juni P, Moher D, Oxman AD,. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011.
7. Gazzerro P., Caruso, M., Notarnicola, M., Misciagna, G., Guerra, V., Laezza, C. and Bifulco, M. Association between cannabinoid type-1 receptor polymorphism and body mass index in a southern Italian population. . *International journal of obesity.* 2007;31(6):908-912.
8. de Luis D., Ovalle, H., Soto, G., Izaola, O., de la Fuente, B. and Romero, E. Role of Genetic Variation in the Cannabinoid Receptor Gene (CNR1) (G1359A Polymorphism) on Weight Loss and Cardiovascular Risk Factors After Liraglutide Treatment in Obese Patients With Diabetes Mellitus Type 2. *Journal of Investigative Medicine.* 2014;62(2):324-327.
9. Hu WC, Feng P., G1359A polymorphism in the cannabinoid receptor-1 gene is associated with metabolic syndrome in the Chinese Han population. *Archives of medical research.* 2010;41(5):378-382.
10. Liu R., Zhang Y. G1359A polymorphism in the cannabinoid receptor-1 gene is associated with coronary artery disease in the Chinese Han population. *Clinical Laboratory.* 2011;57(9-10):689-693.
11. Gazzerro P., Caruso M., Notarnicola M., Misciagna G., Guerra V., Laezza C. and Bifulco M. Association between cannabinoid type-1 receptor polymorphism and body mass index in a southern Italian population. *International journal of obesity.* 2007;31(6):908-912.
12. Wang R., Hu W., Qiang L. G1359A polymorphism in the cannabinoid receptor-1 gene is associated with the presence of coronary artery disease in patients with type 2 diabetes. *Journal of Investigative Medicine.* 2012;60(1):44-48.
13. Frost M., Nielsen, T., Wraae, K., Hagen, C., Piters, E., Beckers, S., De Freitas, F., Brixen, K., Van Hul, W. and Andersen, M. Polymorphisms in the endocannabinoid receptor 1 in relation to fat mass distribution. *European Journal of Endocrinology.* 2010;163(3):407-412.

14. Peeters A., Beckers, S., Mertens, I., Van Hul, W. and Van Gaal, L. The G1422A variant of the cannabinoid receptor gene (CNR1) is associated with abdominal adiposity in obese men. *Endocrine.* 2007;31(2):138-141.
15. Col Araz N., Nacak, M., Oguzkan Balci, S., Benlier, N., Araz, M., Pehlivan, S., Balat, A. and Aynacioglu, A. Childhood Obesity and the Role of Dopamine D2 Receptor and Cannabinoid Receptor-1 Gene Polymorphisms. *Genetic Testing and Molecular Biomarkers.* 2012;16(12):1408-1412.
16. Mutombo P., Yamasaki, M., Nabika, T. and Shiwaku, K. Cannabinoid Receptor 1 (CNR1) 4895 C/T Genetic Polymorphism was Associated with Obesity in Japanese Men. *Journal of atherosclerosis and thrombosis.* 2011;19(8):779-785.
17. Sipe J., Waalen, J., Gerber, A. and Beutler, E. Overweight and obesity associated with a missense polymorphism in fatty acid amide hydrolase (FAAH). *International journal of obesity.* 2005;29(7):755-759.
18. Müller T., Brönner, G., Wandolski, M., Carrie, J., Nguyen, T., Greene, B., Scherag, A., Grallert, H., Vogel, C., Scherag, S., Rief, W., Wichmann, H., Illig, T., Schäfer, H., Hebebrand, J. and Hinney, A. Mutation screen and association studies for the fatty acid amide hydrolase (FAAH) gene and early onset and adult obesity. *BMC Medical Genetics.* 2010;11(1).
19. Monteleone P., Tortorella A., Martiadis V., Di Filippo C., Canestrelli B. and Maj M. The cDNA 385C to A missense polymorphism of the endocannabinoid degrading enzyme fatty acid amide hydrolase (FAAH) is associated with overweight/obesity but not with binge eating disorder in overweight/obese women. *Psychoneuroendocrinology.* 2008;33(4):546-550.
20. Durand E., Delplanque J., Benzinou M., Degraeve F., Boutin P., Marre M., Balkau B., Charpentier G., Froguel P., Meyre D. Evaluating the association of FAAH common gene variation with childhood, adult severe obesity and type 2 diabetes in the French population. *Obesity Facts.* 2008;1(6):305-309.
