UNIVERSITÀ DEGLI STUDI DI TRIESTE

XXXII CICLO DEL DOTTORATO DI RICERCA IN SCIENZE DELLA RIPRODUZIONE E DELLO SVILUPPO

STUDY OF FOOD LIKINGS: GENETIC AND NON-GENETIC INFLUENCES AND RELATIONSHIP WITH HEALTH

Settore scientifico-disciplinare: **MED/03 GENETICA MEDICA**

DOTTORANDA
MARIA PINA CONCAS

COORDINATORE
PROF. PAOLO GASPARINI

SUPERVISORE DI TESI
PROF. PAOLO GASPARINI

ANNO ACCADEMICO 2018/2019

ABSTRACT

Food liking is influenced by a large number of factors including physiological, nutritional, environmental, socio-cultural and genetic ones. Previous studies highlighted that survey-reported food liking may reflect habitual consumption, being simpler to collect and report compared to intake, and may be associated with risk factors for diet-related diseases. Obtaining a better knowledge of genetic and non-genetic factors affecting food liking and the implication of food liking on diet-related diseases, for example obesity or hypertension, is of considerable public health importance.

This work aims to study the genetic and non-genetic factors influencing food liking and to investigate the relationship between food liking and health status.

The study was carried out thanks to the availability of an extensive database of about 3000 individuals coming from three regions of Italy.

Liking for approximately 100 different foods and beverages was evaluated on a 9-point hedonic scale. Food liking was analysed in relationship with personal and lifestyle information, clinical parameters, eating behaviour phenotypes, sensory and genetic data.

The following results were achieved:

- food liking was associated with non-genetic factors, comprising gender, age, educational level, physical activity and eating behaviour. For example, men (compared to women) reported a significantly higher liking for alcoholic beverages, fish and meat and a lower liking for vegetables, fruit and sweet foods; moreover, a higher liking for all foods was associated with higher self-reported willingness to try unfamiliar foods (food adventurousness);
- in a complex interplay with age, sex and educational level, sensory deficits were a risk factor for a decreased liking for vegetables and a reduced food adventurousness;
- a new candidate gene (*CAV1*) for eating disinhibition and food liking was found, through Genome-Wide Association Study and replication analysis. This gene, although not associated in our sample with obesity measures, has been largely investigated for metabolic disorders, and animal models confirmed a link with obesity;

- food liking measures were associated with adiposity, serum lipids, fasting glucose and systolic blood pressure. For instance, greater adiposity was associated with a higher liking for meat and cheeses, while higher HDL-cholesterol was associated with higher vegetables liking;
- through polygenic risk score analysis, a link was found between obesity measures and genetic score obtained using variants previously related to liking for different vegetables.

In conclusion, this work highlights the importance to evaluate food liking in combination with other factors and suggests the possible use of food liking in nutritional studies as a proxy of intake measures. Overall, these results represent a starting point to understand better the very complex interplay existing between food liking, associated factors and diet-related phenotypes.

SOMMARIO

Le preferenze alimentari sono influenzate da un gran numero di variabili come: fattori fisiologici, nutrizionali, ambientali, socioculturali e genetici. Studi precedenti mostrano che le preferenze alimentari ottenute tramite questionari, sono più semplici da rilevare rispetto ai consumi; inoltre possono rispecchiare i consumi abituali e sono associate a fattori di rischio per malattie legate alla dieta. Il conseguimento di una migliore conoscenza dei fattori che influenzano le preferenze alimentari e delle implicazioni delle stesse sulle patologie legate all'alimentazione, come per esempio obesità e ipertensione, è di notevole importanza per la salute pubblica.

Questo lavoro ha lo scopo di studiare i fattori genetici e non genetici che influenzano le preferenze alimentari e di indagare le relazioni tra preferenze alimentari e stato di salute.

Lo studio è stato condotto grazie alla disponibilità di un vasto database con informazioni su circa 3000 persone provenienti da tre regioni d'Italia. Le preferenze alimentari sono state ottenute tramite la somministrazione di un questionario e valutate in una scala edonica a nove punti per circa un centinaio di cibi e bevande diverse. Informazioni personali, sullo stile di vita e sul comportamento alimentare, parametri clinici, dati sensoriali e genetici sono stati valutati in relazione alle preferenze.

Sono stati raggiunti i seguenti risultati:

- le preferenze alimentari sono associate a diversi fattori non genetici, quali sesso, età, livello di istruzione, attività fisica e tratti del comportamento alimentare. Ad esempio, gli uomini (rispetto alle donne) hanno riportato una preferenza significativamente più elevata per bevande alcoliche, pesce e carne e una preferenza meno elevata per verdure, frutta e cibi dolci; sempre a titolo di esempio, una più alta preferenza per tutti gli alimenti è stata associata a una maggiore volontà di provare cibi non familiari;
- in una complessa interazione con età, sesso e livello di istruzione, i deficit sensoriali sono risultati fattore di rischio per una diminuzione della preferenza per le verdure e per la disposizione a provare cibi non familiari;
- attraverso uno studio di associazione su tutto il genoma, un nuovo gene candidato (*CAV1*) è stato trovato associato alla disinibizione alimentare e alle preferenze. Questo gene, sebbene nel nostro campione non sia associato a misure di obesità,

è stato ampiamente studiato riguardo a disordini metabolici, e, tramite modelli animali è stato evidenziato un legame con l'obesità;

- sono state trovate relazioni tra preferenze alimentari e tratti metabolici come adiposità, lipidi, glucosio e pressione arteriosa sistolica. Per esempio, una maggiore adiposità è associata a una maggiore preferenza per carne e formaggi, mentre valori più alti di colesterolo HDL sono associati a una maggiore preferenza per le verdure;
- mediante l'analisi del "polygenic risk score", è stato trovato un legame tra alcune misure di obesità e uno score ottenuto da varianti genetiche già riscontrate in associazione con la preferenza per diverse verdure.

In conclusione, questo lavoro evidenzia l'importanza di valutare le preferenze alimentari in combinazione con altri fattori e suggerisce il possibile utilizzo delle preferenze in studi nutrizionali come misure rappresentative dei consumi. Nel complesso, questi risultati rappresentano un punto di inizio per una migliore conoscenza e comprensione dei complessi meccanismi che intercorrono tra preferenze alimentari, fattori associati e fenotipi legati alla dieta.

CONTENTS

CHAPTER I

INTRODUCTION

It is well known that many common diseases (for instance obesity, hypertension, diabetes, cardiovascular diseases) are complex traits i.e. determined by genetic and non-genetic factors (*Sheikh AB et al, 2017; Kokubo Y et al., 2019; Murea M et al., 2012; Khera AV et al., 2016*). Notably, among non-genetic factors, lifestyle, and specifically diet, plays a prevalent role (*Ziglio E et al., 2004*).

Although the factors shaping a person's food choices are involved, food liking plays a central role in determining food selection and diet quality (*Birch 1999*). Food liking is defined as an individual's reported degree of liking for specific foods and beverages without regard to food intake per se (*de Mendonça et al., 2013*). It has been shown that self-reported food liking might be linked to food choices and can represent habitual food consumption (*Drewnowski & Hann, 1999*; *Drewnowski et al. 2000; Pérez-Rodrigo, Ribas, Serra-Majem & Aranceta, 2003; Wądołowska, Babicz-Zielińska, & Czarnocińskac, 2008*). As a matter of facts, food evaluation through liking is based on affective memories *(M. K. Johnson, 1983; M. K. Johnson, Kim, & Risse, 1985*) rather than factual memory (*M. K. Johnson et al., 1985*), leading to accurate nutritional evaluations (*Duffy et al., 2007*), which are also able to minimize the cognitive limitations of intake measures. Food and beverage liking questionnaire could be a time-efficient and simple task, while intake measures can bring to under- or over-estimate real intakes due to memory issues and dietary restraint. Studies described the effect of dietary restraint and disinhibition on the accuracy of dietary reporting *(Bathalon et al., 2000; David Wang et al., 2014; Lawson et al., 1995; Lindroos et al., 1997*).

Additionally, previous studies have reported that food liking assessment, as a proxy of reported intakes, may be a valid and feasible measure to study the relationship between dietary behaviour and health outcomes (*Pallister et al., 2015*). For example, Duffy and collaborators described that food preferences for fat and fibres are better than self-reported food consumptions explaining variability in adiposity and in blood pressure, suggesting that liking are more reliable markers in estimating the impact of nutrition

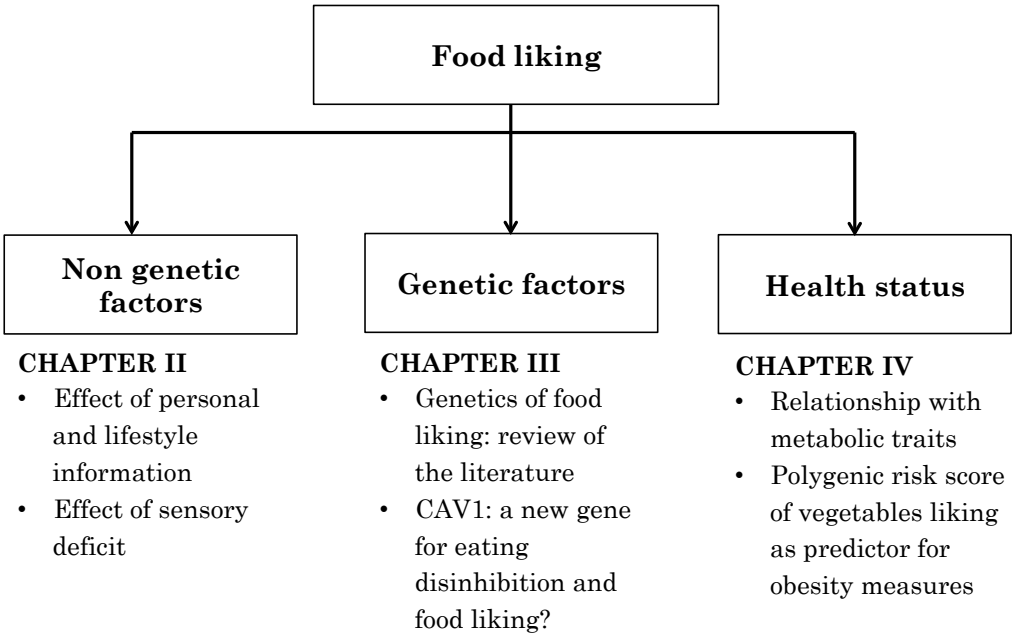
on health *(Duffy, Hayes, Sullivan, & Faghri, 2009; Duffy et al., 2007; Sharafi et al. 2018*).

Individual food liking results from the interaction of several factors working together such as sensory responses to taste and smell (*Bartoshuk, 1991*) but also culture, level of education (*Ventura & Worobey, 2013; Novaković et al., 2014*), eating behaviour (*Jaeger, Rasmussen, & Prescott, 2017; Laureati, Bergamaschi, & Pagliarini, 2014; Laureati, Bergamaschi, & Pagliarini, 2015*) and genetics (*Keskitalo et al., 2008; Törnwall et al., 2014; Feeney et al., 2011; Pirastu et al., 2012; Pirastu et al., 2016*).

In this light, it is clear that a better knowledge of the genetic and non-genetic components affecting food liking and an improved comprehension of the implication of food liking on diet-related diseases, for example obesity or cardiovascular diseases, is of considerable public health importance.

The aims of this work are: 1) to study the genetic and non-genetic factors associated with food liking; 2) to verify the relationship between food liking and health. Figure 1 shows the scheme of the thesis.

Figure 1. The scheme of the thesis.



This work is based on the data collected from three Italian populations. Precisely, a huge database including information of about 3000 individuals from six villages in the

Friuli Venezia Giulia region in the North East of Italy, villages from the Piemonte region (Val Borbera cohort) in the North West, and Carlantino, a village in the South of Italy, was analysed (Figure 2).

These populations belong to the Italian Network of Genetic Isolates (INGI), a large network born to study the genetics of complex diseases taking advantage of the decreased genetic variability and shared environmental of each village. Indeed, isolated populations are derived from a small number of founders and, because of the geographical and/or cultural isolation, low endogamy (within community marriage) and very restricted gene flow (immigration) from neighbouring populations can often be observed. Thus, genomes tend to show higher homogeneity in isolates compared with cosmopolitan populations. Another potentially advantageous characteristic of isolates population is environmental and cultural homogeneity. Indeed, individuals from an isolated population tend to share a common lifestyle, including diet, physical activity levels and other cultural habits and are exposed to similar environmental conditions (Hatzikotoulas et al. 2014).

Figure 2. Map showing approximate location of analyzed Italian samples.

Part of this work has been published:

1. *Factors associated with food liking and their relationship with metabolic traits in Italian cohorts*. Concas MP, Catamo E, Biino G, Toniolo D, Gasparini P, Robino A. Food Quality and Preference 75 (2019) 64–70.

https://doi.org/10.1016/j.foodqual.2019.02.010

2. *A Brief Review of Genetic Approaches to the Study of Food Preferences: Current Knowledge and Future Directions*. Robino A, Concas MP, Catamo E, Gasparini P. Nutrients. 2019 Jul 26;11(8). pii: E1735. doi: 10.3390/nu11081735.

The author (M.P. Concas) contributed to the data analysis, interpreting the results, and she was the corresponding author of the first publication. Help was received from the co-authors in all stages of the work: during the analysis and writing, and the discussion of results and implications.

CHAPTER II

NON-GENETIC FACTORS INFLUENCING FOOD LIKING

As mentioned in the Introduction, individual food liking is the product of several factors. In this chapter, I show the results of two works highlighting the influence of non-genetic factors. In the first section, I present the study about the effect of personal and lifestyle variables on different food liking groups. In the second section, I report a work which aims to evaluate the prevalence of sensory deficits and their relationship with different aspects of eating behaviour such as liking vegetables and food adventurousness.

1. Effect of personal and lifestyle factors on food liking

1.1. Backgrounds and aims

Individual food liking results from the interaction of several factors such as sensory responses to taste, smell and texture (*Bartoshuk, 1991*). Studies have addressed the role of the capacity to perceive bitter taste of PROP (6-n-propylthiouracil) on liking and choice of different bitter and non-bitter compounds (*Tepper, 1998; Tepper et al., 2008; Dinehart, Hayes, Bartoshuk, Lanier, & Duffy, 2006*). However, relationship between PROP tasting and food liking is controversial and several studies could not confirm such association (*Drewnowski, Henderson, & Cockroft, 2007; Feeney, O'Brien, Scannell, Markey, & Gibney, 2011*). Probably other factors associated with food liking should be included in PROP taste studies to better understand its influence on eating behavior and food choices (*Hayes & Keast, 2011*).

Studies in both adults and children have shown that food neophobia, the fear of novel foods, is another factor affecting the degree of food liking (*Jaeger, Rasmussen, & Prescott, 2017; Laureati, Bergamaschi, & Pagliarini, 2014; Laureati, Bergamaschi, & Pagliarini, 2015*).

Additional factors influencing food liking include: level of education, culture, experience and other environmental or socio-economic aspects, such as sex, age and smoking (*Ventura & Worobey, 2013; Novaković et al., 2014*).

In the present study, an analysis of a database of more than 3000 samples and including

a large series of personal, lifestyle and diet related information, was conducted to investigate the factors associated with food liking.

1.2. Materials and methods

Participants

3219 individuals belonging to the Italian Network of Genetic Isolates were included in the study (i.e. 574 from Carlantino (CAR, a small village of the South of Italy situated in the extreme northern part of Puglia Region), 1234 from Val Borbera (VB) in Northwest of Italy and 1411 from six different communities (San Martino del Carso, Erto/Casso, Clauzetto, Illegio, Sauris and Val di Resia) of Friuli Venezia Giulia (FVG). A detailed description of these populations has been previously reported (*Esko et al., 2013; Xue et al., 2017*). All participants gave written informed consent, and the ethical committees of IRCCS Burlo Garofolo and San Raffaele Hospital approved the study.

Data collection

Personal and lifestyle characteristics

Demographic and lifestyle information and living habits, such as cigarettes smoking (current smokers/no smokers), physical activity level (never/light/moderate/intense) and educational attainment (elementary (5 years), lower secondary (3 years), upper secondary (5 years), university (5 years)) were collected for each participant using a standard questionnaire.

Food liking questionnaire

A questionnaire evaluating the liking different foods and beverages was administered. Each subject rated the liking on a 9-point hedonic scale ranging from "dislike extremely" (score 1) to "like extremely" (score 9) (*Tepper et al., 2009; Pirastu et al., 2016*). The foods and beverages included in the questionnaire ranged from 58 in CAR and 106 in FVG and VB. In addition, in FVG and VB another survey was conducted and two subgroups of individuals with evaluation of 61 and 63 foods in FVG and VB respectively, were included in the study.

Taste phenotypes

For each participant the ability to perceive PROP (6-n-propylthiouracil, 50 mmol/l) was evaluated as already reported in other works (*Zhao, Kirkmeyer, & Tepper, 2003; Tepper*

et al., 2009; Robino et al., 2016). Briefly, each subject was asked to place a paper disk impregnated with PROP and to rate the intensity on a labelled magnitude scale (LMS), ranging from 0 ("barely detectable") to 100 ("strongest imaginable") (*Green et al., 1996*).

Food adventurousness, cognitive restraint of eating and disinhibition

Each subject answered the question: "How often do you try unfamiliar foods?". The response categories were: "never", "rarely", "some of the time", "often" and "very often". Subjects were characterized as more food adventurous (willing to try unfamiliar foods some of the time/often/very often) or less food adventurous (willing to try unfamiliar foods never/rarely) (*Ullrich, Touger-Decker, O'Sullivan-Maillet, & Tepper, 2004*).

"Cognitive restraint of eating" and "disinhibition" were assessed for each subject as already reported in *Tepper et al., (2008)* and using statements from the cognitive restraint subscale of the three-factor eating questionnaire (*Stunkard & Messick, 1985).* Briefly, "cognitive restraint of eating" was determined using the answers to the questions "I pay a great deal of attention to changes in my figure", "I do not eat some foods because they make me fat" and "I eat anything I want, any time I want" (reverse). Similarly, "disinhibition" was assessed using the answers to the questions "Sometimes things just taste so good that I keep on eating even when I am no longer hungry", "I usually eat too much at social occasions, like parties and picnics" and "When I feel blue, I often overeat". True answer was scored 1 point each one, with total scores ranging from 0 to 3. Then participants were grouped as: restrained eaters (total score ≥2) or disinhibited eaters (total score ≥2); unrestrained eaters (total score<2) or inhibited eaters (total score<2).

Data analyses

Statistical analyses were performed in R 3.3.0. (www.r-project.org).

To take into account differences in the number of foods included in the questionnaires, five different samples groups were considered: Carlantino, Friuli Venezia Giulia first and second survey, Val Borbera first and second survey.

We aggregated the foods into food groups based on similar liking ratings using cluster analysis. The groups were then confirmed by Cronbach reliability test.

Specifically, the "food liking groups" were defined as the mean of liking given by each individual to the foods belonging to a particular group. Each group was considered as a quantitative trait (*Robino et al., 2016*).

Using linear regression models, different factors (explanatory variables) were tested to study their relationship with food liking groups (outcome variables). The explanatory variables set included: gender, age (5-years groups), cigarettes smoking habit (No/Yes), physical activity (dichotomized variable: never/light versus moderate/intense), educational attainment (measured as the number of years of completed schooling), food adventurousness (considered as binary variable: less adventurous versus more adventurous individuals), cognitive restraint of eating and disinhibition (binary variables) and PROP intensity (quantitative variable).

Each explanatory variable was tested in a base regression model including sex and age, and a final multivariate model, including only the significant covariates in base models (p-value<0.05), was performed for each food liking group.

Although the distributions of preference groups are not perfectly normal, no transformation was applied, but Huber robust standard error was used.

To consider possible differences in food liking groups among sampling, all the analyses were conducted in each population (CAR, FVG first and second survey, VB first and second surveys) and the results were combined using meta-analysis with an inverse variance fixed effect method (R package "rmeta"). We fixed the statistical significance at a p-value of 0.05. The analyses were carried out first on the whole sample set and then stratified by gender.

1.3. Results

Sample characteristics

A total of 3219 individuals were included in the study and their personal and lifestyle characteristics are reported in Table 1, while Table 2 shows the sample characteristics in terms of taste and food behaviour phenotypes.

Table 1. Socio-demographic characteristics of samples included in the study. When not specified, the data are shown in mean and standard deviation (in brackets). In bold are reported significant differences between men and women (p-value<0.05) assessed by Pearson Chi-square test comparing frequencies of categorical variables or to T-test comparing mean values of quantitative variables.

	CAR		**FVG**		**VB**	
	Men (n=254)	Women (n=320)	Men (n=611)	Women (n=800)	Men (n=492)	Women (n=742)
Age, years	52.7 (17.1)	50.9 (16.6)	50.6 (16.3)	50.6 (16.4)	55.8 (17.0)	55.4 (16.9)
Education, years	n=193	n=274	n=541	n=714	n=486	n=735
	8.9 (3.9)	8.8 (3.9)	10.0 (3.6)	9.9 (3.8)	10.0 (4.0)	10.2 (4.3)
Smoking	n=213	n=289	n=595	n=772	n=489	n=741
Yes/No, %	**40.85/59.15**	**18.7/81.3**	20.7/79.3	23.2/76.8	**20.45/79.55**	**11.9/89.1**
Physical activity	n=196	n=279	n=584	n=749	n=220	n=302
Never or Light / Moderate or Intense, %	**48.5/51.5**	**63.4/36.6**	**41.6/58.4**	**54.6/45.4**	**34.1/65.9**	**57.3/42.7**

Table 2. Characteristics of sample: PROP perception, food adventurousness, cognitive restraint of eating and disinhibition. In bold are reported significant differences between men and women (p-value<0.05). SD=standard deviation. FVG1° and 2°-Friuli Venezia Giulia first and second sampling; VB 1° and 2°-Val Borbera first and second sampling.

	CAR		**FVG 1°**		**FVG 2°**		**VB 1°**		**VB 2°**	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
PROP Intensity (mean (SD))	**23.34 (24.41)**	**42.22 (33.69)**	**27.11 (23.31)**	**37.81 (27.55)**	**30.28 (20.97)**	**35.52 (24.52)**	**26.22 (19.01)**	**32.21 (20.18)**	**29.22 (20.6)**	**39.28 (22.6)**
Food adventurousness More food adventurous, %	63.2	65.7	64.7	69.6	**53.1**	**61.4**	57.9	58.0	68.2	73.7
Cognitive restraint of eating Restrained individuals, %	**29.1**	**43.3**	56.0	48.5	**42.6**	**56.7**	39.7	46.1	45.5	51.8
Disinhibition of eating More disinhibited individuals, %	**35.8**	**46.5**	52.8	49.0	51.5	54.3	47.0	48.3	51.4	57.6

Food liking grouping

After cluster analysis and Cronbach reliability test, seven food liking groups were defined: alcoholic beverages, cheeses, fish, fruit, meat, sweet foods and vegetables. Individual foods likings are categorized per food groups based on its similarity, as

already reported in other works (*S. L. Johnson, Boles, & Burger, 2014; Pallister et al. 2015*).

Table 3 shows foods and beverages included in each liking group for each population sampling and the corresponding Cronbach alpha that ranged from 0.59 to 0.9 with the most of values near or exceeding 0.7, supporting internal reliability. The summary statistics for each liking group are reported in Table 4.

Table 3. Composition of food liking groups in each population sampling. In brackets are reported the Cronbach's alphas. FVG 1° and 2°-Friuli Venezia Giulia first and second sampling; VB 1° and 2°-Val Borbera first and second sampling.

Sample	Alcoholic beverages	Cheeses	Fish	Fruit	Meat	Sweet foods	Vegetables
CAR	Grappa, dark beer, red wine, white wine, Cinzano, cherry (0.79)	fontina, gorgonzola, goat cheese, camembert, whole milk, skimmed milk, plain yogurt, mozzarella (0.79)	anchovies, sardines (0.78)	lemons, orange juice, grapefruit juice, avocado (0.59)	pork chops, mortadella, capicola, bacon, ham (0.76)	ice cream, panettone, whipped cream, milk chocolate, marzipan (0.67)	fennel, chicory, cabbage, broccoli, asparagus, artichokes, spinach, radicchio, eggplant, wild mushrooms (0.79)
FVG 1°	Grappa, dark beer, red wine, white wine, Cinzano, Cherry (0.83)	fontina, gorgonzola, goat cheese, whole milk, skimmed milk, plain yogurt, mozzarella, montasio (0.69)	anchovies, sardines (0.78)	lemons, orange juice, grapefruit, avocado, melograno (0.66)	pork chops, mortadella, capicola, bacon, ham (0.78)	Ice cream, panettone, whipped cream, milk chocolate, marzipan (0.63)	fennel, chicory, cauliflower, broccoli, asparagus, artichokes, spinach, green radicchio, red radicchio, beetroot, verza, tomatoes, wild mushrooms, fava beans (0.87)
VB 1°	Grappa, dark beer, red wine, white wine, Cinzano, Cherry (0.80)	fontina, gorgonzola, goat cheese, camembert, whole milk, skimmed milk, plain yogurt, mozzarella (0.64)	anchovies, sardines (0.63)	lemons, orange juice, grapefruit juice, avocado, melograno (0.64)	pork chops, mortadella, capicola, bacon, ham (0.73)	Ice cream, panettone, whipped cream, milk chocolate, marzipan (0.66)	fennel, chicory, cauliflower, broccoli, asparagus, artichokes, spinach, radicchio, eggplant beetroot, broccoli rabe, fava beans, cabbage, wild mushrooms, tomatoes (0.87)
FVG 2°	liquor, Grappa, beer, red wine, white wine, alcohol (0.86)	sheep cheese, fontina, gorgonzola, whole milk, skimmed	salmon, shrimp, fried fish, anchovies,	melon, pear, banana, cherry, strawberry,	meat, grilled meat, pork chops, fried chicken, roast chicken, ham,	ice cream, biscuit, cake, marmalade, panettone,	fennel, chicory, beetroot, verza, broccoli, cauliflower, beans, asparagus,

		milk, plain yogurt, dairy, mozzarella, butter (0.75)	sardines, tuna (0.78)	lemons, orange juice, grapefruit, pineapples (0.78)	baked ham, mortadella, capicola, bacon, sausage (0.90)	Nutella, icing, whipped cream, chocolate with cream (0.85)	artichokes, spinach, raw carrots, green salad, radicchio, eggplant, tomatoes, wild mushrooms, potatoes (0.90)
VB 2°	As above (0.85)	As above (0.73)	As above (0.76)	As above (0.75)	As above (0.83)	As above (0.81)	As above (0.89)

Table 4. Mean, median and standard deviation of food liking group scores in each population sampling and by gender. The ranges are 1-9. FVG1° and 2°-Friuli Venezia Giulia first and second sampling; VB 1° and 2°-Val Borbera first and second sampling.

