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Genetic differences in fat taste sensitivity and dietary intake in a UK female cohort

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ABSTRACT

Over the past decade, a potential sixth taste, fat taste ("oleogustus"), has been identified. Studies in adults and children of various ethnicities have demonstrated that both lifestyle and genetic factors may contribute to fat taste sensitivity (FTS). Data on females in the UK is limited. The aim of this study was to determine, using an ethnically similar, healthy, female cohort, whether known genotypes related to fat taste and dietary intake lead to differences in FTS. A cross-sectional study was carried out on a UK cohort of Caucasian females (32.7 ± 11.4 years, 23.7 ± 3.6 kg/m^2). We report that FTS differed in individuals with differing genotypes; genotypes that have previously been associated with differences in dietary intake. Specifically, FTS was lower in rs1514175 Troponin I-Interacting Protein Kinase (*TNNI3K*) gene AA/AG genotype and was higher in rs6265 Brain Derived Neurotrophic Factor (*BDNF*) gene TT/CT genotype (both $p < 0.05$). We also report that participants in the rs1514175 *TNNI3K* AA/AG genotype group had a higher energy intake, total fat intake, and subsequently, higher monounsaturated fat and saturated fat intake when compared to the GG genotype (all $p < 0.05$). To our knowledge, this is the first study showing associations between genotypes that have been previously associated to dietary intake are also associated to FTS. Due to the heterogeneity of previous research and the infancy of fat taste research, further research is required on a larger, ethnically similar cohort.

1. Introduction

The sensory properties of food are highly influential in motivating consumption, through taste perception and, thus, palatability (Johnson & Wardle, 2014). Palatability is the hedonic reward produced by the consumption of acceptable foods for homeostatic fulfilment of energy needs (Pandurangan & Hwang, 2015). However, hedonic hunger has been shown to be induced by palatability independently of homeostatic dietary needs (Pandurangan & Hwang, 2015). Therefore, palatability can be said to hold a fundamental role in habitual dietary intake. Taste perception is a major contributor to hedonic hunger and may be an influential target for obesity prevention (Johnson & Wardle, 2014).

The five defined human tastes are sweet, sour, bitter, salty and umami (Ikeda, 1909). Over the past decade a potential sixth taste, fat taste ("oleogustus"), has been identified (Mattes, 2010). There is debate regarding fat taste as an independent taste, specifically relating to taste receptor functionality, the type of fatty acid required to elicit a taste response and the additive nature of such a response (Besnard, Passilly-Degrace, & Khan, 2016; Running, Craig, & Mattes, 2015). The ability to taste fat has been demonstrated in rodents (Sclafani, Ackroff, & Abumrad, 2007) and humans, both alone (Mrizak et al., 2015) and in combination with all other defined tastes (Melis et al., 2020).

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Consequently, a related taste receptor has been identified. The receptor-like glycoprotein cluster of difference 36 (*CD36*) is membrane protein belonging to the class B scavenger receptor family expressed in taste bud cells. It has been shown to bind to varying concentrations of saturated and unsaturated long-chain fatty acids (LCFA), and accordingly the LCFA trigger cell signalling (Besnard et al., 2016).

Genetics play an important role in taste receptor functionality (Melis et al., 2020). Functional differences in taste receptors due to differing genotypes (alleles inherited for a particular gene) have been demonstrated with various tastes (Melis et al., 2020). Relating to fat taste sensitivity (FTS), research has shown that the *CD36* rs1761667 (A/G) single nucleotide polymorphism (SNP; a genetic sequence variation occurring when a single nucleotide (or allele) differs between members of a species) is associated with FTS (Daoudi et al., 2015; Karmous et al., 2018; Melis, Sollai, Muroni, Crnjar, & Barbarossa, 2015; Mrizak et al., 2015; Pepino, Love-Gregory, Klein, & Abumrad, 2012; Sayed et al., 2015), fatty acid metabolism (Melis et al., 2017), and dietary fat intake (Fujii et al., 2019; Pepino et al., 2012; Pioltine et al., 2016; Ramos-Lopez et al., 2016). Compared to the G allele, the A allele is characterised by reduced protein expression (Ghosh et al., 2011; Love-Gregory et al., 2011), therefore individuals who carry the A allele have a higher fat detection threshold (hyposensitive), and consequently cannot taste fat as efficiently (Melis et al., 2015; Sayed et al., 2015). These individuals may be at risk of higher consumption of foods containing fatty acids, subsequently leading to weight gain (Besnard et al., 2016), although research is inconclusive (Tucker et al., 2017). Research on the genetic differences of FTS, within a Caucasian cohort, is highly heterogeneous, relating to study design, sample size and method of taste sensitivity assessment (Burgess et al., 2018; Melis et al., 2017, 2020, 2015; Pepino et al., 2012).

In conjunction with SNPs directly impacting FTS, various SNPs have been independently associated with dietary fat intake and overweight/obesity (Khera et al., 2019; Qi et al., 2014), both of which may be contributing factors to differences in taste perception (Stewart & Keast, 2012; Tucker et al., 2017). Stewart and Keast (2012) demonstrated that habitual dietary fat modification for a 4-week period can alter fat taste perception; specifically, the lower fat diet in that study reduced FTS. It can therefore be hypothesised that genetic factors influencing habitual diet, other than those relating directly to taste perception may lead to changes in taste perception, ultimately negatively impacting dietary intake further.

