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Randomized Control Trials

A weight-loss model based on baseline microbiota and genetic scores for selection of dietary treatments in overweight and obese population

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SUMMARY

Background & aims: The response to weight loss depends on the interindividual variability of determinants such as gut microbiota and genetics. The aim of this investigation was to develop an integrative model using microbiota and genetic information to prescribe the most suitable diet for a successful weight loss in individuals with excess of body weight.

Methods: A total of 190 Spanish overweight and obese participants were randomly assigned to two hypocaloric diets for 4 months: 61 women and 29 men followed a moderately high protein (MHP) diet, and 72 women and 28 men followed a low fat (LF) diet. Baseline fecal DNA was sequenced and used for the construction of four microbiota subscores associated with the percentage of BMI loss for each diet (MHP and LF) and for each sex. Bootstrapping techniques and multiple linear regression models were used for the selection of families, genera and species included in the subscores. Finally, two total microbiota scores were generated for each sex. Two genetic subscores previously reported to weight loss were used to generate a total genetic score. In an attempt to personalize the weight loss prescription, several linear mixed models that included interaction with diet between microbiota scores and genetic scores for both, men and women, were studied.

Results: The microbiota subscore for the women who followed the MHP-diet included *Coprococcus, Dorea, Flavonifractor, Ruminococcus albus* and *Clostridium bolteaea*. For LF-diet women, Cytophagaceae, Catabacteriaceae, Flammeovirgaceae, Rhodobacteriaceae, *Clostridium-x1vb, Bacteriodes nordiiay, Alistipes senegalensis, Blautia wexlerae* and *Psedoflavonifractor phocaeensis*. For MHP-diet men, Cytophagaceae, Acidaminococcaceae, Marinilabiliaceae, Bacteroidaceae, *Fusicatenibacter, Odoribacter* and *Ruminococcus faecis;* and for LF-men, Porphyromanadaceae, *Intestinimonas, Bacteroides finegoldii* and *Clostridium bartlettii.* The mixed models with microbiota scores facilitated the selection of diet in 72% of women and in 84% of men. The model including genetic information allows to select the type of diet in 84% and 73%, respectively.

Abbreviations: MHP, Moderately high protein diet; LF, Low fat diet; SNP, Single nucleotide polymorphism; BMI, Body mass index; HDL-c, High-density lipoprotein cholesterol; LDL-c, Low-density lipoprotein cholesterol; HOMA-IR, Homeostatic model assessment insulin resistance; SEM, Standard error of the mean; TC, Total Cholesterol; CLR, Centered log ratio; DEXA, Dual Energy X ray Absorptiometry.

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Conclusions: Decision algorithm models can help to select the most adequate type of weight loss diet according to microbiota and genetic information.
Clinical trial registry number: This trial was registered at www.clinicaltrials.gov as NCT02737267 (https://clinicaltrials.gov/ct2/show/NCT02737267?term=NCT02737267&cond=obekit&draw=2&rank=1).

1. Introduction

Overweight and obesity are recognized as an emerging health problem [1]. The administration of an energy restriction program is the most common approach for obesity treatment [2]. However, the big number of elements involved in body weight regulation trigger that subjects do not respond equally to hypocaloric diets [3]. The recent advances in precision medicine, and specifically in personalized nutrition, have changed and updated the way obesity is being tackled [4]. In this context, personalized nutrition tries to establish decision rules using patients' baseline information for choosing one anti-obesity treatment over another in order to improve the success and reduce the chance of failure [5]. In this context, nutrigenetic studies have identified a large number of single nucleotide polymorphisms (SNPs) and other generic variants associated with body weight regulation and fuel homeostasis, energy expenditure, appetite, adipogenesis, insulin resistance and lipid metabolism [3]. Similarly, in the last years the development of metagenomics has evidenced the connection between gut microbiota and human obesity [6]. A big number of publications have investigated about the role of microbiota in nutrient absorption and the regulation of nutrient harvest and its influence and participation in metabolic outcomes [7,8]. Moreover, some investigations have shown that weight loss is able to modify the composition of the gut microbiome, showing the relationship between microbiota and weight loss process [9–14]. In addition, sex should be also taken into account in personalized medicine. For example, several studies have already elucidate that the gut microbiota composition differ between men and women, which could be attributed to differences in hormone concentration, adiposity, fat distribution [15–19] or even different eating behavior and dietary habits [20]. However, many times this factor had been ignored by researchers in spite of its importance and very few studies have addressed the effects of sex on the gut microbiota in the human intestine.

In this context, the use of prototypes that incorporate diverse precision factors could be a tool for increasing the chance of successful response to dietary treatments for programmed weight loss, as well as for providing clues to understanding the metabolic factors involved in this process [21,22]. The use of these prototypes should be complemented with the differentiation between sexes.

Under this perspective, the aim of this research was to implement an integrative model for selecting a weight loss diet based on microbiota composition and genetic information for the prescription of energy-restricted diets with different macronutrient content in women and men with overweight or obesity.

2. Methods

2.1. Study participants

This study included 190 non-consanguineous Caucasian adults from the Obekit trial with an age range of 18–67 years old. A total of 66 participants presented overweight (BMI: 25–29.9 kg/m^2) and 124 were obese (BMI: 30–40 kg/m^2). Major exclusion criteria were a clinical history of cardiovascular disease; type 1 or type 2 diabetes treated with insulin; pregnant or lactating women; individuals who reported weight change (>3 kg) within the 3 months before the study; and initial or unstable medication doses for hyperlipidemia and/or hypertension. Participants consuming weight-loss medications or other drugs that affect body weight (corticosteroids, antipsychotic or antidepressant drugs) were also excluded. The characteristics of this research project, including study design and registration, have been previously reported [23]. It is registered at clinicaltrials.gov (identifier NCT02737267). All research procedures were performed following the ethical principles of the 2013 Helsinki Declaration [24]. The study protocol was approved by the Research Ethics Committee of the University of Navarra (ref.132/2015). All participants provided a written informed consent before inclusion in the study.

2.2. Nutritional intervention

The volunteers were recruited at the Center for Nutrition Research of the University of Navarra in the city of Pamplona (Spain) between March 2016 and March 2017 and enrolled in the Obekit nutritional intervention during 4 months. Volunteers were randomly assigned to two hypocaloric diets (with 30% energy restriction) with different macronutrient distribution: a moderately high protein (MHP) diet (40% carbohydrates, 30% proteins, 30% lipids) and a low fat (LF) diet (60% carbohydrates, 18% proteins, 22% lipids) [25–27]. Individual energy requirements of each participant were estimated at baseline by calculating their energy expenditure at rest and during physical activity, as previously reported, in order to prescribe hypocaloric diets [28]. Participants were randomly assigned to these diets with a specific algorithm designed in the online MATLAB software (Mathworks; http://www.mathworks.com) by central allocation using stratified block randomization according to sex, age groups (<45 y and ≥45 y), and BMI (25–29.9 and 30–40) following the Cochrane Risk of Bias Tool. Both the LF and MHP diets were designed on the basis of a published food exchange system [29]. In this regard, participants received detailed information from trained dietitians concerning portion size, dietary patterns/eating schedules, and food preparation techniques. Adherence to the diet was subjectively evaluated based on the dietitian's criteria using the following scale: 3 = very good adherence (continuous follow-up); 2 = good adherence (occasionally exceeded recommendations); 1 = regular adherence (follow-up during weekdays but not at the weekend); and 0 = poor adherence (failure to follow the diet at any time). This test was applied twice, in the middle (8th week) and at the end (16th week) of the intervention. Also, dietitians conducted motivational telephone calls during the intervention period for promoting the adherence to the diet. In addition, the real macronutrient distributions of both the MHP and LF diets were monitored using 3-day weighed food records (including 2 weekdays and 1 weekend day), which were applied twice, in the middle (8th week) and at the end (16th week) of the intervention and evaluated by dietitians. Total energy intake and

macronutrient content were obtained following validated Spanish food composition tables and an appropriate software [30].

