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Microbial Phenolic Metabolites Are Associated with Improved Cognitive Health

*Inés Domínguez-López, Polina Galkina, Isabella Parilli-Moser, Camila Arancibia-Riveros, Miguel Ángel Martínez-González, Jordi Salas-Salvadó, Dolores Corella, Mireia Malcampo, J. Alfredo Martínez, Lucas Tojal-Sierra, Julia Wärnberg, Jesús Vioque, Dora Romaguera, José López-Miranda, Ramon Estruch, Francisco J. Tinahones, José Manuel Santos-Lozano, Lluís Serra-Majem, Aurora Bueno-Cavanillas, Josep A. Tur, María Rubín-García, Xavier Pintó, Fernando Fernández-Aranda, Miguel Delgado-Rodríguez, Ana Barabash-Bustelo, Josep Vidal, Clotilde Vázquez, Lidia Daimiel, Emilio Ros, Estefania Toledo, Alessandro Atzeni, Eva M. Asensio, Natàlia Vera, Antonio Garcia-Rios, Laura Torres-Collado, Napoleón Pérez-Farinós, Marian Zulet, Alice Chaplin, Rosa Casas, Sandra Martín-Peláez, Jessica Vaquero-Luna, Ana Maria Gómez-Pérez, Zenaida Vázquez-Ruiz, Sangeetha Shyam, Carolina Ortega-Azorín, Natàlia Talens, Patricia J. Peña-Orihuela, Alejandro Oncina-Canovas, Javier Diez-Espino, Nancy Babio, Montserrat Fitó, and Rosa M. Lamuela-Raventós**

Scope: Diets rich in polyphenols has been associated with better cognitive performance. The aim of this study is to assess the relationship between microbial phenolic metabolites (MPM) in urine and cognition in the context of an older population at high cardiovascular risk.

Methods and results: A cross-sectional analysis is conducted in 400 individuals of the PREDIMED-Plus study. Liquid chromatography coupled to mass spectrometry is used to identify urinary MPM. Mediterranean diet (MedDiet) adherence is estimated with a 17-item questionnaire and cognitive function is evaluated with a battery of neuropsychological tests. Multivariable-adjusted linear regression models are fitted to assess the relationship of urinary MPM with the MedDiet and cognitive tests. Protocatechuic acid and enterolactone glucuronide are associated with higher adherence to the MedDiet. Regarding cognitive function, protocatechuic acid, vanillic acid glucuronide, 3-hydroxybenzoic acid, enterodiol glucuronide, and enterolactone glucuronide are directly associated with a global composite score of all the cognitive tests. Furthermore, protocatechuic acid and enterolactone glucuronide are associated with higher scores in the Mini-Mental State Examination, whereas enterodiol glucuronide is associated with improved Clock Drawing Test scores.

Conclusions: These results suggest that the MedDiet is linked to MPM associated with better cognitive performance in an older population.

1. Introduction

The increasing prevalence of neurodegenerative diseases among the elderly population means there is a pressing need to develop

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I. Domínguez-López, P. Galkina, I. Parilli-Moser, C. Arancibia-Riveros, R. M. Lamuela-Raventós
Polyphenol Research Group
Department of Nutrition
Food Science and Gastronomy
School of Pharmacy and Food Sciences
Barcelona, Catalunya Spain
E-mail: lamuela@ub.edu

early detection and prevention strategies. While an early diagnosis relies on the health care system, prevention can be addressed individually in multiple ways.[1] Modifiable risk factors include smoking, physical inactivity, sleep disturbances, social isolation, and diet.[2]

Dietary patterns and nutrients have been widely studied in relation to cognitive health.[3] Higher adherence to the Mediterranean diet (MedDiet) is reported to delay cognitive decline and reduce the risk of AD.[4,5] The cognitive benefits of the MedDiet might be related to a high intake of nutrients, micronutrients,

I. Domínguez-López, I. Parilli-Moser, C. Arancibia-Riveros, R. Estruch, R. Casas, R. M. Lamuela-Raventós
Institute of Nutrition and Food Safety (INSA-UB)
University of Barcelona
Santa Coloma de Gramanet 08921, Spain

I. Domínguez-López, I. Parilli-Moser, C. Arancibia-Riveros, M. Á. Martínez-González, J. Salas-Salvadó, D. Corella, J. A. Martínez, L. Tojal-Sierra, J. Wärnberg, D. Romaguera, J. López-Miranda, R. Estruch, F. J. Tinahones, J. M. Santos-Lozano, L. Serra-Majem, J. A. Tur, X. Pintó, F. Fernández-Aranda, C. Vázquez, L. Daimiel, E. Ros, E. Toledo, A. Atzeni, E. M. Asensio, A. Garcia-Rios, N. Pérez-Farinós, M. Zulet, A. Chaplin, R. Casas, J. Vaquero-Luna, Z. Vázquez-Ruiz, S. Shyam, C. Ortega-Azorín, P. J. Peña-Orihuela, J. Diez-Espino, N. Babio, M. Fitó, R. M. Lamuela-Raventós
Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y la Nutrición (CIBEROBN)
Instituto de Salud Carlos III
Madrid, Spain

M. Á. Martínez-González, E. Toledo, Z. Vázquez-Ruiz
Department of Preventive Medicine and Public Health
University of Navarra
IDISNA
Pamplona, Spain

M. Á. Martínez-González, E. Toledo, Z. Vázquez-Ruiz
Department of Nutrition
Harvard T.H. Chan School of Public Health
Boston, MA, USA

J. Salas-Salvadó, A. Atzeni, S. Shyam, N. Babio
Universitat Rovira i Virgili
Departament de Bioquímica i Biotecnologia
Grup de Recerca ANut-DSM
Unitat de Nutrició
Reus, Spain

J. Salas-Salvadó, A. Atzeni, S. Shyam, N. Babio
Institut d'Investigació Sanitària Pere Virgili (IISPV)
Reus, Spain

D. Corella, E. M. Asensio, C. Ortega-Azorín
Department of Preventive Medicine
University of Valencia
Valencia, Spain

M. Malcampo, N. Vera, N. Talens, M. Fitó
Unit of Cardiovascular Risk and Nutrition
Institut Hospital del Mar de Investigaciones Médicas Municipal d'Investigació Médica (IMIM)
Barcelona, Spain

J. A. Martínez, M. Zulet
Department of Nutrition
Food Sciences, and Physiology
Center for Nutrition Research
University of Navarra
Pamplona, Spain

J. A. Martínez, M. Zulet
Precision Nutrition and Cardiovascular Health
IMDEA Food
CEI UAM + CSIC
Madrid, Spain

L. Tojal-Sierra, M. Delgado-Rodríguez, J. Vaquero-Luna
Bioaraba Health Research Institute
Cardiovascular, Respiratory and Metabolic Area
Osakidetza Basque Health Service
Araba University Hospital
University of the Basque Country UPV/EHU
Vitoria-Gasteiz, Spain

J. Wärnberg, N. Pérez-Farinós
EpiPHAAN research group
School of Health Sciences
University of Málaga - Instituto de Investigación Biomédica en Málaga (IBIMA)
Málaga, Spain

J. Vioque, L. Torres-Collado, A. Oncina-Canovas
CIBER de Epidemiología y Salud Pública (CIBERESP)
Instituto de Salud Carlos III (ISCIII)
Madrid, Spain

J. Vioque, L. Torres-Collado, A. Oncina-Canovas
Instituto de Investigación Sanitaria y Biomédica de Alicante
Universidad Miguel Hernández (ISABIAL-UMH)
Alicante, Spain

