IMPACT OF DIETARY AND OBESITY GENETIC RISK SCORES ON WEIGHT GAIN

Running head: No gene-diet interaction on weight gain

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LIST OF ABBREVIATIONS

AHEI, Alternative Healthy Eating Index

ANCOVA, analysis of covariance

ANOVA, analysis of variance

BMI, body mass index

FFQ, food frequency questionnaire

MD, Mediterranean diet

SNP, single nucleotide polymorphism

WHO, World Health Organization

WHR, waist to hip ratio

ABSTRACT

BACKGROUND: Whether genetic background and/or dietary behaviours influence weight gain in middle-aged subjects is debated.

AIM: To assess whether genetic background and/or dietary behaviours are associated with changes in obesity markers (body mass index [BMI], weight, waist and hip circumferences) in a Swiss population-based cohort.

METHODS: Cross-sectional and prospective (follow-up of 5.3 years) study. Two obesity genetic risk scores (GRS) based on 31 or 68 SNPs were used. Dietary intake was assessed using a semi-quantitative food frequency questionnaire. Three dietary patterns "Meat & fries" (unhealthy), "Fruits & Vegetables" (healthy), and "Fatty & sugary" (unhealthy), and three dietary scores (two Mediterranean and the alternative healthy eating index [AHEI]) were computed.

RESULTS: On cross-sectional analysis (N=3033, 53.2% females, 58.4±10.6 years), obesity markers were positively associated with unhealthy dietary patterns and GRS, and negatively associated with healthy dietary scores and patterns.

On prospective analysis (N=2542, 54.7% females, age at baseline 58.0±10.4 years), the AHEI and the "Fruits & vegetables" pattern were negatively associated with waist circumference gain: multivariate-adjusted average±standard error 0.96±0.25 vs. 0.11±0.26 cm (p for trend 0.044), and 1.14±0.26 vs. -0.05±0.26 cm (p for trend 0.042) for first and fourth quartiles of the AHEI and the "Fruits & vegetables" pattern, respectively. Similar inverse associations were obtained for changes in waist >5 cm: multivariate-adjusted odds ratio (95% confidence interval): 0.65 (0.50,0.85) and 0.67 (0.51,0.89) for the fourth vs. the first quartile of the AHEI and the "Fruits & vegetables" dietary pattern, respectively. No associations were found

between GRS and changes in obesity markers, and no significant gene-diet interactions were found.

CONCLUSION: Dietary intake, not GRS, are associated with waist circumference in middle-aged subjects living in Lausanne, Switzerland.

Keywords: gene-diet interactions; obesity; weight gain; prospective study; dietary intake

INTRODUCTION

Obesity is a worldwide health concern, with a rising prevalence and increasing morbidity (1, 2), resulting from the interaction of several factors, such as physical activity (3), diet (4) and genetics. Indeed, genome-wide-association studies identified numerous loci related to an increase in body mass index (BMI) levels (5, 6). Furthermore, recent studies hypothesized that obesity's genetic background could interact with environmental factors (7), such as physical activity or diet (3, 8) to impact on obesity markers.

Gene-diet interaction is usually evaluated using diverse dietary markers, such as simple nutrients (9, 10), specific foods (11), dietary scores and dietary patterns (4, 12). Some studies reported gene-diet interaction on obesity markers (11, 13), while others failed to replicate the findings (9, 14). Obesity genetic susceptibility is usually explored using either specific loci or more recently, obesity predisposition genetic risk scores (5, 11, 13, 15), derived from Genome-Wide Association Studies.

To evaluate diet, several dietary scores have previously been developed, such as the Mediterranean diet (MD) score (16) and the Alternative Healthy Eating Index (AHEI) (17). These scores are hypothesis-oriented, as they combine specific foods known to be beneficial. These jointly consumed food groups can usually be categorized into "healthy" and "unhealthy" (18). Alternatively, dietary patterns can be obtained using dimension-reducing methods such as principal components analysis (12). These pattern-oriented dietary studies have the advantage of reflecting in-between food interaction, compared to dietary scores, nutrients or specific food studies (12, 18) .

Little is known regarding the interaction between dietary scores or patterns with genetic risk scores on obesity markers in Switzerland. Hence, we aimed to assess the interaction between known obesity genetic risk scores (GRS) (5, 11, 13, 15) and several

dietary markers (including dietary scores and patterns) on obesity markers (cross sectional analysis) and weight, waist or hip circumferences changes (prospective analysis using a five-year follow-up). We hypothesized that both dietary and obesity GRS would be associated with obesity markers and weight gain, but that no significant gene-diet interaction would be found.

METHODS

Setting and sampling

The CoLaus|PsyColaus study is a prospective survey investigating the biological and genetic determinants of cardiovascular risk factors and cardiovascular disease in the population of Lausanne, Switzerland (19). Recruitment began in June 2003 and ended in May 2006, enrolling 6733 participants who underwent an interview, a physical exam, and a blood analysis. The first follow-up was performed between April 2009 and September 2012, 5.6 years on average after the collection of baseline data. The second follow-up was performed between May 2014 and April 2017, 10.9 years on average after the collection of baseline data. The information collected was similar to that collected in the baseline examination but contained questions regarding food consumption and detailed physical activity information. As dietary intake was first assessed at the first follow-up, the study was based on data from the first (2009-2012) and the second follow-ups (2014-2017) only.

Anthropometric data

At all visits (baseline, first and second follow-ups), body weight and height were measured while participants stood without shoes in light indoor attire (19). Body weight was measured in kilograms to the nearest 100 g using a Seca® scale (Hamburg, Germany) that was frequently calibrated (19). Height was measured to the nearest 5 mm using a Seca® (Hamburg, Germany) height gauge (19). Waist circumference was measured mid-way

between the lowest rib and the iliac crest using a non-stretchable tape. The average of two measurements was taken and rounded to the nearest 0.5 cm.

Body mass index (BMI) was calculated and obesity was defined per World Health Organization (WHO) guidelines as a BMI ≥30 kg/m^2. Changes in obesity variables between studies were computed as the difference between the second and the first follow-up, so that an increase would be registered as a positive value. As performed in a previous study (20) changes in obesity markers were further categorized into clinically significant changes, i.e. at least 5 kg (20) change in weight. This threshold was chosen because the WHO recommends that weight gain in adulthood should not exceed 5 Kg over the entire adult life (21). We also assessed 5 cm change in waist circumference.

For the cross-sectional analyses, body weight, BMI, waist and hip in the first follow-up were the primary outcome variables. For the prospective analyses, changes in body weight, BMI, waist and hip between the first and the second follow-ups were the primary outcome variables (20).

Dietary data

Dietary intake was assessed using a validated, self-administered, semi-quantitative food frequency questionnaire (FFQ) (22-24). Briefly, this FFQ assesses the dietary intake of the previous 4 weeks and consists of 97 different food items accounting for more than 90% of the intake of calories, proteins, fat, carbohydrates, alcohol, cholesterol, vitamin D and retinol, and 85% of fibre, carotene and iron (18). For each item, consumption frequencies ranging from “less than once during the last 4 weeks” to “2 or more times per day” were provided, and the participants indicated the average serving size (smaller, equal or bigger) compared to a reference size (18). Conversion into nutrients was performed based on the French CIQUAL food composition table (18, 25) taking into account portion size.

