International PhD Thesis

LIFESTYLE AND PHYSICAL-MENTAL HEALTH: THE ASSOCIATIONS OF DIET AND PHYSICAL ACTIVITY WITH FITNESS AND DEPRESSION

DOCTORADO EN INVESTIGACIÓN SOCIOSANITARIA Y DE LA ACTIVIDAD FÍSICA
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CERTIFY:

That the International PhD thesis entitled: "*Lifestyle and physical-mental health: the associations of diet and physical activity with fitness and depression*" presented by Bruno Bizzozero Peroni has been carried out under our direction, being an expression of the technical and interpretative capacity of its author in conditions that he deserves the title of Doctor with International Mention, provided by the committee if it considered so.

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Arthur Eumann Mesas
Cuenca, 24 October 2023

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Oscar W. Tabárez once said, “the road is the reward”. Surely many aspects are intangible, but this thesis is an illustration of that statement, a path of numerous academic and personal learnings. And this road is never traveled alone. I thank:

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RESEARCH PROJECTS

This doctoral thesis has been conducted in the context of the Health and Social Research Center (University of Castilla-La Mancha, Spain), an independent knowledge center for research on lifestyle behaviors and health. This thesis is a compendium of publications based on the synthesis of available evidence and the analysis of empirical evidence. The work described in this doctoral dissertation was carried out, in part, within the framework of the following research projects:

- **Lifestyle, adiposity, and vascular function in university students in Castilla-La Mancha, Spain –Manuscript III**–. This research was funded by a grant from the European Regional Development Fund (DOCM 26/02/20).

- **Nuts4Brain Project: The relationship between nut consumption and mental health outcomes throughout adulthood –Manuscript VII**–. Under grant number PI21/01898, this project was funded by the Ministry of Science and Innovation of Spain, the European Union NextGenerationEU program, the Carlos III Health Institute of Spain, and the European Regional Development Fund.

In addition, the Health and Social Research Center collaborated with a project led by the Department of Preventive Medicine and Public Health (Faculty of Medicine, Autonomous University of Madrid) and the Consortium for Biomedical Research Network in Epidemiology and Public Health (Madrid, Spain):

- **The Study on Nutrition and Cardiovascular Risk in Spain (*Estudio de Nutrición y Riesgo cardiovascular en España* [ENRICA]) –Manuscript IV**–. This research was funded by the Carlos III Health Institute of Spain (FIS grants 19/319 and 19/665, State Secretary of R+D+I and FEDER/FSE), the REACT EU Program, the Community of Madrid, and the European Regional Development Fund (FACINGLCOVID-CM project and CB16/10/00477).

“What we know is a drop of water, what we ignore is the ocean.”
“Lo que conocemos es una gota de agua, lo que ignoramos es el océano.”

Isaac Newton

“Life shrinks and expands in proportion to one’s courage.”
“La vida se encoge y se expande en proporción al coraje de cada uno.”

Anaïs Nin Culmell

ABBREVIATIONS AND ACRONYMS

BDNF	Brain-derived neurotrophic factor
CRF	Cardiorespiratory fitness
DALY	Disability-adjusted life year
DII	Dietary Inflammatory Index
DSM	Diagnostic and Statistical Manual of Mental Disorders
HPA	Hypothalamic–pituitary–adrenal
ICD	International Classification of Diseases
MD	Mediterranean diet
MF	Motor fitness
MSF	Musculoskeletal fitness
NCD	Noncommunicable disease
PA	Physical activity
PF	Physical fitness
USA	United States of America
VO_2max	Maximum oxygen consumption
WHO	World Health Organization

These abbreviations and acronyms were used specifically in the introduction of this doctoral thesis. Additional abbreviations can be found in each of the manuscripts comprising this dissertation. In other sections of the thesis (i.e., presentation, methods, aims, conclusions, future research lines, appendix, and other scientific contributions), abbreviations have been avoided to enhance readability.

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PRESENTATION

Physical and mental health are integrated components of a person's overall well-being. A balanced diet and regular physical activity are crucial components of a healthy lifestyle and have a significant impact on maintaining and improving human health. However, these health benefits are being offset by global shifts toward unhealthy diets and insufficient levels of physical activity that have occurred in recent decades. Lifestyle changes have not only amplified the incidence of obesity, noncommunicable diseases, and premature mortality but also contributed to environmental degradation. These trends have been influenced by several factors, including rapid urbanization, sedentary occupations, modern transportation systems, availability of fast food and ultra-processed food, and insufficient access to nutritious foods.

The global increase in the adoption of unhealthy eating habits (i.e., diets rich in ultra-processed foods, which are abundant in fats, added sugars, sodium, and various chemical additives) and sedentary behaviors has generated a large-scale global challenge that disrupts energy balance, movement patterns, and accessibility to natural foods and important sources of healthy nutrients throughout human history, such as fruits, nuts, vegetables, and whole grains. These modern lifestyle structures may play a key role in the activation of the innate immune system that releases proinflammatory cytokines and prooxidant activities. This, in turn, fosters various unfavorable alterations, negatively impacting both physical well-being and mental health.

For some years, the decline in physical fitness and the increase in the prevalence of depressive disorders have represented growing public health problems worldwide. Low levels of physical fitness are indicative of poorer health prognosis, such as an increased risk of premature death. Likewise, depression can have a significant impact on an individual's overall well-being, being associated with impairment of physical and psychosocial functioning and reduced quality of life. Although depression can be prevented and treated through modifiable risk factors and advances in therapy, 280 million people were affected by depression in 2019 according to estimates from the University of Washington's Institute for Health Metrics and Evaluation, and it continues to cause a significant burden of disability across the lifespan. Therefore, despite significant advances along the spectrum of prevention and treatment of depression, these are proving to be insufficient.

In this context, one of the most important public health challenges in industrialized countries is to identify affordable strategies to promote an active and healthy life and aging. Physical and mental health are influenced by a network of biological, genetic, psychosocial, behavioral, and environmental factors. In recent years, lifestyle-related behaviors, such as diet and physical activity, have received special attention as feasible daily living strategies to promote physical fitness and prevent depression. However, while there are data linking healthy dietary patterns to improved physical wellbeing, the impact of specific exposure variables, such as adherence to the Mediterranean diet, on adult physical fitness remains inconclusive. Furthermore, the relationships between lifestyle factors, such as nut consumption or daily step counts, and mental health is a recent topic in scientific research. It is vital to strengthen the evidence base to advance scientific understanding and offer clinical guidance.

Therefore, despite the potential benefits of diet and physical activity on physical fitness and depression during adulthood, to date, there is limited scientific evidence to answer the following questions: Is the Mediterranean diet associated with better physical fitness? What individual components of the Mediterranean diet are related to physical fitness? Is there variability in the relationship between meat consumption and muscle strength according to the type of meat ingested? Is a proinflammatory dietary pattern associated with an increased risk of depression? Does the available evidence substantiate an association between increased nut consumption and a reduced occurrence of depression? Is this relationship influenced by other lifestyle behaviors, such as physical activity? Are Mediterranean diet-based interventions effective in reducing depressive symptoms in people with depression? Does the number of daily steps influence depressive symptoms?

This doctoral thesis is framed by answering these questions and has the following main objectives:

- To synthesize the available evidence regarding the associations of adherence to the Mediterranean diet and its specific foods with physical fitness levels, including each of its components (cardiorespiratory, motor, and musculoskeletal), in adulthood.
- To analyze the associations between the consumption of different types of meat and muscle strength in young adults and to determine whether these relationships are mediated by total protein intake and lean mass.
- To examine the association between a proinflammatory dietary pattern and the risk of depression in community-dwelling older adults.
- To synthesize the available evidence about the effects of Mediterranean diet interventions on the severity of depressive symptoms in adults with depression or mild to severe depressive symptoms.
- To estimate the associations between nut consumption and the incidence of depression in middle-aged and older adults and to determine whether these relationships are affected by other risk factors for depression related to lifestyle behaviors and health status.
- To synthesize the associations between objectively measured daily steps and both depression and depressive symptoms from observational studies in the general adult population.

This thesis incorporates different methodological approaches that cover all adult age groups, drawing upon both systematic reviews and analysis of original data as essential elements to address the underlying research questions and gain a comprehensive understanding of the proposed associations. The doctoral dissertation elaborates the above research questions and objectives and is divided into two sections:

PART I – DIET AND PHYSICAL FITNESS

Chapter 1 provides a concise overview of the importance of physical fitness for adult health and the potential role of the Mediterranean dietary pattern, along with its major parameters and components, in physical fitness. **Manuscripts I**, **II**, and **III** present the results of these associations, including a systematic review and meta-analysis (with its protocol) of observational studies and randomized controlled trials in adults of all ages and a cross-sectional study conducted in Castilla-La Mancha (Spain) with young adults.

PART II – DIET, PHYSICAL ACTIVITY AND DEPRESSION

Chapter 2 contains an introductory description of the definition, pathophysiology, and prevalence of depression. In addition, some important points about the potential role of dietary patterns (i.e., Dietary Inflammatory Index and Mediterranean diet) and food groups (i.e., nuts) in the prevention and treatment of depression are presented. **Manuscripts IV**, **V**, **VI**, and **VII** present the corresponding results. They comprise a systematic review and meta-analysis (with its protocol) of randomized controlled trials, and two prospective cohort studies including national (Spain) and regional (Madrid, Spain) representative samples of older adults, and a large sample of middle-aged and older adults from the United Kingdom.

Finally, **Chapter 3** focuses on the association between physical activity and depression. **Manuscript VIII** presents a systematic review with meta-analysis of observational studies in the general adult population. It provides results and conclusions on the cross-sectional and prospective relationships of the number of daily steps with depression and depressive symptoms.

As a result of this thesis, we can state the following conclusions:

- High adherence to the Mediterranean diet is associated with higher physical fitness levels in adults of all ages.
- A higher consumption of white and fish meat contributes in the same way as red meat to higher muscle strength through the mediation of total protein intake and lean mass percentage in young adults.

- A proinflammatory dietary pattern is associated with increased risk of depression in community-dwelling older adults compared to an anti-inflammatory diet.
- Mediterranean diet-based interventions can be effective in reducing depressive symptoms among young and middle-aged adults with major depression or mild to moderate depressive symptoms.
- Low to moderate daily consumption of nuts is associated with a lower risk of depression in middle-aged and older adults compared to no nut consumption.
- A greater number of daily steps could help reduce both depression and depressive symptoms in the general adult population.

This doctoral thesis was designed by Bruno Bizzozero Peroni, with Arthur Eumann Mesas and Estela Jiménez López as directors. To carry out this thesis, Bruno Bizzozero Peroni has obtained a study leave from his position of professor at the Higher Institute of Physical Education (University of the Republic, Uruguay) and the support of the National Agency for Research and Innovation of Uruguay (POS_EXT_2023_1_175630) and the University of Castilla-La Mancha (2020-PREDUCLM-16746). Furthermore, he became a member of the Health and Social Research Center and the Nutrition, Lifestyle and Mental Health (Nutri&Mental) Research Group, both situated in Cuenca, Spain. Throughout the doctoral thesis, Bruno Bizzozero Peroni undertook a three-month stay at the Research Group in Human Performance Analysis in Rivera, Uruguay.

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PRESENTACIÓN

La salud física y mental son componentes integrados del bienestar general de una persona. Una dieta equilibrada y la actividad física regular son componentes cruciales de un estilo de vida saludable y tienen un impacto significativo en el mantenimiento y la mejora de la salud humana. Sin embargo, estos beneficios para la salud se están viendo contrarrestados por los cambios globales hacia dietas poco saludables y niveles insuficientes de actividad física que se han producido en las últimas décadas. Los cambios en el estilo de vida no sólo amplifican la incidencia de la obesidad, las enfermedades no transmisibles y la mortalidad prematura, sino que también contribuyen a la degradación del medio ambiente. En estas tendencias influyen varios factores, como la rápida urbanización, las ocupaciones sedentarias, los sistemas de transporte modernos, la disponibilidad de comida rápida y ultra procesada, y el acceso insuficiente a alimentos nutritivos.

El aumento mundial de la adopción de hábitos alimentarios poco saludables (es decir, dietas ricas en alimentos ultra procesados, abundantes en grasas, azúcares añadidos, sodio y diversos aditivos químicos) y de comportamientos sedentarios ha generado un desafío global a gran escala que altera el equilibrio energético, los patrones de movimiento y la accesibilidad a alimentos naturales y fuentes importantes de nutrientes saludables a lo largo de la historia de la humanidad, como frutas, frutos secos, verduras y cereales integrales. Estas estructuras de estilo de vida moderno pueden desempeñar un papel clave en la activación del sistema inmunitario innato que libera citoquinas proinflamatorias y actividades prooxidantes. Esto, a su vez, fomenta diversas alteraciones desfavorables, que repercuten negativamente tanto en el bienestar físico como en la salud mental.

Desde hace algunos años, el declive de la condición física y el aumento de la prevalencia de los trastornos depresivos representan un creciente problema de salud pública en todo el mundo. Los bajos niveles de condición física son indicativos de un peor pronóstico sanitario, como un mayor riesgo de muerte prematura. Del mismo modo, la depresión puede tener un impacto significativo en el bienestar general de un individuo, ya que se asocia a un deterioro del funcionamiento físico y psicosocial y a una reducción de la calidad de vida. Aunque la depresión puede prevenirse y tratarse a través de factores de riesgo modificables y avances en la terapia, 280 millones de personas se vieron afectadas por la depresión en 2019 según estimaciones del Instituto de Métricas y Evaluación de la Salud de la Universidad de Washington, y continúa causando una carga significativa de discapacidad a lo largo de la vida. Por lo tanto, a pesar de los avances significativos a lo largo del espectro de la prevención y el tratamiento de la depresión, estos están demostrando ser insuficientes.

En este contexto, uno de los retos de salud pública más importantes en los países industrializados es identificar estrategias asequibles para promover una vida adulta y un envejecimiento activos y saludables. La salud física y mental están influidas por una red de factores biológicos, genéticos, psicosociales, conductuales y ambientales. En los últimos años, los comportamientos relacionados con el estilo de vida, como la dieta y la actividad física, han recibido una atención especial como estrategias factibles de la vida diaria para promover la condición física y prevenir la depresión. Sin embargo, aunque existen datos que relacionan los patrones dietéticos saludables con la mejora del bienestar físico, el impacto de variables de exposición específicas, como la adherencia a la dieta Mediterránea, sobre la condición física de los adultos sigue sin ser concluyente. Además, las relaciones entre los factores del estilo de vida, como el consumo de frutos secos o el recuento de pasos diarios, y la salud mental es un tema reciente en la investigación científica. Es vital reforzar la base de evidencias para avanzar en la comprensión científica y ofrecer orientación clínica.

Por lo tanto, a pesar de los conocidos beneficios potenciales de la dieta y la actividad física sobre la condición física y la depresión durante la edad adulta, hasta la fecha, la evidencia científica para responder a las siguientes preguntas es limitada: ¿Se asocia la dieta Mediterránea con una mejor condición física? ¿Qué componentes individuales de la dieta Mediterránea están relacionado con la condición física? ¿Existe variabilidad en la relación entre el consumo de carne y la fuerza muscular según el tipo de carne ingerida? ¿Se asocia un patrón dietético proinflamatorio con un mayor riesgo de depresión? ¿Confirma la evidencia disponible una asociación positiva entre el consumo de frutos secos y una menor incidencia de depresión? ¿Influyen en esta relación otros comportamientos relacionados con el estilo de vida, como la actividad física? ¿Son eficaces las intervenciones basadas en la dieta Mediterránea para reducir los síntomas depresivos en personas con depresión? ¿Influye el número de pasos diarios en los síntomas depresivos?

Esta tesis doctoral se enmarca en la respuesta a estas preguntas y tiene los siguientes objetivos principales:

- Sintetizar la evidencia disponible sobre las asociaciones de la adherencia a la dieta Mediterránea y sus alimentos específicos con los niveles de condición física, incluyendo cada uno de sus componentes (cardiorrespiratorio, motor y musculoesquelético), en la edad adulta.
- Analizar las asociaciones entre el consumo de diferentes tipos de carne y la fuerza muscular en adultos jóvenes y determinar si estas relaciones están mediadas por la ingesta total de proteínas y la masa magra.
- Examinar la asociación entre un patrón dietético proinflamatorio y el riesgo de depresión en adultos mayores que viven en la comunidad.
- Sintetizar la evidencia disponible sobre los efectos de las intervenciones con dieta Mediterránea en la gravedad de los síntomas depresivos en adultos con depresión.

- Estimar las asociaciones entre el consumo de frutos secos y la incidencia de depresión en adultos de mediana y avanzada edad y determinar si estas relaciones se ven afectadas por otros factores de riesgo de depresión relacionados con los comportamientos del estilo de vida y el estado de salud.
- Sintetizar la evidencia disponible sobre las asociaciones entre los pasos diarios medidos objetivamente y tanto la depresión como los síntomas depresivos a partir de estudios observacionales en la población adulta general.

Esta tesis incorpora diferentes enfoques metodológicos que abarcan todos los grupos de edad adultas, recurriendo a revisiones sistemáticas como al análisis de datos originales como elementos esenciales para abordar las preguntas de investigación subyacentes y obtener una comprensión exhaustiva de las asociaciones propuestas. La disertación doctoral elabora las preguntas y objetivos de investigación mencionados y se divide en dos secciones:

PARTE I – DIETA Y CONDICIÓN FÍSICA

El **Capítulo 1** ofrece una visión general concisa de la importancia de la condición física para la salud de los adultos y del papel potencial del patrón dietético Mediterráneo, junto con sus principales parámetros y componentes, en la condición física. Los **Manuscritos I**, **II** y **III** presentan los resultados de estas asociaciones, incluyendo una revisión sistemática y metaanálisis (con su protocolo) de estudios observacionales y ensayos controlados aleatorizados en adultos de todas las edades, y un estudio transversal realizado en Castilla-La Mancha (España) con adultos jóvenes.

PARTE II – DIETA, ACTIVIDAD FÍSICA Y DEPRESIÓN

El **Capítulo 2** contiene una descripción introductoria de la definición, fisiopatología y prevalencia de la depresión. Además, se presentan algunos puntos importantes sobre el papel potencial de los patrones dietéticos (es decir, la dieta Mediterránea y el Índice Dietético Inflamatorio) y los grupos de alimentos (es decir, los frutos secos) en la prevención y el tratamiento de la depresión. Los **Manuscritos IV**, **V**, **VI** y **VII** presentan los resultados correspondientes. Comprenden una revisión sistemática y metaanálisis (con su protocolo) de ensayos controlados aleatorizados, y dos estudios prospectivos de cohortes que incluyen muestras representativas nacionales (España) y regionales (Madrid, España) de adultos mayores, y una amplia muestra de adultos de mediana edad y mayores del Reino Unido. Por último, el **Capítulo 3** se centra en la asociación entre la actividad física y la depresión. El **Manuscrito VIII**, una revisión sistemática con metaanálisis de estudios observacionales en la población adulta general, proporciona resultados y conclusiones equivalentes a las relaciones transversales y prospectivas del número de pasos diarios con la depresión y los síntomas depresivos.

Como resultado de esta tesis, podemos afirmar las siguientes conclusiones:

- Una alta adherencia a la dieta Mediterránea se asocia con mayores niveles de condición física en adultos de todas las edades.
- Un mayor consumo de carne blanca y de pescado contribuye de la misma manera que la carne roja a una mayor fuerza muscular a través de la mediación de la ingesta total de proteínas y el porcentaje de masa magra en adultos jóvenes.
- Un patrón dietético proinflamatorio se asocia con un mayor riesgo de depresión en adultos mayores que viven en la comunidad en comparación con una dieta antiinflamatoria.
- Las intervenciones basadas en la dieta Mediterránea pueden ser eficaces para reducir los síntomas depresivos entre los adultos jóvenes y de mediana edad con depresión mayor o síntomas depresivos de leves a moderados.
- El consumo diario de frutos secos de bajo a moderado se asocia con un menor riesgo de depresión en adultos de mediana edad y mayores en comparación con el no consumo de frutos secos.
- Un mayor número de pasos diarios podría ayudar a reducir tanto la depresión como los síntomas depresivos en la población adulta general.

Esta tesis doctoral ha sido diseñada por Bruno Bizzozero Peroni, con Arthur Eumann Mesas y Estela Jiménez López como directores. Para la realización de esta tesis, Bruno Bizzozero Peroni ha obtenido una licencia por estudios de su cargo de profesor del Instituto Superior de Educación Física (Universidad de la República, Uruguay) y el apoyo de la Agencia Nacional de Investigación e Innovación de Uruguay (POS_EXT_2023_1_175630) y de la Universidad de Castilla-La Mancha (2020-PREDUCLM-16746). Además, fue miembro del Centro de Investigación Sanitaria y Social y del Grupo de Investigación en Nutrición, Estilo de Vida y Salud Mental (Nutri&Mental), ambos situados en Cuenca, España. A lo largo de la tesis doctoral, Bruno Bizzozero Peroni realizó una estancia de tres meses en el Grupo de Investigación en Análisis del Rendimiento Humano en Rivera, Uruguay.

3

INTRODUCTION

GENERAL INTRODUCTION

Diet and physical activity (PA) play crucial roles in either promoting or compromising health. Humanity has known this for a long time. Although the first large-scale epidemiological studies analyzing the influence of diet and PA on the subsequent development of chronic pathologies (particularly cardiovascular disease) were conducted in the 1950s, interest in these lifestyle factors and their associations with health has been explicit throughout the history of civilizations. Hippocrates (ca. 460-370 BC), considered the father of 'Western medicine', wrote: "food and exercise, while possessing opposite qualities, yet work together to produce health" (1). Identifying his patients' illness as an imbalance of the four humors (black bile, yellow bile, phlegm, and blood), Hippocrates was a pioneering physician who advocated for dietary advice and recommended exercise as essential lifestyle factors to restore equilibrium (2).

This qualitative perception persisted for centuries but was subsequently abandoned in parallel with the paradigm shift in medical thinking (i.e., health is defined as the absence of disease) between the 16th and 19th centuries (3). Concurrently with this transition, public health developed and began to play a key role in disease prevention and treatment (4). Since the 20th century, the concept of health has once more integrated physical, mental, and social components. The World Health Organization's (WHO) establishment in 1948 makes this clear when it states that "health is a state of complete physical, mental, and social wellbeing and not merely the absence of disease or infirmity" (5). Subsequently, health approaches evolved to assess not only mortality and diseases but also health and wellbeing. In this context, the WHO International Classification of Functioning, Disability and Health, which was developed in 2001, delineated six domains encompassing a multidimensional perspective of health. These include health conditions, body functioning, activities in daily life, social participation, and environmental and personal factors (6). In addition, novel definitions of health propose that risk-free well-being is impossible and suggest a dynamic concept of health based on the ability to adapt to one's environment and self-manage emotional, physical, and social challenges (7).

Since biomedical definitions are continually subject to integration and updating, based on the achievements of science and bioethics, the captivating exploration of the concepts of health and disease remains ongoing (8). Currently, health promotion is a relevant concept. It is determined by a complex interplay of factors internal and external to health systems, involving socioeconomic conditions, demographic patterns, family relationships, or cultural and social environment (9). This holistic approach to health goes beyond traditional curative care and involves the personal, community, societal, and political levels to facilitate adaptations (e.g., of lifestyle or environmental conditions) that lead to wellbeing in changing scenarios. In this context, the role of diet quality and PA in promoting a healthy physical-mental state and reducing the development and progression of chronic diseases is becoming increasingly important from scientific and public health perspectives. Epidemiological studies have shown that lifestyle behaviors are relevant factors involved in the etiology of several chronic diseases (10). Currently, the influence of diet and PA on the health of populations are important areas of research and growing areas of health policy, expected to persist as such in the future (11).

The present doctoral thesis analyses the synergistic interactions between lifestyle-related behaviors, such as diet and PA, and both the enhancement of physical functioning and the prevention and treatment of depression. In the proposed study associations, the influence of environmental and individual factors, health conditions, and social support were considered. The approach "the whole is more than the sum of the parts" has served as a pillar for this doctoral dissertation, with the understanding that the study associations are based on the holistic perception of systems (4). In this sense, when examining lifestyle behaviors and their relationship to any health outcome, the influence of other factors must be considered, such as genetic or environmental characteristics, and a wide range of covariates that could act as mediators or confounders of exposure-outcome associations. In other words, to better understand any health phenomena, the question should not solely address whether a variable *X* affects a variable *Y* but should also delve on the mechanisms by which *X* exerts its effect on *Y* (e.g., underlying psychosocial, cognitive, or biological processes). Additionally, it should explore the timing of *X's* impact on *Y* (e.g., under what circumstances or for which population) (12). Therefore, when drawing conclusions from experimental or observational research in the field of lifestyle behaviors and their impact on physical and mental health, it is crucial to interpret the data with caution. As Hayes pointed out, we should acknowledge that we never fully elucidate an association (12).

It is well known that both males and females of all ages benefit from healthy diets and regular PA, which reduces the risk of premature mortality, cardiovascular disease, certain types of cancer, and diabetes (13,14). Dietary patterns and PA can also improve musculoskeletal and mental health (13,14). However, these health benefits can be offset by global shifts to dietary risk factors such as diets high in calories, sodium, trans fats, and ultra-processed foods (15). In the 21st century, easily accessible and affordable calories are plentiful, while PA and movement have nearly been eradicated from our daily work and leisure activities (16). Individuals need to manage two conflicting metabolic impulses: acquiring energy (from food) and expending energy. However, in the current Westernized lifestyle, there is a great imbalance between the energy obtained from food intake and the energy expended in PA. In this sense, global estimates show an alarming disparity that is reflected in the excessive consumption of ultra-processed high-energy foods and reduced levels of PA, which has been associated with numerous noncommunicable diseases (NCDs) (17). For this reason, the WHO recognizes that unhealthy diets and physical inactivity stand as two of the leading global risk factors contributing to physical and mental morbidity, as well as premature mortality (18).

In this framework, navigating within the complex and dynamic fields of nutrition and PA research can be overwhelming for clinicians, policy makers, and researchers (19). Continued analysis of diet and PA is essential to advance our understanding of the relationship between these lifestyle behaviors and health. Evolving knowledge helps to refine recommendations, adapt to changing health challenges, and better address complex interactions. Specifically, some of the study associations proposed in this doctoral dissertation are limited in the current state of nutritional and PA scientific evidence. It is reasonable to consider this fact since both disciplines consolidated their research fields at the end of the 20th century. Therefore, many knowledge gaps and important challenges remain to be unraveled. For example, the associations between lifestyle-related behaviors and mental health are particularly novel to science. From the standpoint of nutrition and PA research, the challenge lies in providing high-quality scientific evidence that aligns with the development of feasible and affordable public health strategies. This includes developing lifestyle interventions based on sustainable food and PA systems to enhance the health status of a growing global population (20,21).

PART I

DIET AND PHYSICAL FITNESS

CHAPTER 1: DIETARY PATTERNS AND PHYSICAL FITNESS

Physical fitness: definitions and components

Physical fitness (PF) refers to the ability to perform daily activities in a highly functional state, as well as capabilities that are associated with a low risk of developing chronic diseases and premature death (22). The set of attributes to perform daily tasks safely and independently requires different physical components, such as aerobic capacity, coordination, or muscular strength, which collectively comprise PF. Specifically, cardiorespiratory fitness (CRF), motor fitness (MF), and musculoskeletal fitness (MSF) are the core components of PF (23). The understanding of these indicators, based on each set of physical attributes, can facilitate the development of practical and public health recommendations (24).

PF and its different components are independent markers of health at all adult ages (24). The CRF represents the integrated capacity of the cardiovascular and respiratory systems to supply oxygen to the mitochondria to perform physical work (25). It therefore quantifies the functional capacity of an individual and interrelates a chain of processes, including pulmonary ventilation and diffusion, ventricular function, ventricular-arterial coupling, the ability of the vascular system to deliver oxygen needs, and the ability of muscle cells to utilize oxygen and nutrients supplied by the blood (26). MF characterizes any physical component that enables an individual to successfully perform a particular motor task (27). Specific MF skills include agility, balance, coordination, reaction time, and speed (25). Finally, MSF implies muscle capabilities related to flexibility (i.e., ability of muscles to move freely through a full range of motion) and muscle strength (i.e., ability of muscles to generate force to withstand repeated contraction over time, to sustain a maximal voluntary contraction for a prolonged period, or to perform a maximal or dynamic contraction in a short period of time) (25).

PF can be measured by field or laboratory methods. Laboratory tests directly measure the function of physiological systems for moderate- to high-intensity exercise related to each component of PF (28). In addition, certain field-based tests of PF are simple, feasible, reliable, and valid alternatives (28), as they provide submaximal measures that assess the integrated responses of physiological systems needed to perform specific exercises under standardized conditions (29). From clinical and research perspectives, field-based tests have become increasingly important as easily applied methods to assess PF (30). Among them, different tests have been identified as valid and reliable for evaluating PF in adults, such as the 20-meter shuttle run test for CRF, the timed up-and-go test for MF, or the handgrip test for MSF (28,31).

The evolution of physical fitness as a health concept

PF is a critical determinant of health throughout adulthood (32). However, its assessment has not always been associated with health status. The measurement of PF has a long history dating back to Adolphe Quételet in the 1830s. The development and decline of body strength throughout life has emerged as a topic of scientific interest since Quetelet's pioneering study in which measurements of handgrip strength were recorded in Belgian children and adults (33). From the early 20th century, PF testing expanded beyond anthropometry and maximal isometric muscle strength to include aerobic exercise capacity and motor skill performance, such as sprints or jumps (34). During World Wars I and II, there was international interest in measuring and improving PF performance for military purposes (34). Later, in the 1970s, research identified significant associations between low levels of PF and poor health outcomes among adults (35). Consequently, PF tests began to focus on a health-related approach (34), not just sport and athletic performance. Evidence supporting a relationship between PF and current and future health in adulthood first appeared for CRF (35,36) and MSF (37) in the 1980s and in the early 1990s for MF (38).

In this context, the concept of health-related PF was introduced by the Toronto model of PA, PF, and health (**Figure 1**). Functional capacity for daily living and health is the cornerstone of this model, extending the traditional concept of PF related to the ability to perform sports and physical exercise (39). This theoretical model focuses on the potential of PA and PF to identify health risks. According to this approach, daily levels of PA and PF have a bidirectional relationship, and in turn, PF is reciprocally associated with health outcomes. Furthermore, the response of a physiological system to PA comprises nonmodifiable (i.e., age, genetics, sex) and modifiable factors (e.g., nutrition, sleep, smoking) that are integrated by systematic responses such as molecular signaling or protein metabolism that consequently result in functional adaptations (40).

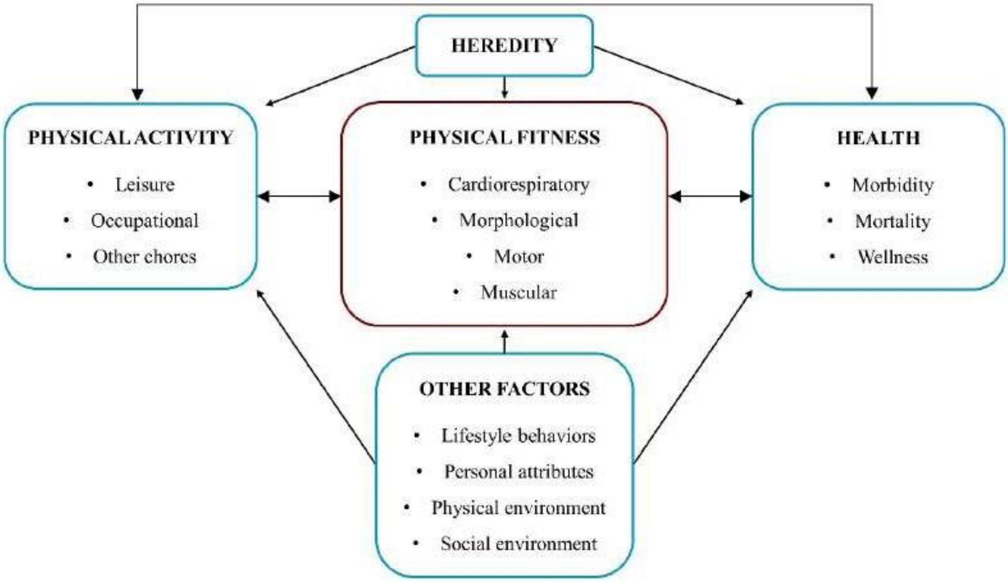

Figure 1. Toronto model on physical activity, physical fitness, and health. Adapted from Bouchard et al. 1994 (39).

Global trends in physical fitness

Although trend analyses on PF in adults are uncommon, levels of CRF and MSF appear to be declining overall (29,41,42). Low PF levels have been increasing for several years and are a strong predictor of deteriorating cardiometabolic health with clear implications for cardiovascular and all-cause mortality (41). National temporal trends in 2,525,827 adults from eight high- and upper-middle-income countries report a meaningful decline in CRF since 1980 (29) (**Figure 2**). These decreased levels could be influenced by a network of behavioral, environmental, socioeconomic, psychosocial, and physiological variables (43) and are indicative of a corresponding deterioration in population health (29). Indeed, PF trends occur in parallel with global physical changes, such as increasing obesity, as well as behavioral changes, such as decreasing PA levels (44) or increasing adherence to a Western dietary pattern (15). Assuming possible interconnections between these temporal trends, strategies that promote PA and healthy dietary patterns may be appropriate population-based approaches to counteract the decline in PF. International ongoing surveillance systems are urgently needed to monitor adult PF trends and report population-representative data (29).

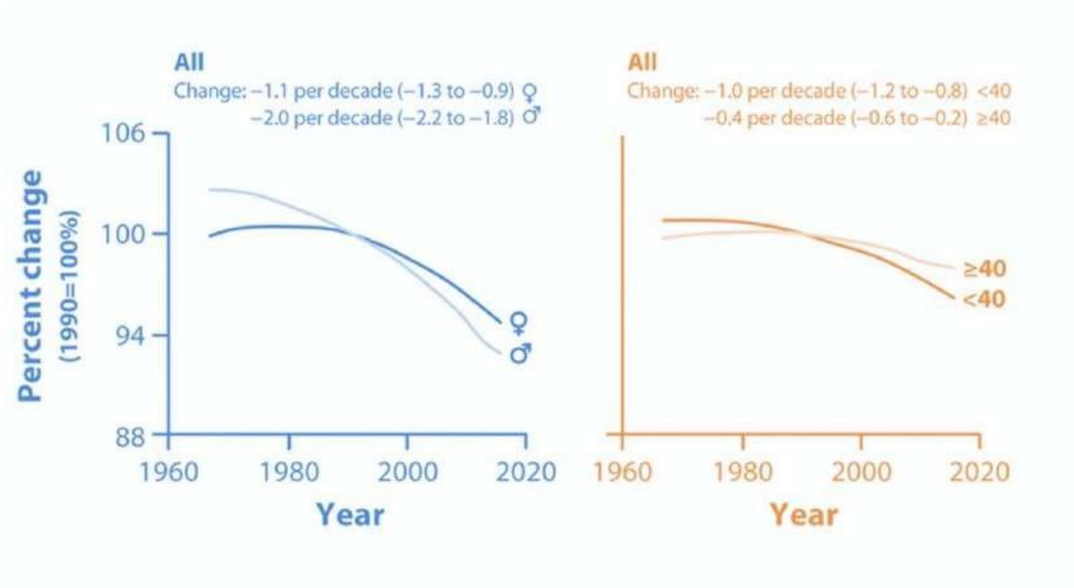

Figure 2. National temporal trends in mean cardiorespiratory fitness at the sex (left side of the panel) and age (right side of the panel) level in 2,525,827 adults of eight countries between 1967 and 2016. Data are standardized to the year 1990 = 100%, with higher values indicating better fitness and lower values indicating poorer fitness. Overall, there was a large collective decline in cardiorespiratory fitness in men, and small declines in women, young adults, and middle-aged adults. Published from Lamoureux et al. 2019 (29).