Participants who dropped out of the study before finishing the intervention period and participants who followed the diet with low adherence (<0.5) were not included in the present investigation. Also, volunteers who did not provide the fecal sample in a correct way and volunteers who used antibiotics before or during the intervention were excluded (supplementary Fig. 1).

2.3. Biochemical and anthropometric determinations

At the beginning and at the end of the nutritional intervention, blood samples were drawn by venipuncture after a 12-h overnight fast. From each volunteer, two tubes with anticoagulant (EDTA) for plasma extraction and two tubes without anticoagulant for serum were collected. Tubes were centrifuged during 15 min at 4500 rpm, aliquoted and stored at − 80 °C. Serum glucose, cholesterol, HDL-c, and triglycerides were quantified using commercial kits (Horiba, Kyoto, Japan) in an automatic analyzer (Pentra C200, HORIBA Medical, Kyoto, Japan) following the instructions provided by the manufacturer. Low-density lipoprotein cholesterol (LDL-c) was estimated using the Friedewald equation (LDL-c = TC−HDL-c−triglycerides/5) [31]. Plasma samples were used for hormonal assays. Adiponectin (BioVendor, Brno, Czech Republic), insulin (Mercodia, Uppsala, Sweden) and leptin (Mercodia, Uppsala, Sweden) were measured using specific enzyme-linked immunosorbent assays and read with an automated analyzer system (Triturus, Grifols, Barcelona, Spain) following the instructions provided by the manufacturers. HOMA-IR was calculated following the formula: fasting insulin (mU/mL) × fasting glucose (mg/dL))/405.

Anthropometric and body composition measurements (body weight, height, waist and hip circumferences) were collected at the beginning and at the end of the intervention (4 months later) by trained nutritionists using conventional validated procedures [32]. BMI was calculated as the ratio between body weight and squared height (kg/m^2) and the BMI classification criteria was following according to the World Health Organization (normalweight BMI <24.9 kg/m^2; overweight BMI <29.9 kg/m^2; obese BMI >30 kg/m^2) [33]. Dual-energy X-ray absorptiometry was applied to estimate fat distribution following the company instructions (DEXA, Lunar Prodigy, software version 6.0, Madison, WI, USA).

2.4. DNA isolation from fecal samples and metagenomic analysis

OMNIgene.GUT kits from DNA Genotek Inc. (Ottawa, ON, Canada) were given to the volunteers to self-collect fecal samples at baseline and at the end of the dietary intervention period, according to the standard guidelines provided by the supplier. In the next hours, samples were aliquoted and stored at − 80 °C. QIAamp ® DNA kit (Qiagen. Hilden, Germany) was used to isolate DNA from the fecal samples following the manufacturer's protocol. Bacterial DNA sequencing was performed by the Servei de Genòmica i Bioinformàtica (Autonomous University of Barcelona, Barcelona, Spain). The Illumina 16S protocol based on the amplification of the V3−V4 variable regions of the 16S rRNA gene was followed. A MiSeq System (Illumina, San Diego, CA, USA) was used for paired-end sequencing. In the process, two PCR reactions were carried out. In the first one, 12.5 ng of genomic DNA and the 16S−F and 16S-R primers were used (16S Amplicon PCR Forward Primer = 50 TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCCTACGGGNGGCWG CAG; 16S Amplicon PCR Reverse Primer = 50 GTCTCGTGGGC TCGGAGATGTGTATAAGAGACAGGACTACHVGGGTATCTAATCC). The protocol in this first PCR was 95 °C for 3 min and 25 cycles of: 95 °C for 30 s, 55 °C for 30 s, 72 °C for 30 s. Finally, 72 °C for 5 min and hold at 4 °C. Five μl of the first PCR was used in the second PCR, after the cleaning process. The primers used in this PCR were part of the Nextera® XT DNA Index Kit (96 indexes, 384 samples) FC-131-1002 (Illumina). The protocol for the second PCR was 95 °C for 3 min, 8 cycles of: 95 °C for 30 s, 55 °C for 30 s, 72 °C for 30 s. Finally, 72 °C for 5 min and hold at 4 °C. After each PCR, the quality of the process was checked in a Labchip Bioanalyzer (Agilent Technologies Inc, Santa Clara, CA, USA). Once all the samples were obtained, up to 40 samples were multiplexed in each run of 2 x 300 cycles. For this purpose, equimolar concentrations of each of the samples were mixed and the pool diluted up to 20 pM. A total of 3 runs were performed on the MiSeq sequencer with the MiSeq® Reagent Kit v3 (600 cycle) MS-102-3003. Negative controls were included in each run. All the samples were processed and sequenced by the same person and with the same kits and technologies. Moreover, the samples were randomized by sex, age, and, category of obesity and type of diet to avoid the batch effect. Adapters and barcodes were removed following the standard Illumina methods. The Basespace Sequence Hub from Illumina and DADA2 pipeline was used for the identification of Amplicon Sequence Variants (ASV) and their abundance matrix generation [34]. Finally, taxonomy was assigned using Ribosomal Data Project (RDP) 11 [35]. In order to apply the statistical analysis adequately, the bacterial abundances compositional were transformed using R packages 'zComposition' [36] for zero replacement using count zero multiplicative method and 'compositions' [37] for performing centered log ratio (CLR) transformation [38]. All sequencing data have been submitted to the NCBI (SRA repository under the accession number PRJNA623853).

2.5. Microbiota subscores and total microbiota score

The construction of the different subscores was performed from baseline microbiota data CLR tranformed and considering families, genera and species. Low abundant bacterial taxa were eliminated, removing those that had less than 4 counts in 80% of the participants. Having into account the role of sex, four microbiota subscores, one for each combination of sex and type of diet (MHP-women, LF-women, MHP-men, and LF-men), were generated following four steps:

The first step was to perform a variable selection procedure for obtaining the best families, genera and species related to BMI loss percentage. Variable selection was made through multiple linear regression using the Furnival-Wilson leaps-and-bounds algorithm, specifying the best option (Stata module "vselect") [39]. All-subsets variable selection provides a R^2 adjusted, Mallows's Cp, Akaike's information criterion, Akaike's corrected information criterion, and Bayesian information criterion for the best regression at each quantity of predictors. The variable combination with the best R^2 adjusted was selected.

In the second step, a bootstrap stepwise multiple linear regression model (Stata module "swboot") was performed using the best combination of microbiota variables provided in the previous step [40]. This method performed a bootstrap to validate the choice of variables in stepwise procedures for linear regression, providing summary counts of the total number of times each variable is selected. We used 1000 repeated models, 0.1 significance level for a variable to enter the model, and 0.11 significance level for a variable to remain in the model. Families, genera and species taxa were selected for further steps when repeated more than 500 times.