Three hypothesis-oriented dietary scores were computed, two based on the Mediterranean diet, the third on a modification of the alternative healthy eating index (AHEI). The first Mediterranean dietary score (hereby designated as "Mediterranean score 1") was derived from Trichopoulou et al. (16), and ranges between zero and eight. The second Mediterranean dietary score (hereby designated as "Mediterranean score 2") is adapted to the Swiss population and was computed according to Vormund et al. (26). Contrary to the score from Trichopoulou et al. (16), dairy products are considered as beneficial. The score thus ranges between zero and nine. The AHEI was adapted from McCullough et al. (17) In our study, the amount of *trans* fat could not be assessed, and we considered all participants taking multivitamins as taking them for a duration ≥5 years. Thus, the modified AHEI score ranged between 2.5 and 77.5 instead of 2.5 and 87.5 for the original AHEI score (17). For all three scores, higher values represented a healthier diet.

Naïve dietary patterns were derived using principal components analysis based on food consumption frequencies. Three dietary patterns were identified: "Meat & fries", "Fruits & Vegetables" and "Fatty & sugary". Detailed description of assessment and characteristics of the dietary patterns is provided elsewhere (18). Prior to analysis, sex-specific quartiles for dietary scores and patterns were computed.

Dietary scores and naïve dietary patterns computed in the first follow-up were used in the prospective analyses assessing the effect of diet on anthropometric changes between the first and the second follow-ups. Similar to other studies (2, 15), dietary scores and patterns were categorized, and quartiles were used.

Genetic data and calculation of obesity genetic risk score

In the baseline survey, nuclear DNA was extracted from whole blood for whole genome scan analysis and genotyping was performed using the Affimetrix 500 K single nucleotide polymorphism (SNP) chip and genome-wide genotyping was performed using the

Affymetrix 500K SNP array (19). Nuclear DNA was extracted from the whole blood of all participants. Genotypes were called using BRLMM (http://www.affymetrix.com/support/technical/whitepapers/brlmm_whitepap).

Duplicate individuals, and first and second-degree relatives, were identified and removed by computing estimates pair-wise genomic kinship coefficients, using KING (27). Subjects were excluded from the analysis in case of inconsistency between sex and genetic data, a genotype call rate of less than 90%, or inconsistencies of genotyping results in duplicate samples. Quality control for SNPs was performed using the following criteria: monomorphic (or with minor allele frequency <1%), call rates less than 90%, deviation from the Hardy-Weinberg equilibrium with $p<10^{-6}$. Phased haplotypes were generated using SHAPEIT2 (28, 29). Imputation was performed using minimac3 and the Haplotype Reference Consortium (version r1.1) (30) hosted on the Michigan Imputation Server.

The GRS for obesity were computed according to previous studies (5, 11, 13, 15), except that the triallelic SNP rs4836133 was not used due to imputation issues. Both scores were derived from large meta-analyses of genome-wide association studies including the CoLaus study (5, 6). Two obesity GRS were computed, based on 31 or 68 SNPs; the list of SNPs used to compute the scores is provided in **Supplemental Tables 1 and 2**. Briefly, weighted GRS were calculated by multiplying each risk allele (0, 1 or 2 risk allele per locus) by its relative effect size as reported by Speliotes et al. (5) and Wang et al. (15). A weighted score reflects the relative contributing effect of each locus on the outcome. The higher the obesity GRS, the higher the predisposition to obesity.

Covariates

Participants were considered as being on a diet if they responded positively to the question ‘are you currently on a diet?’, and the type of diet (i.e. slimming, low salt…) was collected. Smoking status was defined as never, former (irrespective of the time since

quitting) and current (irrespective of the amount smoked) (19). Educational level was categorized into mandatory, apprenticeship, secondary and university (20).

Physical activity was assessed by a questionnaire validated in the population of Geneva (31). This self-reported questionnaire assesses the type and duration of 70 kinds of (non)professional activities and sports during the previous week. Sedentary status was defined as spending more than 90% of the daily energy in activities below moderate- and high-intensity (defined as requiring at least 4 times the basal metabolic rate) (32, 33).

Inclusion and exclusion criteria

The cross sectional analysis of the associations between dietary scores or patterns, GRS and obesity markers included participants from the first follow-up only. The prospective analysis of the associations between dietary scores or patterns and GRS at the first follow-up and changes in obesity markers between the first and the second follow-ups included participants with obesity data for both the first and the second follow-up.

Participants were excluded if they lacked 1) genetic data; 2) follow-up data; 3) any of the dietary scores or patterns; 4) anthropometric data; 5) covariates, or if they were on a slimming diet.

Statistical analysis

Statistical analyses were performed using Stata version 15.1 for windows (Stata Corp, College Station, Texas, USA). Descriptive results were expressed as number of participants (percentage) for categorical variables and as average±standard deviation for continuous variables. Comparison between included and excluded participants was performed using chi-square test for categorical variables and Student's t-test for all variables except total energy intake or nonparametric Kruskal-Wallis (for total energy intake) test for continuous variables.

Cross-sectional analysis of the associations between dietary scores or patterns, GRS and obesity markers were performed for the whole sample and separately for each sex, using data from the first follow-up (2009-2012). Univariate comparisons between quartiles of dietary scores/patterns or GRS were performed using one-way, fixed effects analysis of variance (ANOVA) for continuous variables. Bivariate associations between dietary scores or patterns, GRS and obesity markers were assessed using Spearman nonparametric correlations. Multivariate analyses comparing obesity markers as continuous variables between quartiles of dietary scores or patterns or GRS were performed using covariate-adjusted analysis of variance (ANOVA) and the results were expressed as estimated, multivariate-adjusted average±standard error using the **margins** postestimation command of Stata.

Prospective analysis of the associations between dietary scores or patterns and GRS at the first follow-up and changes in obesity markers between the first and the second follow-ups were performed for the whole sample and separately for each sex. The outcomes were defined as the longitudinal changes in the different measures of adiposity. Univariate comparisons between quartiles of dietary scores/patterns or GRS were performed using chi-square test in case of categorical variables and ANOVA for continuous variables. Multivariate analyses were performed using logistic regression for categorical outcome variables (such as having >5 kg weight gain and >5 cm waist gain) and the results were expressed as odds ratio (OR) and 95% confidence interval. For continuous variables, multivariate analyses were performed using covariate-adjusted ANOVA and the results were expressed as estimated, multivariate-adjusted average±standard error.

Gene-diet interactions were assessed using quartiles of dietary scores or patterns and GRS as 1) a continuous variable using analysis of covariance (ANCOVA), or 2) categorized in quartiles using ANOVA. Interactions were modelled using the syntax

[diet quartile]##[GRS]

where [GRS] can be either a continuous variable (ANCOVA) or a categorical variable (ANOVA). The interactions between sex and quartiles of dietary markers were also assessed.

For both cross-sectional and prospective analyses, covariate-corrected models (logistic regression, ANCOVA and ANOVA) were adjusted for age (continuous), education (primary, apprenticeship, secondary and university), smoking (never, former, current) and sedentary status (yes/no). For analyses including the whole sample, a further adjustment on sex was performed, and for prospective analyses, a further adjustment on the baseline obesity marker as a continuous marker was performed, for all models (logistic, ANCOVA and ANOVA).

