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Associations of taste receptor gene variants with Body Mass Index (BMI) and longevity

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Taste receptors are expressed in the oral cavity and numerous extra-oral tissues, where they share signaling mechanisms. Within this broad context, taste receptors regulate feeding behavior and metabolic homeostasis, potentially contributing to exceptional longevity. We evaluated differences in genotype and allele frequencies at the *TAS1R2*, *TAS1R3*, *TAS2R38*, and *CD36* single-nucleotide polymorphisms (SNPs) and their associations with BMI and sex in two genetically and environmentally distinct populations: a cohort of near centenarian participants (LBZ) and a control cohort (CYME). Significant differences were observed in the genotype and allele distributions of the *TAS1R3*, *TAS2R38*, and *CD36* SNPs. In the LBZ cohort, specific genotypes, such as *TAS1R3* CC, *TAS2R38* PAV/PAV, and *CD36* AA, were most frequent, and likely contributed to favorable phenotypes, whereas they showed no effect in the more heterogeneous urban CYME population. The BMI was significantly higher in the LBZ cohort, particularly among females. The *TAS1R2*, *TAS1R3*, *TAS2R38*, and *CD36* variants modulated BMI in a population- and sex-dependent manner. These results contribute to expanding the understanding of taste receptors as multifunctional chemosensors, with roles that extend beyond gustatory perception to influence systemic physiology, energy balance, and potentially contribute to phenotypic profiles associated with longevity.

Keywords Taste receptor genetic variants, Human longevity, BMI, Sex

The gustatory system is a sensory modality through which taste receptor cells transduce chemical stimuli into neural signals, thereby providing critical information not only about the palatability and nutritional content of ingested substances but also about broader physiological and homeostatic states[1,2]. Recent investigations have expanded this paradigm, revealing that taste receptors are expressed in a wide range of extra-oral tissues, including the respiratory and gastrointestinal systems, pancreas, liver, kidneys, testes, bladder, and central nervous system[3–9]. Within these locations, taste receptors are increasingly recognized as integral components of chemosensory networks that modulate diverse physiological processes. Although the precise mechanisms underlying their function in these tissues are not fully understood, current evidence suggests that they utilize transduction pathways and intracellular signaling cascades analogous to those of lingual taste cells[4,7]. Importantly, alterations in the expression, localization, or sensitivity of these extra-oral taste receptors, as well as their associated signaling pathways, have been implicated in dysregulation of metabolic homeostasis[4]. These findings underscore the relevance of taste receptors as multifunctional chemosensors with emerging roles in physiology and interoceptive signaling.

In humans, taste receptors were characterized by their canonical function within the taste buds of the tongue, where they mediate the detection of five fundamental taste qualities: sweet, sour, salty, umami, and bitter[10]. Fat perception has been described as a potential taste quality[11], as well as kokumi[12], starch[13], and ammonium chloride[14].

Among the various taste receptors implicated in nutrition and systemic health, T1Rs, T2Rs, and CD36 have emerged as key molecular sensors. The T1R family of G-protein-coupled receptors, particularly the T1R2/T1R3 heterodimer, mediates sweet taste perception and plays a crucial role in the detection of energy-dense carbohydrates, while T1R1/T1R3 is responsible for umami detection by signaling the presence of amino acids[15]. These receptors are not only expressed in the oral cavity, but also in the gastrointestinal tract, where they influence nutrient sensing, insulin secretion, and satiety signaling[16–18]. The genes encoding the sweet receptors (T1R2/T1R3) exhibit genetic single-nucleotide polymorphisms (SNPs), such as the *rs35874116* SNP in the *TAS1R2*

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gene, and the *rs307355* SNP in the *TAS1R3* gene, which influence taste sensitivity and food preferences[19–23]. These variants may lead to increased consumption of sugary foods to achieve the same hedonic response, thus contributing to higher caloric intake and increased risk of obesity[24].

T2Rs, traditionally associated with bitter taste, are now recognized for their broader physiological roles, including modulation of immune responses and intestinal motility, and are expressed in tissues such as the gut, airway, and brain[8]. Among them, TAS2R38 has been extensively studied for its role in mediating the perception of bitter taste of phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP) thiourea. Variants of the *TAS2R38* gene, particularly the common haplotypes PAV (taster) and AVI (non-taster), underlie significant interindividual variability in bitter taste perception. This variability influences not only the acceptance or rejection of bitter-tasting foods, such as cruciferous vegetables, but also broader dietary behaviors and nutritional choices[1,25,26]. Consequently, *TAS2R38* SNPs have been linked to differences in body mass composition, nutrient intake, and even non-gustatory physiological mechanisms, including immune responses, metabolic regulation, and the biological process of aging[1,2,8,25–29].

In addition to these families, CD36, a transmembrane glycoprotein expressed on various cell types[30,31], facilitates the uptake and oxidation of fatty acids (FA), and is involved in the pathophysiological mechanisms associated with dysfunctional FA metabolism[32–35]. CD36 is a critical receptor for the sensing of dietary lipids, particularly long-chain fatty acids (LCFAs)[36–39]. Expressed on the apical surface of taste bud cells, CD36 mediates the orosensory perception of fat and initiates cephalic phase responses that prepare the body for lipid digestion and absorption[40]. Genetic inactivation of CD36 in animal models abolishes preference for fatty foods, underscoring its essential role in fat taste perception and dietary fat intake regulation[40]. Beyond the oral cavity, CD36 and its genetic variant that reduce protein expression[41,42], are involved in lipid metabolism, changes in levels of circulating endocannabinoids, inflammation, and energy homeostasis, linking CD36 to metabolic disorders such as obesity, insulin resistance, cardiovascular disease, diabetes, and cancer[43–46].

