

Sweet Taste Perception is Associated with Body Mass Index at the Phenotypic and Genotypic Level

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Investigations on the relationship between sweet taste perception and body mass index (BMI) have been inconclusive. Here, we report a longitudinal analysis using a genetically informative sample of 1,576 adolescent Australian twins to explore the relationship between BMI and sweet taste. First, we estimated the phenotypic correlations between perception scores for four different sweet compounds (glucose, fructose, neohesperidine dihydrochalcone (NHDC), and aspartame) and BMI. Then, we computed the association between adolescent taste perception and BMI in early adulthood (reported 9 years later). Finally, we used twin modeling and polygenic risk prediction analysis to investigate the genetic overlap between BMI and sweet taste perception. Our findings revealed that BMI in early adulthood was significantly associated with each of the sweet perception scores, with the strongest correlation observed in aspartame with $r = 0.09$ ($p = .007$). However, only limited evidence of association was observed between sweet taste perception and BMI that was measured at the same time (in adolescence), with the strongest evidence of association observed for glucose with a correlation coefficient of $r = 0.06$ ($p = .029$) and for aspartame with $r = 0.06$ ($p = .035$). We found a significant ($p < .05$) genetic correlation between glucose and NHDC perception and BMI. Our analyses suggest that sweet taste perception in adolescence can be a potential indicator of BMI in early adulthood. This association is further supported by evidence of genetic overlap between the traits, suggesting that some BMI genes may be acting through biological pathways of taste perception.

■ **Keywords:** taste perception, BMI, sweetness, longitudinal analysis, genetic risk, twin study

A high body mass index (BMI) is associated with increased risk for metabolic, cardiovascular, and respiratory diseases, and several types of cancer, such as breast and colorectal cancers (Solomon & Manson, 1997). Obesity can arise as a result of genetic predisposition (Speliotes et al., 2010), metabolic problems (Wisse, 2004), hormonal changes (Björntorp, 1995), physical activity (Fox & Hillsdon, 2007), and/or eating behavior (Wardle, 2007). The latter is heavily influenced by cognitive factors that allow individuals to assign a subjective reward value to specific kinds of foods (Breslin & Spector, 2008). One of these (cognitive) factors is taste perception, which is the sensory impression of food on the tongue.

Among the five basic human taste qualities (i.e., sweet, bitter, sour, salty, and umami), sweetness is generally considered pleasant at moderate intensities and favored by most individuals (Moskowitz et al., 1974). Sweetness is detected by sweet taste receptors in the oral cavity, which send

a signal to the brain where taste sensation is elicited (Rolls, 2015). Sweet taste receptors are also expressed along the digestive system, including the pancreas, bladder, gastrointestinal, and adipose tissues (Laffitte et al., 2014), where they do not evoke sweet sensation but are involved in many physiological functions, including glucose homeostasis (Laffitte et al., 2014), insulin secretion (Kyriazis et al., 2014), and adipogenesis (Masubuchi et al., 2013).

Earlier studies investigating the association between BMI and sweet taste perception have presented inconsis-

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tent findings. Some studies reported that obese individuals perceive the same candy or sucrose solution as less sweet than their non-obese counterparts (Bartoshuk et al., 2006; Overberg et al., 2012). However, a handful of other studies did not find direct association between BMI and sweet taste perception or sensitivity (Anderson, 1995; Grinker, 1978; Joseph et al., 2016).

Twin studies have reported that individual differences in both sweet taste perception and BMI are partially attributable to genetic variation ($h^2 = 0.30$ – 0.34 for sweet taste perception; Hwang et al., 2015; $h^2 = 0.47$ – 0.90 for BMI; Elks et al., 2012). Recent genome-wide association studies (GWAS) of BMI identified an enrichment of associated genetic variants involved in the central nervous system (CNS) that might be linked to sweet taste perception. These include genetic variants in loci associated with insulin, glucose, and adipogenesis regulation (Locke et al., 2015), as well as energy balance, regulation of appetite, and food intake preferences (Speliotes et al., 2010). However, it is still unclear whether some genes are jointly responsible for both the regulation of sweet taste perception and BMI.