21. Ketterer C., Heni, M., Stingl, K., Tschritter, O., Linder, K., Wagner, R., Machicao, F., Haring, H., Preissl, H., Staiger, H. Polymorphism rs3123554 in CNR2 reveals gender-specific effects on body weight and affects loss of body weight and cerebral insulin action. *Obesity.* 2014;22(3):925-931.
22. Wangensteen T., Akselsen, H., Holmen, J., Undlien, D. and Retterstøl, L. A Common Haplotype in NAPEPLD Is Associated With Severe Obesity in a Norwegian Population-Based Cohort (the HUNT Study). *Obesity.* 2010;19(3):612-617.
23. de Luis D., Sagrado M., Aller R., Izaola O. and Conde R. Relation of G1359A polymorphism of the cannabinoid receptor (CB1) gene with metabolic syndrome by ATP III classification. *Diabetes/metabolism research and reviews.* 2011;27(5):506-511.
24. de Luis D., González Sagrado M., Aller R., Izaola O., Conde R., Pérez Castrillón JL, Romero E. G1359A polymorphism of the cannabinoid receptor gene (CNR1) on anthropometric parameters and cardiovascular risk factors in patients with morbid obesity. *Nutricion Hospitalaria.* 2009;24(6):688-692.
25. Miguel-Yanes J., Manning, A., Shrader, P., McAteer, J., Goel, A., Hamsten, A., Fox, C., Florez, J., Dupuis, J. and Meigs, J. . Variants at the Endocannabinoid receptor CB1 Gene (CNR1) and insulin sensitivity, type 2 diabetes, and coronary heart disease. *Obesity.* 2011;19(10):2031-2037.

26. de Luis D., Izaola, O., Primo, D., de la Fuente, B. and Aller, R. Polymorphism rs3123554 in the cannabinoid receptor gene type 2 (CNR2) reveals effects on body weight and insulin resistance in obese subjects. *Endocrinología, Diabetes y Nutrición.* 2017;64(8):440-445.
27. de Luis D., Gonzalez Sagrado, M., Aller, R., Izaola, O. and Conde, R. Effects of C358A missense polymorphism of the endocannabinoid degrading enzyme fatty acid amide hydrolase on weight loss after a hypocaloric diet. *Metabolism.* 2011;60(5):730-734.
28. de Luis D., Gonzalez Sagrado, M., Aller R., Izaola O., Conde R. and Romero E. C358A missense polymorphism of the endocannabinoid-degrading enzyme fatty acid amide hydrolase (FAAH) and visfatin levels in obese females. *International Journal of Obesity.* 2010;34(3):511-515.
29. de Luis D., Gonzalez Sagrado, M., Aller R., Izaola O. and Conde R. Influence of G1359A polymorphism of the cannabinoid receptor gene on anthropometric parameters and insulin resistance in women with obesity. *Metabolism.* 2011;60(2):272-276.
30. de Luis D., Ballesteros, M., Lopez Guzman, A., Ruiz, E., Muñoz, C., Penacho, M., Iglesias, P., Maldonado, A., San Martin, L., Izaola, O. and Delgado, M. Polymorphism G1359A of the cannabinoid receptor gene (CNR1): allelic frequencies and influence on cardiovascular risk factors in a multicentre study of Castilla-Leon. *Journal of Human Nutrition and Dietetics.* 2015;29(1):112-117.
31. de Luis D., Izaola O., Aller R., Lopez J., Torres B., Diaz G., Gomez E. and Romero E. Association of G1359A polymorphism of the cannabinoid receptor gene (CNR1) with macronutrient intakes in obese females. *Journal of Human Nutrition and Dietetics.* 2015;29(1):118-123.
32. Zhang Y., Sonnenberg G., Baye T., Littrell J., Gunnell J., de la Forest A., MacKinney E., Hillard C., Kissebah A., Olivier M. Obesity-related dyslipidemia associated with FAAH, independent of insulin response, in multigenerational families of Northern European descent. *Pharmacogenomics.* 2009;10(12):1929-1939.
33. Shire D., Calandra, B., Delpech, M., Dumont, X., Kaghad, M., Le Fur, G., Caput, D. and Ferrara, P. Structural features of the central cannabinoid CB1 receptor involved in the binding of the specific CB1 antagonist SR 141716A. *Journal of Biological Chemistry.* 1996;271(12):6941-6946.