For continuous outcomes, test for a linear trend was performed using bivariate or multivariate-adjusted linear regression, using dietary scores or patterns and GRS as continuous variables, and results were expressed as standardized beta coefficients. For categorical outcomes, test for a linear trend was performed using logistic regression using dietary scores or patterns and GRS as continuous variables, and results were expressed as OR and (95%) for a one-unit increment of the independent variable.

As sex was a potential confounder of the associations, stratification on sex was also performed. Statistical significance was considered for a two-sided test with $p<0.05$; no adjustment for multiple testing was performed.

Ethical statement

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the baseline CoLaus study (reference 16/03); the approval was renewed for the first (reference 33/09) and the second (reference 26/14) follow-up. The study was performed in agreement with the

Helsinki declaration and its former amendments, and in accordance with the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

RESULTS

Associations between dietary scores, obesity genetic risk scores and obesity markers, cross-sectional analysis

Of the initial 5064 participants, 3033 (59.9%) were retained for the cross-sectional analysis. The reasons for exclusion are summarized in **Supplemental Figure 1.** The most frequent reason for exclusion was a lack of genetic data (n=955). The comparison between included and excluded participants is provided in **Table 1**. Excluded participants were younger, had higher BMI and waist circumference, were more often smokers and of lower education, reported a lower energy intake and a lower alcohol intake.

The correlations between dietary markers, GRS and obesity markers overall and by sex are summarized in **Supplemental Table 3**. The AHEI, the two Mediterranean scores and the "Fruits & vegetables" dietary pattern were negatively associated, while the "Meat & fries" dietary patterns and the obesity GRS were positively associated with obesity markers (**Supplemental Table 3**). The "Fatty & sugary" dietary pattern was negatively associated with BMI and hip, but not with weight and waist circumference (**Supplemental Table 3**).

The univariate and multivariate analyses of obesity markers according to the quartiles of dietary scores, dietary patterns and obesity GRS are summarized in **Table 2**. On both univariate and multivariate analysis, the AHEI, and the two Mediterranean scores were inversely associated, while the obesity GRS were positively associated with obesity markers (**Table 2**). The "Fruits & vegetables" dietary pattern was inversely associated with all obesity markers on univariate analysis, but the association was no longer significant on multivariate analysis for BMI and hip. The "Meat & fries" dietary pattern was positively associated with

all obesity markers on univariate analysis, but the association was no longer significant on multivariate analysis for weight and hip (**Table 2**). The "Fatty and sugary" pattern was positively associated with BMI on univariate analysis, and with all obesity markers on multivariate analysis. Similar findings were obtained when the analysis was split by sex, although some associations were no longer significant due to the reduced sample size (**Supplemental Tables 4 and 5)**.

The p-values for interaction between dietary and obesity GRS on obesity markers overall and by sex are summarized in **Supplemental Table 6** (GRS categorized in quartiles) and **Supplemental Table 7** (GRS used as continuous variables). No significant interactions were found when using the whole sample. Possible interactions between the 31 SNPs obesity GRS and AHEI and between the 68 SNPs obesity GRS and Fatty & sugary pattern were found in males (**Supplemental Tables 6 and 7**). Finally, with the exception of a possible interaction between sex and the Mediterranean diet score 1, no significant sex-diet interactions were found for all anthropometric markers studied (**Supplemental Table 8**).

Associations between dietary scores, obesity genetic risk scores and changes in obesity markers, prospective analysis

Of the initial 5064 participants, 2545 (50.3%) were retained for the prospective analysis. The reasons for exclusion are summarized in **Supplemental Figure 2**. The most frequent reasons for exclusion were a lack of genetic data (n=955) or follow-up (n=491). The comparison between included and excluded participants is provided in **Supplemental Table 9**: excluded participants had higher BMI and waist circumference, were more frequently current smokers, had a lower educational level, reported a lower total energy intake and were less frequently alcohol drinkers. The mean follow-up time was 5.3 years, with a median and interquartile range of 5.3 and [5.1, 5.4] years, respectively.

312 The univariate and multivariate analyses of changes in obesity markers according to
313 quartiles of dietary scores, dietary patterns and obesity GRS are summarized in **Table 3.** On
314 univariate analysis, the AHEI and the "Fruits & vegetables" dietary pattern were negatively
315 associated with increase in waist circumference; the 68 SNP GRS was negatively associated
316 with increases in hip circumference and the "Meat & fries" dietary pattern was positively
317 associated with increases in weight and waist circumference. On multivariate analysis, the
318 negative associations with the AHEI and the "Fruits & vegetables" dietary pattern persisted,
319 while the associations between the 68 SNP GRS and the "Meat & fries" dietary pattern were
320 no longer significant (**Table 3**). Similar trends were found in both sexes, although the
321 associations were no longer significant due to the reduced sample size (**Supplemental Tables**
322 **10 and 11**). Using quartiles of GRS, possible interactions between the 31 SNPs GRS and
323 AHEI for weight (in females) and with the Mediterranean score 1 for hip (in males) were
324 found (**Supplemental Table 12**). Using GRS as continuous variables, possible interactions
325 between the 31 SNPs GRS and Meat & fries pattern for BMI (overall sample) and AHEI (in
326 females) were found; no other significant gene-diet interactions were found regarding changes
327 in obesity markers (**Supplemental Tables 12 and 13**).

328 The associations between dietary and obesity GRS and increases in weight >5 kg or
329 waist >5 cm are summarized in **Table 4**. On univariate analysis, the AHEI, the Mediterranean
330 score 2 and the "Fruits & vegetables" dietary pattern were negatively associated with increase
331 in waist circumference, and those associations persisted in the multivariate analysis. The
332 AHEI (univariate) and the Mediterranean score 2 (multivariate) were negatively associated
333 and the Meat & Fries (univariate) was positively associated with an increase in weight >5 kg,
334 but the results were less consistent than for waist circumference. No association was found
335 between the "Meat & fries", the "Fatty & sugary" and both genetic markers with increases in

weight or waist circumference in the multivariate analysis (**Table 4**). Similar findings were obtained when the analysis was split by sex (**Supplemental Tables 14 and 15**).

DISCUSSION

Our results show that both dietary and obesity GRS are associated with obesity markers on a cross-sectional analysis. Our results also show that only the AHEI and the Mediterranean 1 dietary scores and the Fruits & vegetables dietary pattern are associated with waist circumference gain (and to a lesser degree with weight gain) in a prospective analysis. Importantly, no consistent gene-diet interactions were found, suggesting that diet exerts the same effect irrespective of the genetic background of the participants.

Associations between dietary scores, obesity genetic risk scores and obesity markers, cross-sectional analysis

A negative association was found between the "healthy" dietary scores and patterns and most obesity markers, while a positive association was found with the "unhealthy" dietary scores and patterns. Those findings are in agreement with current literature that emphasizes the beneficial effects of a healthy diet in obesity prevention (4, 34-36).

No consistent gene-diet interaction was found regarding either fat distribution (waist and hip circumferences) or total adiposity (BMI) when analysing the whole sample; the interaction between the 31 SNPs GRS and the "Meat & fries" regarding BMI was only significant when the GRS was used as a continuous variable. Our findings do not replicate those of Qi et al., who used data from three US studies (overall sample size 33,097), and found a gene-diet interaction, participants in the highest quartiles of obesity GRS and sugar-sweetened beverage intake presenting a higher BMI (13). Similarly, the meta-analysis by Nettelton et al. based on 68,317 participants reported gene-diet interactions mostly for waist to hip ratio (WHR) but less for BMI; the interactions were stronger with a healthier diet (37).