D. Romaguera, A. Bueno-Cavanillas, A. Chaplin
Health Research Institute of the Balearic Islands (IdISBa)
Palma de Mallorca, Spain

J. López-Miranda, A. Garcia-Rios, P. J. Peña-Orihuela
Department of Internal Medicine
Maimonides Biomedical Research Institute of Cordoba (IMIBIC)
Reina Sofia University Hospital
University of Cordoba
Cordoba, Spain

R. Estruch, R. Casas
Internal Medicine Service
Hospital Clínic
University of Barcelona
Barcelona, Spain

F. J. Tinahones, A. M. Gómez-Pérez
Virgen de la Victoria Hospital
Department of Endocrinology
Instituto de Investigación Biomédica de Málaga (IBIMA)
University of Málaga
Málaga, Spain

J. M. Santos-Lozano
Department of Family Medicine
Research Unit
Distrito Sanitario Atención Primaria Sevilla
Sevilla, Spain

L. Serra-Majem
Research Institute of Biomedical and Health Sciences (IUIBS)
University of Las Palmas de Gran Canaria & Centro Hospitalario Universitario Insular Materno Infantil (CHUIMI)
Canarian Health Service
Las Palmas de Gran Canaria, Spain

A. Bueno-Cavanillas, S. Martín-Peláez
Department of Preventive Medicine and Public Health
University of Granada
Granada, Spain

J. A. Tur
Research Group on Community Nutrition & Oxidative Stress
University of Balearic Islands
Palma de Mallorca, Spain

M. Rubín-García
Group of Investigation in Interactions Gene-Environment and Health (GIIGAS)
Institute of Biomedicine (IBIOMED)
Universidad de León
León, Spain

X. Pintó
Lipids and Vascular Risk Unit

and bioactive compounds involved in neurological mechanisms. This plant-based dietary pattern is characterized by a high consumption of fruits, vegetables, legumes, nuts, whole grains, and olive oil.[6] Some of these foods, such as nuts, are valuable sources of healthy fats, including vegetable omega-3 fatty acids, such as alpha-linolenic acid, which is suggested to play an important role in reducing cognitive decline.[7] Moreover, vegetables, fruits, nuts, and virgin olive oil are rich in polyphenols, which possess neuroprotective antioxidant and anti-inflammatory properties.[8]

A positive relationship between dietary polyphenols and cognition has been found in several observational studies and clinical trials.[9–11] However, these studies have not considered the extensive metabolism that polyphenols undergo before they reach the bloodstream. Most of these metabolic changes occur in the colon and are catalyzed by gut microbiota, as polyphenol absorption in the stomach and small intestine is low.[12] The resulting microbial phenolic compounds (MPM) may exert biological activities different to those of the parental polyphenols, corresponding to their altered chemical characteristics. Evidence suggests that the benefits of polyphenols on the host's health are intricately linked to their interactions with the gut microbiota.[13] The gut microbiota plays a crucial role in metabolizing polyphenols, resulting in the production of a wide array of metabolites that can exert different effects on the body, including the central nervous system.[14] Furthermore, the relationship between polyphenols and the gut microbiota is bidirectional, as dietary polyphenols are prebiotics that can influence the composition of the microbiota.[15,16]

The aim of the present study was to assess the relationship between the MedDiet and urinary phenolic metabolites derived from the gut microbiota, as well as the association between these metabolites and neurocognition in an older population at high cardiovascular risk.

2. Experimental Section

2.1. Study Design

A cross-sectional analysis was conducted using baseline data from the PREDIMED-Plus study, an ongoing multicenter, randomized, parallel-group clinical trial conducted in Spain to assess the effects of an energy-reduced MedDiet combined with physical activity and behavioral support on weight loss and cardiovascular disease morbidity and mortality. Details of the study protocol can be found at http://predimedplus.com.[17,18] A total of 6874 participants were recruited from September 2013 to December 2016 in 23 Spanish centers from universities, hospitals, and research institutes. Eligible participants were men aged 55–75 years and women aged 60–80 years who were overweight or obese (body mass index [BMI] = 27–40 kg m^{-2}) and met at least three of the metabolic syndrome criteria established by the International Diabetes Federation and the American Heart Association and National Heart, Lung, and Blood Institute.[19]

The present sub-study was performed in a random subsample of 400 participants with available urinary MPM and data from cognitive tests. Participants who reported extreme total energy intakes (>3500 or <500 kcal day^{-1} in women or >4000 or <800 kcal day^{-1} in men) were excluded from the analysis,[20] as were those with missing data on covariates (diabetes, hypercholesterolemia, or hypertension).

2.2. Ethics Statement

The study was conducted according to the ethical guidelines of the Declaration of Helsinki and all procedures were approved by

Internal Medicine
Hospital Universitario de Bellvitge
Hospitalet de Llobregat
Barcelona, Spain
F. Fernández-Aranda
Clinical Psychology Unit
University Hospital Bellvitge-IDIBELL and University of Barcelona
Barcelona, Spain
M. Delgado-Rodríguez
Division of Preventive Medicine
Faculty of Medicine
University of Jaén
Jaén, Spain
A. Barabash-Bustelo
Department of Endocrinology and Nutrition
Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC)
Madrid, Spain
J. Vidal
CIBER Diabetes y Enfermedades Metabólicas (CIBERDEM)
Instituto de Salud Carlos III (ISCIII)
Madrid, Spain
J. Vidal
Department of Endocrinology
Institut d' Investigacions Biomédiques August Pi Sunyer (IDIBAPS)
Hospital Clinic
University of Barcelona
Barcelona, Spain
C. Vázquez
Department of Endocrinology and Nutrition
Hospital Fundación Jimenez Díaz
Instituto de Investigaciones Biomédicas IISFJD
University Autonoma
Madrid Spain
L. Daimiel
Nutritional Control of the Epigenome Group
Precision Nutrition and Obesity Program
IMDEA Food
CEI UAM + CSIC
Madrid, Spain
L. Daimiel
Departamento de Ciencias Farmacéuticas y de la Salud
Facultad de Farmacia
Universidad San Pablo-CEU
CEU Universities
Urbanización Montepríncipe
Boadilla del Monte 28660, Spain
E. Ros
Lipid Clinic
Department of Endocrinology and Nutrition
Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS)
Hospital Clínic
Barcelona Spain
J. Diez-Espino
Centro de Salud de Tafalla
Gerencia de Atención Primaria
Servicio Navarro de Salud Osasunbidea
Instituto de Investigación Sanitaria de Navarra (IdiSNA)
Pamplona Spain

the Institutional Review Boards of the participating centers. The clinical trial was registered with the ISRCTN (London, England), number 89898870, on July 24, 2014. Written informed consent was obtained from all participants.

2.3. Covariate Assessment

Data on covariates were collected by trained personnel in interviews using general self-report questionnaires on sociodemographics (sex, age, level of education), lifestyle (smoking habits, physical activity, alcohol consumption), and history of illness and medication use.[18] Leisure time physical activity was estimated using the validated Minnesota-REGICOR Short Physical Activity questionnaire.[21] Dietary intake was assessed using the validated, semi-quantitative 143-item PREDIMED-Plus food frequency questionnaire with the assistance of trained dietitians.[22] Adherence to the MedDiet was determined with a 17-item MEDAS questionnaire, adapted from the validated 14-item PREDIMED questionnaire.[23] Trained staff measured anthropometric variables, namely weight and height. Body mass index (BMI) was calculated as the weight in kilograms divided by height in meters^2.

