UNIVERSITÀ
DEGLI STUDI
DI TRIESTE

# UNIVERSITÀ DEGLI STUDI DI TRIESTE

## XXXVIII CICLO DEL DOTTORATO DI RICERCA IN

### Scienze della Riproduzione e dello Sviluppo

# Exploring the genetics of taste and its implications in food preferences and health status

Settore scientifico-disciplinare: **Genetica Medica**


DOTTORANDO / A
**Francesco Piluso**

COORDINATORE
**PROF. Adamo Pio D'Adamo**

SUPERVISORE DI TESI
**PROF. Paolo Gasparini**


**ANNO ACCADEMICO 2024/2025**

# Abstract (English)


**Introduction**

Fat, a newly identified taste, has been associated with the cluster of differentiation 36 (*CD36*) gene, which encodes the CD36 receptor protein, implicated in the perception of dietary free fatty acids in the oral environment. The rs1761667 variant has been associated with fat taste sensitivity; nevertheless, results reported in the literature are often contrasting. Further, umami is a well-established taste with known receptors. The combination of these tastes is common in food, and umami tastants have also been linked to variations in dietary fat intake. Nevertheless, these two taste perceptions have not been extensively investigated together, thereby missing the opportunity to understand better how tastes may interact and how this may influence food choices. This PhD project aimed to assess whether there is an association between fat taste sensitivity and umami taste perception with implications regarding dietary intake, BMI, and body composition. Furthermore, the role of *CD36* rs1761667 in the aforementioned phenotypes was investigated.

**Methods**

Three different studies were conducted: 1) a field study on 235 individuals from Italy, 2) a laboratory study on 49 individuals from the UK, and 3) a laboratory study on 57 individuals conducted at the Lake Lucerne Institute in Switzerland. Common data collected across all three studies included demographics, anthropometrics, BMI, and *CD36* rs1761667 genotyping. Regarding Study 1, liking of fat and umami foods was assessed via questionnaire, and dietary intake data were collected and converted into a Diet Quality Score (DQS). In Study 2, perceptions of fatty and umami foods (intensity and liking) were assessed, and, as in Study 1, dietary intake data were collected and converted into a DQS. For Study 3, fat taste sensitivity (FTS) was assessed using Oleic acid detection threshold measurement, and umami perception (intensity and liking) and fatty food perception (both regular and low-fat versions) were evaluated. Additionally, body composition data were collected (e.g., fat mass percentage, visceral fat score).

**Result**

In Study 1, the rs1761667 A-allele was associated with a reduced liking for fatty and umami foods in individuals with BMI $\geq$ 25 kg/m$^2$; nevertheless, no significant association was found between BMI and DQS. In Study 2, the rs1761667 A-allele was associated with an increased intensity perceived from tasting the umami food samples, and a significant positive association of rs1761667 with BMI and DQS was additionally found. Regarding Study 3, no association was found between fat taste sensitivity and umami perception. Additionally, in our cohort, no association between FTS and adiposity was found. Nevertheless, a positive association was found between the intensity perceived from umami samples and the intensity perceived from fat food samples. Regarding genetics, a negative pattern between *CD36* rs1761667 GG genotype and liking reported from tasting umami samples was observed, and, additionally, the rs1761667 A-allele was associated with reduced perceived intensity from tasting fat food samples.

**Conclusions**

This study is the first to extensively address the potential links between fat taste sensitivity and umami taste perception, thanks to the collection of a wide set of data spanning three different research projects. Our results highlight a possible association between umami perception and fat food perception, and that *CD36* rs1761667, which is related to fat taste sensitivity, may also be a predictor of differences in umami taste perception. Nevertheless, no association between *CD36*

rs1761667 and fat taste sensitivity has been reported, highlighting a previously described issue regarding this link between genetics and the phenotype, and opening up the necessity of a better and standardised approach to assess fat taste perception. Although further studies in wider cohorts are needed to confirm the obtained results, our findings highlight a new potential taste interplay that may be implemented in personalised nutritional practice.

# Abstract (Italiano)


**Introduzione**

Il gusto grasso è stato associato al gene *Cluster of Differentiation 36* (*CD36*), che codifica per il recettore CD36 coinvolto nella percezione degli acidi grassi liberi. La variante rs1761667 è stata associata alla sensibilità verso il gusto grasso; tuttavia, i risultati riportati in letteratura sono contrastanti. L'Umami è un gusto ben consolidato con recettori ben noti. La combinazione di questi sapori è comune a livello alimentare ed è stato osservato che le molecole umami sono state ulteriormente associate anche a differenze nell'assunzione di grassi alimentari. Queste due percezioni gustative non sono state studiate in modo approfondito insieme, perdendo così la possibilità di comprendere meglio come i sapori possano interagire tra loro e come ciò possa influire sulle scelte alimentari. Questo progetto di dottorato mira a valutare se esiste un'associazione tra la sensibilità al gusto grasso e la percezione del gusto umami con implicazioni relative all'assunzione alimentare e alla composizione corporea. Inoltre, abbiamo considerato il ruolo che la variante rs1761667 del gene *CD36* può svolgere in tutti i fenotipi sopra menzionati.

**Metodi**

Sono stati condotti tre studi: 1) uno studio su 235 individui provenienti dall'Italia, 2) uno studio su 49 individui provenienti dal Regno Unito e 3) uno su 57 individui condotto in Svizzera. I dati comuni raccolti in tutti gli studi sono: demografici, antropometrici, IMC e genotipo della variante *CD36* rs1761667. Per quanto riguarda lo studio 1, il gradimento dei cibi grassi e umami è stato valutato tramite questionario e sono stati raccolti dati sull'assunzione alimentare poi convertiti in un punteggio di qualità. Per lo studio 2, è stata valutata la percezione dei cibi grassi e dei cibi umami e, analogamente allo studio 1, sono stati raccolti dati sull'assunzione alimentare poi convertiti in un punteggio di qualità (Diet Quality Score, DQS). Per lo studio 3, il gusto grasso è stata valutato mediante la misurazione della soglia di rilevamento dell'acido oleico, mentre sono state valutate la percezione dell'umami e la percezione dei cibi grassi. Inoltre, sono stati raccolti dati sulla composizione corporea.

**Risultati**

Nello Studio 1, l'allele A di rs1761667 era associato ad un ridotto gradimento per i cibi grassi e umami in individui con IMC $\geq$ 25 kg/m. Nello Studio 2, l'allele A è stato associato a una maggiore intensità percepita dai campioni di alimenti umami ed è stata inoltre riscontrata un'associazione positiva significativa tra la variante, l'IMC e il DQS. Nello Studio 3, non è stata riscontrata alcuna associazione tra la sensibilità al gusto grasso e la percezione dell'umami. Tuttavia, è stata evidenziata un'associazione positiva tra l'intensità percepita dai campioni umani e l'intensità percepita dai campioni grassi. Abbiamo osservato un pattern negativo tra il genotipo GG di rs1761667 e il gradimento riportato dei campioni umani e, inoltre, abbiamo riscontrato che l'allele A era associato a una ridotta intensità percepita dai campioni di cibi grassi.

**Conclusioni**

Questo studio è il primo ad affrontare in modo approfondito i potenziali legami tra la sensibilità al gusto grasso e la percezione del gusto umami grazie alla tre diversi progetti di ricerca. I nostri risultati evidenziano una possibile associazione tra la percezione dell'umami e la percezione dei cibi grassi e che la variante rs1761667 potrebbe anche essere un fattore predittivo delle differenze nella percezione del gusto umami. Tuttavia, non abbiamo osservato alcuna associazione tra questa variante ed il gusto grasso evidenziando una questione già descritta in precedenza riguardo al

legame tra genetica e fenotipo e aprendo la strada alla necessità di un approccio standardizzato per valutare la percezione del gusto del grasso. Sebbene siano necessari ulteriori studi in coorti più ampie per confermare i risultati ottenuti, questi evidenziano una nuova potenziale interazione tra gusti che potrebbe essere implementata nella pratica nutrizionale personalizzata.

# Index

# 1.0 Summary of the project

Taste (or gustation) is one of the five human senses. It is considered the gatekeeper of all ingested substances, allowing individuals to assess the quality of food and potential treats (e.g., poisons, spoiled foods). There are five recognised tastes: sweet, bitter, salty, sour, and umami [1]. In the last decade, a new taste has been proposed: fat taste or *oleogustus* [2]. Fat taste is the perception of dietary non-esterified free fatty acids (NEFAs or FFAs) in the oral environment (e.g., oleic acid, linoleic acid, etc.). Humans can perceive FFAs [3]; however, distinguishing among different tastants is difficult [4], and the scientific community has yet to reach consensus on classifying this perception as a canonical taste.

Nevertheless, researchers have shown significant interest in the topic due to its potential implications for human health. High-fat foods are highly palatable yet high in calories, so excessive consumption may lead to weight gain and, in turn, burden health conditions (e.g., obesity) [4]. Fat taste ability shows high interindividual variability [2,4], with multiple factors involved, including saliva, texture, tongue morphology, and genetics [5]. As with the other tastes, a potential fat taste receptor has been identified: Cluster of Differentiation 36 (CD36), a receptor-like glycoprotein expressed apically on taste bud cells [7], which binds long-chain FFAs.

Genetics has been demonstrated to encompass taste perception [6]. The codifying gene *CD36* for the fat taste receptor has been investigated to elucidate the role of singe nucleotide polymorphisms (SNPs) The most studied common variant rs1761667 (G>A), as reviewed by Jaime-Lara *et al.* [5], has been associated with reduced protein expression [7] and then subsequently fat taste sensitivity (FTS), dietary fat intake, and adiposity. Still, results are often contradictory [10–15], highlighting the need for further research to better understand the role of this SNP in the aforementioned phenotypes. Fat taste perception has already been associated with other taste perceptions (e.g., bitter) [8], but no work has been widely conducted considering umami.

The combination of dietary fats and umami is common in foods (e.g., meats, aged cheeses, etc.). Umami is a well-established taste, first described by Dr. Kikunae Ikeda [1]. In Japanese, umami means "*deliciousness,*" and amino acids elucidate its perception. The main chemical tastant is L-glutamate (glutamic acid), which is found in foods such as meats, fish, aged cheeses, broths, and more [9]. The most common umami compound, used for seasoning and research, is monosodium glutamate (MSG).

Both fat and umami tastes can play a key role in human health. For example, individuals with obesity have shown a high preference for foods that can be labeled as umami but also fatty [10]. High-fat and ultra-processed foods are highly palatable, and their excessive consumption has been associated with weight gain and obesity [11]. On the other hand, MSG has been studied for its possible role in reducing salt intake while maintaining palatability and reducing dietary fat intake [12–14]. These two tastes have never been extensively studied together; thus, how they interact is unknown. This knowledge may influence nutritional practice, for example, developing taste-based personalised nutrition strategies.

This project's main aim is to address this gap by investigating whether there is an association between FTS, umami food perception, fat food perception, BMI, adiposity, and diet quality components, through three independent studies.

## 1.1 Aims of the studies.

Fat and umami have never been extensively studied together; thus, how they may interact is unknown. This knowledge may influence nutritional practice, for example, developing taste-based personalised nutrition strategies.
This project's main aim is to address this gap by investigating whether there is an association between FTS, umami food perception, fat food perception, BMI, adiposity, and diet quality components, through three independent studies.

Considering the literature gap and the lack of comprehensive studies aimed at investigating fat and umami tastes together, this project aimed to:

- Investigate the association between *CD36* rs1761667 and fat and umami-tasting food liking. As secondary aims, differences in BMI and diet quality were assessed based on the *CD36* rs1761667 genotype. This investigation was conducted on Study 1, a study of 235 individuals from a larger data collection carried out in Friuli Venezia Giulia (FVG), a region in north-eastern Italy, in 2014-2015.

- Investigate the association between *CD36* rs1761667 and fat and umami food perception (intensity and liking). As a secondary aim, similar to Study 1, the relationship between CD36 rs1761667, BMI, and diet-quality components was assessed. This investigation was carried out in collaboration with St. Mary's University, London, UK, and conducted on 49 individuals from the United Kingdom (UK) in **Study 2**.

- Investigate whether FTS may encompass umami perception, assessed by food sample tasting, fat food perception, BMI, and adiposity markers. As a secondary aim, *CD36* rs1761667 was investigated for its possible role in the aforementioned phenotypes. These investigations were conducted in Study 3 on 57 individuals from Switzerland, in collaboration with the Lake Lucerne Institute, Vitznau.

This thesis provides a better insight into how fat and umami tastes may interact with each other and influence food preferences and dietary choices. It features such as BMI and adiposity, and subsequently health status. This information could affect personalised nutrition strategies. The content of this thesis is summarised in **Figure 1**.

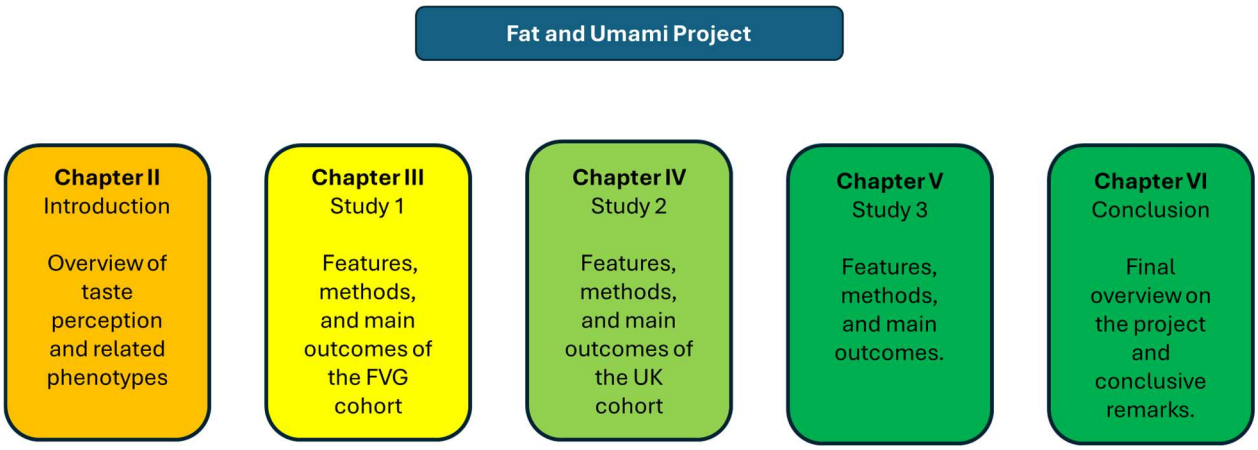


**Figure 1.** Schematic of the structure of the thesis and contents for every chapter.

All the analyses included in this Thesis were performed at the I.R.C.C.S. "Burlo Garofolo" under the supervision of Prof. Paolo Gasparini and Dr. Maria Pina Concas. Data collection for Study 3 was conducted at Lake Lucerne Institute AG under the supervision of Dr. Catherine Anne-Marie Graham. The complete workflow for the studies (Chapters III–V) is shown in **Figure 2.**

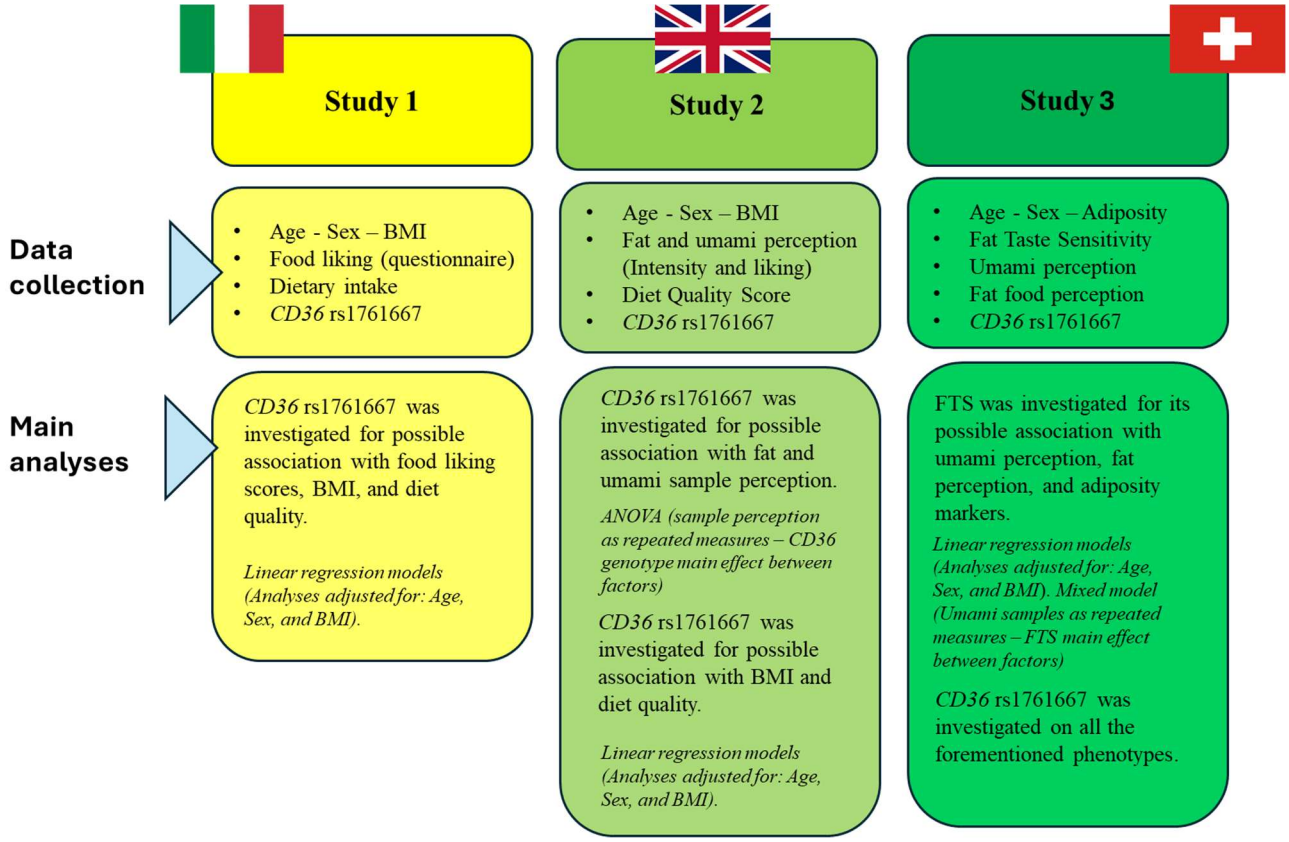


**Figure 2.** Description of the workflow for every project.

# 2.0 Chapter II - Introduction

## 2.1 Taste

Taste (or gustation) is one of the five human senses, along with hearing, sight, touch, and smell. It is crucial to assess the quality of ingested food to identify its health-related components and potential hazards (e.g., toxins). Commonly, taste and flavour are considered synonymous, despite a clearly defined difference between them. Flavour is the integration of different perceptions such as taste, smell, temperature, and texture. Taste is the sensation given by the interaction between chemical tastants in foods and specific receptors on the tongue [15]. Humans can perceive five canonical tastes: sweet, bitter, sour, salty, and umami [1]. A sixth taste is under debate and is called Oleogustus, or fat taste (Figure 3) [2].

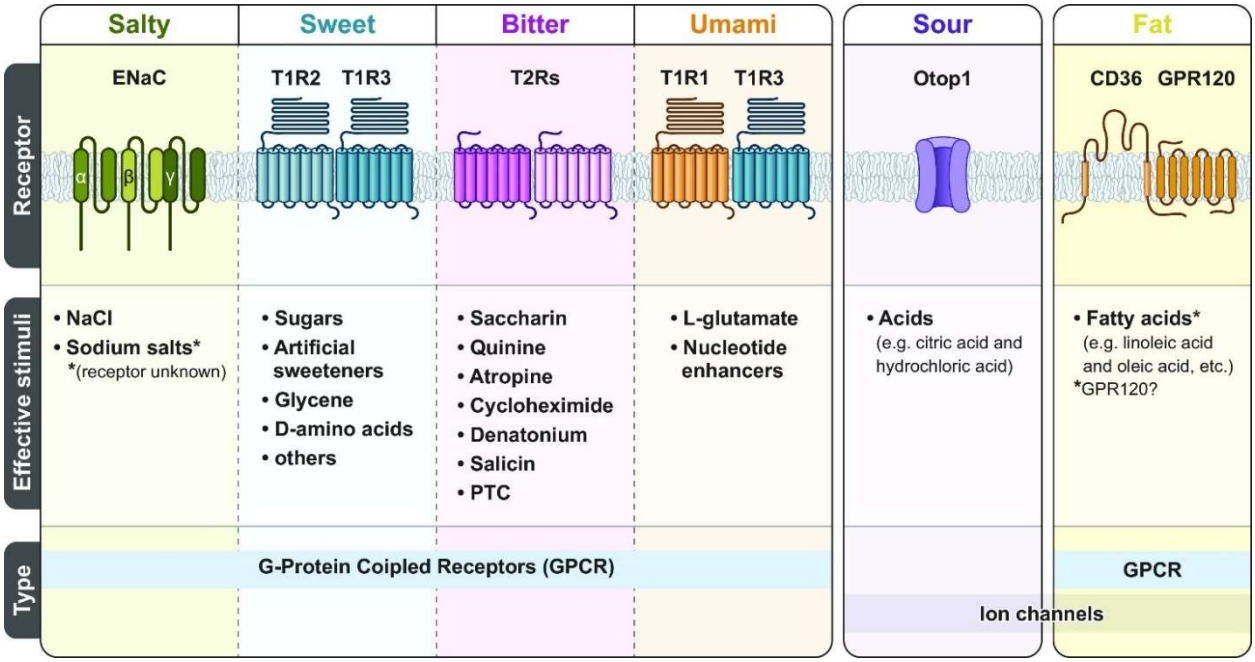


**Figure 3.** A summary of the five established tastes: salty, sweet, bitter, umami, and sour. Also, *Oleogustus*, or fat taste, is described. For every taste, receptors (and type), and chemical tastants (or effective stimuli) are described. Original picture from the work of Jaime-Lara *et al*. 2022 [6].

## 2.2 Structure of the tongue

The tongue is considered the primary organ for taste. The structures labelled *'house of the sensorial perception'* are the papillae. The human tongue has four types of papillae: fungiform, foliate, circumvallate, and filiform (**Figure 4**).

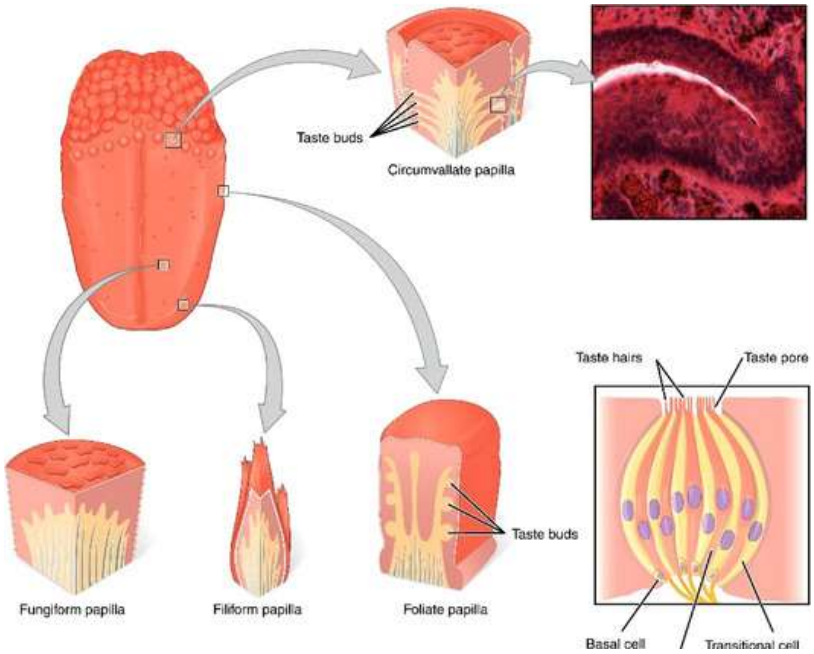


**Figure 4.** Anatomy of the human tongue. Four types of lingual papillae (circumvallate, fungiform, filiform, and foliate) can be observed in detail. A cross-section of a circumvallate papilla is shown upper right. A representation of a taste bud (basal, gustatory, and transitional cells highlighted) is shown lower right (original picture from OpenStax Anatomy & Physiology, 2016) [23].

Filiform papillae transduce sensations such as touch, temperature, and nociception (e.g., pain), whereas the remaining ones harbour taste buds [16,17]. Fungiform papillae are mushroom-shaped structures protruding on the surface of the tongue. On average, humans have ~195 fungiform papillae, of which the majority (~87%) are located at the anterior 2cm of the tongue [17].
Foliate papillae are located on the lateral sides of the tongue, containing ~100 taste buds [17].
Circumvallate papillae are located at the posterior of the tongue, forming an inverted V and harbouring over one hundred taste buds.
Taste buds are the primary sensory unit for taste. They are located under the keratinous layer of the papillae with the taste pore exposed to the external environment. A taste bud is composed of ~150-300 tightly packed epithelial cylindrical cells [23], which can be classified into five types: type I, type II, type III, basal cells, and neuronal processes.
Research has shown that each taste cell corresponds to only one taste modality (e.g., a type 2 cell may express umami receptors but lacks bitter receptors) [18].
The transmission of the sensory information from the tongue to the central nervous system (CNS) appears to be labelled line (each sensory receptor and its corresponding neural pathway are dedicated to a specific sensory modality) [19]. Three CNs innervate the tongue: chorda tympani (CN-VII), glossopharyngeal (CN-IX), and trigeminal (CN-V). Taste information is conducted and processed to the gustatory cortex insula, for which a gustatory map has been developed [20].

# 2.3 Taste perception

### 2.3.1 Sweet, Bitter, Salty, and Sour taste

Sweet taste allows humans to identify foods that are rich in saccharides, which are the primary energy source. Humans are, by instinct, attracted to sweetness (e.g., the positive stereotypical behaviour displayed by children when exposed to sugar solutions) [21]. Genetically, sweet taste is mediated by the expression of two genes, *TAS1R2* and *TAS1R3*, on type II taste cells. The two genes

encode the C-class receptors, G protein–coupled receptors (GPCRs) T1R2 and T1R3. This receptor is a dimer, with two subunits, and the active site features a Venus flytrap module (VFTM) [22]. The module binds the ligand and mediates the activation of the respective G proteins. Regarding sweet taste, the main ligands are small sugars (e.g., glucose), and both subunits of the receptor present a VFTM that can bind a wide range of sweeteners [23]. The sweet taste transduction mechanism is further explained in the dedicated paragraph on umami taste.
From a genetic perspective, SNPs encompassing the genes codifying for the two subunits (*TAS1R2* and *TAS1R3*) have been studied for the effect on sugar sensitivity [24], and, additionally, may be of interest for the possible impact on health status due to the role of sugar intake on obesity development and chronic diseases [25,26]. For example, rs35744813 and rs307355 have been associated with sucrose sensitivity, and both are predicted to encompass the regulatory region of *TAS1R3* [6,27].

Bitter taste perception is, evolutionarily, a defence form against toxins in nature. This mechanism is not exclusive to humans and is common among vertebrates [28]. It has been demonstrated that numerous toxic chemicals in vegetables are perceived as bitter. Nevertheless, this role, in humans, in modern agriculture, is deemed near-redundant. Even if crops still present bitter toxins (e.g., "cassava") and their taste identification is still fundamental [36], bitter-tasting vegetables can also be nontoxic (e.g., cruciferous vegetables) and, for this reason, bitterness is only discouraging consumption, but not excluding it completely [29].
Bitter taste perception is mediated, as sweet taste perception, by GPCRs expressed on type II taste bud cells. These receptors were identified approximately 20 years ago and are designated TAS2Rs [30,31]. Bitter taste transduction, as for sweet taste, will be further explained in the umami taste dedicated paragraph.
From a genetic perspective, the discovery of these receptors occurred simultaneously with the completion of the Human Genome Project. Thirty-three genes, 25 functional loci, and eight pseudogenes were identified that codify for TAS2Rs. These genes are organised in clusters on chromosomes 5, 7, and 12 [30–32]. They are expressed not only in taste bud cells but also, like sweet taste receptor genes, in chemosensory cells in the gut and in bronchial smooth muscle, detecting ingested and inhaled agonists [33,34]. TAS2Rs are usually coexpressed in taste bud cells. On average, a cell may express a random subset of ~5-10 of the 25 possible receptors, mediating sensitivity to a specific compound that differs for every cell [35]. Bitter taste is one of the most studied tastes, and the genetics underlying this perception is among the best characterised. The evolutionary role of bitter taste is to prevent ingestion of toxic agents [36]. Humans have developed a wide family of genes (named *TAS2Rs*) that encode receptors that detect these chemicals. These genes are allocated on chromosomes 7 and 12 [30]. All these genes are encompassed by SNPs that have been associated with a wide range of responses to bitter tastants, from complete insensitivity to the opposite extreme [37–39]. Among this vast gene family, one of the most studied and well-characterised for the effect of genetics is *TAS2R38*. This gene is located on chromosome 7, in a cluster of bitter receptor genes, and the receptor recognizes bitter chemical compounds such as *phenylthiocarbamide* (PTC) and *6-n-propylthiouracil* (PROP) [40], and sinigrin and goitrin in vegetables [41–43]. The most studied variants that affect bitter taste perception are located in the TAS2R38 gene, occurring at three amino acid positions: A49P (alanine or proline encoded), V262A (valine or alanine encoded), and I296V (isoleucine or valine encoded). The combination of these three variants gives rise to two frequent haplotypes, PAV and AVI, plus three less common haplotypes, AAI, PVI, and AAV. These three SNPs and their combination are strongly associated with the perception of PTC and PROP. More specifically, PAV is classified as the "taster" haplotype, while AVI is the "non-taster" [40,44,45]. Individuals heterozygous for PAV/AVI, interestingly, do not elucidate an intermediate phenotype between the two extremes but a wide range of sensitivity to these two chemicals [40,45].

Salt taste perception is mediated by $Na^+$ ions. The presence of $Na^+$ ions dissolved in foods and then saliva triggers specific receptors on taste bud cells, activating and transmitting saltiness signals to the brain. NaCl (table salt) is a condiment used to enhance the flavour of the food. It has been used to prolong the shelf life of food, but it is also fundamental to maintaining body fluid balance and regulating physiological functions. Sodium homeostasis is essential, and for this reason epithelial cells express epithelial sodium channels (ENaC), which regulate the transport of $Na^+$ ions across membranes. These channels are also expressed on taste bud cells, playing a key role in salt taste perception. ENaCs mediate the uptake of Na+ ions from foods and beverages. Signal transduction is mediated by two pathways, amiloride-sensitive (AS) and amiloride-insensitive (AI) [46]. The AS pathway is Na+-specific, whereas the AI pathway is cation-nonselective. Another mechanism involved in saltiness perception is the Transient Receptor Potential (TRP) channels, which are divided into four subtypes and play a crucial role in taste perception (types I to IV) [47]. TRPV1, for example, is a non-selective cation channel, and its role in saltiness perception has already been confirmed [48]. This role differs across animal species [57]; its mechanism of action remains unclear. Genetic variations associated with salt taste sensitivity have been found in genes regulating sodium homeostasis [58] and in genes that may modify individuals' salt preference [49]. The role of genetics on salt sensitivity and, furtherly, intake, is of interest due to the potential impact on health status (e.g., hypertension and cardiovascular diseases) [50,51]. As discussed previously, the TRPV1 channel has been associated with salt taste perception, and common variations in the coding gene have also been investigated. For example, rs4790522 and rs222745 have been associated with salt taste perception and salt preference among children [52,53].