Importantly, the effects of the interactions with specific SNPs were small, with maximum values of 0.017 kg/m^2 for BMI and 2.31×10^{-4} for WHR (37), corresponding to an increase in weight of 52 g for a subject 1.75 m tall. The clinical importance of such tiny effects can thus be considered as irrelevant for individual management. Hence, the likely explanation for the discrepancies between our study and the literature is that our sample size is too small to detect the very small effects of gene-diet interactions. In another study conducted among 2075 participants, McCaffery et al. (38) reported interactions between several obesity risk loci and food consumption habits among overweight or obese individuals with type 2 diabetes, but no results regarding weight or waist were provided. Hence, although genetic loci might contribute to differences in food intake and obesity levels, the effect of gene-diet interactions is very small if non-existent.

Associations between dietary scores, obesity genetic risk scores and changes in obesity markers, prospective analysis

On multivariate analysis, the "healthy" dietary scores (AHEI, Mediterranean score) and pattern ("Fruits and vegetables") were negatively associated with increases in waist circumference and, to a lesser degree, weight. Those findings further emphasize the protective effect of a healthy diet against obesity. Conversely, one of the "unhealthy" dietary patterns ("Meat and fries") and the 31 SNPs (but not the 68 SNP) obesity GRS were positively associated with increases in waist and hip circumferences. Those findings are mostly in line with our initial hypotheses, and confirm the importance of a healthy diet in the prevention of obesity (34-36).

Almost no gene-diet interaction was found for changes in obesity markers. Our findings do not replicate the previous results of Wang et al. in a sample of 14,046 participants, where changes in weight per 1 SD increment of AHEI-2010 score were −0.35, −0.36 and

384 −0.50 kg among participants with low, intermediate, and high genetic risk (15). Interestingly,
385 the authors found no such interaction when another healthy dietary score (Alternate
386 Mediterranean Diet) was used.

387 The lack of gene-diet interaction in our study has several explanations: first, our
388 sample size might be too small to detect minute changes in obesity markers. Second, and as
389 indicated by Nettleton et al. (37), gene-diet interactions depend on diet itself, which differs
390 between cohorts (39). Third, differences in genetic background between cohorts cannot be
391 excluded (40). Finally, the effects of genetics tend to attenuate with age (41), being taken over
392 by environmental factors. As almost three quarters (73%) of our participants were older than
393 50, the effects of the genetic scores might have been smaller. Hence, it would be interesting to
394 replicate this study in a younger cohort.

395 Implications for public health and clinical practice

396 Our results have simple and potential implications for public health and clinical
397 practice. First, to manage the current obesity epidemic, dietary and lifestyle interventions
398 should be implemented, rather than relying on GRS. Indeed, the development of an
399 obesogenic environment during the past decades has favoured the rapid rise of obesity
400 pandemic (7). Thus, better prevention policies targeting unhealthy lifestyles such as sedentary
401 status and unhealthy food are fundamental (34).

402 Second, individual responsibility should be emphasized, instead of attributing obesity
403 control failure solely to genetic background (34). Doctors and health professionals should
404 dedicate more time in providing healthy lifestyle recommendations to patients; given the
405 relatively low nutritional knowledge of doctors (42, 43), dietary counselling should be better
406 provided by dieticians or nutritionists (44).

However, better knowledge of the genetic contribution to the obesity pandemic should progress in parallel. Indeed, personalized nutrition based on nutrigenomic data could lead to future treatment and prevention strategies (45). The focus could be obese patients with a high genetic background, as some studies suggest they respond better to dietary factors (7, 13, 46).

Strengths and limitations

This study has several strengths. First, compared to other studies that explored single nutrients (9, 10), we chose dietary patterns and scores that provide a better outlook of an individual's dietary habits (12). Second, we used two different well-described obesity weighted GRS, which are more strongly associated to obesity markers than single locus.

Our study has also several limitations. First, it was conducted in a single city of a wealthy country and included mostly participants of Caucasian descent. Hence, generalizability to other countries and/or ethnicities is not possible. Second, although our sample's size is large compared to similar studies (4, 38), still it is small to detect gene-diet interactions. Hence, future studies should be based either on a larger sample, or be conducted within a consortium (37). Third, dietary intake was self-reported and (un)voluntary reporting biases cannot be excluded (47). Multiple 24-h recalls should be preferred. Fourth, no adjustment for multiple testing was performed. Had such an adjustment be performed, then a more conservative value of 0.0005, corresponding approximately to 0.05 divided by 96 [6 (number of dietary scores or patterns) × 2 (number of GRS) × 4 (number of obesity markers)] should have been used. Using such a conservative value would have made all gene diet interactions and most of the associations nonsignificant. Finally, the follow-up of 5.6 years may be too short to reveal changes in obesity markers.

Conclusion

Dietary intake, not obesity GRS, are associated with weight and waist circumference gain in subjects aged 40 to 80 living in Lausanne, Switzerland. Health professionals might target dietary behaviours rather than rely on genetics to manage obesity.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

AUTHOR'S CONTRIBUTIONS

LB conducted research and wrote paper. PMV designed research, analysed data, wrote paper and had primary responsibility for final content. MM designed research and revised the manuscript for important scientific content. PMV had full access to the data and is the guarantor of the study. All authors read and approved the manuscript.

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TABLES

Table 1: characteristics of included and excluded participants for the cross-sectional analysis, CoLaus study, Lausanne, Switzerland.

	Included	**Excluded**	**P value**
Sample size	3033	2031	
Females (%)	1612 (53.2)	1095 (53.9)	0.592
Age (years)	58.4 ± 10.6	56.8 ± 10.4	<0.001
Body mass index (kg/m^2)	25.7 ± 4.4	26.9 ± 4.8	<0.001
Body mass index categories (%)			<0.001
Normal + underweight	1432 (47.2)	748 (38.1)	
Overweight	1161 (38.3)	799 (40.6)	
Obese	440 (14.5)	419 (21.3)	
Waist circumference (cm)	91.1 ± 12.9	93.3 ± 13.1	<0.001
Smoking categories (%)			0.009
Never	1245 (41.1)	790 (40.0)	
Former	1171 (38.6)	712 (36.1)	
Current	617 (20.3)	472 (23.9)	
Sedentary (%)	1732 (57.1)	673 (58.6)	0.375
Educational level (%)			<0.001
University	639 (21.0)	440 (21.7)	
Secondary	793 (26.2)	513 (25.3)	
Apprenticeship	1151 (38.0)	645 (31.8)	
Primary	450 (14.8)	428 (21.2)	
Total energy intake (kcal)	1764 [1378, 2226]	1657 [1249, 2151]	<0.001 [1]
Alcohol drinker (%)	2394 (78.9)	1389 (68.4)	<0.001

Results are expressed as number of participants (percentage) for categorical variables and as average±standard deviation for continuous variables. Univariate between-group comparisons were performed using chi-square for categorical variables and Student's t-test or nonparametric Kruskal-Wallis test ([1]) for continuous variables.

Table 2: cross-sectional analysis, obesity markers according to quartiles of dietary and genetic risk scores, all participants (N=3033), univariate and multivariate adjusted, CoLaus study, Lausanne, Switzerland.