Together, these receptors form a complex chemosensory network that integrates peripheral chemosensory signals with central neural circuits to regulate feeding behavior, maintain metabolic balance, and regulate metabolic and systemic homeostasis, which may contribute to phenotypic profiles associated with longevity.

In this work, we analyzed the genotype distribution and allele frequency of polymorphisms in the *TAS1R2*, *TAS1R3*, *TAS2R38*, and *CD36* genes in a cohort of nearcentenarian subjects recruited from a genetically isolated area (Longevity Blue Zone, LBZ) of central-eastern Sardinia Island. This region, which includes six mountainous villages in Ogliastra and Barbagia, has a population of approximately 12,000 inhabitants distributed over 888 km^2 [47]. Long-standing geographic isolation has resulted in a highly homogeneous genetic profile[48] and the preservation of distinct sociocultural and anthropological traits[47,49]. The LBZ presents a compelling case study, exhibiting an Extreme Longevity Index (ELI)[50] for cohorts born between 1880 and 1900, which is more than twice the Sardinian average. Based on the ELI, the longevity rate in the LBZ area was 509 per 100,000, while on the rest of the island, it was only 181 per 100,000 [50]. Accordingly, data from this population were compared with those from an ancestrally diverse cohort of younger, middle-aged, and elderly participants from southern Sardinia. The associations between the gene polymorphisms related to taste and metabolism, body mass index (BMI), and gender were also analyzed.

Materials and methods

Participants

The study size was determined by a priori statistical power analysis using the G*Power software (Düsseldorf, Germany). Setting the parameters to an effect size of 0.4, an alpha error probability of 0.05, a numerator degree of freedom of 2, and a number of groups of 6 resulted in a total sample size of 100. However, to achieve a higher statistical power, we recruited 274 participants, which corresponded to an effect size of 0.24 and a critical F of 3.029. The statistical power decreased when the participants were split into females ($n = 171$, effect size = 0.30, critical F = 3.051) and males ($n = 103$, effect size = 0.39, critical F = 3.090).

A total of 274 participants were enrolled in the study and categorized into two groups based on age and geographic origin: Longevity Blue Zone (LBZ) cohort included 114 individuals aged 90 to 103 years, recruited from the central-eastern region of Sardinia (Ogliastra/Barbagia), and the CYME cohort that included 160 young, middle-aged and elderly participants aged 18 to 67 years, recruited from the urban area of Cagliari. Specifically, for the LBZ cohort, the recruitment was conducted with the assistance of municipal administrations by collecting demographic and personal data from LBZ residents aged 65 and older. Only individuals born in this area and aged 90 years or older were eligible to participate in the study, and their blood samples were collected during in-home interviews. All participants were undergoing a baseline medical screening to investigate their health status. Body height was measured with a portable stadiometer and body weight with an electronic scale with a precision of up to 0.1 kg. BMI was calculated as weight/height^2 (kg/m^2). BMI could not be calculated for 41 participants. Table 1 shows demographic features of the two cohorts. All participants were fully informed about the study's procedures and objectives and provided written informed consent. The study adhered to the principles outlined in the Declaration of Helsinki (1975, revised in 1983), and the local ethics committee (Comitato Etico ASL no. 1 di Sassari, Italy) approved the study protocol (136/CE), approval date: 9 February 2012. In cases of severe cognitive impairment, written informed consent was obtained from all participants or their caregivers.

Molecular analysis

DNA was isolated from blood samples using the QIAamp® DNA Mini Kit (QIAGEN, Hilden, Germany), following the manufacturer's protocol. The concentration and purity of the extracted DNA were assessed by measuring absorbance at 260 nm with a NanoDrop One/One Spectrophotometer (Thermo Fisher Scientific). Participants were genotyped for the *rs35874116* (C/T) variant, which results in an isoleucine-to-valine substitution at position 191 (Ile191Val) in the TAS1R2 gene, and for the *rs307355* (C/T) variant in the *TAS1R3*

	Participants			
	Total	Males	Females	Age range
	(*n*)	(*n*)	(*n*)	(y)
LBZ	114	54	60	90–103
CYME	160	49	111	18–67

Table 1. Demographic features of the LBZ cohort and CYME cohort. LBZ, Longevity Blue Zone cohort; CYME, Cagliari cohort including young, middle-aged, and elderly participants.

gene, located – 1572 base pairs upstream of the coding region. Additionally, genotyping was performed for three single-nucleotide polymorphisms (SNPs) in the *TAS2R38* gene: *rs713598*, *rs1726866*, and *rs10246939*, which cause three amino acid substitutions respectively: Pro49Ala, Ala262Val, and Val296Ile. These SNPs define two main haplotypes, PAV (the dominant taster variant) and AVI (the non-taster recessive one), as well as three less common haplotypes: AAI, AAV, and PVI. Genotyping was also performed for *rs1761667* (G/A) SNP in the *CD36* gene located in the promoter region – 31,118 of exon 1 A. A subset of *TAS2R38* genotyping data previously published in Melis et al. [51] is reused here, integrated with other samples.

Molecular analyses were carried out using the TaqMan® SNP Genotyping Assay, following the manufacturer's guidelines (Applied Biosystems, Life Technologies, Milan, Italy). Reactions were performed in 96-well plates under fast thermal cycling conditions. Each reaction contained 1X TaqMan® Genotyping Master Mix (code: 4371355), 1X TaqMan® Genotyping Assays (C_55646_20, C_188859166_10, C_8876467_10, C_9506827_10, C_9506826_10, and C_8314999_10), 10 ng of DNA, and nuclease-free water.

Amplification and detection were performed using the StepOne™ Real-Time PCR System, and genotypes were determined by allelic discrimination using the Sequence Detection Software (Genotyping—Applied Biosystems, version 2.3; Life Technologies Italia, Monza, Italy). All reactions included positive and negative controls, as well as replicates.