2.4. Neuropsychological Assessment

Participants completed a battery of cognitive tests at baseline administered by trained personnel. The Mini-Mental State Examination (MMSE) was a commonly used brief cognitive screening test that measured five cognitive domains: serial subtraction, language, memory, orientation, and visuospatial skills; higher scores (maximum of 30) indicate an absence of cognitive decline.[24,25] The Clock Drawing Test (CDT) evaluated visuospatial and visuoconstructive capacity.[26,27]

Other neuropsychological tests used were focused on specific cognitive domains. The Verbal Fluency Test (VFT) assessed verbal ability and executive function and consisted of two parts: semantic and phonological verbal fluency tasks (VFT-a and VFT-p, respectively).[28] The Digit Span Test (DST) of the Wechsler Adult Intelligence Scale-III (WAIS-III) included forward recall (DST-f), which evaluated attention and short-term memory, and backward recall (DST-b), which evaluated working memory.[29,30] The Trail Making Test (TMT) assessed attention and processing speed (part A), and cognitive flexibility (part B).[31] The score was the time taken to complete the task, and therefore lower scores implied better performance.

Z-scores were created from raw scores for each cognitive assessment to standardize the results. The Global Cognitive Function (GCF) was calculated as a composite score that was derived from all eight assessments,[32,33] adding or subtracting each individual test value based on whether a higher score indicates higher or lower cognitive performance, respectively.

2.5. Microbial Phenolic Metabolites

2.5.1. Standards and Reagents

Protocatechuic acid (PCA), enterodiol, urolithin-A, and urolithin-B were obtained from Sigma-Aldrich (St. Louis, MO, USA). The internal standard (+) *cis, trans*-abscisic acid D6 was purchased from Santa Cruz (Santa Cruz Biotechnology, Santa Cruz, CA, USA). Vanillic acid, 3-hydroxybenzoic acid (3-OHBz), enterolactone, and creatinine were purchased from Fluka (St. Louis, MO, USA). Standards were stored in powder form and protected from light. The reagents were obtained from the following commercial suppliers: methanol of LC-MS grade and acetonitrile of HPLC grade from Sigma-Aldrich and formic acid (≥98%) from Panreac Química S.A. (Barcelona, Spain). Ultrapure water (Milli-Q) was generated by a Millipore system (Bedford, MA, USA).

2.5.2. Sample Preparation

Urine samples were collected after an overnight fast, coded, and stored at −80 °C until analysis. MPM were analyzed using a method previously validated by the group with minor modifications.[34] The present study focused only on MPM that were mostly or exclusively produced by the gut microbiota. Briefly, 50 µL urine samples were diluted 1:20 (v:v) with Milli-Q Water and 100 µL of the internal standard was added. Then, 2 µL of formic acid was added to acidify the samples before centrifugating at 15 000 × *g* at 4 °C for 4 min. To eliminate undesired compounds, present in urine and to isolate the MPM, the acidified urines underwent a solid-phase extraction in Water Oasis HLB 96-well plates 30 µm (30 mg) (Water Oasis, Milford, MA, USA). The samples were loaded in an activated plate with methanol and 1.5 M formic acid, and a clean-up step was performed with 1.5 M formic acid and methanol (0.5%). The MPM were eluted with methanol acidified with 1.5 M formic acid, evaporated to dryness with nitrogen gas, and reconstituted with 100 µL formic acid (0.05%). The samples were mixed in the vortex for 20 min and filtered through 0.22 µm polytetrafluoroethylene 96-well plate filters (Millipore, MA, USA).

Urinary concentrations of MPM were corrected by urinary creatinine, measured according to the Jaffé alkaline picrate method adapted for Thermo microtiter 96-well plates, as described by Medina-Remón et al.[35]

2.5.3. HPLC-LTQ Orbitrap ESI Analysis

The high-performance liquid chromatography (HPLC) analysis was performed on an Accela chromatograph (Thermo Scientific, Hemel Hempstead, UK) coupled to a linear ion trap quadrupole-Orbitrap mass spectrometer (LTQ-Orbitrap-MS) (Thermo Scientific, Hemel Hempstead, UK) equipped with an ESI source working in negative mode as described.[34] Chromatographic separation was performed on a Kinetex F5 100A (50 × 4.6 mm × 2.6 µm) from Phenomenex (Torrance, CA, USA). Mobile phases A and B were, respectively, 0.05% formic acid in water and 0.05% formic acid in acetonitrile. The following linear gradient was used: held at 98% A for 1.7 min, decreased to 92% A for 3 min, decreased to 80% A for 1.3 min, decreased to 70% A for 1.3 min, decreased to 50% for 0.1 min, decreased to 0% for 1.3 min, then returned to the initial conditions for 1.7 min and re-equilibrated for 3 min. The flow rate was set at 0.750 µL min^{-1} and the injection volume was 5 µL.

2.5.4. Identification and Quantification of MPM

MPM identification and quantification were performed using Trace Finder software version 4.1 (Thermo Fisher Scientific, San Jose, CA, USA). The glucuronidated and sulfated MPM were quantified with their respective aglycone equivalents due to the unavailability of standards.

As microbial phenolic metabolism showed high inter-individual variability, the MPM were not detected in all the participants. For the sake of simplicity and to facilitate comprehension, only metabolites with <20% of missing values were included in the statistical analysis. Thus, a total of seven MPM were considered: PCA, vanillic acid glucuronide (VAG), vanillic acid sulfate (VAS), 3-OHBz, enterodiol glucuronide (EDG), enterolactone glucuronide (ELG), and urolithin B glucuronide (UBG). Missing values of the previously listed metabolites with less than 20% of missing values were replaced by the half of the minimum detectable value.

2.6. Statistical Analyses

Statistical analyses were performed using the PREDIMED-Plus database updated to July 2021. Baseline characteristics were described as means ± standard deviation (SD) for quantitative variables and as *n* (percentages) for qualitative variables. The study used natural logarithmic transformations to approximate a normal distribution of MPM concentrations.

Multivariable adjusted linear regression models were fitted to assess the relationship between MPM and MedDiet adherence and the neuropsychological tests adjusted by confounders. Two adjustment models of increasing complexity were used; Model 1 was minimally adjusted for age (years) and sex (men/women); Model 2 was further adjusted for smoking habits (never, former, or current), educational level (medium-high or low), BMI (obesity/overweight), physical activity (METS min week^{-1}), total energy intake (kcal day^{-1}), hypertension (yes/no), diabetes mellitus (yes/no), dyslipidemia (yes/no), and treatment with cholesterol-lowering and anticholinergic drugs (yes/no). All analyses were conducted with robust estimates of the variance to correct for intracluster correlation.

Statistical analyses were performed using Stata 16.0 (StataCorp. LP, TX, USA) and statistical significance was set at $p < 0.05$.

3. Results

3.1. General Characteristics of Participants

The main characteristics of the 400 PREDIMED-Plus participants are summarized in **Table 1**. There were slightly more men than women, and the average age was 65 years. By study design, all participants had cardiovascular risk factors: nearly one out of four had type-2 diabetes, one-third had hypercholesterolemia, most had hypertension, and only a minority were current smokers. Actual urinary metabolite concentrations are depicted in Table S1, Supporting Information. A heat map of Spearman correlation coefficients of the urinary metabolites analyzed in the present study is presented in Figure S1, Supporting Information.

Table 1. General characteristics of the participants ($n = 400$).