The rs9939609 SNP within the Fat Mass and Obesity (FTO) associated gene was the first defined point associated with obesity (Frayling et al., 2007), and has been linked to dietary intake (Garver et al., 2013; Qi et al., 2014; Timpson et al., 2008) and lowered satiety (Speakman, 2015). Specifically, Qi et al. (2014) demonstrated that the rs9939609 risk allele was associated with a higher dietary protein intake, a lower total EI, and a lower carbohydrate intake. Wåhlén, Sjölin, and Hoffstedt (2008) reported individuals with the rs9939609 risk allele exhibited less lipolysis in adipocytes, suggesting a role of the FTO gene in body fat metabolism. Since discovery of the FTO gene, and its association with obesity, many other genes have been deemed contributory to weight gain, specifically via appetite control. For example, the Brain Derived Neurotrophic Factor *(BDNF)* gene has been deemed a regulator of appetite (Pandit, Behl, Sachdeva, & Arora, 2020) and a contributing factor to weight gain due to its role as an anorexigenic factor within the melanocortin system (Pandit et al., 2020). The rs6265 SNP has previously been associated with differing circulating *BDNF* concentrations, highlighting a potential genetic influence to appetite regulation. Others have demonstrated an interaction between rs6265, body mass, fat mass distribution, and dietary fat intake (Ma et al., 2012), and dietary behaviour (Rosas-Vargas, Martínez-Ezquerro, & Bienvenu, 2011). Similarly, the Melanocortin 4 Receptor (MC4R) gene transcribes the melanocortin 4 receptor, which plays a key role in the melanocortin system and therefore contributes to appetite regulation (Girardet & Butler, 2014). The MC4R rs17782313 SNP has been associated with obesity (Graham et al., 2020; Loos et al., 2008), and dietary intake (Butler & Cone, 2003; Farooqi & O'Rahilly, 2005). Further, the Troponin I-Interacting Protein Kinase (TNNI3K) gene, rs1514175 SNP, associated with obesity (Speliotes et al., 2010), has also been associated with a lower percentage of EI from protein, which was nominally associated with more frequent servings of fats, oils and sweets (McCaffery et al., 2012). The rs1514175 SNP has also been associated with eating behaviour, specifically uncontrollable eating (Cornelis et al., 2014). Although the mechanism of action of this gene is less clear than the above mentioned, it has also been linked to satiety responses (Llewellyn, Trzaskowski, Van Jaarsveld, Plomin, & Wardle, 2014).

Despite mechanistic evidence linking the aforementioned genes to dietary intake, there is currently no research, to our knowledge, assessing whether SNPs related these factors are associated with FTS. Therefore, the aim of this study was to determine whether known genotypes related to fat taste and dietary intake lead to differences in FTS.

2. Methods

2.1. Study design and participants

A cross-sectional study was carried out on a UK cohort of Caucasian females, recruited via university-based advertisement. Sample size was based on a power of 80%, probability of 0.05, a meaningful difference of 3.8 (Haryono, Sprajcer, & Keast, 2014), and an SD of 7.0. From this 59 participants were endeavoured to be recruited (54 plus 10% attrition). Exclusion criteria were: smoking, pregnancy, lactose intolerance or allergy of dairy, diagnosed with type I or II diabetes or any cancer and currently following a diet or weight loss programme. Participants were also excluded if they were not of Caucasian heritage or, had been pregnant or had been following a diet or weight loss programme for more than six months of the previous year (self-reported).

Participants were assessed for FTS, habitual dietary intake, and genotype. This study was conducted in accordance with the Declaration of Helsinki and all procedures involving human subjects were approved by the St Mary's University Ethics Committee; SMEC_2017-18_138. Written informed consent was obtained from all participants. The study is registered: reference: NCT03666182 (https://clinicaltrials.gov/).

2.1.1. Fat taste sensitivity assessment

The Oral Fatty Acid Threshold Assessment and Ascending Forced Choice Triangle Procedure was used to determine each participant's oleic acid (C18:1) detection threshold (FTS). The method is described in full elsewhere (Haryono et al., 2014). Briefly, each participant was presented with three cups containing 30 ml vehicles in a random arrangement, two were controls (oleic-) and the third contained oleic acid (oleic+; 0.02, 0.06, 1, 1.4, 2, 2.8, 3.8, 5, 6.4, 8, 9.8, 12, 20 mM). Participants had to identify the oleic + solution. A participant was required to choose the oleic + solution correctly three times at the same concentration to define their threshold. If they were incorrect at any point they would be presented with three further cups, one containing the higher oleic + concentration and two oleic- solutions. Previous research has detailed that hypersensitive tasters have a fat taste threshold below 3.8 mM, hyposensitive tasters have a fat taste threshold equal to or above 3.8 mM and a proportion of participants fail to identify the oleic + sample at the maximum concentration (20 mM) and are defined as non-tasters (Haryono et al., 2014; Stewart, Newman, & Keast, 2011).

Testing was conducted on one occasion for each participant. Taste vehicles were served at room temperature and presented to participants in individual booths within the St Mary's University Nutrition laboratory. Red lighting was used to disguise visual differences between the samples, nose clips were worn to inhibit olfactory input, textural differences were avoided with the addition of textural agents (gum Arabic and liquid paraffin) and post-ingestive regulation was followed by the sip-and-spit procedure (Haryono et al., 2014). Participants were asked

to refrain from consumption of any food or drink for one hour prior to testing.

2.1.2. Dietary intake

The validated EPIC Norfolk Food Frequency Questionnaire (FFQ) was used to measure dietary intake over the previous year. Dietary intake values were extracted and analysed, using FETA software (Mulligan et al., 2014). The following components were quantified and analysed: total energy intake (EI) (kcal) total carbohydrate (g), total fat (g), monounsaturated fatty acid (MUFA) (g), polyunsaturated fatty acid (PUFA) (g), saturated fatty acid (SFA) (g) and total protein (g).

2.1.3. Anthropometric measurements

Height (m) [Free Standing Height Measure, SECA GmbH & Co., Hamburg, Germany] and weight (kg) [Portable Scale MS-4203, Marsden Weighing Group, Oxfordshire, UK] were recorded by the research team. BMI was calculated using the equation: weight (kg)/height (m^2) (World Health Organization, 2018).