34. Kimchi-Sarfaty C., Oh J., Kim, I., Sauna, Z., Calcagno, A., Ambudkar, S. and Gottesman, M. A "silent" polymorphism in the MDR1 gene changes substrate specificity. *Science.* 2007;315(5811):525-528.
35. Muller T., Reichwald K., Wermter A., Bronner G., Nguyen T., Friedel, S., Koberwitz, K., Engeli, S., Lichtner, P., Meitinger, T. No evidence for an involvement of variants in the cannabinoid receptor gene CNR1 in obesity in German children and adolescents. *Molecular genetics and metabolism.* 2007;90(4):429-434.
36. Benzinou M., Chevre, J., Ward, K., Lecoeur, C., Dina, C., Lobbens, S., Dur, Delplanque, J., Horber, F., Heude, B. Endocannabinoid receptor 1 gene variations increase risk for obesity and modulate body mass index in European populations. *Human molecular genetics.* 2008;17(13):1916-1921.
37. Romero J., Berrendero, F., Garcia-Gil, L., De la Cruz, P., Ramos, J., Fern, and ez-Ruiz, J. Loss of cannabinoid receptor binding and messenger RNA levels and cannabinoid agonist-stimulated 35guanylyl- 5'-O-(thio)-triphosphate binding in the basal ganglia of aged rats. *Neuroscience.* 1998;84(4):1075-1083.

38. Wang L., Liu, J., Harvey-White, J., Zimmer, A. and Kunos, G. Endocannabinoid signaling via cannabinoid receptor 1 is involved in ethanol preference and its age-dependent decline in mice. *Proceedings of the National Academy of Sciences.* 2003;100(3):1393-1398.
39. Diaz S., Farhang, B., Hoien, J., Stahlman, M., Adatia, N., Cox, J. and Wagner, E. Sex differences in the cannabinoid modulation of appetite, body temperature and neurotransmission at POMC synapses. . *Neuroendocrinology.* 2009;89(4):424-440.
40. Mela V., Vargas, A., Meza, C., Kachani, M. and Wagner, E. Modulatory influences of estradiol and other anorexigenic hormones on metabotropic, Gi/o-coupled receptor function in the hypothalamic control of energy homeostasis. *The Journal of Steroid Biochemistry and Molecular Biology.* 2016;160:15-26.
41. Chiang K., Gerber, A., Sipe, J. and Cravatt, B. Reduced cellular expression and activity of the P129T mutant of human fatty acid amide hydrolase: evidence for a link between defects in the endocannabinoid system and problem drug use. *Human molecular genetics.* 2004;13(18):2113-2119.
42. Martins C., Genelhu, V., Pimentel, M., Celoria, B., Mangia, R., Aveta, T., Silvestri, C., Di Marzo, V. and Francischetti, E. Circulating Endocannabinoids and the Polymorphism 385C>A in Fatty Acid Amide Hydrolase (FAAH) Gene May Identify the Obesity Phenotype Related to Cardiometabolic Risk: A Study Conducted in a Brazilian Population of Complex Interethnic Admixture. *PLOS ONE.* 2015;10(11).
43. Milewicz, A., Tworowska-Bardzińska, U., Jędrzejuk, D., Lwow, F., Dunajska, K., Łaczmański, Ł. and Pawlak, M. Are endocannabinoid type 1 receptor gene (CNR1) polymorphisms associated with obesity and metabolic syndrome in postmenopausal Polish women? *International Journal of Obesity*, 2010. 35(3):373-377.
44. de Luis D., G.S.M., Aller R., Izaola O., Conde R. Relation of C358A polymorphism of the endocannabinoid degrading enzyme fatty acid amide hydrolase (FAAH) with obesity and insulin resistance. *Nutricion Hospitalaria*, 2010. 25(6):993-8.
45. Miguel-Yanes, J., Manning, A., Shrader, P., McAteer, J., Goel, A., Hamsten, A., Fox, C., Florez, J., Dupuis, J. and Meigs, J. Variants at the Endocannabinoid receptor CB1 Gene (CNR1) and insulin sensitivity, type 2 diabetes, and coronary heart disease. *Obesity*, 2011. 19(10):2031-2037.
46. de Luis, D., Sagrado, M., Aller, R., Conde, R., Izaola, O., De la Fuente, B. and Primo, D., Roles of G1359A polymorphism of the cannabinoid receptor gene (CNR1) on weight loss and adipocytokines after a hypocaloric diet. *Nutricion Hospitalaria*, 2011. 26(2).