In the present study, we used longitudinal and genetic data from a sample of 1,576 young Australian twins to investigate the relationship between sweet taste and BMI. We first examined the association between sweet taste perception and BMI, both measured during adolescence. Next, we examined whether adolescent taste perception predicted BMI at a later time in life (9 years later). Finally, we assessed the genetic overlap between BMI and sweet perception using twin modeling and polygenic risk scores approaches to determine whether the association between the two traits was due to shared genetic components.

Materials and Methods

Data

Participants were adolescent and young adult twins and their singleton siblings from the Brisbane Adolescent Twin Study (Wright & Martin, 2004), also referred to as the Brisbane Longitudinal Twin Study (BLTS). They completed a taste test at around 15.8 ± 2.6 years old and had their BMI measured at the clinic (two thirds) or self-reported (one third). They reported their BMI again approximately 9 years later as part of a follow-up study. Descriptive statistics for the participants are displayed in Table 1. The study was conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all adult participants and from parents for participants under age of 18 years. Approval for this study was obtained from the Human Research Ethics Committee of QIMR Berghofer Medical Research Institute.

The taste test included 10 different solutions, of which five were bitter, four were sweet (described below), and one was neutral (i.e., water, as control; Hwang et al., 2015). The four sweet solutions included two sugars (0.60 M glucose

TABLE 1
Baseline Characteristics of Participants According to Taste Perception

	Early age (12–26)	Later age (18–38)
N of participants	1,576	998
MZ pairs	205	101
DZ pairs	395	197
Siblings	376	402
Age (years)	15.8 ± 2.6	25.2 ± 4
Female	53.5%	61.1%
Height (cm)	162.7 ± 8.2	171.8 ± 9.7
Weight (kg)	54.9 ± 11.6	70.9 ± 15.1
BMI (kg/m ²)	20.6 ± 3.5	23.8 ± 4.0
Intensity rating		
Glucose	31.2 ± 15.7	
Fructose	31.9 ± 17.6	
NHDC	34.4 ± 18.6	
Aspartame	26.3 ± 16.0	
gSweet	31.1 ± 15.0	

Note: Data are presented as mean \pm standard deviation. Intensity ratings are millimeter on a labeled magnitude scale. NHDC = neohesperidine dihydrochalcone. gSweet = general sweet intensity.

and 0.30 M fructose) and two non-caloric sweeteners (8.0×10^{-5} M NHDC and 1.4×10^{-3} M aspartame). Each solution and the water control were presented twice (i.e., total of 20 solutions) in color-coded 2 mL polypropylene microcentrifuge tubes with flip tops. The first 10 tubes contained one presentation of each compound plus the water control and the next 10 contained the same solutions in a different order. The order of all 20 tubes was the same for all participants. Participants were instructed to: (1) open the tube, swish the solution in the mouth for 5 s, and spit out; (2) rate the perceived intensity of the solution; (3) rinse the mouth out four times with tap water; and (4) repeat steps 1 to 4 for each tube. Perceived intensity was rated on a general labeled magnitude scale (gLMS; Green et al., 1993) with labels of no sensation (0 mm), barely detectable (2 mm), weak (7 mm), moderate (20 mm), strong (40 mm), very strong (61 mm), and strongest imaginable (114 mm). Participants marked a line on the scale where they thought the sensation fitted. The mean intensity ratings from the duplicate presentations were used in this study. As our previous study showed that a common genetic component accounted for most of the variance in intensity scores of each sweetener (71% for glucose, 77% for fructose, 64% for NHDC, and 59% for aspartame; Hwang et al., 2015), here we calculated a general sweet intensity rating (gSweet) using the weighted mean of intensity ratings of the four sweeteners. Intensity scores were square-root transformed to approximate the normal distribution.