2.1.4. Single nucleotide polymorphism genotyping

Saliva samples (2 ml) were collected for DNA analyses (Genefix, Isohelix, Kent, UK). DNA extraction was carried out through use of a PSP® SalivaGene 17 DNA Kit 1011 (STRATEC Molecular, Berlin) following the standard manufacturer protocol. DNA quantification and quality control were assessed with spectroscopy (Nanodrop, ThermoFisher, Waltham, MA, USA). Following this, genotyping of *BDNF* rs6265, *CD36* rs1761667, *FTO* rs9939609, *MC4R* rs17782313 and *TNNI3K* rs1514175 was carried out using prepared TaqMan® SNP genotyping assays (ThermoFisher, Waltham, MA, USA) and a StepOnePlus thermocycler (Applied Biosystems, CA, USA). All samples were analysed in duplicate in accordance with the manufacturer's protocol. Individual samples were accepted with a quality of >98%. All genetic analyses were carried out at St Mary's University, Twickenham. All SNPs were dichotomised by grouping the risk alleles, as per previous research: rs6265 (TT/CT, CC) (Shugart et al., 2009), rs1761667 (GG/AG and AA) (Chamoun et al., 2018), rs9939609 (AA/AT, TT) (Tanofsky-Kraff et al., 2009), rs2867125 (AA/AG, GG) (Graham et al., 2020), rs1514175 (AA/AG, GG) (Graham et al., 2020).

2.1.5. Statistical analysis

Allele frequency in the total study cohort was assessed using the Hardy-Weinberg equilibrium. Allele frequency of the total cohort rather than controls (healthy weight) only was assessed due to the condition (overweight) being common (Wang & Shete, 2011, 2012). Differences in genotype frequency between hyper- and hyposensitive tasters were assessed by Chi Squared or Fishers exact testing, were appropriate. Normality of data were assessed using the Shapiro Wilk's test of normality. Where relevant, the Independent *T* test or Mann Whitney *U* test was used to determine if FTS and dietary intake differed based on dichotomised genotype. SPSS was used throughout (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). All tests were two-tailed, with $p < 0.05$ considered statistically significant.

Table 1
Participant characteristics (mean ± SD), n = 48.

BMI ± SD (kg/m^2)	23.7 ± 3.6
Age ± SD (years)	32.7 ± 11.4
Hyper n (%), Hypo n (%)	22 (46), 26 (54)

SD, Standard Deviation; BMI, Body Mass Index; n, Number; Hypo, Hyposensitive Tasters; Hyper, Hypersensitive Tasters.

3. Results

3.1. Demographics

Participant characteristics are described in Table 1. A total of 55 participants were recruited, 48 participants were categorised on the taste sensitivity scale used (Haryono et al., 2014) and thus used in further analysis. Taste sensitivity was handled as continuous data throughout therefore individuals who failed to identify the oleic + solution at 20 mM were defined as non-tasters (n = 7). Such individuals provided no measurable threshold and were excluded from further analysis, in line with others (Burgess et al., 2018).

Participant genotype frequencies are described in Table 2a. There were no differences in genotype frequency between hyper- and hyposensitive tasters for all SNPs ($p > 0.05$). Genotypes of the excluded participants can be found in Table 2b. All genotypes, excluding the rs17782313 *MC4R*, were within the Hardy Weinberg equilibrium, according to Chi-squared goodness of fit analysis ($p > 0.05$). *MC4R* rs17782313 was therefore excluded from further analysis.

3.2. Difference in fat taste sensitivity based on genotype

The following results explore whether FTS differs based on genotype. Participants in the rs6265 *BDNF* CT/TT genotype group had a lower fat taste threshold (2.0, (4.7) mM; hypersensitive) when compared to the CC genotype (4.4, (6.6) mM; hyposensitive; $p = 0.040$). Participants in the rs1514175 *TNNI3K* AA/AG genotype group had a moderately higher fat taste threshold (4.4, (6.1) mM; hyposensitive) when compared to the GG group (1.5, (6.3) mM; hypersensitive; $p = 0.049$). No differences in FTS were found in relation to rs1761667 CD36 and rs9939609 FTO genotype. All results can be found in Table 3.

3.3. Genotype and dietary intake

The following results explore whether dietary intake differs based on genotype. Participants in the rs1514175 *TNNI3K* AA/AG genotype group had a higher energy intake (1899 ± 572 kcal), total fat intake (82 ± 35 g) and subsequently a higher MUFA (32 ± 15 g) and SFA intake (28 ± 12 g) when compared to the GG genotype (1497 ± 409 kcal; 60 ± 18

Table 2a
Dichotomous genotype frequencies (and percentage distribution) within the total cohort and two subpopulations: those who are hypersensitive and hyposensitive to fat taste.

Gene	SNP	Total Cohort (n = 48)		Hyper (n = 22)		Hyposensitive (n = 26)	
BDNF	rs6265 n (%)	TT/CT	CC	TT/CT	CC	TT/CT	CC
		16 (33)	32 (67)	5 (23)	17 (77)	11 (42)	15 (58)
CD36	rs1761667 n (%)	GG/AG	AA	GG/AG	AA	GG/AG	AA
		34 (71)	14 (29)	16 (73)	6 (27)	18 (69)	8 (31)
FTO	rs9939609 n (%)	AA/AT	TT	AA/AT	TT	AA/AT	TT
		27 (56)	21 (44)	12 (55)	10 (45)	15 (58)	11 (42)
TNNI3K	rs1514175 n (%)	AA/AG	GG	AA/AG	GG	AA/AG	GG
		32 (67)	16 (33)	17 (77)	5 (23)	15 (58)	11 (42)

There were no differences in genotype frequency between hyper- and hyposensitive tasters for all single nucleotide polymorphisms (SNP) ($p > 0.05$; Chi Square/Fishers Exact Testing). BDNF, rs6265 Brain Derived Neurotrophic Factor Gene; CD36, rs1761667 Cluster of Difference 36 Gene; FTO, rs9939609 Fat Mass and Obesity Associated Gene; TNNI3K, rs1514175 Troponin I-Interacting Protein Kinase Gene.

Table 2b
Individual genotypes of the participants that were excluded due to their classification as a non-taster.

Gene	SNP							
Participant no.		1	2	3	4	5	6	7
BDNF	rs6265 n (%)	CC	CT	CC	CC	CT	CC	CC
CD36	rs1761667 n (%)	AA	AG	AG	AG	AG	GG	AG
FTO	rs9939609 n (%)	AT	AT	AT	AT	AT	AT	TT
TNNI3K	rs1514175 n (%)	GG	AA	AG	AG	GG	GG	AG

BDNF, rs6265 Brain Derived Neurotrophic Factor Gene; CD36, rs1761667 Cluster of Difference 36 Gene; FTO, rs9939609 Fat Mass and Obesity Associated Gene; SNP, single nucleotide polymorphism; TNNI3K, rs1514175 Troponin I-Interacting Protein Kinase Gene.