47. Jaeger, J., Mattevi, V., Callegari-Jacques, S. and Hutz, M. , Cannabinoid type-1 receptor gene polymorphisms are associated with central obesity in a Southern Brazilian population. *Disease markers*, 2008. 25(1):67-74.
48. Knoll N, Volckmar AL., Pütter C, Scherag A, Kleber M, Hebebrand J, Hinney A, Reinehr T., The fatty acid amide hydrolase (FAAH) gene variant rs324420 AA/AC is not associated with weight loss in a 1-year lifestyle intervention for obese children and adolescents. *Hormone and Metabolic Research*, 2012. 44(1):75-77.
49. Baye T, Zhang, Y., Smith, E., Hillard, C., Gunnell, J., Myklebust, J., James, R., Kissebah, A., Olivier, M. and Wilke, R. Genetic variation in cannabinoid receptor 1 (CNR1) is associated with derangements in lipid homeostasis, independent of body mass index. *Future Medicine.* 2008. 9(11):1647-56
50. de Luis D, Aller, R., Izaola, O., Conde, R., Sagrado, M., Primo, D. and Castro, M. . Relationship among metabolic syndrome, C358A polymorphism of the

endocannabinoid degrading enzyme fatty acid amide hydrolase (FAAH) and insulin resistance. *Journal of Diabetes and its Complications.* 2012;26(4):328-332.
51. Müller T, Brönner, G., Wandolski, M., Carrie, J., Nguyen, T., Greene, B., Scherag, A., Grallert, H., Vogel, C., Scherag, S., Rief, W., Wichmann, H., Illig, T., Schäfer, H., Hebebrand, J. and Hinney, A. . Mutation screen and association studies for the fatty acid amide hydrolase (FAAH) gene and early onset and adult obesity. *BMC Medical Genetics.* 2010;11(1).
52. de Luis D, Sagrado, M., Pacheco, D., Terroba, M., Martin, T., Cuellar, L. and Ventosa, M. . Effects of C358A missense polymorphism of the endocannabinoid degrading enzyme fatty acid amide hydrolase on weight loss and cardiovascular risk factors 1 year after biliopancreatic diversion surgery. *Surgery for Obesity and Related Diseases.* 2010;6(5):516-520.
53. Zeng J. LJ, Huang G. 385 C/A polymorphism of the fatty acid amide hydrolase gene is associated with metabolic syndrome in the Chinese Han population. *Archives of medical Science.* 2011;7(3):423-427.
54. Grolmusz VK SB, Fekete T, Szendei G, Patócs A, Rácz K, Reismann P. Lack of association between C385A functional polymorphism of the fatty acid amide hydrolase gene and polycystic ovary syndrome. *Experimental and Clinical Endocrinology and Diabetes.* 2013;121(6):338-342.
55. Williams C, Rogers P, TC K. Hyperphagia in pre-fed rats following oral delta 9-THC. *Physiology & Behaviour.* 1998;20:104-110.
56. Williams C, Kirkham T. Reversal of delta 9-THC hyperphagia by SR 141716 and naloxone but not dexfenfluramine. *Pharmacology, Biochemistry & Behaviour.* 2002(71):333-340.
57. Moreira F, Crippa, J. The psychiatric side-effects of rimonabant. *Revista brasileira de psiquiatria.* 2009;31(2):145-153.
58. Gutierrez-Hermosillo H, Diaz De Leon-Gonzalez, E., Palacios-Corona, R., Cedillo-Rodriguez, J. A., Camacho-Luis, A., Reyes-Romero, M. A., Medina-Chavez, J. H., Blandon, P. A. C allele of the rs2209972 single nucleotide polymorphism of the insulin degrading enzyme gene and Alzheimer's disease in type 2 diabetes, a case control study. *Medicina Clinica.* 2013;144(4):151-155.
59. Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. *Endocrine Reviews.* 2006;27(1):73-100.
60. Gomez R., Navarro M., Ferrer B., Trigo JM., Bilbao A., Del Arco I., Cippitelli A., Nava F., Piomelli D., Rodriguez de Fonseca F. A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding. *Journal of Neuroscience.* 2002;22(21):9612-9617.