Age [years]	65.3 ± 4.9
Women, *n* [%]	169 (42.5)
BMI [kg m^{-2}]	32.6 ± 3.3
Type-2 diabetes, *n* [%]	111 (27.75)
Hypertension, *n* [%]	350 (87.5)
Hypercholesterolemia, *n* [%]	275 (68.75)
Medium-high educational level, *n* [%]	222 (55.5)
Current smokers, *n* [%]	43 (10.8)
Physical activity [MET min week^{-1}]	2825.3 ± 2612.4
Total energy intake [kcal day^{-1}]	2384.5 ± 534.4
MedDiet adherence [score]	8 ± 3

Continuous variables are shown as means ± SDs, and categorical variables are shown as *n* (%). BMI, body mass index; MedDiet, Mediterranean diet; MET, metabolic equivalent of task.

3.2. Microbial Phenolic Metabolites and the Mediterranean Diet

The association between individual MPM and MedDiet adherence is described in **Figure 1**. PCA and ELG were found to be significantly associated with higher adherence to the MedDiet ($\beta = 0.14$, 95% CI: 0.01, 0.27 per 1-SD, p-value = 0.038 and $\beta = 0.12$, 95% CI: 0.02, 0.22 per 1-SD, p-value = 0.022, respectively). Results with all adjustment models can be found in Table S2, Supporting Information.

3.3. Association between Microbial Phenolic Metabolites and Cognitive Composite

Table 2 depicts the associations between individual MPM and global cognitive function (GCF). PCA and enterolactone glucuronide showed significant associations with the score ($\beta = 0.04$, 95% CI: 0.02, 0.07 per 1-SD, p-value = 0.002) and ($\beta = 0.02$, 95% CI: 0.01, 0.04 per 1-SD, p-value = 0.010), respectively. Other MPM were also positively associated with the GCF, such as VAG ($\beta = 0.06$, 95% CI: 0.01, 0.12 per 1-SD, p-value = 0.025), 3-OHBz ($\beta = 0.03$, 95% CI: 0.01, 0.06 per 1-SD, p-value = 0.017), or EDG ($\beta = 0.01$, 95% CI: <0.01, 0.02 per 1-SD, p-value = 0.039). VAS and UBG showed no association with the score.

3.4. Microbial Phenolic Metabolites and Neuropsychological Tests

The associations between individual MPM and the scores of MMSE and CDT cognitive tests are shown in **Table 3**. PCA was positively associated with the MMSE score in the fully adjusted model ($\beta = 0.06$, 95% CI: 0.03, 0.13 per 1-SD, p-value = 0.005), as was ELG ($\beta = 0.04$, 95% CI: 0.01, 0.06 per 1-SD, p-value = 0.011). A positive association was also observed between EDG and the CDT score ($\beta = 0.02$, 95% CI: <0.01, 0.04 per 1-SD, p-value = 0.047). No other significant associations were found between other metabolites and these cognitive tests. Results on specific cognitive tests can be found in Table S3, Supporting Information.

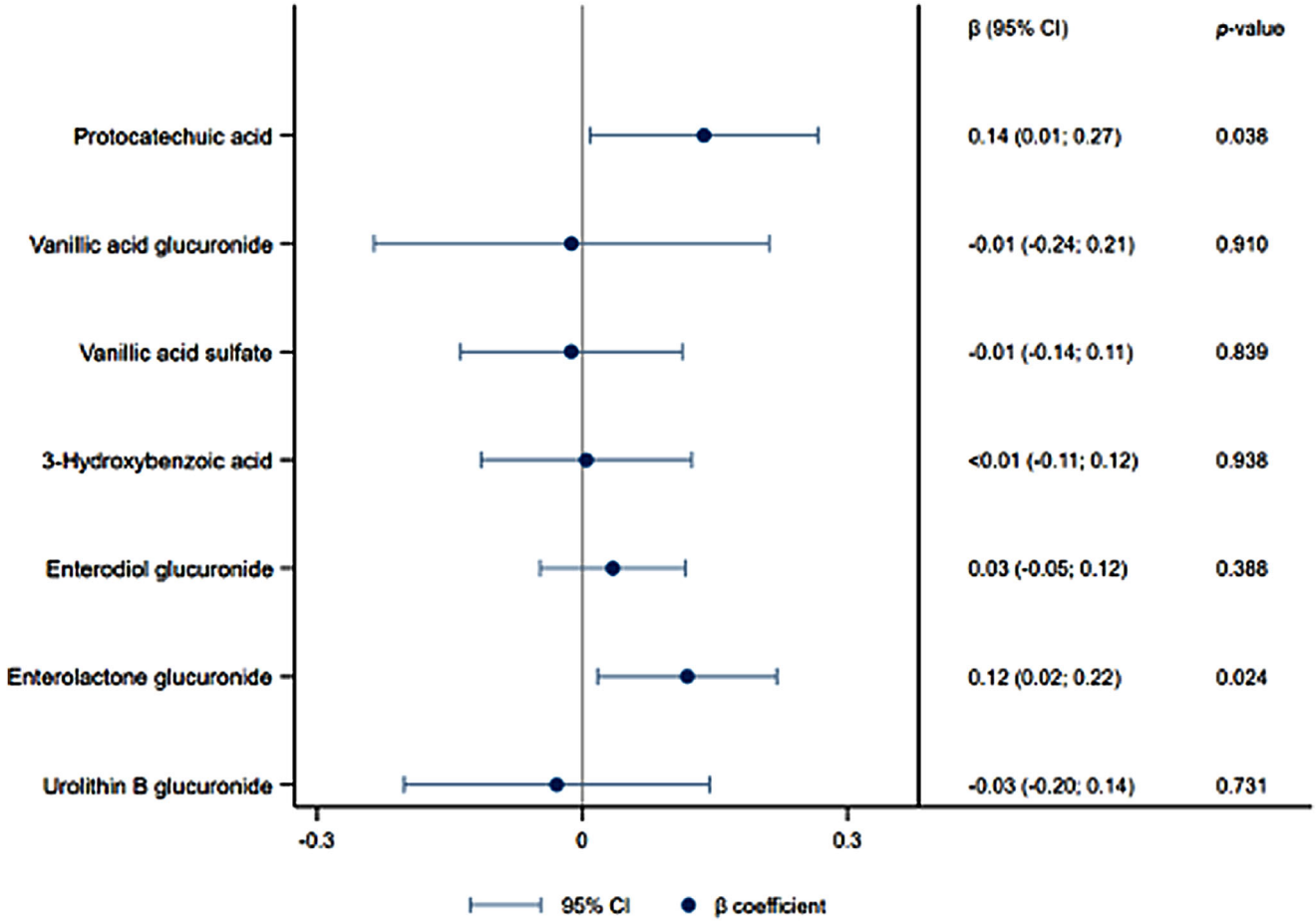

Figure 1. Association between individual MPM and MedDiet adherence (p-17 score) using multivariable adjusted linear regressions models adjusted for age, sex, smoking habit, educational level, obesity/overweight, total energy intake, diabetes, hypertension, hypercholesterolemia, and use of cholesterol-lowering drugs. All analyses were conducted with robust estimates of the variance to correct for intracluster correlation.

4. Discussion

In this cross-sectional study of participants in the PREDIMED-Plus trial, we observed that urinary MPM were directly associated with better cognitive function in an older population at high cardiovascular risk. Moreover, the specific MPM PCA and ELG were directly associated with MedDiet adherence. These results suggest that compliance with the MedDiet is associated with the production of phenolic compounds by the gut microbiota that can contribute to better cognitive function.

