UNIVERSITAT ROVIRA I VIRGILI

BEVERAGE CONSUMPTION IN THE CONTEXT OF A MEDITERRANEAN DIET, CARDIOVASCULAR RISK FACTORS AND MENTAL HEALTH

Indira Paz Graniel

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DOCTORAL THESIS

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Thesis supervised by Prof. Jordi Salas-Salvadó, and co-supervised by Dr. Nancy Babio

UNIVERSITAT ROVIRA i VIRGILI

Human Nutrition Unit
Department of Biochemistry and Biotechnology
Rovira i Virgili University
Reus, Tarragona

2022

UNIVERSITAT ROVIRA i VIRGILI

Jordi Salas Salvadó, Professor of Nutrition and Food Science at the Department of Biochemistry and Biotechnology of Rovira i Virgili University,

I STATE:

*That the present study, entitled "**Beverage consumption in the context of a Mediterranean diet, cardiovascular risk factors and mental health**", presented by Ms. Indira Paz Graniel for the award of the degree of Doctor, has been carried out under my supervision at the Department of Biochemistry and Biotechnology of this university and it is currently up for an international distinction.*

Reus, 10th March 2022

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Nancy Elvira Babio Sánchez, Lecturer at the Department of Biochemistry and Biotechnology of Rovira i Virgili University,

I STATE:

*That the present study, entitled "**Beverage consumption in the context of a Mediterranean diet, cardiovascular risk factors and mental health**", presented by Ms. Indira Paz Graniel for the award of the degree of Doctor, has been carried out under my supervision at the Department of Biochemistry and Biotechnology of this university and it is currently up for an international distinction.*

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"Knowing is not enough; we must APPLY.

Willing is not enough; we must DO."

Johann Wolfgang von Goethe

1749 – 1832

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ACKNOWLEDGMENTS

A todos los seres que amo y he amado,

especialmente a *Ricardo, Indira, Jessica y Génesis*.

Los siguientes párrafos son algunos sobre los que más he reflexionado durante la redacción de esta tesis, son líneas en las que dejo de lado la parte científica-racional dejándome llevar por la emoción y el sentimiento.

Encuentro arriesgado enlistar nombres de personas a quienes estoy agradecida por lo que me han aportado durante estos años, ya que fácilmente puedo dejar de darle el crédito suficiente a alguien cuya casual aparición en mi vida, llegó a ser trascendental y significativa, y… es que no son pocas las casualidades que han tenido lugar hasta este momento.

"*¿Pero un acontecimiento no es tanto más significativo y privilegiado cuantas más casualidades sean necesarias para producirlo?*" (M.K. 1984). La RAE define casualidad como "la combinación *de circunstancias que no se pueden prever ni evitar*". Y cuando digo casualidades me refiero a personas, lugares, momentos y vivencias. Casualidad y causalidad no son lo mismo, sin embargo, una casualidad puede convertirse en la causa, el origen, o el inicio de algo.

Si pensará en este momento como el final de una gran saga, tendría que empezar por agradecer a los personajes del primer episodio, aquellas primeras casualidades que me ayudaron a construir un cimiento e impulsaron a tener una nueva aventura. Aquellos-as que están a 8000kms o más de distancia, que fueron (y son) motor, respaldo, motivación, inspiración. Mi familia y mis amigos, porque, aunque probablemente sigan sin entender lo que he estado haciendo los últimos años lejos de casa, y quienes muchas veces me creyeron en interminables vacaciones, su voz al otro lado del teléfono me daba la *fuerza* necesaria para seguir adelante en los momentos más oscuros; escucharlos o verlos a través de una pantalla me reconforta. A pesar del océano que nos separa me han dejado sentir su amor, y a cada retorno me reciben con los brazos abiertos. Los años no hicieron menos doloroso tener que despedirme de ustedes, pero me hicieron valorar cada segundo que tengo para abrazarlos y saborear la vida a su lado, porque en el mar Caribe, y sobretodo en su compañía, la vida es más sabrosa. *Los quiero tres mil.*

En una misma galaxia pero en un lejano continente, aquellas coincidencias con las que compartí mi primer año en España; aquellos cuyo ejemplo logró despertar en mí el hasta entonces apagado interés por la investigación; a mis tutores por darme la oportunidad de continuar mi formación a su lado, por creer y depositar su confianza en mí; a los compañeros que he tenido dentro y fuera de la unidad, pero especialmente a los amigos y amigas que gané, que fueron mis maestros sin título, con quienes reí, canté y lloré; those that en una mateixa conversaciò nos salían parole in 4 lingues, *a las/los* que he visto partir hacia nuevos retos y aventuras pero que no ha impedido que la amistad continue; a los que me aconsejaron, y me animaron a continuar y no renunciar cuando el sendero se volvía estrecho; a los que en llegaron en mi última etapa de formación, y que con su frescura y risas hicieron más ameno el último *cacho* de camino; y a la casualidad inesperada, por el quien palabras como lealtad, amistad, y familia tomaron otra dimensión, y que a pesar de nuestros continuos e interminables debates sobre la vida (algunas veces también de estadística) es el faro que iluminó nuestro navegar en estos años, mi incondicional amigo.

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Y finalmente, quiero destacar aquellas casualidades muchas veces imperceptibles del día a día como una sonrisa, un saludo, una antena, un abrazo, una palabra amable, cuyo acontecer en el momento oportuno tuvo el impacto suficiente para mantenerme *rodando*.

Aunque tengo curiosidad por saber cuáles serán las nuevas casualidades que me sorprenderán, hoy honro a todos ustedes, las más significativas casualidades de mi vida, a aquellas coincidencias del destino, que me han ayudado a convertirme en la persona que al día de hoy soy, y que me han permitido poder disfrutar (finalmente) de este momento…

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ABSTRACT

English

Cardiovascular diseases had become a worldwide major public health concern due to the exponential increase shown in their prevalence and incidence in the last years. Most of these diseases can be prevented by addressing modifiable lifestyle factors such as diet, physical activity, and smoking habits. However, and despite its daily consumption, epidemiological evidence exploring the association between drinking water, fluids or beverages, and cardiovascular risk factors is limited and contradictory, and sometimes dietary guidelines do not include recommendations on their consumption.

The general objective of the present Doctoral Thesis was to assess the beverage consumption pattern of an elderly Mediterranean population with metabolic syndrome (MetS) and its association with cardiovascular risk factors and cognition. For this purpose data from the *Prevención con Dieta Mediterránea – Plus* (PREDIMED-Plus) study, a multicenter, parallel-group, randomized clinical trial conducted in Spain for the primary prevention of cardiovascular disease (CVD), was analyzed as a prospective cohort design study.

The main findings derived from this dissertation reinforce the role of the Mediterranean beverage consumption pattern in the compliance of European Food Safety Authority (EFSA) recommendations for total water intake (TWI) and total water intake from fluids (TWIF) and its association with a healthy lifestyle; provide evidence for the association between drinking water consumption, body weight and adiposity; contribute with new insights regarding fruit juice consumption and its association with cardiometabolic health; and support the role of coffee consumption and caffeine intake in the prevention of cognitive decline and other dimentions of mental health.

In conclusion, the Mediterranean beverage consumption pattern is associated with a healthier lifestyle, higher compliance with the EFSA's recommendations for water intake, better prognosis in some cardiovascular risk factors, and cognitive performance in elderly individuals with MetS. Further, some molecules present in liquids, such as caffeine, could be associated with aspects of mental health, such as anxiety. If these results are confirmed by intervention studies with an adequate degree of scientific evidence, dietary guidelines should highlight the importance of water and beverages consumption for health maintenance.

Spanish

Debido al aumento exponencial en la prevalencia e incidencia de las enfermedades cardiovasculares en los últimos años, estas se han convertido en un importante problema de salud pública a nivel mundial. La mayoría de estas patologías se pueden prevenir abordando factores de estilo de vida modificables, como la dieta, la actividad física y el hábito tabáquico. Sin embargo, y a pesar de su consumo diario, la evidencia epidemiológica que ha explorado la asociación entre el consumo de agua, líquidos o bebidas y los factores de riesgo cardiovascular es limitada y contradictoria. Aunado a esto, en ocasiones las guías alimentarias no incluyen recomendaciones sobre su consumo.

El objetivo general de la presente Tesis Doctoral fue evaluar el patrón de consumo de bebidas de una población mediterránea de edad avanzada con síndrome metabólico (SM), y su asociación con factores de riesgo cardiovascular y rendimiento cognitivo. Para ello se analizaron los datos del estudio PREDIMED-Plus, un ensayo clínico multicéntrico, aleatorizado y controlado, de grupos paralelos desarrollado en España para la prevención primaria de la enfermedad cardiovascular (ECV). Los análisis se realizaron con el enfoque de un estudio de cohorte prospectivo.

Los principales hallazgos derivados de esta tesis refuerzan el papel del patrón de consumo de bebidas del Mediterráneo en el cumplimiento de las recomendaciones de la EFSA para la ingesta total de agua y la ingesta total de agua procedente de líquidos, así como su asociación con un estilo de vida saludable; proporcionan evidencia acerca de la asociación entre el consumo de agua potable, el peso corporal y la adiposidad; contribuyen con nuevos conocimientos sobre el consumo de zumo de frutas y su asociación con la salud cardiometabólica; y respaldan el papel del consumo de café y la ingesta de cafeína en la prevención del deterioro cognitivo y la salud mental.

En conclusión, el patrón de consumo de bebidas mediterráneas se asoció con un estilo de vida más saludable, mayor cumplimiento de las recomendaciones de la EFSA sobre ingesta de agua, mejor pronóstico en algunos factores de riesgo cardiovascular y rendimiento cognitivo en personas mayores con SM. Además de que, algunas moléculas presentes en los líquidos, tales como la cafeína, podrían estar asociadas con otros aspectos de la salud mental, como la ansiedad. Si estos resultados son confirmados por estudios de intervención con un grado adecuado de evidencia científica, las guías dietéticas deberían resaltar la importancia del consumo de agua y bebidas para el mantenimiento de la salud.

Catalan

A causa de l'augment exponencial en la prevalença i la incidència de les malalties cardiovasculars en els darrers anys, aquestes han esdevingut en un important problema de salut pública a nivell mundial. La majoria d'aquestes patologies es poden prevenir abordant factors d'estil de vida modificables, com la dieta, l'activitat física i l'hàbit tabàquic. Tot i això, i malgrat el seu consum diari, l'evidència epidemiològica que ha explorat l'associació entre el consum d'aigua, líquids o begudes i els factors de risc cardiovascular és limitada i contradictòria. A més a més, a vegades les guies alimentàries no inclouen recomanacions sobre el seu consum.

L'objectiu general de la present Tesi Doctoral va ser avaluar el patró de consum de begudes d'una població mediterrània d'edat avançada amb síndrome metabòlic (SM) i la seva associació amb factors de risc cardiovascular i rendiment cognitiu. Per això es van analitzar les dades de l'estudi PREDIMED-Plus, un assaig clínic multicèntric, aleatoritzat i controlat, de grups paral·lels desenvolupat a Espanya per la prevenció primària de la malaltia cardiovascular (ECV). Les anàlisis es van fer amb l'enfocament d'un estudi de cohort prospectiu.

Els principals resultats derivats d'aquesta tesi reforcen el paper del patró de consum de begudes del Mediterrani en el compliment de les recomanacions de l'EFSA per a la ingesta total d'aigua i la ingesta total d'aigua procedent de líquids, així com la seva associació amb un estil de vida saludable; proporcionen evidència sobre l'associació entre el consum d'aigua, el pes corporal i l'adipositat; contribueixen amb nous coneixements sobre el consum de suc de fruites i la seva associació amb la salut cardiometabòlica; i donen suport al paper del consum de cafè i la ingesta de cafeïna en la prevenció del deteriorament cognitiu i la salut mental.

En conclusió, el patró de consum de begudes mediterrànies es va associar amb un estil de vida més saludable, un major compliment de les recomanacions de l'EFSA sobre ingesta d'aigua, un millor pronòstic en alguns factors de risc cardiovascular i un rendiment cognitiu en persones grans amb SM. A més, algunes molècules presents als líquids, com la cafeïna, podrien estar associades amb altres aspectes de la salut mental, com l'ansietat. Si aquests resultats són confirmats per estudis d'intervenció amb un grau adequat d'evidència científica, les guies dietètiques haurien de ressaltar la importància del consum d'aigua i begudes per al manteniment de la salut.

ABBREVIATIONS

AI, Adequate intake

BMI, Body mass index

BW, Body weight

ccs, Cubic centimeters

CVD, Cardiovascular disease

DALYs, disability-adjusted life years

DBP, Diastolic blood pressure

DST, Digit Span Test

EFSA, European Food Safety Authority

FFQ, Food Frequency Questionnaire

FPG, Fasting blood plasma glucose

g/d, grams per day

HDL-c, High-density lipoprotein cholesterol

HTA, Hypertension

IOM, Institute of Medicine

Kg, Kilograms

LDL-c, Low-density lipoprotein cholesterol

L/d, Litters day

MedDiet, Mediterranean Diet

MetS, Metabolic Syndrome

mg/dL, miligrams per deciliter

MMSE, Mini-mental State Examination test

Mosm, Osmolality

OR, Odds ratio

PA, physical activity

PREDIMED-Plus; PREvención con DIeta MEDiterránea Plus study

SFAs, saturated fatty acids

SBP, Systolic blood pressure

TG, Triglycerides

TMT, Trail Making Test

T2DM, Type 2 diabetes mellitus

VFT, Verbal Fluency Test

VLDL, very low-density lipoprotein

WC, waist circumference

WHO, World Health Organization

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I. INTRODUCTION

1. Water as an essential nutrient

Water is the main constituent of the human body (55-75% of total body weight)[1,2]. Due to its role in several metabolic processes is an essential nutrient for the optimal physiological function of the human body. It is a source of minerals and electrolytes, participates in the homeostasis maintenance of hydro-electrolytic and acid-base balance, vascular volume, and body temperature[1]. It has several functions in cardiovascular, renal, and hepatic processes, and has a role as a nutrients carrier and vehicle for products and toxins excretion[3,4]. Moreover, it also lubricates and provides structural support to cells and tissues, and helps to preserve brain and cognitive functions[5,6]. Total body water is distributed into intracellular (34-65%) and extracellular (26-35%) compartments. The extracellular fluid compartment is further divided into interstitial liquid, plasma, trans-cellular water, and lymphatic liquids[6]. Several factors are prone to influence total body water status, such as body composition, age, sex, physical activity, health status, drug use and environmental temperature.

1.1 Water balance

Hydration status is not a steady state, it is better understood as a dynamic process to maintain water balance, from the continuous human body water loses and its replacement. The three major body water contributors are: 1) water from foods, 2) water from fluids, and 3) metabolic water production. It is estimated that water intake consists largely of the consumption of drinking water and other beverages (80%) and that approximately 20% is consumed through food[7]. Besides, the water intake through fluids and food, there is a small portion of water produced as a result of macronutrient oxidation. Approximately 100g of lipids, 100g of carbohydrates, or 100g proteins produces about 107mL, 60mL, and 40mL of water, respectively[1]. Meanwhile, water is mainly lost through the renal (urine), gastrointestinal tract (feces), respiratory system, and skin (insensible perspiration)[7].

The state of being in water balance is known as euhydration. However, the period between water intake and the replacement of water loses can lead to the status of hyperhydration (positive water balance) or hypohydration (negative water balance). Despite both conditions can affect the ability to maintain homeostasis and health, a negative water balance has been associated with major undesirable effects on health[8,9]. To summarize, water balance disruption can result in decreased plasma volume, altered thermoregulation, impaired cognitive function and decline in exercise performance, among others[10]. Moreover, a severe dehydration status (a total body water loss higher than 10%) could event cause death[9].

Total body water can be estimated through different assessment methods depending on factors like age, health status, physical activity level, and environmental exposure[11,12]. However, to the best of our knowledge, currently, there is not a universally accepted technique to determine hydration status. Methods as dilution techniques (oral or intravenous administration) are considered to be the gold standard for human fluid compartment size assessment[11]. The addition of a tracer to an ingested fluid and the subsequent blood sample collection has also been used to evaluate fluid absorption and balance[13]. Non-invasive methods include body mass differences in short periods (1-4 hours) and the bioelectrical impedance, which allows estimating body composition including body water. Nevertheless, several factors (from the individual and environment) may reduce the accuracy and reliability of this technique, and consequently, it results to be an inappropriate method to measure small changes in body water[14,15]. Because extracellular fluid osmolality stimulates fluid-regulatory mechanisms (as thirst sensation and hormones secretion), it is accepted that the maintenance of total body water content is widely represented by unchanged plasma osmolality. Similarly, urine osmolality can be used as an indicator of hydration status[7,16]. Even so, other indirect indicators can be used to assess body water status, such as hematocrit and hemoglobin (fluids changes on plasma volume), urine indicators (urine specific gravity, color, 24-hour urine volume), and cardiovascular function measures[11,12].

The maintenance of water and mineral balance is the result of the interaction between a network conformed by the central nervous system, neuroendocrine hormones (antidiuretic hormone and atrial natriuretic peptide), and the constant feedback from many organs and neural systems[17]. This network is so sensitive and precise, that small changes in body water can start a homeostatic mechanism to restore water balance[18].

1.2 Water needs determinants

Water needs may vary according to several factors, such as age, sex, body composition, disease, medication use and environmental factors[7].

Body composition, and therefore sex, are the major factors conditioning water requirements. Since the amount of water content in fat-free mass and fat mass are considerable different (approx. 73% and 10%, respectively)[19,20], and because women usually have more fat mass (as percentage) than men (in consequence present lower body water proportion)[21]. This could partly explain the differences in water needs by sex.

The age-related physiological changes that can affect water balance include glomerular filtration rate, urinary concentration ability, thirst mechanism (sensation), free-water clearance, and changes in body composition (with aging muscle mass decrease in parallel with the adipose tissue increase that results in a up to a 50% decrease in total body water)[19,21–24]. In addition, with aging, antidiuretic hormone (ADH) and atrial natriuretic peptide (ANP) tend to increase[25]. Besides these physiological changes, elderly people may face difficulties in gaining access to beverages (mobility reduction, visual troubles, swallowing disorders, cognitive alterations, and sedatives use), the shame of incontinence (restrict liquid intake), and drugs use (diuretic or laxatives)[26,27]. Therefore, elderly individuals compared to younger adults are at higher risk of suffering dehydration.

Both, acute and chronic illness conditions, as constipation, fever, neurological disorders, chronic kidney disease, and cardiovascular diseases [9], and physiological status as pregnancy can modify water needs[28]. Polypharmacy and the chronic consumption of drugs, such as metformin, diuretics (thiazides, loop diuretics, potassium-sparing agents), and corticoids have also been reported to alter the hydration status[27,29], due to their intrinsic mechanism and-or potential side effects which might increase the odds for dehydration.

Besides the aforementioned factors, water intake is also influenced by non-regulated social and cultural behaviours[30,31] and varies widely in children and adults according to physical activity levels (sweat losses, intensity, and duration of the activity)[32–34], environmental factors (temperature, humidity, seasonality)[35,36] and diet[7,37].

At any age, dietary patterns, traditional regional-cultural dishes, dietary sodium, protein intake, and total solute load influence individual water requirements[22,38,39]. Moreover, the consumption of solid food might promote fluid intake to facilitate alimentary bolus formation, swallow, enhance palatability and reduce irritants effect. Plant-based dietary patterns, due to the high content on fruits and vegetables, are more likely to have a higher contribution of water from food[38,40,41] than western-diets. As a consequence, the individual drinking water requirements might be lower in vegetarian people. Drinking water is the main source of water, however other beverages and fluids are important contributors to water intake[42]. Moreover, the consumption of certain drinks such as alcohol-contained beverages and some compounds, as caffeine, might also impact water requirements due to its diuretic effect[7]. For these reasons, the minimal amount of water needed would be determined by the number of end products needed to be excreted.

1.3 Water and fluid recommendations

In view of the several factors prone two influence water requirements, to prevent water balance disruption undesirable effects on health, different worldwide organizations have established water adequate intake (AI) range values for different populations[6,7,43].

Water intake is achieved through two differentiated sources: water from fluids and water from foods. It is held that foods provide approximately 20% of total water intake and the remained 80% is achieved through fluids consumption[7]. However, this percentage might vary according to dietary and beverage patterns followed by the individual[40,41,44,45]. Water content in solid food range from 10% (dry food such as flour) to 90% (fruits and/or vegetables)[7]. Preferences on beverages consumption and selection are determinate by thirst sensation, climate (cold or warm fluids), socio-cultural traditions, and even pleasure (alcoholic beverages consumption) [42]. Besides water, fluids also provide nutrients as minerals, vitamins, and other nutrients such as carbohydrates, proteins, and fats[40,46].

Total water intake recommendations are done by ranges in intake volumes. The Food and Nutrition Board of the Institute of Medicine (IOM) set total water intake recommendations in 3.7L/d and 2.7L/d for men and women, respectively[6]. These recommendations were set based on the median total water intake (drinking water, beverages, and water from food) from U.S. survey data (NHANES III). The European Food Safety Authority (EFSA) established total water intake recommendations at 2.5L/d for men and 2.0 L/d for women[7] based on the observed intakes in different European countries, and on considerations of desirable urine osmolarity (500 mosm/L). Moreover, both organizations recommend an increase of 300ml/day and 700ml/day of water during pregnancy and breastfeeding, respectively[6,7]. Additionally, it has been suggested that water needs are related to body weight and caloric intake, in consequence, recommendations for water intake in 30-35 ml/Kg of body weight or 1.5ml/kcal have been established[6,47]. In Spain, in 2009, the Spanish Society of Community Nutrition (SENC) published the "*The SENC Pyramid of Healthy Hydration*", which presents general recommendations on fluid intake for the Spanish population (**Figure** 1)[48]. This guideline recommends the intake of up to 10 servings/day (1 serving = 200-250ml) of several fluids to maintain good hydration status. Authors classified the beverages into 5 groups according to their energy and nutrients density, and the evidence of their beneficial or detrimental effects on health. However, as the current scientific evidence is focused on total water intake rather than on a specific fluid, concerns on the accuracy of plain water consumption recommendations have been raised[49,50].

Moreover, due to inter-individual variation, a specific water intake recommendation cannot even meet the water needs of an individual under certain conditions. Individual adequate water intake should be based on observed intakes and on the volume needed to maintain body fluids osmolality (290 mosm/L, both intra- and extracellularly). Therefore, in any case, the minimum water requirement would be the amount of water that equals losses and prevents adverse effects of hypohydration.

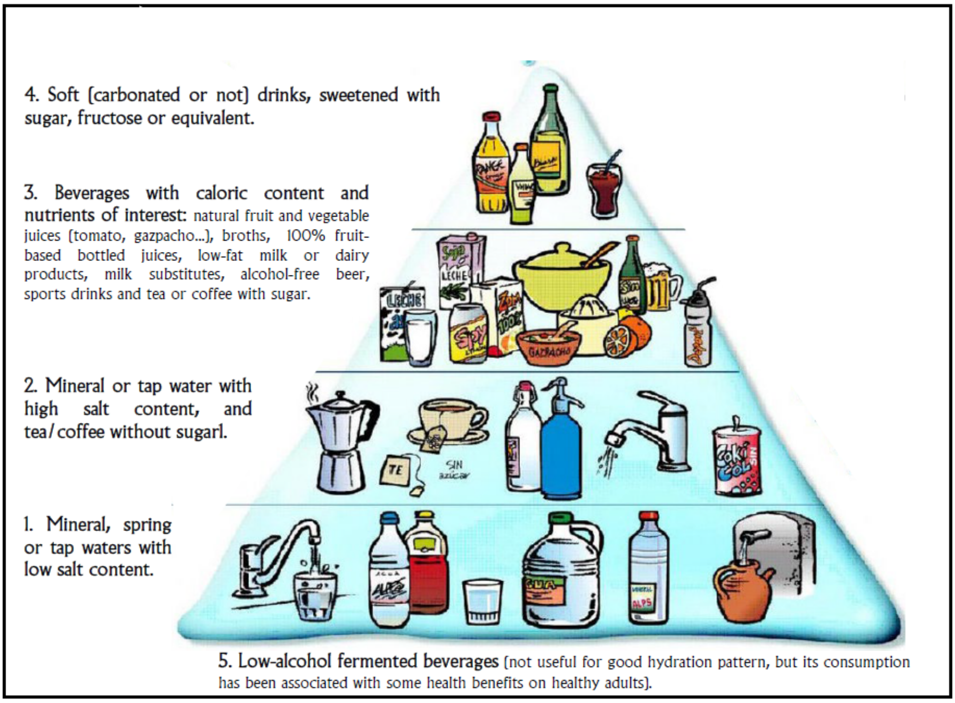

Figure 1. *The SENC Pyramid of Healthy Hydration*

Evidence regarding the compliance with water intake recommendations is scarce[51–54]. In a study conducted with data from 13 countries (3 Americans, 5 Europeans and 4 Asians) it was reported that less than 50 % of women and approximately 60 % of men do not comply with the EFSA water from fluids recommendations[54]. Similarly, in a study conducted on Spanish adults, it was reported that 50.3% of the studied population did not comply with EFSA's recommendations for total water intake[40]. In a French national cohort, the mean TWI for men and women was 2.3 and 2.1 L, respectively. This mean intake was close to the TWI EFSA recommendations, however, only 61.9% of the TWI was reported to come from fluids (less than the EFSA estimation [70-80%])[53]. Finally, in a survey of British adults, the mean TWI (2.53L for men and 2.03L for women) was reported to be almost identical to the EFSA recommendation for both genders. As the scientific literature in the field is limited, and due to the heterogeneity among studies' methodology, further analyses are needed to clarify the grade of compliance with EFSA's recommendations for water intake and its association with health, especially in populations at high risk of dehydration, such as elderly individuals.

2. Assessment methods for fluids and beverages intake

Despite the high significance of water as a nutrient, and the role of beverages as its source on health, few sensitivity tools have been developed to assess fluids consumption. Moreover, in the last decades, more researchers have been interested in the study of beverage consumption and its impact on health, which have evidence the lack of acute, reliable, and precise methods for quantifying water and fluids intake[55].

Commonly, water and-or total fluid intake (both drinking water and other beverages consumption) are estimated through assessments tools mainly designated to evaluate food intake, such as food frequency questionnaires (FFQs), multiple-day food records, or 24-hour recalls[31,44,45,56–58]. However, these tools can lead to miss estimation on fluid intake due to several reasons:

first, because drinking water does not provide calories and usually is not recorded; secondly, because beverages are often consumed all along the day and between meals which might lead to underreported intake and consequently its assessment is commonly forgotten by both the individual and the interviewer. In addition, food diaries and dietary records, which require a longer time to being completed, are more expensive and usually focus on the recent intake data. Because of this, their use might not be feasible to determine habitual intake patterns and neither to be used in large-scale epidemiological studies.

In the last decade, more specific assessment tools for fluids intake have been developed[55,59–61]. In 2010, Hedrick and colleges developed a self-administered beverage intake questionnaire that estimates the mean daily intake of fluids consumed across 19 beverages in the American population[55], of which an abbreviate version has been recently published[59]. However, these questionnaires are mostly focused on energy intake. In 2012, it was developed in Greece a water balance questionnaire aimed to evaluate water intake from drinking water, fluids, and solid foods, Finally, in 2016 it was designed and validated a fluid-specific questionnaire addressed to measure habitual fluids intake (including drinking water and other types of beverages) in Spanish population[61]. To the best of our knowledge, this questionnaire[61] is the only assessment tool validated in the Spanish population addressed to evaluate habitual beverage consumption patterns, and therefore a reliable and optimal tool for nutrition research.

3. Types of beverages

3.1 Drinking water

Drinking plain water (tap or bottled water) is the recommended beverage for the maintenance of healthy hydration status, especially because it is a calorie-free fluid[62], and an important source of minerals such as sodium, calcium, and magnesium; however, minerals intake through water might vary according to its chemical composition, on the source and the amount consumed[6,63].

Since our organism has constant water losses and this nutrient cannot be accumulated in the body, drinking plain water should be daily and frequently consumed. The recommendation on drinking water consumption established by the EFSA was set at 2.0L/d and 1.6L/d for men and women[7], respectively, which under certain conditions (physiological and-or environmental), might be increased. Nevertheless, some dietary guidelines do not focus their recommendations on the amount of water intake; instead, focus the recommendations on the consumption of plain water instead of sugary drinks[64,65].

The association between drinking plain water consumption and health has been poorly explored. Some authors have reported a decreased risk for excess body weight[7,66,67] and type 2 diabetes mellitus (T2DM)[58,68] in individuals that consume high amounts of water, mainly through the replacement of caloric beverages which in consequence decreases overall energy intake[67]. It has also been proposed that drinking water may induce thermogenesis (slightly increasing metabolic rate)[69], and that liquid volume can increase gastric distension and satiety which contributes to lower energy intake at subsequent meals[66]. Concerning kidney function, some authors have reported inverse associations between the amount of drinking plain water consumption and the risk of chronic kidney disease[70,71] or, urinary lithiasis[72] (especially weakly or very weakly mineralized water)[73]. The proposed mechanism is that higher water intake increases the clearance of sodium, urea, and osmolality, preventing kidney damage[2,74]. Further, due to its minerals' content (sodium, calcium, and magnesium), some authors have explored the association between drinking plain water consumption with other health outcomes such as CVD, cerebrovascular mortality bone mineral density, cancer, among others, with controversial results[75,76]. More large-scale epidemiological studies and interventional trials are needed to clarify the effect of drinking plain water consumption on these health outcomes.

3.2 Hot beverages

Coffee and tea are largely consumed worldwide; in Mediterranean countries, they are the most commonly consumed hot beverages[31]. These beverages are characterized by their content of caffeine, polyphenols (as chlorogenic acids and catechins), other bioactive compounds, and micronutrients[77]. Because of its composition, coffee and tea, have been associated with several health outcomes.

Coffee is especially characterized by its high content in caffeine. Coffee and caffeine have been associated with a lower risk of several health outcomes including CVD, T2DM, some types of cancer, gallstones, kidney stones, depression, and neurological diseases (including depression, Parkinson´s, and Alzheimer's disease)[78–80]. Moreover, it has been suggested that the consumption of both could prevent weight gain and promote weight loss[80,81]. It is also known that caffeine has a diuretic and natriuretic effect and decreases water and sodium reabsorption in the kidney[37], however habitual consumption has not shown to significantly affect hydration status. Further, results from large prospective cohort studies suggest that higher consumption of coffee is also associated with moderately lower mortality risk[82]. Nevertheless, the manner it is consumed should be supervised since some brewing methods, such as unfiltered coffee, might content cafestol (a diterpene) which potentially increases serum cholesterol levels (total and LDL-c)[83]. Finally, it has been reported that acute caffeine intake might raise blood pressure, even so, habitual consumption has shown no or a slightly inverse association with hypertension risk[74].

Tea by itself has been associated with the prevention of cancer, chronic inflammation, cardiovascular and liver diseases, diabetes, neurodegenerative disorders, ultraviolet B-induced skin aging, and bone fracture[46,84–86]. Most of these effects have been attributable to its polyphenols content (mostly catechins)[87]. Even so, it has been suggested that tannins content on tea might play an important role in poor iron absorption[88], and therefore, its consumption should be supervised in vulnerable populations, in certain health conditions, and in polypharmaceutical contexts.

The current recommendation on coffee and tea consumption is to "*moderate its consumption*" (up to 4 cups/d)[89]. Besides, the consumption of their nutrient-dense options (along with sweeteners, whole milk, or cream), should be moderate to avoid detrimental effects on health. Regarding caffeine, which is structurally similar to adenosine and which may promote behavioral functions, such as vigilance, attention, mood, and arousal via adenosine A1 and A2A receptors blockade[90], the recommendation is not to exceed 400mg/d. However, this amount might be lower in sensitive people, children, aging, and during pregnancy[78,89]. Further, it has been suggested that caffeine intake at high doses (>200 mg per occasion or >400 mg per day) and in sensitive people can induce anxiety[91]. However, the evidence on the association between caffeine intake and anxiety at low-moderate doses in healthy adults remains unexplored.

3.3 Dairy beverages

Milk, especially cow milk, is one of the most consumed beverages worldwide. In general, it is considered an important daily source of nutrients and energy. Milk has a well-recognized nutrient matrix, which includes water (as its main component 70-90%), lactose (the main carbohydrate), high-quality proteins (especially cow milk), complex fat composition, and a considerable amount of micronutrients as calcium (characterized by its high bioavailability), phosphorus, magnesium, and vitamins D, A, and B complex[92]. Milk from a range animal species (sheep, goats, buffalo, camel, etc.) is also consumed, and with some differences on nutritional composition among them[92].

Milk commonly undergoes several processing procedures (pasteurization, fermentation, fortification) which are prone to affect its composition[93]. Typically, milk is classified according to its fat content into whole milk, skimmed milk, semi-skimmed milk, and low-fat milk; fat-soluble vitamin content might be lower in fat-reduced milks compared to whole milk.

Despite the wide variety of milk products, few studies have particularly explored the association between milk subtypes, and/or dairy-based beverages with health. The current scientific evidence is mostly focused on total dairy products' effect on health outcomes[92]. There is moderate evidence between milk and/or dairy product consumption and decreased risk of T2DM in adults[94]. Further, an inverse association between total milk consumption and MetS risk has been reported[95]. Generally, dairy products consumption has been inversely associated with weight gain and positively associated with improvements in body composition, especially in the short-term and as part of an energy-restricted diet[96]. Despite the concern on milk fat content (particularly SFA), the available scientific evidence shows that milk and total dairy products consumption, with either regular or low fat content, is not associated with increased CVD risk[97]. In early life, milk consumption has an important role as a source of nutrients for bone growth, maturation and metabolism[92]; however, the protective association of milk consumption against osteoporosis, and bone fracture remains unclear[98].

The potential beneficial effect of milk consumption has been attributed to its components, such as calcium which might interact with SFAs, consequently decreasing fat absorption and improving plasma lipid profile). Likewise, it has been proposed that calcium, vitamin D, sphingolipids, butyric acid, and milk proteins may be protective against some types of cancer[99]. Additionally, it has been proposed that proteins on milk might modulate satiety and, consequentially, total energy intake, reducing weight gain[92].

More research is needed to better understand the mechanisms involved and the relationship between milk and milk sub-types consumption with health. Furthermore, in the last years the amount of dairy-based beverages, such as milkshakes, and yogurt drinks, that we can find in the market has increased, and its impact on health needs to be explored.

Health organizations recommend the consumption of 2 -3 servings/day of low-fat dairy products[65]. Similarly in Spain, the general recommendation is to consume 2-4 portions daily of dairy products (1 portion of milk is equivalent to 200 – 250ml)[43]. Nevertheless, lactase deficiency, a normal developmental phenomenon characterized by the down-regulation of lactase activity, increases lactose poor digestion during adulthood[92], has resulted in an increase of plant-based beverages consumption.

3.4 Soups and broths

This group includes a wide range of fluids such as soups, broths, vegetable juices, and *gazpacho*/*salmorejo* (a vegetable-based cold soup typically consumed in Spain). The nutritional properties and calorie content of the fluids included in this group might vary among them as a consequence of the ingredients included and the cooking methods used to prepare them. In general, soups and broths supply high amounts of water and contribute to the intake of vitamins and minerals[100]. Moreover, they may also contain sugar, fats, and salt, especially in their bottled versions[101].

The association between these type of fluids and health has been poorly explored. Regarding *gazpacho* consumption, it was reported an inverse association between the frequency of its consumption and systolic and diastolic BP, as well as the prevalence of hypertension in a Mediterranean population at high cardiovascular risk compared to no-consumption[102]. This association has partly been attributable to its phytochemicals content. Additionally, in comparison with other typically consumed Mediterranean foods (as *ajoblanco*, hummus, bread), *gazpacho* showed the highest satiating scores, despite the low content of protein or fiber[103]. It has been proposed that, despite its energy density, the fluid volume ingested has an effect on satiety sensation, and in consequence has an important role in weight gain (higher volume might cause a lower food intake)[100].

Nevertheless, the addition of salt to these food products might result in high sodium content compared to other fluids and plant foods. The assumption that soups and broths are usually healthy and low-calorie food might induce people to consume larger portions, therefore nutritional advice should focus on cooking methods and the use of healthy ingredients. Further studies are needed to clarify the association between soups, broths, and vegetable juices and health outcomes, and the potentially involved mechanisms.

3.5 Sugary beverages

Sugary drinks, defined as all types of beverages containing free sugars, are recognized as a major source of dietary sugar, especially in developed and developing countries. According to WHO definition, free sugars refer to monosaccharides (such as glucose, fructose) and disaccharides (such as sucrose or table sugar), either added to food and beverages during processing procedures, or which naturally present in the products (as in fruit juices)[64]. In this beverage group can be included carbonated or non-carbonated soft drinks, fruit/vegetable juices and drinks, liquid and powder concentrates, flavoured water, energy and sports drinks, ready-to-drink tea, ready-to-drink coffee, and flavoured milk drinks.

The association between sugary drinks (and subtypes) and health has been extensively studied[104,105]. Its consumption has been associated with an increased risk of weight gain[99,106], TD2M[107], hypertension[108,109], poor cognitive function[110], MetS[107,111], adverse levels of cardiometabolic biomarkers[112] and cardiovascular disease[113], mortality (mainly to due CVD)[114,115], and cancer[116,117].

The observed associations have been attributable to several mechanisms[118]. First, sugary drinks contribute to increasing overall energy intake[118]. Second, fluids have a low satiety effect, maintaining (or even increasing) energy intake in the subsequent meals, leading to a positive energy balance[119]. Third, the intake of free sugars, like fructose, in high amounts can promote lipogenesis resulting in atherogenic dyslipidaemia, insulin resistance, over activation of uric acid pathway and consequently decreasing nitric oxide, lower levels of adiponectin, and increased values of inflammatory biomarkers[109,120]. Finally, these beverages are characterized by their high glycaemic index which stimulates appetite and increases the risk of hyperinsulinemia and insulin resistance[121]. Moreover, its harmful impact on health has not been only attributable to its free sugar content and contribution to energy intake, but also to the presence of ingredients as sodium and caffeine which might act synergically potentiating adverse effects[109], and also to its content of potentially carcinogenic compounds as some colorants and pesticides[116].

Specifically, fruit juice consumption's effect on health is controversial[58,99,111,122]. Despite the free sugar content on fruit juice, it also has some vitamins, nutrients, and other bioactive compounds which may partly explain the less frequent associations reported (compared to other sugar drinks) between fruit juice consumption and health outcomes. In this regard, future research efforts should be focused on comparing the effects on health of the consumption of different types of fruit juices (orange, apple, pineapple, etc.; either natural or bottled).

The current WHO recommendation is to reduce free sugar intake to < 10% of total energy intake, and also it has been suggested a reduction below 5% for higher protection, especially regarding dental caries[64]. However, considering that it was not possible to set an upper level of safe consumption, the EFSA has recommended that the intake of added and free sugars should be as low as possible[123]. Some countries have applied taxes to sugary drinks as a public economic health strategy to reduce sugar consumption with positive results[124,125].

3.6 Artificially sweetened beverages

In an attempt to decrease caloric intake and the potential negative effect of free sugars, artificially sweetened beverages (ASB) are consumed as alternatives to sugary drinks. Even so, their effect on health remains unclear, the current scientific evidence does not support a positive effect on weight loss or in the prevention of cardiometabolic risk factors onset [105,125,126]. ASBs consumption has been associated with a higher risk of hypertension[105], obesity[126], T2DM[127], MetS[111], CVD[113] and mortality[114]. In recent years, it has also been suggested that ASB and its components could lead to alterations in gut microbiota increasing the risk of insulin resistance[128,129]. However, it has been stated that results should be taken with caution, since ASBs are commonly consumed by individuals who already suffer from chronic diseases (as T2DM), and the observed associations might be due to reverse causation.

Despite, substitution analyses have shown that the replacement of sugary drinks by ASB is inversely associated with weight gain, T2DM, and mortality[127]. Moreover, when ASB or sugary drinks were both replaced by water, the risk for weight gain, T2DM and mortality showed a higher decrease[127].

The potential mechanisms which could explain the observed associations include a) ASBs consumption could alter dietary patterns preferences (increase the likeliness for sweet taste, and in consequence increased energy intake)[130,131]; b) ASBs might cause endocrine disruptions[132], and increase blood glucose[133]. Moreover, ASBs are characterized by their scarce nutrient matrix and high content on food additives[101], as aspartame (which has been suggested to be carcinogenic)[134]. For these reasons, their consumption should not be recommended as part of a healthy diet.

Further research is needed in the field to clarify the mechanisms underlying these associations and dismiss the potential bias due to reverse causation.

3.7 Alcoholic beverages

According to the WHO, in 2016 more than 2 billion people were current drinkers, being men those with larger consumption compared to women [135]. The most commonly consumed alcoholic beverages are spirits, wine, and beer, with a great variation in their water and alcohol content among them[136].

Alcoholic beverage consumption is a controversial issue because of the existent evidence in both directions, protection and risk[137]. The effect of alcohol on health outcomes might be conditioned by the type of alcoholic beverage consumed, the habitual amount consumed, and sex [138].

In general, alcoholic beverages do not contribute to hydration, on the contrary, it has a diuretic effect[139], and increases the risk of dehydration. Moreover, alcohol provides 7kcal/g, which contributes to an increased overall energy intake[140], and which not appear to reduce subsequent energy intake from foods. Further, it has been suggested that alcoholic beverages can increase appetite and disturb lipid metabolism [141]. Some types of alcohol-containing beverages have been associated with excess body weight[142], whereas others like wine seem to decrease the risk of central obesity[143].

Harmful alcohol consumption is a cause of premature death and disability[135]. It has been associated with liver disease, certain cancers (colon, breast, liver cancers), and a higher risk of high blood pressure, heart failure, dementia, depression and anxiety[135,137,144]. In pregnant women, might cause fetal alcohol syndrome, along with social implications[99,135,137].

Epidemiological studies have associated low-to-moderate alcohol and wine consumption[138,145] with a positive association on chronic cardiovascular diseases prevention, mostly ischemic heart disease. It has been hypothesized that some wine components (as polyphenols) have cardioprotective effects[146] that might act synergically with ethanol conferring the beneficial effect. Low-to-moderate alcohol consumption has been associated with a reduced risk of T2DM due to improved insulin sensitivity[147]. Nevertheless, excessive chronic consumption might lead to glucose homeostasis disruption and insulin resistance development, and in consequence to an increased risk for T2DM[148].

The evidence supporting the potential positive association of alcoholic beverage consumption on health has been observed mainly in the context of a healthy dietary pattern, such as the MedDiet, where the amount of low-grade fermented alcoholic beverages (wine, beer) is limited and mostly consumed with meals[146,149,150]. It should be noticed that similar beneficial associations as the attributable for alcohol consumption can be observed by adhering to a healthy diet without the potential risk of alcohol consumption. Therefore, people who do not usually consume alcoholic beverages should not start drinking because of their potential beneficial effects.

Worldwide strategies have been developed to reduce alcohol consumption with the intent to reduce its harmful public-health effects[135]. In the European region, in the last decade, the consumption of spirits was reported to decrease by 3%, whereas the consumption of wine and beer showed an increasing trend[135]. In Spain, for people who already consume alcoholic beverages, the current low-risk alcohol consumption is set at 20g alcohol/day for men and 10g alcohol/day for women[151]. Women have more body fat (which delays alcohol metabolism) and lower production of alcohol dehydrogenase (the enzyme required in alcohol metabolism) than men[135,142]. Consequently, the maximal potential beneficial effect (also as the harmful effect) is achieved at lower doses for women than for men[137]. More scientific evidence is needed to clarify the differences observed among alcohol-containing beverages and health.

3.8 Other beverages

There are some fluids which due to the heterogeneity in their nutritional composition do not completely fit on a specific beverage group. This is the case of plant-based drinks, non-alcoholic beer, and liquid meal replacements.

Plant-based drinks include beverages prepared with soy, oat, rice, coconut, almond, walnuts, among others food sources, which are commonly chosen as milk consumption alternatives, and which consumption has increased in the last years[152,153]. The nutritional composition of plant-based drinks varies considerably as their properties depend on a wide range of variables (food source, processing, fortification with micronutrients, addition of sugar and oils)[152,153]. The few studies that have explored the effect of plant-based drinks consumption have been conducted in small samples, and have been focused on the association between plant-based drinks consumption and changes in anthropometric parameters, compared to milk consumption[96,154]. But none of them have studied the association between plant-based drinks consumption and anthropometric changes in the long term. Non-alcoholic beer popularity has increased in recent years and seems to be an option for beer consumers to avoid or moderate ethanol intake. Consumers of non-alcoholic beer might beneficiated from the potential positive effects of some beer components on health, without the increased risk conferred by the ethanol intake[155]. However, the scientific evidence in this regard is scarce and further studies are needed to clarify the association of non-alcoholic beer components and health. Liquid meal replacements are mostly consumed to reduce daily energy intake. Results from a meta-analysis showed that, in the short term, its consumption is associated with weight loss, but its role in the prevention of weight gain, maintenance of weight loss, and its effect on cardiometabolic risk factors remains unclear[156,157].

4. Cardiovascular risk factors and cognition decline

4.1 Overweight, obesity and abdominal obesity

Overweight and obesity are defined as an excess of body fat accumulation. Their onset is the result of an energy imbalance, with a multifactorial background that includes genetics, sedentary lifestyle, excessive caloric intake, among others[158]. Excess of body weight incidence and prevalence has almost triplicated worldwide during last 40 years, with such increasing rate it is estimated that in 2016 near of 2 billion adults had overweight, and from those, approximately 650 million had obesity [159,160]. According to data from the European Survey of Health conducted in 2020, in Spain more than 44% of men and 30% of women had overweight [161](**Figure 2**). For this reason, in addition to their role as a risk factor for the development of non-communicable chronic diseases such as T2DM, MetS, cardiovascular disease, mental health disorders[162], and one of the main causes of premature death, excess of body weight is recognized as a main worldwide public health concern[159].

BMI, weight divided by height (Kg/m^2)[163], is the most common adiposity biomarker used in clinical practice to diagnose the presence of overweight and obesity. BMI values ranging from 25-29 Kg/m^2 indicate overweight, while a BMI ≥ 30 Kg/m^2 indicates obesity[159].