61. Frade A., Teixeira, P. C., Ianni, B. M., Pissetti, C. W., Saba, B., Wang, L. H. T., Kuramoto, A., Nogueira, L. G., Buck, P., Dias, F. . Polymorphism in the Alpha Cardiac Muscle Actin 1 Gene Is Associated to Susceptibility to Chronic Inflammatory Cardiomyopathy. *PLOS ONE.* 2013;8(12):83446.
62. Li Y., Chang, S., Niu, R., Liu, L., Crabtree-Ide, C. R., Zhao, B., Shi, J., Han, X., Li, J., Su, J. TP53 genetic polymorphisms, interactions with lifestyle factors and lung cancer risk: a case control study in a Chinese population. *BMC Cancer.* 2013;13(1):607.

63. Ujike H., Takaki, M., Nakata, K., Tanaka, Y., Takeda, T., Fujiwara, Y., Kodama, M., Sakai, A. and Kuroda, S. CNR1, central cannabinoid receptor gene, associated with susceptibility to hebephrenic schizophrenia. *Molecular psychiatry.* 2002;7(5).
64. Lieb W., Manning, A., Florez, J., Dupuis, J., Cupples, L., Mcateer, J., Vasan, R., Hoffmann, U., O'Donnell, C., Meigs, J. Variants in the CNR1 and the FAAH genes and adiposity traits in the community. *Obesity.* 2009;17(4):755-760.
65. Hariri A., Gorka, A., Hyde, L., Kimak, M., Halder, I., Ducci, F., Ferrell, R., Goldman, D. and Manuck, S. Divergent effects of genetic variation in endocannabinoid signaling on human threat-and reward-related brain function. *Biological psychiatry.* 2009;66(1):9-16.
66. Aller R., De Luis, D., Pacheco, D., Velasco, M., Conde, R., Izaola, O. and Gonzalez Sagrado, M. Influence of G1359A polymorphism of the cannabinoid receptor gene (CNR1) on insulin resistance and adipokines in patients with non-alcoholic fatty liver disease. *Nutricion Hospitalaria.* 2012;27(5):1637-1642.
67. de Luis D., González Sagrado M., Aller R., Izaola O., Conde R., Pérez Castrillón JL, Romero E. G1359A polymorphism of the cannabinoid receptor gene (CNR1) on anthropometric parameters and cardiovascular risk factors in patients with morbid obesity. *Nutricion Hospitalaria.* 2009;24(6):688-692.
68. de Luis D., Gonzalez Sagrado, M., Aller, R., Izaola, O., Conde, R. and Romero, E. . G1359A polymorphism of the cannabinoid receptor gene (CNR1) and insulin resistance in patients with diabetes mellitus type 2. *Nutricion Hospitalaria.* 2010;25(1):34-38.
69. Suárez-Pinilla P., Ortiz-García de la Foz V., Guest PC, Ayesa-Arriola R., Córdova-Palomera A., Tordesillas-Gutierrez D., Crespo-Facorro B. Brain structural and clinical changes after first episode psychosis: Focus on cannabinoid receptor 1 polymorphisms. *Psychiatry Research.* 2015;233(2):112-119.
70. Frost M., Nielsen, T., Wraae, K., Hagen, C., Piters, E., Beckers, S., De Freitas, F., Brixen, K., Van Hul, W. and Andersen, M. . Polymorphisms in the endocannabinoid receptor 1 in relation to fat mass distribution. *European Journal of Endocrinology.* 2010;163(3):407-412.
71. de Luis D., Aller, R., Izaola, O., Díaz Soto, G., López Gómez, J., Gómez Hoyos, E., Torres, B., Villar, A. and Romero, E. Effects of a High-Protein/Low-Carbohydrate versus a Standard Hypocaloric Diet on Weight and Cardiovascular Risk Factors during 9 Months: Role of a Genetic Variation in the Cannabinoid Receptor Gene (CNR1) (G1359A Polymorphism). *Annals of Nutrition and Metabolism.* 2015;66(2-3):125-131.
72. Jensen D., Andreasen, C., Andersen, M., Hansen, L., Eiberg, H., Borch-Johnsen, K., Jørgensen, T., Hansen, T. and Pedersen, O. The functional Pro129Thr variant of the FAAH gene is not associated with various fat accumulation phenotypes in a population-based cohort of 5,801 whites. *Journal of Molecular Medicine.* 2007;85(5):445-449.
73. Dinu I., Popa, S., Mota, M., Mota, E., Ioana, M. and Cruce, M. The association of rs12720071 polymorphism of the CNR1 gene with glucose metabolism abnormalities. *Annals of the Romanian Society of Cell Biology.* 2010;1(15):299-303.