Statistical analysis

The genotype distributions and allele or haplotype frequencies of the *TAS1R2*, *TAS1R3*, *TAS2R38*, and *CD36* SNPs of the two cohorts were compared using Fisher's exact test (Genepop software version 4.2; http://genepop.curtin.edu.au/genepop_op3.html).

Body mass index (BMI) differences between and within cohorts, between sexes, and among genotypes were evaluated using one-way or two-way analyses of variance, as appropriate. All data were checked for the assumptions of homogeneity of variances using Levene's test and for normality using the Shapiro–Wilk test. When the assumption of homogeneity and normality was met, standard ANOVA procedures were applied, followed by Tukey's test for post-hoc comparisons. When the assumption of homogeneity of variances was violated, Welch's ANOVA was used as the omnibus test. In these cases, post-hoc comparisons were conducted using the Games–Howell procedure, which does not assume equal variances or equal sample sizes. When the normality was violated Kruskal–Wallis test followed by the Dwass–Steel–Critchlow–Fligner procedure was used. A Factorial General Linear Model with heteroscedasticity-consistent robust standard errors (HC3) was used for two-way analyses of variance. This test provides reliable inference under heteroscedasticity, deviations from normality, unequal variances, and unbalanced designs, while preserving the interpretability of model parameters and estimated marginal means. In this case, post-hoc comparisons differences were evaluated using Holm-adjusted p-values, a method compatible with robust standard errors and the interpretation of interaction effects. The same analysis was carried out separately in males and females between the two cohorts. Statistical analyses were conducted using STATISTICA for Windows (version 10; StatSoft Inc., Tulsa, OK) and Jamovi (version 2.6.44, The jamovi project, 2025, https://www.jamovi.org). The significance level was set at $p \leq 0.05$.

Results

Genotype distributions and allele frequencies of the TAS1R2, TAS1R3, TAS2R38, and CD36 SNPs in LBZ and CYME cohorts

The genotype distributions and haplotype frequencies of the polymorphisms of *TAS1R2*, *TAS1R3*, *TAS2R38*, and *CD36* genes in the LBZ and CYME cohorts are shown in Fig. 1. The two cohorts differed statistically based on the genotype distributions ($\chi^2 = 13.918$; $p = 0.0009$ Fisher's exact test) and allele frequencies of *TAS1R3* SNPs ($\chi^2 = 13.776$; $p = 0.0010$ Fisher's exact test), the diplotype distributions ($\chi^2 = 8.248$; $p = 0.0181$; Fisher's exact test) and haplotype frequencies of *TAS2R38* SNPs ($\chi^2 = 8.566$; $p = 0.0138$; Fisher's exact test), and the genotype distributions of *CD36* SNP ($\chi^2 = 6.875$; $p = 0.032$; Fisher's exact test), while the allele frequencies for this locus was at the limit of significance ($\chi^2 = 5.887$; $p = 0.052$; Fisher's exact test). No differences were found in the genotype distributions ($\chi^2 = 1.402$; $p = 0.496$; Fisher's exact test) and allele frequencies of *TAS1R2* SNP ($\chi^2 = 1.279$; $p = 0.527$; Fisher's exact test). Specifically, regarding the *TAS1R3* locus, the LBZ cohort was characterized by a very high frequency of genotype CC (97.4%) and allele C (98.7%), a very low frequency of heterozygous CT (2.6%) and allele T (1.3%), and none had genotype TT, while the CYME cohort showed 86.3% of participants with genotype CC, 13.1% of heterozygous and 0.6% of TT genotypes. With respect to the *TAS2R38* locus, the LBZ cohort was characterized by a higher frequency of the diplotype PAV/PAV (30.7%) and a lower frequency of diplotype AVI/AVI (21.9%) compared to the CYME cohort (PAV/PAV, 21.9% and AVI/AVI, 35%, respectively), while with respect to the CD36 locus, the LBZ cohort was characterized by a higher frequency of genotype AA (23.7%) and a lower frequency of genotype GG (21.9%) compared to the CYME cohort (13.8% and 30%, respectively).