Reference values of physical fitness

One of the main challenges in estimating global trends in PF is to determine its reference values and benchmarks. Low PF, associated with increased cardiovascular or all-cause mortality, is usually defined as the lowest quartile or quintile on an exercise test (41,45). Given the importance of PF in estimating health risk, accurate reference values are essential to know what constitutes an optimal or at-risk value (46). To this end, PF levels must be considered in terms of individual characteristics (e.g., age, sex, ethnicity, health status), which poses a significant challenge. For example, PF varies across the lifespan, generally increases with growth in youth and early adulthood, is maintained in midlife, and decreases with aging (47), although these trends may vary by region or ethnicity.

Regarding the main components of PF, worldwide estimates of CRF were established from self-reported variables in 730,432 apparently healthy adults from all continents (48). Mean estimates of CRF values (maximum oxygen consumption [VO_{2max}]) were 50.4 $mL.kg^{-1}.min^{-1}$ for men and 40.6 $mL.kg^{-1}.min^{-1}$ for women (48). The results highlight age- and country-specific mean values. However, values estimated from self-reported data may have errors associated with data collection. For example, in the age group 70–79 years, higher estimated CRF values (~34%) were identified compared with directly measured values (49). In addition, epidemiological research has often identified a CRF threshold of 5 to 6 metabolic equivalents, below which the risk of all-cause mortality is significantly increased (26). However, a nonspecific CRF threshold may be problematic (50) because the significance of 6 metabolic equivalents (i.e., 21 mL O_2.kg^{-1}.min^{-1}) is clearly different depending on an individual's age and sex. For example, using percentile data defined from directly measured CRF (49), a VO_{2max} of 21 mL.kg^{-1}.min^{-1} would place a 75-year-old man at the 25th percentile and a 35-year-old woman at the 10th percentile.

The use of age- and sex-specific reference standards from directly measured CRFs could improve interpretation by researchers and clinicians. However, global reference values are a major challenge (48). Extensive research efforts have been made to establish normative data from directly measured CRF tests (46). A recent study established the first global reference values using cardiopulmonary exercise tests from different countries (i.e., Brazil, Canada, Israel, Japan, Norway, and the United States of America [USA]) (49). The 50th percentile $VO2_{max}$ of men and women aged 20 to 29 years ranged from 46.3 to 38.1 mL.kg^{-1}.min^{-1} and from 29.1 to 22.3 mL.kg^{-1}.min^{-1} for ages 70 to 79 years, respectively (49). This study highlights the international heterogeneity of CRF levels and underscores the need for further development of directly measured CRF data to improve global reference values (49). Furthermore, field CRF tests validated with laboratory measurements are a reliable and useful alternative in epidemiological research (28,31). These tests can estimate VO_{2max} using specific equations and contrast reported levels with reference values (28,31).

Considering MSF, the challenges in obtaining well-documented reference values are considerable. For example, the most widely applied muscle strength field test in research and clinical settings is the handgrip test, which measures maximal isometric handgrip strength. Various normative data have been proposed to define weak muscle strength (47,51,52). In 2014, the first study that provided normative data on lifetime grip strength was conducted in the United Kingdom population and estimated a benchmark of weak grip strength between <16 and <19 kg for women and between <27 and <32 kg for men (51). These results were supported by established cutoff thresholds in older adults for sarcopenia assessments. Specifically, the cutoff points for weakness are grip strength <26 (52) or <27 kg (47) for men and <16 (52) or <17 kg (47) for women. The reference values were developed by the Foundation for the National Institutes of Health Biomarkers Consortium (52) and the European Working Group on Sarcopenia in Older People (47). However, there are some limitations that constitute important obstacles to the establishment of global reference values that should be considered. Specifically, the type of devices used (i.e., handheld dynamometers), as well as their procedures, could restrict comparisons between values obtained with different methods (53). Consequently, this limits the clinical use of existing reference values without knowing the concomitant validity between tools (53). In this sense, the Jamar handheld dynamometer, the most widely used instrument in clinical and research settings, appears to be generally accepted as the gold standard and has the largest amount of normative data (54). In addition, standardized methods have been proposed to provide a more consistent measurement of grip strength (54).

Physical fitness and health outcomes

Adults of any age have the training capacity to increase PF levels, which is vital for short- and long-term health status (55). In fact, higher PF was associated with better health prognosis (56–58) and lower mortality (32,59,60) in youth, middle age, and old life. **Figure 4** shows the important role of PF as a marker of health status. The fraction attributable to low CRF accounts for approximately 16% of all-cause deaths in a large population of men and women, substantially higher than for other risk factors such as obesity or smoking (61). In other words, it was estimated that 16% of deaths would have been avoided in the absence of low CRF regardless of other health risk factors.

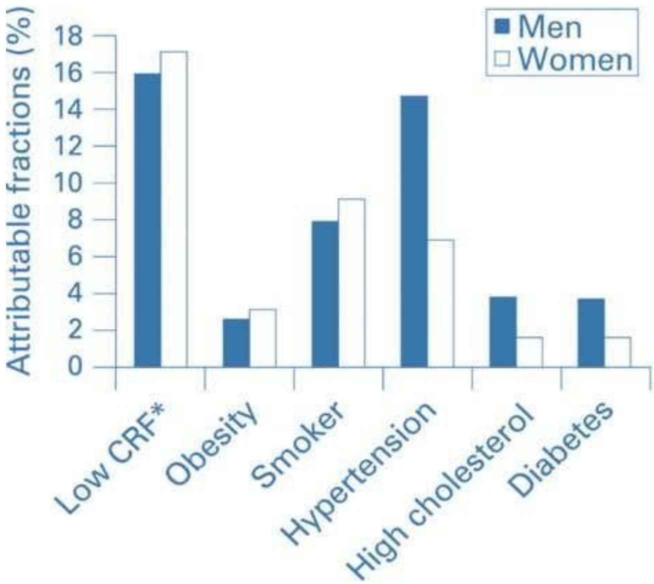

Figure 3. Attributable fractions (%) for all-cause deaths in 40,842 men (3333 deaths) and 12,943 women (491 deaths). The attributable fractions are adjusted for age and each other risk factor in the figure. * Cardiorespiratory fitness determined by a maximal cardiopulmonary exercise test. Published from Blair 2009 (61).
Abbreviations: CRF, cardiorespiratory fitness.

Among the PF components, CRF and MSF (especially muscular strength) have been widely studied and recognized with strong scientific evidence as significant prognostic markers of cardiovascular and all-cause mortality (24). A considerable number of studies have consistently confirmed that CRF and muscle strength are powerful indicators of cardiometabolic health in any adult age, ethnicity, sex, or health status (62,63). Furthermore, elevated PF levels may play an important role in other beneficial health outcomes, such as improved quality of life (64) and reduced risk of some cancers (65), mental disorders (66), and neurogenerative diseases (67). In turn, robust evidence has shown that both small improvements and maintenance of PF performance are related to the maintenance of a favorable health status (55,68). In addition to the strong link of CRF and MSF to health, MF can also be a powerful predictor of health outcomes. Based on available evidence from epidemiologic and clinical research, MF skills, such as gait speed or balance, are associated with survival in middle-aged and older adults (69,70). The critical importance of PF components for health and longevity underscores the paramount value of their assessment in the routine clinical setting in both women and men (71).

Modifiable lifestyle risk factors for physical fitness: the role of dietary behaviors

The components of PF that categorize the set of attributes related to a person's ability to perform daily tasks and PA in a safe and independent functional state are determined primarily by a synergist combination of genetic composition, health status, lifestyle behaviors, and sociodemographic factors (24). Both nonmodifiable and modifiable aspects are related to functional adaptations to PA and PF levels. In this context, PF components such as CRF, MF or MSF could be improved, mainly because they are closely related to modifiable lifestyle behaviors such as diet or PA (24,72).

Data on PF trends in adulthood highlight the importance of lifestyle habits as modifiable behaviors that influence PF levels throughout adulthood (29). In this context, nutrition has received increasing attention as one of the most powerful, feasible, and safe strategies to extend the time in which health status and functional capacity are maintained (73). The synergistic effect of dietary matrix components results in either advantageous or disadvantageous nutrient intake (e.g., high or low antioxidant compounds). This, in turn, affects the development of PF, leading to a more positive or negative scenario (72). For example, a sustained shift at any adult age from a typical Westernized dietary pattern (i.e., high consumption of meat and processed products, saturated fat, soda, sodium, sugar and trans-fat, and deficient consumption of plant-based foods) to a Mediterranean dietary approach can provide substantial health benefits, such as increased life expectancy (19) (**Figure 3**). However, in contrast to traditional lifestyle-related risk factors for cardiovascular disease, there is limited knowledge regarding the interplay between diet and PF (74).

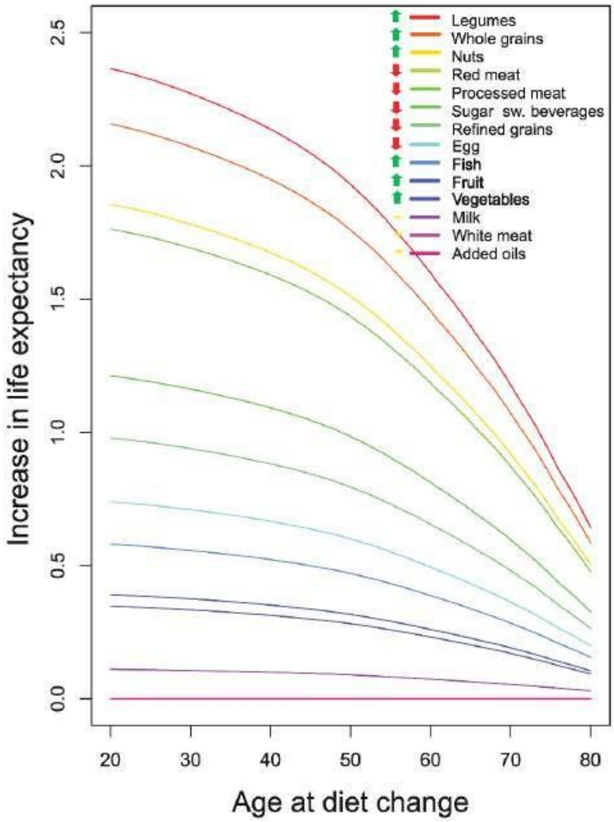

Figure 4. Expected increase in life expectancy for optimizing different food groups with daily dietary changes initiating from various adult ages. Whole grains: from 50 g to 225 g; vegetables: from 250 g to 400 g; fruits: from 200 g to 400 g; nuts: from 0 g to 25 g; legumes: from 0 g to 200 g; fish: from 50 g to 200 g; eggs: from 50 g to 25 g; milk/dairy: from 300 g to 200 g; refined grains: from 150 g to 50 g; red meat: from 100 g to 0 g; processed meat: from 50 g to 0 g; white meat: from 75 g to 50 g; sugar-sweetened beverages: from 500 g to 0 g; and added plant oils: 25 g (without changes). Published from Fadnes et al. 2022 (19).

Within this framework, the nutritional approach should revolve around the concept that "the whole is greater than the sum of its parts" (4). That is, a whole food product or dietary pattern is not reduced to a set of chemical substances but is considered a dynamic and organized unit in which cause–effect chains are modulated by synergistic interactions (4). Dietary patterns, foods, and nutrients are interrelated. The previously termed top-down approach (75), which starts with dietary patterns, then foods, and finally nutrients, enables greater accuracy between dietary orientations and research outcomes (**Table 1**).

The primary consideration should be dietary patterns, given the shifting disease burdens associated with nutrition (76). Traditionally, nutritional epidemiology has focused on the intake or absorption of a particular nutrient and other food components, especially when malnutrition and nutritional deficiencies were the predominant diet-induced disease states (76). However, epidemiologic transitions have modified the burden of disease (77). Chronic conditions such as cardiovascular diseases accounted for 32% of mortality and 40.8 million disability-adjusted life-years (DALYs) globally in 2019 (78). NCDs have multiple interacting dietary determinants consisting of excessive (or insufficient) intake, which cumulatively affect disease risk over the years (15). Consequently, nutritional epidemiological research related to NCDs has moved beyond the single nutrient approach, focusing on foods and food groups and, over the last years, assessing the effect of dietary patterns (76).

Table 1. Summary of the evidence supporting dietary statements.

Focus	Dietary patterns	Foods	Nutrients
Evidence synthesis	Relation between food patterns and health outcomes	Effects of foods on health outcomes	Mechanisms of action (and effects of concentrations) on health outcomes

Adapted from Tapsell et al. 2016 (76).

The results of nutritional research on foods and dietary patterns, as opposed to specific nutrients, are more amenable to translation into dietary guidelines and public health practices (79). In addition, people choose to eat foods, not nutrients. Therefore, the dietary pattern and food group approach is easier for the general population to understand and adopt recommendations for the clinical setting, as opposed to nutrient-specific guidelines (80). Dietary patterns describe the healthful attributes of food groups. For example, vegetables, fruits, nuts, fish, whole grains, and olive oil have consistently emerged as important foods in healthy dietary patterns that support NCD prevention (76). In this framework, studies based on the Mediterranean diet (MD) have demonstrated the feasibility and importance of starting by investigating dietary patterns and then moving on to consider individual foods and the effects of the nutrients they contain (79). In parallel, the application of diet quality indices expanded to assess whether adherence to a particular dietary pattern, such as the Mediterranean matrix, was associated with disease risk (79). Diet quality indices are algorithms that aim to estimate the overall diet and classify individuals according to the extent to which their dietary behavior is healthy or unhealthy (81). Predefined indices assess dietary patterns based on current nutritional knowledge and have been developed primarily for epidemiology to assess dietary risk factors for NCDs (81).

Within the value chain of knowledge generated by dietary guidelines, the impact of dietary patterns and foods on health is examined by different study designs with methodological and practical limitations (82). Some of the main elements that summarize the challenge of advancing knowledge in nutritional research are the following. Human nutrition is highly individualized (e.g., genetics, lifestyles, health conditions), and this variability is extremely complex to address in research (83,84). In addition, self-reported dietary assessments, such as food frequency questionnaires or dietary recall, are most commonly used in studies because of their feasibility and are subject to recall biases and inaccuracies (83). More precise assessments (e.g., biochemical markers) are vital for attributing health effects to dietary behaviors but are often expensive and pose logistical difficulties (84). Furthermore, several nutrition-related health problems, such as NCDs, develop over decades, and long-term studies are resource intensive and may be impractical (84). Finally, intervention studies comparing diet regimens are critical to verify the health effects of specific food matrices; however, some dietary interventions in humans may raise ethical concerns (83).

Global trends in dietary patterns

The metabolism of each species has been genetically adapted to a particular dietary pattern over long periods of evolution that ensures health and survival (85). Present-day humans are genetically adapted to the environment in which our ancestors survived, where the diet consisted mainly of hunting, fishing, and gathering uncultivated plant-based foods such as roots, tubers, berries, nuts, vegetables, or fruits (86). In general, diets were high in proteins and low in carbohydrates, which accounted for 22–40% of energy (87). With the agricultural revolution of approximately 10,000 years ago and especially since the industrial revolution of 250 years ago, nutrition has changed significantly, although the human genome has remained largely unchanged (86). Currently, carbohydrates play a predominant role, and glucose is the most important energy source (i.e., 40–75%) for the human body (86). Western diets consist of large amounts of foods rich in carbohydrates (e.g., refined cereals, corn, potatoes, sugars) and rich in trans fatty acids (88). The significant changes in diet and lifestyle during recent human history cause severe metabolic distortions, including an increased production of reactive oxygen species and oxidative stress, hyperinsulinemia and insulin resistance, low-grade inflammation, and abnormal activation of metabolic systems (e.g., sympathetic nervous, renin angiotensin), all of which play key roles in the development of chronic diseases (86).

A systematic evaluation of global epidemiological evidence showed that, over the past years, the nutritional transition characterized by high adherence to the Western dietary pattern is becoming more pronounced, even in countries of the Mediterranean region (15). Global data from 195 countries reported suboptimal consumption of healthy foods (e.g., fruits, legumes, nuts, seeds, whole grains) in 2017, and in parallel, daily consumption of unhealthy foods and nutrients (e.g., processed meat, sugar-sweetened beverages, trans fats, sodium) exceeded the optimal level (**Figure 5**). This dietary evolution has become a growing public health concern as a relevant contributor to cardiovascular disease, disability, obesity, and mortality (15). Worldwide, dietary behaviors are major risk factors for 11 million deaths (22% of all deaths among adults) and 255 million DALYs (15% of all DALYs among adults), showing a significant increase since 1990 (8 million deaths and 184 million DALYs) (15). Specifically, certain dietary risk components, such as high sodium intake or low intake of whole grains, fruits, nuts, vegetables, and seafood omega-3 fatty acids, had a greater impact on health outcomes (**Figure 5**).

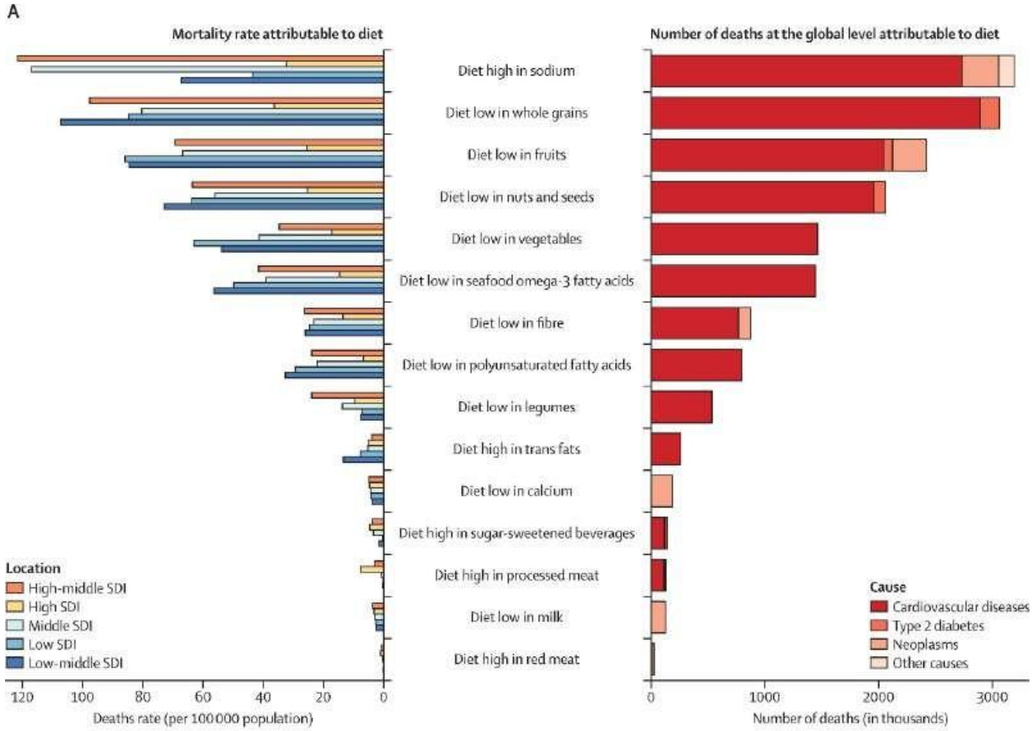

Figure 5. Number of deaths and age-standardized mortality rate (per 100,000 population) attributable to specific dietary risks at the global and sociodemographic index level in 2017. Published from Afshin et al. 2019 (15).

Mediterranean diet

The main dietary characteristics of the MD are as follows (**Figure 6**): virgin olive oil as the principal source of fat; high consumption of fruits, herbs, legumes, nuts, olives, seeds, spices, vegetables, and whole grain cereals; moderate consumption of eggs, fish or seafood, dairy products (preferably low in fat), red wine, and white meat; and occasional consumption of red or processed meat and sweets (e.g., carbonated beverages, pastries, sugar) (89,90). In addition, the concept of MD incorporates cultural and lifestyle elements (e.g., adequate rest, conviviality, regular PA, preference for fresh, local, seasonal, and traditional foods) that should be considered to contribute to the nutritional benefits of this healthy food matrix (90,91) (**Figure 6**).

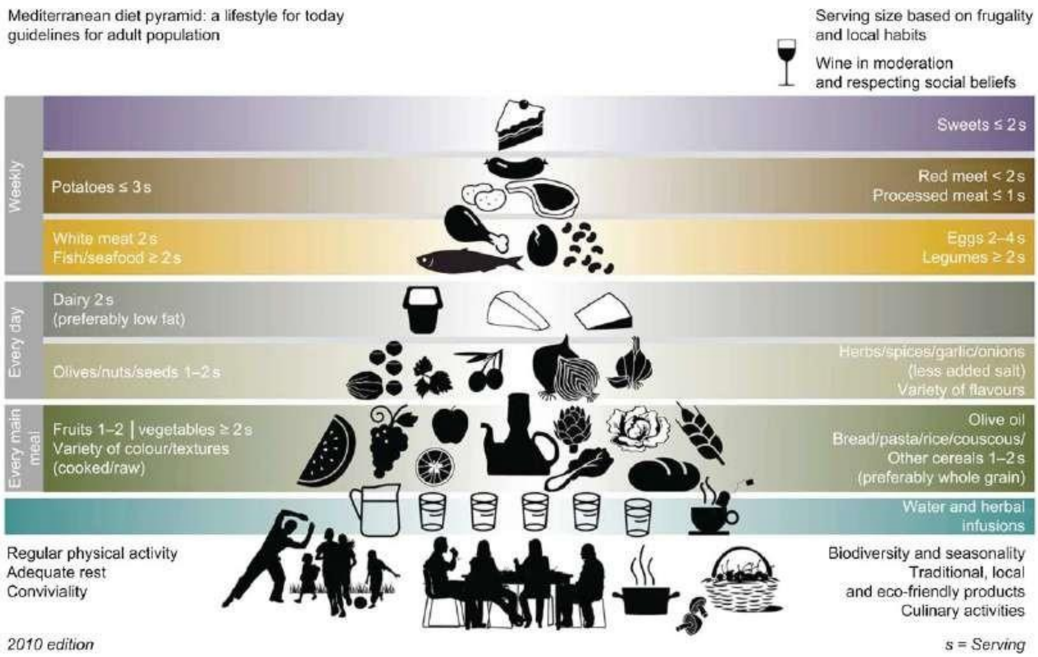

Figure 6. Mediterranean diet pyramid. Published from Bach-Faig et al. 2011 (90).

Typical traditional MD comprises a low intake of saturated fat (~8% of energy), a high intake of total fat (~30% of energy, predominantly from virgin olive oil, nuts, seeds and whole grains), a moderate intake of carbohydrates (~50–60% of energy, mostly from whole grains and with restriction of refined grains) and protein (~20% of energy, primarily from high quality plant-based proteins), and a high content and bioavailability of dietary fiber mainly of plant origin (~30–60 grams per day) (89,90). In this context, for some foods that are configured in the MD within a moderate or occasional consumption category, such as fish, white meat, or red meat, it is relevant to consider that the impact on health presents a U-shaped curve, i.e., only moderate and balanced amounts are potentially beneficial to health (79). However, the complexity and diversity of these associations, marked by elements such as the quality of the food consumed, the mode of preparation, the physiological characteristics and requirements of the individuals, and the interaction with other foods and the dietary pattern, make it difficult to establish healthy limits for the consumption of this type of food. It is important to consider a holistic approach (e.g., food matrix, environment, lifestyle habits) for the overall recommendation of specific MD foods.

The traditional MD is the heritage of millennia of exchanges between the peoples and cultures of the Mediterranean basin (92). It formed the basis of food habits of the entire region until the mid-20th century, when a crossroads of civilizations took place as a point of convergence of peoples, commodities, and religions (93). Conceived as a constantly evolving lifestyle, the MD is a complex system of shared knowledge characterized by diverse food patterns influenced by different cultures (91). In fact, Mediterranean dishes are examples of such exchanges (e.g., the Greek *moussaka*, the Maghreb *harira*, the Arab-Jew *hummus*, the Egyptian *falafel*, the Italian *pesto*, the Spanish *pisto*) (93). Nevertheless, the MD is an entity with common and essential components described above that encompasses variants specific to different cultures and countries. In this context, the concept of MD is undergoing a transformation to recognize different food cultures and a linked ecology that could be described as a Mediterranean cultural food system (92). In this vein, the MD was declared an Intangible Cultural Heritage of Humanity by UNESCO in 2010 (94). In this declaration, the definition of MD deliberately included all disciplinary perspectives regarding food supply and eating habits throughout the Mediterranean, and no single food was identified (93). In fact, this food system model (i.e., retaining the key components mentioned above) can be adapted to the specific agricultural resources and cultures of each country and may have health benefits such as those reported in Mediterranean regions (95).

The MD, considered primarily a plant-based food matrix, is a robust scientific concept associated with several beneficial health outcomes, such as reduced overall mortality and reduced risk of some cancers, cardiovascular and neurogenerative diseases, and diabetes (96–98). The American physiologists Ancel and Margaret Keys can be considered evidence-based discoverers of MD and its potential health benefits (99). The famous Seven Country Study, initiated in 1956 and first published in 1978, was the world's first multinational epidemiological study (100). This longitudinal research not only showed the positive relationships between MD and decreased risk of cardiovascular events but also considered an indivisible and substantial lifestyle to MD (100).

The Mediterranean nutritional scheme, a simple, viable and wholesome food system model, incorporates sustainable development among the economic, environmental, and social dimensions, considering the specific variations of each country (101). In this sense, seasonality, biodiversity, and the use of traditional and local foods are key elements of MD, encompassing conviviality, culinary tradition, and PA (91). Diets closely link human health and environmental sustainability, economics, and sociocultural characteristics. The scientific goals of healthy diets and sustainable food systems are integrated into a common framework (21). MD is much more than a dietary regimen and intrinsically supports the etymology of the word diet (from the Latin *diaeta*, which in turn comes from the Greek *díaita*) that could be translated as “way of living” (93).

Underlying mechanisms between the Mediterranean diet and physical fitness

Some evidence has suggested that the MD may have a positive impact on PF (72,102), mainly because the synergistic effect of its dietary characteristics leads to a high-quality nutrient intake (103). The main elements of the Mediterranean food matrix (fresh fruits and vegetables, herbs, legumes, nuts, olive oil, red wine, seeds, spices, and whole grain cereals) include optimal concentrations of nutrients (104), such as carotenoids (105), fiber (106), omega-3 polyunsaturated fatty acids (107), polyphenols (108), trace elements (109), and vitamins (110), which have been associated with greater benefits on PF status. Specifically, the MD includes a wide variety of antioxidant molecules with anti-inflammatory properties that may influence PF development, such as α-linolenic acid, β-carotene, carboxymethyl-lysine, coenzyme Q10, creatine, flavonoids, hydroxytyrosol, lycopene, oleocanthal, oleuropein, resveratrol, selenium, spermidine, vitamins C and E, and zinc (111–114). This antioxidant capacity of the MD through the synergistic combination of its foods should range between 3500–5300 μmol trolox equivalent per day as an essential indicator of a traditional Mediterranean dietary matrix (106).

Under normal physiological conditions, human cells can restore the balance by regulating antioxidant defense mechanisms (115). Oxidative stress is a multifactorial process caused by an alteration between the components of the antioxidant and prooxidant balance (116). Specifically, it refers to an excessive production of reactive oxygen and nitrogen species. Overproduction of free radicals over a prolonged period can lead to damage to cellular molecules such as deoxyribonucleic acid, lipids, and proteins (116). The main consequence of elevated free radical generation is lipid peroxidation (117), a chain reaction that produces multiple degradative aldehydes (e.g., 4-hydroxy-2-nonenal) that induce alterations in the biochemical properties of biomolecules, which can facilitate the development of various pathological states (118). Some of the mechanisms related to oxidative stress and its consequences (e.g., glycosylated products, lipid peroxidation, oxidized proteins), involved in impaired physical functioning, include release of inflammatory signaling molecules, reduced efficiency of myogenic differentiation, loss of myoblast function, impaired muscle regeneration, or abnormal intramuscular energy metabolism (119,120). These pathways are associated with myogenesis, a process important for maintaining muscle homeostasis and the physiological function of skeletal muscle (120).

Lifestyle-related behaviors, such as diet and PA, can influence the oxidative balancing process that drives important signaling events in PF levels (121,122). Antioxidants are compounds that help protect cellular organs from oxidative damage caused by free radicals (120). Antioxidants can be classified as endogenous (i.e., produced in the body) or exogenous (i.e., taken from external sources such as foods). Evidence suggests that foods rich in antioxidant compounds contribute to the development of PF through different pathways (**Figure 7**), such as reduction of reactive oxygen species and proinflammatory cytokine expression, modulation of gut microbiota, suppression of free radical formation, enhancement and protection of antioxidant defenses, muscle regeneration, or modulation of enzymatic and signaling systems (120,123,124). Traditional antioxidants from nutritional research and included in the beneficial effects of MD are β-carotene, vitamins C and E, and the mineral selenium (125). In turn, polyphenols from MD encompass a wide range of secondary plant metabolites characterized by numerous phenolic groups that make polyphenols potent antioxidants and anti-inflammatories (126).

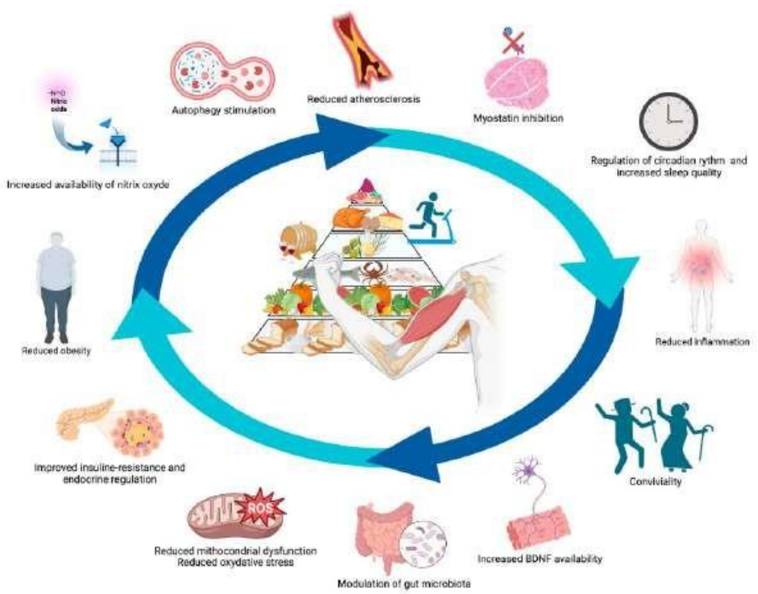

Figure 7. Main mechanisms between the Mediterranean diet and and physical fitness benefits. Published from Cacciatore et al. 2023 (127).

The Mediterranean food matrix provides a complex mixture of antioxidants in food that, when consumed over prolonged periods, is more effective than large doses of a single antioxidant administered over a finite period (124). Indeed, oxidized low-density lipoprotein levels, oxidative lipid damage, and inflammatory markers decreased after MD-based interventions (124,128,129). In turn, the MD could also enhance the endogenous antioxidant activity of the organism (130). Middle-aged and older adults who participated in MD-based interventions reported increased plasma antioxidant capabilities (i.e., catalase and superoxide dismutase activity) and decreased xanthine oxidase prooxidant activity compared with the control group (low-fat diet) after 5 years of follow-up, resulting in increased serum total antioxidant activity (131).

Furthermore, it is important to consider that the relationship between antioxidant activity and the development of PF could act as a bidirectional pathway, i.e., higher levels of antioxidant compounds from the diet could favor PF, and in turn, a higher level of PF could help to maintain lower levels of oxidative stress and better antioxidant defenses (132). In turn, the influence of the Mediterranean lifestyle (e.g., adequate rest, regular PA, social support) could contribute to the positive impact on PF levels. Although the association between MD and PF has shown promising results in a meta-analysis conducted in children and youths (133), a quantitative synthesis on whether and to what extent adherence to the MD and its individual components are associated with PF levels in adulthood remains unknown.

PART II

DIET, PHYSICAL ACTIVITY AND DEPRESSION

CHAPTER 2: DIETARY PATTERNS AND DEPRESSION

Depression: definition and diagnosis

At this point, it should be recalled that the present doctoral thesis is structured into two parts. The first focused on the relationships between diet and PF, while this second part centers on the associations of two specific dietary patterns (i.e., Dietary Inflammatory Index and MD) and one of their major food components (i.e., nuts) with depression.

Depressive disorders include major depressive disorder, major depressive episode, persistent depressive disorder (dysthymia), disruptive mood dysregulation disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder according to the American Psychiatric Association in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (134). The cardinal feature of depressive disorders is the presence of a sad, empty, or irritable mood, accompanied by somatic and cognitive disturbances that significantly affect the individual's capacity to function (134). The duration, timing, or presumed etiology are the factors that differentiate them (134).

Major depressive disorder represents the classic condition of depression. Episodes of major depression can be further described using the specifiers established in the DSM-5, such as illness pattern, clinical features, severity, onset, and remission status (135) (**Figure 8**). The terms major depressive disorder, major depression, and clinical depression generally relate to the same concept and are used interchangeably in the literature. The American Psychiatric Association defines major depression according to five criteria (134). First, the presence of five or more symptoms out of nine over a minimum period of two weeks. At least one of the symptoms must be depressed mood (i.e., most of the day, nearly every day) or loss of interest or pleasure (i.e., in all or almost all activities, most of the day, nearly every day). The other seven symptoms are as follows: significant weight loss when not dieting, weight gain, or decrease or increase in appetite almost every day; insomnia nearly every day; psychomotor agitation or retardation nearly every day; fatigue or loss of energy almost every day; feelings of worthlessness or excessive or inappropriate guilt nearly every day; diminished ability to think or concentrate, or indecisiveness, almost every day; and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan to commit suicide. Second, these symptoms cause clinically significant distress or impairment in familiar, personal, social, or other important contexts. Third, depressive episodes are not attributable to the physiological effects of a substance or other medical conditions. Fourth, the occurrence of a major depressive episode is not best explained by schizophrenia spectrum disorders or other psychotic disorders. Finally, neither a manic episode nor a hypomanic episode has ever occurred.

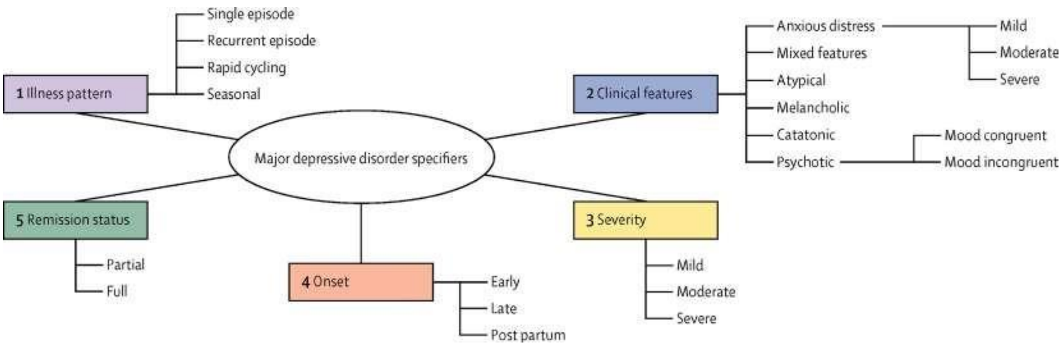

Figure 8. Specifiers of major depressive disorder. Published from Malhi and Mann 2018 (135).