Sour taste is commonly associated with lemons and other acidic substances. It is one of the five basic tastes; nevertheless, its transduction mechanisms have been unclear for a long time [54]. This perception, like the previous ones, occurs in the taste receptor cells (TRCs). The main understanding of this taste coincided with the identification of a specific class of TRCs, Type III cells, which mediate the gustatory response to sourness [55]. Regarding the specific receptor for sour taste, a candidate channel was identified in 2018: Otopetrin 1 (OTOP1) [56]. This channel, encoded by the OTOP1 gene, is expressed on Type III TRCs and induces an inward proton current in response to a decrease in extracellular pH. The channel is a dimeric protein containing 24 transmembrane regions, formed by the shared N and C domains in each monomer [57]. This mechanism, despite not being fully understood, is expected to play an essential role in sour taste transduction [58,59]. A sour taste is commonly associated with spoiled foods and mammals; they usually reject intense acidic stimuli; nevertheless, mild sour stimuli may be found palatable [52].
Genetics has been shown to play a significant role in palatability and consumption of sour foods, compared with environmental conditions [60]. As previously described, acidic chemicals depolarise type III taste bud cells, eliciting a sour taste [61]. The KCNJ2 gene encodes the potassium channel KIR2.1 and may play a significant role in sour taste transduction, making it a good candidate gene for SNP analysis [62].

## 2.3.2 Umami taste

Umami taste, also described as savoury, is the fifth defined basic taste [63]. It was first described by Dr. Kikunae Ikeda in 1908 [1] and, in Japanese, means "*deliciousness*". It is associated with foods such as meats, broths, dried fish (e.g., bonito flakes), aged cheeses, tomatoes, and mushrooms. Like the other canonical tastes, it allows us to identify the quality of ingested food, and, specifically, umami taste has been hypothesized to allow humans to identify food rich in free amino acids, nucleotides, and peptides [64]. Umami taste receptors are part of the taste one receptors (T1Rs) family and, specifically, the predominant receptor, identified in 2002, is the heterodimer T1R1/T1R3 [75], which binds L-amino acids (**Figure 5**).

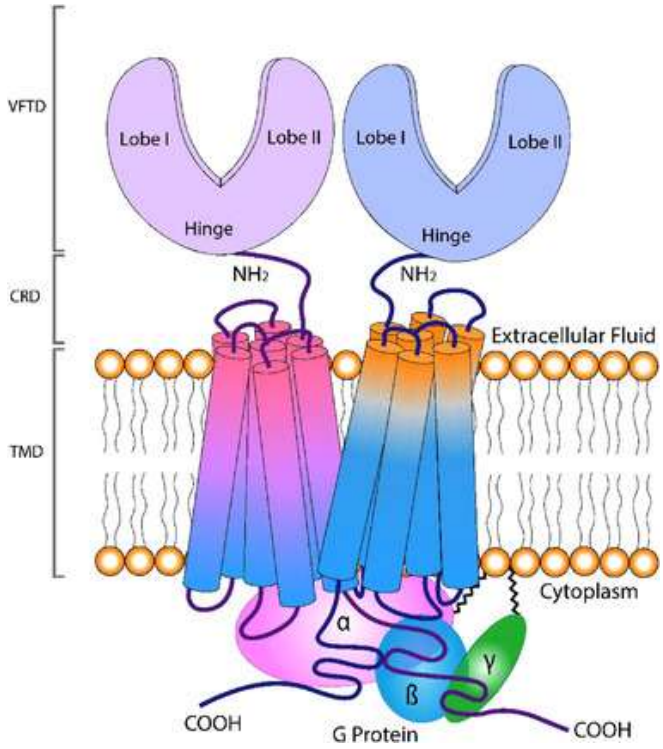


**Figure 5.** The umami taste receptor dimer TAS1R1+TAS1R3 in the plasma membrane and the intracellular G-protein heterotrimer. Highlighted in the figure, seven transmembrane domains (TMD) which stabilise the receptor across the membrane. Each monomer is characterised by two lobes, on the extracellular side, which are stabilised together by CRDs. Both TMDs and CRDs function as possible ligand binding sites. On the intracellular sites, the heterotrimeric G protein interacts with the GPCR by the C-termini of the receptor. Original picture from the work of Adler *et al.* 2000 [39].

Umami tastants are overall described as flavor enhancers, often associated with protein-rich foods, as well as appetite and satiety enhancers [65,66]. The main chemical known to elucidate umami sensation is glutamic acid (L-glutamate), which can be found in the form of monosodium glutamate (MSG). Glutamic acid was the first umami tastant to be discovered, isolated by Dr. Kikunae Ikeda in 1908 [67]. Nevertheless, the heterodimer T1R1/T1R3 has multiple ligand-binding sites and low specificity, allowing it to respond to various ligands. This receptor is embedded in the membrane and, like other GPCRs, has a seven-transmembrane helix structure with intracellular and extracellular loops. The extracellular loops are characterized by cysteine residues (also known as a cysteine-rich domain, or CRD), which participate in stabilizing the GPCR structure by forming disulfide bonds. These loops expose the extracellular environment and bind tastants, triggering downstream activation of second messengers that lead to the activation of afferent nerve fibres [15]. The cascade begins with the associated heterotrimeric G protein, which is composed of the Gα monomer and the heterodimer Gβγ. The first step is the dissociation of the Gα-gustducin subunit from the dimeric Gβ3/Gγ13 subunit, which signals downstream effectors. Phospholipase C (isoform β2) converts phosphatidylinositol 4,5-bisphosphate into diacylglycerol and the second messenger

inositol 1,4,5-triphosphate (IP3). IP3 starts a release of $Ca^{2+}$ from the endoplasmic reticulum (ER) by the type 3 IP3 receptor. The elevated calcium levels activate TRPM5 (transient receptor potential cation channel subfamily M member 5) and induce sodium influx through voltage-gated sodium channels, leading to cell depolarization [54]. This action potential opens calcium homeostasis modulators 1 and 3, releasing adenosine triphosphate (ATP) as a neurotransmitter onto gustatory afferent nerve fibers [68]. This pathway is also shared by sweet and bitter taste perception (**Figure 6**).

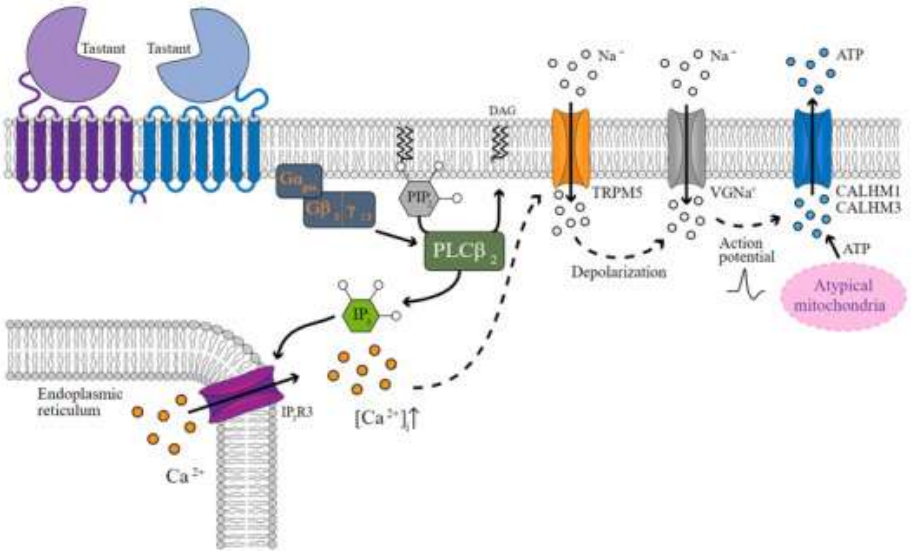


**Figure 6.** Summary of taste transduction pathways for sweet, umami, and bitter taste. Tastant binding enables the GPCR dimer (top left) to cause GTP-driven dissociation of gustducin subunit Gα. This leads the activation of phospholipase $C\beta_2$ ($PLC\beta_2$) to convert phosphatidylinositol 4,5-bisphosphate ($PIP_2$) into inositol 1,4,5-triphosphate ($IP_3$) and diacylglycerol (DAG). Then $Ca^{2+}$ are released from ER by the type 3 $IP_3$ receptor ($IP_3R3$) raising the cytosolic calcium [$Ca^{2+}$] and opening channel protein TRPM5. Subsequent $Na^+$ inflow results in cell depolarization and the opening of calcium homeostasis modulators 1 and 3 (CALHM1 and 3), through which adenosine triphosphate (ATP) is released (original picture from the work of Adler *et al.* 2000) [39].

Umami tastants are also known for their synergistic or suppressive activity over other tastes; for example, umami can modulate sweet perception, enhance saltiness, and reduce bitterness and sourness [69,70]. Most of the L-amino acids are perceived as sweet and bitter, whereas some, such as glycine, alanine, serine, and glutamic acid, elucidate an umami taste [71]. L-glutamate is the predominant umami tastant, often found in the form of MSG. Acetylation, esterification, or methylation of MSG leads to a loss of the ability to elicit umami perception, indicating a robust relationship between the chemical structure and tastant perception, as the tastant must be structurally attached to the umami receptor, as already described by Kaneko in 1963.

In addition to MSG, multiple umami tastants have been discovered, such as amides and derivatives of 5'-ribonucleotides (IMP or GMP), which are generally considered taste enhancers [72]. Umami tastants have also been investigated for possible positive effects on overall health. It is known that sodium enhances palatability, but excessive consumption is related to high blood pressure, heart diseases, and stroke, and currently, according to the WHO, the general population has a sodium intake exceeding the recommendation [73].

Glutamate has been investigated as a component that can reduce the need for sodium in foods without losing palatability [14,74]. Additionally, MSG has been observed to reduce individuals' dietary fat intake. In a study conducted by Imada *et al*., a MSG preload added to broth reduced further fat intake [13]. This observation was further confirmed by Miyaki *et al.,* who found that a vegetable soup, with added MSG, reduced the consumption of high-fat foods in overweight and obese women [75]. Nevertheless, MSG intake was also associated with higher BMI, even after

accounting for energy intake and physical activity [76]. The link between MSG intake, fat consumption, and obesity is of interest for future sensorial research, given MSG's role in eliciting umami perception.

Nevertheless, current research on the genetics of umami taste perception remains limited [77–79]. SNPs (rs11122100 and rs12080675) encompassing the *TAS1R1* gene have been associated with MSG sensitivity [52]. Further research is required to clearly address how much these common variants may explain the interindividual predisposition to preferring umami foods. Exploring these aspects further may be important given the potential role of umami-tastant-rich foods in health status.

### 2.3.6 Fat taste (or *oleogustus*)

Fat taste, or oleogustus, is the perception of non-esterified long-chain free fatty acids (NEFAs) [80]. Dietary free fatty acids (FFAs) include monounsaturated FFAs (e.g., oleic acid), polyunsaturated FFAs (e.g., linoleic acid), and saturated FFAs (e.g., stearic acid).

The ability to taste fat has been demonstrated both in rodents [81] and humans [3]. Rodents tend to show a high degree of identification of FFAs [93], whereas humans struggle to distinguish them [82]. Commonly, in foods, dietary fats are in the form of triglycerides; the lingual lipase in saliva starts the formation of NEFAs in the oral environment. These enzymes exist in multiple isoforms, and their activity on dietary fats results in the perception of FFAs in the oral environment [83]. Nevertheless, NEFAs are less soluble in saliva than other tastants, which may explain the high interindividual variability in fat taste perception in the general population [2,4]. However, individuals can be trained to recognize them [82]. Research is still debating whether oleogustus should be classified as the sixth taste. Nevertheless, there is interest in this perception due to its possible implications for human health, as demonstrated by over 80 articles listed on PubMed since 2016 [5].
CD36 is a transmembrane protein, codified by the *CD36* gene. It has a high affinity for FFAs, such as oleic acid (OA) or linoleic acid (LA) [84], and binding is possible thanks to the protein's hydrophobic region [85]. Like other taste receptors, CD36 is expressed apically on TBCs [84,86] and on multiple other tissues (e.g., nasal epithelium, brain, and cardiovascular tissue) [87]. It has been demonstrated that in human TBCs, the interaction between CD36 and linoleic acid activates downstream pathways shared with those involved in bitter and sweet taste perception. This cascade includes cyclic adenosine monophosphate (cAMP), inositol triphosphate ($IP_3$), and phospholipase C [88] (**Figure 7**).

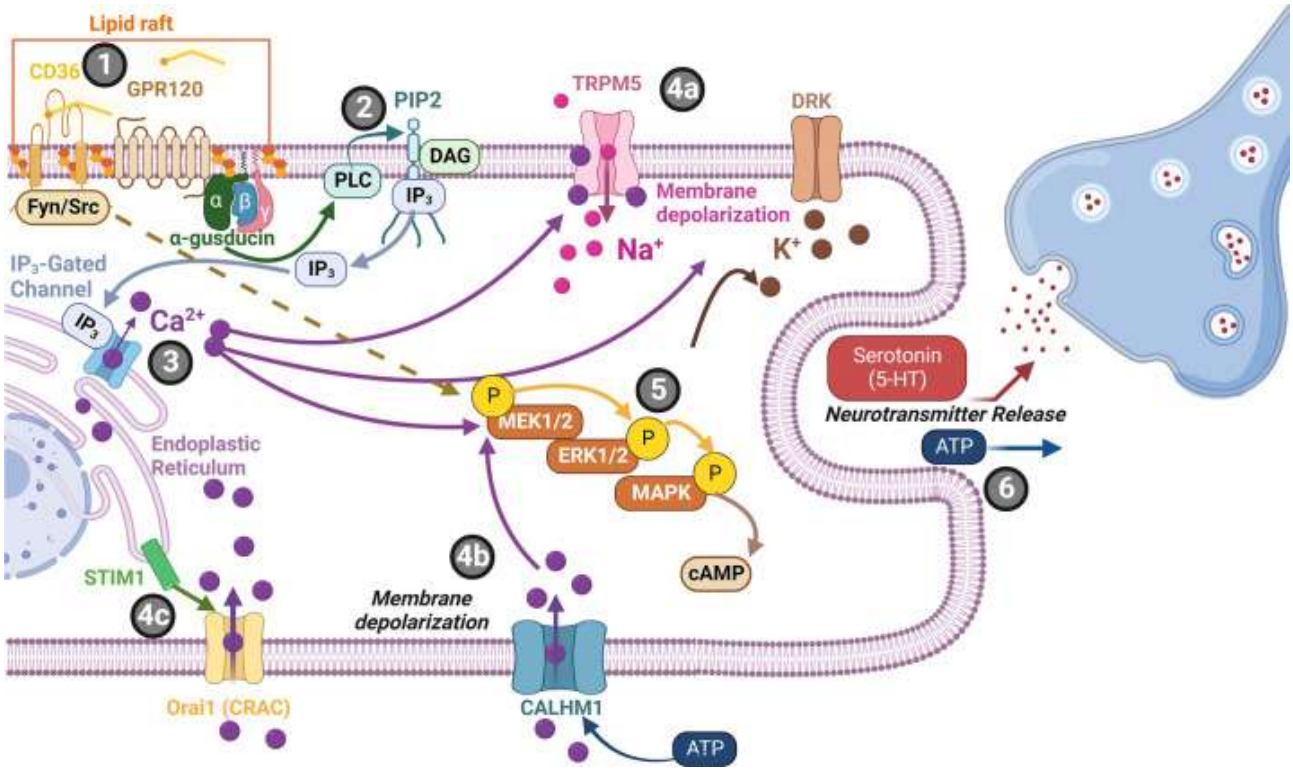


**Figure 7.** The figure highlights the mechanism of signal transduction involved in fat taste. In Section 1: a free fatty acid (FFA) binds Cluster of Differentiation 36 (CD36). This binding leads to a signaling cascade which starts with α-gustducin and $Ca^{2+}$ dependent phospholipase (PLC). In Section 2: PLC converts PIP2 into DAG and IP3. In Section 3: IP3 mediates the release of $Ca^{2+}$ from the endoplasmic reticulum (ER) In Section 4: the increasing [$Ca^{2+}$] triggers multiple events: $Na^{+}$ inflow from TRPM5 and prevention of $K^{+}$ leaving the cytosol; activation of Orai1 and promotion of $Ca^{2+}$ inflow. In section 5: the increasing [$Ca^{2+}$] and the activation of Fyn/Src kinase (CD36 mediated) lead to phosphorylation of ERK1/2 pathway activating cAMP production. In Section 6: cell depolarisation leads to the release of Serotonin and ATP, which are neurotransmitters (Original picture from the work of Jaime-Lara *et al.* 2022) [6].

Furthermore, fat taste perception is also affected by ingestive cues such as texture, saliva, and the tongue itself. Eating is a dynamic event, and when food is ingested, it goes through a series of transformations (mechanical and chemical), and this, as mentioned before, leads to the release of FFAs that contribute to fat taste perception [89]. Fat taste perception, according to recent studies, is independent of texture, but texture contributes to the flavour of fat [90]. For example, high-fat concentrations have been rated as more pleasant in texture by individuals than low-fat concentrations [91,92].

The tongue is the main tasting structure. It possesses papillae and TBCs, which are mandatory for food chemosensation. An individual's tongue features may encompass fat taste perception. For example, Zhou *et al.* observed that individuals classified as hypersensitive to OA, a common FFA used to evaluate fat taste perception, had a higher density of fungiform papillae than hyposensitive individuals. The authors hypothesized that a greater number of fungiform papillae may be associated with a higher density of fat taste receptors [93].

The *CD36* gene has been studied for its possible effects on fat taste perception, including the role of common genetic variants. The importance of these studies lies in the potential link between the consumption of high-fat foods, fat sensitivity, and body weight [94,95]. The most studied SNP regarding fat taste perception is *CD36* rs1761667 (G>A). This variant has been associated with reduced protein expression [7,96], and the possible effect of fat taste sensitivity has been investigated accordingly. The A allele of the variant has been associated with reduced protein

expression and, potentially, with a higher detection threshold (hyposensitivity), reducing individuals' ability to detect fat [10,106]; nevertheless, the association has not always been replicated in the literature [97]. The contrasting results reported in the literature may be due to differences in study designs and methods used to assess fat taste sensitivity [98–101]. The variant may reflect a potential risk of high-fat food consumption and weight gain [102]. *CD36* rs1761667 has also been studied in relation to dietary intake, but the results remain unclear [101,103–105].

## 2.4 Nutrition and dietary intake

Nutrition is the process of eating and absorbing nutrients. It involves breaking down food into nutrients, which are the chemicals that maintain the body's physiology. Diet is defined as the habitual foods an individual consumes. It can be influenced by multiple factors such as taste perception, genetics, socio-economic status, and religious belief [106]. A diet is considered "balanced" when it ensures adequate intake of macro- and micronutrients, according to country/region-specific reference values, based on epidemiological studies of health and well-being [107].

Nutrients are classified as macronutrients (carbohydrates, lipids, and proteins) or micronutrients (e.g., vitamins and minerals), and water. The catabolism of the three macronutrients (carbohydrates, lipids, and proteins) provides energy to perform tasks, maintain homeostasis, and support overall metabolism [108]. "Dietary energy" (or metabolised energy) is the energy remaining after obligatory losses (e.g., incomplete digestion and absorption) [108]. This energy supports all physiological functions by generating high-energy bonds in the form of adenosine triphosphate (ATP) [109]. The energy obtained from macronutrients is measured in kilocalories (or kilojoules). One kilocalorie equals the amount of heat needed to raise the temperature of one kilogram of water by 1 °C, from 14.5 °C to 15.5 °C. The energy obtained from the three macronutrients is as follows: 4kcal/g (17 kJ/g) for carbohydrates, 4kcal/g (17 kJ/g) for proteins, and 9 kg/g (29 kJ/g) for lipids [110]. Alterations in taste perception may encompass dietary patterns and lead to adverse health outcomes. This has been demonstrated in individuals affected by persistent taste alterations, which may lead to reduced appetite and psychological negative implications (e.g., depression) or even generating a shift to unhealthy eating habits (e.g, taste impairments contribute to malnutrition development in cancer patients) [111]

### 2.4.1 Carbohydrates

Carbohydrates usually provide >50% of the total energy requirements and are a major energy source [112]. Usually, men have a higher carbohydrate intake than women. In the human diet, the primary sources of carbohydrates are: grains, vegetables, fruits, seeds, nuts, and dairy [113]. Classification is based on: chemical structure, degree of polymerisation, and functional groups [114]. During digestion, carbohydrates are cleaved into glucose, fructose, and galactose, which are then taken up by gut epithelial cells via transporter proteins [115]. Carbohydrates are used to synthesize ATP through cellular respiration, enabling tissues to perform their biological functions.

### 2.4.2 Lipids

Lipids are a group of small hydrophobic or amphiphilic molecules and provide ~35% of total energy intake. In the human diet, the primary sources of lipids are: meats, dairy, oils, and nuts [116]. The most common dietary lipids are glycerophospholipids and sterol lipids ( 98% of total); nevertheless, the LIPID MAPS Consortium divided lipids into eight classes: fatty acids, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, prenol lipids, saccharolipids, and polyketides [117]. Lipids' digestion starts in the oral cavity and stomach, by lingual and gastric lipases; nevertheless, the primary digestive step is in the small intestine, where these molecules are cleaved into FFAs and glycerol. FFAs are transported into enterocytes, then reassembled into

dietary fats and packed into chylomicrons [115]. Triglycerides (TGs) are the main dietary fats, and in humans, excess nutrients are stored as TGs in adipose tissue. In situations of nutrient deprivation or high energy demand, humans convert TGs into glycerol and FFAs in energy-demanding tissues. Carbon atoms present in glycerol are metabolised in the liver into gluconeogenesis, while FFAs are oxidized into Acetyl-CoA, which enters the Krebs cycle to produce ATP. TGs also play a structural function, being essential in membrane formation and stabilisation [118].

### 2.4.3 Proteins

Proteins are the most abundant and diverse molecules in cells, and their abundance and diversity reflect their wide roles. All proteins are composed of 20 amino acids, linked by peptide bonds. The amino acid sequence of this chain is the main distinction between proteins, and it is genetically determined [119]. On average, proteins provide 12-20% of daily total energy intake (55-62g for women and 71-101g for men). In the human diet, the primary sources of protein are both animal- and plant-based, but animal sources provide all essential amino acids. Animal sources are: meats, fish, eggs, and more, while plant sources are: legumes, seeds, and dried fruits [120].
Protein classification is based on shape and function: globular, membrane, fibrous, and intrinsically disordered proteins [121]. Digestion occurs in the stomach, where the acidic environment converts pepsinogen into pepsin, a protease that cleaves proteins into polypeptides. In the small intestine, polypeptides stimulate the release of CCK, which stimulates the release of pancreatic fluid rich in proteases (e.g., trypsinogen). These enzymes are activated and complete the cleavage of the polypeptides. Peptides are absorbed into the cell by both passive and active transport systems and then are hydrolysed. Free amino acids, then, are excreted in the bloodstream by basolateral membrane transporters [122]. Amino acids are distributed among tissues, including muscles, where they serve as precursors for protein synthesis, as previously described. In a nutrient-deprived condition, the human body can use the amino acids as a secondary energy source. All carbon atoms in amino acids can be converted into pyruvate or intermediates of the Krebs cycle. In the hepatic cells, the amino group is removed and the carbon skeleton is channelled into gluconeogenesis [123]. Excessive nutrient deprivation may lead to the degradation of muscle as a reserve of essential amino acids and, subsequently, to a loss of muscle mass [124]. On the contrary, excessive protein intake may impair renal function through glomerular hyperfiltration [125].

### 2.4.4 Water and micronutrients

Water is the main component of the human body (~60% of total weight) [126]. The balance between loss and gain regarding water is strictly regulated around <2% mass loss. Events (e.g., illness, physical activity) that may alter this balance could potentially compromise overall health [127]. Micronutrients — vitamins and minerals — are consumed at lower levels than macronutrients (mg/d to µg/d) and are involved in multiple physiological processes that sustain the human body [128].
Minerals serve as enzymatic cofactors, as second messengers in several pathways, and as regulators of acid-base balance [129]. According to human requirements, minerals are classified into primary and trace elements [130]. Vitamins are organic compounds present in trace amounts in the human body. They are classified by solubility (water- and fat-soluble), and there are 13 in total. Fat-soluble vitamins are A, D, E, and K. Water-soluble vitamins are B complex (B1, B2, B3, B5, B6, B7, B9, B12) and C. Fat-soluble vitamins are stored in fatty tissues and the liver. In contrast, water-soluble vitamins are stored in the liver and other tissues. The former are stored in fatty tissues and the liver, while the latter are absorbed by diet (excesses are lost from the body) [131].

### 2.4.5 Dietary intake data collection

A precise evaluation of dietary intake is fundamental for revealing and understanding diet effects on human health and for understanding how taste perception contributes to the differences observed in the general population.
The high interindividual variability in eating habits leads to inaccurate measurement of dietary exposures, with significant differences in types and amounts of food consumed. Furthermore, individuals are often unaware of how they perceive what they consume, which can lead to inaccurate self-reports [132].
Dietary assessment methods can be divided by their scope (e.g., total diet or specific nutrients), study design, and time. Short-term tools are relevant for studies that, for example, examine the relationship between sodium intake and pressure [133]. Long-term tools report daily intake over weeks to a year, making them more reliable for assessing daily dietary exposures [133]. Dietary assessment common methods are food record, 24-Hour dietary recall, food-frequency questionnaires, and screening tools [132]:

- A food record is the registration of all food and beverages consumed by an individual within a defined period. The intake track is measured using easy household references (e.g., a spoon or a cup). Visual aids are additionally provided as a reference [134].

- The 24-hour dietary recall (24HR) method is an interview with probing questions to evaluate dietary intake over the past 24 hours. The interview is conducted by a trained investigator or by automated questionnaires. Questions are tailored around preparation methods, recipe ingredients, additions made after preparation, brand-name products, and the consumption time [135].

- A food frequency questionnaire (FFQ) is a tool formed by ~130 commonly and less commonly consumed foods with closed-ended food frequency questions. Participants indicate how often they eat each item using frequency categories (e.g., “never or less than once a month” to “over 6 times per day”) and portion size, based on typical units (e.g., one banana) or household measures [135].

- Screening tools are self-administered or interviewer-administered. A limited number of questions are used to assess intake of a specific macronutrient. They also ask about general or specific dietary habits[136].

### 2.4.6 Taste perception and dietary intake

Variations in taste perception have been associated with dietary intake in the general population. For example, sensitivity to bitterness has been linked to consumption and acceptance of bitter-tasting vegetables. Sensitivity to PROP, a bitter chemical compound, has been linked to the intake of *Brassica* vegetables [137].
Sweet sensitivity has been studied for its possible association with energy (and sugar) intake. Besides being a potential driver of sweet foods, sweetness sensitivity has also been linked to bitter/sour vegetable consumption [138]. Furthermore, as highlighted by Tan and Tucker in their review, only a small proportion of studies found an association between sweetness sensitivity and energy (or sugar) intake [139].

Sourness is linked to innate rejection in newborn children. Nevertheless, it has been reported that children have a higher preference for citric acid, which elicits sourness, and that they consume more fruit [140].
Umami taste has been correlated with protein intake, and sensitivity for this perception has been directly linked to this macronutrient [141]. Additionally, in an Asian population, Kubota *et al.* reported a direct link between umami sensitivity and intake of foods typically associated with these taste perceptions (e.g., dried mushrooms, tomatoes, shellfish) [142]. Additionally, as previously reported in the umami taste-dedicated section, MSG intake, via broth supplementation, has been linked to reduced high-fat food intake [13,75].
Fat taste perception has also been linked to dietary intake. Hyposensitivity to FFAs has been linked to a greater number of eating occasions and, in addition, to higher consumption of meats, eggs, snacks, and fast food [143]. A similar association was reported by Martinez-Ruiz et al., who found that differences in oral fatty acid perception were associated with a higher preference for foods rich in dietary fats [144]. Nevertheless, Costanzo *et al*. found no direct association between fat taste sensitivity and liking for fatty foods or anthropometric measurements [145].

## 2.5 Body composition: as a health indicator

Evaluation of body composition is a key element in nutrition. According to the WHO, the nutritional status of an individual is defined as the condition of the body resulting from the balance of intake, absorption, and utilisation of nutrients, and the influence of particular physiological and pathological states [146]. Nutritional status evaluation is fundamental at both the individual and population levels to understand the risk of nutrition-related conditions among adults and youths, such as overweight and obesity, obesity-related conditions (e.g., diabetes), and undernutrition [147].
Multiple approaches are available for diagnosing obesity. An approach to evaluating health status and obesity is the waist-to-hip ratio (WHR), which is the ratio of the waist circumference to the hip circumference ($^{W}/_{H}$). According to the WHO protocol, waist circumference should be measured at the midpoint between the lower margin of the last palpable ribs and the top of the iliac crest, using a stretch-resistant tape. Hip circumference should be measured around the widest portion of the buttocks, with the tape parallel to the floor. Abdominal obesity is defined as a WHR above 0.90 for males and above 0.85 for females.
Body mass index (BMI) is the most commonly used measure in research, including in taste-related literature [148]. BMI has been used as a health risk indicator; it is calculated as weight (kg) divided by height² (m²). It is a diagnostic tool to classify individuals as: overweight, a BMI greater than or equal to 25kg/m$^2$; obesity, a BMI greater than or equal to 30kg/m$^2$; healthy weight, a BMI between 18.5 and 24.9kg/m$^2$; underweight, a BMI below 18.5kg/m$^2$. Nevertheless, BMI does not give information about actual body composition, which is an assessment that divides an individual's total body mass into fat mass (FM) and fat-free mass (FFM) [149]. FFM is composed of water, muscles, bones, and organs. BMI, lacking this information, has been criticised for failing to reflect true body fatness [150]. One of the best, simplest methods to investigate body composition is bioelectrical impedance analysis (BIA). BIA is a low-level electrical current passing through an individual's body, while the impedance (opposition to the current) is measured. Not only is BIA a diagnostic tool for obesity and a monitoring tool of treatment response and progress, but it is also fundamental for detecting undernutrition, which manifests as a progressive decrease in FFM and FM [151].
Overall, taste perception and body composition markers have already been associated. For example, Papantoni *et al.* reported, in a longitudinal study, that a lower sensitivity to sweet taste was associated with a higher hedonic response to high-sugar foods and, possibly, associated with weight gain [152]. In contrast, in a study by Hardikar et al., individuals with a BMI > 30kg/m2 showed greater sensitivity to sweet, bitter, salty, and sour tastes than individuals with a BMI < 25kg/m$^2$

[153]. Further research is necessary to better define how taste changes according to adiposity markers, and, subsequently, how this may encompass human health.

# 3.0 Chapter III – Study 1

This chapter focuses on elucidating the association between *CD36* rs1761667 and fat and umami food liking, and, as secondary aims, differences in BMI and diet quality were assessed. This investigation has been conducted on 235 individuals from the Friuli-Venezia Giulia region, in Northern East Italy (**Figure 8**). This group is part of the Italian Network of Genetic Isolates (INGI), which is a project created with the aim of identifying genetic variants associated with complex traits [154]. Italy, as a country, has been identified as rich in isolated populations from a genetic point of view, due to its demographic and topographic complexity [155]. Genetic isolates are human populations that, due to isolation (e.g., cultural, geographical), have a limited gene pool and low genetic variability. This can favour the transmission of rare genetic traits, making them ideal populations to investigate complex genetic characteristics (e.g., taste perception). The cohort investigated for this study has been previously confirmed as a genetic isolate due to multiple studies investigating its genetic population structure. The individuals part of the FVG cohort are from several villages in the region: *Clauzetto, Erto-Casso, Resia, Illegio, San Martino del Carso,* and *Sauris* [155].


**Figure 8.** Geographic map of the INGI-FVG Genetic Park. This INGI-FVG genetic cohort includes six villages: Clauzetto, Erto-Casso, Resia, San Martino del Carso, and Sauris (original picture from the thesis work done by Elisabetta Tassin).

## 3.1 Introduction and aims of the study.

The aim of Study 1 was to investigate the role of *CD36* rs1761667 on the liking of fat and umami foods. This variant has been associated with differences in fat taste sensitivity but with inconclusive results [97,99,156]. Palatability is food's pleasantness, and it is proportional to the pleasure that an individual experiences during food consumption. It is strictly associated with food's sensorial properties such as taste, aroma, texture, and even sight and sound [157]. Palatability is a significant driver in food consumption, and genetic variants have been previously associated with food and nutrient intake. For example, Hwang *et al.*, in a study conducted on the UK biobank, found a significant association between the fat mass and obesity associated gene (*FTO*) rs11642841 and total sugar intake [158]. Regarding the same gene, Brunkwall *et al.* found a positive association between the *FTO* rs9939609 A-allele with the consumption of biscuits and pastries, which are energy-dense foods [159]. Additional examples can be found in the literature, as reviewed by Hejazi *et al*. [160].