Table 3
Median observed fat taste, as determined by forced choice triangle taste methodology, by genotype group, n = 48.

Gene SNP	Genotype	Median	IQR	p
BDNF	CT/TT	2.0*	4.7	**0.040**
rs6265	CC	4.4*	6.6	
CD36	GG/AG	1.0	1.0	**0.523**
rs1761667	AA	1.0	1.0	
FTO	AA/AT	2.8	5.4	**0.975**
rs9939609	TT	2.8	7.0	
TNNI3K	AA/AG	4.4*	6.1	**0.049**
rs1514175	GG	1.5 *	6.3	

* , $p < 0.05$ (Mann-Whitney *U* test). IQR, interquartile range; n, number; p, p-value; SNP, single nucleotide polymorphism; BDNF, Brain Derived Neurotrophic Factor Gene; CD36, Cluster of Difference 36 Gene; FTO, Fat Mass and Obesity Associated Gene; TNNI3K, Troponin I-Interacting Protein Kinase Gene.

g; 23 ± 8 g; 20 ± 7 g, respectively) (p = 0.008, 0.009, 0.027, 0.008, respectively). No differences in dietary intake were found between any other genotype analysed. All results can be found in Table 4.

4. Discussion

The first aim of this study was to determine whether known genotypes related to fat taste and dietary intake, influence FTS in a healthy cohort of Caucasian UK females. The main findings of this study were that differences in FTS and fat intake exist based on genotypes that have been associated with dietary intake only previously. Specifically, the rs1514175 *TNNI3K* genotype (for FTS and fat intake), and the rs6265 *BDNF* genotype (for FTS), both of which are novel findings.

4.1. Genotype, fat taste sensitivity and dietary intake

On exploration of a genetic contribution to FTS, researchers have largely focussed on rs1761667 *CD36* (Chamoun et al., 2017). We found no association between rs1761667 *CD36* and FTS or dietary intake, which is in contrast to other published research. For example, Mrizak et al. (2015) investigated how fatty acid detection thresholds differed between Tunisian women (n = 203) of differing *CD36* genotypes (rs1761667, rs1800629 and rs1800795). Results showed that rs1761667 A allele was associated with a 3.3 times higher detection threshold. Similar results have been demonstrated by Karmous et al. (2018), Ong, Tan, and Say (2017) and Sayed et al. (2015) on Tunisian (n = 104), Malaysian (n = 313) and Algerian (n = 116) cohorts, respectively. Our study differs to the aforementioned in relation to ethnicity, which has been shown to modify responses to taste sensitivity (El-Sohemy et al., 2007). Few studies have investigated Caucasian cohorts (Melis et al., 2015; Pepino et al., 2012) of which our findings also do not corroborate. Melis et al. (2015), despite utilising the same fatty acid vehicle and threshold testing method and similar sample size (n = 64), demonstrated participants homozygous for G allele showed a higher sensitivity (lower threshold) to oleic acid than AA subjects. It must be noted, however, that in Melis et al. (2015), both males and females were included and results were reported without controlling for sex, whereas we only tested females. Barragán et al. (2018) reported that sex differences exist in ability to taste; significant associations were noted between a higher perception and preference for sour in females only, but a higher perception of sweet was significantly associated with a higher preference for bitter in both males and females. No such research has been undertaken regarding FTS, however it has been stated that a heterogeneous cohort may reduce the validity of results (Grimaldi et al., 2017), which may explain why the current study does not corroborate the findings of Melis et al. (2015). Furthermore Pepino et al. (2012) examined genetic differences in FTS, using two fatty acids (oleic acid and triolein), with an obese cohort (n = 21), consisting of males and females of Caucasian and African American decent. Results displayed that those homozygous for the rs1761667 G allele had lower detection thresholds for oleic acid and triolein than subjects homozygous for the A allele. To date, it is evident that research exploring genetic contributions to FTS is largely heterogeneous, therefore in order to determine the impact differing rs1761667 genotypes have on taste perception further research on a homogenous cohort is required.

We have reported original findings in relation to associations between *BDNF* rs6265 and *TNNI3K* rs1514175, and FTS. Firstly, we present that participants carrying the *BDNF* wildtype (T) allele, previously associated with a decreased BMI, had a lower fat taste threshold (increased sensitivity) when compared to those without. The rs6265 SNP has been associated with differing circulating *BDNF* concentrations, with a 0.772 ng/mL increase per minor allele (C), highlighting potential genetic influence to appetite regulation (Pandit et al., 2020). Circulating *BDNF* was not analysed in the current study, however future research should endeavour to include this alongside genetic analysis. In addition, the rs6265 SNP has been linked to dietary behaviour on many occasions, specifically restricted eating patterns related to eating disorders (Rosas-Vargas et al., 2011). Baseline diet can influence taste sensitivity, and it has been demonstrated that diet modification can lead to changes in FTS (Costanzo et al., 2018; Newman, Bolhuis, Torres, & Keast, 2016). It can therefore be hypothesised that FTS may be indirectly affected by rs6265

Table 4
Mean ± SD dietary intake, as determined by food frequency questionnaire, by genotype group, n = 48.

