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Original Research Article

A single-blinded, randomized, parallel intervention to evaluate genetics and omics-based personalized nutrition in general population via an e-commerce tool: The PREVENTOMICS e-commerce study

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A B S T R A C T

Background: Personalized nutrition (PN) has been proposed as a strategy to increase the effectiveness of dietary recommendations and ultimately improve health status.

Objectives: We aimed to assess whether including omics-based PN in an e-commerce tool improves dietary behavior and metabolic profile in general population.

Methods: A 21-wk parallel, single-blinded, randomized intervention involved 193 adults assigned to a control group following Mediterranean diet recommendations ($n = 57$, completers = 36), PN ($n = 70$, completers = 45), or personalized plan (PP, $n = 68$, completers = 53) integrating a behavioral change program with PN recommendations. The intervention used metabolomics, proteomics, and genetic data to assist participants in creating personalized shopping lists in a simulated e-commerce retailer portal. The primary outcome was the Mediterranean diet adherence screener (MEDAS) score; secondary outcomes included biometric and metabolic markers and dietary habits.

Results: Volunteers were categorized with a scoring system based on biomarkers of lipid, carbohydrate metabolism, inflammation, oxidative stress, and microbiota, and dietary recommendations delivered accordingly in the PN and PP groups. The intervention significantly increased MEDAS scores in all volunteers (control—3 points; 95% confidence interval [CI]: 2.2, 3.8; PN—2.7 points; 95% CI: 2.0, 3.3; and PP—2.8 points; 95% CI: 2.1, 3.4; $q < 0.001$). No significant differences were observed in dietary habits or health parameters between PN and control groups after adjustment for multiple comparisons. Nevertheless, personalized recommendations significantly (false discovery rate < 0.05) and selectively enhanced the scores calculated with biomarkers of carbohydrate metabolism (β: −0.37; 95% CI: −0.56, −0.18), oxidative stress (β: −0.37; 95% CI: −0.60, −0.15), microbiota (β: −0.38; 95% CI: −0.63, −0.15), and inflammation (β: −0.78; 95% CI: −1.24, −0.31) compared with control diet.

Abbreviations: BMI, body mass index; CHP, core health process; CRP, C-reactive protein; DBP, diastolic blood pressure; DMA, dimethylamine; ELISA, enzyme linked immunosorbent analysis; FFQ, food frequency questionnaire; GWAS, genome-wide association studies; HDL, high density lipoprotein; ICT, information and communications technologies; LDL, low density lipoprotein; MCP, monocyte chemoattractant protein; MEDAS, Mediterranean Diet Adherence screener; MPB, metabolic or proteomic biomarker; PN, personalized nutrition; PP, personalized plan; SBP, systolic blood pressure; sCD14, soluble subtype of CD14; SNP, single nucleotide polymorphism; TMA, trimethylamine.

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Conclusions: Integration of personalized strategies within an e-commerce–like tool did not enhance adherence to Mediterranean diet or improved health markers compared with general recommendations. The metabotyping approach showed promising results and more research is guaranteed to further promote its application in PN.
This trial was registered at clinicaltrials.gov as NCT04641559 (https://clinicaltrials.gov/study/NCT04641559?cond=NCT04641559&rank=1).

Keywords: physiologic characterization, genome-wide association studies, lifestyle intervention, targeted nutrition, precision nutrition, health status, healthy diets, dietary patterns

Introduction

Diseases linked to unhealthy dietary habits are increasing steadily in developing and developed countries [1,2]. This is indicative of the inefficiency of general nutritional recommendations, which do not succeed in changing consumers' dietary behavior [3]. It has been proposed that adapting nutritional recommendations to individuals' needs and preferences may fill the current gap between the availability of knowledge in nutrition and its adoption by general population [4]. Thus, personalized nutrition (PN) has gained great interest during the last decade [5]. To evaluate the effectiveness of PN approaches, several nutritional intervention trials have been conducted. However, the results of meta-analyses and systematic reviews have been inconsistent, with some reporting positive outcomes [4,6] and others negative outcomes [7]. This discrepancy may be due to the use of different information for personalizing nutritional recommendations. Nutrigenetics-based personalization is a widely used strategy [5], but other disciplines, such as metabolomics, proteomics, and metagenomics, have gained prominence in recent years [8–10]. The use of omics has also facilitated research on metabotypes, which are groups of subjects with similar metabolic features that influence their responses to the same food [8,11,12]. Along with the characterization of physiology, behavioral change strategies have gained significant interest in recent years, as sustained changes in dietary habits and behavior can be achieved through a holistic approach that takes into account individual behavior and personality traits [4].

Although regulatory bodies have yet to adopt robust standards, current proposals for defining PN guidelines emphasize the use of individual data to improve dietary behavior and ultimately optimize consumers' health status [13,14]. The PREVENTOMICS Project [15] aims to empower consumers to prevent diet-related diseases through an integrated system that assesses the status of 5 CHP (oxidative stress, systemic inflammation, carbohydrate and lipid metabolism, and microbiota-derived metabolites) using metabolomics, proteomics, and genetics data. A score is calculated for each process to simplify the system for its use in different information and communication technology (ICT) applications for delivering personalized recommendations [16]. We hypothesized that omics-based and genetics-based personalized recommendations delivered through a retailer's e-commerce portal enhance dietary behavior and consequently health markers when compared with the same digital tool delivering general recommendations based on the Mediterranean diet and that a behavioral change strategy combined with the personalized approach increases the response.

Based on the abovementioned premises, a simulated e-commerce portal integrating PREVENTOMICS was developed. A control group used the ICT tool after receiving general recommendations based in the Mediterranean diet and with no personalization features. Two groups used the tool with real-time personalized recommendations. One group received recommendations based on metabotype and genotype data. For the other group, a personalized behavioral change program was added on top of the physiologic characterization to assess whether addition of a psychological dimension could enhance dietary behavior and health outcomes.

Methods

Participants and study design

A randomized, parallel, and single-blind nutrition intervention trial was conducted for 16 wk in healthy participants. A total of 192 participants were recruited from December 2020 to July 2021 at Eurecat, Centre Tecnològic de Catalunya, Unitat de Nutrició i Salut, in Reus, Spain. Participants were recruited from general databases of participants from previous studies and via media and social networks. Eurecat has its own profile and experience in the recruitment of participants for clinical trials.

Participants were randomly assigned into the following 3 arms of intervention: *1*) control group, which used the e-commerce tool delivering general recommendations of the Mediterranean diet; *2*) PN group, which had recommendations based on the status of their 5 core health processes (CHPs) as described previously [16]; *3*) personalized plan (PP) group, receiving the same recommendations than PN and including a personalized behavioral change program [17].

Three face-to-face visits were performed at Eurecat, Reus: a screening visit to verify inclusion and exclusion criteria (V0); a baseline visit (V1) to provide biological samples to be analyzed (blood, saliva, and urine) and allocate participants to the 5 CHPs (lipid metabolism, carbohydrate metabolism, systemic inflammation, oxidative stress, and microbiota status) according to omics and genetic data, complete online questionnaires related to dietary habits and behavior, and learn how to use the study website (V1); and a final visit on the last day of the intervention, after 16 wk, to provide biological samples and complete online questionnaires (V2). After baseline visit (V1) analyses of biological samples took 1 mo and subsequently participants were allocated to 1 of the 3 arms of intervention and informed by e-mail and a telephone call to start the intervention.

All participants signed an informed consent form before participation in the study. All protocols had been approved by the Clinical Research Ethical Committee of Institut d'Investigació sanitaria Pere Virgili, Reus, Catalonia, Spain (Ref. CEIm: 076/2020 and 02/2021). The protocol and trial were conducted in accordance with the Helsinki Declaration and Good Clinical Practice Guidelines of the International Conference of Harmonization (ICH GCP) and reported according to CONSORT criteria. The study was registered at clinicaltrials.gov with the identifier number NCT04641559.

Inclusion and exclusion criteria

Participants were eligible for enrollment in the study if they met the following criteria: *1*) males and females aged ≥18 y; *2*) all participants signed the informed consent form; and *3*) having access to internet.

Exclusion criteria were as follows: *1*) having diabetes (or fasting blood glucose clinical laboratory assessment ≥126 mg/dL or

pharmacologic treatment); *2*) having hypertension [systolic blood pressure (SBP) ≥160 mm Hg and/or diastolic blood pressure (DBP) ≥100 mm Hg or using blood pressure medicines); *3*) having dyslipidemia [LDL cholesterol ≥4.9 mmol/L and/or triglycerides ≥4.5 mmol/L and/or HDL cholesterol <1.03 mmol/L in males and <1.29 mmol/L in females] or using lipid-lowering medication; *4*) using a prescribed medicine to control acute or chronic inflammation; *5*) having anemia (hemoglobin ≤13 g/dL in males and ≤12 g/dL in females); *6*) having a body mass index (BMI, in kg/m^2) <18.5 or >35; *7*) being pregnant or planning to become pregnant within the study or being in lactation period; *8*) current smokers; *9*) being participating in or have participated in a clinical trial or a nutritional intervention study in the last 30 d before inclusion in the study; *10*) experiencing chronic gastrointestinal disorders or chronic disease with clinical manifestation, such as coronary heart diseases, cardiovascular disease, coeliac disease, Crohn disease, and chronic kidney disease; *11*) following a prescribed diet for any reason, including weight loss, in the last 3 mo; *12*) following a pharmacologic treatment of weight loss or intake of food supplements or medications that could affect body weight; *13*) having allergies or food intolerances; *14*) no or limited access to the internet; *15*) consumption of >14 drinks of alcoholic beverages per week; *16*) having a Mediterranean Diet Adherence Score (MEDAS) > 8 of 14 points, which is a food pattern already highly concordant with the Mediterranean diet [18]; and *17*) being unable to follow the study guidelines.