	CAR		**FVG 1°**		**FVG 2°**		**VB 1°**		**VB 2°**	
Food liking groups	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
Alcoholic beverages	6.21, 6.5, 1.9	4.62, 4.55, 2.4	5.41, 5.5, 1.63	4.52, 4.67, 2.01	5.37, 5.5, 1.8	3.92, 3.83, 1.86	5.15, 5.17, 1.61	4.03, 4, 1.79	5.32, 5.67, 1.8	4.07, 4.08, 1.86
Cheeses	6.26, 6.54, 1.73	5.95, 6.29, 1.79	6.18, 6.4, 1.36	6.33, 6.43, 1.35	5.9, 6.11, 1.37	5.97, 6.11, 1.35	6.06, 6.25, 1.26	6.08, 6.25, 1.3	6.23, 6.33, 1.18	6.36, 6.56, 1.28
Fish	6.83, 8, 2.34	6.21, 7, 2.49	6.28, 7, 2.16	5.2, 5.5, 2.53	6.19, 6.5, 1.65	5.85, 6.17, 1.75	6.15, 6.5, 2.04	5.5, 5.5, 2.19	6.94, 7.17, 1.15	6.43, 6.67, 1.49
Fruit	6.45, 6.75, 1.62	6.28, 6.5, 1.74	6.05, 6.2, 1.44	6.25, 6.4, 1.51	6.76, 6.89, 1.21	6.97, 7.11, 1.16	5.44, 5.63, 1.55	5.65, 5.6, 1.49	6.8, 6.89, 1.04	7.09, 7.22, 1.02
Meat	7.94, 8, 1.05	7.59, 8, 1.31	7.34, 7.6, 1.24	6.96, 7.2, 1.36	6.9, 7.09, 1.18	6.21, 6.48, 1.57	7.11, 7.4, 1.17	6.9, 7.2, 1.41	7.06, 7.09, 0.96	6.78, 6.91, 1.17
Sweet foods	6.25, 6.6, 1.88	6.49, 6.75, 1.73	6.56, 6.8, 1.46	6.72, 7, 1.46	5.95, 6.25, 1.65	6.3, 6.44, 1.52	6.18, 6.4, 1.52	6.39, 6.6, 1.61	6.21, 6.39, 1.37	6.69, 6.89, 1.31
Vegetables	7.16, 7.6, 1.5	7.45, 7.6, 1.09	6.64, 6.79, 1.33	6.91, 7.07, 1.29	6.39, 6.56, 1.33	6.85, 7, 1.24	5.64, 5.93, 1.51	6.24, 6.35, 1.32	6.22, 6.33, 1.25	6.68, 6.78, 1.17

Factors associated with food liking groups

As summarised in Table 5, different factors showed association with food liking groups, as assessed by multivariate regression models.

Differences between men and women were found in all liking groups except for cheeses. Women showed higher liking of sweet foods, vegetables and fruits (p-values<0.0001)

than men, while men showed higher liking of alcoholic beverages, meat and fish (p-values<0.0001) compared to women.

Food liking also showed associations with age groups: greater liking for vegetables and fish were observed with 5-year age group increases (p-values<0.0001).

Smoking habit was associated with liking of sweet foods, fish and alcoholic beverages, with smokers having lower liking for sweet foods (p-value<0.0001) and higher liking for fish (p-value=0.0001) and alcoholic beverages (p-value=0.016) compared to non-smokers.

Individuals with high education level showed lower liking for meat (p-value<0.0001) and greater liking for alcoholic beverages (p-value<0.0001) and vegetables (p-value=0.014).

As regard physical activity, subjects practicing moderate/intense physical activity show a greater liking for fish (p-value=0.0054), fruit (p-value=0.008) and vegetables (p-value<0.0001).

The relationship between food groups and bitter intensity of PROP was also tested detecting a relationship between PROP intensity and sweet foods: increasing of PROP intensity perception corresponded to higher sweet foods liking (p-value 0.0094).

The analysis of eating behaviour phenotypes in our samples highlighted that food adventurousness was associated with all food liking groups (p-values<0.005). In particular, subjects showing a food adventurous behaviour present a higher liking of all food groups compared to those being less adventurous. Moreover, cognitive restraint of eating was associated with the liking of meat and sweet foods: in individuals with high self-control a lower liking of meat (p-value<0.0001) and sweet foods (p-value=0.0029) was observed compared to individuals with low self-control. Finally, eating disinhibition was associated with liking for all foods except for fruit and vegetables. Specifically, individuals with higher disinhibition showed greater liking for alcoholic beverages (p-value=0.0059), cheeses (p-value<0.0001), fish (p-value=0.0023), meat (p-value<0.0001) and sweet foods (p-value<0.0001), compared to individuals with less eating disinhibition.

Overall, the explained variability of each liking group (response variable) by the explanatory variables as expressed by the determination coefficients (R^2) of the models described in Table 5 was: 12.1% for alcoholic beverages, 9.3% for vegetables, 7.8% for fish, 6.3% for meat, 4.5% for sweet foods, 3.0% for cheeses and 2.8% for fruit.

Table 5. Factors related to liking groups as assessed by multivariate regression models implemented in each population sample and aggregated by meta-analysis. The values are beta and p-value in brackets. Significant results (p-value<0.05) were reported in bold. The explanatory variables are reported in rows, and response variables in columns. For non-quantitative variables, the reference categories are: (1) women, (2) non-smokers, (3) none/light physical activity, (4) less adventurous individuals, (5) less conscious individuals, (6) inhibited individuals. Each variable was first tested on a base model with sex and age and if not significant (p-value<0.05) it was not included in final multivariate model. Not included variables are indicated by "Not included".

Explanatory variables	Alcoholic beverages	Cheeses	Fish	Fruit	Meat	Sweet Foods	Vegetables
Gender (1)	**1.368 (<0.0001)**	Not included	**0.477 (<0.0001)**	**-0.195 (<0.0001)**	**0.303 (<0.0001)**	**-0.275 (<0.0001)**	**-0.413 (<0.0001)**
Age (5-years)	-0.003 (0.85)	Not included	**0.085 (<0.0001)**	Not included	Not included	-0.01 (0.275)	**0.107 (<0.0001)**
Smoking (2)	**0.227 (0.016)**	Not included	**0.339 (<0.0001)**	Not included	Not included	**-0.314 (<0.0001)**	Not included
Education (years)	**0.048 (<0.0001)**	-0.001 (0.84)	0.015 (0.18)	0.007 (0.24)	**-0.027 (<0.0001)**	Not included	**0.018 (0.014)**
Exercise (3)	Not included	Not included	**0.203 (0.0054)**	**0.14 (0.008)**	Not included	Not included	**0.238 (<0.0001)**
PROP Intensity	-0.003 (0.057)	Not included	Not included	Not included	Not included	**0.003 (0.0094)**	Not included
Food adventurousness (4)	**0.403 (<0.0001)**	**0.394 (<0.0001)**	**0.619 (<0.0001)**	**0.305 (<0.0001)**	**0.265 (<0.0001)**	**0.175 (0.0037)**	**0.485 (<0.0001)**
Cognitive restraint (5)	Not included	Not included	Not included	Not included	**-0.229 (<0.0001)**	**-0.167 (0.0029)**	Not included
Disinhibition (6)	**0.202 (0.0059)**	**0.22 (<0.0001)**	**0.202 (0.0023)**	Not included	**0.189 (<0.0001)**	**0.416 (<0.0001)**	Not included

The results of the analyses in men and women separately are displayed in Appendix section in Table A.1. a) e b) respectively.

1.4. Discussion

This cross-sectional observational study examined a large database of 3219 Italian adults aimed to study factors related with food liking.

In the present work, we showed that personal characteristics, such as gender and age, or eating behaviour phenotypes (i.e. food adventurousness, cognitive restraint and disinhibition) are very important factors to take into consideration when studying food liking.

For example, we found that men preferred high-fat foods like meat and alcoholic beverages, while women preferred healthier foods such as fruits and vegetables (*Logue*

& Smith, 1986; Frewer & van Trijp, 2007). A possible explanation for these differences might be the highest awareness of women to health benefits and weight control (*Westenhoefer, 2005*). Differently from other studies on food intake measures (*Karlsson et al., 2017; Wennberg et al., 2012; O'Doherty Jensen & Holm, 1999*), in our work men reported higher fish liking compared to women. To our knowledge, no other study showed gender differences in fish liking, therefore further investigation is necessary.

Age is another very important factor shaping food liking and, in agreement with past works, we have observed that ageing is associated with an increased liking for vegetables (*Kossioni & Bellou, 2011; Guido et al., 2016*) and fish.

A role of food adventurousness (to be willing to try novel and unfamiliar foods) and neophobia (reluctance to try novel and unfamiliar foods) on food liking and intake in adults and children was already reported (*Ullrich et al., 2004; Jaeger et al., 2017; Russell & Worsley, 2008; Laureati et al., 2014; Laureati et al., 2015*). In the present work, food adventurousness resulted associated with an increase of liking for all food groups, suggesting that more food adventurous subjects tend to prefer a wide variety of foods. Furthermore, higher cognitive restraint resulted associated with a decrease in sweet and meat liking while increased eating disinhibition is associated with a higher liking for several food groups, but not for vegetables and fruit (*Contento, Zybert, & Williams, 2005; Habhab, Sheldon, & Loeb, 2009; Mela, 1996; Lähteenmäki & Tuorila, 1995*).

Additionally, our results showed that other factors, such as smoking, education and physical activity, might play a role in modelling some specific food liking groups. Smoking people show a higher alcohol liking and lower sweet food liking as compared to non-smokers, partially in agreement with previous reports (*Zizza et al., 2015; Lampuré et al., 2015*). Moreover, liking of alcoholic beverages and vegetables increases according to the level of education attainment, while liking of meat decreases (*Mullie, Clarys, Hulens, & Vansant, 2010*). As regards to physical activity, our data (i.e. increased liking of fish, fruit and vegetables in individuals practicing moderate to intense physical activity) further confirms previous findings linking differences in food liking or intake to healthy behaviors (*Mullie et al., 2010; Ball, Jeffery, Abbott, McNaughton, & Crawford, 2010; Masic, Christiansen, & Boyland, 2017; Rodenburg, Oenema, Pasma, Kremers, & van de Mheen, 2013*).

When it comes to taste perception, higher ability to perceive the bitter taste of PROP resulted weakly associated with higher liking for sweet foods. Although controversial results have been reported on the relationship between PROP perception and liking/disliking of sweet foods, our results agree with some studies showing that subjects sensitive to PROP also perceive more sweetness (*Bachmanov et al., 2003; Peterson, Bartoshuk, & Duffy, 1999; Looy & Weingarten, 1992; Drewnowski, Henderson, Shore, & Barratt-Fornell, 1997; Drewnowski, Henderson, Levine & Hann, 1999*).

In conclusion, this work shows that many factors may influence questionnaire-reported food liking. As a limitation, the variables measured only explained a moderate level of variance for liking of the food groups. This suggests that additional factors (e.g., social, cultural, environmental, etc.) or greater precision in self-reported variables (such as physical activity or smoking) are required. Another limitation may concern the use of the 9-point scale that, despite it being very brief and easy to use for both participants and researchers, does not permit to define the full range of hedonic due to its limited number of responses.

Despite these limitations, the main strength of this study remains the availability of comprehensive data on lifestyle, food experiences behavior in a very large adult population.

2. Sensory deficits and their link with eating behaviour

2.1. Backgrounds and aims

Sensory dysfunctions may play a critical role in the health and quality of life *(Fischer ME et al., 2009; Genther DJ et al., 2014; Li L et al., 2013; Schiffman SS et al., 2000; Solemdal K et al., 2014; Pinto JM et al., 2014)*.

It is well known that single sensory impairments are common, especially in older people *(Kern DW et al., 2014; Crews JE et al., 2004; Murphy C et al., 2002; Welge-Leussen A., 2009)*. Otherwise, studies showed that multiple dysfunctions exacerbate the effect of single *(Chia E-M et al, 2006; Kiely KM et al., 2013)*, highlighting the importance of investigating also multisensory impairments. Many studies focused on the prevalence, the risk factors and the impact of sensory deficits in individuals aged 40 years and more *(Liu G et al., 2016; Correia C et al., 2016; Pinto JM et al., 2014; Crews JE et al., 2004)*, but little is known about the prevalence, the risk factors and the effect of impairments of single or multiple senses in general population, across the life spectrum of adults *(Khil L et al., 2015)*.

Sensory dysfunctions could modify eating habit. In particular, smell and taste disorders, but also hearing, could affect nutrition (*Mathieu ME et al., 2019*). Studies in older adults showed that olfactory dysfunction affect either overall perception as well as single preferences of odorants (*Seow Y-X et al., 2016*) and this deficit affects food selection, nutrition, and consequently health (*Kong IG et al., 2016, Kershaw JC et al., 2018*). For example, some studies highlighted that, in older adults, decreased smell is associated with appetite suppression, weight loss, and malnutrition (*Gopinath B, et al, 2012; Boyce JM et al, 2006*). Declining taste acuity or taste loss predisposes the elderly to a higher risk of developing cardiovascular diseases, overweight, obesity and other diseases (*Schiffman SS, 2009*). Hearing dysfunction can lead to social isolation (*Mick P et al, 2014*) and depression (*Mener DJ et al, 2013*), both of which are associated with an increased risk of malnutrition in older individuals (*Schiffman SS, 2007*).

The aims of the present study are:

1. to describe the prevalence of single and multiple sensory impairments in Italian adult samples;
2. to investigate the relationship between sensory deficits and environmental and personal variables as possible risk factors;

3. to evaluate the impact of sensory dysfunctions on eating behaviour investigating the relationship of the number of impaired senses with food adventurousness and liking for vegetables foods.

2.2. Materials and methods

Participants

1151 individuals from two Italian populations, Friuli Venezia Giulia (FVG) and Val Borbera (VB), were included in the study. All participants gave written informed consent, and the ethical committees of IRCCS Burlo Garofolo and San Raffaele Hospital approved the study. For further details, see section 1.2..

Personal and lifestyle characteristics

Personal, socio-demographic information and living habits were collected for each participant using a standard questionnaire, as explained in section 1.2.. In particular, in this work, we used information about gender, age, smoking status (non-smokers/smokers), educational level (measured in years of schooling) and alcohol consumption (in grams/die).

Sensory measurements

Smell

Each participant was presented with 12 odorants in 12 commercially available felt-tip pens ("Sniffin' Sticks" Burghart GmbH, Wedel, Germany) (*Hummel T et al., 1997*). Olfactory test consists in odour identification (4-alternative forced choice). In this study, 5 odorants (leather, cinnamon, lemon, cloves and pineapple) were excluded because were not recognized by more than the 20% of the subjects (data not shown), in accordance with (*Parola S and Liberini P, 1999).* The odorants included in the study were orange, peppermint, banana, liquorice, coffee, rose and fish.

The number of errors was counted. The smell score was created categorizing the individual smell ability as "good" if the individual showed 0 or 1 error, "medium" for 2 errors and "poor" for number of errors ≥ 3 in similar manner to other studies (*Khil et al., 2015; Vennemann et al., 2008*).

Hearing

For each participant different frequencies (0.25, 0.5, 1, 2, 4 and 8 kHz) were measured using standard audiometers.

To classify the hearing ability, the mean of frequency thresholds of 0.5, 1, 2, and 4 kHz were taken into account, in accordance with Bureau International d'Audiophonologie (BIAP) recommendation no. 02/01 bis (*http://www.biap.org/en/recommendations/65-ct-2-classification-des- surdites/5-recommandation-biap-021-bis*).

For each individual the hearing score was defined as "good" for average threshold ≤ 20, "poor" for average threshold>40, "medium" otherwise.

Taste

Taste responsiveness was determined using the Burghart filter paper method (*Zhao L et al, 2003*). The tastes were sweet (sucrose, 0.2 g/ml), sour (citric acid, 0.165 g/ml), salty (NaCl, 1.0 mol/l) and bitter (quinine hydrochloride, 0.0024 g/ml). At each subject was asked to individuate the correct taste (4-alternative forced choice). A possible choice was also "I don't perceive any taste" and this answer was considered as error. The number of errors was counted.

The taste score was defined categorizing the individual taste ability as "good" if the individual showed 0 error, "medium" for 1 error and "poor" for number of errors ≥ 2, in agreement with other studies (*Khil et al., 2015*; *Vennemann et al., 2008*; *Correia et al., 2016*).

Definition of the number of impairments

For each sensory score, "medium" and "poor" conditions were considered as signal of impairment. A multisensory score was defined as the number of impairments: 0 if the individual does not show impairments ("good" in all the senses), 1 for impairment in only one sense etc.

Vegetables liking group

As explained in section 1.2., liking for about 100 foods and beverages were assessed by means of questionnaire in a 9-point scale. A vegetables liking group was defined as the average of liking given by each individual for the following foods: fennel, chicory, beetroot, savoy cabbage, broccoli, cauliflower, beans, asparagus, artichokes, spinach, raw carrots, green salad, radicchio, eggplant, tomatoes, wild mushrooms and potatoes.

Cronbach reliability test confirms the goodness of the group (0.90 in FVG and 0.89 in VB).

Food adventurousness

Food adventurousness (to be willing to try novel and unfamiliar foods) was assessed by the answer to the question: "How often do you try unfamiliar foods?". The response categories were: "never", "rarely", "some of the time", "often" and "very often". In the statistical analysis this trait was considered as score ranging from 0 ("never") to 4 ("very often").

Statistical analysis

Statistical analyses were performed in R 3.4.1. (www.r-project.org).

Individuals without all three sensory phenotypes and individuals with pathologies that can cause damage to senses (cancers, neurodegenerative diseases, severe hearing-related problems like as tinnitus) were excluded from the study.

The prevalence of impairments was evaluated in all samples and by gender and age groups.

The relationships between independent variables, as possible risk factors, and sensory impairments were assessed by means of ordinal logistic regression models (*polr* function in MASS R library) for each sense function (classified as good, medium and poor) and by means of linear regression model for the number of impairments. The explanatory variables set included gender, age, smoking habit and alcohol consumption. Age was considered in groups of 10 years in order to better capture the effect. Alcohol consumption was classified as low and high: a consumption of more than 30 grams/die in men and more than 20 grams/die in women was considered as high (*Khil L et al., 2015*).

To evaluate the association of eating behaviour phenotypes and the number of impairments, multiple regression analyses were conducted. Moreover, to better understand the complex interplay between variables, models were developed and tested with Structural Equation Modelling (SEM, lavaan R package, *Rosseel Y (2012)*). SEM (*Wright SS, 1921*) is a statistical technique that allows identifying the direct and indirect influences of variables and it is used when the response variable in one regression equation becomes a predictor in another. Potential confounders (sex, age and educational level) were included in the models. Criteria for overall fit were chosen a

priori: chi-square p-value non-significant ($\chi 2$ $p>0.05$), Confirmatory Fit Index (CFI) ≥ 0.92, Tucker-Lewis Index (TLI) > 0.87 and Root Mean Square Error of Approximation (RMSEA) < 0.05 (*Tabachnick, B.G. and Fidell L.S., 2001*).

2.3. Results

Sample characteristics

The number of individuals included in the study was 1155, exactly 713 in FVG and 442 in VB. Age ranged from 18 to 89 in FVG and from 18 to 88 in VB and the percentage of female population was 57.1% in FVG and 56.6% in VB. Preliminary analysis conducted in each population separately (data not shown) revealed a similar trend, thus, we decided to combine the individuals in a single dataset. Sample characteristics are summarized in Table 6.

Table 6. Characteristics of individuals included in the study. *P-value is referred to difference in no sensory/any sensory impairments groups (T-test for continuous variables, Chi-square for categorical).

	All (n=1155)	**No impairment (n=361)**	**Any impairment (n=794)**	**P-value***
Age (years), mean (SD)	51.7 (16.7)	43.9 (13.9)	55.2 (16.6)	<0.0001
Age groups, % (n)				<0.0001
18-29	12.6 (145)	18.3 (66)	9.9 (79)	
30-39	13.2 (153)	22.7 (82)	8.9 (71)	
40-49	16.8 (194)	23.0 (83)	14.0 (111)	
50-59	22.2 (256)	21.3 (77)	22.5 (179)	
60-69	19.4 (224)	11.6 (42)	22.9 (182)	
70+	15.8 (183)	3.0 (11)	21.7 (172)	
Men, % (n)	43.1 (498)	32.4 (117)	48.0 (381)	<0.0001
Education (years), mean (SD)	11.0 (3.8)	12.4 (3.4)	10.4 (3.8)	<0.0001
Current smokers, % (n)	19.5 (225)	23.3 (84)	17.8 (141)	0.035
High alcohol consumption, % (n)	25.9 (299)	22.7 (82)	27.3 (217)	NS
Food adventurousness, mean, median, SD	2.0, 2.0, 1.05	2.2, 2.0, 1.03	1.9, 2.0, 1.05	<0.0001
Vegetables liking, mean, median, SD	6.6, 6.7, 1.3	6.6, 6.8, 1.2	6.6, 6.7, 1.3	NS

Prevalence of sensory impairments

Sensory damages were identified as medium or poor condition. The percentage of individuals without sensory damages (i.e. all the senses "good") was 31.25%. As displayed in Figure 3, taste damages were the most prevalent (55.32% in total and 31.17% without co-occurrence of other senses) followed by hearing (32.29% in total and 9.61% without co-occurrence). Smell impairments were the less prevalent: 13.07% in total and 1.65% without co-occurrence. 20.62% of population showed dual co-occurrence: taste plus hearing was the most prevalent (14.86%) and hearing plus smell the less prevalent (2.16%). 5.63% of population showed all the three senses impaired.

Figure 3. Venn diagram of prevalence of single and multiple sensory impairments.

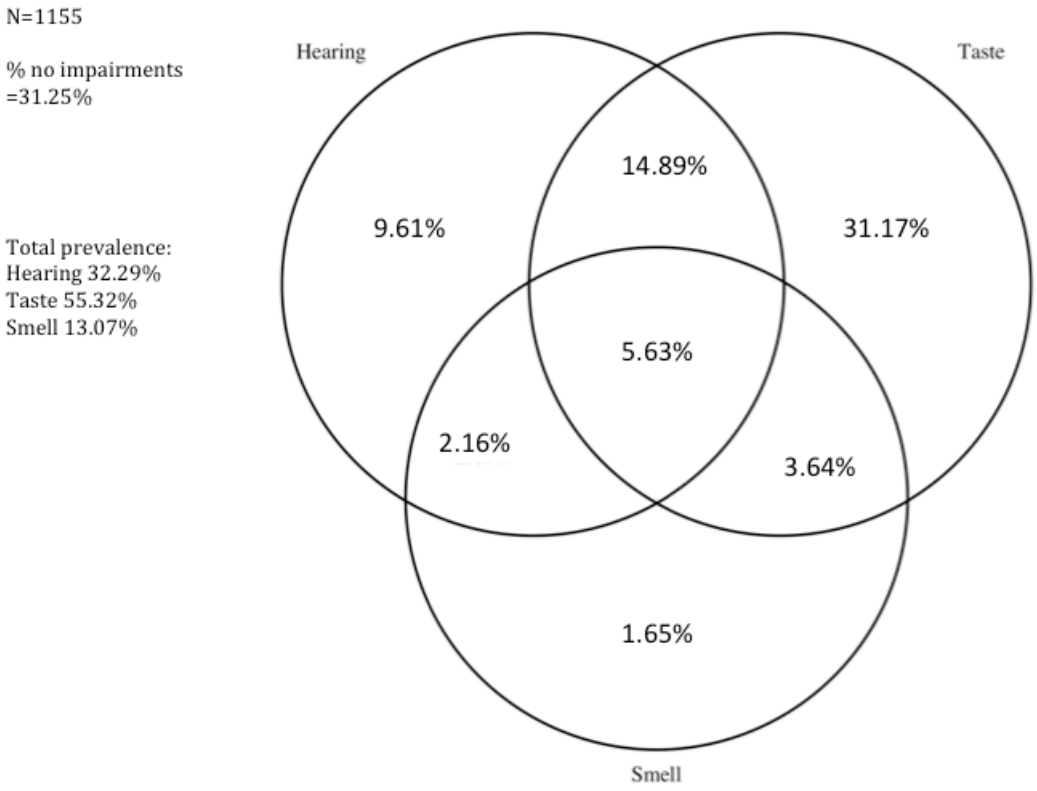
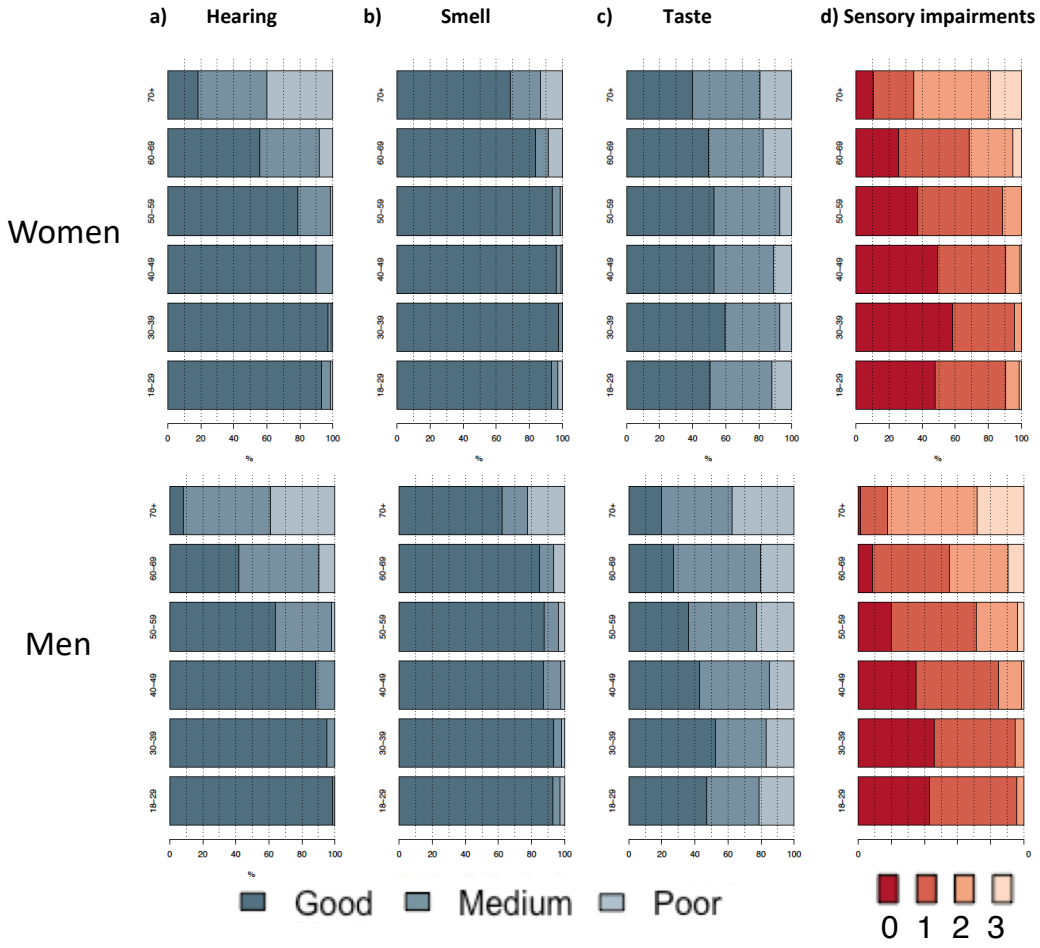


Figure 4 shows the percentage of individuals with "good" (darkest shade), "medium" (medium shade) and "poor" function (lightest shade) for hearing (a), smell (b) and taste (c) in each age group for women (in the top) and men (in the bottom). It is evident the influence of age in decreasing of good function both for men and women, especially for hearing. In addition, men showed higher prevalence for medium and poor status, specifically in old age, compared to women. Considering the number of impairments (Figure 4 d)), the percentage of individuals with 2 or 3 senses damaged (lightest colours)

increased by aging. Men, compared to women, showed lower percentage of absence of impairments (darkest shade) in all the age classes. For example, while in the whole dataset analysed the percentage of all the senses impaired was 5.6% (Figure 3), in older adults (aged 70 and over) the prevalence becomes about 20% for women and 30% for men (lightest shade).