Gene, SNP	GT	TE	p	CHO	p	Protein	p	Fat	p	MUFA	p	PUFA	p	SFA	p
BDNF	CC	1609 ± 453	0.197	173 ± 49	0.202	79 ± 26	0.929	68 ± 21	0.518	26 ± 9	0.760	12 ± 5	0.254	23 ± 8	0.512
rs6265	CT/TT	1833 ± 586		203 ± 60		84 ± 35		78 ± 36		30 ± 15		16 ± 8		26 ± 12	
CD36	GG/AG	1821 ± 609	0.597	200 ± 60	0.504	85 ± 37	0.239	78 ± 36	0.364	30 ± 15	0.596	15 ± 8	0.405	27 ± 12	0.364
rs1761667	AA	1646 ± 383		187 ± 51		73 ± 16		67 ± 20		26 ± 8		12 ± 4		23 ± 8	
FTO	AA/AT	1807 ± 547	0.932	194 ± 59	0.588	79 ± 21	0.918	78 ± 36	0.718	30 ± 16	0.884	14 ± 8	0.79	27 ± 12	0.705
rs9939609	TT	1723 ± 575		192 ± 57		85 ± 43		71 ± 28		27 ± 11		14 ± 7		24 ± 9	
TNNI3K	AA/AG	1899 ± 572	0.008	206 ± 56	0.893	87 ± 36	0.159	82 ± 35	0.009	32 ± 15	0.027	16 ± 8	0.051	28 ± 12	0.008
rs1514175	GG	1497 ± 410		170 ± 56		73 ± 21		60 ± 18		23 ± 8		12 ± 5		20 ± 7	

*, $p < 0.05$ (Mann-Whitney U Test/Independent T Test, as appropriate); SD, standard deviation; SNP, single nucleotide polymorphism; GT, genotype; TE, total energy intake; CHO, carbohydrate; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; BDNF, Brain Derived Neurotrophic Factor Gene; CD36, cluster of differentiation 36; FTO, fat mass and obesity associated gene; TNNI3K, Troponin I-Interacting Protein Kinase Gene.

genotype via differences in habitual dietary pattern, however this is speculative and warrants further research. It is noteworthy to mention that the mechanistic actions relating to weight gain (and subsequently metabolic disease) of both *BDNF* and CD36 have recently been linked in rodent studies (Liu, Tso, & Woods, 2018). Mice containing the human $BDNF^{(Met/Met(M/M))}$ variant fed a normal diet presented with a significantly increased body weight compared to $BDNF^{(Val/Val(V/V))}$ mice, and that $BDNF^{(M/M)}$ mice had a higher level of *CD36* mRNA, serum and protein (Yang, Park, & Cho, 2018). As our study is the first human study to investigate both genes in relation to FTS and dietary intake, future research is needed to confirm whether differences in FTS and/or dietary fat intake are related to both rs6265 and rs1761667 SNPs, and whether these are associated with markers of metabolic disease.

Lastly, we presented that participants carrying the rs1514175 A-allele had a moderately higher fat taste threshold compared to those without, and that the AA/AG genotype group had a higher EI, total fat intake, and subsequently a higher MUFA and SFA intake when compared to the GG genotype. As no mechanism has been described, it is difficult to fully elucidate the link between FTS and dietary fat intake, however previous research has reported effects on dietary intake. McCaffery et al. (2012) demonstrated an association between TNNI3K and lower percentage EI from protein, which was nominally associated with more frequent servings of fats, oils and sweets. Later, Cornelis et al. (2014) investigated rs1514175 and eating behaviour, showing that rs1514175 and uncontrollable eating were positively associated.

4.1.1. Strengths and limitations

A strength of this study was the homogeneity of the cohort. Grimaldi et al. (2017) states that genotypic assessment should explicitly specify the subgroup investigated (e.g. sex, ancestral background etc.), in order for results to be considered probable. Nevertheless, due to the heterogeneity of published research involving FTS, further studies are required to assess the accuracy of the results within the specified population. Another strength of this study is the method of FTS assessment used (force-choice triangle test) (Haryono et al., 2014). Forced-choice paradigms are stated to produce a criterion-free, unbiased threshold estimates (Green & Swets, 1966). Also, many others utilise the same method (Karmous et al., 2018; Mrizak et al., 2015; Sayed et al., 2015) and thus allows direct comparison. Furthermore, many, including our study, measure taste sensitivity on one occasion only. Validity of results could be improved by measuring on multiple occasions. In addition, when assessing FTS confounding factors can be present, such as non-taste sensory cues. Based on the reliable methodology used these non-taste sensory cues were minimised (Haryono et al., 2014). Moreover, diet records may be prone to bias and under-reporting. The average total energy intake was below UK recommendations, despite evidence suggesting that this is common in dietary intake research (Qi et al., 2014) it should be considered when interpreting and applying results. Lastly, the study sample size allowed only for exploratory analysis, despite being similar to other relevant published research (Burgess et al., 2018; Melis et al., 2015), study groups were not balanced, and in order to confirm these results, future studies are required that consider both minor allele frequency and attrition for non-tasters when recruiting participants.

5. Conclusions

The results of this study present that differences in FTS and dietary intake were apparent based on SNPs analysed. To the best of our knowledge, this is the first study to report that SNPs that have been previously associated with dietary intake (rs6265 *BDNF* and rs1514175 *TNNI3K*) are also associated with FTS. Due to the evident heterogeneity of previous research and the infancy of fat taste research in general, further research is required on a larger but equally ethically similar cohort.

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CRediT authorship contribution statement

Catherine A.M. Graham: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Project administration. **Leta Pilic:** Conceptualization, Investigation, Writing - original draft. **Alexandra King:** Conceptualization, Investigation, Writing - original draft. **Jonathan E. Nixon:** Investigation. **Julie Pipe:** Conceptualization, Investigation. **Juliet Holton:** Conceptualization, Investigation. **Krisztina Tamba:** Conceptualization, Investigation. **Gary Hearne:** Formal analysis. **Charles R. Pedlar:** Writing - original draft. **Silvia Lorente-Cebrián:** Conceptualization, Data curation, Writing - original draft. **Pedro González Muniesa:** Conceptualization, Data curation, Writing - original draft. **Yiannis Mavrommatis:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Project administration, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Barragán, R., Coltell, O., Portolés, O., Asensio, E. M., Sorlí, J. V., Ortega-Azorín, C., … Corella, D. (2018). Bitter, sweet, salty, sour and umami taste perception decreases with age: Sex-specific analysis, modulation by genetic variants and taste-preference associations in 18 to 80 year-old subjects. *Nutrients, 10*(10). https://doi.org/10.3390/nu10101539

Besnard, P., Passilly-Degrace, P., & Khan, N. A. (2016). Taste of fat: A Sixth taste modality? *Physiological Reviews, 96*(1), 151–176. https://doi.org/10.1152/physrev.00002.2015

Burgess, B., Melis, M., Scoular, K., Driver, M., Schaich, K. M., Keller, K. L., & Tepper, B. J. (2018). Effects of CD36 genotype on oral perception of oleic acid supplemented safflower oil emulsions in two ethnic groups: A preliminary study. *Journal of Food Science, 83*(5), 1373–1380. https://doi.org/10.1111/1750-3841.14115

Butler, A. A., & Cone, R. D. (2003). Knockout studies defining different roles for melanocortin receptors in energy homeostasis. *Annals of the New York Academy of Sciences, 994*, 240–245. http://www.ncbi.nlm.nih.gov/pubmed/12851322.