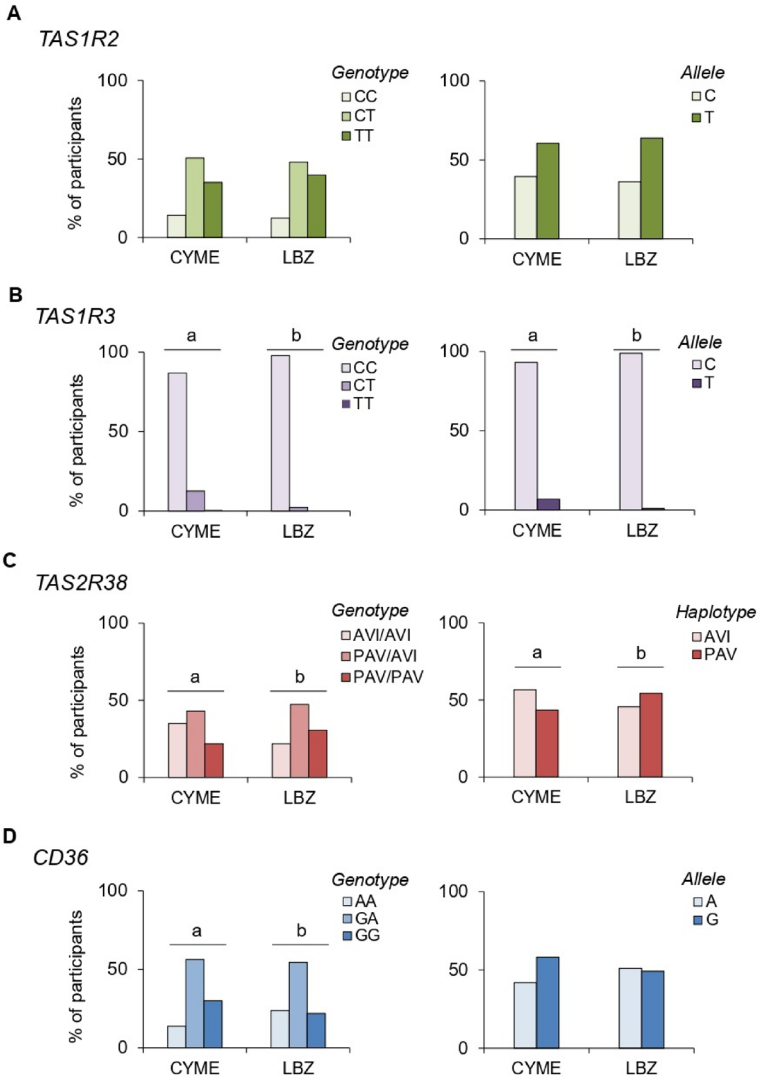

Fig. 1. Genotype distributions and allele or haplotype frequencies of polymorphisms of the *TAS1R2***(A)**, *TAS1R3***(B)**, *TAS2R38***(C)** and *CD36***(D)** genes in the Longevity Blue Zone cohort (LBZ) ($n = 114$) and Cagliari Young, Middle-aged, and Elderly participants (CYME) ($n = 160$). Different letters indicated significant differences ($\chi^2 > 6.38$; $p \leq 0.041$; Fisher's exact test).

Considering only females, the two cohorts differed statistically based on the genotype distributions ($\chi^2 = 13.215$; $p = 0.0013$ Fisher's exact test) and allele frequencies of *TAS1R3* SNPs ($\chi^2 = 12.731$; $p = 0.0017$ Fisher's exact test). No other differences in the genotype distributions and haplotype frequencies were found between the two cohorts in females and males (Table S1).

Associations between the TAS1R2, TAS1R3, TAS2R38, and CD36 SNPs, BMI, and gender in LBZ and CYME cohorts

The mean values ± SEM of body mass index (BMI) in the LBZ were significantly higher than those of CYME participants ($F_{[1,168]} = 20.7$; $p < 0.001$; Welch's ANOVA) (Fig. 2A). When data were analyzed stratified by gender, the Factorial General Linear Model HC3 revealed a significant two-way interaction of GENDER × LBZ/CYME cohort for the BMI values ($F_{[1,270]} = 5.204$; $p = 0.023$) (Fig. 2B). Post hoc comparisons showed that the BMI of LBZ females was significantly higher than that of CYME females ($p < 0.001$; Holm's test), who showed lower BMI values than males of the two cohorts ($p < 0.001$; Holm test). No differences were found between males of the two cohorts. One-way ANOVA showed significant differences between females and males only within the CYME cohort ($F_{[1,158]} = 19.521$; $p < 0.001$).

The mean values ± SEM of BMI in the LBZ and CYME participants, according to polymorphisms in the *TAS1R2*, *TAS1R3*, *TAS2R38*, and *CD36* loci, are shown in Fig. 3. The Factorial General Linear Model HC3 revealed significant two-way interactions of the *TAS1R2* SNP × LBZ/CYME cohort, at the limit of statistical significance ($F_{[2,268]} = 2.966$; $p = 0.05$), and the *CD36* SNP × LBZ/CYME cohort for the BMI values and ($F_{[2,268]} = 6.675$; $p = 0.002$). Figure 3A shows BMI values of the two cohorts according to *TAS1R2* genotypes. Post hoc comparisons showed that the BMI of TT genotype of LBZ participants was higher than that of the

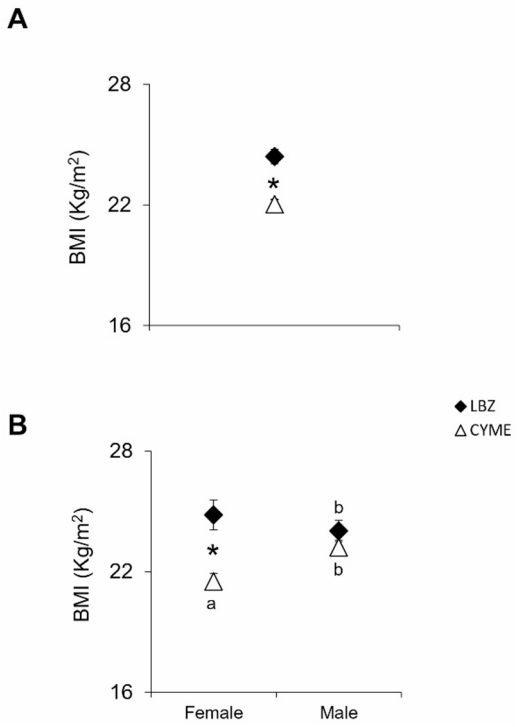

Fig. 2. Mean values ± SEM of body mass index (BMI) in the Longevity Blue Zone cohort (LBZ) ($n = 114$) and Cagliari Young, Middle-aged, and Elderly participants (CYME) ($n = 160$) **(A)**. The same data spitted by sex **(B)**. * Indicates a significant difference between the corresponding values in participants of the LBZ and CYME cohorts (A: Welch's ANOVA, $p < 0.001$; B: Holm's test, subsequent Factorial General Linear Model HC3, $p < 0.001$). Different letters (a and b) denote significant differences from Holm's test, subsequent Factorial General Linear Model HC3, $p < 0.001$.