Genotyping Quality Control

Participants were genotyped using the Illumina-Human610W-Quad bead chip. Standard quality control was performed on genotyped variants: single nucleotide polymorphism (SNP) with call rate <0.95 , deviation from Hardy–Weinberg equilibrium (HWE) p value $<10^{-6}$, or

minor allele frequency (MAF) <0.01 were excluded (Medland et al., 2009). To control for population stratification, we excluded individuals which lay beyond six standard deviations from the first two genotypic principal components centroid of the 1,000 Genome European descent populations. Imputation was carried out based on the August 4, 2010 version of the publicly released 1,000 Genomes Project European genotypes using MACH (Li et al., 2010). We implemented a filtering threshold of 0.3 on the r^2 metric for each of the SNPs in line with recommended practice in MACH, and a MAF >0.01 .

Twin Modeling

Phenotypic and genetic correlations between measures of taste intensity and BMI were estimated using bivariate variance components modeling in the structural equation software package Mx, which utilizes maximum likelihood estimation procedures (Neale & Cardon, 1992). Variance components modeling partitions the variation of a trait into genetic and environmental sources by leveraging the degree of genetic differences between monozygotic twins (MZ; share all genes) and dizygotic twins (DZ; share half of genes) pairs. These known differences allow the estimation of additive genetic (A), common environment (C), and unique environment (E, which also includes experimental error and random noise) parameters in a variance components model (ACE). The comparative fit of models was assessed by calculating the Log-likelihood Ratio Test (LRT) statistics (Wilks, 1938). All the models were adjusted for sex and the participants' corresponding age.

Polygenic Risk Scores

To complement the genetic correlation estimates, we also carried out a polygenic risk prediction analysis by computing polygenic risk scores (PGRS) of our trait of interest (in this case, BMI) and then using this genetic profile to predict another trait (i.e., taste perception) (International Schizophrenia Consortium et al., 2009). In short, the PGRS describes predicted phenotypic values that are genetically derived. It is computed by aggregating the estimated effects of many variants multiplied by the number of observed effect allele into a single score for each individual, to mimic a genetic proxy (profile scoring) for the underlying phenotypic trait. In our analysis, we used the association estimates from the latest GWAS meta-analysis summary statistics of BMI from the Genetic Investigation of Anthropometric Traits (GIANT) consortium including up to 339,225 participants (Locke et al., 2015). We extracted effect estimates of the SNPs that were computed based on participants ($n = 322,154$) of European ancestry only. This approach could yield increased power to detect genetic correlations due to the large sample size of the GIANT analysis. Given that the samples in this study were also part of the GIANT BMI GWAS, these GWAS estimates were

recomputed after removing the overlapping samples. Next, we selected variants to compute the PGRS based on 10 different p -value thresholds ($<.00001$, $.001$, $.01$, $.05$, $.1$, $.2$, $.3$, $.4$, $.5$, $.75$). Linkage disequilibrium (LD) clumping was performed to remove redundant SNPs ($r^2 > 0.2$) within a 500 kb window for each of the variants in the PGRS. The computation of PGRS and LD clumping were carried out using PLINK (Chang et al., 2015) by multiplying the number copies of each effect allele with the reported magnitude of association and summing over all the relevant SNPs. Ambiguous SNPs with complementary strands (A/T, G/C) were removed. Specifically, the number of independent genetic variants for each of the thresholds was 2,071, 8,403, 27,638, 79,871, 136,195, 237,876, 333,747, 424,237, and 511,295 SNPs. Finally, we converted each of the PGRS to standard z scores ($\mu = 0$ and $\sigma = 1$) and tested their association with the different sweet taste perception scores using a linear mixed model, fitting the first three principal components derived from the genotypes, age, and sex as covariates, and the family ID as random effect.

The polygenic risk prediction approach carries a high multiple testing burden given that each of the PGRS is tested for their association with sweet taste perception. However, given that the different sweet taste perception are correlated between each other and that each of the PGRS are highly redundant, we estimated the number of independent tests using a matrix spectral decomposition algorithm (Nyholt, 2004). This algorithm estimates the equivalent number of independent variables from a correlation matrix, by examining the ratio of observed eigenvalue variance to its theoretical maximum. Using this, we estimated the number of independent test to be 7, thus our bonferroni-corrected significance threshold was $p = .05/7 = .007$.