Previous research has been conducted on *CD36* to elucidate its role in food liking and, consequently, intake. Nevertheless, results are contrasting at present. Shen *et al.*, in an adult UK cohort, found no association between *CD36* rs1761667 and ice cream liking, with different fat concentrations [161], whereas Keller *et al.* found a positive association with the rs761667 AA genotype and high acceptance of "added fats and oils" (seasoning and cooking purposes) [162]. As previously mentioned, *CD36* rs1761667 has been studied for its possible association with dietary fat intake, with contrasting results [103,104,163]. Nevertheless, a role is also played by MSG, which is the main umami chemical tastant. Umami, overall, has been associated with appetite and, at the same time, satiety [66], and MSG supplementation has been shown to reduce the intake of dietary fats [13].

Considering the significant role that liking has on food intake, and how palatable high-fat foods are, with consequences on human health in case of excessive intake, this study aimed to better understand the role that this SNP may play in food liking, with respect to both fat and umami foods.

The aims of this study are as follows:

- Elucidate the role of *CD36* rs1761667 on food liking, considering food groups, considering both fat and umami flavour.

- Considered how strictly interconnected the consumption of high-fat foods is with weight gain and then, obesity, the possible role that CD36 rs1761667 may play on BMI, as a health status indicator and diagnostic parameter for obesity, and, as well, on elements of diet quality was investigated.

## 3.2 Methods

Study 1 cohort is formed by 235 individuals from the INGI-FVG of European ancestry, as determined by Principal Component Analysis using the genetic data (SNP array), The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethical Committee and Institutional Review Board of IRCCS "Burlo Garofolo" (under the univocal code Prot. CE/V-78, approval date: 6 August 2007).

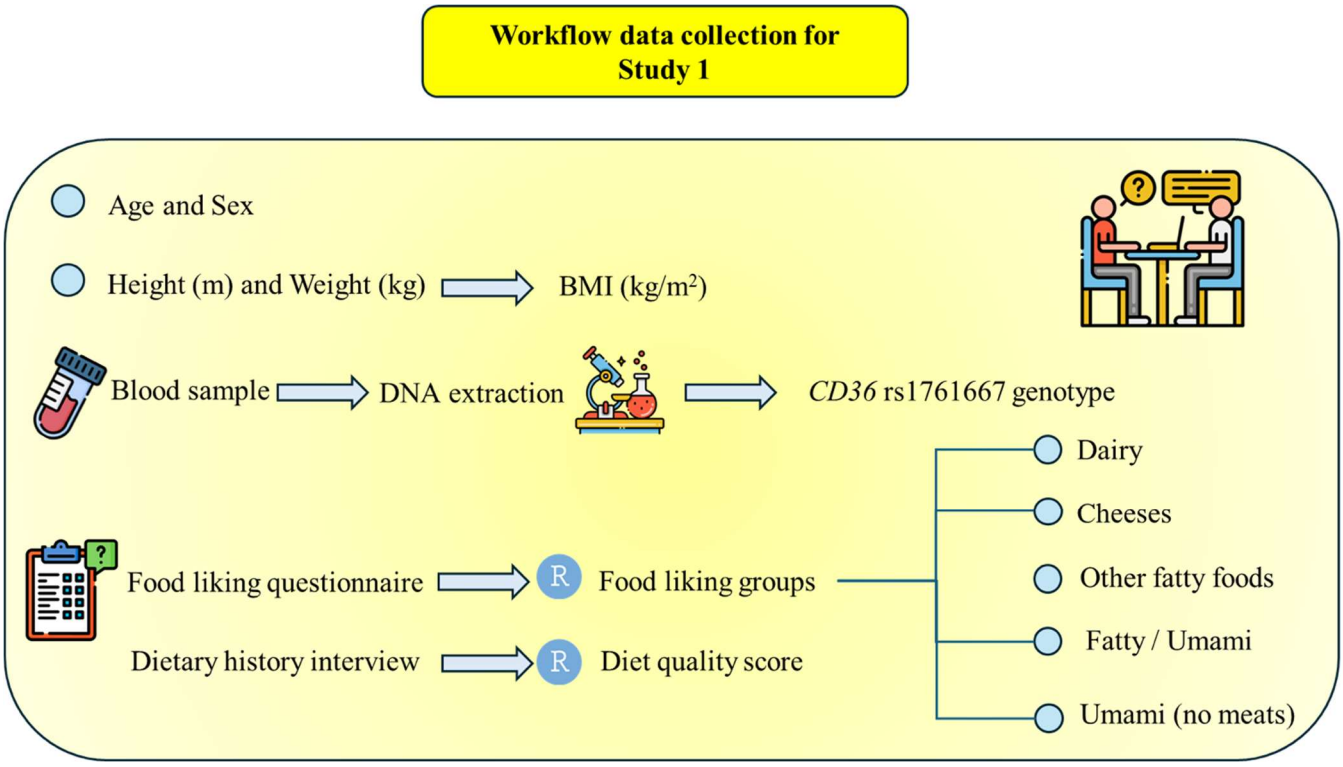


**Figure 9.** Workflow for the data collection adopted for Study 1. Participants were instructed by trained staff, available during the entire data collection process. Age and sex were collected by a self-administered questionnaire. Height (m) and weight (kg) were measured, and then BMI (kg/m2) was calculated. Fasting blood samples were collected from all participants. DNA was extracted using the phenol-chloroform extraction protocol. All participants were genotyped for *CD36* rs1761667. Food liking was investigated by questionnaire (a 9-point Hedonic scale) and food liking groups calculated (R Studio). Forty-eight participants agreed to conduct a dietary history interview (EPIC-FFQ). Average daily nutritional intake, compared to population reference values, was used to create a Diet Quality Score.

### 3.2.1 Data collection

An age range of 18 to 56 years was selected for the cohort, both males and females, and with the following data available: BMI, food liking questionnaire, and *CD36* rs1761667 genotype. A subset of the cohort has available dietary intake data. Informed consent was obtained from all participants in the study. A summary of the data collection workflow is described in **Figure 9**.
Demographic data were collected for both cohorts by a self-administered questionnaire after a detailed explanation by trained staff who were available during the process. All data collection happened in government-provided accommodations. Anthropometric data, including height (m) and weight (kg), were also measured, and body mass index (BMI; kg/m2) was calculated.

### 3.2.2 Genetic analysis

Fasting blood samples were collected during separate early morning sessions; blood was either processed on the same day or aliquoted and stored for future analysis. Genomic DNA was extracted using a phenol-chloroform extraction protocol. *CD36* rs1761667 was genotyped in the FVG cohort as previously described [164]. Briefly, all samples were genotyped with an *Illumina 370/700 k high-density SNP array*, and the genotypes of rs1761667 were extracted.

### 3.2.3 Food liking

Food liking was assessed by questionnaire due to the lack of a laboratory setting for testing and the high number of individuals enrolled.
The questionnaire consisted of approximately 100 foods and beverages, using a 9-point Hedonic scale: from 1 (dislike extremely) to 9 (like extremely) [165].
Food liking groups were created, and their reliability was assessed by the *Cronbach* alpha function available in the *R* package *psy*. For each participant, the mean liking value for all foods selected was used for group creation**.** Non-available data were excluded from the calculation.
The food groups were named, according to the content, as:

- Dairy
- Cheeses
- Other Fatty Foods (meats excluded)
- Fatty / Umami
- Umami (meats excluded)

A single food used for every group can be found in **Supplementary Table 3.1**.

### 3.2.3 Dietary intake

Only 48 individuals agreed to attend a dietary history interview, conducted by professionals, to evaluate the average daily food intake for each participant. The interview was conducted using the EPIC-FFQ, created by the *European Prospective Investigation of Cancer and Nutrition*. It is characterised by a list of 130 foods with a multiple response grid where volunteers estimate the average frequency of consumption for each food.

Participants must choose between nine response categories:

- “Ever or less than once a month”
- “1-3 times per month”
- “Once a week,” “2-4 per week”
- “5-6 per week”
- “Once a day”
- “2-3 per day”
- “4-5 per day”
- “6 or more times per day”

Once these data were collected, the software WinFood, 2.7. (Medimatica; San Benedetto del Tronto, Italy) was used to process, calculate, and return quantitative estimates of average daily dietary intake.

Dietary intake data were used to assess compliance with the nutritional guidelines for Italy [166], creating a DQS. Each dietary component was rated from 0 for non-compliance to 1 for compliance. In Study 1, the following data were available: carbohydrates (g/die), total fats (g/die), saturated fatty acids (g/die), fibre (g/die), and sodium (mg/die). The final DQS assigned to each participant ranged from 0 (no compliance at all) to 5 (compliance for every component).

### 3.2.4 Statistical analyses

Association of the *CD36* rs1761667 genotypes with food liking groups, DQS, and BMI was assessed using linear regression models. An additive inheritance model was used for all analyses performed (0 = GG, 1 = GA, 2 = AA). Additionally, the possible association between food liking groups and DQS was investigated using a linear regression model.
Covariates used for the model were age, sex, and BMI for every analysis performed. In study 1, participants were divided into those with a BMI ≥ 25 kg/m$^2$ (overweight / obesity) and those with a BMI < 25 kg/m$^2$ (healthy weight/underweight) according to the WHO guidelines in adults [167]. Stratification by sex was also assessed.
R Studio was used throughout (*R version 4.4.0 (2024-04-24 ucrt) -- "Puppy Cup" Copyright (C) 2024 The R Foundation for Statistical Computing*). Throughout, the significance criterion was $p \leq 0.05$. The Hardy-Weinberg Equilibrium (HWE) of *CD36* rs1761667 was assessed using the "R" package "*genetics*". We performed a priori power analyses using G*Power (version 3.1. for Mac) [168,169]. As there was limited prior research, we assumed a medium effect size of the SNP. For this study, which employed a linear multiple regression with four predictors, a sample of 55 individuals was necessary to detect a medium effect size ($f^2 = 0.15$) for a single predictor with 80% power at alpha = 0.05.

## 3.3 Results

### 3.3.1 Participants' features and food liking.

Two hundred and thirty-five participants were analysed. A summary of the cohort's main features can be found in **Table 1**. For every food liking group, the Cronbach alpha value was > 0.5. The *CD36* rs1761667 genotype followed HWE ($p > 0.05$).

**Table 1.** Participants' features and food liking scores were described according to the *CD36* rs1761667 genotype in Study 1 (FVG cohort).

| | **Total (n = 235)** | **AA rs1761667 (n = 58, 25%)** | **AG rs1761667 (n = 108, 46%)** | **GG rs1761667 (n = 69, 29%)** |
|---|---|---|---|---|
| **Female % (n)** | 54 (128) | 45 (26) | 56 (61) | 59 (41) |
| **Age (years), mean ± SD** | 34 ± 9.2 | 33 ± 9.7 | 34 ± 9.3 | 34 ± 8.8 |
| **BMI (kg/m$^2$), mean ± SD** | 24 ± 4.4 | 24 ± 5.1 | 24 ± 4.2 | 24 ± 4.2 |
| **BMI≥25 (kg/m$^2$), mean ± SD** | 28.75 ± 3.75 | 29.21 ± 5.15 | 28.53 ± 3.28 | 28.67 ± 2.97 |
| **BMI<25 (kg/m$^2$), mean ± SD** | 21.63 ± 2.22 | 21.69 ± 2.36 | 21.64 ± 2.23 | 21.55 ± 2.13 |
| **Dairy, mean ± SD** | 6.0 ± 1.19 | 6.1 ± 1.22 | 5.8 ± 1.11 | 6.2 ± 1.25 |
| **Cheeses, mean ± SD** | 6.3 ± 1.44 | 6.4 ± 1.48 | 6.1 ± 1.35 | 6.6 ± 1.51 |

| | | | | |
|---|---|---|---|---|
| **Other Fatty Foods, mean ± SD** | 6.2 ± 1.5 | 6.0 ± 1.69 | 6.2 ± 1.5 | 6.3 ± 1.37 |
| **Fatty / Umami, mean ± SD** | 6.3 ± 1.44 | 6.3 ± 1.35 | 6.4 ± 1.41 | 6.2 ± 1.57 |
| **Umami foods (meats excluded), mean ± SD** | 5.9 ± 1.22 | 5.9 ± 1.14 | 5.7 ± 1.27 | 6.3 ± 1.15 |
| **DQS, mean ± SD*** | 2.39 ± 1.31 | 2.71 ± 1.49 | 2.6 ± 1.22 | 1.93 ± 1.34 |

FVG, Friuli-Venezia Giulia; AA/AG/GG, rs1761667 genotype; DQS, diet quality score; SD, Standard deviation; n: sample size. *DQS data available for 48 participants.

### 3.3.2 Associations between *CD36* rs1761667 and food liking

A summary of all analyses is reported in **Table 2.** No significant association was found between *CD36* rs1761667 and liking for all food liking groups ($p > 0.05$). Models revealed that BMI was a positive significant predictor for the liking of Cheeses ($\beta = 0.04$, $SE = 0.02$, $p = 0.05$), Other Fatty Foods ($\beta = 0.07$, $SE = 0.02$, $p = 0.03$) and for, in male participants only, for Fatty / Umami group liking ($\beta = 0.05$, $SE = 0.03$, $p = 0.05$) (**Supplementary Table 3.3**).
After BMI stratification, in those with a BMI ≥ 25 kg/m$^{2,}$ a significant, negative association was found between the rs1761667 A-allele ($\beta = -0.47$, $SE = 0.18$, $p = 0.01$) and liking of Cheeses, and with liking of Umami (no meat) ($\beta = -0.47$, $SE = 0.16$, $p = 0.02$). No other significant associations were found with BMI, nor sex ($p > 0.05$).

**Table 2.** Results of the linear regression models assessing the association between the SNP rs1761667 (independent variable) and food liking (dependent variable) in the entire sample and stratified by BMI and sex**.**

| | **All FVG (n = 235)** | | **BMI<25kg/m$^2$ (n = 155)** | | **BMI≥25kg/m$^2$ (n = 80)** | | **Only females (n = 128)** | | **Only males (n = 107)** | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Food groups** | ***β (SE)*** | ***p*** | ***β (SE)*** | ***p*** | ***β (SE)*** | ***p*** | ***β (SE)*** | ***p*** | ***β (SE)*** | ***p*** |
| **Dairy** | -0.07 (0.1) | 0.5 | 0.08 (0.1) | 0.5 | -0.33 (0.2) | 0.06 | -0.08 (0.15) | 0.6 | -0.06 (0.15) | 0.7 |
| **Cheeses** | -0.14 (0.13) | 0.3 | 0.05 (0.17) | 0.7 | -0.47 (0.18) | 0.01* | -0.20 (0.19) | 0.3 | -0.07 (0.17) | 0.7 |
| **Other Fatty Foods** | -0.19 (0.13) | 0.1 | -0.17 (0.17) | 0.3 | -0.18 (0.19) | 0.3 | -0.08 (0.19) | 0.7 | -0.29 (0.17) | 0.09 |
| **Fatty / Umami** | 0.002 (0.12) | 0.9 | 0.04 (0.15) | 0.8 | -0.07 (0.21) | 0.8 | -0.01 (0.20) | 0.9 | 0.008 (0.14) | 0.9 |
| **Umami foods** | -0.18 (0.11) | 0.1 | -0.03 (0.13) | 0.8 | -0.47 (0.16) | 0.02* | -0.23 (0.16) | 0.16 | -0.23 (0.16) | 0.2 |

β, effect size (Beta value); SE, Standard error; p, p-value. The following covariates were included in the models: age, sex, and BMI, in the whole sample; age and sex in the BMI subsamples; age and BMI in the sex specific analyses. * Indicates significant results.

### 3.3.3 Associations between *CD36* rs1761667 and DQS, and DQS and Food Liking

Regarding the DQS, no significant associations were found ($p > 0.05$) (**Supplementary Table 3.2**). No stratification was applied due to the sparse number of individuals due to the lack of dietary intake data.

### 3.3.4 Associations between *CD36* rs1761667 and BMI

No significant association was found between *CD36* rs1761667 with BMI. The same was true also after stratification according to BMI (≥/< 25 kg/m$^2$) and sex ($p > 0.05$).

## 3.4 Discussion for Study 1

This study aimed to investigate the possible association between *CD36* rs1761667 and fat and umami food liking, as part of the overall aim of this PhD project. The study has been conducted on 235 individuals from the FVG region in Italy as part of the INGI dataset.

### 3.4.1 *CD36* rs1761667 and food liking

In this population-based study, for which food liking was assessed by questionnaire, the *CD36* rs1761667 A-allele was negatively associated with liking for the fatty food group "Cheeses" in participants with a BMI ≥ 25 kg/m$^2$.

This result does not align with Keller *et al.,* where AA genotype carriers reported higher liking for the "added fats and oils" food group, also assessed by questionnaire [162], and Shen *et al.,* where no differences for ice cream liking with differing fat contents were found, assessed by food tasting [161]. Furthermore, the A-allele was associated with reduced umami food group liking in participants with a BMI ≥ 25 kg/m$^2$. Due to the complexity of the components that are found in real food, this aspect is not to be excluded. Dietary fats are present in umami-based foods, for example, in hard cheese, the fat content is generally >30g/per serving, and in sardines, the fat content is approximately 5g/per serving [170]. This may account for the genetic association between *CD36*, the possible fat taste receptor gene, and the liking of umami foods, which highlights the complex interplay between flavours and food liking. This is not the first study to identify an association between genetics and umami food liking in a variant that has previously been associated with a different taste. Han *et al.* reported an association between *TAS1R3* rs307355 and rs35744813, previously associated with sugar intake, and a higher consumption of protein-rich and savoury foods in a buffet setting [171,172].

These results support that BMI is a positive predictor for fatty and umami food liking, as observed in previous works [173], and may alter food choices [174–178]. Nevertheless, the effect size reported between BMI and food liking groups, even if statistically significant, is small, and no definitive conclusions can be drawn regarding health outcomes. It has been suggested that obesity may impact gene expression in type II taste bud cells [179], which may respond to free fatty acid stimuli [84], possibly causing differences in food liking across the general population.

This warrants further research assessing genetic differences in taste receptors and food liking, whilst considering body composition. This lack has been further investigated in Study 3, where not only BMI was calculated but also fat mass percentage and visceral fat score were gathered from all the participants.

### 3.4.2 *CD36* rs1761667 and dietary intake

Whether taste receptor genes that have been associated with food liking influence actual dietary intake is not known. Regarding rs1761667, previous literature has returned contrasting results [163,180,181]. These studies were conducted in different populations with distinct cultural backgrounds. In Study 1, there was no association with rs1761667, and dietary intake was found. This may be due to the distinct cultural food behaviour. Italy, traditionally, has always been

associated with a “Mediterranean” dietary pattern [182], and the strong role of this cultural behaviour around food may also encompass the reproducibility of the results.

# 4.0 Chapter IV – Study 2

This chapter focuses on Study 2 which was conducted on a cohort of 49 individuals from the United Kingdom (UK) to study the role of common genetic variants and their association with food perception, dietary intake, and BMI as a health status marker.

## 4.1 Introduction and aims of the study.

As previously defined in Chapter I, Taste, or *gustation*, is part of the human senses. It allows the quality assessment of the food ingested, and it is elucidated by the interaction between chemical tastants (e.g., L-glutamate) and specific receptors on taste buds. Taste and flavour are often considered synonyms, but they are different. Taste is the specific sensation given by the interaction between chemicals and receptors on the taste buds. Flavour is the integration of multiple sensorial perceptions such as taste, smell, texture, and temperature [183].
As previously described, *CD36* rs1761667 has been associated with differences in individuals' fat taste sensitivity, with contrasting results also regarding food liking, dietary intake [5], and an increased risk of developing overweight/obesity [102], although results are inconsistent [94,98,184–186]. Further, carrying the A-allele has been shown to influence consumption of other tastes in humans [187], and rodent models allow the hypothesis of the interaction of *CD36* with both sweet and umami tastes [188].

Individuals with obesity have shown a preference for foods labelled as salty, umami, and fatty [10]. However, the combination of taste may influence consumption; for example, a preload of monosodium glutamate (MSG), the most common umami compound used for seasoning, can reduce dietary fat intake and salt consumption [11,12,14,189], although clear conclusions cannot be drawn because fat and umami have not been extensively studied together. Therefore, further research is required to assess the perception and liking of fatty foods and umami foods.

This study aimed to:

- Investigate the possible association between *CD36* rs1761667 and fat and umami food perceptions, rating both intensity and liking perceived, using actual food samples.

- Considering how food perception is strongly associated with food consumption, investigate the possible association between *CD36* rs1761667 and BMI, as a health status indicator, and elements of diet quality.

## 4.2 Methods

The cohort for study 2 (laboratory-based) was derived from a novel data collection in the UK. The study was approved by the ethical committee of St Mary's University (SMU_ETHICS_2021-22_217). Inclusion criteria were any sex, healthy, aged 18-65 years. Majority of participants identified themselves as white Europeans (67%). Exclusion criteria were pregnancy, affected by diseases (e.g., hypertension, cardiovascular diseases, any illness that permanently alters taste, food allergies), and lactose intolerance. Informed consent was obtained from all subjects involved in the studies. The workflow for data collection in Study 2 is summarized in **Figure 10**.

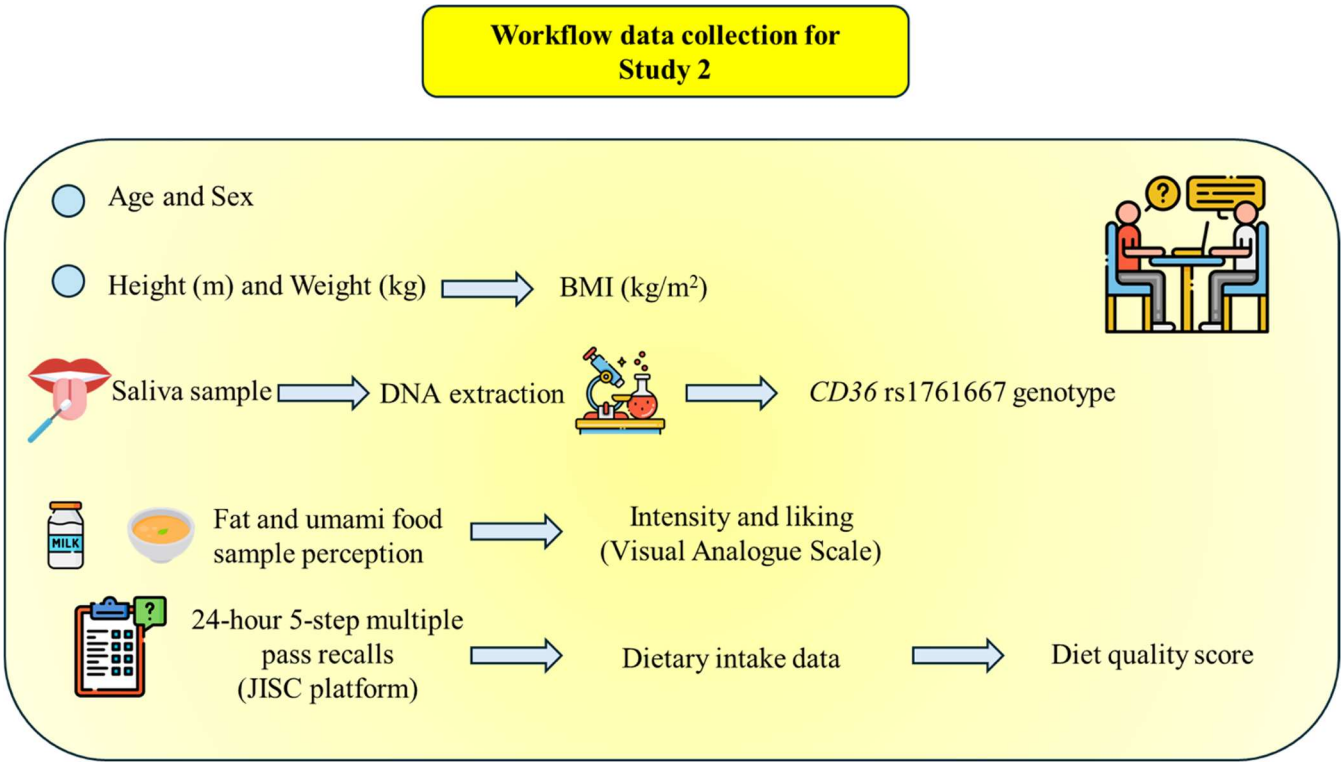


**Figure 10.** Workflow for the data collection adopted for Study 2. Participants were instructed by trained staff, available during the entire data collection process. Age and sex were collected by a self-administered questionnaire. Height (m) and weight (kg) were measured, and then BMI (kg/m2) was calculated. Saliva samples were collected from all participants. DNA was extracted by the *PSP® SalivaGene 17 DNA Kit 1011* (Stratec Molecular GmbH). All participants were genotyped for *CD36* rs1761667. Food perception (intensity and liking) for fat and umami food samples was assessed by a 10cm Visual Analogue Scale (VAS). Dietary intake data were assessed by 24-hour 5-step multiple pass recalls (JISC platform). Average daily dietary intake, compared to population reference values, was used to create a Diet Quality Score.

### 4.2.1 Demographic and Anthropometric data

Demographic data were collected by a self-administered questionnaire. All questionnaires were conducted on the same day, after a detailed explanation by trained staff. Anthropometric data, including height (m) and weight (kg), were also measured, and body mass index (BMI; kg/m2) was calculated.

### 4.2.2 Genetic analysis

For Study 2, 2ml saliva samples were provided, and pure genomic DNA was isolated by the *PSP® SalivaGene 17 DNA Kit 1011* (Stratec Molecular GmbH), in agreement with the manufacturer's procedures. Genotyping was then conducted using the predesigned TaqMan SNP genotyping assay by quantitative real-time polymerase chain reaction (qPCR) technique (*StepOnePlus thermocycler; Applied Biosystems*). Two technical replicates of each sample were performed, and individual samples were accepted with a quality of >98%.

### 4.2.3 Food perception

Participants were assessed for fat and umami food perception using three food samples per flavour, due to the laboratory setting. Fatty flavour was assessed using commercially available foods with differing fat contents, similar to previous literature [190,191]. Milk samples were selected specifically: skimmed milk (0.6g per 200ml), semi-skimmed milk (3.6g per 200ml), and whole milk (7.4g per 200ml) (*TESCO*). Umami flavour was assessed by dilution of commercially available vegetable stock cubes (*OXO*), prepared according to the manufacturer's instructions, as per previous

literature [189]. Three MSG concentrations were used: 0.3%, 0.75%, and 1.5%. Concentrations were piloted internally due to the lack of commercially available reference values.
Participants were instructed to swirl the sample in their mouth for approximately 10 seconds before expectorating. A five-minute break was given between the fatty and umami tastings. Liking and intensity perceived were rated by a visual analogue scale (VAS) (0.0 cm = lowest to 10.0 cm = highest) as per previous literature [192].

### 4.2.4 Dietary intake and Diet Quality Score (DQS)

Dietary intake data were measured using two 24-hour 5-step multiple pass recalls. Participants provided information regarding all food and drinks consumed within the past 24-hour period, together with quantities and a detailed description. The recall was administered online using the JISC survey platform.
Dietary intake data were used to assess compliance with the dietary guidelines in each respective country [193], creating a DQS. The following data were available: free sugars (g/die), total fats (g/die), saturated fatty acids (g/die), fibre (g/die), and sodium (mg/die). The final DQS assigned to each participant ranged from 0 (no compliance at all) to 5 (compliance for every component).

### 4.2.5 Statistical analyses

Differences in intensity and liking ratings for the three fat and umami samples were evaluated using repeated measures analysis of variance (ANOVA), with fat and MSG concentration as the repeated measures for the respective food samples (*within* factor). The main effect of *CD36* rs1761667 genotypes (*between* factor) as well as the interactions with concentrations were examined in the ANOVA models. Testing for normality was done with the Shapiro–Wilk test. Post hoc comparisons were made using Tukey's test following Bonferroni adjustment. The effect of *CD36* rs1761667 genotypes on DQS and BMI was investigated using the same statistical approach as in Study 1. Then, the relationship between the perception of the fatty and umami food samples was assessed by Pearson correlation, and as an exploratory analysis, the possible association between fatty and umami food perception on DQS by a linear regression model was investigated.
Age, sex, and BMI were included in the model as covariates for every analysis performed.
No stratification was applied during the analyses due to the reduced number of participants in Study 2. R Studio was used throughout (*R version 4.4.0 (2024-04-24 ucrt) -- "Puppy Cup" Copyright (C) 2024 The R Foundation for Statistical Computing*). Throughout, the significance criterion was $p \leq 0.05$. The Hardy-Weinberg Equilibrium (HWE) of *CD36* rs1761667 was assessed using the "R" package "*genetics*". We performed a priori power analyses using G*Power (version 3.1. for Mac) [168,169]. As there was limited prior research, we assumed a medium effect size of the SNP. Regarding this study, for which a mixed ANOVA design was used (between-subjects: 3 groups; within-subjects: 3 measurements), a sample of 36 participants (12 per group) was needed to detect a medium effect size (Cohen's f = 0.25) with 80% power at alpha = 0.05.

## 4.3 Results

### 4.3.1 Participants' characteristics and food perception

A total of 49 participants were analysed, as summarised in Table 3. The *CD36* rs1761667 genotype followed HWE ($p > 0.05$).

**Table 3.** Participants' features and food samples perception and liking according to *CD36* rs1761667 genotype in study 2 (UK cohort).

| | | **Total (n =49)** | **AA rs1761667 (n =7, 14%)** | **AG rs1761667 (n = 28, 57%)** | **GG rs1761667 (n = 14, 29%)** |
|---|---|---|---|---|---|
| **Female % (n)** | | 63 (31) | 86 (6) | 57 (16) | 64 (9) |
| **Age (year), mean ± SD** | | 32 ± 11.1 | 36 ± 12.3 | 30 ± 9.7 | 35 ± 12.8 |
| **BMI (kg/m$^2$), mean ± SD** | | 23.6 ± 3.9 | 24.7 ± 2.5 | 24.4 ± 4.4 | 21.4 ± 2.6 |
| **Fat (Milk) Intensity** | Skimmed | 2.9 ± 1.9 | 4.3 ± 1.7 | 2.9 ± 2.2 | 2.3 ± 1.3 |
| | Semi-skimmed | 4.3 ± 1.8 | 5.4 ± 1.5 | 4.2 ± 1.8 | 4.0 ± 1.9 |
| | Whole | 6.3 ± 2.2 | 6.8 ± 1.8 | 6.1 ± 2.1 | 6.4 ± 2.5 |
| **Fat (Milk) Liking** | Skimmed | 4.6 ± 2.4 | 5.2 ± 2.2 | 4.1 ± 2.4 | 5.4 ± 2.4 |
| | Semi-skimmed | 5.4 ± 2.4 | 5.8 ± 2.4 | 5.0 ± 2.6 | 5.9 ± 1.9 |
| | Whole | 5.5 ± 2.9 | 5.2 ± 3 | 5.0 ± 2.9 | 6.5 ± 2.8 |
| **MSG (Broth) Intensity** | 0.3% | 5.7 ± 1.8 | 6.4 ± 1.1 | 6.0 ± 1.7 | 4.7 ± 1.9 |
| | 0.75% | 6.7 ± 1.6 | 7.3 ± 1.4 | 7.0 ± 1.5 | 5.7 ± 1.6 |
| | 1.5% | 7.3 ± 1.9 | 7.8 ± 1.0 | 7.6 ± 2.1 | 6.4 ± 1.5 |
| **MSG (Broth) Liking** | 0.3% | 5.3 ± 2.7 | 6.0 ± 2.5 | 4.9 ± 2.9 | 5.8 ± 2.3 |
| | 0.75% | 4.9 ± 2.6 | 5.9 ± 2.6 | 4.4 ± 2.7 | 5.7 ± 2.3 |
| | 1.5% | 5.1 ± 2.8 | 5.8 ± 2.7 | 4.8 ± 2.9 | 5.5 ± 2.6 |
| **Diet Quality Score, mean ± SD** | | 1.8 ± 1.3 | 2.6 ± 1.4 | 1.8 ± 1.2 | 1.5 ± 1.2 |

UK, United Kingdom; AA/AG/GG, rs1761667 genotype; SD, Standard deviation; n, sample size; MSG, Monosodium Glutamate; DQS: diet quality score. In the second column, the type of milk (based on the concentration of fat) is reported, while for the broth, the concentration of MSG is reported.