In the third step, the relationship of the baseline percentage abundance of these pre-selected taxa with BMI loss percentage in each type of diet was evaluated using fit plot graphs. Those taxa which presented a similar relation with the two types of diets (or no relation with any) were discarded. Bacterial taxa that presented a positive or negative association with only one of the diets but an

inverse relation (or no relation) with the other type of diet were selected for the next step. This procedure was essential to achieve an interaction term between microbiota and diet, necessary for derivation of the individualized treatment effects. In every step, the variance inflation factor was used to check and discard collinearity between bacterial taxa.

In the fourth step, four subscores (one for each combination of sex and type of diet) were finally calculated. For that, a multiple linear regression model was built using BMI loss percentage after treatment as dependent variable and the taxa selected in the third step for each combination of sex and type of diet as independent variables. The subscores were calculated by adding the CLR transformed values of each taxa multiplied by its corresponding beta value from the previous regression models.

Finally, two different total microbiota scores for women and men were obtained doing a subtraction of the score for each type of diet.

2.6. Genotyping, SNP selection and genetic subscores

For the DNA genotyping assay, oral epithelium samples were collected with a liquid-based kit (ORAcollect-DNA, OCR-100, DNA Genotek Inc). Genomic DNA was isolated with the Maxwell® 16 Buccal Swab LEV DNA Purification Kit (Promega Corp, Madison,WI, USA). Genotyping of 95 genetic variants related to obesity and weight loss, which were selected after an exhaustive bibliographic review [3,41,42], was performed by targeted next-generation sequencing in an Ion Torrent PGM™ equipment (Thermo Fisher Scientific Inc, Waltham, MA, USA) using a pre-designed panel (Ion AmpliSeq Custom NGS DNA Panels, Thermo Fisher Scientific Inc), as previously described [43]. The construction of two genetic risk subscores (one for each diet MHP y LF) based on these 95 single nucleotide polymorphisms (SNPs) has been carefully detailed in a previous paper [21]; briefly, the two subscores were calculated by adding the number of risk genotypes at each locus. The list of the selected SNPs statistically or marginally associated with percentage BMI decrease, all of which were different between the MHP and LF diets, is shown as supplementary material (supplementary table 1). The genetic subscore for the MHP diet included 6 SNPs (rs1801133, *MTHFR*; rs2605100, *LYPLAL1*; rs3123554, *CNR2*; rs10767664, *BDNF*; rs659366, *UCP2*; rs1052700, *PLIN1*) whereas the genetic subscore for the LF diet was composed by 7 SNPs (rs2943641, *IRS1*; rs1018218, *ADCY3*; rs1042713, *ADRB2*; rs1800544, *ADRA2A*; rs662799, *APOA5*; rs6123837, *GNAS*; rs3813929, *HTR2C*). The total genetic score for this study was calculated doing a subtraction of the score for each type of diet.

As described in a previous article [1], Anova tests followed by post hoc tests (Bonferroni's and Dunnett's) were performed in order to differentially codify each SNP genotype as a risk or non-risk variant. A risk genotype was defined as the one that was associated with lower BMI decrease due to the intervention. SNPs with a low prevalence (<10%) in either genotype category (risk and non-risk) were excluded.

2.7. Statistical analyses

Continuous variables were expressed as means ± standard error of the mean (SEM). The normality of analyzed variables was screened with the Shapiro–Wilk test. Statistical differences at baseline between intervention diets and sex, were assessed by Student's t-test or Mann–Whitney test according to the distribution of data. Significant changes after 4 months of nutritional intervention in each diet stratified by sex were assessed by Student t-test or Mann–Whitney test according to the distribution of data. Changes between before and after weight loss intervention were evaluated using paired t-test or Wilcoxon signed-ranks test. Alpha diversity indexes (Shannon, Chao1 and Simpson) were calculated using MicrobiomeAnalyst platform for including in the models [44]. Linear mixed models were implemented to predict BMI loss according to two total microbiota scores (one for each sex), the total genetic score, and the interactions with the diet. An interaction term between total microbiota score and genetic score with diet was intentionally sought in order to select the best type of diet for weight loss. Age and baseline energy intake were used as adjusting variables as well as Chao1 index alpha diversity. Subjects were used as random effects. Statistical analyses and graph designs were carried out using Stata 16 (StataCorp LLC, College Station, TX, USA; http://www.stata.com).

3. Results

3.1. Anthropometric, biochemical and dietary values at baseline

A total of 190 participants from Obekit project met the criteria for this research (Supplementary Fig. 1).

Baseline characteristics stratified by dietary intervention group and sex are shown in Table 1. At baseline, the population did not present statistically relevant differences in anthropometric and biochemical parameters according to the type of diet randomly assigned. Minor significant differences were found (fat mass, insulin and HOMA-IR in women and HDL and LDL-cholesterol in men). Some of the variables were different between men and women in both groups of diets. For example, men presented significantly higher values of waist circumference, visceral fat mass and triglycerides, whereas women had higher values of hip circumference, HDL-cholesterol, adiponectin and leptin. Energy and macronutrients intake did not show significant differences by sexes and intervention diet groups.

3.2. Anthropometric, biochemical and dietary values after the dietary intervention

The statistical analysis of changes of anthropometric and biochemical determinations in response to the dietary treatment are shown in Table 2. After 4 months of dietary intervention, all variables showed a significant improvement independently of type of diet and sex, showing that the two diets were effective in the reduction of anthropometric and biochemical parameters both in women and men (excepting adiponectin values which did not decrease significantly in the MHP-women and LF-women groups). Minor differences were found between groups of diets depending on sex. In women, the analysis of the changes after the dietary intervention showed that, in those assigned to the LF group, HDL-cholesterol presented a significantly higher increase and triglycerides showed a significantly lower decrease compared to the MHP group. In men, total cholesterol presented a higher decrease in those who followed the LF diet. Following the dietary pattern, a significantly increase in protein consumption and a moderate significantly decrease in fat consumption were observed in the groups that followed the MHP-diet, while the LF-diet group showed an increase in carbohydrate and a significant decrease in fat consumption. Differences between sexes were also found after the dietary intervention. For example, women presented significant lower values of hip circumference following the MHP diet and leptin following the LF diet, but an important increase of HDL-cholesterol after the LF diet. Men presented significantly higher decreases in weight, waist circumference, LDL-cholesterol and triglycerides following the LF diet, but a higher decrease in HOMA and adiponectin levels with the MHP diet. Interestingly, adiponectin decreased more in men (despite lower baseline values) than in

women, independently of the diet. As expected, percentage of macronutrient intake presented significant changes according to the diet prescribed in each group.

3.3. Selected bacteria for microbiota subscores

Table 3 shows the families, genera and bacterial species selected after applying the algorithms described in material and methods (step 1 and 2) to calculate the subscores. For the final linear mixed model to be effective is necessary to include an interaction term between the microbiota score and the diet. For this reason, a selection of taxa was carried out studying the association between the percentage of its basal abundance with the percentage of BMI loss. After that, we selected (in bold type, Table 3) the taxa that presented a positive or a negative relation with BMI loss in a non-coincidental way in both diets (see step 3 of Methods section 2.5) and did not show collinearity. Supplementary Fig. 2 shows the behaviors of the taxa marked in bold type from Table 3.

Once the most appropriate taxa were selected following the steps 1, 2 and 3 described in Methods section, four multiple linear regression models were performed to predict the percentage of BMI loss by diet and sex (see Table 4). The adjusted R^2 values ranged from 0.18 to 0.68.