Despite that BMI allows to evaluate the excess of body weight, might not be the best tool to assess body fat accumulation, since it does not distinguish between weight associated with muscle and weight associated with fat or bone[160,164]. Central or abdominal obesity, characterized by intra-abdominal fat accumulation has been postulated as a better predictor of adiposity status, in addition to that, it has been associated with higher metabolic and cardiovascular disease risk[165,166]. Central obesity can be indirectly assessed by the waist circumference measurement, which has shown to be highly correlated with intra-abdominal fat content[167]. The cut-off points for central obesity diagnosis are established at >102 cm in men and >88 cm in women[168], however lower cut-off points have been proposed for different ethnic groups[168,169].

Due to its impact on public health, several organizations have proposed several strategies to prevent and treat overweight and obesity. However, the most common recommendations concern lifestyle factors, such as lowering total energy intake, decreasing the consumption of high-calorie beverages, adhering to a healthy dietary pattern, increasing physical activity, the avoidance of sedentary behaviors, and stress and anxiety management[169,170].

4.2 Plasma glucose impairment

In normal conditions, plasma glucose is regulated by insulin which stimulates glucose uptake into muscle and adipose tissue and inhibits hepatic gluconeogenesis during the fed state. Expected values for FPG concentration are between 70 mg/dL (3.9 mmol/L) and 100 mg/dL (5.6 mmol/L). However, reduced insulin sensitivity and insulin secretion, either by the dysfunction or destruction of pancreatic β-cells can lead to plasma glucose regulation impairment[171]. Moreover, insulin resistance is closely associated with overweight, obesity, and excess of body fat. In the long term, increased FPG concentration (hyperglycemia) is a risk factor for the development of non-communicable chronic diseases such as dyslipidemia, T2DM, MetS, CVD, cognitive decline, Alzheimer's disease, among others[172,173]. In 2014, the WHO estimated that 422 million adults were living with diabetes and that the number will continue increasing until 2045 when it is expected that more than 600 million will be living with diabetes[174]. In 2011, T2DM prevalence in Spain was near 14%, and its incidence has continued to increase in the last years (**Figure 2**)[175]. The cut-off point for T2DM has been set at fasting plasma glucose ≥ 7.0mmol/l (126mg/dl), 2–h plasma glucose ≥ 11.1mmol/l (200mg/dl) or glycated haemoglobin ≥ 6.5%[171]. Strategies to prevent its onset are focused on lifestyle interventions: maintenance of healthy body weight; physical activity practice; adherence to a healthy diet; smoking cessation, and avoidance of harmful alcohol use[171,176].

4.3 Dyslipidemia

Atherogenic dyslipidemia, which is recognized as one of the most important risk factors for CVD[177], is defined as alteration on lipids profile characterized by an increase in plasma levels of total TG ((>150 mg/dL) and VLDL-cholesterol, and a decrease in HDL-cholesterol levels (<40 mg/dL in men and <45 mg/dL in women) [178]. Additionally, high plasma levels of LDL-cholesterol (>100 mg/dL) can be observed. The presence of factors such as excess body weight and adiposity have been associated with an increased risk for developing these metabolic disruptions[162,179]. In the last years, it was reported that over 20% of the European population had some lipid disorder[179180]. Similarly, high atherogenic dyslipidemia prevalence has been reported in the

Spanish population with overweight (37%), obesity (17%), T2DM (34%), and MetS (30%)[181]. Lifestyle modifications (healthy diet, high physical activity level, smoking cessation) have been proposed to improve plasma lipid profile. Dietary recommendations are mostly focused on reducing the intake of free and simple sugars (especially sugar-sweetened beverages)[64], limiting saturated and trans fat intake, and moderating alcohol consumption; Along with the preferred consumption of foods rich in unsaturated fat, dietary fibre, and/or with a low glycaemic index[177,178]. Physical activity association with lipid metabolism has been explained by the reduction of the total cholesterol and TG concentrations, the increase of 3-9% in the HDL-c levels, and by a higher proportion of large, less atherogenic LDL particles[182,183]. The last WHO guidelines on PA for adults aged>65, recommend performing at least 150–300 minutes of moderate-intensity aerobic PA; or at least 75–150 minutes of vigorous-intensity aerobic PA; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week, for substantial health benefits[184].

4.4 Hypertension

In 2010, it was estimated that more than 1.3 billion people worldwide had HTA [185]. However, disparities in its prevalence among low- and middle-income countries have been reported. It was estimated that in Spain HTA prevalence was higher than 28%[186,187]. Due to its association with chronic kidney disease, CVD, and premature death, along with its financial burden, nowadays is considered a public health concern. The cut-off points for hypertension diagnosis have been settled at SBP ≥140 mmHg and/or DBP ≥90 mmHg. However, they might vary in the presence of comorbidities (T2DM, chronic kidney disease, etc.)[188]. Strategies to prevent and control hypertension are focused on reducing the risk factors such as high sodium intake, low potassium intake, obesity, alcohol consumption, sedentary lifestyle, stress management, and diet[184,189].

4.5 Cognitive decline and mental health

In the last decade, mental health, which is understood as the absence of mental disorders/disabilities, and by a general state of well-being, in which the individual can conduct usual daily life activities and manage stressful situations, has been recognized as an important component of public health.

Regarding cognition, it is estimated that 50 million individuals around the world suffer from some type of dementia, and it is predicted that the number of people affected by this illness will increase to 75 million in 2030 and 132 million by 2050[190]. With such several individuals affected by this mental condition and its potential negative impact on individual life quality, society, and economy, cognitive dysfunction has become a major public health concern[191].

Cognitive decline can be described as the loss of cognitive (memory, orientation, registration, concentration, processing speed, visual search, and hemi attention) and behavioral (vigilance, attention, mood, and arousal) functions. The progressive loss of these functions can result in a more severe cognitive impairment status, including some types of dementia and even Alzheimer's disease (AD)[192]. Certainly, non-modifiable factors as age (recognized as the strongest one), sex, some gene polymorphisms, race/ethnicity, and family history can increase the risk of developing some type of cognitive dysfunction including dementia and Alzheimer's disease [193]. However, in the last decades, cognitive decline/impairment development and progression has been associated with lifestyle related-risk factors (sedentary behavior, unhealthy dietary pattern, tobacco, and alcohol abuse)[190,193]. There is also evidence that certain medical conditions such as obesity, T2DM, hypocholesteremia, and hypertension may increase the risk of vascular dementia, the risk of progression from cognition impairment to dementia in aged individuals, and Alzheimer's disease[194–196]. Additionally, social isolation, low educational attainment, cognitive inactivity, and mid-life depression have been specifically associated with dementia[192].

Unfortunately, nowadays does not exists cure for cognitive impairment nor dementia, a fact that highlights the need for strategies to prevent its onset and progression to late stages. Therefore, these interventions should be specially focused on modifying lifestyle risk factors such as dietary and beverage patterns and physical activity promotion.

Meanwhile, the prevalence of mental conditions, such as depression and anxiety disorders, have been reported to have increased in the last years. According to WHO, the prevalence of anxiety disorders has increased worldwide by 15% since 2005[197]. These conditions have been associated with the greatest disease burden and the risk of other mental and chronic physical conditions[198], which highlights urgent strategies development for the prevention of mental illnesses.

Anxiety is characterized by a sense of tension, apprehension, and fear, with an intensity that can range from mild to severe[199]. Several risk factors such as life experiences in early life, family history of mental illness, biological predispositions, environmental events, heavy use of alcohol and/or illicit drugs, chronic medical conditions, etc. might trigger its onset[200]. It has been suggested that prevention strategies should be focused on potentially modifiable factors, such as diet. In this regard, previous studies have suggested an inverse association between anxiety and adherence to healthy dietary patterns, while diets with a high content of saturated fatty acids, simple sugars and salt have been positively associated with anxiety[201,202]. Further, the association with certain compounds such as alcohol and caffeine has been mostly explored in susceptible individuals (i.e., those with specific psychopathological conditions, genetic predisposition, etc.), and the research has been especially focused on the effect of very large doses (>200 mg per drinking occasion or >400 mg/d)[91]. Nevertheless, evidence of the role of low to moderate doses of caffeine intake in healthy individuals, analyzed by sex is scarce and inconsistent and scarce.

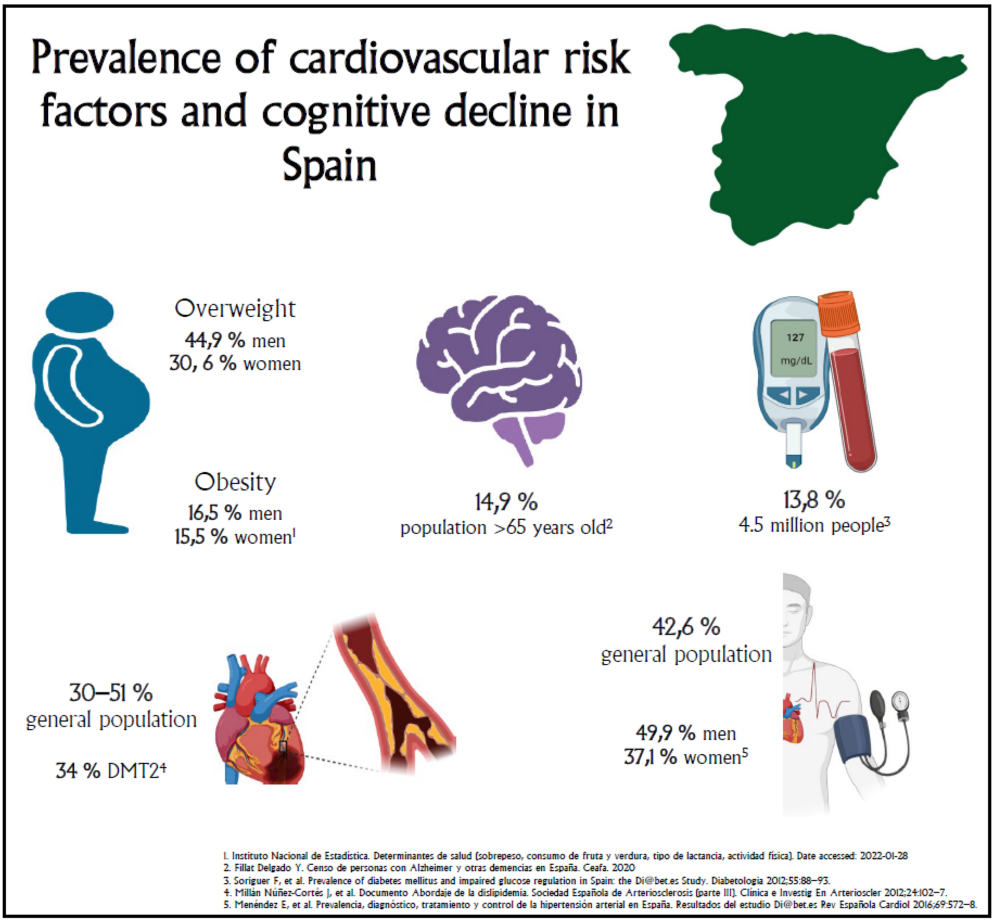

Figure 2. *Prevalence of cardiovascular risk factors and cognitive decline in Spain*

II. JUSTIFICATION

The prevalence and incidence of CVD has become a worldwide major public health concern since its onset increases the risk of other illnesses and pathological disorders which are linked to a reduced quality of life and less expectancy. According to the WHO, almost 19 million people die each year from CVDs. In Spain, CVDs are the main cause of death followed by AD and other types of dementia. Further, these chronic diseases have significant costs (either social or economic). Most of these diseases can be prevented by addressing behavioral risk factors, and therefore strategies have been sought for their prevention, emphasizing on modifiable lifestyle factors such as dietary pattern, physical activity, and smoking habit. However, advice on water intake and fluids consumption remains controversial.

Water plays a crucial role in the well-being of the individual, and therefore ensuring an adequate state of hydration is essential for life. However, an adequate hydration status does not depend exclusively on the consumption of drinking water, but also on the intake from other water sources, such as food moisture and other beverages. These sources differ in their total water content and nutritional composition, and in consequence, its contribution of energy, nutrients, and other compounds such as caffeine or additives to the human body varies and might induce disturbances in homeostasis and metabolism.

Hydration recommendations by worldwide organisms are usually done without differentiation between drinking water, total fluid intake, and/or total water intake. This is an important issue since it might result confuse for the general population to understand and to comply with them. It should be noticed that drinking water refers to the consumption of tap water and bottled water (still or sparkling); the total fluid intake represents the intake of drinking water and all kinds of beverages (milk and dairy beverages, hot beverages, juices, soups, regular sweet beverages, artificially sweetened beverages, and alcoholic beverages); and finally, total water intake it should be understood as the intake of water through fluids and food. In the last decade with the aim to restrict caloric intake, most worldwide dietary guidelines have included advice on the preferential consumption of plain water instead of sugary drinks.

Nevertheless, the impact of drinking water per se on body weight, and cardiometabolic factors has been poorly explored. In addition, despite the association between the consumption of some types of beverages (sugary drinks, milk, coffee, fruit juice, or alcoholic beverages), and metabolic disorders (as T2DM, dyslipidemia, MetS, and some types of beverages) has been further explored, evidence is inconsistent to setup clear recommendations.

Due to the lack of scientific evidence in the field, particularly regarding drinking water consumption, the study of the potential associations between beverage consumption, body weight, adiposity, and other cardiovascular risk factors and the plausible mechanisms by which do they impact health, has great relevance for public health, especially for the population at high cardiometabolic risk.

Like dietary preferences, previous studies have suggested a sociocultural and geographical influence on behavior related to beverage patterns. For this reason, it is interesting to evaluate the usual consumption of different fluids within the context of a Mediterranean Diet, which is recognized for its beneficial effect on cardiometabolic health, will allow us to establish recommendations on beverage consumption, favor the generation of public policies, and food-beverages industry regulation.

Considering the scarcity of evidence regarding drinking water, along with the existing controversial results about other types of fluids, the findings of the present doctoral thesis sought to get an in-depth view regarding the potential role of drinking water and other beverages on body weight, adiposity, and cardiometabolic health in a senior Mediterranean population at high CVD risk.

III. HYPOTHESIS AND AIMS

Hypothesis 1: Mediterranean elderly individuals follow a healthy beverage consumption pattern which is associated with better compliance with the EFSA's recommendations for total water intake.

- **Objective 1:** To describe the fluid intake pattern of a senior Mediterranean population with overweight/obesity and Metabolic Syndrome.
- **Objective 2:** To evaluate the associations between compliance with recommendations for total water intake and total water intake from fluids, and socio-demographic and lifestyle factors of a senior Mediterranean population at high cardiovascular risk.

Hypothesis 2: Drinking water consumption is associated with weight loss and changes in adiposity in the medium-long term in an elderly Mediterranean population.

- **Objective 1:** To evaluate the associations between the frequency of drinking water consumption, body weight and waist circumference changes in an elderly Mediterranean population.
- **Objective 2:** To assess the theoretical effect of substituting one type of beverage for water on body weight and waist circumference in an elderly Mediterranean population.

Hypothesis 3: Natural fruit juice consumption rather than bottled juices, is associated with cardiometabolic risk factors profile in a senior Mediterranean population with metabolic syndrome.

- **Objective 1:** To assess the associations between total juices, natural juices, and bottled juices consumption with different cardiometabolic parameters in a senior Mediterranean population with metabolic syndrome.

Hypothesis 4: Coffee consumption is associated with better cognitive functioning in a senior Mediterranean population with metabolic syndrome.

- **Objective 1:** To assess the association of coffee consumption and cognitive functioning in a population of elderly overweight/obese adults with metabolic syndrome.
- **Objective 2:** To evaluate the association between different types of coffee (caffeinated or decaffeinated) consumption and cognitive functioning in an elderly population with metabolic syndrome.
- **Objective 3:** To evaluate the association between caffeine intake and cognitive functioning in a senior Mediterranean population with metabolic syndrome.

Hypothesis 5: High mean daily caffeine intake is associated with higher odds of anxiety in a general population cohort.

- **Objective 1:** To assess the sex-specific associations of caffeine intake and trait anxiety in a population of healthy French adults.
- **Objective 2:** To evaluate the potential modifying effect of perceived stress and sugar intake over the relationship between caffeine intake and the odds of anxiety trait.

IV. MATERIAL AND METHODS

1. The PREDIMED-Plus study

1.1 PREDIMED-Plus study objective and design

PREDIMED-Plus study objective

The PREDIMED-Plus study is an ongoing parallel-group, randomized, and controlled clinical trial conducted in 23 Spanish centers, for the primary prevention of CVD in overweight and obese elderly adults with MetS. The main hypothesis of the trial is that by addressing three lifestyle aspects (energy-restricted MedDiet, physical activity promotion, and motivational behavior changes) a higher reduction on cardiovascular events will be attained, in comparison with an intervention based only on energy-unrestricted traditional MedDiet.

The main objective of the PREDIMED-Plus study is to evaluate the effect of an intensive lifestyle intervention on:

- The incidence of cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death).
- Weight change (weight loss and long-term weight-loss maintenance).

Additionally, trial secondary objectives comprise the evaluation of the effect of interventions on waist circumference, and some of the following adiposity excess-driven conditions: total mortality, myocardial infarction, stroke, heart failure, atrial fibrillation, peripheral artery disease, T2DM and its complications, total and site-specific cancer incidence, osteoporotic fractures, cholelithiasis, cataracts, neurodegenerative disorders (dementia and Parkinson's disease), unipolar depression and eating behavior disorders. Furthermore, it will be assessed the effect of the intervention in several intermediate outcomes: overall dietary pattern and nutrients intake, blood pressure, biochemical indicators (serum lipid concentrations, fasting plasma glucose, C-reactive protein, glycated hemoglobin A1c, renal function, uric acid, pharmacological treatment (antihypertensive, lipid-lowering, and/or antidiabetic medication), liver function, quality of life, and psychopathological symptoms.

The PREDIMED-Plus trial was registered at the International Standard Randomized Controlled Trial (ISRCTN89898870).

Study population

Study recruitment started in October 2013 and finished in December 2016. Medical doctors from primary health care centers associated with the recruitment centers were the main responsible for recruiting participants. The established inclusion criteria[61] were men aged 55-75 years and women aged 60-75 years, with overweight or obesity (BMI 27–40 kg/m^2), who at baseline were free of CVD and who met at least three components of the MetS, in accordance with the updated harmonized criteria between the International Diabetes Federation, the American Heart Association and National Heart, Lung and Blood Institute [168].

Moreover, individuals were excluded if they met any of the following criteria:

- Illiteracy, or inability or unwillingness to give written consent or communicate with the study staff
- Documented history of previous CVD, including angina; myocardial infarction; coronary revascularization procedures; stroke (either ischemic or hemorrhagic, including transient ischemic attacks); symptomatic peripheral artery disease that required surgery or was diagnosed with vascular imaging techniques; ventricular arrhythmia; uncontrolled atrial fibrillation; congestive heart failure (New York Heart Association Class II or IV); hypertrophic myocardiopathy; and history of aortic aneurism ≥5.5 cm in diameter or aortic aneurism surgery
- Current or previous history of malignancy cancer within the last 5 years (with exception of non-melanoma skin cancer)
- Inability to follow the recommended diet (religious reasons, swallowing disorders, etc…)
- Low predicted likelihood to change dietary habits according to the Prochaska and DiClemente stages of change mode[203]
- Inability to follow the scheduled intervention visits

- Inclusion in another program providing advice on weight loss (> 5kg weight-loss within the six months before the selection visit)
- History of weight-loss surgery or intention to undergo bariatric surgery in the next 12 months
- History of small bowel resection
- History of inflammatory bowel disease
- Obesity of known endocrine origin (except for treated hypothyroidism).
- Food allergy to any Mediterranean diet component
- Immunodeficiency or HIV-positive status
- Cirrhosis or severe liver dysfunction
- Psychiatric disorders: schizophrenia, bipolar disease, eating disorders, or depression with hospitalization within the last 6 months
- Any severe co-morbidity condition with limited life expectancy
- Alcohol (total daily alcohol intake >50 g/d) or drug abuse within the past 6 months.
- History of major organ transplantation
- Concurrent therapy with immunosuppressive drugs, cytotoxic agents, or systemic corticosteroids
- Current use of weight loss medication
- Concurrent participation in another randomized clinical trial.
- Patients with an acute infection or inflammation (i.e., pneumonia) were allowed to participate in the study 3 months after the resolution of their condition
- Any other condition that may interfere with the adherence to the study protocol

A total of 6874 participants were enrolled in the trial. Participants with T2DM at baseline did not exceed 25% of the final population.

All participants provided written informed consent, and the study protocol and procedures were approved according to the ethical standards of the Declaration of Helsinki.

Study design

The overview of the PREDIMED-Plus study design is presented in **Figure 3** Initially, potential candidates were identified by physicians from primary health care centers and were further contacted by telephone to briefly explain the study. If they were interested in participating, a face-to-face interview was scheduled to explain in detail the study purpose, characteristics, and interventions. Candidates who agreed to participate signed informed consent at this first screening visit, and data on anthropometric measurements (height, weight, and waist circumference), blood pressure, medical history, and lifestyle habits, was collected. Moreover, questionnaires on physical activity and diverse psychopathological aspects were administered, along with a 3-day food registry and records for self-measured body weight, WC, and hip circumference; to be completed at home and be returned at the last screening visit. In the last screening visit candidates who met eligibility criteria and who correctly full-filled the administered questionnaires and records were invited to attend a baseline visit in which randomization was taking place.

Participants of the PREDIMED-Plus study were randomly and equally assigned in a 1:1 ratio to one of two intervention groups:

- Intervention group: Intensive lifestyle intervention based on an energy-restricted MedDiet (energy reduction of ~600 kcal/day according to each participants' basal metabolic rate and PA level), physical activity promotion, and behavioral therapy.
- Control group: Energy un-restricted traditional MedDiet advice.

The randomization process was performed using a centrally controlled, computer-generated random number system. Participants were randomly assigned with stratification by center, sex, and age group (<65, 65-70, >70 years). Couples living in the same household who both met eligibility criteria were randomized together as clusters.

As part of the trial intervention, participants in both groups attended periodical group sessions which were conducted by study dietitians. The group sessions consisted of a set of informative talks including lifestyle-related topics and motivational aspects. Moreover, free extra virgin olive oil (1 liter/month) and raw nuts (125g/month, during the first year of intervention) were provided to reinforce participants' adherence to their assigned study group.

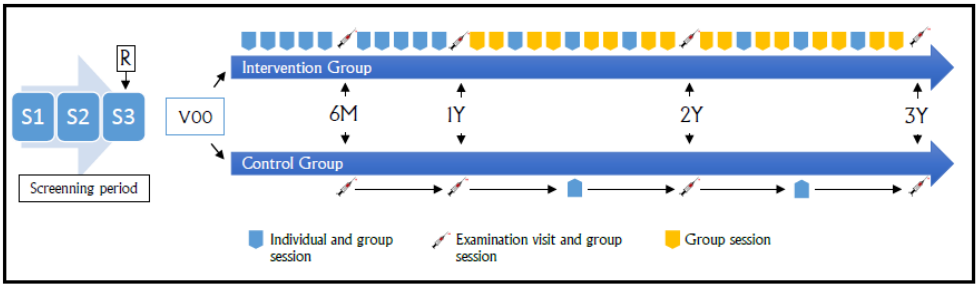

Figure 3. *PREDIMED-Plus study design*

1.2 Exposure assessment methods

Fluid consumption assessment sub-study

The fluid consumption assessment is a sub-study conducted in 10 out of the 23 PREDIMED-Plus recruiting centers. Out of 6874 total participants enrolled in the PREDIMED-Plus trial, 2075 individuals who full-filled, at baseline, the validated 32-item Spanish fluid-intake questionnaire(54) object of this sub-study, were included.

At baseline and yearly, in a face-to-face interview with a trained dietitian, using a validated questionnaire[61], it was recorded the consumption frequency of the last month about each beverage.

The questionnaire items on beverages included: tap water, bottled water, natural fruit juices, bottled fruit juices, natural vegetable juices, bottled vegetable juices, whole milk, semi-skimmed milk, skimmed milk, drinking yogurt (100 and 200 ccs), milkshakes, vegetable drinks, soups, jellies and sorbets, soda (200 and 330 ccs), light/zero soda (200 and 330 ccs), expresso (sweetened and unsweetened), white coffee (sweetened and unsweetened), tea (sweetened and unsweetened), other infusions (sweetened and unsweetened), beer 200 and 330 ccs), non-alcoholic beer (200 and 330 ccs), wine, spirits, mixed alcoholic drinks, energy drinks, sports drinks (200 and 330 ccs), meal replacement shakes and other beverages.

Exposure: Assessment of nutrients intake through the validated 32-item Spanish fluid-intake questionnaire

Nutrients content in beverages was estimated mainly with data from the Higher Education in Nutrition and Dietetics Center (CESNID) Food Composition Tables [101], data from the Spanish Database of Food Composition (BEDCA)[204], and nutritional data from nutritional information labels[205].

To estimate the mineral content of bottled water, we used data from previous studies, which compared mineral content from different bottled water brands commercialized in Spain[206]. Likewise, to estimate the mineral intake through tap water, we used data from previous studies[207], which compared its mineral content according to the geographical location within the Spanish peninsula. To estimate the nutrient intake from natural juices, bottled juices, vegetable drinks, wine, spirits, and mixed alcoholic drinks, the mean content from two or more representative types from each of these beverages was calculated: natural juices (orange and pomelo juice); bottled juices (orange, pineapple, and apple bottled juices); vegetable drinks (almonds and soymilk); wine (white, pink and red wine); spirits (tequila, rum, whiskey, and vodka); and mixed alcoholic drinks (daiquiri, gin tonic, and rum-cola).

Finally, it was estimated that every portion of sweetened coffee, sweetened tea, and other sweetened infusions content 8% sugar.

Nutrients intake through fluids are expressed in the following units:

- Energy: kilocalories/day

- Water, protein, lipids, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, cholesterol, carbohydrates, sugars, polysaccharides, fiber, ethanol: grams/day
- Sodium, potassium, calcium, magnesium, phosphorus, iron, zinc, vitamin E, vitamin C, vitamins B1, B2, and B3: mg/day.
- Vitamin A, retinol, carotenoids, vitamin D, folic acid, vitamin B12: ug/day.

1.3 Covariate and outcome measurements

At baseline, 6 months, and yearly during the follow-up, participants attended a face-to-face visit with PREDIMED-Plus staff (dietitians and nurses) in their primary care centers in which different questionnaires were administered and several anthropometric and biochemical measurements were collected (see **Table 1**).

Table 1. Overview of data collection used for the present doctoral thesis scheduled per visit in the PREDIMED-Plus trial.

	S	Baseline	6-m	1-y	2-y
Eligibility questionnaire	•				
Anthropometric measurements*	•	•	•	•	•
General questionnaire		•	•	•	•
143-item FFQ			•	•	•
32-item Spanish fluid-intake questionnaire		•	•	•	•
Mediterranean diet questionnaire (17/14-items)		•	•	•	•
Physical activity questionnaire	•	•	•	•	•
Blood pressure measurement	•	•	•	•	•
Blood sample collection		•	•	•	
Cognitive-neuropsychological tests	•				•
Psychopathological questionnaire	•			•	•

S: Screening visit; FFQ: Food-frequency questionnaire; M: Month; Y: Year.
*Anthropometric measurements included: weight, height, waist circumference, and hip circumference

1.3.1 Questionnaires

a. <u>General and follow-up questionnaires:</u> These questionnaires included different items related to personal and medical data such as socioeconomic status, education level, conjugal status, family history of disease, illness history, smoking status, alcohol consumption, previous and current CVD risk factors, medication use, new onset of cardiovascular events and-or other medical conditions.

b. Mediterranean diet questionnaires (17/14-items): Short questionnaires used to assess the adherence to the MedDiet diet. The 14-item validated Spanish version questionnaire was answered by the control group[208]. Meanwhile, the intervention group answered the 17-item energy-restricted Mediterranean diet questionnaire (see **Table 2**)[209].

Table 2. 17-item questionnaire of adherence to an energy-restricted Mediterranean Diet

Foods and frequency of consumption	Criteria for 1 point*
1. Do you use extra-virgin olive oil as the main culinary fat?	Yes
2. How many servings of vegetables do you consume per day? (Count garnish and side servings as ½ point; 1 serving =200g)	≥ 2
3. How many pieces of fruit or 100% natural fruit juice do you consume per day?	≥ 3
4. How many servings of red meat, hamburgers, or meat products (ham, sausages, etc.) do you consume per week? (1 serving = 100-150g)	≤ 1
5. How many servings of butter, margarine, or cream do you consume per week? (1 serving = 12g)	< 1
6. How many sugar-sweetened beverages (sodas, tonic waters, energy drinks, fruit juices with added sugar) do you consume per week?	< 1
7. How many servings of legumes do you consume per week? (1 serving = 150g)	≥ 3
8. How many servings of fish/shellfish do you consume per week? (1 serving = 100-150g, or 4 – 5 pieces of fish, or 200g of shelfish)	≥ 3
9. How many times per week do you consume pastries, such as cookies, sweets, or cakes?	< 3
10. How many times per week do you consume nuts[ǂ]? (1 serving = 30g)	≥ 3
11. Do you preferentially consume chicken, turkey, or rabbit meat instead of beef, pork, hamburgers, or sausage?	Yes
12. How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with *sofrito* (sauce made with tomato and onion, leek or garlic and simmered with olive oil)	≥ 2
13. Do you add sugar to beverages (coffee, tea)?	No/use of artificial sweeteners
14. How many servings of white bread do you consume per day? (1 serving = 75 g)	≤ 1
15. How many servings of whole grains (bread, rice, pasta) do you consume per week?	≥ 5
16. How many servings of refined bread, rice, and/or pasta do you consume per week?	< 3
17. Do you drink wine? How much do you consume per week? (One glass=100ml)	Men: 2-3 glasses/day Women:1-2 glasses /day

*0 points if the criteria is not met.
ǂincluding peanuts

c. Leisure-time physical activity questionnaire: a validated Spanish version of the Minnesota Leisure-time Physical Activity Questionnaire[210] was administered to each participant. This questionnaire included information about the monthly frequency (number of days) and duration (min/day) of several physical activities during the previous month. Total physical activity was estimated as the summed product of frequency and duration divided by 30 to obtain the amount of min/day. The intensity of each activity (expressed in metabolic equivalent task, MET) was assigned based on the 2015 Compendium of Physical Activity[211], and further categorized into light (< 4.0 MET), moderate (4 ± 5.5 MET), and vigorous (≥ 6.0 MET) physical activity.

d. Food frequency questionnaire: a semi-quantitative FFQ of 143-items was administered for the evaluation of dietary intake over the last year. Participants were asked to report their frequency consumption, on an incremental scale (from 'never' or 'rarely' to 'more than 6 times per day'), which were transformed into grams or milliliters per day using the standard portion size of each item. Nutrient and energy consumption were derived from these responses using Spanish food composition tables[136,212].

Anthropometric and blood pressure measurements

PREDIMED-Plus trained dietitians were responsible for measuring height, weight, waist circumference, and blood pressure to all PREDIMED-Plus study participants, by using standardized techniques and calibrated scales.

- Weight and height were measured in duplicate with participants wearing light clothes, without shoes nor accessories, using a calibrated balance beam scale and a wall-mounted stadiometer. BMI was calculated as the weight in kg divided by the square of the height in meters.
- Waist circumference: was measured in duplicate and midway between the lowest rib and the iliac crest using an anthropometric tape.
- Blood pressure: was determined in triplicate with the use of a validated semiautomatic oscillometer (Omron HEM-705CP, The Netherlands) while

the participant was in a seated position after 5 minutes of rest in between measurements.

Measurement averages were calculated later for analysis purposes.

Biological samples and biochemical determinations

PREDIMED-Plus nursing staff collected participants' blood samples in fasting conditions. After extraction blood samples were immediately centrifuged, processed, and stored accordingly to PREDIMED-Pus protocol. Biochemical determinations included FPG, HDL-c, LDL-c, total cholesterol, TG, HbA1c, glycated hemoglobin, among others.

Neuropsychological assessment

Cognitive functioning was assessed using a battery of neuropsychological tests which included:

a. The Mini-Mental State Examination test questionnaire was validated for the Spanish population[213]. The MMSE is a 30-item questionnaire that examines cognitive functions including orientation, registration, concentration, memory, language, and copying a figure. It has a maximum total score of 30, and higher scores indicate the absence of cognitive decline[214]. The cut-off point for poor cognitive functioning was established as MMSE score ≤ 24 points.

b. The Clock Drawing Test evaluates visuo-constructive and visuospatial skills, symbolic and conceptual representation, hemi-attention, semantic memory, and executive function (including organization, planning, and parallel processing)[215,216]. For this study, we used a validated Spanish version ranging from 0 to 7[217]. The Clock Test cut-off point was established as ≤ 4 points.

c. The Verbal Fluency Test assesses verbal ability and executive control and consists of two parts: the phonemic fluency task and the semantic fluency task. The total raw score for each task is the number of words the participant produces[218].

d. The Digit Span Test of the Wechsler Adult Intelligence Scale-III Spanish version[219] is made up of two different subtests: DST forward recall and DST backward recall. DST In this study, the performance on the DST was reported via a direct score of 1 to 16 for the forward performance and a direct score of 1 to 14 for backward performance.
e. The Trail Making Test is a tool used to assess executive function, and tests processing speed, sequence alternation, cognitive flexibility, visual search, motor performance, and executive functioning[220]. It consists of part A and part B. Each part is scored according to the time taken to complete the task (lower scores imply better performance).

There is no gold standard cut off point for the VFT, the DST, and the TMT, therefore, cut-off points were established according to the Petersen diagnostic criteria for mild cognitive impairment, which included, among others, scores <1.5 SDs of the mean of a reference population on an episodic memory test[221].

1.4 Study population for the analyses

For the present doctoral thesis, data from the PREDIMED-Plus trial was analyzed as it was an observational prospective cohort design study. Detailed inclusion and exclusion criteria have been extensively described in each article included in this doctoral thesis.

Briefly, from the 6874 participants enrolled in the trial, there were excluded those individuals with lack of information regarding FFQ at baseline or those who reported implausible total energy intake (≤500 and ≥3500 kcal/d in women and ≤800 and ≥4000 kcal in men) (n = 241).

Further, the fluid intake questionnaire is only performed in 10 of the 23 centers participating in PREDIMED-Plus, and therefore, from the 6874 participants enrolled in the trial, only 2067 participants full-filled the validated 32-item Spanish fluid-intake questionnaire at baseline. In consequence, when the fluid intake questionnaire was used as the main assessment tool for fluids consumption, the sample size was smaller. In addition, there were excluded baseline outliers of total fluid intake (established based on 2SDs from the median value (n = 107)).

Finally, participants with missing data on the variables of interest (body weight, waist circumference, cardiovascular risk factors, and cognition) were excluded from the analyses.

2. The Nutrinet-Santé study

2.1 NutriNet-Santé study objective and design

The NutriNet-Santé study is a French large-scale (n=171,000) ongoing web-based cohort, launched in 2009 which aims to explore the associations between nutrition and health as well as the determinants of dietary behaviors and nutritional status. A detailed description of the NutriNet-Santé study has been previously published[222]. The NutriNet-Santé study was registered at www.clinicaltrial.gov as #NCT03335644, and was approved by the Institutional Review Board of the French Institute for Health and Medical Research (INSERM # 00000388FWA00005831) and by the National Commission on Informatics and Liberty (CNIL # 908450 and # 909216).

Briefly, the study population is recruited via traditional methods, multimedia campaigns and online strategies. Eligible participants are adults ≥18 years from the general population with internet access, comprehension of written French, and the ability to self-report information using the study web platform[222]. At inclusion, participants are asked to complete a set of five self-report questionnaires to assess socio-demographic and lifestyle characteristics, physical activity, anthropometric, dietary intake, physical and mental health status[223–228].

Additionally, as part of the follow-up, all participants are asked to complete about one nutrition- or health-related questionnaire per month. All major health events reported by the participants are validated by an expert committee of physicians based on medical records, and/or retrieved from the French National Health Insurance medico-administrative databases. Data on mortality is obtained from the exhaustive French National Mortality Registry (CépiDC). Finally, a sub-sample of the cohort (n=20,000) provided blood and urine samples.

2.2 Exposure assessment methods

Dietary intake assessment

Dietary intake is assessed at baseline and every 6 months thereafter. Participants are asked to complete 3 non-consecutive (two weekdays and one weekend day) 24h dietary records, in which individuals are asked to declare all food and beverages consumed during the previous 24 hours, considering the three main meals (breakfast, lunch, dinner) and any other eating occasion. The tool used for collecting dietary data has been validated against dietitian interviews and nutritional status biomarkers[223,228].

All dietary data are weighted to account for weekdays and weekend usual consumption. Portion sizes were estimated using previously validated photographs[224] or usual containers. To calculate mean daily energy and nutrient intake, the NutriNet-Santé food composition database (>3,500 items) was used[229]. Participants with under-reported energy intake, identified via Black's method[230] considering participants' age, sex, weight, height, physical activity level, and basal metabolic rate, are excluded from the analysis.

2.3 Covariate and outcome assessment

Assessment of covariates

At inclusion and during the follow-up, participants provide self-reported information by completing validated general questionnaires on:

a. Sociodemographic characteristics and lifestyle: marital status, number, and characteristics of family members, education level, professional status, income, smoking, alcohol consumption habits, among others[226].
b. Anthropometric measurements: current height, weight, hip and waist circumferences, weight history, the practice of restrictive diets, body self-perception[225]. BMI (kg/m^2) is calculated based on self-reported height and weight.

c. Health status: past medical history, past and current medication use, dietary supplements consumption, familial medical history, among others. For women information on obstetrical history, pregnancies, menopausal status, contraception, and hormone replacement therapy is also collected[222].

d. Physical and sedentary activity: assessed through the short French version of the International Physical Activity questionnaire[227]. Physical activity is described according to 3 levels of exercise intensity, frequency per week (days/week), and daily duration of each performed activity. Sedentary behavior is estimated by screentime (TV, computer, etc.).

Trait anxiety

Trait anxiety was assessed using the validated French version of Spielberger's State-Trait Anxiety Inventory Form Y (STAI-T)[231], which was once self-completed by participants between 2013 and 2016 as part of the NutriNet-Santé web cohort follow-up. Briefly, Spielberger's State-Trait Anxiety Inventory is one of the most widely used screening tools for anxiety state (STAI-S) and trait anxiety (STAI-T)[232]. In the analysis included in the present doctoral thesis, trait anxiety was the outcome of interest, which is considered a relatively stable personal characteristic displayed in a wide range of daily life situations[232]. The STAI-T sub-scale consists of 20 items based on a 4-point Likert scale with responses ranging from "Almost never" to "Almost always". The total score ranges from 20 to 80, with higher scores corresponding to higher levels of general anxiety symptoms[233].

There is no established cut-off point for defining high trait anxiety, therefore, cut-off points were established according to the methodology applied in prior studies[234,235] (first the value distribution was explored and then applied the sex-specific top quartile as cut-off).

2.4 Study population for the analysis

For the present doctoral thesis, data from the NutriNet-Sante cohort was analyzed as a cross-sectional design study. Detailed inclusion and exclusion criteria have been described in the article included in this doctoral thesis. Briefly, participants with data on caffeine intake and who had responded to STAI-T were included.

3. Statistical analyses

All the studies included in this doctoral thesis have a cross-sectional or prospective cohort design. Statistical analyses conducted are extensively described in each publication presented in the results section. Briefly, all the analyses were performed using the statistical software STATA version 14 and 15 (StataCorp LP). The level for all statistical tests was set at $P < 0.05$ for bilateral contrast.

Generally:

- To compare differences among exposure categories, ANOVA or Pearson chi-square tests were used for continuous and categorical variables, respectively.
- In cross-sectional studies, to assess the risk of main outcomes according to exposure categories in the cross-sectional analyses, logistic regression models adjusted for potential confounder factors were used.
- To assess changes (β-coefficients) on outcomes according to exposure categories, multivariable linear regression models were fitted.
- Mathematical models were used to assess the theoretical effect of substituting one type of beverage for another. Both variables were simultaneously added to the models and the difference in beta-coefficients from the same model was used to estimate the theoretical effect of substituting one type of beverage for another.
- To assess the linear trend, it was assigned the median value to each exposure category and the new variables were modeled as continuous.
- Interaction between covariates and exposure variables was tested with likelihood ratio tests, which involved comparing models with and without cross-product terms.

- All analyses were conducted with robust variance estimators to correct for intra-cluster correlations (considering the members of the same household to be clustered).

V. RESULTS

Table 3. Original articles included in the present thesis doctoral

Chapter 1

Paz-Graniel I, Babio N, Serra-Majem L, et al. *Fluid and total water intake in a senior mediterranean population at high cardiovascular risk: demographic and lifestyle determinants in the PREDIMED-Plus study*. Eur J Nutr. 2020 Jun;59(4):1595-1606. doi: 10.1007/s00394-019-02015-3.
Impact Factor: 5.619
Category and Rank: Nutrition & Dietetics, Q1

Chapter 2

Paz-Graniel I, Becerra-Tomás N, Babio N, et al *Baseline drinking water consumption and changes in body weight and waist circumference at 2-years of follow-up in a senior Mediterranean population*. Clin Nutr. 2021 Jun;40(6): 3982-3991. doi: 10.1016/j.clnu.2021.05.014. Epub 2021 May 23.
Impact Factor: 7.325
Category and Rank: Nutrition & Dietetics, D1

Chapter 3

Becerra-Tomás N, **Paz-Graniel I**, Tresserra-Rimbau, et al. *Fruit consumption and cardiometabolic risk in the PREDIMED-plus study: a cross-sectional analysis*. Nutr Metab Cardiovasc D. 2021. Jun 7; 31(6):1702-1713. doi.org/10.1016/j.numecd.2021.02.007. Epub 2021 Feb 17.
Impact Factor: 4.222
Category and Rank: Nutrition & Dietetics, Q2

Chapter 4

Paz-Graniel I, Babio N, Becerra-Tomás N, et al. *Association between coffee consumption and total dietary caffeine intake with cognitive functioning: cross-sectional assessment in an elderly Mediterranean population*. Eur J Nutr. 2020 Oct 30. doi: 10.1007/s00394-020-02415-w
Impact Factor: 5.619 (2020)
Category and Rank: Nutrition & Dietetics, Q1

Chapter 5

Paz-Graniel I, Kose J, Babio N, et al. *Caffeine intake and its sex-specific association with general anxiety: a cross-sectional analysis among general-population adults.* . Nutrients 2022, 14, 1242. https://doi.org/10.3390/nu14061242
Impact Factor: 5.719
Category and Rank: Nutrition & Dietetics, Q1

D, Decile; Q, Quartile
*Accessed date: March 10th, 2022 (Journal Citation Reports of the ISI web of Knowledge, Thompson Reuters).

Chapter 1

Fluid and total water intake in a senior Mediterranean population at high cardiovascular risk: demographic and lifestyle determinants in the PREDIMED-Plus study.

Paz-Graniel I, Babio N, Serra-Majem L, Vioque J, Zomeño M, Corella D, Díaz-López A, Pintó X, Bueno-Cavanillas A, Tur J, Daimiel L, Martínez J, Becerra-Tomás N, Navarrete-Muñoz E, Schröder H, Fernández-Carrión R, Ortiz-Andrellucchi A, Corbella E, Riquelme-Gallego B, Gallardo-Alfaro L, Micó V, Zulet M, Barrubés L, Fitó M, Ruiz-Canela M, Salas-Salvadó J

Key teaching points:

- Water is an essential nutrient for life. The excess or deficiency of water or other types of beverages intake and its micronutrients can determine the state of health or disease.

- Few studies have analyzed the demographic and lifestyle determinants of beverage consumption pattern and the compliance with current public health recommendations.

- A cross-sectional assessment using a validated fluid intake questionnaire with 1902 senior Mediterranean population at high CVD risk was conducted in the framework of the PREDIMED-Plus study.

- The present study is the first one that analyses the TWI determinants and describes the fluid intake pattern of a Mediterranean population at high cardiovascular risk.

- Results suggest that a healthy lifestyle, characterized by high adherence to the MedDiet and spending more time on PA, is associated with compliance with TWI recommendations.

European Journal of Nutrition
https://doi.org/10.1007/s00394-019-02015-3

ORIGINAL CONTRIBUTION

Fluid and total water intake in a senior mediterranean population at high cardiovascular risk: demographic and lifestyle determinants in the PREDIMED-Plus study

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Abstract

Purpose We aimed to evaluate associations between compliance with recommendations for total water intake (TWI) and total water intake from fluids (TWIF), and some socio-demographic and lifestyle factors of a senior Mediterranean population at high cardiovascular risk.

Methods Cross-sectional analysis with data of 1902 participants from the PREDIMED-Plus study. A validated 32-item Spanish fluid-intake questionnaire was used to assess beverage consumption and water intake. Multivariable logistic regression models were used to assess the odds ratio (OR) and the 95% confidence interval (CI) for complying with European Food Safety Agency recommendations for TWI and TWIF according to various socio-demographic and lifestyle factors, and for the joint associations of Mediterranean diet (MedDiet) adherence and moderate–vigorous physical activity (MVPA).

Results The mean total volume of fluid intake in the population studied was 1934 ± 617 mL/day. Water was the most frequently consumed beverage. Significant differences between sex were only observed in alcoholic and hot beverage consumption. Compliance with TWIF was associated with being women (OR 3.02; 2.40, 3.80), high adherence to MedDiet (OR 1.07; 1.02, 1.12), and participants who were more engaged in physical activity (PA) (OR 1.07; 1.02, 1.13). Age was inversely associated (OR 0.96; 0.94, 0.98). Similar results for TWI recommendations compliance were observed in relation to being women (OR 5.34; 3.85, 7.42), adherence to MedDiet (OR 1.16; 1.02, 1.31) and PA (OR 1.07; 1.00, 1.15). The joint association of PA and MedDiet, showed that participants with higher adherence to MedDiet and meeting WHO recommendations for MVPA complied better with the TWI recommendations (OR 1.66; 1.19, 2.32).

Conclusions High compliance with recommendations for TWI was associated with being a woman, and a healthy lifestyle characterized by high adherence to the MedDiet and PA.

Keywords Total water intake (TWI) · Fluid intake · Beverages · Mediterranean diet

Introduction

Water is essential for the optimal physiological function of the human body, because it is a source of minerals and electrolytes and is involved in metabolic processes [1]. Low fluid consumption and inadequate water intake could induce dehydration and its consequences, increase the risk of urolithiasis and non-communicable chronic diseases [2] and have some undesirable effects on cognitive function and physical performance [3]. Consequently, adequate water intake is

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necessary to maintain a good health status. The elderly are at special risk of low water intake because they lose their sensation of thirst and appetite, and their renal ability to concentrate urine is impaired [4, 5]. In fact, a previous study in US citizens reported that elderly population had inadequate water intake [4], and higher risk of dehydration.