Apart from the DSM-5 description of major depressive disorder, there is another common method for defining clinical diagnosis, i.e., the WHO International Classification of Diseases 11th revision (ICD-11) (136). Both procedures (i.e., DSM-5 and ICD-11) are similar and are the most widely used worldwide to define clinical depression. In the ICD-11, the threshold for the diagnosis of major depressive disorder is the same as in the DSM-5: at least five symptoms (137). However, the ICD-11 requires at least five symptoms from a list of 10, instead of nine as in the DSM-5. The additional symptom is “hopelessness”, which has been shown to outperform more than half of the DSM symptoms in differentiating people with major depression from those without (138). The American Psychiatric Association and the WHO have made a great effort to harmonize their diagnostic systems (i.e., DSM-5 and ICD-11) (137). In fact, the organizational framework is now the same in the two approaches.

Moreover, in epidemiological studies on lifestyle behaviors and mental health, mainly self-reported scales or blind-observer instruments that assess depressive symptoms to categorize their severity (none, mild, moderate, severe, extremely severe) are used. Some of the most commonly used measures of depressive symptoms in the scientific literature are the Beck Depression Inventory, Center for Epidemiologic Studies Depression Scale, Geriatric Depression Scale, Hamilton Rating Scale for Depression, Inventory of Depressive Symptomatology, Montgomery–Åsberg Depression Rating Scale or the Patient Health Questionnaire (139).

A prior study reported that DSM-5 core symptoms (i.e., sad mood and loss of interest), along with loss of energy and concentration problems, were the four of the 14 depressive symptoms analyzed with the greatest impact on impaired psychosocial functioning (140). In turn, a network analysis showed that non-DSM symptoms could also act as core symptoms (141). Specifically, sympathetic arousal (e.g., palpitations, tremors, blurred vision), featuring strong connections with somatic complaints (e.g., limb heaviness, pain), gastrointestinal problems, and anxiety symptoms (e.g., panic, phobia), exhibited high node strength values and documented an important role in depression (141).

These findings highlight the complex clinical picture of depression. Some of these core symptoms for depression, from both DSM and non-DSM criteria, do not receive any special attention in common depression rating scales, such as the Beck Depression Inventory or the Center for Epidemiologic Studies Depression Scale (140,141). In addition, standard assessment measures do not differentiate between core and secondary symptoms, and because of the emerging evidence on depressive symptoms and associated factors, a model that focuses on hierarchical levels is needed (141). Finally, the growing body of evidence emphasizes the need to differentiate between depressive symptom profiles and to consider disaggregated symptom analysis (141,142). The substantial symptomatic variation among individuals with major depression questions the status of this mental disorder as a specific consistent syndrome and offers a potential explanation for the difficulty in treatment efficacy (143). Analysis of individual symptoms and their patterns could provide relevant information that studies based solely on summative scores would not be able to encompass (143). Considering the heterogeneity of depression in pathophysiological research is fundamental and an important challenge for future studies.

Pathophysiology, etiology, and risk factors

Chronic diseases typically have a gradual onset, a crucial consideration, particularly in the context of lifestyle-related illnesses. As discussed in the general introduction, a state of complete physical, mental, and social well-being is fundamentally impossible (144). Assuming the dynamic, multidimensional, and time-dependent changes that occur during the transition from the health to disease state, the physiological principle of homeostasis becomes significant (145) because it considers health in terms of the ability to adapt to environmental challenges (4). In this context, the onset and gradual development of disease begins when adaptive processes start to deteriorate (146). Lifestyle-related factors, including diet and PA, significantly contribute to maintaining and enhancing physiological resilience (145). This could be termed phenotypic flexibility, being the result of multiple factors, such as the individual's genotype or physiological and psychological states (146). In this sense, the different regulatory mechanisms fluctuate within a certain homeostatic range (**Figure 9**). Chronic diseases develop when an organism is no longer able to maintain homeostatic processes within a certain limit (145).

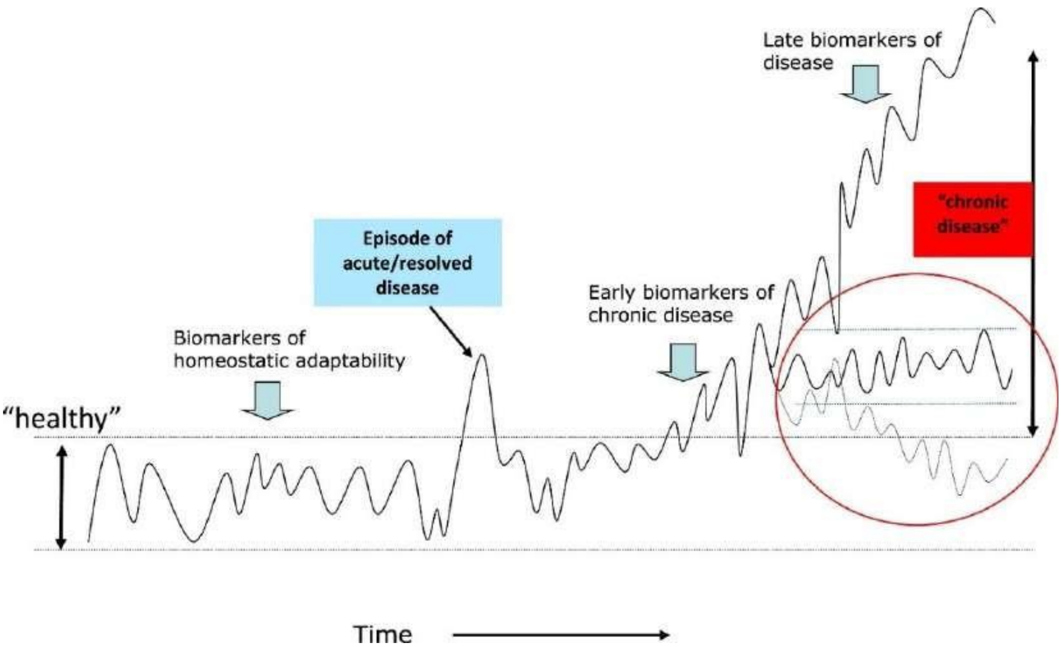

Figure 9. Biomarker patterns in relation to homeostatic adaptability. Schematic representation of physiological balance and biomarker pattern development in time from homeostasis via dysfunction to chronic disease. An organism (individual) maintains homeostasis for as long as possible by changes in its metabolic pathway dynamics. Lifestyle behaviors, such as diet and physical activity, aim to support this homeostasis. Chronic disease develops when an organism is no longer able to maintain physiological balance processes within a certain limit. A disease process may deteriorate further or stabilize in a new homeostatic state. Published from Witkamp and van Norren 2019 (145).

Although the causes of depression remain unclear, a complex interplay of environmental, genetic, psychosocial, and behavioral factors has been proposed (147). Despite genetic vulnerability to depression, environmental influences, and the individual's ability to adapt to them (e.g., acceptance, community involvement, enjoyment, resilience, self-management, life experiences, intentions, choices, and actions) should be considered of vital importance in exploring the pathways leading to depressive disorders (148). The learned helplessness theory of depression relates depressive phenomena to the experience of uncontrollable life events and not only to specific cognitive distortions present in susceptible individuals (i.e., cognitive theory) (148).

Environmental factors can facilitate the dysregulation of the stress response system and could play a major role in the occurrence of depression (149). Stressful life events that can precede depression, such as job loss, social isolation, or childhood trauma, could lead to structural changes in the prefrontal cortex, amygdala, and hippocampus, contributing to the development of depression (150). Stressful life events are important risk factors for depressive disorders but may have a greater effect in individuals with a specific genetic liability for the disorder (151). Evidence supports gene–environment interactions, i.e., the strong causal role of the environment could be modified by genetic factors (150). Genetic polymorphisms appear to exert control over the degree of sensitivity to an adverse life event (151). Thus, individuals may respond differently to the same stressful event due to epigenetic factors (i.e., heritable changes in gene expression or cellular phenotype) (151).

The gene–environmental interaction model supports the biogenic amine hypothesis, which focuses on the role of specific neurotransmitters in the development and clinical manifestations of depression (152). That is, the biogenic amine theory proposes that reduced availability of these major monoaminergic neurotransmitters (i.e., dopamine, norepinephrine, and serotonin) results in decreased neurotransmission and impaired cognitive performance that can lead to depression (152). In addition, recent approaches implicate several critical pathways as possible contributors to the etiology of depression, such as decreased function of transporter proteins, abnormalities of receptor and endocrine system functions (i.e., altered growth hormone levels, thyroid hormone abnormalities, hypothalamic–pituitary–adrenal [HPA] axis dysfunction), elevated levels of inflammatory cytokines (e.g., interleukin-6, interleukin-1, tumor necrosis factor, C-reactive protein), neuroinflammation, and reduced capacity for neurogenesis (153).

Furthermore, there is some evidence that factors derived from cognitive and personality-based theories (i.e., dysfunctional attitudes and negative emotionality) may predict the onset of major depression (154). A recent review identified transdiagnostic factors (e.g., neuroticism, implicit low self-esteem, repetitive negative thinking) that may help explain comorbidity between depression and symptom overlap and indications of disorder-specific risk factors (e.g., cognitive responsiveness) that support the relevance of distinct disorder categories and disorder-specific mechanisms (155). Several psychosocial risk factors, such as extraversion or conscientiousness, have been associated with the development and chronicity of depressive disorders (155). In contrast, psychosocial factors have been associated with mental resilience (i.e., good mental health despite stressor exposure), including factors such as general self-efficacy, optimism, perceived good stress, negative neuroticism, or social support (156). Resilience is an important protective factor against psychological distress (157), and greater resilience has been associated with fewer depressive symptoms (158). All these psychological factors are likely to be involved in the progression of depressive disorders.

Social determinants include a range of social and economic aspects, such as income inequality or social support, that influence people's mental health. These structural social and economic arrangements confer advantages or disadvantages, differential exposure to adverse life events, and the specific conditions of vulnerability and resilience that these arrangements and exposures produce (159). The social determinants of mental health encompass five key domains, including demographic (e.g., age, ethnicity), economic (e.g., employment, food security), neighborhood (e.g., built environment, housing), environmental (e.g., exposure to violence, migration), and sociocultural (e.g., education, social capital) factors, which act as distal (i.e., the upstream, structural arrangements of society) and proximal (i.e., the way these arrangements are experienced by individuals) levels (159). These domains frequently cluster and interact (160), and a combination of two or more social determinants of mental health could establish highly vulnerable populations (159). Studies have identified adverse mental health consequences of exposure to negative economic, neighborhood, environmental or sociocultural events (159).

Finally, lifestyle factors can trigger increases in inflammatory activity, which in turn may influence physiological domains relevant to depressive symptoms, such as neurotransmitter metabolism, neuroendocrine function, and functional brain activity (147). Unhealthy diets, insufficient PA, sedentary behaviors, frequent alcohol consumption, smoking, or poor sleep quality could increase the activation of proinflammatory cytokines or inflammasomes that drive inflammatory responses relevant to depression (10). The synergistic combination of unhealthy lifestyle behaviors could potentiate depressive symptoms. In addition, lifestyle factors could influence certain risk factors related to depression, such as disability or loneliness (159).

Therefore, considering that the causes of depression are multifaceted and not fully understood, a multifactorial interaction of biological, genetic, psychosocial, behavioral, and environmental aspects that affect each individual suffering from depression differently must be considered. Despite their complexity, depressive disorders could be positively affected by lifestyle modifications. Healthy dietary patterns and regular PA could be crucial in preventing or treating depressive symptoms. While the emerging scientific evidence supports the protective role of dietary patterns and PA against depression, many questions remain to be answered, such as the role of MD as an effective complementary treatment or the influence of daily steps as a preventive strategy.

Prevalence

In recent years, mental illnesses are on the rise worldwide (161). According to the Institute for Health Metrics and Evaluation, lifetime prevalence estimates in 2019 showed that 13.1% (~970 million) and 3.8% (~280 million) of the world's population suffer from some form of mental or depressive disorder, respectively (162). In contrast, these values were approximately 12.7% and 3.3% in 1990 (162) and near 0.03% for mental disorders in 1960 according to estimates by Torrey and Miller (163).

According to the last report of the Global Burden Disease Study in 2019, mental disorders were the seventh leading cause of disease burden worldwide (161). Specifically, 125 million DALYs could be attributable to mental disorders (4.9% of global DALYs) (161) and, using a composite approach that considers premature mortality due to mental disorders, estimates increased to 418 million DALYs (164). Among them, depressive disorders were the primary cause of disability burden from early adulthood to old age (**Figure 10**).

In this framework, the COVID-19 pandemic in 2020 has created a high-risk scenario where some determinants (e.g., mobility, social interactions) of the cardinal features of all depression phenotypes (i.e., the presence of a sad, empty, or irritable mood and loss of interest or pleasure in life) have been affected (165). The clustering of multiple social determinants of mental health could generate or aggravate mental health problems on a global scale (166). In fact, the worldwide prevalence of major depressive disorder increased by 53.2 million additional cases in 2020 (165) (**Figure 11**).

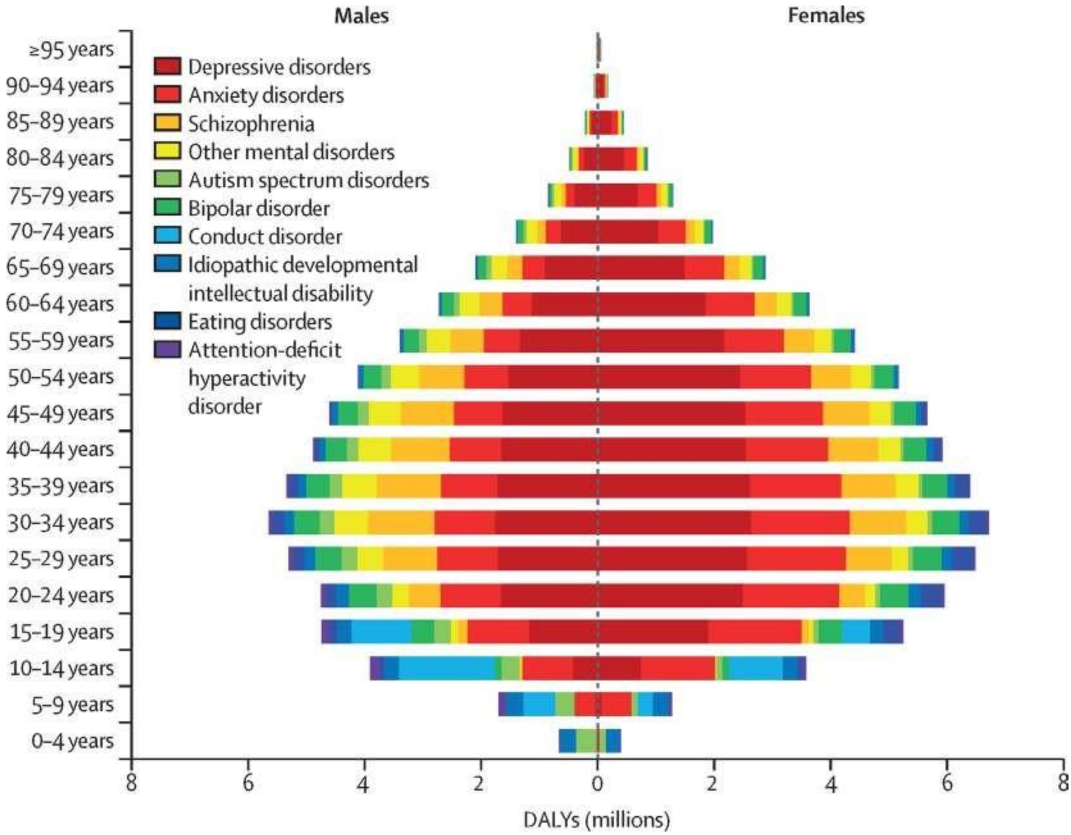

Figure 10. Global disability-adjusted life years by mental disorder, sex, and age in 2019. Published from Global Burden Disease 2019 Mental Disorders Collaborators (161).

Furthermore, the elevated economic cost associated with DALYs from mental disorders (estimated at US$ 4.7 trillion per year) highlights a considerable problem in global society (164). The direct and indirect effects of depression on the economy are significant and have alarming implications (164). For instance, functional impairment in depression affects workplace productivity and could account for approximately 20% of lost workdays (167). Specifically, lost productivity associated with the most common mental disorders (i.e., anxiety and depression) costs the global economy US$ 1 trillion per year (164).

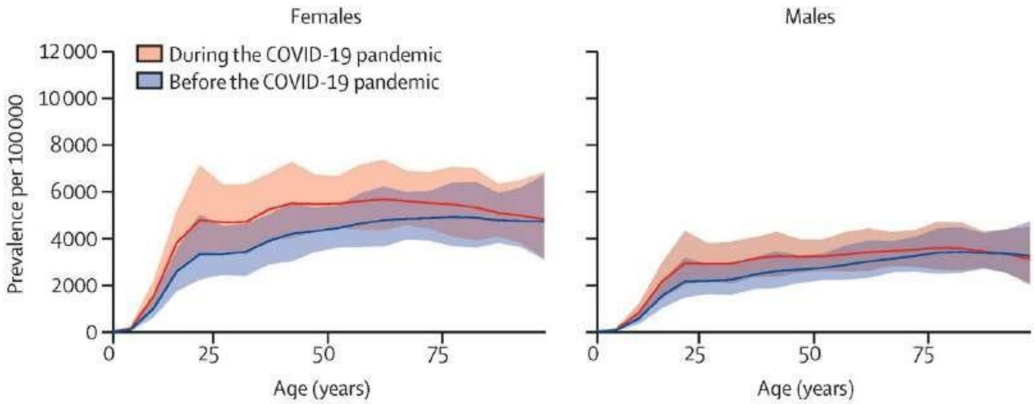

Figure 11. Global prevalence of major depressive disorder in 2020 before and after adjustment for (i.e., during) the COVID-19 pandemic by age and sex. Before adjustment for the COVID-19 pandemic, the estimated global prevalence of major depression was 2470.5 cases per 100 000 population, equivalent to 193 million people. After adjustment for the COVID-19 pandemic, the estimated prevalence of major depression was 3152.9 cases per 100 000 population, equivalent to 246 million people. Published from Santomauro et al. 2021 (165).

Epidemiological and economic estimates are probably conservative, as the complex clinical picture of depression, covered by other problems (e.g., memory difficulties with distress, bipolar disorder), leads to a high proportion of undiagnosed cases (168). These estimates suggest that the global burden of mental disorders, and depression in particular, is considerable, both in terms of their impact on human health and losses in societal well-being (164). In turn, even below the clinical threshold, depressive symptoms exert a significant impact on quality of life and a considerable likelihood of progressing to clinical depression (169).

Depression and health impacts

The health impact of depressive disorders is associated with serious consequences in terms of increased mortality, disability, and secondary morbidity. Scientific evidence supports that depression is a significant risk factor for mortality (170,171) and the development of other chronic conditions, such as cardiovascular diseases and diabetes (172). Depressive burden, even in the absence of clinical depression, appears to be related to the development of multimorbidity, especially in individuals presenting somatic and mood symptoms (173). Associations between depression and chronic diseases share common risk factors (e.g., poor diet quality, physical inactivity, sleep disorders) and pathophysiological pathways such as biological (e.g., cerebral vascular dysfunction, endocrine system disturbances, inflammation) and psychosocial (e.g., low socioeconomic status, stress, loneliness)

(174,175). Furthermore, depressive symptoms significantly affect quality of life (176), and depending on their severity, they result in negative impacts on physical and psychosocial functions (177,178). Thus, it has been estimated that a high proportion of individuals with depression have some impairment in their daily functioning (159).

The increased frequency and its clinical, physical, socioemotional, and economic implications make depression a major global public health problem (4). These estimates confirm the emerging challenge facing both the developed and developing world, which now must cope with a growing population with chronic NCDs and mental health problems (172). Moreover, although the psychological impact of COVID-19 in 2020 is already evident, its effects will be far-reaching (166). This calls for urgent public health interventions to promote mental wellbeing and reduce both the prevalence and burden of depressive disorders as well as their health-related consequences (179).

Modifiable lifestyle risk factors for depression: the role of dietary behaviors

Although substantial advances in research have demonstrated the efficacy of psychological and pharmacological treatments for clinical depression (180,181), translation to real-world benefits remains a global challenge, as not all individuals with depression achieve or maintain symptom remission with standard treatment alone (159). In fact, an important proportion of patients fail to respond to pharmacological treatments and psychotherapies (182). It is important to consider that the same antidepressant may be effective in some patients and ineffective in others, as well as the long-term side effects of medication (183). Moreover, individuals with depressive symptoms who do not meet the criteria for a diagnosis of depressive disorder (i.e., subthreshold or subsyndromal depression) represent a challenge for clinical settings because few treatment options are available (169). The multifactorial etiology and phenotypic heterogeneity of depression are constant difficulties for treatment effectiveness (159).

In addition, large-scale implementation and translation into real-world benefits of pharmacological and psychosocial treatments have been slow. The direct and indirect costs of mental health care are many and may involve social services, primary, secondary, and tertiary care, administration, management, or supervision. The WHO's Mental Health Atlas 2020 estimated that mental health spending accounted for less than 2.5% of the global average for government public health (184). Consequently, the Lancet Commission on Global Mental Health and Sustainable Development stated that "all countries can be thought of as developing countries in the context of mental health" (159).

Given the high burden of depression and the complexity of treatment, it is essential that preventative strategies be developed through the identification of both risk and protective factors and the subsequent design and implementation of prevention programs targeting these modifiable aspects (185). In this context, lifestyle behaviors have emerged as potential strategies in the prevention and treatment of depression (10). Optimizing diet quality could act as a central determinant of mental health. In recent years, there has been unprecedented growth in the quantity and methodological quality of research exploring the relationship between nutrition and mental health. Epidemiological data, basic science, and clinical evidence suggest that diet might influence both the prevention and symptom management of mental disorders (186). The strength of the scientific evidence has allowed nutritional medicine to take place in mainstream psychiatric discourse (186).

At this point, the 2015 consensus position statement of the International Society for Nutritional Psychiatry Research advocated that nutrition should be considered central to psychiatric practice and that research, education, policy, and health promotion should reflect this new paradigm (186). That same year, a group of experts with diverse backgrounds related to epidemiology, psychiatry, and nutrition structured the first dietary recommendations for the prevention of depression (187). The five key dietary recommendations comprised: (i) following 'traditional' dietary patterns, such as the Mediterranean, Norwegian or Japanese diets; (ii) increasing consumption of fruits, vegetables, legumes, whole grain, nuts and seeds; (iii) including a high intake of foods rich in omega-3 polyunsaturated fatty acids; (iv) replacing unhealthy foods with nutritious and healthy foods; and (v) limiting intake of processed foods, fast foods, commercial pastries, and sweets. Position statements and recommendations such as these are crucial steps toward the widespread implementation of healthy dietary patterns as preventive measures for depression (188).

Nutrition has received more attention in the last decade as a modifiable lifestyle risk factor for depression (186), with particular attention to dietary matrices (189) and specific foods (190) that might modulate inflammatory factors. Consistent epidemiological and clinical evidence, particularly for depression, suggests positive associations between optimal diet quality and mental health. Indeed, current quantitative syntheses highlight the role of healthy dietary patterns in decreasing the risk of depression (191) and of diet-based interventions in reducing depressive symptoms (192). The main challenge for evidenced-based nutrition is to determine the temporal relationship between diet and mental health and to consider the complex multifactorial nature of depressive disorders. Nutritional epidemiological research in mental health is especially prone to reverse causality; there may be a cyclical pattern and a bidirectional relationship between diet quality and depression (193).

The current increase in the adoption of unhealthy eating habits (i.e., diets rich in ultra-processed foods and abundant in fat, added sugar, sodium, and various chemical additives) has created a large-scale global challenge that alters the accessibility of traditional foods and important sources of healthy nutrients throughout human history, such as fruits, nuts, and vegetables. This trend in dietary structure toward low-quality food matrices plays a key role in the activation of the innate immune system that releases proinflammatory cytokines, promoting, among other mental health dysregulations, depressive symptoms. The rising number of depression cases since the 1990s and the increased risk attributed to the COVID-19 pandemic in 2020, together with its clinical and socioeconomic implications, characterizes depression as a critical public health concern that requires urgent mitigation strategies.

Diet may act as a modifiable protective or risk factor for depression (189) and as a potential complementary strategy for the treatment of depression (194). However, there is limited evidence on specific dietary patterns, such as the Dietary Inflammatory Index, on specific foods, such as nuts, or on dietary interventions, such as MD-based approaches, in the prevention and treatment of depression.

Dietary Inflammatory Index

Of the latter, diet has increasingly emerged as a possible independent predictor of depression risk (186). One of the key factors is that dietary habits modulate inflammatory factors (195), and in recent years, links have been established between chronic inflammation and depression (196). The inflammatory potential of diet and increased levels of inflammatory biomarkers have been reported to be major contributors to the incidence of depression (195,196). In this regard, the Dietary Inflammatory Index (DII) was developed to estimate the inflammatory potential of the overall diet according to the pro- and anti-inflammatory effect of different dietary parameters on various circulating inflammatory biomarkers (197). The DII provides a novel tool to explore the mechanistic inflammatory contribution of different dietary components (197).

The inflammatory potential of the diet could be calculated from the DII according to Shivappa's procedure (197). The DII is a scoring algorithm based on a robust review of the literature published up to 2010, which included 1943 articles analyzing the effect of dietary components on inflammation. A total of 45 dietary parameters, including foods, individual nutrients, and other bioactive compound components, were scored based on their effects on six inflammatory biomarkers (i.e., C-reactive protein, interleukin-6, interleukin-1β, interleukin-4, interleukin-10, and tumor necrosis factor-α) (**Table 2**). Dietary parameters were standardized using the world averages from 11 data sets provided in the procedure and formed the basis of a composite data set containing the means of intakes for each of the 45 dietary parameters. These values were converted to centered percentiles, which were then multiplied by the 'overall dietary parameter-specific inflammatory effect score' to obtain the 'dietary parameter-specific DII score'. The sum of all 'dietary parameter-specific DII scores' resulted in the 'overall DII score'.

The DII has been validated in more than 25 studies with a range of inflammatory markers, including C-reactive protein, interleukin-6, and tumor necrosis factor-α (198). Since the development of the DII in 2014, over 500 studies have investigated the association between the DII and a diverse range of chronic disease-related outcomes, including depression (199). A recent synthesis of meta-analytic data from observational studies provided a credibility assessment of these relationships (13). Although suggestive evidence was presented between a proinflammatory dietary pattern and an increased risk of depression, the strength of the evidence was limited, and further cohort studies are needed to improve the precision of the estimates.

Table 2. Inflammatory effect of the dietary parameters included in the Dietary Inflammatory Index. [1]

Parameter	Effect [2]	Parameter	Effect [2]	Parameter	Effect [2]
Carbohydrate	▲	Green/black tea	▼	Flavones	▼
Cholesterol	▲	Riboflavin	▼	Magnesium	▼
Energy	▲	Selenium	▼	MUFAs	▼
Iron	▲	Thiamin	▼	Niacin	▼
Protein	▲	Vitamin A	▼	ω-3 fatty acids	▼
Saturated fat	▲	Vitamin B_6	▼	ω-6 fatty acids	▼
Total fat	▲	Vitamin C	▼	Onion	▼
Trans fat	▲	Vitamin D	▼	PUFAs	▼
Vitamin B_{12}	▲	Vitamin E	▼	Flavonols	▼
Alcohol	▼	Zinc	▼	Anthocyanidins	▼
β-Carotene	▼	Eugenol	▼	Isoflavones	▼
Caffeine	▼	Ginger	▼	Pepper	▼
Fiber	▼	Saffron	▼	Thyme/oregano	▼
Folic acid	▼	Turmeric	▼	Rosemary	▼
Garlic	▼	Flavan-3-ol	▼	Flavononels	▼

[1] Specific mean intakes and effect scores of each dietary parameter are detailed in the world composite database published from Shivappa et al. 2013 (197). [2] Upward arrows (▲) indicate proinflammatory effects and downward arrows (▼) indicate anti-inflammatory effects associated with the mean intake of each dietary parameter detailed in the world composite database.
Abbreviations: MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.

Mediterranean diet

A recent umbrella review comprising 19 meta-analyses of observational studies and randomized controlled trials highlighted the role of healthy dietary patterns on depression incidence (191). In particular, the most consistent evidence concerned MD, for which higher adherence was associated with a lower risk of depression. This dietary pattern, rich in fruits, herbs, virgin olive oil, whole grains, nuts, and vegetables, among other foods, has been associated with reductions in systemic inflammatory markers (200). This has been supported by a meta-analysis of randomized controlled trials reporting significant reductions in C-reactive protein and interleukin-6, as well as an increase in adiponectin, following the effects of MD-based interventions (201). In addition, some nutrient-rich food compounds, such as fiber (202), omega-3 fatty acids (203) or polyphenols (204), have demonstrated anti-inflammatory properties. In contrast, adherence to Western dietary patterns, characterized by low consumption of plant-based foods and high consumption of calorie-dense ultra-processed foods, is associated with increased levels of inflammatory markers (205,206).

Lifestyle interventions, without side effects, based mainly on the promotion of healthy diets and active routines, has demonstrated encouraging results in alleviating depressive symptoms (207). As commented regarding the role of PF, nutrition also plays a key role in promoting mental health. However, whether MD is an effective evidence-based treatment for depression is unknown. Upcoming results from recent trials (194,208) will aid in elucidating the mechanisms underlying the effects of diet on depression, in addition to discerning the effects of MD-based interventions on the severity of depressive symptoms in people with depression.

Underlying mechanisms between diet and depression

The dietary pathways to depression are related to inflammation, oxidative stress, HPA axis function, tryptophan–kynurenine metabolism, neurogenesis, brain-derived neurotrophic factor (BDNF), epigenetics, mitochondrial function, and gut microbiota (147) (**Figure 12**).

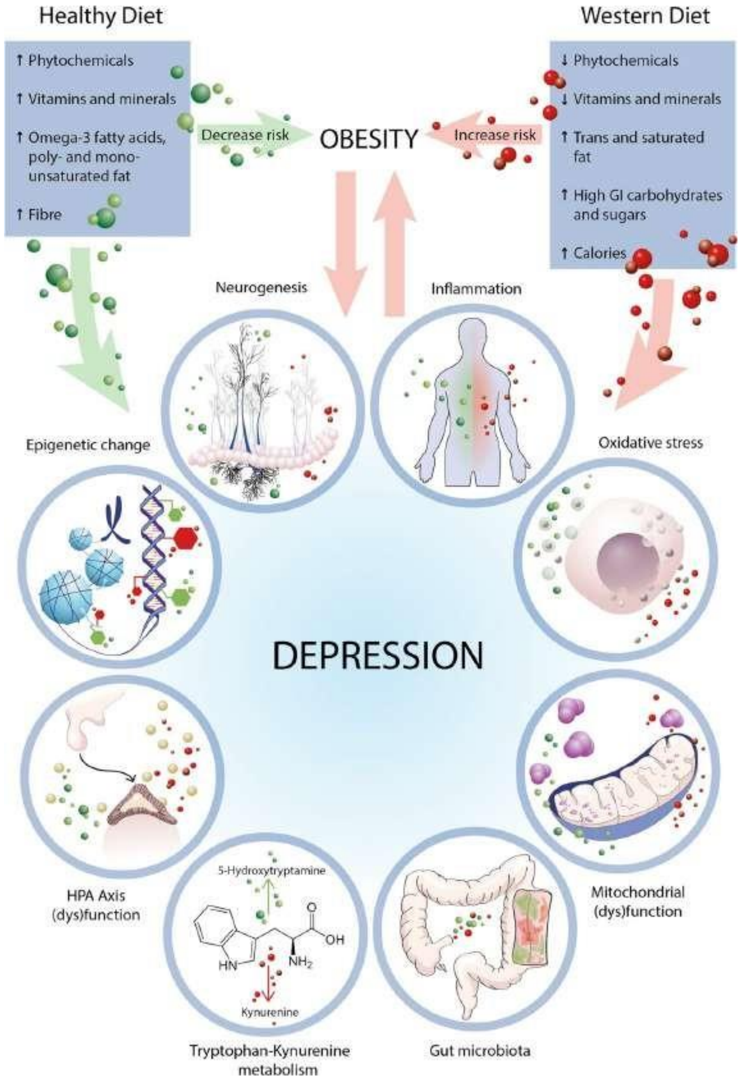

Figure 12. The role of diet quality on the pathways implicated in depression. Published from Marx et al. 2021 (147).

While there is still much to be discovered, available evidence suggests that certain cytokines can cross the blood–brain barrier, transmitting signals to the brain through afferent nerves that influence brain functions and promote depressive-like behaviors (209). Activation of immune cells can lead to excessive production of reactive oxygen species, resulting in oxidative stress. This is likely to affect brain neuronal cells because of their requirement for higher oxygen consumption and relatively weak antioxidant defense (147).

In addition, stimulation of proinflammatory cytokine production might be attributed to diet-induced intestinal microecological disruption, which may lead to increased intestinal mucosal permeability, implicated in the pathogenesis of depression (147). Furthermore, proinflammatory cytokines could affect the HPA axis, which is associated with decreased hippocampal volume, impaired neuronal plasticity, and decreased neurochemical function (210).

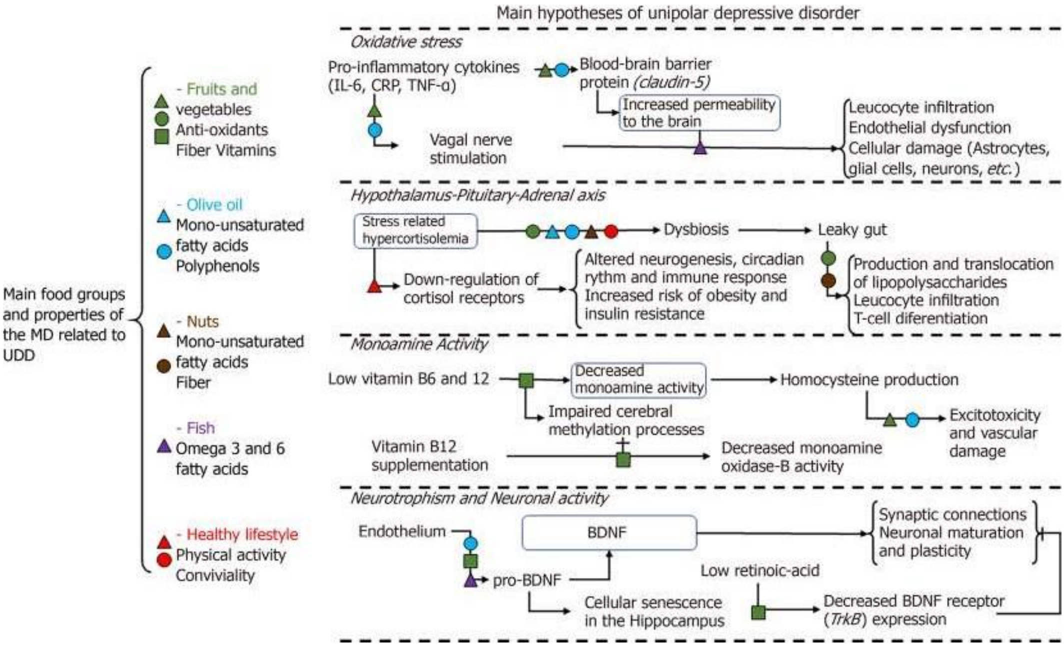

Figure 13. Main interactions between some of the main components of the Mediterranean diet and depression. Published from Pano et al. 2021 (188).