	Univariate				Multivariate			
	Weight (kg)	**BMI (kg/m²)**	**Waist (cm)**	**Hip (cm)**	**Weight (kg)**	**BMI (kg/m²)**	**Waist (cm)**	**Hip (cm)**
AHEI								
Q1 [3; 25]	76.1 ± 0.5	26.4 ± 0.2	93.3 ± 0.5	100.5 ± 0.3	74.8 ± 0.5	26.1 ± 0.1	92.3 ± 0.4	100.2 ± 0.3
Q2 [25.5; 32]	74.4 ± 0.5	25.8 ± 0.2	91.5 ± 0.4	99.7 ± 0.3	73.9 ± 0.4	25.8 ± 0.1	91.3 ± 0.4	99.6 ± 0.3
Q3 [32.5; 39]	72.1 ± 0.6	25.5 ± 0.2	90.1 ± 0.5	98.9 ± 0.4	72.8 ± 0.5	25.6 ± 0.2	90.5 ± 0.4	99.1 ± 0.4
Q4 [39.5; 69.5]	71.0 ± 0.6	25.2 ± 0.2	89.2 ± 0.5	98.5 ± 0.4	72.4 ± 0.5	25.4 ± 0.2	90.3 ± 0.4	98.9 ± 0.4
Test for trend								
Beta coefficient §	-0.135	-0.107	-0.126	-0.080	-0.065	-0.065	-0.061	-0.050
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.005
Mediterranean 1								
Q1 [0; 3]	74.8 ± 0.4	26.2 ± 0.1	92.5 ± 0.4	100.4 ± 0.3	75.0 ± 0.4	26.2 ± 0.1	92.4 ± 0.3	100.3 ± 0.3
Q2 [4]	73.2 ± 0.5	25.6 ± 0.2	91.0 ± 0.5	99.3 ± 0.4	73.4 ± 0.5	25.6 ± 0.2	91.0 ± 0.4	99.3 ± 0.3
Q3 [5]	72.2 ± 0.6	25.2 ± 0.2	89.7 ± 0.5	98.7 ± 0.4	72.2 ± 0.5	25.3 ± 0.2	90.0 ± 0.5	98.9 ± 0.4
Q4 [6; 8]	72.6 ± 0.7	25.5 ± 0.2	90.1 ± 0.6	98.6 ± 0.4	72.0 ± 0.6	25.5 ± 0.2	89.7 ± 0.5	98.5 ± 0.4
Test for trend								
Beta coefficient §	-0.058	-0.065	-0.072	-0.065	-0.074	-0.062	-0.080	-0.061
P-value	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001

Mediterranean 2								
Q1 [0; 3]	74.8 ± 0.5	26.1 ± 0.1	92.6 ± 0.4	100.3 ± 0.3	74.7 ± 0.4	26.1 ± 0.1	92.4 ± 0.4	100.2 ± 0.3
Q2 [4; 5]	73.6 ± 0.5	25.8 ± 0.1	91.1 ± 0.4	99.7 ± 0.3	73.5 ± 0.4	25.7 ± 0.1	90.9 ± 0.4	99.6 ± 0.3
Q3 [6]	72.6 ± 0.6	25.5 ± 0.2	89.9 ± 0.6	98.8 ± 0.4	72.6 ± 0.6	25.5 ± 0.2	89.9 ± 0.5	98.8 ± 0.4
Q4 [7; 9]	72.4 ± 0.6	25.4 ± 0.2	90.1 ± 0.5	98.4 ± 0.4	72.7 ± 0.5	25.5 ± 0.2	90.6 ± 0.5	98.7 ± 0.4
Test for trend								
Beta coefficient §	-0.070	-0.077	-0.091	-0.085	-0.065	-0.063	-0.074	-0.070
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Meat & fries								
Q1 [-3.06; -0.82]	70.4 ± 0.5	25.2 ± 0.2	88.7 ± 0.5	99.0 ± 0.4	73.4 ± 0.5	25.5 ± 0.2	90.2 ± 0.4	99.2 ± 0.4
Q2 [-0.81; -0.22]	72.4 ± 0.5	25.5 ± 0.2	90.4 ± 0.5	99.3 ± 0.4	73.4 ± 0.5	25.6 ± 0.2	91.0 ± 0.4	99.3 ± 0.4
Q3 [-0.21; 0.53]	74.3 ± 0.5	25.7 ± 0.2	91.2 ± 0.5	99.1 ± 0.4	73.2 ± 0.5	25.7 ± 0.2	90.7 ± 0.4	99.1 ± 0.3
Q4 [0.54; 70.75]	77.1 ± 0.5	26.4 ± 0.2	93.7 ± 0.5	100.3 ± 0.4	74.3 ± 0.5	26.2 ± 0.2	92.3 ± 0.4	100.1 ± 0.4
Test for trend								
Beta coefficient §	0.116	0.089	0.109	0.046	0.020	0.051	0.045	0.030
P-value	<0.001	<0.001	<0.001	0.013	0.205	0.005	0.007	0.098
Fruits & vegetables								
Q1 [-4.05; -1.09]	78.0 ± 0.5	26.6 ± 0.2	94.5 ± 0.5	100.7 ± 0.4	74.7 ± 0.5	26.1 ± 0.2	92.2 ± 0.4	100.1 ± 0.4
Q2 [-1.08; -0.20]	74.2 ± 0.5	25.6 ± 0.2	90.9 ± 0.5	99.1 ± 0.4	73.7 ± 0.5	25.6 ± 0.2	90.7 ± 0.4	99.1 ± 0.3
Q3 [-0.19; 0.87]	71.9 ± 0.5	25.5 ± 0.2	89.9 ± 0.5	99.2 ± 0.4	73.1 ± 0.5	25.6 ± 0.2	90.6 ± 0.4	99.3 ± 0.4
Q4 [0.88; 12.8]	70.1 ± 0.5	25.2 ± 0.2	88.9 ± 0.5	98.7 ± 0.4	72.7 ± 0.5	25.5 ± 0.2	90.6 ± 0.4	99.2 ± 0.4