To prevent dehydration and its undesirable effects on health, reference values for water intake have been established. The European Food Safety Agency's (EFSA) recommendation for total water intake (TWI) for the elderly is 2.5 L/day and 2.0 L/day for men and women, respectively, in conditions of moderate environmental temperature and moderate physical activity [5]. Water intake consists largely of the consumption of drinking water and other beverages (80%), although it is generally held that approximately 20% is consumed through food [5]. Beverages provide not only water, but also some minerals, vitamins and other nutrients such as carbohydrates, proteins, and fats. Therefore, total fluid intake and the beverage pattern, as well as food consumption, are fundamental to determine the health and disease, not just hydration.

There are several determinants of total fluid intake and beverage consumption. For example, healthy dietary patterns and regular physical activity (PA) have proved to be associated with a healthier beverage pattern and general lifestyle [6, 7]. The Mediterranean diet (MedDiet), a healthy dietary pattern associated with a reduced risk of several chronic health conditions, is characterized by the consumption of water as the main drinking fluid, a daily but moderate consumption of red wine especially with meals, a moderate consumption of milk or yogurt, and a low consumption of sugar-sweetened beverages (such as soda and sugar-sweetened fruit juice or tonic) [7, 8]. PA has also been associated with healthier dietary patterns. People who are more physically active are more likely to adhere to the MedDiet [9] and, therefore, consume healthier beverages. In fact, a previous study by our research group reported that healthy young and adult individuals who adhere more closely to the MedDiet and who engage in more physical exercise had a healthier fluid intake pattern, and a greater probability of complying with EFSA's recommended total daily fluid intake and the World Health Organization's recommendations on the intake of free sugars to reduces the risk of non-communicable diseases [10]. These associations have been especially explored in adolescents or healthy adults, but not in individuals at high cardiovascular risk.

Since fluid consumption has been the object of few studies and these relationships have been poorly studied in old populations, the aim of the present study was to describe the fluid intake pattern of a senior Mediterranean population with overweight/obesity and Metabolic Syndrome (MetS), and to evaluate possible associations between compliance with TWI and TWIF recommendations and some socio-demographic and lifestyle factors.

Materials and methods

Study design and participants

The present study is a cross-sectional baseline analysis within the frame of the PREDIMED-Plus study, a large, multicentre, parallel-group, randomized and controlled clinical trial conducted in Spain to assess the effect of an intensive weight loss intervention program based on an energy-restricted traditional MedDiet, PA promotion and behavioural support, in comparison with an intervention based on energy-unrestricted traditional MedDiet (control group) on cardiovascular disease (CVD) morbi-mortality. A more detailed description of the PREDIMED-Plus study is available at https://www.predimedplus.com. This study was registered at the International Standard Randomized Controlled Trials (ISRCT; http://www.isrctn.com/ISRCTN89898870) on 24 July 2014.

From October 2013 to October 2016, 6874 participants were recruited and randomized in 23 centres from various universities, hospitals and research institutes in Spain. The eligible participants were adults (aged 55–75 for men; 60–75 for women) with overweight/obesity [body mass index (BMI) ≥ 27 and < 40 kg/m^2], who had at least three components of the Metabolic Syndrome according to the updated harmonized criteria between the International Diabetes Federation, the American Heart Association and National Heart, Lung and Blood Institute [11]. The age cutoff has been defined to have enough power to find differences between groups in relation to the primary end-point of the trial (a composite of CVD incidence and mortality). Detailed inclusion and exclusion criteria have been extensively described elsewhere [12].

This is a sub study conducted in 10 out of the 23 PREDIMED-Plus recruiting centres. Out of 6874 total participants enrolled in the PREDIMED-Plus trial, 2068 individuals full-filled the validated 32-item Spanish fluid-intake questionnaire. From those 2068 participants with Spanish fluid-intake questionnaire, we excluded participants without the baseline food frequency questionnaire (FFQ), or who reported implausible total energy intakes (≤ 500 and ≥ 3500 kcal/day in women and ≤ 800 and ≥ 4000 kcal/day in men; $n = 55$), and, those participants who reported a total fluid intake above or below two standard deviations from the median value (< 303 and > 3684 mL/day in men and < 474 and > 3295 mL/day women; $n = 111$). Hence, the final sample analysed in present study was 1902 individuals (945 men and 957 women).

As the present cross-sectional analysis has been conducted with baseline data of the study participants (before the intervention was started), results of the present study were not reported separately by intervention or control group.

All participants provided written informed consent, and the study protocol and procedures were approved according to the ethical standards of the Declaration of Helsinki.

Assessment of fluid and water intake

At baseline a trained dietitian held a face-to-face interview with participants and completed a validated 32-item Spanish fluid-intake questionnaire [13], which recorded the frequency of consumption of various beverage types over the previous month. The average daily fluid intake from beverages was estimated from the servings of each type of beverage. The questionnaire items on beverages included: tap water, bottled water, natural fruit juices, bottled fruit juices, natural vegetable juices, bottled vegetable juices, whole milk, semi-skimmed milk, skimmed milk, drinking yogurt (100 and 200 cc), milkshakes, vegetable drinks, soups, jellies and sorbets, soda (200 and 330 cc), light/zero soda (200 and 330 cc), espresso (sweetened and unsweetened), white coffee (sweetened and unsweetened), tea (sweetened and unsweetened), other infusions (sweetened and unsweetened), beer (200 and 330 cc), non-alcoholic beer (200 and 330 cc), wine, spirits, mixed alcoholic drinks, energy drinks, sports drinks (200 and 330 cc), meal replacement shakes and other beverages. The water and nutrient content of the beverages were estimated mainly with the CESNID Food Composition Tables [14], with complementary data from the BEDCA Spanish Database of Food Composition [15] and nutritional information from the food industry website [16].

Beverages were classified into eight groups for further analysis: water (tap and bottled water), milk and dairy beverages (milk, milkshakes, drinking yogurt, other milk beverages), hot beverages (coffee, tea and other infusions), sugar-sweetened beverages (SSBs, including carbonated soft drinks, natural and bottled fruit juice, energy drinks and sports drinks), artificial sweetened beverages (ASBs, including light/zero carbonated soft drinks), alcoholic beverages (spirits, mixed alcoholic drinks, wine, beer, cider), broths (vegetable soups and natural and bottled vegetable juice), and other beverages (soy drinks, non-alcoholic beer, sorbets and jellies, and meal replacement shakes).

To compute the TWI, the water contained in food was also calculated. Additionally, foods from the FFQ were classified into 10 food groups: vegetables, fruits, legumes, cereals, dairy beverages, meat and poultry, fats, nuts, fish/seafood, and other foods to assess their contribution to total water intake.

Total daily consumption of fluids (mL) was computed as the sum of all the beverages consumed. Total water intake from fluids (TWIF) (mL) was computed as the water intake through fluids and beverages. TWI (mL) was computed as the sum of the water content of the beverages and foods consumed.

Covariate assessment

At baseline, trained dietitians in a face-to-face interview with the participants completed questionnaires with their socio-demographic information (sex, age, education, and marital status), lifestyle factors (smoking habits, physical activity, and sedentary behaviours), personal medical history, medication use and a 143-item FFQ.

Trained staff in the PREDIMED-Plus operations protocol determined anthropometric variables. Weight and height were measured with calibrated scales and a wall-mounted stadiometer, respectively. BMI was calculated as the weight in kilograms divided by the height in meters squared. Waist circumference was measured midway between the lowest rib and the iliac crest, after normal exhalation, using an anthropometric tape.

In accordance with the PREDIMED-Plus protocol, participants in the control group completed a validated 14-item MedDiet adherence questionnaire [17], while participants in the intervention group completed a 17-item questionnaire to assess adherence to an energy-restricted MedDiet. Eleven items were the same in both of them, and they differed in the amount or number of portions of olive oil, red meat and sugar-sweetened beverages' consumption. To measure adherence to the MedDiet in both groups, these three items were calculated using baseline data from the FFQ. The correlation coefficient between the 14-item MedDiet adherence score and the estimation using the FFQ data was 0.8590 ($n=960$, $P\leq 0.001$) in the control group.

Sedentary behaviours were evaluated using the validated Nurses' Health Study questionnaire for sedentary behaviours [18]. It consists of a set of open-ended questions assessing the average daily time spent over the last year watching TV, sitting while using a computer, sitting on journeys and total sitting. Answers were divided into 12 categories ranging from 0 to 9 h/day of sitting time for the corresponding activity.

Leisure-time PA was assessed using the validated Registre Gironí del Cor (REGICOR) questionnaire [19], which collects information about the type of activity, frequency (days) and duration (min/day) in a month. The intensity was assigned using the compendium of PA [20]. A trained interviewer collected the information for six types of activity during a conventional month: brisk walking (5 MET), walking at a slow/normal pace (4 MET), walking in the countryside (6 MET), climbing stairs (7 MET), working in the garden (5

MET), exercise or playing sports either at home, outdoors or in a gym (11 MET). Depending on the PA intensity, activities were categorized into light PA ≤ 4.0 MET or moderate and vigorous PA > 4.0 MET.

Statistical analysis

For the present report we used the PREDIMED-Plus database updated until October 2018. To report differences in beverage consumption and water intake between male and female individuals, all analyses were conducted separately by sex. Socio-demographic characteristics, beverage consumption, total fluid intake and TWI are reported as mean values and standard deviation (SD) for continuous variables or numbers and percentages (%) for dichotomous variables. Pearson's χ^2 tests or Student's t tests were used to compare the quantitative or general categorical characteristics of the studied population.

The odds ratio (OR, 95% CI) for meeting the EFSA recommendations for TWIF (2 L/day and 1.6 L/day, for men and women, respectively) and TWI (2.5 L/day and 2 L/day, for men and women, respectively) (dependent variables) was assessed by logistic regression models adjusted for age (continuous), sex, educational level (primary education, secondary education and academic/graduate), smoking status (never smoker, former smoker and current smoker), sedentary time (h/day), leisure-time physical activity (30 min./day), MedDiet adherence (< 9, low or ≥ 9, high adherence) and recruitment centre (in quartiles by number of recruited participants). The percentage of individuals who met EFSA recommendations for TWIF and TWI was calculated.

We also explored the joint associations of MedDiet adherence and moderate–vigorous physical activity (MVPA) and the compliance with EFSA TWIF and TWI recommendations by logistic regressions adjusted by the variables mentioned above except for sedentary time, leisure-time physical activity and MedDiet adherence. For both analyses, each participant was cross-allocated to one of the four joint categories in which low adherence to MedDiet and not meeting MVPA recommendations was considered as the reference category. MVPA was first dichotomized into meeting (≥ 150 min/week) or not meeting (< 150 min/week) based on current World Health Organization's recommendations for elderly population [21]. Since the EFSA recommendations are reported by sex, we present the results for the total population and separately by sex. We then conducted stratified analyses to investigate whether the observed associations were modified by sex and age. Interaction was tested with likelihood ratio tests, which involved comparing models with and without cross-product terms.

All analyses were conducted with robust estimates of the variance to correct for intra-cluster correlation in the logistic regression models. Intra-cluster was defined as the participants sharing the same household. Significance level was set at $P < 0.05$. All analyses were cross-sectional, and performed using Stata (14.0, StataCorp LP, TX. USA).

Results

The present analysis included 1902 participants (945 men and 957 women) with a mean age of 65 ± 5 years. The general characteristics of the studied population are shown in Table 1. There were no statistically significant differences between women and men in terms of diabetes or hypertension prevalence and adherence to MedDiet. However, the men were younger, had low BMI values, spent more time on PA, were more likely to smoke, and had a higher educational level. Participants involved in the present analysis did not differ from the rest of the participants enrolled in the PREDIMED-Plus trial in terms of age, sex, BMI, and prevalence of obesity and T2D ($P > 0.05$ for all comparisons)

Table 2 shows the fluid consumption pattern by sex. The mean total volume of fluid intake in the studied population was 1934 ± 617 mL/day. Total fluid intake was higher in men than in women (women 1876 ± 574 and men 1991 ± 653). Although water was the most frequently consumed beverage followed by milk and dairy beverages, differences by sex were only significant for alcoholic and total hot beverage consumption. The consumption of alcoholic beverages was higher in men than women. We also observed that alcohol consumption decreased with age ($P < 0.01$, data not shown). In contrast, women consumed more hot beverages than men. No significant differences were observed by sex in terms of drinking water, dairy beverages, soup or vegetable juices, sugar and sweetened beverages and artificially sweetened beverages.

Total water intake was 2,845 mL (men 2861 ± 656 and women 2830 ± 628). Fluids contributed to total water intake by 1819 ± 558 mL/day (women 1778 ± 536 and men 1861 ± 577). The contribution of each beverage group to total fluid intake is shown in Fig. 1. Drinking water constitutes more than 50% of total fluid intake.

The mean total intake of macro and some micronutrients through fluids for the total population and separated by sex is shown in Supplementary Table 1. In the total sample, energy, carbohydrate, protein and fat intake from fluids was 420 ± 257 kcal/day, 51 ± 39 g/day (more than 70% was from sugars), 23 ± 15 g/day, and 7 ± 6 g/day, respectively. The mean total alcohol intake was 8 ± 13 g/day. Significant differences were observed between sex in terms of energy, sugar, alcohol and potassium intake, which proved to be higher in men than in women.

Mean water intake from food was 1026 ± 286 mL/day (women 1553 ± 289 and men 1000 ± 280). The contribution of water from various food groups is shown

Table 1 General characteristics of the PREDIMED-PLUS population

Variables	All population (n = 1902)	Women (n = 957)	Men (n = 945)	P value[a]
Age, years	65 ± 5	66 ± 4	64 ± 5	< 0.01
Weight, kg	86.6 ± 13.0	80.5 ± 10.8	92.7 ± 12.1	< 0.01
BMI, kg/m^2	32.6 ± 3.5	33.0 ± 3.6	32.3 ± 3.4	< 0.01
BMI classification, % (n)[b]				
Overweight	26.0 (493)	23.8 (228)	28.0 (265)	0.04
Obesity	74.0 (1409)	76.2 (729)	72.0 (680)	
Central obesity, % (n)	93.8 (1784)	98.4 (942)	89.1 (842)	< 0.01
Prevalence of type 2 diabetes, % (n)	28.3 (539)	26.5 (254)	30.2 (285)	0.08
Prevalence of hypertension, % (n)	83.9 (1596)	84.4 (808)	83.4 (788)	0.54
Prevalence of hypercholesterolemia, % (n)	74.1 (1409)	78.2 (748)	70.0 (661)	< 0.01
Marital status, % (n)				< 0.01
Single or divorced	12.5 (237)	13.8 (132)	11.1 (105)	
Married	77.1 (1467)	69.1 (661)	85.3 (806)	
Widower	10.4 (198)	17.1 (164)	3.6 (34)	
Education, % (n)				< 0.01
Primary education	52.5 (998)	63.6 (609)	41.2 (389)	
Secondary education	27.7 (527)	23.7 (227)	31.8 (300)	
Academic or graduate	19.8 (377)	12.6 (121)	27.1 (256)	
Smoking habit, % (n)				< 0.01
Never smoker	46.1 (877)	71.3 (682)	20.6 (195)	
Former smoker	41.9 (796)	21.2 (203)	62.8 (593)	
Current smoker	12.0 (229)	7.5 (72)	16.6 (157)	
Sedentary time, h/day	6.1 ± 2.0	5.9 ± 2.0	6.4 ± 1.9	< 0.01
Leisure-time physical activity, min/sem.	459 ± 384	385 ± 317	535 ± 430	< 0.01
14-Item MedDiet Adherence Score	7.9 ± 2.0	7.9 ± 2.0	7.9 ± 2.1	0.96

Data expressed as mean ± SD or percentages (n)

BMI body mass index, *MedDiet* Mediterranean diet

[a] P values for comparisons between groups were tested by Student's t test or χ^2 as appropriate

[b] BMI (kg/m^2) was divided into the following categories: overweight (BMI between 25 and < 30 kg/m^2) and obese (BMI = > 30 kg/m^2)

in Supplementary Table 2. The mean volume of TWI was 2845 ± 642 mL/day (women 2830 ± 628 and men 2861 ± 656). The percentage contributed by fluids and various food groups to total water intake is shown in Fig. 2. Fluids contributed to 65% of TWI, while food contributed to the rest. Fruits and vegetables were the two food groups that contributed most to TWI (11% each). Supplementary Fig. 1 shows the contribution of various food groups and fluids to total water intake by sex. Statistically significant differences by sex in the percentage of water contributed were observed for several food groups and fluids at exception for legumes, fish/seafood, fats and nuts (P < 0.01).

In total, 80% of the studied population (91% of women and 69% of men) met EFSA's recommendations for TWI (2.5 L/day for men and 2 L/day for women). In contrast, only 51% of the study population (62% of women and 39% of men) met the EFSA's recommendation for TWIF (Supplementary Fig. 2). Table 3 shows the associations (OR and 95% CI) between various socio-demographic and lifestyle factors and compliance with the EFSA recommendations for TWIF and TWI. As far as TWIF is concerned, women are more likely to comply with the EFSA's recommendations than men (OR 3.02, 95% CI 2.40, 3.80, P <0.001). Besides, women with higher adherence to the MedDiet were 8% more likely to meet EFSA recommendations than women with low adherence (OR 1.08, 95% CI 1.01, 1.16, P <0.025). PA in leisure time was also positively associated with complying with TWIF EFSA recommendations (OR 1.07, 95% CI 1.02, 1.13, P <0.05). In addition, we observed an unexpected positive association between time spent on sedentary behaviours and compliance with the EFSA recommendations for TWIF in the total population (OR 1.06, 95% CI 1.01, 1.12, P <0.05). In contrast, for both sexes a significant inverse association between age and compliance with TWIF EFSA recommendations (OR 0.96, 95% CI 0.94, 0.98, P <0.001)

Table 2 Total daily consumption of various types of beverage (mL/day) in all population and stratified by sex

Variables	All population ($n=1902$)	Women ($n=957$)	Men ($n=945$)	P value[a]
Drinking water	1022 ± 454	1026 ± 445	1018 ± 463	0.70
Hot beverages	236 ± 213	254 ± 221	218 ± 204	< 0.01
Coffee	135 ± 118	133 ± 117	138 ± 119	0.38
Tea	101 ± 185	121 ± 193	80 ± 174	< 0.01
Milk and derivates	259 ± 213	262 ± 214	255 ± 213	0.47
Soups and vegetable juices	57 ± 94	57 ± 98	57 ± 88	0.92
Sugar-sweetened beverages	117 ± 203	114 ± 206	120 ± 201	0.50
Soda	33 ± 137	30 ± 135	36 ± 139	0.36
Juices	82 ± 149	82 ± 152	82 ± 147	0.95
Isotonic drinks	1.5 ± 18	1 ± 15	2 ± 20	0.40
Energy drinks	0 ± 5	0 ± 3	0 ± 6	0.34
Artificially sweetened beverages	38 ± 133	32 ± 118	44 ± 146	0.06
Alcoholic beverages	150 ± 267	72 ± 149	229 ± 330	< 0.01
Wine	63 ± 106	35 ± 78	92 ± 122	< 0.01
Beer	81 ± 222	35 ± 115	128 ± 285	< 0.01
Spirits	2 ± 11	0 ± 5	4 ± 15	< 0.01
Alcoholic mixed drinks	3 ± 26	0 ± 14	6 ± 35	< 0.01
Other beverages	54 ± 143	59 ± 144	49 ± 142	0.13
Total daily fluid volume	1934 ± 617	1876 ± 574	1991 ± 653	< 0.01

Data expressed as mean values ± SD

Other beverages category include soy drinks, beer without alcohol, sorbets and jellies, and meal replacement shakes

[a]P values for comparisons by sex were tested by Student's t test

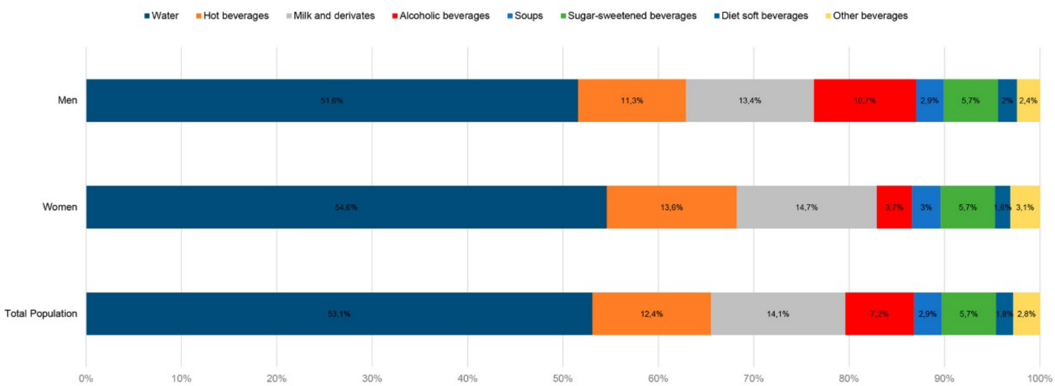

Fig. 1 Contribution of various beverages (%) to total fluid intake in all participants stratified by sex

was found. Similar results were observed for TWI. Being a woman (OR 5.34, 95% CI 3.85, 7.42, $P<0.001$) with high adherence to the MedDiet (OR 1.16, 95% CI 1.02, 1.31, $P<0.02$) was associated to better compliance with EFSA recommendations for TWI. We also observed that populations that engaged most in PA in their leisure time (OR 1.07, 95% CI 1.00, 1.15, $P<0.05$) and in sedentary behaviours were more likely to comply with TWI EFSA recommendations (OR 1.11, 95% CI 1.04, 1.18, $P<0.001$).

Figure 3 shows the association between MedDiet adherence and moderate–vigorous physical activity (MVPA) and compliance with EFSA TWIF (a) and TWI (b) recommendations. Compared to the reference category (low adherence to the MedDiet and non-compliance with MVPA

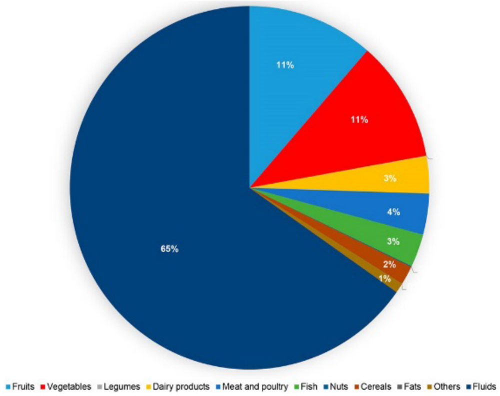

Fig. 2 Various food groups and fluids contributions (%) to total water intake in the studied population

recommendations), low adherence to the MedDiet and compliance with MVPA recommendations (OR 1.30, 95% CI 1.01, 1.65, P<0.039), high adherence to the MedDiet and non-compliance with MVPA recommendations (OR 1.43, 95% CI 1.09, 1.89, P<0.011) and high adherence to the MedDiet and high compliance with MVPA recommendations (OR 1.63, 95% CI 1.26, 2.10, P<0.001) showed to be positively associated with higher compliance with EFSA TWIF recommendations. Also compared to the reference category, those participants with higher adherence to the MedDiet and who complied with World Health Organization's recommendations for MVPA were more likely to comply with TWI recommendations (OR 1.66, 95% CI 1.19, 2.32, P<0.003).

Table 3 Association (multivariable adjusted, odds ratio, 95% CI) between different socio-demographic and lifestyle factors and compliance with EFSA recommendations for water intake from fluids and total water intake

Variables	Total water intake from fluids			Total water intake		
	All population (n=1902)	Women (n=957)	Men (n=945)	All population (n=1902)	Women (n=957)	Men (n=945)
Population complying with EFSA recommendations, n (%)	965 (51.70)	592 (61.90)	373 (39.50)	1523 (80.10)	875 (91.40)	648 (68.60)
Sex	–	3.02 (2.40–3.80)**	1 (ref.)	–	5.34 (3.85–7.42)	1 (ref)
Age[a]	0.96 (0.94–0.98)**	0.97 (0.94–1.00)	0.95 (0.93–0.98)**	0.99 (0.97–1.02)	1.03 (0.97–1.09)	0.99 (0.96–1.02)
Education						
Primary education	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Secondary education	1.01 (0.80–1.27)	1.09 (0.78–1.51)	0.96 (0.69–1.32)	1.16 (0.86–1.55)	1.07 (0.59–1.95)	1.23 (0.88–1.72)
Academic or graduate	0.96 (0.74–1.27)	0.71 (0.46–1.09)	1.14 (0.80–1.61)	1.06 (0.76–1.46)	0.55 (0.29 -1.07)	1.28 (0.90–1.84)
Smoking habit						
Never smoker	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Former smoker	0.99 (0.79–1.26)	1.15 (0.80–1.64)	0.99 (0.70–1.39)	0.92 (0.68–1.25)	0.80 (0.43–1.49)	1.13 (0.80–1.60)
Current smoker	0.91 (0.66–1.27)	0.72 (0.43–1.20)	1.07 (0.69–1.66)	0.73 (0.48–1.09)	0.39 (0.19–0.81)*	1.03 (0.65–1.61)
Sedentary time, h/day[a]	1.06 (1.01–1.12)*	1.09 (1.02–1.17)*	1.03 (0.96–1.11)	1.11 (1.04–1.18)	1.18 (1.06–1.31)*	1.08 (1.01–1.17)*
Leisure-time physical activity, 30 min/day[a]	1.07 (1.02–1.13)*	1.09 (0.99–1.19)	1.07 (0.99–1.15)	1.07 (1.00–1.15)	1.08 (0.99–1.27)	1.08 (0.91–1.16)
MedDiet adherence 14 items[a]	1.07 (1.02–1.12)*	1.08 (1.01–1.16)*	1.07 (0.99–1.14)	1.06 (1.00–1.13)	1.16 (1.02 -1.31)*	1.04 (0.97–1.11)

Multivariable results (simultaneous adjustment). In addition, model was adjusted by recruitment center (in quartiles by number of recruited participants). All analyses were conducted with robust estimates of the variance to correct for intra-cluster correlation. Data expressed as ORs (95% CI)

*P<0.05; **P<0.001; compared to the reference category

[a]Variable expressed as continues. Total water intake from fluids was defined as water consumed through fluids sources and total water intake was computed as the sum of water content in the consumed beverages and foods

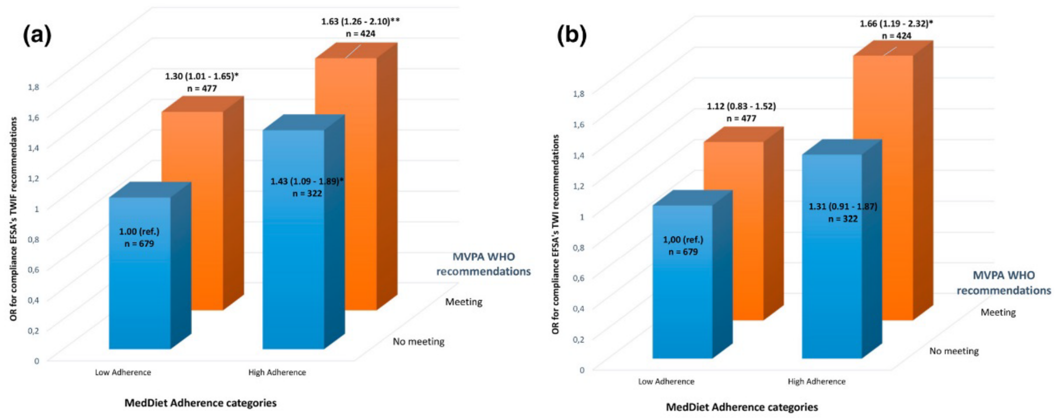

Fig. 3 Percentage of individuals from the studied population complying or not with the EFSA recommendation for total water intake from fluids (TWIF) and total water intake (TWI). **a** OR (95% CI) for compliance with EFSA recommendations for total water intake from fluids for the joint association of Mediterranean diet adherence and MVPA recommendations ($n = 1902$). **b** OR (95% CI) for compliance with EFSA recommendations for Total Water Intake for joint associations of Mediterranean Diet Adherence and MVPA recommendations ($n = 1902$)

Discussion

Few studies have analysed the demographic and lifestyle determinants of fluid intake, and to the best of our knowledge the present study is the first one, which analyses the TWI (considering water from fluids and water contained in food) determinants. In the present analysis, we have described the fluid intake pattern of a Mediterranean population at high cardiovascular risk and its determinants. We have reported that 80% of the study population met the water recommendations established by the EFSA. High compliance with TWI recommendations was associated with age, being a woman, and having a healthier lifestyle characterized by high adherence to the MedDiet and spending more time on PA. Furthermore, when we analysed the joint association of PA and MedDiet with the EFSA's recommendation for TWI and TWIF we observed that people with higher adherence to the MedDiet and who spent more time on MVPA were more likely to meet the recommendations.

In our study a higher percentage of men (69%) and women (91%) complied with the TWI recommendations than in the recent Anthropometry, Intake and Energy Balance (ANIBES) study conducted in a representative healthy Spanish sample [22], in which only 67% and 79% of men and women, respectively, complied with these recommendations. These differences might be explained in part by the fact that we used a specific validated fluid intake assessment questionnaire to assess the water intake from fluids whereas the ANIBES study method estimated the water intake was through a non-validated 3-day record of all the food and drinks consumed using photographic records for estimating the consumed amounts.

According to EFSA's recommendations, 80% of the TWI comes from drinking water and beverages, whereas food only accounts for the remaining 20%. In our study, however, approximately 65% of water intake was supplied by drinking water and other fluids whereas food contributed to the remaining 35%. The MedDiet pattern followed by our studied population could partly explain this discrepancy, since it is characterized by a high consumption of fruits and vegetables, which are known to provide significant amounts of water [14]. In fact, in our study these two food groups by themselves made up 22% of the TWI (62.8% of water intake through food). In addition, in a previous study it has been shown that those individuals with high adherence to MedDiet reported to drink more water and wine than those with low adherence to the Mediterranean diet [10]. This also occurred in the present study in relation to wine consumption (data not shown).

In a seminal study conducted by our group in the context of a healthy Mediterranean population we have also reported that sex and age were important determinants of fluid intake [23]. In the present study, we extended the results to TWI in a population at high risk of CVD with overweight/obesity and MetS. The positive association between being women and the compliance with EFSA's recommendations for TWI and TWIF, might be explained by the fact that women are more likely to adhere to a healthier lifestyle [24], and, in general, adults with healthier dietary pattern usually have a healthier fluid intake pattern [6]. The inverse association observed in both studies between age and TWI, TWIF or TFI might be related to the elderly's inability to perceive thirst [25] regardless of health status, although other cultural or socio-demographic determinants cannot be excluded as explanations for this association.

Along the same lines, a previous study of healthy Spanish adults had shown that adherence to the MedDiet and PA was positively associated with Total Fluid Intake (TFI) [10]. However, the previous study reported these associations for TFI instead of TWI, which may not assure that TWI EFSA's recommendations were complied. Furthermore, we observed that participants who showed a higher adherence to MedDiet and who engaged in MVPA were more likely to comply with EFSA's recommendations for TWI.

It has been suggested that high compliance with TWI recommendations by people who engage in physical activity might be partly explained by the fact that they tend to drink more as they have increased fluid demands [26]. However, future studies need to be carried out to better understand the determinants/mechanisms that explain why more active people are less prone to be below the fluid intake recommendations. In addition, studies should be conducted to verify if people practising MVPA are meeting their water individual demands, since it has been reported that daily water requirements could increase in the performance of modest physical activity [27].

Our results on the beverage pattern are in agreement with those reported for Spain in a previous multicentre study conducted in different continents [28], but specially with those reported in a healthy Spanish population [7, 22, 23]. Drinking water was the most consumed beverage, followed by a moderate–low milk consumption, hot beverages (mainly coffee) and moderate–low alcohol beverages (mainly wine and beer). Although men had a higher alcohol consumption than women, mean alcohol intake was in accordance with Spanish recommendations (no more than 40 g/day and 20 g/day for men and women, respectively) [29]. Interestingly, although the MedDiet is characterized by a moderate–low consumption of red wine (one cup for women, two cups for men), in the studied population mean consumption was less than 1 cup per day for both sexes. We also observed that alcohol consumption tended to decrease with age. A study conducted on a Spanish elderly population observed that the consumption of alcoholic beverages tends to decrease with age, suboptimal health status, a diagnosis of diabetes or drug use, and CVD, which might partly explain our findings [30]. The consumption of sugar-sweetened beverages in our population was lower than the mean consumption reported in healthy and younger populations [23]. Previous studies reported a positive association between age and higher adherence to the MedDiet [31]. Investigators have suggested that elderly populations at high risk of developing chronic diseases are more likely to adopt healthy dietary habits than young adults [32], which might partly explain the differences observed in our study with other healthy and younger populations.

Fluids contribute not only to water but also to energy intake, mostly from sugars [14]. In addition, some beverages (mainly dairy) can contribute to the intake of fat and protein and micronutrients such as calcium, vitamin C, sodium and potassium [14]. The relatively high intake of fats, protein and calcium through beverages could be explained by the moderate consumption of milk and dairy drinks in the studied population. Furthermore, fluids contributed to almost 50% of the recommended daily vitamin C intake in a Spanish healthy population [33], because of the high consumption of fruit and vegetable juices. In our study a low-to-moderate amount of sugar comes from beverages compared to other countries. This deserves a comment because drinking water or low-calorie beverages' consumption should be prioritized to decrease energy intake through beverages, especially from SSB, that are characterized by a high content of added sugar and has been related to weight gain [34] and an increase in the risk of non-communicable chronic diseases [35].

Our study has some limitations that should be mentioned. First, it is a cross-sectional analysis, therefore, causal relationships cannot be proven. Second, the studied population is a senior Mediterranean population at high cardiovascular risk, so the results cannot be extrapolated to the general population. Third, the period of food or fluid consumption addressed by each questionnaire differs (in case of the FFQ during the last year, and in case of the Spanish fluid intake during the last month), which could lead to bias in total water intake estimation. Fourth, hydration biomarkers, such as urine osmolality, were not used. If hydration biomarkers had been used, we would have been able to better assess if the individual water demands to maintain an optimal hydration status were covered.

One of the strengths, in our study is that we assessed not only water intake from beverages as is standard in studies using a fluid-specific assessment questionnaire validated in Spanish population, but we also assessed water consumption from food. In addition, to the best of our knowledge, this is the first study to assess the association between compliance with TWI and TWIF, and several social-demographic and lifestyle factors, and it has been able to describe the joint association of MedDiet adherence and physical activity with compliance with the EFSA's recommendations in a senior Mediterranean population at high cardiovascular risk.

Conclusion

Our study showed that a high percentage of elderly Mediterranean individuals (aged 55–75) at high cardiovascular risk meet the EFSA's recommendation for TWI. We demonstrated that high compliance with TWI recommendations is inversely associated with age, and positively associated with being a woman, and having a healthier lifestyle characterized by high adherence to the MedDiet and PA. These results suggest that a healthy lifestyle is associated with compliance with water recommendations and a lower risk of dehydration and the potential unhealthy effects of excess salt and sugar from beverages.

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Author contributions IP-G, NB-T, NB and JS-S conducted the statistical analyses and drafted the article. IP-G, JS-S, NB and NB-T made substantial contributions to the conception and design of the work. All authors contributed substantially in the acquisition of data or analysis and interpretation of data. All authors revised the article critically for important intellectual content. All authors approved the final version to be published.

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Compliance with ethical standards

Conflict of interest J. S.-S. reports serving on the board of the International Nut and Dried Fruit Council from which he has also received grant support through his institution, receiving consulting fees from Danone, Font Vella Lanjaron, Nuts for Life, and Eroski, and being given grant support through his institution from Eroski. J.S.-S is member of the executive committee of the Instituto Danone Spain and member of the scientific committee of the Institute Danone International. L. D. reports to receive a Grant from the Fundación Cerveza y Salud. N.-B. declares that she received payments from Danone S.A. for the purposes of scientific and technical consulting but not for preparing this study and grant support through his institution from Font Vella Lanjaron. No other potential conflicts of interest relevant to this article were reported.

Ethical standards All participants provided written informed consent, and the study protocol and procedures were approved according to the ethical standards of the Declaration of Helsinki.

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Online Supplementary Material

Supplementary Table 1. Energy and nutrient intake from fluids in all population and stratified by sex.

Variables	*All population* (*n* = 1902)	*Women* (*n* = 957)	*Men* (*n* = 945)	*P value*[a]
Energy (kcal/d)	420 ± 257	391 ± 258	450 ± 252	<0.01
Water (mL/d)	1,819 ± 558	1,778 ± 536	1,861 ± 577	<0.01
Carbohydrate (g/d)	51 ± 39	50 ± 41	51 ± 35	0.74
Sugar (g/d)	36 ± 25	34 ± 24	38 ± 27	<0.01
Proteins(g/d)	23 ± 15	23 ± 16	23 ± 15	0.36
Lipids (g/d)	7 ± 6	7 ± 6	7 ± 6	0.38
Alcohol (g/d)	8 ± 13	4 ± 8	12 ± 15	<0.01
Sodium (mg/d)	340 ± 284	338 ± 296	342 ± 269	0.78
Potassium (g/d)	2.6 ± 2.9	2.4 ± 2.7	2.8 ± 3.0	<0.01
Calcium (mg/d)	535 ± 273	541 ± 270	530 ± 277	0.38
Vitamin C (mg/d)	32 ± 56	32 ± 56	31 ± 55	0.85

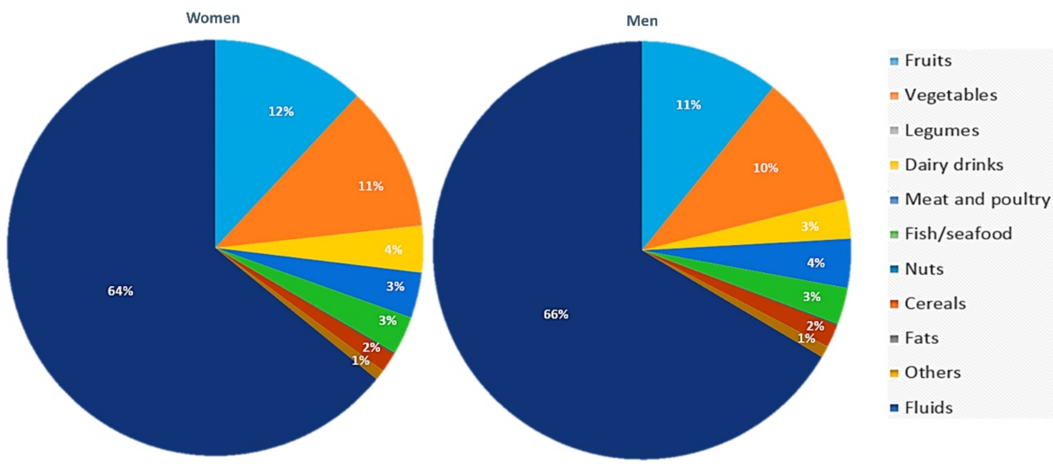
Data expressed as means ± SD. [a]P values for comparisons by sexes were tested by Student's t-test.

Supplementary Table 2. Daily contribution of water (mL/day) from various food groups in the whole population and stratified by sex.

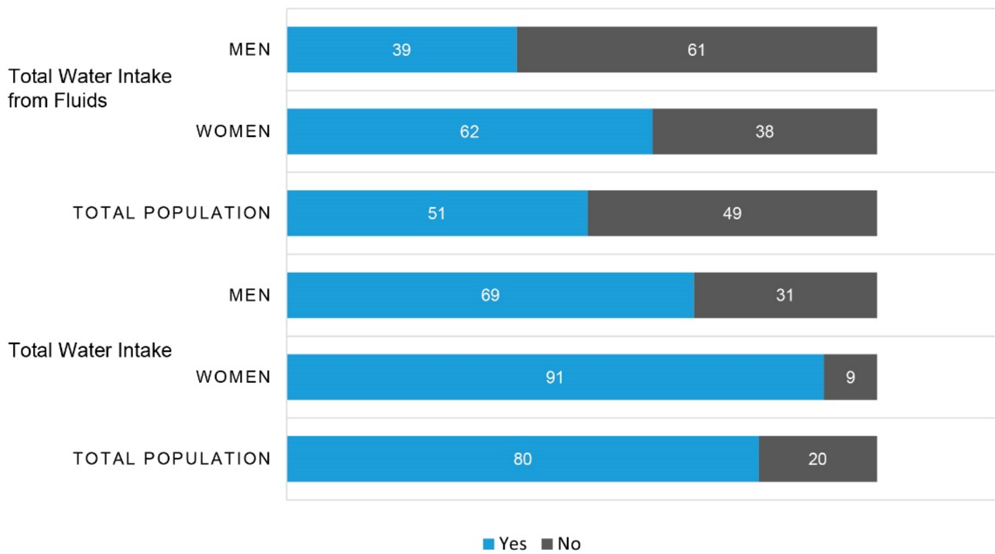
Variables	*All population* (*n* = 1902)	*Women* (*n* = 957)	*Men* (*n* = 945)	*P value*[a]
Vegetables	301 ± 127	313 ± 127	288 ± 125	<0.01
Fruits	317 ± 177	332 ± 187	302 ± 166	<0.01
Legumes	1 ± 0.6	1 ± 0.6	1 ± 0.6	0.27
Cereals	47 ± 24	43 ± 22	50 ± 25	<0.01
Dairy drinks	92 ± 73	100 ± 76	84 ± 70	<0.01
Meat and poultry	102 ± 40	98 ± 38	106 ± 41	<0.01
Fish/seafood	82 ± 38	83 ± 38	80 ± 38	0.07
Fats	0.5 ± 0.7	0.5 ± 0.8	0.5 ± 0.7	0.70
Nuts	2 ± 2	2 ± 2	2 ± 2	0.71
Other foods	24 ± 10	22 ± 8	25 ± 11	<0.01

Data express as means ± SD. [a]P values for comparisons by sex were tested by Student's t-test.

Online Supplementary Material



Supplemental Fig 1. Contribution of various food groups and fluids (%) to total water intake by sex.



Supplemental Fig 2. Percentage of individuals from the studied population complying or not with EFSA's recommendation for Total Water Intake from Fluids (TWIF) and Total Water Intake (TWI).

Chapter 2

Baseline drinking water consumption and changes in body weight and waist circumference at 2-years of follow-up in a senior Mediterranean population.

Paz-Graniel I, Becerra-Tomás N, Babio N, Serra-Majem L, Vioque J, Zomeño MD, Corella D, Pintó X, Bueno-Cavanillas A, Tur JA, Daimiel L, Zulet MA, Palau-Galindo A, Torres-Collado L, Schröder H, Gimenez-Alba IM, Nissenshon M, Galera A, Riquelme-Gallego B, Bouzas C, Micó V, Martínez JA, Canudas S, Castañer O, Vázquez-Ruiz Z, Salas-Salvadó J.

Key teaching points:

- The consumption of energy-containing beverages has increased in parallel with the rise in the incidence of overweight and obesity.

- Recommendations to decrease the consumption of high-calorie beverages and to increase drinking water consumption are done. Despite the association between drinking water consumption and other beverages with body weight has been poorly explored.

- A prospective analysis was performed with data from 1,832 participants from the PREDIMED-Plus fluid intake assessment sub-study.

- Drinking water consumption was inversely associated with 1-year and 2-year changes in body weight and waist circumference.

- The replacement of some energy-containing beverages consumption by drinking water was associated with reductions in body weight

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Original article

Baseline drinking water consumption and changes in body weight and waist circumference at 2-years of follow-up in a senior Mediterranean population

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SUMMARY

Background & aims: The association between drinking water consumption and adiposity has been poorly explored. Therefore, we aimed to analyse the associations between the frequency of drinking water consumption and body weight and waist circumference changes in an elderly Mediterranean cohort.
Methods: A total of 1832 elderly participants (aged 55–75 years) with metabolic syndrome from the PREDIMED-Plus study with baseline data on drinking water and other beverages assessed by a validated 32-item Spanish fluid-intake questionnaire and with data on body weight (BW) and waist circumference (WC) at 1-year and 2-year were included in these prospective analyses. Multivariable linear regression models were fitted to assess the β-coefficients and 95% confidence interval (CI) for BW and WC changes

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Central obesity
Alcoholic beverages
Sugary drinks

in terms of categories of baseline drinking water consumption (tap water and bottled water). The theoretical effect on BW and WC of replacing several beverages with drinking water was assessed using mathematical models.

Results: The baseline frequency of drinking water consumption was inversely associated with 1-year and 2-year changes in BW. β-coefficients (95%CI) across categories of water consumption (<2.5, 2.5 to <5, 5 to < 7.5, ≥7.5 servings/d) expressed in % of weight changes at 2 years of follow-up were 0.0, 0.80 (1.48, 0.12), 1.36 (2.18, 0.54), and 1.97 (3.09, 0.86), respectively. Individuals in the two highest categories of drinking water consumption (5 to < 7, and ≥7.5 servings/d) also showed a higher decrease in WC (expressed as % of change) after 2 years of follow-up: 1.11 (1.96, 0.25) and 1.45 (2.66, 0.24) compared to the reference intake (<2.5 servings/day), after adjustment for potential confounding factors. The theoretical replacement of soups, beers, spirits, hot beverages, dairy beverages, and other beverages group with drinking water was associated with greater reductions in BW at one- and two-years of follow-up.

Conclusions: Drinking water consumption was inversely associated with 2-year adiposity changes in an elderly Mediterranean cohort at high cardiovascular risk. Our results also suggest that the consumption of drinking water instead of energy-containing beverages is associated with lower weight gain.

The trial registration: ISRCTN89898870.

1. Introduction

Excess body weight (BW) is a recognized worldwide public health concern because it is a risk factor for the development of non-communicable chronic diseases such as diabetes and cardiovascular disease [1]. The onset of overweight and obesity is the result of an energy imbalance, with a multifactorial background that includes genetics, a sedentary lifestyle, and excessive caloric intake, among others [2]. As its incidence and prevalence have increased worldwide in recent decades [3], intervention strategies have been proposed to prevent its onset and also for treatment [4,5]. The most common recommendations concern lifestyle factors, such as a lower caloric intake, a healthy dietary pattern, physical activity, less sedentary behaviours, and stress and anxiety management, among others [5]. Although drinking water is recommended for the maintenance of healthy hydration status [6,7], in recent decades the consumption of other types of beverage has increased in parallel with the rise in incidence of overweight/obesity [8]. Beverages can be dietary sources of water, vitamins, and minerals, but also of carbohydrates, proteins, and fat, which can contribute to increase total energy intake [6,9]. Consequently, in recent years health professionals have stressed the importance of decreasing the consumption of high-calorie beverages, especially sugary drinks, and increasing the consumption of drinking water [10]. It has been reported that replacing caloric beverages [11–13], such as sugary drinks and beer with drinking water, contributes to decreasing total energy intake, and thus might prevent weight gain. Unfortunately, the association between drinking water consumption and body weight (BW) changes in the long-term has been poorly explored and results are inconclusive. Due to the lack of evidence in the field, the study of the potential associations between drinking water and body weight or adiposity has greater relevance for public health. Therefore, the present analysis aimed to assess the associations between drinking water consumption and changes in BW and waist circumference (WC) in a cohort of overweight/obese elderly adults with metabolic syndrome (MetS). We hypothesized that individuals who consumed more drinking water at baseline will be more likely to lose weight after 1 and 2 years of follow-up.