In our study, individuals with higher adherence to the MedDiet presented more PCA and ELG in urine. Evidence indicates that the MedDiet induces changes in the gut microbiota and increases short-chain fatty acid production.[36] Mitsou et al. reported that higher adherence to the MedDiet was associated with greater amounts of total bacteria and lower levels of *Escherichia coli* in the gut,[37] whereas in another study this dietary pattern induced an increase of Bifidobacteria sp., which are involved in the synthesis of MPM.[38–40] Therefore, the MedDiet may influence the composition of the gut microbiota and enhances the production of specific MPM.

Several studies have demonstrated that polyphenol-enriched diets may improve cognition and reduce the risk of developing neurodegenerative diseases.[9,41] Previously, a study has shown the protective association between metabolites related to the consumption of polyphenol-rich foods and cognitive decline.[42] In the present work, PCA was one of the urinary metabolites most strongly associated with cognitive function and was also related to MedDiet adherence. PCA is present in the circulation for significantly longer periods and at higher concentrations than the parent compounds and easily crosses the blood–brain barrier.[43] The parent compounds of PCA, present in fruits, are anthocyanins and procyanidins, such as cyanidin-3-*O*-glucoside, which after ingestion are metabolized to PCA by intestinal microbiota and can be detected in blood and urine.[44–46] Experimental and clinical studies strongly support a preventative role for PCA in neurodegenerative processes, including AD and Parkinson's disease. A favorable influence of PCA on factors underlying cognitive and behavioral disorders has been described, such as the accumulation of β-amyloid plaques in brain tissues and neuroinflammation.[43] Experiments conducted by Ban et al. on cultured rat cortical neurons revealed that PCA exerts concentration-dependent protective effects against neuronal cell

Table 2. Multivariable adjusted regression between microbial phenolic metabolites and global cognitive function.

	Global cognitive function	
	β (CI 95%) per 1-SD	*p*-value
Protocatechuic acid		
Model 1	0.04 (0.01; 0.07)	0.011
Model 2	0.04 (0.02; 0.07)	0.002
Vanillic acid glucuronide		
Model 1	0.05 (←0.01; 0.11)	0.069
Model 2	0.06 (0.01; 0.12)	0.025
Vanillic acid sulfate		
Model 1	0.01 (-0.01; 0.02)	0.499
Model 2	←0.01 (-0.02; 0.02)	0.942
3-Hydroxybenzoic acid		
Model 1	0.02 (-0.01; 0.05)	0.118
Model 2	0.03 (0.01; 0.06)	0.017
Enterodiol glucuronide		
Model 1	0.01 (←0.01; 0.03)	0.061
Model 2	0.01 (<0.01; 0.02)	0.039
Enterolactone glucuronide		
Model 1	0.03 (0.01; 0.06)	0.020
Model 2	0.02 (0.01; 0.04)	0.010
Urolithin B glucuronide		
Model 1	0.01 (-0.01; 0.02)	0.236
Model 2	0.01 (-0.01; 0.02)	0.345

A natural logarithmic transformation was applied to the raw values of individual metabolites. Model 1 was adjusted for age and sex. Model 2 was further adjusted for smoking habit, educational level, obesity/overweight, total energy intake, diabetes, hypertension, hypercholesterolemia, and use of cholesterol-lowering and anticholinergic drugs. All analyses were conducted with robust estimates of the variance to correct for intracluster correlation.

death and prevents neurotoxicity.[47] A study in mice revealed that PCA reduced the number of β-amyloid deposits in the hippocampus and cerebral cortex, diminished inflammatory responses, and improved learning and memory performance.[48]

Another compound strongly associated with cognitive function that was detected in participants with high adherence to the MedDiet was ELG. This MPM is metabolized from dietary lignans such as pinoresinol, sesamolin, or syringaresinol, present in whole grains, nuts, and legumes.[49] A positive association with global cognition was also found for EDG, another compound of the lignan family with a similar origin to that of ELG. Even though other lignans have been associated with improvements in neurocognition,[50,51] the role of ELG and EDG has been scarcely studied. It has been suggested that the enterolactone aglycone may possess neuroprotective properties due to its capacity to inhibit the activities of carbonic anhydrase, acetylcholinesterase, and butyrylcholinesterase.[52] The few clinical and observational studies that have examined the association between dietary lignans and cognitive performance have found them to be positively related.[53–55] Altogether, these results suggest that the microbial lignans ELD and EDG may have a beneficial impact on neurocognitive health.

3-OHBz was associated with higher GCF scores and, more specifically, with better attention and short-term memory. This MPM is derived from dietary polyphenols such as epicatechin and procyanidin B, and produced after the intake of cocoa, coffee, grapes, and other plant food sources.[56] Although not previously associated with memory or cognition in humans, in vitro and animal studies have shown that 3-OHBz has a significant protective effect against AD and Parkinson's disease. Capable of penetrating the blood–brain barrier, it accumulates in the brain, and exerts neuroprotective effects.[57] An in vitro study reported that 3-OHBz potentially interferes with the self-assembly of β-amyloid peptides, which play a key role in AD neuropathogenesis.[57]

In our study, VAG was positively associated with global cognition and especially with verbal ability and executive function, as well as with short-term and working memory. A glucuronidated form of vanillic acid, VAG has been detected after the consumption of berries, being one of the main metabolites of cyanidin-3-*O*-glucoside.[58,59] Vanillic acid is reported to reduce streptozotocin-induced neurodegeneration, improve learning and memory, and exert specific anti-inflammatory and antioxidant effects that down-regulate neuroinflammatory processes.[60] Moreover, experimental studies in mice revealed that vanillic acid has a neuroprotective effect against Aβ-induced neurotoxicity, resulting in improved memory function.[61] A possible mechanism to explain the memory-enhancing effect of vanillic acid is an increased expression of nuclear factor erythroid 2-related factor 2 (Nrf2) protein, which provides neuroprotection in AD.[61] The activation of Akt/Nrf2 signaling pathways is another feasible mechanism, since their inhibition plays an important role in the development of AD.[61] Interestingly, we observed that VAS was negatively associated with attention and processing speed, a relationship not previously reported in the literature, which may indicate that glucuronidation metabolism is more beneficial than sulfation.

Our study has limitations. The sample size was relatively small, although comparable to that in similar studies[62] and given the cross-sectional nature of the study, we cannot exclude the possibility of reverse causation or residual confounding. Due to the study design, only older Mediterranean individuals at high cardiovascular risk were studied, hence the results cannot be generalized to other populations, since pre-existing conditions, age, or lifestyle factors could potentially influence the composition and function of the microbiota as well as the resulting metabolites. In the PREDIMED-trial only spot urine samples were available, however a previous study observed that both samples can be used for large scale studies.[63] Finally, since not all existing MPM have been quantified, there may be other compounds with effects on the cognitive system. The study also has strengths, such as the use of biological samples, which provide the most accurate indication of the metabolic state of participants. Furthermore, the use of high-precision equipment such as HPLC coupled with LTQ-Orbitrap MS detectors facilitated the detection, identification, and quantification of polyphenols and their metabolites with high sensitivity. Moreover, we included a comprehensive battery of neuropsychological tests to assess cognitive function.

In conclusion, our findings suggest that the MedDiet is linked to the production of MPM, especially PCA and ELG, which are associated with better cognitive functions in an older population at high cardiovascular risk. These results underscore the poten-

Table 3. Multivariable adjusted regression between microbial phenolic metabolites and cognitive tests.