Abbreviations: MD, Mediterranean diet; UDD: unipolar depressive disorder; IL-6: interleukin-6; CRP: C-reactive protein; TNF-α: tumor necrosis factor-α; BDNF: brain-derived neurotrophic factor.

Inflammatory markers such as C-reactive protein or tumor necrosis factor-α have been useful in demonstrating that inflammatory activity could be related to depression. In fact, adults with depression have increased inflammatory reactions and exhibit dysfunctional physiological stress system responses (211). In this context, healthy dietary patterns provide a rich variety of phytochemicals that might be associated with various mechanisms, such as anti-inflammatory or antioxidant activities, involved in the progression of pathogenic diseases (212). Some evidence suggests that healthy food matrices encompassing the consumption of antioxidant-rich food groups, such as fish, fruits, legumes, nuts, olive oil, seeds, and vegetables, reduce the onset and symptomatology of depression (191,213). The synergistic effect of healthy diet prototypes, such as MD, leads to favorable nutrient intake (i.e., rich in dietary fiber, unsaturated fatty acids, probiotics, vitamins B-D-E, selenium, zinc, carotenoids, phytosterols, polyphenols) associated with reduced reactive oxygen species (124) and proinflammatory cytokine expression (123) that drive important signaling events in the depressed state (196). **Figure 13** details the interactions between significant MD food groups and their bioactive compounds and the etiological hypotheses of depression with their major contributors (188).

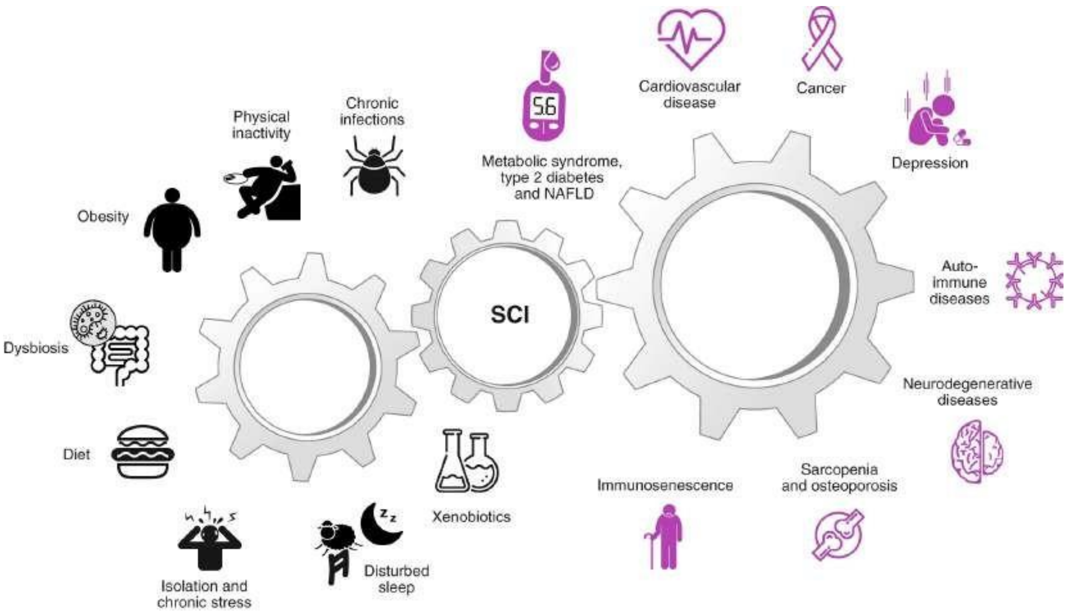

Figure 14. The most common triggers (left) of low-grade systemic chronic inflammation and their consequences (right). Published from Furman et al. 2019 (209).
Abbreviations: SIC, systemic chronic inflammation.

Chronic inflammation in adulthood is influenced in part by a complex process called cellular senescence, which is characterized by the arrest of cell proliferation and the development of a multifaceted senescence-associated secretory phenotype (214). This senescent phenotype converts senescent fibroblasts into proinflammatory cells (secretion of proinflammatory cytokines, chemokines, and other proinflammatory molecules) (214), and health consequences include an increased risk of depression (195). A combination of social, environmental and lifestyle risk factors is part of the explanation for cells acquiring the senescent phenotype (209) (**Figure 14**).

Of the nonendogenous contributors, diet has been conceived as a major component in increased activation of the inflammatory response system in adults (195). Over time, low-grade systemic inflammation may pave the way for chronic conditions such as depression (209). In other words, inflammation only becomes harmful when it persists for a long time and begins to damage healthy cells, resulting in a proinflammatory state. A healthy diet aimed at interrupting the chronic systemic depression-inflammation cycle should consider favorable nutrient intake and anti-inflammatory dietary components associated with the pathophysiologic pathways of depression (215–218). Specifically, MD provides a rich source of bioactive compounds with strong antioxidant properties (106) that may affect the major biological mechanisms (i.e., oxidative stress and proinflammatory state) of depression (147).

Other potential pathways that could be beneficially modulated by healthy diets include BDNF (related to synaptic plasticity and neuronal survival and differentiation) (219), endothelial function (increased percentage of flow-mediated dilatation) (220), gut microbiota (modulation of taxonomic composition and short-chain fatty acid production) (221), and lipid metabolism (improved triglyceride content of high-density lipoproteins) (222). In addition, healthy dietary patterns have been closely associated with several beneficial health outcomes (95) and could encompass different lifestyle elements (e.g., adequate rest, conviviality, regular PA) (90) that can contribute to reducing the severity of depressive symptoms (223).

A traditional food in the human diet: nuts

Definitions of nuts could be based on botanical and nutritional perspectives. The botanical classification defined nuts as a dry one-seeded fruit with an extremely hard pericarp (outer layer of the ovary wall), which includes chestnuts and hazelnuts (224). Dietary guidelines do not follow botanical definitions and include nuts according to their nutritional composition. As defined by nutrition research (224), nuts are nutrient-dense foods that include a wide variety of types, such as almonds, Brazil nuts, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios, and walnuts. Peanuts, which are legumes, are also integrated among nuts because they share a similar nutritional profile. However, coconut and chestnuts are excluded from the above definition because of their high saturated fat and high carbohydrate and water content, respectively (224). In the present thesis, nuts are considered for the purpose of health outcome analysis and, accordingly, are based on the nutritional research classification that includes both tree nuts and peanuts (224).

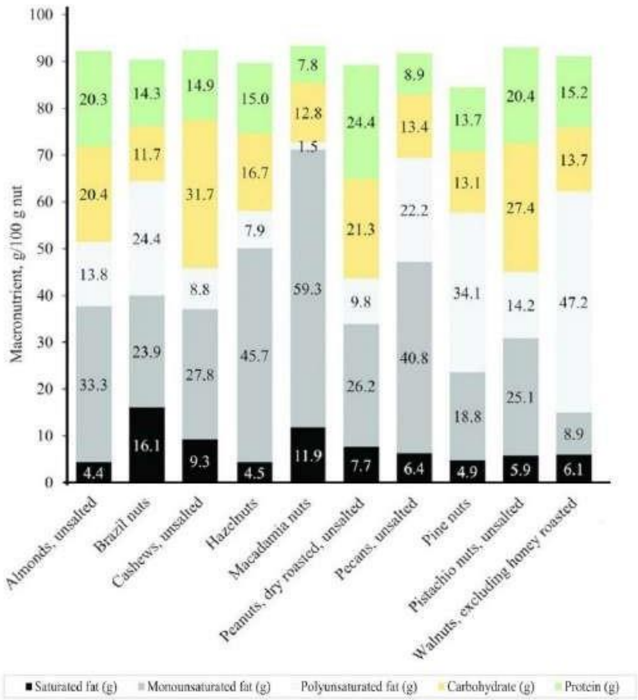

Figure 15. The content of carbohydrate, protein, and fat (saturated, mono-, and polyunsaturated fats) in grams per 100 grams of nuts. Published from George et al. 2022 (224).

Despite their diversity, nuts share essential nutritional properties (i.e., bioactive substances such as phenols or phytosterols, essential micronutrients, fiber, high-quality protein, monounsaturated and polyunsaturated fatty acids, and vitamins) (224) that could play a beneficial role in mental health (225). The specific breakdown of macronutrients and micronutrients per 100 grams of nuts is shown in **Figure 15** and **Table 3**. Nuts provide a rich variety of bioavailable phytochemicals that might be associated with various mechanisms involved in the progression of pathogenic processes (226). Alterations in oxidative-antioxidant balance and elevated levels of inflammation are two key pathways in depression. The nutritional composition of nuts (e.g., dietary fiber, omega-3 fatty acids, phenols, polyphenols, and vitamin E) may affect mental health primarily through anti-inflammatory and antioxidant mechanisms (227), including downregulation of proinflammatory cytokines, neutralization of reactive oxidative species, and enhancement of innate antioxidant defenses. Additionally, nuts are rich in amino acids, including arginine, glutamine, serine, and tryptophan (228), and lower levels of these amino acids have been associated with depression (229).

Other mechanisms underlying the possible impact of nuts on mental health have been suggested, such as increased BDNF levels and tryptophan metabolism and stimulation of the interplay between the gut microbiome and brain health (226,230,231). Metabolites produced along the tryptophan-kynurenine pathway (i.e., kynurenic acid as neuroprotective and quinolinic acid or 3-hydroxykynurenine as neurotoxic) (232) are vital neurobiological mediators in depression (229). In addition, previous studies have reported beneficial associations between an MD enriched with nuts and BDNF (231), a molecule highly expressed in the hippocampus that is involved in synaptic plasticity and cellular metabolism, playing a key role in mood (219). Finally, the gut microbiota, a mediating pathway between diet and brain health that can partially modulate inflammatory activities, serves as another potential mechanism of action implicated in depression (233).

Nuts are frequently included in current dietary guidelines and healthy dietary patterns as a food with multiple health benefits (234), such as potential antidepressant activity (235). In general, dietary guidelines recommend a daily intake of 30 grams of nuts (234), which coincides with the estimated amount supported by scientific evidence on their health benefits (236). However, the role of nut consumption in mental health has been little explored. Specifically, it is still uncertain whether nuts may play an important role in the prevention of depression.

Table 3. Nutrient composition of commonly consumed nuts. [1]

Nutrients, unit/100 g	Alm	Braz	Cas	Haz	Mac	Pea	Pec	Pine	Pist	Wal
Energy, kcal	607	659	583	628	716	587	697	673	581	654
Tot sugars, g	4.7	2.3	4.9	4.3	4.1	4.9	3.9	3.6	7.5	2.6
Tot dietary fiber, g	10.6	7.5	2.9	9.7	8.0	8.4	9.3	3.7	10.0	6.7
Total fat, g	54.0	67.1	48.0	60.8	76.1	49.7	72.8	68.4	47.4	65.2
Vitamin A, RE	0	0	0	1.0	0	0	3.0	1.0	13.0	1.0
α-Carotene, µg	0	0	0	3.0	0	0	0	0	0	0
β-Carotene, µg	1	0	0	11	0	0	28	17	154	12
β-Cryptoxanthin, µg	0	0	0	0	0	0	9.0	0	0	0
Lutein + zeaxanthin, µg	1	0	22	92	0	0	16.0	9	1125	9
Thiamin, mg	0.07	0.6	0.1	0.6	0.7	0.1	0.6	0.3	0.6	0.3
Riboflavin, mg	1.1	0.03	0.1	0.1	0.08	0.1	0.1	0.2	0.2	0.1
Niacin, mg	3.5	0.2	1.3	1.8	2.2	14.4	1.1	4.3	1.3	1.1
Vitamin B-6, mg	0.13	0.10	0.24	0.56	0.35	0.46	0.20	0.09	1.09	0.53
Tot folate, µg	53	22	67	113	10	9	21	34	49	98
Tot choline, mg	50.5	28.8	59.2	45.6	44.6	64.6	39.3	55.8	69.3	39.2
Vitamin C, mg	0	0.7	0	6.3	0.7	0	1.1	0.8	2.9	1.3
Vitamin E, mg	23.5	5.6	1.2	15.0	0.5	4.9	1.7	9.3	2.4	0.7
Vitamin K, µg	3.5	0	37.2	14.2	0	0	6.9	53.9	16.3	2.7
Calcium, mg	260	160	44	114	70	58	68	16	104	98
Phosphorus, mg	457	725	475	290	198	363	269	575	455	346
Magnesium, mg	271	376	252	163	118	178	117	251	106	158
Iron, mg	3.6	2.4	5.8	4.7	2.6	1.5	2.4	5.5	3.9	2.9
Zinc, mg	3.2	4.0	5.4	2.4	1.2	2.7	4.3	6.4	2.2	3.0
Copper, mg	1.0	1.7	2.1	1.7	0.5	0.4	1.1	1.3	1.2	1.5
Selenium, µg	1.9	1920	11.3	2.4	11.7	9.3	3.7	0.7	9.7	4.9
Potassium, mg	692	659	548	680	363	634	398	597	977	441
Sodium, mg	3.0	3.0	16.0	0	353.0	6.0	0	2.0	6.0	2.0

[1] Nutrient breakdown obtained from the USA Food and Nutrient Database for Dietary Studies' 2017–2018 in George et al. 2022 (224).
Abbreviations: Alm, almonds; Braz, Brazil nuts; Cas, cashews; Haz, hazelnuts; Mac, macadamia nuts; Pea, peanuts; Pec, pecans; Pine, pine nuts; Pist, pistachio nuts; RE, retinol equivalents; Tot, total; Wal, walnuts.

CHAPTER 3: PHYSICAL ACTIVITY AND DEPRESSION

Physical activity: definition, health impact and prevalence

PA is defined as any bodily movement produced by skeletal muscles that requires energy expenditure (237) and can be performed at different intensities and accumulated through work, domestic chores, transportation or during leisure time or by participating in sport activities, walking, cycling, and active play. Conversely, physical inactivity is defined as doing insufficient PA to meet current recommendations (237).

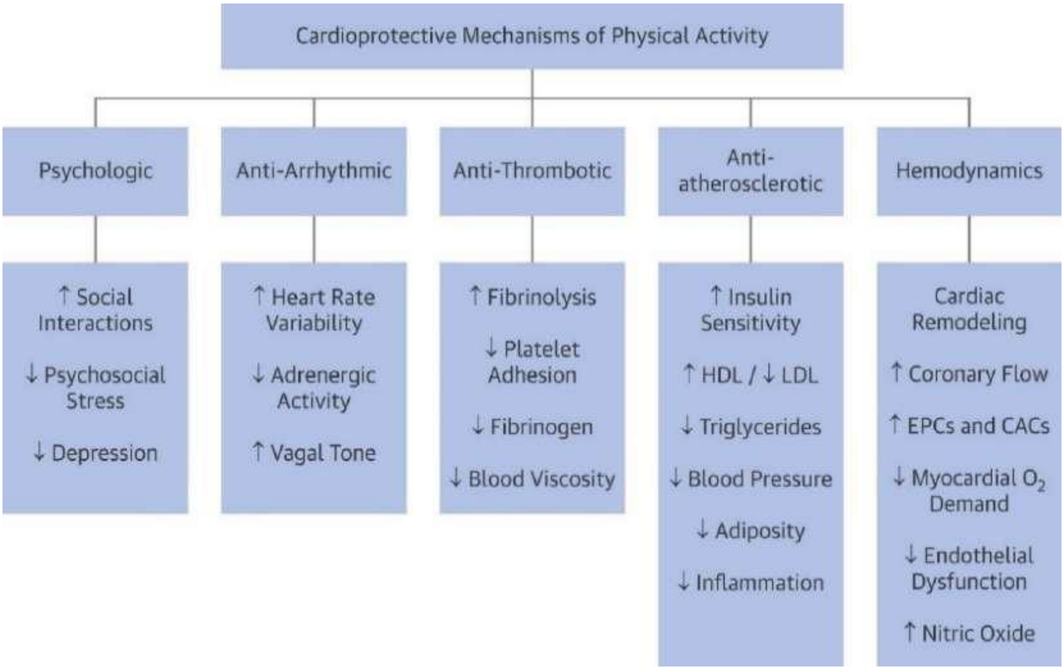

Figure 16. Cardioprotective mechanisms by which physical activity may reduce the risk for noncommunicable diseases. Published from Kachur et al. 2017 (238).
Abbreviations: BP, blood pressure; CAC, circulating angiogenic cell; EPC, endothelial progenitor cell; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

PA is a fundamental pillar in the health and well-being of adults. Regular PA promotes both physical and mental health, independent of age, sex, and functional abilities (14). The health benefits of PA are associated with several outcomes, such as improved musculoskeletal system, PF, cognitive function, and quality of life, or reduced risk of mortality and various diseases (e.g., cancer, cardiovascular diseases, dementia, depression, type 2 diabetes)

(14). Daily PA is a key protective factor for the prevention and management of NCDs due to multiple positive pathways (e.g., biological, psychosocial) with beneficial health consequences (14) (**Figure 16**).

Conversely, insufficient levels of PA are one of the major modifiable risk factors for mortality and NCDs worldwide (17,239). Physical inactivity has even been called the greatest public health problem of the 21st century (74). Insufficient PA is associated with systemic pathophysiology that contributes to the development of health imbalances (14). Current global estimates indicate that insufficient levels of PA cause 7.2% and 7.6% of deaths from all causes and cardiovascular disease, respectively (239). In turn, the most recent global estimates published in 2018 show that approximately one in four adults, out of a total of 1.9 million, were insufficiently active (44). Specifically, 27.5% of adults do not meet the recommended level of PA (i.e., not accumulating at least 150 minutes per week of moderate intensity, 75 minutes per week of vigorous intensity, or any equivalent combination of the two) to improve and protect their health (44). Worryingly, this trend remained largely unchanged from 2000 to 2016 (240) (**Figure 17**).

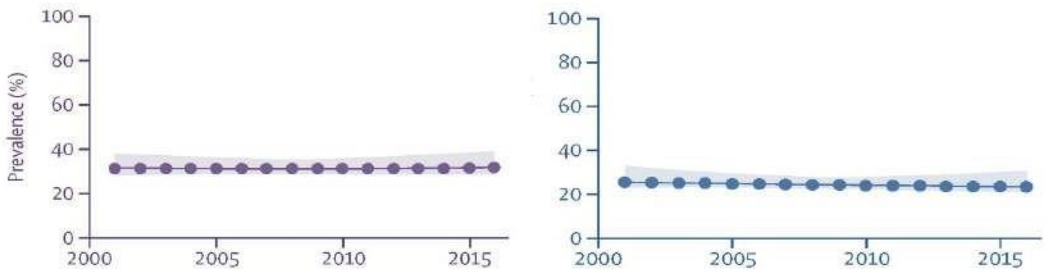

Figure 17. Worldwide trends in insufficient physical activity in women (left side of the panel) and men (right side of the panel) from 2000 to 2016. Published from Guthold et al. 2018 (44).

In this context, the economic burden of insufficient levels of PA on health systems and society is large and substantial. Globally, 449.2 million new cases of preventable NCDs are expected to occur between 2020 and 2030 worldwide if there is no change in the prevalence of physical inactivity (241). The global cost of all preventable NCDs is likely to result in treatment costs of approximately US$301.8 billion (241). These estimations also indicate that nearly half of new NCD cases will result from depression (~43%) and will account for 28% of total direct health care costs (241) (**Figure 18**). Consequently, urgent public health strategies are needed to increase population PA levels and reduce the burden of NCDs and health-related consequences (242).

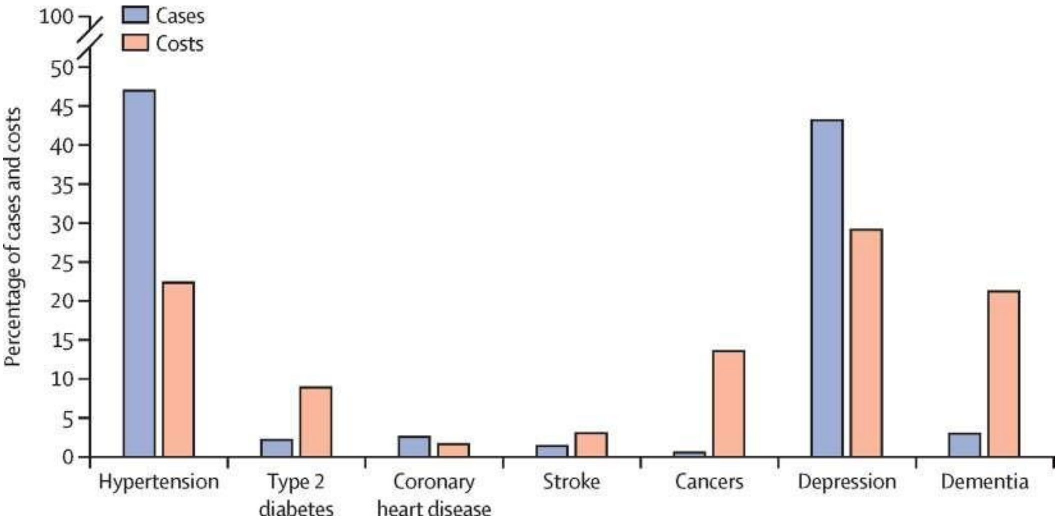

Figure 18. Total global proportion of new cases and direct health-care costs of noncommunicable diseases attributed to physical inactivity between 2020 and 2030. Published from Santos et al. 2023 (241).

Modifiable lifestyle risk factors for depression: the role of physical activity

A meta-review published in 2020 summarized the critical role of modifiable health behaviors, such as PA, in public health strategies focused on depression prevention (10). Moreover, two meta-analyses of prospective cohort studies consistently reported that adults with high levels of PA had between 17% (243) and 21% (244) lower risk of developing depression than their counterparts with low levels of PA. Specifically, habitual and increasing levels of moderate to vigorous PA in cohort studies are inversely associated with incident depression and the occurrence of depressive symptoms among adults regardless of age, sex, or geographic region (244).

In turn, meta-analytic evidence supports that any level of PA confers protection against the onset of depression (223,243). Indeed, light-intensity activities such as walking, which are potentially feasible, safe, and cost-effective, have been shown to be as effective as more vigorous forms of PA in reducing the risk of depression (245). Even small amounts of PA (e.g., walking <150 minutes per week) have been associated with a lower incidence of depressive episodes (245). This may be especially significant in people with depression, who are less likely to achieve the recommended levels of PA (e.g., performing 150 minutes of moderate-intensity PA per week) compared to people without major depression (246).

Evidence syntheses on the associations between PA and risk of depression have focused on self-reported data (243–245) and, to a lesser extent, on objectively measured data (223,248). The different methods used to measure PA could produce contrasting results and inconsistent conclusions (248). Indeed, self-reports and wearable devices capture different constructs, i.e., questionnaires cover continuous blocks of time during which episodes of activity occur, whereas devices cover actual PA episodes of any duration, including those that occur intermittently (247) (**Figure 19**).

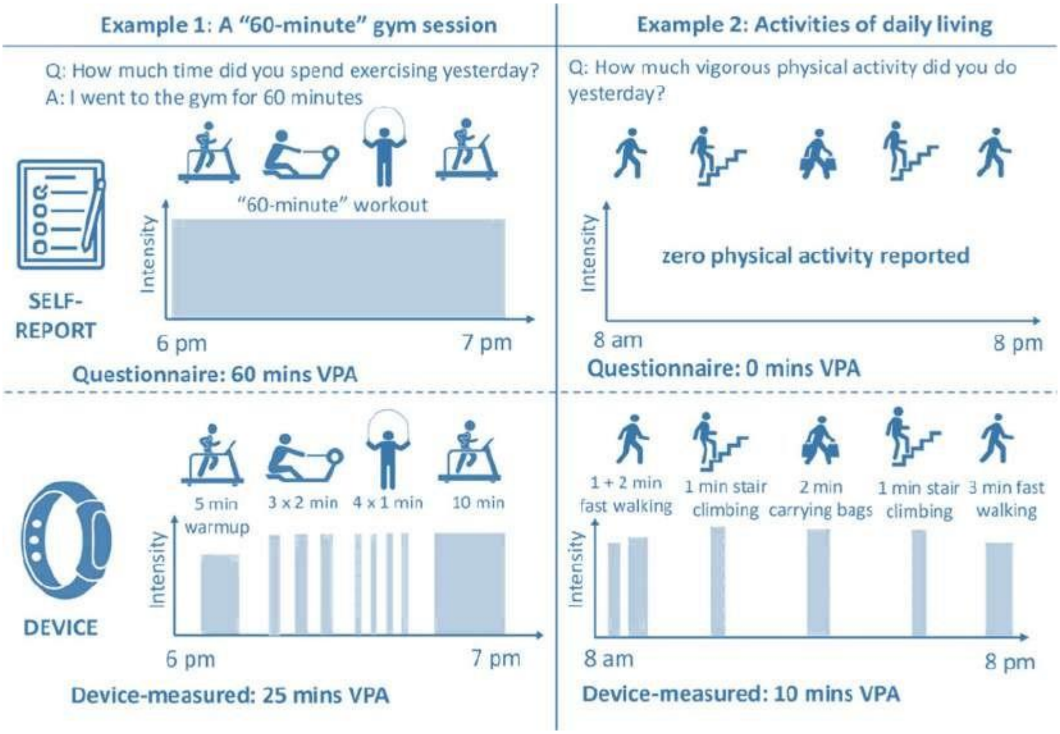

Figure 19. Physical activity captured by self-report questionnaire (top panels) and wearable device (bottom panels) in two different situations: a session in the gym (example 1, left panels) and during intermittent activities of daily living (example 2, right panels). Self-reported data overestimate physical activity in the former but underestimate physical activity in the latter. Published from Gill et al. 2023 (247).

Abbreviations: VPA, vigorous physical activity.

Recent studies using wearable devices have affected our understanding of the study associations between PA and health outcomes (247). Although quantifying real-world PA data is challenging (243), a genome-wide association study pointed out the importance of objectively assessing PA in epidemiological studies focusing on mental health to elucidate the PA-depression relationship (249). In fact, there is increasing evidence that objectively measured PA is more accurate than self-reported PA (248). In this sense, emerging evidence from wearable devices offers important opportunities for the development of future PA guidelines that report simple and achievable goals for the general adult population.

Underlying mechanisms between physical activity and depression

Different potential mechanisms have been proposed to explain the interaction between PA and depression, such as biological (e.g., inflammatory changes, mesolimbic pathway activation, neuroplasticity, regulation of the HPA axis) and psychosocial (e.g., self-efficacy, self-esteem, sleep quality, social support) mechanisms (250) (**Figure 20**).

Certain benefits of PA are thought to stem from its potential to prevent disruptions in neuroplasticity, a factor that may play a role in the pathophysiology of depression (251). Depression has been associated with structural brain alterations, such as white matter hyperintensities (252) and reductions in hippocampal and prefrontal volumes (253,254). Considering the subcortical brain alterations, a robust meta-analysis reported smaller hippocampal volumes (i.e., 1.24%) in people with depression compared to healthy controls (255). The 'neurotrophic hypothesis of depression' suggests that elevated glucocorticoid levels associated with chronic HPA axis hyperactivity in individuals experiencing depression may induce brain atrophy by remodeling and downregulating of growth factors such as BDNF (251). This process may preferentially affect the hippocampus, an important glucocorticoid sensor in relation to the stress response (256). Systematic reviews and intervention studies have found positive associations of PA with increased volumes of white matter, hippocampus, and various cortical regions in healthy adults (257–259). PA stimulates several cellular and molecular processes in the brain that support its functioning (250). Specifically, improvements in cerebral blood flow, circulation of neurotrophic factors and hippocampal functionality could be crucial for PA-induced neuroplasticity and neurogenesis in adults (260,261). PA stimulates these mechanisms associated with growth in various brain regions and a more efficient vascular delivery system, which are adversely affected in individuals with depression (262).

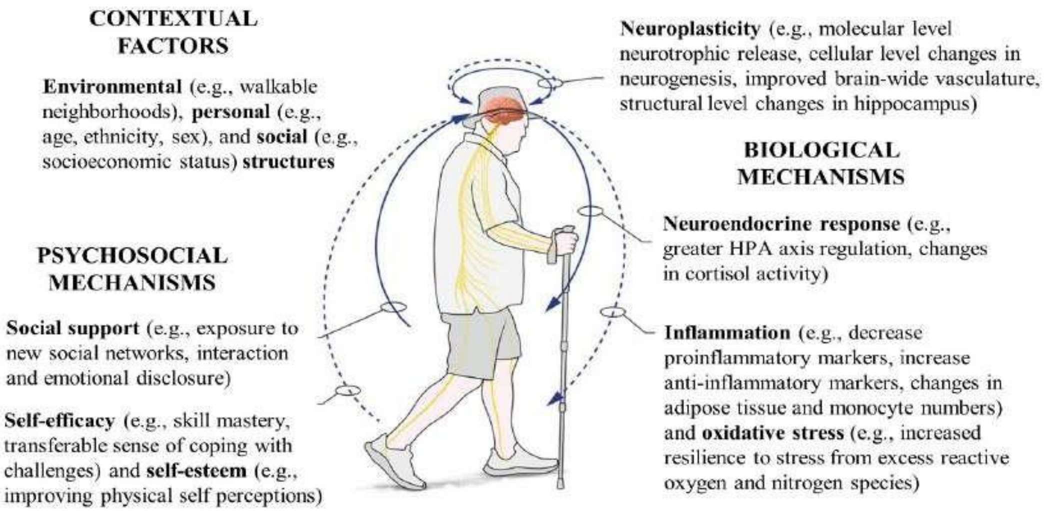

Figure 20. Protective mechanisms (biological and psychosocial) and influencing factors (contextual) of the relationship between physical activity and depressive symptoms. Adapted from O'Mara 2023 (263).
Abbreviations: HPA, hypothalamic–pituitary–adrenal.

A wide range of evidence suggests that chronic low-grade inflammation plays a role in the pathophysiology of depression (209). Of the nonendogenous contributors, insufficient PA has been conceived as a major component in the increased activation of the inflammatory response system in adults (209). Physical inactivity leads to visceral fat accumulation and deconditioned muscles that promote persistent low-grade systemic inflammation (264). Indeed, low levels of PA have been associated with elevated C-reactive protein and fibrinogen levels (265). Conversely, the cytokine profile induced by PA is overall anti-inflammatory (e.g., increases in interleukin-10) (266). PA acts through different mechanisms to create an anti-inflammatory environment. Muscles are myokine-secreting organs and elicit homeostatic adjustments to reduce levels of inflammation (266). Specifically, upregulation of interleukin-6 through PA could be associated with the release of anti-inflammatory cytokines such as interleukin-10 and inhibition of the production of the proinflammatory cytokine tumor necrosis factor-α (267,268). In addition, PA could reduce inflammation by modulating adipokine circulation, counteracting adipose tissue accumulation, and reducing inflammasome activation (264).

When maintained at low to moderate concentrations, free radicals and oxidants in cells and tissues perform physiological functions beneficial to the organism, such as elimination of pathogenic microbes, synthesis of cell signaling molecules, or mitogenic response (269).

However, when reactive oxygen species begin to outcompete antioxidants, they can adversely affect various cellular structures, such as lipids, proteins, lipoproteins, and deoxyribonucleic acid (270). This harmful process, known as oxidative stress, ensues from an imbalance between the formation of free radicals and the ability of cellular processes to detoxify these reactive products (269). Organs such as the brain are especially vulnerable to this damaging imbalance process because they have a high metabolic rate and low antioxidant levels (270). Oxidative stress pathways have been linked to depression through different mechanisms, such as degradation of antioxidant defenses or stimulation of proinflammatory cytokine production (270). Regular PA could produce an adaptative response to free radicals by reducing oxidative stress markers and increasing the production of antioxidant enzymes (271,272).

Moreover, the neuroendocrine system maintains homeostasis by regulating the internal environment of the organism (250). The HPA axis mediates physiological responses to stress in healthy individuals. However, depression has been associated with dysregulation of the HPA axis (273). Habitual PA could lead to physical (good) stress associated with increased inactivation of cortisol (active steroid) into cortisone (inert steroid) and increased levels of anandamide, BDNF, and serotonin (274). These factors could play important roles in amygdala hyperactivity, emotional processing, and neuronal plasticity (274). Thus, regular PA may act as a positive stressor for certain neuroendocrine pathways, regulating HPA axis tone and cortisol sensitivity (250).

Psychosocial and behavioral explanations have also been suggested. PA could act by improving physical and body image self-perceptions, social interactions, and personal development of coping strategies (250). The social aspect of activity participation and the environmental context could be important moderators of the association between PA and depression. For example, the use of green space is associated with a lower risk of depression (275), and neighborhood deprivation might reduce the mental health benefits of PA (276). Specifically, the biopsychosocial antidepressant framework induced by PA could occur in a reciprocal context in which a specific activity such as walking interacts from the inside out (i.e., neurobiological modulation of molecular and organ systems, stabilizing and consolidating changes in brain and body structure and function) and from the outside in (socially moderated biological adaptation of geographic locations and community contexts) (263).

Overall, more studies are needed to understand how daily PA influences the multifactorial interaction of the causes of depression. Most of the scientific evidence underlying the mechanisms between PA and depression examines the effects of both leisure-time PA and specific physical exercise programs. Although it is important to note that the impact of PA on oxidative and inflammatory responses depends on the modality, intensity and frequency of the activity, the crucial factor in triggering antidepressant mechanisms is the maintenance and consistency of regular PA (both unplanned and planned) over time. Indeed, regardless of the mechanism or combination of mechanisms responsible for PA to prevent depression, a daily active lifestyle emerges as a crucial factor in regulating and reinforcing these pathways (245). In this sense, daily steps could play a pivotal role in accumulating regular PA in an unstructured way and are a good option to break the cycle of some common adult's perceived PA barriers, such as low energy or fear of injury (277), which are particularly relevant in individuals experiencing depressive symptoms (278).

A simple and intuitive indicator of physical activity: daily steps

Robert Burton's Anatomy of Melancholy, first published in 1621, already recognized that lack of PA was the ruin of body and mind (279). The beginnings of the epidemiology of daily PA date back nearly 350 years ago (280), when the Italian physician Bernardini Ramazzini compared the diseases of various tradesmen, observing that fast runners (e.g., professional couriers) avoided the occupational hazards of sedentary tailors and shoemakers (281). The modern history of regular PA began in 1949 (280), when Morris and colleagues examined the risk of cardiovascular disease among various occupations and found that physically active workers suffered less ischemic-coronary heart disease than sedentary workers (282). Meanwhile, classical epidemiology (i.e., the study of decreasing infections and increasing various disorders) adapted to societal needs (i.e., "new" NCD problems related to lifestyle behaviors) and translated into both modern advances in methodological designs (e.g., cohort follow-up, family studies, international comparisons) and research extensions (e.g., genetic-environmental, physical-psychological, morbidity-mortality) (283).