2. Materials and methods

2.1. Study design and participants

A prospective analysis was conducted within the frame of the PREDIMED-Plus (PREvención con DIeta MEDiterránea) cohort. PREDIMED-Plus is a large, multicentre, parallel-group, randomized controlled clinical trial conducted in Spain to compare the effect on cardiovascular disease (CVD) morbi-mortality of two interventions: an intensive weight loss program based on an energy-restricted traditional Mediterranean diet (MedDiet), physical activity (PA) promotion and behavioural support (intervention group, IG), and an energy-unrestricted traditional MedDiet (control group, CG). A detailed explanation of the trial design has been published elsewhere [14] and the study protocol can be accessed at www.predimedplus.com. The trial was registered in 2014 as ISRCTN89898870.

Eligible participants were overweight or obese males and females (BMI 27–40 kg/m^2 and aged 55–75 years) who satisfied at least three of the following criteria for the metabolic syndrome (MetS): waist circumference >102 cm in men and >88 cm in women; serum triglyceride ≥150 mg/dL or drug treatment for elevated triglycerides; HDL-c <40 mg/dL in men and <50 mg/dL in women or drug use for low HDL-c; blood pressure ≥130/85 mmHg or antihypertensive drug treatment; and fasting plasma glucose level ≥100 mg/dL or hypoglycemic treatment [15]; and were free from CVD at baseline. Detailed PREDIMED-Plus inclusion and exclusion criteria have been extensively described elsewhere [16]. Between October 2013 and December 2016, 6874 participants were recruited from 23 centres in Spain (universities, hospitals, and research institutes), and randomly allocated in a 1:1 ratio to an intensive lifestyle intervention or the usual medical care group.

The fluid intake assessment is a PREDIMED-Plus sub-study in which only 10 of the 23 centres agreed to participate. The present analysis has been conducted with data from those recruiting centres, where information on water and beverage consumption was collected using a specific validated beverage questionnaire. A total of 2067 individuals completed the validated 32-item Spanish fluid-intake questionnaire [17]. Of these, we excluded participants who had not responded to the baseline food frequency questionnaires (FFQ) or who reported implausible total energy intakes (≤500 and ≥ 3500 kcal/day in women and ≤800 and ≥ 4000 kcal/day in men; n = 55), and those who reported a total fluid intake above or below two standard deviations from the median value (≤397 and ≥ 3590 mL/day in men and ≤490 and ≥ 3262 mL/day women; n = 107). For our main analysis, we included those participants with data on BW after a 1-year (n = 1832) and 2-year follow-up (n = 1813). Figure 1 shows participants flow diagram.

All participants provided written informed consent and the institutional review boards of each participating centre approved the final protocol and procedures.

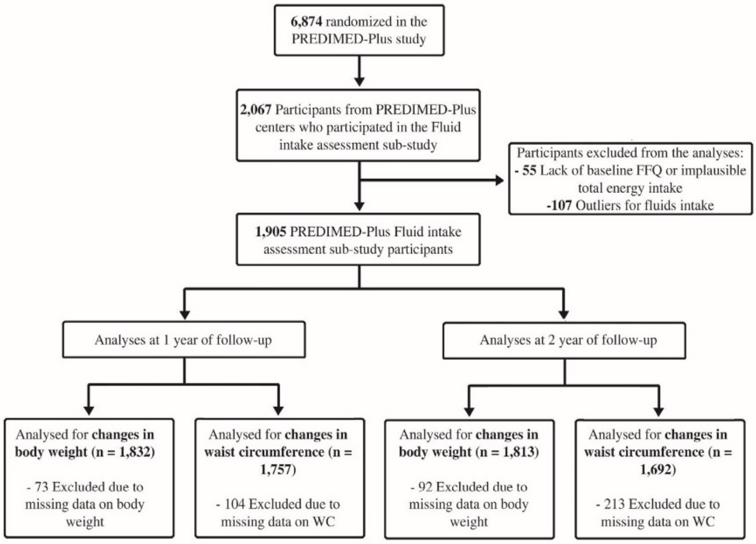

Fig. 1. Flow diagram for study participants. FFQ, food frequency questionnaire; WC, waist circumference.

2.2. Beverage assessment

At baseline, a trained dietitian held a face-to-face interview with participants and completed a validated 32-item Spanish fluid-intake questionnaire [17], which recorded the frequency of consumption of various beverage types over the previous month. For each type, frequencies of consumption were measured in eight categories, ranging from never/almost-never to >8 servings/day. The daily total fluid intake from beverages was computed as the sum of all beverages consumed.

For the present analysis, beverages were categorized into eight groups: drinking water (tap and bottled water), total dairy beverages (sub-categorized into whole-dairy beverages, which include whole milk, milkshakes, and other milk beverages; and reduced-dairy beverages, which include reduced-fat and skimmed milk), hot beverages (coffee, tea, and other infusions), sugary drinks (including carbonated soft drinks, natural and bottled fruit juice, energy drinks and sports drinks), artificially sweetened beverages (including light/zero carbonated soft drinks), alcoholic beverages (spirits, mixed alcoholic drinks, wine, beer/cider), broths (soups and natural and bottled vegetable juice), and other beverages (plant-based drinks, non-alcoholic beer, sorbets and jellies, and meal replacement shakes; we decided to categorize these beverages as a group since their consumption in our cohort is too low to be analysed separately). A serving of drinking water, dairy beverages (whole and reduced dairy beverages), sugary beverages and artificially sweetened beverages was defined as 200 mL, a serving of soups was defined as 100 mL. The hot beverage group includes servings of all kinds of coffee (50 mL) and tea (200 mL). The alcoholic beverage group includes servings of wine (100 mL), beer (200 mL), spirits (50 mL) and mixed alcoholic beverages (200 mL). A serving of the other beverage group was defined as 180 mL. Serving size reported in the fluid-intake questionnaire assessment tool was considered for beverages servings size categorization.

2.3. Outcomes and assessment of covariables

The primary outcome of the current study was BW changes at 1-yr and 2-yr of follow-up according to categories of drinking water consumption at baseline. We also assessed WC changes at 1 and 2-years of follow-up using the same exposure categories.

At baseline and yearly, participants provided information, by responding to general questionnaires on sociodemographic characteristics, physical activity, lifestyle and MedDiet adherence, among others. Also, in accordance with the study protocol, height, weight, and WC were measured in duplicate by PREDIMED-Plus trained staff using standardized techniques and calibrated scales. Weight and height were measured with participants wearing light clothes and no shoes. Body mass index (BMI) was calculated as the weight in kg divided by the square of the height in meters. WC was measured using an anthropometric tape midway between the lowest rib and the iliac crest. Measurement averages were calculated later for analysis purposes. Adherence to the MedDiet was evaluated using the 14-item Mediterranean diet score [18], where the adherence to each item reflecting the MedDiet were scored with 1 point, and with 0 points otherwise, therefore a total score equal to 14 means maximum adherence. When the beverage that we evaluated was included in this score (fruit juices, soft drinks, or wine), it was recalculated after the item that we analysed had been excluded to avoid overlap with the main exposure.

2.4. Statistical analysis

For the present study, we used the PREDIMED-Plus database updated until June 2020. Study participants were categorized according to servings per day (s/d) of drinking water consumption into < 2.5, 2.5 to < 5.5, 5.5 to < 7.5, and ≥7.5 servings per day. To compare the baseline characteristics of the study participants in terms of categories of drinking water consumption the Chi-square test and the ANOVA test were used, as appropriate.

Multivariable linear regression models were fitted to assess the β-coefficients and 95% confidence interval (CI) for BW and WC changes according to categories of drinking water consumption. Model 1 was adjusted for age (years) and sex; Model 2 was additionally adjusted for intervention group (CG/IG), smoking (never, former, or current), educational level (primary, secondary or academic/graduate), BMI (kg/m^2), leisure-time physical activity (METs.min/week) and the 14-point MedDiet adherence score (continuous); Model 3 was additionally adjusted for total energy intake (kcal/day, continuous) and total fluid intake (mL/day, continuous).

To assess the linear trend across categories of drinking water consumption and changes in BW and WC, we assigned the median value to each drinking water category and treated the variable as continuous. We also assessed the possible interactions between categories of drinking water consumption and sex, age, and intervention group of the trial by including cross-product terms in adjusted models.

Moreover, we used mathematical models to assess the association between substituting one serving per day of water for each beverage or beverage group (increasing by one serving of water and decreasing by one serving of the beverage/group in question) and the adjusted absolute mean BW and WC changes (and 95% CI). The theoretical effect of substituting one type of beverage for another was assessed by simultaneously adding both variables to the model and we estimated the theoretical effect of substituting one type of beverage for another by using the difference in beta-coefficients from the same model. These substitutions were made only to the consumption reported at baseline; changes in beverage intake over time were not assessed. The multivariable model was adjusted for the baseline covariates age (years), sex, intervention group (CG/IG), smoking habit (never, former, or current), educational level (primary, secondary or academic/graduate), baseline body mass index (kg/m^2), leisure-time physical activity (METs.min/week), the 14-point MedDiet adherence score (continuous), and total energy intake from fluids other than the exchanged beverages (continuous). When the analyses were carried out for a beverage group, we additionally adjusted for servings per day of other groups.

All analyses were conducted with robust variance estimators to correct for intra-cluster correlations in linear regression models (considering the members of the same household to be clusters). Analyses were performed using Stata software, version 15.0 (StataCorp LP) and the level of significance for all of them was set at $P < 0.05$.

3. Results

The general characteristics of the studied population according to categories of drinking water consumption at baseline are shown in Table 1. Compared to participants in the lowest category of drinking water consumption, those in the highest category were younger, had higher body weight and BMI, and reported higher total fluid intake. For other groups and subgroups of beverages, the participants in the highest category of drinking water consumption reported a lower consumption frequency of total and reduced dairy beverages, sugary and artificially sweetened drinks, alcoholic beverages, wine, and beer, than participants in the lowest category. No other significant associations were observed.

Table 2 displays non-standardized β-coefficients and 95%CI for BW changes at 1- and 2-year follow-up according to categories of drinking water consumption at baseline. Participants in higher consumption categories (2.5 to < 5.5 servings/day, 5.5 to < 7.5, and ≥7.5 servings/day) showed significant BW reductions after one-year follow-up after adjustment for potential confounders including total energy intake and total fluid intake compared to participants who consumed less than 2.5 servings per day of drinking water, after adjusting for potential confounders. Results were similar at the two-year follow-up for all consumption categories of drinking water compared to the reference category, even after adjustment for potential confounders.

Table 3 shows non-standardized β-coefficients (95%CI) for WC changes at the 1- and 2-year follow-up according to categories of drinking water consumption at baseline. At two-years of follow-up, participants who consumed between 5 and 7.5 servings/day and those consuming ≥7.5 servings/day showed higher reductions in WC compared to the reference category of consumption (<2.5 servings/day) after adjustment for total energy intake and total fluid intake.

We did not observe significant interactions between sex, age, randomized intervention group and drinking water consumption categories. Additionally, sensitivity analyses were performed excluding participants who reported total energy intake <1200 kcal/day (n = 18), being the results similar (data not shown).

The mean absolute BW and WC changes and 95%CI of the substitution of one serving/day of water for beverage subgroups at 1- and 2-year follow-up are shown in Table 4 and Table 5, respectively. At 1-year follow-up, the replacement of one serving of soups/vegetable juices, alcoholic beverages, beer, spirits/mixed-alcoholic beverages and other beverages by one serving of drinking water was associated with a reduction of −403 (95%CI, −602, −205), −150 (95%CI, −278, −22), −230 (95%CI, −385, −74), 702 (95% CI, −1329, −76) and 343 (95%CI, −641, −45) grams in body weight, respectively. The substitution of one serving of spirits/mixed-alcoholic beverages with drinking water was associated with a decrease of −1.16 cm (95%CI, −2.04, −0.29) in WC at one-year follow-up. At 2-year follow-up, significant inverse associations were observed between the consumption of one serving of drinking water instead of one serving of hot beverages (−152 (95%CI,-279, −25)), total dairy beverages (−279 (95%CI,-479, −77)), reduced dairy beverages (−268 (95%CI,-480, −56)), soups and vegetable juices (−277 (95%CI,-499, −56)), and other beverages (−385 (95% CI,-715, −54)) and absolute BW changes in grams. No other significant associations were observed in the substitution models.

4. Discussion

To the best of our knowledge, this is the first epidemiological study to prospectively analyse the association between drinking water consumption and long-term BW changes in an elderly population with overweight/obesity and MetS. The results of our analyses showed that participants who reported a higher consumption of drinking water at baseline had a greater reduction in BW at 1- and 2- years of follow-up. Furthermore, the theoretical substitution of alcoholic beverages (beer and spirits/mixed alcoholic beverages), soups/vegetable juices, and other beverages by water was significantly associated with a greater reduction in weight at one year of follow-up. At two years of follow-up the consumption of one serving of drinking water instead of one serving of hot beverages, total and reduced-dairy beverages, and soups/vegetable juices was associated with a significant decrease in BW.

The association between drinking water consumption and BW in the long-term has been poorly studied [11,19]. To date, most research efforts have focused on the short-term effects of drinking water on total energy intake [20–23] and BW [24]. Intervention studies which have explored the effect of fluid consumption before a meal on energy intake have reported inconsistent results [20–23]. Two of them reported that participants who drank fluids before meals had lower energy intakes than those who did not drink any [20,21], although this association was not observed in other studies [22,23]. In a 12-week intervention trial [24], pre-meal

Table 1
Baseline characteristics of study participants with data on BW at a 1-year follow-up according to categories of baseline drinking water consumption.

N	Categories of Drinking Water Consumption (servings/day)				
	<2.5	2.5 - < 5	5 - < 7.5	>7.5	P value
	357	713	515	247	
Drinking water consumption,[1] mL	355 (0, 500)	892 (800, 1000)	1300 (1071, 1400)	1800 (1800, 3100)	<0.01
Intervention group, % (n)	52 (185)	50 (353)	45 (234)	52 (128)	0.20
Women, % (n)	48 (173)	51 (364)	51 (264)	51 (126)	0.85
Age, years	65 ± 5	65 ± 5	65 ± 5	64 ± 5	<0.01
Body weight, kg	85.7 ± 13.0	86.0 ± 12.7	85.6 ± 11.9	89.5 ± 14.3	<0.01
BMI, kg/m^2	32.2 ± 3.4	32.7 ± 3.5	32.4 ± 3.5	33.5 ± 3.4	<0.01
Waist circumference, cm	107.1 ± 9.6	107.7 ± 9.9	107.3 ± 9.5	108.8 ± 10.4	0.15
Smoking status, % (n)					0.29
Current	11.5 (41)	14.0 (100)	11.5 (59)	8.5 (21)	
Former	41.5 (148)	41.1 (293)	39.8 (205)	45.3 (112)	
Never	47.0 (168)	44.9 (320)	48.7 (251)	46.2 (114)	
Education, % (n)					0.43
Primary or less	48.5 (173)	53.4 (381)	55.3 (285)	51.0 (126)	
Secondary	28.9 (103)	27.6 (197)	26.4 (136)	30.8 (76)	
Academic/graduate	22.7 (81)	18.9 (135)	18.3 (94)	18.2 (45)	
Leisure-time physical activity, METs.min/week	2351 ± 2275	2416 ± 2303	2580 ± 2472	2481 ± 2290	0.50
Total energy intake, Kcal/day	2431 ± 560	2396 ± 528	2372 ± 545	2368 ± 534	0.39
14-points MedDiet score	8.0 ± 2.2	7.8 ± 2.0	8.1 ± 1.9	8.1 ± 2.0	0.19
Total fluid intake, mL	1368 ± 537	1798 ± 457	2170 ± 438	2600 ± 390	<0.01
Groups and subgroups of beverages (servings/week)					
Drinking water	12.4 ± 4.3	31.2 ± 1.1	45.5 ± 0.5	63.7 ± 4.6	<0.01
Hot beverages	21.9 ± 18.5	21.7 ± 17.0	23.4 ± 17.3	22.9 ± 17.3	0.34
Total dairy beverages	10.0 ± 7.9	9.5 ± 7.2	8.6 ± 7.7	7.4 ± 7.2	<0.01
Whole-fat dairy beverages	1.8 ± 4.7	1.4 ± 3.9	1.2 ± 3.7	1.1 ± 3.3	0.10
Reduced-fat dairy beverages	8.2 ± 7.5	8.1 ± 7.1	7.4 ± 7.3	6.2 ± 7.0	<0.01
Soups	3.6 ± 6.3	3.6 ± 6.1	4.3 ± 6.4	4.6 ± 7.4	0.05
Sugary beverages	4.7 ± 7.3	4.1 ± 6.3	3.9 ± 6.0	2.5 ± 4.4	<0.01
Artificially sweetened beverages	2.1 ± 6.0	1.2 ± 4.3	1.0 ± 3.5	1.0 ± 3.6	<0.01
Alcoholic beverages	9.7 ± 14.0	8.1 ± 12.1	6.1 ± 10.3	5.3 ± 8.7	<0.01
Wine	5.6 ± 8.6	4.6 ± 7.3	3.7 ± 6.5	3.2 ± 6.4	<0.01
Beer	3.6 ± 9.2	3.0 ± 8.0	2.1 ± 6.3	1.9 ± 4.9	<0.01
Spirits and mixed alcoholic beverages	0.5 ± 2.2	0.5 ± 2.0	0.4 ± 1.5	0.2 ± 1.1	0.15
Other beverages	1.3 ± 4.0	1.3 ± 4.1	1.6 ± 4.8	1.9 ± 4.9	0.24

Data expressed as percentage (number) and mean ± standard deviation or [1] Median, minimum and maximum.
BMI, Body Mass Index; MedDiet, Mediterranean diet. P-value for comparisons between servings of drinking water consumption was calculated by Pearson's chi-square test for categorical variables or One-factor ANOVA for continuous variables.
A serving of water, dairy beverages (whole and reduced dairy beverages), sugary beverages and artificially sweetened beverages is defined as 200 mL; a serving of soups is defined as 100 mL; the hot beverage group includes servings of any kind of coffee (50 mL) and tea (200 mL); the alcoholic beverage group includes servings of wine (100 mL), beer (200 mL), spirits (50 mL) and mixed alcoholic beverages (200 mL); a serving from other beverages group (plant-based drinks, non-alcoholic beer, sorbets and jellies, and meal replacement shakes) is defined as (180 mL).

water intake combined with a hypocaloric diet was associated with a greater weight loss than a hypocaloric diet alone in middle-aged and older adults. In a prospective study conducted by Pan et al. [11] it was observed that each 1 cup/day increment of water intake was associated with less weight gain in three separate large prospective cohorts of healthy individuals. Moreover, our analyses showed that baseline consumption of five or more servings per day of drinking water was also associated with a decrease in WC, at one and two years of follow-up. These results are in line with observations reported by Stookey et al. [19] and Dennis et al. [24] who reported a positive association between increased water consumption and weight loss.

Some of the mechanisms by which drinking water may contribute to weight maintenance are: a) liquid volume can increase gastric distension and satiety, which contributes to a lower energy intake at subsequent meals [24], and b) the replacement of energy-containing beverages with water might contribute to a reduction in overall energy intake [19]. Moreover, the adjustment by total energy intake and total fluid intake at baseline, as stable variables, give robustness to our observed results suggesting that drinking water has potential effects on body weight and adiposity in the long-term, independently of caloric or fluid intake. Actually, experimental studies have reported that drinking water may induce thermogenesis and slightly increase metabolic rate, thus increasing energy expenditure [25,26], although this has to be further explored [27].

The associations between alcohol consumption, BW and WC have been explored but the results from different studies are inconclusive [28,29]. The effect of alcohol on weight seems to be conditioned by the type of alcoholic beverage consumed, the habitual amount consumed and sex differences [30]. Our results are supported by prospective studies that have demonstrated positive associations between changes in the consumption of alcoholic beverages and gain in BW and WC in different populations [28,31–33]. Similar to our observations, Fresán et al. [12], reported that the theoretical replacement of beer with one serving of water per day was related to a greater weight loss and lower incidence of obesity over a four-year period in a Mediterranean cohort of healthy young adults. Additionally, as in our study, Fresán and collaborators [12] did not observed this association for wine. The detrimental effects of alcoholic beverages (beer and spirits) on BW and adiposity have been explained by their high energy content, which increases the overall energy intake [34], and their ability to increase appetite and disturb lipid metabolism [28].

Contrary to what has been reported by other authors [11,19], our analysis did not show a significant decrease in BW or WC when sugary drinks were theoretically replaced by drinking water. The differences in the type of participants, the drinking pattern and

Table 2
Crude and multivariate β-coefficients and 95% CI of 1- and 2-year changes (%) in body weight per servings of drinking water at baseline.

	Categories of Drinking Water Consumption (servings/day)						
	<2.5 s/d	2.5 - < 5 s/d	5 - < 7.5 s/d	>7.5 s/d	P value	Per 200 mL increase[a]	P trend
Change in weight at 1-year follow-up							
N	357	713	515	247			
Drinking water consumption, mL/d[b]	355 ± 122	892 ± 30	1300 ± 13	1821 ± 130	<0.01		
Body weight at baseline, kg[b]	85.7 ± 13.0	86.0 ± 12.7	85.6 ± 11.9	89.5 ± 14.3	<0.01		
Body weight 1-year follow-up, kg[b]	83.4 ± 13.1	83.5 ± 12.9	83.2 ± 12.1	86.6 ± 14.3	<0.01		
Change in weight (%)[b]	−3.0 ± 5.2	−3.2 ± 5.0	−3.1 ± 5.3	−3.6 ± 5.4	0.47		
Model 1[c]	0 (ref.)	−0.28 (−0.93, 0.38)	−0.14 (−0.59, 0.56)	−0.68 (−1.55, 0.19)		−0.07 (−0.18, 0.04)	0.22
Model 2[c]	0 (ref.)	−0.35 (−0.95, 0.25)	−0.44 (−1.09, 0.20)	−0.67 (−1.50, 0.15)		−0.09 (−0.20, 0.01)	0.09
Model 3[c]	0 (ref.)	−0.69 (−1.33, −0.06)	−1.07 (−1.79, −0.36)	−1.64 (−2.59, −0.68)		−0.24 (−0.36, −0.12)	<0.01
Change in weight at 2-year follow-up							
N	360	707	503	243			
Drinking water consumption, mL/d[b]	355 ± 122	892 ± 30	1300 ± 13	1821 ± 131	<0.01		
Body weight at baseline, kg[b]	85.7 ± 13.0	86.0 ± 12.7	85.6 ± 11.9	89.5 ± 14.3	<0.01		
Body weight 2-years follow-up, kg[b]	83.7 ± 13.3	83.7 ± 13.1	83.3 ± 12.3	86.6 ± 14.3	<0.01		
Change in weight (%)[b]	−2.6 ± 5.5	−2.9 ± 5.3	−2.9 ± 5.6	−3.5 ± 5.8	0.29		
Model 1[c]	0 (ref.)	−0.35 (−1.04, 0.35)	−0.33 (−1.08, 0.43)	−0.98 (−1.92, −0.04)		−0.11 (−0.22, 0.01)	0.06
Model 2[c]	0 (ref.)	−0.44 (−1.09, 0.21)	−0.69 (−1.39, 0.02)	−0.97 (−1.86, −0.08)		−0.13 (−0.24, −0.02)	0.02
Model 3[c]	0 (ref.)	−0.80 (−1.48, −0.12)	−1.36 (−2.18, −0.54)	−1.97 (−3.09, −0.86)		−0.28 (−0.42, −0.13)	<0.01

Linear regression models and median regression analyses: Model 1 was adjusted for age (years) and sex; Model 2 was additionally adjusted for intervention group (a/b), smoking habit (never, former or current), educational level (primary, secondary or academic/graduate), body mass index (kg/m^2), leisure time physical activity (METs.min/week) and the 14-item Mediterranean diet score (continuous); Model 3 was additionally adjusted for total energy intake (Kcal/day) and total fluid intake (mL/day).
The p-value for comparisons between servings of drinking water consumption and changes in weight were calculated by One-factor ANOVA.
[a] Calculated per 200 mL increment on drinking water.
[b] Data were expressed as means ± SD.
[c] Non-standardized coefficient (Confidence Interval).

Table 3
Crude and multivariate β-coefficients and 95% CI of 1- and 2-year changes in waist circumference per servings of drinking water at baseline.

	Categories of Drinking Water Consumption (servings/day)						
	<2.5 s/d	2.5 - < 5 s/d	5 - < 7.5 s/d	>7.5 s/d	P value	Per 200 mL increase[a]	P trend
Change in waist circumference at 1-year follow-up							
N	344	682	494	237			
Drinking water consumption, mL/d[b]	354 ± 123	892 ± 31	1300 ± 13	1821 ± 133	<0.01		
Waist circumference at baseline, kg[b]	107.1 ± 9.6	107.7 ± 9.9	107.3 ± 9.5	108.8 ± 10.4	0.15		
Waist circumference 1-year follow-up, kg[b]	103.7 ± 10	104.6 ± 10.1	104.2 ± 9.9	105.7 ± 10.8	0.12		
Change in waist circumference (%)[b]	−3.5 ± 5.5	−3.2 ± 5.2	−3.0 ± 5.4	−3.2 ± 5.4	0.50		
Model 1[c]	0 (ref.)	0.37 (−0.34, 1.07)	0.56 (−0.20, 1.32)	0.28 (−0.62, 1.18)		0.05 (−0.07, 0.16)	0.36
Model 2[c]	0 (ref.)	0.24 (−0.42, 0.90)	0.26 (−0.45, 0.97)	0.20 (−0.67, 1.07)		0.02 (−0.09, 0.13)	0.61
Model 3[c]	0 (ref.)	−0.08 (−0.77, 0.60)	−0.33 (−1.13, 0.47)	−0.70 (−1.70, 0.30)		−0.11 (−0.25, 0.02)	0.15
Change in waist circumference at 2-year follow-up							
N	325	666	476	225			
Drinking water consumption, mL/d[b]	353 ± 124	892 ± 31	1300 ± 14	1819 ± 126	<0.01		
Waist circumference at baseline, kg[b]	107.1 ± 9.6	107.7 ± 9.9	107.3 ± 9.5	108.8 ± 10.4	0.15		
Waist circumference 2-years follow-up, kg[b]	104.4 ± 10.2	105.1 ± 10.5	104.3 ± 10.1	105.8 ± 10.3	0.25		
Change in waist circumference (%)[b]	−2.6 ± 5.6	−2.8 ± 5.8	−2.7 ± 5.7	−3.0 ± 5.8	0.92		
Model 1[c]	0 (ref.)	−0.14 (−0.90, 0.61)	−0.07 (−0.87, 0.74)	−0.35 (−1.34, 0.63)		−0.03 (−0.15, 0.09)	0.58
Model 2[c]	0 (ref.)	−0.27 (−0.99, 0.44)	−0.39 (−1.15, 0.38)	−0.38 (−1.34, 0.58)		−0.05 (−0.17, 0.07)	0.36
Model 3[c]	0 (ref.)	−0.66 (−1.40, 0.08)	−1.11 (−1.96, −0.25)	−1.45 (−2.66, −0.24)		−0.21 (−0.36, −0.05)	0.01

Linear regression models and median regression analyses: Model 1 was adjusted for age (years) and sex; Model 2 was additionally adjusted for intervention group (a or b), smoking habit (never, former or current), educational level (primary, secondary or academic/graduate), body mass index (kg/m^2), leisure time physical activity (METs.min/week) and the 14-item Mediterranean diet score (continuous); Model 3 was additionally adjusted for total energy intake (Kcal/day) and total fluid intake (mL/day).
The p-value for comparisons between servings of drinking water consumption and changes in waist were calculated by One-factor ANOVA.
[a] Calculated per 200 mL increment on drinking water.
[b] Data were expressed as means ± SD.
[c] Non-standardized coefficient (Confidence Interval).

methods used to assess drinking water and the time of follow-up might explain the discrepancies between the aforementioned studies and our results. However, our results are in line with those reported by Fresán et al. [12] who did not find a correlation between substitution of water for sugary drinks and weight changes. A long follow-up would probably be needed to achieve statistical significance in the replacement models [35]. Besides, the consumption of sugary drinks in the PREDIMED-Plus cohort [36] might be too low for any association to be detected. Artificially sweetened beverages (ASB) are commonly consumed as replacements for sugary drinks in an attempt to decrease calorie intake, although their effect on weight loss and weight maintenance remains

Table 4
Mean 1-year body weight and waist circumference changes (95% CI) associated with the substitution of one serving/day of water for different beverage groups (increasing water consumption by 1 serving/day and decreasing the relative beverage consumption by 1 serving/day) at baseline, using mathematical models.

	Absolute weight change (in grams)	Absolute waist circumference change (in centimeters)
Water for Hot beverages[b]	−92 (−197, 13)	0.08 (−0.07, 0.23)
Water for Total dairy beverages[b]	−131 (−301, 40)	−0.11 (−0.35, 0.13)
Water for Whole dairy beverages[a]	−112 (−373, 150)	−0.16 (−0.50, 0.18)
Water for Reduced dairy beverages[a]	−141 (−318, 34)	−0.11 (−0.35, 0.14)
Water for Sugary beverages[b]	−0.04 (−205, 205)	−0.10 (−0.37, 0.18)
Water for Artificially sweetened beverages[b]	−131 (−464, 201)	−0.13 (−0.65, 0.38)
Water for Soups/vegetable juices[b]	−403 (−602, −205)	−0.20 (−0.52, 0.13)
Water for Alcoholic beverages[b]	−150 (−278, −22)	−0.01 (−0.19, 0.17)
Water for Wine[a]	−37 (−220, 146)	0.09 (−0.15, 0.33)
Water for Beer[a]	−230 (−385, −74)	−0.04 (−0.28, 0.19)
Water for Spirits/Mixed alcoholic beverages[a]	−702 (−1329, −76)	−1.16 (−2.04, −0.29)
Water for Other beverages	−343 (−641, −45)	−0.42 (−0.81, 0.02)

[a] Multivariable-adjusted model for baseline covariates: age (years), sex, intervention group (a/b), smoking habit (never, former or current), educational level (primary, secondary or academic/graduate), baseline body mass index (kg/m^2), leisure time physical activity (METs.min/week) and the 14-item Mediterranean diet score (continuous) and total energy intake from fluids other than the exchanged beverages.
[b] Model additionally adjusted for servings per day from other groups of beverages.

Table 5
Mean 2-year absolute body weight and waist circumference changes (95% CI) associated with the substitution of one serving/day of water for different beverage groups (increasing water consumption by 1 serving/day and decreasing relative beverage consumption by 1 serving/day) at baseline, using mathematical models.

	Absolute weight change (in grams)	Absolute waist circumference change (in centimeters)
Water for Hot beverages[b]	−152 (−279, −25)	−0.07 (−0.25, 0.10)
Water for Total dairy beverages[b]	−279 (−479, −77)	−0.13 (−0.42, 0.15)
Water for Whole dairy beverages[a]	−171 (−488, 146)	0.04 (−0.34, 0.42)
Water for Reduced dairy beverages[a]	−268 (−480, −56)	−0.19 (−0.49, 0.10)
Water for Sugary beverages[b]	−22 (−238, 194)	−0.11 (−0.42, 0.20)
Water for Artificially sweetened beverages[b]	−144 (−465, 177)	−0.35 (−0.924, 0.23)
Water for Soups/vegetables juices[b]	−277 (−499, −56)	−0.38 (−0.81, 0.04)
Water for Alcoholic beverages[b]	−103 (−271, 65)	−0.06 (−0.27, 0.14)
Water for Wine[a]	−2.8 (−259, 253)	0.07 (−0.23, 0.37)
Water for Beer[a]	−148 (−381, 86)	−0.15 (−0.51, 0.20)
Water for Spirits/Mixed alcoholic beverages[a]	−367 (−1071, 337)	−0.91 (−1.91, 0.09)
Water for Other beverages	−385 (−715, −54)	−0.38 (−0.87, 0.11)

[a] Multivariable-adjusted model for baseline covariates: age (years), sex, intervention group (a/b), smoking habit (never, former or current), educational level (primary, secondary or academic/graduate), baseline body mass index (kg/m^2), leisure time physical activity (METs.min/week) and the 14-item Mediterranean diet score (continuous) and total energy intake from fluids other than the exchanged beverages.
[b] Model additionally adjusted for servings per day from other groups of beverages.

unclear [37,38]. However, the association between ASB consumption and BW compared to drinking water has been less explored. When we assessed the effect of replacing drinking water with ASB, we observed no effect on BW or WC. Similar results were recently reported in a young Mediterranean cohort [12]. In a parallel randomized-controlled weight-loss trial [39], ASB consumption was reported to be associated with greater weight loss and weight maintenance than water consumption during a structured weight loss program. Unfortunately, authors could not explain the potential mechanism responsible of the differences observed between groups. More studies are needed to clarify the long-term effect of ASB consumption instead of drinking water on BW and WC.

The published results on the association between types of dairy products, BW and WC are inconclusive. The consumption of dairy products has been inversely associated with weight gain and positively associated with improvements in body composition, especially in the short-term and as part of an energy-restricted diet [40]. In the long-term, these associations seem to be controversial [11,41–43]. Although reduced-fat dairy beverages are lower in energy content than whole-fat and sugary dairy beverages, in our study, their substitution by drinking water was associated with a greater decrease in BW at two-years of follow-up. The discrepancies between the aforementioned studies and our results could be attributed to differences in exposure (the amount consumed or changes over time) and to the fact that whole-dairy beverage consumption is low in our cohort, which makes it difficult to detect potential associations. It should also be taken into account that most previous longitudinal studies and meta-analyses focused on total dairy products and milk, and very few studies have analysed this effect on milk subtypes, milkshakes, and liquid yogurt.

The association between coffee and/or tea with BW and adiposity also remains unclear. Discrepancies between studies are mostly related to sex and ethnicity among others [44,45]. Coffee and tea are characterized by their content of caffeine, catechins, and other bioactive compounds which have been proposed as the potential mechanisms by which these beverages could prevent weight gain and promote weight loss [46,47]. However, when we assessed the effect of replacing hot beverages with drinking water a significant association with a decrease in BW was observed at two-years of follow-up. A possible explanation to our observations could be that, although coffee and tea are calorie-free beverages their consumption is often associated with calorie sweeteners, such as sugar, or other beverages such as milk or vegetable drinks (such as soy or almond beverages), which may contribute to increased energy intake, and therefore, their replacement with water could lead to a reduction in total energy intake.

In our analyses, replacing one serving of soups, broths, or vegetable juices with water was associated with weight and WC reductions. The assumption that soups and broths are usually a healthy and low-calorie food might induce people to consume larger portions. However, its nutritional properties and calorie content might vary as a consequence of cooking methods and the addition of other ingredients [48].

In our study, due to the heterogeneity of the other beverages group, it is difficult to clarify which of the beverages has the greatest influence on BW and WC. The few studies that have explored the effect of the consumption of plant-based drinks ("soy, almond, oats, rice milk", etc.) have been conducted in small samples and have focused on how the consumption of plant-based drinks and milk changes anthropometric parameters [40,49]. None of them have studied the association in the long-term. Except for one study that reported slight decreases in WC [49], no significant differences were observed between the effects of consuming milk or plant-based drinks on anthropometric parameters [40]. The nutrient density of plant-based drinks varies considerably between and within types, and their nutritional properties depend on a wide range of variables (food source, processing, fortification with vitamins and minerals, and the addition of other ingredients such as sugar and oils). Meal replacements, usually used to reduce daily energy intake, have proved to be positively associated with weight loss in the short-term, however their effectiveness preventing weight gain and maintaining weight loss still remain controversial [50]. Finally, sorbets and jellies are sources of sugars and saturated fat, with low satiating effects that contribute to increase energy intake [35,51]. All these reasons might explain the reduction observed in BW when these beverages were replaced by drinking water.

Some strengths of our study deserve to be mentioned: its prospective design, which reduces the possibility of reverse causation bias, the use of a specific validated fluid-intake questionnaire to assess beverage consumption, large sample size, and adjustment for several confounding factors. As far as limitations are concerned, we cannot discount that beverage consumption changed during the follow-up, and that the positive associations observed are due to other confounding factors not covered by the statistical analysis. Third, results from substitution models are based on mathematical theoretical estimations, therefore intervention trials are warranted in the future to prove the observed effect. Finally, we focused on elderly individuals with overweight/obesity and MetS and undergoing a planned weight loss program, so our results cannot be generalized to other populations.

5. Conclusions

The results of our study suggest that drinking tap and bottled water is inversely associated with adiposity changes in the long-term in an elderly Mediterranean cohort at high cardiovascular risk. Although further studies are warranted in the future, our results suggest that drinking water rather than energy-containing beverages is associated with lower weight gain. Recommendations to drink water, then, should be part of dietary advice on weight loss and its maintenance in the long-term.

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Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are not expected to be made available outside the core research group, as neither participants' consent forms or ethics approval included permission for open access. However, the researchers will follow a controlled data sharing collaboration model, as in the informed consent participants agreed with a controlled collaboration with other investigators for research related to the project's aims. Therefore, investigators who are interested in this study can contact the PREDIMED Plus Steering Committee by sending a request letter to predimed_plus_scommittee@googlegroups.com. A data sharing agreement indicating the characteristics of the collaboration and data management will be completed for the proposals that are approved by the Steering Committee.

Ethical standards

All participants provided their written informed consent. The study protocol and procedures were approved in accordance with the ethical standards of the Declaration of Helsinki.

Author contributions

Study concept and design: I.P-G, N.B and J.S-S. Statistical analyses: I.P-G, N.B.-T., and J.S-S. Drafting the manuscript: I.P-G, N.B, and J.S-S. All authors reviewed the manuscript for important intellectual content and approved the final version to be published.

Conflict of interest

JS-S serves on the board of (and is provided grant support by his institution from) the International Nut and Dried Fruit Council and the Eroski Foundation. He also serves on the Executive Committee of the Instituto Danone, Spain, and on the Scientific Committee of the Danone International Institute. He has received research support from the Patrimonio Comunal Olivarero, Spain, and Borges S.A., Spain. He receives consulting fees or travel expenses from

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.05.014.

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Online Supplementary Material

Supplementary Table 1. Correlation coefficients among variables considered in the models.

	BW at 1 year	BW at 2 year	WC at 1 year	WC at 1 year	Sex	Age	IG	BMI	LT PA	EL	SH	TFI	TEI	MEDAS	DW
BW at 1 year	1.00														
BW at 2 year	0.76**	1.00													
WC at 1 year	0.67**	0.55**	1.00												
WC at 1 year	0.51**	0.67**	0.72**	1.00											
Sex	0.01	0.00	0.04	0.03	1.00										
Age	-0.01	-0.05*	0.00	-0.00	0.25**	1.00									
IG	-0.42**	-0.35**	-0.35**	-0.30**	-0.00	-0.04	1.00								
BMI	-0.01	-0.03	0.03	0.03	0.11	-0.02	-0.04	1.00							
LT PA	0.03	0.04	0.03	0.02	-0.20**	0.00	0.03	-0.15*	1.00						
EL	-0.00	-0.00	0.00	0.02	-0.24**	-0.26**	0.03	-0.06*	-0.00	1.00					
SH	0.00	0.00	-0.05*	-0.03	-0.44**	-0.26**	0.00	-0.12**	0.07**	0.24**	1.00				
TFI	0.04	0.02	0.06*	0.03	-0.08**	-0.10**	-0.02	0.02	0.04	0.04	0.04	1.00			
TEI	-0.03	-0.06*	-0.03	-0.05*	-0.28	-0.11**	-0.03	-0.01	0.07**	0.14**	0.13**	0.10**	1.00		
MEDAS	0.04	0.05*	0.01	0.01	-0.00	0.10**	-0.04	-0.09**	0.15**	0.05*	0.00	0.04	0.05*	1.00	
DW	-0.03	-0.04	0.02	-0.01	0.02	-0.07	-0.02	0.07**	0.03	-0.04	-0.03	0.63**	-0.04	0.03	1.00

*Correlation is significant at the < 0.05 level. **Correlation is significant at the < 0.01 level.

BMI, body mass index; BW, body weight; DW, categories of drinking water; EL, education level; IG, intervention group; LT PA, leisure-time physical activity; MEDAS, Mediterranean Diet score; SH, smoking habit; TEI, total energy intake; TFI, total fluid intake; WC, waist circumference.

Chapter 3

Fruit consumption and cardiometabolic risk in the PREDIMED-plus study: a cross-sectional analysis.

Becerra-Tomás N, Paz-Graniel I, Tresserra-Rimbau A, Martínez-González MÁ, Barrubés L, Corella D, Muñoz-Martínez J, Romaguera D, Vioque J, Alonso-Gómez ÁM, Wärnberg J, Martínez JA, Serra-Majem L, Estruch R, Bernal-López MR, Lapetra J, Pintó X, Tur JA, Garcia-Rios A, Riquelme-Gallego B, Delgado-Rodríguez M, Matía-Martín P, Daimiel L, Velilla-Zancada S, Vidal J, Vázquez C, Ros E, Buil-Cosiales P, Babio N, Fernández-Carrión R, Pérez-Vega KA, Morey M, Torres-Collado L, Tojal-Sierra L, Pérez-López J, Abete I, Pérez-Cabrera J, Casas R, Fernandez-García JC, Santos-Lozano JM, Esteve-Luque V, Bouzas C, Fernandez-Lázaro CI, Sorlí JV, Martín M, García-Muñoz M, Salaverria-Lete I, Toledo E, Castañer O, Salas-Salvadó J.

Key teaching points:

- Public health organizations widely recommended fruit consumption to prevent CVD. It has been suggested that not only the quantity but the variety may contribute to reducing CVD risk. There is no consensus about the role of fruit juices on cardiometabolic health.
- Cross-sectional analysis assessing the association between the quantity, variety, and how fruit is consumed with different cardiometabolic risk factors in 6,633 elderly Mediterranean individuals with MetS.
- Higher fruit consumption was associated with lower WC, plasma glucose, and LDL-cholesterol levels, and unexpectedly, with higher SBP and DBP. Subgroup analyses suggested that not all varieties of fruits are associated in the same way with CVD risk.
- Total and natural fruit juice consumption was associated with lower WC and glucose levels, despite the low fiber content.

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Fruit consumption and cardiometabolic risk in the PREDIMED-plus study: A cross-sectional analysis

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Abbreviations: BP, blood pressure; CVDs, cardiovascular diseases; DBP, diastolic blood pressure; FFQ, food frequency questionnaire; MedDiet, Mediterranean Diet; MetS, metabolic syndrome; PREDIMED, Prevención Dieta MEDiterránea; SBP, systolic blood pressure; WC, waist circumference.

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Abstract *Background and aims:* Total fruit consumption is important for cardiovascular disease prevention, but also the variety and form in which is consumed. The aim of the study was to assess the associations between total fruit, subgroups of fruits based on their color and fruit juices consumption with different cardiometabolic parameters.
Methods and results: A total of 6633 elderly participants (aged 55–75 years) with metabolic syndrome from the PREDIMED-Plus study were included in this analysis. Fruit and fruit juice consumption was assessed using a food frequency questionnaire. Linear regression models were fitted to evaluate the association between exposure variables (total fruit, subgroups based on the color, and fruit juices) and different cardiometabolic risk factors. Individuals in the highest category of total fruit consumption (≥3 servings/d) had lower waist circumference (WC) (β = −1.04 cm; 95%CI:-1.81, −0.26), fasting glucose levels (β = −2.41 mg/dL; 95%CI(-4.19, −0.63) and LDL-cholesterol (β = −4.11 mg/dL; 95%CI:-6.93, −1.36), but, unexpectedly, higher systolic blood pressure (BP) (β = 1.84 mmHg; 95%CI: 0.37, 3.30) and diastolic BP (β = 1.69 mmHg; 95%CI:0.83, 2.56) when compared to those in the lowest category of consumption (<1 servings/d). Participants consuming ≥1 serving/day of total fruit juice had lower WC (β = −0.92 cm; 95%CI:-1.56, −0.27) and glucose levels (β = −1.59 mg/dL; 95%CI:-2.95, −0.23) than those consuming <1 serving/month. The associations with cardiometabolic risk factors differed according to the color of fruits.
Conclusion: Fruit consumption is associated with several cardiometabolic risk factors in Mediterranean elders with metabolic syndrome. The associations regarding BP levels could be attributed, at least partially, to reverse causality bias inherent to the cross-sectional design of the study.

Introduction

Cardiovascular diseases (CVDs) are among the top causes of mortality worldwide [1]. High body mass index (BMI), abnormal lipid profile and elevated blood pressure (BP) are well recognized CVDs risk factors [2]. Importantly, these modifiable risk factors are susceptible to improve by dietary changes, as demonstrated in nutritional intervention studies [3]. In this context, an increased consumption of fruits, which are rich in fiber, vitamins, minerals and bioactive compounds, has been widely recommended by public health organizations in order to prevent CVDs [4]. These guidelines are supported by a recent meta-analysis of prospective cohort studies where a 16% lower risk of CVDs was observed when comparing highest *versus* lowest categories of fruit consumption [5]. However, evidence from the last years suggests that not only total fruit intake may contribute to reduce the risk of CVDs, but also the variety and the way in which fruit is consumed (whole fruit or fruit juice) are important factors determining the disease risk [6–8]. For instance, whereas it is generally accepted that whole fruit consumption reduces the risk of

CVDs, there is no consensus about the role of fruit juices [9]. Moreover, it has been suggested that not all varieties of fruit are associated in the same manner with CVD risk. In a dose–response meta-analysis, consumption of apples, pears and citrus fruits was inversely associated with coronary heart disease, total stroke and CVD risk, whereas bananas, berries, grapes, strawberries and watermelon intakes were not significantly associated [10]. Another study classifying fruit and vegetables according to the color of the edible portion, which reflects the presence of pigmented phytochemicals and other components, showed that different colors of fruit and vegetables subgroups are differently associated with CVD risk factors [6]. Nonetheless, to the best of our knowledge, no previous study has investigated the association between various colors of fruits subgroups, independently of vegetable consumption, and CVDs risk factors. Therefore, we cross-sectionally evaluated the association between total fruit consumption, different forms of fruit consumption (whole and juices) and different varieties of fruit according to color groups with cardiometabolic risk factors (BMI, fasting glucose, lipid profile and blood pressure) in a large cohort of individuals with metabolic syndrome (MetS) participating in the PREDIMED-Plus study.