	Mini-Mental State Examination *Z*-score		Clock drawing test *Z*-score	
	β (CI 95%) per 1-SD	*p*-value	*β* (CI 95%) per 1-SD	*p*-value
Protocatechuic acid				
Model 1	0.08 (0.03; 0.13)	0.005	0.02 (−0.04; 0.08)	0.569
Model 2	0.06 (0.03; 0.13)	0.005	0.03 (−0.03; 0.09)	0.379
Vanillic acid glucuronide				
Model 1	0.03 (−0.07; 0.13)	0.550	0.05 (−0.03; 0.14)	0.191
Model 2	0.04 (−0.04; 0.13)	0.266	0.06 (−0.02; 0.13)	0.120
Vanillic acid sulfate				
Model 1	0.01 (−0.03; 0.04)	0.769	<0.01 (−0.03; 0.03)	0.951
Model 2	<0.01 (−0.03; 0.03)	0.984	<0.01 (−0.03; 0.04)	0.917
3-Hydroxybenzoic acid				
Model 1	0.04 (−0.02; 0.10)	0.214	0.03 (−0.03; 0.09)	0.280
Model 2	0.05 (−0.01; 0.11)	0.102	0.04 (−0.02; 0.09)	0.152
Enterodiol glucuronide				
Model 1	0.02 (−0.01; 0.05)	0.109	0.02 (←0.01; 0.04)	0.056
Model 2	0.02 (←0.01; 0.05)	0.067	0.02 (<0.01; 0.04)	0.047
Enterolactone glucuronide				
Model 1	0.04 (0.02; 0.07)	0.005	0.02 (−0.03; 0.06)	0.442
Model 2	0.04 (0.01; 0.06)	0.011	0.02 (−0.03; 0.06)	0.458
Urolithin B glucuronide				
Model 1	0.03 (0.01; 0.06)	0.022	−0.03 (−0.09; 0.02)	0.202
Model 2	0.03 (←0.01; 0.05)	0.055	−0.03 (−0.08; 0.03)	0.276

A natural logarithmic transformation was applied to the raw values of individual metabolites. Model 1 was adjusted for age and sex. Model 2 was further adjusted for smoking habit, educational level, obese/overweight, total energy intake, diabetes, hypertension, hypercholesterolemia, and use of cholesterol-lowering and anticholinergic drugs. All analyses were conducted with robust estimates of the variance to correct for intracluster correlation.

tial role of the MedDiet in reducing age-related cognitive decline. Further studies are needed to investigate the molecular mechanisms linking these metabolites to cognition.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

J.S.-S. reported receiving research support from the Instituto de Salud Carlos III, Ministerio de Educación y Ciencia, Departament de Salut Pública de la Generalitat de Catalunya, the European Commission, the USA National Institutes of Health; receiving consulting fees or travel expenses from Eroski Foundation, Instituto Danone, Nestle, and Abbott Laboratories, receiving nonfinancial support from Hojiblanca, Patrimonio Comunal Olivarero, the California Walnut Commission, Almond Board of California, La Morella Nuts, Pistachio Growers and Borges S.A; serving on the board of and receiving grant support through his institution from the International Nut and Dried Foundation and the Eroski Foundation; and grants and personal fees from Instituto Danone; Serving in the Board of Danone Institute International. D.C. reported receiving grants from Instituto de Salud Carlos III. R.E. reported receiving grants from Instituto de Salud Carlos III, Fundación Dieta Mediterránea and Cerveza y Salud and olive oil for the trial from Fundación Patrimonio Comunal Olivarero and personal fees from Brewers of Europe, Fundación Cerveza y Salud, Interprofesional del Aceite de Oliva, Instituto Cervantes in Albuquerque, Milano and Tokyo, Pernod Ricard, Fundación Dieta Mediterránea (Spain), Wine and Culinary International Forum and Lilly Laboratories; non-financial support from Sociedad Española de Nutrición and Fundación Bosch y Gimpera; and grants from Uriach Laboratories. E.R. reports grants, personal fees, non-financial support and other from California Walnut Commission, during the conduct of the study; non-financial support from The International Nut Council; grants, personal fees, non-financial support and other from Alexion; grants from Amgen and Pfizer; grants, personal fees and other from Sanofi Aventis; personal fees, non-financial support and other from Ferrer International, Danone and Merck Sharp & Dohme, personal fees and other from Amarin, outside the submitted work. R.M.L.-R. reports personal fees from Cerveceros de España, personal fees and other from Adventia, other from Ecoveritas, S.A., outside the submitted work. The rest of the authors have declared that no competing interests exist. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Author Contributions

I.D.L. and R.M.L.R. conceptualized this study; I.D.L., I.P.M., and C.A.R. performed the investigation and the formal analysis. I.D.-L. and P.G. wrote the original draft. M.A.M.G, J.S.S., D.C., M.C., J.A.M., L.T.S., J.W., J.V., D.R., J.L.M., R.E., F.J.T., J.L., L.S.M., A.B.C., J.A.T., M.R.G., X.P., F.F.A., M.D.R., A.B.B., J.V., C.V., L.D., E.R., E.T., A.A., E.M.A., N.V., A.G.R., L.T.C., N.P.F., M.Z., A.C., R.C., S.M.P., J.V.L., A.M.G.P., Z.V.R., S.S., C.O.A., N.T., P.J.P.O., A.O.C., J.D.E., N.B., M.F., and R.M.L.R. reviewed and edited the manuscript. All authors have read and approved the final manuscript.

Data Availability Statement

There are restrictions on the availability of data for the PREDIMED-Plus trial, due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project purposes. Requestors wishing to access the PREDIMED-Plus trial data used in this study can make a request to the PREDIMED-Plus trial Steering Committee chair: jordi.salas@urv.cat. The request will then be passed to members of the PREDIMED-Plus Steering Committee for deliberation.

The PREDIMED-Plus study was registered at the ISRCTN of London, England: 89898870