However, insufficient PA is currently a major unsolved public health problem. Alarmingly, if trends in adult PA levels continue, the global target of a 15% relative reduction by 2030 will not be met (284) (**Figure 17**). In turn, global daily step counts in 1,255,811 individuals from 200 countries have not returned to pre-pandemic levels (i.e., ~5300 steps/day) in the 2 years since the onset of the COVID-19 pandemic (i.e., ~4600 steps/day) (285) (**Figure 21**). These current daily step patterns correspond to a sedentary lifestyle, leading to a correlated increase in NCDs such as type 2 diabetes or major depressive disorder (286,287). In the 21st century, the daily life movement of work and leisure in Western societies has been greatly threatened (16).

In this context, there is an urgent need to prioritize and scale up public health policies and strategies to increase PA levels in the population (44). In recent years, more countries have been monitoring the prevalence of PA levels, although evidence of any improvement is still scarce (240). Some obstacles to the implementation and progress of national policies hinder the increase in PA levels, with policy operationalization and lack of clarity about which actions are most likely to be effective and feasible being two of the most relevant challenges (240). At this point, daily steps could be a valuable strategy to set simple targets to increase levels of PA and achieve current recommendations for health benefits (288).

Available evidence underscores the importance of modifiable health behaviors, including PA, in public health strategies for depression prevention (10). Nevertheless, the impact of regular PA, such as daily steps, on depression remains uncertain. Daily steps may serve as a simple and intuitive measure of PA (288). Since the 1990s, scientific research has focused on evaluating the impacts of ambulatory activity on health (289). With the increasing popularity of wearable devices, monitoring daily steps has become a practical possibility for the general population (290). Undoubtedly, objectively measuring daily steps provides a more accurate representation of PA behavior than self-reported data (**Figure 19**). Although recent meta-analyses have presented compelling evidence that increased step counts can reduce the risk of cardiovascular diseases (291) and all-cause mortality (292), the 2018 USA Department of Health and Human Services (293) and 2020 WHO (294) expert committees on PA guidelines emphasized the need for additional research on other health outcomes.

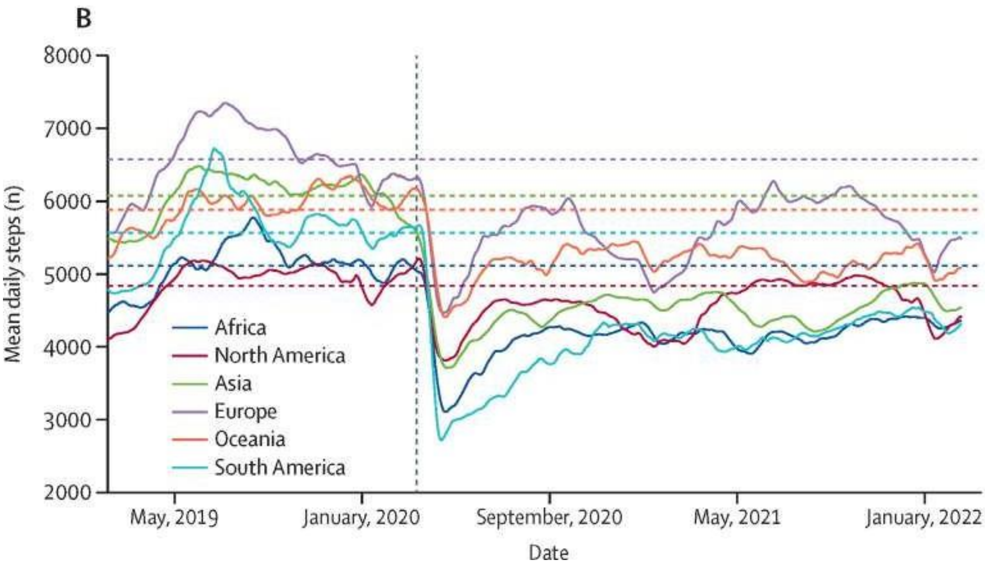

Figure 21. Global daily step reductions in all continents after COVID-19 onset (activity measures from 1 year before to 2 years after). Published from Tison et al. 2022 (285).

The more recent USA PA Guidelines released in 2018 indicate that some activity is better than none because any amount of PA provides some health benefits (293). Indeed, recent evidence suggests that taking between 2500 (295) and 4000 (296) steps/day significantly reduces the risk of all-cause mortality by 8% and 16%, respectively. This highlights the prevailing message that "something is better than nothing" (297), currently in force (296), regardless of the individual's capacity to perform PA or the spectrum of daily PA patterns (active-sedentary). Every step in chronic disease prevention may be especially important for specific populations (e.g., older adults, individuals with limited activities of daily living) in whom daily steps emerge as an accessible PA strategy (298).

A recent meta-analysis of 15 cohort studies suggested that even small doses of PA (2.5 hours per week at moderate intensity, such as brisk walking) were associated with a decreased incidence of depression (223). However, their results are based on studies in which PA metrics were self-reported and estimated in marginal MET task hours per week. The relationship between daily steps measured with wearable activity trackers and depression has not been examined in a synthesized form. Setting PA goals based on the number of daily steps is easy to understand and integrate into daily routines of the general population and may be valuable to consider in depression prevention guidelines.

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METHODS AND BASIS FOR THIS DOCTORAL DISSERTATION

METHODS

This doctoral thesis incorporates different methodological approaches as an essential element to address the underlying research questions and gain a comprehensive understanding of the proposed associations. The doctoral dissertation comprises different study designs to obtain a more realistic and integrated picture of the relationships between exposure (diet and physical activity) and outcome (physical fitness and depression) variables. Each manuscript details the proposed methodology along with its ethical aspects, data synthesis and statistical analyses. Overall, the present thesis is based on the following methodological approaches:

- **Systematic review protocol**

  A systematic review protocol outlines the reasoning, hypothesis, and methods intended for the subsequent systematic review. It is created in advance and serves as a guide for conducting the review. Elaborate protocols are designed beforehand, made accessible to the public, and registered in an international database such as PROSPERO. Systematic review protocols could provide important steps toward a rigorous and methodical approach, an essential component of systematic reviews according to prespecified methods and analyses. Publishing or registering review protocols not only serves as a roadmap for research but also enables minimizing the risk of duplicate studies. **Manuscripts I** and **V** cover this study design, generating detailed methodological plans for conducting two systematic reviews and meta-analyses.

- **Systematic review and meta-analysis**

  Systematic reviews aim to summarize evidence using transparent and clearly defined rules. Prior to conducting systematic reviews, research questions are established, and there is an explicit and reproducible methodology through which studies are selected and reviewed. The objective of systematic reviews is to cover all available evidence objectively and to evaluate the validity of that evidence using predefined standards. Outcomes are synthesized in a systematic manner, resulting in a comprehensive evaluation of the evidence. In addition, meta-analyses aim to produce a numerical estimate that summarizes the data collected. They quantitatively combine results from prior evidence, making primary studies the basis of analyses. In this doctoral thesis, three systematic reviews with different methodological approaches were conducted in relation to the research questions: (i) a systematic review and meta-analysis of observational and intervention studies synthesizing evidence of cross-sectional and prospective associations between adherence to the Mediterranean diet and physical fitness levels (**Manuscript II**); (ii) a systematic review and meta-analysis of randomized controlled trials summarizing the effect of Mediterranean diet-based interventions on the severity of depressive symptoms in adults with depression (**Manuscript VI**); and (iii) a systematic review and meta-analysis of observational studies estimating the cross-sectional and prospective relationships between the number of daily steps and the prevalence or risk of depression or depressive symptoms (**Manuscript VIII**).

- **Cross-sectional study**

Observational study designs are distinguished by specific characteristics of the research study, such as the main objectives, how subjects are sampled and the timeline of data collection. Among them, cross-sectional studies analyze exposure and outcome simultaneously (i.e., at one specific point in time) for a population. In medical research, they are often employed to measure the prevalence of health outcomes, examine determinants of health, or describe population characteristics. Cross-sectional studies do not follow individuals over time. Once the subjects are selected, the investigators collect the data at a single point in time. They are useful for providing initial evidence and exploring possible associations between exposure and outcome. Participants for a cross-sectional study are chosen from an available population of potential relevance to the proposed research question. **Manuscript III** comprises a panel study with a cross-sectional design that collected data on cardiovascular risk factors, body composition, nutritional and lifestyle habits, and physical fitness in 18–30-year-old university students from Castilla-La Mancha (Spain) during the 2016/2017 academic year.

- **Cohort studies**

Cohort studies are a type of longitudinal study that follows the research population over time. Specifically, they include the recruitment and following of participants who share a common characteristic, such as a particular occupation or demographic similarity. Cohort studies help to build an understanding of what factors increase or decrease the likelihood of developing adverse health outcomes. Thus, as a portion of the cohort is exposed to a particular characteristic during the follow-up period, potential connections between exposure and outcome can be investigated by tracking health outcomes over time. Therefore, prospective cohort studies are an essential tool in epidemiology to discern the factors that influence disease incidence (i.e., the occurrence of new cases in a specific period). In this doctoral thesis, two prospective studies were conducted using three large-scale biomedical databases, the Seniors-ENRICA (I and II) and UK Biobank cohorts. The Seniors-ENRICA studies were established between 2008–2010 (Seniors-ENRICA I, first follow-up: 2012) and 2015–2017 (Seniors-ENRICA II, first follow-up: 2019) and included non-institutionalized participants older than 60 years. Between both Seniors-ENRICA cohorts, data on body composition, cardiovascular risk factors, nutritional and lifestyle habits, and mental health were collected using similar procedures, questionnaires, and instruments in more than 5000 older adults. **Manuscript IV** examines the influence of a proinflammatory dietary pattern on the risk of depression in two national (Spain) and regional (Madrid, Spain) representative samples of older adults. **Manuscript VII** analyzes a large sample of adults over 40 years from the United Kingdom who participated in the UK Biobank cohort. At the start of the study in 2006–2010, more than 500,000 participants completed a tactile questionnaire and underwent a clinical assessment to record anthropometric measurements, respond to self-report scales on a wide range of health outcomes, and collect blood samples. The UK Biobank provides updated information at additional time points from 2012–2013, with ongoing follow-up of subsamples of participants.

BASIS FOR THIS DOCTORAL DISSERTATION

This doctoral thesis is based on the following statements:

PART I – Chapter 1

a) **Manuscripts I and II: The influence of adherence to the Mediterranean diet on physical fitness in adults of all ages**

Nutrition has received increasing attention as one of the most potent, feasible, and safest strategies to extend the time in which health status and functional capacity are maintained. In this context, the Mediterranean diet is a robust scientific concept associated with favorable health outcomes over the entire life span. Specifically, the synergistic effect of their dietary characteristics leads to a high-quality nutrient intake that could promote greater physical fitness, a key determinant of health. A previous meta-analysis showed promising results in the associations between Mediterranean diet adherence and physical fitness levels in children and youth. However, available evidence syntheses in adults are limited and inconclusive, focusing primarily on musculoskeletal impairment outcomes rather than physical fitness. A meta-analytic approach could help to better understand whether and to what extent adherence to the Mediterranean dietary pattern and its individual components are associated with each indicator of physical fitness in adulthood.

b) **Manuscript III: Relationships between the consumption of different types of meat and muscle strength in young adults.**

Meat represents an important dietary source of protein, in addition to providing a substantial content of saturated and unsaturated fats, minerals, and vitamins. The density of each of these nutrients varies considerably according to the type of meat, and therefore, the associations of meat consumption on health parameters may differ according to the type of meat consumed. Moreover, current dietary recommendations consider that some types of meat, such as fish, are optimal for frequent consumption, while others, such as processed meat, should be consumed occasionally. In this context, some studies reported that higher total and animal protein intake was positively associated with greater musculoskeletal fitness in adulthood. However, less consideration has been given to the differential contributions of meat types to muscle strength, specifically in young adults, a critical stage in the development of muscle function.

PART II – Chapter 2

c) Manuscript IV: Associations between a proinflammatory diet and the risk of depression in older adults.

Diet has received special consideration within lifestyle behaviors as a feasible strategy to promote mental health and, specifically, as a modifiable risk factor for depression. Evidence suggests that chronic low-grade inflammatory processes could contribute to depression through different pathways, such as exposure to a diet high in ultra-processed foods. Previous follow-up studies have investigated the associations between the potential inflammatory effects of diet through the Dietary Inflammatory Index and the incidence of depression or depressive symptoms throughout adulthood. However, cohort-based evidence among older adults is currently sparse and inconclusive.

d) Manuscripts V and VI: The impact of the Mediterranean diet on alleviating depressive symptoms in adults.

Interventions based on lifestyle behaviors have emerged as potentially beneficial strategies in the treatment of depression. Specifically, a previous meta-analysis reported benefits of dietary interventions in the reduction of depressive symptoms in the general adult population. Current evidence highlights the potential role of healthy dietary patterns, with convincing data for the Mediterranean dietary matrix, a simple, feasible, sustainable, and wholesome food system model, on depression risk. However, although studies supporting the role of dietary strategies in mental health have grown in the last decade, there is limited evidence regarding the effects of Mediterranean diet-based interventions in people suffering depression. A synthesis of randomized controlled trials could provide valuable findings for considering the Mediterranean diet as a possible component of health care for the treatment of depression.

e) Manuscript VII: Associations between nut consumption and the risk of depression in middle-aged and older adults.

Scientific evidence from follow-up studies supports the role of optimal dietary patterns and specific food sources in modulating depression risk and symptom management. In this context, nuts are frequently included in current dietary guidelines and healthy dietary patterns as a food with potential preventive and supportive antidepressant activity. A previous systematic review from observational and randomized controlled trial studies supported that higher nut consumption may be associated with fewer depressive symptoms. Despite this, more comparable cohort-based studies with an adequate follow-up period and a large sample size are still needed to provide meaningful evidence, due to the paucity and inconsistency of existing data.

PART II – Chapter 3

f) Manuscript VIII: Associations between daily step count and depression in the general adult population.

The number of daily steps determined with wearable devices is an objective, simple and intuitive measure of physical activity. In this context, daily steps could play a pivotal role in accumulating physical activity in an unstructured and accessible manner for the general population. Recent meta-analyses have provided robust evidence that higher step counts can reduce the risk of cardiovascular diseases and all-cause mortality. However, the 2020 World Health Organization expert committee on physical activity guidelines established the need for further research to encompass additional health outcomes. A quantitative synthesis regarding the associations of objectively measured daily steps with depression and depressive symptoms is lacking. A deeper understanding of the mental health implications of daily steps would provide complementary information to current physical activity guidelines and allow targeted interventions in adulthood for depression preventive strategies.

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MÉTODOS Y PLANTEAMIENTOS PARA ESTA DISERTACIÓN DOCTORAL

MÉTODOS

Esta tesis doctoral incorpora diferentes enfoques metodológicos como elemento esencial para abordar las preguntas de investigación subyacentes y obtener una comprensión exhaustiva de las asociaciones propuestas. La disertación doctoral aborda diferentes diseños de estudio para obtener una imagen más realista e integrada de las asociaciones entre las variables de exposición (dieta y actividad física) y de resultado (condición física y depresión). Cada manuscrito detalla la metodología propuesta junto con sus aspectos éticos, la síntesis de datos y los análisis estadísticos. En general, la presente tesis se basa en los siguientes enfoques metodológicos:

- **Protocolo de revisión sistemática**

  Un protocolo de revisión sistemática describe el razonamiento, la hipótesis y los métodos previstos para la revisión sistemática posterior. Se elabora con antelación y sirve de guía para llevar a cabo la revisión. Los protocolos elaborados se diseñan de antemano, se ponen a disposición del público y se registran en una base de datos internacional como PROSPERO. Los protocolos de revisión sistemática podrían proporcionar pasos importantes hacia un enfoque riguroso y metódico, un componente esencial de las revisiones sistemáticas según métodos y análisis preespecificados. La publicación o el registro de los protocolos de revisión no sólo sirve como hoja de ruta para la investigación, sino que también permite minimizar el riesgo de duplicación de estudios. Los **Manuscritos I** y **V** abarcan este diseño de estudio, generando planes metodológicos detallados para conducir dos revisiones sistemáticas y metaanálisis.

- **Revisión sistemática y metaanálisis**

  El objetivo de las revisiones sistemáticas es resumir la evidencia utilizando reglas transparentes y claramente definidas. Antes de realizar revisiones sistemáticas, se establecen las preguntas de investigación y existe una metodología explícita y reproducible mediante la cual se seleccionan y revisan los estudios. El objetivo de las revisiones sistemáticas es cubrir toda la evidencia disponible de forma objetiva y evaluar la validez de dicha evidencia utilizando normas predefinidas. Los resultados se sintetizan de forma sistemática, lo que da lugar a una evaluación exhaustiva de la evidencia. Además, los metaanálisis pretenden producir una estimación numérica que resuma los datos recopilados. Combinan cuantitativamente los resultados de la evidencia previa, haciendo de los estudios primarios la base del análisis. En esta tesis doctoral se realizaron tres revisiones sistemáticas con diferentes aproximaciones metodológicas en relación a su pregunta de investigación: (i) una revisión sistemática y metaanálisis de estudios observacionales y de intervención sintetizando la evidencia de las asociaciones transversales y prospectivas entre la adherencia a la dieta Mediterránea y los niveles de condición física (**Manuscrito II**); (ii) una revisión sistemática y metaanálisis de ensayos controlados aleatorios resumiendo el efecto de intervenciones basadas en la dieta Mediterránea sobre la severidad de los síntomas depresivos en adultos con depresión (**Manuscrito VI**); y (iii) una revisión sistemática y metaanálisis de estudios observacionales estimando las relaciones transversales y prospectivas entre el número de pasos diarios y la prevalencia o riesgo de depresión (**Manuscrito VIII**).

- **Estudio transversal**

Los diseños de estudios observacionales se distinguen por características específicas del estudio de investigación, como los objetivos principales, la forma de muestreo de los sujetos y el calendario de recogida de datos. Entre ellos, los estudios transversales analizan la exposición y el resultado simultáneamente (es decir, en un momento concreto) para una población. En la investigación médica suelen emplearse para medir la prevalencia de resultados sanitarios, conocer los determinantes de la salud o describir las características de la población. Los estudios transversales no realizan un seguimiento de los individuos a lo largo del tiempo. Una vez seleccionados los sujetos, los investigadores recogen los datos en un único momento. Son útiles para proporcionar pruebas iniciales y explorar posibles asociaciones entre exposición y resultado. Los participantes de un estudio transversal se eligen de una población disponible de relevancia potencial para la pregunta de investigación propuesta. El **Manuscrito III** comprende un estudio de panel con diseño transversal que recolectó datos sobre factores de riesgo cardiovascular, composición corporal, hábitos nutricionales y de estilo de vida, y condición física en estudiantes universitarios de 18–30 años de Castilla-La Mancha (España) durante el curso 2016/2017.

- **Estudios de cohorte**

Los estudios de cohortes son un tipo de estudio longitudinal que sigue a una población en investigación a lo largo del tiempo. En concreto, incluyen el reclutamiento y seguimiento de participantes que comparten una característica común, como una ocupación concreta o una similitud demográfica. Los estudios de cohortes ayudan a comprender qué factores aumentan o disminuyen la probabilidad de desarrollar resultados adversos para la salud. Así, como una parte de la cohorte está expuesta a una característica concreta durante el periodo de seguimiento, pueden investigarse las posibles conexiones entre la exposición y el resultado mediante el seguimiento de los resultados sanitarios a lo largo del tiempo. Por lo tanto, los estudios de cohortes prospectivos son una herramienta esencial en epidemiología para discernir los factores que influyen en la incidencia de enfermedades (es decir, la aparición de nuevos casos en un periodo específico). En esta tesis doctoral se realizaron dos estudios prospectivos utilizando tres bases de datos biomédicas a gran escala, las cohortes Seniors-ENRICA (I y II) y UK Biobank. Los estudios Seniors-ENRICA se establecieron entre 2008–2010 (Seniors-ENRICA I, primer seguimiento: 2012) y 2015–2017 (Seniors-ENRICA II, primer seguimiento: 2019) incluyendo participantes no institucionalizados mayores de 60 años. Entre ambas cohortes se recogieron datos sobre composición corporal, factores de riesgo cardiovascular, hábitos nutricionales y de estilo de vida, y salud mental mediante procedimientos, cuestionarios e instrumentos similares en más de 5000 adultos mayores. El **Manuscrito IV** analizó la influencia de un patrón dietético proinflamatorio sobre el riesgo de depresión en dos muestras representativas nacionales (España) y regionales (Madrid, España) de adultos mayores. A su vez, el **Manuscrito VII** analiza a una amplia muestra de adultos mayores de 40 años del Reino Unido que participaron de la cohorte UK Biobank. Al inicio del estudio en 2006–2010, más de 500,000 participantes rellenaron un cuestionario táctil y se sometieron a una evaluación clínica para registrar medidas antropométricas, a escalas de autoinforme sobre una amplia gama de resultados de salud y recoger muestras de sangre. El UK Biobank proporciona información actualizada en puntos temporales adicionales a partir del año 2012–2013, realizando un seguimiento continuo de submuestras de participantes.

PLANTEAMIENTOS PARA ESTA DISERTACIÓN DOCTORAL

Esta tesis doctoral se enmarca en los siguientes supuestos:

PARTE I – Capítulo 1

a) Manuscritos I y II: La influencia de la adherencia a la dieta Mediterránea sobre la condición física en adultos de todas las edades.

La nutrición ha recibido una atención creciente como una de las estrategias más potentes y seguras para prolongar el tiempo en el que se mantienen el estado de salud y la capacidad funcional. En este contexto, la dieta Mediterránea es un concepto científico sólido asociado a resultados de salud favorables a lo largo de toda la vida. En concreto, el efecto sinérgico de sus características dietéticas conduce a una ingesta de nutrientes de alta calidad que podría promover una mayor condición física, un determinante clave de la salud. Un metaanálisis previo mostró resultados prometedores en las asociaciones entre la adherencia a la dieta Mediterránea y los niveles de condición física en niños y jóvenes. Sin embargo, las síntesis de la evidencia disponible en adultos son limitadas y poco concluyentes, y se centran en resultados de deterioro musculoesquelético en lugar de condición física. Un enfoque meta-analítico podría ayudar a comprender mejor si la adherencia al patrón dietético Mediterráneo y sus componentes individuales se asocian, y en qué medida, con cada uno de los indicadores de la condición física en la edad adulta.

b) Manuscrito III: Relaciones entre el consumo de diferentes tipos de carne y la fuerza muscular en adultos jóvenes.

La carne representa una importante fuente dietética de proteínas, además de aportar un contenido sustancial de grasas saturadas e insaturadas, minerales y vitaminas. La densidad de cada uno de estos nutrientes varía considerablemente según el tipo de carne y, por lo tanto, las asociaciones del consumo de carne sobre los parámetros de salud pueden diferir según el tipo de carne consumida. Además, las recomendaciones dietéticas actuales consideran que algunos tipos de carne, como el pescado, son óptimos para un consumo frecuente, mientras que otros, como la carne procesada, deben consumirse ocasionalmente. En este contexto, algunos estudios informaron de que una mayor ingesta de proteínas totales y animales se asociaba positivamente con una mayor fuerza muscular en la edad adulta. Sin embargo, se ha prestado menos atención a las contribuciones diferenciales de los tipos de carne a la fuerza muscular, específicamente en adultos jóvenes, una etapa crítica en el desarrollo de la función muscular.

PARTE II – Capítulo 2

c) Manuscrito IV: Asociaciones entre una dieta proinflamatoria y el riesgo de depresión en adultos mayores.

La dieta ha recibido especial consideración dentro de los comportamientos del estilo de vida como una estrategia factible para promover la salud mental y, en concreto, como un factor de riesgo modificable para la depresión. La evidencia sugiere que los procesos inflamatorios crónicos de bajo grado podrían contribuir a la depresión a través de diferentes vías, como la exposición a una dieta rica en alimentos ultra procesados. Estudios de seguimiento previos han investigado las asociaciones entre los posibles efectos inflamatorios de la dieta a través del Índice Dietético Inflamatorio y la incidencia de depresión o síntomas depresivos a lo largo de la edad adulta. Sin embargo, las pruebas basadas en cohortes entre adultos mayores son actualmente escasas y no concluyentes.

d) Manuscritos V y VI: El impacto de la dieta Mediterránea en el alivio de los síntomas depresivos en adultos.

Las intervenciones basadas en comportamientos del estilo de vida han emergido como estrategias potencialmente beneficiosas en el tratamiento de la depresión. En concreto, un metaanálisis previo informó de los beneficios de las intervenciones dietéticas en la reducción de los síntomas depresivos en la población adulta general. La evidencia actual destaca el papel de los patrones dietéticos saludables, con datos convincentes de la matriz dietética Mediterránea, un modelo de sistema alimentario sencillo, factible, sostenible y saludable, sobre el riesgo de depresión. Sin embargo, aunque en la última década han aumentado los estudios que apoyan el papel de las estrategias dietéticas en la salud mental, la evidencia sobre los efectos de las intervenciones basadas en la dieta Mediterránea en personas que sufren depresión es limitada. Una síntesis de ensayos controlados aleatorizados podría aportar valiosos hallazgos para considerar la dieta Mediterránea como un posible componente de la atención sanitaria para el tratamiento de la depresión.

e) Manuscrito VII: Asociaciones entre el consumo de frutos secos y el riesgo de depresión en adultos de mediana edad y mayores.

La evidencia científica procedente de estudios de seguimiento respalda el papel de los patrones dietéticos óptimos y las fuentes alimentarias específicas en la modulación del riesgo de depresión y la gestión de los síntomas. En este contexto, los frutos secos se incluyen con frecuencia en las directrices dietéticas actuales y en los patrones dietéticos saludables como un alimento con potencial actividad antidepresiva preventiva y de apoyo. Una revisión sistemática previa sintetizó la evidencia procedente de estudios transversales y de ensayos controlados aleatorizados y descubrió que un mayor consumo de frutos secos podría asociarse con menos síntomas depresivos. A pesar de ello, sigue siendo necesario disponer de más pruebas comparables basadas en cohortes con un periodo de seguimiento adecuado y un gran tamaño de muestra para aportar evidencia significativa debido a la escasez e inconsistencia de los datos existentes.

PARTE II – Capítulo 3

f) Manuscrito VIII: Asociaciones entre el recuento de pasos diarios y la depresión en la población general adulta.

El número de pasos diarios determinados con dispositivos wearables es una medida objetiva, sencilla e intuitiva de la actividad física. En este contexto, los pasos diarios podrían desempeñar un papel fundamental en la acumulación de actividad física de forma no estructurada y accesible para la población general. Recientes metaanálisis han aportado pruebas sólidas de que un mayor recuento de pasos puede reducir el riesgo de enfermedades cardiovasculares y la mortalidad por todas las causas. Sin embargo, el comité de expertos de la Organización Mundial de la Salud de 2020 sobre directrices de actividad física estableció la necesidad de realizar más investigaciones para abarcar resultados de salud adicionales. Falta una síntesis cuantitativa sobre las asociaciones de los pasos diarios con la depresión y los síntomas depresivos. Un conocimiento más profundo de las implicaciones para la salud mental de los pasos diarios proporcionaría información complementaria a las directrices actuales sobre actividad física y permitiría intervenciones específicas en la edad adulta para estrategias preventivas de la depresión.

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AIMS

The aims of each manuscript included in this doctoral dissertation are shown below:

PART 1 – Chapter 1

Manuscript I

1) To provide the methodology of a systematic review and meta-analysis to update the evidence on the associations between adherence to the Mediterranean diet and physical fitness in young, middle-aged, and older adults.

Manuscript II

2) To synthesize the associations of high (vs. low) adherence to the Mediterranean diet and its specific foods with physical fitness levels, including each of its components (cardiorespiratory, motor, and musculoskeletal), in adulthood.

Manuscript III

3) To analyze the associations between the consumption of different types of meat and muscle strength in Spanish young adults and to determine whether these relationships are mediated by total protein intake and percentage of lean mass.

PART II – Chapter 2

Manuscript IV

4) To examine the associationsbetween a proinflammatory dietary pattern and the incidence of depression in community-dwelling older adults in Spain.

Manuscript V

5) To determine the methodological approach for a systematic review and meta-analysis that will summarize the available evidence on the efficacy of Mediterranean diet interventions on depressive symptoms in adults with depressive disorders.

Manuscript VI

6) To synthesize the effects of Mediterranean diet-based interventions on the severity of depressive symptoms in adults with depression or mild to severe depressive symptoms.

Manuscript VII

7) To estimate the associations between nut consumption and the risk of depression in middle-aged and older UK adults and to determine whether these relationships are affected by other risk factors for depression related to lifestyle and health status.

PART II – Chapter 3

Manuscript VIII

8) To synthesize the associations between objectively measured daily steps and both depression and depressive symptoms from observational studies in the general adult population.

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OBJETIVOS

A continuación, se indican los objetivos de cada uno de los manuscritos incluidos en esta disertación doctoral:

PARTE I – Capítulo 1

Manuscrito I

1) Proporcionar la metodología de una revisión sistemática y metaanálisis para actualizar la evidencia sobre las asociaciones entre la adherencia a la dieta Mediterránea y la condición física en adultos jóvenes, de mediana edad y mayores.

Manuscrito II

2) Sintetizar las asociaciones de la adherencia alta (frente a la baja) a la dieta Mediterránea y sus alimentos específicos con los niveles de condición física, incluyendo cada uno de sus componentes (cardiorrespiratorio, motor y musculoesquelético), en la edad adulta.

Manuscrito III

3) Analizar las asociaciones entre el consumo de diferentes tipos de carne y la fuerza muscular en adultos jóvenes españoles y determinar si estas relaciones están mediadas por la ingesta total de proteínas y el porcentaje de masa magra.

PARTE II – Capítulo 2

Manuscrito IV

4) Examinar las asociaciones entre un patrón dietético proinflamatorio y la incidencia de depresión en adultos mayores residentes en la comunidad en España.

Manuscrito V

5) Determinar el enfoque metodológico para una revisión sistemática y metaanálisis que resumirá la evidencia disponible sobre la eficacia de las intervenciones con dieta Mediterránea sobre los síntomas depresivos en adultos con trastornos depresivos.

Manuscrito VI

6) Sintetizar los efectos de las intervenciones basadas en la dieta Mediterránea sobre la gravedad de los síntomas depresivos en adultos con depresión o síntomas depresivos de leves a moderados.

Manuscrito VII

7) Estimar las asociaciones entre el consumo de frutos secos y el riesgo de depresión en adultos de mediana y avanzada edad del Reino Unido y determinar si estas relaciones se ven afectadas por otros factores de riesgo de depresión relacionados con los comportamientos del estilo de vida y el estado de salud.

PARTE II – Capítulo 3

Manuscrito VIII

8) Sintetizar las asociaciones entre los pasos diarios medidos objetivamente y tanto la depresión como los síntomas depresivos a partir de estudios observacionales en la población adulta general.

8

ABSTRACT OF THE MANUSCRIPTS

PART I – CHAPTER 1

MANUSCRIPT I

The associations between adherence to the Mediterranean diet and physical fitness in young, middle-aged, and older adults: A protocol for a systematic review and meta-analysis.

Introduction: A healthy diet and high health-related physical fitness (PF) levels may be part of an overall healthy lifestyle. The relationship between adherence to the Mediterranean diet (MD) and PF levels has been analyzed in several studies. However, no studies have synthesized evidence on this relationship throughout adulthood. Moreover, in addition to the overall Mediterranean dietary pattern, the associations of individual components of the MD with PF indicators are also unclear.

Methods: This protocol for a systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols statement and the Cochrane Collaboration Handbook. Systematic literature searches will be performed in the MEDLINE (PubMed), Scopus, Web of Science, SPORTDiscus and Cochrane CENTRAL databases to identify studies published up to 31 January 2022. The inclusion criteria will comprise observational studies and randomized controlled trials reporting the associations between adherence to the MD and PF levels on general healthy or unhealthy adults (≥18 years). When at least five studies addressing the same outcome are available, meta-analysis will be carried out to estimate the standardized mean difference of PF according to the adherence to MD. Subgroup analyses will be performed according to the characteristics of the population, the individual dietary components of the MD and PF parameters if there are sufficient studies.

Ethics and dissemination: This systematic review and meta-analysis protocol is designed for updating evidence on the associations between adherence to overall MD (and specific Mediterranean foods) and PF levels in young, middle-aged, and older adults. Findings from this review may have implications for public health. The results will be disseminated through peer-reviewed publication, conference presentation, and infographics.

Keywords: Adulthood; Diet; Fitness; Meta-analysis.

Trial registration number: PROSPERO CRD42022308259.

MANUSCRIPT II

High Adherence to the Mediterranean Diet is Associated with Higher Physical Fitness in Adults: a Systematic Review and Meta-Analysis.

Abstract: Although prior research has synthesized the relationships between the Mediterranean diet (MD) and components of physical fitness (PF) in adults, they are limited and inconclusive. This study aimed to synthesize the associations between high (compared with low) MD adherence and PF levels with each of its components (cardiorespiratory, motor, and musculoskeletal) in adulthood. We conducted a systematic search in 5 databases from inception to January 2022. Observational studies and randomized controlled trials were included. Pooled odds ratios (ORs) and effect sizes (Cohen d index) with their 95% CIs were calculated via a random effects model. A total of 30 studies were included (19 cross-sectional in young, middle-aged, and older adults; 10 prospective cohort in older adults; and 1 randomized controlled trial in young adults) involving 36,807 individuals (mean age range: 20.9-86.3 y). Pooled effect sizes showed a significant cross-sectional association between higher MD adherence scores (as a continuous variable) and overall PF ($d = 0.45$; 95% CI: 0.14, 0.75; $I2 = 91.0\%$, $n = 6$). The pooled ORs from cross-sectional data showed that high adherence to MD was associated with higher cardiorespiratory fitness (OR: 2.26; 95% CI: 2.06, 2.47; $I2 = 0\%$, $n = 4$), musculoskeletal fitness (OR: 1.26; 95% CI: 1.05, 1.47; $I2 = 61.4\%$, $n = 13$), and overall PF (OR: 1.44; 95% CI: 1.20, 1.68; $I2 = 83.2\%$, $n = 17$) than low adherence to MD (reference category: 1). Pooled ORs from prospective cohort studies (3- to 12-y follow-up) showed that high adherence to MD was associated with higher musculoskeletal fitness (OR: 1.20; 95% CI: 1.01, 1.38; $I2 = 0\%$, $n = 4$) and overall PF (OR: 1.14; 95% CI: 1.02, 1.26; $I2 = 9.7\%$, $n = 7$) than low adherence to MD (reference category: 1). Conversely, no significant association was observed between MD and motor fitness. High adherence to MD was associated with higher PF levels, a crucial marker of health status throughout adulthood.

Keywords: Mediterranean diet adherence; Mediterranean foods; Adulthood; Aerobic capacity; Healthy diet; Motor skills; Muscular strength.

Systematic review registration: PROSPERO CRD42022308259.

MANUSCRIPT III

The association between meat consumption and muscle strength index in young adults: the mediating role of total protein intake and lean mass percentage.

Purpose: The aim of this study was to analyze the associations between the consumption of different types of meat and the muscle strength index (MSI) and to examine whether this relationship is mediated by total protein intake (TPI) and lean mass percentage (LM%) in young adults.