Results

We investigated whether sweet taste perception in adolescence was predictive of BMI in adolescence (15.8 ± 2.6 years old) and early adulthood (25.2 ± 4.0 years old). In our regression analyses, we found an association between the perceived intensity of sweetness and BMI at the same age in adolescence, with glucose and aspartame showing significant correlations of $r = 0.056$ ($p = .035$) and $r = 0.058$ ($p = .029$), respectively (Table 2). When investigating whether sweet taste perception was predictive of early adulthood BMI, we found stronger associations with all sweet perception scores ranging from $r = 0.07$ for fructose to $r = 0.09$ for aspartame (Table 2). Intensity ratings of water were used as a negative control, and, as expected, they were not associated with BMI.

Using twin modeling, we found a positive genetic correlation between perceived intensity of all the tastes and BMI at same and later age. However, only the perceived intensity of glucose showed a significant association (same age: $r_g = 0.13$, $p = .03$; later age: $r_g = 0.21$, $p = .017$; Table 2). The

TABLE 2
Summary of Phenotypic and Genetic Correlations Between Taste Intensity Ratings and BMI

Phenotypic correlations	BMI same age		BMI later age	
	$r_p \pm SE$	p	$r_p \pm SE$	p
gSweet	.05 ± .03	.059	.08 ± .03	.012
Glucose	.06 ± .03	.035	.08 ± .03	.020
Fructose	.04 ± .03	.196	.07 ± .03	.034
NHDC	.04 ± .03	.122	.07 ± .03	.025
Aspartame	.06 ± .03	.029	.09 ± .03	.007
H ₂ O	-.02 ± .03	.579	-.03 ± .03	.406
Genetic correlations	$r_g \pm SE$	p	$r_g \pm SE$	p
gSweet	.10 ± .06	.092	.16 ± .08	.053
Glucose	.13 ± .06	.030	.21 ± .08	.017
Fructose	.08 ± .06	.173	.14 ± .08	.150
NHDC	.07 ± .06	.260	.10 ± .08	.267
Aspartame	.12 ± .06	.077	.18 ± .08	.090
H ₂ O	.00 ± .06	.955	-.12 ± .08	.172

Note: All values are calculated using bivariate variance components modeling in the structural equation software package Mx. Genetic correlations are calculated from bivariate AE model as C components can be dropped without worsening the model fit ($p = .28 - .87$ for each trait). gSweet = general sweet intensity. NHDC = neohesperidine dihydrochalcone. Estimates in bold are statistically different from zero.

environmental correlations were not significantly different from zero (data not shown).

To further assess the genetic overlap between BMI and sweet taste perception, we carried out a polygenic risk prediction analysis. Based on the GWAS of BMI from the GIANT consortium, we computed individual BMI PGRS, including a different number of variants based on p -value thresholds, and tested their association with sweet taste perception and BMI itself. As anticipated, each of the PGRS were strongly associated with BMI (e.g., the PGRS based on SNPs with a p value $< .2$ in the GIANT GWAS had an $r = 0.2$; $p < 1.0 \times 10^{-15}$; Figure S1). Through this approach, we found a significant genetic correlation between BMI and NHDC (Figure 1) but not with glucose, as with the twin modeling analysis.

Discussion

We found that the perceived intensity of sweet solutions measured during adolescence was positively associated with BMI measured at the same age, and that the association was stronger with BMI measured 9 years later. We also found evidence of a positive genetic correlation of glucose and NHDC with BMI.

In contrast to findings from previous cross-sectional studies, which showed negative associations (Bartoshuk et al., 2006; Overberg et al., 2012) or no associations between sweet taste perception and BMI (Anderson, 1995; Grinker, 1978; Joseph et al., 2016), we found a subtle but positive association with BMI measured at the same age. The differences may result from variation in study designs and sample demographics. Bartoshuk et al. (2006) reported a negative association between perceived sweetness of a candy and BMI in a large sample of college students

($n = 3,700$), whereas the taste measures in our study were adolescents' intensity ratings of sweet solutions. Overberg et al. (2012) collected data from adolescents as well as children (age ranged from 6 to 18 years) and they reported a negative association by dichotomizing participants into either obese (BMI > 97th percentile) or normal weight (BMI < 90th percentile). In our study, BMI was defined as a continuous variable, which provided us more robust estimates with respect to the magnitude and direction of the correlation. In addition, studies (Anderson, 1995; Grinker, 1978; Joseph et al., 2016) that showed no association typically have relatively small sample sizes ($n < 100$), which suggests that larger samples are necessary to detect a significant association.