A total of 3 genera (*Coprococcus*, *Dorea* and *Flavonifractor*) and 2 species (*Rumminococcus albus* and *Clostridium bolteaea*) were used for generating this subscore in MHP-women.

For LF-women, 4 families (Cytophagaceae, Catabacteriaceae, Flammeovirgaceae and Rhodothermaceae), 1 genera (*Clostridium_x1vb*) and 4 species (*Bacteroides nordiiay, Alistipes senegalensis, Blautia wexleraee* and *Pseudoflavonifractor phocaeensis*) were included in this subscore.

For MHP-men, 4 families (Cytophagaceae, Acidaminococcaceae, Marinilabiliaceae and Bacteroidaceae), 2 genera (*Fusicatenibacter* and *Odoribacter*) and 1 species (*Ruminococcus faecis*) were used for this subscore.

For LF-men, 1 family (Porphyromonadaceae), 1 genus (*Intestinimonas*) and 2 species (*Bacteroides finegoldii* and *Clostridium bartlettii*) was included in this subscore.

3.4. Total microbiota score and total genetic score calculation

The subscores for each group of sex and type of diet were calculated with the formulas showed in Table 5 using the β coefficient from the multiple regression models obtained in the previous steps and bacterial CLR-transformed data abundance. Finally, two total microbiota scores were calculated, one for each sex, subtracting the subscores of each diet as shown in Table 5. Similarly, a total genetic score was calculated by subtracting the two subscores obtained by our group in a previous publication [21], as shown in Table 5.

3.5. Linear mixed-effect regression models to select the weight loss diet

The equation for prediction BMI changes by diet was evaluated using a linear mixed regression model including the total microbiota score calculated for each sex and the interaction term with diet as fixed effects, and the subjects as random effects. Age, energy at baseline and Chao1 diversity index were also included as adjusting variables. Figure 1A and C shows the models, including β-coefficient and p-values, for both, women (A) and men (C). In both models, the interaction Diet X Total Microbiota score was statistically significant ($p = 0.001$).

Figure 1B and D shows the estimated values of BMI percentage loss for each type of diet according to the total microbiota score values in both models, women (B) and in men (D). As shown in Figure 1B, the prediction of BMI loss among women when the total microbiota score was lower than 2 was higher following the MHP diet. On the contrary, when the total microbiota score was higher than 4 points, the BMI loss was higher following the LF diet. The confidence interval of each estimation was calculated for each diet and sex.

Figure 1D shows that the estimation of BMI loss among men. When the total microbiota score was lower than 3 points, BMI loss was higher following the MHP diet. Meanwhile, when the total microbiota score was higher than 6, the BMI loss was higher following the LF dietary treatment.

Table 1
Anthropometric, biochemical and dietary characteristics of MHP-women, LF-women, MHP-men and LF-men groups at baseline.

	MHP- women (n = 61)	LF-women (n = 72)	P value[1] MHP-LF women	MHP-men (n = 29)	LF-men (n = 28)	P value[2] MHP-LF men	P value[3] women-men MHP	P value[4] women-men LF
Age (y)	47.3 ± 1.2	46.8 ± 1.2	0.78	43.6 ± 1.9	47.1 ± 1.4	0.16	0.10	0.91
BMI (kg/m^2)	31.0 ± 0.4	32.2 ± 0.4	0.11	31.7 ± 0.5	31.9 ± 0.6	0.79	0.31	0.79
Waist circumference (cm)	99 ± 1	101 ± 2	0.17	110 ± 2	107 ± 1	0.19	**<0.001**	**0.004**
Hip circumference (cm)	112 ± 1	114 ± 1	0.06	108 ± 1	108 ± 1	0.74	0.07	**0.004**
Fat mass (kg)	35.9 ± 0.9	38.8 ± 0.9	**0.02**	36.3 ± 1.3	33.4 ± 1.2	0.18	0.81	**0.001**
Visceral fat mass (kg)	1.2 ± 0.1	1.1 ± 0.1	0.21	2.2 ± 0.2	2.2 ± 0.1	0.98	**<0.001**	**<0.001**
Glucose (mg/dL)	94 ± 1	95 ± 1	0.48	101 ± 3	97 ± 2	0.29	**0.002**	0.28
Total cholesterol (mg/dL)	215 ± 5	214 ± 5	0.98	211 ± 8	230 ± 8	0.09	0.65	0.09
HDL-cholesterol (mg/dL)	59 ± 2	60 ± 2	0.52	43 ± 1	48 ± 2	**0.02**	**<0.001**	**0.001**
LDL-cholesterol (mg/dL)	45 ± 1	43 ± 1	0.40	45 ± 2	54 ± 3	**0.01**	0.94	**<0.001**
Triglycerides (mg/dL)	90 ± 5	90 ± 5	0.97	122 ± 13	127 ± 11	0.49	**0.005**	**0.006**
Adiponectin (μg/mL)	12.4 ± 0.6	13.1 ± 0.6	0.49	8.0 ± 0.4	8.8 ± 0.5	0.28	**<0.001**	**0.002**
Insulin (mU/L)	6.8 ± 0.6	8.2 ± 0.5	**0.03**	9.7 ± 1.0	7.2 ± 0.6	0.10	**0.008**	0.32
Leptin (ng/mL)	41.3 ± 3.0	49.9 ± 3.4	0.07	16.1 ± 1.9	12.6 ± 1.5	0.12	**<0.001**	**<0.001**
HOMA-IR	1.6 ± 0.1	2.0 ± 0.1	**0.04**	2.5 ± 0.3	1.8 ± 0.2	0.11	**0.005**	0.58
Total energy (kcal)	2902 ± 97	2905 ± 115	0.78	2969 ± 116	3436 ± 241	0.17	0.67	0.14
Carbohydrate intake (%)	55 ± 6	53 ± 6	0.34	53 ± 6	52 ± 7	0.19	0.27	0.86
Protein intake (%)	23 ± 4	22 ± 4	0.76	24 ± 3	23 ± 4	0.27	0.33	0.43
Fat intake (%)	21 ± 4	22 ± 4	0.53	20 ± 4	20 ± 3	0.38	0.23	0.17

Values correspond to the mean ± SEM. HOMA-IR: insulin resistance index. [1] P value of the comparison of means at baseline between women assigned to MHP diet and women assigned to LF diet. [2] P value of the comparison of means at baseline between men assigned to MHP diet and men assigned to LF diet. [3] P value of the comparison of means at baseline between sexes in the MHP diet group. [4] P value of the comparison of means at baseline between sexes in the LF diet group. Each variable was compared by t-test or Mann-Whitney test according to the distribution of data.

Table 2
Anthropometric, biochemical and dietary changes after the four-month nutritional intervention with the two diets (MHP and LF), separated by sex.