Chamoun, E., Hutchinson, J. M., Krystia, O., Mirotta, J. A., Mutch, D. M., Buchholz, A. C., & Ma, D. W. L. (2018). Single nucleotide polymorphisms in taste receptor genes are associated with snacking patterns of preschool-aged children in the guelph family health study: A pilot study. *Nutrients, 10*(2), 1–11. https://doi.org/10.3390/nu10020153

Chamoun, E., Mutch, D. M., Allen-Vercoe, E., Buchholz, A. C., Duncan, A. M., Spriet, L. L., … Ma, D. W. L. (2017). A review of the associations between single nucleotide polymorphisms in taste receptors, eating behaviors, and health. *Critical Reviews in Food Science and Nutrition, 58*(2), 194–207. https://doi.org/10.1080/10408398.2016.1152229

Cornelis, M. C., Rimm, E. B., Curhan, G. C., Kraft, P., Hunter, D. J., Hu, F. B., & van Dam, R. M. (2014). Obesity susceptibility loci and uncontrolled eating, emotional eating and cognitive restraint behaviors in men and women. *Obesity (Silver Spring Md.), 22*(5), E135–41. https://doi.org/10.1002/oby.20592

Costanzo, A., Nowson, C., Orellana, L., Bolhuis, D., Duesing, K., & Keast, R. (2018). Effect of dietary fat intake and genetics on fat taste sensitivity: a co-twin randomized controlled trial. *The American Journal of Clinical Nutrition, 107*(5), 683–694. https://doi.org/10.1093/ajcn/nqy022

Daoudi, H., Plesník, J., Sayed, A., Šerý, O., Rouabah, A., Rouabah, L., & Khan, N. A. (2015). Oral Fat Sensing and CD36 Gene Polymorphism in Algerian Lean and Obese Teenagers. *Nutrients, 7*(11), 9096–9104. https://doi.org/10.3390/nu7115455

El-Sohemy, A., Stewart, L., Khataan, Ln, Fontaine-Bisson, B., Kwong, P., Ozsungur, S., & Cornelis, M. C. (2007). Nutrigenomics of taste – Impact on food preferences and food