corresponding genotype of the CYME cohort ($p < 0.001$; Holm's test), while Kruskal-Wallis' test showed that the BMI values varied with genotype only in LBZ participants ($H_{(2)} = 7.303$; $p = 0.026$), with the values of TT genotypes higher than those of CT genotypes ($p = 0.027$; Dwass-Steel-Critchlow-Fligner test). The BMI values in participants with genotype CC of *TAS1R3* in the LBZ cohort were significantly higher than those of CYME participants ($p < 0.001$; Holm's test) (Fig. 3B). The BMI values in participants with genotype PAV/AVI of *TAS2R38* in the LBZ cohort were significantly higher than those of CYME participants ($p = 0.004$; Holm's test) (Fig. 3C). In addition, Fig. 3D shows BMI values of the two cohorts according to *CD36* genotypes. Post hoc comparison showed that the BMI of LBZ participants with the GG genotype of the *CD36* locus was significantly lower than that of LBZ participants with GA genotype ($p = 0.012$; Holm's test), who showed higher BMI values than those of the corresponding genotype of the CYME cohort ($p < 0.001$; Holm's test). Kruskal-Wallis's test showed that the BMI values varied with genotype only in LBZ participants ($H_{(2)} = 7.323$; $p = 0.0257$), with the values of GG genotype participants lower than those of GA genotypes ($p = 0.019$; Dwass-Steel-Critchlow-Fligner test). In the CYME cohort, the genotypes of the four loci had BMI values that did not differ from each other ($p > 0.05$).

Figure 4 shows the mean values ± SEM of body mass index (BMI) based on polymorphisms in the *TAS1R2*, *TAS1R3*, *TAS2R38*, and *CD36* genes in females of the LBZ and CYME cohorts. The Factorial General Linear Model HC3 revealed significant two-way interactions of the *CD36* SNP × LBZ/CYME cohort for the BMI values ($F_{[2,165]} = 4.916$; $p = 0.009$). Figure 4A shows BMI values of the two cohorts according to *TAS1R2* genotypes. Post hoc comparisons showed that the BMI of TT genotype of LBZ participants was higher than that of the corresponding genotype of the CYME cohort ($p = 0.008$; Holm's test), while Kruskal-Wallis' test showed that the BMI values varied with genotype only in LBZ participants ($H(2) = 5{,}901$; $p = 0.05$), with the values of TT genotypes higher than those of CT genotypes ($p = 0.05$; Dwass-Steel-Critchlow-Fligner test). In the CYME cohort, the three genotypes of this locus exhibited BMI values that did not differ from each other ($p > 0.05$). One-way ANOVA showed that BMI values in females with genotype CC of *TAS1R3* in the LBZ cohort were significantly higher than those of CYME participants ($F_{[1,129]} = 29.351$; $p < 0.0001$) (Fig. 4B). In the CYME cohort, no difference related to this locus was found ($p > 0.05$). The BMI values in participants with genotype PAV/AVI of *TAS2R38* in the LBZ cohort were significantly higher than those of CYME participants ($p = 0.011$; Holm's test). Kruskal-Wallis' test showed that the BMI values varied with genotype only in CYME participants ($H_{(2)} = 6.275$; $p = 0.043$), with the values of AVI/AVI genotypes higher than those of PAV/AVI genotypes ($p = 0.044$; Dwass-Steel-Critchlow-Fligner test) (Fig. 4C). In addition, Fig. 4D shows BMI values of the two cohorts according to *CD36* genotypes. Post hoc comparison showed that the BMI of LBZ females who had the GG genotype of the *CD36* locus was significantly lower than that of LBZ females with the GA genotype ($p = 0.04$; Holm's test), who showed higher BMI values than those of the corresponding genotype of the CYME cohort ($p = 0.002$; Holm's test). One-way

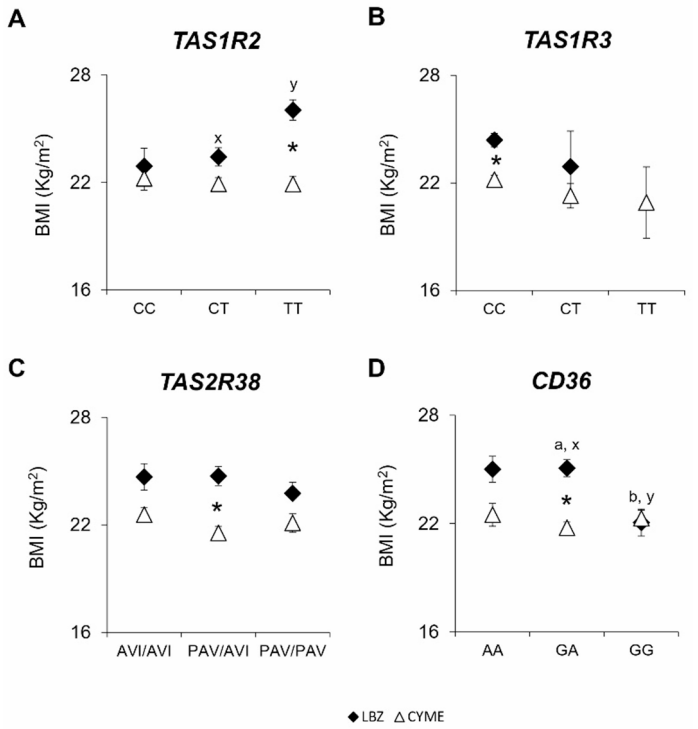

Fig. 3. Mean values ± SEM of body mass index (BMI) according to polymorphisms in the *TAS1R2*, *TAS1R3*, *TAS2R38*, and *CD36* genes in the Longevity Blue Zone cohort (LBZ) ($n = 114$) and Cagliari young, middle-aged, and elderly participants (CYME) ($n = 160$). * Indicates a significant difference between the corresponding genotypes of the two cohorts ($p < 0.004$; Holm's test, subsequent Factorial General Linear Model HC3). Different letters denote significant differences, a and b from Holm's test after Factorial General Linear Model with HC3 robust standard errors ($p = 0.012$), while x and y from Dwass-Steel-Critchlow-Fligner test, after Kruskal-Wallis' test ($p < 0.027$).