	MHP- women (n = 61)	LF-women (n = 72)	P value[1] MHP-LF women	MHP-men (n = 29)	LF-men (n = 28)	P value[2] MHP-LF men	P value[3] women-men MHP	P value[4] women-men LF
Δ BMI (kg/m^2)	−3.2*** ± 0.2	−3.2*** ± 0.1	0.90	−2.9*** ± 0.2	−3.6*** ± 0.2	0.06	0.31	0.13
Δ Weight (kg)	−8.3*** ± 0.4	−8.6*** ± 0.3	0.64	−9.2*** ± 0.7	−11.1*** ± 0.7	0.09	0.27	**0.001**
Δ Waist circumference (cm)	−8.9*** ± 0.9	−9.4*** ± 1.3	0.21	−9.3*** ± 1.3	−10.0*** ± 1.3	0.38	0.06	**0.04**
Δ Hip circumference (cm)	−7.1*** ± 0.4	−7.3*** ± 0.4	0.76	−5.1** ± 0.4	−6.3*** ± 0.5	0.06	**0.003**	0.23
Δ Fat mass (kg)	−6.7*** ± 0.4	−7.8*** ± 0.8	0.29	−7.8*** ± 0.5	−8.1*** ± 1.0	0.84	0.13	0.87
Δ Visceral fat mass (kg)	−0.3*** ± 0.02	−0.4*** ± 0.03	0.39	−0.8*** ± 0.08	−0.8*** ± 0.09	0.71	**<0.001**	**<0.001**
Δ Glucose (mg/dL)	−3.3*** ± 0.9	−5.2*** ± 1.7	0.35	−6.0*** ± 1.8	−5.6*** ± 1.9	0.86	0.14	0.91
Δ Total cholesterol (mg/dL)	−20.8*** ± 2.6	−21.4*** ± 4.1	0.91	−17.6*** ± 4.8	−34.5*** ± 5.2	**0.02**	0.53	0.08
Δ HDL-cholesterol (mg/dL)	3.8*** ± 1.0	7.5*** ± 1.1	**0.01**	0.05 ± 0.9	0.4 ± 1.5	0.66	**0.01**	**0.008**
Δ LDL-cholesterol (mg/dL)	−7.9*** ± 1.0	−5.5*** ± 1.3	0.17	−7.9*** ± 1.7	−16.1*** ± 2.9	0.20	0.98	**0.003**
Δ Triglycerides (mg/dL)	−17.7*** ± 3.7	−7.0* ± 3.6	**0.04**	−24.3*** ± 9.6	−35.1*** ± 9.1	0.42	0.44	**0.008**
Δ Adiponectin (μg/mL)	−0.06 ± 0.27	−0.3 ± 0.2	0.28	−1.3** ± 0.4	−1.2* ± 0.5	0.91	**0.007**	**0.009**
Δ Insulin (mU/L)	−2.3*** ± 0.5	−2.6*** ± 0.5	0.68	−4.0*** ± 0.8	−2.9*** ± 0.5	0.26	0.08	0.73
Δ Leptin (ng/mL)	−21.1*** ± 2.4	−25.6*** ± 2.5	0.21	−8.3*** ± 1.3	−6.9*** ± 0.9	0.42	**0.008**	**<0.001**
Δ HOMA-IR	−0.6*** ± 0.1	−0.7*** ± 0.1	0.55	−1.2*** ± 0.3	−0.8*** ± 0.1	0.22	**0.03**	0.72
Δ Total energy (kcal)	−495*** ± 99	−682*** ± 160	0.34	−697*** ± 144	−991*** ± 266	0.35	0.26	0.31
Δ Carbohydrate intake (%)	−5.3* ± 1.7	10.0 *** ± 2.3	**<0.001**	−2.1 ± 0.8	9.4*** ± 3.0	**<0.001**	0.12	0.91
Δ Protein intake (%)	10.2*** ± 2.4	−0.4 ± 0.1	**<0.001**	8.3*** ± 2.1	−0.9 ± 0.6	**<0.001**	0.87	0.11
Δ Fat intake (%)	−4.6** ± 2.2	−10.0*** ± 2.8	**<0.001**	−4.1*** ± 1.9	−7.1*** ± 1.9	**0.03**	0.68	0.33

Values correspond to the mean of changes after calorie restriction treatment ± SEM. HOMA-IR: insulin resistance index. [1] P value of the comparison of change means after weight loss between women assigned to MHP diet and women assigned to LF diet. [2] P value of the comparison of change means after weight loss between men assigned to MHP diet and men assigned to LF diet. [3] P value of the comparison of change means after weight loss between men and women assigned to MHP diet. [4] P value of the comparison of change means after weight loss between men and women assigned to LF diet.
***Represents a significant change (p<0.001), ** (p<0.01) and * (p<0.05) after 4 months of weight loss intervention comparing baseline and final data sets in each group. Each variable was compared by t-test or Mann-Whitney test according to the distribution of data for independent data and paired t-test or Wilcoxon rank sum test for paired data.

Statistical differences between the predictions of BMI percentage loss with both diets were analyzed using a Z test involving the standard errors of each estimation in order to test the capacity of this model for prescribing the most suitable diet to each individual in this population. Thus, a total of 72% of women and 84% of men participating in this study were significantly assigned to a most successful weight loss diet following this model.

Table 3
Bacterial families, genera and species preselected for the construction of the microbiota subscores according to type of diet (MHP and LF) and sex.

MHP-women (n = 61)	LF-women (n = 72)	MHP-men (n = 29)	LF-men (n = 28)
FAMILY			
Lachnospiraceae	**Cytophagaceae**	**Cytophagaceae**	**Cytophagaceae**
Clostridiales_incertae_sedis_xi	**Catabacteriaceae**	**Acidaminococcaceae**	**Porphyromonadaceae**
Lactobacillaceae	Verrucomicrobiaceae	Rhodospirillaceae	**Catabacteriaceae**
	Flammeovirgaceae	**Marinilabiliaceae**	**Streptococcaceae**
	Rhodothermaceae	**Caldilineaceae**	**Fibrobacteraceae**
	Prolixibacteraceae	**Bacteroidaceae**	Prevotellaceae
	Clostridiaceae_2	**Clostridiaceae_3**	Clostridiaceae_2
		Erysipelotrichaceae	Bifidobacteriaceae
			Chthonomonadaceae
GENUS			
Coprococcus	*Akkermansia*	*Acetivibrio*	***Henriciella***
Dorea	*Alkaliphilus*	***Anaerostipes***	***Intestinimonas***
Flavonifractor	*Blautia*	*Clostridium_xviii*	*Lactobacillus*
Fusicatenibacter	***Butyricicoccus***	***Dorea***	*Veillonella*
Intestinimonas	***Clostridium_xlvb***	***Eubacterium***	
	Holdemania	***Fusicatenibacter***	
	Marvinbryantia	***Intestinibacter***	
	Niabella	***Odoribacter***	
	Oribacterium		
	Paraprevotella		
SPECIES			
Dorea formicigenerans(L34619)	*Roseburia inulinivorans270473*	***Ruminococcus faecisfj611794***	*Bacteroides fluxusab490802*
Bacteroides eggerthii(AB050107)	***Bacteroides nordiiay608697***	*Culturomica massiliensi~14474*	*Eubacterium oxidoreducens1047*
Bacteroides xylanisolvens(AM230650)	*Emergencia timonensis~1447371*	*Bacteroides plebeiusab200217*	***Bacteroides finegoldii222699***
Ruminococcus albus(L76598)	***Alistipes senegalensis1182191***	***Negativibacillus massiliensis***	***Clostridium bartlettii438672***
Mordavella massiliensis(NR_147406.1)	***Blautia wexleraeef036467***	*Fusicatenibacter saccharivōa*	*Eubacterium ramulusl34623*
Pseudoflavonifractor capillosus(AY136666)	***Pseudoflavonifractor phocaeensiss***	***Prevotella copriab064923***	*Parabacteroides distasonis2389*
Blautia luti(AJ133124)			***Catabacter hongkongensis574991***
Bacteroides uniformis(AB050110)			
Bacteroides vulgatus(CP000139)			
Phocea massiliensis(NR_144748.1)			
Lachnospira multipara(FR733699)			
Clostridium bolteae(AJ508452)			

In bold type, bacterial taxa preselected for the subscores due to they presented a different abundance-change for each type of diet (Fig. 2 supplementary material).