### 4.3.2 Associations between CD36 rs1761667 and food samples perception

A statistically significant effect of the concentration of fat on the perceived intensities from the three milk samples was found ($p < 0.001$). More specifically, post-hoc tests revealed that each comparison between the intensities reported for the three different concentrations (Skimmed-; Semi-skimmed-; Whole) was statistically significant ($p < 0.05$). Nevertheless, we found no significant effect of *CD36* rs1761667 genotype ($p = 0.252$) (**Figure 11.A**).
Regarding the umami perception, both the effect of the three different MSG concentrations ($p < 0.001$) and the *CD36* rs1761667 genotype were detected ($p = 0.009$) (**Figure 11.B**). No interaction between concentration and genotypes was observed ($p = 0.9$). All comparisons of intensity between different concentrations (0.3%, 0.75%, 1.5%) were statistically significant, as were the comparisons between genotypes, except for the comparison between AA and AG.
Additionally, we found no statistically significant effect of concentrations or *CD36* rs1761667 genotype, for both fatty and umami liking in food samples ($p > 0.05$).

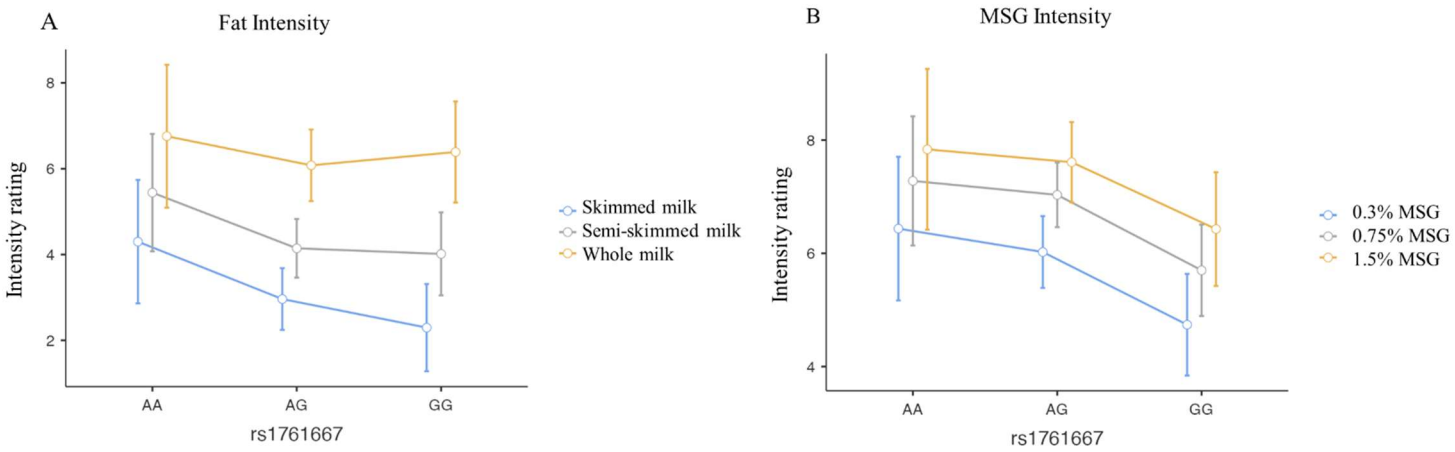


**Figure 11.** Line plots describing the perceived intensity of fat (A) and umami (B) flavour in food samples for each concentration according to *CD36* rs1761667 genotype. Blue lines represent the lowest concentration, grey solid lines represent the intermediate concentrations, and yellow lines represent the highest concentration. The legend is reported on the right for both graphs. Dots represent the average value for every genotype, and bars represent the standard error. The effect of different concentrations is statistically significant for both fatty and umami samples ($p < 0.001$), while the effect of the SNP is significant only for umami (p = 0.009), for which the GG carriers perceived the lowest intensity compared to AA and AG individuals at each concentration. No interaction effect was detected ($p = 0.963$)**.**

### 4.3.3 Correlation between intensity and liking for fat and umami food samples.

A significant, negative correlation was observed between the intensity and liking of umami food samples (Broth 0.3% MSG, cor = -0.35, $p$ =0.01; Broth 0.75% MSG, cor = -0.37, $p$ = 0.009; Broth 1.5% MSG, cor = -0.32, $p$ = 0.03; Figure 12.B). No correlation was observed between the intensity and liking of fatty food samples (Figure 12.A), or the intensity of fatty and umami food samples, the liking of fatty and umami food samples, the intensity of fatty food samples and the liking of umami food samples, and the intensity of umami food samples and the liking of fatty food samples ($p > 0.05$; **Supplementary Table 4.1**).

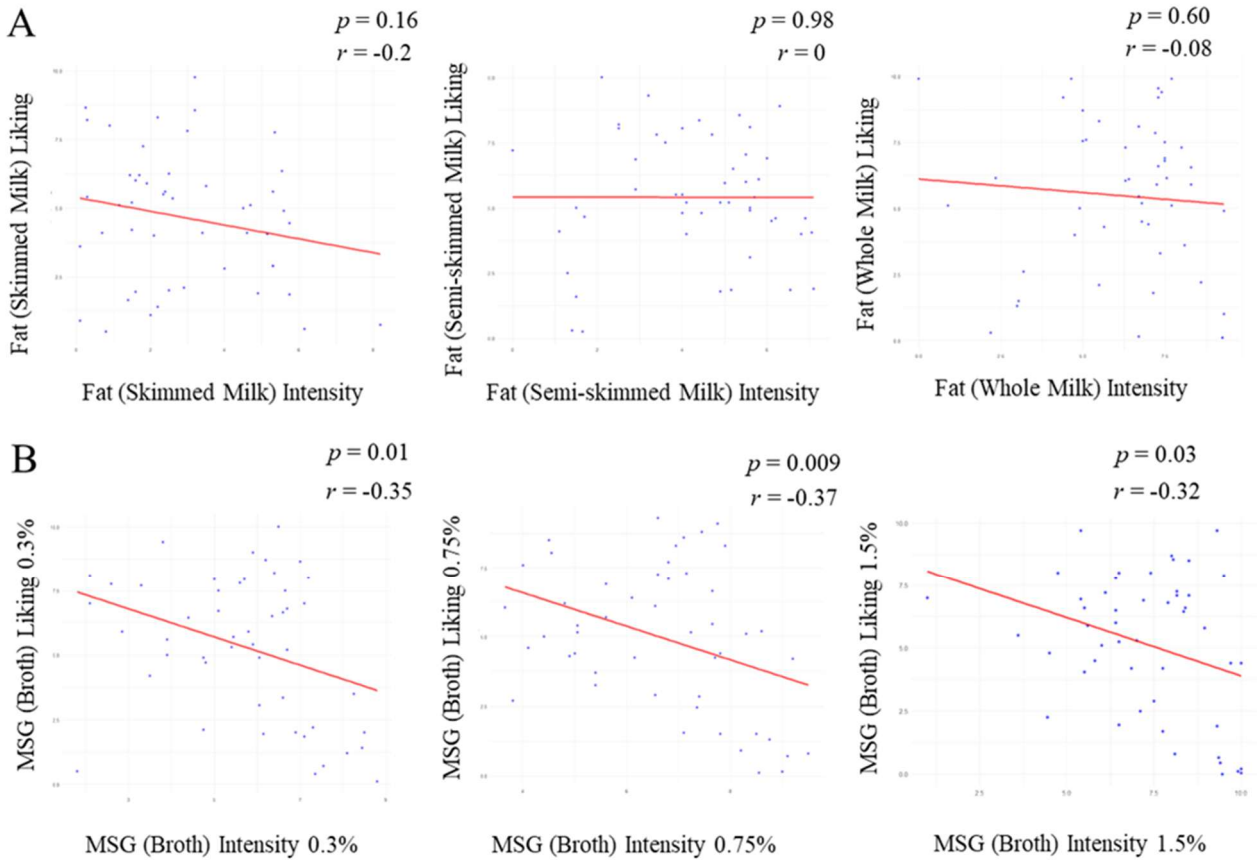

**Figure 12.** Scatter plot illustrating the correlation between intensity and liking for the three fat (milk) samples (A) and for the three MSG (broth) samples (B). The X-axis represents intensities for each sample. The y-axis represents the liking for each sample. Points represent individual observations, while the solid red line indicates the linear regression line and direction of the correlation. The Pearson correlation coefficient (*r*) and p-value (*p*) are indicated, for every analysis, in the top right corner of each plot.

### 4.3.4 The role of CD36 rs1761667 on DQS and BMI

A significant, positive association was found between the *CD36* rs1761667 A-allele and DQS ($\beta$ = 0.64*,* *SE* = 0.30, $p$ = 0.03). Additionally, the *CD36* rs1761667 A-allele was associated with an increased BMI ($\beta$ = 2.0, *SE* = 0.8, $p$ = 0.02). However, BMI as a covariate showed no significant association with DQS.

### 4.3.5 The role of food sample perception on DQS

As an exploratory analysis, the possible association between fat and umami perception with DQS and BMI was investigated. A significant, positive association was found between intensity perceived from the skimmed milk sample and DQS ($\beta$ = 0.2, *SE* = 0.13, $p$ = 0.04). Additionally, a significant, negative association was found between liking of the whole milk sample and DQS ($\beta$ = -0.14, *SE* = 0.06, $p$ = 0.03). No other associations regarding DQS were apparent ($p > 0.05$) (**Supplementary Table 4.2**).

## 4.4 Discussion for Study 2

This study has been conducted on 49 individuals from the United Kingdom, aiming to investigate the possible association between *CD36* rs1761667 and fat and umami food perception as part of the overall aim of this project.

### 4.4.1 *CD36* rs1761667 and food sample perception

In this exploratory laboratory-based study, the role of genetics and food perception was assessed. Regarding fat, no associations were found between the *CD36* rs1761667 SNP and intensity of perception or liking. In contrast, Melis *et al.* found that carriers of the AA genotype showed reduced sensitivity to oleic acid compared to carriers of the GG genotype [8]. Nevertheless, multiple studies have failed to demonstrate any associations as seen in our work [156,185]. The heterogeneity reported in the literature may be due to the different methodologies adopted to investigate fat taste; for example, this study (study 2) utilised commercially available foods as per previous literature [190,191]. While this allows for better translation to nutrition practice, whole foods are often a complex mixture of tastes with a vast array of fat types and concentrations, which may confound results. However, even with consistent, simple taste mediums, results can differ potentially due to other sensory aspects, i.e., texture, which may also influence results when using whole foods. For example, Daoudi *et al.* utilised oleic acid water emulsion to evaluate fat taste sensitivity [156], finding no association with rs1761667, contrasting the association reported in Graham *et al.*, which used oleic acid fat-free UHT milk emulsion [12], considered to be more homogeneous than water emulsion [194]. Further research is required to assess the differences between fat taste assessment vehicles and their relationship to fat taste receptor genetic variability, to ensure clear conclusions can be drawn.

Regarding umami, in this study, there was an association between rs1761667 and umami flavour perception but not liking. This is the first time, to our knowledge, that an association between umami flavour perception and *CD36* has been reported. However, associations between other genetic variants and umami perception have previously been shown (e.g., *TAS1R1* rs11122100 and rs12080675) [52], and genetic interactions between taste perception and dietary intake have been

reported, for example, the *TAS1R1* rs34160967 SNP has been associated with umami taste perception [195] and is separately related to a higher dietary fat intake [171]. Additionally, the *TAS1R1* rs34160967 SNP has been associated with umami, sweet, and salty taste sensitivity [196]. All considered, and accounting for the exploratory nature of our study, our results warrant further research to assess genetic interactions between all known taste-related genes and all known tastes, and whether this may influence dietary intake and other health markers.

### 4.4.2 Correlation between intensity and liking for food samples.

Study 2 demonstrates a negative correlation between intensity and liking for all the umami food samples, following the assumption that the degree of liking changes according to the intensity of the sensation [197]; however, this was not observed for the fatty food samples. The correlation between intensity and liking may vary according to the taste studied [198]. Additionally, the familiarity of foods assessed may be confounding; for example, individuals may show higher liking for the type of milk they have regularly been exposed to [199]**.** Future research should be conducted to further validate the results previously discussed, including all known tastes, with an adequate sample size, which will provide better insight into how we perceive tastes and how this can influence our food choices.

### 4.4.3 *CD36* rs1761667 and DQS, and DQS and food perception

Taste perception has previously been identified as a driver for different dietary patterns [200], as well as genetics [180]. Study 2 revealed a positive association with DQS and the *CD36* rs1761667 A-allele and with skimmed milk sample intensity. Conversely, liking for the whole milk sample was negatively associated with DQS. The role of *CD36* rs1761667 on dietary intake has been investigated previously. For example, Fujii *et al.,* in a Japanese cohort, observed a positive association between total fat intake and the *CD36* rs1761667 A-allele. In contrast, Pioltine *et al*. found the same allele associated with a lower daily fat consumption in a South American cohort [186], while Chmurzynska et al. showed no association with fat food consumption in a Polish cohort [163]. These works included three differing ethnicities and three different methodologies to investigate dietary intake (Food Frequency Questionnaire, 24-h food recalls, and a mobile phone application, respectively), making direct comparison challenging. Dietary intake data are commonly considered limited and challenging to interpret [201], which may explain the heterogeneity in results observed. Taste is one of the major factors that influences dietary choice [202–204]; thus, the potential effect that CD36 rs1761667 may have on food perception, and food perception on dietary intake and quality, warrants further research.

### 4.4.4 *CD36* rs1761667 and BMI

Fat food consumption has previously been associated with increased adiposity parameters [184,205]. Here we report that rs1761667 A-allele carriers had an increased BMI, which is a disease risk indicator [206] that has been linked to eating habits [207]. However, BMI, although associated with body fat, does not directly measure body fat [208]. When discussing body fat and taste perception, various mechanisms have been hypothesised related to increasing dietary intake [209], including reward circuitry and microbiota, factors that are related to body composition, of which BMI does not reliably measure. Therefore, to better understand the relationship between rs1761667 and adiposity alluded to in this current study, it is recommended that future research integrate measurements of body composition (hip-to-waist ratio/bio-electrical impedance/dual-energy X-ray absorptiometry) with an adequate sample size for such stratification.

# 5.0 Chapter V – Study 3

This chapter focuses on Study 3, which has been conducted to validate, using a better-characterised cohort, the results obtained in Studies 1 and 2, which were limited by a lack of specific data and, in Study 2, by a low sample size. This study was conducted on a cohort of 57 individuals gathered at the Lake Lucerne Institute AG, Vitznau, in Switzerland.

## 5.1 Introduction and Aim

In the previous chapters, fat taste, or *Oleogustus*, has been introduced and described. Briefly, it is the sensation elucidated by interaction between long-chain free fatty acids and the possible fat taste receptor, cluster of differentiation 36, codified by the *CD36* gene, as reviewed by Jaime-Lara *et al.* 2022 [210]. This perception, even if not confirmed yet as a taste, may be implicated in the consumption of dietary fats [2].

It has been hypothesized that a lower sensitivity to FFAs may lead to increased intake of high-fat food [190]. In humans, for example, previous studies have reported that individuals hypersensitive to FFAs consumed less dietary fat and showed a lower BMI compared to individuals classified as hyposensitive [94]. The key role that fat taste perception may play in defining human diet and then, health status is at the basis of the high number of research articles published in the last decade. Umami, opposingly, is a canonical taste, and it has never been studied with regard to fat taste, as described in the previous chapters, even if the combination of the two tastes is common in foods, and umami tastants have been associated with different dietary intake for dietary fats [10,189]. In Study 1 and Study 2, the *CD36* common variant rs1761667 (G>A) was investigated, due to its previously described association with differences in FTS among individuals, and fat and umami food liking and perception. A novel association between *CD36* rs1761667 A-allele and a higher intensity perceived from tasting umami food samples, in Study 2, and between the same allele and reduced liking for umami food, in Study 1, was described in the previous chapters.

The experience of these studies warrants further research to better understand these new associations and overcome the previous limitations.

The main aims of the study are:

- Elucidated the possible association between FTS and umami perception, fat food perception, and anthropometric data.

- Investigate the possible association between umami food perception, fat food perception, and anthropometric data.

- Re-investigate the *CD36* rs1761667 (G>A) and the possible associations with the previously mentioned phenotypes to replicate the previous observations.

## 5.2 Methods

The cohort for study 3 (laboratory-based) was derived from a novel data collection in Switzerland at the Lake Lucerne Institute, Vitznau. The study was approved by the ethical committee of SwissEthics (BASEC number: 2023 - 01441). Fifty-seven participants were recruited via word of mouth and emails. Majority of participants identified themselves as White Europeans (87%). Exclusion criteria were pregnancy, breastfeeding, allergies, or intolerances to any of the compounds used for testing, or being affected by diabetes or cancer. Informed consent was obtained from all individuals enrolled. A summary of the data collection workflow can be found in **Figure 13**.

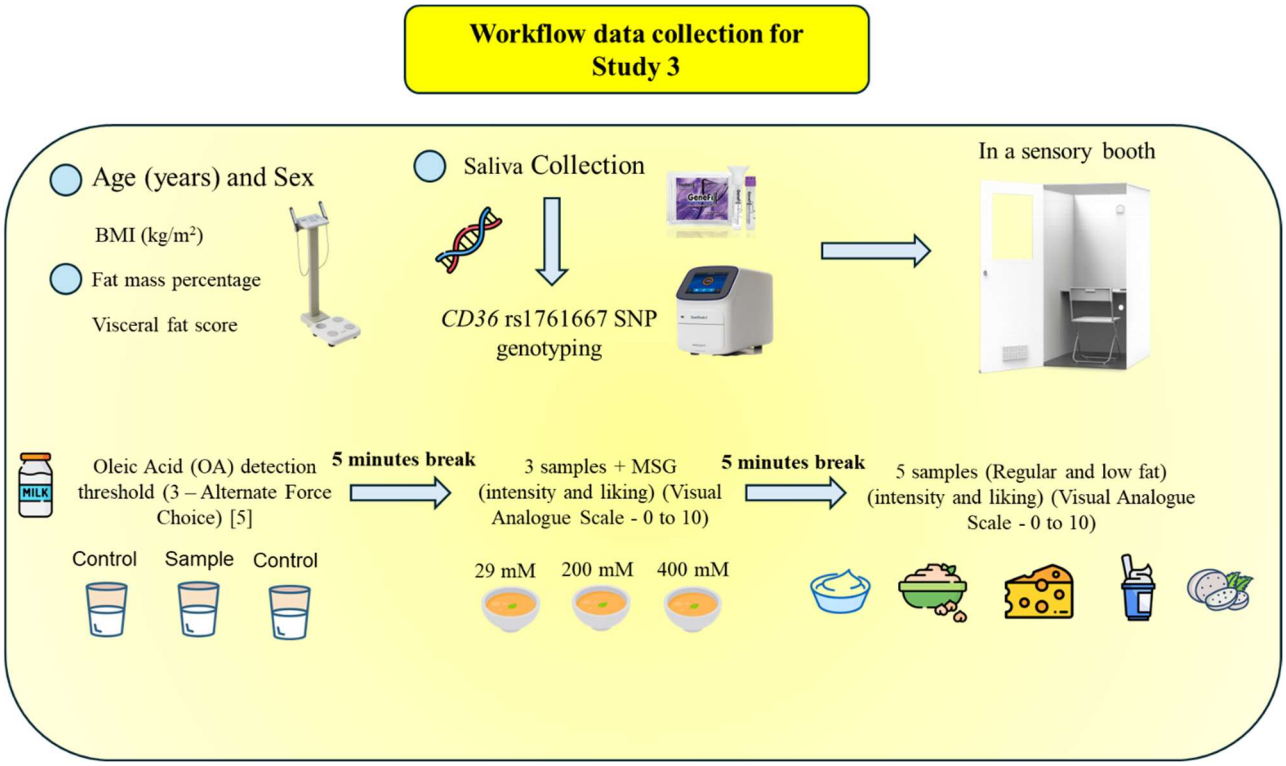


**Figure 13.** Workflow for the data collection adopted for Study 3. Participants were instructed by trained staff, available during the entire data collection process. Age and sex were collected by a self-administered questionnaire. Height (m) was self-reported by the participants, and weight (kg) was measured (*TANITA MC-780*). BMI (kg/m$^2$), fat mass percentage, and visceral fat score were measured by the instruments and then reported. Saliva samples were collected from all participants. DNA was extracted using the *Isohelix GeneFix™ Saliva-Prep 2 DNA Kit*. All participants were genotyped for *CD36* rs1761667. OA detection threshold was measured using the 3-Alternate Forche Choice method as per previous literature [194]. The perception of umami food samples was assessed by tasting three broth samples with increasing MSG concentration by rating intensity and liking. The perception of fat food samples was assessed by tasting five different fatty foods (regular and low-fat versions) by rating intensity and liking. Rating was performed using a 10cm Visual Analogue Scale (0.0 lowest – 10.0 highest) as per previous literature [192].

### 5.2.1 Demographic and Anthropometric data

Individuals were interviewed to collect all the main demographic information. Instructions were explained by trained personnel that was available all the time during the testing procedure. All participants reported age (years), sex, and height (m). Allergies and intolerances were asked about during the interview. Participants were asked to refrain from eating and drinking anything except water for 3 hours before testing. Additionally, they were asked not to do intense training before the test.

Data regarding BMI (kg/m$^2$), fat mass percentage, and visceral fat score were assessed by electric bioimpedance (*TANITA MC-780*). All participants were asked to remove any metallic objects. Individuals with a pacemaker or metallic prosthesis were excluded from the measurement. Individuals were instructed by the personnel regarding the right position to keep during the measurement.

### 5.2.2 Genetic data collection

Saliva collection samples were collected by all participants (*IsoHelix GFX-02 2ml saliva*). DNA was extracted using the *Isohelix GeneFix™ Saliva-Prep 2 DNA Kit*. Concentration for all samples was assessed by *Nanodrop One* (ThermoScientific). Genotyping was conducted with a 10µl reaction volume using the 96-well Fast thermal cycling parameters and predesigned TaqMan SNP genotyping assay by quantitative real-time polymerase chain reaction (qPCR) technique (*Quant Studio 3; Applied Biosystems*). The primers and the probes were pre-designed by Applied Biosystems with the following code: C___8314999_10. Two negative controls were included during the process, as well as two positive controls. Two technical replicates of each sample were performed, and individual samples were accepted with a quality of >98%.

### 5.2.3 Fat Taste Sensitivity (Oleic Acid detection threshold)

Oral Fatty Acid Threshold Assessment and Ascending Forced Choice Triangle Procedure was used to determine each participant's oleic acid (OA) detection threshold (FTS). Full description of the methodology can be found in the original manuscript [194]. Testing was conducted in a sensory booth under red light to avoid any risk of bias given by visual cues, and participants were instructed to wear nose clips to avoid any cues from smell.
Each participant was presented randomly with three cups (randomly two-digit number for labelling) containing 15 ml of vehicles at room temperature, two were controls, and the third contained oleic acid (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 cup with the added OA. To define the OA threshold, individuals were required to choose the OA solution sample correctly three times at the same concentration. If they were incorrect at any point, they would be presented with three further cups at the upper concentration level (1 sample and two controls). 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 [194].

### 5.2.4 Umami food perception

Testing was conducted in a sensory booth, under red light, after a 5-minute break from the previous test. Participants were presented with three broth samples at room temperature with increasing concentrations of MSG to evaluate umami perception. A vegetable broth (*Knorr* brand) was selected that did not list MSG as an ingredient. Broth was prepared according to the manufacturer's instructions. The three concentrations used were: 29 mM (low), 200 mM (medium), and 400 mM (high) as per previous literature [211]. All samples were presented at room temperature.
Participants were presented with the three broth samples and were instructed by the available personnel. Samples were tasted for 5-10 seconds and then expectorated. Water was used to rinse the mouth between each sample. Intensity and liking for each sample were rated with a VAS (0.0cm – 10.0 cm) as per previous literature [192].

### 5.2.5 Fat food perception

Testing was conducted in a sensory booth. Participants were presented with five different fatty foods in regular and low-fat versions using the same brand for each couple.
Samples were as follows:

- Cream cheese (*Philadelphia Original and Balance*, *Mondelez*),
- Hummus (*Karma Hummus Nature and 45% reduced, Coop*),
- Yogurt, unsweetened (*Yaos Natural Greek Style Yogurt Original and 0%*),
- Cheese (*Leerdammer Sliced Cheese Original and Lightlife*),
- Mozzarella (*Mollini Mozzarella Original and 60% Less Fat*).

Samples were presented at room temperature. Presentation order was randomised, and all samples were labelled with a random 3-digit ID number. Samples were presented in pairs (regular and low-fat order randomised). Water was given to allow mouth rinsing between each sample. Participants were instructed to taste each sample and rate both intensity and liking using a VAS (0.0cm – 10.0 cm) as per previous literature [192].

### 5.2.6 Statistical analyses

Mean intensity and liking scores for the umami food samples were calculated for each participant. Internal reliability for each group was assessed by the Cronbach alpha function available in R.
A sum score, for both intensity and liking (regular and low-fat), was calculated for each participant. Differences in distribution of categorical variables (e.g., OA taster status) by biological sex and BMI ($< 25 kg/m^2$ or $\geq 25 kg/m^2$) [167] were assessed by *Pearson's Chi-squared test* or *Fisher's Exact Test for Count Data* according to the number of observations for each group. The differences in distribution of continuous variables (e.g., umami perception scores) by biological sex and BMI categories (< 25kg/m2 or ≥ 25kg/m2) were assessed by *Student's T test* (for parametric variables) or *Mann–Whitney U test* (for non-parametric variables). Normal distribution of the data was assessed by the *Shapiro-Wilk* test.
To investigate the associations between FTS (Non taster – 0; Hyposensitive - 1; Hypersensitive - 2) and umami perception (intensity and liking) scores, linear regression models were used.
The associations between FTS and umami single samples perception (as repeated measurements) were assessed using a mixed model (*Type III Analysis of Variance*). Umami samples concentrations (29 mM, 200mM, and 400mM) were investigated as *within factor*, while FTS (status) was the *between* factor. The possible association between FTS and fat food perception (intensity and liking) scores was evaluated with the previously described methodology in Chapter III. The same was true also regarding the possible association between fat mass percentage and visceral fat score.
Additionally, we have also investigated the possible association between umami perception scores (intensity and liking) with fat food perception, BMI, fat mass percentage, and visceral fat score, using the same statistical approach previously described.
To assess any differences in the distribution of *CD36* rs1761667 and FTS, a *Fisher's Exact Test for Count Data* was used to assess the differences in the distribution of the genotype according to OA taste status.
To investigate the association between *CD36* rs1761667 and umami and fat food perception (scores), linear regression models were used. The *CD36* rs1761667 genotype was assessed with an additive inheritance model (GG = 0; AG = 1; AA = 2).

To investigate the associations between *CD36* rs1761667 and umami sample perception (as repeated measurements), a mixed model (*Type III Analysis of Variance*) was used. Umami samples concentrations (29 mM, 200mM, and 400mM) were investigated as within factor, while the CD36 rs1761667 genotype (GG-AG-AA) was the *between* factor. For the linear regression model, analyses were adjusted according to age, sex, and BMI ($kg/m^2$). No stratification according to sex or BMI was performed in the analyses due to the resulting low sample size after applying the stratification. Throughout, the significance criterion was $p \leq 0.05$.

Analyses were performed on *R version 4.4.2 (2024-10-31 ucrt) -- "Pile of Leaves" Copyright (C) 2024 The R Foundation for Statistical Computing Platform: x86_64-w64-mingw32/x64*. The Hardy-Weinberg Equilibrium (HWE) of *CD36* rs1761667 was assessed using the "R" package "*genetics*".

## 5.3 Results

### 5.3.1 Participants' features

A total of 57 participants were included in the study, as summarised in **Table 4**.

**Table 4.** Participants' features and food samples perception and liking according to FTS (OA taster status) in Study 3.

| | **Total (n = 57)** | **OA non-taster (n = 15, 26%)** | **OA hyposensitive (n = 24, 42%)** | **OA hypersensitive (n = 18, 32%)** |
|---|---|---|---|---|
| **Female % (n)** | 53% (30) | 53% (8) | 50% (12) | 56% (10) |
| **Age (year), mean ± SD** | 28.0 ± 7.6 | 27.0 ± 5.7 | 29.0 ± 9.6 | 28.0 ± 6.0 |
| **BMI (kg/m$^2$), mean ± SD** | 23.0 ± 3.3 | 22.0 ± 3.2 | 23.5 ± 3.5 | 23.1 ± 2.9 |
| **Fat mass percentage, mean ± SD** | 21.4 ± 7.2 | 20.8 ± 6.7 | 21.2 ± 7.8 | 22.2 ± 7.2 |
| **Visceral fat score, mean ± SD** | 3.0 ± 2.5 | 3.0 ± 1.7 | 3.2 ± 3.1 | 3.0 ± 2.1 |
| **Umami intensity score, mean ± SD** | 7.7 ± 1.2 | 8.0 ± 0.9 | 7.6 ± 1.1 | 7.3 ± 1.5 |
| **Umami liking score, mean ± SD** | 6.4 ± 1.7 | 5.8 ± 1.7 | 6.9 ± 1.6 | 6.1 ± 1.8 |
| **Fat intensity (regular) score, mean ± SD** | 24.3 ± 6.2 | 24.3 ± 6.5 | 24.1 ± 5.4 | 24.5 ± 7.1 |
| **Fat liking (regular) score, mean ± SD** | 31.9 ± 6.1 | 31.3 ± 5.6 | 31.6 ± 6.6 | 32.8 ± 6.0 |
| **Fat intensity (low-fat) score, mean ± SD** | 24.4 ± 6.7 | 24.6 ± 6.9 | 23.6 ± 5.3 | 25.3 ± 8.4 |
| **Fat liking (low-fat) score, mean ± SD** | 28.9 ± 5.6 | 28.3 ± 5.7 | 28.9 ± 6.2 | 29.6 ± 5.0 |

n, sample size; OA, Oleic Acid; SD, standard deviation,

### 5.3.2 FTS and umami food perception

All participants were classified according to the OA detection threshold [194]. Fifteen participants failed to identify three samples in a row at the same concentration across all 13 concentrations and were then classified as non-tasters (OA detection threshold >20mM). Twenty-four participants showed a detection threshold ≥ 3.8mM and were classified as hyposensitive. Eighteen participants showed a detection threshold < 3.8mM and were classified as hypersensitive. No differences in the distribution of the OA taster status were found between the two biological sexes ($p > 0.05$).
No statistically significant association between OA taster status and both intensity and liking umami perception scores was found ($p > 0.05$).
When investigating the three samples as repeated measurements, a statistically significant effect of the MSG concentration (29mM; 200mM; 400mM) in the perceived intensities from the three broth samples was found ($p < 0.001$). Nevertheless, no significant effect of the OA taster status was found ($p > 0.1$). Regarding liking, as per intensity, a statistically significant effect of the MSG concentration (29mM; 200mM; 400mM) in the liking rating for the three broth samples was found ($p < 0.001$). Nevertheless, like intensity, no statistically significant effect of the OA taster status was found (**Figure 14**).