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[1] W. H. Organization, *Global Action Plan on the Public Health Response to Dementia 2017 - 2025*, W. H. Organization, Geneva **2017**.
[2] M. Baumgart, H. M. Snyder, M. C. Carrillo, S. Fazio, H. Kim, H. Johns, *Alzheimers Dement.* **2015**, *11*, 718.
[3] S. Norton, F. E. Matthews, D. E. Barnes, K. Yaffe, C. Brayne, *Lancet Neurol.* **2014**, *13*, 788.
[4] L. Wu, D. Sun, *Sci. Rep.* **2017**, *7*, 41317.
[5] J. Fu, L. J. Tan, J. E. Lee, S. Shin, *Front. Nutr.* **2022**, *9*, 946361.
[6] A. Bach-Faig, E. M. Berry, D. Lairon, J. Reguant, A. Trichopoulou, S. Dernini, F. X. Medina, M. Battino, R. Belahsen, G. Miranda, L. Serra-Majem, J. Aranceta, T. Atinmo, J. M. Barros, S. Benjelloun, I. Bertomeu-Galindo, B. Burlingame, M. Caballero-Bartolí, C. Clapés-Badrinas, S. Couto, I. Elmadfa, R. Estruch, A. Faig, F. Fidanza, S. Franceschi, J. Hautvast, E. Helsing, D. Julià-Llobet, C. La Vecchia, A. Lemtouni, et al., *Public Health Nutr.* **2011**, *14*, 2274.
[7] A. Sala-Vila, J. Fleming, P. Kris-Etherton, E. Ros, *Adv. Nutr.* **2022**, *13*, 1584.
[8] F. di Meo, A. Valentino, O. Petillo, G. Peluso, S. Filosa, S. Crispi, *Int. J. Mol. Sci.* **2020**, *21*, 2564.
[9] C. Valls-Pedret, R. M. Lamuela-Raventós, A. Medina-Remón, M. Quintana, D. Corella, X. Pintó, M. Á. Martínez-González, R. Estruch, E. Ros, *J. Alzheimers Dis.* **2012**, *29*, 773.
[10] J. Godos, F. Caraci, A. Micek, S. Castellano, E. D'amico, N. Paladino, R. Ferri, F. Galvano, G. Grosso, *Antioxidants* **2021**, *10*, 1.
[11] N. Cheng, L. Bell, D. J. Lamport, C. M. Williams, *Mol. Nutr. Food Res.* **2022**, *2100976*, 1.
[12] F. Cardona, C. Andrés-Lacueva, S. Tulipani, F. J. Tinahones, M. I. Queipo-Ortuño, *J. Nutr. Biochem.* **2013**, *24*, 1415.
[13] S. Mithul Aravind, S. Wichienchot, R. Tsao, S. Ramakrishnan, S. Chakkaravarthi, *Food Res. Int.* **2021**, *142*, 110189.
[14] E. Connell, G. Le Gall, M. G. Pontifex, S. Sami, J. F. Cryan, G. Clarke, M. Müller, D. Vauzour, *Mol. Neurodegener.* **2022**, *17*, 1.
[15] G. Peron, G. Gargari, T. Meroño, A. Miñarro, E. V. Lozano, P. C. Escuder, R. González-Domínguez, N. Hidalgo-Liberona, C. Del Bo, S. Bernardi, P. A. Kroon, B. Carrieri, A. Cherubini, P. Riso, S. Guglielmetti, C. Andrés-Lacueva, *Clin. Nutr.* **2021**, *40*, 5288.
[16] G. Zhu, J. Zhao, H. Zhang, G. Wang, W. Chen, *Adv. Nutr.* **2023**, *14*, 819.
[17] J. Salas-Salvadó, A. Díaz-López, M. Ruiz-Canela, J. Basora, M. Fitó, D. Corella, L. Serra-Majem, J. Wärnberg, D. Romaguera, R. Estruch, J. Vidal, J. Alfredo Martínez, F. Arós, C. Vázquez, E. Ros, J. Vioque, J. López-Miranda, A. Bueno-Cavanillas, J. A. Tur, F. J. Tinahones, V. Martín, J. Lapetra, X. Pintó, L. Daimiel, M. Delgado-Rodríguez, P. Matía, E. Gómez-Gracia, J. Díez-Espino, N. Babio, O. Castañer, et al., *Diabetes Care* **2019**, *42*, 777.
[18] M. A. Martínez-González, P. Buil-Cosiales, D. Corella, M. Bulló, M. Fitó, J. Vioque, D. Romaguera, J. Alfredo Martínez, J. Wärnberg, J. López-Miranda, R. Estruch, A. Bueno-Cavanillas, F. Arós, J. A. Tur, F. Tinahones, L. Serra-Majem, V. Martín, J. Lapetra, C. Vázquez, X. Pintó, J. Vidal, L. Daimiel, M. Delgado-Rodríguez, P. Matía, E. Ros, F. Fernández-Aranda, C. Botella, M. P. Portillo, R. M. Lamuela-Raventós, A. Marcos, et al., *Int. J. Epidemiol.* **2019**, *48*, 387.