Methods

Study population

Briefly, PREDIMED-Plus is a 6-year, multicenter, parallel group clinical trial conducted in Spain aiming to evaluate the effect of an intensive intervention focused on weight loss (based on an energy-restricted Mediterranean diet, promotion of physical activity and behavioral support) on CVD events compared to usual care advices in individuals with MetS. A detailed explanation of the trial design has been published elsewhere [11], and the study protocol can be accessed at www.predimedplus.com. The study was registered at ClinicalTrials.gov (ISRCTN89898870). Recently, the results of the pilot study in relation to the effect of changes in body weight on CVD risk factors have been published [12].

From October 2013 to December 2016, we recruited 6784 community-dwelling men (aged 55–75 years) and women (aged 60–75 years) with overweight/obesity (BMI ≥27 kg/m^2 and <40 kg/m^2), free from CVD at baseline and harboring the MetS (meeting at least three criteria for the updated harmonized criteria of the International Diabetes Federation and the AHA/National Heart, Lung, and Blood Institute [13]. Therefore, individuals were considered as having MetS if they had three or more of the following components: elevated waist circumference for European individuals (≥88 cm in women and ≥102 cm in men), hypertriglyceridemia (>150 mg/dL) or drug treatment for elevated triglycerides, low concentrations of HDL-cholesterol (<50 mg/dL and <40 mg/dL in women and men, respectively) or drug treatment for low HDL-cholesterol, elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥ 85 mmHg) or taking antihypertensive medication; and high fasting plasma glucose (≥100 mg/dL) or drug treatment for hyperglycemia. Institutional review boards of each center approved the final protocol and all participants provided written informed consent. More information about the timeline of the data collection can be found elsewhere [11].

Among the 6874 participants, we excluded 53 participants who did not complete the food frequency questionnaire (FFQ) at baseline. Furthermore, we also excluded 188 participants with extreme total energy intakes according to predefined limits [14] (<500 or >3500 kcal/d for women and <800 or >4000 kcal/d for men). Therefore, the final sample size for the analyses was 6633 participants. The data were analyzed using the latest available complete PREDIMED-Plus database, dated March 25th 2019.

Dietary assessment

Trained dietitians administered a 143-item semi-quantitative FFQ, based on the validated FFQ used in PREDIMED study [15], in a face-to-face interviews at baseline. The frequency consumption of each item, with nine possible answers (never, one to three servings per month, one serving per week, two to four servings per week, five to six servings per week, one serving per day, two to three servings per day, four to six servings per day or more than six servings per day) during the preceding year, was asked to each participant. Ten items from the FFQ specifically addressed fruit consumption and three items to fruit juice intake. For the present analysis, we considered total fruit consumption as the sum of: 1) oranges, grapefruits or tangerines; 2) bananas; 3) apples or pears; 4) strawberries; 5) cherries or plums; 6) peaches, apricots or nectarines; 7) watermelon; 8) melon; 9) kiwi; and 10) grapes. Furthermore, as it has previously been reported [6,7], we also categorized fruit consumption according to the color of the edible part in orange fruits (oranges, tangerines, grapefruits and peaches); green fruits (kiwis and melons); red/purple fruits (strawberries, cherries, watermelons and grapes); and white fruits (bananas, apples and pears). Total fruit juice consumption was considered as the sum of natural orange juice, natural juice from other fruits and bottled fruit juice. Two Spanish food composition databases were used to calculate total energy and nutrient intake [16,17].

Other covariates assessment

At baseline, trained personnel (dietitians or nurses) collected socio demographic and lifestyle variables including age, sex, marital status, educational level, smoking habit, physical activity and Mediterranean diet (MedDiet) adherence as well as medication use and personal and family history of illness.

A validated version of the Minnesota Leisure Time Physical Activity Questionnaire was used to estimate leisure time physical activity [18,19].

Adherence to an energy-reduced MedDiet was assessed using a 17-item questionnaire adapted from a previous validated one [20]. The score obtained from the questionnaire ranged from 0 to 17 and one item related to fruit consumption. To control the analysis for the overall dietary pattern, we removed this item from the questionnaire, hence, the total score ranged from 0 to 16 points.

Outcomes

The outcomes of the present study were cross-sectional differences in BMI, waist circumference (WC), fasting blood glucose, triglycerides, LDL-cholesterol, HDL-cholesterol, systolic BP (SBP) and diastolic BP (DBP) between categories of fruit and juice consumption. These outcomes were selected because, although several cardiovascular risk factors have been identified, these are the main modifiable ones recorded in PREDIMED-Plus [21].

Following the study protocol, which can be found at www.predimedplus.com, trained staff of the PREDIMED-Plus study collected anthropometric and BP measurements. Weight and height were measured with participants with light clothes and no shoes using calibrated scales and wall-mounted stadiometers, respectively. BMI was calculated dividing the weight in kilograms by the square of height in meters. WC was measured at the midway between the lowest rib and the iliac crest using an anthropometric tape.

SBP and DBP were measured, in triplicate, after 5 min of rest with the participant seated using a validated semi-automatic oscillometer (Omron HEM-705CP, Netherlands). The mean of the three measures was recorded.

At baseline, blood samples were collected after an overnight fast, and laboratory technicians, who were blinded to the intervention group, performed biochemical analyses on fasting plasma glucose, triglycerides, and HDL-cholesterol using standard enzymatic procedures. The Friedewald formula was used to estimate LDL-cholesterol when levels of triglycerides were less than 400 mg/dL.

Statistical analyses

Analyses were performed using Stata software, version 15.0 (StataCorp LP, College Station, TX). Prior to analyses, we used multiple imputation with chained equations (STATA "mi" command) and created 20 imputed datasets to deal with missing data. The proportion of missing data ranged from 0.42% to 2.64%. Binary variables were imputed using the "logit" function, nominal variables using "mlogit", ordinal variables using "ologit" and continuous variables using "regress" function or "pmm" function (when the distribution was slightly skewed). The imputation model included all confounder variables used in the full-adjusted model as well as all exposures and outcomes. Diagnostic for multiple imputation was performed using the STATA command "midiagplots" [22].

Study participants were categorized by the frequency of consumption of servings of total fruit in: < 1 serving per day, 1 serving per day, 2 servings per day and ≥3 servings per day). We used this categorization to ensure that the highest category represented the recommendation of eating at least 3 servings of fruit per day [23]. For total juices and different types of juices (natural and bottled) participants were also classified based on the frequency of servings consumed in less than one serving per month, 1–4 servings per month, 2–6 servings per week and one or more servings per day. We followed this classification because the fruit juice intake was lower compared to fruit consumption. For subgroups according to fruit color, due to the low amount consumed in some groups because their availability is lower as they are seasonal fruits, individuals were categorized in tertiles of servings/week to ensure a homogeneous distribution of participants across categories.

Continuous variables were assessed for normality using the Shapiro Wilk test and the visual inspection of the histograms and scatter plots. To compare baseline characteristics of the study participants according to categories of total fruit consumption and total fruit juice consumption the Chi-square test and the ANOVA or Kruskal–Wallis test were conducted, as appropriate. Multivariable linear regression models or median regression analyses (if data were skewed) were carried out to evaluate the adjusted β-coefficients and 95% confidence interval for different CVD risk factors (BMI, WC, fasting glucose, LDL-cholesterol, HDL-cholesterol, tryglicerides, SBP and DBP) according to categories of total fruit consumption, tertiles of colors of fruit subgroups, and categories of total, natural and bottled fruit juices. All models were adjusted for potential confounders including: age (years), sex, diabetes prevalence (yes/no), hypertension prevalence (yes/no), hypercholesterolemia prevalence (yes/no), recruitment center (in categories by number of participants), leisure time physical activity (METs, min/week), BMI (kg/m^2; except for waist circumference and BMI outcomes), smoking habit (never, current or former smoker), educational level (primary, secondary or university/graduate), alcohol consumption (in grams per day and adding the quadratic term), energy intake (kcal/day) and 16-point screener (excluding the fruit item) of MedDiet adherence. We used the robust variance estimators to account for intra-cluster correlations in linear regression models (considering as clusters the members of the same household). In a sensitivity analysis, we conducted a complete case analysis (including only those individuals who had available data for all the variables) in 6190 participants. Statistical significance was set at a 2-tailed P-value <0.05.

Results

Baseline characteristics of the study population according to extreme categories of total fruit and total fruit juice consumption are shown in Table 1. Regarding total fruit

Table 1 Baseline characteristics of the study population according to categories of total fruit and total fruit juice consumption[a].

	Total fruit consumption			Total fruit juice consumption		
	<1 serving/day (n = 785)	≥3 servings/day (n = 1857)	P-value	<1 serving/month (n = 2876)	≥1 servings/day (n = 957)	P-value
Age, years	63 ± 5	66 ± 5	<0.01	65 ± 5	65 ± 5	<0.01
Women, % (n)	37.58 (295)	53.85 (1000)	<0.01	46.94 (1350)	46.50 (445)	0.01
BMI, kg/m^2	32.74 ± 3.48	32.42 ± 3.42	0.09	32.58 ± 3.40	32.25 ± 3.33	0.04
Leisure time physical activity, METs.min/week	2061 ± 2056	2617 ± 2421	<0.01	2403 ± 2259	2638 ± 2348	0.01
Smoking habit, % (n)			<0.01			<0.01
Never	31.75 (248)	49.27 (912)		42.32 (1210)	43.65 (416)	
Former	46.09 (360)	40.95 (758)		45.23 (1293)	42.81 (408)	
Current	22.15 (173)	9.78 (181)		12.45 (356)	13.54 (129)	
Education, % (n)			<0.01			<0.01
Primary or less	38.67 (302)	52.42 (965)		50.82 (1448)	43.86 (418)	
Secondary	34.19 (267)	26.89 (495)		29.06 (828)	28.86 (275)	
University/graduate	27.14 (212)	20.70 (381)		20.11 (573)	27.28 (260)	
Hypertension, % (n)	82.20 (642)	84.79 (1561)	0.22	84.99 (2429)	82.72 (785)	0.20
Diabetes, % (n)	30.70 (241)	30.86 (573)	0.99	34.77 (1000)	25.29 (242)	<0.01
Hypercholesterolemia, % (n)	68.98 (536)	70.09 (1289)	0.68	68.76 (1963)	70.83 (675)	0.05
Total energy intake, Kcal/day	2209 ± 593	2532 ± 531	<0.01	2291 ± 541	2531 ± 571	<0.01
Orange fruits, servings/day	0.13 [0.14]	1.07 [0.57]	<0.01	0.57 [0.86]	0.86 [0.86]	<0.01
Green fruits, servings/day	0.07 [0.13]	0.57 [0.79]	<0.01	0.14 [0.43]	0.21 [0.43]	<0.01
Red/purple fruits, servings/day	0.14 [0.20]	0.63 [0.86]	<0.01	0.28 [0.37]	0.34 [0.37]	<0.01
White fruits, servings/day	0.14 [0.23]	1.14 [0.93]	<0.01	0.85 [0.64]	0.86 [0.71]	<0.01
Natural fruit juices, servings/day	0 [0.13]	0.07 [0.43]	<0.01	0 [0]	1.00 [0.21]	<0.01
Bottled fruit juices, servings/day	0 [0]	0 [0]	0.15	0 [0]	0 [1.00]	<0.01
MedDiet score (16-points)	7.34 ± 2.45	8.41 ± 2.59	<0.01	8.03 ± 2.54	8.22 ± 2.67	0.03

Data expressed as percentage (number) and mean ± standard deviation or median [interquartile range] for categorical and continuous variables, respectively.
In the analyses, there were missing data for smoking habit in 28 participants (0.42%), education in 54 participants (0.81%), hypertension in 42 participants (0.63%) and hypercholesterolemia in 48 participants (0.72%).
[a] All categories were included in the analyses. P-value for comparisons between categories of total fruit consumption and total fruit juice consumption was calculated by Pearson's chi-square test for categorical variables or one-factor ANOVA and Kruskal–Wallis tests for continuous variables.

consumption, compared to participants who consumed less than one serving per day, those who consumed three or more servings per day, were more likely to be women, older, and physically more active. They also were less likely to smoke, had lower educational level, and had higher energy intake and MedDiet adherence. When participants were compared according to their fruit juice consumption, those who consumed one or more servings per day were more likely to be men, presented lower BMI values, had lower diabetes prevalence, and were more physically active. They also were more likely to smoke, had higher educational level, higher energy intake and higher adherences to the MedDiet. Significant differences among categories of total fruit and total fruit juice consumption were also observed on the type of fruit according to the color of the edible part.

The mean consumption of total fruit in the study population was 2.43 servings/day. The main type of fruit consumed was oranges, grapefruits or tangerines (24.73%), apples or pears (23.80%) and bananas (10.70%). The other 40% of total fruit consumption came from kiwis (7.89%), watermelon (7.38%), melon (7.07%), peaches (6.65%), cherries or plums (4.59%), strawberries (4.12%), and grapes (3.05%). Regarding fruit juice, the mean consumption of the study population was 0.21 servings/day, being natural fruit juices the most consumed (69.80%). The correlation between total fruit consumption and total fruit juice intake was low (correlation coefficient = 0.089).

Table 2 displays β-coefficients and 95%CI for different cardiovascular risk factors according to categories of total fruit consumption and total juice consumption, after adjusting for multiple potential confounders. Compared to participants who consumed less than one serving per day of total fruit, those who consumed three or more servings per day of total fruit had 1.04 cm, 2.41 mg/dL and 4.11 mg/dL lower values of WC, fasting glucose and LDL-cholesterol, respectively. In contrast, individuals who consumed three or more servings of total fruit had 1.84 mmHg and 1.69 mmHg higher values of SBP and DBP, respectively. Similar results for total fruit juice consumption were observed. WC and glucose levels were lower (0.92 cm and 1.59 mg/dL, respectively) in participants who consumed more than one serving per day compared to those who consumed less than one serving of fruit juice per month. However, LDL-cholesterol levels and SBP and DBP, did not differ across categories of total fruit juice consumption.

Results for multivariable linear regression analyses according to tertiles of colors of fruit consumption are shown in Table 3. In relation to orange fruit consumption,

Table 2 Multivariate-adjusted β-coefficients and 95%CI for different cardiovascular risk factors according to categories of total fruit consumption and total juice consumption.

Total Fruit consumption	**<1 serving/day (n = 785)**	**≥1 to <2 servings/day (n = 2019)**	**≥2 to <3 servings/day (n = 1972)**	**≥3 servings/day (n = 1857)**	***P*-trend**
BMI, kg/m^2	0 Ref.	−0.20 (−0.48, 0.08)	−0.04 (−0.33, 0.25)	−0.24 (−0.55, 0.06)	0.14
Waist circumference, cm	0 Ref.	−0.67 (−1.41, 0.06)	−0.82 (−1.56, −0.08)	−1.02 (−1.80, −0.24)	0.01
Glucose, mg/dL[a]	0 Ref.	−1.08 (−2.81, 0.65)	−1.45 (−3.18, 0.28)	−2.30 (−4.14, −0.45)	0.01
Triglycerides, mg/dL[a]	0 Ref.	−5.56 (−11.29, 0.17)	−3.72 (−9.50, 2.05)	−5.40 (−11.29, 0.50)	0.42
LDL-cholesterol, mg/dL	0 Ref.	−2.15 (−4.80, 0.49)	−3.67 (−6.36, −1.00)	−4.08 (−6.87, −1.30)	<0.01
HDL-cholesterol, mg/dL	0 Ref.	−0.25 (−1.14, 0.65)	−0.44 (−1.36, 0.48)	0.33 (−0.64, 1.29)	0.19
SBP, mmHg	0 Ref.	1.58 (0.21, 2.96)	1.25 (−0.15, 2.66)	1.81 (0.35, 3.28)	0.06
DBP, mmHg	0 Ref.	1.01 (0.20, 1.82)	1.37 (0.55, 2.20)	1.67 (0.81, 2.53)	<0.01
Total Fruit Juice consumption	**< 1 serving/month (n = 2876)**	**1–4 servings/month (n = 1481)**	**2–6 servings/week (n = 1319)**	**≥ 1 servings/day (n = 957)**	***P*-trend**
BMI, kg/m^2	0 Ref.	0.04 (−0.18, 0.25)	0.04 (−0.18, 0.26)	−0.22 (−0.47, 0.03)	0.15
Waist circumference, cm	0 Ref.	0.04 (−0.52, 0.61)	−0.23 (−0.81, 0.35)	−0.90 (−1.55, −0.26)	<0.01
Glucose, mg/dL[a]	0 Ref.	−0.93 (−2.03, 0.16)	−1.93 (−3.21, −0.65)	−1.72 (−3.06, −0.38)	<0.01
Triglycerides, mg/dL[a]	0 Ref.	−2.31 (−6.68, 2.05)	2.04 (−2.48, 6.56)	−1.95 (−7.02, 3.12)	0.45
LDL-cholesterol, mg/dL	0 Ref.	0.37 (−1.59, 2.33)	0.39 (−1.69, 2.46)	−0.80 (−3.22, 1.61)	0.39
HDL-cholesterol, mg/dL	0 Ref.	0.03 (−0.64, 0.70)	0.14 (−0.57, 0.85)	−0.17 (−0.99, 0.65)	0.72
SBP, mmHg	0 Ref.	−0.92 (−1.96, 0.12)	−1.28 (−2.39, −0.17)	−0.58 (−1.80, 0.64)	0.23
DBP, mmHg	0 Ref.	−0.77 (−1.38, −0.16)	−0.22 (−0.85, 0.39)	−0.25 (−0.97, 0.46)	0.93

Abbreviations: BMI, body mass index; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure. Linear regression models and median regression analyses: were adjusted for sex, age (in years), smoking habit (never, former or current smoker), educational level (primary or less, secondary or university/graduate), diabetes prevalence (yes/no), hypertension prevalence or antihypertensive use (yes/no), hypercholesterolemia prevalence (yes/no), leisure time physical activity (METs.min/week), recruitment center (in quartiles by number of participants), energy intake (Kcal/day), alcohol intake (g/d and adding the quadratic term), 16-point screener (excluding fruit item) of Mediterranean diet adherence (continuous) and BMI (except for BMI and waist circumference). Total fruit consumption and total fruit juice consumption were mutually adjusted.

[a] Data are median (95%CI).

participants located in the highest tertile of consumption had 1.90 mg/dL lower levels of triglycerides. Contrary, same participants exhibited 2.32 mmHg and 1.65 mmHg higher values of SBP and DBP, respectively. Regarding to green fruit consumption, participants in the highest tertile had 0.84 mg/dL higher HDL-cholesterol levels. Individuals located in the highest tertile of red purple fruit consumption had 2.10 mg/dL lower levels of fasting glucose compared to those individuals in the lowest tertile. Finally, those participants in the highest tertile of white fruit consumption had 0.40 kg/m^2 lower BMI and 1.13 cm lower WC than those in the bottom tertile.

In addition, we evaluated whether the type of fruit juice consumed (natural or bottled) was associated with different cardiovascular risk factors. Fig. 1 shows multivariate-adjusted β-coefficients and 95% CI for various cardiovascular risk factors according to frequency of natural fruit juice consumption. The consumption of one or more servings of natural fruit juice was only associated with lower values of WC (0.93 cm) and glucose levels (1.26 mg/dL).

Bottled fruit juice consumption was not associated with any of the cardiovascular risk factors considered (Fig. 2).

Sensitivity analyses were conducted with data from completers only and results remained essentially unchanged (Supplemental Table 1, Supplemental Table 2, Supplemental Fig. 1 and Supplemental Fig. 2). However, the association between tertiles of orange fruit consumption and triglycerides levels and HDL-cholesterol became non-significant and significant, respectively (Supplemental Table 2).

Discussion

As far as we know, this is the first study that depicts the association between not only the amount of fruit consumed, but also the variety and the way in which it is consumed with different cardiometabolic risk factors in individuals with metabolic syndrome. The results showed that the higher fruit consumption, the lower WC, plasma glucose and LDL-cholesterol levels, but unexpectedly, the higher SBP and DBP. Subgroup analyses according to the color of fruits showed different associations with cardiometabolic risk factors, suggesting that not all varieties of fruits are associated in the same way with CVD risk. Moreover, total fruit juice and natural juice intake was inversely associated with WC and fasting glucose levels, while bottled juice consumption was not associated with cardiometabolic risk factors.

Our results regarding total fruit consumption and WC are in line with a meta-analysis of prospective cohort studies [24] where fruit intake was associated with a decreased WC over time (β-coefficient: −0.04 cm/year; 95%CI: −0.05 to −0.02). Since WC is a well-known risk factor for CVD, fruit intake could help to prevent its development. The findings in relation to glucose levels also

Table 3 Multivariate-adjusted β-coefficients and 95%CI for different cardiovascular risk factors according to tertiles of colors of fruit consumption in servings/week.

	Tertiles of fruit consumption			*P*-trend
	T1 (Lowest)	T2	T3 (Highest)	
Orange fruits, median (P25–P75)	1.47 (0.93–3.00)	5.97 (4.00–6.00)	8.00 (7.47–10.00)	
BMI, kg/m^2	0 Ref.	0.11 (−0.11, 0.33)	0.06 (−0.14, 0.26)	0.59
Waist circumference, cm	0 Ref.	0.44 (−0.13, 1.02)	0.32 (−0.20, 0.84)	0.97
Glucose, mg/dL[a]	0 Ref.	0.23 (−0.86, 1.33)	0.53 (−0.61, 1.66)	0.61
Triglycerides, mg/dL[a]	0 Ref.	−3.63 (−7.99, 0.73)	−1.77 (−5.54, −2.00)	0.53
LDL-cholesterol, mg/dL	0 Ref.	−0.72 (−2.77, 1.33)	−1.38 (−3.29, 0.53)	0.05
HDL-cholesterol, mg/dL	0 Ref.	−0.07 (−0.77, 0.63)	−0.63 (−1.26, 0.01)	0.44
SBP, mmHg	0 Ref.	0.54 (−0.52, 1.61)	2.27 (1.26, 3.29)	<0.01
DBP, mmHg	0 Ref.	0.41 (−0.20, 1.03)	1.64 (1.06, 2.22)	<0.01
Green fruits, median (P25–P75)	0.47 (0–0.47)	1.47 (1.00–2.00)	5.97 (4.00–7.47)	
BMI, kg/m^2	0 Ref.	0.15 (−0.06, 0.36)	0.17 (−0.07, 0.39)	0.22
Waist circumference, cm	0 Ref.	0.01 (−0.46, 0.64)	0.01 (−0.59, 0.60)	0.48
Glucose, mg/dL[a]	0 Ref.	−0.10 (−1.32, 1.11)	−1.04 (−2.25, 0.16)	0.01
Triglycerides, mg/dL[a]	0 Ref.	6.58 (2.42, 10.74)	−0.11 (−4.44, 4.22)	0.46
LDL-cholesterol, mg/dL	0 Ref.	−1.28 (−3.27, 0.70)	−1.99 (−4.12, 0.14)	0.08
HDL-cholesterol, mg/dL	0 Ref.	−0.15 (−0.82, 0.53)	0.83 (0.11, 1.56)	0.01
SBP, mmHg	0 Ref.	−1.01 (−2.07, 0.05)	−0.97 (−2.09, 0.16)	0.10
DBP, mmHg	0 Ref.	0.26 (−0.35, 0.87)	−0.25 (−0.89, 0.39)	0.93
Red/purple fruits, median (P25–P75)	0.93 (0.47–1.40)	2.40 (1.87–2.47)	5.47 (4.00–8.00)	
BMI, kg/m^2	0 Ref.	−0.10 (−0.31, 0.11)	0.01 (−0.22, 0.24)	0.32
Waist circumference, cm	0 Ref.	−0.07 (−0.62, 0.49)	0.16 (−0.45, 0.77)	0.13
Glucose, mg/dL[a]	0 Ref.	−1.66 (−2.80, −0.53)	−2.20 (−3.50, −0.91)	0.01
Triglycerides, mg/dL[a]	0 Ref.	4.48 (0.30, 8.67)	3.62 (−0.93, 8.18)	0.92
LDL-cholesterol, mg/dL	0 Ref.	0.52 (−1.45, 2.50)	−0.59 (−2.83, 1.65)	0.11
HDL-cholesterol, mg/dL	0 Ref.	0.23 (−0.45.0.91)	0.39 (−0.36, 1.14)	0.60
SBP, mmHg	0 Ref.	−0.32 (−1.36, 0.73)	−0.83 (−2.00, 0.35)	0.36
DBP, mmHg	0 Ref.	0.38 (−0.23, 0.99)	0.06 (−0.61, 0.74)	0.57
White fruits, median (P25–P75)	2.00 (0.93–3.00)	6.00 (4.00–6.50)	10.00 (8.00–14.00)	
BMI, kg/m^2	0 Ref.	−0.06 (−0.26, 0.13)	−0.40 (−0.61, −0.19)	<0.01
Waist circumference, cm	0 Ref.	−0.09 (−0.61, 0.42)	−1.14 (−1.67, −0.60)	<0.01
Glucose, mg/dL[a]	0 Ref.	0.21 (−0.93, 1.34)	−0.42 (−1.52, 0.69)	0.89
Triglycerides, mg/dL[a]	0 Ref.	0.82 (−3.34, 4.97)	−0.19 (−3.95, 3.56)	0.72
LDL-cholesterol, mg/dL	0 Ref.	−1.98 (−3.83, −0.14)	−0.42 (−2.38, 1.55)	0.67
HDL-cholesterol, mg/dL	0 Ref.	−0.17 (−0.79, 0.46)	0.43 (−0.25, 1.10)	0.78
SBP, mmHg	0 Ref.	0.15 (−0.81, 1.11)	−0.11 (−1.15, 0.94)	0.50
DBP, mmHg	0 Ref.	0.12 (−0.43, 0.68)	0.08 (−0.51, 0.66)	0.30

Abbreviations: BMI, body mass index; LDL. Low-density lipoprotein; HDL, High-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Linear regression models and median regression analyses were adjusted for: sex, age (in years), smoking habit (never, former or current), educational level (primary or less, secondary or university/graduate), diabetes prevalence (yes/no), hypertension prevalence or antihypertensive use (yes/no), hypercholesterolemia prevalence (yes/no) leisure time physical activity (METs.min/week), center (in quartiles by number of participants), energy intake (Kcal/day), alcohol intake (g/d and adding the quadratic term), 16-point screener (excluding fruit item) of Mediterranean diet adherence (continuous), fruit juice intake (<1 serving/month, 1–4 servings/month, 2–6 servings/week or ≥1 serving/day) and BMI (except for BMI and waist circumference). Individual fruit consumption was mutually adjusted.
[a] Data are median (95%CI).

concur with prior research. In an additional meta-analysis of prospective cohort studies, a non-linear dose–response association was observed between fruit consumption and type 2 diabetes risk, with a 10% decreased risk in intakes up to 200–300 g/day, although, no more apparent benefits above this value were reported [25]. However, it should be noted that in another recent meta-analysis of randomized clinical trials, fruit intake had no effect on fasting glucose levels in the substitution (replacement of foods rich in refined starches for equal amounts of calories from fruits) or addition studies (excess energy from sugars added to diets), but a beneficial effect on glycated hemoglobin in substitution studies was detected [26]. Of note, our results are consistent with previous studies despite the fact that they come from a cross-sectional analysis and that fruit and juice intake were assessed using an FFQ, while in other studies different dietary assessment methods could have been used.

Previous cross-sectional studies evaluating fruit and vegetable consumption in relation to LDL-cholesterol levels reported inverse correlations [27,28], results that are consistent with our findings.

Contrary to previous epidemiological studies [29,30], our results surprisingly revealed a positive association between fruit consumption and SBP and DBP. However, in the INTERMAP study [31], despite non-statistically significant results, a trend toward higher levels of SBP and DBP was observed per >50 g/1000 kcal of fruit consumption.

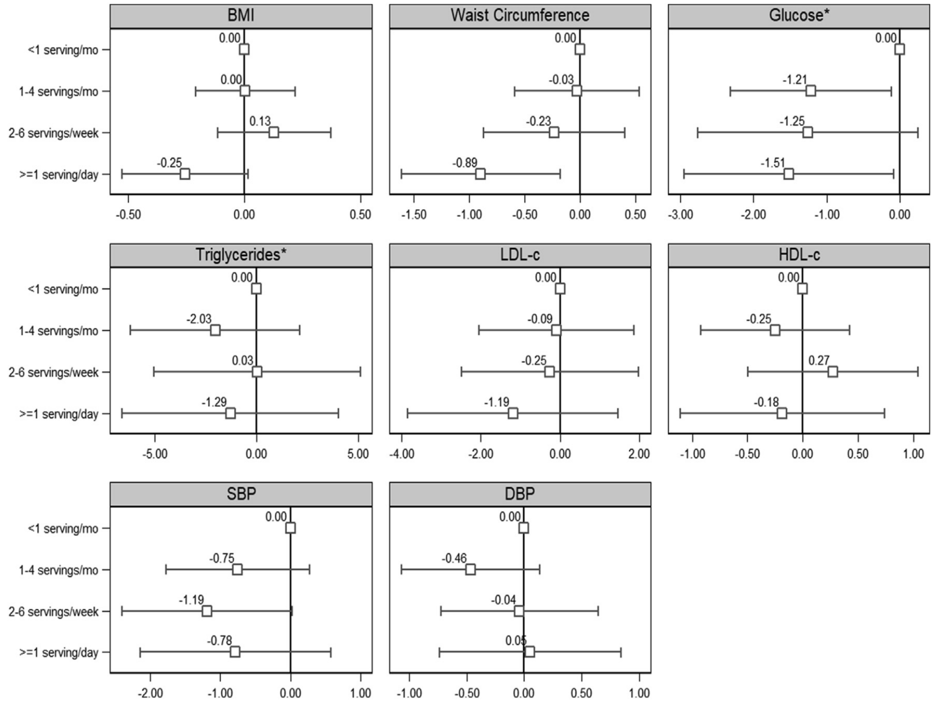

Figure 1 Multivariate-adjusted β-coefficients and 95%CI for different cardiovascular risk factors according to categories of natural fruit juice consumption. Linear regression models and median regression analyses were adjusted for sex, age (in years), smoking habit (never, former or current smoker), educational level (primary, secondary or university/graduate), diabetes prevalence (yes/no), hypertension prevalence or antihypertensive use (yes/no), hypercholesterolemia prevalence (yes/no) leisure time physical activity (METs.min/week), recruitment center (in quartiles by number of participants), energy intake (Kcal/day), alcohol intake (g/d and adding the quadratic term), 16-point screener (excluding fruit item) of Mediterranean diet adherence (continuous), total fruit consumption (<1 serving/day, ≥1 to <2 servings/day, ≥ 2 to <3 servings/day or ≥3 servings/day) and BMI (except for BMI and waist circumference). *Data are median (95%CI).

When analysis were stratified by regions, fruit consumption was associated with high DBP (0.37 mmHg; 95%CI: 0.02, 0.71) in participants from East Asian countries, whereas no association was observed in those from Western countries. Of note, fruits are a fructose-rich food, and high consumption of fructose has been related to adverse effects on blood pressure. Although the exact mechanisms are not well understood, it could be related to the impact of fructose on uric acid [32,33] and its interaction with salt absorption in the gut [34]. However, due to the cross-sectional design of both the aforementioned and the present study, as well as the paucity of evidence and the contradictory results in this field, it is premature to make inference about causality. Future studies, with a prospective design, evaluating the effect of fructose derived solely from fruits on BP could help to clarify these associations and to elucidate the exact mechanisms implicated.

To the best of our knowledge, this is the first study examining the association between groups of fruits (and not vegetables) based on the color of the edible part and different cardiometabolic risk factors. The present results suggest that certain colors of fruit, may be more relevant than others for cardiovascular disease prevention. Whereas For instance, only white fruits were associated with WC and BMI (anthropometrical features), only orange fruits associated with BP, only green fruits were associated with HDL-cholesterol and only green and red/purple fruits were associated with glucose levels. Limited previous research has focused on evaluating the association between fruit and vegetable consumption according to its color and cardiometabolic risk factors, stroke and coronary heart disease. Our results support those obtained from the Tehran lipid and glucose study [6], where different color of fruits and vegetables were differently associated with cardiometabolic risk factors. Besides, in a Dutch cohort of men and women aged 20–65 years, only white fruit and vegetable consumption was inversely associated with the incidence of stroke [7], and deep orange fruit and vegetables with lower risk of coronary heart disease [35]. Nevertheless, due to the limited evidence in this field, the extent to which fruit color groups contribute to cardiometabolic risk factors is uncertain.

In the present study we also evaluated the association between fruit juices consumption (total, natural and bottled) and different cardiometabolic risk factors, since there is still debate about their role on cardiovascular disease prevention due to the amount of naturally occurring sugar they contain and the presence of most of the nutrients found in whole fruit. Our results showed a

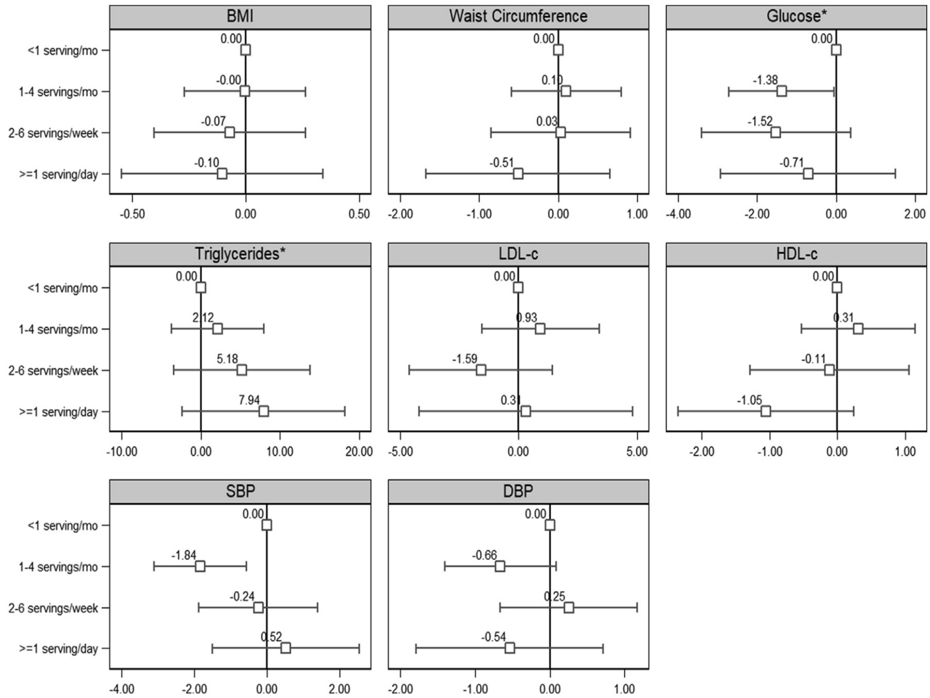

Figure 2 Multivariate-adjusted β-coefficients and 95%CI for different cardiovascular risk factors according to categories of bottled fruit juice consumption. Linear regression models and median regression analyses were adjusted for: sex, age (in years), smoking habit (never, former or current), educational level (primary, secondary or university/graduate), diabetes prevalence (yes/no), hypertension prevalence or antihypertensive use (yes/no), hypercholesterolemia prevalence (yes/no) leisure time physical activity (METs.min/week), center (in quartiles by number of participants), energy intake (Kcal/day), alcohol intake (g/d and adding the quadratic term), 16-point screener (excluding fruit item) of Mediterranean diet adherence (continuous), total fruit consumption (<1 serving/day, ≥1 to <2 servings/day, ≥ 2 to <3 servings/day or ≥3 servings/day)and BMI (except for BMI and waist circumference). *Data are median (95%CI).

significant inverse association between total and natural fruit juice intake with WC and fasting glucose levels. Similarly, previous cross-sectional studies also reported an inverse association between fruit juice consumption and BMI [36], and between 100% fruit juice intake and BMI, WC, and homeostasis model assessment (HOMA) insulin resistance [37]. Of note, bottled fruit juice usually contains a significant amount of sugar, which could counteract the beneficial effects of other nutrients. This fact could explain the lack of association between bottled fruit juices and cardiometabolic risk factors in the present study. However, there is still some controversy about the potential health impact of fruit juice consumption. Therefore, further longitudinal and clinical trials are needed to clarify this issue.

The mechanisms by which fruit consumption may protect against cardiometabolic risk are unlikely to be related to a single constituent [38]. Besides the high fiber content, fruit contains other nutrient and non-nutrient components, such as beta-carotenes, vitamins C and E, potassium and polyphenols that could act synergistically through the reduction of oxidative stress, inflammation, platelet aggregation, cholesterol levels and the improvement of the endothelial function [39,40]. Moreover, the high fiber content could increase satiation and modulate gut microbiota in a positive way [41]. Finally, fruit consumption may displace other unhealthy foods rich in saturated fatty acids, sugar and sodium that are detrimental for cardiovascular health. It is important to highlight, that color pigments of food correspond to specific phytonutrients. For instance, orange to beta-carotenes, purple to flavonoids and green to chlorophyll. These molecules seems to have different health effects, which could explain the diverse associations reported in the present analysis. Accordingly to a recent review, orange pigments are mainly antioxidant for fat-soluble tissues; red pigments have anti-inflammatory properties and are implicated in general antioxidant activity; green pigments are frequently antioxidants and are involved in blood vessel support; and red/purple pigments have antioxidant capacities [42].

Regarding fruit juices, although their fiber content is low, other healthy components such as polyphenols and vitamins and minerals are still present, which could explain the beneficial associations reported in the current analysis [43].

Our study has several limitations that deserve to be discussed. First, the results cannot be extrapolated to other populations since participants included in the analysis were elderly Mediterranean individuals with metabolic syndrome. Therefore, as they were already at risk of cardiovascular disease the results of the present study could be influenced by this condition. Second, the cross-sectional study design does not allow to draw inference about causation, and, importantly, reverse causality is a well-known concern in this type of studies, which could explain the unexpected results observed regarding SBP and DBP. Finally, the assessment of food intake through a FFQ is prone to possible measurements errors. Moreover, fruit and juice intake could be underestimated since our FFQ has a food-based design that does not take into account other ways of eating fruits or juices as do the dish-based FFQs. However, despite this limitation, food-based FFQs have been widely used as a tool in epidemiological studies since the 1990s [44].

The present study also has some strengths that need to be highlighted such as the control for several potential confounding factors, the use of multiple imputation to deal with missing data, and the analysis of different fruit groups based on the color of their edible part.

In conclusion, the present findings showed that higher total fruit consumption is associated with lower WC, plasma glucose and LDL-cholesterol levels, and higher SBP and DBP in elderly individuals with metabolic syndrome. However, varieties of fruits, based on their color, are differently associated with each cardiometabolic risk factor. In addition, despite the low fiber content, total and natural fruit juice consumption was associated with lower WC and glucose levels. The present study adds new insights into the potential association between different fruits based on their colors and cardiometabolic risk. So far science has been mainly focused on fruit quantity, but in the last years, it has been demonstrated that variety could be even more important for human health. Therefore, the results of the present study open a new line of research for better understanding the potential benefits of consuming different types of fruit (variety) using observational prospective design studies and randomized clinical trials. The obtained results will help to update evidence-based clinical practice guidelines for the prevention of cardiovascular diseases emphasizing the consumption of a variety of colorful fruits. This strategy could serve not only to increase the consumption of thousands of phytochemicals but also to increase the quantity of fruit intake which continues to be less than what is recommended.

Contribution statement

Study concept and design: N.B and J.S–S. Statistical analyses: N.B-T and J.S–S. Drafting the manuscript: N.B-T, I.P-G and J.S–S. All authors reviewed the manuscript for important intellectual content and approved the final version to be published. N.B-T and J.S–S had full access to all the data for the present study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data statement

Data described in the article, code book, and analytic code will be made available upon request pending.

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Conflict of interest

The authors declare that they have no conflict of interest related to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2021.02.007.

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Supplemental Table 1. Multivariate-adjusted β-coefficients and 95%CI for different cardiovascular risk factors according to categories of total fruit consumption and total juice consumption in completers (n=6,190)

	Total Fruit consumption				
	<1 serving/day (n= 730)	**≥1 to <2 servings/day (n= 1,889)**	**≥2 to <3 servings/day (n= 1,845)**	**≥ 3servings/day (n= 1,726)**	***P*-trend**
BMI, kg/m²	0 Ref.	-0.24 (-0.53, 0.06)	-0.08 (-0.38, 0.22)	-0.29 (-0.61, 0.02)	0.08
Waist circumference, cm	0 Ref.	-0.74 (-1.49, 0.02)	-0.86 (-1.62, -0.10)	-1.13 (-1.93, -0.33)	0.01
Glucose, mg/dL¥	0 Ref.	-1.13 (-2.79, 0.53)	-1.52 (-3.14, -0.11)	-2.24 (-3.98, -0.50)	0.02
Triglycerides, mg/dL¥	0 Ref.	-5.95(-11.76, -0.13)	-4.79 (-10.74, 1.17)	-6.00 (-12.05, 0.07)	0.36
LDL-cholesterol, mg/dL	0 Ref.	-2.75 (-5.44, -0.06)	-4.52 (-7.24, -1.80)	-4.93 (-7.77, -2.09)	<0.01
HDL-cholesterol, mg/dL	0 Ref.	-0.11 (-1.04, 0.81)	-0.32 (-1.26, 0.63)	0.41 (-0.58, 1.41)	0.15
SBP, mmHg	0 Ref.	1.67 (0.25, 3.08)	1.49 (0.04, 2.95)	2.07 (0.54, 3.59)	0.02
DBP, mmHg	0 Ref.	1.23 (0.40, 2.07)	1.62 (0.77, 2.47)	1.95 (1.06, 2.84)	<0.01
	Total Fruit Juice consumption				
	<1 serving/month (n= 2,673)	**1-4 servings/month (n= 1,378)**	**2-6 servings/week (n= 1,245)**	**≥ 1servings/day (n= 894)**	***P*-trend**
BMI, kg/m²	0 Ref.	0.04 (-0.18, 0.26)	0.01 (-0.22, 0.24)	-0.23 (-0.48, 0.02)	0.11
Waist circumference, cm	0 Ref.	0.05 (-0.54, 0.63)	-0.24 (-0.83, 0.36)	-0.91 (-1.57, -0.24)	<0.01
Glucose, mg/dL¥	0 Ref.	-1.00 (-2.28, 0.28)	-1.76 (-3.09, -0.42)	-1.90 (-3.41, -0.39)	0.01
Triglycerides, mg/dL¥	0 Ref.	-0.77 (-4.71, 3.18)	1.93 (-2.195, 6.04)	2.41 (-6.94, 3.78)	0.45
LDL-cholesterol, mg/dL	0 Ref.	0.23 (-1.77, 2.23)	0.10 (-1.99, 2.19)	-1.05 (-3.48, 1.38)	0.18
HDL-cholesterol, mg/dL	0 Ref.	-0.08 (-0.78, 0.61)	0.09 (-0.64, 0.81)	-0.28 (-1.11, 0.56)	0.61
SBP, mmHg	0 Ref.	-0.94 (-2.02, 0.15)	-1.21 (-2.37, -0.06)	-0.41 (-1.67, 0.83)	0.48
DBP, mmHg	0 Ref.	-0.77 (-1.40, -0.15)	-0.23 (-0.87, 0.41)	-0.11 (-0.84, 0.62)	0.49

Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Linear regression models and median regression analyses were adjusted for sex, age (in years), smoking habit (never, former or current smoker), educational level (primary or less, secondary or university/graduate), diabetes prevalence (yes/no), hypertension prevalence or antihypertensive use (yes/no), hypercholesterolemia prevalence (yes/no) leisure time physical activity (METs.min/week), recruitment center (in quartiles by number of participants), energy intake (Kcal/day), alcohol intake (g/d and adding the quadratic term), 16-point screener (excluding the fruit item) of Mediterranean diet adherence (continuous) and BMI (except for BMI and waist circumference). Total fruit consumption and total fruit juice consumption were mutually adjusted. ¥Data are median (95%CI).