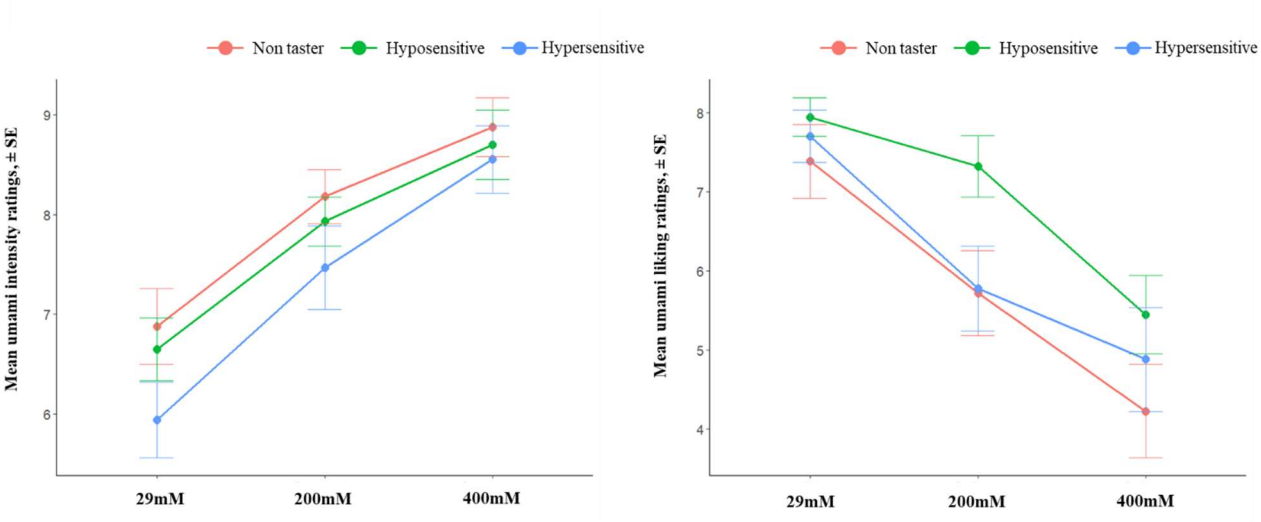


**Figure 14.** Line plots describing the perceived intensity (left) and liking (right) for umami food samples according to MSG concentration (X-axis) and variation according to OA taster status. Red lines represent the OA non-taster participants. Green lines represent the OA hypo-sensitive participants. Blue lines represent the OA hypersensitive participants. Legend is reported on the top right for both graphs. Dots represent the average value for every MSG concentration, and bars represent the standard error. The effect of different concentrations is statistically significant for both intensity and liking ($p < 0.001$), while no significant effect of the OA taster status has been observed ($p > 0.05$).

### 5.3.3 FTS and fat food perception

For all participants, a sum score regarding fat food perception (separately for regular and low-fat versions) was calculated. A summary of the values can be found in **Table 4**. Using a linear regression model, we have found no statistically significant association ($p < 0.05$) between the OA taster status and intensity and liking scores (both regular and low-fat) for the fat food samples perceptions. A summary of these analyses can be found in **Supplementary Table 5.1**
We have then investigated the perception of the single foods rated by the participants. A positive statistically significant association ($\beta = 0.8$ / $SE = 0.3$ / $p = 0.03$) between liking for hummus (regular) and OA taster status was reported. Individuals with a higher sensitivity to this fatty acid showed a higher liking for this specific food sample. No other statistically significant association was found regarding FTS and fat food samples perception ($p > 0.05$). A summary of all analyses conducted can be found in **Supplementary Table 5.2**.

### 5.3.4 FTS, BMI, and adiposity

No significant differences in the distribution of the OA taster status were found by dividing all participants according to BMI (underweight / normal-weight and overweight / obesity) using *Fisher's Exact Test for Count Data* ($p > 0.05$). No statistically significant association was found between OA taster status and fat mass percentage ($p > 0.05$). Additionally, the same was true for visceral fat score ($p > 0.05$). A summary of all analyses conducted can be found in **Supplementary Table 5.3**.

### 5.3.5 Umami food perception and fat food perception

There was no difference between intensity and liking umami score by the two biological sexes ($p > 0.05$). Additionally, the same was true also for fat food intensity and liking (regular and low-fat) scores ($p > 0.05$). As exploratory analyses, we have investigated the possible association between umami food perception (as an independent variable) and fat food perception. A positive significant association ($\beta = 3.0$ / $SE = 0.6$ / $p < 0.0001$) was found between fat intensity score (regular) and umami intensity score, as described in **Figure 15**. A similar significant association ($\beta = 2.8$ / $SE =$

0.7 / $p$ = 0.0002) was found between fat intensity score (low-fat) and umami intensity score. No statistically significant association was found between fat food liking scores (regular and low-fat) and umami intensity score ($p$ > 0.05).

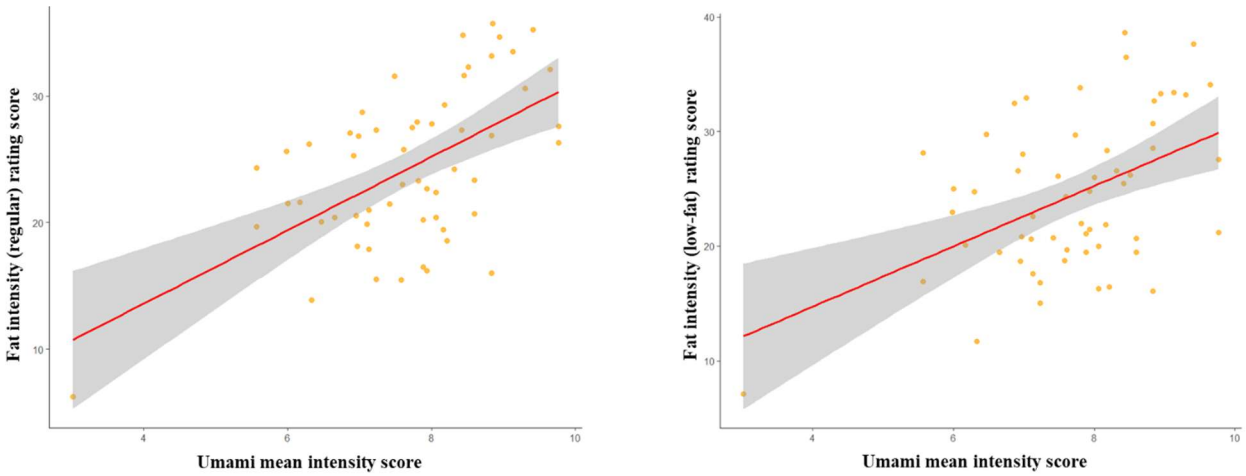


**Figure 15.** Scatter plots illustrating the association between umami mean intensity score (*X-axis) and fat intensity rating score (regular – left / low-fat right) (Y-axis*). Yellow dots represent single observations. The solid red line indicates the linear regression line and direction of the correlation.

No statistically significant association was found between fat food intensity and liking score (regular and low-fat) and umami liking score ($p$ > 0.05).
Furthermore, as previously done regarding OA taster status, we have investigated single fat food perception (regular and low-fat). Similar positive association were found between umami intensity scored and regular ($\beta$ = 0.7 / $SE$ = 0.2 / $p$ = 0.0001) and low-fat hummus intensity ($\beta$ = 0.5 / $SE$ = 0.2 / $p$ = 0.008), regular ($\beta$ = 0.7 / $SE$ = 0.2 / $p$ = 0.001) and low-fat ($\beta$ = 0.7 / $SE$ = 0.2 / $p$ = 0.008) cheese intensity and regular cheese liking ($\beta$ = 0.7 / $SE$ = 0.2 / $p$ = 0.005), regular yogurt intensity ($\beta$ = 0.8 / $SE$ = 0.2 / $p$ = 0.0009), and low-fat yogurt intensity ($\beta$ = 0.9 / $SE$ = 0.2 / $p$ = 0.0009). No other statistically significant associations were apparent ($p$ > 0.05).
No statistically significant associations were found between fat food samples perception and umami liking score ($p$ > 0.05). A summary of all analyses can be found in **Supplementary Table 5.4**.

## 5.3.6 Umami food perception, BMI, and adiposity

Dividing individuals by BMI (< 25kg/m$^2$ or ≥ 25kg/m$^2$), a significant difference for the umami intensity score ($p$ = 0.02) was reported. Participants classified as underweight or normal-weight showed a lower intensity score rating (7.5) compared to participants with overweight or obesity (8.3). No significant difference was found regarding umami liking score ($p$ > 0.05).
No significant association was found between fat mass percentage and umami intensity and liking score ($p$ >0.05). Additionally, the same was true for visceral fat score ($p$ > 0.05). A summary of all analyses can be found in **Supplementary Table 5.5**.

## 5.3.7 Fat food perception, BMI, and adiposity

Dividing individuals by BMI (< 25kg/m$^2$ or ≥ 25kg/m$^2$), no significant difference was found for the fat intensity and liking (regular and low-fat) scores ($p$ > 0.05), and the same was true also for single fat foods perception ($p$ > 0.05).

No statistically significant associations were found between fat mass percentage and fat intensity and liking (regular and low-fat) scores ($p > 0.05$). The same was true also for visceral fat score ($p > 0.05$).
When investigating single food perception, a positive significant association was found between fat mass percentage and regular ($\beta = 0.6$ / $SE = 0.2$ / $p = 0.01$) and low-fat ($\beta = 0.8$ / $SE = 0.3$ / $p = 0.01$) cheese liking, as described in **Figure 16.** No other statistically significant associations were reported. A summary of all analyses can be found in **Supplementary Table 5.6**.

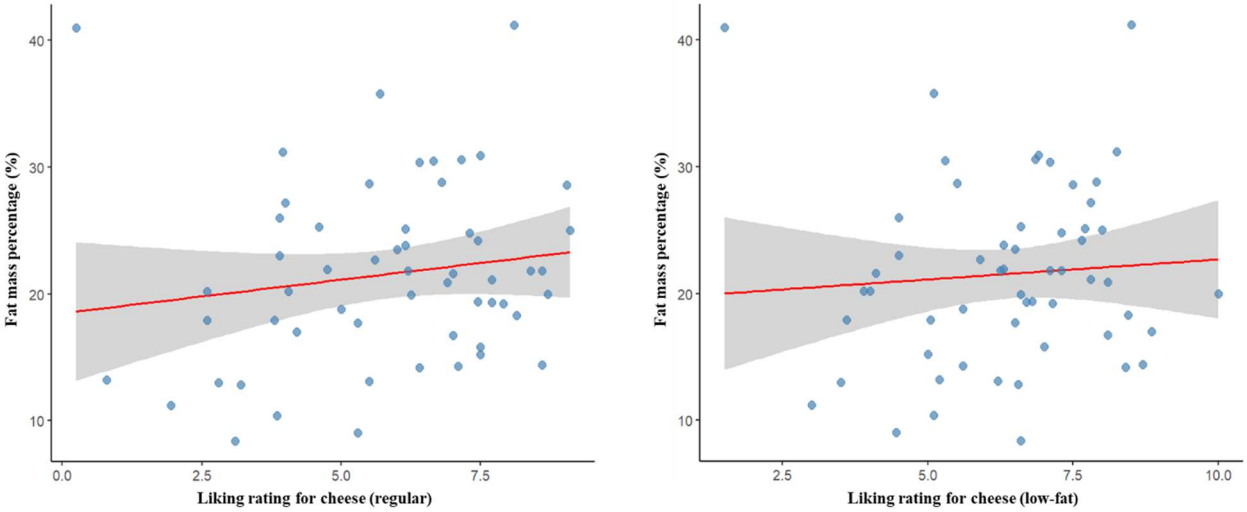


**Figure 15.** Scatter plots illustrating the association between liking rating for regular (left) and low-fat (right) cheese (*X-axis) and fat mass percentage (Y-axis*). Blue dots represent single observations. The solid red line indicates the linear regression line and direction of the correlation.

Regarding visceral fat score, a negative and significant association was found with intensity perceived from cheese (regular) ($\beta = -0.2$ / $SE = 0.1$ / $p = 0.05$) and with liking for yogurt (low-fat) ($\beta = -0.2$ / $SE = 0.1$ / $p = 0.02$). Additionally, a positive and significant association was found with liking for cheese (low-fat) ($\beta = 0.2$ / $SE = 0.1$ / $p = 0.03$). No other statistically significant associations were reported. A summary of all analyses can be found in **Supplementary Table 5.6**.

### 5.3.8 *CD36* rs1761667 and FTS

A total of 36 individuals were genotyped for *CD36* rs1761667 (AA = 10; AG = 17; GG = 9). The distribution of the genotypes was in line with the Hardy-Weinberg equilibrium ($p > 0.05$). No differences in the distribution were found according to sex using *Fisher's Exact Test for Count Data* ($p > 0.05$). No difference in the distribution of the *CD36* rs1761667 was found according to OA detection threshold status using *Fisher's Exact Test for Count Data* ($p > 0.05$).

### 5.3.9 *CD36* rs1761667 and umami food perception

No associations were found between *CD36* and umami perception mean scores (both intensity and liking) ($p > 0.05$). When investigating the three samples as repeated measurements, a statistically significant effect of the MSG concentration (29mM; 200mM; 400mM) in the perceived intensities from the three broth samples was found ($p < 0.001$). Nevertheless, no significant effect of the *CD36* rs1761667 genotype was found ($p > 0.1$). Regarding liking, as per intensity, a statistically significant effect of the MSG concentration (29mM; 200mM; 400mM) in the liking rating for the three broth samples was found ($p < 0.001$). Nevertheless, a suggestive trend was observed according to *CD36* rs1761667 genotype ($p = 0.06$) (**Figure 17**), and, more specifically, individuals carrying *CD36* rs1761667 GG genotype seem to perceive a reduced liking for MSG samples at higher concentrations (200mM; 400mM).

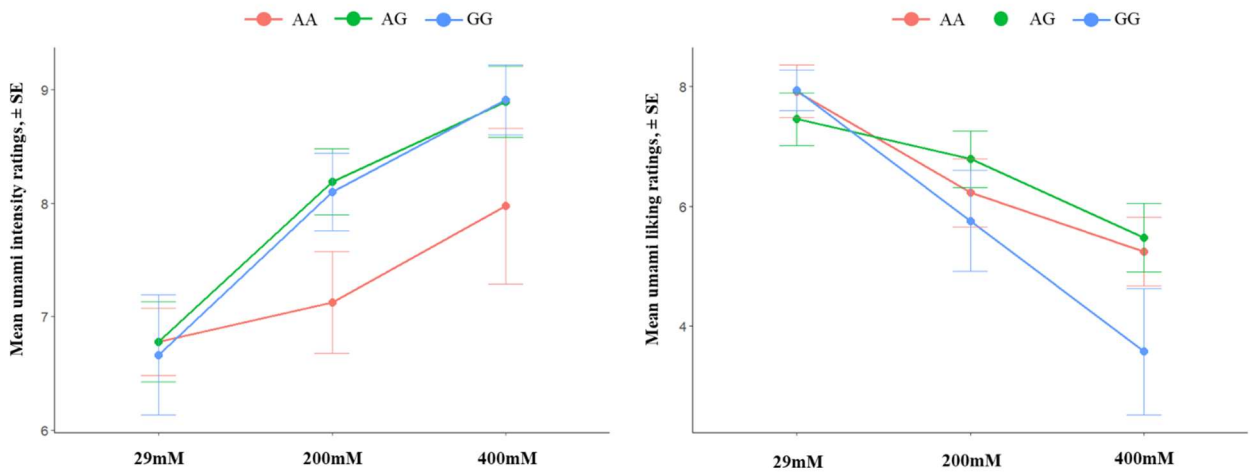


**Figure 16.** Line plots describing the perceived intensity (left) and liking (right) for umami food samples according to MSG concentration (X-axis) and variation according to *CD36* rs1761667. Red lines represent *CD36* rs1761667 AA individuals. Green lines represent *CD36* rs1761667 AG individuals. Blue lines represent *CD36* rs1761667 GG individuals. Legend is reported on the top right for both graphs. Dots represent the average value for every MSG concentration, and bars represent the standard error. The effect of different concentrations is statistically significant for both intensity and liking ($p < 0.001$), while no significant effect of *CD36* rs1761667 genotypes was observed for intensity ($p > 0.05$); a suggestive pattern was observed for liking ($p = 0.06$).

### 5.3.10 *CD36* rs1761667 and fat food perception

No significant associations between *CD36* rs1761667 genotypes and fat food perception scores (intensity and liking), both for regular and low-fat versions, were found. A summary of these analyses can be found in **Supplementary Table 5.7.** Then, we have investigated the perception of the single foods rated by the participants according to the *CD36* rs1761667 genotype. We have suggestive patterns regarding the association with the rs1761667 A-allele. More specifically, the *CD36* rs1761667 A-allele was associated with a reduced intensity perceived from tasting regular ($\beta = -0.9$ / $SE = 0.5$ / $p = 0.06$) and low-fat ($\beta = -0.9$ / $SE = 0.5$ / $p = 0.08$). A similar pattern was reported for the intensity perceived from tasting regular yogurt ($\beta = -0.8$ / $SE = 0.5$ / $p = 0.09$). No other significant or suggestive statistical associations were found. A summary of all analyses can be found in **Supplementary Table 5.8**.

### 5.3.11 *CD36* rs1761667, BMI, and adiposity

In our cohort, we found no differences in the distribution of *CD36* rs1761667 genotypes, dividing all participants according to BMI (underweight / normalweight and overweight / obesity), using *Fisher's Exact Test for Count Data* ($p > 0.05$). No significant association between *CD36* rs1761667 and fat mass percentage using linear regression models ($p > 0.05$) was found. The same was true also for visceral fat score ($p > 0.05$). A summary of all analyses can be found in **Supplementary Table 5.9**.

## 5.4 Discussion

In study 3, the possible interplay between FTS and umami perception was investigated in a cohort of 57 individuals gathered at the Lake Lucerne Institute, Switzerland. We have reported no significant associations between FTS and umami food perception; nevertheless, we have found a positive and significant association between the umami food perception and fat food perception.

### 5.4.1 FTS and umami food perception

In our study, the majority of the participants were classified as hyposensitive or non-tasters for OA as per previous literature [185]. We have found no statistically significant association between FTS

and umami food perception (as mean score and as repeated measurement), highlighting that, at the current state, we exclude that OA detection threshold status may encompass umami perception. An explanation may be found in the methods used in this study. To assess FTS, we have selected the method described by Haryono *et al.*, which consists of oleic acid milk solutions [194]. To the best of our knowledge, this technique is one of the most used in research to assess FTS [185,185,190], and this choice was made to ensure replicability. Nevertheless, it is important to mention that this approach has multiple issues. The preparation of solutions is not free from the risk of human error (e.g., pipetting, volume measuring), and grouping based on the detection threshold reported by each participant can only partially reduce the risk of bias. This is demonstrated by the lack of replication of previous results that can be found in the literature. For example, Graham *et al.* found no associations between FTS and *CD36* rs1761667 [185], even if the effect of the variant on FTS has been alluded to in multiple studies [210]. Additionally, using milk, even if considered to be more stable for an oleic acid emulsion compared to water [194], may generate bias due to the flavour that may not be appreciated by all participants, causing underperformance during the testing phase. Further research should consider the use of different approaches that do not involve actual food for the emulsion. A new protocol has been developed by Costanzo *et al.* that avoids the use of milk without losing any emulsion stability and avoiding the risk of bias due to the possible averse reaction to milk flavour among individuals [212].

### 5.4.2 FTS and fat food perception

In our study, we have reported that there was no association between FTS and fat food perception score, both intensity and liking, regular and low-fat versions. This result is in contrast to previous literature, where individuals marked as hyposensitive regarding fat taste showed higher acceptance for fatty foods compared to hypersensitive individuals [213]. Nevertheless, opposing results have also been reported in the literature [214]. For example, Costanzo *et al.*, in a cohort of Australian adult women, found no association between FTS and fatty food liking [145]. In our study, we have evaluated intensity and liking perceived from tasting a panel of five different fatty foods. We have found no association between FTS and intensity of the flavour perceived; nevertheless, we have reported that higher FTS was associated with higher liking for regular hummus samples. As previously described, literature reports contrasting results regarding FTS and fatty food liking, but overall, it has been observed that a higher sensitivity to fatty acids may lead to a reduced liking for high-fat foods [121,213]. Our result contrasts this association; nevertheless, an explanation may also be found in hummus's extraordinarily complex flavour that may not be related to fattiness. Nevertheless, these results are in line with those observed in Study 1, where individuals carrying the CD36 rs1761667 A-allele, commonly related to fat taste hyposensitivity, were also related to reduced liking for fatty foods. The inconsistencies found in the literature may be due to the difference between taste and flavour, which is elucidated by actual food and may not be directly associated with OA detection threshold. Further research should include multiple sensorial taste assessments to validate replicability and association with food perception.

### 5.4.3 FTS, BMI, and adiposity

In our study, no association between FTS and adiposity/health markers (BMI, fat mass percentage, and visceral fat score) was found. The association between FTS and adiposity is quite controversial in the literature. When assessing the association between FTS and BMI, studies have reported that individuals with a lower FFA sensitivity showed higher BMI [213,215,216] while others reported no association [217–219]. Furthermore, a meta-analysis by Tucker *et al.*, conducted in 2017 on

seven cross-sectional studies, found that FTS does not contribute to or result from obesity [217]. The investigation between FTS and adiposity lies in the assumption that an FFA hypersensitivity may lead to higher liking, and consequently, intake of fatty foods; nevertheless, the current evidence regarding the association between fat perception and overall health status is weak [220]. In our study, we have not only investigated BMI as a health status marker, but also fat mass percentage and visceral fat score, which are direct and accurate measures of adiposity [149], but we have found no significant association. A limitation of our study is the lack of data regarding the physical activity levels, and, also, due to the young age of our cohort, it is possible that a possible association may have been masked; nevertheless, considering the current research, our results confirm the non-association between fat taste and obesity [217].

### 5.4.4 Umami perception and fat food perception

In this new cohort, a higher sensitivity score for the umami samples was strongly associated with the fat food intensity score. Individuals who rated a higher intensity score for umami samples also reported a higher intensity score for the perception of single fat food samples. To the best of our knowledge, this is a novel association. In Study 2, we found no direct association between umami food perception and fat food perception. Nevertheless, in Study 2, fat food perception was assessed by tasting milk at different dietary fat concentrations (Skimmed-; Semi-skimmed-; and Whole Milk), while in Study 3, fat food perception was assessed by a wider panel of different fatty food, avoiding again the selection of milk for which the flavour was possibly linked to bias to the strong exposition factor related to milk liking [197]. In literature, it has been reported that individuals with umami taste impairments reported an overall improvement in food palatability after umami taste was improved separately [221], linking to a possible taste interplay. Nevertheless, it is important to specify that we cannot exclude the multisensorial aspect of flavour perception coming from food tasting. It is known that food flavour cannot be associated with only one taste component and with only one sensorial perception (e.g. smell, texture, temperature), so future research, in order to confirm a possible association between fat and umami perceptions, should also consider a direct assessment of umami taste sensitivity, as example reporting for participants MSG detection threshold [222]. Additionally, in our study, to avoid additional burden for the participants, we have not reported other possible taste-associated variables such as papillae density [223] and salivary flow rate [224]. Nevertheless, the strong association highlights an interplay between fat and umami flavour perception, assessed by actual food tasting. Future research should focus on how this interplay may encompass dietary patterns and then, subsequently, health status.

### 5.4.5 Umami perception, BMI, and adiposity markers

In Study 3, we found that individuals with a BMI $\geq 25 kg/m^2$ reported a higher intensity score compared to individuals with a BMI $< 25 kg/m^2$. Nevertheless, no association was found regarding fat mass percentage and visceral fat score levels. Literature is inconsistent regarding the association between BMI and umami perception. In a study conducted by Pepino *et al.* to assess differences in umami taste perception in women, the authors reported that women with obesity showed a higher MSG detection threshold [225], whereas, in a study conducted by Feeney *et al.*, no differences in umami sensitivity were found according to BMI and body fat [226]. An explanation for this association may be found in the effect that MSG has on energy intake. MSG plays a biphasic role in food intake, increasing appetite during a meal and, consequently, enhancing satiety and reducing further energy intake [227]. It is possible that an individual reporting a higher intensity score may have an adverse reaction to MSG containing foods and, for this reason, have a higher energy intake leading to a higher BMI. Nevertheless, it is important to mention that in our study, only 14 individuals out of 57 showed a BMI $\geq 25 kg/m^2$. To confirm the association reported, further

research should be conducted in a cohort with a higher number of individuals with a BMI ≥ 25kg/m$^2$.

### 5.4.6 Fat food perception, BMI, and adiposity

It is known that high-fat foods are palatable and high-energy dense, thus possibly leading to overconsumption of these foods and weight gain with negative outcomes on human health [4]. As previously observed in our study, we found no association between FTS and adiposity markers (e.g., BMI, fat mass percentage, and visceral fat score), and the literature has reported conflicting results regarding the topic [217]. In Study 3, no association was found between FTS and adiposity markers, in line with previous literature [222–224]; nevertheless, we have additionally investigated fat food samples perception, which may better reflect a real-world scenario. We have found no association between BMI (< 25kg/m$^2$ or ≥ 25kg/m$^2$) and fat food perception (as a score and as single food perception). Nevertheless, when investigating fat mass percentage, even if no significant association was found regarding fat food perception scores, we have reported a positive and significant association with liking for cheese, both regular (27.5g of fat per 100 g of product) and low-fat versions (16g of fat per 100 g of product). In our study, we have not investigated dietary intake; nevertheless, it is known that liking is one of the major drives of food intake [228–230]. The association reported is in line with previous literature, where it has been observed that a major preference for fats is linked to a major risk of obesity [231]; nevertheless, the association between cheese consumption and obesity is controversial. For example, in a study conducted by Alegría-Lertxundi *et al.*, it was observed that a lower or moderate intake of cheese was associated with a higher prevalence of excess weight compared to a higher consumption [232].

When investigating visceral fat score, we have found no associations with fat food perception scores; nevertheless, when investigating single food perception, we have reported multiple associations. We have found negative associations with regular cheese flavour intensity and liking for low-fat yogurt. It is possible that a stronger sensitivity to fatty flavour may lead to a reduced consumption of high-fat food. This trend has been previously alluded to in research. For example, in a study conducted by Cornelis *et al.*, it was reported that the recalled intensity of fatty foods was negatively related to liking and consumption [233]. Opposingly, a preference for a low-fat version of a food (e.g., yogurt) may lead to a reduced intake of the regular whole-fat version of it. Regarding the topic, the literature is still controversial. In a study conducted by Raynor *et al.*, it was reported that a preference for high-fat food and lower liking for low-fat foods was predictive of a higher dietary fat intake, and the authors concluded that dietary interventions, in order to reduce dietary fat intake, should focus on increasing acceptance for low-fat foods [233].

### 5.4.7 *CD36* rs1761667 and FTS

In our cohort, we have found no difference in the distribution of the *CD36* rs1761667 genotype. In literature, the A-allele variant of this SNP has been previously associated with fat taste hyposensitivity [8]. Nevertheless, these associations have not always been replicated. Our study is in line with previous literature where no direct association between *CD36* rs1761667 and FTS was reported [156,185]. In our study, we selected the same methodology used by Graham *et al.*, resulting in a similar outcome; nevertheless, our results are still preliminary due to the lack of data for 21 individuals, and all the analyses will be repeated when all data are available. As previously described in the discussion for Study 2, it is possible that the contrasting results reported regarding *CD36* rs1761667 and FTS may be due to the different methods used to assess FTS. Even if the OA-milk emulsion is considered to be more stable than a water emulsion [194], it is possible that the

flavour of the milk samples may lead to bias in participants with an aversion to it [10]. For future research, the development of a standardised and commercial kit to assess FTS would be an improvement for the replicability of the results in order to clarify the contrasting associations between *CD36* and FTS.

### 5.4.8 *CD36* rs1761667 and umami perception

In our preliminary results, we have found no associations between *CD36* rs1761667 and umami perception scores (both intensity and liking). Nevertheless, when investigating umami perception considering the three samples as repeated measurements, we have found a suggestive pattern regarding liking, but again not for intensity. At this preliminary stage, we have, then, not replicated the previous association between *CD36* rs1761667 and intensity from tasting umami samples. Currently, in our study, the *CD36* rs1761667 GG genotype carriers showed a negative pattern with umami sample liking. Carriers of the GG genotypes showed reduced liking at the intermediate and highest (200mM and 400mM) levels of MSG added in broth samples. These results contrast with the associations found in Study 1, where the *CD36* rs1761667 A-allele was associated with reduced liking for umami food groups, assessed by questionnaire. An explanation may be found in the different methodologies used for the two studies. Due to the high number of individuals enrolled in Study 1, a food liking questionnaire (9-Point Hedonic Scale) was used. This approach is cost-effective for larger cohorts, but results often are affected, and the correlation between the two methods is usually weak or moderate and may not fully represent food hedonic response [234]. It is known that the *CD36* rs1761667 G-allele is associated with a higher protein expression [9] and, possibly, with fat taste hypersensitivity [8,235]. If these associations are confirmed in the full dataset, it may indicate that differences in FTS may also encompass umami perception.

### 5.4.9 *CD36* rs1761667 and fat food perception

In this study, we have evaluated the direct association between *CD36* rs1761667 and the perception of actual fat food samples. This has been scarcely studied in previous literature. For example, a study conducted by Ong *et al.* investigated commercially available foods with different fat content, but *CD36* rs1761667 only significantly affected the perception of cream crackers [191]. Furthermore, a study conducted by Shen *et al.* found no direct effect of *CD36* rs1761667 on ice-cream liking at different fat content [161]. In our preliminary analyses, we have found several suggestive patterns that showed the A-allele, commonly related to fat taste hyposensitivity [12,108], associated with reduced intensity ratings for cream cheese and yogurt samples. It is known that different sensitivities to fat taste can encompass dietary patterns with negative health outcomes [236]. If these results are confirmed in the full-size dataset, a direct link between genetics and food perception will be identified, opening the possibility to investigate how these changes may encompass dietary choices. Future research should consider gathering a wider range of food panels, covering all the tastes, and multiple health markers (e.g., adiposity, cholesterol levels, glycemia) to better understand how food perception may encompass the aforementioned phenotypes.

### 5.4.10 *CD36* rs1761667 and adiposity

In this study, we have investigated the possible association between *CD36* rs1761667 and adiposity markers such as BMI, fat mass percentage, and visceral fat score. *CD36* rs1761667 has been previously investigated for its possible role in adiposity markers due to its possible impact of fat food intake [210]. Literature has reported contrasting results regarding *CD36* rs1761667 and obesity markers. For example, the variant AA genotype has been associated with lower BMI compared to carriers of AG or GG genotype [237]. Opposingly, in the study conducted by Boghdady *et al.*, the AG genotype was observed to be involved in obesity development and higher BMI [238], while in

the study conducted by Pioltine *et al.*, no associations between *CD36* rs1761667 and adiposity were found [181]. In our study, we found no association between *CD36* rs1761667 and BMI, and the same was true also for fat mass percentage and visceral fat score, which are direct markers of body composition [149]. This outcome is in line with a large meta-analysis conducted by Yazdanpanah *et al.* in 2022, where no associations were found between CD36 rs1761667, using different inheritance models, and BMI [239]; nevertheless, the analyses will be replicated when the full-size dataset is genotyped to confirm the described associations. At the current state, we can not define a conclusive association between this common genetic variant and adiposity markers. Future research should consider investigating not only markers such as BMI and fat mass percentage, but also information regarding physical activity levels, dietary intake, other health markers such as glycemia and cholesterol, and consider not only one variant but multiple SNPs that together may have a larger and wider effect on the aforementioned phenotypes.

# 6.0 Chapter VI – Conclusions

During this PhD project, I have deepened my understanding of the possible interplay between fat and umami taste perception, conducting three different studies.