ANOVA showed that the BMI values varied with genotype only in LBZ participants ($F_{[2,57]} = 3.269$; $p = 0.051$), with the values of the GG genotype lower than those of the GA genotype ($p = 0.041$; Tukey's test). In the CYME cohort, the three genotypes of this locus exhibited BMI values that did not differ from each other ($p > 0.05$).

Figure 5 shows the mean values ± SEM of body mass index (BMI) across polymorphisms in the *TAS1R2*, *TAS1R3*, *TAS2R38*, and *CD36* genes in males of the LBZ and YCME cohorts. The Factorial General Linear Model HC3, Welch ANOVA or Kruskal-Wallis' test showed no difference related to the genotypes of the four loci ($p > 0.05$).

Discussion

This study investigated the distribution of polymorphisms in the *TAS1R2*, *TAS1R3*, *TAS2R38*, and *CD36* genes and their associations with BMI in two genetically and environmentally distinct Sardinian populations: the Longevity Blue Zone (LBZ) cohort and the Cagliari Young, Middle-aged, and Elderly (CYME) cohort. The results provide novel insights into how taste receptor gene variants, traditionally associated with oral gustation, may contribute to phenotypic profiles potentially linked to metabolic traits observed in long-lived populations, with sex-specific implications for BMI.

Molecular analysis revealed significant differences in genotype distributions and allele frequencies of *TAS1R3*, *TAS2R38*, and *CD36* between the LBZ and CYME cohorts, reflecting the genetic isolation and homogeneity of the LBZ population. This suggests potential genetic contributions to phenotypic profiles associated with longevity in the LBZ population. These findings align with previous studies showing that taste receptor gene variants can vary significantly across populations and may be subject to positive selection due to their roles in nutrient sensing and metabolic regulation[52–55]. In particular, the LBZ cohort exhibited a highly homogeneous profile in the *TAS1R3* locus, with nearly all individuals carrying the CC genotype and C allele, and no TT genotypes. This contrasts with the CYME cohort, which displays greater genetic diversity. *TAS1R3* encodes a subunit of the sweet and umami taste receptors and is known to be highly conserved across populations[56]. Variants in *TAS1R3* have been associated with differences in sweet taste sensitivity and dietary sugar intake. Subjects carrying the heterozygous or homozygous genotype for the T allele had a lower sweet sensitivity than those with two C alleles[22,23,57]. Although the *TAS1R3* SNP was not correlated with BMI in this study, based on previous research that has associated the C allele with higher sweet taste sensitivity and lower sugar intake, the near-fixation of the CC genotype in the LBZ cohort may reflect a genetic trait protective against energy imbalance due a high caloric intake[58]. However, fortuitous recruitment cannot be excluded in a cross-sectional study. Conversely, no

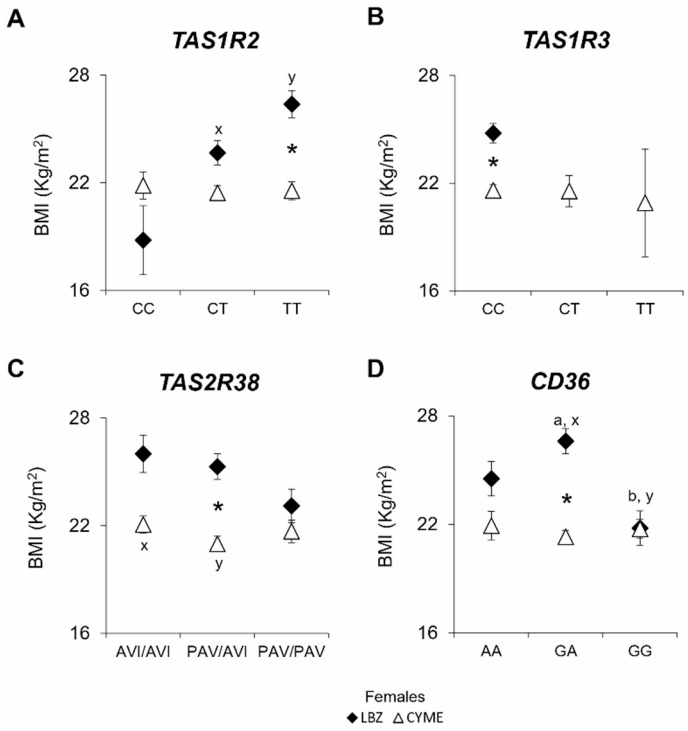

Fig. 4. Mean values ± SEM of body mass index (BMI) according to polymorphisms in the *TAS1R2*, *TAS1R3*, *TAS2R38*, and *CD36* genes in females of the Longevity Blue Zone cohort (LBZ) ($n = 60$) and the Cagliari young, middle-aged, and elderly cohort (CYME) ($n = 111$). * Indicates a significant difference between the corresponding genotypes of participants of the LBZ and CYME cohorts ($p < 0.011$; Holm's test, subsequent Factorial General Linear Model HC3). Different letters denote significant differences, a and b from Holm's test after Factorial General Linear Model HC3 ($p = 0.04$), while x and y from Dwass-Steel-Critchlow-Fligner test, after Kruskal-Wallis' test ($p < 0.05$).

significant differences were found in the *TAS1R2* genotype distributions or allele frequencies, suggesting a minor role for this gene in differentiating the two populations.