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Supplemental Table 2. Multivariate-adjusted β-coefficients and 95%CI for different cardiovascular risk factors according to tertiles of colors of fruit consumption (in servings/week) in completers (n=6,190)

	Tertiles of fruit consumption			
	T1 (Lowest)	**T2**	**T3 (Highest)**	*P*-trend
Orange fruits, median (P25-P75)	1.47 (0.93, 3.00)	5.97 (4.00, 6.00)	8.00 (7.47, 10.00)	
BMI, kg/m^2	0 Ref.	0.08 (-0.15, 0.31)	0.08 (-0.13, 0.29)	0.69
Waist circumference, cm	0 Ref.	0.43 (-0.16, 1.03)	0.32 (-0.22, 0.86)	0.88
Glucose, mg/dL$^¥$	0 Ref.	0.51 (-0.65, 1.66)	0.77 (-0.37, 1.91)	0.31
Triglycerides, mg/dL$^¥$	0 Ref.	-4.40 (-8.65, -0.14)	-2.64 (-6.41, 1.12)	0.65
LDL-cholesterol, mg/dL	0 Ref.	-0.75 (-2.80, 1.31)	-1.24 (-3.19, 0.71)	0.05
HDL-cholesterol, mg/dL	0 Ref.	-0.11 (-0.83, 0.61)	-0.72 (-1.37, -0.06)	0.29
SBP, mmHg	0 Ref.	0.81 (-0.30, 1.91)	2.46 (1.42, 3.51)	<0.01
DBP, mmHg	0 Ref.	0.48 (-0.16, 1.11)	1.69 (1.10, 2.29)	<0.01
Green fruits, median (P25-P75)	0.47 (0, 0.47)	2.00 (1.00, 2.00)	5.97 (3.47, 7.47)	
BMI, kg/m^2	0 Ref.	0.13 (-0.09, 0.34)	0.14 (-0.10, 0.37)	0.19
Waist circumference, cm	0 Ref.	-0.03 (-0.61, 0.54)	-0.12 (-0.74, 0.50)	0.49
Glucose, mg/dL$^¥$	0 Ref.	-0.41 (-1.64, 0.83)	-1.26 (-2.51, -0.01)	<0.01
Triglycerides, mg/dL$^¥$	0 Ref.	6.25 (2.10, 10.39)	-0.12 (-4.32, 4.08)	0.19
LDL-cholesterol, mg/dL	0 Ref.	-1.09 (-3.10, 0.92)	-1.84 (-4.01, 0.32)	0.12
HDL-chlesterol, mg/dL	0 Ref.	-0.14 (-0.83, 0.56)	0.85 (0.10, 1.60)	<0.01
SBP, mmHg	0 Ref.	-0.96 (-2.06, 0.14)	-0.87 (-2.04, 0.30)	0.19
DBP, mmHg	0 Ref.	0.29 (-0.33, 0.92)	-0.15 (-0.81, 0.51)	0.47
Red/purple fruits, median (P25-P75)	0.93 (0.47, 1.40)	2.40 (1.87, 2.47)	5.46 (4.00, 7.97)	
BMI, kg/m^2	0 Ref.	-0.09 (-0.31, 0.12)	-0.04 (-0.28, 0.20)	0.42
Waist circumference, cm	0 Ref.	-0.14 (-0.72, 0.43)	-0.06 (-0.70, 0.56)	0.27
Glucose, mg/dL$^¥$	0 Ref.	-1.63 (-2.80, -0.46)	-2.25 (-3.60, -0.90)	<0.08
Triglycerides, mg/dL$^¥$	0 Ref.	4.78 (0.69, 8.87)	4.05 (-0.39, 8.50)	0.91

LDL-cholesterol, mg/dL	0 Ref.	0.81 (-1.19, 2.80)	-1.15 (-3.42, 1.13)	0.04
HDL-cholesterol, mg/dL	0 Ref.	0.22 (-0.48, 0.92)	0.26 (-0.51, 1.04)	0.69
SBP, mmHg	0 Ref.	-0.23 (-1.31, 0.85)	-1.00 (-2.22, 0.22)	0.37
DBP, mmHg	0 Ref.	0.47 (-0.16, 1.09)	0.10 (-0.60, 0.79)	0.76
White fruits, median (P25-P75)	2.00 (0.93, 3.00)	6.00 (4.00, 6.50)	10.00 (8.00, 14)	
BMI, kg/m^2	0 Ref.	-0.07 (-0.27, 0.14)	-0.44 (-0.66, -0.23)	<0.01
Waist circumference, cm	0 Ref.	-0.13 (-0.66, 0.40)	-1.11 (-1.68, -0.56)	<0.01
Glucose, mg/dL[¥]	0 Ref.	0.15 (-0.99, 1.29)	-0.59 (-1.72, 0.54)	0.99
Triglycerides, mg/dL[¥]	0 Ref.	0.73 (-3.12, 4.67)	-0.09 (-3.90, 3.72)	0.53
LDL-cholesterol, mg/dL	0 Ref.	-2.60 (-4.47, -0.74)	-0.93 (-2.94, 1.07)	0.35
HDL-cholesterol, mg/dL	0 Ref.	-0.18 (-0.82, 0.46)	0.58 (-0.11, 1.28)	0.37
SBP, mmHg	0 Ref.	0.18 (-0.81, 1.17)	0.01 (-1.07, 1.09)	0.40
DBP, mmHg	0 Ref.	0.321 (-0.36, 0.78)	0.10 (-0.60, 0.80)	0.44

Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Linear regression models and median regression analyses were adjusted for sex, age (in years), smoking habit (never, former or current smoker), educational level (primary or less, secondary or university/graduate), diabetes prevalence (yes/no), hypertension prevalence or antihypertensive use (yes/no), hypercholesterolemia prevalence (yes/no) leisure time physical activity (METs.min/week), center (in quartiles by number of participants), energy intake (Kcal/day), alcohol intake (g/d and adding the quadratic term), 16-point screener (excluding fruit item) of Mediterranean diet adherence (continuous), fruit juice intake (<1 serving/month, 1-4 servings/month, 2-6 servings/week or ≥1serving/day) and BMI (except for BMI and waist circumference). Individual fruit consumption was mutually adjusted. [¥]Data are median (95%CI).

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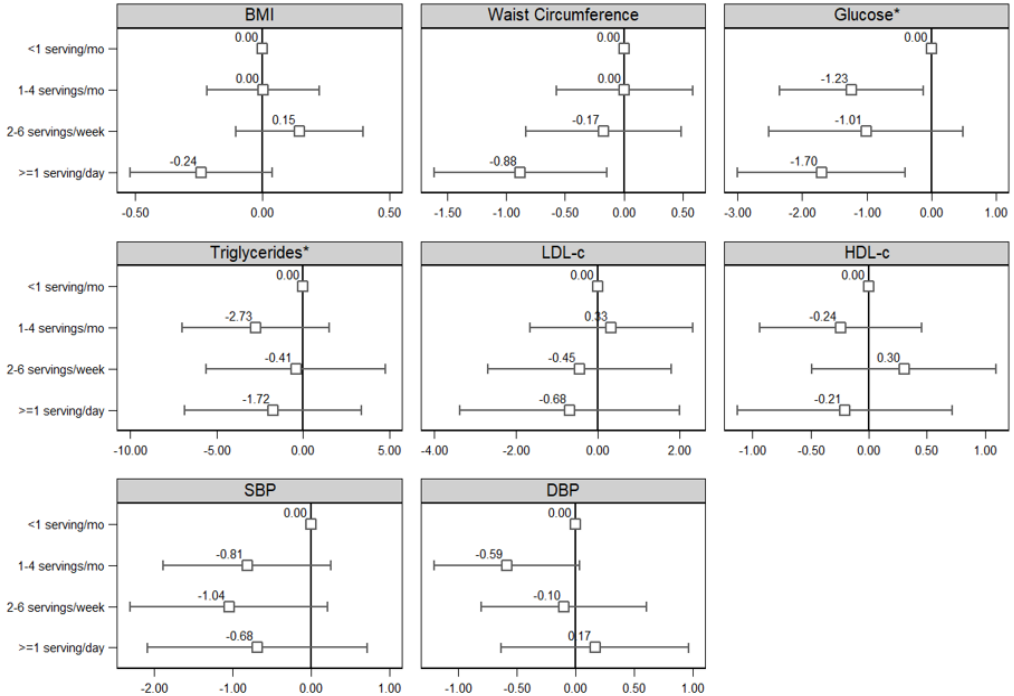
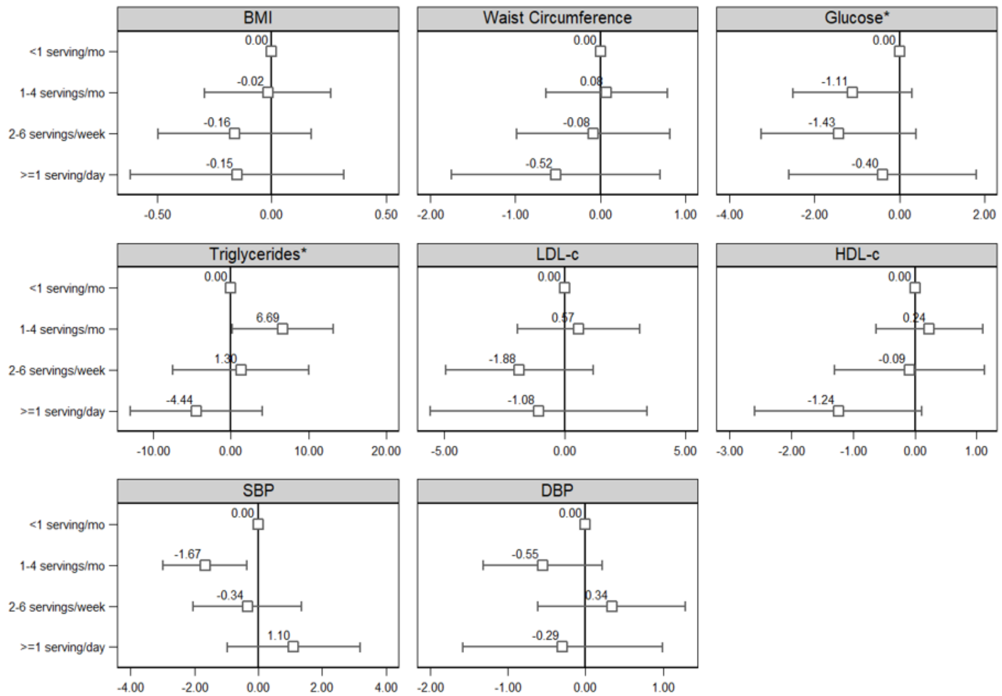


Supplemental Figure 1. Multivariate-adjusted β-coefficients and 95%CI for different cardiovascular risk factors according to categories of natural fruit juice consumption in completers (n=6,190). Linear regression models and median regression analyses were adjusted for, sex, age (in years), smoking habit (never, former or current smoker), educational level (primary or less, secondary or university/graduate), diabetes prevalence (yes/no), hypertension prevalence or antihypertensive use (yes/no), hypercholesterolemia prevalence (yes/no) leisure time physical activity (METs.min/week), recruitment center (in quartiles by number of participants), energy intake (Kcal/day), alcohol intake (g/d and adding the quadratic term), 16-point screener (excluding fruit item) of Mediterranean diet adherence (continuous), total fruit consumption (<1 serving/day, ≥1 to <2 servings/day, ≥ 2 to <3 servings/day or ≥3 servings/day) and BMI (except for BMI and waist circumference). *Data are median (95%CI). Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Online Supplementary Material



Supplemental Figure 2. Multivariate-adjusted β-coefficients and 95%CI for different cardiovascular risk factors according to categories of bottled fruit juice consumption in completers (n=6,190). Linear regression models and median regression analyses were adjusted for sex, age (in years), smoking habit (never, former or current smoker), educational level (primary or less, secondary or university/graduate), diabetes prevalence (yes/no), hypertension prevalence or antihypertensive use (yes/no), hypercholesterolemia prevalence (yes/no) leisure time physical activity (METs.min/week), recruitment center (in quartiles by number of participants), energy intake (Kcal/day), alcohol intake (g/d and adding the quadratic term), 16-point screener (excluding fruit item) of Mediterranean diet adherence (continuous), total fruit consumption (<1 serving/day, ≥1 to <2 servings/day, ≥ 2 to <3 servings/day or ≥3 servings/day) and BMI (except for BMI and waist circumference). *Data are median (95%CI). Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP systolic blood pressure; DBP, diastolic blood pressure.

Chapter 4

Association between coffee consumption and total dietary caffeine intake with cognitive functioning: cross-sectional assessment in an elderly Mediterranean population.

Paz-Graniel I, Babio N, Becerra-Tomás N, Toledo E, Camacho-Barcia L, Corella D, Castañer-Niño O, Romaguera D, Vioque J, Alonso-Gómez ÁM, Wärnberg J, Martínez JA, Serra-Majem L, Estruch R, Tinahones FJ, Fernandez-Aranda F, Lapetra J, Pintó X, Tur JA, García-Rios A, Bueno-Cavanillas A, Gaforio JJ, Matía-Martín P, Daimiel L, Sánchez VM, Vidal J, Prieto-Sanchez L, Ros E, Razquin C, Mestres C, Sorli JV, Cuenca-Royo AM, Rios A, Torres-Collado L, Vaquero-Luna J, Pérez-Farinós N, Zulet MA, Sanchez-Villegas A, Casas R, Bernal-Lopez MR, Santos-Lozano JM, Corbella X, Mateos D, Buil-Cosiales P, Jiménez-Murcia S, Fernandez-Carrion R, Forcano-Gamazo L, López M, Sempere-Pascual MÁ, Moreno-Rodriguez A, Gea A, de la Torre-Fornell R, Salas-Salvadó J; PREDIMED-Plus Investigators.

Key teaching points:

- It has been suggested that individuals with MetS are at higher risk for developing neurological alterations characterized by cognitive decline.
- Coffee is rich in caffeine, which may act as psychoactive stimulants that improve cognitive performance in the short term, and polyphenols, which might have a protective effect on cognition.
- Epidemiological studies have reported inconsistent results regarding the association between coffee consumption and cognitive function or the risk of dementia.
- This is the first study to evaluate the association between coffee consumption (and its subtypes) and cognition in an elderly population with MetS using a cross-sectional design.

- Coffee consumption and total dietary caffeine intake were associated with better cognitive functioning measured by a battery of neurophysiological tests.

- Decaffeinated coffee consumption showed a not significant protective trend against poor cognitive performance, reinforcing the hypothesis of a synergic effect between coffee compounds against cognitive impairment.

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ORIGINAL CONTRIBUTION

Association between coffee consumption and total dietary caffeine intake with cognitive functioning: cross-sectional assessment in an elderly Mediterranean population

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Abstract

Purpose Coffee is rich in compounds such as polyphenols, caffeine, diterpenes, melanoidins and trigonelline, which can stimulate brain activity. Therefore, the possible association of coffee consumption with cognition is of considerable research interest. In this paper, we assess the association of coffee consumption and total dietary caffeine intake with the risk of poor cognitive functioning in a population of elderly overweight/obese adults with metabolic syndrome (MetS).

Methods PREDIMED-plus study participants who completed the Mini-Mental State Examination test (MMSE) ($n = 6427$; mean age $= 65 \pm 5$ years) or a battery of neuropsychological tests were included in this cross-sectional analysis. Coffee consumption and total dietary caffeine intake were assessed at baseline using a food frequency questionnaire. Logistic regression models were fitted to evaluate the association between total, caffeinated and decaffeinated coffee consumption or total dietary caffeine intake and cognitive impairment.

Results Total coffee consumers and caffeinated coffee consumers had better cognitive functioning than non-consumers when measured by the MMSE and after adjusting for potential confounders (OR 0.63; 95% CI 0.44–0.90 and OR 0.56; 95% CI 0.38–0.83, respectively). Results were similar when cognitive performance was measured using the Clock Drawing Test (CDT) and Trail Making Test B (TMT-B). These associations were not observed for decaffeinated coffee consumption. Participants in the highest tertile of total dietary caffeine intake had lower odds of poor cognitive functioning than those in the reference tertile when screened by the MMSE (OR 0.64; 95% CI 0.47–0.87) or other neurophysiological tests evaluating a variety of cognitive domains (i.e., CDT and TMT-A).

Conclusions Coffee consumption and total dietary caffeine intake were associated with better cognitive functioning as measured by various neuropsychological tests in a Mediterranean cohort of elderly individuals with MetS.

A complete list of PREDIMED-Plus investigators is included as an acknowledgements.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00394-020-02415-w) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

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Keywords Cognitive impairment · Mini-Mental State Examination · Coffee · Caffeine · PREDIMED-plus

Introduction

The metabolic syndrome (MetS) is a recognized risk factor in the development of non-communicable chronic diseases such as diabetes and cardiovascular disease (CVD). In recent years, it has been suggested that individuals with MetS are also at high risk of developing neurological alterations characterized by cognitive decline, which may progress to Alzheimer's disease (AD) or other types of dementia [1–3]. According to the latest World Health Organization guidelines for reducing the risk of cognitive decline and dementia [4], the net number of individuals with dementia is increasing exponentially in parallel with population aging. This important public health concern is expected to have a considerable negative effect on society and the economy.

Lifestyle changes such as modifications in diet, physical activity, social enrichments and cognitive training may preserve and enhance cognitive performance in older adults [4]. In terms of diet, numerous studies have indicated that adherence to healthy dietary patterns is associated with better cognitive performance throughout the adult life span [5, 6] and therefore might play an important role in preventing cognitive decline and dementia. The association between cognitive performance and certain food groups, nutrients and/or bioactive compounds such as coffee consumption and caffeine intake has also been of research interest [7–9].

It has been reported that coffee and caffeine may act as psychoactive stimulants that improve cognitive performance in the short term. Studies on animals have demonstrated that caffeine [10, 11] and other bioactive components of coffee [12] have a protective effect on cognition. The few randomized clinical trials that have studied the potential effect of coffee or caffeine consumption on cognitive performance have focused on short-term effects, and none of them has analyzed the effect on cognitive decline or the risk of dementia [8]. Studies evaluating decaffeinated coffee consumption are even more scarce and have focused on the acute effects on cognitive performance.

Epidemiological studies that have analyzed potential associations between coffee and caffeine consumption and cognitive function or the risk of dementia in humans have provided inconsistent results [13–15]. This is partly due to the differences in the populations studied, the study design, the exposure variables and the method for assessing them (studies have focused on total coffee consumption but excluded the type of coffee consumed (caffeinated/decaffeinated) from their analyses, the reported outcome (AD, dementia, cognitive impairment, cognitive decline) and the criteria or tools used to define the outcome [14].

Moreover, most epidemiological studies have been conducted on healthy or non-Mediterranean populations and their results cannot be extrapolated to elderly populations at high risk of developing neurological disorders. Since there is evidence to suggest that MetS may increase the incidence of vascular dementia and the risk of progression from cognition impairment to dementia in aged individuals, studying the possible associations between coffee/caffeine consumption and cognition is of great value.

In this paper, we aimed to assess the association of coffee consumption and caffeine intake with the odds of poor cognitive functioning in a population of overweight/obese elderly adults with MetS. We hypothesize that individuals who consume higher amounts of coffee or caffeine have better cognitive functioning.

Methods

Study design and participants

A cross-sectional analysis using baseline data from the PREDIMED-Plus study was conducted. Briefly, the PREDIMED-Plus is an ongoing parallel-group, randomized and controlled clinical trial conducted in 23 Spanish centers, which aims to evaluate the effect of an intensive weight loss intervention (based on an energy-restricted Mediterranean diet, physical activity promotion and behavioral support) on CVD events compared to a control group that is given usual care advice. A detailed description of the PREDIMED-Plus study is also available at https://www.predimedplus.com. This study was registered at the International Standard Randomized Controlled Trials (ISRCTN; https://www.isrctn.com/ISRCTN89898870) on July 24, 2014.

Between October 2013 and December 2016, 6,874 participants were recruited at 23 centers from various universities, hospitals and research institutes in Spain and randomly allocated in a 1:1 ratio to an intensive lifestyle intervention or to usual medical care. Eligible participants were overweight or obese (BMI 27–40 kg/m^2) men and women (aged 55–75 years) who satisfied at least three criteria for the MetS (waist circumference > 102 cm in men and > 88 cm in women; serum triglyceride ≥ 150 mg/dL or drug treatment for elevated triglycerides; HDL-c < 40 mg/dL in men and < 50 mg/dL in women or drug use for low HDL-c; blood pressure ≥ 130/85 mmHg or antihypertensive drug treatment; and fasting plasma glucose level ≥ 100 mg/dL or hypoglycemic treatment) [16] and were free of CVD. Detailed inclusion and exclusion criteria have been extensively described elsewhere [17].

All participants provided written informed consent, and the institutional review boards of each participating center approved the final protocol and procedures.

For the present study, PREDIMED-Plus participants who had baseline information missing from the food frequency questionnaire (FFQ) or whose total energy intake was extreme (women < 500 and > 3500 kcal/day, and men < 800 and > 4000 kcal/day) were excluded ($n = 241$). Participants with missing data on covariates (education level, hypertension, hypercholesterolemia) or who had been diagnosed with dementia were excluded from our analyses ($n = 19$). Associations were tested for those participants who had completed the various cognitive tests. As not all participants completed every cognitive test, there were slightly different samples for the Mini-Mental State Examination test ($n = 6427$), the semantic and phonemic Verbal Fluency Test ($n = 6563$), the Clock Drawing Test ($n = 6400$), Trail Making Test A ($n = 6533$) and B ($n = 6457$) and the Digit Span Test forward score ($n = 5128$).

Assessment of coffee consumption and caffeine intake

At baseline, a trained dietitian administered a 143-item FFQ during a face-to-face visit. Participants were asked about their frequency of consumption of each item in the preceding year. The nine possible answers ranged from never to more than six times per day, which were transformed into grams or milliliters per day using the standard portion size of each item. Two items on the FFQ were specifically related to coffee consumption (one for caffeinated coffee and one for decaffeinated coffee). Total coffee consumption was considered to be the sum of caffeinated and decaffeinated coffee consumption. Two Spanish food composition tables were used to calculate total energy and nutrient intake [18, 19]. Total dietary caffeine consumption was computed from the FFQ using the caffeine contained in caffeinated coffee (400 mg/l), decaffeinated coffee (10.7 mg/l), tea (100 mg/l), regular sodas (79.2 mg/l), artificially sweetened soda (128 mg/l) and chocolate (180 mg/kg). Reference values from the European Food Safety Authority [20] were used to calculate caffeine intake.

Neuropsychological assessment

The MMSE questionnaire validated for the Spanish population [21] was administered by trained PREDIMED-Plus staff. MMSE is the most commonly used brief cognitive screening test. This 30-point questionnaire examines cognitive functions including orientation, registration, concentration, memory, language and copying a figure. It is divided into two sections, the first of which requires vocal responses only (maximum score of 21). The second section tests the respondent's ability to name, follow verbal and written commands, write a sentence spontaneously and copy a complex polygon similar to a Bender–Gestalt figure (maximum score of 9). The MMSE, therefore, has a maximum total score of 30, and higher scores indicate the absence of cognitive decline [22].

We also evaluated other cognitive domains using several neuropsychological tests such as the Verbal Fluency Test (VFT), the Digit Span Test (DST) of the Wechsler Adult Intelligence Scale-III (WAIS-III), the Trail Making Test (TMT) and the Clock Drawing Test (CDT).

The VFT assesses verbal ability and executive control and consists of two parts: (1) the phonemic fluency task, in which participants are asked to recite, in 60 s, as many words as possible that start with the letter P (not including the names of people or places or repetitions of the same word with different suffixes), and (2) the semantic fluency task, in which the participants name as many animals as they can without repetition in 60 s. The total raw score for each task is the number of words the participant produces [23].

The DST of the WAIS-III Spanish version [24] is made up of two different subtests: DST forward recall and DST backward recall. DST forward recall requires participants to orally repeat a series of three to nine random single digits in the same order they hear them. On the other hand, DS backward recall requires participants to repeat a series of two to eight random single digits in reverse order. In this study, the performance on the DST was reported via a direct score of 1–16 for the forward performance and a direct score of 1–14 for backward performance.

The TMT is a tool that assesses executive function and tests processing speed, sequence alternation, cognitive flexibility, visual search, motor performance and executive functioning [25]. It is considered sensitive enough to detect cognitive impairment associated with dementia (i.e., AD). The TMT consists of 25 circles spread over two sheets of paper (parts A and B). In part A (TMT-A), participants are asked to connect consecutive numbers (1–2–3–4–…) in the correct order by drawing a line. In part B (TMT-B), they are asked to connect consecutive numbers and letters in an alternating numeric and alphabetic sequence (1-A, 2-B, 3-C-…). Each part is scored according to the time taken to complete the task (lower scores imply better performance).

The CDT [26] is used as a neuropsychological screening tool to detect cognitive impairment and dementia [27]. It evaluates visuoconstructive and visuospatial skills, symbolic and conceptual representation, hemiattention, semantic memory and executive function (including organization, planning and parallel processing). For this study, we used a validated Spanish version ranging from 0 to 7 [28].

Assessment of covariates

Covariates were evaluated by trained staff in a face-to-face interview using self-reported general questionnaires on socio-demographics (sex, age, level of education and employment status), and lifestyle (smoking habits, physical activity), history of illness and medication use. Trained PREDIMED-Plus staff followed the study protocol to measure anthropometric variables and blood pressure. Blood samples were collected in fasting conditions, and biochemical analyses were performed on fasting plasma glucose, triglycerides, cholesterol and other biochemical parameters by routine laboratory methods. Leisure time physical activity was estimated using a validated short version of the Minnesota Leisure Time Physical Activity Questionnaire [29, 30]. Adherence to an energy-reduced MedDiet was assessed using a 17-item questionnaire [31] adapted from a previously validated one [32]. The score obtained from the questionnaire ranged from 0 to17. Finally, depressive symptoms were evaluated using the Beck Depression Inventory II (BDI-II). Cutoff points for depressive status risk were established as scores ≤ 19 for mild depression and scores > 19 for moderate-to-severe depression [33].

Statistical analysis

For our analyses, we used the PREDIMED-Plus database updated to March 2019. Participants were categorized as non-coffee consumers and coffee consumers. Coffee consumers were further differentiated according to the type of coffee they consumed (caffeinated coffee consumers and decaffeinated coffee consumers). The Chi-square test and *t* test were used to compare the baseline characteristics between non-consumers and coffee consumers, or non-consumers and caffeinated coffee consumers or decaffeinated coffee consumers, respectively.

The MMSE was used for our main analyses to evaluate the odds of poor cognitive functioning (established as MMSE score ≤ 24 points). Several logistic regression models were fitted to assess the association [odds ratio (OR); 95% confidence interval (CI)] between coffee consumption and the odds of poor cognitive functioning. Model 1 was adjusted for age (years), sex, body mass index (kg/m^2), educational level (primary or lower, secondary or academic or graduate), smoking habit (never, former or current), total energy consumption (kcal/day), physical activity (METs. min/week), alcohol consumption (g/day, and adding the quadratic term), prevalence of diabetes (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no) and participating center (in quartiles by number of participants). Model 2 was further adjusted for food groups [consumption of vegetables, fruits, nuts and dried fruits, biscuits, fish, dairy products, meat and poultry, legumes, olive oil and cereals (g/day)]. Finally, model 3 was further adjusted for depression status (mild/moderate to severe). Models 2 and 3 for caffeinated coffee consumers and decaffeinated coffee consumers were further adjusted for decaffeinated coffee consumption (ml/day) or caffeinated coffee consumption (ml/day), respectively.

We also evaluated the associations between coffee consumption and the odds of poor cognitive functioning using other neuropsychological tests. The cutoff points for the VFTs and DSTs were established as ≤ than the mean − 1.5SD. The TMT's cutoff points were established as ≥ the mean + 1.5SD. The clock test cutoff point was established as ≤ 4 points. The same covariates as above were used to fit the fully adjusted models. The models for caffeinated coffee consumers and decaffeinated coffee consumers were further adjusted for decaffeinated or caffeinated coffee consumption (ml/day), respectively. It was not possible to run logistic regression models for the DST backward test because of the low number of impairment cases. We also explored the associations (OR, 95% CI) between servings of caffeinated coffee, decaffeinated coffee, and total coffee consumed and the odds of poor cognitive functioning as assessed by the MMSE test. The same adjustments were used to analyze these models.

We also evaluated the association (OR, 95% CI) between total dietary caffeine intake and the odds of poor cognitive functioning as assessed by the aforementioned neuropsychological tests. For each test, tertiles of caffeine intake were calculated and the lowest tertile was used as the reference category. The fully adjusted model was used.

To assess the linear trend in the logistic regression models, the median value of each serving category of total, caffeinated and decaffeinated coffee consumption and the median value of each tertile of total caffeine intake were assigned to each participant, and this new variable was modeled as continuous.

We conducted statistical analyses to evaluate whether the associations observed could be modified by age (years) and sex (men/women). Interaction was tested with likelihood ratio tests, which involved comparing models with and without cross-product terms.

All analyses were conducted with robust estimates of the variance to correct for intracluster correlation. The data were analyzed using the Stata 14 software program (StataCorp), and statistical significance was set at a two-tailed p value < 0.05.

Results

Table 1 shows the general characteristics of the population under study according to coffee consumption. Among coffee consumers, mean coffee consumption was 85 ± 52 ml/day, of which 45 ± 55 ml/day and 39 ± 49 ml/day were consumed in the form of caffeinated coffee and decaffeinated coffee, respectively. Coffee consumers were younger, more likely to smoke, and more likely to present T2DM or hypercholesterolemia than non-coffee consumers. Coffee consumers also had higher energy intake, consumed higher amounts of red meat/poultry, dairy products and alcohol (irrespective of the type of coffee consumed) and had a lower consumption of vegetables, nuts and legumes. In addition, their MMSE scores were higher and their adherence to the MedDiet was lower than that of non-coffee consumers. No other significant associations were observed. The general characteristics of the study population in terms of MMSE performance are shown in Supplementary Table 1.

The association (OR, 95% CI) between coffee consumption and the odds of poor cognitive functioning (MMSE test) is shown in Table 2. Compared to non-coffee consumers, coffee consumers and caffeinated coffee consumers proved to have better cognitive functioning (0.59, 0.42–0.82) and (0.47, 0.33–0.67), respectively, even after adjusting for potential confounders [(0.63, 0.44–0.90) and (0.56, 0.38–0.83), respectively]. No significant associations were found between decaffeinated coffee consumers and the odds of poor cognitive functioning by the MMSE test.

Table 3 shows the association (OR, 95% CI) between the number of servings (50 ml) of total coffee, caffeinated coffee and decaffeinated coffee and the odds of poor cognitive functioning using the MMSE test. Compared to those participants with < 1 serving/day of total coffee intake, participants who consumed > 2 servings/day of total coffee were more likely to have better cognitive performance in the test even after adjusting for potential confounders. For caffeinated coffee, participants who consumed 1 to < 2 servings/day and > 2 servings/day had significantly lower odds of cognitive impairment (37% and 46%, respectively) than those who consumed < 1 serving per day. There were no significant associations between the consumption of servings of decaffeinated coffee and the odds of cognitive impairment. Supplementary Table 2 shows the association (OR, 95% CI) between the number of servings (50 ml) of total coffee and its subtypes and the odds of poor cognitive functioning when non-consumers (0 servings/day) category is considered as the referent group, and results remain in the same direction.

Table 4 shows the association (OR, 95% CI) between cognitive status and coffee consumption measured using various neuropsychological tests. Regardless of the type of coffee consumed, coffee consumers were more likely to have better cognitive functioning, when cognitive status was evaluated by TMT-B. No other significant associations were observed with any other neuropsychological test.

Figure 1 and Supplementary Table 3 show the association (OR, 95% CI) between tertiles of total dietary caffeine intake and various neuropsychological tests. Coffee consumption contributed to 68.6% of total dietary caffeine intake in our population (data not shown). Participants in the highest tertile of caffeine intake performed better in the cognition domains than those in the lowest tertile (reference category) when evaluated by MMSE, CDT and TMT-A.

When the heart rate and systolic blood pressure were added to our models as covariates, the results were in the same direction and remain significant (data not shown). Interactions between sex ($p = 0.07$) and age ($p = 0.27$) with coffee consumption were not significant.

Discussion

To the best of our knowledge, this is the first study to evaluate the association between coffee consumption and cognition in an elderly population at high cardiovascular risk using a cross-sectional design. We observed that total coffee consumers and caffeinated coffee consumers have lower odds of poor cognitive functioning than non-coffee consumers measured by the MMSE, CDT and TMT-B tests. In addition, participants in the highest tertile of total dietary caffeine intake had lower odds of poor cognitive functioning than those in the reference tertile when screened by the MMSE and other neuropsychological tests that evaluate different cognitive domains (i.e., CDT and TMT-B).

Coffee is one the most widely consumed beverages around the world, and the level of consumption by the Spanish population is no exception [34–36]. Coffee is a seed, made of complex matrices rich in vitamins, minerals, and bioactive phytochemicals that protect the plant's DNA from oxidative stress, thus facilitating the perpetuation of the species [37]. As such, coffee is rich in polyphenols (with antioxidant properties), caffeine, diterpenes, melanoidins and trigonelline [38]. For these reasons, the effect of coffee consumption on several health outcomes has been the object of research interest, especially in relation to cardio-metabolic health, cancer incidence and mortality [38–40]. However, coffee composition can depend on the type of coffee bean and the brewing process, which may influence the biological effects it has on the human body [39].

Previous studies have explored the association coffee and caffeine intake has with cognitive performance. In a cross-sectional study conducted on a representative British population, it was observed that total coffee consumption, and

Table 1 General characteristics of the studied population according to coffee consumption and subtype

	Non-coffee consumers (n=537)	Coffee consumers (n=5890)	p value[a]	Caffeinated coffee consumers (n=3419)	p value[b]	Decaffeinated coffee consumers (n=3365)	p value[c]
Coffee consumption, ml/day	0	85 ± 52	<0.01	91 ± 54	<0.01	83 ± 51	<0.01
Caffeinated coffee consumption, ml/day	0	45 ± 55	<0.01	78 ± 52	<0.01	15 ± 33	<0.01
Decaffeinated coffee consumption, ml/day	0	39 ± 49	<0.01	14 ± 30	<0.01	69 ± 46	<0.01
Age, years	66 ± 5	65 ± 5	<0.01	64 ± 5	<0.01	65 ± 5	0.04
Women, % (n)	58 (311)	47 (2794)	<0.01	43 (1474)	<0.01	51 (1719)	<0.01
BMI, kg/m^2	32 ± 4	33 ± 3	0.37	32 ± 3	0.80	33 ± 3	0.15
Central obesity, % (n)	92 (495)	93 (5483)	0.43	93 (3171)	0.64	93 (3141)	0.32
Type 2 diabetes, % (n)	23 (125)	32 (1856)	<0.01	31 (1049)	<0.01	33 (1102)	<0.01
Hypertension % (n)	94 (505)	94 (5522)	0.79	93 (3171)	0.28	95 (3199)	0.31
Hypercholesterolemia, % (n)	56 (303)	61 (3590)	0.04	61 (2088)	0.04	61 (2059)	0.04
MMSE > 24, % (n)	92 (494)	95 (5604)	<0.01	96 (3285)	<0.01	94 (3173)	0.04
MMSE ≤ 24, % (n)	8 (43)	5 (286)		4 (134)		6 (192)	
BDI-II score	9 ± 8	8 ± 7	0.16	8 ± 7	0.06	9 ± 7	0.33
Education level, % (n)							
Up to primary education	52 (282)	49 (2902)	0.33	44 (1519)	<0.01	53 (1771)	0.90
Secondary education	28(148)	29 (1700)		30 (1028)		28 (949)	
Academic or graduate	20 (107)	22 (1288)		26 (872)		19 (645)	
Smoking habit, % (n)							
Never a smoker	55 (297)	43 (2549)	<0.01	39 (1336)	<0.01	46 (1564)	<0.01
Former smoker	37 (196)	44 (2589)		47 (1595)		42 (1415)	
Current smoker	8 (44)	13 (752)		14 (488)		12 (386)	
Leisure time physical activity, METs. min./week	1986 [895–3469]	1867 [848–3382]	0.36	1846 [848–3390]	0.46	1888 [863–3357]	0.21
Total energy intake (Kcal/day)	2284 ± 570	2372 ± 549	<0.01	2405 ± 553	<0.01	2351 ± 539	<0.01
Food group consumption, g/day							
Fruits	371 ± 227	358 ± 203	0.17	349 ± 198	0.02	365 ± 208	0.54
Vegetables	339 ± 142	327 ± 139	0.04	326 ± 139	0.03	326 ± 139	0.03
Nuts	16 ± 18	15 ± 17	0.03	15 ± 17	0.02	15 ± 17	0.04
Olive oil	41 ± 18	40 ± 17	0.20	39 ± 17	0.07	40 ± 17	0.29
Cereals	149 ± 78	151 ± 78	0.61	152 ± 78	0.38	149 ± 78	0.88
Red meat and poultry	138 ± 56	149 ± 58	<0.01	152 ± 61	<0.01	147 ± 56	<0.01
Fish and seafood	98 ± 46	102 ± 48	0.05	103 ± 48	0.03	102 ± 47	0.09
Dairy products	301 ± 210	349 ± 199	<0.01	342 ± 197	<0.01	365 ± 201	<0.01
Biscuits	26 ± 30	27 ± 30	0.46	27 ± 31	0.40	28 ± 30	0.20
Legumes	22 ± 13	21 ± 11	0.03	21 ± 11	0.04	20 ± 11	0.01
Alcohol	2 [0–10]	5 [0.7–14.8]	<0.01	6 [1.5–17]	<0.01	4[0.7–13]	<0.01
MedDiet score (17 points)	9 ± 3	8 ± 3	<0.01	8 ± 3	<0.01	9 ± 3	<0.01

Data were expressed as means ± SD or median [P25–P75] and percentages (number) for continuous and categorical variables, respectively. p values for comparisons between non-coffee consumers and coffee consumers[a], non-coffee consumers and caffeinated coffee consumers[b], and non-coffee consumers and decaffeinated coffee consumers[c] were tested by t test or Chi-square test, as appropriate

BDI-II Beck Depression Inventory, *BMI* body mass index, *MedDiet* Mediterranean diet, *MMSE* Mini-Mental State Examination

Table 2 Association (odds ratio, 95% CI) between type of coffee consumption and odds of poor cognitive functioning (MMSE)

	Non-coffee consumers (n=537)	Coffee consumers (n=5890)	p value[a]	Caffeinated coffee consumers (n=3419)	p value[b]	Decaffeinated coffee consumers (n=3365)	p value[c]
MMSE ≤ 24, % (n)	8 (43)	5 (286)		4 (134)		6 (192)	
Crude model	1 (ref.)	0.59 (0.42–0.82)	<0.01	0.47 (0.33–0.67)	<0.01	0.70 (0.49–0.98)	0.04
Model 1	1 (ref.)	0.66 (0.46–0.93)	0.02	0.58 (0.40–0.84)	<0.01	0.73 (0.51–1.05)	0.09
Model 2	1 (ref.)	0.63 (0.45–0.90)	0.01	0.57 (0.39–0.84)	<0.01	0.70 (0.48–1.03)	0.07
Fully adjusted	1 (ref.)	0.63 (0.44–0.90)	0.01	0.56 (0.38–0.83)	<0.01	0.70 (0.48–1.02)	0.06

Risk of cognitive impairment was defined as a MMSE score ≤ 24 points. Multivariable logistic regression models were fitted: outcome: MMSE score > 24 (0) vs. MMSE score ≤ 24 points (1). Model 1: adjusted for age (years), sex, body mass index (kg/m^2), educational level (up to primary, secondary or university/graduate), smoking habit (never, former or current), total energy consumption (kcal/day), physical activity (METs. min/week), alcohol consumption (g/day, and adding the quadratic term), diabetes prevalence risk (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no) and participating center (in quartiles by number of participants). Model 2: additionally, adjusted for food groups [consumption of vegetables, fruits, dried fruits, biscuits, fish, dairy products, meat and poultry, legumes, olive oil and cereals (g/day)]. Fully adjusted: model 2 additionally adjusted for depression status (mild/moderate-to-severe depression). Models 2 and fully adjusted for caffeinated coffee consumers and decaffeinated coffee consumers were additionally adjusted by decaffeinated coffee consumption (ml/day) or caffeinated coffee consumption (ml/day), respectively. All analyses were conducted with robust estimates of the variance to correct for intracluster correlation

MMSE Mini-Mental State Examination, *CI* confidence interval, *OR* odds ratio

p values between non-consumers and coffee consumers[a], between non-consumers and caffeinated coffee consumers[b], and between non-consumers and decaffeinated coffee consumers[c]

especially caffeine intake, had a dose–response relationship with improving several domains of cognitive performance [7]. The same study also reported that older participants had a greater scope than younger participants for increasing their level of cognitive functioning in relation to caffeine intake [7]. This might suggest that individuals at risk of cognitive impairment (i.e., older age) are more prone to the benefits of coffee consumption and its components. However, we cannot discard reverse causation. In the ELSA-Brasil cohort, a battery of neuropsychological tests (including semantic and phonemic VFTs and TMT-B) was used to cross-sectionally assess the association between coffee consumption and cognitive function [41]. The above study reported that elderly individuals who consumed ≥ 3 cups/day of total coffee performed better on the semantic verbal fluency test than those who rarely consumed coffee or did not consume it at all. However, these associations were not observed among elderly participants in the phonemic verbal fluency test or the TMT-B. Although, in our study conducted in a senior population, this association was observed in the Trail Making Test B. Neither were any associations reported between coffee consumption and cognitive performance in younger adults in the ELSA-Brasil cohort.

A systematic review and meta-analysis of nine prospective studies [13] reported that individuals who consumed between 1 and 2 cups/day had a lower risk of incidence of cognitive disorders such as Alzheimer's disease, dementia, cognitive decline and cognitive impairment than low coffee consumers (< 1 cup/day). The review also reported a J-shaped association between total coffee consumption and incident cognitive disorders, with the lowest risk observed at a consumption level of 1–2 cups of coffee per day. This association was not observed in our study, where no difference was observed between participants who consumed between 1–2 servings/day and those who consumed more than 2 servings/day. However, this may be due to the different tests used by each study.

Our results on total dietary caffeine intake are in line with those of previous studies that have reported that caffeine can act as a psychoactive stimulant, improving cognitive performance in the short term and decreasing the risk of cognitive impairment, dementia and AD in the long term [7–9, 14]. The mechanisms underlying the association between caffeine intake and cognitive ability or dementia are not completely understood. Some animal studies have demonstrated that caffeine intake has a beneficial effect on cognitive performance in the short term. Moreover, some in vitro and preclinical animal models suggest that some of the bioactive components of coffee have neuroprotective mechanisms of action that attenuate β-amyloid peptide (Aβ) production and prevent neuronal damage, synaptotoxicity and cognitive deficit in rats induced by Aβ in the long term [42]. Unfortunately, to the best of our knowledge, there was no evidence of this in humans.

In a double-blind placebo-controlled trial conducted in 2018 [8], healthy Japanese adults completed a battery of four tests that measured performance in several cognitive domains, including reaction time, cognitive flexibility, processing speed, executive function, working memory and sustained attention. The authors found that participants who were acutely given 200 mg/day of caffeine performed

Table 3 Association (odds ratio, 95% CI) between servings of total coffee, caffeinated coffee and decaffeinated coffee consumption and the odds of cognitive impairment (MMSE test)

Servings of total coffee consumption (50 ml)	< 1/day n = 1201	1–2/day n = 2891	> 2/day n = 2335	p trend
Odds of poor cognitive functioning, % (n)	6.2 (75)	5.4 (156)	4.2 (98)	
Crude model	1 (ref.)	0.86 (0.65–1.14)	0.66 (0.48–0.90)	< 0.01
Model 1	1 (ref.)	0.79 (0.59–1.06)	0.74 (0.54–1.01)	0.11
Model 2	1 (ref.)	0.77 (0.57–1.03)	0.70 (0.50–0.97)	0.06
Fully adjusted	1 (ref.)	0.77 (0.57–1.03)	0.70 (0.50–0.97)	0.06
Servings of caffeinated coffee (50 ml)	< 1/day n = 3492	1–2/day n = 1629	> 2/day n = 1306	p trend
Odds of poor cognitive functioning, % (n)	6.2 (218)	4.0 (66)	3.5 (45)	
Crude model	1 (ref.)	0.63 (0.48–0.84)	0.54 (0.39–0.74)	< 0.01
Model 1	1 (ref.)	0.76 (0.57–1.01)	0.80 (0.57–1.12)	0.10
Model 2	1 (ref.)	0.65 (0.47–0.89)	0.66 (0.46–0.97)	0.02
Fully adjusted	1 (ref.)	0.65 (0.47–0.90)	0.66 (0.45–0.96)	0.02
Servings of decaffeinated coffee (50 ml)	< 1/day n = 3694	1–2/day n = 1678	> 2/day n = 1055	p trend
Odds poor cognitive functioning, % (n)	4.8 (176)	5.9 (99)	5.1 (54)	
Crude model	1 (ref.)	1.25 (0.97–1.62)	1.08 (0.79–1.47)	0.40
Model 1	1 (ref.)	1.00 (0.77–1.30)	0.93 (0.67–1.28)	0.68
Model 2	1 (ref.)	0.91 (0.68–1.22)	0.79 (0.54–1.15)	0.21
Fully adjusted	1 (ref.)	0.92 (0.69–1.22)	0.79 (0.54–1.15)	0.69

CI confidence interval, *OR* odds ratio

Risk of cognitive impairment was defined as a MMSE score ≤ 24 points. Multivariable logistic regression models and median regression models were fitted: Outcome: MMSE score > 24 points (0) vs. MMSE score ≤ 24 points (1). Model 1: adjusted for age (years), sex, body mass index (kg/m^2), educational level (primary, secondary or university/graduate), smoking habit (never, former or current), total energy consumption (kcal/day), physical activity (METs. min/week), alcohol consumption (g/day, and adding the quadratic term), diabetes prevalence (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no) and participating center (in quartiles by number of participants). Model 2: additionally adjusted for food groups [consumption of vegetables, fruits, dried fruits, biscuits, fish, dairy products, meat, legumes, olive oil and cereals (g/day)]. Fully adjusted: Model 2 additionally adjusted for depression status (mild/moderate-to-severe depression). Models for caffeinated coffee consumers and decaffeinated coffee consumers were additionally adjusted by decaffeinated coffee consumption (ml/day) or caffeinated coffee consumption (ml/day), respectively. All analyses were conducted with robust estimates of the variance to correct for intracluster correlation

better on the shifting attention test but not in other cognitive domains.

Caffeine is structurally similar to adenosine, an endogenous neurotransmitter with mostly inhibitory effects on the central nervous system, when acting through A1 receptors. In general, adenosine inhibits adenyl cyclase via A1 receptors and stimulates adenyl cyclase via A2 receptors [43]. The effects of caffeine on the brain are mediated through the blockade of adenosine A1 and A2A receptors, which disable the capacity of adenosine to bind the receptors. The ability of caffeine to interact with neurotransmission in different regions of the brain may promote behavioral functions, such as vigilance, attention, mood and arousal [12].

The association between long-term caffeine consumption in humans and cognition or cognitive disorders has been explored using cross-sectional and prospective study designs. A cross-sectional analysis conducted in more than 9000 British adults [6] showed that caffeine intake had a dose–response relationship with better cognitive performance when measured by several tests and after adjusting for potential confounders. A systemic review and meta-analysis published in 2010 [14] that included nine prospective cohort studies and two case–control studies reported a trend towards a protective relationship of caffeine intake on various measures of cognitive impairment/decline, although considerable methodological heterogeneity between studies made it difficult to interpret the results. After this meta-analysis, a new prospective study conducted in the context of the Women's Health Initiative Memory Study [9] also showed an inverse association between total caffeine intake and the risk of age-related cognitive impairments in women aged ≥ 65 years.