In Study 1, we assessed population-level food liking regarding both fatty foods and umami foods and the role played by *CD36* rs1761667, which may be implicated in fat taste sensitivity. In this study, we have reported that the A-allele is negatively associated with the liking of fatty foods and, additionally, with the liking of umami foods in individuals with overweight or obesity. Food liking is one of the major drivers for food choices, and the possible role of *CD36* rs1761667 has been previously investigated with mixed results. Our results corroborate that genetics may play a role in driving individuals' food preferences; nevertheless, no association was found regarding BMI and elements of diet quality, highlighting the complexity of these associations, often conflicting and not replicated between studies, as already reported in the literature. Dietary patterns are not only influenced by sensorial perceptions (e.g., taste and smell), but a role is also played by socio-economic elements (e.g., income, cultural background), and future research should also consider these aspects to obtain a clear understanding of how genetics and environmental elements shape food choices among the general population. In Study 2, we assessed laboratory-based real food perception, assessing both intensity and liking, selecting fatty food samples, but also umami food samples. Even if we found no association between *CD36* rs1761667 and fat food samples perception, which has been a controversial topic in previous literature, we have observed that the A-allele was positively associated with perceived intensity from tasting umami food samples, which was, to the best of our knowledge, a novel association. Additionally, we have also reported that the A-allele was positively associated with BMI and elements of diet quality. Again, these results highlight the complexity of the association between this common variant and the aforementioned phenotypes, hinting that future research should aim to gather a wider range of data that are known to influence these traits (e.g., socio-economic elements, physical activity). Considering that the gustatory features of whole foods are extremely complex and involve multiple sensorial perceptions (e.g., taste, smell, texture, temperature), a new study was designed after the associations found in Study 1 and Study 2 in order to obtain further validation in a larger and better characterised cohort, in order to overcome the limitations previously highlighted.

In Study 3, we gathered a new cohort in a laboratory and standardised environment, with data collection centred around fat and umami perception. In our new cohort, we found no association between FTS and umami perception. Nevertheless, as previously highlighted, there could be an elevated risk of bias regarding the OA detection threshold assessment method, due to human error

and participants' aversion towards milk flavour. Future research should, then, move to a different method to assess FTS that should avoid the use of actual food for solution or samples preparation (e.g., milk, custard) and minimize the risk of human error (e.g., commercial kit). Furthermore, we have found a strong association between the intensities perceived when tasting umami samples and fat food samples. This association may highlight, as previously hinted in Study 1 and Study 2, an interplay between fat and umami taste perception that was further highlighted using actual food samples, which may be a better approach to translate scientific observations into real-world scenarios. This is also highlighted by the preliminary results obtained regarding *CD36* rs1761667. The variant, currently, seems not to be associated with FTS, as previously observed in multiple studies, but seems to encompass, with the reported suggestive patterns, umami samples perception and fat food samples perception. The analyses will be repeated once all participants' data are available. If the results are confirmed in the whole dataset, they may corroborate the hypothesis that genetics influences food perception and, consequently, dietary patterns. Further, considering that gustatory characteristics of whole foods cannot be associated solely with one taste, future research should explore the interactions between all six researched tastes, including their genetic receptor variability. Future research should focus on gathering a wider range of genetic data to have a better insight into how common genetic variants shape individuals' sensorial profiles and affect food choices.

In conclusion, this thesis is the first study to investigate the potential links among the fat taste sensitivity, *CD36* gene, flavour perception, and liking of both fat and umami foods, and population-level food liking, with comments on dietary patterns, BMI, and body composition. Due to the limitations previously highlighted regarding the methods used to assess FTS and low sample size which limits the generalizability of the findings and statistical power for some sub-group analyses, future research would benefit from replicating these findings in larger, more diverse and better characterized populations by a wider range of data that are necessary to have a complete view of all elements that shape individuals' food choices, dietary patterns, and adiposity. These results represent a starting point for highlighting the possible interplay between fat and umami taste perception and, possibly, for implementing the associations reported into personalised nutritional practice and real-world scenarios.

# 7.0 Supplementary Materials

**Supplementary Table 3.1** Single foods used to create the food groups in Study 1 (FVG cohort from the Italian Network of Genetic Isolates).

| FOOD GROUP NAME | SINGLE FOOD USED |
|---|---|
| DAIRY FOODS | Butter, dairy, fontina, gorgonzola, mozzarella, plain yogurt, sheep cheese, skimmed milk, whipped cream, whole milk, ice cream. |
| CHEESES | Sheep cheese, fontina, mozzarella, dairy. |
| OTHER FATTY FOODS | Hazelnut spread , French fries, chips, mayonnaise, fat food. |
| UMAMI / FATTY MEAT | Bacon, capicola, fried chicken, grilled meat, meat, mortadella, pork chops, sausage, fried fish, salmon, sardines. |
| UMAMI (no meat) | Wild mushrooms, tomatoes, fontina, tuna, sardines, sheep cheese, soy sauce. |

**Supplementary Table 3.2** Summary of analyses conducted to assess the association between food liking groups and DQS in Study 1 (FVG cohort from the Italian Network of Genetic Isolates).

| **Food group liking (as independent variable)** | **FVG** | |
|---|---|---|
| | **DQS (as dependent variable)** | |
| | ***β* (SE)** | ***p*** |
| **Dairy** | -0.30 (0.17) | 0.07 |
| **Cheeses** | -0.17 (0.14) | 0.24 |
| **Other fatty foods** | -0.19 (0.15) | 0.2 |
| **Fatty / Umami** | -0.15 (0.14) | 0.3 |
| **Umami foods** | -0.24 (0.16) | 0.14 |

**Supplementary Table 3.3** Summary of the analyses to assess the association of BMI as a covariate with food liking groups (as dependent variables) in Study 1 (FVG cohort from the Italian Network of Genetic Isolates).

| BMI as covariate | | | | | | |
|---|---|---|---|---|---|---|
| Food liking group | **All FVG** | | **Only females** | | **Only males** | |
| | **Beta (standard error)** | **p-value** | **Beta (standard error)** | **p-value** | **Beta (standard error)** | **p-value** |
| Dairy | 0.024 (0.02) | 0.2 | 0.03 (0.03) | 0.2 | 0.01 (0.03) | 0.7 |
| Cheeses | 0.04 (0.02) | 0.05* | 0.05 (0.03) | 0.1 | 0.04 (0.03) | 0.3 |
| Other fatty foods | 0.07 (0.02) | 0.003* | 0.07 (0.03) | 0.03* | 0.07 (0.03) | 0.04* |
| Fatty / Umami | 0.03 (0.02) | 0.18 | 0.01 (0.03) | 0.7 | 0.05 (0.03) | 0.05* |
| Umami foods | 0.001 (0.002) | 0.9 | 0.01 (0.03) | 0.7 | -0.01 (0.03) | 0.7 |

**Supplementary Table 4.1** Correlation between fat and umami food samples perception in Study 2 (UK cohort).

| Food perception | | | UK | |
|---|---|---|---|---|
| | | | ***Cor.*** | ***p*** |
| Fat (Milk) Intensity / Fat (Milk) Liking | Skimmed | | -0.2 | 0.16 |
| | Semi-skimmed | | -0 | 0.98 |
| | Whole | | -0.07 | 0.6 |
| MSG (Broth) Intensity / MSG (Broth) Liking | | 0.30% | -0.35 | 0.01* |
| | | 0.75% | -0.37 | 0.009* |
| | | 1.50% | -0.32 | 0.03* |
| Fat (Milk) Intensity / MSG (Broth) Intensity | Skimmed | 0.30% | 0.14 | 0.36 |
| | Semi-skimmed | 0.75% | 0.19 | 0.2 |
| | Whole | 1.50% | 0.2 | 0.17 |
| Fat (Milk) Liking / MSG (Broth) Liking | Skimmed | 0.30% | 0.14 | 0.33 |
| | Semi-skimmed | 0.75% | 0.16 | 0.29 |
| | Whole | 1.50% | 0.2 | 0.17 |
| Fat (Milk) Intensity / MSG (Broth) Liking | Skimmed | 0.30% | 0.01 | 0.93 |
| | Semi-skimmed | 0.75% | 0.1 | 0.48 |
| | Whole | 1.50% | -0.09 | 0.5 |
| Fat (Milk) Liking / MSG (Broth) Intensity | Skimmed | 0.30% | -0.01 | 0.92 |
| | Semi-skimmed | 0.75% | -0.05 | 0.74 |
| | Whole | 1.50% | -0.06 | 0.7 |

**Supplementary Table 4.2:** Summary of the analyses conducted to assess the possible association. Between food perception and DQS in Study 2 (UK cohort).

| **Food perception (as independent variable)** | | **UK** | |
|---|---|---|---|
| | | **DQS (as dependent variable)** | |
| | | ***β* (SE)** | ***p*** |
| Fat (Milk) Intensity | Skimmed | 0.2 (0.1) | 0.04* |
| | Semi-skimmed | 0.06 (0.1) | 0.57 |
| | Whole | 0.05 (0.09) | 0.57 |
| Fat (Milk) Liking | Skimmed | -0.15 (0.08) | 0.07 |
| | Semi-skimmed | -0.14 (0.08) | 0.08 |
| | Whole | -0.14 (0.06) | 0.03* |
| MSG (Broth) Intensity | 0.30% | 0.19 (0.1) | 0.08 |
| | 0.75% | 0.19 (0.11) | 0.096 |
| | 1.50% | 0.03 (0.1) | 0.75 |
| MSG (Broth) Liking | 0.30% | -0.06 (0.07) | 0.4 |
| | 0.75% | -0.05 (0.07) | 0.52 |
| | 1.50% | -0.02 (0.07) | 0.72 |

**Supplementary Table 5.1:** Summary of the analyses to assess the possible association between FTS and fat food perception scores in Study 3.

| Fat food perception (as dependent variable) | Study 3 | |
|---|---|---|
| | FTS (as independent variable) | |
| | *β* (SE) | *p* |
| Fat intensity score (regular) | 0.005 (1.1) | 0.9 |
| Fat liking score (regular) | 0.9 (1.0) | 0.4 |
| Fat intensity score (low-fat) | 0.4 (1.2) | 0.8 |
| Fat liking score (low-fat) | 0.8 (0.9) | 0.4 |

**Supplementary Table 5.2:** Summary of the analyses to assess the possible association between FTS and single fat food samples perception in Study 3.

| Fat food perception (as dependent variable) | Study 3 | |
|---|---|---|
| | FTS (as independent variable) | |
| | $\beta$ (SE) | $p$ |
| Cream Cheese intensity (regular) | 0.1 (0.4) | 0.8 |
| Cream Cheese liking (regular) | 0.1 (0.3) | 0.7 |
| Cream Cheese intensity (low-fat) | 0.2 (0.4) | 0.6 |
| Cream Cheese liking (low-fat) | 0.001 (0.4) | 0.9 |
| Hummus intensity (regular) | 0.1 (0.3) | 0.7 |
| Hummus liking (regular) | 0.8 (0.3) | 0.03* |
| Hummus intensity (low-fat) | -0.01 (0.3) | 0.9 |
| Hummus liking (low-fat) | 0.07 (0.3) | 0.8 |
| Cheese intensity (regular) | -0.03 (0.3) | 0.9 |
| Cheese liking (regular) | -0.2 (0.4) | 0.6 |
| Cheese intensity (low-fat) | 0.08 (0.4) | 0.8 |
| Cheese liking (low-fat) | 0.009 (0.3) | 0.9 |
| Yogurt intensity (regular) | -0.4 (0.4) | 0.3 |
| Yogurt liking (regular) | 0.2 (0.3) | 0.6 |
| Yogurt intensity (low-fat) | 0.1 (0.4) | 0.8 |
| Yogurt liking (low-fat) | 0.2 (0.4) | 0.6 |
| Mozzarella intensity (regular) | 0.2 (0.3) | 0.6 |
| Mozzarella liking (regular) | 0.05 (0.9) | 0.9 |
| Mozzarella intensity (low-fat) | -0.01 (0.3) | 0.9 |
| Mozzarella liking (low-fat) | 0.5 (0.4) | 0.2 |

**Supplementary Table 5.3:** Summary of the analyses to assess the possible association between FTS and adiposity markers in Study 3.

| Adiposity markers (as dependent variable) | Study 3 | |
|---|---|---|
| | FTS (as independent variable) | |
| | $\beta$ (SE) | $p$ |
| Fat mass percentage | -0.2 (0.7) | 0.8 |
| Visceral fat score | -0.2 (0.2) | 0.6 |

**Supplementary Table 5.4** Summary of the analyses to assess the possible association between umami perception scores (intensity and liking) with single fat food samples perception in Study 3.

| Fat food perception (as dependent variable) | Study 3 | | Study 3 | |
|---|---|---|---|---|
| | Umami intensity score (as independent variable) | | Umami liking score (as independent variable) | |
| | $\beta$ (SE) | *p* | $\beta$ (SE) | *p* |
| Cream Cheese intensity (regular) | 0.4 (0.2) | 0.06 | -0.04 (0.2) | 0.8 |
| Cream Cheese liking (regular) | 0.2 (0.2) | 0.3 | -0.04 (0.1) | 0.8 |
| Cream Cheese intensity (low-fat) | 0.3 (0.3) | 0.2 | -0.2 (0.2) | 0.4 |
| Cream Cheese liking (low-fat) | -0.2 (0.2) | 0.3 | 0.06 (0.2) | 0.7 |
| Hummus intensity (regular) | 0.7 (0.2) | 0.0001* | -0.07 (0.1) | 0.6 |
| Hummus liking (regular) | 0.02 (0.2) | 0.9 | 0.2 (0.2) | 0.2 |
| Hummus intensity (low-fat) | 0.5 (0.2) | 0.009* | 0.04 (0.1) | 0.8 |
| Hummus liking (low-fat) | 0.2 (0.2) | 0.3 | -0.02 (0.2) | 0.9 |
| Cheese intensity (regular) | 0.7 (0.2) | 0.001* | 0.03 (0.2) | 0.8 |
| Cheese liking (regular) | 0.7 (0.2) | 0.005* | 0.3 (0.2) | 0.1 |
| Cheese intensity (low-fat) | 0.7 (0.2) | 0.008* | -0.004 (0.2) | 0.9 |
| Cheese liking (low-fat) | 0.08 (0.2) | 0.7 | 0.1 (0.1) | 0.4 |
| Yogurt intensity (regular) | 0.8 (0.2) | 0.0001* | -0.09 (0.2) | 0.6 |
| Yogurt liking (regular) | 0.04 (0.2) | 0.9 | 0.2 (0.1) | 0.3 |
| Yogurt intensity (low-fat) | 0.9 (0.2) | 0.0009* | -0.1 (0.2) | 0.5 |
| Yogurt liking (low-fat) | -0.2 (0.2) | 0.3 | 0.3 (0.2) | 0.07 |
| Mozzarella intensity (regular) | 0.2 (0.2) | 0.3 | -0.1 (0.1) | 0.3 |
| Mozzarella liking (regular) | -0.07 (0.2) | 0.8 | -0.1 (0.2) | 0.4 |
| Mozzarella intensity (low-fat) | 0.3 (0.2) | 0.07 | 0.07 (0.1) | 0.6 |
| Mozzarella liking (low-fat) | -0.1 (0.3) | 0.6 | 0.1 (0.2) | 0.5 |

**Supplementary Table 5.5:** Summary of the analyses to assess the possible association between umami perception scores (intensity and liking) with adiposity markers in Study 3.

| Adiposity markers (as dependent variables) | Study 3 | | Study 3 | |
|---|---|---|---|---|
| | Umami intensity score (as independent variable) | | Umami liking score (as independent variable) | |
| | $\beta$ (SE) | *p* | $\beta$ (SE) | *p* |
| Fat mass percentage | 0.01 (0.5) | 0.9 | 0.3 (0.3) | 0.3 |
| Visceral fat score | 0.04 (0.1) | 0.8 | -0.2 (0.1) | 0.1 |

**Supplementary Table 5.6:** Summary of the analyses to assess the possible association between single fat food samples perception (intensity and liking) with adiposity markers in Study 3.

| Fat food perception (as independent variable) | Study 3 | | Study 3 | |
|---|---|---|---|---|
| | Fat mass percentage (as dependent variable) | | Visceral fat score (as dependent variable) | |
| | $\beta$ (SE) | *p* | $\beta$ (SE) | *p* |
| Cream Cheese intensity (regular) | 0.08 (0.3) | 0.8 | -0.0 (0.1) | 0.8 |
| Cream Cheese liking (regular) | 0.1 8 (0.3) | 0.8 | 0.1 (0.1) | 0.3 |
| Cream Cheese intensity (low-fat) | 0.2 (0.2) | 0.5 | -0.01 (0.1) | 0.9 |
| Cream Cheese liking (low-fat) | 0.1 (0.3) | 0.8 | -0.06 (0.1) | 0.5 |
| Hummus intensity (regular) | -0.1 (0.3) | 0.7 | 0.01 (0.1) | 0.9 |
| Hummus liking (regular) | 0.1 (0.3) | 0.6 | 0.01 (0.01) | 0.8 |
| Hummus intensity (low-fat) | 0.2 (0.3) | 0.6 | -0.08 (0.1) | 0.5 |
| Hummus liking (low-fat) | 0.01 (0.3) | 0.9 | 0.04 (0.01) | 0.6 |
| Cheese intensity (regular) | -0.5 (0.3) | 0.08 | -0.2 (0.1) | 0.05* |
| Cheese liking (regular) | 0.6 (0.2) | 0.01* | 0.1 (0.1) | 0.08 |
| Cheese intensity (low-fat) | -0.3 (0.2) | 0.3 | -0.08 (0.1) | 0.3 |
| Cheese liking (low-fat) | 0.8 (0.3) | 0.01* | 0.2 (0.1) | 0.03* |
| Yogurt intensity (regular) | 0.1 (0.3) | 0.8 | 0.07 (0.3) | 0.8 |
| Yogurt liking (regular) | -0.01 (0.3) | 0.9 | 0.02 (0.1) | 0.8 |
| Yogurt intensity (low-fat) | -0.2 (0.2) | 0.5 | -0.1 (0.1) | 0.4 |
| Yogurt liking (low-fat) | -0.3 (0.3) | 0.3 | -0.2 (0.1) | 0.02* |
| Mozzarella intensity (regular) | 0.2 (0.3) | 0.6 | -0.01 (0.1) | 0.9 |
| Mozzarella liking (regular) | 0.4 (0.3) | 0.2 | 0.1 (0.1) | 0.2 |
| Mozzarella intensity (low-fat) | -0.002 (0.3) | 0.9 | -0.1 (0.1) | 0.6 |
| Mozzarella liking (low-fat) | 0.5 (0.2) | 0.07 | 0.1 (0.1) | 0.5 |

**Supplementary Table 5.7:** Summary of the analyses to assess the possible association between *CD36* rs1761667 genotype and fat food perception scores in Study 3.

| Fat food perception scores (as dependent variable) | Study 3 | |
|---|---|---|
| | *CD36* rs1761667 (as independent variable) | |
| | $\beta$ (SE) | *p* |
| Fat intensity score (regular) | -1.9 (1.5) | 0.2 |
| Fat liking score (regular) | 0.7 (1.6) | 0.7 |
| Fat intensity score (low-fat) | -1.2 (1.6) | 0.4 |
| Fat liking score (low-fat) | -0.3 (1.4) | 0.8 |

**Supplementary Table 5.8:** Summary of the analyses to assess the possible association between *CD36* rs1761667 genotype and single fat food samples in Study 3.

| Fat food perception (as independent variable) | Study 3 | |
|---|---|---|
| | CD36 rs1761667 (as dependent variable) | |
| | $\beta$ (SE) | *p* |
| Cream Cheese intensity (regular) | -0.9 (0.5) | 0.06 |
| Cream Cheese liking (regular) | 0.03 (0.5) | 0.9 |
| Cream Cheese intensity (low-fat) | -0.9 (0.5) | 0.08 |
| Cream Cheese liking (low-fat) | -0.02 (0.5) | 0.9 |
| Hummus intensity (regular) | -0.4 (0.4) | 0.4 |
| Hummus liking (regular) | 0.4 (0.5) | 0.5 |
| Hummus intensity (low-fat) | 0.5 (0.4) | 0.2 |
| Hummus liking (low-fat) | -0.02 (0.4) | 0.9 |
| Cheese intensity (regular) | 0.2 (0.4) | 0.7 |
| Cheese liking (regular) | -0.03 (0.6) | 0.9 |
| Cheese intensity (low-fat) | -0.5 (0.5) | 0.4 |
| Cheese liking (low-fat) | -0.2 (0.4) | 0.6 |
| Yogurt intensity (regular) | -0.8 (0.5) | 0.09 |
| Yogurt liking (regular) | 0.1 (0.4) | 0.8 |
| Yogurt intensity (low-fat) | -0.5 (0.5) | 0.3 |
| Yogurt liking (low-fat) | -0.4 (0.5) | 0.5 |
| Mozzarella intensity (regular) | -0.001 (0.5) | 0.9 |
| Mozzarella liking (regular) | 0.2 (0.5) | 0.7 |
| Mozzarella intensity (low-fat) | 0.2 (0.4) | 0.6 |
| Mozzarella liking (low-fat) | 0.3 (0.6) | 0.6 |

**Supplementary Table 5.9:** Summary of the analyses to assess the possible association between *CD36* rs1761667 genotype and adiposity markers in Study 3.

| Adiposity markers (as dependent variables) | Study 3 | |
|---|---|---|
| | *CD36* rs1761667 genotype (as independent variable) | |
| | $\beta$ (SE) | *p* |
| Fat mass percentage | -0.7 (1.1) | 0.5 |
| Visceral fat score | -0.04 (0.3) | 0.9 |

# References


1. Ikeda, K. New Seasonings. *Chem Senses* **2002**, *27*, 847–849, doi:10.1093/chemse/27.9.847.
2. Running, C.A.; Craig, B.A.; Mattes, R.D. Oleogustus: The Unique Taste of Fat. *Chemical Senses* **2015**, *40*, 507–516, doi:10.1093/chemse/bjv036.
3. Mrizak, I.; Šerý, O.; Plesnik, J.; Arfa, A.; Fekih, M.; Bouslema, A.; Zaouali, M.; Tabka, Z.; Khan, N.A. The A Allele of Cluster of Differentiation 36 (CD36) SNP 1761667 Associates with Decreased Lipid Taste Perception in Obese Tunisian Women. *British Journal of Nutrition* **2015**, *113*, 1330–1337, doi:10.1017/S0007114515000343.
4. Golay, A.; Bobbioni, E. The Role of Dietary Fat in Obesity. *Int J Obes Relat Metab Disord* **1997**, *21 Suppl 3*, S2-11.
5. Jaime-Lara, R.B.; Brooks, B.E.; Vizioli, C.; Chiles, M.; Nawal, N.; Ortiz-Figueroa, R.S.E.; Livinski, A.A.; Agarwal, K.; Colina-Prisco, C.; Iannarino, N.; et al. A Systematic Review of the Biological Mediators of Fat Taste and Smell. *Physiological Reviews* **2023**, *103*, 855–918, doi:10.1152/physrev.00061.2021.
6. Chamoun, E.; Mutch, D.M.; Allen-Vercoe, E.; Buchholz, A.C.; Duncan, A.M.; Spriet, L.L.; Haines, J.; Ma, D.W.L. A Review of the Associations between Single Nucleotide Polymorphisms in Taste Receptors, Eating Behaviors, and Health. *Critical Reviews in Food Science and Nutrition* **2018**, *58*, 194–207, doi:10.1080/10408398.2016.1152229.
7. Love-Gregory, L.; Sherva, R.; Schappe, T.; Qi, J.-S.; McCrea, J.; Klein, S.; Connelly, M.A.; Abumrad, N.A. Common CD36 SNPs Reduce Protein Expression and May Contribute to a Protective Atherogenic Profile. *Hum Mol Genet* **2011**, *20*, 193–201, doi:10.1093/hmg/ddq449.
8. Melis, M.; Sollai, G.; Muroni, P.; Crnjar, R.; Tomassini Barbarossa, I. 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* **2015**, *7*, 2068–2084, doi:10.3390/nu7032068.
9. Kurihara, K. Umami the Fifth Basic Taste: History of Studies on Receptor Mechanisms and Role as a Food Flavor. *Biomed Res Int* **2015**, *2015*, 189402, doi:10.1155/2015/189402.
10. van Langeveld, A.W.B.; Teo, P.S.; de Vries, J.H.M.; Feskens, E.J.M.; de Graaf, C.; Mars, M. Dietary Taste Patterns by Sex and Weight Status in the Netherlands. *Br J Nutr* **2018**, *119*, 1195–1206, doi:10.1017/S0007114518000715.
11. Hall, K.D.; Ayuketah, A.; Brychta, R.; Cai, H.; Cassimatis, T.; Chen, K.Y.; Chung, S.T.; Costa, E.; Courville, A.; Darcey, V.; et al. Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain: An Inpatient Randomized Controlled Trial of Ad Libitum Food Intake. *Cell Metab* **2019**, *30*, 226, doi:10.1016/j.cmet.2019.05.020.
12. Magerowski, G.; Giacona, G.; Patriarca, L.; Papadopoulos, K.; Garza-Naveda, P.; Radziejowska, J.; Alonso-Alonso, M. Neurocognitive Effects of Umami: Association with Eating Behavior and Food Choice. *Neuropsychopharmacology* **2018**, *43*, 2009–2016, doi:10.1038/s41386-018-0044-6.
13. Imada, T.; Hao, S.S.; Torii, K.; Kimura, E. Supplementing Chicken Broth with Monosodium Glutamate Reduces Energy Intake from High Fat and Sweet Snacks in Middle-Aged Healthy Women. *Appetite* **2014**, *79*, 158–165, doi:10.1016/j.appet.2014.04.011.
14. Tanaka, S.; Yoneoka, D.; Ishizuka, A.; Adachi, M.; Hayabuchi, H.; Nishimura, T.; Takemi, Y.; Uneyama, H.; Nakamura, H.; Lwin, K.S.; et al. Modelling of Salt Intake Reduction by Incorporation of Umami Substances into Japanese Foods: A Cross-Sectional Study. *BMC Public Health* **2023**, *23*, 1–14, doi:10.1186/s12889-023-15322-6.

15. Gravina, S.A.; Yep, G.L.; Khan, M. Human Biology of Taste. *Ann Saudi Med* **2013**, *33*, 217–222, doi:10.5144/0256-4947.2013.217.
16. Brouwer, J.N.; Wiersma, A. Location of Taste Buds in Intact Taste Papillae by a Selective Staining Method. *Histochemistry* **1978**, *58*, 145–151, doi:10.1007/BF00495713.
17. Miller, I.J.; Preslar, A.J. Spatial Distribution of Rat Fungiform Papillae. *Anat Rec* **1975**, *181*, 679–684, doi:10.1002/ar.1091810309.
18. Zhang, Y.; Hoon, M.A.; Chandrashekar, J.; Mueller, K.L.; Cook, B.; Wu, D.; Zuker, C.S.; Ryba, N.J.P. Coding of Sweet, Bitter, and Umami Tastes: Different Receptor Cells Sharing Similar Signaling Pathways. *Cell* **2003**, *112*, 293–301, doi:10.1016/s0092-8674(03)00071-0.
19. Hellekant, G.; Ninomiya, Y.; Danilova, V. Taste in Chimpanzees. III: Labeled-Line Coding in Sweet Taste. *Physiol Behav* **1998**, *65*, 191–200, doi:10.1016/s0031-9384(97)00532-5.
20. Chen, X.; Gabito, M.; Peng, Y.; Ryba, N.J.P.; Zuker, C.S. A Gustotopic Map of Taste Qualities in the Mammalian Brain. *Science* **2011**, *333*, 1262–1266, doi:10.1126/science.1204076.
21. Rosenstein, D.; Oster, H. Differential Facial Responses to Four Basic Tastes in Newborns. *Child Dev* **1988**, *59*, 1555–1568.
22. Bessis, A.-S.; Rondard, P.; Gaven, F.; Brabet, I.; Triballeau, N.; Prézeau, L.; Acher, F.; Pin, J.-P. Closure of the Venus Flytrap Module of mGlu8 Receptor and the Activation Process: Insights from Mutations Converting Antagonists into Agonists. *Proc Natl Acad Sci U S A* **2002**, *99*, 11097–11102, doi:10.1073/pnas.162138699.
23. Masuda, K.; Koizumi, A.; Nakajima, K.; Tanaka, T.; Abe, K.; Misaka, T.; Ishiguro, M. Characterization of the Modes of Binding between Human Sweet Taste Receptor and Low-Molecular-Weight Sweet Compounds. *PLoS One* **2012**, *7*, e35380, doi:10.1371/journal.pone.0035380.
24. Keskitalo, K.; Knaapila, A.; Kallela, M.; Palotie, A.; Wessman, M.; Sammalisto, S.; Peltonen, L.; Tuorila, H.; Perola, M. Sweet Taste Preferences Are Partly Genetically Determined: Identification of a Trait Locus on Chromosome 161. *The American Journal of Clinical Nutrition* **2007**, *86*, 55–63, doi:10.1093/ajcn/86.1.55.
25. Gross, L.S.; Li, L.; Ford, E.S.; Liu, S. Increased Consumption of Refined Carbohydrates and the Epidemic of Type 2 Diabetes in the United States: An Ecologic Assessment123. *The American Journal of Clinical Nutrition* **2004**, *79*, 774–779, doi:10.1093/ajcn/79.5.774.
26. Bray, G.A.; Nielsen, S.J.; Popkin, B.M. Consumption of High-Fructose Corn Syrup in Beverages May Play a Role in the Epidemic of Obesity. *The American Journal of Clinical Nutrition* **2004**, *79*, 537–543, doi:10.1093/ajcn/79.4.537.
27. Fushan, A.A.; Simons, C.T.; Slack, J.P.; Manichaikul, A.; Drayna, D. Allelic Polymorphism within the *TAS1R3* Promoter Is Associated with Human Taste Sensitivity to Sucrose. *Current Biology* **2009**, *19*, 1288–1293, doi:10.1016/j.cub.2009.06.015.
28. Reed, D.R.; Knaapila, A. Genetics of Taste and Smell: Poisons and Pleasures. *Prog Mol Biol Transl Sci* **2010**, *94*, 213–240, doi:10.1016/B978-0-12-375003-7.00008-X.
29. Dinehart, M.E.; Hayes, J.E.; Bartoshuk, L.M.; Lanier, S.L.; Duffy, V.B. Bitter Taste Markers Explain Variability in Vegetable Sweetness, Bitterness, and Intake. *Physiol Behav* **2006**, *87*, 304–313, doi:10.1016/j.physbeh.2005.10.018.
30. Adler, E.; Hoon, M.A.; Mueller, K.L.; Chandrashekar, J.; Ryba, N.J.; Zuker, C.S. A Novel Family of Mammalian Taste Receptors. *Cell* **2000**, *100*, 693–702, doi:10.1016/s0092-8674(00)80705-9.
31. Hoon, M.A.; Adler, E.; Lindemeier, J.; Battey, J.F.; Ryba, N.J.; Zuker, C.S. Putative Mammalian Taste Receptors: A Class of Taste-Specific GPCRs with Distinct Topographic Selectivity. *Cell* **1999**, *96*, 541–551, doi:10.1016/s0092-8674(00)80658-3.
32. Lander, E.S.; Linton, L.M.; Birren, B.; Nusbaum, C.; Zody, M.C.; Baldwin, J.; Devon, K.; Dewar, K.; Doyle, M.; FitzHugh, W.; et al. Initial Sequencing and Analysis of the Human Genome. *Nature* **2001**, *409*, 860–921, doi:10.1038/35057062.