The TAS2R38 receptor, and its genetic variants, have been extensively studied for their roles in the taste perception of the bitter compound 6-*n*-propylthiouracil (PROP), which has been considered as an oral marker for interindividual differences in general taste perception, general food preferences and dietary behaviour, variations in body mass composition and other non-tasting physio-pathological mechanisms, including longevity[1,2,8,25–29]. The molecular analysis of the *TAS2R38* SNPs showed significant differences in diplotype distributions and haplotype frequencies between the two cohorts. Consistent with our previous work[51], the LBZ cohort exhibited a significantly higher frequency of the PAV/PAV diplotype and PAV haplotype, both of which have been associated with physiological processes[59–61], an efficient immune response[8,62–67], and a favourable body composition[1,68,69]. In contrast, the CYME cohort had a higher frequency of the AVI/AVI diplotype and AVI haplotype, which have been associated with a higher risk of developing various dysfunctions and diseases[59–65,70–72]. These differences, which are not surprising in a cohort with exceptional longevity, also suggest that the genetics of taste perception may diverge among populations with distinct lifestyles and longevity profiles. The higher prevalence of the PAV variant in the LBZ cohort may reflect dietary adaptations or preferences that contribute to healthier aging. Differently from a recent meta-analysis that reported inconsistent associations between *TAS2R38* and longevity across populations[73], our findings support population-specific effects possibly influenced by lifestyle and environmental context.

The analysis at the *CD36* locus (which encodes a fatty acid translocase involved in fat perception and lipid metabolism[40,45] showed significant differences in genotype distribution between cohorts. The LBZ cohort had a higher frequency of the AA genotype, while the CYME cohort had a higher frequency of the GG genotype. These differences could indicate variations in fat taste sensitivity and lipid metabolism between cohorts, potentially contributing to dietary habits and metabolic health. The higher frequency of the A allele in the LBZ cohort might be associated with a more efficient fat metabolism or an altered preference for fat, which could contribute to the lower prevalence of obesity and metabolic disorders observed in long-lived populations[74].

These results indicate that the genetic profiles of the LBZ and CYME cohorts differ significantly at loci associated with taste perception and fat metabolism, highlighting a near-fixation of the *TAS1R3* CC genotype, a higher prevalence of the *TAS2R38* PAV/PAV diplotype and the *CD36* AA genotype in the LBZ. These patterns may reflect adaptive genetic traits, long-standing dietary patterns, and environmental pressures that contribute to phenotypic profiles associated with exceptional longevity and metabolic health. Further studies integrating

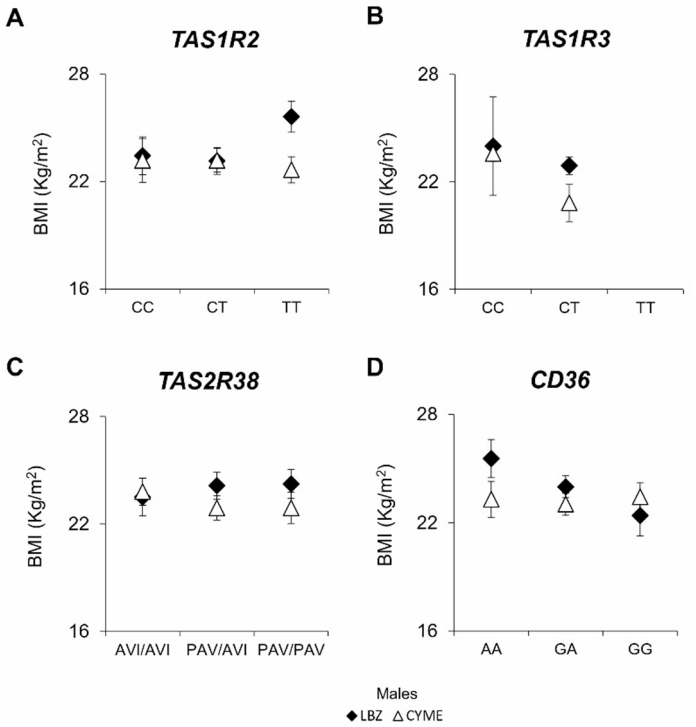

Fig. 5. Mean values ± SEM of body mass index (BMI) according to polymorphisms in the *TAS1R2*, *TAS1R3*, *TAS2R38*, and *CD36* genes in males of the two cohorts (LBZ, $n = 54$; CYME, $n = 49$).

dietary data, metabolic markers, and longitudinal health outcomes would help clarify the functional implications of these genetic variations.

Interestingly, significant differences between the two cohorts in the *TAS1R3* genotype distribution were observed only in females, but not in males. Instead, no significant differences were observed in the *TAS1R2*, *TAS2R38*, and *CD36* genes between the two cohorts in females and males, suggesting that the genetic differences observed for these three genes are population-wide rather than sex-specific.

BMI was significantly higher in the LBZ cohort, particularly in females, compared to the CYME cohort, despite LBZ being a longevity hotspot. Despite having a higher BMI, LBZ individuals are known for their exceptional longevity. This result, which appears to be a paradox, suggests that BMI alone is not a sufficient predictor of health span, and that genetic resilience, metabolic flexibility, and lifestyle factors may attenuate the effects of adiposity[74]. These findings challenge conventional BMI thresholds and support a more nuanced understanding of metabolic health, particularly in aging populations. In addition, the higher BMI we found in the LBZ cohort agrees with data showing exceptional longevity associated with modest overweight, suggesting that hypocaloric diets should not be recommended for mildly overweight elderly patients[74]. In addition, the analysis performed within each cohort showed variation in BMI related to sex only in the CYME cohort.

The associations that we found between taste receptor gene SNPs and BMI were cohort-specific, suggesting that gene–environment interactions play a critical role in modulating metabolic outcomes. A significant interaction between *TAS1R2* genotype and cohort (LBZ vs. CYME) was observed for BMI values, indicating that the effect of *TAS1R2* variants on BMI differs depending on the population context. In the LBZ cohort, the *TAS1R2* TT genotype was consistently associated with higher BMI. This supports the hypothesis that individuals with this genotype, particularly females, may have reduced sweet taste sensitivity, leading to increased sugar consumption to achieve the same hedonic response, as previously reported in other populations[24]. In contrast, no BMI differences related to *TAS1R2* genotype in CYME were found.