[19] K. G. M. M. Alberti, R. H. Eckel, S. M. Grundy, P. Z. Zimmet, J. I. Cleeman, K. A. Donato, J. C. Fruchart, W. P. T. James, C. M. Loria, S. C. Smith, *Circulation* **2009**, *120*, 1640.
[20] W. C. Willett, G. Howe, L. Kushi, *Am. J. Clin. Nutr.* **1997**, *65*, 1220S.
[21] L. Molina, M. Sarmiento, J. Peñafiel, D. Donaire, J. Garcia-Aymerich, M. Gomez, M. Ble, S. Ruiz, A. Frances, H. Schröder, J. Marrugat, R. Elosua, *PLoS One* **2017**, *12*, 1.
[22] J. D. Fernández-Ballart, J. L. Piñol, I. Zazpe, D. Corella, P. Carrasco, E. Toledo, M. Perez-Bauer, M. Á. Martínez-González, J. Salas-Salvadó, J. M. Martn-Moreno, *J. Nutr.* **2010**, *103*, 1808.
[23] H. Schröder, M. D. Zomeño, M. A. Martínez-González, J. Salas-Salvadó, D. Corella, J. Vioque, D. Romaguera, J. A. Martínez, F. J. Tinahones, J. L. Miranda, R. Estruch, A. Bueno-Cavanillas, A. M. Alonso Gómez, J. A. Tur, J. Warnberg, L. Serra-Majem, V. Martín, C. Vázquez, J. Lapetra, X. Pintó, J. Vidal, L. Daimiel, J. J. Gaforio, P. Matía-Martín, E. Ros, C. Lassale, M. Ruiz-Canela, N. Babio, J. v. Sorlí, A. García-Arellano, et al., *Clin. Nutr.* **2021**, *40*, 4971.
[24] M. Folstein, S. Folstein, *J. Psychiatr. Res.* **1975**, *12*, 189.
[25] R. Blesa, M. Pujol, M. Aguilar, P. Santacruz, I. Bertran-Serra, G. Hernández, J. M. Sol, J. Peña-Casanova, T. Soler, C. Zabay, M. Riera, M. Castellví, L. Torner, I. Charques, H. Toirán, R. M. Manero, G. E. Peter Böhm, A. M. Martí, M. Meza, M. C. Crespo, *Neuropsychologia* **2001**, *39*, 1150.
[26] T. del Ser Quijano, M. J. García de Yébenes, F. Sánchez Sánchez, B. Frades Payo, Á. Rodríguez Laso, M. P. Bartolomé Martínez, Á. Otero Puime, *Med. Clin. (Barc)* **2004**, *122*, 727.
[27] A. Paganini-Hill, L. J. Clark, *Dement. Geriatr. Cogn. Dis. Extra* **2011**, *1*, 75.
[28] A. L. Benton, K. de S. Hamsher, A. B. Sivan, *Multilingual Aphasia Examination*, AJA Associates, Iowa City **1994**.
[29] D. Wechsler, *Escala de Inteligencia de Wechsler Para Adultos-III (WAIS III)*, TEA Ediciones, Madrid **1999**.
[30] M. S. Lopetegui, L. E. Rossi Casé, R. H. Neer, *Revista de Psicol.*, **2008**.
[31] J. Llinàs-Reglà, J. Vilalta-Franch, S. López-Pousa, L. Calvó-Perxas, D. Torrents Rodas, J. Garre-Olmo, *Assessment* **2015**, *24*, 183.
[32] C. Gómez-Martínez, N. Babio, J. Júlvez, N. Becerra-Tomás, M. Martínez-González, D. Corella, O. Castañer, D. Romaguera, J. Vioque, Á. M. Alonso-Gómez, J. Wärnberg, J. A. Martínez, L. Serra-Majem, R. Estruch, F. J. Tinahones, J. Lapetra, X. Pintó, J. A. Tur, J. López-Miranda, A. Bueno-Cavanillas, J. J. Gaforio, P. Matía-Martín, L. Daimiel, V. Martín-Sánchez, J. Vidal, C. Vázquez, E. Ros, S. Dalsgaard, C. Sayón-Orea, J. v. Sorlí, et al., *Front Endocrinol (Lausanne)* **2021**, *12*, 1.
[33] R. C. Shah, A. L. Janos, J. E. Kline, L. Yu, S. E. Leurgans, R. S. Wilson, P. Wei, D. A. Bennett, K. M. Heilman, J. W. Tsao, *PLoS One* **2013**, *8*, e64111.
[34] E. P. Laveriano-Santos, M. Marhuenda-Muñoz, A. Vallverdú-Queralt, M. Martínez-Huélamo, A. Tresserra-rimbau, E. Miliarakis, C. Arancibia-riveros, O. Jáuregui, A. M. Ruiz-León, S. Castro-baquero, P. Bodega, M. de Miguel, A. de Cos-Gandoy, J. Martínez-Gómez, G. Santos-Beneit, J. M. Fernández-Alvira, R. Fernández-Jiménez, R. M. Lamuela-Raventós, **2022**.
[35] A. Medina-Remón, A. Barrionuevo-González, R. Zamora-Ros, C. Andres-Lacueva, R. Estruch, M. Á. Martínez-González, J. Diez-Espino, R. M. Lamuela-Raventos, *Anal. Chim. Acta* **2009**, *634*, 54.
[36] G. Merra, A. Noce, G. Marrone, M. Cintoni, M. G. Tarsitano, A. Capacci, A. de Lorenzo, *Nutrients* **2020**, *13*, 1.
[37] E. K. Mitsou, A. Kakali, S. Antonopoulou, K. C. Mountzouris, M. Yannakoulia, D. B. Panagiotakos, A. Kyriacou, *J. Nutr.* **2017**, *117*, 1645.
[38] I. Garcia-Mantrana, M. Selma-Royo, C. Alcantara, M. C. Collado, *Front. Microbiol.* **2018**, *9*, 1.
[39] M. v. Selma, F. A. Tomás-Barberán, D. Beltrán, R. García-Villalba, J. C. Espín, *Int. J. Syst. Evol. Microbiol.* **2014**, *64*, 2346.
[40] T. Clavel, G. Henderson, W. Engst, J. Doré, M. Blaut, *FEMS Microbiol. Ecol.* **2006**, *55*, 471.
[41] G. Caruso, S. A. Torrisi, M. P. Mogavero, W. Currenti, S. Castellano, J. Godos, R. Ferri, F. Galvano, G. M. Leggio, G. Grosso, F. Caraci, *Pharmacol. Ther.* **2022**, *232*, 108013.
[42] R. González-Domínguez, P. Castellano-Escuder, F. Carmona, S. Lefèvre-Arbogast, D. Y. Low, A. Du Preez, S. R. Ruigrok, C. Manach, M. Urpi-Sarda, A. Korosi, P. J. Lucassen, L. Aigner, M. Pallàs, S. Thuret, C. Samieri, A. Sánchez-Pla, C. Andres-Lacueva, *Mol. Nutr. Food Res.* **2021**, *65*, 1.
[43] K. Krzysztoforska, D. Mirowska-Guzel, E. Widy-Tyszkiewicz, *Nutr. Neurosci.* **2019**, *22*, 72.
[44] F. J. Olivas-Aguirre, J. Rodrigo-García, N. D. R. Martínez-Ruiz, A. I. Cárdenas-Robles, S. O. Mendoza-Díaz, E. Álvarez-Parrilla, G. A. González-Aguilar, L. A. de La Rosa, A. Ramos-Jiménez, A. Wall-Medrano, *Molecules* **2016**, *21*, 1264.
[45] S. W. Min, S. N. Ryu, D. H. Kim, *Int. Immunopharmacol.* **2010**, *10*, 959.
[46] C. D. Kay, P. A. Kroon, A. Cassidy, *Mol. Nutr. Food Res.* **2009**, *53*, S92.
[47] J. Y. Ban, S. O. Cho, S. Y. Jeon, K. H. Bae, K. S. Song, Y. H. Seong, *Neurosci* **2007**, *420*, 184.
[48] Y. Song, T. Cui, N. Xie, X. Zhang, Z. Qian, J. Liu, *Int. Immunopharmacol.* **2014**, *20*, 276.
[49] N. Han, Y. Wen, Z. Liu, J. Zhai, S. Li, J. Yin, *Front Pharmacol* **2022**, *13*, 960112.
[50] T. Yan, L. Shang, M. Wang, C. Zhang, X. Zhao, K. Bi, Y. Jia, *Metab. Brain Dis.* **2016**, *31*, 653.
[51] S. Shimoyoshi, D. Takemoto, Y. Ono, Y. Kitagawa, H. Shibata, S. Tomono, K. Unno, K. Wakabayashi, *Nutrients* **2019**, *11*, 1582.
[52] L. P. Köse, I. Gulcin, *Nat. Prod.* **2017**, *11*, 558.
[53] F. Giampieri, J. Godos, G. Caruso, M. Owczarek, J. Jurek, S. Castellano, R. Ferri, F. Caraci, G. Grosso, *Biomolecules* **2022**, *12*, 760,
[54] A. R. Miranda, M. v. Cortez, A. v. Scotta, L. Rivadero, S. v. Serra, E. A. Soria, *Nutr. Res.* **2021**, *85*, 1.
[55] G. A. Greendale, M. H. Huang, K. Leung, S. L. Crawford, E. B. Gold, R. Wight, E. Waetjen, A. S. Karlamangla, *Menopause* **2012**, *19*, 894.
[56] M. Marhuenda-Muñoz, E. P. Laveriano-Santos, A. Tresserra-Rimbau, R. M. Lamuela-Raventós, M. Martínez-Huélamo, A. Vallverdú-Queralt, *Nutrients* **2019**, *11*, 2725.
[57] D. Wang, L. Ho, J. Faith, K. Ono, E. M. Janle, P. J. Lachcik, B. R. Cooper, A. H. Jannasch, B. R. D'Arcy, B. A. Williams, M. G. Ferruzzi, S. Levine, W. Zhao, L. Dubner, G. M. Pasinetti, *Mol. Nutr. Food Res.* **2015**, *59*, 1025.
[58] J. J. Mendoza-Velásquez, J. F. Flores-Vázquez, E. Barrón-Velázquez, A. L. Sosa-Ortiz, B. M. W. Illigens, *T. Siepmann, Front. Neurol.* **2019**, *10*, 363.
[59] R. Hu, S. Wu, B. Li, J. Tan, J. Yan, Y. Wang, Z. Tang, M. Liu, C. Fu, H. Zhang, J. He, *Anim. Nutr.* **2022**, *8*, 144.
[60] J. C. H. Singh, R. M. Kakalij, R. P. Kshirsagar, B. H. Kumar, S. S. B. Komakula, P. V. Diwan, *Pharm. Biol.* **2015**, *53*, 630.
[61] F. Ul Amin, S. A. Shah, M. O. Kim, *Sci. Rep.* **2017**, *7*, 40753.
[62] M. Marhuenda-Muñoz, I. Domínguez-López, E. P. Laveriano-Santos, I. Parilli-Moser, C. Razquin, M. Ruiz-Canela, F. J. Basterra-Gortari, D. Corella, J. Salas-Salvadó, M. Fitó, J. Lapetra, F. Arós, M. Fiol, L. Serra-Majem, X. Pintó, E. Gómez-Gracia, E. Ros, R. Estruch, R. M. Lamuela-Raventós, *Antioxidants* **2022**, *8*, 1540.
[63] R. Zamora-Ros, M. Rabassa, A. Cherubini, M. Urpi-Sarda, R. Llorach, S. Bandinelli, L. Ferrucci, C. Andres-Lacueva, *Anal. Chim. Acta* **2011**, *704*, 110.