Intervention

Participants accomplishing selection criteria were derived to the basal visit (V1). In V1, participants provided biological samples and anthropometrics. Next, participants logged into the Preventomics Dashboard to fill in the different questionnaires described further. One month after providing data and samples, participants started the intervention through the e-commerce platform. A figure summarizing the intervention is provided in Supplemental Figure 1.

Dietary recommendations were elaborated for each of the 5 CHPs and the control group as food categories and subcategories to increase or decrease in the diet. Detailed description is provided in Supplemental Table 1 and **Supplemental References**. Recommendations for the control group were based in general Mediterranean diet guidelines, whereas recommendations for the 5 CHPs were more detailed, reaching the level of subcategory in order to include foods rich in specific bioactive compounds or micronutrients and macronutrients that have been described as beneficial for the main metabolic pathways included in the 5 overarching CHPs and to exclude those described as detrimental.

The food selection was performed according to 18 food categories: starchy foods, vegetables, fruits, legumes, dairy products, nuts and seeds, eggs, meat, fish, oils and fats, sweets and desserts, snacks, nonalcoholic beverages, alcoholic beverages, dietary supplements, sauces and dressings, meat and dairy imitates, and convenience food. Food categories were divided into 155 subcategories. Subcategories were used in the recommender system to define those foods to be increased and those to decrease in the diet of the participant. A real full retailer catalog was provided and continuously updated by ALDI Central de Compras (Barcelona, Spain), and products of the catalog were matched to the subcategories described above in order to show in the ICT application specific products of the catalog to decrease and to increase.

The 5 dietary recommendation plans, the blood and urine test results, and descriptions about metabolic status were delivered through the e-commerce tool in the 3 intervention groups (control, PN, and PP). However, in the control group, participants received standard recommendations aligned with the Mediterranean diet, without specific information regarding their metabolic, genetic, and clinical parameters. Individuals in the PN group were provided with insights into their metabolic status and received personalized advice. The PP group, in addition to the information given to the PN group, participated in a personalized behavioral change program delivered through notifications within the e-commerce tool.

The e-commerce tool facilitated the creation of personalized shopping lists by allowing participants to select items from a retailer catalog. For those in the PN and PP groups, foods on the shopping list were dynamically flagged in real time as either beneficial or nonbeneficial based on their individual recommendations for increased or decreased consumption, respectively. Foods without specific recommendations were not highlighted. Participants in the control group did not receive guidance from the system.

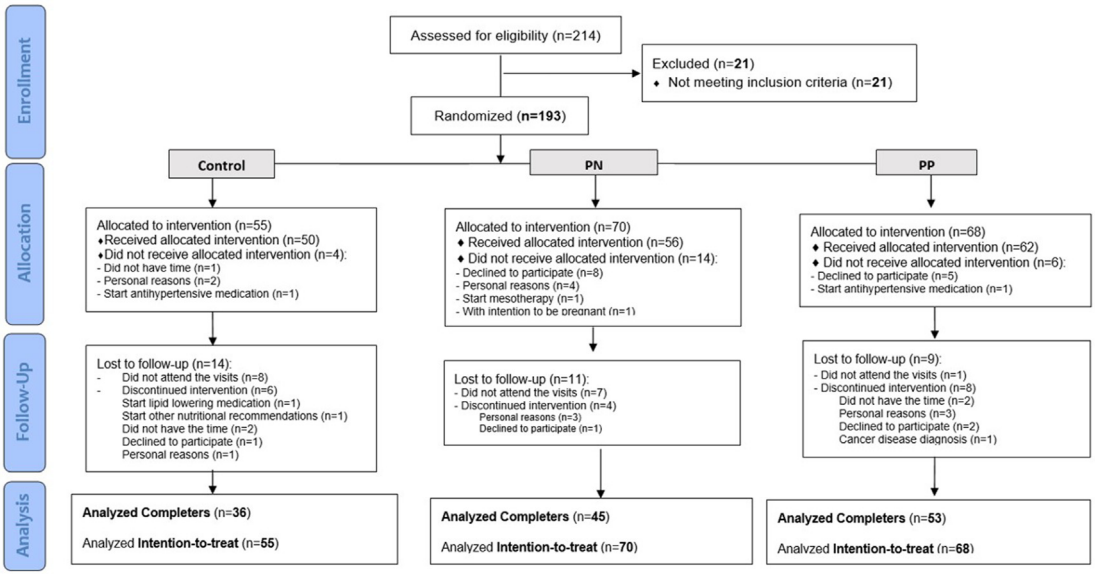

FIGURE 1. CONSORT diagram of the intervention.

TABLE 1
Baseline characteristics of the participants according to intervention groups.[1]

Characteristic	Overall (n = 134)[2]	Control (n = 36)[2]	PN (n = 45)[2]	PP (n = 53)[2]
Sex				
Female	95 (71)	25 (69)	31 (69)	39 (74)
Male	39 (29)	11 (31)	14 (31)	14 (26)
Age (y)	44 (36, 51)	47 (38, 53)	44 (37, 50)	43 (32, 51)
Dietary plan assigned				
Carbohydrate	31 (23)	10 (28)	9 (20)	12 (23)
Inflammation	17 (13)	5 (14)	4 (8.9)	8 (15)
Lipid	38 (28)	13 (36)	15 (33)	10 (19)
Microbiota	16 (12)	3 (8.3)	7 (16)	6 (11)
Oxidative stress	32 (24)	5 (14)	10 (22)	17 (32)
BMI (kg/m^2)	24.3 (21.8, 28.4)	24.3 (22.2, 28.9)	25.1 (21.5, 28.2)	24.2 (21.6, 28.0)
BMI category				
Normal weight	70 (52)	19 (53)	21 (47)	30 (57)
Obese	19 (14)	5 (14)	7 (16)	7 (13)
Overweight	45 (34)	12 (33)	17 (38)	16 (30)
Physical activity[3]				
0	37 (28)	8 (22)	14 (31)	15 (28)
1	33 (25)	11 (31)	8 (18)	14 (26)
2	64 (48)	17 (47)	23 (51)	24 (45)
Body weight (kg)	68 (60, 78)	71 (62, 78)	68 (59, 79)	68 (60, 77)
Waist circumference (cm)	84 (75, 93)	86 (77, 93)	84 (74, 94)	84 (75, 93)
Hip circumference (cm)	103 ± 9	104 ± 10	104 ± 9	103 ± 9
Conicity index	0.80 (0.78, 0.87)	0.81 (0.78, 0.86)	0.80 (0.76, 0.89)	0.82 (0.78, 0.87)
SBP (mm Hg)	113 ± 15	114 ± 17	110 ± 17	115 ± 11
DPB (mm Hg)	70 ± 10	70 ± 13	69 ± 9	70 ± 8
Pulse pressure (beats/min)	68 ± 12	65 ± 10	67 ± 11	70 ± 13
Fat mass %	28 ± 11	28 ± 12	29 ± 10	27 ± 11
MEDAS score				
2	2 (1.5)	1 (2.8)	1 (2.2)	0 (0)
3	1 (0.7)	0 (0)	0 (0)	1 (1.9)
4	6 (4.5)	2 (5.6)	1 (2.2)	3 (5.7)
5	18 (13)	6 (17)	9 (20)	3 (5.7)
6	32 (24)	6 (17)	11 (24)	15 (28)
7	35 (26)	12 (33)	8 (18)	15 (28)
8	40 (30)	9 (25)	15 (33)	16 (30)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[1] Data based on completers.
[2] Values are n (%); median (IQR); or mean ± SD.
[3] According to IPAQ.

Furthermore, the e-commerce tool featured a dedicated section for all groups offering suggestions on recommended and non-recommended food intake according to the assigned dietary plan (i.e., control, carbohydrates, lipids, inflammation, microbiota, and oxidative stress) to aid in decision-making. Finally, participants had free access to the whole catalog in order to allow freedom of selection. Participants submitted their completed shopping lists on a weekly basis, encompassing all foods purchased for the week. At weekends, participants reported their consumption of each listed food. Shopping activities were conducted at participants' preferred retailers, with a recommendation to adapt specific products listed in the e-commerce tool to their preferred brands. No compensation or free food was provided to participants. The e-commerce tool did not present commercial options and was not linked to commercial activities, it was designed and used for elaborating the shopping list exclusively.

Randomization and allocation to dietary plans

The list of the randomization sequence was generated by SAS 9.2 (SAS Institute) statistical software PROC PLAN by an independent researcher who was not enrolled in the study to guarantee dietitians blinding. Stratified randomization, using blocking (60 participants per block), was conducted to achieve a 1:1:1 ratio for BMI and the 5 CHPs between groups in order to accommodate to technical analytical constrains.

Each participant was classified, first, in the CHPs with the highest score according to the results of urine, plasma, and saliva analyses. Second, each participant was blindly randomly assigned in 1 of the 3 arms of the study: control, PN or PP group.

Clinical data collection

Anthropometric parameters were collected at V0, V1, and V2, while the participants were wearing lightweight clothing and without shoes. Trained nutritionist measured the body weight, and composition of the participants using a body composition analyzer (Tanita SC 330-S; Tanita). Height of participants was obtained by a wall-mounted stadiometer (Tanita Leicester Portable; Tanita). Waist and hip circumference were measured at the umbilicus level and in largest part of the hips, respectively, using a 150-cm anthropometric steel measuring tape. Blood pressure was measured when participants were rested for 2–5 min while seated at V0, V1, and V2. The SBP and DBP were measured twice at 1 min difference using an automatic sphygmomanometer (OMRON HEM-907; Peroxfarma). The mean value of 2 measurements were used for analyses.

TABLE 2
Baseline characteristics according to the classification obtained with the Preventomics algorithm.