Although the BMI of the females with the CC genotype in the *TAS1R3* (with 100% frequency in the LBZ cohort and 88% in the CYME cohort), was significantly higher than that of CC females of the CYME cohort, the very low variability in the *TAS1R3* that we observed in both cohorts limits the possibility of detecting a significant effect on BMI.

Interestingly, while *TAS2R38* diplotypes did not show important BMI differences within cohorts, LBZ individuals had a higher BMI across all diplotypes compared to CYME participants, particularly in heterozygous and female participants. This may reflect broader population-level differences, potentially mediated by dietary preferences or extra-oral functions of the receptor, such as its role in gut motility and immune modulation[75,76]. These results suggest that *TAS2R38* variations might influence BMI in a genotype- and environment-specific manner, particularly in heterozygous females.

From our findings, the *CD36* gene emerged as a particularly important modulator of BMI in the LBZ cohort. A significant interaction between *CD36* genotype and cohort (LBZ vs. CYME) was observed for BMI values, indicating that the effect of *CD36* variants on BMI is context-dependent. In the LBZ cohort, the GG genotype,

which is associated with enhanced fat taste sensitivity, efficient lipid metabolism, and reduced fat intake[38,45,77,78], was associated with lower BMI compared to those with the GA genotype, particularly in females. Only LBZ females with the GA genotype had higher BMI than its CYME counterpart, suggesting that this genotype may be more metabolically disadvantageous in the LBZ environment in females. Interestingly, no BMI differences were observed among *CD36* genotypes in the CYME cohort, indicating that the GG genotype may confer a protective effect, likely due to lifestyle or dietary factors unique to the LBZ population. These findings are consistent with the known roles of *CD36* in fatty acid uptake, energy homeostasis, and inflammation, and suggest that genetic variation in fat-sensing pathways may contribute to the metabolic resilience observed in long-lived populations[74]. Furthermore, the role of *CD36* in cephalic phase responses and lipid sensing may explain the observed BMI differences, especially in a population like the LBZ, where traditional diets and metabolic adaptations may amplify genetic effects.

These results suggest that these genetic variants may influence BMI through alterations in taste perception, food preferences, and metabolism in the LBZ cohort. Unfortunately, due to practical limitations, in this work, no data is presented on the participants' diet, caloric intake, physical activity, or other lifestyle factors. Therefore, it is correct to state that without these additional measures, the causal pathway linking taste receptor genotypes to BMI remains hypothetical. Future studies will focus on verifying our speculative hypothesis. Although relying exclusively on BMI limits the interpretation of our results, it is necessary to highlight that BMI is easy to measure and could be considered a proxy for metabolic health, especially in older adults. Epidemiological and interventional data consistently link higher BMI to insulin resistance, inflammation, and chronic disease risks[79], and some reports suggested that gene-by-age interactions influence known BMI loci, making cross-sectional findings inconsistent over the lifespan[57,80].

Our results also showed sex-specific genetic effects. Remarkably, we found BMI differences related to genotypes only in female participants, while no differences were found in males. This could reflect hormonal influences on taste receptor expression or inherent sex -related differences in energy storage and metabolism, consistent with previous findings obtained in both human and animal models[81,82]. Notably, despite a higher BMI, LBZ individuals, particularly those with metabolically favorable genotypes, may benefit from protective genetic profiles that mitigate the adverse effects of adiposity, supporting the concept of "healthy obesity" in the context of exceptional longevity. These results emphasize the need to consider sex as a biological variable in genetic and nutritional research. However, because BMI does not distinguish fat mass from lean or water mass, higher BMI in the LBZ cohort may not directly correspond to higher adiposity and could instead reflect altered body composition typical of advanced age.

We do not rule out causal links between the SNPs, BMI, gender, and longevity, or other factors that contribute to phenotypic profiles associated with longevity that could not be measured. Therefore, the observed genetic differences could reflect population-level genetic structures and lifestyle interactions rather than direct determinants of longevity.

Conclusions

This work contributes to the understanding of taste receptors as complex and multifunctional chemosensors that integrate peripheral chemosensory signals with central neural circuits. In addition to mediating gustatory perception, taste receptors influence feeding behaviors, systemic metabolic regulation, and phenotype profiles potentially associated with longevity. By analyzing polymorphisms in *TAS1R2*, *TAS1R3*, *TAS2R38*, and *CD36* genes and their associations with BMI and gender in two distinct Sardinian populations, our results revealed that specific genetic variants may interact with environmental and lifestyle factors to influence BMI in a longevity context, with notable sex-specific effects. In the LBZ cohort, where longevity and metabolic health are prominent, specific genotypes, such as *TAS1R3* CC, *TAS2R38* PAV/PAV, and *CD36* AA, may contribute to favorable phenotypes, whereas these genotypes have no effect in a more heterogeneous urban population like CYME. However, the high genetic homogeneity of the LBZ cohort, while offering a unique opportunity to study longevity-associated traits, may limit the generalizability of these findings to more heterogeneous populations. These insights could inform personalized nutrition and public health strategies tailored to genetic background and environmental context.

Data availability

The dataset generated during the current study is available in the European Genome-Phenome Archive repository. The study and dataset are available at the following link: https://ega-archive.org/studies/EGAS00001008403. Request for data access referred directly to Data Access Committee: https://ega-archive.org/dacs/EGAC00001003627.

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Author contributions

Conceptualization, I.T.B. and G.M.P.; methodology, M.M. and A.E.; formal analysis, M.M.; data curation, M.M. and I.T.B.; writing—original draft preparation, I.T.B.; writing—review and editing, M.M., A.E. and G.M.P.; funding acquisition, M.M. All authors have read and agreed to the published version of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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