In our analysis, a protective trend against poor cognitive performance was observed for decaffeinated coffee consumption, although it was not statistically significant. Few studies have analyzed the potential effect of decaffeinated

Table 4 Association (odd ratio, 95% CI) between type of coffee consumed and cognitive status measured by various neuropsychological tests

Neuropsychological tests	Non-coffee consumers	Coffee consumers	Caffeinated coffee consumers	Decaffeinated coffee consumers
Phonological verbal fluency of letter P ($n=6563$)	($n=553$)	($n=6010$)	($n=3500$)	($n=3435$)
Odds of poor cognitive functioning, % (n)	6.7 (37)	5.1 (308)	4.1 (143)	5.7 (196)
Crude model	1 (ref.)	0.75 (0.53–1.07)	0.59 (0.41–0.86)	0.84 (0.59–1.21)
Fully adjusted model	1 (ref.)	0.83 (0.57–1.20)	0.71 (0.47–1.06)	0.95 (0.65–1.40)
Semantic verbal fluency of animals ($n=6563$)	($n=553$)	($n=6010$)	($n=3500$)	($n=3435$)
Odds of poor cognitive functioning, % (n)	5.4 (30)	4.5 (269)	3.6 (125)	5.0 (173)
Crude model	1 (ref.)	0.82 (0.55–1.22)	0.65 (0.42–0.98)	0.92 (0.61–1.39)
Fully adjusted model	1 (ref.)	0.93 (0.62–1.41)	0.84 (0.54–1.30)	0.98 (0.64–1.52)
Clock test ($n=6400$)	($n=534$)	($n=5866$)	($n=3403$)	($n=3353$)
Odds of poor cognitive functioning, % (n)	13.9 (74)	10.9 (640)	9.3 (318)	12.0 (402)
Crude model	1 (ref.)	0.76 (0.59–0.99)	0.64 (0.49–0.84)	0.85 (0.65–1.11)
Fully adjusted model	1 (ref.)	0.80 (0.61–1.05)	0.72 (0.54–0.96)	0.89 (0.67–1.18)
Trail making test: A, total time (seconds), ($n=6533$)	($n=547$)	($n=5986$)	($n=3489$)	($n=3418$)
Odds of poor cognitive functioning, % (n)	7.5 (41)	5.9 (351)	5.1 (177)	6.7 (228)
Crude model	1 (ref.)	0.77 (0.55–1.08)	0.66 (0.46–0.94)	0.88 (0.62–1.25)
Fully adjusted model	1 (ref.)	0.88 (0.61–1.25)	0.83 (0.56–1.21)	0.95 (0.66–1.37)
Trail making test: B, total time (s), ($n=6457$)	($n=542$)	($n=5915$)	($n=3452$)	($n=3375$)
Odds of poor cognitive functioning, % (n)	14.2 (77)	9.4 (556)	8.7 (300)	9.6 (323)
Crude model	1 (ref.)	0.63 (0.48–0.81)	0.57 (0.44–0.75)	0.64 (0.49–0.84)
Fully adjusted model	1 (ref.)	0.63 (0.48–0.84)	0.67 (0.49–0.90)	0.63 (0.47–0.86)
Digit forward score ($n=5128$)	($n=423$)	($n=4705$)	($n=2707$)	($n=2715$)
Odds of poor cognitive functioning, % (n)	5.9 (25)	5.9 (277)	4.5 (123)	6.6 (178)
Crude model	1 (ref.)	1.00 (0.65–1.52)	0.76 (0.49–1.18)	1.12 (0.73–1.72)
Fully adjusted model	1 (ref.)	1.19 (0.77–1.82)	1.03 (0.64–1.65)	1.33 (0.84–2.09)

Cutoff points for the phonological verbal fluency, the semantic verbal fluency and the digit forward score were established as $\leq$ the mean − 1.5SD. For Trail Making Tests A and B cutoff points were established as $\geq$ of the mean + 1.5SD. For the clock test, the cutoff point was established as $\leq$ 4 points. Multivariable logistic regression models were fitted. Outcome (several neuropsychological tests). Fully adjusted model: adjusted for age (years), sex, body mass index (kg/m^2), educational level (primary, secondary or university/graduate), smoking habit (never, former or current), total energy consumption (kcal/day), physical activity (METs. min/week), alcohol consumption in g/day (and adding the quadratic term), diabetes prevalence risk (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), consumption of vegetables (g/day), fruits (g/day), dried fruits (g/day), biscuits (g/day), fish (g/day), dairy products (g/day), meat (g/day), legumes (g/day), olive oil (g/day), cereals (g/day), depression status (mild/moderate-to-severe depression), and participating center (in quartiles by number of participants). The models for caffeinated coffee consumers and decaffeinated coffee consumers were additionally adjusted by decaffeinated coffee consumption (ml/day) or caffeinated coffee consumption (ml/day), respectively. All analyses were conducted with robust estimates of the variance to correct for intracluster correlation. Data are expressed as ORs (95%, CI)

CI confidence interval, *OR* odds ratio

coffee on cognition although the results are inconsistent [15, 44–46]. It has been suggested that coffee compounds other than caffeine, which are also found in decaffeinated coffee, may also have a protective effect on cognition [47, 48]. These include chlorogenic acids (polyphenols with antioxidant properties), which may help to reduce oxidative stress and neuroinflammation [49]. It has been suggested that the antioxidant capacity of coffee depends on its ability to increase the concentration of glutathione in plasma [38], while levels of glutathione in the brain tend to decrease with aging, Parkinson's disease and Alzheimer's disease [50]. A prospective study conducted with healthy Afro-American adults reported an association between increased levels of oxidative stress, as reflected by low or progressively decreasing glutathione levels, and a decline in executive function with aging [51]. Furthermore, coffee components such as quinic acid, caffeic acid, quercetin, and phenylindane have been associated with anti-inflammatory properties, protection against amyloid toxicity, tau aggregation and Aβ inhibition [47, 48]. However, the results from a recently published study conducted in older American adults reported no significant association between decaffeinated coffee and different dimensions of cognitive performance [15], which is in line with our

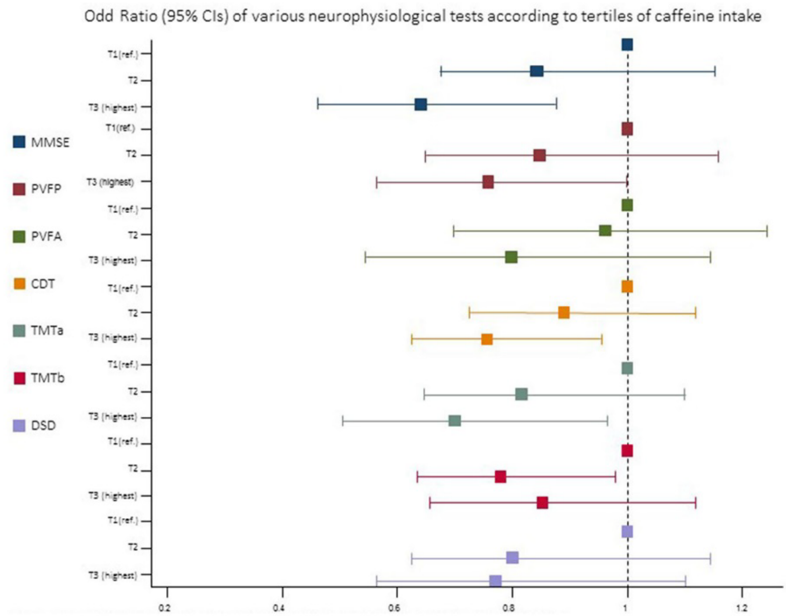

Fig. 1 Odds ratio (95% CIs) of various neurophysiological tests according to tertiles of caffeine intake. *MMSE* Mini-Mental State Examination, *PVFP* phonological verbal fluency, *SVFA* semantic verbal fluency, *Clock T* clock test, *TMTa* trail making tests A, *TMTb* trail making tests B, *DSD* digit forward score. Multivariable logistic regression model. Adjusted for age (years), sex, body mass index (kg/m^2), educational level (primary, secondary or university/graduate), smoking habit (never, former or current), total energy consumption (kcal/day), physical activity (METs. min/week), alcohol consumption (g/day, and adding the quadratic term), diabetes prevalence (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), consumption of vegetables (g/day), fruits (g/day), dried fruits (g/day), biscuits (g/day), fish (g/day), dairy products (g/day), meat (g/day), legumes (g/day), olive oil (g/day), cereals (g/day), depression status (mild/moderate-to-severe depression) and participating center (in quartiles by number of participants). All analyses were conducted with robust estimates of the variance to correct for intracluster correlation

observations and the results reported by Johnson-Kozlow et al. [44].

The results for total and decaffeinated coffee reinforce the hypothesis that it is the synergic effect of polyphenols, caffeine and other coffee compounds, not only caffeine, that gives coffee consumption its protective effect against cognitive impairment. It should be noticed that the positive associations between total coffee and caffeinated coffee consumption and cognitive performance observed in our study and others [9, 44] have been reported using various neuropsychological screening tests. The different results provided by the different tests may be the consequence of each test measuring different cognitive domains that are more prone to influence by coffee consumption and its components in different forms. For example, it is accepted that caffeine can increase alertness, improve sustained attention and working memory and reduce reaction time and fatigue [43, 52]. This may explain the associations observed for the MMSE, CDT and TMT tests which examine cognitive functions such as memory, orientation, registration, concentration, processing speed, visual search and hemiattention, which are prone to be affected by coffee consumption.

Our study has certain limitations that must be considered. Firstly, as MMSE and the battery of neuropsychological tests used in this study are screening tools that cannot substitute a complete diagnostic workup, the results must be taken with caution. However, using several neuropsychological tests to evaluate cognitive status gives our findings greater value. Secondly, given the cross-sectional design, it is not possible to determine causality between coffee consumption and caffeine intake, and cognitive function. Thirdly, the caffeine content in coffee, other beverages (e.g., tea and soft drinks) and food varies greatly, which may lead to under- or overestimation. However, we should point out that we have explored the association between cognitive performance and decaffeinated coffee, which gives greater insight into the potential effect of coffee consumption as a whole and not just caffeine on cognition. Finally, our study has been conducted in aged individuals with overweight/obesity and metabolic syndrome; therefore, our findings cannot be extrapolated to other population groups.

Conclusion

In this cross-sectional study, total and caffeinated coffee consumption and total caffeine intake were associated with lower odds of poor cognitive functioning measured by a battery of neurophysiological tests in a Mediterranean cohort of elderly individuals with MetS. Long-term and interventional studies are needed to clarify these associations, and if they are confirmed, dietary recommendations on coffee consumption and caffeine intake could be part of strategies for preventing cognitive decline.

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Compliance with ethical standards

Conflict of interest JS-S serves on the board of (and receives grant support through his institution from) the International Nut and Dried Fruit Council and the Eroski Foundation. He also serves on the Executive Committee of the Instituto Danone, Spain, and on the Scientific Committee of the Danone International Institute. He has received research support from the Patrimonio Comunal Olivarero, Spain, and Borges S.A., Spain. He receives consulting fees or travel expenses from Danone, the Eroski Foundation, the Instituto Danone, Spain, and Abbot Laboratories. ER has received research funding through his institution from the California Walnut Commission, Folsom, CA, USA; was a paid member of its Health Research Advisory Group; and is a nonpaid member of its Scientific Advisory Council.

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Online Supplementary Material

Supplementary Table 1. General characteristics of the studied population according to cognitive status (MMSE)

	MMSE > 24 (n = 6,098)	MMSE ≤ 24 (n = 329)	*P value*[a]
Total coffee consumption, ml/day	78 ± 55	67 ± 50	< 0.01
Caffeinated coffee consumption, ml/day	42 ± 54	30 ± 49	< 0.01
Decaffeinated coffee consumption, ml/day	36 ± 48	37 ± 44	< 0.56
Age, years	65 ± 5	67 ± 4	< 0.01
Women, % (n)	47 (2,859)	75 (246)	< 0.01
BMI, kg/m^2	32 ± 3	33 ± 3	< 0.01
Central obesity, % (n)	93 (5,661)	96 (317)	0.02
Type 2 diabetes, % (n)	30 (1,857)	38 (124)	< 0.01
Hypertension % (n)	94 (5,718)	94 (309)	0.01
Hypercholesterolemia, % (n)	61 (3,680)	65 (213)	0.11
BDI-II score	8 ± 7	11 ± 10	< 0.01
Education level, % (n)			
Up to primary education	47 (2,895)	88 (289)	
Secondary education	30 (1,818)	9 (30)	< 0.01
Academic or graduate	23 (1,371)	3 (10)	
Smoking habit, % (n)			
Never a smoker	43 (2,622)	68 (224)	
Former smoker	44 (2,698)	26 (87)	< 0.01
Current smoker	13 (778)	5 (18)	
Leisure time physical activity, METs. min. /week.	1,888 [848-3,413]	1,855 [965-3,180]	0.78
Total energy intake (Kcal/day)	2,372 ± 548	2,229 ± 597	< 0.01
Food group consumption, g/day			
Fruits	358 ± 204	380 ± 222	0.06
Vegetables	328 ± 139	332 ± 137	0.54
Nuts	15 ± 17	15 ± 21	0.74
Olive oil	40 ± 17	36 ± 17	< 0.01
Cereals	151 ± 78	142 ± 76	0.05
Red meat and poultry	148 ± 58	138 ± 61	< 0.01
Fish and seafood	102 ± 48	97 ± 47	0.04
Dairy products	343 ± 199	390 ± 221	< 0.01
Biscuits	27 ± 30	21 ± 30	< 0.01
Legumes	21 ± 11	22 ± 12	< 0.01
Alcohol	5 [1-15]	1 [0-7]	< 0.01
MedDiet score (17 points)	8 ± 3	9 ± 3	< 0.01

Data expressed as means ± SD or median [P25–P75] and percentages (number) for continuous and categorical variables, respectively.
[a] *P value* for comparisons between groups were tested by t-test or x^2, as appropriate.
Abbreviations: BDI-II, Beck Depression Inventory; BMI, body mass index; MedDiet, Mediterranean Diet; MMSE, Mini-Mental State Examination.

Online Supplementary Material

Supplementary Table 2. Association (odds ratio, 95%CI) between servings of total coffee, caffeinated coffee and decaffeinated coffee consumption and the odds of cognitive impairment (MMSE test)

Servings of total coffee consumption (50ml)	**0/d n = 537**	**0 - <1/day n = 664**	**1 - <2/day n = 2,575**	**>2/day n = 2,651**	***P - trend***
Odds of poor cognitive functioning, % (n)	8.0 (43)	4.8 (32)	5.7 (146)	4.1 (108)	
Crude model	1 (ref.)	0.58 (0.36 -0.93)	0.69 (0.49 - 0.98)	0.49 (0.34 - 0.70)	< 0.01
Model 1	1 (ref.)	0.70 (0.43 - 1.15)	0.68 (0.47 - 0.99)	0.61 (0.42 - 0.89)	< 0.05
Model 2	1 (ref.)	0.70 (0.43 - 1.15)	0.66 (0.46 - 0.96)	0.57 (0.39 - 0.85)	0.03
Fully adjusted	1 (ref.)	0.69 (0.42 - 1.13)	0.66 (0.45 - 0.95)	0.57 (0.38 - 0.85)	0.03
Servings of caffeinated coffee (50ml)	**0/d n = 3,008**	**0 - <1/day n = 484**	**1 - <2/day n = 1,629**	**>2/day n = 1,306**	
Odds of poor cognitive functioning, % (n)	6.5 (195)	4.8 (23)	4.1 (66)	3.5 (45)	
Crude model	1 (ref.)	0.72 (0.46 - 1.12)	0.61 (0.46 - 0.81)	0.51 (0.37 - 0.72)	< 0.01
Model 1	1 (ref.)	0.97 (0.62 - 1.53)	0.76 (0.56 - 1.02)	0.80 (0.57 - 1.12)	0.11
Model 2	1 (ref.)	0.85 (0.53 - 1.37)	0.63 (0.45 - 0.88)	0.64 (0.44 - 0.95)	0.02
Fully adjusted	1 (ref.)	0.86 (0.54 - 1.38)	0.63 (0.45 - 0.88)	0.64 (0.44 - 0.95)	0.02
Servings of decaffeinated coffee (50ml)	**0/d n = 3,062**	**0 - <1/day n = 632**	**1 - <2/day n = 1,678**	**>2/day n = 1,055**	
Odds of poor cognitive functioning, % (n)	4.5 (137)	6.2 (39)	5.9 (99)	5.1 (54)	
Crude model	1 (ref.)	1.40 (0.97 - 2.03)	1.34 (1.03 - 1.75)	1.15 (0.83 - 1.59)	0.29
Model 1	1 (ref.)	1.37 (0.93 - 2.01)	1.07 (0.81 - 1.41)	0.99 (0.71 - 1.38)	0.85
Model 2	1 (ref.)	1.32 (0.87 - 2.01)	0.99 (0.72 - 1.37)	0.86 (0.57 - 1.29)	0.30
Fully adjusted	1 (ref.)	1.31(0.86 - 1.99)	0.99 (0.72 - 1.36)	0.86 (0.57 - 1.29)	0.88

Abbreviations; CI, confidence interval; OR, Odds Ratio.

Risk of cognitive impairment was defined as a MMSE score ≤ 24 points. Multivariable logistic regression models and median regression models were fitted: Outcome: MMSE score >24 points (0) vs. MMSE score ≤24 points (1). Model 1: adjusted for age (years), sex, body mass index (kg/m^2), educational level (primary, secondary or university/graduate), smoking habit (never, former or current), total energy consumption (kcal/day), physical activity (METs.min/week), alcohol consumption (g/day, and adding the quadratic term), diabetes Prevalence risk (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no) and participating center (in quartiles by number of participants).

Model 2: additionally, adjusted for food groups (consumption of vegetables, fruits, dried fruits, biscuits, fish, dairy products, meat, legumes, olive oil and cereals (g/d)).Fully adjusted: Model 2 additionally adjusted for depression status (mild/moderate-to-severe depression).

Models for caffeinated coffee consumers and decaffeinated coffee consumers were additionally adjusted by decaffeinated coffee consumption (ml/day) or caffeinated coffee consumption (ml/day), respectively. All analyses were conducted with robust estimates of the variance to correct for intra-cluster correlation.

Online Supplementary Material

Supplementary Table 3. Association (odds ratio, 95%CI) between tertiles of total dietary caffeine consumption and cognitive status measured by various neuropsychological tests

Neuropsychological tests	Tertiles of total dietary caffeine consumption in mg/day			*P* value	*P-trend*
	T1 (lowest)	T2	T3 (highest)		
Mini-Mental State Examination (n = 6,427)	(*n* = 2,143)	(*n* = 2,148)	(*n* = 2,136)		
Total caffeine consumption, median (P25-P75)	2.4 (1.2 – 4.2)	20 (12.4 – 21.8)	51.2 (37.1 – 57.7)	< 0.01	
Prevalence risk of poor cognitive functioning, % (n)	7.1 (152)	5.1 (110)	3.1 (67)		
Crude model	1 (ref.)	0.71 (0.55 - 0.91)	0.42 (0.32 - 0.57)		< 0.01
Fully adjusted model	1 (ref.)	0.84 (0.65 - 1.10)	0.64 (0.47 - 0.87)		< 0.01
Phonological verbal fluency of letter P (n = 6,563)	(*n* = 2,188)	(*n* = 2,194)	(*n* = 2,181)		
Total caffeine consumption, median (P25-P75)	2.4 (1.2 - 4.2)	20.0 (12.5 - 21.8)	51.0 (36.9 - 57.7)	< 0.01	
Prevalence risk of poor cognitive functioning, % (n)	6.9 (151)	5.1 (111)	3.8 (83)		
Crude model	1 (ref.)	0.72 (0.56 - 0.93)	0.53 (0.41 - 0.70)		< 0.01
Fully adjusted model	1 (ref.)	0.86 (0.66 - 1.12)	0.76 (0.57 - 1.00)		0.06
Semantic verbal fluency of animals (n = 6,563)	(*n* = 2,188)	(*n* = 2,194)	(*n* = 2,181)		
Total caffeine consumption, median (P25-P75)	2.4 (1.2 - 4.2)	20.0 (12.5 - 21.8)	51.0 (36.9 - 57.7)	< 0.01	
Prevalence risk of poor cognitive functioning, % (n)	5.9 (129)	4.7 (103)	3.1 (67)		
Crude model	1 (ref.)	0.79 (0.60 - 1.03)	0.51 (0.38 - 0.68)		< 0.01
Fully adjusted model	1 (ref.)	0.97 (0.73 - 1.27)	0.80 (0.58 - 1.09)		0.15
Clock Test Score (n = 6,400)	(*n* = 2,134)	(*n* = 2,138)	(*n* = 2,128)		
Total caffeine consumption, median (P25-P75)	2.4 (1.2 - 4.2)	20 (12.5 – 21.9)	51.3 (37.1 – 57.7)	< 0.01	
Prevalence risk of poor cognitive functioning, % (n)	13.5 (289)	11.3 (241)	8.7 (184)		
Crude model	1 (ref.)	0.81 (0.68 - 0.97)	0.60 (0.50 - 0.73)		< 0.01
Fully adjusted model	1 (ref.)	0.89 (0.74 - 1.08)	0.75 (0.61 - 0.93)		< 0.01
Trail Making Test: A, total time (seconds), (n = 6,533)	(*n* = 2,178)	(*n* = 2,184)	(*n* = 2,171)		
Total caffeine consumption, median (P25-P75)	2.4 (1.2 - 4.2)	20.0 (12.5 - 21.9)	51.3 (37.2 - 58.1)	< 0.01	
Prevalence risk of poor cognitive functioning, % (n)	8.3 (181)	5.7 (125)	4.0 (86)		
Crude model	1 (ref.)	0.67 (0.53 - 0.85)	0.46 (0.35 - 0.59)		< 0.01
Fully adjusted model	1 (ref.)	0.83 (0.65 - 1.07)	0.72 (0.54 - 0.97)		0.03
Trail Making Test: B, total time (seconds), (n = 6,457)	(*n* = 2,156)	(*n* = 2,149)	(*n* = 2,152)		
Total caffeine consumption, median (P25-P75)	2.4 (1.2 - 4.2)	20.0 (12.7 - 21.9)	51.3 (37.1 - 58.2)	< 0.01	
Prevalence risk of poor cognitive functioning, % (n)	12.5 (269)	9.0 (194)	7.9 (170)		
Crude model	1 (ref.)	0.70 (0.57 - 0.85)	0.60 (0.49 - 0.74)		< 0.01
Fully adjusted model	1 (ref.)	0.79 (0.64 - 0.98)	0.86 (0.69 - 1.08)		0.15
Digit: forward score (n = 5,128)	(*n* = 1,711)	(*n* = 1,708)	(*n* = 1,709)		

Total caffeine consumption, median (P25-P75)	2.4 (1.3 - 4.2)	20.0 (12.3 - 21.8)	51.1 (36.5 - 57.7)	< 0.01	
Prevalence risk of poor cognitive functioning, % (n)	8.0 (137)	5.4 (93)	4.2 (72)		
Crude model	1 (ref.)	0.66 (0.50 - 0.87)	0.51 (0.38 - 0.68)		< 0.01
Fully adjusted model	1 (ref.)	0.82 (0.62 - 1.09)	0.78 (0.57 - 1.07)		0.14

Abbreviations: CI, confidence interval; OR, Odds Ratio; SD, Standard Deviation.
Caffeine consumption was computed from FFQs considering the caffeine contained in caffeinated coffee, decaffeinated coffee, tea, regular sodas, artificially sweetened soda, and chocolate.
Cut-off points for the Phonological verbal fluency, the Semantic verbal fluency and the Digit forward score were established as ≤ the mean – 1.5SD. For Trail Making Tests A and B cut-off points were established as ≥ the mean + 1.5SD. For the Clock Test, the cut-off point was established as ≤ 4 points. Multivariable logistic regression models and median regression models were fitted:
Fully – adjusted model: adjusted for age (years), sex, body mass index (kg/m^2), educational level (primary, secondary or university/graduate), smoking habit (never, former or current), total energy consumption (kcal/day), physical activity (METs.min/week), alcohol consumption (g/day, and adding the quadratic term), diabetes Prevalence risk (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), consumption of vegetables (g/d), fruits (g/d), dried fruits (g/d), biscuits (g/d), fish (g/d),dairy products (g/d), meat(g/d), legumes (g/d), olive oil (g/d), cereals (g/d), depression status (mild/moderate-severe depression) and participating center (in quartiles by number of participants)
All analyses were conducted with robust estimates of the variance to correct for intra-cluster correlation. Data are expressed as ORs (95%, CI).

Chapter 5

Caffeine intake and its sex-specific association with general anxiety: a cross-sectional analysis among general-population adults.

Paz-Graniel I, Kose J, Babio N, Hercberg S, Galan P, Touvier M, Salas-Salvadó J, Andreeva VA.

Key teaching points:

- Anxiety disorders prevalence has increased worldwide by 15% since 2005. Moreover, during the COVID-19 the global anxiety disorder prevalence increased by an estimated 25%.

- These disorders have been associated with the risk of other mental and chronic health conditions, and are recognized as one of the most common causes of the reduction in DALYs.

- Caffeine intake at large doses (>200 mg per drinking occasion or >400 mg/d) has been suggested to induce anxiety, especially in susceptible individuals.

- The role of low to moderate caffeine intake in healthy individuals is scarce and inconsistent. Some studies have reported that low doses of caffeine might produce stimulation, improve alertness, decrease depression and even anxiety.

- This large epidemiological study is the first to assess the association between caffeine intake and trait anxiety in general adult population.

- Caffeine intake was positively associated with general anxiety among women but not among men.

nutrients

MDPI

Article

Caffeine Intake and Its Sex-Specific Association with General Anxiety: A Cross-Sectional Analysis among General Population Adults

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Abstract: (1) Background: Caffeine is one of the most consumed psychoactive stimulants worldwide. It has been suggested that caffeine intake at large doses can induce anxiety, whereas evidence of the role of low to moderate caffeine intake is scarce and inconsistent. Therefore, we aimed to assess the association between caffeine intake and general anxiety in adults recruited from the general population. (2) Methods: Participants from the French NutriNet-Santé web cohort with data on caffeine intake and general anxiety (assessed during 2013–2016 through the trait subscale of Spielberger's State-Trait Anxiety Inventory Form Y; STAI-T, sex-specific top quartile = high trait anxiety) were included in this cross-sectional analysis (n = 24,197; 74.1% women; mean age = 53.7 ± 13.9 years). Mean dietary intake was estimated using ≥2 self-reported 24-h dietary records. Sex-specific tertiles of caffeine intake and low/high trait anxiety were calculated. Multivariable logistic regression models were fitted to assess the odds ratio (OR) and 95% confidence interval (CI) for the association between caffeine intake and general anxiety by sex. (3) Results: In the total sample, the mean caffeine intake (mg/day) from all dietary sources combined was 220.6 ± 165.0 (women = 212.4 ± 159.6; men = 243.8 ± 177.7, $p < 0.01$). Women in the highest tertile of caffeine intake showed significantly higher odds for high trait anxiety compared to those in the lowest tertile (reference), even after adjustment for potential confounders (OR: 1.13; 95% CI: 1.03–1.23). No significant associations were detected among men. Sensitivity analyses according to perceived stress level and sugar intake, respectively, showed similar results. (4) Conclusions: The results suggest that higher caffeine intake is associated with higher odds of general anxiety among women but not among men. Further research is needed to confirm the sex-specific findings and elucidate the potential causal relationship between caffeine intake and anxiety status.

Keywords: caffeine; dietary intake; anxiety; STAI-T; mental health; epidemiological study

1. Introduction

In the last decade, mental health has been recognized as an important component of public health; it is characterized not only by the absence of mental disorders or disabilities but also by a general state of well-being, allowing the individual to conduct his or her daily life activities and to manage stressful situations [1]. The DSM-5 includes a wide range of mental conditions [2]; among them, anxiety disorders (along with depression) have been associated with the greatest disease burden [3]. They have been identified as one of the most common causes of the reduction in disability-adjusted life years, and have been associated with the risk of other mental and chronic physical conditions [3].

According to the World Health Organization (WHO), the prevalence of anxiety disorders, which are characterized by a sense of tension, apprehension, and especially fear, with an intensity that can range from mild to severe [2], has increased worldwide by 15% since 2005, and in 2015 nearly 264 million individuals had anxiety [4]. Moreover, it was recently reported that during the Coronavirus disease 2019 (COVID-19) pandemic, the global anxiety disorder prevalence increased by an estimated 25% [5], placing these conditions near the top of the list of urgent health concerns and highlighting the necessity of designing prevention strategies.

Anxiety disorder onset can be triggered by the interplay of several risk factors, such as adverse life experiences in early life, shyness, family history of mental illness, biological predispositions, environmental events, socio-economic disadvantage, heavy use of alcohol and/or illicit drugs, chronic medical conditions, etc. [6]. In addition, as a higher prevalence among women than men has been reported [4], it has been proposed that sex hormones might also play an important role in its etiology and chronicity [6].

As anxiety onset results from complex gene–environment interactions, prevention strategies should be especially focused on potentially modifiable factors, such as diet and physical activity. In this regard, it has been proposed that due to its ability to modulate the gut microbiome, inflammation, oxidative stress, and immune function, diet might play an important role in the prevention and management of anxiety [7,8]. Some evidence has suggested an inverse association between anxiety and adherence to healthy dietary patterns (characterized by a high content of fruit, vegetables, nuts, whole grains, and fish) [9], while a "Western diet" (with a high content of red meat, processed and/or fried food, simple sugars, and salt) has been positively associated with anxiety [10]. However, most research in this field has focused on dietary patterns, food consumption, or nutrient intake, while research about the relationship between beverage consumption and mental health has been scarce and mainly explored through the association with certain compounds such as alcohol and—to a lesser extent—caffeine [11,12]. Moreover, research on caffeine intake and its association with anxiety has been especially focused on the effect of very large doses (>200 mg per drinking occasion or >400 mg/day), and most of it has been conducted in susceptible individuals (i.e., those with specific psychopathological conditions, genetic predisposition, etc.) [12]. A handful of studies have reported that low doses of caffeine might produce stimulation, improve the performance of activities that require alertness, and decrease depression and even anxiety [13–17]. Nevertheless, evidence of the role of low to moderate doses of caffeine intake in healthy individuals or by sex is inconsistent and scarce [12–14]. As caffeine might be the most consumed psycho-stimulant around the world, and due to its likely complex effect on anxiety, further research in this field is needed. Moreover, results from recent studies suggested an increase in coffee, tea, and energy drink consumption during the COVID-19 pandemic [18–20]; as these beverages are the principal caffeine sources, caffeine intake might have also increased, and have become an additional risk factor for anxiety during this period and possibly beyond. The reported increased anxiety disorder prevalence during the COVID-19 pandemic in 2020–2021 underscores the urgency to strengthen mental illness prevention strategies.

In this context, the main objective of the present study was to explore the association between the usual intake of low–moderate caffeine doses and general anxiety in a large sample of adults recruited from the general population. We hypothesized that participants with a higher mean daily caffeine intake would present higher odds of anxiety. In addition, as women show a higher prevalence of anxiety disorders than do men, we further hypothesized that women would be more prone to show an unfavorable association between caffeine intake and anxiety.

2. Materials and Methods

2.1. Study Population

A cross-sectional analysis using data from the NutriNet-Santé web cohort was performed. Briefly, the NutriNet–Santé study is an ongoing web-based general population prospective cohort launched in France in 2009. It aims to elucidate the multifaceted association between nutrition and health, as well as the determinants of dietary behaviors and nutritional status. A detailed description of the NutriNet-Santé study has been published elsewhere [21]. It is registered at clinicaltrial.gov as NCT03335644 and was approved by the Institutional Review Board of the French Institute for Health and Medical Research (INSERM # 00000388FWA00005831) and by the National Commission on Informatics and Liberty (CNIL # 908,450 and # 909216).

Eligible participants are adults aged ≥18 years with internet access; recruitment relies on recurrent large multimedia campaigns. After providing electronic informed consent, the participants complete a set of five self-report questionnaires to assess sociodemographic and lifestyle characteristics, anthropometrics, dietary intake, physical activity, and health status (outlined below, and extensively described in prior publications [22–27]). The present analysis has been conducted with those participants who had data on caffeine intake and who had responded to the Spielberger's State-Trait Anxiety Inventory Form Y (STAI-T) (both described below).

2.2. Assessment of Caffeine and Dietary Intake

At inclusion and every six months thereafter, participants are asked to complete three 24-h dietary records covering two weekdays and one weekend day. The tool used for collecting dietary data has been validated against dietitian interviews and nutritional status biomarkers [22,27]. Participants are asked to report all food and beverages consumed during the previous 24 h, considering the three main meals (breakfast, lunch, and dinner) and any other eating occasions. For the present analysis, we aimed to capture usual dietary intake, thus participants who had completed ≥ 2 dietary records within 2.5 years around the completion date of the STAI-T scale were eligible. All dietary data were weighted to account for weekday and weekend day consumption. Portion sizes were estimated using previously validated photographs [23] or usual containers. To calculate mean daily energy and nutrient intake, the NutriNet-Santé food composition database which includes > 3500 different items was used [28]. Participants with under-reported energy intake, identified via Black's method [29] considering the participant's age, sex, weight, height, physical activity level, and basal metabolic rate, were excluded from the analysis.

In the present study, caffeine intake (mg/day) was the main exposure variable. Total dietary caffeine consumption was estimated from 24-h dietary records [22] taking into consideration the average amount of caffeine contained in caffeinated coffee drinks (including Viennese coffee, Americano, espresso, mocha, Liège, gourmet, instant coffee, etc.), decaffeinated coffee, tea (including white, green, and black teas), regular soda, artificially sweetened soda, energy drinks, and alcohol-containing caffeinated beverages.

2.3. Trait Anxiety

Trait anxiety was assessed using the validated French version of the STAI-T scale [30], which was completed by participants only once between 2013 and 2016 as part of the NutriNet-Santé follow-up. Briefly, the STAI is one of the most widely used screening tools for assessing anxiety as a temporary state (STAI-S) and anxiety as a personality trait (STAI-T) reflecting general anxiety proneness [31]. In this study, trait anxiety was the outcome of interest, which is considered a relatively stable personal characteristic displayed in a wide range of daily life situations [31]. The STAI-T subscale consists of 20 items based on a 4-point Likert scale with responses ranging from "Almost never" to "Almost always". The total score ranges from 20 to 80, with higher scores corresponding to higher levels of general anxiety symptoms [32]. As there is no established cut-off point for defining high trait anxiety, we first explored the value distribution and then applied the sex-specific top quartile as cut-off, which is consistent with prior studies [33,34]. In addition, as a higher prevalence of anxiety disorders in women compared to men has been reported [4], sex-specific analyses were conducted (described below).

2.4. *Assessment of Covariates*

At inclusion and yearly thereafter, participants provide self-reported information by completing validated questionnaires on sociodemographic characteristics and lifestyle [25], anthropometric measurements, and health status. Body mass index (BMI, kg/m^2) was calculated based on self-reported height and weight [24]. Leisure-time physical activity was assessed through the short version of the International Physical Activity Questionnaire [26]. For each participant, we used covariate data obtained within a 2.5-year window around the date of STAI-T completion. As there is evidence that stress can trigger anxiety [6], we assessed whether the association between caffeine intake and trait anxiety might vary according to stress level. The validated French version of Cohen's 10-item Perceived Stress Scale (PSS-10) was administered at the same time as the STAI-T. The PSS-10 is commonly used in epidemiological research; it assesses the degree to which situations in daily life were appraised as stressful during the previous month [35]; higher scores indicate higher perceived stress, without an established cut-off. In the total studied sample, the Pearson correlation coefficient between the PSS-10 and STAI-T was 0.74 (n = 24,197, $p < 0.01$), which served as further justification for the interaction tests and subgroup analyses (described below).

Participants with missing data on covariables were excluded, except for covariables with >5% missing values, in which case a "Missing data/not reported" category was created. Regarding the "socio-professional category" variable, if the value was missing and age was <25 or >60 years, the respective status of "student" and "retired" was attributed.

2.5. *Statistical Analysis*

Study participants were categorized into sex-specific tertiles of caffeine intake due to the value distribution of the caffeine intake variable and also for purposes of interpretability of the results. To compare study participants' characteristics in terms of tertiles of caffeine intake, the x^2 test and the ANOVA test were used, as appropriate. Participants in the highest quartile were considered as having high trait anxiety (i.e., STAI-T score = Q4 defined as "high trait anxiety" versus STAI-T < Q4 "low trait anxiety"). Interaction between caffeine intake tertiles and sex was tested including cross-product terms in crude and adjusted models (p-value for interaction < 0.01), considering the higher prevalence of anxiety disorders among women than among men. Given the significant results of these tests, the main analyses were stratified by sex. Interaction tests with age and smoking status with regard to caffeine intake were also performed but the results were not significant. Multivariable logistic regression models according to sex were fitted to assess the association (odds ratio (OR); 95% confidence interval (CI)) between tertiles of caffeine intake (lowest tertile as reference category) and the odds of high trait anxiety. Model 1 was adjusted for age (continuous scale). Model 2 was additionally adjusted for marital status (living alone, and married/cohabiting), educational level (less than high school, high school, college, and graduate), physical activity (low, moderate, and high), smoking status (never, former, and current smoker), socio-professional category (homemaker, manual work, professional, and retired), BMI (continuous scale, kg/m^2), mean total energy intake (Kcal/d), alcohol consumption (continuous scale, g/dayay), and number of 24-h dietary records (continuous scale).

Sensitivity analyses by degree of perceived stress (PSS-10 score $\geq$ sex-specific mean) [36] were conducted to evaluate whether the associations observed in the main analysis were varied by perceived stress level. Further, we performed another set of sensitivity analyses, fitting statistical models where intakes of total sugar (g/day), simple sugars (g/day), and added sugars (g/day) were added as covariates to take into account the plausible association of these nutrients with anxiety [37] as well as the frequently combined intake of sugar and caffeine. The data were analyzed using the Stata 14 software (StataCorp, College Station, TX, USA), and statistical significance was set at a two-tailed p-value < 0.05.

3. Results

3.1. Sample Description

From the 40,809 NutriNet-Santé participants who completed the anxiety questionnaire, we excluded from the present analysis individuals: (1) with non-valid or incomplete STAI-T data, (2) without data on caffeine intake, (3) with under-reported dietary intake or with < 2 24-h dietary records, and (4) with <5% missing data on sociodemographic and/or lifestyle variables. Therefore, the present analysis included 24,197 individuals (6274 men and 17,923 women) (Figure 1) with a mean age of 53.7 ± 13.9 years. In the full sample, the mean number of 24-h dietary records for the assessment period considered was 8.2 ± 3.8. The descriptive characteristics of the final sample according to sex-specific tertiles of caffeine intake are presented in Table 1. In the total studied population, the mean caffeine intake was 220.6 ± 165 mg/day. Significant differences by tertiles of caffeine intake were observed for all characteristics in men, except for educational level and perceived stress. Similarly, among women, except for high trait anxiety prevalence and perceived stress, all descriptive characteristics were significantly different across tertiles of caffeine intake ($p < 0.05$).

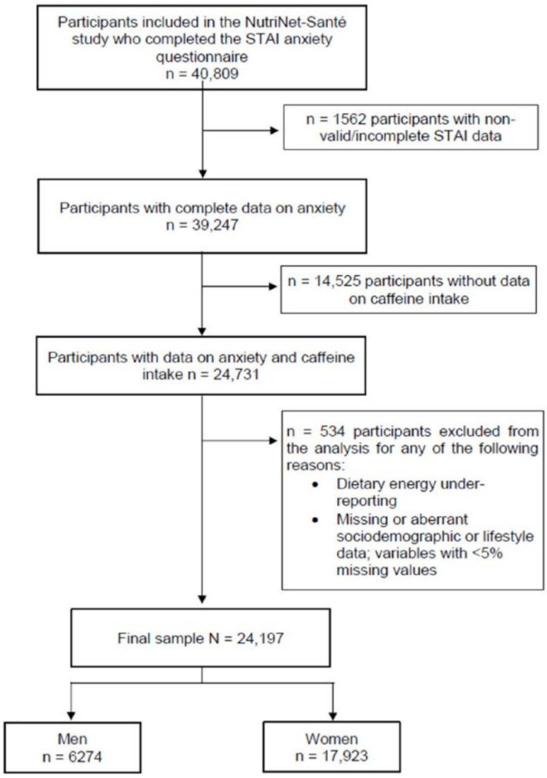

Figure 1. Participant flow diagram for NutriNet-Santé e-cohort participants included in the current analysis. Abbreviations: STAI-T, Spielberger's State-Trait Anxiety Inventory Form Y.

Table 1. Descriptive characteristics of the NutriNet-Santé participants according to sex and tertiles of caffeine intake.

	Full Sample	Men				Women			
	n = 24,197	T1 n = 2092	T2 n = 2091	T3 n = 2091	p Value [a]	T1 n = 5975	T2 n = 5974	T3 n = 5974	p Value [b]
Caffeine intake, mg/day	220.6 ± 165	76.0 ± 47.7	218.8 ± 38.5	436.8 ± 157.8	<0.01	62.3 ± 36.8	186.4 ± 35.8	388.6 ± 139.5	<0.01
High trait anxiety †		23.4 (489)	20.7 (433)	20.4 (427)	0.03	23.8 (1419)	24.1 (1438)	24.4 (1459)	0.69
Age, mean (SD), years	53.7 ± 13.9	57.1 ± 14.8	60.8 ± 12.4	59.1 ± 12.0	<0.01	47.8 ± 14.7	53.5 ± 13.3	54.3 ± 11.9	<0.01
Age category					<0.01				<0.01
<40 years	20.7 (5019)	17.7 (370)	8.8 (184)	8.9 (185)		36.9 (2204)	19.9 (1191)	14.8 (885)	
40–60 years	39.1 (9454)	28.4 (595)	27.7 (579)	34.9 (730)		36.5 (2179)	42.1 (2515)	47.8 (2856)	
>60 years	40.2 (9724)	53.9 (1127)	63.5 (1328)	56.2 (1176)		26.6 (1592)	38.0 (2268)	37.4 (2233)	
Educational level					0.51				<0.01
Less than high school	13.9 (3372)	16.3 (340)	18.4 (384)	18.4 (386)		11.5 (686)	13.7 (818)	12.7 (758)	
High school or equivalent	16.8 (4058)	18.6 (389)	17.4 (364)	17.4 (364)		16.0 (955)	16.6 (992)	16.6 (994)	
College, undergraduate degree	27.9 (6746)	22.9 (479)	21.9 (458)	22.6 (472)		30.9 (1843)	29.2 (1746)	29.3 (1748)	
Graduate degree	36.3 (8788)	40.0 (837)	39.4 (825)	39.2 (819)		36.7 (2194)	34.1 (2,037)	34.8 (2076)	
Not reported	5.10 (1233)	2.2 (47)	2.9 (60)	2.4 (50)		5.0 (297)	6.4 (381)	6.7 (398)	
Socio-professional category					<0.01				<0.01
Homemaker/disabled/unemployed/student	8.30 (2016)	4.3 (91)	2.2 (46)	3.4 (70)		11.5 (685)	9.3 (555)	9.5 (569)	
Manual/office work/administrative staff	30.5 (7389)	20.8 (436)	14.5 (304)	18.6 (389)		40.0 (2390)	32.1 (1920)	32.6 (1950)	
Professional/executive staff	23.1 (5578)	22.7 (475)	21.8 (4555)	24.5 (513)		23.4 (1398)	22.7 (1357)	23.1 (1380)	
Retired	38.10 (9214)	52.1 (1090)	61.5 (1286)	53.5 (1119)		25.1 (1502)	35.9 (2142)	34.7 (2075)	
Marital status					<0.01				<0.01
Living alone (single, divorced, widowed)	23.4 (5674)	20.5 (428)	14.8 (310)	14.9 (311)		24.6 (1470)	24.6 (1472)	28.2 (1683)	
Married/cohabiting	76.6 (18,523)	79.5 (1664)	85.2 (1781)	85.1 (1780)		75.4 (4505)	75.4 (4502)	71.8 (4291)	
Physical activity *					<0.01				<0.01
Low	36.8 (8906)	44.6 (932)	48.6 (1,107)	45.2 (944)		30.4 (1814)	34.5 (2058)	35.8 (2141)	
Moderate	41.3 (9986)	34.9 (730)	35.5 (742)	36.1 (755)		43.9 (2620)	43.3 (2588)	42.7 (2551)	
High	21.9 (5305)	20.5 (430)	15.9 (332)	18.7 (392)		25.8 (1541)	22.2 (1328)	21.5 (1282)	
Smoking status					<0.01				<0.01
Never smoker	51.0 (12,351)	52.7 (1103)	39.3 (821)	33.4 (699)		66.1 (3949)	52.6 (3142)	44.1 (2637)	
Former smoker	39.4 (9519)	41.9 (877)	53.0 (1110)	54.4 (1138)		27.3 (1629)	38.0 (2267)	41.8 (2498)	
Current smoker	9.6 (2327)	5.4 (112)	7.7 (160)	12.2 (254)		6.6 (397)	9.5 (565)	14.0 (839)	
Body Mass Index (BMI), kg/m^2	23.8 ± 4.1	24.5 ± 3.5	25.0 ± 3.5	25.4 ± 3.6	<0.01	23.1 ± 4.2	23.4 ± 4.2	23.5 ± 4.3	<0.01
BMI category					<0.01				<0.01
Underweight (<18.5)	4.6 (1123)	1.7 (36)	0.9 (19)	0.6 (13)		6.7 (398)	5.7 (338)	5.3 (319)	
Normal weight (18.5–24.9)	64.4 (15,588)	59.7 (1250)	56.1 (1173)	50.1 (1048)		68.8 (4108)	67.9 (4056)	66.2 (3953)	
Overweight (25.0–29.9)	23.6 (5699)	32.3 (675)	35.7 (746)	39.8 (33)		17.5 (1048)	19.3 (1154)	20.8 (1243)	
Obese (≥30)	7.4 (1787)	6.3 (131)	7.3 (153)	9.4 (197		7.0 (421)	7.1 (426)	7.7 (459)	
Total energy intake, kcal/d	1910.8 ± 440.4	2223.1 ± 452.5	2286.1 ± 454.0	2,324.3 ± 463.3	<0.01	1759.8 ± 356.5	1772.5 ± 344.6	1814.8 ± 355.7	<0.01
Alcohol consumption, g ethanol/d	8.5 ± 11.6	12.4 ± 16.3	16.6 ± 16.0	16.8 ± 15.4	<0.01	4.5 ± 7.4	6.6 ± 8.3	7.5 ± 9.4	<0.01
Number of 24-h dietary records	8.2 ± 3.8	8.5 ± 3.7	9.0 ± 3.6	8.8 ± 3.7	<0.01	7.5 ± 3.8	8.1 ± 3.7	8.3 ± 3.7	<0.01
Perceived stress score‡	13.5 ± 6.9	11.6 ± 6.3	11.2 ± 6.2	11.3 ± 6.5	0.21	14.3 ± 6.9	14.2 ± 6.8	14.2 ± 6.9	0.48

Abbreviations: SD, standard deviation. Data expressed as percentage (number) or mean ± standard deviation, as appropriate. *p*-values for comparisons between tertiles of caffeine intake for men [a] and women [b] were calculated by Pearson's chi-square test for categorical variables or one-factor ANOVA for continuous variables. † Spielberger Trait Anxiety Inventory (STAI-T) Form Y; score range between 20 and 80 points, with higher scores indicating higher anxiety symptomatology, high trait anxiety STAI-T score in Q4. * Assessed with the International Physical Activity Questionnaire-Short Form; scoring followed established protocol. ‡ Assessed with Cohen's Perceived Stress Scale-10 (PSS-10) where higher scores indicate higher levels of perceived stress.