Figure 4. Percentage of individuals with good, medium and poor sensory functions by age groups, respectively for a) hearing, b) smell and c) taste for women (top) and men (down). d) Percentage of number of impairments by age groups for women and men: medium and poor conditions of smell, taste and hearing were considered as sign of impairment; 0=no impairment, 1=impairment in one sense, 2= impairment in two senses, 3= impairment in all the three senses.



Factors influencing sensory ability

The influence of gender, age (10 years groups), education (years of schooling), high alcohol consumption (no/yes) and smoking habit (no/yes) on single sensory impairments, assessed by ordinal probit regression, are shown in Table 7 a). Table 7 b) shows the

influence of the same independent variables, assessed by linear regression, on the number of impairments.

Table 7. a) Factors influencing smell, taste and hearing abilities tested by ordinal logistic regression (category good, medium and poor). b) Factors associated to numbers of sensory impairments by linear regression. OR=Odds Ratio, CI= Confidence Interval. In bold significant associations (p-value<0.05).

a)

	Smell	**Taste**	**Hearing**
	OR 95%CI (p-value)	**OR 95%CI (p-value)**	**OR 95%CI (p-value)**
Sex (men)	**1.5 [1.04;2.18] (0.03)**	**2.0 [1.59;2.52] (<0.00001)**	**1.64 [1.22;2.21] (0.001)**
Age, 10-y groups	**1.47 [1.26;1.72] (<0.0001)**	**1.11 [1.02;1.21] (0.019)**	**3.15 [2.71;3.68] (<0.00001)**
Education, years of schooling	**0.91 [0.86;0.96] (0.0008)**	**0.94 [0.91;0.97] (0.0005)**	**0.95 [0.91;0.99] (0.02)**
High alcohol consumption, yes	1.44 [0.97;2.11] (NS)	0.8 [0.61;1.03] (NS)	0.79 [0.57;1.09] (NS)
Current smoker	0.93 [0.55;1.51] (NS)	1.04 [0.79;1.38] (NS)	0.97 [0.65;1.44] (NS)

b)

	Number of impairments
	Beta 95% CI (p-value)
Sex (men)	**0.28 [0.19;0.37] (<0.0001)**
Age, 10-y groups	**0.21 [0.18;0.24] (<0.0001)**
Education, years of schooling	**-0.03 [-0.05;-0.02] (<0.0001)**
High alcohol consumption, yes	-0.03 [-0.13;0.07] (NS)
Current smoker	-0.02 [-0.12;0-09] (NS)

As already observed in terms of prevalence, male gender was a significant risk factor for all the three senses and for the number of impairments and affects particularly taste with an odds ratio of 2.0. All the sensory abilities were affected by aging: a 10-years increase in aging produced an increase of the risk of 1.47 for smell ability, 1.11 for taste

and 3.15 for hearing (p-values < 0.05). In addition, a 10-years increase in aging corresponded to an increase of 0.21 in number of impairments (p-value < 0.0001).
Increasing educational level was a protective factor for each sense (OR for smell 0.91, taste 0.94, hearing 0.95, p-value < 0.05). Education was also related to the number of impairments with a significant decrease of number of impairments of 0.03 (p-value < 0.0001) for the increase of one year of schooling.
No significant associations were observed for smoking status and high alcohol consumption.

Relationship between the number of impairments and eating behaviour

Linear regression models were used to explore the relationship of the number of impairments with food adventurousness and vegetables liking, including as confounding variables, gender, age and educational level. As shown in Table 8, the number of impairments was associated with both food adventurousness and vegetables liking: higher number of sensory impairments corresponded to lower values of food adventurousness and vegetables liking.

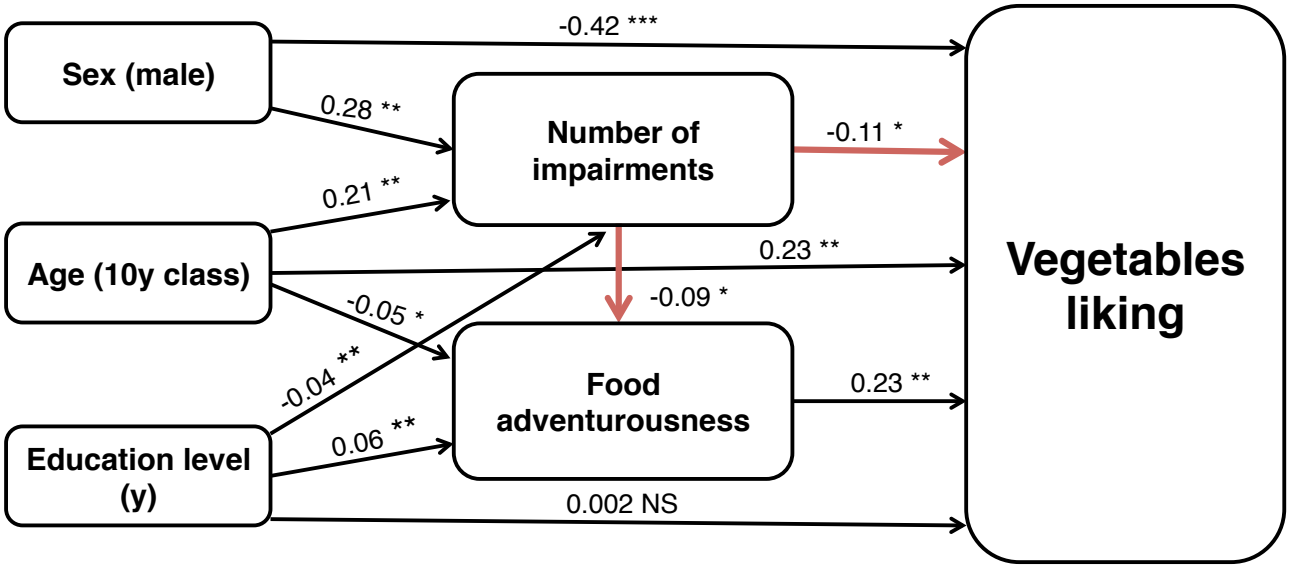
Table 8. Results of linear regression models to assess the relationship between the number of sensory impairments and eating behaviour. The explanatory variables are in rows and the response variables (food adventurousness and vegetables liking) are in columns). Food adventurousness has been included in the model for vegetables liking. The values are betas, confidence interval in square brackets and p-value in round brackets.

	Food Adventurousness	**Vegetables liking**
Sex (male)	-0.09 [-0.21;0.03] (NS)	-0.42 [-0.56;-0.28] (<0.0001)
Age (10y)	0.03 [-0.07;0.02] (NS)	0.23 [0.17;0.28] (<0.0001)
Education (y)	0.06 [0.04;0.08] (<0.0001)	0.002 [-0.02; 0.02] (NS)
Food adventurousness	-	0.23 [0.16;0.3] (<0.0001)
Number of impairments	-0.08 [-0.16;-0.0008] (0.048)	-0.10 [-0.2;-0.01] (0.03)

Because the effect of the number of impairments on vegetables liking could be mediated by the food adventurousness (Table 8), SEM models were performed to test the direct

and indirect associations. As shown in Figure 5, a direct effect of the number of sensory impairments on vegetables liking and food adventurousness emerged, controlling for sex, age and education. The model has a good fit.

Figure 5. Results of SEM models (Lavaan R package). The model showed a good fit (CFI=0.998, TLI=0.978, p-value Chi-square=0.15, RMSEA=0.031). Reported value are the effect of the variables in left side on the variable in right side and p-values *<0.05, **<0.001. NS=not significant; y=years.



2.4. Discussion

This study examined the prevalence of hearing, smell and taste impairments and their association with possible risk factors as well as their link with eating behaviour.

In our sample, taste deficits were the most prevalent impairments followed by hearing and smell. In a past work, *Khil and co-authors* (*2015*) investigated the sensory deficit in a total of 1208 Germany individuals aged 25-74. They found a prevalence of one or more deficits comparable to ours (73.6% versus 68.75% in our sample) and reported a similar co-occurrence of the deficits of the three senses together (3.2% versus 5.6% in our work). Indeed, their results showed a prevalence of single senses deficit different from ours, higher for hearing and smell and lower for taste. *Liu et al. (2016)*, found a prevalence for smell impairments of 13.5% in about 3500 US individuals aged 40 and older, which is comparable with our results, while the prevalence of taste dysfunctions was very different (17.3%). In addition, they found a percentage for the co-occurrence of smell and taste deficits of 2.2% in line with our results. In a study of 2968 US individuals

aged 57-85, *Correia et al.* (*2016*) used the same method, the same tastes and the same classification as we did. They found that taste impairment was the most prevalent sensory deficit with 74%, similar to our results for older people.

We found an association of both single sensory deficit and the number of impairments with age, gender and educational level, while no link was found with smoking habit and high alcohol consumption. Our results on the effect of aging were in agreement with other studies (*Khil et al., 2015; Correia et al., 2016).* Indeed, it is already well known that the aging process is associated with a decline in the function of senses (*Murphy C et al., 2002; Michikawa T et al., 2011*; *Mathieu et al., 2019).* Many studies reported that male gender is a risk factor for sensory decline. For example, *Khil et al. (2015)* results were very similar to ours, while *Liu et al. (2016)* reported an association only for smell impairments but not for taste. *Khil et al. (2015)* found, like us, that a low educational level was a risk factor for smell, hearing, taste decline and the grade of impairments, whereas *Liu et al. (2016)* reported association only for smell but not taste. Regarding the relationship of hearing, smell and taste with smoking and alcohol habit, controversial results were reported, some of which in accordance with ours. For example, *Khil et al. (2015)* found smoking as a risk factor for smell deficit and the grade of impairments, but not for taste and hearing decline, and found high alcohol consumption as a risk factor only for hearing impairments. *Liu et al. (2016)* found no association of smell and taste impairments with smoking habit while found that alcohol consumption was a risk factor for smell.

In our study the increase of the number of sensory impairments was associated with lower food adventurousness and lower liking for vegetables. Our results are in line with the ones from previous studies, which showed that taste, smell and hearing alterations could affect nutritional response (*Mathieu et al., 2019).* In particular, other studies agree with our results, even though the considered eating phenotypes were different, and a single deficit was taken into account (*Mathieu et al., 2019*). For example, some studies showed that individuals with smell deficits had a reduced preference for fruits and vegetables (*Duffy VB et al., 1995*) or consumed low quality diet (*Gopinath B et al., 2016*). Other studies showed that food neophobia (i.e. the reluctance to try novel foods,

almost the opposite measure of food adventurousness) is associated with impaired chemosensory abilities such as the smell and taste (*Wildes et al., 2012*).

In conclusion, we observed that the relationship between sensory deficits and diet-related phenotypes is complex. This aspect highlights that many factors could have been included in this kind of studies and appropriate statistical instruments, such as Structural Equation Modelling, are needed.

CHAPTER III

GENETIC FACTORS AFFECTING FOOD LIKING

In this chapter, the genetics of food liking is investigated. The first part is a brief review of the current knowledge, starting from heritability to candidate genes and Genome-Wide Association Studies (GWAS). Precisely, I report the results of past studies that have investigated the role of taste and olfactory genes on food liking. Subsequently, are explored the results of GWAS on food liking, some of which were performed in INGI populations in the previous years. In the second part, I present my work about the discovery (by GWAS) and the replication of a new gene (*CAV1*) found associated with eating disinhibition and food liking.

3. Genetics of food liking: a review of the current knowledge

3.1. Background and aim

The first evidence for genetic influences on food liking came from family and twin studies (*Faust J, 1980; Falciglia GA, Norton PA, 1994; Reed DR et al, 1997; Breen FM et al, 2006; Keskitalo K, Knaapila A et al., 2007; Keskitalo K, Tourila H et al, 2007; Törnwall O et al., Physiol Behav 2012; Törnwall O et al., Appetite 2012; Fildes A et al, 2014; Smith AD et al, 2016; Pallister T e al., 2015*).

However, over the last decades, rapid advances in molecular genetics have revolutionized the understanding of individual differences in many aspects of human behavior. These advances give researchers the tools to conduct genetic association studies on a large scale, to better understand the role of specific gene loci in sensory perceptions, food liking, intake as well as on food-related habits (*Reed DR et al., 2010; Hwang LD et al., 2019; Pirastu N et al., 2012; Pirastu N et al., 2015; Pirastu N et al., 2016; Eriksson N et al., 2012*).

To date, the vast majority of genetic studies on food liking have focused on identifying specific loci associated with sensory perceptions (mainly taste and smell perception). The effects of taste and smell genes on food habits (*Kim UK et al., 2003; Guo SW et al., 2001; Bufe et al., 2002; Kuhn et al., 2004; Pronini AN et al, 2007; Beherens M et al, 2006; Mainland JD et al., 2009; Fushan AA et al, 2009; Shigemura N et al., PlosOne 2009; Shigemura N et al., Am J Clin Nutr 2009; Dias AG et al., 2013; Laugerette F et al, 2005;*

Keller KL et al., 2012; Reed DR et al, 2015; Ugawa S, 2003; Ishimaru Y, Matsunami H, 2009; Bachmanov AA et al, 2007; Bachmanov AA et al, 2014) and health status (*Keller KL et al., 2012; Reed DR et al., 2015; Hayes JE et al., 2011; Tepper BJ, 2008; Feeney E, 2011; Hayes JE et al., 2013; Feeney E et al, Proc Nutr Soc 2011; Negri R et al., 2012; Garcia-Bailo B et al., 2009; Chamoun E et al., 2018; Eny KM et al., 2010; Kulkarni GV et al, 2013; Ma X et al., 2004; Dotson CD et al, 2010*) have also been extensively investigated.

However, gaps in understanding still exist, and emerging evidence suggests that novel genes (not necessarily related to taste or smell perception) may play a critical role in these relationships (*Reed DR et al, 2010; Hwang LD et al, 2019; Pirastu N et al, 2012; Pirastu N et al, 2015*).

Thus, a potential new area in nutrition research is the investigation of the genetic bases of food liking to include both taste/smell-related and non-related genes.

Specifically, this is a brief review of studies on both food preferences (defined as the selection of one food rather than another) and food liking (meaning the degree of liking or disliking towards a food). In the text these terms are used as synonyms.

3.2. Genetic dissection of food preferences

The genetic background of a trait can be investigated through several methods. Firstly, heritability analysis allows one to estimate the proportion of variation of a phenotype, which is due to genetic differences between individuals. However, heritability studies do not provide any information on specific genes and polymorphisms related to a given trait. Specific information can be identified through genetic association analysis such as candidate gene and genome-wide approaches.

A candidate gene study investigates variations within specific genes of interest selected on the bases of the existing knowledge or hypotheses. In contrast, a GWAS is conducted without suppositions or previous knowledge and the whole genome is scanned, so that new genetic variants may be discovered (*Mackay TF, 2001; Yang J et al., 2011; Rao DC, 2008*).

Here, different approaches through which the genetic of food liking can be dissected are reported: firstly, studies that provided evidence for a genetic basis of food liking (heritability studies) and then studies that identified associations with genes (candidate gene and genome-wide association).

Heritability studies

Heritability is the proportion of the phenotypic variation in a population explained by genetic effects; it is a measure of inheritance of a trait. Usually, heritability estimation requires data where familial relationships are known (twins or family studies) and does not provide information about which genes are responsible for the trait. Heritability has been widely estimated in twin studies, where monozygotic twins (identical twins with almost no differences in their DNA) are compared to dizygotic twins (fraternal twins who share on average half of their DNA). This comparison allows one to evaluate the proportion of variation of a trait ascribable to genetic factors, while the remaining variance is assumed to derive from environmental factors. Heritability estimation ranges from 0 to 1: a high value indicates that genetics plays a major role, while low values indicate that most of the variation is due to environmental factors. High heritability does not necessarily imply a single gene is the cause of trait variation. It is possible that multiple genes, each of them having a small effect, contribute to this variation (*Visscher PM et al., 2008*).

Evidences on the heritability of food liking have been reported in both adults and children twin studies. For example, studies in 3-5 years old children provide evidence for high or moderate heritability for liking of vegetables (from 0.37 and 0.54), fruits (from 0.51 to 0.53) and proteins (from 0.48 to 0.78) (*Breen FM et al, 2006; Fildes et al, 2014*). Moderate heritability for specific food liking such as vegetables (0.54), fruits (0.49), meat or fish (0.49) and dairy (0.44) has also been observed in adolescents (18–19 years of age) (*Smith AD et al, 2016*). Similar findings have been reported in adults. In a cohort of about 600 adult female twins in the UK, Keskitalo and colleagues reported that 49%, 54%, and 53% of the variation in liking for a sweet solution, liking and use-frequency of different sweet foods (sweet desserts, sweets, sweet pastry, ice cream, hard candy, and chocolate) respectively, was explained by genetic factors (*Keskitalo K, Knaapila A et al, 2007; Keskitalo K, Tuorila H et, 2007*). Similarly, a study in young adult Finnish twins showed that genetic effects account for 18%-58% of the variation in the pleasantness of oral pungency, spicy foods and pungent sensations (*Törnwall O et al., Physiol Behav 2010*). In the same cohort, genetic influences on sour foods were studied, and 14% and 31% of the variation in pleasantness and intensity of orange juice spiked with citric acid was reported (*Törnwall O et al., Appetite 2012*). Moreover, these same authors also found that genetic effects accounted for 34%-50% of the variation in

pleasantness and use-frequency of sour foods categorized in three groups as follow: sour fruits and berries (red currant, red currant juice, cranberry, lingonberry, lemon and rhubarb), sour dairy products (natural cultured milk, natural yogurt and sour milk) and less-sour berries and fruits (strawberry, orange, blueberry, peach and banana) (*Törnwall O et al., Appetite 2012*).

Differences in heritability results across studies can be explained by the small sample size of most studies and by the minimal number of foods analyzed (i.e. different from study to study and mainly focused on taste perception of foods). Moreover, differences in the data collection and analysis (i.e. age differences of participants, use of different questionnaires and measurements, analysis of single foods or a set of clustered foods) could also be responsible for this variability.

More recently, a large study of more than 2,000 UK twins analyzed heritability of different liking patterns using data from an online food liking-disliking questionnaire including 87 different foods and beverages. This study revealed four food-liking patterns by principal component analysis (PCA): fruit and vegetables; sweet and high carbohydrates; meat; distinctive tastes (including chilly paper, garlic or other foods with strong taste). Moderate heritability was obtained for all of them (fruit and vegetables: 0.36; sweet and high carbohydrates: 0.52; meat: 0.44; distinctive tastes: 0.58), corroborating past works on genetic influences of food liking-disliking (*Pallister T et al, 2015*). However, similar heritability estimates reached by studies with both large and small sample size suggest that environmental factors also play a crucial role.

Overall, these studies are useful in providing a quantitative estimate of the heritability of food liking and in supporting the idea that genetic determinants play a role. However, as already mentioned, they do not give information concerning specific genes accounting for food liking.

Candidate gene studies

A candidate gene study requires "*a priori"* hypothesis based on a potential role of a given gene on a given trait of interest (*Zhu M, Shuhong Zhao S., 2007*). Regarding food liking, this approach has been used to examine the possible role of polymorphisms in genes already known to be involved in taste or smell perceptions. These two senses allow us to recognize and to discriminate foods and are among the most important determinants of food liking (*Glanz K et al, 1998; Drewnowski A et al, 1999; Boesveldt S et al, 2017*).

For these reasons, DNA polymorphisms in taste and smell genes have played an important role in individual variability on food choices.

Taste receptor genes

It is well ascertained that genetic factors influence taste perception. Genes encoding taste receptors have been identified and genetic variability of sweet, umami and bitter perceptions have been intensely investigated; although knowledge gaps exist for sour and salty perception (*Tepper BJ, 2008; Feeney E., Nutrition Bulletin 2011; Hayes JE et al., 2013; Feeney E et al, Proc Nutr Soc, 2011; Negri R et al, 2012; Garcia-Bailo B et al, 2009; Chamoun E et al, 2018*).

A very well known example is that of the *TAS2R38* bitter receptor, a major contributor to individual differences in bitter taste perception of PROP (6-n-propylthiouracil) or PTC (phenylthiocarbamide). About 30-40% of the European population is taste-blind to these compounds or perceive them weakly bitter (so-called non tasters), while the remaining 70-60% can perceive them moderately or intensely bitter (so-called tasters). Three SNPs in *TAS2R38* gene (rs1726866, rs10246939, rs713598) result in three amino acid substitutions defining two main haplotypes, namely AVI and PAV that confer differences in the ability to taste PTC/PROP. Indeed, individuals homozygous for the AVI haplotype are mainly non taster, while homozygous for the PAV haplotype and heterozygous individuals are likely to be tasters (*Kin UK et al, 2003; Guo SW, Reed DR, 2001; Kin UK et al, 2005; Bufe B et al, 2005*).

Although controversial results have emerged in the literature, the variation in the ability to perceive PROP has been widely related to liking for different foods such as brassica vegetables, other bitter foods, sweets, added fat, spicy foods and alcoholic beverages (*Hayes JE et al, 2011; Tepper BJ, 2008; Dinehart ME et al, 2006; Keller KL et al, 2002; Ullrich NV et al 2004; Hayes JE, Duffy VB, 2008*). For example, Mennella and collaborators showed that in children, but not in adults, *TAS2R38* variations partially explained individual preferences for sucrose or beverages and cereals with high sugar content (*Mennella et al, 2005*). A study in Malaysian adults showed mixed results. Specifically, the authors reported that aversions to individual foods such as green tea, mayonnaise and whipped cream were associated to *TAS2R38* genotypes, while no associations were observed for vegetables and sweet/fat foods (*Ooi SX et al, 2010*). More recently, a study by Shen et al. showed that AVI/AVI subjects liked brassica vegetables

more than PAV/AVI and PAV/PAV individuals (*Shen Y et al, 2016*). In another recent work, *Perna* and collaborators reported that one specific polymorphism in the *TAS2R38* gene was associated with liking for beer, butter and cured meat (*Perna S et al, 2018*). However, a link between *TAS2R38* genetic variants and food liking has not been observed in other studies and several reasons could be responsible for the inconsistent findings such as food assessment methods, sample size, cultural habits or other environmental factors that may influence the association.

Evidences of a relationship between other bitter taste receptors genes and liking of common foods and beverages have also been reported. For example, variation in the *TAS2R19* bitter-taste gene showed associations with grapefruit juice bitterness and liking (*Hayes JE et al, 2011*), while another bitter-taste gene, *TAS2R43,* has been related to coffee liking (*Mennella JA et al, 2005*). Data also suggested a possible influence of genetic variation in the *TAS1R3* sweet receptor gene on sweet liking in children (*Mennella JA et al, 2012*), as well as a link between variations in *CD36* gene (responsible for fat taste perception) and fat preferences (*Keller KL et al, 2012*).

The studies mentioned above have limited implications for general food liking because they analyze only one or few genes (or SNPs) and they examine liking for just one or few foods. To address this shortcoming, our group examined the relationship between a broad spectrum of food liking and DNA variants in 27 taste and olfaction genes in a large cohort of > 400 individuals coming from Caucasus and Central Asia (*Pirastu N et al, 2012*). Statistically significant associations were identified for genes involved in chemosensory functions (i.e., *TRPV1* and *TAS1R2*) or in signal transduction (i.e. *PLCβ2* and *ITPR3*). One of the most interesting associations was found between the *TAS1R2* gene (coding for a sweet taste receptor) and liking of alcoholic beverages, according to data reporting a link between ethanol preference and liking for sweet taste. In particular, the less frequent alleles for two different SNPs (rs3935570 and rs4920566) in the *TAS1R2* gene were positively associated with the liking of vodka and white wine. Another noteworthy association was detected for tea and the *PLCβ2* gene, a marker for type II taste bud cells, involved in caffeine response and also expressed in the sensory cells of the olfactory epithelium. In this case, the rarest allele of rs2290550 SNP was negatively correlated with tea liking.

Olfactory receptor genes

Humans vary in the capacity to perceive several odors and variation in olfactory receptor (OR) genes may be responsible for these differences (*Wysocki CJ and Beauchamp GK, 1984; Keller A et al, 2007*). Despite more than 400 genes/receptors being involved in smell perception, little is known about the link between these genes and specific odorants as well as their possible influence on food liking. One of the most recognized examples is the role of olfactory receptor gene *OR7D4* that is partially responsible for individual differences in the ability to smell androsterone (*Wysocki CJ and Beauchamp GK, 1984*). Androsterone is undetectable for some people while others define it as foul smelling or urine and sweat smelling and others describe it as sweet or floral smelling. Two SNPs in *OR7D4* gene are responsible for two amino acid substitutions that impair the ability to perceive androstenone (*Keller A et al, 2007*). Androstenone is present in male pork meat. A recent study confirmed that *OR7D4* variants were associated with the sensory perception of pork meat containing androstenone as well as lower liking for the flavor and odor of pork meat by androstenone-sensitive individuals (*Lunde K et al, 2012*).

Another example is the *OR2J3* gene associated with individual differences in detecting *Cis*-3-hexen-1-ol (C3HEX), an odorant with green/grassy smell present in several fruits and vegetables. Polymorphisms in this gene are responsible for amino acid substitutions impairing the ability to smell C3HEX. Subjects can be classified in C3HEX-sensitive or C3HEX-insensitive (*Jaeger SR et al, 2010; McRae JF et al, 2012*). Moreover, foods spiked with C3HEX were less acceptable than the unspiked foods; however, the reductions in acceptability were more marked in C3HEX-sensitive individuals if compared to C3HEX-insensitive individuals (*Jaeger SR et al, 2012*).