Methods: We conducted a cross-sectional study with first-year university students from Castilla-La Mancha, Spain. Different types of meat consumption (total, red, processed, and white and fish) were separately evaluated using a Food-Frequency Questionnaire. MSI was determined from the handgrip and standing long jump tests. ANCOVA models were used to test the mean differences in MSI by categories of meat consumption. Serial multiple mediation models were used to explore the mediating role of TPI and LM% in the relationship between meat consumption and MSI. All analyses were adjusted for age, sex, and socioeconomic level, identified through a directed acyclic graph. Additional analyses were performed with a small subsample including alcohol intake, tobacco smoking, physical activity, cardiorespiratory fitness, and total energy intake as covariates in the multiple mediation models.

Results: A total of 230 students (mean age 21.1 ± 2.1 years, 66.5% women) were included in the analysis. Young adults with higher meat consumption (total, red, and white and fish) had higher MSI adjusted means than their peers with lower meat consumption ($p < 0.05$). These associations did not remain after controlling for TPI and LM%. In adjusted mediation analyses, a significant indirect effect was observed through TPI and LM% in the associations between each of the types of meat consumption and MSI. In the additional analyses, a greater effect of white and fish meat consumption on muscle strength through mediation of TPI and LM% was reported compared to red or processed meat consumption, and no significant effects were observed between processed meat consumption and MSI.

Conclusion: Higher consumption of total, red, and white and fish meat was associated with increased MSI in young adults. TPI and LM% mediated this relationship.

Keywords: Lean body mass; Meat consumption; Muscle strength; Protein; University students.

PART II – CHAPTER 2

MANUSCRIPT IV

Proinflammatory dietary pattern and depression risk in older adults: Prospective analyses from the Seniors-ENRICA studies.

Background & aims: Only a few studies have assessed the association between a proinflammatory diet and the risk of depression in older adults, and they have rendered weak results. The present study analyzed the association between the Dietary Inflammatory Index (DII) and incident self-reported diagnosis or symptoms of depression in two cohorts of community-dwelling older adults in Spain.

Methods: We used data from the Seniors-ENRICA-I (SE-I) and Seniors-ENRICA-II (SE-II) cohorts. In both cohorts, the baseline DII was calculated from habitual food consumption estimated with a validated computer-based diet history. The incidence of both physician self-reported diagnosis of depression and mild-to-major depressive symptoms (≥3 on the 10-item Geriatric Depression Scale) was analyzed. Logistic regression models were adjusted for the main potential confounders, such as sociodemographic, lifestyles, and comorbidities. The results of both cohorts were pooled using a random effects model.

Results: Among the 1627 participants in SE-I (mean age 71.5 ± 5.5 y, 53.1% women) and the 1579 in SE-II (mean age 71.4 ± 4.2, 46.7% women), 86 (5.3%) and 140 (8.9%) incident cases of depression were identified after a mean 3.2-y and 2.3-y follow-up, respectively. The fully adjusted odds ratio (95% confidence interval) of incident depression for the highest (the highest proinflammatory diet) versus the lowest quartile of DII was 2.76 (1.25-6.08, p-for-trend = 0.005) in the SE-I, 1.90 (1.04-3.40, p-for-trend = 0.005) in the SE-II and 2.07 (1.01-3.13) in the pooled cohorts. The results were consistent across strata defined by sex, age, physical activity, loneliness/poor social network, and morbidity.

Conclusions: A proinflammatory dietary pattern is associated with depression risk in older adults. Future research should evaluate whether reducing the inflammatory component of diet leads to reduced depression symptoms in this population.

Keywords: Dietary inflammatory index; Health behavior; Mental health; Older age.

MANUSCRIPT V

Mediterranean Diet Interventions for Depressive Symptoms in Adults with Depressive Disorders: A Protocol for a Systematic Review and Meta-Analysis.

Abstract: The associations between Mediterranean diet (MD) adherence and depression levels have been synthesized from observational studies. However, a systematic review with meta-analysis including randomized controlled trials on this relationship in adults with depressive disorders remains lacking. This protocol was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols statement. MEDLINE (PubMed), Cochrane CENTRAL, PsycINFO, Scopus, and Web of Science databases will be systematically searched to identify studies published from database inception up to 30 September 2022. The inclusion criteria will comprise randomized controlled trials reporting pre-post changes in depression status (symptoms or remission) after a MD intervention compared to a control condition in adults over 18 years with depressive disorders. Pooled effect sizes and 95% confidence intervals will be calculated using the DerSimonian random-effects model. This study protocol determines the methodological approach for the systematic review and meta-analysis that will summarize the available evidence on the efficacy of MD interventions on depressive symptoms in adults with depressive disorders. The findings from this review may have implications for public mental health programs. The results will be disseminated through peer-reviewed publication, conference presentation, and infographics. No ethical approval will be required since only published data will be used.

Keywords: Mediterranean foods; Adulthood; Depression; Healthy diet; Study protocol; Systematic review.

Systematic review registration: PROSPERO CRD42022341895.

MANUSCRIPT VI

The impact of the Mediterranean diet on alleviating depressive symptoms in adults: a systematic review and meta-analysis of randomized controlled trials.

Context: High adherence to the Mediterranean diet (MD) has been associated with a reduced risk of depression in prospective cohort studies, but whether MD interventions are effective among adults with depression is uncertain.

Objective: This study aimed to synthesize the effects of MD interventions on the severity of depressive symptoms in adults with depression.

Methods: PubMed, Cochrane CENTRAL, PsycINFO, Scopus and Web of Science were systematically searched from database inception to March 2023. The Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines and the Cochrane recommendations were followed. Randomized controlled trials comparing MD interventions vs. control conditions in adults with depressive disorders or depressive symptoms were included. Pooled standardized mean differences and 95% confidence intervals (CIs) were calculated using a random-effects model. The Sidik-Jonkman estimator, the I^2 metric, and the prediction interval were used to estimate between-study heterogeneity. To determine the risk of bias and certainty of evidence from randomized controlled trials, the RoB 2 and GRADE tools were used, respectively.

Results: In total, 1,507 participants (mean age range: 22.0–53.3 years) with depression were initially included in the five randomized controlled trials of this review. Compared to control conditions, MD interventions significantly reduced depressive symptoms among young and middle-aged adults with major depression or mild to moderate depressive symptoms (SMD: -0.53; 95% CI: -0.89 to -0.16; I2 = 87.1%). The prediction interval ranged from -1.86 to 0.81. The overall risk of bias was within the range of ‘some concerns’ to ‘high’, while the certainty of evidence was low.

Conclusion: MD interventions appear to have substantial potential for alleviating depressive symptoms in people experiencing major or mild depression. However, to establish robust recommendations, there remains a need for high-quality, large-scale, and long-term randomized controlled trials.

Keywords: Depressive disorder; Diet therapy; Healthy diet; Mental health; Mental disorders; Nutrition therapy; Psychiatry.

Systematic review registration: PROSPERO CRD42022341895.

MANUSCRIPT VII

Nut consumption is associated with a lower risk of depression in adults: A prospective analysis with data from the UK Biobank cohort.

Background & aims: Evidence on the association between nut consumption and depression is mainly based on cross-sectional studies. This study aims to analyze whether nut consumption is prospectively associated with the risk of depression in adults.

Methods: This study was conducted using the United Kingdom (UK) Biobank resource. Data from middle-aged and older UK adults who participated in this cohort between 2007-2012 (baseline) and 2013-2020 (follow-up) were analyzed. Baseline information on nut consumption was obtained with the Oxford WebQ 24-h questionnaire. Depression, defined as a self-reported physician diagnosis of depression or antidepressant use, was assessed at baseline and follow-up. Hazard regression models estimating the predictive ability of nut consumption for the risk of developing depression were adjusted for sociodemographic, lifestyle, and health confounders.

Results: A total of 13,504 participants (mean age 57.5 ± 7.2 years, 50.7% female) free of depression at baseline were included in the analyses. After a mean follow-up of 5.3 ± 2.4 years, 1122 (8.3%) incident cases of depression were identified. Compared with no nut consumption, the daily consumption of >0 to 1 serving of 30 g of nuts was associated with a lower risk of depression (hazard ratio, HR = 0.83; 95% confidence interval, CI: 0.71-0.97) regardless of all potential confounders considered. In stratified analyses, a decreased risk of depression was more clearly observed in UK adults with adequate weight control, a healthy lifestyle, and better health status than in their counterparts ($p < 0.05$).

Conclusions: Low-to-moderate nut consumption (>0 to 1 serving of 30 g/day) was associated with a 17% lower risk of depression during a 5.3-year follow-up compared with no nut consumption in a large sample of middle-aged and older UK adults. This protective association is enhanced in the absence of other known risk factors for depression.

Keywords: Adulthood; Depressive disorder; Longitudinal; Mental health; Nuts.

PART II – CHAPTER 3

MANUSCRIPT VIII

Daily step count and depression in the general adult population: a systematic review and meta-analysis of observational studies.

Objective: This study aims to synthesize the associations between daily steps and depression in observational studies of the general adult population.

Design: Systematic review and meta-analysis.

Data sources: The MEDLINE, PsycINFO, SPORTDiscus and Web of Science databases.

Eligibility criteria: Observational studies reporting associations between objectively measured daily steps and depression or depressive symptoms in adults. Pooled effect sizes (correlation coefficients or standardized mean differences [SMDs]) with their 95% confidence intervals (CIs) were estimated using the Sidik-Jonkman random-effects method.

Results: Thirty studies (25 cross-sectional and 5 prospective cohorts) involving 23,656 adults (range of mean ages: 18.6 to 79.1 years) were included. Daily steps were inversely correlated with the number of depressive symptoms in both cross-sectional and cohort studies. When compared with <5000 steps/day, pooled SMDs from cross-sectional studies showed that ≥10,000 steps/day (SMD=−0.32, 95% CI: −0.46 to −0.17), 7500–9999 steps/day (SMD=−0.24, 95% CI: −0.38 to −0.09), and 5000–7499 steps/day (SMD=−0.22, 95% CI: −0.34 to −0.10) were associated with a lower frequency of depression or fewer depressive symptoms. Furthermore, pooled SMDs from cohort studies (follow-up from 2 to 5 years) showed that participants with ≥7000 steps/day were less likely to develop depression or depressive symptoms than their counterparts with <7000 steps/day (SMD=−0.23, 95% CI: −0.31 to −0.14).

Conclusion: A greater number of daily steps could help reduce both depression and depressive symptoms in the general adult population. Health practitioners should encourage regular physical activity, specifically ≥5000 steps/day, to prevent depression and reduce depressive symptoms.

Keywords: Physical activity; Step count; Depressive symptoms; Mental health; Adulthood.

Systematic review registration: PROSPERO CRD42023404793.

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ORIGINAL MANUSCRIPTS

PART I – CHAPTER 1

MANUSCRIPT I

Title:
The associations between adherence to the Mediterranean diet and physical fitness in young, middle-aged, and older adults: A protocol for a systematic review and meta-analysis.

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Systematic review and meta-analysis protocol.

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STUDY PROTOCOL

The associations between adherence to the Mediterranean diet and physical fitness in young, middle-aged, and older adults: A protocol for a systematic review and meta-analysis

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Abstract

Introduction

A healthy diet and high health-related physical fitness levels may be part of an overall healthy lifestyle. The relationship between adherence to the Mediterranean diet and physical fitness levels has been analyzed in several studies. However, no studies have synthesized evidence on this relationship throughout adulthood. Moreover, in addition to the overall Mediterranean dietary pattern, the associations of individual components of the Mediterranean diet with physical fitness indicators are also unclear.

Methods

This protocol for a systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols statement and the Cochrane Collaboration Handbook. Systematic literature searches will be performed in the MEDLINE (PubMed), Scopus, Web of Science, SPORTDiscus and Cochrane CENTRAL databases to identify studies published up to 31 January 2022. The inclusion criteria will comprise observational studies and randomized controlled trials reporting the associations between adherence to the Mediterranean diet and physical fitness levels on general healthy or unhealthy adults ($\geq$18 years). When at least five studies addressing the same outcome are available, meta-analysis will be carried out to estimate the standardized mean difference of physical fitness according to the adherence to Mediterranean diet. Subgroup

Data Availability Statement: Our article does not report data and the data availability policy is not applicable.

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Competing interests: The authors have declared that no competing interests exist.

analyses will be performed according to the characteristics of the population, the individual dietary components of the Mediterranean diet and physical fitness parameters as long as there are sufficient studies.

Ethics and dissemination

This systematic review and meta-analysis protocol is designed for updating evidence on the associations between adherence to overall Mediterranean diet (and specific Mediterranean foods) and physical fitness levels in young, middle-aged, and older adults. Findings from this review may have implications for public health. The results will be disseminated through peer-reviewed publication, conference presentation, and infographics. No ethical approval will be required since only published data will be used.

PROSPERO registration number

CRD42022308259.

Introduction

The Mediterranean diet (MD) has been a robust scientific concept in health research for many years [1]. High adherence to the MD has been associated with several beneficial health outcomes, such as reduced overall mortality, reduced risk of some cancers, cardiovascular and neurogenerative diseases and diabetes [2]. Consistent evidence has demonstrated that following an MD is a key factor in preserving favorable health over the entire lifespan [3]. The main characteristics of the MD include an abundance of plant foods (fruits, vegetables, whole-grain cereal, nuts, and legumes), olive oil as the main source of fat, moderate consumption of fish and seafood, and reduced consumption of red and processed meats [4, 5]. The synergistic effect of the dietary components included in the MD scoring systems [4] leads to a favorable nutrient intake (i.e., low contents of saturated and *trans* fatty acids and high contents of unsaturated fatty acids, dietary fiber, vitamins, and minerals) associated with several health benefits such as better metabolic and inflammatory risk parameters [2].

A progressive nutritional transition characterized by a high adherence to the Western dietary pattern (i.e., high consumption of meat products, processed foods, saturated fat, soda, sodium, sugar, and trans-fat) and a decline in adherence to the MD has been observed among adults worldwide, including in Mediterranean countries [6, 7]. The increase in the Western dietary pattern is a growing public health concern because of its relevant contributory factor for obesity, cardiovascular disease, disability, and mortality worldwide [6, 8, 9].

Meanwhile, the average population levels of health-related physical fitness (PF) have been reduced for several years [10], being a strong predictor of deteriorating cardiometabolic health [11] with clear implications and cardiovascular and all-cause mortality [10, 12]. On the other hand, some evidence points to the potential benefits of healthy dietary patterns on PF levels [13, 14], showing the relevance of diet in improving and preserving PF performance, which is an important marker of health status at different time points in adulthood [15, 16].

Although the association between adherence to the MD and PF levels in adults has been analyzed in several studies [14, 17–19], a systematic review with a meta-analytical understanding of how adherence to the MD is associated with PF levels remains unknown. Thus, the aim of this protocol is to provide a detailed plan for conducting a review synthesizing the evidence regarding the relationship between adherence to the MD and PF levels throughout adulthood (young adults, middle-aged adults, and elderly adults) and to determine which individual dietary components are associated with each PF parameter.

Methods

Protocol and registration

This systematic review and meta-analysis protocol was drafted using the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA-P) statement [20] (S1 Table). The systematic review and meta-analysis have been previously registered in PROSPERO (CRD42022308259). It will be conducted according to the PRISMA 2020 guidelines and following the Cochrane Collaboration Handbook [21]. Ethics committee approval and/or informed consent from patients will not be required since no primary data will be collected.

Eligibility criteria

To be included, studies retrieved from the peer-reviewed literature must report the following: (i) population: healthy or unhealthy adults ($\geq$18 years); (ii) intervention/exposure: the adherence of the MD according to the overall score of different scales (e.g., Mediterranean Diet Score, Mediterranean Diet Adherence Screener) and to specific components (foods and nutrients) of these scoring systems; (iii) outcome: PF components (cardiorespiratory fitness, musculoskeletal fitness, and motor fitness) by using standardized tests; (iv) designs: observational studies (cross-sectional, case–control, prospective/retrospective cohort and longitudinal) and randomized controlled trials; and (v) period: published before January 31st, 2022. Moreover, studies will be excluded if they report: (i) duplicate data published in another included study; (ii) diet in terms of intake of single nutrients, food items, and food groups; (iii) special interest group data (e.g., elite athletes or firefighters); (iv) PF measured by self-report; (v) qualitative data; and (vi) data published as conference/meeting abstracts.

Search methods for study identification

The systematic search will be conducted in MEDLINE (PubMed), Scopus, Web of Science, SPORTDiscus and Cochrane CENTRAL from database inception up to 31 January 2022. No filters will be used in the systematic search. Further studies will be located by additional searches where reference lists of included studies and relevant systematic reviews will be screened for potential relevance. In case of a lack of data, experts will be contacted requesting information.

The electronic database searches will be limited to keywords, title and abstract. The search terms were identified and grouped from the main components (PICO elements) of the research question. To perform the search strategy, free text terms will be used in combination with Boolean operators, as shown in Table 1.

Data collection and analysis

Study selection. All database references will be imported into Mendeley Manager (v1.19.8; Elsevier, London, UK) and checked for duplications. Following this step and based on inclusion/exclusion criteria, two researchers will independently examine the titles and abstracts. The full text of the identified studies will be screened by two researchers independently against the inclusion/exclusion criteria, with consensus required for final inclusion. Discrepancies between researchers will be resolved by reaching consensus or with the

Table 1. Search strategy for the MEDLINE database.

#1 Population	Adult* OR "young adult" OR "middle aged" OR aged OR elderly OR olde*
#2 Intervention/ exposure	"Mediterranean index" OR adherence OR "Mediterranean score" OR "Mediterranean diet" OR MedDiet OR "Mediterranean-style diet" OR "Mediterranean eat" OR "Mediterranean food" OR "dietary pattern" OR "diet quality"
#3 Outcome	fitness OR "fitness level" OR "physical fitness" OR "physical performance" OR "functional fitness" OR "physical function" OR "muscle strength" OR "muscular power" OR "muscular fitness" OR "muscle endurance" OR "explosive strength" OR flexibility OR "musculoskeletal fitness" balance OR coordination OR agility OR speed OR "motor fitness" OR "aerobic fitness" OR "aerobic capacity" OR "cardiorespiratory fitness" OR "cardiorespiratory endurance" OR "aerobic endurance"
Search strategy: [(**#1**) AND (**#2**) AND (**#3**)]	

Proximity operators (*) will be used to search for root words.

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intervention of a third reviewer. The results of the search and selection process will be described using the PRISMA 2020 flow diagram (Fig 1).

Data collection process. One researcher will perform data extraction on a standardized template, and a second researcher will check for accuracy. If necessary, additional data will be requested from the corresponding authors via email.

The following study-specific data will be extracted: 1) name of the first author and year of publication; 2) country; 3) study design; 4) sample size; 5) participant information (sex and age); 6) adult age group (young, middle-aged, or older adults); 7) MD adherence indices; 8) specific Mediterranean foods; 9) PF component; and 10) main findings. The information will be summarized in a "Table of characteristics" (S2 Table).

Intervention/Exposure. The adherence of the MD will be defined with different scoring systems previously identified [4, 22, 23]. Both the earlier (e.g., Mediterranean Diet Score) and newer (e.g., Mediterranean Dietary Serving Score) MD scoring systems, as well as the more widely validated Mediterranean Diet Adherence Screener, will be considered for the assessment of the MD [4].

Outcomes. PF refers to the ability to perform daily activities with vigor, as well as the full range of physical qualities that have a relationship with health, such as aerobic capacity or muscle strength [24]. Based on a previous definition [25], PF outcomes for which data will be sought in this review include cardiorespiratory fitness, musculoskeletal fitness, and motor fitness. PF outcomes should be assessed by using standardized tests (e.g., 20-meter shuttle run test, 1.5-mile run/walk test, 12 minutes run/walk test, handgrip strength test, sit-and-reach test) in the general adult population [26].

Risk of bias in individual studies. Risk of bias will be independently assessed at the study level by two researchers using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [27] and the Cochrane Collaboration's tool for assessing risk of bias (RoB2) [28]. In case of discrepancies that could not be resolved by discussion, a third reviewer resolved the disagreements.

Certainty of the evidence. The Grading of Recommendations Assessment, Development and Evaluation approach will be used for assessing the certainty of evidence and providing recommendations [29]. The GRADE method will be used involving five steps: 1) Assign an a priori ranking of 'high' to randomized controlled trials and 'low' to observational studies; 2) 'Downgrade' or 'upgrade' initial ranking; 3) Assign final grade for the quality of evidence as 'high', 'moderate', 'low', or 'very low' for all critically important outcomes; 4) Consider other factors that impact the strength of recommendation for a course of action; 5) Make a 'strong' or 'weak' recommendation [30].

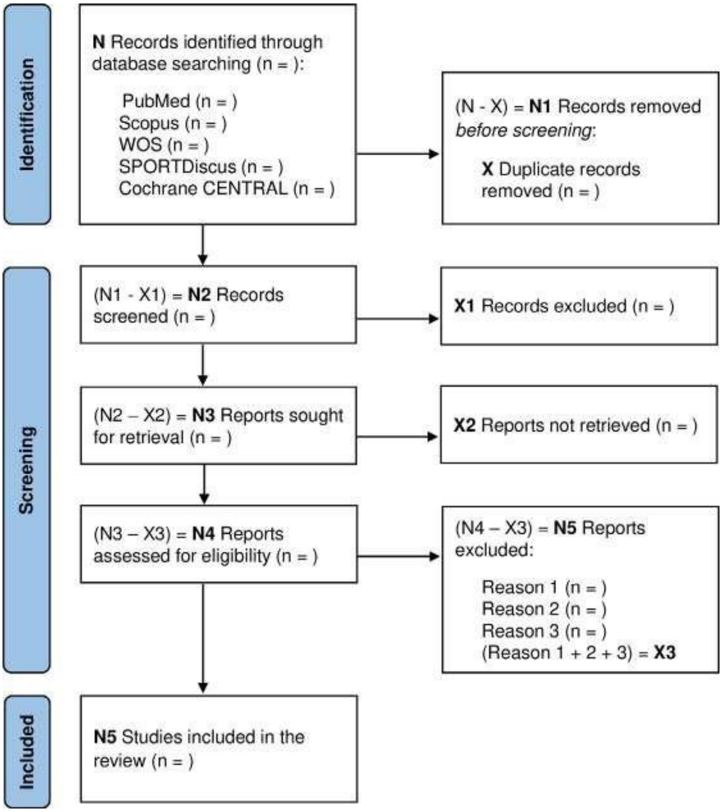

Fig 1. PRISMA flow diagram for identifying, screening, and determining the eligibility and inclusion of studies.

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Synthesis of data

Once the main characteristics of the included studies have been extracted, higher vs lower MD exposures will be compared for each PF outcome, and these data will be synthesized narratively sub-grouped by sex, adult age group, and health status. Where a minimum of five studies addressing the same outcome have been identified, a meta-analysis will be conducted. Effect sizes (ESs) and their 95% confidence intervals (95% CIs) will be calculated for each included study using Cohen's d index [31]. If the included studies presented statistical adjustment models, the fully adjusted model will be selected. A pooled ES will be estimated using the DerSirmonian and Laird random effects method [32, 33]. The heterogeneity of results will be assessed using the I^2 statistic, categorizing as not important (0% - 30%), moderate (30% - 60%), substantial (60% - 75%), or considerable (75–100%) (21). In addition, the corresponding p values and 95% CIs for I^2 will be considered [34].

If there is available information, subgroup analyses will be performed according to the characteristics of the population (sex, adult age group, health status), intervention (MD scoring systems, individual dietary components of the MD), and outcome (PF tests). Furthermore, the methodological quality of the included studies will be considered for the subgroup analyses.

Random-effects meta-regression analyses will be conducted considering potential main factors causing heterogeneity (e.g., sex, age, study design, body mass index, health status).

To evaluate the robustness of the pooled estimates and detect whether any specific study represents a large proportion of heterogeneity, sensitivity analyses will be conducted by eliminating the included studies one by one.

Finally, publication bias will be tested by visual inspection of funnel plots and using Egger's regression asymmetry test [35].

We will perform all statistical analyses in StataSE software, version 15 (StataCorp, College Station, TX, USA).

Results

The results of this research will be submitted to a peer-reviewed journal.

Discussion

This protocol describes the methodology that will be applied for the first systematic review and meta-analysis synthesizing the relationships between adherence to the Mediterranean diet (MD) and health-related physical fitness (PF) levels in young, middle-aged, and older adults. Moreover, the systematic review will intend to provide evidence on the associations of individual components of the MD with PF indicators.

Available evidence indicates that MD is one of the healthiest dietary matrix patterns [36], and PF is an important marker of health in adults [37]. While systematic reviews analyzed the associations between MD patterns and PF levels during adulthood [38–42], they examined only older adults [41, 42], did not specifically analyze adherence to the MD [39, 40], reported results only for one component of PF [40, 42] and did not perform meta-analyses [38–40, 42]. Furthermore, no previous systematic review analyzed the relationships between specific Mediterranean foods and PF levels.

To our knowledge, there are no systematic reviews and meta-analyses that have answered the following questions: Does the available evidence support a relationship between adherence to the MD and PF levels throughout adulthood (young adults, middle-aged adults, and elderly adults)? Which individual dietary components, in conjunction with MD adherence, are associated with each PF component? Since current global dietary transitions have become a growing challenge and public health problem during adulthood, this study may potentially have future implications for public health policies.

The limitations of the review may include the usual limitations of systematic reviews and meta-analyses, such as publication bias, low methodological quality, and heterogeneity of the included studies. Differences among the study designs, sample characteristics, dietary data, PF assessments and methodological quality may restrict comparisons among the included studies and affect the generalizability of the findings.

Conclusions

This study facilitates the protocol methodology for a systematic review and meta-analysis that will provide updated evidence on the associations between adherence to the MD and PF levels throughout adulthood. Findings from this review may be useful for researchers and health professionals responsible for adult lifestyle surveillance and health promotion. The results obtained will be disseminated through peer-reviewed publications, conferences, symposia, social networks, educational talks, and infographics.

Supporting information

S1 Table. PRISMA-P 2015 checklist to address the systematic review protocol, adapted from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1.
(PDF)

S2 Table. Characteristics of studies included in the systematic review and meta-analysis. Abbreviations: CRF, cardiorespiratory fitness; MD, Mediterranean Diet; MF, motor fitness; MSF, musculoskeletal fitness.
(PDF)

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MANUSCRIPT II

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High Adherence to the Mediterranean Diet is Associated with Higher Physical Fitness in Adults: a Systematic Review and Meta-Analysis.

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REVIEW

High Adherence to the Mediterranean Diet is Associated with Higher Physical Fitness in Adults: a Systematic Review and Meta-Analysis

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ABSTRACT

Although prior research has synthesized the relationships between the Mediterranean diet (MD) and components of physical fitness (PF) in adults, they are limited and inconclusive. This study aimed to synthesize the associations between high (compared with low) MD adherence and PF levels with each of its components (cardiorespiratory, motor, and musculoskeletal) in adulthood. We conducted a systematic search in 5 databases from inception to January 2022. Observational studies and randomized controlled trials were included. Pooled odds ratios (ORs) and effect sizes (Cohen *d* index) with their 95% CIs were calculated via a random effects model. A total of 30 studies were included (19 cross-sectional in young, middle-aged, and older adults; 10 prospective cohort in older adults; and 1 randomized controlled trial in young adults) involving 36,807 individuals (mean age range: 20.9–86.3 y). Pooled effect sizes showed a significant cross-sectional association between higher MD adherence scores (as a continuous variable) and overall PF ($d = 0.45$; 95% CI: 0.14, 0.75; $I^2 = 91.0\%$, $n = 6$). The pooled ORs from cross-sectional data showed that high adherence to MD was associated with higher cardiorespiratory fitness (OR: 2.26; 95% CI: 2.06, 2.47; $I^2 = 0\%$, $n = 4$), musculoskeletal fitness (OR: 1.26; 95% CI: 1.05, 1.47; $I^2 = 61.4\%$, $n = 13$), and overall PF (OR: 1.44; 95% CI: 1.20, 1.68; $I^2 = 83.2\%$, $n = 17$) than low adherence to MD (reference category: 1). Pooled ORs from prospective cohort studies (3- to 12-y follow-up) showed that high adherence to MD was associated with higher musculoskeletal fitness (OR: 1.20; 95% CI: 1.01, 1.38; $I^2 = 0\%$, $n = 4$) and overall PF (OR: 1.14; 95% CI: 1.02, 1.26; $I^2 = 9.7\%$, $n = 7$) than low adherence to MD (reference category: 1). Conversely, no significant association was observed between MD and motor fitness. High adherence to MD was associated with higher PF levels, a crucial marker of health status throughout adulthood. This trial was registered at PROSPERO as CRD42022308259. *Adv Nutr* 2022;0:1–12.

Statement of Significance: This is the first systematic review and meta-analysis to provide a comprehensive picture of the associations between adherence to the Mediterranean diet and physical fitness levels with each of its components (cardiorespiratory, motor, and musculoskeletal) in adulthood.

Keywords: adulthood, healthy diet, Mediterranean diet adherence, Mediterranean foods, aerobic capacity, motor skills, muscular strength

Introduction

Physical fitness (PF) is a critical determinant of health throughout adulthood (1). The core components of overall PF include cardiorespiratory fitness (CRF) (i.e., the functional capacity of the cardiovascular and respiratory systems during sustained physical activity), motor fitness (MF) (i.e., motor skills such as agility or speed), and musculoskeletal fitness (MSF) (i.e., muscle abilities such as flexibility or muscular strength) (2). These health-related PF components categorize the set of attributes related to a person's ability to perform physical activities, facilitating the development of practical and public health recommendations according to each component (3). Adults of any age have the trainability capacity to increase PF levels, which is vital for short- and long-term health status (4). In fact, higher PF was associated with improved health prognosis (5, 6) and reduced mortality (1, 7) in young, mid-, and old life.

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Nutrition has received increasing attention as one of the most potent, feasible, and safest strategies to extend the time in which health status and functional capacity are maintained (8, 9). In this context, the Mediterranean diet (MD) appears to be a robust scientific concept (10) associated with favorable health outcomes over the entire life span (11). Some evidence has suggested that the MD could have a positive impact on PF (12), mainly because the synergistic effect of its food features—olive oil as the principal source of fat; high consumption of fruits, herbs, legumes, nuts, olives, seeds, spices, vegetables, and whole grain cereals; moderate consumption of eggs, fish or seafood, dairy products (preferably low in fat), red wine, and white meat; and occasional consumption of red or processed meat and sweets (carbonated beverages, pastries, sugar) (13, 14)—leads to high-quality nutrient intake [i.e., rich in unsaturated fatty acids (especially monounsaturated), essential amino acids, and antioxidant capacity (from carotenoids, phenolic compounds, trace elements, and vitamins)] (15), which in turn promotes greater PF (16). Moreover, the concept of MD incorporates lifestyle and cultural elements (e.g., adequate rest, conviviality, regular physical activity; preference for fresh, local, seasonal, and traditional foods) that should be considered to contribute to the nutritional benefits of this healthy and sustainable food matrix (10, 14).

Syntheses of the available evidence on MD–PF relationships among adults are limited and inconclusive. Most systematic reviews analyzing the associations between MD patterns and PF levels during adulthood (12, 17–20) are mainly focused on musculoskeletal impairment outcomes (i.e., frailty, mobility disability, sarcopenia) rather than PF components (19, 20). However, some of them did not specifically analyze adherence to the MD (17–19), did not perform meta-analysis (17–20), and were based on few cross-sectional and prospective cohort studies (n 2–5), showing mixed results on PF components (12, 17–20). The only meta-analysis on MD and PF components showed that high MD adherence was cross-sectionally associated with MF in older adults, although inconsistent results were found regarding MSF parameters (12). Considering this body of evidence, a systematic review and meta-analysis remain lacking to address whether adherence to the MD is associated with each PF component (CRF, MSF, MF) in observational and interventional studies throughout adulthood. Therefore, this study was aimed at synthesizing the cross-sectional, prospective observational (i.e., from cohort studies), and interventional [i.e., from randomized controlled trials (RCTs)] associations between high (compared with low) MD adherence and PF levels in the adult population.

This work was supported by the University of Castilla-La Mancha and cofinanced by the European Social Fund under grant 2020-PREDUCLM-16746; the National Agency for Research and Innovation under grant POS_EXT_2020_20_1_165371; the Spanish Ministry of Education, Culture and Sport under grant FPU 19/00167; and the Spanish Ministry of Education, Culture and Sport under Beatriz Galindo contract BEAGAL18/00093. The funders played no role in the study design, the data collection or analysis, the decision to publish, or the preparation of the manuscript. The conclusions and interpretations provided, based on the scientific data reviewed, are those of the authors and not of the public funding agencies of the study.
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Supplemental Tables 1–10, Supplemental Material, and Supplemental Figures 1–9 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Abbreviations used: CRF, cardiorespiratory fitness; MD, Mediterranean diet; MF, motor fitness; MSF, musculoskeletal fitness; PF, physical fitness; RCT, randomized controlled trial.

Materials and Methods

The systematic review and meta-analysis were conducted in accordance with the 2020 PRISMA guidelines (21) and the Cochrane Collaboration handbook (22). The study protocol was registered in PROSPERO (CRD42022308259) and has been published elsewhere (23). The literature search, data extraction, and risk-of-bias assessment were independently performed by 2 researchers (BB-P and JB-S) with any disagreements resolved by a third researcher (AEM).

Search strategy and study selection

The systematic search was conducted in the following databases from inception until 31 January 2022: MEDLINE–PubMed (January 1975), Cochrane CENTRAL (March 1982), Scopus (July 1974), SPORTDiscus (June 1993), and Web of Science (January 1972). The full detailed search strategy for each database is presented in **Supplemental Table 1**. All identified studies were pooled into a single database, and duplicate articles were excluded via Mendeley Manager (version 1.19.8). Next, studies that clearly did not address the MD–PF relationship were first excluded by title and abstract. In a second step, the remaining studies were analyzed by reading the full text to determine whether they met the eligibility criteria.

Eligibility criteria

To be included, studies retrieved from the peer-reviewed literature had to meet the following inclusion criteria according to the PI(E)COS strategy:

- Participants: general adult population ($\geq$ 18 y)
- Intervention or exposure: for observational studies, high MD adherence according to the overall score of different scales (e.g., 9-point MD scale, 14-point MD scale) and to their specific elements (foods and nutrients); for RCTs, a treatment strategy directly related to the MD (e.g., dietary advice or cooking workshops)
- Comparison: for observational studies, low adherence to the MD; for RCTs, control condition as a non-MD strategy (e.g., habitual diet or usual care)
- Outcome: PF components, including CRF (maximal or submaximal aerobic capacity), MF (agility, balance, or speed), and MSF (flexibility; maximal, endurance, explosive, or isokinetic strength) measured by standardized tests;
- Study design: observational studies (cross-sectional, case–control, and prospective/retrospective cohort) or RCTs

Moreover, studies were excluded if they reported on the following: *1*) only data for populations with specific activities (e.g., elite athletes); *2*) diet in terms of single-nutrient intake, food items, or food groups; *3*) neuromusculoskeletal impairment as the outcome (i.e., frailty, sarcopenia, and physical disability); *4*) PF measured exclusively by self-report; *5*) duplicate data published in another included study; and *6*) noneligible publications, such as qualitative studies, conference or meeting abstracts, preprints, editorials, and letters to the editor.

Data extraction

The following data were extracted from the included studies: name of the first author and year of publication, country, study design, sample size, participant information (sex, age, high MD adherence, and health condition), diet assessment, MD assessment instrument and cutoff score for high MD adherence, specific MD elements (foods and nutrients), PF components, main results, and statistical methods and covariates used.