3.2. Description of Caffeine Intake

Table 2 shows the total daily consumption (mL/day) of various caffeinated beverages in the sample. In the total studied population, the mean total caffeinated beverages consumption was 385.0 ± 290.4 mL/day, and tea was the most consumed caffeine-containing beverage. Compared to men, women reported higher consumption of caffeinated beverages, especially tea. Caffeinated coffee was the most consumed caffeinated beverage in men.

Table 2. Total daily consumption (mL/day) of various caffeinated beverages in the NutriNet-Santé study (n = 24,197).

Caffeine Sources	Total Sample	Men (n = 6274)	Women (n = 17,923)	*p* Value [a]
Total caffeinated beverages	385.0 ± 290.4	343.8 ± 259.7	399.5 ± 299.1	<0.01
Total coffee	160.5 ± 179.9	188.3 ± 188.9	150.7 ± 175.6	<0.01
Caffeinated coffee	152.2 ± 174.9	179.9 ± 185.3	142.5 ± 170.1	<0.01
Decaffeinated coffee	8.2 ± 46.1	8.4 ± 47.9	8.2 ± 45.5	0.73
Tea	211.7 ± 280.5	143.0 ± 229.2	235.7 ± 292.6	<0.01
Other caffeinated beverages [b]	12.9 ± 63.3	12.5 ± 53.4	13.0 ± 66.4	0.54

Data expressed as mean ± standard deviation. [a] *p*-value for comparisons between sexes was obtained by Student's *t*-test. [b] Other caffeinated beverages category includes sodas, energy drinks, and alcohol-containing caffeinated beverages.

3.3. Association between Caffeine Intake and Trait Anxiety

Table 3 summarizes the results of the sex-specific associations (OR, 95% CI) between tertiles of caffeine intake and the odds of high trait anxiety. No significant associations were observed for men in crude or adjusted models. In turn, women in the two higher tertiles of caffeine intake were more likely to present high trait anxiety (Model 2: aOR = 1.10, 95% CI: 1.01–1.20; aOR = 1.13 95% CI: 1.03–1.23, respectively) compared to those in the lowest tertile.

Table 3. Sex-specific associations (odds ratios, 95% CI) between tertiles of caffeine intake and odds of high trait anxiety in the NutriNet-Santé study (n = 24,197).

	Men			Women		
	T1 n = 2092	T2 n = 2091	T3 n = 2091	T1 n = 5975	T2 n = 5974	T3 n = 5974
Caffeine intake, mg/day ^	76.0 ± 47.7	218.8 ± 38.5	436.8 ± 157.8	62.3 ± 36.8	186.4 ± 35.8	388.6 ± 139.5
Trait anxiety † (% (n) high) ^	23.4 (489)	20.7 (433)	20.4 (427)	26.3 (1572)	26.2 (1566)	26.7 (1597)
Model 1	1 (ref.)	0.94 (0.81–1.08)	0.89 (0.76–1.03)	1 (ref.)	1.08 (0.99–1.18)	**1.11 (1.02–1.21)**
Model 2	1 (ref.)	0.96 (0.83–1.12)	0.88 (0.75–1.02)	1 (ref.)	**1.10 (1.01–1.20)**	**1.13 (1.03–1.23)**

Abbreviations: ref, reference category. ^ Data expressed as percentage (number) or mean ± standard deviation. Multivariable logistic regression models were fitted: outcome: STAI-T < Q4 (0) vs. STAI-T score in Q4 (1) †; reference category: lowest tertile of caffeine intake. Model 1 adjusted for age. Model 2 additionally adjusted for marital status, education, physical activity, smoking status, socio-professional category, BMI, mean total energy intake, alcohol consumption, and number of 24-h dietary records. Bold means highlight significant results.

3.4. Sensitivity Analysis

As noted above, PSS-10 and STAI-T were significantly correlated (n = 24,197, $r = 0.74$), thus we proceeded with subgroup models. Results from the sensitivity analyses, stratified by perceived stress (Sensitivity analysis 1) are displayed in Table 4. Among women with high perceived stress, trait anxiety was positively associated with the highest tertile of caffeine intake (aOR = 1.17, 95% CI: 1.02–1.34), whereas no significant associations were observed for men. Results following the additional adjustment for total sugars, simple sugars, and added sugars (Sensitivity analysis 2, Table 5) remained virtually unchanged and at the same significance level as the main results.

Table 4. Sensitivity analyses of the association (odds ratio, 95% CI) between tertiles of caffeine intake and odds of high trait anxiety according to perceived stress level in women and men from the NutriNet-Santé cohort.

	Women (n = 12,923)					
	Low Perceived Stress (PSS-10 Score < Sex-Specific Mean)			High Perceived Stress (PSS-10 Score ≥ Sex-Specific Mean)		
	T1 n = 3216	T2 n = 3216	T3 n = 3216	T1 n = 2759	T2 n = 2758	T3 n = 2758
Caffeine intake, mg/day ^	62.4 ± 37.3	186.9 ± 35.7	388.3 ± 135.1	62.2 ± 36.2	185.8 ± 36.0	389.0 ± 144.6
Trait anxiety † (% (n) high) ^	24.6 (790)	23.6 (759)	25.0 (805)	20.8 (574)	22.6 (623)	23.4 (646)
Model S3	1 (ref.)	0.96 (0.86–1.08)	1.05 (0.93–1.18)	1 (ref.)	1.14 (0.99–1.30)	**1.17 (1.02–1.34)**
	Men (n = 6274)					
	Low Perceived Stress (PSS-10 Score < Sex-Specific Mean)			High Perceived Stress (PSS-10 Score ≥ Sex-Specific Mean)		
	T1 n = 1114	T2 n = 1113	T3 n = 1113	T1 n = 978	T2 n = 978	T3 n = 978
Caffeine intake, mg/day^	78.7 ± 48.8	221.2 ± 37.2	435.8 ± 155.5	73.0 ± 46.4	215.9 ± 39.9	437.9 ± 160.5
Trait anxiety † (% (n) high)^	23.9 (267)	24.8 (276)	23.9 (266)	24.3 (238)	25.2 (246)	24.3 (238)
Model S3	1 (ref.)	1.09 (0.89–1.33)	1.02 (0.83–1.24)	1 (ref.)	1.17 (0.95–1.45)	1.04 (0.84–1.30)

Abbreviations: ref, reference category. ^ Data expressed as percentage (number) or mean ± standard deviation. Multivariable logistic regression models were fitted: outcome: STAI-T < Q4 (0) vs. STAI-T score in Q4 (1) †; reference category: lowest tertile of caffeine intake. All models were adjusted for age, marital status, education, physical activity, smoking status, socio-professional category, BMI, mean total energy intake, alcohol consumption, and number of 24-h dietary records. Bold means highlight significant results.

Table 5. Sensitivity analyses of the association (odds ratio, 95% CI) between tertiles of caffeine intake and odds of high trait anxiety in women and men from the NutriNet-Santé cohort (n = 12,923) according to sugar intake.

	Men			**Women**		
	T1 n = 2092	**T2 n = 2091**	**T3 n = 2091**	**T1 n = 5975**	**T2 n = 5974**	**T3 n = 5974**
Caffeine intake, mg/day ^	76.0 ± 47.7	218.8 ± 38.5	436.8 ± 157.8	62.3 ± 36.8	186.4 ± 35.8	388.6 ± 139.5
Trait anxiety † (% (n) high) ^	23.4 (489)	20.7 (433)	20.4 (427)	26.3 (1572)	26.2 (1566)	26.7 (1597)
Model S1	1 (ref.)	1.01 (0.85–1.21)	0.90 (0.75–1.07)	1 (ref.)	**1.10 (1.01–1.20)**	**1.13 (1.03–1.23)**
Model S2	1 (ref.)	1.00 (0.85–1.21)	0.89 (0.75–1.07)	1 (ref.)	**1.10 (1.01–1.20)**	**1.13 (1.03–1.23)**
Model S3	1 (ref.)	1.01 (0.85–1.21)	0.89 (0.75–1.07)	1 (ref.)	**1.10 (1.01–1.20)**	**1.13 (1.03–1.23)**

Abbreviations: ref, reference category. ^ Data expressed as percentage (number) or mean ± standard deviation. Multivariable logistic regression models were fitted: outcome: STAI-T < Q4 (0) vs. STAI-T score in Q4 (1) †; reference category: lowest tertile of caffeine intake. All models were adjusted for age, marital status, education, physical activity, smoking status, socio-professional category, BMI, mean total energy intake, alcohol consumption, and number of 24-h dietary records. Model S1 additionally adjusted for total sugars (g/day). Model S2 additionally adjusted for simple sugars (g/day). Model S3 additionally adjusted for added sugars (g/day). Bold means highlight significant results.

4. Discussion

To the best of our knowledge, this large epidemiological study is the first to assess the association between caffeine intake and trait anxiety in a cohort recruited from the general adult population. The results of our analyses showed that among women caffeine intake was positively associated with trait anxiety, supporting our hypothesis. No significant associations were observed among men, however, this merits confirmation before a conclusion could be drawn. In our sample, women allocated in the highest tertile of caffeine intake, generally reported a 50 mg/day lower mean caffeine intake than did men in the top caffeine intake tertile, which is in line with data reported from two European cohorts [38].

It has been reported that anxiety prevalence is twice as high among women compared to men [4]. The increased odds of anxiety disorders in women compared to men have been partly attributed to differences in hormonal and neurotransmitter profiles (e.g., estrogen, progesterone, corticotropin-releasing factor, serotonin, etc.) [39]. Further, consistent with the evidence in the literature [40], in our study population, men had higher mean alcohol consumption than did women. It has been suggested that men are more likely than women to use substances with depressant effects on the central nervous system to cope with anxiety symptoms [41]. These factors might contribute to partly explain the different results among men and women. Interestingly, men and women also seem to differ regarding their motives for caffeine consumption [42].

Unlike our findings, some previous studies have reported significant associations between caffeine intake and anxiety in men; the discrepancies might be due to methodological differences (study design, individuals' health status, age distribution, assessment tools, etc.). For example, in an experimental study (n = 99; 39 men, 60 women) conducted by Botella et al. [43], it was reported that after the consumption of coffee containing 150 mg or 300 mg of caffeine, men showed higher state anxiety than did women. In contrast, some authors have reported that low to moderate doses of caffeine reduced anxiety and increased mood in men [44]. In another experimental study conducted by Rogers et al., it was observed that at baseline higher habitual caffeine intake was associated with greater anxiety; however, after the intake of two caffeine doses (100 + 150 mg), participants who did not usually consume it showed increased anxiety [45]. In the latter three studies, samples did not include women [44] or results were not reported by sex [45], which does not allow comparisons with our observations. Overall, it should be noted that results from experimental studies largely pertain to the acute effect of caffeine intake in state anxiety but it has been weakly correlated with trait anxiety, which reflects a more habitual reaction to adverse events or stimulants [12,46]. In this regard, as caffeine intake can result in the development of tolerance, future studies of the association between caffeine and trait anxiety should be focused on long-term exposure. Moreover, caffeine intake at high doses (>400 mg/day, 200 mg per occasion) has been described as inducing anxiety disorders [2] but the effect of habitually lower doses remains unclear [47]. In turn, anxiogenic effects of caffeine have been more commonly reported in sensitive individuals, i.e., those with a genetic predisposition, younger age, with certain psychiatric disorders, and those with a predisposition to anxiety disorders than among their counterparts without such sensitivity profiles [12,48]. In our sample, largely composed of healthy French adults, mean caffeine intake (220.6 $\pm$ 165 mg/day) was somewhat lower than the quantities reported in previous studies in which caffeine intake was associated with anxiety [12,47]. This might serve as an additional explanation for the non-significant results in men. Caffeine intake in our sample was within the range of the reported usual consumption in the general French population (mean: 168 mg/day, P95: 438 mg/day) [49].

As stress has been associated with anxiety [6], we conducted sensitivity analyses by additionally stratifying the sample by level of perceived stress. The associations observed in the main analysis remained significant among women who reported having high perceived stress (PSS-10 score $\geq$ sex-specific mean); in men, perceived stress did not make a difference in the results. Stress is a biological response of the organism to situations perceived as threatening, in which the hypothalamic–pituitary–adrenocortical axis and the sympathetic–adrenal–medullary axis are activated, leading to stress hormone release (cortisol and catecholamines) [50]. Moreover differences in the biological and psychological stress response by sex have been described. It has been suggested that women are more susceptible to stress-induced anxiety than men, especially due to lower basal stress hormone levels in women, in addition to the role of sex hormones involved in the stress response [50–52]. It has also been suggested that women and men react to stressful life situations differently; while women might be more likely to ruminate (through disturbing and repetitive thoughts that are distressing and debilitating, and consequently might have increased anxiety symptoms), men tend to engage in more active pathways for problem-solving (i.e., behavioral and cognitive strategies focused on changing the stressful condition, and its perception and meaning), problem avoidance, and social withdrawal [41] that may increase the risk for stress-induced anxiety. Next, we previously reported an association between intakes of added sugars (g/day) and trait anxiety [37]. As caffeine is frequently consumed along with sugar, and to take into consideration the previously observed plausible associations, a second set of sensitivity analyses was performed by additionally adjusting our models for total sugar (g/day), simple sugars (g/day), and added sugars (g/day), and found that the results remained virtually unchanged. This gives greater robustness to our results about the potential effect of caffeine intake on trait anxiety.

As previous studies have reported a positive association between smoking habits and coffee consumption [53], and increased caffeine metabolism in smokers has been suggested [38], we tested the interaction between smoking status and caffeine intake, yet the result was non-significant. In our sample, men did not seem to be heavier smokers than women; that might partially explain this result. In addition, previous evidence has suggested a weaker association between smoking habits and tea consumption, in this regard, the differences observed in caffeinated beverage (tea and coffee) consumption among the sexes might be one reason for the lack of significant interactions. Future specific analyses are needed to clarify these potential interactions and their relationship with anxiety.

Several mechanisms underlying the observed associations between caffeine intake and general anxiety have been suggested in the literature. It has been proposed that the caffeine effect might be mediated via (a) the antagonism of adenosine receptors, (b) the inhibition of phosphodiesterase, (c) intracellular stores/calcium release, and (d) the antagonism of $GABA_A$ receptors [54]. Due to its similarity to adenosine, the most accepted mechanism regarding the impact of caffeine is its antagonistic property at the level of adenosine receptors. It has been proposed that caffeine might bind to adenosine receptors and promote behavioral alertness, such as vigilance, attention, elevated mood, and arousal [55]. Meanwhile, phosphodiesterase inhibition and calcium release mechanisms require very high doses (>25 mg/kg/day) of caffeine to occur, and therefore, the pathway of their impact is less pertinent [54]. Next, some polymorphisms of A2A adenosine receptors have been described which may explain discrepancies in findings among different populations [12]. Finally, the source of caffeine might play an important role in its effect on trait anxiety. In our study, men were more likely to consume coffee than women. Coffee, due to its complex matrix featuring vitamins, minerals, bioactive phytochemicals, and polyphenols with antioxidant properties [56], might present a synergistic interaction of caffeine with the other components, thus potentially promoting a protective effect against anxiety. Further, tea has usually been associated with relaxation states, however, a cup of tea provides approximately 35–61 mg of caffeine and 4.5–22.5 mg of theanine [57], and therefore its consumption might promote anxiety symptoms, especially when such consumption is increased. Nevertheless, in an experimental analysis conducted by Smith et al., the effect of caffeine on mood and performance was not modified by the type of drink from which it was obtained [14]. Future studies should explore the potential interaction among the various beverage compounds and their individual and combined effects on mood and anxiety.

Our study has certain limitations that must be considered. One of the main limitations is the potential reverse causation bias, inherent in the cross-sectional design; in addition it is not possible to determine a causal relationship between caffeine intake and general anxiety. Second, despite the STAI-T being one of the most commonly used assessment tools regarding general anxiety proneness in epidemiological research, it cannot substitute for a complete clinical diagnosis. Third, caffeine intake was estimated from dietary sources and no other potential sources (such as dietary supplements) were considered; it is, therefore, possible that mean caffeine intake might have been underestimated. Still, as noted above, the reported mean caffeine intake in our studied population was within the range of the reported usual consumption in the general French population [49]. Fourth, our study used data from the NutriNet-Santé cohort, in which women and well-educated individuals are somewhat over-represented in comparison with the general French population [58], therefore the findings should be extrapolated prudently. Finally, we cannot discount the possibility that the observed associations might be due to residual confounding by factors not taken into account in the statistical analysis (clinical and family history of anxiety disorders, ethnoracial status, etc.). As study strengths, however, it should be highlighted that the analysis was based on a large and heterogeneous sample and data were obtained via validated assessment tools. Moreover, dietary (and caffeine) intake was estimated using a large number of previously validated 24-h dietary records [22], reducing the risk of over- or under-estimation.

5. Conclusions

In this large cross-sectional study conducted in a sample of adults recruited from the French general population, higher caffeine intake was positively associated with higher odds of general anxiety in women but not in men. Further research is needed to confirm the sex-specific findings and to elucidate the potential mechanisms involved in the observed association. The findings could inform future mental health promotion initiatives, especially among women.

Author Contributions: M.T., S.H. and P.G. designed and implemented the NutriNet-Santé cohort study; P.G. and V.A.A. implemented the STAI questionnaire and coordinated anxiety data collection; V.A.A. conceptualized the study, designed the analytic strategy, and provided theoretical and empirical guidance; I.P.-G. performed the literature review, statistical analyses, and led the writing; J.K. assisted with the literature review and statistical analysis; all authors assisted with interpretation of the data and critically revised the manuscript for important intellectual content. Writing—review & editing, J.K., N.B., J.S.-S. and V.A.A. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The NutriNet-Santé study is conducted according to the Declaration of Helsinki guidelines. It was approved by the Institutional Review Board of the French Institute for Health and Medical Research (INSERM # 00000388FWA00005831) and by the National Commission on Informatics and Liberty (CNIL # 908450 and # 909216). NutriNet-Santé is registered (# NCT03335644) at www.clinicaltrials.gov.

Informed Consent Statement: Electronic informed consent was obtained from all participants included in the study.

Data Availability Statement: Researchers at public institutions can submit a project collaboration request that includes information about their institution and a brief description of the project to: collaboration@etude-nutrinet-sante.fr. All requests are reviewed by the steering committee of the NutriNet-Santé study. In case of approval, a signed data access agreement will be requested and additional authorizations from the competent administrative authorities may be needed regarding human subjects' data protection. In accordance with existing regulations, no personally identifiable data will be made available.

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VI. DISCUSSION

Previous studies have recognized fluids as an important component for health maintenance and disease prevention. The present doctoral thesis has sought to evaluate more deeply the association between water intake, beverages consumption, cardiovascular risk factors, and cognition in elderly Mediterranean individuals with MetS.

Figure 4 resume the main findings of this work: 1) Reinforce the evidence that Mediterranean beverage consumption pattern is associated with better compliance of EFSA recommendations for TWI and TWIF, and with a healthier lifestyle; 2) Provide evidence for the association between drinking water consumption, body weight, and adiposity; 3) Contribute with new insights regarding fruit juice consumption and its association with cardiometabolic health; 4) Support the role of coffee consumption and caffeine intake in the prevention of cognitive functioning decline, in individuals at high risk; and 5) Highlight the sex-specific associations between caffeine intake and odds of general anxiety.

The following general discussion section aims to integrate the results from this investigation work, as well as to discuss new scientific evidence, and to deeply comment on some points that were not previously extensively addressed in each of the five published chapters.

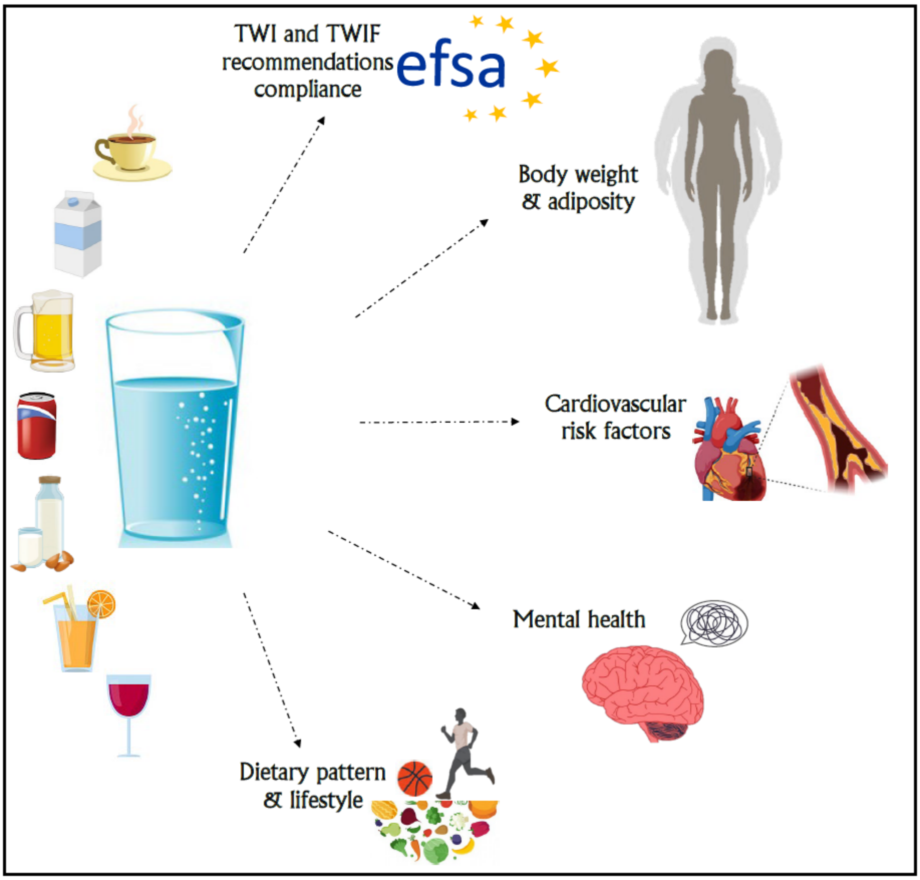

Figure 4. *Main associations between beverages consumption, health and lifestyle observed in the PREDIMED-Plus cohort*

1. General discussion

There is little evidence regarding beverage consumption in the European region and its association with hydration and health. In addition, methodological differences in fluids intake assessment difficult the comparison of the result among studies. Despite that, several tools and assessing methods have been developed to evaluate beverage intake and hydration status, to date there is only a fluid-specific intake questionnaire validated in the Spanish population. The use of this questionnaire allowed us to identify several types of beverages commonly consumed in the Mediterranean population. Moreover, in combination with the FFQ, we were able to estimate TWI, and in consequence, achieve a greater perspective of fluids intake.

Results from *chapter 1* showed that in an elderly Spanish population drinking water was the most consumed beverage followed by milk and other dairy beverages. Sex differences were observed for alcoholic and hot beverages (coffee and tea) consumption. These results are similar to what has been reported in other European populations[53,236,237]. In our study, TWI and TWIF were associated with some socio-demographic and lifestyle factors such as sex, age, physical activity, and adherence MedDiet. In this line, our results were in accordance with previous studies reporting an inverse association between water intake and age, and a positive association with women[53,238]. In this regard, it is known that with aging the ability to perceive thirst decreases and might be one reason for the low water intake in the elderly population, in addition to the onset of other health and psycho-social conditions[23,25]. Further, it has been suggested that women are more likely to adhere to a healthy lifestyle than men, and consequently their beverage consumption pattern it will also be healthier[237]. In contrast, compared with studies conducted in populations that are not strongly adhered to MedDiet[51], in our population water from foods contributed to 35% of TWI, suggesting that the MedDiet pattern (characterized by its high content on fruits and vegetables) greatly contributes to compliance with EFSA's recommendations for TWI. Similarly, we observed that physical activity was positively associated with fluid intake. As known, when exercising water requirements might be increased[33] and water intake recommendations may not be enough, for this reason, our results should be taken with caution. However, even if we could not assess the level of physical activity during the day fluid intake questionnaire was full-filled, it should be noticed that both questionnaires (leisure-time PA questionnaire and fluid intake assessment questionnaire) aimed to reflect the usual fluids consumption and physical activity habit[35,61,239]. Therefore, in terms of lifestyle, we could assess the joint effect of the physical activity level and MedDiet on water intake. In contrast with our analyses, some studies conducted in other European countries have reported differences in mean fluids intake and water intake according to daytime, seasonality, and holidays[51,53,240]. In studies to be conducted in the Spanish population, factors that are prone to modify water requirements and fluids consumption as seasonality, weekdays, holidays, costumes, and medication use should be considered and explored. Finally, it should be borne in mind that the EFSA's reference values for adequate water intake were established based on a standard value aiming to avoid the harmful effects of dehydration. However, these water needs are susceptible to inter- and intra- individual variation. Hence, the use of biomarkers would give a wide and better comprehensive view of hydration status, beverage consumption pattern, and its determinants.

To the best of our knowledge, *chapter 2*, was the first time an epidemiological study prospective explored the association between drinking water consumption and long-term BW changes in an elderly population at high cardiovascular risk. Previous studies have focused on the short-term effect of drinking water on BW[66,119,241,242]. We reported that participants with higher consumption of drinking water at baseline had a greater reduction in BW at 1- and 2- years of follow-up. This association has been mostly explained by the effect on energy intake of drinking water consumption, either due to increased gastric distension and satiety sensation caused by liquid volume which has been suggested to contribute to decreasing energy intake at subsequent meals[66]; as by the replacement of energy-containing beverages with water[67]. Beverages other than drinking water are dietary sources of water, vitamins, minerals, and bioactive compounds, but also of carbohydrates, proteins, and fat, which can contribute to increased total energy intake[2,7]. In our theoretical substitution analyses alcoholic beverages (beer and spirits/mixed alcoholic beverages), soups/vegetable juices, hot beverages, total and reduced-dairy beverages, and other beverages group by water were significantly associated with a greater reduction in BW at one year or two years of follow-up, supporting results from previous studies[57,141,243,244]. Contrary to what has been reported by other authors[67,245,246], we did not observe a significant decrease in BW or WC when sugary drinks or ASB were theoretically replaced by water. It should be noticed that these beverages have been reported to be low consumed in our study population[40], which along with sample nature and methodological differences might be some reason for the discrepancies observed with other studies Nevertheless, results from experimental studies have suggested that drinking water has potential effects on body weight and adiposity in the long-term, independently of caloric or fluid intake by inducing thermogenesis and slightly increasing metabolic rate, thus increasing energy expenditure[69,247]. Taking into consideration this previous evidence, our statistical models were adjusted by total energy intake and total fluid intake, as stable variables, giving robustness to our results.

Fruit juices are an important source of micronutrients and bioactive compounds with potential beneficial effects on health[122]. Nonetheless, because of its free sugar content and its low content on dietary fiber, it has been suggested that fruit juice consumption induces less satiety than whole fruit ingestion, and in consequence, its consumption could promote an over energy intake[248]. Therefore, recommendations on fruit juice consumption remain controversial[249]. In *chapter 3*, we aimed to explore the association between fruit consumption in several manners and cardiometabolic risk factors. Specifically, for total fruit juice consumption, we reported that participants who consumed ≥1 s/d had lower WC and glucose levels compared to those consuming <1 s/month. This association was not observed for bottled juices. In this regard, other authors have suggested that natural fruit juice has not the same effect on health outcomes as sugar-sweetened beverages[114,250,251]. It has been hypothesized that the high fiber content, micronutrients, and bioactive components present in natural fruit juices might act synergistically to counteract the potentially harmful effect of simple sugars, reduce oxidative stress, inflammation, platelet aggregation, cholesterol levels, and improvement of the endothelial function at low-moderate fruit juice consumption doses[251–253]. However, as reported in other studies when the consumption is high this protective effect might not be enough and the risk of developing cardiometabolic risk factors would increase[111,113,254].

In *chapter 4*, we reported a positive association between total coffee consumption, caffeinated coffee consumption, and cognitive functioning in an elderly population at high cardiovascular risk. Caffeine, probably, is the most recognized molecule on coffee, and because of its structural similarity to adenosine and its potential effect on the central nervous system[90], is the molecule on coffee to which most properties are attributable. However, coffee has a complex nutrient matrix (polyphenols, diterpenes, melanoidins, trigonelline, etc.) that has been proposed to act synergically to produce benefits for the human body[255,256]. Our results for decaffeinated coffee consumption support this hypothesis. Previous studies have explored the acute effect of coffee and caffeine on mood, and cognition decline[257,258], however, in the long-term epidemiological evidence is scarce and remains unclear. One of the main reasons is that caffeine intake can develop tolerance[259], which difficult the study of its effects in the long term. However, in a recent longitudinal study (10.5 years of follow-up) conducted in cognitively average Australian elderly adults, it was observed that coffee consumption was associated with slower cognitive decline and slower cerebral Aβ-amyloid accumulation[260]. It has been proposed that the bioactive coffee compounds might attenuate β-amyloid peptide (Aβ) production (protection against amyloid toxicity), tau aggregation, and prevent neuronal damage, synaptotoxicity, and cognitive deficit[261]. In addition, they may contribute to reduce oxidative stress and neuroinflammation and increase the concentration of glutathione in plasma (glutathione brain levels decrease with aging, Parkinson's disease, and Alzheimer's disease)[262–265]. However, further studies should be conducted to establish a range of coffee consumption recommendations as J-shape associations have been reported for the risk of dementia and other health outcomes[78,266].

As significant associations have been previously described between large doses of caffeine intake and an increased risk of anxiety (especially in sensitive individuals)[78,267,268], in *chapter 5*, we explored the association between the usual intake of low-moderate caffeine doses and general anxiety in healthy adults. We reported that higher caffeine intake was positively associated with higher odds of general anxiety in women but not in men. Sex-specific associations between caffeine intake and odds for general anxiety might be attributable to certain factors such as differences in hormonal and neurotransmitter profiles, lifestyle habits use to cope with mental disorders and anxiety trigger agents[269,270]. In addition in our study population, mean caffeine was lower than the amount reported in previous studies in which caffeine intake was associated with anxiety[258], as an additional explanation for the non-significant results in men. Nonetheless, previous experimental studies have reported significant associations in men[271–273]. It should be considered that results from experimental studies mostly report the acute effects of caffeine intake in state anxiety but not in trait anxiety, which reflects a more habitual reaction to adverse events or stimulants[274]. The caffeine association with the odds of trait anxiety has been suggested to be mediated mainly via the antagonism of adenosine receptors. Other proposed, but less commonly accepted pathways (because of the requirement of high doses to occur), are the inhibition of phosphodiesterase, intracellular stores/calcium release, and the antagonism of benzodiazepine receptors[275].

The current advice is not to exceed the upper limit caffeine intake recommendation (400mg/d). However, as mentioned caffeine intake may develop tolerance, and also the presence of some bioactive compounds in coffee and tea might contribute to counteracting these symptoms[255,276]. In this regard, previous studies on mental health had associated coffee consumption and caffeine at moderate amounts with reduced risks of depression and suicide in diverse populations[78]. Besides the nature of the studied populations and study design, variation in cup sizes, coffee brew methods, caffeine sources, and consumption habits along populations could be the reason for discrepancies among studies. Finally, future studies should also address coffee/tea-sugar and coffee/tea non-caloric sweeteners interactions and their association with mental health, since sugar, commonly added to caffeine-containing beverages, has been linked to cognitive functioning, brain activity and mood in the short and long term[269,277].

In summary, the results presented from different analyses included in this Doctoral Thesis highlighted the role of beverages and fluids consumption on health, particularly its associations with cardiovascular risk factors and mental health. Our results suggest that not only to comply with the recommendations for water intake but also the source of water (or beverages) is important for health maintenance, as it has been observed for the different associations with body weight, cardiovascular risk factors, cognitive functioning, and energy intake. Health care professionals should encourage individuals to consume enough water as their body claims, recommend the avoidance of high calorie beverages, and specific fluid consumption recommendations should be given according to population health status. As drinking water was reported to be the most consumed beverage, and because of the observed associations it results strongly recommended its consumption as the healthiest option for health maintenance.

2. Strengths and limitations

The results from the present doctoral thesis should be interpreted with caution considering its strengths and limitations.

The first limitation is regarding sample nature. The present work was conducted with data from Mediterranean elderly individuals at high cardiovascular risk. Therefore, results can not be extrapolated to others and, consequently, further studies should be conducted in distinct populations to confirm the main findings. Second, all the studies included in the present investigation have an observational design which only allows to describe associations but not to establish causal inference. In the same line, despite we adjusted all the statistical models by several lifestyle factors, we can not discard that residual confounding factors (e.g. medication use, seasonality, etc) may still be present. Further, results from substitutions models are based on mathematical estimations, and therefore intervention trials should be driven to prove the observed effect. Fourth, the use of FFQs and fluid intake questionnaires to estimate dietary habitual intake, are susceptible to error measurement, mainly due to participants being unable to exactly report their consumption of foods during the preceded year or month. However, FFQ is the dietary data collection method most used in large epidemiological studies and has proven reliability for dietary intake assessment. Further, the fluid intake assessment questionnaire was previously validated in an elderly Spanish population using hydration and intake biomarkers which increase study reliability.

The main strengths that should be highlighted included: The relatively large sample size, statistical models adjusted for potential confounding factors, and the use of a specific validated fluid-intake questionnaire which allows us to assess the consumption of several types and subtypes of beverages often forgotten in dietary recalls or which are not included in FFQs.

VII. CONCLUSIONS

The main conclusion derived from the doctoral thesis driven in a cohort of elderly Mediterranean individuals at high cardiovascular risk is that the Mediterranean beverage consumption pattern is associated with a healthier lifestyle, higher compliance with the EFSA's recommendations for water intake, better prognosis in some cardiovascular risk factors and cognitive functioning.

Further, due to epidemiological evidence exploring the association between drinking water, some types of beverages, and cardiovascular risk factors in elderly individuals was limited, this thesis has contributed to increasing the scientific knowledge of the field.

The conclusions of the present dissertation are presented in accordance with the hypotheses raised previously in the present document.

Hypothesis 1: Mediterranean elderly individuals follow a healthy beverage consumption pattern which is associated with better compliance with the EFSA's recommendations for total water intake.

- A high percentage of elderly Mediterranean individuals at high cardiovascular risk meet the EFSA's recommendation for TWI.
- High compliance with TWI recommendations was inversely associated with age, and positively associated with being a woman, and a healthier lifestyle characterized by high adherence to the MedDiet and PA.

Hypothesis 2: Drinking water consumption is associated with weight loss and changes in adiposity in the long term in an elderly Mediterranean population.

- Drinking water was inversely associated with body weight and adiposity changes in the long term in an elderly Mediterranean cohort at high cardiovascular risk.

- The theoretical replacement of energy-containing beverages by drinking water was associated with lower weight gain.

Hypothesis 3: Natural fruit juice consumption rather than bottled juice is associated with lower values on cardiometabolic risk factors in a senior Mediterranean population with metabolic syndrome.

- Total and natural fruit juice consumption was associated with lower values on two cardiovascular risk factors: WC and glucose levels. No association was observed for bottled juice consumption.

Hypothesis 4: Coffee consumption is associated with better cognitive functioning in a senior Mediterranean population with metabolic syndrome.

- Total and caffeinated coffee consumption and total caffeine intake were associated with lower odds of poor cognitive functioning measured by a battery of neurophysiological tests in a Mediterranean cohort of elderly individuals with MetS.

Hypothesis 5: Higher mean daily caffeine intake is associated with higher odds of anxiety in a cohort drawn from the general population.

- In a large sample of adults recruited from the French general population, higher caffeine intake was positively associated with higher odds of general anxiety in women but not in men.

VIII. GLOBAL AND FUTURE INSIGHTS

This doctoral thesis adds new evidence to the current scientific literature regarding the nutritional epidemiology of certain beverages consumption and CVD. The findings from this work have exposed the relevance of beverages on health maintenance and may stimulate future research perspectives.

Future analyses should address the recognized limitations of the present work for clarifying and for a better understanding of the reported associations between beverage consumption and health or disease:

- Prospective studies are needed, both in the general and in specific populations, as in other geographical areas to confirm our results. This would help to compare findings across different studies and to translate the results to the general population in a clear, and easily understandable manner.
- Studies exploring the effect of factors as seasonability, weather, and time of consumption on fluid intake would allow the establishment of more specific recommendations.
- Future studies should include the use of biomarkers for a better assessment of hydration status and beverages consumption. In this regard, omics sciences, in particular metabolomics, can be helpful to identify biomarkers of beverages intake, its effects on metabolism, and give a better understanding of the pathways involved in the pathogenesis of cardiometabolic diseases.
- As associations could differ according to several factors including the genetic background, studies based on gene-diet interactions are also warranted.
- Finally, some nutrients present in beverages, as caffeine, fructose and-or polyphenols, have been suggested to alter microbiota (which changes in composition have been linked to several metabolic diseases). Therefore, exploring the effect of fluid intake-microbiota interactions and cardiometabolic risk factors would be of great

interest to describe other plausible mechanisms regarding the observed associations in the present doctoral thesis.

These new research lines will permit to evaluate the effect of several and new varieties of beverages on the cardiometabolic risk factors onset and to establish solid based-evidence dietary guidelines recommendations.

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X. APPENDICES

Scientific contributions

Publications derivate from the present work

Paz-Graniel I, Babio N, Serra-Majem L, Vioque J, Zomeño M, Corella D, Díaz-López A, Pintó X, Bueno-Cavanillas A, Tur J, Daimiel L, Martínez J, Becerra-Tomás N, Navarrete-Muñoz E, Schröder H, Fernández-Carrión R, Ortiz-Andrellucchi A, Corbella E, Riquelme-Gallego B, Gallardo-Alfaro L, Micó V, Zulet M, Barrubés L, Fitó M, Ruiz-Canela M, Salas-Salvadó J. *Fluid and total water intake in a senior mediterranean population at high cardiovascular risk: demographic and lifestyle determinants in the PREDIMED-Plus study*. Eur J Nutr. 2020 Jun;59(4):1595-1606. doi: 10.1007/s00394-019-02015-3. Epub 2019 Jun 1. PubMed Central PMID: 31154492

Paz-Graniel I, Becerra-Tomás N, Babio N, Serra-Majem L, Vioque J, Zomeño MD, Corella D, Pintó X, Bueno-Cavanillas A, Tur JA, Daimiel L, Zulet MA, Palau-Galindo A, Torres-Collado L, Schröder H, Gimenez-Alba IM, Nissenshon M, Galera A, Riquelme-Gallego B, Bouzas C, Micó V, Martínez JA, Canudas S, Castañer O, Vázquez-Ruiz Z, Salas-Salvadó J. *Baseline drinking water consumption and changes in body weight and waist circumference at 2-years of follow-up in a senior Mediterranean population.* Clin Nutr. 2021 May 23;40(6):3982-3991. doi: 10.1016/j.clnu.2021.05.014. PubMed Central PMID: 34139471.

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Paz-Graniel, I, Babio, N, Mendez, I, Salas-Salvadó, J. *Association between Eating Speed and Classical Cardiovascular Risk Factors: A Cross-Sectional Study*. Nutrients. 2019 Jan 4,11(1):83. doi: 10.3390/nu11010083. PubMed Central PMID: 30621124

Participation in national and international conferences

Conference: 14th. Congress on Nutrition. Food, Nutrition and Health: A place where science meets practice. Belgrade, Serbia. 11th – 13th November 2021.

Authors: Paz-Graniel I, Kose J, Babio N, Hercberg S, Galan P, Touvier M, Salas-Salvadó, Andreeva VA.

Title: *Caffeine intake and its association with high trait anxiety: cross-sectional analysis among general-population French adults*

Format: Speaker

Conference: 14th. Congress on Nutrition. Food, Nutrition and Health: A place where science meets practice. Belgrade, Serbia. 11th – 13th November 2021.

Authors: Figueiredo N, Kose J, Srour B, Julia C, Kesse-Guyot E, Péneau S, Allès B, **Paz-Graniel I**, Chazelas E, Deschasaux-Tanguy M, Debras C, Hercberg S, Galán P, Monterios CA., Touvier M, Andreeva VA.

Title: *Ultra-processed food intake and eating disorders: cross-sectional associations among French adults.*

Format: Oral presentation

Conference: 51 Congreso Nacional de la S.E.N. 15 – 18 October 2021

Authors: Ruiz-García V, Díaz-López A, **Paz-Graniel I**, Toledo E, Becerra-Tomás N, Corella D, Castañer O, Martínez JA, Alonso-Gómez A, Salas-Salvadó J.

Title: *Asociación entre el consumo de bebidas cafeinadas y el deterioro de la función renal en una población mediterránea mayor con síndrome metabólico.*

Format: Oral presentation

Conference: 38th. International Symposium on Diabetes and Nutrition. Virtual Event 21 – 24 June 2021.

Authors: **Paz-Graniel I**, Becerra-Tomás N, Babio N, Serra-Majem L, Vioque J, Zomeño MD, Corella D, Pintó X, Bueno-Cavanillas A, Tur JA, Daimiel L, Zulet MA, Salas-Salvadó J.

Title: *Drinking water consumption and 2-year changes in body weight in a senior Mediterranean population*

Format: e-Poster

Conference: 38th. International Symposium on Diabetes and Nutrition. Virtual Event 21 – 24 June 2021.

Authors: García-Gavilán JF, **Paz-Graniel I**, Babio N, Romaguera D, Martínez JF, Martin V, Martinez MA, Konieczna J, Ruiz-Canela M, de Paz-Fernandez JA, Goday A, Martinez-Gonzalez MA, Bullo M, Salas-Salvadó J.

Title: *Inflammatory potential of diet and bone mineral density in a senior Mediterranean population: a cross-sectional analysis in the PREDIMED-Plus*

Format: e-Poster

Conference: 38th. International Symposium on Diabetes and Nutrition. Virtual Event 21 – 24 June 2021.

Authors: Díaz-López A, **Paz-Graniel I**, Ruiz V, Toledo E, Becerra-Tomás N, Corella D, Castañer O, Martínez JA, Alonso-Gómez AM, Wärnberg J, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinahones FJ, Lapetra J, Serra-Majem L, Bueno-Cavanillas A, Tur JA, Martín Sánchez V, Pintó X, Delgado-Rodríguez M, Matía-Martín P, Vidal J, Vázquez C, Daimiel L, Fernandez-Villa T, Ros E, Eguaras S, Babio N, Sorlí JV, Goday A, Abete I, Tojal-Sierra L, Barón-López FJ, Torres-Collado L, Morey M, García-Rios A, Casas R, Bernal-López

MR, Santos-Lozano JM, Navarro A, Gonzalez JI, Zomeño MD, Zulet MA, Vaquero-Luna J, Raul Ramallal, Montse Fitó, Salas-Salvadó J.

Title: *Consumption of caffeinated beverages and kidney function decline in an elderly Mediterranean population with metabolic syndrome*

Format: e-Poster

Conference: 38th. International Symposium on Diabetes and Nutrition. Virtual Event 21 – 24 June 2021.

Authors: Garcidueñas-Fimbres TE, **Paz-Graniel I**, Nishi SK, Salas-Salvadó J, Babio N

Title: *Eating speed, eating frequency and their relationships with diet quality, adiposity and metabolic syndrome or its components*

Format: e-Poster

Conference: Simposio Anual CIBERobn "Obesity and nutrition in the 21st Century". Madrid Spain. October 26th- 29th, 2020.

Authors: Díaz-López A, **Paz-Graniel I**, Becerra-Tomás N, Martínez-González M.A., Babio N, Corella D, Fitó M, Martínez JA, Alonso-Gómez AM, Wärnberg J, Vioque J, Romaguera D, López-Miranda J, Estruch R, Tinahones FJ, Lapetra J, Serra-Majem L, Bueno-Cavanillas A, Tur JA, Martín-Sánchez V, Pintó X, Delgado-Rodríguez M, Matía-Martín P, Vidal J, Vázquez C, Daimiel L, Ros E, Hernández-Alonso P, Salas-Salvadó J

Title: *Caffeinated beverages consumption and kidney function decline in an elderly Mediterranean population with metabolic syndrome*

Format: Poster

Conference: FENS 2019 - 13th European Nutrition Conference. Malnutrition in an obese world: European Perspectives. Dublin, Ireland. October 15th-18th,2019.

Authors: Paz-Graniel I, Babio N, Salas-Salvadò J, Díaz-López A, Becerra-Tomas N, Vioque J, Fitó M, Corella D, Serra-Majem L, Pintó X, Bueno-Canavillas A, Tur JA, Daimiel L, Martínez JA, Ruiz-Canela M.

Title: *Fluid and total water intake: Demographic and lifestyle determinants in the PREDIMED-PLUS study.*

Format: Poster

Conference: FENS 2019 - 13th European Nutrition Conference. Malnutrition in an obese world: European Perspectives. Dublin, Ireland. October 17th, 2019.

Authors: Paz Graniel I

Title: *Association between eating speed and classical cardiovascular risk factors: A cross-sectional study.*

Format: Speaker

Conference: FENS 2019 - 13th European Nutrition Conference. Malnutrition in an obese world: European Perspectives. Dublin, Ireland. October 15th-18th, 2019.

Authors: Paz Graniel I, Babio N, Mendez I, Salas-Salvadó J.

Title: *Association between eating speed and classical cardiovascular risk factors: A cross-sectional study.*

Format: Poster

Conference: Genetics of complex diseases. Reus, Spain. May 10th, 2019.

Authors: Paz Graniel I

Title: *Fluid and Total Water Intake in a senior Mediterranean Population at high cardiovascular risk: Demographic and lifestyle determinants in the PREDIMED-PLUS study.*

Format: Speaker

Mobility

Length: 3 months (April – July 2021)

Institution: Nutritional Epidemiology Research Group (EREN) at Sorbonne Paris Nord University (Bobigny, France).

Supervisor: Prof. Valentina A. Andreeva

Objective: To collaborate in an ongoing research project dealing with the link between caffeine intake and anxiety status in the framework of the general population-based NutriNet-Santé cohort.

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