Characteristic	Overall ($n = 134$)[1]	Carbohydrate ($n = 31$)[1]	Inflammation ($n = 17$)[1]	Lipid ($n = 38$)[1]	Microbiota ($n = 16$)[1]	Oxidative stress ($n = 32$)[1]	q[2]
Group							0.5
Control	36 (27)	10 (32)	5 (29)	13 (34)	3 (19)	5 (16)	
PN	45 (34)	9 (29)	4 (24)	15 (39)	7 (44)	10 (31)	
PP	53 (40)	12 (39)	8 (47)	10 (26)	6 (38)	17 (53)	
Sex							0.067
Female	95 (71)	21 (68)	12 (71)	26 (68)	16 (100)	20 (63)	
Male	39 (29)	10 (32)	5 (29)	12 (32)	0 (0)	12 (38)	
Age (y)	44 (36, 51)	45 (35, 52)	45 (39, 51)	49 (43, 54)	40 (36, 52)	38 (28, 42)	0.002
BMI (kg/m^2)	24.3 (21.8, 28.4)	28.3 (24.1, 29.6)	22.3 (20.6, 23.8)	25.2 (22.4, 28.1)	25.9 (22.2, 29.6)	22.0 (20.8, 24.8)	<0.001
BMI category							0.008
Normal weight	70 (52)	9 (29)	13 (76)	18 (47)	6 (38)	24 (75)	
Obese	19 (14)	7 (23)	1 (5.9)	6 (16)	4 (25)	1 (3.1)	
Overweight	45 (34)	15 (48)	3 (18)	14 (37)	6 (38)	7 (22)	
Physical activity							0.7
0	37 (28)	12 (39)	4 (24)	11 (29)	4 (25)	6 (19)	
1	33 (25)	9 (29)	5 (29)	8 (21)	4 (25)	7 (22)	
2	64 (48)	10 (32)	8 (47)	19 (50)	8 (50)	19 (59)	
Body weight (kg)	68 (60, 78)	76 (69, 88)	63 (58, 66)	71 (60, 79)	70 (58, 81)	65 (58, 70)	0.001
Waist circumference (cm)	84 (75, 93)	93 (86, 99)	75 (71, 86)	88 (78, 95)	89 (72, 92)	77 (72, 81)	<0.001
Hip circumference (cm)	103 ± 9	108 ± 8	99 ± 7	105 ± 8	106 ± 12	99 ± 8	0.001
Conicity index	0.80 (0.78, 0.87)	0.87 (0.82, 0.91)	0.79 (0.72, 0.86)	0.81 (0.78, 0.87)	0.80 (0.78, 0.83)	0.79 (0.76, 0.82)	0.002
Fat mass %	28 ± 11	35 ± 9	23 ± 9	28 ± 9	32 ± 11	21 ± 11	<0.001
SBP (mm Hg)	113 ± 15	116 ± 14	110 ± 16	118 ± 14	106 ± 16	110 ± 15	0.038
DPB (mm Hg)	70 ± 10	74 ± 10	66 ± 10	72 ± 8	68 ± 9	65 ± 9	0.001
Pulse pressure (beats/min)	68 ± 12	70 ± 9	69 ± 14	67 ± 11	67 ± 11	67 ± 14	0.8
MEDAS score							0.079
2	2 (1.5)	1 (3.2)	0 (0)	1 (2.6)	0 (0)	0 (0)	
3	1 (0.7)	0 (0)	0 (0)	1 (2.6)	0 (0)	0 (0)	
4	6 (4.5)	2 (6.5)	3 (18)	0 (0)	1 (6.3)	0 (0)	
5	18 (13)	4 (13)	3 (18)	8 (21)	3 (19)	0 (0)	
6	32 (24)	7 (23)	2 (12)	7 (18)	5 (31)	11 (34)	
7	35 (26)	11 (35)	4 (24)	11 (29)	3 (19)	6 (19)	
8	40 (30)	6 (19)	5 (29)	10 (26)	4 (25)	15 (47)	

[3]According to IPAQ.
Abbreviation: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[1] Values are n (%); median (IQR); and mean ± SD.
[2] False discovery rate (FDR) adjustment for multiple comparisons of Fisher exact test or Kruskal–Wallis rank sum test.

Lifestyle data collection

Data on diet composition and mean daily energy and nutrients intake were assessed through a 3-d dietary record (2 weekdays and 1 weekend day), at the baseline visit (V1, week 0) and final visit (V2, week 16), and calculated by European food composition tables (CIQUAL) [19]. Dietary patterns were assessed prebaseline and at the end of the study by using a validated self-administered electronic form of the European Prospective Investigation of Cancer-Norfolk Study food frequency questionnaire (FFQ) [20]. In the same visit, nutritionist and participants revised the dietary record to ensure that all necessary information was collected, and in the case of missing food quantities, the nutritionist used a portion book to complete the dietary record. Physical activity was evaluated at the baseline visit (V1, week 0) and final visit (V2, week 16) in all participants by completion of the International Physical Activity Questionnaire [21].

Adherence to Mediterranean diet was measured trough the MEDAS questionnaire, which consists of 2 questions about eating habits, 8 questions about the frequency of consumption of typical foods of the Mediterranean diet, and 4 questions about the consumption of foods not recommended in this diet. Each question is scored with 0 (noncompliant) or 1 (compliant), and the total score (from 14 questions) ranges from 0 to 14, so a score of 14 points means maximum adherence.

Metabolic analyses

Blood samples were taken in overnight fasting conditions at V1 and V2 and resulting serum and plasma stored at −80 °C in Eurecat, Centre Tecnològic de Catalunya, Unitat de Nutrició i Salut, in Reus, Spain, until use for batch analyses. Urine samples were collected in a special container over a 24-h period previous to V1 and V2. The supernatants of centrifuged urine samples were kept at −80 °C until analysis. Targeted proton nuclear magnetic resonance metabolomics and ELISA assays are further explained in **Supplemental Methods**. In brief, ELISA kits were used to analyze concentrations of hormones leptin, insulin, and adiponectin and inflammatory and oxidative stress-related markers [tumor necrosis factor; IL-6; IL-10; C-reactive protein (CRP); soluble cluster of differentiation (sCD) 14; monocyte chemoattractant protein (MCP)-1; soluble intercellular adhesion molecule 1; LPS binding protein; and oxidized LDL] according to the manufacturer's instructions. Urine 8-oxo-2'-deoxyguanosine (8-OH-dG) and isoprostanes were determined with commercially available ELISA kits and results were expressed relative to the amount of creatinine. Plasma