Test for trend								
Beta coefficient §	-0.177	-0.095	-0.139	-0.060	-0.041	-0.035	-0.032	-0.024
P-value	<0.001	<0.001	<0.001	0.001	0.013	0.061	<0.001	0.193
Fatty & sugary								
Q1 [-3.97; -0.92]	73.9 ± 0.6	26.2 ± 0.2	91.5 ± 0.5	100.1 ± 0.4	74.7 ± 0.5	26.3 ± 0.2	92.2 ± 0.4	100.4 ± 0.3
Q2 [-0.91; -0.05]	73.7 ± 0.6	25.9 ± 0.2	91.2 ± 0.5	99.7 ± 0.4	74.0 ± 0.5	25.9 ± 0.2	91.2 ± 0.4	99.6 ± 0.3
Q3 [-0.04; 0.89]	72.8 ± 0.6	25.3 ± 0.2	90.4 ± 0.5	98.6 ± 0.4	72.6 ± 0.5	25.3 ± 0.2	90.3 ± 0.4	98.6 ± 0.3
Q4 [0.90; 9.67]	73.8 ± 0.6	25.5 ± 0.2	91.1 ± 0.5	99.2 ± 0.4	72.9 ± 0.5	25.4 ± 0.2	90.4 ± 0.4	99.0 ± 0.3
Test for trend								
Beta coefficient §	0.003	-0.051	0.003	-0.026	-0.043	-0.076	-0.039	-0.047
P-value	0.884	0.006	0.866	0.164	0.006	<0.001	0.016	0.008
GRS 31 SNPs								
Q1 [28.1; 50.6]	71.8 ± 0.5	25.1 ± 0.2	89.4 ± 0.5	98.3 ± 0.4	72.2 ± 0.5	25.2 ± 0.2	90.0 ± 0.4	98.6 ± 0.3
Q2 [50.7; 55.5]	72.5 ± 0.5	25.4 ± 0.2	90.3 ± 0.5	98.7 ± 0.4	72.3 ± 0.5	25.4 ± 0.2	90.2 ± 0.4	98.6 ± 0.3
Q3 [55.6; 60.8]	73.6 ± 0.5	25.9 ± 0.2	91.4 ± 0.5	99.6 ± 0.4	73.8 ± 0.5	25.9 ± 0.2	91.4 ± 0.4	99.6 ± 0.3
Q4 [60.9; 82.1]	76.3 ± 0.5	26.6 ± 0.2	93.4 ± 0.5	101.3 ± 0.4	75.9 ± 0.5	26.5 ± 0.2	92.9 ± 0.4	101.0 ± 0.3
Test for trend								
Beta coefficient §	0.097	0.115	0.098	0.103	0.089	0.102	0.078	0.087
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
GRS 68 SNPs								
Q1 [40.6; 57.8]	71.4 ± 0.5	25.0 ± 0.2	89.1 ± 0.5	97.7 ± 0.4	71.5 ± 0.5	25.1 ± 0.2	89.4 ± 0.4	97.9 ± 0.3

Q2 [57.9; 61.2]	73.7 ± 0.5	25.8 ± 0.2	91.4 ± 0.5	99.6 ± 0.4	73.7 ± 0.5	25.8 ± 0.2	91.4 ± 0.4	99.7 ± 0.3
Q3 [61.3; 64.5]	73.1 ± 0.5	25.7 ± 0.2	91.0 ± 0.5	99.3 ± 0.4	73.2 ± 0.5	25.7 ± 0.2	90.9 ± 0.4	99.2 ± 0.3
Q4 [64.6; 78.9]	75.9 ± 0.5	26.5 ± 0.2	93.1 ± 0.5	101.2 ± 0.4	75.7 ± 0.5	26.5 ± 0.2	92.9 ± 0.4	101.1 ± 0.3
Test for trend								
Beta coefficient §	0.099	0.118	0.101	0.114	0.097	0.110	0.089	0.104
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

BMI, body mass index; AHEI, alternative healthy eating index; Q, quartile; GRS, genetic risk score; SNP, single nucleotide polymorphism. Quartile boundaries are indicated in square brackets. Results are expressed as average ± standard error for bivariate analysis and as multivariate adjusted average ± standard error. Univariate statistical analysis performed using analysis of variance. Multivariate statistical analysis performed using analysis of covariance adjusted for sex; age (continuous); educational level (primary, apprenticeship, secondary and university); smoking status (never, former, current) and sedentary status (yes/no). §, standardized beta coefficient as obtained by linear regression, using dietary scores or patterns and GRS as continuous variables.

Table 3: prospective analysis, changes in obesity markers according to quartiles of dietary and genetic risk scores, all participants (N=2542), univariate and multivariate adjusted, CoLaus study, Lausanne, Switzerland.

	Univariate				Multivariate			
	Weight (kg)	**BMI (kg/m^2)**	**Waist (cm)**	**Hip (cm)**	**Weight (kg)**	**BMI (kg/m^2)**	**Waist (cm)**	**Hip (cm)**
AHEI								
Q1 [3; 25]	0.57 ± 0.18	0.40 ± 0.06	0.97 ± 0.25	3.15 ± 0.24	0.57 ± 0.18	0.41 ± 0.06	0.96 ± 0.25	3.45 ± 0.20
Q2 [25.5; 32]	0.32 ± 0.18	0.31 ± 0.06	0.34 ± 0.25	2.65 ± 0.23	0.31 ± 0.17	0.31 ± 0.06	0.32 ± 0.24	2.78 ± 0.20
Q3 [32.5; 39]	0.33 ± 0.19	0.31 ± 0.07	-0.13 ± 0.26	2.86 ± 0.24	0.32 ± 0.18	0.31 ± 0.07	-0.15 ± 0.25	2.67 ± 0.21
Q4 [39.5; 67.5]	0.55 ± 0.19	0.37 ± 0.07	0.05 ± 0.26	3.25 ± 0.25	0.57 ± 0.19	0.37 ± 0.07	0.11 ± 0.26	2.96 ± 0.21
Test for trend								
Beta coefficient §	0.011	0.008	-0.059	0.017	0.017	0.010	-0.041	-0.005
P-value	0.575	0.673	0.003	0.394	0.393	0.626	0.044	0.803
Mediterranean 1								
Q1 [0; 3]	0.41 ± 0.15	0.35 ± 0.05	0.48 ± 0.21	2.88 ± 0.20	0.42 ± 0.15	0.35 ± 0.05	0.69 ± 0.20	3.09 ± 0.17
Q2 [4; 4]	0.55 ± 0.18	0.39 ± 0.06	0.14 ± 0.26	3.00 ± 0.24	0.59 ± 0.18	0.40 ± 0.06	0.13 ± 0.25	2.99 ± 0.21
Q3 [5; 5]	0.38 ± 0.20	0.31 ± 0.07	0.10 ± 0.28	2.74 ± 0.26	0.30 ± 0.20	0.29 ± 0.07	-0.03 ± 0.27	2.49 ± 0.22
Q4 [6; 8]	0.45 ± 0.23	0.33 ± 0.08	0.50 ± 0.32	3.45 ± 0.29	0.46 ± 0.22	0.34 ± 0.08	0.21 ± 0.31	3.27 ± 0.25
Test for trend								
Beta coefficient §	-0.001	-0.006	-0.012	0.021	0.005	-0.001	-0.015	0.028
P-value	0.956	0.744	0.539	0.296	0.799	0.942	0.438	0.137