74. Buraczynska M WP, Zukowski P, Dragan M, Ksiazek A. Common polymorphism in the cannabinoid type 1 receptor gene (CNR1) is associated with microvascular complications in type 2 diabetes. *Journal of Diabetes and its Complications.* 2014;28(1):35-39.

75. Dinu I., Popa, S., Mota, M., Mota, E., Stanciulescu, C., Ioana, M. and Cruce, M. The association of the rs1049353 polymorphism of the CNR1 gene with hypoadiponectinemia. *Romanian Journal of Morphology and Embryology.* 2011;52(3):791-795.
76. de Luis D., Aller, R., Sagrado, M., Conde, R., Izaola, O. and de la Fuente, B. Genetic variation in the cannabinoid receptor gene (CNR1) (G1359A polymorphism) and their influence on anthropometric parameters and metabolic parameters under a high monounsaturated vs. high polyunsaturated fat hypocaloric diets. *The Journal of nutritional biochemistry.* 2013;24(8):1431-1435.
77. Silver H., Niswender, K., Keil, C., Jiang, L., Feng, Q., Chiu, S., Krauss, R. and Wilke, R. . CNR1 genotype influences HDL-cholesterol response to change in dietary fat intake. *PLOS ONE.* 2012;7(5):361-366.
78. Feng Q., Jiang, L., Berg, R., Antonik, M., MacKinney, E., Gunnell-Santoro, J., McCarty, C. and Wilke, R. A common CNR1 (cannabinoid receptor 1) haplotype attenuates the decrease in HDL cholesterol that typically accompanies weight gain. *PLOS ONE.* 2010;5(12):15779.
79. Feng Q., Vickers, K., Anderson, M., Levin, M., Chen, W., Harrison, D. and Wilke, R. A common functional promoter variant links CNR1 gene expression to HDL cholesterol level. *Nature communications.* 2013;4.
80. Chmelikova M., Pacal L., Spinarova, L. and Vasku, A. Association of polymorphisms in the endocannabinoid system genes with myocardial infarction and plasma cholesterol levels. *Biomedical Papers.* 2014;159(4):535-539.
81. Aberle J., Flitsch, J., Beck, N., Mann, O., Busch, P., Peitsmeier, P. and Beil, F. Genetic variation may influence obesity only under conditions of diet: analysis of three candidate genes. *Molecular genetics and metabolism.* 2008;95(3):188-191.
82. Lenarcik-Kabza A, Łaczmański Ł, Milewicz A, Bidzińska-Speichert B, Pawlak M, Kolackov K, Kuliczkowska-Płaksej J, Trzmiel-Bira A, Brona A. . The influence of endocannabinoid receptor 1 gene variations on anthropometric and metabolic parameters of women with polycystic ovary syndrome. *Endokrynologia Polska.* 2014;65(3):181-188.
83. Schleinitz D, Carmienke, S., Böttcher, Y., Tönjes, A., Berndt, J., Klöting, N., Enigk, B., Müller, I., Dietrich, K., Breitfeld, J., Scholz, G., Engeli, S., Stumvoll, M., Blüher, M. and Kovacs, P. Role of genetic variation in the cannabinoid type 1 receptor gene (CNR1) in the pathophysiology of human obesity. *Pharmacogenomics.* 2010;11(5):693-702.
84. de Luis D., Sagrado, M., Aller, R., Conde, R., Izaola, O., de la Fuente, B. and Primo, D. Role of G1359A polymorphism of the cannabinoid receptor gene on weight loss and adipocytokines levels after two different hypocaloric diets. *The Journal of Nutritional Biochemistry.* 2011;23(3):287-291.
85. Aberle J FI, Klages N, George E, Beil FU. Genetic variation in two proteins of the endocannabinoid system and their influence on body mass index and metabolism under low fat diet. *Hormone and Metabolic Research.* 2007;39(5):395-397.
86. Wei R, Yang, F., Urban, T., Li, L., Chalasani, N., Flockhart, D. and Liu, W. . Impact of the interaction between 3'-UTR SNPs and microRNA on the expression of human xenobiotic metabolism enzyme and transporter genes. *Frontiers in Genetics.* 2012;21(3):248.