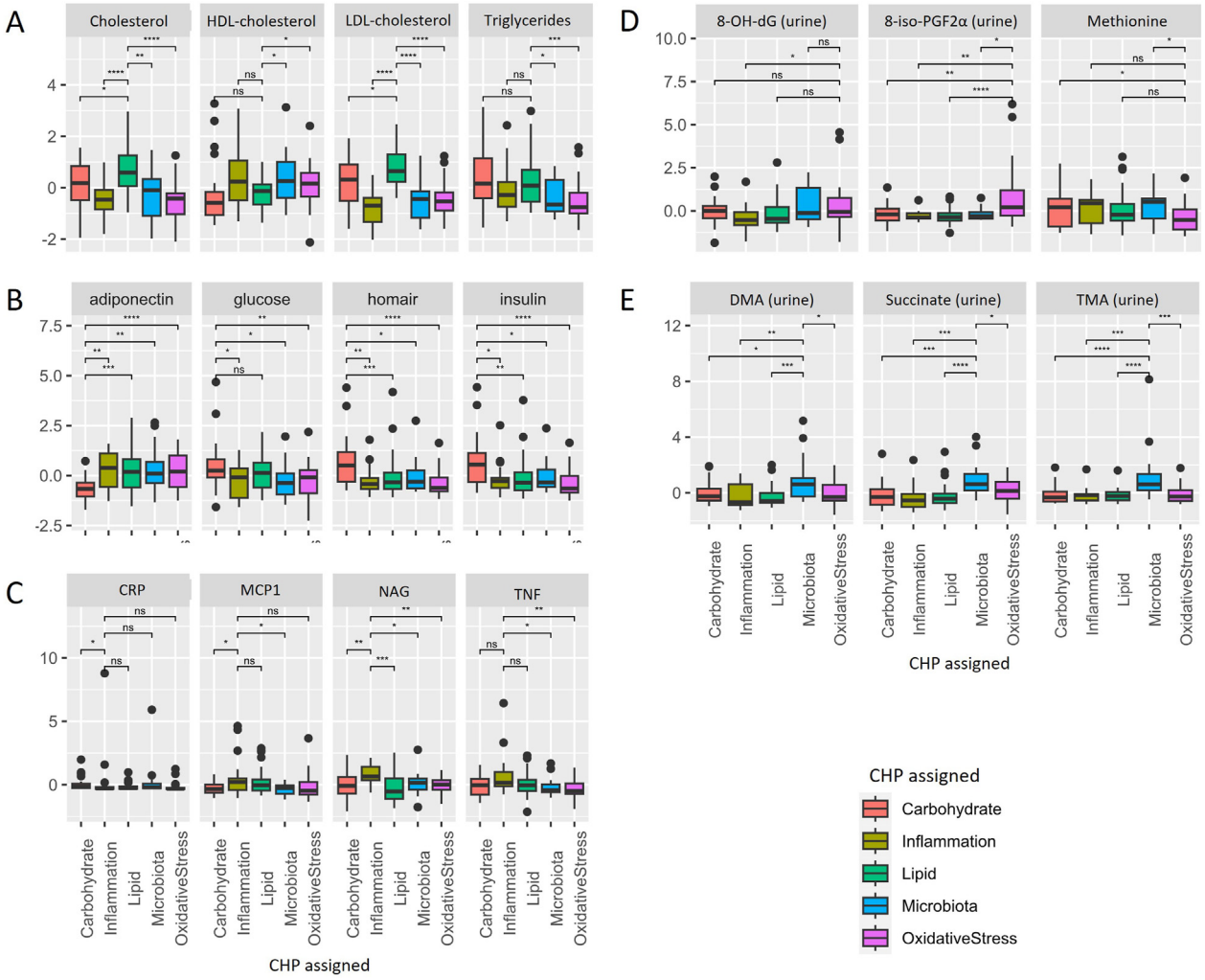

FIGURE 2. Blood and urine concentrations of selected biomarkers in participants grouped according to their most altered CHP. Blood and urine biomarkers were combined to calculate a score for each of the 5 CHP, namely carbohydrate metabolism, lipid metabolism, systemic inflammation, microbiota, and oxidative stress. Participants were assigned to 1 of the 5 CHPs according to the highest score and representative biomarkers are shown for each group of participants. Box and whisker plot of scaled data are presented. (A) Biomarkers of lipid metabolism, (B) biomarkers of carbohydrate metabolism, (C) biomarkers of inflammation, (D) biomarkers of oxidative stress, and (C) biomarkers of microbiota metabolism. Analysis conducted on completers: carbohydrate, $n = 31$; inflammation, $n = 17$; lipid, $n = 38$; microbiota, $n = 16$; oxidative stress, $n = 32$. Differences between groups are indicated as $^{*}P < 0.05$; $^{**}P < 0.01$, $^{***}P < 0.005$, $^{****}P < 0.001$ after Wilcoxon test for nonnormally distributed data and Student *t* test for normally distributed data and FDR adjustment for multiple testing. *P* values are shown only for descriptive purposes and not for hypothesis testing. CHP, core health process; DMA, dimethylamine; CRP, C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; MCP-1, monocyte chemoattractant protein 1; NAG, *N*-acetyl glycosylated protein; TNF, tumor necrosis factor; 8-OH-dG, 8-oxo-2'-deoxyguanosine; 8-iso-PGF2α, 8-iso-prostaglandin F2α; TMA, trimethylamine.

acylcarnitines were quantified in plasma by LC-MS/MS. Serum and urine samples were measured using targeted high throughput ^{1}H nuclear magnetic resonance metabolomics as explained elsewhere [22] for measuring blood hydroxybutyrate, choline, DHA, glutamine, glutamate, glycine, isoleucine, leucine, linoleic acid, methionine, monounsaturated fatty acids, *N*-acetyl-glycosilated proteins, oleic acid, phenylalanine, PUFAs, SFAs, tyrosine and valine; and urine acetate, allantoin, betaine, dimethylamine (DMA), dimethylglycine, pseudouridine, succinate, trimethylamine (TMA). Detailed description of the methodology is provided in **Supplemental Methods**.

Subject metabotyping

The rationale, principles, and detailed algorithms followed for subject characterization in the 5 CHPs have been discussed previously [16]. In brief, for phenotyping, each CHP was quantified as the sum of *z*-scores of the biomarkers within the CHP corrected by a weight for each biomarker. Weights were introduced in order to consider the relevance of each biomarker in their respective CHP. To define weight values, the 49 biomarkers used in the algorithms were analyzed in 329 samples representative of Spanish and Danish population from previous studies [23–26]. With these data, the following steps were applied: *1*) 1 or more reference biomarkers were defined for each CHP. Thus, glucose and HOMA-IR as gold standards and branched chain amino acids as predictive biomarkers were considered; LDL cholesterol and triglycerides were selected for lipids; isoprostanes and 8-OH-dG for oxidative stress; CRP, *N*-acetylated proteins and MCP-1 for inflammation in order to consider different components of the inflammatory process, such as the clinical gold standard, a composite biomarker and an adipose tissue-derived inflammatory signal, respectively; and TMA for microbiota; *2*) partial least squared regressions were applied using the reference biomarkers as predicted variables and the rest of biomarkers as predictors; *3*)

TABLE 3
Changes in food dietary habits in control and personalized nutrition groups.

Characteristic	Group[1]	Basal[2]	After 21 wk[2]	Difference[3]	P_{Time}[4]	q_{Time}[5]	P_{Group}[6]	q_{Group}[7]	P_{GxT}[8]	q_{GxT}[9]
MEDAS score	Control	7.00 (5.75, 7.25)	10.00 (9.00, 10.25)	3 (2.2, 3.8)	<0.001	<0.001	0.9	>0.9	0.7	0.9
	PN	7.00 (6.00, 8.00)	9.00 (8.00, 10.00)	2.7 (2.0,3.3)						
	PP	7.00 (6.00, 8.00)	10.00 (8.00, 11.00)	2.8 (2.1,3.4)						
Cereals (FFQ)										
Wholegrain cereals (g/d)	Control	74 (24, 121)	93 (53, 123)	21 (−18, 59)	0.1	0.4	0.8	0.9	0.5	0.7
	PN	69 (14, 114)	98 (52, 187)	61 (17, 105)*						
	PP	75 (31, 105)	92 (66, 161)	39 (0.76, 77)						
Refined cereal products (g/d)	Control	62 (35, 101)	40 (10, 83)	−30 (−61, 1.9)	0.002	0.028	0.6	0.9	0.9	0.9
	PN	69 (30, 124)	33 (19, 68)	−39 (−70, −7.8)*						
	PP	60 (26, 111)	27 (13, 62)	−38 (−62, −14)*						
Vegetables										
Root vegetables (g/d)	Control	43 (18, 60)	45 (26, 104)	19 (−4.3, 42)	0.048	0.2	0.5	0.9	0.5	0.79
	PN	38 (20, 71)	42 (23, 78)	8.8 (−12, 29)						
	PP	43 (23, 78)	46 (34, 84)	5 (−17, 27)						
Other vegetables, fresh, frozen[10] (g/d)	Control	194 (133, 217)	226 (165, 303)	71 (14, 127)*	0.002	0.025	0.2	0.8	0.7	0.9
	PN	211 (157, 293)	252 (184, 367)	65 (4.9, 124)*						
	PP	193 (133, 247)	296 (212, 376)	85 (41, 130)*						
Berries (g/d	Control	64 (26, 73)	18 (5, 32)	−53 (−90, −16)*	<0.001	0.001	0.023	0.4	0.075	0.5
	PN	64 (17, 107)	14 (8, 35)	−48 (−76, −20)						
	PP	24 (10, 71)	24 (7, 39)	−19 (−35, −3.0)*						
Oleaginous fruits (g/d)	Control	10 (4, 19)	14 (5, 35)	6.9 (−1.8, 16)	0.03	0.2	0.4	0.8	0.5	0.83
	PN	12 (5, 34)	12 (7, 34)	0.99 (−7.1, 9.1)						
	PP	13 (9, 34)	18 (9, 36)	6.1 (−1.7, 14)						
Nuts and seeds (g/d)	Control	21 (14, 41)	25 (11, 33)	−5.4 (−19, 8.5)	0.3	0.6	0.3	0.8	0.036	0.5
	PN	15 (6, 32)	23 (15, 35)	10 (−4.0, 24)	$P = 0.011$, $\beta = 16.44$ (3.8, 29.0)					
	PP	17 (8, 32)	23 (17, 30)	2.9 (−6.7, 12)	$P = 0.2$, $\beta = 8.43$ (−3.7, 20.6)					
Meats (FFQ)										
Red meat (g/d)	Control	29 (10, 73)	18 (8, 39)	−19 (−36, −2.1)*	0.02	0.1	0.8	0.9	0.8	0.9
	PN	28 (16, 66)	18 (8, 30)	−17 (−31, −2.9)*						
	PP	28 (18, 64)	18 (8, 31)	−16 (−30, −1.3)*						
Processed meat (g/d)	Control	20 (10, 36)	15 (10, 28)	−6.2 (−15, 2.1)	0.15	0.36	0.3	0.8	0.009	0.24
	PN	21 (13, 34)	19 (10, 25)	−7.7 (−16, 0.72)	$P = 0.4$, $\beta = -0.18$ (−0.59, 0.22)[11]					
	PP	30 (15, 41)	14 (3, 27)	−15 (−22, −7.7)	$P = 0.004$, $\beta = -0.57$ (−0.97, −0.18)[11]					
Dairy (FFQ)										
Fresh cheese (g/d)	Control	3 (0, 7)	3 (0, 7)	−0.99 (−6.1, 4.2)	0.09	0.3	0.8	0.9	<0.001	0.023
	PN	3 (0, 7)	7 (3, 21)	6.2 (0.99, 11)*	$P < 0.001$, $\beta = -0.89$ (0.42, 1.6)[11]					
	PP	3 (0, 7)	3 (3, 21)	3.6 (0.22, 6.9)	$P = 0.003$, $\beta = -0.68$ (0.23, 1.13)[11]					
Other (FFQ)										
Meat and dairy imitates (plant based) (g/d)	Control	0 (0, 13)	0 (0, 27)	12 (−15, 40)	0.03	0.2	0.3	0.9	0.2	0.55
	PN	0 (0, 17)	0 (0, 17)	2.6 (−5.3, 10)						
	PP	5 (0, 11)	0 (0, 20)	4.4 (−21, 30)						
Tea, infusions (g/d)	Control	25 (7, 61)	21 (3, 51)	−14 (−40, 12)	0.04	0.2	0.6	0.9	0.2	0.7
	PN	44 (7, 96)	30 (3, 95)	−3.5 (−33, 26)						
	PP	31 (0, 57)	21 (1, 56)	−2.5 (−24, 19)						
Other oils and fats[12] (g/d)	Control	0.80 (0.00, 1.71)	0.80 (0.00, 1.20)	−0.77 (−4.0, 2.5)	0.02	0.2	0.4	0.9	0.2	0.6
	PN	0.8 (0.0, 5.1)	0.8 (0.0, 2.0)	−0.45 (−1.8, 0.94)						

(*continued on next page*)

TABLE 3 (*continued*)