Mediterranean 2								
Q1 [0; 3]	0.58 ± 0.17	0.40 ± 0.06	0.60 ± 0.24	2.83 ± 0.22	0.61 ± 0.17	0.40 ± 0.06	0.82 ± 0.23	3.06 ± 0.19
Q2 [4; 5]	0.17 ± 0.16	0.26 ± 0.05	0.28 ± 0.22	2.70 ± 0.20	0.20 ± 0.15	0.27 ± 0.05	0.28 ± 0.21	2.83 ± 0.17
Q3 [6; 6]	0.64 ± 0.22	0.41 ± 0.08	0.31 ± 0.30	3.39 ± 0.28	0.61 ± 0.21	0.40 ± 0.08	0.06 ± 0.29	3.16 ± 0.24
Q4 [7; 9]	0.54 ± 0.21	0.37 ± 0.07	-0.02 ± 0.29	3.28 ± 0.27	0.47 ± 0.21	0.35 ± 0.07	-0.09 ± 0.28	2.9 ± 0.24
Test for trend								
Beta coefficient §	0.010	0.003	-0.023	0.044	0.008	0.003	-0.025	0.038
P-value	0.625	0.867	0.240	0.027	0.673	0.899	0.214	0.049
Meat & fries								
Q1 [-3.06; -0.83]	0.13 ± 0.19	0.27 ± 0.07	-0.37 ± 0.26	2.95 ± 0.24	0.26 ± 0.19	0.28 ± 0.07	-0.09 ± 0.26	2.76 ± 0.21
Q2 [-0.83; -0.24]	0.67 ± 0.19	0.43 ± 0.07	0.65 ± 0.26	3.17 ± 0.24	0.69 ± 0.18	0.43 ± 0.07	0.74 ± 0.25	3.08 ± 0.21
Q3 [-0.24; 0.48]	0.46 ± 0.19	0.36 ± 0.07	0.43 ± 0.26	3.21 ± 0.24	0.45 ± 0.18	0.36 ± 0.07	0.30 ± 0.25	3.27 ± 0.21
Q4 [0.48; 70.75]	0.71 ± 0.19	0.39 ± 0.07	0.69 ± 0.26	2.79 ± 0.24	0.57 ± 0.19	0.38 ± 0.07	0.45 ± 0.26	3.02 ± 0.22
Test for trend								
Beta coefficient §	0.051	0.038	0.048	0.007	0.037	0.034	0.019	0.016
P-value	0.012	0.057	0.018	0.712	0.066	0.096	0.342	0.406
Fruits & vegetables								
Q1 [-4.05; -1.04]	0.55 ± 0.19	0.36 ± 0.07	1.31 ± 0.26	2.50 ± 0.24	0.50 ± 0.19	0.37 ± 0.07	1.14 ± 0.26	3.08 ± 0.22
Q2 [-1.04; -0.17]	0.57 ± 0.19	0.39 ± 0.07	0.55 ± 0.26	3.46 ± 0.24	0.53 ± 0.18	0.38 ± 0.06	0.43 ± 0.25	3.32 ± 0.21
Q3 [-0.17; 0.88]	0.17 ± 0.19	0.26 ± 0.07	-0.19 ± 0.26	2.87 ± 0.24	0.20 ± 0.18	0.26 ± 0.07	-0.13 ± 0.25	2.74 ± 0.21
Q4 [0.88; 12.79]	0.68 ± 0.19	0.44 ± 0.07	-0.27 ± 0.26	3.30 ± 0.24	0.74 ± 0.19	0.44 ± 0.07	-0.05 ± 0.26	2.99 ± 0.21

Test for trend								
Beta coefficient §	0.017	0.025	-0.081	0.044	0.034	0.031	-0.043	0.020
P-value	0.393	0.222	<0.001	0.030	0.157	0.147	0.042	0.332
Fatty & sugary								
Q1 [-3.97; -0.9]	0.82 ± 0.19	0.48 ± 0.07	0.42 ± 0.26	3.10 ± 0.24	0.81 ± 0.18	0.47 ± 0.07	0.68 ± 0.25	3.16 ± 0.21
Q2 [-0.89; -0.04]	0.46 ± 0.19	0.36 ± 0.07	0.48 ± 0.26	3.12 ± 0.24	0.50 ± 0.18	0.36 ± 0.06	0.55 ± 0.25	3.17 ± 0.21
Q3 [-0.04; 0.87]	0.17 ± 0.19	0.25 ± 0.07	0.13 ± 0.26	2.89 ± 0.24	0.17 ± 0.18	0.25 ± 0.07	-0.01 ± 0.25	2.74 ± 0.21
Q4 [0.87; 9.67]	0.51 ± 0.19	0.36 ± 0.07	0.37 ± 0.26	3.02 ± 0.24	0.49 ± 0.18	0.36 ± 0.07	0.16 ± 0.25	3.05 ± 0.21
Test for trend								
Beta coefficient §	-0.029	-0.033	-0.012	-0.021	-0.026	-0.028	-0.026	0.001
P-value	0.153	0.107	0.539	0.307	0.198	0.163	0.202	0.972
GRS 31 SNPs								
Q1 [28.3; 50.7]	0.45 ± 0.18	0.35 ± 0.06	0.33 ± 0.26	3.12 ± 0.24	0.32 ± 0.18	0.31 ± 0.06	0.18 ± 0.25	2.62 ± 0.21
Q2 [50.7; 55.5]	0.75 ± 0.18	0.44 ± 0.06	0.70 ± 0.26	3.00 ± 0.24	0.74 ± 0.18	0.43 ± 0.06	0.58 ± 0.25	2.83 ± 0.20
Q3 [55.5; 60.7]	0.32 ± 0.18	0.31 ± 0.06	-0.03 ± 0.26	2.97 ± 0.24	0.35 ± 0.18	0.32 ± 0.06	0.00 ± 0.25	3.05 ± 0.20
Q4 [60.7; 79.9]	0.25 ± 0.18	0.29 ± 0.06	0.29 ± 0.26	2.8 ± 0.24	0.36 ± 0.18	0.32 ± 0.06	0.53 ± 0.25	3.38 ± 0.21
Test for trend								
Beta coefficient §	-0.026	-0.019	-0.005	-0.021	-0.013	-0.009	-0.005	0.000
P-value	0.192	0.349	0.796	0.297	0.499	0.653	0.815	0.990
GRS 68 SNPs								
Q1 [40.6; 57.7]	0.57 ± 0.18	0.38 ± 0.06	0.44 ± 0.26	3.36 ± 0.24	0.45 ± 0.18	0.35 ± 0.06	0.23 ± 0.25	2.86 ± 0.21

Q2 [57.7; 61.2]	0.51 ± 0.18	0.36 ± 0.06	0.26 ± 0.26	3.04 ± 0.24	0.47 ± 0.18	0.35 ± 0.06	0.21 ± 0.25	2.93 ± 0.21
Q3 [61.2; 64.5]	0.53 ± 0.18	0.36 ± 0.06	0.22 ± 0.26	2.89 ± 0.24	0.60 ± 0.18	0.38 ± 0.06	0.29 ± 0.25	3.00 ± 0.20
Q4 [64.5; 78.9]	0.15 ± 0.18	0.28 ± 0.06	0.36 ± 0.26	2.59 ± 0.24	0.24 ± 0.18	0.30 ± 0.06	0.55 ± 0.25	3.08 ± 0.21
Test for trend								
Beta coefficient §	-0.031	-0.026	-0.010	-0.043	-0.022	-0.019	-0.009	-0.030
P-value	0.117	0.193	0.598	0.029	0.262	0.330	0.660	0.113

BMI, body mass index; AHEI, alternative healthy eating index; Q, quartile; GRS, genetic risk score, SNP, single nucleotide polymorphism. Quartile boundaries are indicated in square brackets. Results are expressed as average ± standard error for bivariate analysis and as multivariate adjusted average ± standard error. Univariate statistical analysis performed using analysis of variance separately for each score. Multivariate statistical analysis performed using analysis of covariance adjusted for sex; age (continuous); educational level (primary, apprenticeship, secondary and university); smoking status (never, former, current), sedentary status (yes/no) and baseline anthropometric value (continuous). §, standardized beta coefficient as obtained by linear regression, using dietary scores or patterns and GRS as continuous variables.

Table 4: prospective analysis, association between quartiles of dietary and genetic scores and increases in weight>5 kg and waist >5 cm, all participants (N=2542), univariate and multivariate adjusted, CoLaus study, Lausanne, Switzerland.