Finally, studies examined variation in the *OR5A1* gene, related to β-ionone odor sensitivity. β-ionone aroma is a fruity/floral aroma present in several foods and beverages (*Etievant PX et al, 1983; Larsen M et al, 1991; Tandon KS et al, 2000; Mahattanatawee K et al, 2005*). A series of studies by Jaeger and co-workers showed that a DNA variation (rs6591536 SNP) in the *OR5A1* gene is the causal variant for β-ionone odor sensitivity, explaining the 96,3% of the phenotypic variation. They also reported that β-ionone sensitive individuals can easily differentiate between foods (such as milk chocolate or apple juice) with and without added β-ionone, and they can also recognize β-ionone in foods when compared to less-sensitive individuals. Moreover,

sensitive individuals prefer foods without β-ionone rather than with β-ionone (*Jaeger SR et al 2013*).

GWA studies

Over the past decade, the GWAS approach has become one of the most common tools for the identification of genes associated with complex traits and diseases. In this kind of studies, a large number of participants are genotyped for a hundreds of thousands of genetic markers (usually SNPs) covering the whole genome and their relationships with the trait of interest are examined, allowing the identification of novel gene variants and genomic loci (*Visscher PM et al, 2017*).

To date, very few GWAS have been conducted on food liking, which are summarized in Table 9. Although a genome-wide scan typically analyzes thousands or even millions of SNPs, Table 9 reports only GWAS significant SNPs with p-value $<5x10^{-8}$. This p-value is equivalent to the Bonferroni-corrected threshold ($\alpha=0.05$) for 1 million independent variants (approximately the number of independent SNPs analyzed in a GWAS).

The first GWAS was carried out on cilantro (or coriander) liking in a large cohort of unrelated European subjects belonging to the 23andMe cohort (*Eriksson N et al, 2010*), who responded to an online questionnaire asking whether they taste cilantro as soapy and whether they like it. An association among the rs72921001 SNP, soapy taste and disliking of cilantro was found. This SNP falls within a cluster of eight olfactory receptor genes on chromosome 11. Among them, the authors suggested that a good candidate for cilantro preferences could be the *OR6A2* gene coding for a receptor that can be activated by several aldehydes responsible for the characteristic odor of cilantro (*Eriksson N et al, 2012*). More recently, in our lab was conducted the first GWAS on red and white wine liking assessed by survey-reported food liking in 3885 adults coming from different geographic areas (Italy, the Netherland and Central Asia) (*Pirastu N et al, 2015*). In this work, a significant association between white wine liking and rs9276975 SNP in the *HLA-DOA* gene, encoding for a non-canonical MHC (major histocompatibility complex) II molecule was detected. Although the mechanism of how MHC could be linked to wine liking is unknown, the possible involvement of the olfactory system was hypothesized.

Table 9. GWA studies of food liking. Only genome-wide significant SNPs (p-value< $5x10^{-8}$) were included. Associated trait refers to the associated food liking; SNP shows the name polymorphism; Locus refers to the gene closest to the most significant SNP.

Reference	Subjects (n)	Population	Food liking assessment	Associated trait	SNP	Locus
Eriksson et al. 2012	26455	Unrelated (European)	Responses to an online survey asking the following questions: - Does fresh cilantro taste like soap to you?" (Yes/No/I'm not sure) -Do you like the taste of fresh (not dried) cilantro?" (Yes/No/I'm not sure)	Cilantro	rs72921001	*OR6A2*
Pirastu et al. 2015	3885	Isolated population (European and Central Asia)	Survey-reported food liking (5-point scale or 9-point scale)	White wine	rs9276975	*HLA-DOA*
Pirastu et al. 2016	4611	Isolated population (European and Central Asia)	Survey-reported food liking (5-point scale or 9-point scale)	Artichokes	rs28849980	CCRN4L
				Artichokes	rs28849980	ADAMTS19-CHSY3
				Artichokes	rs8034691	LOC100128714
				Broccoli	rs2530184	NA
				Broccoli	rs9832668	RYBP
				Broccoli	rs138369603	CSMD1
				Bacon	rs140738262	CNTN5
				Oil or Butter on Bread	rs6661761	BPNT1
				Blue Cheese	rs12994253	KCMF1-TCF7L1
				Ice Cream	rs2035613	IRX4
				Liver	rs34088951	RNU6-66
				Coffee	rs145671205	FIBIN

Moreover, another GWAS on the liking of 20 different foods was carried out on a large cohort of 4611 individuals from Europe and Central Asia, which identified 15 novel significant variants associated with 12 different foods (*Pirastu N et al, 2016*). Some of these variants are located within genes that might represent good candidates for food choices. Interestingly, none of them belong to taste or olfactory receptors gene families but are likely to be involved in reward response to food (i.e., *BPNT1, IRX4, CNTN5* and

CSMD1 genes). For example, an association was detected between the liking of bacon and rs140738262 SNP in the *CNTN5* gene. This polymorphism showed marginal association also with the liking of other fatty foods such as lamb, pork chops and goat cheese. This gene is expressed in the brain and has previously been associated with anorexia nervosa, suggesting a possible link with preferences for palatable food and response of the brain reward system to these foods. For vegetables, an association between chicory liking and rs138369603 SNP in the *CSMD1* gene has emerged. Pirastu and colleagues hypothesized a possible role of this gene in the regulation of food reward response since its variants were linked to differential activation of the cuneus, an area possibly involved in central reward processing.

Overall, these results represent a step in understanding the biological bases of food liking and suggest that the GWAS approach may be useful in identifying novel candidate genes for food preferences. Nowadays, thanks to the reduction of SNP genotyping costs as well as to the existence of large population biobanks, GWA studies could contribute to identifying many more loci that will enhance insight into the genetic architecture of food liking. Thus, further studies should be conducted to confirm previous findings, to extend the range of examined foods and analyze also food groups.

4. *CAV1*: a new candidate gene for eating disinhibition and food liking?

4.1. Background and aim

Human eating disinhibition, a loss of restraint resulting in overeating, is a complex trait influenced by genetic and environmental factors (*Grimm and Steinle 2011*).

High disinhibition has been associated with making less healthy food choices. Indeed, a positive correlation with higher liking or consumption of alcohol and high-fat and high-sugar foods was reported in previous studies, as well as a negative association with the consumption of vegetables, fruit and high-fiber bread (*Contento et al. 2005; Lahteenmaki et al. 1995; Bryant et al. 2006; Bryant et al. 2008; Borg et al. 2008; Higgs et al. 2007*). A relationship between disinhibition and high-energy intakes was also reported in obese subjects (*Lindroos et al. 1997*) and several studies have shown a link between this eating behavior and BMI, weight gain over time and the development of obesity (*Löffler et al. 2015; Bryant et al. 2008; Bellisle et al. 2004; Hays et al. 2008; Williamson et al. 1995*). Higher disinhibition was also associated with diabetes, increased insulin levels and glycemic control (*Schwab et al. 2016; Straub et al. 1996*) as well as hypertension or hyperlipidemia (*Hainer et al. 2006*).

Moreover, evidence for a genetic contribution to individual eating disinhibition has been reported. Heritability was estimated between 0.19 and 0.45 (*Steinle et al. 2002; Provencher et al. 2003; Neale et al. 2003*) and through linkage analysis two loci on chromosomes 7 and 16 were identified as likely linked to this eating behavior (*Steinle et al. 2002*). Another genome-wide linkage analysis led to the identification of a locus on chromosome 15 surrounding the *neuromedin β* gene (*NMB*). NMB is widely expressed in the brain, pancreas, adrenals, and gastrointestinal tract; it is known to inhibit food intake in rat and it is involved in the modulation of the serotonergic (5-HT) system and the stimulation of pancreatic hormones. A missense mutation in this gene resulted associated with disinhibition and susceptibility to hunger as well as changes in body fat (*Bouchard et al 2004*).

Candidate gene studies have also been conducted, supporting the role of genetics in eating behavior. For example, genes associated with taste perception, have been studied in relation to eating disinhibition and an association with genetic variation in *TAS2R38* bitter taste gene has been reported in Old Order Amish (*Dotson et al. 2010*).

Furthermore, genes previously associated with BMI or obesity, such as *FTO* gene, have been investigated**.** For instance, a study reported that rs9939609 SNP in *this* gene resulted also linked with loss of control overeating and selection of fat foods (*Tanofsky-Kraff et al. 2009*). Another obesity-related gene studied as a possible candidate gene linked to eating disinhibition has been *GAD2 (glutamate decarboxylase),* implicated in the GABA (gamma-aminobutyric acid) formation, a neurotransmitter involved in food intake regulation. In a French cohort, a functional polymorphism in the 5' promoter region of this gene was related to disinhibition and hunger scores in obese subjects (*Boutin et al. 2003*). Meyre et al. (2005) further reported an association between the promoter variant in *GAD2* and lower birth weight and subsequently higher BMI in French children. Moreover, another SNP in *GAD2* gene (rs992990) was associated with increased disinhibition, emotional susceptibility to disinhibition, susceptibility to hunger and weight gain over time in women from the Quebec Family Study (*Choquette et al. 2009*).

In other work, the relation between eating disinhibition and genetic variants located in the *AKR1B10* gene was investigated. AKR1B10 encodes for an enzyme involved in detoxifying processes during digestion and its expression in brain regions potentially involved in eating behavior, such as nucleus accumbens and the frontal cortex, is diminished (*Rohde et al. 2015*).

Nonetheless, to date little is yet known about genetic influences on eating disinhibition. In this work, a GWAS and replication study for eating disinhibition were carried out. Moreover, we evaluated the relationship between disinhibition (and identified variants) with food liking groups and anthropometric phenotypes such as BMI and waist-hip ratio.

4.2. Materials and methods

Study populations

The discovery sample was comprised of 1124 individuals belonging to the Val Borbera cohort, while replication analysis was carried out in 426 individuals coming from the Carlantino village. More details about these populations are reported in section 1.2.. The ethical committees of San Raffaele and IRCCS Burlo Garofolo approved the study, and all participants signed written informed consent.

Eating disinhibition

Eating disinhibition was evaluated based on the statements from the three-factor eating questionnaire, as already described in section 1.2.. Briefly, disinhibition was assessed with the following three questions: "Sometimes things just taste so good that I keep on eating even when I am no longer hungry", "I usually eat too much at social occasions, like parties and picnics" and "When I feel blue, I often overeat". An affirmative answer was marked 1 point each one, with total scores ranging from 0 to 3.

Food liking groups

As explained in section 1.2., liking of different foods and beverages was assessed utilizing a questionnaire administered to each subject in a 9-point hedonic scale ranging from "dislike extremely" (score 1) to "like extremely" (score 9). The foods were aggregated into food groups based on similar liking ratings using cluster analysis and then confirmed by Cronbach reliability test. Each "food liking group" was defined as the average of liking given by each individual to the foods belonging to a particular group. In this work three food liking groups were studied: alcoholic beverages (alcohol, Grappa, beer, dark beer, red wine, white wine, Cinzano, Cherry), sweet foods (ice cream, panettone, whipped cream, milk chocolate, marzipan, biscuit, cake, icing, Nutella, chocolate with cream) and high-fat foods (gorgonzola, goat cheese, pork chops, capicola, bacon, mortadella). The Cronbach alpha of each group was higher than 0.6, supporting internal reliability.

Anthropometric traits

Body Mass Index (BMI) was obtained by the Bioelectrical Impedance Analysis technique using the Body Composition Analyzer (Tanita BC-420MA; Tanita, Tokyo, Japan). Waist and hip circumference (both in cm) were measured and waist-hip ratio (WHR) was calculated.

Genotyping and imputation

All discovery and replication samples have been genotyped with Illumina 370 k high-density SNP array. Genotype imputation was conducted after standard quality control using IMPUTE2 (*Howie et al., 2009*) considering as reference a custom panel generated merging the 1000 Genomes phase 3 reference panel (*Abecasis GR et al., 2012*) and whole genome sequences of INGI samples (*Cocca M et al., 2019*). After imputation, SNPs with

MAF<0.01 and Info Score<0.4 were discarded from the statistical analyses.

Genome Wide Association study and replication analysis

Association studies were conducted using mixed linear models as implemented in ABEL R packages (*Aulchenko YS et al., 2007*). Genomic kinship matrices were used as random effects in order to take into account the relatedness. The models were adjusted by sex and age.

A two-step approach was used. First, a genome-wide discovery was carried out in 1124 individuals of the VB cohort. The SNPs showing association with the trait at the significance level of p-value<$1x10^{-5}$ were selected to be replicated in 426 individuals of the CAR population. The results were meta-analyzed using an inverse-variance method (*METAL, Willer CJ et al. 2010*). After meta-analysis, SNPs with p-value<$5x10^{-8}$ were considered as significant.

Linkage disequilibrium between SNPs was assessed in 424 whole genome sequences from VB and 124 from CAR using R library Genetics.

Relationship between eating disinhibition/SNPs and food liking groups and anthropometric traits

In order to evaluate the association of eating disinhibition and associated polymorphisms with food liking groups and anthropometric parameters, linear mixed models were constructed. Food liking groups and anthropometric traits were considered as dependent variables and disinhibition and polymorphisms genotypes as explanatory variables. Age and sex were added as covariates in all models. Because of the relatedness structures of VB and CAR samples, genomic pairwise kinship coefficients matrices were included in the models as a random effect, as implemented in 'coxme' R package. The analyses were performed in each population separately and then the results were meta-analyzed ('rmeta' R package). Statistical significance was set at p-value < 0.05.

Moreover, to better understand the complex interplay with variables, models were developed and tested with Structural Equation Modeling (SEM, lavaan R package; more details are reported in section 2.2.) in order to identify the direct and indirect influences of polymorphisms on food liking. Gender, age and population (CAR or VB) were included in the models as potential confounders. Criteria for overall fit were chosen a priori: chi-

square p-value non-significant ($\chi 2$ p>0.05), Confirmatory Fit Index (CFI) ≥ 0.92, Tucker-Lewis Index (TLI) > 0.87 and Root Mean Square Error of Approximation (RMSEA) < 0.05 (*Tabachnick, B.G. and Fidell L.S., 2001*).

4.3. Results

Sample characteristics

1124 adults (age range 18-90 years) were included in the discovery sample and 426 (age range 18-89) in replication sample. Table 10 shows the sample characteristic for both populations.

Table 10. Characteristics of individuals included in the study. The values are median and interquartile interval when not specified.

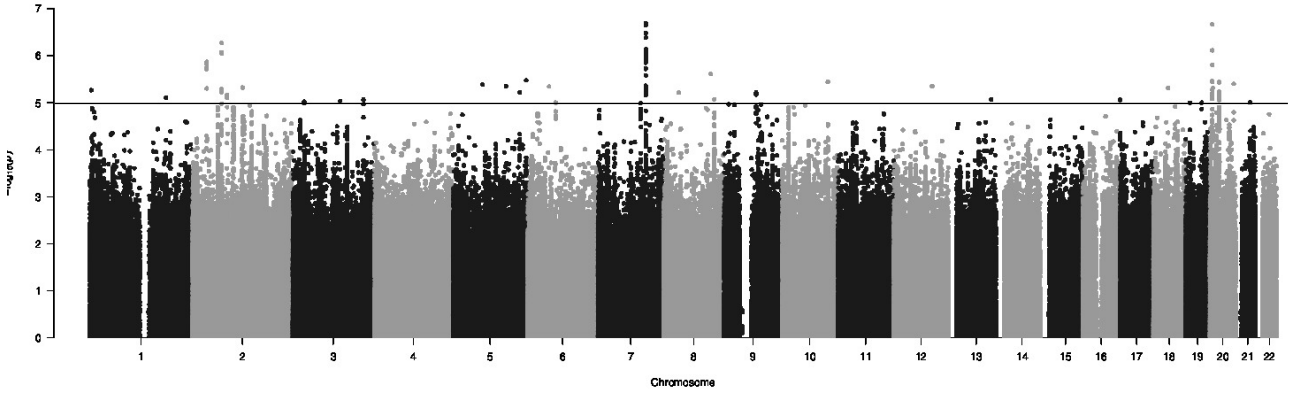
	Discovery sample VB	**Replication sample CAR**
N (% women)	1124 (60.7%)	426 (54.2%)
Age, mean (standard deviation)	56.1 (16.5)	51.8 (17.1)
Disinhibition	2 [1-2]	1 [1-2]
Liking of Sweet foods	6.6 [5.4-7.4]	6.6 [5.2-7.7]
Liking of Alcoholic beverages	4.5 [3.2-6.0]	5.6 [3.8-7.0]
Liking of high-fat foods	6.8 [5.8-7.5]	7.2 [6.2-8.0]
BMI (Kg/m^2), n, mean (sd)	1118, 25.6 (4.4)	365, 26.4 (4.8)
Hip (cm), n, mean (sd)	1105, 89.9 (12.3)	310, 88.02 (13.87)
Waist (cm), n, mean (sd)	405, 98.72 (9.75)	310, 100.97 (11.44)
Waist Hip ratio, n, mean (sd)	405, 0.90 (0.07)	310, 0.87 (0.08)

GWAS and meta-analysis results

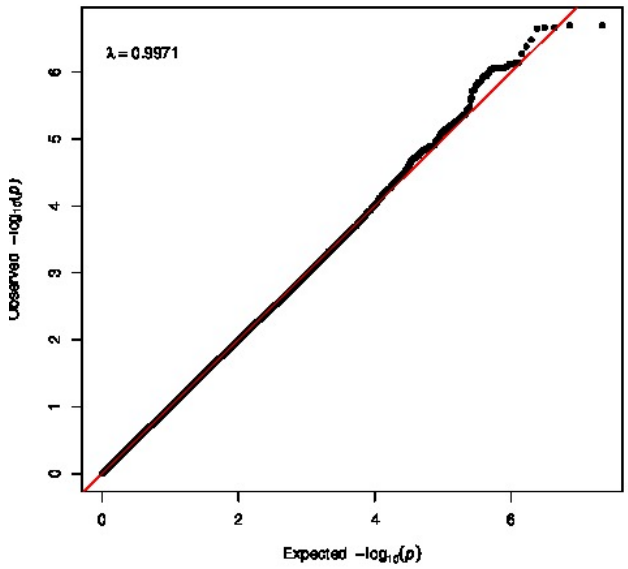
The effect of population stratification on the GWAs on discovery sample was negligible as confirmed by the value of the genomic inflation factor (lambda=0.9971). QQ-plot and Manhattan-plot were shown in Figure 6 a) and b)).

Figure 6 a). Manhattan plot of GWAs of eating disinhibition on 1124 individuals of Val Borbera. The line is set at p-value=1×10^{-5} and the SNPs above the line were selected for replication step. b). QQ-plot of GWAs of eating disinhibition on 1124 individuals of Val Borbera.

a)



b)



118 SNPs achieved the suggestive threshold of p-value < 1x10^{-5} and were selected for replication in the CAR cohort (data not shown). After meta-analysis, 7 SNPs achieved the genome-wide significant threshold of 5x10^{-8} (Table 11).

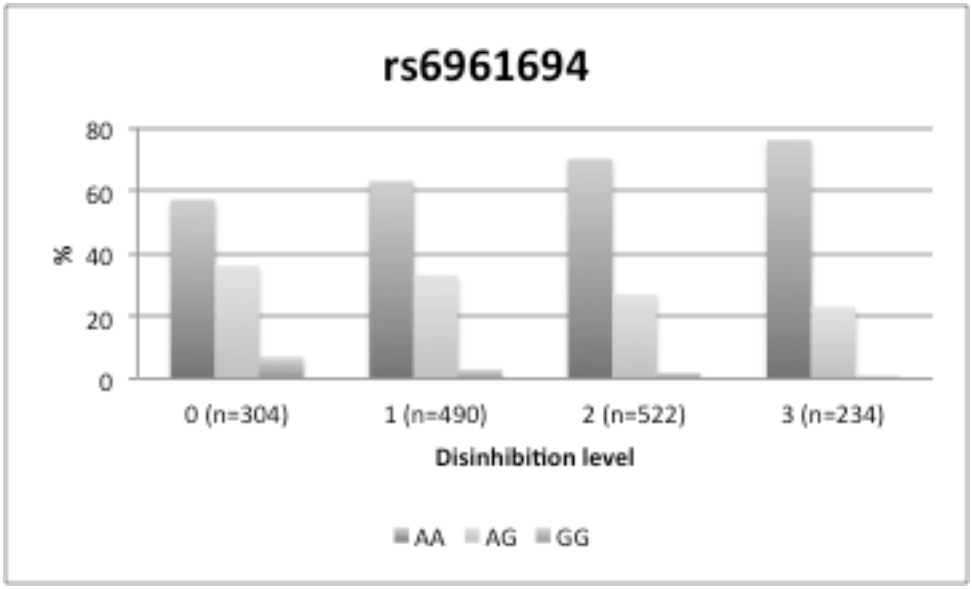
Table 11. Top SNPs from the meta-analysis of GWAS and replication study results for eating disinhibition. All SNPs are in *CAV1* gene in chromosome 7 and showed info score>0.9. *Effect allele/Other allele; ** frequency of effect allele; beta=effect; se=standard error.

			Discovery sample VB (n=1124)			Replication sample CAR (n=426)			Combined sample (n=1550)	
SNP	**Genomic location**	**Alleles***	**freq A1****	**Beta (se)**	**p-value**	**freq A1****	**Beta (se)**	**p-value**	**Beta (se)**	**p-value**
rs6466582	upstream variant 2KB	A/G	0.84	0.2854 (0.058)	8.55E-07	0.80	0.223 (0.0802)	5.42E-03	0.264 (0.047)	1.98E-08
rs6950593	upstream variant 2KB	T/C	0.84	0.2876 (0.0581)	7.27E-07	0.81	0.2124 (0.0810)	8.77E-03	0.2622 (0.0473)	2.86E-08
rs2215448	upstream variant 2KB	G/A	0.84	0.2876 (0.0581)	7.30E-07	0.81	0.1997 (0.0813)	1.40E-02	0.2581 (0.0473)	4.89E-08
rs3807986	intron	A/G	0.77	0.2547 (0.0499)	3.30E-07	0.79	0.1771 (0.0776)	2.25E-02	0.2321 (0.042)	3.28E-08
rs976739	intron	C/A	0.81	0.2821 (0.0543)	2.01E-07	0.82	0.1945 (0.0825)	1.85E-02	0.2558 (0.0454)	1.75E-08
rs3779514	intron	C/T	0.81	0.2821 (0.0544)	2.19E-07	0.82	0.1954 (0.0826)	1.80E-02	0.256 (0.0455)	1.85E-08
rs6961694	intron	A/G	0.81	0.2821 (0.0543)	2.01E-07	0.82	0.1945 (0.0825)	1.85E-02	0.2558 (0.0454)	1.75E-08

These SNPs are located in a region of about 39 Kb in Caveolin 1 (*CAV1*) gene in chromosome 7. All SNPs are in linkage disequilibrium (LD) in both samples: the minimum D' score was 0.94 in VB and 0.9994 in CAR. Because of this high LD, only one SNP was selected for the follow-up analysis: the hit rs6961694.

The results showed that individuals carrying the A allele in homozygous state for the selected SNP showed higher disinhibition level than individuals carrying G allele (AG or GG), as shown in Figure 7.

Figure 7. Distribution of eating disinhibition levels by rs6961694 genotypes.

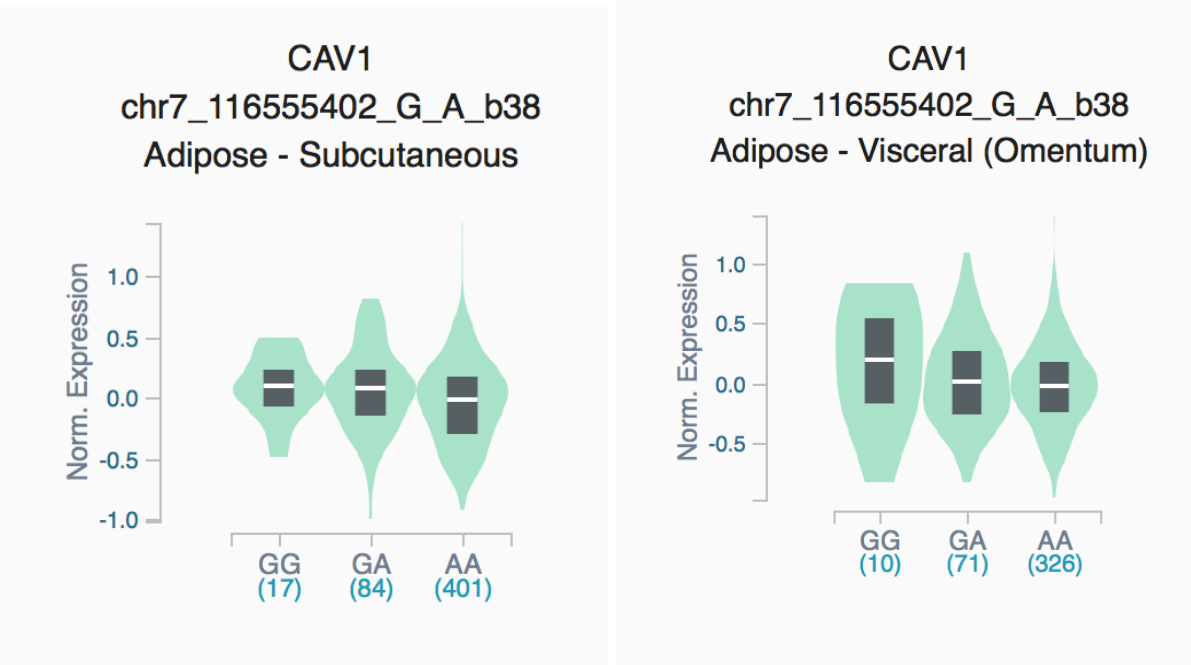


rs6961694 and CAV1 gene expression levels

The association between rs6961694 and *CAV1* gene expression levels was analysed in multiple tissues using the GTEx (Genotype-Tissue Expression) Database ("*Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans", 2015).* GTEx eQTL browser is a central resource that records and shows the results of a national research project for determining the association between genetic variation and high-throughput molecular-level expression phenotypes, and this information can help to understand better the biological relevance of results from GWA studies.

A significant eQTL association between rs6961694 SNP and *CAV1* expression levels was observed in adipose subcutaneous and visceral tissues (p-value = 0.00028 and p-value = 0.047 respectively). As shown in Figure 8, A allele was correlated with reduced expression of *CAV1* gene.

Figure 8. GTEx eQTL analysis of rs6961694.



Effect of disinhibition and rs6961694 on food liking

We checked the association of eating disinhibition and rs6961694 with food liking groups. Different models were carried out in order to better understand the effect of disinhibition and rs6961694 genotypes and their interplay. Table 12 shows the results of association of food liking groups with eating disinhibition and *CAV1* variant. Associations with disinhibition were found for the all food liking groups (p-values <0.05): increasing disinhibition corresponded to higher foods liking. The SNP resulted associated with alcohol beverages and sweet liking groups, but no high-fat foods, with the same direction of the association with eating disinhibition: AA carriers showed higher disinhibition and higher liking compared to AG or GG carriers.