production. In *Nutrigenomics - Opportunities in Asia* (pp. 176–182). Basel: KARGER. https://doi.org/10.1159/000107194.
Farooqi, I. S., & O'Rahilly, S. (2005). Monogenic Obesity in Humans. *Annual Review of Medicine, 56*(1), 443–458. https://doi.org/10.1146/annurev.med.56.062904.144924
Frayling, T. M., Timpson, N. J., Weedon, M. N., Zeggini, E., Freathy, R. M., Lindgren, C. M., & McCarthy, M. I. (2007). A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science (New York, N.Y.), 316*(5826), 889–894. https://doi.org/10.1126/science.1141634
Fujii, R., Hishida, A., Suzuki, K., Imaeda, N., Goto, C., Hamajima, N., & Kondo, T. (2019). Cluster of differentiation 36 gene polymorphism (rs1761667) is associated with dietary MUFA intake and hypertension in a Japanese population. *British Journal of Nutrition, 121*(11), 1215–1222. https://doi.org/10.1017/S0007114519000679
Garver, W. S., Newman, S. B., Gonzales-Pacheco, D. M., Castillo, J. J., Jelinek, D., Heidenreich, R. A., & Orlando, R. A. (2013). The genetics of childhood obesity and interaction with dietary macronutrients. *Genes & Nutrition, 8*(3), 271–287. https://doi.org/10.1007/s12263-013-0339-5
Ghosh, A., Murugesan, G., Chen, K., Zhang, L., Wang, Q., Febbraio, M., & Silverstein, R. L. (2011). Platelet CD36 surface expression levels affect functional responses to oxidized LDL and are associated with inheritance of specific genetic polymorphisms. *Blood, 117*(23), 6355–6366. https://doi.org/10.1182/blood-2011-02-338582
Girardet, C., & Butler, A. A. (2014). Neural melanocortin receptors in obesity and related metabolic disorders. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1842*(3), 482–494. https://doi.org/10.1016/J.BBADIS.2013.05.004
Graham, C. A. M., Pedlar, C. R., Hearne, G., Lorente-Cebrián, S., González-Muniesa, P., & Mavrommatis, Y. (2020). The association of parental genetic, lifestyle, and social determinants of health with offspring overweight. *Lifestyle Genomics, 13*(2), 99–106. https://doi.org/10.1159/000505749
Green, D. M., & Swets, J. A. (1966). *Signal detection theory and psychophysics*. John Wiley & Sons Inc.
Grimaldi, K. A., van Ommen, B., Ordovas, J. M., Parnell, L. D., Mathers, J. C., Bendik, I., … Bouwman, J. (2017). Proposed guidelines to evaluate scientific validity and evidence for genotype-based dietary advice. *Genes and Nutrition, 12*(1), 1–12. https://doi.org/10.1186/s12263-017-0584-0
Haryono, R. Y., Sprajcer, M. A., & Keast, R. S. J. (2014). Measuring oral fatty acid thresholds, fat perception, fatty food liking, and papillae density in humans. *Journal of Visualized Experiments : JoVE*, (88)https://doi.org/10.3791/51236
Ikeda, K. (1909). New seasonings. *Journal of the Chemical Society of Tokyo, 30*, 820–836.
Johnson, F., & Wardle, J. (2014). Variety, palatability, and obesity. *Advances in Nutrition (Bethesda, Md.), 5*(6), 851–859. https://doi.org/10.3945/an.114.007120
Karmous, I., Plesník, J., Khan, A. S., Šerý, O., Abid, A., Mankai, A., & Khan, N. A. (2018). Orosensory detection of bitter in fat-taster healthy and obese participants: Genetic polymorphism of CD36 and TAS2R38. *Clinical Nutrition, 37*(1), 313–320. https://doi.org/10.1016/j.clnu.2017.06.004
Khera, A. V., Chaffin, M., Wade, K. H., Zahid, S., Brancale, J., Xia, R., & Kathiresan, S. (2019). Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood. *Cell, 177*(3), 587–596.e9. https://doi.org/10.1016/J.CELL.2019.03.028
Liu, M., Tso, P., & Woods, S. C. (2018). Receptor CD36 links a risk-associated allele to obesity and metabolic disorders. *Journal of Biological Chemistry, 293*(34), 13349–13350. https://doi.org/10.1074/jbc.H118.004818
Llewellyn, C. H., Trzaskowski, M., Van Jaarsveld, C. H., Plomin, R., & Wardle, J. (2014). Satiety mechanisms in genetic risk of obesity. *JAMA Pediatrics, 168*(4), 338–344. https://doi.org/10.1001/jamapediatrics.2013.4944
Loos, R. J. F., Lindgren, C. M., Li, S., Wheeler, E., Zhao, J. H., Prokopenko, I., … Mohlke, K. L. (2008). Common variants near MC4R are associated with fat mass, weight and risk of obesity. *Nature Genetics, 40*(6), 768–775. https://doi.org/10.1038/ng.140
Love-Gregory, L., Sherva, R., Schappe, T., Qi, J. S., McCrea, J., Klein, S., … Abumrad, N. A. (2011). Common CD36 SNPs reduce protein expression and may contribute to a protective atherogenic profile. *Human Molecular Genetics, 20*(1), 193–201. https://doi.org/10.1093/hmg/ddq449
Ma, X., Qiu, W. Q., Smith, C. E., Parnell, L., Jiang, Z., Ordovas, J. M., … Lai, C. Q. (2012). Association between BDNF-rs6265 and obesity in the Boston Puerto Rican Health Study. *Journal of Obesity*.
Mattes, R. D. (2010). Fat taste in humans: Is it a primary?. In *Fat Detection: Taste, Texture, and Post Ingestive Effects* (pp. 167–193). Florida, USA: CRC Press.
McCaffery, J. M., Papandonatos, G. D., Peter, I., Huggins, G. S., Raynor, H. A., Delahanty, L. M., … Look AHEAD Research Group. (2012). Obesity susceptibility loci and dietary intake in the Look AHEAD Trial. *The American Journal of Clinical Nutrition, 95*(6), 1477–1486. https://doi.org/10.3945/ajcn.111.026955
Melis, M., Carta, G., Pintus, S., Pintus, P., Piras, C. A., Murru, E., … Tomassini Barbarossa, I. (2017). Polymorphism rs1761667 in the CD36 gene is associated to changes in fatty acid metabolism and circulating endocannabinoid levels distinctively in normal weight and obese subjects. *Frontiers in Physiology, 8*, 1006. https://doi.org/10.3389/fphys.2017.01006
Melis, M., Mastinu, M., Sollai, G., Paduano, D., Chicco, F., Magrì, S., & Barbarossa, I. T. (2020). Taste changes in patients with inflammatory bowel disease: Associations with PROP phenotypes and polymorphisms in the salivary protein, gustin and CD36 receptor genes. *Nutrients, 12*(2), 1–17. https://doi.org/10.3390/nu12020409
Melis, M., Sollai, G., Muroni, P., Crnjar, R., & Barbarossa, I. T. (2015). Associations between orosensory perception of oleic acid, the common single nucleotide polymorphisms (rs1761667 and rs1527483) in the CD36 gene, and 6-n-propylthiouracil (PROP) tasting. *Nutrients, 7*(3), 2068–2084. https://doi.org/10.3390/nu7032068
Mrizak, I., Šerý, O., Plesnik, J., Arfa, A., Fekih, M., Bouslema, A., … Khan, N. A. (2015). The A allele of cluster of differentiation 36 (CD36) SNP 1761667 associates with decreased lipid taste perception in obese Tunisian women. *The British Journal of Nutrition, 113*(8), 1330–1337. https://doi.org/10.1017/S0007114515000343