Table 4
Linear regression models constructed with percentage of BMI loss as dependent variable and the groups of bacteria selected for the microbiota score in each group of sex and diet.

Models	[a] coefficient	SEM	p value	R^2 adjusted	P value model
Women MHP-diet (n = 61)					
BMI loss (%)				0.18	0.007
Coprococcus	1.60	0.67	0.02		
Dorea	−2.24	0.62	0.002		
Flavonifractor	1.28	0.77	0.11		
Rumminococcus albus	0.41	0.25	0.11		
Clostridium bolteaea	0.58	0.43	0.19		
Constant	−10.72	1.88	<0.001		
Women LF-diet (n = 72)					
BMI loss (%)				0.34	<0.001
Cytophagaceae	1.35	0.65	0.04		
Catabacteriaceae	0.43	0.24	0.08		
Flammeovirgaceae	−1.87	0.76	0.02		
Rhodothermaceae	1.77	0.70	0.01		
Clostridium_x1vb	0.64	0.36	0.07		
Bacteroides nordiiay	0.63	0.43	0.09		
Alistipes senegalensis	−0.58	0.21	0.008		
Blautia wexleraee	−0.91	0.40	0.03		
Pseudoflavonifractor phocaeensis	−0.64	0.29	0.03		
Constant	−8.14	1.79	<0.001		
Men MHP-diet (n = 29)					
BMI loss (%)				0.68	<0.001
Cytophagaceae	−1.29	0.55	0.03		
Acidaminococcaceae	−0.42	0.18	0.03		
Marinilabiliaceae	2.51	0.91	0.01		
Bacteroidaceae	−1.66	0.58	0.01		
Fusicatenibacter	1.52	0.57	0.01		
Odoribacter	1.50	0.43	0.002		
Rumminococcus faecis	1.58	0.59	0.01		
Constant	−2.83	3.81	0.46		
Men LF-diet (n = 28)					
BMI loss (%)				0.22	0.04
Porphyromonadaceae	−1.72	0.93	0.07		
Intestinimonas	−2.03	1.25	0.12		
Bacteroides finegoldii	−0.41	0.30	0.19		
Clostridium bartlettii	0.44	0.30	0.16		
Constant	0.75	5.08	0.88		

[a] represents changes in outcomes for the increasing number of units of percentage of BMI loss separating by groups of sex and type of diet. SEM: standard error of the mean.

A previous publication encompassing the same study population reported the personalization of weight loss by using genetic scores for each type of diet [21]. In order to complement the previous model and to determine whether the inclusion of these genetic score could improve the diet assignment, linear mixed models were performed including the such genetic subscores (Table 5) as a new independent variable in the analysis. Since the term of the interaction with diet is essential for discriminating the optimum treatment, the genetic score was included as an interaction term with diet. Figure 2 shows the β coefficient and p-values of these models for women and men. Age, energy at baseline and Chao1 diversity index were also included as adjusting variables.

Predicted BMI loss values from the mixed models according to the new models that include the total genetic score are represented in Fig. 2B and D. The effect of the genetic score was represented dividing by the mean (5 points of genetic score). Two lines for each diet are showing, one when the values are above or equal to the mean value of the total genetic score (5 genetic score points) and

Table 5
Construction of the microbiota subscores and the total microbiota score for each group of diet MHP and LF) and sex.

Scores	Calculating formula
MHP-women subscore	(1.60*_Coprococcus_) + (−2.24*_Dorea_) + (1.28*_Flavonifractor_) + (0.41*_Ruminococcus albus_) + (0.57*_Clostridium bolteaea_)
LF-women subscore	(1.35*Cytophagaceae) + (0.43*Catabacteriaceae) + (−1.88*Flammeovirgaceaeae) + (1.78*Rhodothermaceae) + (0.64*_Clostridium_xlvb_) + (0.73*_Bacteroides nordiiay_) + (0.58*_Alistipes senegalensis_) + (−0.91*_Blautia wexleraee_) + (0.65*_Pseudoflavonifractor phocaeensis_)
MHP-men subscore	(-1.29*Cytophagaceae) + (−0.42*Acidaminococcaceae) + (2.51*Marinilabiliaceae) + (−1.66*Bacteroidaceae) + (1.52*_Fusicatenibacter_).+ (1.50*_Odoribacter_) + (1.57*_Ruminococcus faecis_)
LF-men subscore	(-1.73*Porphyromonadaceae) + (−2.04*_Intestinimonas_) + (−0.41*_Bacteroides finegoldii_) + (0.44*_Clostridium bartlettii_)
Total microbiota score for women	MHP-women subscore − LF-women subscore
Total microbiota score for men	MHP-men subscore − LF-men subscore
Total genetic score	MHP-genetic subscore − LF-genetic subscore [21]

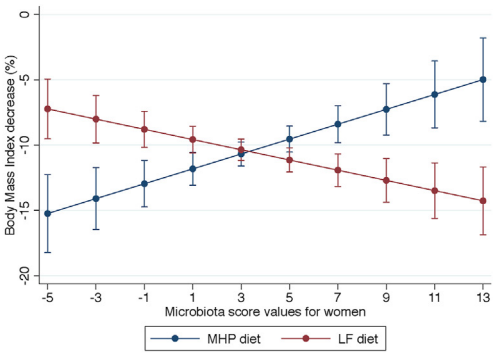
A.

Microbiota Score model in women (n= 133).
P value Wald-chi square = 0.02

Independent variable	*β coefficient ± SEM*	*P value Z test*
Age	-0.01 ± 0.03	0.637
Diet	3.20 ± 0.97	0.001
Total Microbiota Score	0.57 ± 0.17	0.001
Diet * Total Microbiota score	-0.96 ± 0.21	<0.001
Energy intake at baseline	-0.0005 ± 0.0003	0.197
Chao1 diversity	0.004 ± 0.001	0.014
constant	-13.77 ± 2.03	0.000

B.

Predicted values of BMI percentage loss in women



C.

Microbiota Score model in men (n= 57).
P value Wald-chi square <0.001

Independent variable	*β coefficient ± SEM*	*P value Z test*
Age	-0.03 ± 0.04	0.495
Diet	4.51 ± 1.52	0.003
Total Microbiota Score	0.69 ± 0.14	<0.001
Diet * Total Microbiota score	-1.05 ± 0.22	<0.001
Energy intake at baseline	-0.0006 ± 0.0005	0.239
Chao1 diversity	0.001 ± 0.002	0.538
constant	-10.97 ± 3.43	0.001

D.