Characteristic	Group[1]	Basal[2]	After 21 wk[2]	Difference[3]	P_{Time}[4]	q_{Time}[5]	P_{Group}[6]	q_{Group}[7]	P_{GxT}[8]	q_{GxT}[9]
	PP	0.80 (0.00, 1.71)	0.00 (0.00, 0.80)	−0.59 (−1.5, 0.31)*						
Sauces, dressings, and condiments (g/d)	Control	13 (7, 26)	6 (4, 14)	−9.3 (−16, −2.7)*	<0.001	0.001	0.6	0.9	0.6	0.9
	PN	16 (10, 31)	6 (3, 13)	−12 (−18, −6.9)*						
	PP	14 (10, 20)	7 (4, 9)	−9.8 (−16, −4.0)*						
Sweets and desserts (g/d)	Control	37 (20, 89)	33 (12, 55)	−32 (−62, −1.4)*	0.002	0.02	0.4	0.8	0.6	0.9
	PN	42 (24, 63)	31 (16, 46)	−16 (−35, 3.7)						
	PP	40 (13, 78)	22 (5, 53)	−21 (−41, −1.9)*						
Macronutrients (3DR)										
Energy (kJ/d)	Control	8223 (7008, 9783)	8222 (7208, 9591)	−224 (−1478, 1031)	0.4	0.9	0.085	0.4	0.6	>0.9
	PN	9412 (8009, 10720)	8844 (,436, 10148)	−700 (−1653, 254)						
	PP	8745 (7412, 10059)	8262 (6889, 9161)	−378 (−1161, 405)						
Protein (g/d)	Control	82 (69, 95)	86 (71, 94)	0.33 (−9.9, 11)	>0.9	>0.9	0.5	0.7	>0.9	>0.9
	PN	90 (80, 99)	88 (74, 107)	−1.7 (−10, 7.0)						
	PP	81 (71, 98)	81 (70, 95)	−2.1 (−11, 6.7)						
Carbohydrates (g/d)	Control	200 (165, 230)	199 (159, 237)	−5.5 (−35, 24)	0.5	0.9	0.2	0.5	0.4	>0.9
	PN	209 (174, 241)	202 (174, 228)	−22 (−46, 1.1)*						
	PP	194 (157, 239)	179 (151, 226)	−11 (−34, 12)						
Fats (g/d)	Control	83 (72, 118)	84 (74, 99)	−2.7 (−20, 15)	0.5	0.9	0.4	0.7	>0.9	>0.9
	PN	103 (87, 124)	97 (82, 114)	−5.2 (−18, 7.5)						
	PP	100 (75, 120)	92 (73, 111)	−4.4 (−15, 6.2)						
Sugar (g/d)	Control	74 (62, 87)	77 (66, 94)	1.4 (−13, 15)	0.8	0.9	0.003	0.07	0.014	0.19
	PN	90 (65, 106)	82 (61, 95)	−13 (−26, 0.76)*	$P = 0.021$, $\beta = -14.6$ (−26.9, −2.27)					
	PP	71 (57, 86)	74 (62, 84)	1.6 (−11, 7.8)	$P > 0.9$, $\beta = 0.54$ (−11.2, 12.3)					
Fiber (g/d)	Control	23 (20, 29)	24 (18, 31)	0.82 (−3.4, 5.0)	0.5	0.9	0.056	0.3	0.036	0.4
	PN	29 (22, 32)	24 (19, 30)	−3 (−6.9, 0.86)	$P = 0.055$, $\beta = -3.8$ (−7.7, −0.09)					
	PP	22 (18, 28)	22 (17, 29)	1.5 (−2.1, 5.2)	$P = 0.8$, $\beta = -0.6$ (−3.18, −4.3)					
Salt (g/d)	Control	5.18 (3.91, 6.48)	3.97 (3.10, 6.33)	−0.49 (−1.6, 0.63)	0.2	0.9	0.5	0.9	0.4	0.9
	PN	5.75 (4.35, 7.41)	5.65 (4.36, 7.41)	0.21 (−0.88, 1.3)						
	PP	4.91 (3.93, 6.45)	4.69 (3.86, 6.11)	−0.33 (−1.1, 0.46)						

Variables reporting significant changes in time or time per group interactions are shown.

Abbreviations: 3DR, 3-day report; FFQ, food frequency questionnaire; MEDAS, Mediterranean Diet adherence screener; PN, personalized nutrition; PP, personalized plan.

[1] Data based in completers ($n_{Control} = 36$, n_P $n = 45$, $n_{PP} = 53$).

[2] Median (IQR) or mean ± SD.

[3] Difference between basal and final values (95% CI).

[4] *P* values of factor time after mixed linear model analyses.

[5] *q* values for factor time resulting from Benjamini–Hochberg correction of *P* values.

[6] *P* values of factor group after ANOVA assessment of fixed effects of the mixed linear models.

[7] *q* values for overall factor group resulting from Benjamini–Hochberg correction of *P* values.

[8] *P* values of the interaction between factors group and time for the ANOVA of fixed effects of the mixed linear models. For a value of $P < 0.05$, the *P* values, coefficients, and corresponding CIs are provided for the interaction between factors group and time for PN and PP groups vs. the control group after mixed linear model analyses.

[9] *q* values for the interaction between factors group and time resulting from Benjamini–Hochberg correction of *P* values

[10] Different from green leafy, root, fermented, and cruciferous.

[11] Coefficients and CIs according to square root transformation of the variable to comply with normal distribution of residuals in mixed linear models assessment.

[12] Different from vegetable oils.

* $q < 0.05$ according to false discovery rate adjustment of *P* values from Wilcoxon signed rank test for paired comparisons between basal and at 21 wk.

TABLE 4
Biometric parameters and vital signs.

Characteristic	Group[1]	Basal[2]	After 21 wk[3]	Difference[3]	P_{Time}[4]	q_{Time}[5]	P_{Group}[6]	q_{Group}[7]	P_{GxT}[8]	q_{GxT}[9]
Weight (kg)	Control	71 (62, 78)	71 (61, 78)	0.21 (−5.2, 5.6)	0.6	0.7	0.9	>0.9	0.022	0.16
	PN	68 (59, 79)	67 (58, 78)	−1.2 (−7.6, 5.1)*	$P = 0.012$, $\beta = -0.009$ (−0.0016, −0.002)[10]					
	PP	68 (60, 77)	69 (60, 77)	−1 (−5.6, 3.5)*	$P = 0.021$, $\beta = -0.008$ (−0.014, −0.0014)[10]					
BMI (kg/m^2)	Control	24.3 (22.2, 28.9)	24.5 (22.3, 28.1)	0.09 (−2.2, 2.0)	0.4	0.4	>0.9	>0.9	0.009	0.08
	PN	25.1 (21.5, 28.2)	24.8 (21.6, 27.2)	−0.45 (−2.2, 1.3)*	$P = 0.005$, $\beta = -0.01$ (−0.016, −0.003)[10]					
	PP	24.2 (21.6, 28.0)	24.0 (21.6, 27.6)	−0.37 (−2.0, 1.2)*	$P = 0.011$, $\beta = -0.009$ (−0.015, −0.002)[10]					
Conicity index score	Control	0.81 (0.78, 0.86)	0.83 (0.79, 0.89)	0.02 (−0.02, 0.06)	0.008	0.02	0.4	0.9	0.4	0.6
	PN	0.80 (0.76, 0.89)	0.82 (0.77, 0.88)	0.01 (−0.02, 0.04)						
	PP	0.82 (0.78, 0.87)	0.81 (0.78, 0.90)	0.01 (−0.02, 0.04)						
Fat mass (%)	Control	29 (20, 39)	24 (16, 34)	−4.1 (−9.7, 1.4)*	0.018	0.03	0.4	0.9	0.3	0.6
	PN	28 (24, 35)	26 (22, 33)	−1.9 (−5.7, 2.0)						
	PP	26 (19, 36)	27 (19, 33)	−1.1 (−5.3, 3.1)						
SBP (mm Hg)	Control	114 (97, 127)	119 (108, 126)	4.1 (−3.5, 12)*	0.02	0.03	0.05	0.5	0.026	0.08
	PN	109 (99, 122)	113 (107, 120)	5 (−1.4, 11)*	$P = 0.6$, $\beta = 0.005$ (−0.013, −0.024)[10]					
	PP	114 (107, 122)	114 (103, 125)	0.17 (−4.7, 5.0)	$P = 0.065$, $\beta = -0.017$ (−0.035, 0.001)[10]					
DBP (mm Hg)	Control	69 (59, 79)	72 (65, 80)	3.3 (−2.7, 9.2)	0.006	0.023	0.4	0.9	0.2	0.4
	PN	66 (62, 75)	70 (64, 74)	1.2 (−2.4, 4.7)						
	PP	71 (66, 74)	72 (64, 78)	0.7 (−2.7, 4.1)						

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; PN personalized nutrition; PP, personalized plan; SBP, systolic blood pressure.

[1] Data based in completers ($n_{Control} = 36$, n_P $n = 45$, $n_{PP} = 53$).

[2] Median (IQR) or mean ± SD.

[3] Difference between 21 wk and basal values (95% CI).

[4] P values of factor time after mixed linear model analyses.

[5] q values for factor time resulting from Benjamini–Hochberg correction of P values.

[6] P values of factor group for the ANOVA of fixed effects of the mixed linear models.

[7] q values for factor group resulting from Benjamini–Hochberg correction of P values.

[8] P values of the interaction between factors group and time for the ANOVA of fixed effects of the mixed linear models. For a value of $P < 0.05$, the P values, coefficients, and corresponding CIs are provided for the interaction between factors group and time for PN and PP groups vs. the control group after mixed linear model analyses.

[9] q value for the interaction between factors group and time resulting from Benjamini–Hochberg correction of p values.

[10] Coefficients and CIs according to logarithmic transformation of the variable to comply with normal distribution of residuals in linear mixed models assessment.

* $q < 0.05$ according to false discovery rate adjustment of P values from Wilcoxon signed rank test for paired comparisons between basal and at 21 wk.