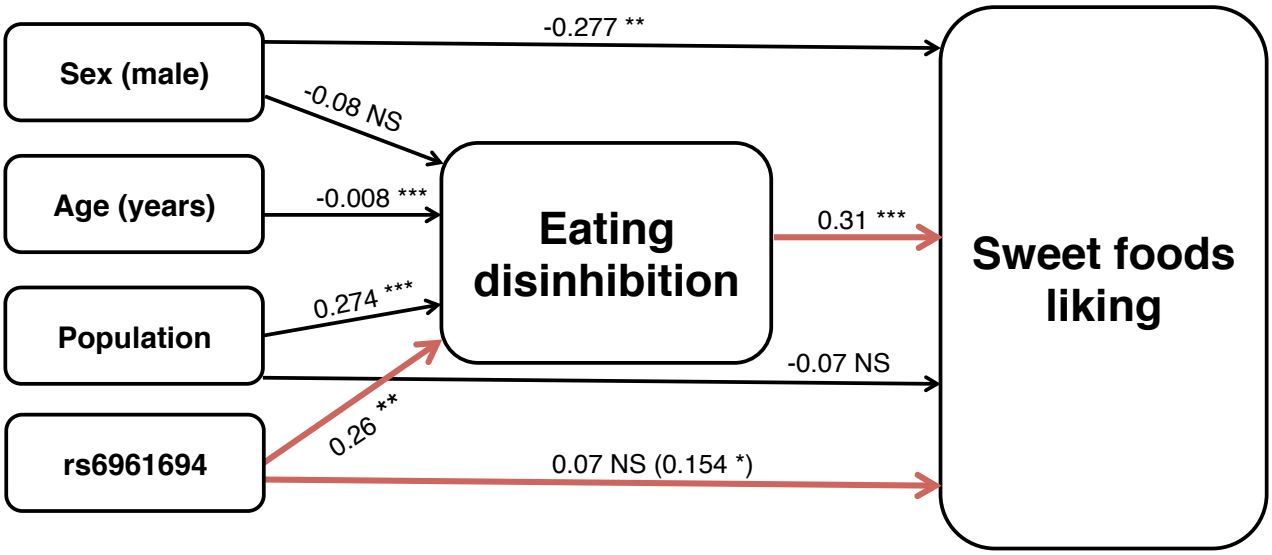
Table 12. Results of association of food liking (response variable) with eating disinhibition and rs6961694 (independent variables). Models are sex and age adjusted.

	Disinhibition		**rs6961694**	
Liking group	**Effect (95% CI)**	**p-value**	**Effect (95% CI)**	**p-value**
Alcoholic beverages	0.127 (0.032,0.223)	0.0088	0.265 (0.44, 0.092)	0.00258
Sweet foods	0.317 (0.237,0.397)	<0.0001	0.154 (0.302,0.006)	0.041
High-fat foods	0.149 (0.08,0.217)	<0.0001	0.056 (-0.068,0.18)	0.37

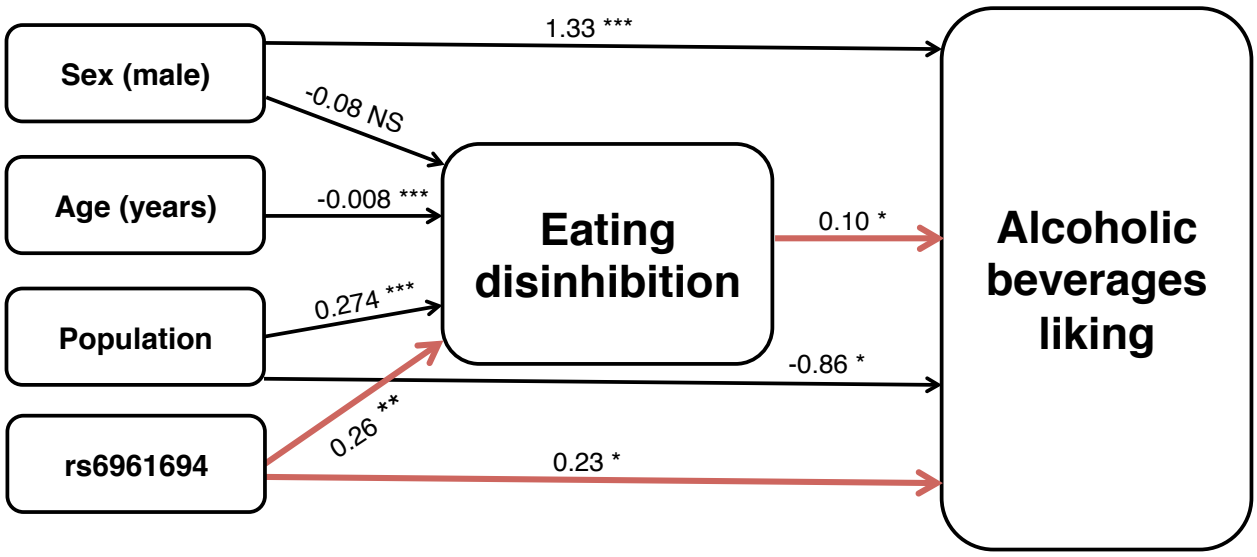
Because of the association of both SNP and disinhibition with alcoholic beverages and sweet liking, SEM models were performed to test the direct and indirect effects of the SNP. Figure 9 shows the results of the models: the effect of rs6961694 on sweet food liking was completely mediated by disinhibition (Figure 9 a)) while the effect on alcoholic beverages was both direct and indirect (Figure 9 b)). Both models had a good fit.

Figure 9. Results of SEM models (Lavaan R package) for sweet liking (a) and alcoholic beverages (b) liking groups. Reported values are betas and p-values *≤0.05, **≤0.01, ** ≤0.0001. Pop=population (CAR/VB). In brackets are the values before eating disinhibition was added to the model. Both models had a good fit (CFI=1.0, TLI=1.04, p-value Chi-square=0.63, RMSEA=0.0 for sweet foods and CFI=0.999, TLI=0.994, p-value Chi-square=0.269, RMSEA=0.012 for alcoholic beverages). The relationship of the SNP with sweet liking was completely mediated by eating disinhibition while the relationship with alcoholic beverages was both direct and indirect.

a)



b)



Effect of disinhibition and rs6961694 on anthropometric traits

In Table 13 the results of mixed models used to test the association between anthropometric measures and disinhibition and rs6961694 are displayed. Eating disinhibition showed significant association with all the traits except WHR: increasing disinhibition corresponded to higher values of BMI, waist and hips. No association was found with the SNP.

Table 13. Results of association of anthropometric measures (response variables) with eating disinhibition and *rs6961694* as independent variables (sex and age adjusted).

	Disinhibition		**rs6961694**	
Anthropometric traits	**Effect (95% CI)**	**p-value**	**Effect (95% CI)**	**p-value**
BMI, Kg/m^2	0.751 (0.537,0.966)	<0.0001	-0.202 (-0.619,0.215)	0.34
WHR	0.003 (-0.002,0.007)	0.23	-0.001 (-0.009,0.007)	0.81
Waist, cm	1.794 (1.230,2.358)	<0.0001	-0.655 (-1.732,0.423)	0.23
Hips, cm	1.82 (1.098,2.542)	<0.0001	-0.775 (-2.141,0.59)	0.27

4.4. Discussion

Through GWAS and replication study, we found an association between *CAV1* gene and eating disinhibition. The top SNP rs6961694 resulted also associated with the liking for alcoholic beverages and sweet foods, but not with the liking for high-fat foods and anthropometric measures. Finally, using GTEx, a significant eQTL association between rs6961694 and *CAV1* expression levels was observed in adipose tissues.

Based on our knowledge, this is the first GWAS on eating disinhibition. Indeed, most of the researches about the genetics influences on this trait were linkage analysis based (*Steinle et al. 2002; Bouchard et al 2004*) or studies on candidate genes involved in taste (*Dotson et al. 2010*) or related to obesity (*Tanofsky-Kraff et al. 2009; Boutin et al. 2003; Meyre et al. 2005; Choquette et al. 2009*).

Although in our samples no association was found between *CAV1* SNP and anthropometric measures, many studies showed relationship between this gene and

obesity related traits such as hypertension (*Grilo A et al., 2006; Yamada Y et al., 2007; Pojoga LH et al., 2011*) or metabolic syndrome (*Baudrand R et al., 2015; Baudrand R et al, 2015; Grilo A et al., 2006*). The link between *CAV1* and obesity was also investigated using animal models. For example, *Razani et al (2002)* showed that *CAV1* knockout mice are protected from diet-induced obesity.

As expected, in our sample high eating disinhibition resulted associated with higher obesity related traits such as BMI, waist and hips, in agreement with other studies (*Löffler et al. 2015; Bryant et al. 2008; Bellisle et al. 2004; Hays et al. 2008; Williamson et al. 1995*). Moreover, a link between high eating disinhibition and higher liking for alcoholic beverages, sweet foods and high-fat foods was confirmed (*Concas et al., 2019*).

In conclusion, our results suggest that *CAV1* is a possible candidate gene for eating disinhibition and specific food liking groups and represent a starting point for further studies linking eating behaviors and health status. Additional studies are needed to confirm our results and to better understand these relationships.

CHAPTER IV

RELATIONSHIP BETWEEN FOOD LIKING AND HEALTH

In this chapter, I present my work on the association between food liking and health. This section is divided into two parts: the first is about the relationship between food liking and metabolic parameters and the second about genetic variants found in association with food liking and their link with health through polygenic risk score analysis.

5. Relationship between food liking and metabolic traits

5.1. Background and aim

Past works assessed the relationship between liking for fat-rich foods and adiposity, reporting a positive correlation between fat preference and body fat or anthropometric measurements such as Body Mass Index and waist to hip circumference ratio *(Nakamura, Shimai, Kikuchi, & Tanaka, 2001; D J Mela & Sacchetti, 1991*). Studies on children also showed that preferences for fat-rich foods correlate positively with high dietary fat intake and BMI (*Ricketts, 1997*). Duffy and collaborators have reported that food preferences for fat and fibres are better than reported food consumptions, explaining variability in adiposity and in blood pressure, suggesting that preferences are more reliable markers in estimating the impact of nutrition on health (*Duffy, Hayes, Sullivan, & Faghri, 2009; Duffy et al., 2007; D J Mela & Sacchetti, 1991; Sharafi et al. 2018*). More recently, a study conducted in our laboratory showed a positive association between caries prevalence and sweet food liking, but not with simple sugar intake, suggesting that food liking, rather than reported food intake, can be a valid determinant of health outcomes (*Robino et al., 2015*).

Here, the results of a study of more than 3000 samples to investigate the relationship between food liking groups and some metabolic phenotypes, such as BMI, cholesterol, glucose and blood pressure, are shown.

Despite past works have already examined the relationship between food liking measures and metabolic parameters, comparing them also with intake measures, most of these works analysed small cohorts and focused on few health parameters and liking for specific foods or food groups. On the contrary, although our study did not measure

reported dietary intake, we can exploit the advantages of a large sample size to analyse simultaneously demographic variables, metabolic traits and liking for different food groups.

5.2. Materials and methods

Data collection

3219 individuals belonging to the INGI populations were included in the study. More details are reported in section 1.2..

BMI and Fat Mass were obtained by the Bioelectrical Impedance Analysis technique using the Body Composition Analyzer (Tanita BC-420MA; Tanita, Tokyo, Japan). Waist and Hip circumference (both in cm) were measured and WHR was calculated. Fasting venous blood was collected and used to perform routine biochemical analyses through Cobas 6000 analyzer (Roche). Blood pressure measurements were obtained in the sitting position and with at least a two-minute interval between each measurement. A standard mercury sphygmomanometer was used.

Data analyses

Statistical analyses were performed in R 3.3.0. (www.r-project.org).

Food liking groups were defined as already explained in section 1.2..

To assess the relationship between food liking groups and health, for each metabolic parameter (anthropometric measures, lipids and blood pressure) as outcome variable, a multivariate regression model was carried out using food liking groups as predictors. Gender, age, education and physical activity were included in all models. BMI was also included as explanatory variable in regression models for serum lipids, glucose and blood pressure.

A log-transformation was applied, since the glucose and triglycerides were not normally distributed.

To consider possible differences in food liking groups among sampling, all the analyses were conducted in each sampling separately (CAR, FVG first and second survey, VB first and second surveys) and the results were combined using meta-analysis with an inverse variance fixed effect method (R package “rmeta”). We fixed the statistical significance at a p-value of 0.05. The analyses were carried out first on the whole sample and then stratified by gender.

5.3. Results

A total of 3219 individuals were included in the study and their personal and lifestyle characteristics are already reported in section 1.3.. Table 14 describes the features of samples as regards to anthropometric parameters, lipids, glucose and blood pressure.

Table 14. Characteristics of samples: anthropometric measures, lipids, glucose and blood pressure. The values are mean (standard deviation). In bold are reported significant differences between men and women (p-value<0.05). BMI=Body Mass Index; WHR=Waist to Hip Ratio; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure.

	CAR		**FVG**		**VB**	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
BMI, kg/m²	26.733 (4.107)	26.792 (5.634)	**26.818 (4.289)**	**24.223 (4.683)**	**26.229 (3.863)**	**24.996 (4.623)**
Normal (BMI<25), %	**34.9**	**44.6**	**37.7**	**61.8**	**41.3**	**56.6**
Overweight (25≤BMI<30), %	**45.0**	**23.9**	**42.0**	**26.3**	**43.6**	**30.3**
Obese (BMI≥30), %	**20.1**	**31.5**	**20.3**	**11.9**	15.1	13.1
WHR	**0.923 (0.063)**	**0.83 (0.064)**	**0.939 (0.083)**	**0.832 (0.078)**	**0.959 (0.06)**	**0.853 (0.062)**
Fat Mass, Kg	NA	NA	**19.948 (8.952)**	**21.236 (9.681)**	**17.312 (7.566)**	**20.18 (8.845)**
LDL Cholesterol, mg/dL	NA	NA	134.211 (40.4)	133.147 (40.288)	**125.444 (35.591)**	**129.525 (33.789)**
HDL Cholesterol, mg/dL	NA	NA	**53.265 (13.884)**	**64.677 (16.386)**	**52.643 (13.523)**	**63.238 (14.899)**
Total Cholesterol,mg/dL	200.856 (45.353)	199.785 (47.311)	213.096 (46.166)	217.944 (43.614)	**203.669 (40.774)**	**213.47 (37.882)**
Tryglicerides, mg/dL	**137.016 (65.326)**	**109.926 (54.205)**	**120.635 (62.944)**	**99.266 (46.524)**	**122.851 (68.079)**	**101.912 (52.906)**
Glucose, mg/dL	**97.091 (16.761)**	**92.427 (15.146)**	**96.212 (17.213)**	**91.01 (14.915)**	**90.694 (14.727)**	**86.955 (14.62)**
SBP, mmHg	131.121 (18.166)	127.793 (20.572)	**137.82 (20.505)**	**132.133 (22.52)**	**129.636 (16.482)**	**125.224 (19.996)**
DBP, mmHg	80.719 (9.965)	79.174 (11.069)	**86.136 (10.141)**	**81.86 (10.846)**	**79.17 (8.738)**	**75.445 (9.117)**

After cluster analysis and Cronbach reliability test, seven food liking groups were defined as explained in section 1.3..

Results of multivariate models assessing the relationship between food liking groups and some metabolic phenotypes, such as BMI, cholesterol, glucose and blood pressure are shown in Table 15.

Table 15. Results of multivariate models for health parameters. In rows are the explanatory variables and in columns the dependent variables. The values are beta and p-value in brackets. In bold are the results with p-value <0.05. BMI=Body Mass Index; WHR=Waist to Hip Ratio; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure. * logarithm of trait.

	BMI kg/m²	**Fat Mass Kg**	**WHR**	**HDL-Chol mg/dL**	**LDL-Chol mg/dL**	**Total-Chol mg/dL**	**Glucose mg/dL***	**Triglycerides mg/dL***	**SBP mmHg**	**DBP mmHg**
Gender, male	**1.513 (<0.0001)**	**-1.868 (<0.001)**	**0.099 (<0.0001)**	**-9.361 (<0.0001)**	-3.414 (0.055)	**-9.095 (<0.0001)**	**0.013 (<0.0001)**	**0.052 (<0.0001)**	**4.271 (<0.0001)**	**3.132 (<0.0001)**
Age, years	**0.066 (<0.0001)**	**0.132 (<0.0001)**	**0.002 (<0.0001)**	**0.082 (0.001)**	**0.457 (<0.0001)**	**0.641 (<0.0001)**	**0.001 (<0.0001)**	**0.002 (<0.0001)**	**0.536 (<0.0001)**	**0.13 (<0.0001)**
Education, years	**-0.139 (<0.0001)**	**-0.223 (0.002)**	**-0.001 (0.007)**	0.142 (0.16)	0.113 (0.67)	0.307 (0.25)	0 (0.83)	0 (0.79)	**-0.279 (0.009)**	0.06 (0.32)
Physical activity	**-1.392 (<0.0001)**	**-3.481 (<0.0001)**	**-0.013 (<0.0001)**	1.08 (0.15)	1.464 (0.47)	-0.124 (0.95)	-0.003 (0.31)	-0.007 (0.44)	-1.338 (0.10)	-0.019 (0.97)
BMI	Not included	Not included	Not included	**-1.013 (<0.0001)**	**0.651 (0.0004)**	**0.449 (0.018)**	**0.003 (<0.0001)**	**0.013 (<0.0001)**	**0.808 (<0.0001)**	**0.543 (<0.0001)**
Meat	**0.362 (<0.0001)**	**0.557 (0.006)**	0.003 (0.055)	-0.063 (0.82)	-0.399 (0.58)	-0.428 (0.56)	0.001 (0.33)	0.003 (0.45)	0.403 (0.17)	-0.02 (0.90)
Cheeses	**0.155 (0.026)**	0.351 (0.077)	0 (0.92)	0.441 (0.10)	-0.84 (0.23)	-0.826 (0.23)	-0.001 (0.16)	**-0.008 (0.0087)**	0.131 (0.63)	-0.036 (0.82)
Vegetables	-0.144 (0.069)	-0.127 (0.57)	-0.002 (0.12)	**0.606 (0.036)**	0.79 (0.28)	0.658 (0.39)	0 (0.97)	-0.004 (0.33)	0.474 (0.12)	0.188 (0.28)
Sweet foods	-0.036 (0.55)	-0.159 (0.37)	**-0.002 (0.041)**	-0.254 (0.27)	**-1.461 (0.013)**	**-2.121 (0.0004)**	0 (0.68)	**-0.007 (0.016)**	-0.403 (0.086)	-0.085 (0.53)
Fruit	-0.089 (0.21)	-0.125 (0.60)	0 (0.91)	-0.484 (0.08)	0.351 (0.62)	0.487 (0.48)	-0.002 (0.083)	0.006 (0.063)	0.105 (0.70)	0.037 (0.81)
Fish	0.003 (0.95)	-0.064 (0.67)	0 (0.63)	-0.258 (0.15)	0.60 (0.20)	0.635 (0.18)	**0.002 (0.022)**	0.001 (0.79)	**-0.711 (0.0001)**	-0.102 (0.35)
Alcoholic beverages	-0.044 (0.36)	0.022 (0.87)	0.001 (0.14)	**0.599 (0.001)**	0.303 (0.52)	**0.968 (0.041)**	0 (0.55)	-0.001 (0.50)	-0.093 (0.62)	-0.143 (0.19)

Overall, it emerged that specific food liking groups affect adiposity measures in addition to gender, age, education and physical activity. Specifically, the strongest association emerged between meat liking, BMI and fat mass (p-value<0.0001, p-value=0.006 respectively). Independent of physical activity, age and education level, a greater liking of meat was associated with a greater adiposity (beta=0.362 for BMI and 0.557 for fat

mass). Moreover, a weaker association was found between higher cheese liking and greater BMI (beta=0.155, p-value=0.026). Finally, higher sweet foods liking resulted weakly associated with lower WHR (beta=-0.002, p-value=0.04).

As regard lipids different associations were found: HDL cholesterol was higher in older women with lower BMI and higher preference for alcohol beverages and vegetables; greater LDL cholesterol was seen in older individuals with greater BMI and lower liking for sweet foods; total cholesterol resulted higher in older women with higher BMI and lower liking for sweets and higher for alcoholic beverages; higher triglycerides were seen in older men with high BMI and lower liking for cheeses and sweet foods.

Our results also show that higher levels of glucose are present in older men with higher BMI and higher liking for fish.

Additionally, we found associations between food liking groups and blood pressures: individuals with higher systolic blood pressure are older men with higher BMI, lower education level and with low liking for fish. Diastolic blood pressure is not influenced by food liking but only by age, gender and BMI.

The results of the analyses in men and women separately are displayed in Appendix section in Table A.2. a) e b) respectively.

5.4. Discussion

Our results confirm previous findings (*Duffy et al., 2007; Duffy et al., 2009; Robino et al., 2015; Sharafi et al. 2018*) showing that food preferences are associated with measures of health status. In particular, we found that adiposity measures, such as BMI and fat mass, are associated with food liking measures in addition to factors as age, gender, education and physical activity. In the present work, higher liking for meat was associated with an increase in BMI and fat mass and higher liking of cheeses was associated with an increase in BMI. These findings are in line with previous data showing an association between fat liking and increased cardiovascular disease risk factors, such as waist circumference, BMI and cholesterol (*Duffy et al., 2007; Duffy et al., 2009*).

Nonetheless, present efforts led to the identification of other interesting associations between food liking and serum lipids. The liking for specific food groups showed associations with serum lipids that were separate from effects of age, gender and level

of adiposity. For example, vegetable liking resulted associated with favourable serum lipid level and specifically older women with lower BMI also showed higher liking for vegetables and higher HDL cholesterol.

Furthermore, in agreement with what reported on sugar consumption (*Stanhope, 2016; Bravo, Lowndes, Sinnett, Yu, & Rippe, 2013; David Wang et al., 2014*), we did not find adverse effects on lipid levels associated with sweet foods liking.

The data obtained also shows that higher alcohol liking was associated with increased HDL-cholesterol levels, again in line with literature on intake measure reporting that light-to-moderate alcohol consumption increase HDL-cholesterol levels (*Choudhury et al., 1994; Tolstrup, Grønbaek, & Nordestgaard, 2009; Tabara et al., 2017; Duffy et al., 2007*). Finally, a higher fish liking resulted associated with increased fasting glucose levels and decreased systolic blood pressure (always in cooperation with other factors). Although we did not distinguish between fatty and non-fatty fish, these results agree with past works on fish consumption (*Lee et al., 2013; Panagiotakos et al., 2007; Appel, Miller, Seidler, & Whelton, 1993*).

6. From genetic variations in food liking genes to health

6.1. Background

There is a well-developed body of research examining relationships between taste receptor genes and their downstream effects on food preferences and intake, that may in turn affect nutritional and health status (*Keller KL et al., 2012; Garcia-Bailo B et al., 2009; Chamoun E et al., 2018; Eny KM, Wolever TM et al., 2010; Kulkarni GV et al., 2013; Ma X et al., 2004; Dotson CD et al., 2010*). For instance, SNPs in the *TAS1R2* and *TAS1R3* genes, which codify for sweet taste receptors and are related to a higher preference and intake of sweet foods, have also been associated to increased dental caries (*Kulkarni GV et al., 2013; Haznedaroglu E et al., 2015; Robino A et al., 2015*). Another example is the relationship between variations in the *TAS2R38* bitter taste gene and eating behaviour as well as anthropometric and adiposity measures. Increased disinhibition (i.e., loss of eating control) has been described in women carrying the PROP-insensitive allele for the rs1726866 SNP (*Dotson CD et al., 2010*); while another finding reported higher BMI and waist circumference among PROP non-taster women with low dietary restraint (*Tepper BJ e al., 2008*). In another study, differences in body fat percentage were associated with the three *TAS2R38* genetic variants, while no significant relationships with BMI and eating behaviour were found (*Keller M et al., 2013*). Other studies did not support a relationship between *TAS2R38* variants and adiposity measures (*Ooi SX et al., 2010; Tepper BJ et al., 2008; Keller M et al., 2013; Timpson NJ et al., 2005*). These inconsistent results could be ascribed to the presence of several confounding factors (i.e., sex, age, ethnicity, etc.) that may modulate the relationship among taste receptors and health status parameters. Differences in bitter taste perception have also been associated with bitter taste receptor mRNA levels in taste cells (*Lipchock SV et al., 2013; Lipchock SV et al., 2017*), suggesting that gene expression is another factor to consider when the relationship with health measures is studied. Moreover, recent findings showed that the gene expression profile of fungiform taste papillae differs between lean and obese subjects (*Archer N et al., 2019*). Together, these findings highlight the need to conduct future studies to clarify their association.

Recent evidence also raises the possibility that taste and smell receptors residing in different bodily tissues, may have multiple functions in health and disease. For example, taste receptors are also expressed in extra-oral tissues such as the

gastrointestinal tract, where they seem to be involved in digestive functions or homeostasis and energy metabolism (*Wu SV et al., 2002; Kokrashvili Z et al., 2009; Pham H et al., 2016; Kok BP et al., 2018; Avau B et al., 2015; Jang HJ et al., 2007; Behrens M et al., 2010; Finger TE & Kinnamon SC, 2011; Depoortere I., 2014; Avau B & Depoortere I, 2016; Feng R et al., 2017; Lee SJ et al., 2018*).

It is also well known that the sense of smell is impaired in neurodegenerative diseases (*Doty RL, 2017; Marin C et al., 2018*) and associations between olfactory genes (expressed in olfactory and non-olfactory tissues) and diet-related diseases such as obesity have also been demonstrated (*Doty RL , 2017; Riera CE et al, 2017; Mariman EC et al, 2015*).

Notably, the *OR7D4* gene, recently related to preference for pork meat containing androstenone (described in *Lunde K et al, 2012*), was previously associated with adiposity, cognitive dietary restraint and susceptibility to hunger in another study (*Choquette AC et al, 2012*).

Despite these positive findings, very large GWAS on BMI or other health-related parameters have not found associations with SNPs in chemosensory genes (*Locke AE et al., 2015; Yengo L et al., 2018; Evangelou E et al., 2018*), suggesting that their effects are likely to be very small and limited in predictive power.

6.2. Combining several genetic variants: the polygenic risk score

The evidence presented above suggests a new paradigm may be needed to accelerate progress in understanding the relationships between food preferences and nutrition and health.

Studies (*Pirastu N et al, 2016*) using the GWAS approach identified novel genes associated with food preferences with no known effects on chemosensory function. Thus, looking beyond the involvement of traditional chemosensory genes in food preferences may be important for gaining new insights.

Although GWA studies have led to progress in identifying common variations associated with many complex traits, the modest effect sizes have prevented risk prediction based on single genetic variants. More recently, polygenic risk score analyses that combine the effects of several genetic variants have shown some predictive ability for a wide range of complex traits (*Torkamani A et al, 2018*). In polygenic score (PGS) analysis, a

set of SNPs identified in a GWAS is used to build a score that is used for association testing or risk prediction.