Our finding that sweet taste perception has a higher association with BMI at a later age (as compared to BMI obtained at the same time of taste perception measurement) yields several possible explanations. The first could be the cumulative effect of sweet preferences. Individual differences in sweet perception may gradually contribute to a bigger variation in preferences for sweetness, which directly influence sweet food consumption, and further lead to a bigger variation in BMI later in life. Second, during adolescence, diet preferences are strongly influenced by cultural practice and familial influences (Scaglioni et al., 2008), rather than the true taste preferences. Also, BMI at a young age is susceptible to body and hormonal changes rather than sweet food consumption, compared to that in a later age when body mass change becomes more stable.

Our two genetic approaches independently identified significant correlations between BMI and sweet taste perception; one with glucose and the other with NHDC. Nevertheless, these correlations were all positive regardless of taste stimuli and the underlying modeling approaches. In the context of our study, the twin modeling and PGRS analyses complement each other in the sense that the PGRS models the cross-trait genetic overlap based on common genetic variants, while conventional twin models incorporate a larger spectrum of information, including undiscovered causal SNPs and rare variants, in determining heritability.

Our genetic overlap observation is consistent with the biological literature. Simple carbohydrates (sugars) as well as complex carbohydrates (oligosaccharides and polysaccharides) are the main source of energy for the human body, and over-consumption of these sweet compounds can result in weight gain as excess energy intake is transformed and stored as body fat (Aarsland et al., 1997). While the GIANT consortium's analysis identified several BMI-associated genes with putative functions in the brain, some of those genes could be responsible for sweet taste perception, such that genetic variants might affect BMI by influencing dietary behaviors. Similarly, there is some evidence that individual differences in taste responses are due to differences in signal processing in the CNS (Green &