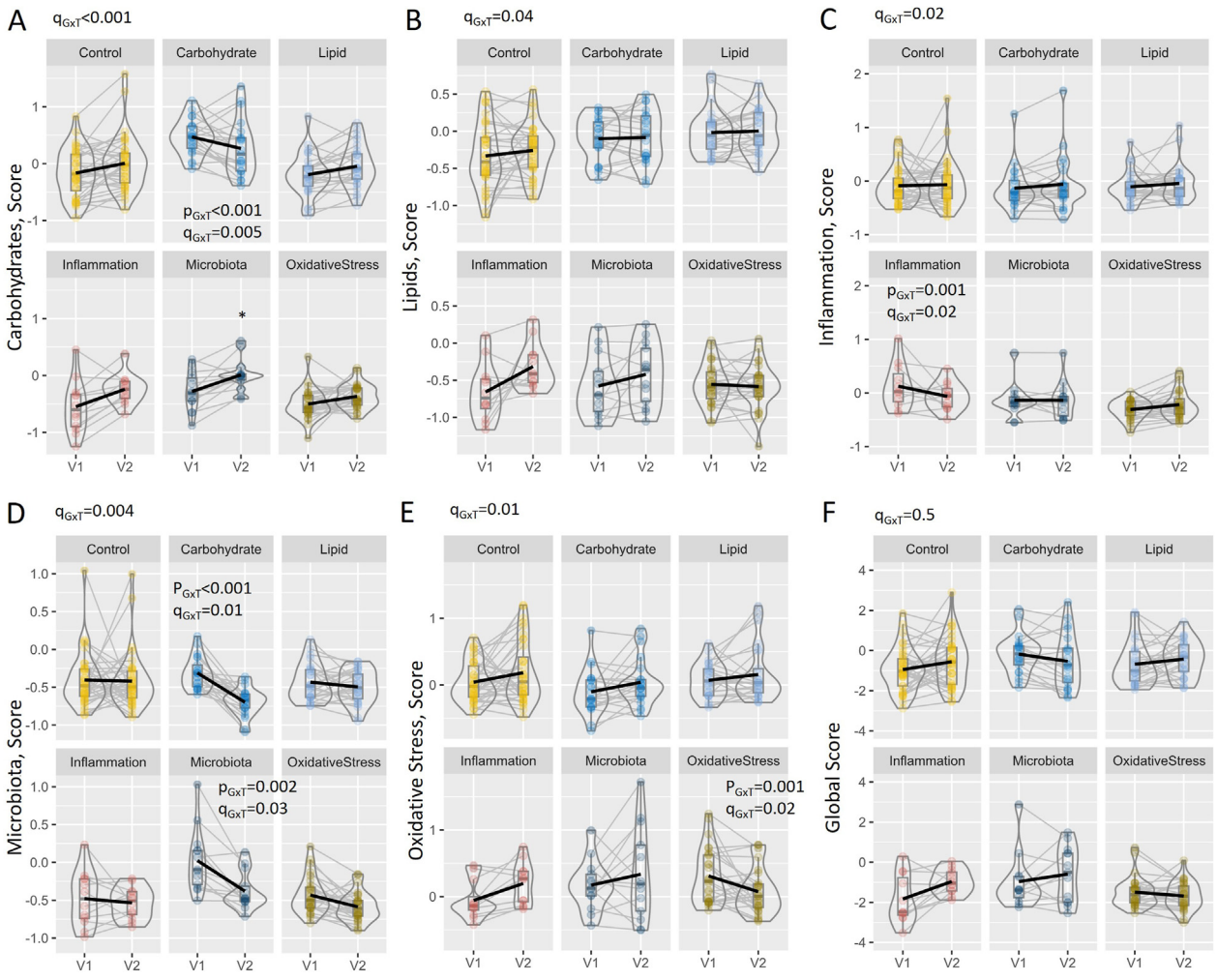

FIGURE 3. Specific dietary plans effectively target their respective CHP. Violin plots with boxplots showing median and IQR with scattered participants, showing trajectories from basal conditions (V1) to the end point of the intervention after 21 wk (V2) for the 6 different dietary interventions (control group and interventions targeting carbohydrate metabolism, lipid metabolism, inflammation, oxidative stress and microbiota) of scores for the carbohydrate CHP (A); lipids CHP (B); inflammation CHP (C); microbiota CHP (D); oxidative stress CHP (E), and global score (F). The bold line represents the mean trajectory. The *q* value for the interaction between factor time and dietary plan according to linear mixed model analysis is reported for each CHP. The *P* value and corresponding *q* value for the interaction between factors time and dietary group resulting from the comparison of each dietary plan with the control group by means of linear mixed models is reported when lower than 0.05. *$q < 0.05$ after adjustment for multiple comparisons by the Benjamini–Hochberg method of *P* values of intragroup assessment by Wilcoxon signed rank test. Analysis conducted on completers: control, $n = 36$; carbohydrate, $n = 31$; inflammation, $n = 17$; lipid, $n = 38$; microbiota, $n = 16$; oxidative stress, $n = 32$. CHP, core health process.

biomarker variable importance in the projection score was calculated for each biomarker in the different PLS models; and *4*) variable importance in the projection scores were used to rank predictor biomarkers according to their relevance when predicting the values of the reference biomarkers and for assigning the weights to each biomarker as explained previously [16].

Genetic analysis

Saliva samples, or alternatively blood samples, were used to assess the volunteer's genetic background (by ALIMENTOMICA, Palma, Spain). Saliva samples were collected by volunteers themselves at home following a standardized procedure. Specifically, the participants were requested to not eat, drink, smoke, and/or chew gum in the 30 min before sample collection. Then, ~2 mL of saliva was taken by means of the Collection and Stabilization Kit consisting of a saliva collection tube, a mini transfer pipette, and a saliva preservation solution (DANASALIVA Sample Collection Kit; Danagen-Bioted). In specific cases where it was not possible to genotype from saliva samples, DNA was isolated from blood. Isolation of genomic DNA, from saliva or blood samples, was performed using a commercial kit (High Pure PCR template Preparation Kit; Roche) following the manufacturer guidelines. A panel of 180 genetic variants [single nucleotide polymorphisms (SNPs)] was determined using a Custom OpenArray for genotyping analysis (ThermoFisher Scientific).

Participants genotyping

The selection of genetic variants was carried out under specific search criteria—in order of relevance: *1*) SNPs associated with each metabolic or proteomic biomarker (MPB) were selected for their relationship with the biomarker in published evidence from genome-wide association studies (GWAS), or in case of absence of GWAS evidence, the search for genetic variants associated with specific biomarker was extended to meta-analysis studies. *2*) Most of the literature searches were performed in PubMed up to 30 December

2019. *3*) The definitive list of SNPs selected for each MPB and its relationship with each CHP has been published before [27]. In order to obtain a genetic score for each participant, the potential impact/influence of each SNP on the MPB of interest was characterized mainly from association human studies using regression coefficients (β) as units of variation of the mean or units of SD, the effect size (in case of meta-analysis or meta-analysis of GWAS) or the percentage variability explained by the risk allele. Individual genetic data of 503 subjects from European populations were extracted from the 1000genomes database [28] and used as reference to normalize the variability explained by genetics. Three genetic risk ranges (low, medium, and high risk) were established. Thus, to establish the individual's risk range, the mean and the SD of the variability explained by genetics on each MPB from 1000genomes data set were used, based on the following criteria: Participants with genetic values above the European theoretical (mean + SD) were included in the high-risk range; participants with values (mean − SD) were classified in the low-risk range; and individuals with intermediate genetic value were classified in the medium range. In the specific case of the inflammation CHPs, because it did not follow a normal distribution according to data from European populations, individuals with values above the SD were classified in the high-risk range. Finally, the SD values of the variability explained by genetics (lipid CHP: 0.124; carbohydrate CHP: 0.153; oxidative stress CHP: 0.137; and inflammation CHP: 0.18.8) were applied to all those individuals classified as "high genetic risk" in the corresponding CHP and were used to refine the corresponding CHP scoring result.

Physiologic characterization and participant allocation to dietary plans

Both metabotypic and genotypic scores were combined, as described previously [16] to obtain a score for the 5 CHPs. It was assumed arbitrarily that the personalized dietary plan assigned to participants would target their most deviated CHP. Because scores were designed to positively increase or decrease with deleterious or beneficial physiologic status, respectively, participants were allocated to a specific dietary plan according to their highest score. Global scores were calculated as the sum of the 5 CHP scores for each participant in order to provide a measure of global status.

Behavioral change program

Behavioral change was assessed through a behavioral change questionnaire designed by ONMI, which collected data on mental wellbeing levels, cognitive health, social inclusion, and behaviors as explained previously [17]. The behavioral change program was integrated into the e-commerce tool proposing a series of personalized, goal-oriented achievable actions to the participant based on the translation of data from the ONMI questionnaire into selection algorithms. The program consisted in weekly personalized messages delivered as push notifications in the notifications area of the ALDI microsite.

Sample size calculation

The sample size was estimated using the Gpower 3.1 software, considering adherence to Mediterranean diet as the main variable and to detect significant differences of 1 point in changes on MEDAS score between PN and PP groups and control group. The total number of individuals, considering basal levels of MEDAS score of 8.1 with a SD of 1.8 [29], a power of 80%, and a confidence level of 95%, and carrying out a student *t* test, was of 52 individuals per group. It was assumed that 15% of volunteers would not complete the study, so that the total number of individuals that were recruited to perform the study were 180 (60 individuals per group). A MEDAS score between 7 and 8 was considered a moderate adherence to Mediterranean diet, whereas a score of 9 or greater was considered a high adherence to Mediterranean diet [18].