To our knowledge, polygenic risk score analyses for food preferences have not yet been conducted. Although the link between vegetable intake and adiposity measures was widely investigated (Ledoux TA et al., 2011; Schwingshackl L et al., 2015; Nour M et al, 2018), few studies focusing on the relationship between hedonic measures and adiposity have been conducted. These studies have identified none or weak association (*Duffy VB et al, 2009; Laureati M et al., 2015; Concas MP et al, 2019*), suggesting that this complex relationship could be modulated by several factors, including genetic ones. Here, we report the data obtained from a polygenic risk score analysis to evaluate the predictive power of SNPs associated with food liking on adiposity measures (BMI and fat mass).

A total of 1140 individuals belonging to the INGI were used in this study for calculation of polygenic risk score (PGS): 706 coming from six villages located in the Friuli Venezia Giulia Region in Northern-Eastern Italy and 434 from the Val Borbera Valley in Northern-Western Italy. All participants gave written informed consent, and the ethical committees of IRCCS Burlo Garofolo and San Raffaele Hospital approved the study.

Personal information, such as physical activity level (never/light/moderate/intense) and educational level (elementary (5 years), lower secondary (3 years), upper secondary (5 years), university (5 years)) were assessed in each participant by standard questionnaires. BMI and fat mass were measured by the Bioelectrical Impedance Analysis technique using the Body fat Composition Analyzer (Tanita BC-420MA; Tanita, Tokyo, Japan).

Genotyping was carried out with Illumina 370k high-density SNP array. Genotype imputation was conducted after standard quality control using a custom reference panel integrating Whole Genome Sequence data available for INGI samples with resources from the 1000 Genomes project using the method implemented by the IMPUTE2 software (*Cocca M et al, 2019*).

Statistical analyses for PGS calculation were carried out with R 3.3.0. (www.r-project.org). For this analysis, 6 SNPs previously associated at genome wide significance p-value (p-value $<5x10^{-8}$) with liking of different vegetables were selected (*Pirastu N et al., 2016*). Specifically, artichokes liking resulted associated with rs28849980 (β=–0.052), rs10050951 (β=0.031) and rs8034691 (β=0.040), broccoli liking with rs2530184 (β=–0.048) and rs9832668 (β=–0.127) and chicory liking with rs138369603 (β=0.084).

For each SNP, the individual's genotypic score (0, 1, or 2 for genotyped SNPs or any value between 0-2 for imputed SNPs) was extracted and for each individual this value was multiplied by the effect size (β) of the SNP. All SNPs were coded according to higher preference for the associated vegetable. Then, for each individual a PGS-vegetables was the summed values obtained for each SNP, as follow:

$$\text{PGS-vegetables} = \beta_1 * X_1 + \beta_2 * X_2 + \ldots + \beta_6 * X_6$$

in which βi is the effect of SNP_i on the vegetable and X_i is the genotypic score of the SNP_i.

Linear regression analysis was conducted to test the associations between adiposity measures (BMI and fat mass as dependent variables) and PGS-vegetables as the predictor variable, in models adjusted for sex, age, education level and physical activity. Table 16. shows the characteristics of samples.

Table 16. Sample characteristics

	Friuli Venezia Giulia	**Val Borbera**
N	706	434
Women, %	60.74	39.26
Age (years), mean (standard deviation)	52 (16.4)	58.7 (15.2)
Education level (years), mean (standard deviation)	10.6 (3.6)	10.5 (4.1)
Physical activity, %		
Never	13.2	19.4
Light	29.3	28.6
Moderate	45.3	46.5
Intense	12.2	5.5
BMI, Kg mean (standard deviation)	25.5 (4.9)	25.1 (4.1)
Fat Mass, Kg mean (standard deviation)	20.9 (9.5)	19.6 (8.5)
Waist Hip ratio mean (standard deviation)	0.9 (0.1)	0.9 (0.08)

In Figure 10 the distribution of PGS-vegetables by sex (A) and by population (B) are shown.

Figure 10. PGS-vegetables distribution by sex (A) and population (B).

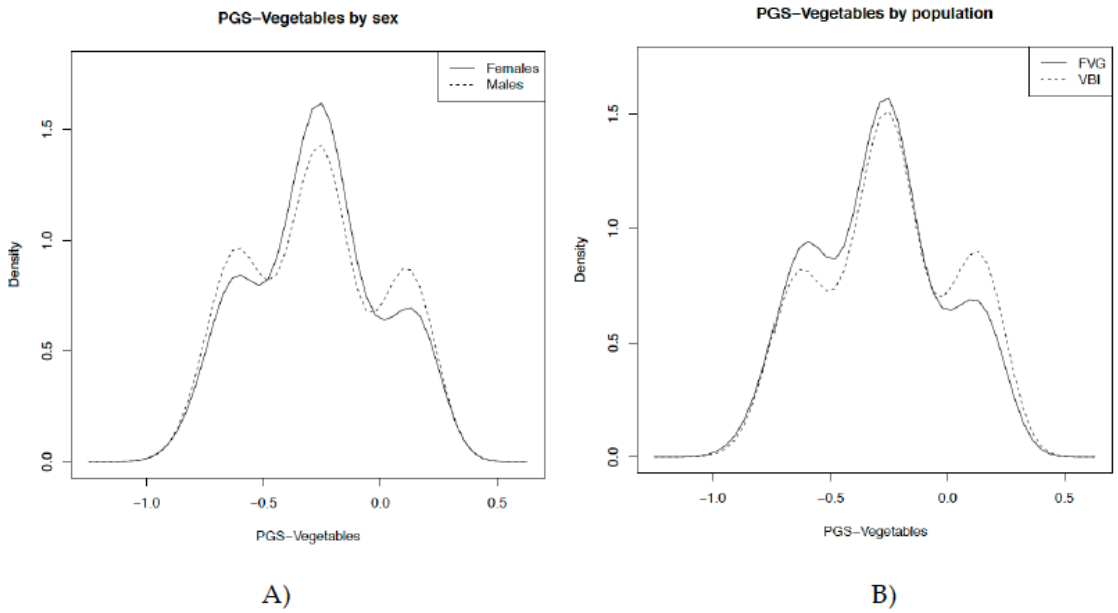


Table 17 shows that PGS-vegetables was a significant negative predictor of BMI and fat mass (p-value <0.05), in cooperation with sex, age, education and physical activity. Specifically, higher PGS-vegetables (corresponding to higher preferences for vegetable foods) was predictive of lower BMI and fat mass.

Table 17. Results of association analysis of polygenic risk score for vegetables and anthropometric measures. The results are beta and p-value in brackets.

	BMI, Kg/m^2	Fat Mass, Kg
Sex, male	2.85 (<0.0001)	-0.67 (0.2)
Age, years	0.04 (<0.0001)	0.09 (<0.0001)
Education level, years	-0.14 (<0.001)	-0.26 (0.002)
Physical activity	-1.19 (<0.0001)	-2.56 (<0.0001)
Vegetables PGS	-0.98 (0.028)	-2.08 (0.023)

The PGS-vegetables variable accounted for 0.28% of the variation in BMI and 0.33% of the variation in fat mass.

6.3. Discussion

These results on PGS represent a starting point in studying polygenic effects of food preferences on health status. As the number of GWAS on food preferences increase,

further studies considering more SNPs and other food categories should be conducted. Adopting the PGS approach would allow the development of more powerful genetic profiles to better predict the risk of disease. Although the PGS-vegetables variable accounted for only 0.28% of the variation in BMI and 0.33% of the variation in fat mass, the low number of SNPs included in the study could explain this finding.

In conclusion, these data highlight the role of genetic variations in food liking and their important contributions for nutrition and health. There is a need to identify and investigate other genes involved in food preferences, besides those already implicated in olfactory and taste perception. These novel genes can be discovered through GWAS or other genomic approaches. The use of polygenic risk analysis to assess associations between food preferences and disease outcomes could lead to important new insights in nutrition research.

CHAPTER V

CONCLUSIONS

The purpose of these three years of my doctoral program was to examine the genetic and non-genetic bases of food liking and investigate the possible relationships between food-related phenotypes and health status, analysing a large database of three Italian isolated populations.

Overall, the reported results indicate that:

- food liking is associated with genetic and non-genetic factors (including gender, age, educational level, physical activity and eating behaviour traits) (CHAPTER II and III).
- a complex relation between sensory deficits and eating behaviour exists (CHAPTER II);
- Genome-Wide Association Study and replication analysis allowed the identification of a new candidate gene (*CAV1*) associated with eating disinhibition and food liking (CHAPTER III);
- food liking is associated with metabolic measures (adiposity, serum lipids, fasting glucose and systolic blood pressure) (CHAPTER IV);
- a polygenic risk score analysis based on genetic variants previously associated with food liking may be predictive of health parameters (CHAPTER IV).

Despite some limitations already discussed in the above chapters, the main strength of this study consists in the availability of comprehensive information on lifestyle, food behaviour, clinical parameters and genetic data in a large adult individuals' cohort. Moreover, the use of genetic isolated populations turned out effective in the study of determinants of a complex trait such as food liking and eating behaviour.
Besides, the use of appropriate statistical approaches as Structural Equational Modelling allowed us to understand the complex relationship between food liking, eating behaviour and associated factors (both genetic and non-genetic) better. It emerged that the interplay between genetic and environment is a crucial aspect in the study of food liking. Thus, as a future perspective, other studies could be carried out to

extricate better the complex structure of food liking considering the gene-environment interaction. For example, examine social and cultural effects may provide new insight into the comprehension of the biological mechanisms of food preferences as well as their impact on health outcomes.

In conclusion, this work emphasizes the importance of the study of food liking in combination with other factors and suggests the possible use of liking as a proxy of food intake measures in nutritional studies. These results also represent a starting point for a better knowledge of the complex interplay existing between food liking, associated factors and diet-related phenotypes.

APPENDIX

Table A.1. Factors related to liking groups as assessed by multivariate regression models implemented in each population sample in men (a) and women (b) and aggregated by meta-analysis. The values are beta and p-value in brackets. Significant results (p-value<0.05) were reported in bold. The explanatory variables are reported in rows, and response variables in columns. For non-quantitative variables, the reference categories are: (1) non-smokers, (2) none/light physical activity, (3) less adventurous individuals, (4) less conscious individuals, (5) inhibited individuals. Each variable was first tested on a base model with age and if not significant (p-value<0.05) it was not included in final multivariate model. Not included variables are indicated by "Not included".

a)

Explanatory variables	Alcoholic beverages	Cheeses	Fish	Fruit	Meat	Sweet Foods	Vegetables
Age (5-years)	-0.02 (0.30)	Not included	**0.064 (<0.0001)**	Not included	Not included	**-0.037 (0.010)**	**0.138 (<0.0001)**
Smoking (1)	0.106 (0.39)	Not included	0.177 (0.102)	Not included	Not included	**-0.481 (<0.0001)**	Not included
Education (years)	0.012 (0.46)	0.006 (0.547)	-0.012 (0.389)	-0.007 (0.475)	**-0.029 (0.00031)**	Not included	0.015 (0.228)
Exercise (2)	Not included	Not included	0.163 (0.100)	0.125 (0.131)	Not included	Not included	**0.266 (0.0013)**
PROP Intensity	Not included	Not included	Not included	Not included	Not included	0.004 (0.083)	Not included
Food adventurousness (3)	**0.365 (0.0008)**	**0.428 (<0.0001)**	**0.582 (<0.0001)**	**0.243 (0.0019)**	**0.298 (<0.0001)**	0.137 (0.148)	**0.542 (<0.0001)**
Cognitive restraint (4)	Not included	Not included	Not included	Not included	**-0.212 (0.0006)**	-0.15 (0.096)	Not included
Dishinibition (5)	**0.277 (0.0067)**	0.143 (0.055)	**0.291 (0.0012)**	Not included	**0.242 (<0.0001)**	**0.398 (<0.0001)**	Not included

b)

Explanatory variables	Alcoholic beverages	Cheeses	Fish	Fruit	Meat	Sweet Foods	Vegetables
Age (5-years)	0.019 (0.34)	Not included	**0.101 (<0.0001)**	Not included	Not included	Not included	**0.084 (<0.0001)**
Smoking (1)	**0.351 (0.0083)**	Not included	**0.47 (0.00016)**	Not included	Not included	-0.16 (0.085)	Not included
Education (years)	**0.079 (<0.0001)**	-0.006 (0.46)	**0.037 (0.016)**	0.016 (0.051)	**-0.024 (0.0021)**	Not included	0.019 (0.052)
Exercise (2)	Not included	Not included	0.182 (0.072)	**0.138 (0.043)**	-0.094 (0.19)	Not included	**0.22 (0.0006)**
PROP Intensity	**-0.004 (0.038)**	Not included	Not included	Not included	Not included	Not included	Not included

Food adventurousness (3)	**0.435 (<0.0001)**	**0.37 (<0.0001)**	**0.641 (<0.0001)**	**0.353 (<0.0001)**	**0.25 (0.00014)**	**0.172 (0.022)**	**0.438 (<0.0001)**
Cognitive restraint (4)	Not included	Not included	Not included	Not included	**-0.244 (<0.0001)**	**-0.184 (0.0098)**	Not included
Dishinibition (5)	Not included	**0.277 (<0.0001)**	Not included	Not included	**0.134 (0.028)**	**0.441 (<0.0001)**	Not included

Table A.2. Results of multivariate models for health parameters in men (a) and women (b) separately. In rows are the explanatory variables and in columns the dependent variables. The values are beta and p-value in brackets. In bold are the results with p-value <0.05. BMI=Body Mass Index; WHR=Waist to Hip Ratio; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure. * logarithm of trait.

a)

	BMI kg/m²	**Fat Mass Kg**	**WHR**	**HDL-Chol mg/dL**	**LDL-Chol mg/dL**	**Total-Chol mg/dL**	**Glucose mg/dL***	**Triglycerides mg/dL***	**SBP mmHg**	**DBP mmHg**
Age, years	**0.054 (<0.0001)**	**0.134 (<0.0001)**	**0.001 (<0.0001)**	**0.094 (0.0069)**	0.184 (0.063)	**0.299 (0.0042)**	**0.001 (<0.0001)**	0.001 (0.14)	**0.426 (<0.0001)**	**0.065 (0.0035)**
Education, years	-0.075 (0.055)	-0.079 (0.45)	-0.001 (0.48)	-0.139 (0.34)	0.191 (0.64)	0.026 (0.95)	0.001 (0.29)	0 (0.84)	**-0.352 (0.024)**	0.005 (0.96)
Physical activity	**-1.333 (<0.0001)**	**-3.042 (<0.0001)**	**-0.019 (0.00015)**	1.889 (0.097)	-2.116 (0.52)	-5.517 (0.087)	-0.004 (0.42)	**-0.033 (0.022)**	-1.992 (0.11)	-0.814 (0.27)
BMI	Not included	Not included	Not included	**-1.06 (<0.0001)**	0.441 (0.15)	0.332 (0.31)	**0.003 (<0.0001)**	**0.012 (<0.0001)**	**0.798 (1<0.0001)**	**0.554 (<0.0001)**
Meat	**0.356 (0.0063)**	**0.947 (0.0095)**	0 (0.86)	0.479 (0.31)	-2.285 (0.088)	-1.968 (0.16)	0.002 (0.27)	-0.003 (0.66)	0.707 (0.17)	-0.163 (0.59)
Cheeses	0.118 (0.26)	0.185 (0.54)	0.001 (0.77)	0.121 (0.77)	-2.054 (0.076)	**-2.713 (0.019)**	0 (0.84)	**-0.015 (0.0076)**	0.191 (0.66)	-0.103 (0.69)
Vegetables	-0.068 (0.55)	-0.024 (0.94)	0 (0.91)	**0.875 (0.038)**	0.898 (0.45)	0.997 (0.42)	0.001 (0.49)	-0.004 (0.49)	0.701 (0.11)	**0.62 (0.019)**
Sweet foods	-0.06 (0.49)	-0.193 (0.46)	-0.001 (0.76)	-0.58 (0.090)	-0.562 (0.56)	-1.451 (0.14)	-0.002 (0.22)	-0.004 (0.44)	**-0.805 (0.023)**	-0.293 (0.17)
Fruit	-0.124 (0.23)	-0.391 (0.27)	-0.002 (0.28)	-0.755 (0.070)	1.506 (0.197)	0.674 (0.56)	-0.003 (0.051)	0.008 (0.15)	0.305 (0.46)	0.175 (0.48)
Fish	0.022 (0.77)	-0.126 (0.61)	0 (0.87)	-0.393 (0.18)	0.352 (0.69)	0.568 (0.49)	**0.003 (0.024)**	0.004 (0.296)	**-0.95 (0.0018)**	-0.295 (0.108)
Alcoholic beverages	0.043 (0.57)	0.035 (0.86)	0.002 (0.14)	**0.811 (0.0049)**	1.549 (0.058)	**2.163 (0.0097)**	-0.001 (0.26)	0.003 (0.499)	0.022 (0.94)	-0.086 (0.64)

b)

	BMI kg/m²	Fat Mass Kg	WHR	HDL-Chol mg/dL	LDL-Chol mg/dL	Total-Chol mg/dL	Glucose mg/dL*	Triglycerides mg/dL*	SBP mmHg	DBP mmHg
Age, years	**0.077 (<0.0001)**	**0.129 (<0.0001)**	**0.002 (<0.0001)**	**0.071 (0.047)**	**0.679 (<0.0001)**	**0.925 (<0.0001)**	**0.001 (<0.0001)**	**0.003 (<0.0001)**	**0.626 (<0.0001)**	**0.187 (<0.0001)**
Education, years	**-0.178 (<0.0001)**	**-0.331 (0.0016)**	**-0.002 (0.0050)**	**0.325 (0.025)**	0.253 (0.45)	0.632 (0.066)	-0.001 (0.19)	0.001 (0.50)	-0.151 (0.30)	0.122 (0.139)
Physical activity	**-1.457 (<0.0001)**	**-3.908 (<0.0001)**	**-0.009 (0.025)**	0.672 (0.519)	2.743 (0.267)	2.47 (0.319)	-0.001 (0.707)	0.008 (0.478)	-0.742 (0.501)	0.631 (0.31)
BMI	Not included	Not included	Not included	**-0.956 (<0.0001)**	**0.657 (0.0032)**	0.384 (0.094)	**0.003 (<0.0001)**	**0.013 (<0.0001)**	**0.792 (<0.0001)**	**0.511 (<0.0001)**
Meat	**0.326 (0.00065)**	0.323 (0.202)	**0.004 (0.015)**	-0.304 (0.38)	0.274 (0.73)	0.215 (0.80)	0.001 (0.64)	0.004 (0.28)	0.345 (0.35)	0.081 (0.69)
Cheeses	0.159 (0.090)	0.464 (0.085)	-0.001 (0.71)	0.683 (0.061)	-0.255 (0.77)	0.131 (0.88)	**-0.003 (0.041)**	-0.006 (0.16)	0.023 (0.95)	-0.081 (0.68)
Vegetables	-0.189 (0.089)	-0.295 (0.34)	**-0.005 (0.015)**	0.35 (0.38)	0.327 (0.73)	0.515 (0.60)	-0.001 (0.55)	-0.003 (0.53)	0.358 (0.40)	0.011 (0.96)
Sweet foods	-0.011 (0.89)	-0.122 (0.62)	**-0.003 (0.019)**	-0.099 (0.75)	**-1.723 (0.0195)**	**-2.345 (0.0017)**	0.002 (0.12)	-0.007 (0.053)	-0.138 (0.66)	0.081 (0.65)
Fruit	-0.099 (0.31)	-0.021 (0.95)	0.001 (0.46)	-0.192 (0.60)	-0.038 (0.97)	0.485 (0.58)	-0.001 (0.66)	0.007 (0.10)	0.036 (0.92)	-0.055 (0.79)
Fish	-0.007 (0.92)	0.033 (0.87)	-0.001 (0.57)	-0.208 (0.38)	0.898 (0.11)	0.645 (0.26)	0 (0.61)	-0.001 (0.75)	**-0.599 (0.012)**	-0.042 (0.76)
Alcoholic beverages	-0.088 (0.16)	0.017 (0.92)	0.001 (0.46)	0.459 (0.056)	-0.316 (0.58)	0.194 (0.73)	**0.002 (0.047)**	-0.005 (0.077)	-0.099 (0.68)	-0.174 (0.20)

BIBLIOGRAPHY

1. Appel L J, Miller E R, Seidler A J, & Whelton P K, (1993). Does supplementation of diet with “fish oil” reduce blood pressure? A meta-analysis of controlled clinical trials. Archives of Internal Medicine, 153(12), 1429–1438.
2. 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 (Lond) 2019 doi: 10.1038/s41366-018-0303-y. Epub ahead of print.
3. Avau B, Depoortere I. The bitter truth about bitter taste receptors: beyond sensing bitter in the oral cavity. Acta Physiol (Oxf). 2016 216(4), 407-20.
4. Avau B, Rotondo A, Thijs T, Andrews CN, Janssen P, Tack J1 Depoortere I.Targeting extra-oral bitter taste receptors modulates gastrointestinal motility with effects on satiation. Sci Rep 2015 6, 5:15985.
5. Bachmanov AA, Beauchamp GK. Taste receptor genes. Annu Rev Nutr 2007 27, 389-414.
6. Bachmanov AA, Bosak NP, Lin C, Matsumoto I, Ohmoto M, Reed DR, Nelson TM. Genetics of taste receptors. Curr Pharm Des 2014, 20(16), 2669-83.
7. Bachmanov, A. A., Kiefer, S. W., Molina, J. C., Tordoff, M. G., Duffy, V. B., Bartoshuk, L. M., & Mennella, J. A. (2003). Chemosensory factors influencing alcohol perception, preferences, and consumption. Alcoholism, Clinical and Experimental Research, 27(2), 220–231. https://doi.org/10.1097/01.ALC.0000051021.99641.19
8. Ball, K., Jeffery, R. W., Abbott, G., McNaughton, S. A., & Crawford, D. (2010). Is healthy behavior contagious: associations of social norms with physical activity and healthy eating. International Journal of Behavioral Nutrition and Physical Activity, 7(1), 86. https://doi.org/10.1186/1479-5868-7-86
9. Bartoshuk, L. M. (1991). Sensory factors in eating behavior. Bulletin of the Psychonomic Society, 29(3), 250–255. https://doi.org/10.3758/BF03342692
10. Bathalon, G. P., Tucker, K. L., Hays, N. P., Vinken, A. G., Greenberg, A. S., McCrory, M. A., & Roberts, S. B. (2000). Psychological measures of eating behavior and the accuracy of 3 common dietary assessment methods in

healthy postmenopausal women. The American Journal of Clinical Nutrition, 71(3), 739–745. https://doi.org/10.1093/ajcn/71.3.739

11. Behrens M, Meyerhof W. Bitter taste receptors and human bitter taste perception. Cell Mol Life Sci. 2006 63(13), 1501-9.
12. Behrens M, Meyerhof W. Oral and extraoral bitter taste receptors. Results Probl Cell Differ. 2010 52, 87-99.
13. Bellisle F, Clement K, Le Barzic M, Le Gall A, Guy-Grand B, Basdevant A. The Eating Inventory and body adiposity from leanness to massive obesity: A study of 2509 adults. Obes. Res. 2004; 12:2023–2030.
14. Birch LL. Development of food preferences. Annu. Rev. Nutr. 1999. 19:41–62.
15. Boesveldt S, de Graaf K. The Differential Role of Smell and Taste For Eating Behavior. Perception. 2017 46(3-4), 307-319.
16. Borg P, Fogelholm M, Kukkonen-Harjula K. Food selection and eating behaviour during weight maintenance intervention and 2-y follow-up in obese men 48. Int J Obes Relat Metab Disord 2004; 28: 1548–1554.
17. Bouchard L, Drapeau V, Provencher V, Lemieux S, Chagnon Y, Rice T, Rao DC, Vohl MC, Tremblay A, Bouchard C, Pérusse L. Neuromedin beta: a strong candidate gene linking eating behaviors and susceptibility to obesity. Am J Clin Nutr. 2004; 80(6):1478-86.
18. Boutin P, Dina C, Vasseur F, Dubois S, Corset L, Séron K, Bekris L, Cabellon J, Neve B, Vasseur-Delannoy V, Chikri M, Charles MA, Clement K, Lernmark A, Froguel P. GAD2 on chromosome 10p12 is a candidate gene for human obesity. PLoS Biol. 2003; 1(3):E68.
19. Boyce JM, ShoneGR. Effects of ageing on smell and taste. PostgradMed J 2006;82:239–41.
20. Bravo, S., Lowndes, J., Sinnett, S., Yu, Z., & Rippe, J. (2013). Consumption of sucrose and high-fructose corn syrup does not increase liver fat or ectopic fat deposition in muscles. Applied Physiology, Nutrition, and Metabolism, 38(6), 681–688. https://doi.org/10.1139/apnm-2012-0322
21. Breen FM, Plomin R, Wardle J. Heritability of food preferences in young children. Physiol Behav 2006 88(4-5), 443-7.

22. Bryant E, Finlayson G, King N, Blundell J. The influence of acute exercise on liking and preference for food on high trait Disinhibition women. Obes Rev 2006; 7: 343
23. Bryant EJ, King NA, Blundell JE. Disinhibition: its effects on appetite and weight regulation. Obes Rev. 2008; 9(5):409-19.
24. Bufe B, Breslin PAS, Kuhn C, Reed DR, Tharp CD, et al. The molecular basis of individual differences in phenylthiocarbamide and propylthiouracil bitterness perception. Curr Biol 2005 15, 322–327.
25. Bufe B, Hofmann T, Krautwurst D, Raguse JD, Meyerhof W. The human TAS2R16 receptor mediates bitter taste in response to beta-glucopyranosides. Nat Genet 2002 32(3), 397–401.
26. Chamoun E, Mutch DM, Allen-Vercoe E, Buchholz AC, Duncan AM, Spriet LL, Haines J, Ma DWL; Guelph Family Health Study. A review of the associations between single nucleotide polymorphisms in taste receptors, eating behaviors, and health. Crit Rev Food Sci Nutr 2018 58(2), 194-207
27. Chia E-M, Mitchell P, Rochtchina E, Foran S, Golding M, Wang JJ. Association between vision and hearing impairments and their combined effects on quality of life. Arch Ophthalmol. 2006;124:1465-1470.
28. Choquette AC, Bouchard L, Drapeau V, Lemieux S, Tremblay A, Bouchard C, Vohl MC, Pérusse L. Association between olfactory receptor genes, eating behavior traits and adiposity: results from the Quebec Family Study. Physiol Behav. 2012 105(3), 772-6.
29. Choquette AC, Lemieux S, Tremblay A, Drapeau V, Bouchard C, Vohl MC, Pérusse L. GAD2 gene sequence variations are associated with eating behaviors and weight gain in women from the Quebec family study. Physiol Behav. 2009; 98(4):505-10.
30. Choudhury, S. R., Ueshima, H., Kita, Y., Kobayashi, K. M., Okayama, A., Yamakawa, M., … Miyoshi, Y. (1994). Alcohol intake and serum lipids in a Japanese population. International Journal of Epidemiology, 23(5), 940–947.
31. Concas, M.P.; Catamo, E.; Biino, G.; Toniolo, D.; Gasparini, P.; Robino, A. Factors associated with food liking and their relationship with metabolic traits in Italian cohorts. Food Qual. Prefer. 2019, 75, 64–70.