Mulligan, A. A., Luben, R. N., Bhaniani, A., Parry-Smith, D. J., O'Connor, L., Khawaja, A. P., & Khaw, K. T. (2014). A new tool for converting food frequency questionnaire data into nutrient and food group values: FETA research methods and availability. *BMJ Open, 4*(3). https://doi.org/10.1136/bmjopen-2013-004503
Newman, L. P., Bolhuis, D. P., Torres, S. J., & Keast, R. S. J. (2016). Dietary fat restriction increases fat taste sensitivity in people with obesity. *Obesity, 24*(2), 328–334. https://doi.org/10.1002/oby.21357
Ong, H.-H., Tan, Y.-N., & Say, Y.-H. (2017). Fatty acid translocase gene CD36 rs1527483 variant influences oral fat perception in Malaysian subjects. *Physiology & Behavior, 168*, 128–137. https://doi.org/10.1016/j.physbeh.2016.11.006
Pandit, M., Behl, T., Sachdeva, M., & Arora, S. (2020). Role of brain derived neurotropic factor in obesity. *Obesity Medicine, 17*(January). https://doi.org/10.1016/j.obmed.2020.100189
Pandurangan, M., & Hwang, I. (2015). Systemic Mechanism of Taste, Flavour and Palatability in Brain. *Applied Biochemistry and Biotechnology, 175*(6), 3133–3147. https://doi.org/10.1007/s12010-015-1488-3
Pepino, M. Y., Love-Gregory, L., Klein, S., & Abumrad, N. A. (2012). The fatty acid translocase gene CD36 and lingual lipase influence oral sensitivity to fat in obese subjects. *Journal of Lipid Research, 53*(3), 561–566. https://doi.org/10.1194/jlr.M021873
Pioltine, M. B., de Melo, M. E., Santos, A., Machado, A. D., Fernandes, A. E., Fujiwara, C. T., … Mancini, M. C. (2016). Genetic variation in CD36 Is Associated With Decreased Fat And Sugar Intake In Obese Children And Adolescents. *Journal of Nutrigenetics and Nutrigenomics, 9*(5–6), 300–305. https://doi.org/10.1159/000455915
Qi, Q., Downer, M. K., Tanaka, T., Smith, C. E., Kilpela, T. O., Sonestedt, E., … Renstro, F. (2014). FTO genetic variants, dietary intake and body mass index : insights from 177330 individuals. *Human Molecular Genetics, 23*(25), 6961–6972. https://doi.org/10.1093/hmg/ddu411
Ramos-Lopez, O., Roman, S., Martinez-Lopez, E., Fierro, N. A., Gonzalez-Aldaco, K., Jose-Abrego, A., & Panduro, A. (2016). CD36 genetic variation, fat intake and liver fibrosis in chronic hepatitis C virus infection. *World Journal of Hepatology, 8*(25), 1067–1074. https://doi.org/10.4254/wjh.v8.i25.1067
Rosas-Vargas, H., Martínez-Ezquerro, J. D., & Bienvenu, T. (2011). Brain-Derived Neurotrophic Factor, Food Intake Regulation, and Obesity. *Archives of Medical Research, 42*(6), 482–494. https://doi.org/10.1016/j.arcmed.2011.09.005
Running, C. A., Craig, B. A., & Mattes, R. D. (2015). Oleogustus: The unique taste of fat. *Chemical Senses, 40*(7), 507–516. https://doi.org/10.1093/chemse/bjv036
Sayed, A., Šerý, O., Plesnik, J., Daoudi, H., Rouabah, A., Rouabah, L., & Khan, N. A. (2015). CD36 AA genotype is associated with decreased lipid taste perception in young obese, but not lean, children. *International Journal of Obesity (2005), 39*(6), 920–924. https://doi.org/10.1038/ijo.2015.20
Sclafani, A., Ackroff, K., & Abumrad, N. A. (2007). CD36 gene deletion reduces fat preference and intake but not post-oral fat conditioning in mice. *American Journal of Physiology - Regulatory Integrative and Comparative Physiology, 293*(5). https://doi.org/10.1152/ajpregu.00211.2007
Shugart, Y. Y., Chen, L., Day, I. N. M., Lewis, S. J., Timpson, N. J., Yuan, W., … Davey-Smith, G. (2009). Two British women studies replicated the association between the Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) and BMI. *European Journal of Human Genetics, 17*(8), 1050–1055. https://doi.org/10.1038/ejhg.2008.272
Speakman, J. R. (2015). The 'Fat Mass and Obesity Related' (FTO) gene: Mechanisms of impact on obesity and energy balance. *Current Obesity Reports, 4*(1), 73–91. https://doi.org/10.1007/s13679-015-0143-1
Speliotes, E. K., Willer, C. J., Berndt, S. I., Monda, K. L., Thorleifsson, G., Jackson, A. U., … Loos, R. J. F. (2010). Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nature Genetics, 42*(11), 937–948. https://doi.org/10.1038/ng.686
Stewart, J. E., & Keast, R. (2012). Recent fat intake modulates fat taste sensitivity in lean and overweight subjects. *International Journal of Obesity, 36*(6), 834–842. https://doi.org/10.1038/ijo.2011.155
Stewart, J. E., Newman, L. P., & Keast, R. S. (2011). Oral sensitivity to oleic acid is associated with fat intake and body mass index. *Clinical Nutrition, 30*(6), 838–844. https://doi.org/10.1016/j.clnu.2011.06.007
Tanofsky-Kraff, M., Han, J. C., Anandalingam, K., Shomaker, L. B., Columbo, K. M., Wolkoff, L. E., … Yanovski, J. A. (2009). The FTO gene rs9939609 obesity-risk allele and loss of control over eating. *The American Journal of Clinical Nutrition, 90*(6), 1483–1488. https://doi.org/10.3945/ajcn.2009.28439
Timpson, N. J., Emmett, P. M., Frayling, T. M., Rogers, I., Hattersley, A. T., McCarthy, M. I., & Davey Smith, G. (2008). The fat mass- and obesity-associated locus and dietary intake in children. *The American Journal of Clinical Nutrition, 88*(4), 971–978. http://www.ncbi.nlm.nih.gov/pubmed/18842783.
Tucker, R. M., Kaiser, K. A., Parman, M. A., George, B. J., Allison, D. B., & Mattes, R. D. (2017). Comparisons of fatty acid taste detection thresholds in people who are lean vs. overweight or obese: A systematic review and meta-analysis. *PloS One*. https://doi.org/10.1371/journal.pone.0169583
Wåhlén, K., Sjölin, E., & Hoffstedt, J. (2008). The common rs9939609 gene variant of the fat mass- and obesity-associated gene FTO is related to fat cell lipolysis. *Journal of Lipid Research, 49*(3), 607–611. https://doi.org/10.1194/jlr.M700448-JLR200
Wang, J., & Shete, S. (2011). Testing Hardy-Weinberg proportions in a frequency-matched case-control genetic association study. *PLoS ONE, 6*(11). https://doi.org/10.1371/journal.pone.0027642

Wang, J., & Shete, S. (2012). In *Chapter 6 Testing Departure from Hardy – Weinberg Proportions*. https://doi.org/10.1007/978-1-61779-555-8

World Health Organization. (2018). WHO | Obesity and overweight. Retrieved April 12, 2018, from <http://www.who.int/mediacentre/factsheets/fs311/en/>.

Yang, J., Park, K. W., & Cho, S. (2018). Inhibition of the CD36 receptor reduces visceral fat accumulation and improves insulin resistance in obese mice carrying the BDNF-Val66Met variant. *Journal of Biological Chemistry, 293*(34), 13338–13348. https://doi.org/10.1074/jbc.RA118.002405