87. Dunajska K, Lwow, F., Jedrzejuk, D., Milewicz, A., Tworowska-Bardzinska, U. and Laczmanski, L. Are endocannabinoid type 1 receptor gene (CNR1) polymorphisms

associated with obesity and metabolic syndrome in postmenopausal Polish women? *Nature Publishing Group.* 2009;35(3):373-377.
88. Bordicchia M, Battistoni, I., Mancinelli, L., Giannini, E., Refi, G., Minardi, D., Muzzonigro, G., Mazzucchelli, R., Montironi, R., Piscitelli, F. Cannabinoid CB1 receptor expression in relation to visceral adipose depots, endocannabinoid levels, microvascular damage, and the presence of the CNR1 A3813G variant in humans. *Metabolism.* 2010;59(5):734-741.
89. Greenwood TA., Kelsoe Jr. Promoter and intronic variants affect the transcriptional regulation of the human dopamine transporter gene. *Genomics.* 2003;82(5):511-520.
90. Egertova M, Cravatt, B. and Elphick, M. Comparative analysis of fatty acid amide hydrolase and CB1 cannabinoid receptor expression in the mouse brain: evidence of a widespread role for fatty acid amide hydrolase in regulation of endocannabinoid signaling. *Neuroscience.* 2003;119(2):481-496.
91. Łaczmański Ł, Milewicz, A., Dunajska, K., Jędrzejczuk, D., Pawlak, M. and Lwow, F. Endocannabinoid type 1 receptor gene (CNR1) polymorphisms (rs806381, rs10485170, rs6454674, rs2023239) and cardiovascular risk factors in postmenopausal women. *Gynecological Endocrinology.* 2011;27(12):1023-1027.
92. Tiwari AK ZC, Likhodi O, Lisker A, Singh D, Souza RP, Batra P, Zaidi SH, Chen S, Liu F, Puls I, Meltzer HY, Lieberman JA, Kennedy JL, Müller DJ. A common polymorphism in the cannabinoid receptor 1 (CNR1) gene is associated with antipsychotic-induced weight gain in Schizophrenia. *Neuropsychopharmacology.* 2010;35(6):1315-1324.
93. Caruso M.G. GP, Notarnicola M., Cisternino A.M., Guerra V., Misciagna G., Laezza C., Bifulco M.c Cannabinoid Type 1 Receptor Gene Polymorphism and Macronutrient Intake. *Journal of Nutrigenetics and Nutrigenomics.* 2012;5(6):305-313.
94. Zhuang M, Yang, Y., Cao, F., Lu, M., Wang, X., Zhang, J., Chen, X., Cheng, P., Zhang, N., Ye, W. Associations of variants of CNR1 with obesity and obesity-related traits in Chinese women. *Gene.* 2012;495(2):194-198.
95. Bellini G. GA, Torella M., Miraglia del Giudice E., Nobili B., Perrone L., Maione S., and Rossi F. The Cannabinoid Receptor 2 Q63R Variant Modulates the Relationship between Childhood Obesity and Age at Menarche. *PLOS ONE.* 2015;10(10).
96. Papazoglou D PI, Papanas N, Gioka T, Papadopoulos T, Papathanasiou P, Kaitozis O, Papatheodorou K, Maltezos E. The fatty acid amide hydrolase (FAAH) Pro129Thr polymorphism is not associated with severe obesity in Greek subjects. *Hormone and Metabolic Research.* 2008;40(12):907-910.
97. Reinhard W., Stark K, Neureuther K, Sedlacek K, Fischer M, Baessler A, Weber S, Kaess B, Wiedmann S, Erdmann J, Lieb W, Jeron A, Riegger G, Hengstenberg C. Common polymorphisms in the cannabinoid CB2 receptor gene (CNR2) are not associated with myocardial infarction and cardiovascular risk factors. *International Journal of Molecular Medicine*. 2008;22(2):165-74.
98. Vazquez-Roque M., Camilleri M, Vella A, Carlson P, Laugen J, Zinsmeister AR. Association of genetic variation in cannabinoid mechanisms and gastric motor functions and satiation in overweight and obesity. *Neurogastroenterology & Motility*. 2011;23(7):637-e257.
99. Harismendy O., Bansal V, Bhatia G, Nakano M, Scott M, Wang X, Dib C, Turlotte E, Sipe JC, Murray SS, Deleuze JF, Bafna V, Topol EJ, Frazer KA. Population sequencing of two endocannabinoid metabolic genes identifies rare and common regulatory variants

associated with extreme obesity and metabolite level. *Genome Biology.* 2010;11(11):R118