Predicted values of BMI percentage loss in men

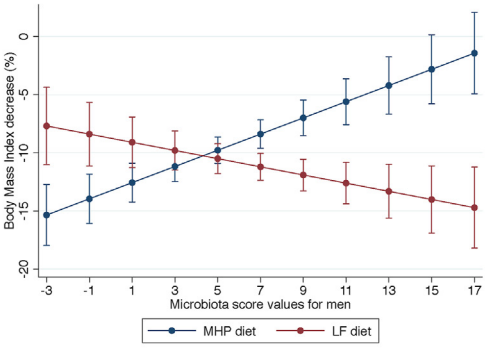


Fig. 1. Linear mixed regression models to predict percentage of BMI loss (Body mass index decrease, %) based on the total microbiota scores for women (A) and for men (C). The models include diet, total microbiota score calculated for each sex, and the interaction term between the microbiota score and diet as fixed effects, and the subjects as random effects. Age, baseline energy intake and Chao1 diversity index were used as adjusting variables. The graphs B and D show the interaction between the total microbiota scores and the diet (MHP or LF) in the linear mixed regression models for women (B) and for men (D). Dark blue line represents MHP- diet and red line represents LF-diet. A confidence interval of 95% is depicted.

another when the values are lower than the mean. Women with the same genetic score punctuation (5 points, red and blue lines in Fig. 2B) but microbiota score higher than 8 could achieve a greater BMI loss following the LF diet. Women with a genetic score higher than 5 points and a microbiota score lower than −3 could reach more BMI loss following the MHP diet (green line, Fig. 2B). On the contrary, women with more than 5 points in the genetic score but a microbiota score higher than 2 could accomplish higher BMI loss with the LF diet yellow line, Fig. 2B).

In men, the estimated values (Fig. 2D) showed that the participants with a genetic score lower or equal to 5 points could benefit from the MHP diet if the microbiota score is lower than 3 points (dark blue line, Fig. 2D). However, if the microbiota score is higher than 7, the LF diet should be prescribed (red line, Fig. 2D). Men with a genetic score higher than 5 points and a microbiota score lower than 1 could be treated with the MHP diet for a greater BMI loss (green line, Fig. 2D). On the contrary, men with genetic values higher than 5 but microbiota score values higher than 7 could obtain a greater BMI loss following the LF diet (yellow line, Fig. 2D).

In order to prescribe the most suitable diet for each individual, statistical differences were calculated between the prediction of the percentage of BMI loss with each diet (MDP and LF) in the new models using a Z test. Thus, a total of 84% of women and 73% of men belonging to this study were significantly assigned to one of the diet following these models.

To test the improvement of selection capacity in the models that include the genetic score (and its interaction with diet), a comparison of the Wald chi-square values was performed with the model without the genetic score. In women, the comparison of the models (with and without genetic score) resulted in a p value of 0.046, showing that the inclusion of the genetic score significantly improved the model; in the case of men, a non-significant p value was obtained.

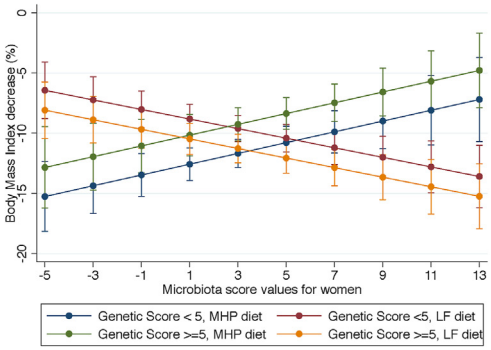
A.

Microbiota Score + Genetic Score model in women (n= 133). P value Wald-chi square <0.001

Independent variable	*β coefficient ± SEM*	*P value Z test*
Age	-0.01 ± 0.03	0.447
Diet	4.89 ± 1.33	<0.001
Total Microbiota Score	0.49 ± 0.17	0.005
Diet * Total Microbiota Score	-0.88 ± 0.22	<0.001
Total Genetic Score	0.21 ± 0.16	0.010
Diet * Total Genetic Score	-0.43 ± 0.23	0.001
Energy intake at baseline	-0.0005 ± 0.0003	0.162
Chao1 diversity	0.004 ± 0.001	0.006
constant	-14.50 ± 2.09	<0.001

B.

Predicted values of BMI percentage loss in women



C.

Microbiota Score + Genetic Score model in men (n= 57). P value Wald-chi square <0.001

Independent variable	*β coefficient ± SEM*	*P value Z test*
Age	-0.03 ± 0.05	0.545
Diet	5.08 ± 1.91	0.002
Total Microbiota Score	0.67 ± 0.15	<0.001
Diet * Total Microbiota Score	-1.01 ± 0.23	<0.001
Total Genetic Score	0.08 ± 0.21	0.221
Diet * Total Genetic Score	-0.16 ± 0.32	0.326
Energy intake at baseline	-0.0005 ± 0.005	0.281
Chao1 diversity	0.0009 ± 0.002	0.732
constant	-11.03 ± 3.60	0.002

D.

Predicted values of BMI percentage loss in men

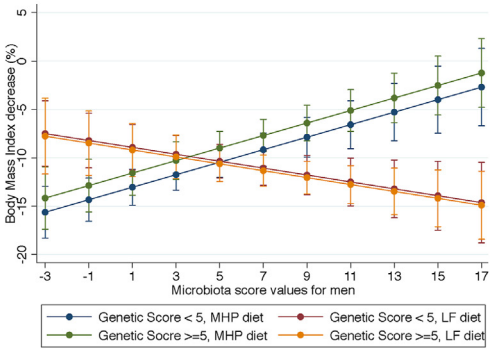


Fig. 2. Linear mixed regression models to predict percentage of BMI loss (Body mass index decrease, %) based on the Total genetic score and the Total microbiota score for women (A) and for men (C). The models include diet, total genetic score, total microbiota score calculated for each sex, and the interaction terms between both scores (microbiota and genetics) with diet as fixed effects, and the subjects as random effects. Age, baseline energy intake and Chao1 diversity index were used as adjusting variables. The graphs B and D show the interaction between the microbiota score for women (B) or for men (D) and the diet in each model, and the influence of the genotype score. Dark blue line represents MHP-diet and total genetic score lower or equal to 5 points; green line represents MHP-diet and total genetic score higher than 5 points; red line represents LF-diet and total genetic score lower or equal to 5 yellow line represents LF-diet and total genetic score higher than 5 points. A confidence interval of 95% is depicted.

4. Discussion

In the current study, we show that integrative models based on baseline microbiota composition and genetic scores could be useful tools to prescribe the most suitable weight loss diet for women and men.

At baseline, biochemical and anthropometrical parameters were similar between both dietary groups (MHP and LF), with some differences due to sexual dimorphism for example in waist and hip circumference. In general, biochemical and anthropometric measurements improved after 4 months of weight loss intervention with both diets in both sexes, demonstrating that energy restriction was equally effective for women and men. At the present, advances in personalized medicine and "omics" technologies have allowed to look into the different factors influencing interindividual weight loss variability [45,46]. Using patients' baseline information (such as ethnicity, clinical history, eating behavior, food preferences, etc.) and phenotypic characteristics is possible to select which type of diet would be adequate [47]. In this regard, some polymorphisms have been described to be associated with different metabolic outcomes in response to various dietary prescriptions [21,42,48,49] and have already been used in a previous investigation to build a genetic risk score [21]. On the other hand, several bacterial taxa have been involved in physiological processes directly or indirectly related to energy homeostasis and body weight regulation [50–52]. In this study, different bacterial taxa have been associated with

weight loss in each sex and diet, and they were used for the construction of a microbiota score.