32. Contento IR, Zybert P, Williams SS. Relationship of cognitive restraint of eating and disinhibition to the quality of food choices of Latina women and their young children. Prev Med. 2005 Mar;40(3):326-36.
33. Correia C, Lopez KJ, Wroblewski KE, Huisingh-Scheetz M, Kern DW, Chen RC, et al. Global sensory impairment in older adults in the United States. J Am Geriatr Soc. 2016; 64(2):306±13.
34. Crews JE, Campbell VA. Vision impairment and hearing loss among community dwelling older Americans: Implications for health and functioning. Am J Public Health 2004;94:823–829.18. 19.
35. David Wang, D., Sievenpiper, J. L., de Souza, R. J., Cozma, A. I., Chiavaroli, L., Ha, V., … Jenkins, D. J. A. (2014). Effect of fructose on postprandial triglycerides: A systematic review and meta-analysis of controlled feeding trials. Atherosclerosis, 232(1), 125–133. https://doi.org/10.1016/J.ATHEROSCLEROSIS.2013.10.019
36. de Mendonça, S. N. T. G., Brandão, H. C. A. D. N. T. M., Brandão, W. A. P. L. N. T. M., Quintino, C. A. A., De Francisco, A., & Teixeira, E. (2013). Food preferences of middle aged and elderly subjects in a Brazilian city. The Journal of Nutrition, Health & Aging, 17(2), 130–135. https://doi.org/10.1007/s12603-012-0384-6
37. Depoortere I. Taste receptors of the gut: emerging roles in health and disease. Gut 2014 63(1), 179-90.
38. Dias AG, Rousseau D, Duizer L, Cockburn M, Chiu W, Nielsen D, El-Sohemy. Genetic variation in putative salt taste receptors and salt taste perception in humans. Chem Senses, 2013 38(2), 137–45.
39. Dinehart ME, Hayes JE, Bartoshuk LM, Lanier SL, Duffy VB. Bitter taste markers explain variability in vegetable sweetness, bitterness, and intake. Physiol Behav 2006 87: 304–313.
40. Dotson CD, Shaw HL, Mitchell BD, Munger SD, Steinle NI. Variation in the gene TAS2R38 is associated with the eating behavior disinhibition in Old Order Amish women. Appetite. 2010; 54(1):93-9.
41. Dotson CD, Vigues S, Steinle NI, Munger SD. T1R and T2R receptors: the modulation of incretin hormones and potential targets for the treatment of type 2 diabetes mellitus. Curr Opin Investig Drugs 2010, 11(4), 447–454.

42. Doty RL. Olfactory dysfunction in neurodegenerative diseases: is there a common pathological substrate? Lancet Neurol. 2017 16(6):478-488.
43. Drewnowski, A., & Hann, C. (1999). Food preferences and reported frequencies of food consumption as predictors of current diet in young women. The American Journal of Clinical Nutrition, 70(1), 28–36.
44. Drewnowski, A., Hann, C., Henderson, S.A., & Gorenflo, D. (2000). Both food preferences and food frequency scores predict fat intakes of women with breast cancer. Journal of the American Dietetic Association, 100(11), 1325-1333.
45. Drewnowski, A., Henderson, S. A., & Cockroft, J. E. (2007). Genetic Sensitivity to 6-n-Propylthiouracil Has No Influence on Dietary Patterns, Body Mass Indexes, or Plasma Lipid Profiles of Women. Journal of the American Dietetic Association, 107(8), 1340–1348. https://doi.org/10.1016/J.JADA.2007.05.013
46. Drewnowski, A., Henderson, S.A., Levine, A. & Hann, C. (1999). Taste and food preferences as predictors of dietary practices in young women. Public Health Nutrition, 2(4), 513–519.
47. Drewnowski, A., Henderson, S.A., Shore, A.B. & Barratt-Fornell A. (1997). Nontasters, tasters, and supertasters of 6-n-propylthiouracil (PROP) and hedonic response to sweet. Physiology and Behavior, 62 (3), 649-55.
48. Duffy VB, Backstrand JR, Ferris AM. Olfactory dysfunction and related nutritional risk in free-living, elderly women. 1995. JAm Diet Assoc 95:879–884
49. Duffy VB, Hayes JE., Sullivan BS, Faghri P. Surveying food and beverage liking. Annals of the New York Academy of Sciences 2009 1170(1), 558–568.
50. Duffy, V. B., Lanier, S. A., Hutchins, H. L., Pescatello, L. S., Johnson, M. K., & Bartoshuk, L. M. (2007). Food Preference Questionnaire as a Screening Tool for Assessing Dietary Risk of Cardiovascular Disease within Health Risk Appraisals. Journal of the American Dietetic Association, 107(2), 237–245. https://doi.org/10.1016/J.JADA.2006.11.005
51. Eny KM, Wolever TM, Corey PN, El-Sohemy A. Genetic variation in TAS1R2 (Ile191Val) is associated with consumption of sugars in overweight and obese individuals in 2 distinct populations. Am J of CliN Nutr 2010 92(6), 1501–10.

52. Eriksson N, Macpherson JM, Tung JY, Hon LS, Naughton B, Saxonov S, Avey L, Wojcicki A, Pe'er I, Mountain J: Web-based, participant-driven studies yield novel genetic associations for common traits. PLoS Genet. 2010, 6:e1000993.
53. Eriksson N, Wu S, Do CB, Kiefer AK, Tung JY, Mountain JL, Hinds DA, Francke U. A genetic variant near olfactory receptor genes influences cilantro preference, Flavour, 2012 1, 1-7
54. Esko, T., Mezzavilla, M., Nelis, M., Borel, C., Debniak, T., Jakkula, E., … D'Adamo, P.. Genetic characterization of northeastern Italian population isolates in the context of broader European genetic diversity. European Journal of Human Genetics, (2013) 21(6), 659–665. https://doi.org/10.1038/ejhg.2012.229
55. Etievant PX, Issanchou SN, Bayonove CL. The flavour of muscat wine: the sensory contribution of some volatile compounds.J. Sci. Food Agric 1983 34, 497-504
56. Evangelou E et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. Nat Genet 2018 50(12):1755.
57. Falciglia G, Couch S, Gribble L, Pabst S, Frank R. 2000. Food neophobia in childhood affects dietary variety. J Am Diet Assoc 100:1474-1481
58. Falciglia GA, Norton PA. Evidence for a genetic influence on preference for some foods. J Am Diet Assoc. 1994 94(2), 154-8.
59. Faust J. A twin study of personal preferences. J Biosoc Sci 1974 6, 75–91.
60. Feeney E, O'Brien S, Scannell A, Markey A, Gibney ER. Genetic variation in taste perception: does it have a role in healthy eating? Proc Nutr Soc. 2011 70(1), 135-43.
61. Feeney E. The impact of bitter perception and genotypic variation of TAS2R38 on food choice. Nutrition Bulletin 2011 36(1), 20–33.
62. Feng R, Qian C, Liu Q, Jin Y, Liu L, Li S, Liao Y, Zhou H, Liu W, Rayner CK, Ma J. Expression of sweet taste receptor and gut hormone secretion in modelled type 2 diabetes. Gen Comp Endocrinol. 2017 252, 142-149.
63. Fildes A, van Jaarsveld CH, Llewellyn CH, Fisher A, Cooke L, Wardle J. Nature and nurture in children's food preferences. Am J Clin Nutr. 2014 99(4), 911-7.

64. Finger TE, Kinnamon SC. Taste isn't just for taste buds anymore. F1000 Biol Rep 2011 3:20.
65. Fischer ME, Cruickshanks KJ, Klein BEK, Klein R, Schubert CR, Wiley TL. Multiple sensory impairment and quality of life. Ophthalmic Epidemiol. 16, 346–353 (2009)
66. Frewer, L. J., & van Trijp, H. (2007). 30 – Looking to the future. In Understanding Consumers of Food Products (pp. 643–649). https://doi.org/10.1533/9781845692506.5.643
67. Fushan AA, Simons CT, Slack JP, Manichaikul A, Drayna D. Allelic polymorphism within the TAS1R3 promoter is associated with human taste sensitivity to sucrose. Curr Biol 2009 19(15), 1288–93.
68. Garcia-Bailo B, Toguri C, Eny KM, El-Sohemy A. Genetic variation in taste and its influence on food selection. OMICS 2009 13(1), 69-80.
69. Genther DJ, Betz J, Pratt S et al. Association of hearing impairment and mortality in older adults. J Gerontol Ser A Biol Sci Med Sci 2014;70A:85–90.
70. 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. J Am Diet Assoc 1998, 98, 1118–1126.
71. Goodrick, C. L. (1975). Behavioral differences in young and aged mice: Strain differences for activity measures, operant learning, sensory discrimination, and alcohol preference. Experimental Aging Research, 1(2), 191–207. https://doi.org/10.1080/03610737508257960
72. Gopinath B, Russell J, Sue CM, Flood VM, Burlutsky G, Mitchell P. Olfactory impairment in older adults is associated with poorer diet quality over 5 years. Eur J Nutr. 2016; 55(3):1081±1087. doi: 10.1007/s00394-015-0921-2 PMID: 25957862.
73. Gopinath B, Sue CM, Kifley A, Mitchell P. The association between olfactory impairment and total mortality in older adults. J Gerontol A Biol Sci Med Sci 2012;67:204–9.
74. Green, B. G., Dalton, P., Cowart, B., Shaffer, G., Rankin, K., & Higgins, J. (1996). Evaluating the "Labeled Magnitude Scale" for measuring sensations of taste and smell. Chemical Senses, 21(3), 323–334.

75. Grimm ER, Steinle NI. Genetics of eating behavior: established and emerging concepts. Nutr Rev. 2011;69(1):52-60.

76. Guido, D., Perna, S., Carrai, M., Barale, R., Grassi, M., & Rondanelli, M. (2016). Multidimensional Evaluation of Endogenous and Health Factors Affecting Food Preferences, Taste and Smell Perception. The Journal of Nutrition, Health & Aging, 20(10), 971–981. https://doi.org/10.1007/s12603-016-0703-4

77. Guo SW, Reed DR. The genetics of phenylthiocarbamide perception. Ann Hum Biol. 2001 28(2), 111-42.

78. Habhab, S., Sheldon, J. P., & Loeb, R. C. (2009). The relationship between stress, dietary restraint, and food preferences in women. Appetite, 52(2), 437–444. https://doi.org/10.1016/J.APPET.2008.12.006

79. Hainer V, Kunesova M, Bellisle F, Parizkova J, Braunerova R, Wagenknecht M, Lajka J, Hill M, Stunkard A. The Eating Inventory, body adiposity and prevalence of diseases in a quota sample of Czech adults. Int J Obes (Lond). 2006; 30(5):830-6.

80. Hatzikotoulas K, Gilly A and Zeggini E. Using population isolates in genetic association studies. Briefings In Functional Genomics. vol 13. no 5. 371-377 doi:10.1093/bfgp/elu022

81. Hayes JE, Duffy VB. Oral sensory phenotype identifies level of sugar and fat required for maximal liking. Physiol Behav 2008 95, 77–87.

82. Hayes JE, Feeney EL, Allen AL. Do polymorphisms in chemosensory genes matter for human ingestive behavior? Food Qual Prefer. 2013 30(2), 202-216.

83. Hayes JE, Wallace MR, Knopik VS, Herbstman DM, Bartoshuk LM, Duffy VB. Allelic variation in TAS2R bitter receptor genes associates with variation in sensations from and ingestive behaviors toward common bitter beverages in adults. Chemical Senses 2011 36(3), 311–9.

84. Hayes, J. E. & Keast, R. S. (2011). Two decades of supertasting: where do we stand? Physioliogy & Behaviour, 104 (5):1072-4. https://doi.org/10.1016/j.physbeh.2011.08.003

85. Hays NP, Roberts SB. Aspects of eating behaviors disinhibition and restraint are related to weight gain and BMI in women. Obes. Res. 2008;16:52–58.

86. Haznedaroglu E, Koldemir-Gunduz M, Bakir-Coskun N, Bozkus HM, Cagatay P, Susleyici-Duman B, Mentes A. Association of Sweet Taste Receptor Gene Polymorphisms with Dental Caries Experience in School Children. Caries Res. 2015 49, 275–281.

87. Higgs S, Eskenazi T. Dietary restraint and disinhibition are associated with increased alcohol use behaviours and thoughts in young women social drinkers. Eat Behav 2007; 8: 236–243.

88. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' Sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses. 1997;22:39-52.

89. Hwang LD, Lin C, Gharahkhani P, Cuellar-Partida G, Ong JS, An J, Gordon SD, Zhu G, MacGregor S, Lawlor DA, Breslin PAS, Wright MJ, Martin NG, Reed DR. 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(6):1724-1737.

90. Kong IG, Kim SY, Kim MS, Park B, Kim JH, Choi HG. Olfactory Dysfunction Is Associated with the Intake of Macronutrients in Korean Adults PLoS One. 2016; 11(10): e0164495. Published online 2016 Oct 10. doi: 10.1371/journal.pone.0164495.

91. Intranuovo, L. R., & Powers, A. S. (1998). The perceived bitterness of beer and 6-n-propylthiouracil (PROP) taste sensitivity. Annals of the New York Academy of Sciences, 855, 813–815.

92. Inui-Yamamoto, C., Yamamoto, T., Ueda, K., Nakatsuka, M., Kumabe, S., Inui, T., & Iwai, Y. (2017). Taste preference changes throughout different life stages in male rats. PLOS ONE, 12(7), e0181650. https://doi.org/10.1371/journal.pone.0181650

93. Ishimaru Y, Matsunami H. Transient receptor potential (TRP) channels and taste sensation. J Dent Res 2009 88(3), 212-8.

94. Jaeger SR, McRae JF, Bava CM, Beresford MK, Hunter D, Jia Y, Chheang SL, Jin D, Peng M, Gamble JC, Atkinson KR, Axten LG, Paisley AG, Tooman L, Pineau B, Rouse SA, Newcomb RD. A Mendelian trait for olfactory sensitivity affects odor experience and food selection. Curr Biol 2013 23(16), 1601-5.

95. Jaeger SR, McRae JF, Salzman Y, Williams L, Newcomb RD. A preliminary investigation into a genetic basis for cis-3-hexen-1-ol odour perception: a genome-wide association approach. Food Qual Prefer. 2010 21, 121–131.

96. Jaeger SR, Pineau B, Bava CM, Atkinson KR, AMcRae JF, Axten LG, Chheang SL, Beresford MK, Peng M, Paisley AG, Reinbach HC, Rouse SA, Wohlers MW, Jia Y, Newcomb RD. Investigation of the impact of sensitivity to cis-3-hexen-1-ol (green/grassy) on food acceptability and selection. Food Qual and Prefer. 2012 24(2), 230–242.

97. Jaeger, S. R., Rasmussen, M. A., & Prescott, J. (2017). Relationships between food neophobia and food intake and preferences: Findings from a sample of New Zealand adults. Appetite, 116, 410–422. https://doi.org/10.1016/J.APPET.2017.05.030

98. Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, Zhou J, Kim HH, Xu X, Chan SL, Juhaszova M, Bernier M, Mosinger B, Margolskee RF, Egan JM. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. Proc Natl Acad Sci U S A 2007 104(38), 15069-74.

99. Johnson, M. K. (1983). A multiple-entry, modular memory system. Psychology of Learning and Motivation - Advances in Research and Theory. https://doi.org/10.1016/S0079-7421(08)60097-3

100. Johnson, M. K., Kim, J. K., & Risse, G. (1985). Do alcoholic Korsakoff's syndrome patients acquire affective reactions? Journal of Experimental Psychology: Learning, Memory, and Cognition, 11(1), 22–36. https://doi.org/10.1037/0278-7393.11.1.22

101. Johnson, S. L., Boles, R. E., & Burger, K. S. (2014). Using participant hedonic ratings of food images to construct data driven food groupings. Appetite, 79, 189–196. https://doi.org/10.1016/J.APPET.2014.04.021

102. Kershaw JC, Mattes RD. Nutrition and taste and smell dysfunction.World J Otorhinolaryngol Head Neck Surg. 2018 Mar 23;4(1):3-10. doi: 10.1016/j.wjorl.2018.02.006. eCollection 2018 Mar. Review.

103. Karlsson, T., Rosendahl-Riise, H., Dierkes, J., Drevon, C. A., Tell, G. S., & Nygård, O. (2017). Associations between fish intake and the metabolic syndrome and its components among middle-aged men and women: the

Hordaland Health Study. Food & Nutrition Research, 61(1), 1347479. https://doi.org/10.1080/16546628.2017.1347479

104. Keller A, Zhuang H, Chi Q, Vosshall LB, Matsunami H. Genetic variation in a human odorant receptor alters odour perception. Nature 2007 449, 468–472.

105. Keller KL, Liang, LCH., Sakimura J, May D, van Belle C, Breen C, Driggin E, Tepper BJ, Lanzano PC, Deng L, Chung WK. Common variants in the CD36 gene are associated with oral fat perception, fat preferences, and obesity in African Americans Obesity 2012 20(5), 1066-73.

106. Keller KL, Steinmann L, Nurse RJ, Tepper BJ. Genetic taste sensitivity to 6-n-propylthiouracil influences food preference and reported intake in preschool children. Appetite 2002 38: 3–12.

107. Keller M, Liu X, Wohland T, Rohde K, Gast MT, Stumvoll M, Kovacs P, Tönjes A, Böttcher Y. TAS2R38 and its influence on smoking behavior and glucose homeostasis in the German Sorbs. PLoS One 2013 8(12), e80512.

108. Kern DW, Wroblewski KE, Schumm LP et al. Field survey measures of olfaction: The Olfactory Function Field Exam (OFFE). Field Methods 2014;26:421–434.

109. Keskitalo K, Knaapila A, Kallela M, et al. Sweet taste preferences are partly genetically determined; identification of a trait locus on chromosome 16. Am J Clin Nutr 2007 86, 55–63.

110. Keskitalo K, Tuorila H, Spector TD, Cherkas LF, Knaapila A, Silventoinen K, Perola M.
Same genetic components underlie different measures of sweet taste prefere nce. Am J Clin Nutr 2007 86(6), 1663-9.

111. Keskitalo, K., Silventoinen, K., Tuorila, H., Perola, M., Pietiläinen, K. H., Rissanen, A., & Kaprio, J. (2008). Genetic and environmental contributions to food use patterns of young adult twins. Physiology & Behavior, 93(1–2), 235–242. https://doi.org/10.1016/J.PHYSBEH.2007.08.025

112. Khera AV, Emdin CA, Drake I, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. N Engl J Med. 2016;375(24):2349-2358. doi:10.1056/NEJMoa1605086

113. Khil L., Wellmann J., and Berger K., Determinants of Single and Multiple Sensory Impairments in an Urban Population, Otolaryngol Head Neck Surg. 2015 Sep;153(3):364-71. doi: 10.1177/0194599815588913. Epub 2015 Jun 17.
114. Kiely KM, Anstey KJ, Luszcz MA. Dual sensory loss and depressive symptoms: the importance of hearing, daily functioning and activity engagement. Front Hum Neurosci. 2013;7:837.
115. Kim UK, Drayna D. Genetics of individual differences in bitter taste perception: lessons from the PTC gene. Clin Genet 2005 67, 275–280.
116. Kim UK, 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(5610), 1221–1225.
117. Kok BP, Galmozzi A, Littlejohn NK, Albert V, Godio C, Kim W, Kim SM, Bland JS, Grayson N, Fang M, Meyerhof W, Siuzdak G, Srinivasan S, Behrens M, Saez E. Intestinal bitter taste receptor activation alters hormone secretion and imparts metabolic benefits. Mol Metab 2018 16,76-87.
118. Kokrashvili Z, Mosinger B, Margolskee RF. Taste signaling elements expressed in gut enteroendocrine cells regulate nutrient-responsive secretion of gut hormones. Am J Clin Nutr. 2009 90(3):822S-825S.
119. Kokubo Y, Padmanabhan S, Iwashima Y, Yamagishi K, Goto A., Gene and environmental interactions according to the components of lifestyle modifications in hypertension guidelines. Environ Health Prev Med. 2019 Mar 11;24(1):19. doi: 10.1186/s12199-019-0771-2. Review
120. Kossioni, A., & Bellou, O. (2011). Eating habits in older people in Greece: The role of age, dental status and chewing difficulties. Archives of Gerontology and Geriatrics, 52(2), 197–201. https://doi.org/10.1016/J.ARCHGER.2010.03.017
121. Kuhn C, Bufe B, Winnig M, Hofmann T, Frank O, Behrens M, Meyerhof W. Bitter taste receptors for saccharin and acesulfame K. J Neurosci 2004 24(45), 10260–5.
122. Kulkarni GV, Chng T, Eny KM, Nielsen D, Wessman C, El-Sohemy A. Association of GLUT2 and TAS1R2 genotypes with risk for dental caries. Caries Res 2013 47(3), 219–25.
123. Lahteenmaki L, Tuorila H. Three-factor eating questionnaire and the use and liking of sweet and fat among dieters. Physiol Behav 1995; 57: 81–88.

124. Lampuré, A., Schlich, P., Deglaire, A., Castetbon, K., Péneau, S., Hercberg, S., & Méjean, C. (2015). Sociodemographic, Psychological, and Lifestyle Characteristics Are Associated with a Liking for Salty and Sweet Tastes in French Adults. The Journal of Nutrition, 145(3), 587–594. https://doi.org/10.3945/jn.114.201269

125. Larsen M, Poll L, Callesen O, Lewis M. Relations between the content of aroma compounds and the sensory evaluation of 10 raspberry varieties (Rubus idaeus L). Acta Agric. Scand 1991 41, 447-454

126. Laugerette F, Passilly-Degrace P, Patris B, Niot I, Febbraio M., Montmayeur, J.-P., & Besnard, P. CD36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions. J Clinical Invest 2005 15(11), 3177–84.

127. Laureati M, Simona Bertolia S, Bergamaschi V, Leone A, Lewandowski L, Giussani B, Battezzati A, Pagliarini E. Food neophobia and liking for fruits and vegetables are not related to Italian children's overweight. Food Quality and Preference 2015 40:125-131.

128. Laureati, M., Bergamaschi, V., & Pagliarini, E. (2015). Assessing childhood food neophobia: Validation of a scale in Italian primary school children. Food Quality and Preference, 40, 8–15. https://doi.org/10.1016/J.FOODQUAL.2014.08.003

129. Laureati, M., Bergamaschi, V., & Pagliarini, E. School-based intervention with children. Peer-modeling, reward and repeated exposure reduce food neophobia and increase liking of fruits and vegetables. Appetite, 2014, 83, 26–32. https://doi.org/10.1016/J.APPET.2014.07.031.

130. Lawson, O. J., Williamson, D. A., Champagne, C. M., DeLany, J. P., Brooks, E. R., Howat, P. M., … Ryan, D. H. (1995). The association of body weight, dietary intake, and energy expenditure with dietary restraint and disinhibition. Obesity Research, 3(2), 153–161.

131. Ledoux TA, Hingle MD, Baranowski T. Relationship of fruit and vegetable intake with adiposity: a systematic review. Obes Rev 2011 12(5):e143-50.

132. Lee SJ, Depoortere I, Hatt H. Therapeutic potential of ectopic olfactory and taste receptors. Nat Rev Drug Discov 2018 [Epub ahead of print]

133. Lee, C., Liese, A., Wagenknecht, L., Lorenzo, C., Haffner, S., & Hanley, A. (2013). Fish consumption, insulin sensitivity and beta-cell function in the Insulin Resistance Atherosclerosis Study (IRAS). Nutrition, Metabolism and Cardiovascular Diseases, 23(9), 829–835. https://doi.org/10.1016/J.NUMECD.2012.06.001
134. Li L, Simonsick EM, Ferrucci L et al. Hearing loss and gait speed among older adults in the United States. Gait Posture 2013;38:25–29
135. Lindroos AK, Lissner L, Mathiassen ME, Karlsson J, Sullivan M, Bengtsson C, Sjöström L. Dietary intake in relation to restrained eating, disinhibition, and hunger in obese and nonobese Swedish women. Obes Res. 1997; 5(3):175-82.
136. Lipchock SV, Mennella JA, Spielman AI, Reed DR. Human bitter perception correlates with bitter receptor messenger RNA expression in taste cells. Am J Clin Nutr.2013 98(4):1136-43.
137. Lipchock SV, Spielman AI, Mennella JA, Mansfield CJ, Hwang LD, Douglas JE, Reed DR. Caffeine Bitterness is Related to Daily Caffeine Intake and Bitter Receptor mRNA Abundance in Human Taste Tissue. Perception. 2017 46(3-4):245-256
138. Liu G, Zong G, Doty RL, Sun Q. Prevalence and risk factors of taste and smell impairment in a nationwide representative sample of the US population: a cross-sectional study. BMJ Open. 2016 Nov 9;6(11):e013246. doi: 10.1136/bmjopen-2016-013246.
139. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J, et al., LifeLines Cohort Study, ADIPOGen Consortium, AGEN-BMI Working Group, CARDIOGRAMplusC4D Consortium, CKDGen Consortium, GLGC, ICBP, MAGIC Investigators, MuTHER Consortium, MIGen Consortium, PAGE Consortium, ReproGen Consortium, GENIE Consortium, International Endogene Consortium Nature 2015 518:197-206
140. Löffler A, Luck T, Then FS, Sikorski C, Kovacs P, Böttcher Y, Breitfeld J, Tönjes A, Horstmann A, Löffler M, et al. Eating behaviour in the general population: An analysis of the factor structure of the German version of the

three-factor-eating-questionnaire (TFEQ) and its association with the body mass index. PLoS One. 2015; 10(7):e0133977.

141. Logue, A. W., & Smith, M. E. (1986). Predictors of food preferences in adult humans. Appetite, 7(2), 109–125.

142. Looy, H. & Weingarten H. (1992). Facial expressions and genetic sensitivity to 6-n-propylthiouracil predict hedonic response to sweet. Physiology & Behavior, 52 (1), 75-82.

143. Lunde K, Egelandsdal B, Skuterud E, Mainland JD, Lea T, Hersleth M, Matsunami H. Genetic variation of an odorant receptor OR7D4 and sensory perception of cooked meat containing androstenone. PLoS One 2012 7(5), e35259.