Statistical analysis

Data analysis was performed using R and Rstudio [30,31]. The package gtsummary was used to generate summary tables [32]. Differences between groups in basal levels of variables were analyzed by Pearson χ^2 test for categorical variables and Kruskal–Wallis rank sum test for continuous variables. Intragroup differences between visits were analyzed by Wilcoxon signed rank test. Differences between groups in the primary outcome (MEDAS) and all other outcomes (biometric and vital signs, blood and urine markers, and dietary habits) were evaluated by linear mixed models (LMM) analysis that included random intercepts for participants, fixed effects for time (2 levels: before compared with after the intervention) and personalization (3 levels with control group as the reference: PN compared with control and PP compared with control), and their interaction, with sex and age as covariates. A secondary LMM analysis was performed in which participants in PN and PP groups were pooled and dietary plans (i.e., inflammation, oxidative stress, carbohydrate metabolism, lipid metabolism, and microbiota), time (2 levels: before compared with after the intervention), and their interaction were used as a fixed effect to assess the effects of each dietary plan compared with the control group, with sex and age as covariates. All LMM analyses were conducted with the nlme package for R [33] as both intent-to-treat analysis considering all randomly assigned participants (Supplemental Tables 9 and 10) and as analysis of completers, which has been included in the main text. All models were verified for normality and homogeneity of variance by visual inspection of histograms and Q–Q plots and plots of residuals against fitted values. Dependent variables with nonnormally distributed residuals were log-transformed or cube root transformed. The models were fitted using restricted maximum likelihood to accommodate data from participants with missing values at random in a single response variable. Adjustment for multiple comparisons were conducted with the Benjamini–Hochberg method in all analysis. Variables with values over 3 times the SD compared with the mean were considered as potential outliers, reinspected, and maintained in the analyses if considered both technically and physiologically feasible.

Results

Baseline characteristics

A total of 214 participants were assessed for eligibility, of whom 21 did not meet eligibility criteria and 193 meeting eligibility criteria were enrolled. Participants were randomly assigned into 3 groups: control group ($n = 55$), PN group ($n = 70$), and PP group ($n = 68$), and distributed as shown in Figure 1. A total of 168 participants provided complete data and samples at V1, whereas 134 participants completed the study, resulting in a total dropout rate of 30%. The baseline characteristics of completers were comparable between the 3 groups (Table 1) as well as baseline characteristics based on randomly assigned participants (intent-to-treat: Supplemental Table 8).

In the baseline, distribution among CHP (Table 2) resulted in statistically significant differences for age, BMI, body weight, waist and hip circumference, conicity index, fat mass and SBP, and DBP. Participants with highest scores for carbohydrates metabolism CHP and

microbiota CHP presented the highest proportion of overweight and obese participants, whereas individuals classified under inflammation and oxidative stress CHP presented the highest proportion of participants with normal weight. In contrast, blood pressure was higher in participants classified into carbohydrates and lipids CHP, whereas those under microbiota CHP presented the lowest values. In terms of blood and urine selected representative biomarkers (Figure 2), participants under the lipids CHP showed increased concentrations of blood total cholesterol and LDL cholesterol compared with individuals in the other CHP, lower concentrations of HDL cholesterol compared with participants in inflammation, microbiota, and oxidative stress CHP; and higher concentrations of triglycerides than participants classified under microbiota and oxidative stress CHP (Figure 2A). Participants with the highest score in carbohydrates CHP presented higher concentrations of glucose, insulin, and HOMA-IR, and lower concentrations of adiponectin than the rest of participants (Figure 2B). Participants under the inflammation CHP were characterized by higher concentrations of *N*-acetyl glycosylated proteins, higher concentrations of tumor necrosis factor than individuals classified under microbiota and oxidative stress CHPs, and higher MCP-1 than participants in the microbiota and carbohydrate CHPs (Figure 2C). Those participants with the highest score in oxidative stress CHP presented higher concentrations of urine isoprostanes than the rest of participants and lower concentrations of methionine than participants under microbiota and carbohydrate CHPs (Figure 2D). Participants with the highest score in the microbiota CHP presented increased DMA, TMA, and succinate than the rest of participants (Figure 2E). No significant differences were found in MEDAS between participants classified in the different CHP, neither in dietary habits assessed through FFQ (Supplemental Table 2).

Effects of personalized interventions compared with the control group

Effect on dietary intake

Table 3 summarizes results of the intervention on FFQ and 3-d registry variables for the 3 groups and *P* values resulting from LMM analysis. The intervention increased the MEDAS score, showing a significant difference in factor time but no differences between PN and control groups in the interaction between factors time and group, suggesting that groups did not differ with respect to change from baseline. According to false discovery rate–adjusted analyses, intake of refined cereals, berries, sauces and dressings, and sweets and desserts reduced in all groups, whereas consumption of other vegetables (including all vegetables that are not cruciferous, green leafy vegetables, or root vegetables) increased. In addition, unadjusted *P* values support trends toward reduction of effects sizes of red meat and other fats and oils together with increased consumption of tea and infusions, meat and dairy imitates, oleaginous fruits, and root vegetables.

Personalized interventions showed additional changes in the unadjusted interaction between factors group and time when both PN and PP were compared with control group as the reference. Thus, PN intervention increased the consumption of raw nuts and seeds and fresh cheese and decreased sugar consumption compared with the control group. Volunteers in PP group decreased consumption of processed meat and berries and increased consumption of fresh cheese when compared with the control group. Nevertheless, all those changes were not maintained when *P* values were adjusted by false discovery rate, suggesting that dietary behavior was not significantly changed by the personalized interventions. No significant differences were detected between PN and PP groups (data not shown). Analogous results were obtained when dietary habits were assessed in all randomly assigned participants (intent-to-treat analysis, Supplemental Table 10).

Effect on anthropometrics and vital signs

According to LMM assessment (Table 4), both PN and PP interventions decreased body weight (1.8% and 1.5%, respectively) and BMI (1.8% and 1.5%, respectively) between visits compared with the control group, although adjustment for multiple comparisons did not result in statistically significant differences. Conicity index increased slightly but significantly, and %fat mass decreased by the intervention in the 3 groups. SBP and DBP increased during the intervention differently depending on the intervention group. Thus, SBP significantly increased in control and PN groups but remained unchanged in the PP group. Nevertheless, differences between PP and control groups did not reach statistical significance. To note, when PN and PP were compared, the interaction between factors visit and group reached a statistical significant change that was not maintained after adjusting for multiple comparisons ($P_{GxT} = 0.02$, q_{GxT}=0.09). Analysis by intent-to-treat reported no significant differences between PN and PP groups in SBP or DBP (Supplemental Table 10).

Effect on blood and urine biomarkers

Results for blood and urine biomarkers are summarized in Supplemental Table 3. According to statistics adjusted for multiple comparison the intervention increased the concentrations of total cholesterol in the 3 groups, being numerically higher in the control (7.7%) than in that PN (4.3%) and PP (6.7%) groups. Glutamate, DHA, valine, leucine, isoleucine, glutamine, allantoin, methionine, and sCD14 increased and oleic acid, 8-hydroxy-2′-deoxyguanosine, *N*-acetyl-glycoproteins, and adiponectin decreased, as indicated by statistically significant effects in factor time and trends in the 3 groups. Personalized interventions did not show additional effects in blood and urine biomarkers when compared with the control group by means of LMM and further adjusted by multiple comparisons (Supplemental Table 3). Unadjusted *P* values revealed similar trends for dimethylglycine, sCD14, and DMA, suggesting that, overall, both PN and PP interventions had very similar outcomes.

The scores obtained by combining biomarkers and genetic data relevant to the different 5 CHPs are summarized in Supplemental Table 4. No significant differences were found after the results of LMM analyses were adjusted by multiple comparisons. Unadjusted statistics pointed to an increase in carbohydrate score taking place in the 3 intervention groups, which is indicative of generalized unfavorable outcomes. The score calculated with biomarkers of microbiota metabolism decreased by the intervention in the PP group when compared with the control group. This result suggests decreased detrimental circulating metabolites produced by the host microbiota. The PN group showed a similar trend ($P_{GxT} = 0.061$).

Effects of specific dietary plans

In order to assess the effects of the different dietary plans (i.e., targeting carbohydrate metabolism, lipid metabolism, inflammation, oxidative stress, and microbiota), participants in PN and PP groups were considered together and subsequently distributed according to the dietary plan assigned during the intervention, therefore obtaining 6 different dietary plan groups (i.e., control, carbohydrate metabolism,

lipid metabolism, inflammation, oxidative stress, and microbiota). Analyses were conducted comparing participants in each personalized dietary plan with those in the control group.

Effects of dietary plans on dietary intake

Supplemental Table 5 tabulates a summary of FFQ assessment by LMM of participants in the 5 distinct dietary plans and intragroup changes from baseline to final visit. After adjustment for multiple comparisons, significant differences pointed exclusively to increased consumption of fermented vegetables in those participants under personalized intervention targeting microbiota. Unadjusted statistics pointed to increased consumption of nuts and seeds and canned fish in participants under personalized groups targeting carbohydrate metabolism. Participants under dietary plan targeting inflammation decreased green leafy vegetables consumption. Lipid subgroup showed increased consumption of raw nuts and canned fish compared with the control group. Participants in the oxidative stress subgroup decreased consumption of meat and dairy imitates and processed meat compared with the control group.

Effect of dietary plans on anthropometrics and biomarkers

Supplemental Table 6 summarizes the effects of the different dietary plans in anthropometrics, vital signs, and physical activity. Compared with participants in the control group, physical activity decreased in participants under the dietary plan targeting inflammation. Body weight and BMI also showed a significant decrease for those participants under dietary plans targeting oxidative stress. Effects on blood and urine biomarkers are summarized in Supplemental Table 7. Compared with the control group, participants under the dietary plan targeting carbohydrate metabolism presented marginal effects on glutamate. Branched chain amino acids valine, leucine, isoleucine, and aromatic amino acid phenylalanine, which have been described as predictors of insulin resistance [34,35], decreased significantly. Moreover, circulating trimethylamine N-oxide, a microbiota-associated metabolite which share associations with cardiometabolic alterations [36,37], decreased significantly by the intervention when compared with the control group. Finally, as a result of combining the corresponding biomarkers, both carbohydrate and microbiota scores decreased in participants on the dietary plan targeting carbohydrate metabolism when compared with control participants, reaching statistical significance in the interaction between factors time and dietary plan adjusted by multiple comparisons (Figure 3A,D). Moreover, the global score followed a similar trend, although did not reach statistical significance after adjustment by multiple comparisons (Figure 3F). Other scores (i.e., inflammation, lipid, and oxidative stress) paralleled the trends shown by participants in the control group.