Regarding the microbial taxa found, there were no coincidences between bacteria included in each subscore, excepting Cytophagaceae family. *Coprococcus, Dorea* and *Flavonifractor* genera were included in the MHP-women subscore. There are some studies that associate these bacterial taxa with body weight regulation and diet, but we are the first proposing that these taxa could be used in a score to optimize the response to weight loss. *Coprococcus* has been previously associated with a decrease of adiposity [53]. *Dorea* has been reported to decrease in parallel with a decrease in BMI following a diet high in protein [54]. *Flavonifractor* has been associated with browning promotion in white adipose tissues of HFD-fed mice [55], but results in humans are scarce. *Ruminococcus albus* has not been previously related to weight loss in women in the literature, although this species produces cellulose, an enzyme that mediates the cellulose digestion producing starch-glucose [56]. *C.lostridium bolteaea* has been previously associated with non-obese subjects in Japanese population [57].

The microbiota subscore in women who followed the LF diet revealed that baseline abundances of the families Cytohagaceae, Catabacteriaceae, Flammeovirgaceae and Rhodothermaceae could be used as markers for a successful weight loss.

These families have been no associated with weight loss in the scientific literature, although Catabacteriaceae has been associated with low grade of inflammation [58]. *Clostridium* genus has been found to correlate with weight loss in an adolescent population [59], although its role as a biomarker for weight loss in women is not described in the bibliography.

Alistipes senegalensis belongs to a genus of bacteria that is highly relevant in disease-related dysbiosis and correlated negatively with BMI [60], although this species has not been previously associated with weight loss specifically in women. *Blautia wexlerae* belongs to a genus with potential applications as probiotics [61] and a depletion in *Blautia* species has been reported to be associated with gut inflammation, which could suggest that *Blautia* might be an intestinal protective genus [62]. Specifically, *Blautia wexlerae* abundance has been associated with non-obese subjects in a study with Japanese population [57].

On the other hand, the analysis of the basal microbiota included the families Cytophagaceae, Acidaminococcaceae, Marinilabiliaceae and Bacteroidaceae as biomarkers for prescribing MHP diet in men. In a previous study, Lv et al. described that the relative abundance of Acidaminococcaceae was negatively associated with BMI [63]. Despite the association of Acidaminococcaceae with BMI, the relationship of this family with a successful weight loss process in men as far as we know is not detailed in the bibliography. Marinilabiliaceae has not been previously associate with obesity or weight loss in the scientific literature. Bacteria from the Bifidobacteriaceae family have been largely described in the literature. The increase of Bifidobacteriaceae facilitates a cross-feeding interaction that results in an increase in butyrate producers and butyrate synthesis, which contributes to gut barrier function immunomodulation and anti-inflammatory properties [64,65]. The subscore for MHP-men also included *Fusicatenibacter* and *Odoribacter* genera. *Fusicatenibacter* has been previously associated with greater weight loss [66], whereas *Odoribacter* abundance was found to be increased after weight loss, but there is a little information about this relation in men [67]. *Ruminococcus faecis* has not been described as a potential biomarker for weight loss, but it has been associated with a protective effect on liver damage [68].

In the LF-men group, we found that Porphyromonadaceae, *Intestinimonas, Bacteriodes finegoldii* and *Clostridium bartlettii* could be used as biomarkers to prescribe a LF diet in men. Porphyromonadaceae has been associated with reduced visceral adipose tissue and healthier metabolic profile [69]. The abundance of *Intestinimonas* genus has been associated with an increase in fat intake [70]. *Bacteroides finegoldii* belongs to *Bacteroides*, a genus that has been related to obesity and weight loss in some studies [71–73]. For example, the ratio between *Bacteroides* and *Prevotella* has been described in the literature as a predictive tool for weight loss trajectory [74]. However, this species has not been previously related to weight loss. *Clostridium bartlettii* has been found to be increased in healthy control patients compared to patients with metabolic syndrome [75].

In this study we have pioneerly shown that several microbiota taxa could be useful to predict the best dietary treatment but also that genetic information must be taken into account in the prescription of anti-obesity treatment. These results indicate that the introduction of the genetic score and its interaction with the diet improved the models. However, it is necessary to be cautious with these results because in this study the inclusion of the genetic score into the men model did not improved it, showing that the microbiota score was better predictor of weight loss for men. By the contrary, the model including genetic score showed an improvement of the predictive capacity of the model for assigning a dietary treatment in women. This could be explained because the number of men was lower than women subjects and should be tested in a larger number of male subjects to verify if the genetic score should be considered in the weight loss prediction model.

These results suggest that the use of these integrative models may help to predict BMI decrease, allowing to prescribe the best diet considering the microbiota composition, genotype and the individual phenotype. In addition, epigenetic signatures or metabolomic fingerprints could also be included in a weight loss model similar to the one explained in this manuscript for a more accurate dietary prescription. Moreover, these type of models show that some participants cannot be significantly assigned to one of these diets for a better BMI loss. In this sense, these subjects might choose the type of diet according to individual food preferences since both diets would result in similar weight loss. As conclusion, this holistic approach may lead to personalized dietary advice using precision nutrition standards for the management of excessive body weight and an increase in the success of weight-loss treatments, where sex is included as an important variable in the individualization process. In fact, these type of statistical models have been previously proposed in the scientific literature. A study of Ritz et al. (2019) followed similar statistical methods (mixed model) and determined that fasting glucose and insulin measurements were able to predict individualized treatment effect of introducing more fiber and whole grain in the diet [29]. Moreover, this methodology has been used in other publications for personalized dietary treatment using gut microbiota to discriminate weight loss success with specific diets by applying similar linear mixed models [72,76]. However, our results indicate that gut microbiota composition depends greatly on sex, and these sex-related differences must be taken into account for the dietary interventions efficacy [77]. The main strength of this investigation is the new conceptual modeling for selecting the best type of diet (MHP and LF) for a successful weight loss using baseline microbiota, genetic and phenotypic information. Also, robust statistical approaches were applied to select the best multiple linear regression models explaining BMI decrease difference in each type of diet. On the other hand, some limitations of this research include the screening of only two types of diets for weight loss (more types of diet could improve the model and reach a higher personalization). Moreover, as it has been performed in a Spanish population, caution must be taken before applying these findings in other ethnic groups. Thus, further studies including

other different cohorts, a larger number of individuals, different hypocaloric diets, longer follow-ups and other ethnic backgrounds are necessary. Also, discussing the obtained results is complex due to the lack of similarities with the dietary design and methods in the present bibliography. Finally, the design of this experiment should be considered as a proof-of-concept in order to evaluate if combining information from microbiota composition, genetic variants and phenotypic characteristics may be useful to personalize the treatments.

5. Conclusions

This investigation demonstrates that the success of a BMI loss treatment could be estimated based on gut microbiota composition (as represented by the specific microbiota scores for both women and men), but is also dependent on the genetic information in the case of women subjects. As a conclusion, this investigation presents a novel tool for selecting weight loss treatments based on baseline gut microbiota and host genetics information as factors for the selection of the most suitable weight loss diet.

Author contributions

Conceptualization: FIM, JAM and JIR-B; Data curation: AC-S and LG; Formal analysis and software: *AC-S, MG-G and JIR-B*; Funding acquisition: FIM, JAM, MC and JIR-B; Investigation: AC-S and JIR-B; Methodology: AC-S, JIR-B, MC, LG and MG-G; Project administration: JAM and MC; Supervision: FIM and JAM; Validation: FIM, MG-G and JAM; Visualization: FIM and JIR-B; Original draft writing: AC-S and JIR-B; Review and editing: FIM, JAM, MC and LG.

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Conflicts of interest

Authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.06.008.

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