33. Deshpande, D.A.; Wang, W.C.H.; McIlmoyle, E.L.; Robinett, K.S.; Schillinger, R.M.; An, S.S.; Sham, J.S.K.; Liggett, S.B. Bitter Taste Receptors on Airway Smooth Muscle Bronchodilate by Localized Calcium Signaling and Reverse Obstruction. *Nat Med* **2010**, *16*, 1299–1304, doi:10.1038/nm.2237.
34. Egan, J.M.; Margolskee, R.F. Taste Cells of the Gut and Gastrointestinal Chemosensation. *Mol Interv* **2008**, *8*, 78–81, doi:10.1124/mi.8.2.5.
35. Behrens, M.; Foerster, S.; Staehler, F.; Raguse, J.-D.; Meyerhof, W. Gustatory Expression Pattern of the Human TAS2R Bitter Receptor Gene Family Reveals a Heterogenous Population of Bitter Responsive Taste Receptor Cells. *J Neurosci* **2007**, *27*, 12630–12640, doi:10.1523/JNEUROSCI.1168-07.2007.
36. Drewnowski, A.; Gomez-Carneros, C. Bitter Taste, Phytonutrients, and the Consumer: A Review. *Am J Clin Nutr* **2000**, *72*, 1424–1435, doi:10.1093/ajcn/72.6.1424.
37. Hayes, J.E.; Wallace, M.R.; Knopik, V.S.; Herbstman, D.M.; Bartoshuk, L.M.; Duffy, V.B. Allelic Variation in TAS2R Bitter Receptor Genes Associates with Variation in Sensations from and Ingestive Behaviors toward Common Bitter Beverages in Adults. *Chem Senses* **2011**, *36*, 311–319, doi:10.1093/chemse/bjq132.
38. Pronin, A.N.; Xu, H.; Tang, H.; Zhang, L.; Li, Q.; Li, X. Specific Alleles of Bitter Receptor Genes Influence Human Sensitivity to the Bitterness of Aloin and Saccharin. *Curr Biol* **2007**, *17*, 1403–1408, doi:10.1016/j.cub.2007.07.046.
39. Reed, D.R.; Zhu, G.; Breslin, P.A.S.; Duke, F.F.; Henders, A.K.; Campbell, M.J.; Montgomery, G.W.; Medland, S.E.; Martin, N.G.; Wright, M.J. The Perception of Quinine Taste Intensity Is Associated with Common Genetic Variants in a Bitter Receptor Cluster on Chromosome 12. *Hum Mol Genet* **2010**, *19*, 4278–4285, doi:10.1093/hmg/ddq324.
40. Bufe, B.; Breslin, P.A.S.; Kuhn, C.; Reed, D.R.; Tharp, C.D.; Slack, J.P.; Kim, U.-K.; Drayna, D.; Meyerhof, W. The Molecular Basis of Individual Differences in Phenylthiocarbamide and Propylthiouracil Bitterness Perception. *Curr Biol* **2005**, *15*, 322–327, doi:10.1016/j.cub.2005.01.047.
41. Meyerhof, W.; Batram, C.; Kuhn, C.; Brockhoff, A.; Chudoba, E.; Bufe, B.; Appendino, G.; Behrens, M. The Molecular Receptive Ranges of Human TAS2R Bitter Taste Receptors. *Chem Senses* **2010**, *35*, 157–170, doi:10.1093/chemse/bjp092.
42. Behrens, M.; Gunn, H.C.; Ramos, P.C.M.; Meyerhof, W.; Wooding, S.P. Genetic, Functional, and Phenotypic Diversity in TAS2R38-Mediated Bitter Taste Perception. *Chem Senses* **2013**, *38*, 475–484, doi:10.1093/chemse/bjt016.
43. Wooding, S.; Gunn, H.; Ramos, P.; Thalmann, S.; Xing, C.; Meyerhof, W. Genetics and Bitter Taste Responses to Goitrin, a Plant Toxin Found in Vegetables. *Chem Senses* **2010**, *35*, 685–692, doi:10.1093/chemse/bjq061.
44. Kim, U.; Jorgenson, E.; Coon, H.; Leppert, M.; Risch, N.; Drayna, D. Positional Cloning of the Human Quantitative Trait Locus Underlying Taste Sensitivity to Phenylthiocarbamide. *Science* **2003**, *299*, 1221–1225, doi:10.1126/science.1080190.
45. Mennella, J.A.; Pepino, M.Y.; Duke, F.F.; Reed, D.R. Age Modifies the Genotype-Phenotype Relationship for the Bitter Receptor TAS2R38. *BMC Genet* **2010**, *11*, 60, doi:10.1186/1471-2156-11-60.
46. Lewandowski, B.C.; Sukumaran, S.K.; Margolskee, R.F.; Bachmanov, A.A. Amiloride-Insensitive Salt Taste Is Mediated by Two Populations of Type III Taste Cells with Distinct Transduction Mechanisms. *J. Neurosci.* **2016**, *36*, 1942–1953, doi:10.1523/JNEUROSCI.2947-15.2016.
47. Matsumoto, K.; Ohishi, A.; Iwatsuki, K.; Yamazaki, K.; Takayanagi, S.; Tsuji, M.; Aihara, E.; Utsumi, D.; Tsukahara, T.; Tominaga, M.; et al. Transient Receptor Potential Vanilloid 4 Mediates Sour Taste Sensing via Type III Taste Cell Differentiation. *Sci Rep* **2019**, *9*, 6686, doi:10.1038/s41598-019-43254-y.

48. Masenga, S.K.; Pilic, L.; Kirabo, A. Salt Taste and Salt Sensitive Hypertension in HIV. *Curr Hypertens Rep* **2023**, *25*, 25–33, doi:10.1007/s11906-023-01236-6.
49. Dias, A.G.; Rousseau, D.; Duizer, L.; Cockburn, M.; Chiu, W.; Nielsen, D.; El-Sohemy, A. Genetic Variation in Putative Salt Taste Receptors and Salt Taste Perception in Humans. *Chem Senses* **2013**, *38*, 137–145, doi:10.1093/chemse/bjs090.
50. Strazzullo, P.; D'Elia, L.; Kandala, N.-B.; Cappuccio, F.P. Salt Intake, Stroke, and Cardiovascular Disease: Meta-Analysis of Prospective Studies. *BMJ* **2009**, *339*, b4567, doi:10.1136/bmj.b4567.
51. Elliott, P.; Stamler, J.; Nichols, R.; Dyer, A.R.; Stamler, R.; Kesteloot, H.; Marmot, M. Intersalt Revisited: Further Analyses of 24 Hour Sodium Excretion and Blood Pressure within and across Populations. *BMJ* **1996**, *312*, 1249–1253, doi:10.1136/bmj.312.7041.1249.
52. Chamoun, E.; Liu, A.S.; Duizer, L.M.; Feng, Z.; Darlington, G.; Duncan, A.M.; Haines, J.; Ma, D.W.L. Single Nucleotide Polymorphisms in Sweet, Fat, Umami, Salt, Bitter and Sour Taste Receptor Genes Are Associated with Gustatory Function and Taste Preferences in Young Adults. *Nutrition Research* **2021**, *85*, 40–46, doi:10.1016/j.nutres.2020.12.007.
53. Chamoun, E.; Carroll, N.A.; Duizer, L.M.; Qi, W.; Feng, Z.; Darlington, G.; Duncan, A.M.; Haines, J.; Ma, D.W.L.; The Guelph Family Health Study The Relationship between Single Nucleotide Polymorphisms in Taste Receptor Genes, Taste Function and Dietary Intake in Preschool-Aged Children and Adults in the Guelph Family Health Study. *Nutrients* **2018**, *10*, 990, doi:10.3390/nu10080990.
54. Liman, E.R.; Zhang, Y.V.; Montell, C. Peripheral Coding of Taste. *Neuron* **2014**, *81*, 984–1000, doi:10.1016/j.neuron.2014.02.022.
55. Huang, A.L.; Chen, X.; Hoon, M.A.; Chandrashekar, J.; Guo, W.; Tränkner, D.; Ryba, N.J.P.; Zuker, C.S. The Cells and Logic for Mammalian Sour Taste Detection. *Nature* **2006**, *442*, 934–938, doi:10.1038/nature05084.
56. Tu, Y.-H.; Cooper, A.J.; Teng, B.; Chang, R.B.; Artiga, D.J.; Turner, H.N.; Mulhall, E.M.; Ye, W.; Smith, A.D.; Liman, E.R. An Evolutionarily Conserved Gene Family Encodes Proton-Selective Ion Channels. *Science* **2018**, *359*, 1047–1050, doi:10.1126/science.aao3264.
57. Saotome, K.; Teng, B.; Tsui, C.C.A.; Lee, W.-H.; Tu, Y.-H.; Kaplan, J.P.; Sansom, M.S.P.; Liman, E.R.; Ward, A.B. Structures of the Otopetrin Proton Channels Otop1 and Otop3. *Nat Struct Mol Biol* **2019**, *26*, 518–525, doi:10.1038/s41594-019-0235-9.
58. Richter, T.A.; Caicedo, A.; Roper, S.D. Sour Taste Stimuli Evoke Ca2+ and pH Responses in Mouse Taste Cells. *J Physiol* **2003**, *547*, 475–483, doi:10.1113/jphysiol.2002.033811.
59. Lyall, V.; Alam, R.I.; Phan, D.Q.; Ereso, G.L.; Phan, T.H.; Malik, S.A.; Montrose, M.H.; Chu, S.; Heck, G.L.; Feldman, G.M.; et al. Decrease in Rat Taste Receptor Cell Intracellular pH Is the Proximate Stimulus in Sour Taste Transduction. *Am J Physiol Cell Physiol* **2001**, *281*, C1005-1013, doi:10.1152/ajpcell.2001.281.3.C1005.
60. Törnwall, O.; Silventoinen, K.; Keskitalo-Vuokko, K.; Perola, M.; Kaprio, J.; Tuorila, H. Genetic Contribution to Sour Taste Preference. *Appetite* **2012**, *58*, 687–694, doi:10.1016/j.appet.2011.12.020.
61. Huang, Y.A.; Maruyama, Y.; Stimac, R.; Roper, S.D. Presynaptic (Type III) Cells in Mouse Taste Buds Sense Sour (Acid) Taste. *The Journal of Physiology* **2008**, *586*, 2903–2912, doi:10.1113/jphysiol.2008.151233.
62. Ye, W.; Chang, R.B.; Bushman, J.D.; Tu, Y.-H.; Mulhall, E.M.; Wilson, C.E.; Cooper, A.J.; Chick, W.S.; Hill-Eubanks, D.C.; Nelson, M.T.; et al. The K+ Channel KIR2.1 Functions in Tandem with Proton Influx to Mediate Sour Taste Transduction. *Proc Natl Acad Sci U S A* **2016**, *113*, E229-238, doi:10.1073/pnas.1514282112.
63. Hartley, I.E.; Liem, D.G.; Keast, R. Umami as an 'Alimentary' Taste. A New Perspective on Taste Classification. *Nutrients* **2019**, *11*, 182, doi:10.3390/nu11010182.
64. Chaudhari, N.; Pereira, E.; Roper, S.D. Taste Receptors for Umami: The Case for Multiple Receptors1234. *Am J Clin Nutr* **2009**, *90*, 738S-742S, doi:10.3945/ajcn.2009.27462H.

65. Uematsu, A.; Tsurugizawa, T.; Kitamura, A.; Ichikawa, R.; Iwatsuki, K.; Uneyama, H.; Torii, K. Evaluation of the 'Liking' and 'Wanting' Properties of Umami Compound in Rats. *Physiology & Behavior* **2011**, *102*, 553–558, doi:10.1016/j.physbeh.2011.01.005.
66. Masic, U.; Yeomans, M.R. Umami Flavor Enhances Appetite but Also Increases Satiety123. *The American Journal of Clinical Nutrition* **2014**, *100*, 532–538, doi:10.3945/ajcn.113.080929.
67. Nakamura, E. One Hundred Years since the Discovery of the "Umami" Taste from Seaweed Broth by Kikunae Ikeda, Who Transcended His Time. *Chemistry – An Asian Journal* **2011**, *6*, 1659–1663, doi:10.1002/asia.201000899.
68. Romanov, R.A.; Lasher, R.S.; High, B.; Savidge, L.E.; Lawson, A.; Rogachevskaja, O.A.; Zhao, H.; Rogachevsky, V.V.; Bystrova, M.F.; Churbanov, G.D.; et al. Chemical Synapses without Synaptic Vesicles: Purinergic Neurotransmission through a CALHM1 Channel-Mitochondrial Signaling Complex. *Science Signaling* **2018**, *11*, eaao1815, doi:10.1126/scisignal.aao1815.
69. Shim, J.; Son, H.J.; Kim, Y.; Kim, K.H.; Kim, J.T.; Moon, H.; Kim, M.J.; Misaka, T.; Rhyu, M.-R. Modulation of Sweet Taste by Umami Compounds via Sweet Taste Receptor Subunit hT1R2. *PLoS One* **2015**, *10*, e0124030, doi:10.1371/journal.pone.0124030.
70. Dewis, M.L.; Phan, T.-H.T.; Ren, Z.; Meng, X.; Cui, M.; Mummalaneni, S.; Rhyu, M.-R.; DeSimone, J.A.; Lyall, V. N-Geranyl Cyclopropyl-Carboximide Modulates Salty and Umami Taste in Humans and Animal Models. *J Neurophysiol* **2013**, *109*, 1078–1090, doi:10.1152/jn.00124.2012.
71. M, K.; Y, S.-H.; A, O.; Y, N. Gustatory Sensation of (L)- and (D)-Amino Acids in Humans. *Amino acids* **2012**, *43*, doi:10.1007/s00726-012-1315-x.
72. Winkel, C.; de Klerk, A.; Visser, J.; de Rijke, E.; Bakker, J.; Koenig, T.; Renes, H. New Developments in Umami (Enhancing) Molecules. *Chemistry & Biodiversity* **2008**, *5*, 1195–1203, doi:10.1002/cbdv.200890096.
73. Thout, S.R.; Santos, J.A.; McKenzie, B.; Trieu, K.; Johnson, C.; McLean, R.; Arcand, J.; Campbell, N.R.C.; Webster, J. The Science of Salt: Updating the Evidence on Global Estimates of Salt Intake. *The Journal of Clinical Hypertension* **2019**, *21*, 710–721, doi:10.1111/jch.13546.
74. Rosa, M.S. do C.; Pinto-e-Silva, M.E.M.; Simoni, N.K. Can Umami Taste Be an Adequate Tool for Reducing Sodium in Food Preparations? *International Journal of Food Science and Technology* **2021**, *56*, 5315–5324, doi:10.1111/ijfs.15061.
75. Miyaki, T.; Imada, T.; Hao, S.S.; Kimura, E. Monosodium L-Glutamate in Soup Reduces Subsequent Energy Intake from High-Fat Savoury Food in Overweight and Obese Women. *British Journal of Nutrition* **2016**, *115*, 176–184, doi:10.1017/S0007114515004031.
76. He, K.; Zhao, L.; Daviglus, M.L.; Dyer, A.R.; Van Horn, L.; Garside, D.; Zhu, L.; Guo, D.; Wu, Y.; Zhou, B.; et al. Association of Monosodium Glutamate Intake with Overweight in Chinese Adults: The INTERMAP Study. *Obesity (Silver Spring)* **2008**, *16*, 1875–1880, doi:10.1038/oby.2008.274.
77. Raliou, M.; Wiencis, A.; Pillias, A.-M.; Planchais, A.; Eloit, C.; Boucher, Y.; Trotier, D.; Montmayeur, J.-P.; Faurion, A. Nonsynonymous Single Nucleotide Polymorphisms in Human Tas1r1, Tas1r3, and mGluR1 and Individual Taste Sensitivity to Glutamate123. *The American Journal of Clinical Nutrition* **2009**, *90*, 789S-799S, doi:10.3945/ajcn.2009.27462P.
78. Raliou, M.; Grauso, M.; Hoffmann, B.; Schlegel–Le-Poupon, C.; Nespoulous, C.; Débat, H.; Belloir, C.; Wiencis, A.; Sigoillot, M.; Preet Bano, S.; et al. Human Genetic Polymorphisms in T1R1 and T1R3 Taste Receptor Subunits Affect Their Function. *Chemical Senses* **2011**, *36*, 527–537, doi:10.1093/chemse/bjr014.
79. Shigemura, N.; Shirosaki, S.; Ohkuri, T.; Sanematsu, K.; Islam, A.S.; Ogiwara, Y.; Kawai, M.; Yoshida, R.; Ninomiya, Y. Variation in Umami Perception and in Candidate Genes for

the Umami Receptor in Mice and Humans1234. *Am J Clin Nutr* **2009**, *90*, 764S-769S, doi:10.3945/ajcn.2009.27462M.
80. Mattes, R.D. Fat Taste and Lipid Metabolism in Humans. *Physiology & Behavior* **2005**, *86*, 691–697, doi:10.1016/j.physbeh.2005.08.058.
81. Sclafani, A.; Ackroff, K.; Abumrad, N.A. 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* **2007**, *293*, R1823–R1832, doi:10.1152/ajpregu.00211.2007.
82. Tucker, R.M.; Laguna, L.; Quinn, R.; Mattes, R.D. The Effect of Short, Daily Oral Exposure on Non-Esterified Fatty Acid Sensitivity. *Chem. Percept.* **2013**, *6*, 78–85, doi:10.1007/s12078-013-9147-y.
83. Voigt, N.; Stein, J.; Galindo, M.M.; Dunkel, A.; Raguse, J.-D.; Meyerhof, W.; Hofmann, T.; Behrens, M. The Role of Lipolysis in Human Orosensory Fat Perception. *Journal of Lipid Research* **2014**, *55*, 870–882, doi:10.1194/jlr.M046029.
84. Reed, D.R.; Xia, M.B. Recent Advances in Fatty Acid Perception and Genetics. *Advances in Nutrition* **2015**, *6*, 353S-360S, doi:10.3945/an.114.007005.
85. Hao, J.-W.; Wang, J.; Guo, H.; Zhao, Y.-Y.; Sun, H.-H.; Li, Y.-F.; Lai, X.-Y.; Zhao, N.; Wang, X.; Xie, C.; et al. CD36 Facilitates Fatty Acid Uptake by Dynamic Palmitoylation-Regulated Endocytosis. *Nature Communications* **2020**, *11*, 4765, doi:10.1038/s41467-020-18565-8.
86. Simons, P.J.; Kummer, J.A.; Luiken, J.J.F.P.; Boon, L. Apical CD36 Immunolocalization in Human and Porcine Taste Buds from Circumvallate and Foliate Papillae. *Acta Histochemica* **2011**, *113*, 839–843, doi:10.1016/j.acthis.2010.08.006.
87. Xavier, A.M.; Ludwig, R.G.; Nagai, M.H.; Almeida, T.J. de; Watanabe, H.M.; Hirata, M.Y.; Rosenstock, T.R.; Papes, F.; Malnic, B.; Glezer, I. CD36 Is Expressed in a Defined Subpopulation of Neurons in the Olfactory Epithelium. *Scientific Reports* **2016**, *6*, 25507, doi:10.1038/srep25507.
88. Pepino, M.Y.; Kuda, O.; Samovski, D.; Abumrad, N.A. Structure-Function of CD36 and Importance of Fatty Acid Signal Transduction in Fat Metabolism. *Annual Review of Nutrition* **2014**, *34*, 281–303, doi:10.1146/annurev-nutr-071812-161220.
89. Méjean, C.; Morzel, M.; Neyraud, E.; Issanchou, S.; Martin, C.; Bozonnet, S.; Urbano, C.; Schlich, P.; Hercberg, S.; Péneau, S.; et al. Salivary Composition Is Associated with Liking and Usual Nutrient Intake. *PLoS One* **2015**, *10*, e0137473, doi:10.1371/journal.pone.0137473.
90. Mattes, R.D. Oral Detection of Short-, Medium-, and Long-Chain Free Fatty Acids in Humans. *Chem Senses* **2009**, *34*, 145–150, doi:10.1093/chemse/bjn072.
91. Appelqvist, I. a. M.; Poelman, A. a. M.; Cochet-Broch, M.; Delahunty, C.M. Impact of Model Fat Emulsions on Sensory Perception Using Repeated Spoon to Spoon Ingestion. *Physiol Behav* **2016**, *160*, 80–86, doi:10.1016/j.physbeh.2016.03.035.
92. Grabenhorst, F.; Rolls, E.T. The Representation of Oral Fat Texture in the Human Somatosensory Cortex. *Hum Brain Mapp* **2013**, *35*, 2521–2530, doi:10.1002/hbm.22346.
93. Zhou, X.; Yeomans, M.; Thomas, A.; Wilde, P.; Linter, B.; Methven, L. Individual Differences in Oral Tactile Sensitivity and Gustatory Fatty Acid Sensitivity and Their Relationship with Fungiform Papillae Density, Mouth Behaviour and Texture Perception of a Food Model Varying in Fat. *Food Quality and Preference* **2021**, *90*, 104116, doi:10.1016/j.foodqual.2020.104116.
94. Stewart, J.E.; Feinle-Bisset, C.; Golding, M.; Delahunty, C.; Clifton, P.M.; Keast, R.S.J. Oral Sensitivity to Fatty Acids, Food Consumption and BMI in Human Subjects. *British Journal of Nutrition* **2010**, *104*, 145–152, doi:10.1017/S0007114510000267.

95. Stewart, J.E.; Feinle-Bisset, C.; Keast, R.S.J. Fatty Acid Detection during Food Consumption and Digestion: Associations with Ingestive Behavior and Obesity. *Progress in Lipid Research* **2011**, *50*, 225–233, doi:10.1016/j.plipres.2011.02.002.
96. Ghosh, A.; Murugesan, G.; Chen, K.; Zhang, L.; Wang, Q.; Febbraio, M.; Anselmo, R.M.; Marchant, K.; Barnard, J.; Silverstein, R.L. Platelet CD36 Surface Expression Levels Affect Functional Responses to Oxidized LDL and Are Associated with Inheritance of Specific Genetic Polymorphisms. *Blood* **2011**, *117*, 6355–6366, doi:10.1182/blood-2011-02-338582.
97. Graham, C.A.M.; Pilic, L.; King, A.; Nixon, J.E.; Pipe, J.; Holton, J.; Tamba, K.; Hearne, G.; Pedlar, C.R.; Lorente-Cebrián, S.; et al. Genetic Differences in Fat Taste Sensitivity and Dietary Intake in a UK Female Cohort. *Food Quality and Preference* **2021**, *92*, 104202, doi:10.1016/j.foodqual.2021.104202.
98. Burgess, B.; Melis, M.; Scoular, K.; Driver, M.; Schaich, K.M.; Keller, K.L.; Tomassini Barbarossa, I.; Tepper, B.J. 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* **2018**, *83*, 1373–1380, doi:10.1111/1750-3841.14115.
99. Melis, M.; Sollai, G.; Muroni, P.; Crnjar, R.; Barbarossa, I.T. 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* **2015**, *7*, 2068–2084, doi:10.3390/nu7032068.
100. Melis, M.; Carta, G.; Pintus, S.; Pintus, P.; Piras, C.A.; Murru, E.; Manca, C.; Di Marzo, V.; Banni, S.; Tomassini Barbarossa, I. 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* **2017**, *8*.
101. Pepino, M.Y.; Love-Gregory, L.; Klein, S.; Abumrad, N.A. The Fatty Acid Translocase Gene CD36 and Lingual Lipase Influence Oral Sensitivity to Fat in Obese Subjects. *J Lipid Res* **2012**, *53*, 561–566, doi:10.1194/jlr.M021873.
102. Besnard, P.; Passilly-Degrace, P.; Khan, N.A. Taste of Fat: A Sixth Taste Modality? *Physiol Rev* **2016**, *96*, 151–176, doi:10.1152/physrev.00002.2015.
103. Fujii, R.; Hishida, A.; Suzuki, K.; Imaeda, N.; Goto, C.; Hamajima, N.; Wakai, K.; Kondo, T. Cluster of Differentiation 36 Gene Polymorphism (Rs1761667) Is Associated with Dietary MUFA Intake and Hypertension in a Japanese Population. *British Journal of Nutrition* **2019**, *121*, 1215–1222, doi:10.1017/S0007114519000679.
104. Pioltine, M.B.; de Melo, M.E.; Santos, A.; Machado, A.D.; Fernandes, A.E.; Fujiwara, C.T.; Cercato, C.; Mancini, M.C. Genetic Variation in CD36 Is Associated with Decreased Fat and Sugar Intake in Obese Children and Adolescents. *J Nutrigenet Nutrigenomics* **2016**, *9*, 300–305, doi:10.1159/000455915.
105. Ramos López, O.O.; Panduro, A.; Martinez-Lopez, E.; Fierro, N.; Ojeda-Granados, C.; Sepulveda-Villegas, M.; Roman, S. Genetic Variant in the CD36 Gene (Rs1761667) Is Associated with Higher Fat Intake and High Serum Cholesterol among the Population of West Mexico. *Journal of Nutrition & Food Sciences* **2014**, *05*, doi:10.4172/2155-9600.1000353.
106. *The Impact of Nutrition and Diet on Oral Health*; S.Karger AG, 2019; ISBN 978-3-318-06517-6.
107. Dietary Reference Values | EFSA Available online: https://www.efsa.europa.eu/en/topics/topic/dietary-reference-values (accessed on 31 July 2025).
108. Roberts, S.B.; Flaherman, V. Dietary Energy. *Adv Nutr* **2022**, *13*, 2681–2685, doi:10.1093/advances/nmac092.
109. Chu, X.-Y.; Xu, Y.-Y.; Tong, X.-Y.; Wang, G.; Zhang, H.-Y. The Legend of ATP: From Origin of Life to Precision Medicine. *Metabolites* **2022**, *12*, 461, doi:10.3390/metabo12050461.

110. *Food Energy: Methods of Analysis and Conversion Factors: Report of a Technical Workshop, Rome, 3-6 December 2002*; MacLean, W.C., Warwick, P., Food and Agriculture Organization of the United Nations, Eds.; FAO food and nutrition paper; Food and Agriculture Organization of the United Nations: Rome, 2003; ISBN 978-92-5-105014-9.
111. Risso, D.; Drayna, D.; Morini, G. Alteration, Reduction and Taste Loss: Main Causes and Potential Implications on Dietary Habits. *Nutrients* **2020**, *12*, 3284, doi:10.3390/nu12113284.
112. Liu, A.G.; Ford, N.A.; Hu, F.B.; Zelman, K.M.; Mozaffarian, D.; Kris-Etherton, P.M. A Healthy Approach to Dietary Fats: Understanding the Science and Taking Action to Reduce Consumer Confusion. *Nutr J* **2017**, *16*, 53, doi:10.1186/s12937-017-0271-4.
113. Slavin, J.; Carlson, J. Carbohydrates. *Adv Nutr* **2014**, *5*, 760–761, doi:10.3945/an.114.006163.
114. Mann, J.; Cummings, J.H.; Englyst, H.N.; Key, T.; Liu, S.; Riccardi, G.; Summerbell, C.; Uauy, R.; van Dam, R.M.; Venn, B.; et al. FAO/WHO Scientific Update on Carbohydrates in Human Nutrition: Conclusions. *Eur J Clin Nutr* **2007**, *61 Suppl 1*, S132-137, doi:10.1038/sj.ejcn.1602943.
115. Jackson, A.D.; McLaughlin, J. Digestion and Absorption. *Surgery (Oxford)* **2009**, *27*, 231–236, doi:10.1016/j.mpsur.2009.03.003.
116. Leturque, A.; Brot-Laroche, E.; Le Gall, M. Carbohydrate Intake. In *Progress in Molecular Biology and Translational Science*; Bouchard, C., Ordovas, J.M., Eds.; Recent Advances in Nutrigenetics and Nutrigenomics; Academic Press, 2012; Vol. 108, pp. 113–127.
117. Fahy, E.; Cotter, D.; Sud, M.; Subramaniam, S. Lipid Classification, Structures and Tools. *Biochim Biophys Acta* **2011**, *1811*, 637–647, doi:10.1016/j.bbalip.2011.06.009.
118. Glycerolipid Structure, Function, and Synthesis in Eukaryotes Available online: https://www.researchgate.net/publication/323706689_Glycerolipid_Structure_Function_and_Synthesis_in_Eukaryotes (accessed on 31 July 2025).
119. Peptides and Proteins - an Overview | ScienceDirect Topics Available online: https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/peptides-and-proteins (accessed on 31 July 2025).
120. Phillips, S.M.; Fulgoni, V.L.; Heaney, R.P.; Nicklas, T.A.; Slavin, J.L.; Weaver, C.M. Commonly Consumed Protein Foods Contribute to Nutrient Intake, Diet Quality, and Nutrient Adequacy. *Am J Clin Nutr* **2015**, *101*, 1346S-1352S, doi:10.3945/ajcn.114.084079.
121. Alberts, B.; Johnson, A.; Lewis, J.; Raff, M.; Roberts, K.; Walter, P. The Shape and Structure of Proteins. In *Molecular Biology of the Cell. 4th edition*; Garland Science, 2002.
122. Bhutia, Y.D.; Ganapathy, V. Chapter 47 - Protein Digestion and Absorption. In *Physiology of the Gastrointestinal Tract (Sixth Edition)*; Said, H.M., Ed.; Academic Press, 2018; pp. 1063–1086 ISBN 978-0-12-809954-4.
123. (PDF) Lehninger Principles of Biochemistry Available online: https://www.researchgate.net/publication/48376766_Lehninger_Principles_of_Biochemistry (accessed on 8 August 2025).
124. Rr, W. The 2017 Sir David P Cuthbertson Lecture. Amino Acids and Muscle Protein Metabolism in Critical Care. *Clinical nutrition (Edinburgh, Scotland)* **2018**, *37*, doi:10.1016/j.clnu.2017.12.010.
125. Ko, G.-J.; Rhee, C.M.; Kalantar-Zadeh, K.; Joshi, S. The Effects of High-Protein Diets on Kidney Health and Longevity. *J Am Soc Nephrol* **2020**, *31*, 1667–1679, doi:10.1681/ASN.2020010028.
126. Serra-Prat, M.; Lorenzo, I.; Palomera, E.; Ramírez, S.; Yébenes, J.C. Total Body Water and Intracellular Water Relationships with Muscle Strength, Frailty and Functional Performance in an Elderly Population. *J Nutr Health Aging* **2019**, *23*, 96–101, doi:10.1007/s12603-018-1129-y.

127. Bossingham, M.J.; Carnell, N.S.; Campbell, W.W. Water Balance, Hydration Status, and Fat-Free Mass Hydration in Younger and Older Adults. *Am J Clin Nutr* **2005**, *81*, 1342–1350, doi:10.1093/ajcn/81.6.1342.
128. Cena, H.; Calder, P.C. Defining a Healthy Diet: Evidence for The Role of Contemporary Dietary Patterns in Health and Disease. *Nutrients* **2020**, *12*, 334, doi:10.3390/nu12020334.
129. Stathopoulou, M.G.; Kanoni, S.; Papanikolaou, G.; Antonopoulou, S.; Nomikos, T.; Dedoussis, G. Mineral Intake. In *Progress in Molecular Biology and Translational Science*; Bouchard, C., Ordovas, J.M., Eds.; Recent Advances in Nutrigenetics and Nutrigenomics; Academic Press, 2012; Vol. 108, pp. 201–236.
130. Vitamins and Minerals in Older Adults. In *ResearchGate*.
131. Stevens, S.L. Fat-Soluble Vitamins. *Nurs Clin North Am* **2021**, *56*, 33–45, doi:10.1016/j.cnur.2020.10.003.
132. Shim, J.-S.; Oh, K.; Kim, H.C. Dietary Assessment Methods in Epidemiologic Studies. *Epidemiol Health* **2014**, *36*, e2014009, doi:10.4178/epih/e2014009.
133. Bailey, R.L. Overview of Dietary Assessment Methods for Measuring Intakes of Foods, Beverages, and Dietary Supplements in Research Studies. *Curr Opin Biotechnol* **2021**, *70*, 91–96, doi:10.1016/j.copbio.2021.02.007.
134. Thompson, F.E.; Subar, A.F. Dietary Assessment Methodology. In *Nutrition in the Prevention and Treatment of Disease*; Academic Press, 2017; pp. 5–48.
135. Willett, W. *Nutritional Epidemiology*; Oxford University Press, 2012;
136. Thompson, F.E.; Kirkpatrick, S.I.; Krebs-Smith, S.M.; Reedy, J.; Schap, T.E.; Subar, A.F.; Wilson, M.M. The National Cancer Institute's Dietary Assessment Primer: A Resource for Diet Research. *J Acad Nutr Diet* **2015**, *115*, 1986–1995, doi:10.1016/j.jand.2015.08.016.
137. Exploring the Effects of Genotypical and Phenotypical Variations in Bitter Taste Sensitivity on Perception, Liking and Intake of Brassica Vegetables in the UK. *Food Quality and Preference* **2016**, *50*, 71–81, doi:10.1016/j.foodqual.2016.01.005.
138. Rodrigues, L.; Silverio, R.; Costa, A.R.; Antunes, C.; Pomar, C.; Infante, P.; Cristina Conceição, null; Amado, F.; Lamy, E. Taste Sensitivity and Lifestyle Are Associated with Food Preferences and BMI in Children. *Int J Food Sci Nutr* **2020**, *71*, 875–883, doi:10.1080/09637486.2020.1738354.
139. Tan, S.-Y.; Tucker, R.M. Sweet Taste as a Predictor of Dietary Intake: A Systematic Review. *Nutrients* **2019**, *11*, 94, doi:10.3390/nu11010094.
140. Liem, D.G.; Bogers, R.P.; Dagnelie, P.C.; de Graaf, C. Fruit Consumption of Boys (8–11 Years) Is Related to Preferences for Sour Taste. *Appetite* **2006**, *46*, 93–96, doi:10.1016/j.appet.2005.11.002.
141. Teo, P.S.; van Langeveld, A.W.B.; Pol, K.; Siebelink, E.; de Graaf, C.; Yan, S.W.; Mars, M. Similar Taste-Nutrient Relationships in Commonly Consumed Dutch and Malaysian Foods. *Appetite* **2018**, *125*, 32–41, doi:10.1016/j.appet.2018.01.020.
142. Kubota, M.; Toda, C.; Nagai-Moriyama, A. Relationship between Umami Taste Acuity with Sweet or Bitter Taste Acuity and Food Selection in Japanese Women University Students. *Asia Pac J Clin Nutr* **2018**, *27*, 107–112, doi:10.6133/apjcn.042017.01.
143. Skoczek-Rubińska, A.; Chmurzynska, A.; Muzsik-Kazimierska, A.; Bajerska, J. The Association between Fat Taste Sensitivity, Eating Habits, and Metabolic Health in Menopausal Women. *Nutrients* **2021**, *13*, 4506, doi:10.3390/nu13124506.
144. Martínez-Ruiz, N.R.; López-Díaz, J.A.; Wall-Medrano, A.; Jiménez-Castro, J.A.; Angulo, O. Oral Fat Perception Is Related with Body Mass Index, Preference and Consumption of High-Fat Foods. *Physiol Behav* **2014**, *129*, 36–42, doi:10.1016/j.physbeh.2014.02.010.
145. Costanzo, A.; Orellana, L.; Nowson, C.; Duesing, K.; Keast, R. Fat Taste Sensitivity Is Associated with Short-Term and Habitual Fat Intake. *Nutrients* **2017**, *9*, 781, doi:10.3390/nu9070781.