In participants under the dietary plan targeting inflammation, biomarkers of inflammation (Supplemental Table 6) showed different trends over time compared with the control group. Thus, glycine showed a trend to increase (q_{DxT}= 0.1) and dimethylglycine decreased. *N*-acetyl glycoproteins, an emerging composite biomarker of inflammation [38,39], presented a clear trend to decrease compared with the control group (q_{DxT} = 0.099), as well as the gold standard CRP, which was reduced a mean value of 250-fold compared with the control group during the intervention but did not reach statistical significance (P_{DxT} = 0.026, q_{DxT} = 0.17). The inflammatory score obtained by aggregation of inflammation biomarkers was reduced over time in participants under the inflammation-targeted dietary plan compared with the control group (Figure 3C). Clinical parameters related with lipid metabolism such as LDL cholesterol increased a 31% in those participants under the dietary plan targeting inflammation, whereas an increase of a 12% was observed in participants of the control group, although differences between both groups did not reach statistical significance. Concentrations of HDL cholesterol showed an inverse pattern, decreasing a nonsignificant 18% in participants on the dietary pattern targeting inflammation, whereas remained unchanged in the control group. Nevertheless, both LDL cholesterol and HDL cholesterol remained within concentrations of normolipidemia after the intervention.

When compared with the control group, the dietary plan targeting lipid metabolism (Supplemental Table 6) tended to increase circulating polyunsaturated fatty acids (P_{DxT} = 0.007), although did not reach statistical significance when the global P_{DxT} was adjusted by multiple comparisons. No differences were detected between the lipid CHP scores and the control group for any dietary plan (Figure 3B).

Compared with the control group (Supplemental Table 6), dietary plan targeting microbiota showed a significant reduction of DMA and tended to decrease dimethylglycine (q_{DxT} = 0.07) and TMA (q_{DxT} = 0.052), precursors of trimethylamine *N*-oxide [36], an emerging risk factor of cardiovascular disease [37], when *P* values were adjusted by multiple comparisons. The combination of the different biomarkers associated to microbiota resulted in a statistically significant decrease of the microbiota CHP score compared with the control group (Figure 3D). Finally, participants under the dietary plan targeting oxidative stress did not show statistically significant changes over time compared with those in the control group in blood or urine biomarkers when adjusted *P* values were considered (Supplemental Table 6). Nevertheless, the contribution of oxidative stress biomarkers into the respective CHP score resulted in a statistically significant decrease (Figure 3E). These results stem from changes in oxidative stress biomarkers such as, among others, the gold standard biomarker urine isoprostanes, which was decreased a 7-fold compared with the control group (*P* = 0.014) or 8-hydroxy-2′-deoxyguanosine, decreased a 1.88-fold compared with the control group.

Discussion

Our results show that personalization of dietary recommendations through an e-commerce-like tool induced beneficial changes in food choices, although results did not reach statistical significance when compared with participants using the same tool under control conditions. Concomitantly, the slight improvements observed in markers of health did not reach statistical significance or clinical relevance. Nevertheless, the phenotyping strategy used in this work resulted in a promising approach to identify a priori those individuals with a higher metabolomic response to specific dietary interventions. Introduction of a behavioral change program on top of the personalization strategy based in physiologic characterization did not result in a significant effect, suggesting that, under the studied conditions, psychological reinforcement do not increase efficacy to dietary plans.

The findings from this study suggest that using ICT tools to aid in decision-making while elaborating a shopping list is an effective strategy for promoting healthy food choices in the general population. These findings are in line with previous studies [40,41]. The clear trends toward beneficial effects in dietary behavior contrast with generalized trends toward worsened cardiometabolic parameters such as increased SBP, LDL cholesterol, or total cholesterol among others. The Mediterranean diet has been widely recognized as a healthy diet associated to reduced incidence of cardiometabolic diseases [42]. Therefore, we ruled out Mediterranean diet as a cause of the observed

effects. Because the intervention was conducted during the COVID pandemic, it is plausible to hypothesize that the effects of lockdowns and restrictions on lifestyle habits such as sedentariness or other factors such as mood, sleep patterns, or psychological distress and stress [43–45] underlie the observed changes. Alternatively, the general changes observed in our study are consistent with the natural seasonal rhythms of cardiometabolic parameters that take place in humans [46–48]. Because the intervention started in late spring and summer and finished in late autumn and winter, this natural variation provides a feasible hypothesis to explain our results. The actual cause for the discrepancies observed between increased adherence to Mediterranean diet and worsened cardiometabolic parameters remains elusive.

Previous studies [4,49,50] reinforce the idea that personalization may represent an added value to general healthy eating guidelines. Nevertheless, other studies assessing whether self-knowledge has an impact on consumer's behavior have shown dissimilar outcomes [51–54]. In this work, trends observed in personalized groups suggest different effects of personalization aligned with the requirements highlighted by the global burden of disease (GBD) study 2017, which found that the most relevant dietary risks for health were a diet low in fruits, vegetables, legumes, whole grains, nuts and seeds, milk, fiber, calcium, seafood omega (ω)-3 fatty acids, and polyunsaturated fat and high in red meat, processed meat, sugar-sweetened beverages, trans fatty acids, and sodium [1]. More research with larger cohorts and longer interventions is still needed to underscore whether the trends observed in our study result in unambiguous significant improvements in dietary habits.

The final goal of PN is to improve consumers' health status [13]. In this study, both PN and PP strategies led to slight, clinically irrelevant changes in health-related parameters such as BMI or blood and urine classical clinical biomarkers such as cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and glucose. Nevertheless, the interpretation of results requires careful consideration, as both the PN and PP groups encompass distinct interventions stemming from diverse dietary recommendations designed to target carbohydrate metabolism, lipid metabolism, inflammation, oxidative stress and microbiota. Within this context, the secondary analysis of these 5 interventions in comparison with the control group revealed some insights that may allow for nuances in the interpretation of results that are exposed below.

We propose a novel metabotyping approach based on combining biomarkers according to their relevance in different overarching processes key for maintaining health [16]. Our approach allows to classify individuals according to shared deviations of carbohydrate metabolism, lipid metabolism, systemic inflammation, oxidative stress, and microbiota-related metabolites with potential effect on individual's metabolism. Moreover, applying specific dietary interventions to these metabotypes showed that our approach may serve as a powerful tool for differentiating a priori those individuals with a highest response to a specific dietary intervention from those who need another nutritional approach [8]. Thus, assessment of the 5 personalized dietary plans compared with the control group revealed changes that were specific to the metabolic pathways targeted by each dietary plan. Interestingly, despite several specific changes resulted statistically unsignificant, the harmonized contribution of different biomarkers as a score allowed to underscore metabolic effects of the interventions that would have remained elusive by studying biomarkers separately. Despite the promising results, further research is still necessary to validate this approach and to quantify the clinical significance of the different scores.

The study has several limitations. The restrictions and social impact of the COVID pandemic resulted in higher than expected dropouts. Nevertheless, a post hoc power calculation revealed that with the actual data the a priori expected changes in MEDAS score would have been detected. The short duration of the study can be considered another limitation because it prevented the assessment of long-term outcomes. Moreover, larger cohorts, offering higher statistical power, may be required to assess the real potential of personalization based in the metabotyping approach exposed in this work. Finally, our study did not include a group of participants with no access to the e-commerce tool, and therefore, conclusions may be considered only under the perspective of digitally driven PN. Another limitation relies on the potential bias associated to the single-blind design, which was inevitable because the digital tool included characteristic elements in each experimental group that were distinguishable by the researcher. Further studies considering wider populations, longer interventions, and including a group with no access to the e-commerce tool would overcome the aforementioned limitations discussed.

In conclusion, our results suggest that PN based in integrating omics and genetics does not improve adherence to Mediterranean diet when compared with general recommendations delivered through an e-commerce–like tool, either with or without a behavioral change program. Nevertheless, positive trends in healthy food choices and improvements in metabolomics and proteomics health-related parameters associated with dietary recommendations targeting specific metabotypes warrant further investigation in larger cohorts to fully comprehend the real potential of this targeted metabotyping approach. This may represent an opportunity for innovative models aiming to optimize the health status of consumers or to optimize consumer experience in current ones. Thus, health professionals might benefit of such tools as part of a holistic approach that puts individuals in the center of a personalization strategy that considers the different dimensions of consumer relation with food.

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Author contributions

The authors' responsibilities were as follows – FS, ACaimari, BG, JMdB: conceptualized the study; MR, JMdB: visualized the study; XE, MR, NT, RMV, APedret, RM, KG, JMdB: were responsible for the methodology; LC, XE, JC, MB, MR, NT, PS, JMA, DS, MGalofré: performed investigation and data curation; RM, KG, MAR, HP, MGuirro, AdP, SG, FS: performed investigation; ACrescenti, RS, NC, APalou: were responsible for the resources; MR, DS, MGalofré;, SG, FS, JMdB: performed formal analysis; ACrescenti, XE, JMA, APalou, BG: administered the project. DS, MGalofré: performed software analysis; JMdB: wrote the original draft; LC, XE, JC, SG, FS: reviewed and edited the manuscript; JMA, JMdB: supervised the study; and all authors: have read and approved the final version.

Conflict of interest

The authors declare no conflict of interests.

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Data availability

Data described in the manuscript, code book, and analytic code will be made available on request pending application and approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2024.04.004.

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