Risk-of-bias assessment

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (24) and the Risk of Bias tool for crossover trials (25) were used to evaluate the risk of bias of observational studies and RCTs, respectively. Assessment details of the risk-of-bias rating are synthesized in the **Supplemental Material** (Risk of Bias Appendix).

Data synthesis and statistical analysis

For meta-analysis, MD intervention compared with control condition (for RCTs) and higher compared with lower MD adherence (for observational studies) as exposures were considered to compare their association with overall PF levels and, where possible, separately with each PF component (CRF, MF, and MSF; outcomes). The results of the studies were synthesized narratively, and a meta-analysis was performed when at least 4 studies addressed the same outcome (26). In the meta-analysis, ORs and 95% CIs were calculated according to the estimator used in each study (means, ORs, standardized regression coefficients, and unstandardized regression coefficients) by applying the appropriate formula (27–30). We conducted separate meta-analyses depending on the study design. Pooled ORs were estimated with the DerSimonian and Laird random effects method (31). Associations between adherence to the MD as a categorical variable (high compared with low adherence as the reference category) and PF levels as categorical and continuous variables were combined in forest plots according to PF components. Heterogeneity among studies was assessed with the I^2 statistic, categorized as not important (0%–30%), moderate (30%–60%), substantial (60%–75%), or considerable (75%–100%) (22). Additionally, the corresponding *P* values for I^2 were considered (32).

Other methodological considerations for data collection and analysis should be noted. According to a previous meta-analysis (33), studies in which MD adherence was analyzed as a continuous score (i.e., no categorical high compared with low MD adherence was presented) were excluded from the calculation of the ORs to provide more homogeneous results and accurate quantification of associations between high MD adherence and PF levels. For studies analyzing MD adherence as a continuous score, effect sizes and 95% CIs were calculated for each observed correlation and regression coefficient with the Cohen *d* index (28, 30, 34, 35). A pooled effect size was estimated with the DerSimonian and Laird random effects method (31).

Moreover, if the studies presented adjustment models, the results of the fully adjusted model were selected. When studies presented results stratified by sex groups separately and where >1 measure was used for the exposure or for the same PF component, we combined the respective measures to calculate a single pooled OR for each study. In those cases where studies stratified the level of MD adherence into group percentiles, high MD adherence was defined as the highest group and low MD adherence as the lowest group. In prospective cohort studies reporting results for >1 follow-up length, the longest period was selected. Furthermore, prospective cohort studies reporting baseline associations between MD adherence and PF levels were included in the cross-sectional meta-analyses.

Subgroup analyses were performed according to geographic location (Mediterranean region compared with non-Mediterranean region), adult age group (older compared with young or middle-aged), and scale used to assess adherence to the MD (9-point MD scale compared with other scales). Random effects meta-regressions were performed considering the following sample characteristics as continuous independent variables in the model: sex (percentage women), age (mean years), BMI (mean kg/m^2), health status (percentage of ≥ 1 chronic diseases), current smoker (percentage), and total energy intake (mean kilocalories per day). Moreover, sensitivity analyses were conducted to evaluate the robustness of the summary estimates by removing each study one by one. Additional analyses were carried out by combining the measurements of the PF components (CRF, MF, and MSF) into a single pooled OR (overall PF) for each study. Finally, publication bias was assessed with Egger's regression asymmetry test (36) and by evaluating funnel plots through visual inspection when $\geq$ 10 studies were included in the meta-analysis to distinguish chance from real asymmetry (37).

All statistical analyses were performed in Stata/SE software (version 15.0; StataCorp).

Results

Study selection

A total of 3631 studies were considered for title–abstract review after removal of duplicates, of which 80 were fully assessed for eligibility and 50 were excluded for various reasons (**Supplemental Table 2**). Thirty studies were included in the systematic review: 19 cross-sectional (38–56), 10 prospective cohort (57–66), and 1 RCT (67) (**Supplemental Figure 1**).

Study characteristics

Table 1 and **Supplemental Table 3** summarize the characteristics of the studies. The studies were conducted between 2011 (59) and 2021 (44, 50, 51, 55, 58, 65). Twenty-two studies were conducted with older adults (38, 39, 41, 44–49, 53, 55–66). Five cross-sectional (44, 47, 48, 53, 54) and 3 prospective cohort (63–65) studies analyzed adherence to the MD as a continuous score. The insufficient number of prospective cohort studies ($n < 4$) (63–65) estimating associations between MD adherence as a continuous score and PF levels did not allow meta-analysis. The crossover RCT compared two 4-d dietary interventions (MD compared with Western diet) based on verbal and written instructions for each diet (i.e., following the recommended dietary goals through general meal plans for the MD and the Western diet), separated by a washout period from 9 to 16 d (67). Insufficient RCTs addressing the same outcome did not allow meta-analysis regarding this study design (67).

Participants

The studies included 36,807 adults from Mediterranean (38, 39, 41, 43, 46–48, 51, 52, 54, 55, 57, 59, 60, 63) and non-Mediterranean (40, 42, 44, 45, 49, 50, 53, 55, 56, 58, 61, 62, 64–67) countries. The mean age ranged from 20.9 (43) to 86.3 (41) y. Six studies (39, 44, 48–50, 53) analyzed participants with specific health conditions, such as autosomal dominant polycystic kidney disease (50), obesity (44, 48, 49), and type 2 diabetes mellitus (39, 44, 53).

Exposure: MD

MD was calculated via the 9-point MD scale (68) in 12 studies (38–40, 42, 57–62, 64, 66) and the 14-point MD scale (69) in 9 studies (43, 44, 47–49, 53–55, 67). The specific MD index items analyzed were butter and cream (47), cereals (51), commercial sweets and confectionery (47), fish (51, 55), fish and seafood (47, 53), legumes (47, 55), nuts (47), olive oil (47, 51), red meat (47, 51, 55), soda drinks (47), sofrito sauce (47), vegetables and fruits (47, 51, 61), and wine (47).

Outcome: PF

CRF was assessed with 6-min walking test (39, 46, 48), maximal or submaximal bicycle or treadmill ergometry test (42, 51, 64, 67), and 20-m shuttle run test (43, 54). MF was measured with the Short Physical Performance Battery derived from gait speed, functional performance of lower limbs, and standing balance (41, 44, 49, 53, 55, 59–61, 63) and the gait speed test (38, 45, 46, 52, 57, 58, 61, 62, 65, 66). MSF was evaluated with the handgrip strength test (40, 43–47, 49, 50, 52–57, 61–63, 65, 67).

Risk-of-bias assessment

According to the Quality Assessment Tool (24), cross-sectional studies scored between 5 and 8 points (36.8% were rated good quality and 63.2% poor quality), and prospective cohort studies scored between 9 and 11 points (20% were rated good quality and 80% fair quality). The 4 criteria where most of the articles lacked information were sample size justification, varying levels of exposure, repeated exposure assessment, and outcome blinding of the assessors to the participants' exposure status (**Supplemental Table 4**). The RCT (67) was rated as having "some concerns" according to the Risk of Bias tool for crossover trials (25) (**Supplemental Figure 2**).

MD and PF associations

Systematic review.

The results of the studies in the systematic review, not in the meta-analysis, are displayed in **Supplemental Table 5**. The prospective associations between higher MD continuous scores and PF levels provided mixed results, with studies showing significant (63) and nonsignificant (64, 65) improvements. Concerning the RCT, a 4-d MD intervention as compared with a 4-d Western diet reported significant increases in CRF and no significant changes in MSF (67).

When studies analyzed MD-specific elements, higher consumption of fish and seafood (53), nuts (47), and vegetables and fruits (47, 51, 61) and lower consumption of butter and cream, commercial sweets and confectionery, red meat, and soda drinks (47) were significantly associated with higher PF, specifically for CRF (51), MF (53, 61), and MSF (47). Meanwhile, other studies showed no significant association between consumption of cereals (51), fish (47, 51, 55), legumes (47, 55), olive oil (47, 51), red meat (51), and wine (47) and PF levels, specifically for CRF (51), MF (55), and MSF (47, 55). Finally, 1 study showed that higher consumption of red meat was significantly associated with higher MSF (55).

Meta-analysis.

The meta-analysis comparing high and low MD adherence included 16 studies with cross-sectional data (38–43, 45, 46, 49, 51, 52, 55, 56, 59, 61, 66) in 29,866 adults (mean age range: 20.9–86.3 y) and 7 prospective cohort studies (57–62, 66) in 6912 older adults (mean age range: 67.8–74.6 y). Moreover, 5 cross-sectional studies (44, 47, 48, 53, 54) reporting adherence to the MD as a continuous score in 695 adults (mean age range: 20.9–71.7 y) were included in a second meta-analysis.

The pooled ORs from cross-sectional associations (**Figure 1**) showed that high adherence to MD was statistically associated with higher CRF (OR: 2.26; 95% CI: 2.06, 2.47; $I^2 = 0\%$; $n = 4$), MSF (OR: 1.26; 95% CI: 1.05, 1.47; $I^2 = 61.4\%$, $n = 13$), and overall PF (OR: 1.44; 95% CI: 1.20, 1.68; $I^2 = 83.2\%$, $n = 17$) when compared with low adherence to MD (reference category: 1). Moreover, the association between high (compared with low) MD adherence and MF was not statistically significant (OR: 1.27; 95% CI: 0.96, 1.58; $I^2 = 52.9\%$, $n = 10$). The pooled ORs from prospective cohort associations (**Figure 2**) showed that high adherence to MD was statistically associated with higher MSF (OR: 1.20; 95% CI: 1.01, 1.38; $I^2 = 0\%$, $n = 4$) and overall PF (OR: 1.14; 95% CI: 1.02, 1.26; $I^2 = 9.7\%$, $n = 7$) than low adherence to MD (reference category: 1). Moreover, the association between high (compared with low) MD adherence and MF

TABLE 1 Main characteristics of the studies included in the systematic review and meta-analysis

Studies			Participants			Exposure		Outcome		
Reference	Country	Design	Women, *n* (%)	Age, y, mean ± SD or range	haMD, %	Dietary assessment	MD scale/cutoff score for haMD	CRF test	MF test	MSF test
Baker (2019) (67)	Spain	RCT (4 d)	11 (64)	28.0 ± 3.0	—	DH, 3- and 4-d DR	MEDAS/—	5-km treadmill ergometer	—	VHJ, WAn
Barrea (2019) (47)	Italy	Cross-sectional	84 (100)	71.7 ± 5.5	26.2	DH, 7-d DR	MEDAS/≥10	—	—	HGS
Bibiloni (2017) (46)	Spain	Cross-sectional	380 (54.9)	55–80	24.9	FFQ	MP/—	6-min walk	30-m gait speed	Arm curl, HGS, chair stands
Bollwein (2013) (45)	Germany	Cross-sectional	192 (64.6)	83.0 ± 4.0	23.9	FFQ	aMED/≥6	—	4.6-m gait speed	HGS
Buchanan (2021) (44)[1]	Australia	Cross-sectional	87 (33.3)	71.2 ± 8.2	—	—	MEDAS/≥10	—	SPPB	HGS
			65 (66.1)	68.7 ± 5.6						
Cervo (2021) (65)	Australia	Prospective cohort (3 y)	794 (0.0)	81.1 ± 4.5	—	DH, 4-d DR	MEDI-LITE/—	—	6-m gait speed	HGS
Chan (2019) (64)	China	Prospective cohort (7 y)	1235 (39.1)	70.4 ± 4.2	—	FFQ	MDS, MIND/—	Maximal bicycle ergometry	—	—
Cobo-Cuenca (2019) (43)	Spain	Cross-sectional	310 (65.2)	20.9 ± 2.5	24.0	FFQ	MEDAS/≥9	20-m shuttle run	—	HGS, SLJ
Cuenca-García (2014) (42)[2]	US	Prospective cohort (11.6 y)	12,449 (23.3)	46.2 ± 10.1	17.4	3-d DR	MDS/>7	Maximal treadmill ergometry	—	—
Fougère (2016) (41)	Italy	Cross-sectional	304 (59.5)	86.3 ± 6.8	—	—	MSDPS/—	—	SPPB	—
Gallucci (2019) (63)	Italy	Prospective cohort (3 y)	190 (56.8)	83.8 ± 4.5	—	—	MSDPS/—	—	SPPB	HGS
Huang (2021) (62)	Japan	Prospective cohort (3 y)	666 (56.5)	69.4 ± 4.4	—	FFQ	MDS/—	—	5-m gait speed	HGS
Isanejad (2018) (61)[3]	Finland	Prospective cohort (3 y)	503 (100)[4]	67.8 ± 1.8	15.7	3-d DR	MDS/≥7	—	10-m gait speed, 30-s leg stance, SPPB	HGS, knee extension, chair stands
Jin (2017) (60)	Italy	Prospective cohort (9 y)	906 (55.3)	74.0 ± 6.7	—	FFQ	MDS/—	—	SPPB	—
Kelaiditi (2016) (40)[1]	UK	Cross-sectional	2570 (100)	48.3 ± 12.7	—	FFQ	MDS/≥6	—	—	NPR
			949 (100)	59.1 ± 9.3						HGS
Kim (2019) (56)	Korea	Cross-sectional	3675 (53.5)	72.6 ± 0.2	41.7	24-h recall survey	aMED/—	—	—	HGS
Marcos-Pardo (2020) (48)	Spain	Cross-sectional	62 (—)	62.7 ± 8.02	50.0	—	MEDAS/—	6-min walk	—	—
Marcos-Pardo (2021) (55)	Finland, Ireland, Italy, Spain	Cross-sectional	1880 (51.6)	65.4 ± 8.5	34.4	—	MEDAS/≥7	—	SPPB	HGS
Martín-Espinosa (2020) (54)	Spain	Cross-sectional	310 (65.2)	20.9 ± 2.5	24.0	FFQ	MEDAS/>9	20-m shuttle run	—	HGS

(*Continued*)

TABLE 1 (*Continued*)

Studies			Participants			Exposure		Outcome		
Reference	Country	Design	Women, *n* (%)	Age, y, mean ± SD or range	haMD, %	Dietary assessment	MD scale/cutoff score for haMD	CRF test	MF test	MSF test
McClure (2019) (53)	Australia	Cross-sectional	87 (33.3)	71.2 ± 8.2	—	FFQ	MEDAS, aMED/≥10, ≥6	—	SPPB	HGS
Milaneschi (2011) (59) [3]	Italy	Prospective cohort (9 y)	935 (55.6)[5]	74.1 ± 6.8	29.3	FFQ	MDS/≥6	—	SPPB	Knee extension
Mohseni (2017) (52)	Iran	Cross-sectional	250 (100)	57.7 ± 6.2	33.3	FFQ	MP/—	—	4-m gait speed	HGS
Payandeh (2021) (51)	Iran	Cross-sectional	270 (56.3)	36.5 ± 13.1	24.2	FFQ	Med-DQI/≥7	Maximal treadmill ergometry	—	—
Ryu (2021) (50)	Korea	Cross-sectional	68 (60.3)	57.1 ± 10.5	—	FFQ	aMED/—	—	—	HGS
Saadeh (2021) (58)	Sweden	Prospective cohort (12 y)	1686 (57.6)	69.0 ± 8.1	30.8	FFQ	MDS/—	—	6- or 2.4-m gait speed	Chair stands
Shahar (2012) (66) [3]	US	Prospective cohort (8 y)	2225 (49.9)	74.6 ± 2.8	5.1	FFQ	MDS/≥6	—	20-m gait speed	—
Stanton (2019) (49)	Australia	Cross-sectional	65 (63.1)	68.7 ± 5.6	35.4	—	MEDAS/≥6	—	SPPB	HGS
Talegawkar (2012) (57)	Italy	Prospective cohort (6 y)	690 (51.7)	73.0 ± 6.2	27.4	FFQ	MDS/≥6	—	4-m gait speed	HGS
Tepper (2018) (39)	Israel	Cross-sectional	117 (39.3)	70.6 ± 6.5	26.5	FFQ	MDS/≥5	6-min walk	—	—
Zbeida (2014) (38)	Israel	Cross-sectional	2791 (49.3)	71.3 ± 7.8	14.2	24-h recall survey	MDS/≥6	—	6-m gait speed	Knee extension

aMED, alternate Mediterranean diet; CRF, cardiorespiratory fitness; DH, diet history; DR, dietary registration; haMD, high adherence to the Mediterranean diet; HGS, handgrip strength; MD, Mediterranean diet; MDS, Mediterranean Diet Score; MEDAS, Mediterranean Diet Adherence Screener; Med-DQI, Mediterranean Dietary Quality Index; MEDI-LITE, Literature-Derived Mediterranean Diet; MF, motor fitness; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay Diet; MP, Mediterranean Pattern; MSDPS, Mediterranean-Style Dietary Pattern Score; MSF, musculoskeletal fitness; NPR, Nottingham Power Rig; RCT, randomized controlled trial; SLJ, standing long jump; SPPB, Short Physical Performance Battery; VHJ, vertical height jump; WAn, Wingate Anaerobic.

[1] Data from 2 samples.

[2] Only cross-sectional data were included in the meta-analysis.

[3] Cross-sectional data were also included in the meta-analysis.

[4] Among the participants in the cross-sectional analyses, 253 had available data at the 3-y follow-up.

[5] Among the participants in the cross-sectional analyses, 486 had available data at the 9-y follow-up.

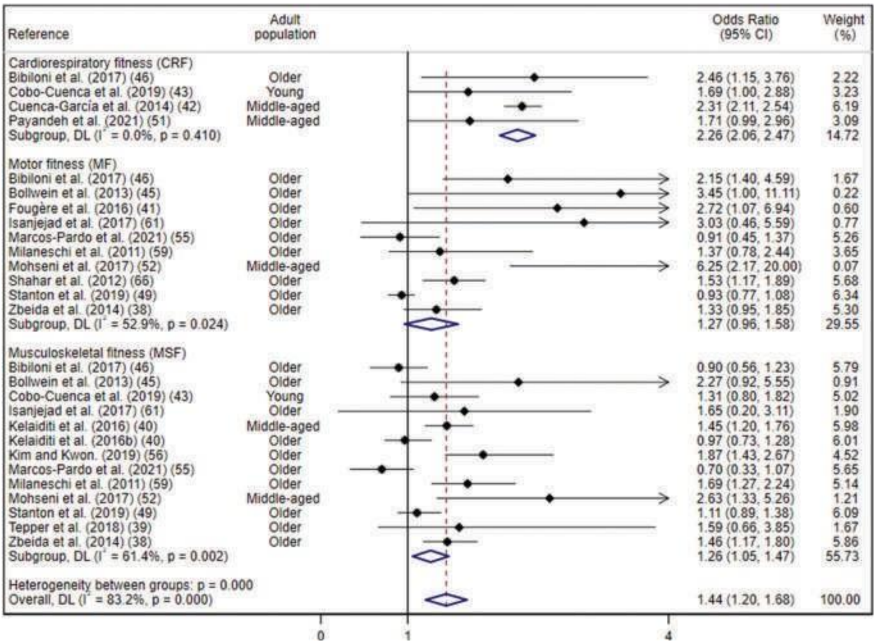

FIGURE 1 Forest plot for the cross-sectional associations between high adherence to the Mediterranean diet and physical fitness components in adults of all ages.

was not statistically significant (OR: 1.17; 95% CI: 0.95, 1.38; I^2 = 36.5%, n = 7). Finally, the pooled effect sizes between higher MD adherence scores (as a continuous variable) and overall PF (**Figure 3**) showed a significant cross-sectional association (d = 0.45; 95% CI: 0.14, 0.75; I^2 = 91.0%, n = 6).

Subgroup analyses and meta-regressions

Subgroup analyses are displayed in **Supplemental Table 6** and **Supplemental Figures 3** and **4**. The pooled estimates for the cross-sectional subgroup analyses were similar to the main pooled OR for overall PF in the Mediterranean and non-Mediterranean regions, in older adults and in young or middle-aged adults, and when MD adherence was assessed by the 9-point MD scale and by other MD indices. Moreover, high (compared with low) MD adherence and PF levels were statistically significant for MF in the Mediterranean region and for CRF and MSF in the Mediterranean and non-Mediterranean regions. Concerning the prospective cohort studies, the pooled estimates for subgroup analyses were similar to the main pooled ORs for MF and overall PF in the Mediterranean region. Additionally, meta-regression models showed that none of the variables considered (sex, age, BMI, health status, current smoker, and total energy intake) influenced the relationship between high (compared with low) MD adherence and PF levels for the cross-sectional or prospective cohort models (**Supplemental Table 7**).

Sensitivity analyses

Sensitivity analyses for the cross-sectional estimates (**Supplemental Table 8**) showed that the association between high (compared with low) MD adherence and MF became significant after excluding the studies by Marcos-Pardo et al. (55) and Stanton et al. (49). The pooled ORs for CRF, MSF, and overall PF were not modified when removing each study one by one. Sensitivity analyses for the prospective cohort estimates (**Supplemental Table 9**) showed that the association between high (compared with low) MD adherence and MSF was no longer significant after excluding the study performed

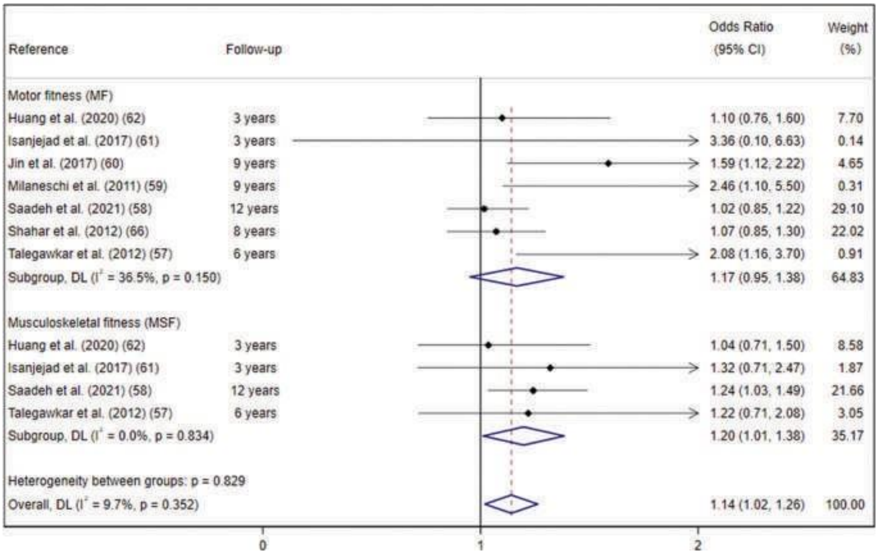

FIGURE 2 Forest plot for the prospective cohort associations between high adherence to the Mediterranean diet and physical fitness components in older adults.

by Saadeh et al. (58). Moreover, the association between high (compared with low) MD adherence and overall PF was no longer significant after excluding the studies conducted by Jin et al. (60), Saadeh et al., and Talegawkar et al. (57). The pooled ORs for MF were not modified when removing each study one by one. Finally, after combining measurements for all PF components from each study, cross-sectional and prospective cohort estimates showed that the association between high (compared with low) MD adherence and overall PF remained significant (**Supplemental Figures 5** and **6**).

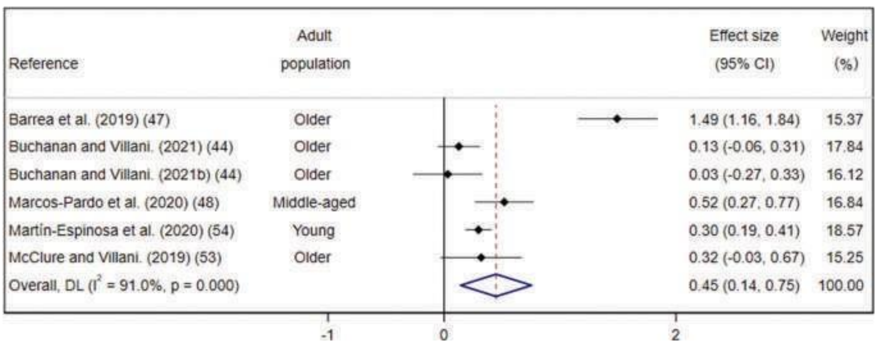

FIGURE 3 Forest plot for the cross-sectional association between higher Mediterranean diet adherence scores (as a continuous variable) and overall physical fitness in adults of all ages.

Publication bias

According to Egger's test and funnel plot asymmetry, publication bias was found for MF in the cross-sectional analysis (**Supplemental Table 10** and **Supplemental Figures 7–9**).

Discussion

This systematic review and meta-analysis synthesized the relationships between adherence to the MD and PF components (cardiorespiratory, motor, and musculoskeletal) in adulthood. Our results support a significant positive association between high (compared with low) MD adherence and PF levels in cross-sectional studies specifically for CRF, MSF, and overall PF in adults of all ages. Furthermore, the improvement in PF among those with higher MD adherence was observed in prospective cohorts (3- to 12-y follow-up), specifically for MSF and overall PF, but only older adults were included in these studies. No significant association was observed between MD adherence and MF. Sex, age, BMI, health status, current smoking status, and total energy intake did not influence the strength of these associations.

Thus far, the available evidence regarding associations between high (compared with low) MD adherence and PF levels among adults has been inconclusive (12, 17, 18). Previous systematic reviews included a limited number of observational studies and showed mixed results in CRF (18) and MSF (12) in late adulthood. Regarding other plant-based dietary patterns (MD can be considered mainly, but not exclusively, a plant-based food matrix) (10), a recent systematic review reported a positive trend in associations between a vegetarian or vegan dietary pattern and PF levels, although the evidence is scarce and does not allow drawing consistent conclusions (70). Our results extend knowledge by providing a comprehensive picture of MD–PF associations in adulthood, pointing out that adults of all ages with high MD adherence have greater CRF, MSF, and overall PF levels than their counterparts with low MD adherence. These findings suggest the potential role of following the MD, which is associated with higher levels of PF, thus reducing the risk of critical outcomes such as mortality (1, 5–7).

Subgroup analyses showed that high cross-sectional adherence to the MD was associated with higher PF levels in Mediterranean and non-Mediterranean countries (for MSF and overall PF). However, changes were observed in the MF component according to geographic region. Indeed, high (compared with low) MD adherence was cross-sectionally and prospectively associated with higher MF only in countries from the Mediterranean region. A potential explanation is the influence of the Mediterranean lifestyle (e.g., adequate rest, regular practice of moderate physical activity, social support), which contributes to the effectiveness of high MD adherence (71). While this applies to all PF factors (71), according to our results, it may play a key role in the motor component. MF parameters (e.g., speed or balance), whose results were reported by the studies in older adults, are complex neuromuscular tasks that could require greater neurocognitive demands than measures of CRF and MSF in late adulthood (72). Therefore, MF improvements in older adults may require the whole structure of the Mediterranean lifestyle and not just MD adherence to improve their condition. The influence of this demographic characteristic needs to be confirmed because of the lack of studies to draw consistent conclusions.

Significant heterogeneity was observed in some of the pooled analyses and was explored in the subgroup and meta-regression analyses based on participant characteristics. Although sex, age, BMI, chronic diseases, smoking status, and total energy intake have been identified as factors related to MD adherence (73), the results of the meta-regressions did not confirm that the relationship between high (compared with low) MD adherence and PF levels could be influenced by these factors. Additionally, data from subgroup analyses suggest that geographic position could be a source of heterogeneity. This may be related to the variability of other factors in assessing the MD–PF relationships not available for the present analyses, such as inconsistencies in food and nutrient intakes in MD adherence (74) or country-typical food products and customs (75).

Different mechanisms have been proposed to explain the effects of MD on PF. Optimal concentrations of nutrients linked to high MD adherence, such as advanced glycation end products (76), carotenoids (77), n-3 polyunsaturated fatty acids (78), polyphenolic compounds (79), trace elements (80), and vitamins (81), have been associated with greater benefits on PF status. Notably, the main elements of the Mediterranean food matrix (extra virgin olive oil, fresh fruits and vegetables, legumes, nuts, red wine, seeds, and whole grain cereals) include a wide variety of antioxidant molecules that can influence the MD–PF links, such as carboxymethyl-lysine, coenzyme Q10, creatine, flavonoids, hydroxytyrosol, lycopene, oleocanthal, selenium, spermidine, vitamins D and E, α-linolenic acid, β-carotene, and others (82, 83). Evidence suggests that these components are rich in antioxidant compounds and contribute to PF development through different pathways, such as reduced reactive oxygen species (84) and proinflammatory cytokine expression (85), which drive important signaling events in PF status (86, 87). The results of our systematic review showed inconsistent results regarding specific MD elements, mainly because studies analyzing MD adherence in conjunction with specific foods and PF status are scarce. However, preliminary evidence showed positive associations between high consumption of vegetables and fruits and higher PF levels (47, 51, 61).

Two main strengths of this study were identified. First, to date, this is the first systematic review and meta-analysis, to the best of our knowledge, synthesizing the relationships between MD adherence and PF components (CRF, MF, and MSF) from cross-sectional, prospective cohort, and RCT studies in the general adult population. Second, we found several research gaps in MD–PF relationships that will play a key role in understanding these relationships through future scientific evidence. In particular, our findings identified a need for more prospective cohort studies (particularly on CRF and MSF outcomes and in young and middle-aged adults) and long-term RCTs to provide consistent conclusions for all PF components. Concerning PF outcomes, more studies analyzing CRF (particularly in older adults) and MF and MSF (particularly in young and middle-aged adults) and considering underanalyzed parameters (e.g., flexibility for MSF) could provide essential information. Moreover, there are still fundamental gaps in the knowledge about the role of specific MD elements, with high MD adherence, on PF status that must be clarified. Last, diet efficacy can be specific to age ranges, health conditions, geographic regions, sex, and PF components. It is desirable to promote high-quality research that, in addition to providing a better understanding of the MD–PF links, provides vital evidence to identify specific nutritional requirements related to MD according to PF outcomes and associated factors (sex, age, health status, and region).

Some limitations of our systematic review and meta-analysis should be acknowledged. First, some pooled estimates were accompanied by moderate to considerable unexplained between-study heterogeneity. The studies were performed in different types of populations (e.g., healthy, with obesity or type 2 diabetes, young, older) and with high variability in confounding factors and measurements of MD, which may have increased heterogeneity and limited the implications of our results. In particular, the high variability in the levels of evidence of validity and reliability of PF tests (88, 89) developed in the studies might lead to some bias. Moreover, we cannot rule out residual confounding due to factors unavailable in most of the studies, such as cooking techniques, eating behavior, genetic variants, or social support. Second, the overall risk of bias for observational studies showed fair quality in most studies, and sensitivity analyses revealed variation in the pooled estimates concerning specific studies. Finally, there was evidence of publication bias per Egger's test for MF in cross-sectional studies. Therefore, our findings should be considered and extrapolated with caution.

In conclusion, pooled analysis of cross-sectional studies showed that high MD adherence was associated with higher levels of CRF, MSF, and overall PF in the entire adult population. Moreover, high (compared with low) MD adherence significantly improved MSF and overall PF levels in the pooled analysis of prospective cohort studies (3- to 12-y follow-up) in which only older adults were included. Promoting optimal adherence to MD during adulthood, which was positively associated with a powerful health indicator such as PF, should be a cornerstone of public health initiatives to prevent different diseases. Future long-term clinical trials and prospective cohort studies are needed to provide evidence on the biological and environmental mechanisms underlying the associations between high MD adherence with specific Mediterranean foods and higher PF levels.

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Data Availability

The data used in this review are available from the corresponding author upon reasonable request.

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MANUSCRIPT III

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The association between meat consumption and muscle strength index in young adults: the mediating role of total protein intake and lean mass percentage.

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ORIGINAL CONTRIBUTION

The association between meat consumption and muscle strength index in young adults: the mediating role of total protein intake and lean mass percentage

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Abstract

Purpose The aim of this study was to analyse the associations between the consumption of different types of meat and the muscle strength index (MSI) and to examine whether this relationship is mediated by total protein intake (TPI) and lean mass percentage (LM%) in young adults.

Methods We conducted a cross-sectional study with first-year university students from Castilla-La Mancha, Spain. Different types of meat consumption (total, red, processed, and white and fish) were separately evaluated using a Food-Frequency Questionnaire. MSI was determined from the handgrip and standing long jump tests. ANCOVA models were used to test the mean differences in MSI by categories of meat consumption. Serial multiple mediation models were used to explore the mediating role of TPI and LM% in the relationship between meat consumption and MSI. All analyses were adjusted for age, sex, and socioeconomic level, identified through a directed acyclic graph. Additional analyses were performed with a small subsample including alcohol intake, tobacco smoking, physical activity, cardiorespiratory fitness, and total energy intake as covariates in the multiple mediation models.

Results A total of 230 students (mean age 21.1 ± 2.1 years, 66.5% women) were included in the analysis. Young adults with higher meat consumption (total, red, and white and fish) had higher MSI adjusted means than their peers with lower meat consumption ($p < 0.05$). These associations did not remain after controlling for TPI and LM%. In adjusted mediation analyses, a significant indirect effect was observed through TPI and LM% in the associations between each of the types of meat consumption and MSI. In the additional analyses, a greater effect of white and fish meat consumption on muscle strength through mediation of TPI and LM% was reported compared to red or processed meat consumption, and no significant effects were observed between processed meat consumption and MSI.

Conclusion Higher consumption of total, red, and white and fish meat was associated with increased MSI in young adults. TPI and LM% mediated this relationship.

Keywords Lean body mass · Meat consumption · Muscle strength · Protein · University students

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Introduction

The consumption of meat has been increasing exponentially worldwide since the 1960s, and projections support a continuous increase in this trend in the coming years [1]. Currently, 92.1% of the adult Spanish population consumes meat daily [2]. Meat represents an important dietary source of protein, in addition to providing a substantial content of saturated and unsaturated fats, minerals, and vitamins [3]. The density of each of these nutrients varies considerably according to the type of meat (i.e. red, processed, white and fish meat) [4]. Differences in protein content occur, especially in terms of density, composition, digestibility, and amino acids provided [5]. Therefore, it is reasonable to consider that the effects of meat consumption on health parameters, such as muscle strength or body composition, vary according to the type of meat consumed [6].

Muscle strength is an important indicator of health status in the general adult population [7]. The intake of high-quality protein, such as that from meat, is essential for lean mass development and maintenance and muscle strength [8]. However, in addition to increased total protein intake, increasing meat consumption may increase total energy intake and, consequently, contribute to body fat storage with adverse effects on body composition and energy regulation [9]. In this context, meat consumption leads to greater muscle strength if the protein and energy provided promote positive changes in lean mass [10, 11]. Therefore, protein intake, lean mass, and muscle strength are closely linked to protein metabolism, energy expenditure, and consequently weight control [12].

Some studies reported that higher total and animal protein intake was positively associated with greater muscle strength in adulthood [10, 13]. However, less consideration has been given to the differential contributions of protein, particularly food sources, to muscle strength [14]. Regarding meat consumption, a meta-analysis of randomized controlled trials (RCTs) showed that beef consumption combined with exercise training represented an effective strategy for increasing lower-limb maximal muscle strength in young adults [15]. Nevertheless, because of the small number of studies and their small sample sizes, the available evidence did not allow for consistent conclusions to be drawn [15].

Considering that eating habits are modifiable aspects of lifestyle and that muscle structure and function in younger adults determine musculoskeletal health and quality of life in adulthood [16], further knowledge of the associations between consumption of different types of meat and muscle strength in young adults is relevant from a public health perspective. In fact, both muscle mass and strength decline progressively after young adulthood [17], so it is imperative to prevent these age-associated losses to maintain whole-body metabolic homeostasis and locomotory capabilities throughout the life span [18]. Additionally, there is also a need to advance the understanding of the role of total protein intake and percentage of lean mass in the relationship between meat consumption and muscle strength. Therefore, this study aimed to (i) analyse the associations between the consumption of different types of meat and muscle strength in young adults and (ii) examine whether these associations are mediated by total protein intake and lean mass percentage.