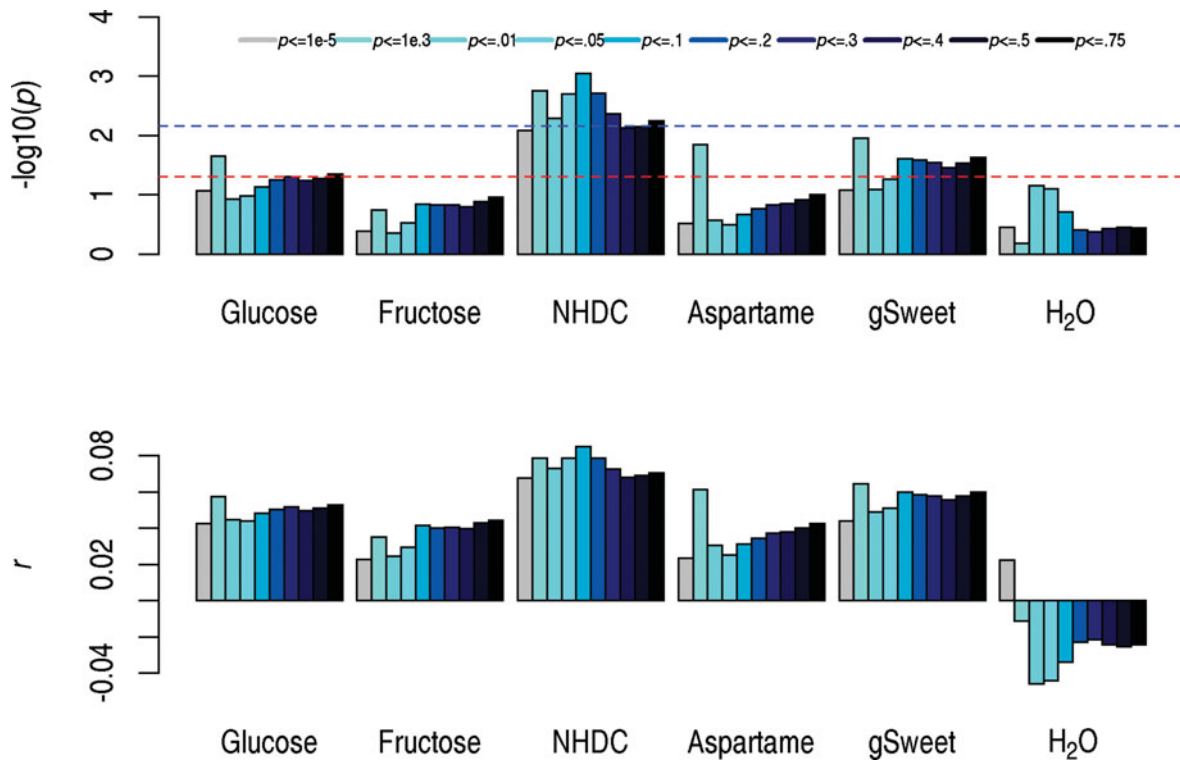


FIGURE 1

(Colour online) Results of the polygenic risk prediction. Note: The bars correspond to the association between each of the polygenic risk scores (PGRS) of BMI computed based on the specified p -value thresholds ($<.00001$, $.001$, $.01$, $.05$, $.1$, $.2$, 0.3 , 0.4 , 0.5 , 0.75) and the different sweet taste intensity scores. p values of the association are shown in the logarithmic scale in the upper part of the figure while spearman correlations (r) are shown in the bottom part. Red dotted line shows the nominal p -value ($.05$) on $-\log_{10}$ scale. Blue dotted line shows the significance threshold after accounting for multiple testing. As an example, the first bar should be interpreted as the correlation between a genetically predicted BMI value based on SNPs with a p value $<1.0 \times 10^{-5}$ in the GIANT BMI GWAS and glucose. gSweet = general sweet intensity. NHDC = neohesperidine dihydrochalcone.

George, 2004). Other pathways may also contribute to explaining the genetic overlap between sweet perception and BMI. For example, the neurobiology of food reward might help explain why the use of non-caloric sweeteners can result in weight gain without affecting calorie intake (Heid et al., 2010). Lastly, apart from the neurological and other possible mechanisms explained above, sweet taste receptors in the mouth or guts can also control metabolism through various mechanisms, such as influencing insulin secretion (Kyriazis et al., 2014; Laffitte et al., 2014). Regardless of the scenario, sweet taste perception appears to play an important role in regulating BMI. However, in this study, we were not able to prove the directionality of this association.

The strengths of our study included that the twin data allowed us to estimate the genetic and environmental contributions to the correlation between sweet taste and BMI. Also, the PGRS of BMI derived from common variants provided further support for the genetic correlation between the two and made our findings more robust. Lastly, the longitudinal data for BMI measured 9 years apart allowed us to

test the long-term effects of sweet taste perception on BMI. We must also acknowledge some limitations; for example, the effective sample size ($N_{\text{same age}} = 1,576$ and $N_{\text{later age}} = 998$) could be considered small for a twin study, and the use of self-reported BMI might potentially introduce some modest bias, as it has been pointed out that participants tend to slightly overestimate their height and underestimate their weight (Reed & Price, 1998).

In conclusion, we showed that adolescent sweet taste perception in adolescence is associated with BMI at both adolescence and early adulthood, and that this association is partly explained through their genetic overlap. Identification of the shared genetic architecture could improve our understanding of the genetic pathways underlying both sweet taste perception and weight gain. As we obtain more study samples in the future, we will use the SNPs that strongly associate with sweet taste perception as genetic instruments to make causal inference (i.e., Mendelian randomization studies) about the effect of sweet taste perception on weight gain and diet-related disorders, which may provide insights into their prevention and treatment.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Supplementary Material

To view supplementary material for this article, please visit <http://dx.doi.org/10.1017/thg.2016.60>.

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