	Univariate		**Multivariate**	
	Weight	**Waist**	**Weight**	**Waist**
AHEI				
Q1 [3; 25]	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2 [25.5; 32]	0.77 (0.56, 1.05)	0.63 (0.49, 0.81)	0.78 (0.57, 1.08)	0.64 (0.50, 0.82)
Q3 [32.5; 39]	0.68 (0.49, 0.95)	0.60 (0.46, 0.78)	0.71 (0.50, 0.99)	0.60 (0.46, 0.79)
Q4 [39.5; 67.5]	0.68 (0.49, 0.95)	0.63 (0.49, 0.82)	0.72 (0.51, 1.02)	0.65 (0.50, 0.85)
Test for trend				
OR (95%) §	0.99 (0.97 - 0.99)	0.98 (0.97 - 0.99)	0.99 (0.98 - 1.00)	0.98 (0.97 - 0.99)
P-value	0.026	<0.001	0.075	<0.001
Mediterranean 1				
Q1 [0; 3]	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2 [4; 4]	0.85 (0.63, 1.15)	0.75 (0.59, 0.96)	0.86 (0.64, 1.16)	0.75 (0.59, 0.95)
Q3 [5; 5]	0.81 (0.59, 1.11)	0.79 (0.62, 1.02)	0.81 (0.58, 1.12)	0.79 (0.61, 1.01)
Q4 [6; 8]	0.54 (0.37, 0.80)	0.74 (0.56, 0.98)	0.55 (0.37, 0.82)	0.73 (0.55, 0.97)
Test for trend				
OR (95%) §	0.88 (0.82 - 0.96)	0.92 (0.86 - 0.98)	0.89 (0.82 - 0.96)	0.91 (0.86 - 0.97)
P-value	0.002	0.007	0.005	0.005
Mediterranean 2				

Q1 [0; 3]	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2 [4; 5]	0.75 (0.56, 1.01)	0.88 (0.70, 1.10)	0.77 (0.57, 1.03)	0.87 (0.69, 1.10)
Q3 [6; 6]	0.93 (0.67, 1.31)	0.83 (0.63, 1.09)	0.94 (0.67, 1.33)	0.81 (0.61, 1.07)
Q4 [7; 9]	0.64 (0.44, 0.92)	0.58 (0.43, 0.78)	0.63 (0.43, 0.91)	0.57 (0.43, 0.77)
Test for trend				
OR (95%) §	0.94 (0.88 - 0.99)	0.92 (0.88 - 0.97)	0.94 (0.88 - 0.99)	0.92 (0.88 - 0.97)
P-value	0.032	0.001	0.038	0.001
Meat & fries				
Q1 [-3.06;-0.83]	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2 [-0.83;-0.24]	1.46 (1.03, 2.08)	1.28 (0.98, 1.67)	1.38 (0.96, 1.98)	1.23 (0.94, 1.62)
Q3 [-0.24; 0.48]	1.21 (0.84, 1.74)	1.13 (0.86, 1.48)	1.09 (0.75, 1.59)	1.06 (0.80, 1.39)
Q4 [0.48; 70.75]	1.61 (1.14, 2.27)	1.11 (0.85, 1.45)	1.33 (0.91, 1.92)	0.98 (0.73, 1.30)
Test for trend				
OR (95%) §	1.19 (1.07 - 1.31)	1.05 (0.99 - 1.12)	1.12 (1.01 - 1.24)	1.04 (0.98 - 1.09)
P-value	0.001	0.113	0.032	0.201
Fruits & vegetables				
Q1 [-4.05;-1.04]	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2 [-1.04;-0.17]	0.81 (0.59, 1.13)	0.81 (0.63, 1.05)	0.87 (0.62, 1.22)	0.83 (0.64, 1.08)
Q3 [-0.17; 0.88]	0.57 (0.40, 0.81)	0.60 (0.46, 0.78)	0.63 (0.44, 0.91)	0.62 (0.47, 0.82)
Q4 [0.88; 12.79]	0.86 (0.62, 1.19)	0.64 (0.49, 0.83)	1.00 (0.71, 1.41)	0.67 (0.51, 0.89)
Test for trend				

OR (95%) §	1.01 (0.93 - 1.09)	0.91 (0.85 - 0.97)	1.06 (0.97 - 1.15)	0.92 (0.86 - 0.99)
P-value	0.818	0.003	0.189	0.019
Fatty & sugary				
Q1 [-3.97; -0.9]	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2 [-0.89;-0.04]	0.72 (0.51, 1.00)	0.89 (0.69, 1.15)	0.73 (0.52, 1.03)	0.89 (0.68, 1.15)
Q3 [-0.04; 0.87]	0.59 (0.42, 0.84)	0.75 (0.57, 0.98)	0.61 (0.43, 0.87)	0.75 (0.57, 0.98)
Q4 [0.87; 9.67]	0.94 (0.68, 1.29)	0.86 (0.66, 1.11)	0.94 (0.68, 1.29)	0.84 (0.64, 1.09)
Test for trend				
OR (95%) §	0.99 (0.91 - 1.08)	0.96 (0.90 - 1.03)	0.99 (0.91 - 1.08)	0.95 (0.89 - 1.02)
P-value	0.876	0.232	0.851	0.180
GRS 31 SNPs				
Q1 [28.3; 50.7]	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2 [50.7; 55.5]	0.94 (0.67, 1.32)	1.10 (0.85, 1.42)	1.00 (0.71, 1.41)	1.11 (0.85, 1.43)
Q3 [55.5; 60.7]	0.93 (0.66, 1.30)	0.86 (0.66, 1.12)	0.99 (0.71, 1.40)	0.86 (0.66, 1.12)
Q4 [60.7; 79.9]	1.12 (0.81, 1.55)	0.97 (0.74, 1.25)	1.22 (0.88, 1.71)	0.97 (0.75, 1.26)
Test for trend				
OR (95%) §	1.00 (0.99 - 1.02)	1.00 (0.99 - 1.01)	1.01 (0.99 - 1.02)	1.00 (0.99 - 1.01)
P-value	0.760	0.863	0.405	0.928
GRS 68 SNPs				
Q1 [40.6; 57.7]	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2 [57.7; 61.2]	1.33 (0.95, 1.88)	1.15 (0.88, 1.50)	1.36 (0.96, 1.93)	1.15 (0.88, 1.49)

Q3 [61.2; 64.5]	1.33 (0.95, 1.88)	1.13 (0.87, 1.47)	1.46 (1.03, 2.07)	1.15 (0.88, 1.50)
Q4 [64.5; 78.9]	1.23 (0.87, 1.74)	1.08 (0.83, 1.41)	1.31 (0.92, 1.86)	1.08 (0.83, 1.41)
Test for trend				
OR (95%) §	1.01 (0.99 - 1.04)	1.00 (0.99 - 1.02)	1.02 (0.99 - 1.04)	1.01 (0.99 - 1.02)
P-value	0.298	0.639	0.158	0.589

AHEI, alternative healthy eating index; Q, quartile; GRS, genetic risk score; ref, reference; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval. Quartile boundaries are indicated in square brackets. Results are expressed as univariate or multivariate-adjusted odds ratio and (95% confidence interval). Statistical analysis performed separately for each score using logistic regression, simple or adjusted for sex, age (continuous), educational level (primary, apprenticeship, secondary and university); smoking status (never, former, current) and sedentary status (yes/no). §, OR and 95% CI for one unit increase, using dietary scores or patterns and GRS as continuous variables.