144. Ma X, Bacci S, Mlynarski W, Gottardo L, Soccio T, Menzaghi C, Iori E, Lager RA, Shroff AR, Gervino EV, Nesto RW, Johnstone MT, Abumrad NA, Avogaro A, Trischitta V, Doria A. A common haplotype at the CD36 locus is associated with high free fatty acid levels and increased cardiovascular risk in Caucasians. Hum Mol Genet 2004 13(19), 2197–205.

145. Mackay TF. The genetic architecture of quantitative traits. Annu. Rev. Genet. 2001 35, 303–339.

146. Mahattanatawee K, Rouseff R, Valim MF, Naim M. Identification and aroma impact of norisoprenoids in orange juice.J. Agric. Food Chem. 2005 53, 393-397

147. Mainland JD, Matsunami H. Taste perception: how sweet it is (to be transcribed by you). Curr Biol 2009 19(15), R655–6.

148. Mariman EC, Szklarczyk R, Bouwman FG, Aller EE, van Baak MA, Wang P. Olfactory receptor genes cooperate with protocadherin genes in human extreme obesity. Genes Nutr 2015 10(4), 465.

149. Marin C, Vilas D, Langdon C, Alobid I, López-Chacón M, Haehner A, Hummel T, Mullol J. Olfactory Dysfunction in Neurodegenerative Diseases. Curr Allergy Asthma Rep. 2018 18(8), 42.

150. Masic, U., Christiansen, P., & Boyland, E. J. (2017). The influence of calorie and physical activity labelling on snack and beverage choices. Appetite, 112, 52–58. https://doi.org/10.1016/J.APPET.2017.01.007

151. Mathieu ME, Reid RER, King NA. Sensory Profile of Adults with Reduced Food Intake and the Potential Roles of Nutrition and Physical Activity Interventions. Adv Nutr 2019 Nov 1;10(6):1120-1125. doi: 10.1093/advances/nmz044.
152. McRae JF, Mainland JD, Jaeger SR, Adipietro KA, Matsunami H, Newcomb RD.Genetic variation in the odorant receptor OR2J3 is associated with the ability to detect the "grassy" smelling odor, cis-3-hexen-1-ol. Chem Senses 2012 37(7), 585-93.
153. Mela, D. J. (1996). Eating behaviour, food preferences and dietary intake in relation to obesity and body-weight status. Proceedings of the Nutrition Society, 55(3), 803–816. https://doi.org/10.1079/PNS19960080
154. Mela, D. J., & Sacchetti, D. A. (1991). Sensory preferences for fats: relationships with diet and body composition. The American Journal of Clinical Nutrition, 53(4), 908–915.
155. Mener DJ, Betz J, Genther DJ, Chen D, Lin FR. Hearing loss and depression in older adults. J Am Geriatr Soc 2013;61(9):1627–9.
156. Mennella JA, Finkbeiner S, Reed DR. The proof is in the pudding: children prefer lower fat but higher sugar than do mothers. Int J Obes (Lond) 2012 36(10), 1285–1291.
157. Mennella JA, Pepino MY, Reed DR. Genetic and environmental determinants of bitter perception and sweet preferences. Pediatrics 2005 115(2), e216-22.
158. Meyre D, Boutin P, Tounian A, Deweirder M, Aout M, Jouret B, Heude B, Weill J, Tauber M, Tounian P, Froguel P. Is glutamate decarboxylase 2 (GAD2) a genetic link between low birth weight and subsequent development of obesity in children? J Clin Endocrinol Metab. 2005; 90(4):2384-90.
159. Cocca M, Barbieri C, Concas MP, Robino A, Brumat M, Gandin I, Trudu M, Sala C, Vuckovic D, Girotto G, Matullo G, Polasek O, Kolcic I, Gasparini P, Soranzo N, Toniolo D, Mezzavilla M. A bird's-eye view of Italian genomic variation through whole genome sequencing, Eur J Hum Genet, 2019, doi: 10.1038/s41431-019-0551-x.
160. Michikawa T, Nishiwaki Y, Takebayashi T. Are you conscious of any age-related taste impairments? Prevalence of and factors associated with taste impairment in Japan. J Am Geriatr Soc. 2011;59:951-953.

161. Mick P, Kawachi I, Lin FR. The association between hearing loss and social isolation in older adults. Otolaryngol Head Neck Surg 2014;150(3):378–84.
162. Monteleone, E., Spinelli, S., Dinnella, C., Endrizzi, I., Laureati, M., Pagliarini, E., … Tesini, F. (2017). Exploring influences on food choice in a large population sample: The Italian Taste project. Food Quality and Preference, 59, 123–140. https://doi.org/10.1016/J.FOODQUAL.2017.02.013
163. Mullie, P., Clarys, P., Hulens, M., & Vansant, G. (2010). Dietary patterns and socioeconomic position. European Journal of Clinical Nutrition, 64(3), 231–238. https://doi.org/10.1038/ejcn.2009.145
164. Murea M, Ma L, Freedman BI. Genetic and environmental factors associated with type 2 diabetes and diabetic vascular complications. Rev Diabet Stud. 2012 Spring;9(1):6-22. doi: 10.1900/RDS.2012.9.6. Epub 2012 May 10. Review.
165. Murphy C, Schubert CR, Cruickshanks KJ et al. Prevalence of olfactory impairment in older adults. JAMA 2002;288:2307–2312.20.
166. Nakamura, K., Shimai, S., Kikuchi, S., & Tanaka, M. (2001). Correlation between a liking for fat-rich foods and body fatness in adult Japanese: a gender difference. Appetite, 36(1), 1–7. https://doi.org/10.1006/APPE.2000.0377
167. Neale BM, Mazzeo SE, Bulik CM. A twin study of dietary restraint, disinhibition and hunger: an examination of the eating inventory (three factor eating questionnaire). Twin Res. 2003 Dec;6(6):471-8.
168. Negri R, Di Feola M, Di Domenico S, Scala MG, Artesi G, Valente S, Smarrazzo A, Turco F, Morini G, Greco L. Taste perception and food choices. J Pediatr Gastroenterol Nutr 2012 54(5), 624-9.
169. Nour M, Lutze SA, Grech A, Allman-Farinelli M. The Relationship between Vegetable Intake and Weight Outcomes: A Systematic Review of Cohort Studies. Nutrients 2018 10(11). pii: E1626.
170. Novaković, R., Cavelaars, A., Geelen, A., Nikolić, M., Altaba, I. I., Viñas, B. R., … de Groot, L. C. (2014). Review Article Socio-economic determinants of micronutrient intake and status in Europe: a systematic review. Public Health Nutrition, 17(5), 1031–1045. https://doi.org/10.1017/S1368980013001341

171. O'Doherty Jensen, K., & Holm, L. (1999). Preferences, quantities and concerns: socio-cultural perspectives on the gendered consumption of foods. European Journal of Clinical Nutrition, 53(5), 351–359.
172. Ooi SX, Lee PL, Law HY, Say YH. Bitter receptor gene (TAS2R38) P49A genotypes and their associations with aversion to vegetables and sweet/fat foods in Malaysian subjects. Asia Pac. J. Clin. Nutr 2010 19, 491–498.
173. Pallister T, Sharafi M, Lachance G, Pirastu N, Mohney RP, MacGregor A, Feskens EJ, Duffy V, Spector TD, Menni C. Food Preference Patterns in a UK Twin Cohort. Twin Res Hum Genet. 2015 18(6), 793-805.
174. Panagiotakos, D. B., Zeimbekis, A., Boutziouka, V., Economou, M., Kourlaba, G., Toutouzas, P., & Polychronopoulos, E. (2007). Long-term fish intake is associated with better lipid profile, arterial blood pressure, and blood glucose levels in elderly people from Mediterranean islands (MEDIS epidemiological study). Medical Science Monitor : International Medical Journal of Experimental and Clinical Research, 13(7), CR307-12.
175. Parola S and Liberini P, Assessing olfaction in the Italian population: methodology and clinical application, Ital J Neurol Sci. 1999 Oct;20(5):287-96.
176. Pérez-Rodrigo, C., Ribas, L., Serra-Majem, L.l. & Aranceta, J. (2003). Food preferences of Spanish children and young people: the enKid study. European Journal of Clinical Nutrition, 57, S45–S48. https://doi.org/10.1038/sj.ejcn.1601814
177. Perna S, Riva A, Nicosanti G, Carrai M, Barale R, Vigo B, Allegrini P, Rondanelli M. Association of the bitter taste receptor gene TAS2R38 (polymorphism RS713598) with sensory responsiveness, food preferences, biochemical parameters and body-composition markers. A cross-sectional study in Italy. Int J Food Sci Nutr 2018 69(2), 245-252.
178. Peterson, J. M., Bartoshuk, L. M., & Duffy, V. B. (1999). Intensity and Preference for Sweetness is Influenced by Genetic Taste Variation. Journal of the American Dietetic Association, 99(9), A28. https://doi.org/10.1016/S0002-8223(99)00486-1
179. Pham H, Hui H, Morvaridi S, Cai J, Zhang S, Tan J, Wu V, Levin N, Knudsen B, Goddard WA 3rd, Pandol SJ, Abrol R. A bitter pill for type 2 diabetes? The

activation of bitter taste receptor TAS2R38 can stimulate GLP-1 release from enteroendocrine L-cells. Biochem Biophys Res Commun 2016 475(3), 295-300.

180. Pinto JM, Wroblewski KE, Kern DW et al. Olfactory dysfunction predicts 5-year mortality in older adults. PLoS ONE 2014;9:e107541.

181. Pirastu N, Kooyman M, Traglia M, Robino A, Willems SM, Pistis G, Amin N, Sala C, Karssen LC, van Duijn CM, Toniolo D, Gasparini P. Genome-wide association analysis on five isolated populations identifies variants of the HLA-DOA gene associated with white wine liking. Eur J Hum Genet. 2015 23(12), 1717-22.

182. Pirastu N, Kooyman M, Traglia M, Robino A, Willems SM, Pistis G, d'Adamo P, Amin N, d'Eustacchio A, Navarini L, Sala C, Karssen LC, van Duijn C, Toniolo D, Gasparini P. Association analysis of bitter receptor genes in five isolated populations identifies a significant correlation between TAS2R43 variants and coffee liking. PLoS One 2014 9(3), e92065.

183. Pirastu N, Kooyman M, Traglia M, Robino A, Willems SM, Pistis G, Amin N, Sala C, Karssen LC, Van Duijn C, Toniolo D, Gasparini, P, A Genome-Wide Association Study in isolated populations reveals new genes associated to common food likings. Reviews in Endocrine and Metabolic Disorders, 17(2), 209–219. (2016). https://doi.org/10.1007/s11154-016-9354-3.

184. Pirastu N, Robino A, Lanzara C, Athanasakis E, Esposito L, Tepper BJ, Gasparini P. Genetics of food preferences: a first view from silk road populations. J Food Sci. 2012 77(12), S413-8.

185. Precone V, Beccari T, Stuppia L, Baglivo M, Paolacci S, Manara E, Miggiano GAD, Falsini B, Trifirò A, Zanlari A, Herbst KL, Unfer V, Bertelli M; Geneob Project. Taste, olfactory and texture related genes and food choices: implications on health status. Eur Rev Med Pharmacol Sci. 2019 23(3):1305-1321.

186. Prescott, J., & Swain-Campbell, N. (2000). Responses to repeated oral irritation by capsaicin, cinnamaldehyde and ethanol in PROP tasters and non-tasters. Chemical Senses, 25(3), 239–246.

187. Pronin AN, 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(16), 1403–8.

188. Provencher V, Pérusse L, Drapeau V, Tremblay A, Després J, Lemieux S. Familial resemblance in eating behaviors in men and women from the Québec Family Study. J Am Diet Assoc 2003;102(suppl 2):A-35.
189. Rao DC. An Overview of the Genetic Dissection of Complex Traits. Adv Genet. 2008 60,3-34
190. Reed DR, Bachmanov AA, Beauchamp GK, Tordoff MG, Price RA. Heritable variation in food preferences and their contribution to obesity. Behav Genet. 1997 27(4), 373-87.
191. Reed DR, Xia MB. Recent advances in fatty acid perception and genetics. Adv Nutr 2015 6(3), 353S-6.
192. Reed DR, Zhu G, Breslin PA, Duke FF, Henders AK, Campbell MJ, Montgomery GW, Medland SE, Martin NG, Wright MJ. 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(21):4278-85.
193. Ricketts, C. D. (1997). Fat preferences, dietary fat intake and body composition in children. European Journal of Clinical Nutrition, 51(11), 778–781.
194. Riera CE, Tsaousidou E, Halloran J, Follett P, Hahn O, Pereira MMA, Ruud LE, Alber J, Tharp K, Anderson CM, Brönneke H, Hampel B, Filho CDM, Stahl A, Brüning JC, Dillin A. The Sense of Smell Impacts Metabolic Health and Obesity. Cell Metab. 2017 26(1), 198-211.e5.
195. Robino A, Bevilacqua L, Pirastu N, Situlin R, Di Lenarda R, Gasparini P, Navarra CO. Polymorphisms in sweet taste genes (TAS1R2 and GLUT2), sweet liking, and dental caries prevalence in an adult Italian population. Genes Nutr 2015 10(5), 485.
196. Robino, A., Mezzavilla, M., Pirastu, N., La Bianca, M., Gasparini, P., Carlino, D., & Tepper, B. J. (2016). Understanding the role of personality and alexithymia in food preferences and PROP taste perception. Physiology & Behavior, 157, 72–78. https://doi.org/10.1016/J.PHYSBEH.2016.01.022
197. Rodenburg, G., Oenema, A., Pasma, M., Kremers, S. P. J., & van de Mheen, D. (2013). Clustering of food and activity preferences in primary school children. Appetite, 60, 123–132. https://doi.org/10.1016/J.APPET.2012.10.007

198. Rohde K, Federbusch M, Horstmann A, Keller M, Villringer A, Stumvoll M, Tönjes A, Kovacs P, Böttcher Y. Genetic variants in AKR1B10 associate with human eating behavior. BMC Genet. 2015; 16:31.
199. Rolls, B. J. (1999). Do Chemosensory Changes Influence Food Intake in the Elderly? Physiology & Behavior, 66(2), 193–197. https://doi.org/10.1016/S0031-9384(98)00264-9
200. Rosseel Y (2012). "lavaan: An R Package for Structural Equation Modeling." Journal of Statistical Software, 48(2), 1–36. http://www.jstatsoft.org/v48/i02/.
201. Russell, C. G., & Worsley, A. (2008). A Population-based Study of Preschoolers' Food Neophobia and Its Associations with Food Preferences. Journal of Nutrition Education and Behavior, 40(1), 11–19. https://doi.org/10.1016/j.jneb.2007.03.007
202. Schiffman SS, Graham BG. Taste and smell perception affect appetite and immunity in the elderly. Eur J Clin Nutr 2000;54:S54–S63.12.
203. Schiffman SS. Critical illness and changes in sensory perception. ProcNutr Soc 2007;66(3):331–45.
204. Schiffman, S. S. Effects of aging on the human taste system. Ann. N. Y. Acad. Sci. 1170, 725–729 (2009).
205. Schwab S, Xu T, Ryan K, Steinle N. Eating Behavior Disinhibition Predicts Insulin Insensitivity in Old Order Amish. Advances in Nutrition. 2016; 7:40A.
206. Schwingshackl L, Hoffmann G, Kalle-Uhlmann T, Arregui M, Buijsse B, Boeing H. Fruit and Vegetable Consumption and Changes in Anthropometric Variables in Adult Populations: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. PLoS One 2015 10(10):e0140846.
207. Seow, Y.-X., Ong, P. K. C. & Huang, D. Odor-Specific Loss of Smell Sensitivity with Age as Revealed by the Specific Sensitivity Test. Chem. Senses 41, 487–495 (2016).
208. Sharafi, M. S., Fernandez, M. L., Huedo-Medina, T. B., & Duffy, V. B. (2018). Taste phenotype associates with Rawal cardiovascular disease risk factors via diet quality in multivariate modeling. Physiology & Behavior, 194, 103–112.
209. Sheikh AB, Nasrullah A, Haq S, Akhtar A, Ghazanfar H, Nasir A, Afzal RM, Bukhari MM, Chaudhary AY, Naqvi SW. The Interplay of Genetics and

Environmental Factors in the Development of Obesity. Cureus. 2017 Jul 6;9(7):e1435. doi: 10.7759/cureus.1435. Review.

210. Shen Y, Kennedy OB, Methven L. 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

211. Shigemura N, Shirosaki S, Ohkuri T, Sanematsu K, Islam AA, Ogiwara Y, Kawai M, Yoshida R, Ninomiya Y. Variation in umami perception and in candidate genes for the umami receptor in mice and humans. Am J Clin Nutr 2009 90(3), 764S-769S.

212. Shigemura N, Shirosaki S, Sanematsu K, Yoshida R, Ninomiya Y. Genetic and molecular basis of individual differences in human umami taste perception. PloS One 2009 4(8), e6717.

213. Smith AD, Fildes A, Cooke L, Herle M, Shakeshaft N, Plomin R, Llewellyn C. Genetic and environmental influences on food preferences in adolescence. Am J Clin Nutr. 2016 104(2), 446-53.

214. Solemdal K, Møinichen-Berstad C, Mowe M et al. Impaired taste and increased mortality in acutely hospitalized older people. Chem Senses 2014;39:263–269.

215. Stanhope, K. L. (2016). Sugar consumption, metabolic disease and obesity: The state of the controversy. Critical Reviews in Clinical Laboratory Sciences, 53(1), 52–67. https://doi.org/10.3109/10408363.2015.1084990

216. Steinle N, Hsueh W, Snitker S, et al. Eating behavior in the Old Order Amish: heritability analysis and a genome-wide linkage analysis. Am J Clin Nutr 2002;75:1098–106.

217. Straub RH, Lamparter-Lang R, Palitzsch KD, Schölmerich J. Association between eating behaviour and current glycaemic control, body mass or autonomic nervous function in long-term type I and type II diabetic patients. Eur J Clin Invest. 1996; 26(7):564-8.

218. Stunkard, A. J., & Messick, S. (1985). The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. Journal of Psychosomatic Research, 29(1), 71–83.

219. Tabachnick, B.G.; Fidell, L.S. Using Multivariate Statistics; Allyn and Bacon: Boston, MA, USA, 2001; Volume xxvi.

220. Tabara, Y., Arai, H., Hirao, Y., Takahashi, Y., Setoh, K., Kawaguchi, T., … Matsuda, F. (2017). The causal effects of alcohol on lipoprotein subfraction and triglyceride levels using a Mendelian randomization analysis: The Nagahama study. Atherosclerosis, 257, 22–28. https://doi.org/10.1016/j.atherosclerosis.2016.12.008

221. Tandon KS, Baldwin EA, Shewfelt RL. Aroma perception of individual volatile compounds in fresh tomatoes (Lycopersicon esculentum, Mill.) as affected by the medium of evaluation. Postharvest Biology and Technology 2000 20 (3), 261-268.

222. Tanofsky-Kraff M, Han JC, Anandalingam K, Shomaker LB, Columbo KM, Wolkoff LE, Kozlosky M, Elliott C, Ranzenhofer LM, Roza CA, Yanovski SZ, Yanovski JA. The FTO gene rs9939609 obesity-risk allele and loss of control over eating. Am J Clin Nutr. 2009; 90(6):1483-8.

223. Tepper BJ, Koelliker Y, Zhao L, Ullrich NV, Lanzara C, d'Adamo P, Ferrara A, Ulivi S, Esposito L, Gasparini P. Variation in the bitter-taste receptor gene TAS2R38, and adiposity in a genetically isolated population in Southern Italy. Obesity (Silver Spring). 2008 16(10), 2289-95.

224. Tepper BJ. Nutritional implications of genetic taste variation: the role of PROP sensitivity and other taste phenotypes. Annu Rev Nutr 2008 28, 367–388.

225. Tepper, B. J. (1998). 6-n-Propylthiouracil: A Genetic Marker for Taste, with Implications for Food Preference and Dietary Habits. The American Journal of Human Genetics, 63(5), 1271–1276. https://doi.org/10.1086/302124

226. Tepper, B. J., White, E. A., Koelliker, Y., Lanzara, C., D'Adamo, P., & Gasparini, P. (2009). Genetic Variation in Taste Sensitivity to 6-n-Propylthiouracil and Its Relationship to Taste Perception and Food Selection. Annals of the New York Academy of Sciences, 1170(1), 126–139. https://doi.org/10.1111/j.1749-6632.2009.03916.x

227. Timpson, NJ, Christensen, M., Lawlor, D. A., Gaunt, T. R., Day, I. N., Ebrahim, S. and Davey Smith, G. TAS2R38 (phenylthiocarba- mide)

haplotypes, coronary heart disease traits, and eating behavior in the British Women's Heart and Health Study. Am. J. Clin. Nutr. 2005 81, 1005–1011.

228. Tolstrup, J. S., Grønbaek, M., & Nordestgaard, B. G. (2009). Alcohol intake, myocardial infarction, biochemical risk factors, and alcohol dehydrogenase genotypes. Circulation. Cardiovascular Genetics, 2(5), 507–514. https://doi.org/10.1161/CIRCGENETICS.109.873604
229. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. Nat Rev Genet 2018 19(9):581-590.
230. Törnwall O, Silventoinen K, Kaprio J, Tuorila H. Why do some like it hot? Genetic and environmental contributions to the pleasantness of oral pungency. Physiol Behav 2012 107(3), 381-9.
231. Törnwall O, Silventoinen K, Keskitalo-Vuokko K, Perola M, Kaprio J, Tuorila H. Genetic contribution to sour taste preference. Appetite. 2012 58(2), 687-94.
232. Törnwall, O., Silventoinen, K., Hiekkalinna, T., Perola, M., Tuorila, H., & Kaprio, J. (2014). Identifying flavor preference subgroups. Genetic basis and related eating behavior traits. Appetite, 75, 1–10. https://doi.org/10.1016/J.APPET.2013.11.020
233. Ugawa S. Identification of sour-taste receptor genes. Anat Sci Int 2003, 78(4), 205-10.
234. Ullrich N V, Touger-Decker R, O'sullivan-Maillet J, Tepper BJ. PROP taster status and self-perceived food adventurousness influence food preferences. J Am Diet Assoc 2004 104: 543–549.
235. Vennemann MM, Hummel T, Berger K. The association between smoking and smell and taste impairment in the general population. J Neurol. 2008;255:1121-1126.].
236. Ventura, A. K., & Worobey, J. (2013). Early Influences on the Development of Food Preferences. Current Biology, 23(9), R401–R408. https://doi.org/10.1016/J.CUB.2013.02.037
237. Visscher PM, Hill WG, Wray NR. Heritability in the genomics era--concepts and misconceptions. Nat Rev Genet 2008 9(4), 255-66.
238. Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA, Yang J. 10 Years of GWAS Discovery: Biology, Function, and Translation. Am J Hum Genet. 2017 6, 101(1):5-22.

239. Wądołowska, L., Babicz-Zielińska, E. & Czarnocińskac, J. (2008). Food choice models and their relation with food preferences and eating frequency in the Polish population: POFPRES study. Food Policy, 33, 122-134. https://doi.org/10.1016/j.foodpol.2007.08.001

240. Welge-Leussen A. Ageing, neurodegeneration, and olfactory and gustatory loss. B-ENT 2009;5(Suppl 13):129–132.

241. Wennberg, M., Tornevi, A., Johansson, I., Hörnell, A., Norberg, M., & Bergdahl, I. A. (2012). Diet and lifestyle factors associated with fish consumption in men and women: a study of whether gender differences can result in gender-specific confounding. Nutrition Journal, 11(1), 101. https://doi.org/10.1186/1475-2891-11-101

242. Westenhoefer, J. (2005). Age and gender dependent profile of food choice. Forum of Nutrition, (57), 44–51.

243. Wildes, J. E., Zucker, N. L., & Marcus, M. D. (2012). Picky eating in adults: Results of a web-based survey. International Journal of Eating Disorders, 45(4), 575-582.

244. Williamson DA, Lawson OJ, Brooks ER, Wozniak PJ, Ryan DH, Bray GA, Duchmann EG. Association of Body Mass with Dietary Restraint and Disinhibition. Appetite. 1995; 25:31–41.

245. Wright SS: Correlation and causation. J Agric Res 1921, 20:557–585.

246. Wu SV, Rozengurt N, Yang M, Young SH, Sinnett-Smith J, Rozengurt E. Expression of bitter taste receptors of the T2R family in the gastrointestinal tract and enteroendocrine STC-1 cells. Proc Natl Acad Sci U S A 2002 99(4), 2392–7.

247. Wysocki CJ, Beauchamp GK. Ability to smell androstenone is genetically determined. Proc Natl Acad Sci U S A 1984 81(15), 4899–4902.

248. Xue, Y., Mezzavilla, M., Haber, M., McCarthy, S., Chen, Y., Narasimhan, V., ... Zeggini, E.. Enrichment of low-frequency functional variants revealed by whole-genome sequencing of multiple isolated European populations. Nature Communications (2017), 8, 15927. https://doi.org/10.1038/ncomms15927.

249. Yang J, Manolio TA, Pasquale LR, Boerwinkle E, Caporaso N, Cunningham JM, de Andrade M, Feenstra B, Feingold E, Hayes MG, Hill WG, Landi MT, Alonso A, Lettre G, Lin P, Ling H, Lowe W, Mathias RA, Melbye M, Pugh E,

Cornelis MC, Weir BS, Goddard ME, Visscher PM. Genome partitioning of genetic variation for complex traits using common SNPs. Nat Genet 2011, 43(6), 519-25.

250. Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, Frayling TM, Hirschhorn J, Yang J, Visscher PM, GIANT Consortium. Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. Hum Mol Genet 2018 27(20):3641-3649.

251. Zhao L, Kirkmeyer SV, Tepper BJ. A paper screening test to assess genetic taste sensitivity to 6-n-propylthiouracil. Physiol Behav 2003;78(4-5):625-33. doi: 10.1016/s0031-9384(03)00057-x.

252. Zhu M, Shuhong Zhao S. Candidate Gene Identification Approach: Progress and Challenges. Int J Biol Sci 2007, 3(7), 420–427

253. Ziglio E, Currie C, Rasmussen VB. The WHO cross-national study of health behavior in school aged children from 35 countries: findings from 2001-2002. J School Health (2004), 74 (6): 204-206.

254. Zizza, C. A., Sebastian, R. S., Wilkinson Enns, C., ISIK, Z., Goldman, J. D., & Moshfegh, A. J. (2015). The Contribution of Beverages to Intakes of Energy and MyPlate Components by Current, Former, and Never Smokers in the United States. Journal of the Academy of Nutrition and Dietetics, 115(12), 1939–1949. https://doi.org/10.1016/j.jand.2015.07.015

Acknowledgements

I want to thank my supervisor, Prof Gasparini, and all the collaborators who have contributed to the different stages of this project.
I am particularly grateful to Antonietta Robino for her invaluable help during all the three PhD years and in providing indispensable suggestions and advice.