146. Organization, W.H. *Diet, Nutrition, and the Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation*; World Health Organization, 2003; ISBN 978-92-4-120916-8.
147. Andreoli, A.; Garaci, F.; Cafarelli, F.P.; Guglielmi, G. Body Composition in Clinical Practice. *Eur J Radiol* **2016**, *85*, 1461–1468, doi:10.1016/j.ejrad.2016.02.005.
148. Hajimaghsoodi, S.; Hajiebrahimi, F.; Owlia, F. Variations in Basic Taste Perception and Body Mass Index. *J Diabetes Metab Disord* **2025**, *24*, 122, doi:10.1007/s40200-025-01628-2.
149. AMA Adopts New Policy Clarifying Role of BMI as a Measure in Medicine Available online: https://www.ama-assn.org/press-center/ama-press-releases/ama-adopts-new-policy-clarifying-role-bmi-measure-medicine (accessed on 28 September 2025).
150. Lavie, C.J.; Milani, R.V.; Ventura, H.O. Obesity and Cardiovascular Disease: Risk Factor, Paradox, and Impact of Weight Loss. *J Am Coll Cardiol* **2009**, *53*, 1925–1932, doi:10.1016/j.jacc.2008.12.068.
151. Thibault, R.; Pichard, C. The Evaluation of Body Composition: A Useful Tool for Clinical Practice. *Ann Nutr Metab* **2012**, *60*, 6–16, doi:10.1159/000334879.
152. Papantoni, A.; Shearrer, G.E.; Sadler, J.R.; Stice, E.; Burger, K.S. Longitudinal Associations Between Taste Sensitivity, Taste Liking, Dietary Intake and BMI in Adolescents. *Front. Psychol.* **2021**, *12*, doi:10.3389/fpsyg.2021.597704.
153. Hardikar, S.; Höchenberger, R.; Villringer, A.; Ohla, K. Higher Sensitivity to Sweet and Salty Taste in Obese Compared to Lean Individuals. *Appetite* **2017**, *111*, 158–165, doi:10.1016/j.appet.2016.12.017.
154. Cocca, M.; Barbieri, C.; Concas, M.P.; Robino, A.; Brumat, M.; Gandin, I.; Trudu, M.; Sala, C.F.; Vuckovic, D.; Girotto, G.; et al. A Bird's-Eye View of Italian Genomic Variation through Whole-Genome Sequencing. *Eur J Hum Genet* **2020**, *28*, 435–444, doi:10.1038/s41431-019-0551-x.
155. Esko, T.; Mezzavilla, M.; Nelis, M.; Borel, C.; Debniak, T.; Jakkula, E.; Julia, A.; Karachanak, S.; Khrunin, A.; Kisfali, P.; et al. Genetic Characterization of Northeastern Italian Population Isolates in the Context of Broader European Genetic Diversity. *Eur J Hum Genet* **2013**, *21*, 659–665, doi:10.1038/ejhg.2012.229.
156. Daoudi, H.; Plesník, J.; Sayed, A.; Šerý, O.; Rouabah, A.; Rouabah, L.; Khan, N.A. Oral Fat Sensing and CD36 Gene Polymorphism in Algerian Lean and Obese Teenagers. *Nutrients* **2015**, *7*, 9096–9104, doi:10.3390/nu7115455.
157. Schiffman, S.S.; Graham, B.G. Taste and Smell Perception Affect Appetite and Immunity in the Elderly. *Eur J Clin Nutr* **2000**, *54 Suppl 3*, S54-63, doi:10.1038/sj.ejcn.1601026.
158. Hwang, L.-D.; Lin, C.; Gharahkhani, P.; Cuellar-Partida, G.; Ong, J.-S.; An, J.; Gordon, S.D.; Zhu, G.; MacGregor, S.; Lawlor, D.A.; et al. New Insight into Human Sweet Taste: A Genome-Wide Association Study of the Perception and Intake of Sweet Substances. *Am J Clin Nutr* **2019**, *109*, 1724–1737, doi:10.1093/ajcn/nqz043.
159. Brunkwall, L.; Ericson, U.; Hellstrand, S.; Gullberg, B.; Orho-Melander, M.; Sonestedt, E. Genetic Variation in the Fat Mass and Obesity-Associated Gene (FTO) in Association with Food Preferences in Healthy Adults. *Food Nutr Res* **2013**, *57*, doi:10.3402/fnr.v57i0.20028.
160. Hejazi, J.; Amiri, R.; Nozarian, S.; Tavasolian, R.; Rahimlou, M. Genetic Determinants of Food Preferences: A Systematic Review of Observational Studies. *BMC Nutrition* **2024**, *10*, 24, doi:10.1186/s40795-024-00828-y.
161. Shen, Y.; Kennedy, O.B.; Methven, L. The Effect of Genotypical and Phenotypical Variation in Taste Sensitivity on Liking of Ice Cream and Dietary Fat Intake. *Food Quality and Preference* **2017**, *55*, 79–90, doi:10.1016/j.foodqual.2016.08.010.
162. Keller, K.L.; Liang, L.C.H.; Sakimura, J.; May, D.; van Belle, C.; Breen, C.; Driggin, E.; Tepper, B.J.; Lanzano, P.C.; Deng, L.; et al. Common Variants in the CD36 Gene Are

Associated With Oral Fat Perception, Fat Preferences, and Obesity in African Americans. *Obesity (Silver Spring)* **2012**, *20*, 1066–1073, doi:10.1038/oby.2011.374.
163. Chmurzynska, A.; Mlodzik-Czyzewska, M.A.; Galinski, G.; Malinowska, A.M.; Radziejewska, A.; Mikolajczyk-Stecyna, J.; Bulczak, E.; Wiebe, D.J. Polymorphism of CD36 Determines Fat Discrimination but Not Intake of High-Fat Food in 20- to 40-Year-Old Adults. *The Journal of Nutrition* **2020**, *150*, 2016–2022, doi:10.1093/jn/nxaa136.
164. Graham, C.A.-M.; Spedicati, B.; Pelliccione, G.; Gasparini, P.; Concas, M.P. Regulator of G-Protein Signalling 9: A New Candidate Gene for Sweet Food Liking? *Foods* **2023**, *12*, 1739, doi:10.3390/foods12091739.
165. Pirastu, N.; Kooyman, M.; Traglia, M.; Robino, A.; Willems, S.M.; Pistis, G.; Amin, N.; Sala, C.; Karssen, L.C.; Van Duijn, C.; et al. A Genome-Wide Association Study in Isolated Populations Reveals New Genes Associated to Common Food Likings. *Rev Endocr Metab Disord* **2016**, *17*, 209–219, doi:10.1007/s11154-016-9354-3.
166. LARN_ing_web.Pdf Available online: https://drive.google.com/file/d/1mBDPBG__Jop06_NqVTVvBfsLc0VAeHG4/preview?usp=embed_facebook (accessed on 31 July 2024).
167. Body Mass Index (BMI) Available online: https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/body-mass-index?introPage=intro_3.html (accessed on 5 August 2025).
168. Faul, F.; Erdfelder, E.; Lang, A.-G.; Buchner, A. G*Power 3: A Flexible Statistical Power Analysis Program for the Social, Behavioral, and Biomedical Sciences. *Behav Res Methods* **2007**, *39*, 175–191, doi:10.3758/bf03193146.
169. Faul, F.; Erdfelder, E.; Buchner, A.; Lang, A.-G. Statistical Power Analyses Using G*Power 3.1: Tests for Correlation and Regression Analyses. *Behav Res Methods* **2009**, *41*, 1149–1160, doi:10.3758/BRM.41.4.1149.
170. *McCance and Widdowson's: The Composition of Foods*; The Royal Society of Chemistry, 2014; ISBN 978-1-84973-636-7.
171. Han, P.; Keast, R.; Roura, E. TAS1R1 and TAS1R3 Polymorphisms Relate to Energy and Protein-Rich Food Choices from a Buffet Meal Respectively. *Nutrients* **2018**, *10*, 1906, doi:10.3390/nu10121906.
172. Fushan, A.A.; Simons, C.T.; Slack, J.P.; Manichaikul, A.; Drayna, D. Allelic Polymorphism within the TAS1R3 Promoter Is Associated with Human Taste Sensitivity to Sucrose. *Curr Biol* **2009**, *19*, 1288–1293, doi:10.1016/j.cub.2009.06.015.
173. Lampuré, A.; Castetbon, K.; Deglaire, A.; Schlich, P.; Péneau, S.; Hercberg, S.; Méjean, C. Associations between Liking for Fat, Sweet or Salt and Obesity Risk in French Adults: A Prospective Cohort Study. *Int J Behav Nutr Phys Act* **2016**, *13*, 74, doi:10.1186/s12966-016-0406-6.
174. Tanofsky-Kraff, M.; Han, J.C.; Anandalingam, K.; Shomaker, L.B.; Columbo, K.M.; Wolkoff, L.E.; Kozlosky, M.; Elliott, C.; Ranzenhofer, L.M.; Roza, C.A.; et al. The FTO Gene Rs9939609 Obesity-Risk Allele and Loss of Control over Eating12345. *Am J Clin Nutr* **2009**, *90*, 1483–1488, doi:10.3945/ajcn.2009.28439.
175. Peng, S.; Zhu, Y.; Xu, F.; Ren, X.; Li, X.; Lai, M. FTO Gene Polymorphisms and Obesity Risk: A Meta-Analysis. *BMC Med* **2011**, *9*, 71, doi:10.1186/1741-7015-9-71.
176. Proserpio, C.; Laureati, M.; Bertoli, S.; Battezzati, A.; Pagliarini, E. Determinants of Obesity in Italian Adults: The Role of Taste Sensitivity, Food Liking, and Food Neophobia. *Chemical Senses* **2016**, *41*, 169–176, doi:10.1093/chemse/bjv072.
177. Bartoshuk, L.M.; Duffy, V.B.; Hayes, J.E.; Moskowitz, H.R.; Snyder, D.J. Psychophysics of Sweet and Fat Perception in Obesity: Problems, Solutions and New Perspectives. *Philos Trans R Soc Lond B Biol Sci* **2006**, *361*, 1137–1148, doi:10.1098/rstb.2006.1853.

178. Goldstein, G.L.; Daun, H.; Tepper, B.J. Adiposity in Middle-Aged Women Is Associated with Genetic Taste Blindness to 6-n-Propylthiouracil. *Obesity Research* **2005**, *13*, 1017–1023, doi:10.1038/oby.2005.119.
179. Archer, N.; Shaw, J.; Cochet-Broch, M.; Bunch, R.; Poelman, A.; Barendse, W.; Duesing, K. Obesity Is Associated with Altered Gene Expression in Human Tastebuds. *Int J Obes* **2019**, *43*, 1475–1484, doi:10.1038/s41366-018-0303-y.
180. Fujii, R.; Hishida, A.; Suzuki, K.; Imaeda, N.; Goto, C.; Hamajima, N.; Wakai, K.; Kondo, T. Cluster of Differentiation 36 Gene Polymorphism (Rs1761667) Is Associated with Dietary MUFA Intake and Hypertension in a Japanese Population. *Br J Nutr* **2019**, *121*, 1215–1222, doi:10.1017/S0007114519000679.
181. Pioltine, M.B.; de Melo, M.E.; Santos, A.; Machado, A.D.; Fernandes, A.E.; Fujiwara, C.T.; Cercato, C.; Mancini, M.C. Genetic Variation in CD36 Is Associated with Decreased Fat and Sugar Intake in Obese Children and Adolescents. *Journal of Nutrigenetics and Nutrigenomics* **2017**, *9*, 300–305, doi:10.1159/000455915.
182. Keys, A.; Menotti, A.; Karvonen, M.J.; Aravanis, C.; Blackburn, H.; Buzina, R.; Djordjevic, B.S.; Dontas, A.S.; Fidanza, F.; Keys, M.H. The Diet and 15-Year Death Rate in the Seven Countries Study. *Am J Epidemiol* **1986**, *124*, 903–915, doi:10.1093/oxfordjournals.aje.a114480.
183. Chen, Y.; Liu, Y.; Feng, X. Food Perception: Taste, Smell and Flavour. *Foods* **2023**, *12*, 3628, doi:10.3390/foods12193628.
184. Bajit, H.; Mohammed, O.A.S.; Guennoun, Y.; Benaich, S.; Bouaiti, E.; Belghiti, H.; Mrabet, M.; Elfahime, E.M.; El Haloui, N.E.; Saeid, N.; et al. Single-Nucleotide Polymorphism Rs1761667 in the CD36 Gene Is Associated with Orosensory Perception of a Fatty Acid in Obese and Normal-Weight Moroccan Subjects. *Journal of Nutritional Science* **2020**, *9*, doi:10.1017/jns.2020.18.
185. Graham, C.A.M.; Pilic, L.; King, A.; Nixon, J.E.; Pipe, J.; Holton, J.; Tamba, K.; Hearne, G.; Pedlar, C.R.; Lorente-Cebrián, S.; et al. Genetic Differences in Fat Taste Sensitivity and Dietary Intake in a UK Female Cohort. *Food Quality and Preference* **2021**, *92*, 104202, doi:10.1016/j.foodqual.2021.104202.
186. Tucker, R.M.; Kaiser, K.A.; Parman, M.A.; George, B.J.; Allison, D.B.; Mattes, R.D. Comparisons of Fatty Acid Taste Detection Thresholds in People Who Are Lean vs. Overweight or Obese: A Systematic Review and Meta-Analysis. *PLoS One* **2017**, *12*, e0169583, doi:10.1371/journal.pone.0169583.
187. Khan, A.S.; Murtaza, B.; Hichami, A.; Khan, N.A. A Cross-Talk between Fat and Bitter Taste Modalities. *Biochimie* **2019**, *159*, 3–8, doi:10.1016/j.biochi.2018.06.013.
188. Nagai, Y.; Tokita, K.; Yasumatsu, K. Fatty Acid Taste Quality Information via GPR40 and CD36 in the Posterior Tongue of Mice. *Acta Physiol (Oxf)* **2025**, *241*, e70071, doi:10.1111/apha.70071.
189. Imada, T.; Hao, S.S.; Torii, K.; Kimura, E. Supplementing Chicken Broth with Monosodium Glutamate Reduces Energy Intake from High Fat and Sweet Snacks in Middle-Aged Healthy Women. *Appetite* **2014**, *79*, 158–165, doi:10.1016/j.appet.2014.04.011.
190. Costanzo, A.; Orellana, L.; Nowson, C.; Duesing, K.; Keast, R. Fat Taste Sensitivity Is Associated with Short-Term and Habitual Fat Intake. *Nutrients* **2017**, *9*, 781, doi:10.3390/nu9070781.
191. Ong, H.-H.; Tan, Y.-N.; Say, Y.-H. Fatty Acid Translocase Gene CD36 Rs1527483 Variant Influences Oral Fat Perception in Malaysian Subjects. *Physiol Behav* **2017**, *168*, 128–137, doi:10.1016/j.physbeh.2016.11.006.
192. Pilic, L.; Lubasinski, N.J.; Berk, M.; Ward, D.; Graham, C.A.-M.; Da Silva Anastacio, V.; King, A.; Mavrommatis, Y. Pilic, Leta, Nicole Jane Lubasinski, Melis Berk, et al. «The Associations between Genetics, Salt Taste Perception and Salt Intake in Young Adults». Food Quality and Preference 84 (Settembre 2020): 103954.

Https://Doi.Org/10.1016/j.Foodqual.2020.103954. *Food Quality and Preference* **2020**, *84*, 103954, doi:10.1016/j.foodqual.2020.103954.
193. SACN Dietary Reference Values for Energy Available online: https://www.gov.uk/government/publications/sacn-dietary-reference-values-for-energy (accessed on 31 July 2024).
194. Haryono, R.Y.; Sprajcer, M.A.; Keast, R.S.J. Measuring Oral Fatty Acid Thresholds, Fat Perception, Fatty Food Liking, and Papillae Density in Humans. *J Vis Exp* **2014**, 51236, doi:10.3791/51236.
195. Feeney, E.; O'Brien, S.; Scannell, A.; Markey, A.; Gibney, E.R. Genetic Variation in Taste Perception: Does It Have a Role in Healthy Eating? *Proc Nutr Soc* **2011**, *70*, 135–143, doi:10.1017/S0029665110003976.
196. Rawal, S.; Hayes, J.E.; Wallace, M.R.; Bartoshuk, L.M.; Duffy, V.B. Do Polymorphisms in the TAS1R1 Gene Contribute to Broader Differences in Human Taste Intensity? *Chem Senses* **2013**, *38*, 719–728, doi:10.1093/chemse/bjt040.
197. Pangborn, R.M. Individual Variation in Affective Responses to Taste Stimuli. *Psychon Sci* **1970**, *21*, 125–126, doi:10.3758/BF03335798.
198. Endrizzi, I.; Cliceri, D.; Menghi, L.; Aprea, E.; Charles, M.; Monteleone, E.; Dinnella, C.; Spinelli, S.; Pagliarini, E.; Laureati, M.; et al. Relationships between Intensity and Liking for Chemosensory Stimuli in Food Models: A Large-Scale Consumer Segmentation. *Foods* **2022**, *11*, 5, doi:10.3390/foods11010005.
199. Tuorila, H. Selection of Milks with Varying Fat Contents and Related Overall Liking, Attitudes, Norms and Intentions. *Appetite* **1987**, *8*, 1–14, doi:10.1016/s0195-6663(87)80022-3.
200. Gervis, J.E.; Fernández-Carrión, R.; Chui, K.K.H.; Ma, J.; Coltell, O.; Sorli, J.V.; Asensio, E.M.; Ortega-Azorín, C.; Pérez-Fidalgo, J.A.; Portolés, O.; et al. Associations between Taste Perception Profiles and Empirically Derived Dietary Patterns: An Exploratory Analysis among Older Adults with Metabolic Syndrome. *Nutrients* **2021**, *14*, 142, doi:10.3390/nu14010142.
201. Bingham, S.A. Limitations of the Various Methods for Collecting Dietary Intake Data. *Ann Nutr Metab* **1991**, *35*, 117–127, doi:10.1159/000177635.
202. Cornelis, M.C.; Tordoff, M.G.; El-Sohemy, A.; van Dam, R.M. Recalled Taste Intensity, Liking and Habitual Intake of Commonly Consumed Foods. *Appetite* **2017**, *109*, 182–189, doi:10.1016/j.appet.2016.11.036.
203. Drewnowski, A. Taste Preferences and Food Intake. *Annual Review of Nutrition* **1997**, *17*, 237–253, doi:10.1146/annurev.nutr.17.1.237.
204. Glanz, K.; Basil, M.; Maibach, E.; Goldberg, J.; Snyder, D. Why Americans Eat What They Do: Taste, Nutrition, Cost, Convenience, and Weight Control Concerns as Influences on Food Consumption. *Journal of the American Dietetic Association* **1998**, *98*, 1118–1126, doi:10.1016/S0002-8223(98)00260-0.
205. Wang, L.; Wang, H.; Zhang, B.; Popkin, B.M.; Du, S. Elevated Fat Intake Increases Body Weight and the Risk of Overweight and Obesity among Chinese Adults: 1991–2015 Trends. *Nutrients* **2020**, *12*, 3272, doi:10.3390/nu12113272.
206. A Healthy Lifestyle - WHO Recommendations Available online: https://www.who.int/europe/news-room/fact-sheets/item/a-healthy-lifestyle---who-recommendations (accessed on 11 May 2024).
207. Platikanova, M.; Yordanova, A.; Hristova, P. Dependence of Body Mass Index on Some Dietary Habits: An Application of Classification and Regression Tree. *Iran J Public Health* **2022**, *51*, 1283–1294, doi:10.18502/ijph.v51i6.9672.
208. National Academies of Sciences, E.; Division, H. and M.; Board, F. and N.; Solutions, R. on O.; Callahan, E.A. The Science, Strengths, and Limitations of Body Mass Index. In

*Translating Knowledge of Foundational Drivers of Obesity into Practice: Proceedings of a Workshop Series*; National Academies Press (US), 2023.
209. Şeref, B.; Yıldıran, H. A New Perspective on Obesity: Perception of Fat Taste and Its Relationship with Obesity. *Nutr Rev* **2025**, *83*, e486–e492, doi:10.1093/nutrit/nuae028.
210. Jaime-Lara, R.B.; Brooks, B.E.; Vizioli, C.; Chiles, M.; Nawal, N.; Ortiz-Figueroa, R.S.E.; Livinski, A.A.; Agarwal, K.; Colina-Prisco, C.; Iannarino, N.; et al. A Systematic Review of the Biological Mediators of Fat Taste and Smell. *Physiological Reviews* **2022**, *103*, 855, doi:10.1152/physrev.00061.2021.
211. Hartley, I.; Costanzo, A.; Liem, D.G.; Keast, R. Glutamate-Sodium Discrimination Status in Adults Is Associated with Salt Recognition Threshold and Habitual Intake of Discretionary Food and Meat: A Cross-Sectional Study. *Int J Environ Res Public Health* **2022**, *19*, 11101, doi:10.3390/ijerph191711101.
212. Costanzo, A.; Hartley, I. A Simple Emulsion for Measuring Fat Taste Sensitivity. *Food Research International* **2025**, *213*, 116515, doi:10.1016/j.foodres.2025.116515.
213. Martínez-Ruiz, N.R.; López-Díaz, J.A.; Wall-Medrano, A.; Jiménez-Castro, J.A.; Angulo, O. Oral Fat Perception Is Related with Body Mass Index, Preference and Consumption of High-Fat Foods. *Physiology & Behavior* **2014**, *129*, 36–42, doi:10.1016/j.physbeh.2014.02.010.
214. Mattes, R.D. Oral Fatty Acid Signaling and Intestinal Lipid Processing: Support and Supposition. *Physiology & Behavior* **2011**, *105*, 27–35, doi:10.1016/j.physbeh.2011.02.016.
215. Stewart, J.E.; Feinle-Bisset, C.; Golding, M.; Delahunty, C.; Clifton, P.M.; Keast, R.S.J. Oral Sensitivity to Fatty Acids, Food Consumption and BMI in Human Subjects. *Br J Nutr* **2010**, *104*, 145–152, doi:10.1017/S0007114510000267.
216. Asano, M.; Hong, G.; Matsuyama, Y.; Wang, W.; Izumi, S.; Izumi, M.; Toda, T.; Kudo, T. Association of Oral Fat Sensitivity with Body Mass Index, Taste Preference, and Eating Habits in Healthy Japanese Young Adults. *The Tohoku Journal of Experimental Medicine* **2016**, *238*, 93–103, doi:10.1620/tjem.238.93.
217. Tucker, R.M.; Nuessle, T.M.; Garneau, N.L.; Smutzer, G.; Mattes, R.D. No Difference in Perceived Intensity of Linoleic Acid in the Oral Cavity between Obese and Nonobese Individuals. *Chem Senses* **2015**, *40*, 557–563, doi:10.1093/chemse/bjv040.
218. Stewart, J.E.; Keast, R.S.J. Recent Fat Intake Modulates Fat Taste Sensitivity in Lean and Overweight Subjects. *Int J Obes (Lond)* **2012**, *36*, 834–842, doi:10.1038/ijo.2011.155.
219. Running, C.A.; Mattes, R.D.; Tucker, R.M. Fat Taste in Humans: Sources of within- and between-Subject Variability. *Prog Lipid Res* **2013**, *52*, 438–445, doi:10.1016/j.plipres.2013.04.007.
220. Cox, D.N.; Hendrie, G.A.; Carty, D. Sensitivity, Hedonics and Preferences for Basic Tastes and Fat amongst Adults and Children of Differing Weight Status: A Comprehensive Review. *Food Quality and Preference* **2016**, *48*, 359–367, doi:10.1016/j.foodqual.2015.01.006.
221. Sasano, T.; Satoh-Kuriwada, S.; Shoji, N. The Important Role of Umami Taste in Oral and Overall Health. *Flavour* **2015**, *4*, 1–5, doi:10.1186/2044-7248-4-10.
222. Yoshida, R.; Ninomiya, Y. Umami and MSG. In *Umami: Taste for Health*; San Gabriel, A., Rains, T.M., Beauchamp, G., Eds.; Springer International Publishing: Cham, 2024; pp. 7–42 ISBN 978-3-031-32692-9.
223. Khan, A.M.; Ali, S.; Jameela, R.V.; Muhamood, M.; Haqh, M.F. Impact of Fungiform Papillae Count on Taste Perception and Different Methods of Taste Assessment and Their Clinical Applications. *Sultan Qaboos Univ Med J* **2019**, *19*, e184–e191, doi:10.18295/squmj.2019.19.03.003.
224. Spielman, A.I. Interaction of Saliva and Taste. *J Dent Res* **1990**, *69*, 838–843, doi:10.1177/00220345900690030101.
225. Pepino, M.Y.; Finkbeiner, S.; Beauchamp, G.K.; Mennella, J.A. Obese Women Have Lower Monosodium Glutamate Taste Sensitivity and Prefer Higher Concentrations than Do Normal-Weight Women. *Obesity (Silver Spring)* **2010**, *18*, 959–965, doi:10.1038/oby.2009.493.

226. Feeney, E.L.; Leacy, L.; O'Kelly, M.; Leacy, N.; Phelan, A.; Crowley, L.; Stynes, E.; de Casanove, A.; Horner, K. Sweet and Umami Taste Perception Differs with Habitual Exercise in Males. *Nutrients* **2019**, *11*, 155, doi:10.3390/nu11010155.
227. Masic, U.; Yeomans, M.R. Monosodium Glutamate Delivered in a Protein-Rich Soup Improves Subsequent Energy Compensation. *J Nutr Sci* **2014**, *3*, e15, doi:10.1017/jns.2014.15.
228. Boesveldt, S.; Bobowski, N.; McCrickerd, K.; Maître, I.; Sulmont-Rossé, C.; Forde, C.G. The Changing Role of the Senses in Food Choice and Food Intake across the Lifespan. *Food Quality and Preference* **2018**, *68*, 80–89, doi:10.1016/j.foodqual.2018.02.004.
229. Clark, J.E. Taste and Flavour: Their Importance in Food Choice and Acceptance. *Proc Nutr Soc* **1998**, *57*, 639–643, doi:10.1079/pns19980093.
230. Boesveldt, S.; de Graaf, K. The Differential Role of Smell and Taste For Eating Behavior. *Perception* **2017**, *46*, 307–319, doi:10.1177/0301006616685576.
231. Lampuré, A.; Castetbon, K.; Deglaire, A.; Schlich, P.; Péneau, S.; Hercberg, S.; Méjean, C. Associations between Liking for Fat, Sweet or Salt and Obesity Risk in French Adults: A Prospective Cohort Study. *International Journal of Behavioral Nutrition and Physical Activity* **2016**, *13*, 74, doi:10.1186/s12966-016-0406-6.
232. Alegría-Lertxundi, I.; Rocandio Pablo, A.; Arroyo-Izaga, M. Cheese Consumption and Prevalence of Overweight and Obesity in a Basque Adult Population: A Cross-Sectional Study. *Int J Food Sci Nutr* **2014**, *65*, 21–27, doi:10.3109/09637486.2013.836741.
233. Cornelis, M.C.; Tordoff, M.G.; El-Sohemy, A.; van Dam, R.M. Recalled Taste Intensity, Liking and Habitual Intake of Commonly Consumed Foods. *Appetite* **2017**, *109*, 182–189, doi:10.1016/j.appet.2016.11.036.
234. Wanich, U.; Sayompark, D.; Riddell, L.; Cicerale, S.; Liem, D.G.; Mohebbi, M.; Macfarlane, S.; Keast, R. Assessing Food Liking: Comparison of Food Liking Questionnaires and Direct Food Tasting in Two Cultures. *Nutrients* **2018**, *10*, 1957, doi:10.3390/nu10121957.
235. Graham, C.A.-M.; Pilic, L.; Mcgrigor, E.; Brown, M.; Easton, I.J.; Kean, J.N.; Sarel, V.; Wehliye, Y.; Davis, N.; Hares, N.; et al. The Associations Between Bitter and Fat Taste Sensitivity, and Dietary Fat Intake: Are They Impacted by Genetic Predisposition? *Chem Senses* **2021**, *46*, bjab029, doi:10.1093/chemse/bjab029.
236. Karmous, I.; Ben Othman, R.; Dergaa, I.; Ceylan, H.İ.; Bey, C.; Dhahbi, W.; Khan, A.S.; Jamoussi, H.; Muntean, R.I.; Khan, N.A. Sweet and Fat Taste Perception: Impact on Dietary Intake in Diabetic Pregnant Women—A Cross-Sectional Observational Study. *Nutrients* **2025**, *17*, 2515, doi:10.3390/nu17152515.
237. Enciso Ramírez, M.A.; Reyes Castillo, Z.; Valdés Miramontes, E.H. [Genetic variants in CD36: emerging role in oral fat perception and food preferences]. *Nutr Hosp* **2023**, doi:10.20960/nh.04711.
238. Boghdady, A.; Arafa, U.A.; Sabet, E.A.; Salama, E.; El Sharawy, A.; Elbadry, M.I. Association between Rs1761667 Polymorphism of CD36 Gene and Risk of Coronary Atherosclerosis in Egyptian Population. *Cardiovasc Diagn Ther* **2016**, *6*, 120–130, doi:10.21037/cdt.2015.12.15.
239. Yazdanpanah, Z.; Mozaffari-Khosravi, H.; Mirzaei, M.; Sheikhha, M.H.; Salehi-Abargouei, A. A Systematic Review and Meta-Analysis on the Association between CD36 Rs1761667 Polymorphism and Cardiometabolic Risk Factors in Adults. *Sci Rep* **2022**, *12*, 5916, doi:10.1038/s41598-022-09908-0.