Methods

Experimental design, sample size, and participants

This cross-sectional study is based on data obtained from first-year university students in Castilla-La Mancha, Spain, during the 2017–2018 academic year. The data analysed in this study are part of the database of the investigation "Lifestyle, adiposity and vascular function in university students in Castilla-La Mancha, Spain", which aimed to estimate the prevalence of obesity in the target population. The sample size was calculated with Epidat software, estimating an obesity prevalence of 23%, an alpha error of 0.05, a statistical power of 80%, and a precision of 5% [19]. Considering a nonresponse rate of 20%, the total sample size was calculated at 300 students. Taking as a sampling frame the list of students enrolled in these university courses, 560 random students aged 18–30 years were invited to participate in the study, of whom 360 (64.3%) agreed and met the following inclusion criteria: not having a learning disability and not having any type of physical or mental disorder. After the exclusion of 130 individuals with missing values for the variables of interest, 230 university students aged 19–29 years were finally included in this analysis. There was no difference in age, sex, or parental socioeconomic status between the invited and finally included students. The study protocol was approved by the Clinical Research Ethics Committee of the "Virgen de la Luz" of Cuenca (REG: 2016jPI1116) and adhered to the principles of the Declaration of Helsinki. Informed consent to participate was obtained from all subjects involved in the study. "A Guideline for Reporting Mediation Analyses" [20] was used for reporting this study (Supplementary material: Table S1).

Study variables

Outcome variable: muscle strength index (MSI)

A muscle strength index (MSI) was calculated as the sum of the standardized *z*-score of handgrip/body mass and *z*-score of the standing long jump. Muscle strength variables were assessed after a 4-min warm-up of calisthenic exercises and static stretching. In the handgrip test, a dynamometer

(TKK 5401 Grip-D, Takeya, Tokyo, Japan) was used to measure the maximum isometric handgrip muscle strength. With the elbow in extension, participants had to squeeze the dynamometer gradually and continuously as hard as possible for at least 2 s. The test was performed twice with each hand, and the mean average of the four measurements was reported in kilograms. Additionally, the standing long jump was used to measure the explosive lower body muscular strength. Participants stood behind the jump line, feet shoulder width apart. From this position, they jumped as far as possible, and the test was accepted if they were able to land with both legs in a stable position. The distance jumped was measured in centimetres from the jump line to the back of the heel closest to this line. The best distance of three attempts was recorded and used in the analyses.

Outcome variable–exposure variable: meat consumption

A 137-item Food-Frequency Questionnaire (FFQ) was used to estimate the meat consumption of each meat type [21]. This FFQ contains nine levels of consumption frequencies for each item (never or almost never, 1–3 times per month, once per week, 2–4 times per week, 5–6 times per week, once per day, 2–3 times per day, 4–6 times per day, and more than 6 times per day). In the FFQ questionnaire, all meat servings were specified in grams. Meat consumption was estimated by multiplying the frequency of consumption for each item and the typical portion size specified in the FFQ according to the Spanish food composition tables [22]. For this study, meat consumption was determined in grams per kilogram of body mass (BM) per day (g/kg BM/d). The study sample was classified into three categories of total meat consumption (low, intermediate, and high) based on tertile splits.

Four major groups of meat consumption were created based on the type of meat consumed. Red meat consumption (RMC) was defined as the consumption of beef, veal, lamb, pork, liver (veal, pork), other entrails (brains, heart, sweetbreads), and bacon. Processed meat consumption (PMC) included the consumption of salami, blood sausage, sausage, *sobrassada*, *serrano* and york ham, mortadella, and hamburger. White and fish meat consumption (WFMC) was defined for the consumption of poultry (chicken and turkey), hare, rabbit, white fish (sole, sea bream, hake, whiting, grouper, cod), blue fish (sardine, tuna, bonito, salmon, mackerel), oysters, clams, mussels, squid, octopus, squid, cuttlefish, crustaceans (prawn, shrimp, crayfish), canned fish, and seafood (sardines, anchovies, tuna, bonito). Finally, total meat consumption (TMC) was defined as the sum of RMC, PMC, and WFMC.

Potential mediators: total protein intake (TPI) and lean mass percentage (LM%)

Total protein intake (TPI) was assessed with the 137-item FFQ [21] and determined in g/kg BM/d.

Lean mass (LM) (g) and body fat mass (g) were measured using dual-energy X-ray absorptiometry (DXA) (Lunar iDXA, GE Medical Systems Lunar, Madison, WI 53718, USA). The variable lean mass percentage (LM%) was calculated as follows: [(LM/total body mass) * 100]. All DXA scans were examined using Physician's Viewer, APEX System Software Version 3.1.2. (Bedford, USA). DXA equipment precision was examined daily before each checking session using the GE Lunar calibration phantom, as suggested by the manufacturer. All measurements were performed at high resolution with students in a supine decubital position. Seven trained health researchers performed data collection following standardized procedures to reduce interobserver variability.

Covariates

Information on potential confounders of the study associations was also assessed. Self-reported information was obtained for age (years), sex (female, male), socioeconomic level based on the level of education of the participants' parents (high, intermediate, low), alcohol intake (alcoholic beverages drinker, nondrinker), and tobacco smoking (current smoker, nonsmoker). Moreover, BMI was calculated as mass divided by the square of the height (kg/m^2), both objectively measured under standardized conditions. Total energy intake was estimated based on the answers to the 137-item FFQ [21] and determined in total calories/day [22]. Likewise, data on carbohydrate intake and lipid intake were also obtained. Cardiorespiratory fitness was assessed with the Course Navette test, and the maximal oxygen consumption (VO_2 max) was estimated using the Leger 20-m shuttle-run formula (31.025 + (3.238 × velocity) − (3.248 × age) + (0.1536 × age × velocity)) [23]. Finally, information on objectively measured physical activity was obtained for a small subsample (n = 118) and used specifically in the additional analyses. Participants wore GENEActive accelerometers (ActivInsights) on their wrists for seven consecutive days. The devices were set at a fixed frequency of 30.0 Hz for collecting raw acceleration data measured in milli-g (1000 mg = 1 g = 9.81 m/s^2) for each movement axis (x, y, and z) to estimate the young adult's physical activity. We considered valid measurements those available for at least five consecutive days, including one weekend day. For this study, the mean minutes per day of moderate and vigorous physical activity were estimated according to previous studies [24].

Body mass (BM) is associated with meat consumption, muscle strength, and the two mediators analysed regardless of sex and age [12, 25]. For this reason, instead of considering BM as another possible adjustment covariate, we considered that incorporating BM in the definition of the exposure, outcome, and mediator variables would be more appropriate. Therefore, meat consumption and TPI were calculated in terms of daily intake in grams per kg of BM. LM%, being a proportion of BM, did not require any specific procedure in this regard. Likewise, BM was considered for the calculation of MSI (the sum of the standardized *z*-score of handgrip/BM and *z*-score of the standing long jump). In summary, BM was not included as a possible adjustment variable because its potential biasing effect was intrinsically controlled in the definition of the main study variables.

To identify the minimum sufficient adjustment set (MSAS) for the total effect of meat consumption on muscle strength, we built a theoretical causal diagram based on previous knowledge available in the scientific literature. We used the online tool DAGitty [26] to construct a directed acyclic graph (DAG) [27]. The covariates sex, age, and socioeconomic level were identified as the MSAS.

Statistical analysis

Initially, statistical (Kolmogorov–Smirnov) and graphical (normal probability plots) methods were used to evaluate the normal distribution of continuous variables. One-way analysis of variance and the Kruskal–Wallis test were used to analyse the associations between characteristics of the study sample by the TMC categories (low, intermediate, and high). Moreover, the associations between categorical variables and TMC categories were tested through the Chi-square test (Table 1).

Bivariate correlation coefficients were calculated to examine the relationship between MSI, TPI, LM%, and each group of meat consumption (Table 2).

To test the mean differences in MSI by categories of all groups of meat consumption, analysis of covariance models controlled for age, sex, and socioeconomic level (model 1), and additionally for TPI and LM% (model 2) were used. Post hoc pairwise multiple comparisons using the Bonferroni test to identify significant differences between means of MSI by the categories of meat consumption were used (Fig. 1).

Mediation analyses were conducted to examine whether TPI and LM% mediate the association between meat consumption and MSI using PROCESS SPSS Macro, version 3.5 [28]. This macro used bootstrapping methods for testing mediation hypotheses [28]. For these analyses, we selected a serial multiple mediation model using 5000 bootstrap samples to calculate confidence intervals (CI 95%) with TPI as the first mediator, controlling for age, sex, and socioeconomic level (i.e. the MSAS covariates identified through the DAG). ###We separately analysed TMC, RMC, PMC, and WFMC as the main independent variables. The mediation model used (Model 6 with 2 mediators) [28] explores the total (c) and direct effects (a_1, a_2, b_1, b_2, d, and c') that indicate the unstandardized regression coefficient and significance between meat consumption and MSI. Additionally, this model examines three indirect effects (IE_1, IE_2, and IE_3) that indicate the change in MSI for each unit change in meat consumption that is mediated by TPI and LM%. The IEs were considered significant when the 95% CI did not contain zero. Pairwise contrasts calculate all possible comparisons between specific IEs. Following the Hayes recommendation [28], the complete and partial mediation concepts were not used in this study. As shown in Supplementary material: Fig. S1, when controlling the analyses for the MSAS covariates, the bias pathways were completely closed, and only the causal pathways (both direct and indirect, i.e. through mediators) remained open. Therefore, age, sex and socioeconomic level were added as covariates in these analyses. Additional mediation analyses were performed with the adjustment for other covariates identified through the DAG (Fig. S1) as relevant confounding factors in the diet-muscle strength relationship available for a subsample (n = 118) in our dataset, such as alcohol intake, tobacco smoking, physical activity, cardiorespiratory fitness, and total energy intake. The mediation analyses in this study are exploratory.

All statistical analyses were performed using IBM SPSS Statistics software (Version 24.0; IBM Corp., Armonk, NY, USA), and $p < 0.05$ was considered to indicate significance.

Results

Of the 360 students who agreed to participate in the study, a total of 230 young adults (mean age 21.1 ± 2.1, 66.5% female) were finally included in this analysis. Table 1 presents the descriptive characteristics of the study participants. Compared with the low category of TMC, those with high TMC presented lower BMI values, higher intake of all macronutrients, and higher values of total energy intake and MSI.

Bivariate correlations among meat consumption, MSI, TPI and LM% are presented in Table 2. TMC, RMC, and WFMC were significantly associated with MSI, TPI, and LM%.

Figure 1 depicts the mean differences in MSI by categories of meat consumption (TMC, RMC, PMC, and WFMC). When adjusted for age, sex, and socioeconomic level (model 1), participants with high TMC, RMC, and WFMC showed significantly higher values in MSI than those with low categories of meat consumption. When TPI and LM% were added to model 1 as covariates (model 2), the aforementioned associations lost statistical significance. No association between PMC and LM% was observed (Fig. 1).

Table 1 Descriptive characteristics of the study sample by total meat consumption

Characteristic	Total[a] ($n=230$)	Total meat consumption (g/kg BM/d)			p-value[b]
		Low ($n=77$)	Intermediate ($n=77$)	High ($n=76$)	
Sociodemographic					
Age (years)	21.1 ± 2.1	21.0 ± 1.7	21.2 ± 2.4	21.1 ± 2.2	0.740
Female (%)	66.5	58.4	68.8	72.4	0.165
Socioeconomic level (level of parental education, %)					
University studies (high)	22.5	21.3	24.0	22.1	
Secondary studies (intermediate)	60.4	58.7	64.0	58.4	0.712
Primary studies or no education (low)	17.1	20.0	12.0	19.5	
Lifestyle habits					
Alcohol intake (%)	87.3	81.8	89.6	90.7	0.199
Tobacco smoking (%)	14.7	10.8	18.4	14.9	0.421
Moderate and vigorous physical activity (min/d)	145.51 ± 249.51	225.99 ± 48.62	222.62 ± 82.08	224.32 ± 78.12	0.608
Cardiorespiratory fitness (VO_2 max estimate, mL/kg/min)	38.65 ± 8.18	38.05 ± 8.74	38.12 ± 7.94	39.61 ± 7.94	0.455
Anthropometric					
Lean mass (%)	70.1 ± 9.4	69.3 ± 9.4	69.1 ± 10.3	72.0 ± 8.1	0.108
Fat mass (%)	29.3 ± 9.0	30.3 ± 9.4	30.0 ± 9.4	27.5 ± 7.9	0.115
BMI (kg/m^2)	23.1 ± 3.5	24.5 ± 4.4	23.1 ± 2.9	21.8 ± 2.5	**< 0.001**
Dietary intake					
Meat consumption (g/kg BM/d)					
Total meat	4.1 ± 2.4	2.2 ± 0.7	3.7 ± 0.5	6.6 ± 2.5	**< 0.001**
Red meat	1.0 ± 0.7	0.5 ± 0.3	0.9 ± 0.4	1.6 ± 0.8	**< 0.001**
Processed meat	0.7 ± 0.6	0.4 ± 0.3	0.7 ± 0.4	1.1 ± 0.7	**< 0.001**
White and fish meat	2.4 ± 1.7	1.2 ± 0.5	2.1 ± 0.6	3.9 ± 2.1	**< 0.001**
Macronutrient intake (g/kg BM/d)					
Protein	1.8 ± 0.8	1.2 ± 0.5	1.7 ± 0.4	2.6 ± 0.9	**< 0.001**
Carbohydrate	4.7 ± 2.5	3.5 ± 2.0	4.5 ± 2.2	6.1 ± 2.7	**< 0.001**
Lipids	1.9 ± 1.0	1.3 ± 0.7	1.7 ± 0.6	2.7 ± 1.2	**< 0.001**
Total energy intake (kcal)	2703 ± 1223	2060 ± 956	2514 ± 841	3545 ± 1321	**< 0.001**
Muscle strength					
Muscle strength index[c]	−0.07 ± 1.8	−0.33 ± 1.9	−0.03 ± 1.7	0.15 ± 1.6	**0.042**
Handgrip strength (kg)	29.4 ± 8.6	28.1 ± 7.2	29.4 ± 8.4	30.8 ± 10.0	0.528
Standing long jump (cm)	160.0 ± 47.3	154.9 ± 52.5	161.4 ± 48.2	163.5 ± 41.4	0.632

BM body mass

[a]For the following variables, the total number of participants was lower due to missing data: alcohol intake and BMI ($n = 229$), tobacco smoking ($n = 224$), and physical activity ($n = 118$)

[b]Obtained for continuous variables with one-way analysis of variance (normally distributed: moderate and vigorous physical activity; lean mass; fat mass; muscle strength index; and standing long jump) or Kruskal–Wallis test (nonnormally distributed: age; BMI; cardiorespiratory fitness; total, red, processed, and white and fish meat consumption; protein, carbohydrate, and lipids intake; total energy intake; and handgrip strength) and for categorical variables with the Chi-square test

[c]Sum of the BM-standardized z-score of dynamometry and standing long jump test. P values marked with bold indicate statistically significant differences between the tertiles of meat consumption

The results of the multiple serial mediation models are presented in Fig. 2. Total effects were found, indicating that the higher the TMC, RMC, PMC, and WFMC were, the higher the MSI (paths c). Furthermore, similarly for each type of meat studied, TPI and LM% mediated the associations between meat consumption and MSI. Indirect effect 3 (IE_3) was the only statistically significant pathway for these mediation analyses. The IE_3 means that the higher the consumption of all types of meat was, the higher the TPI, which would be associated with improvements in LM% and, therefore, with gains in MSI (Fig. 2).

Additional mediation analyses in a subsample adjusted for alcohol intake, tobacco smoking, physical activity, cardiorespiratory fitness, and total energy intake showed overall

Table 2 Bivariate correlations among muscle strength, protein intake, lean mass, and each group of meat consumption

Meat consumption (g/kg BM/d)	MSI	TPI (g/kg BM/d)	LM%
Total meat	0.174**	0.872**	0.177*
Red meat	0.171**	0.641**	0.138*
Processed meat	0.112**	0.613**	0.164*
White and fish meat	0.165**	0.735**	0.132*

BM body mass, *LM%* lean mass percentage, *MSI* muscle strength index, *TPI* total protein intake

Values are the correlation coefficients. $*p<0.05$, $**p<0.01$

similar results (Supplementary material: Fig. S2). However, the following changes in the mediation effects should be noted: the IE_3 between PMC and MSI did not remain statistically significant, and the IE_3 among WFMC and MSI was higher compared to the IE_3 between RMC and MSI.

Discussion

This study analysed the associations of total meat consumption (TMC), red meat consumption (RMC), processed meat consumption (PMC), and white and fish meat consumption (WFMC) with muscle strength index (MSI) in Spanish young adults and explored the mediating roles of total protein intake (TPI) and lean mass percentage (LM%) in these relationships. The main findings were as follows: (i) university students with high meat consumption (TMC, RMC and WFMC) had higher MSI than their peers with lower meat consumption, regardless of age, sex, and socioeconomic level; and (ii) TPI

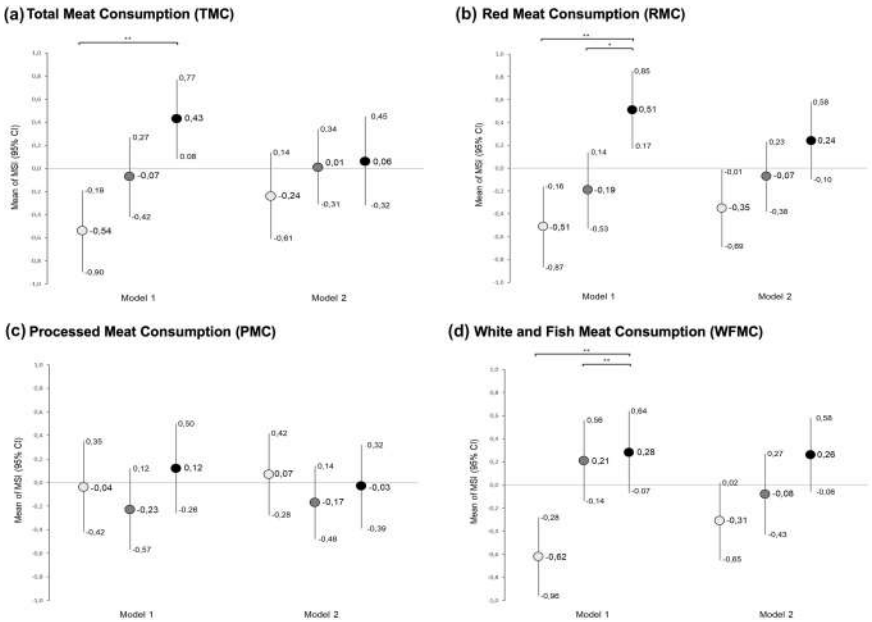

Fig. 1 Mean differences (95% confidence intervals) in muscle strength index by categories of consumption (g/kg BM/d) of different types of meat. Model 1: adjusted for age (y), sex (female, male), and socioeconomic level (level of parental education); Model 2: Model 1 adjusted for total protein intake (g/kg BM/d) and lean mass (%). The Bonferroni post hoc test was used to identify statistical significance in pairwise mean comparisons of muscle strength index by the categories (low, intermediate, and high) of total (**A**), red (**B**), processed (**C**), and white and fish (**D**) meat consumption. The colour of the figures indicates low (white), intermediate (grey), and high (black) meat consumption. $*p<0.05$, $**p<0.01$. *MSI* muscle strength index

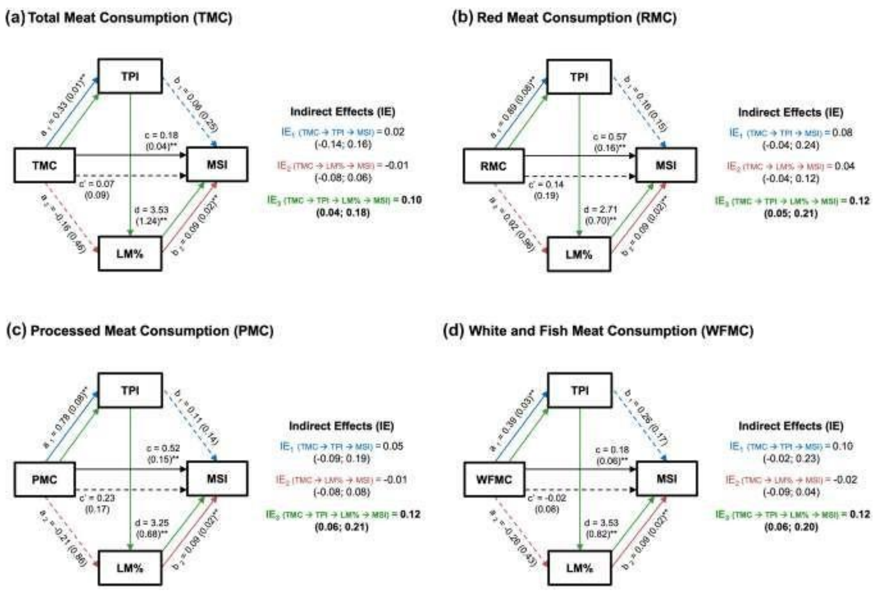

Fig. 2 Mediation analysis of the association between meat consumption (g/kg BM/d) and muscle strength index. Serial multiple mediation models were used with total protein intake (g/kg BM/d) and lean mass (%) as mediators, controlled for age (y), sex (female, male), and socioeconomic level (level of parental education). Values for the a_1, a_2, b_1, b_2, d, c, and c' paths are expressed as the unstandardized regression coefficient (standard error). IE_1, IE_2, and IE_3 are expressed as unstandardized regression coefficients (95% confidence intervals). Continuous lines (pathways) and bold values (IEs) indicate a statistically significant effect. *$p < 0.05$, **$p < 0.01$. *IE* indirect effect, *LM%* lean mass percentage, *MSI* muscle strength index, *PMC* processed meat consumption, *RMC* red meat consumption, *TMC* total meat consumption, *TPI* total protein intake, *WFMC* white and fish meat consumption

and LM% mediated the association between meat consumption (TMC, RMC, PMC and WFMC) and MSI.

The association of high meat consumption with higher MSI is consistent with a prospective study in which the consumption of different types of meat (red meat, chicken, and fish) had a similar positive association with muscle strength in the general adult population [10]. Concerning the consumption of different types of meat in young adults, consumption of lean beef (~ 113 g/d) increases muscle protein synthesis after ingestion in healthy young adults [29]. However, compared with no meat consumption, lean beef consumption (~ 135 g/d) after exercise sessions (3 times per week) for 9 weeks showed no significant difference in maximum leg and chest strength [30]. Consistently, the findings from another RCT indicated that no muscle adaptations were found in maximum leg and chest strength with consumption (~46 g/d) of different types of meat (beef and chicken) during 8 weeks of periodized exercise training in resistance-trained university students [31]. Nevertheless, because these studies did not analyse the mediating effects of TPI and LM%, their role in MSI changes cannot be ruled out. Furthermore, it should be considered that in this study, the increase in MSI according to higher meat consumption was regardless of socioeconomic level (and age and sex), and this association may be due to the mediating effect of TPI and LM%. Therefore, it seems premature to state that meat consumption positively or negatively influences muscle strength without considering TPI and LM%.

Three major differences between our study and other existing studies should be noted. First, studies associating meat consumption with muscle strength typically refer to changes in the maximum muscle strength for the upper or lower body regions separately. Second, other studies have analysed meat consumption, especially beef consumption, along with a resistance training component. Third, our definition of meat consumption (g/kg BM/d) is different from others more frequently used (i.e. g/d). Therefore, it is possible that the characteristics of the methodology adopted to collect and analyse dietary data were behind some differences observed between studies and difficult the comparison across studies.

The serial multiple mediation model revealed one probable pathway to understand the association between meat consumption and MSI (IE_3). The IE_3 is a specific pathway from increasing meat consumption groups to higher MSI by increasing TPI and subsequently increasing LM%. First, the association of high meat consumption with higher TPI and LM% is consistent with a prospective study that found that protein intake (~ 4.3% of total energy intake) from meat consumption (red, processed, and white) during puberty was related to greater levels of fat-free mass index in young adults [32]. Our data indicated that the increase in LM% following higher meat consumption could be attributed to the high protein content of meat consumed, although we cannot be certain that other dietary protein sources (e.g. eggs, dairy, and vegetables) influence this association. Additionally, it is necessary to highlight that although PMC was associated with higher MSI through the IE_3 pathway in the main mediation analysis, additional mediation models with further adjustment including physical activity reported no significant effects (total, direct or indirect) between PMC and MSI. Moreover, no significant differences were found in the means of MSI according to the different categories of PMC (ANCOVA results). It should be considered that this is partially because in our sample, the PMC was the lowest proportion among all types of meat, so differences in MSI exclusively related to PMC could be expected to be difficult to detect. Therefore, according to our findings, the association between PMC and MSI remains inconclusive, and future research is certainly warranted in this regard.

Finally, the IE_3 indicated that meat consumption, through the mediation of TPI and LM%, increased MSI. Meat consumption exhibits rapid protein digestion and amino acid absorption, resulting in greater postprandial plasma amino acid availability and peak plasma leucine concentrations [33]. Both muscle strength and lean mass improve with increased essential amino acid availability, especially leucine, which has been established as a key factor in muscle protein synthesis [5]. Lean mass, which is predominantly represented by skeletal muscle, has been positively associated with muscle strength because it influences the development of muscle fibres, noncontractile tissue (i.e. collagen, fat), muscle metabolism, oxidative stress, and neuromuscular junctions [34]. Regarding our results, LM% appears to be a key factor in understanding the improvement of MSI through meat consumption and TPI. However, a direct causal pathway cannot be assumed because TPI also influences other characteristics (i.e. insulin resistance, serum metabolites) that affect muscle function [35]. Therefore, meat consumption is important for building and maintaining muscle strength in young adults [25], always with a positive net protein balance that is influenced by TPI and physical activity [12]. Specifically, it has been suggested that moderate to vigorous physical activity is the most important intensity for developing muscle strength in young adults [36].

It is important to consider a holistic approach (e.g. environment, lifestyle habits, dietary pattern, protein food, food matrix, and constituent of protein) for the overall recommendation of protein and meat intake [37]. In this sense, in our study sample, those who reported higher TMC showed higher total energy intake and better body composition levels (i.e. BMI, fat mass, lean mass). According to previous studies, high meat consumption has been associated with higher nutrient and overall dietary quality compared to low meat consumption [38], which is consistent with better body composition levels [32, 39]. Furthermore, although the higher TMC group did not report a greater amount of moderate to vigorous physical activity, it is important to consider that the type of activity performed (e.g. high-intensity intervals, aerobic, strength) [40] and light physical activities [41] can lead to considerable differences in energy expenditure and muscle function. Therefore, the interactions between food protein quality, diet quality, type of physical activity and energy expenditure are important factors in analysing the associations of meat consumption with body composition and muscle strength levels.

In this context, the impact of both total protein and meat intake on health outcomes should be considered a U-shaped curve; that is, only in moderate and balanced quantities are they potentially beneficial for health [42]. However, the complexity and diversity of these associations, marked by different elements such as the type of meat consumed or the physiological characteristics/requirements of individuals, make it difficult to establish healthy limits for meat consumption [5, 43]. To meet functional needs and promote skeletal muscle protein synthesis and muscle strength, the intake of good-quality protein between 0.8 and 3.5 g/kg BM/d is recommended for healthy adults [5, 44]. Regarding the recommendations for meat consumption ranges, the evidence is mostly related to red meat [29, 30, 45]. An adequate (i.e. without health risks) RMC has been reported between 100 and 200 g/d in interventional studies [29, 30, 45], although the evidence is still not conclusive and may vary according to individual anthropometric and metabolic characteristics. Previous evidence recommended limiting [46] or reducing RMC to an average of 70 g/d [43] or less than 500 g/week [1]. Considering that a typical serving of meat (i.e. 100–160 g) contains between 15 and 45 g of protein depending on the type-quality-preparation of meat [21, 45], the abovementioned range of TPI and RMC coincides with the average consumption observed in our study sample.

Although the health effects of high RMC and PMC are still inconclusive, most evidence points out an adverse effect for colorectal cancer [46]. Regarding muscle function, processed meat contains a considerable amount of sodium, nitrite, and saturated and trans fats [47], which may yield increased inflammation and endothelial dysfunction [48] and can consequently reduce physical functioning [49]. It should be considered that, in this study, the increase in MSI according to higher meat consumption was for all types of meat, except for processed meat, according to the results of both ANCOVA and additional meditation analyses. Meanwhile, global evidence of WFMC is more consistent to support beneficial associations with different health outcomes, such as a lower risk of total mortality [50] or a reduced risk of incident cardiovascular diseases [51]. The nutritional composition of white and fish meat has greater cardioprotective properties than red or processed meat because of its lower total fat content and higher polyunsaturated and monounsaturated fat content and because it is a less plentiful source of heme iron [47]. In turn, both proteins and fatty acids from fish meat have shown better digestibility, which improves absorption and, consequently, the bioavailability of their end products (i.e. amino acids and unsaturated fatty acids) [52]. Moreover, dietary effects have been proven to be more related to the food matrix than to specific foods [53]. In this context, the Mediterranean diet is a healthy dietary pattern associated with higher WFMC rather than RMC or PMC. Finally, the production of white and fish meat has a lower environmental impact than that of red or processed meat [54]. Considering that in this study the potential benefits of WFMC for MSI are comparable to those of other types of meat (and with a greater effect in the results of the additional mediation analyses), our findings reinforce the body of evidence supporting the recommendation for increased white and fish meat consumption as a healthier substitute for red and processed meat.

Our study has some limitations that should be acknowledged. First, the cross-sectional design limits us from stating causal associations, and the results must be read with caution. Specifically, longitudinal studies are needed to determine whether our highest meat consumption category has prospective beneficial effects for MSI and, importantly, is safe in terms of cardiovascular and metabolic health parameters. Second, dietary variables were collected through a questionnaire, which might have some degree of measurement error due to recall and information biases. Third, the dietary behaviour, lifestyle and body composition of university students are specific to the early stage of adult life, so the generalization of our results to middle-aged and older adult populations will require additional testing. Fourth, although we analysed an MSI normalized by BM, other anthropometric parameters related to muscle performance could alternatively be used in this normalization procedure, such as height or hand size. Finally, although serial mediation analyses were performed, they were exploratory and, thus, we cannot exclude other dietetic components or mediators that could have influenced the association between meat consumption and MSI. Likewise, although we adjusted the analyses for some major potential confounders identified through the DAG method (i.e. age, sex, and socioeconomic level), residual confounding cannot be eliminated. This limitation was partially overcome because additional analyses in a smaller subsample also included the adjustment of the covariate's alcohol intake, smoking, physical activity, cardiorespiratory fitness, and total energy intake.

In conclusion, the relationship between regular meat consumption and muscle strength, although still lacking confirmation from prospective observational and experimental studies, reinforces the importance of this food group as an essential item in a healthy diet, especially in young adults. More importantly, with respect to the benefits for muscle function and body composition, our data suggest that the consumption of white and fish meat contributes in the same way as red or processed meat through the mediation of total protein intake and lean mass percentage. In fact, the additional mediation analyses through this same pathway indicate a greater effect of white and fish meat consumption on muscle strength than red or processed meat consumption. Thus, our findings agree with dietary guidelines of healthy diets such as the Mediterranean diet, which recommends the preferential consumption of white and fish meat over the consumption of red or processed meat.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00394-022-03014-7.

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Author contributions Conceptualization, BB-P, AEM, and VM-V; methodology and formal analysis, BB-P and AEM; writing—original draft, BB-P and AEM; writing—review and editing, BB-P, AEM, VM-V, MG-M, RF-R, AT-C, AF-G, and NMM-E; funding acquisition, AEM and VM-V; supervision, AEM and VM-V. All authors approved the final manuscript.

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Availability of data and materials The datasets generated and analysed in this study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and consent to participate The study protocol was approved by the Clinical Research Ethics Committee of the "Virgen de la Luz" of Cuenca (REG: 2016jPI1116) and adhered to the principles of the Declaration of Helsinki. Informed consent to participate was obtained from all subjects involved in the study.

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PART II – CHAPTER 2

MANUSCRIPT IV

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Proinflammatory dietary pattern and depression risk in older adults: Prospective analyses from the Seniors-ENRICA studies.

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Original article

Proinflammatory dietary pattern and depression risk in older adults: Prospective analyses from the Seniors-ENRICA studies

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Background & aims: Only a few studies have assessed the association between a proinflammatory diet and the risk of depression in older adults, and they have rendered weak results. The present study analysed the association between the Dietary Inflammatory Index (DII) and incident self-reported diagnosis or symptoms of depression in two cohorts of community-dwelling older adults in Spain.
Methods: We used data from the Seniors-ENRICA-I (SE-I) and Seniors-ENRICA-II (SE-II) cohorts. In both cohorts, the baseline DII was calculated from habitual food consumption estimated with a validated computer-based diet history. The incidence of both physician self-reported diagnosis of depression and mild-to-major depressive symptoms (�3 on the 10-item Geriatric Depression Scale) was analysed. Logistic regression models were adjusted for the main potential confounders, such as sociodemographics, lifestyles, and comorbidities. The results of both cohorts were pooled using a random effects model.
Results: Among the 1627 participants in SE-I (mean age 71.5 ± 5.5 y, 53.1% women) and the 1579 in SE-II (mean age 71.4 ± 4.2, 46.7% women), 86 (5.3%) and 140 (8.9%) incident cases of depression were identified after a mean 3.2-y and 2.3-y follow-up, respectively. The fully adjusted odds ratio (95% confidence interval) of incident depression for the highest (the highest proinflammatory diet) *versus* the lowest quartile of DII was 2.76 (1.25e6.08, *p-for-trend* ¼ 0.005) in the SE-I, 1.90 (1.04e3.40, *p-for-trend* ¼ 0.005) in the SE-II and 2.07 (1.01e3.13) in the pooled cohorts. The results were consistent across strata defined by sex, age, physical activity, loneliness/poor social network, and morbidity.
Conclusions: A proinflammatory dietary pattern is associated with depression risk in older adults. Future research should evaluate whether reducing the inflammatory component of diet leads to reduced depression symptoms in this population.

1. Introduction

Mental disorders were the seventh leading cause of burden of disease worldwide in 2019 [1]. Among them, depression is the most common [1], with approximately 280 million people suffering from depression every year [2]. Projections support a continuous increase in the prevalence of depression in the coming years, mainly because some determinants of poor mental health, such as lack of social support, have intensified due to the COVID-19 pandemic [3]. Older age is also one of the main risk factors for depression [2]. Therefore, there is an urgent need for public health strategies to prevent depression or reduce the severity of symptoms as well as its health-related consequences in older adults [4].

Although the causes of depression remain unclear, a complex interaction of genetic, social, psychological, behavioural, environmental, and biological factors has been proposed [5e8]. Evidence suggests that inflammatory processes contribute to depression

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through different pathways, such as exposure to psychosocial stress or a processed-food diet, increasing the activation of proinflammatory cytokines or inflammasomes that drive inflammatory responses relevant to depression [9]. Accordingly, nutrition has received more attention in the last decade as a modifiable lifestyle risk factor for depression [10], with a particular focus on the consumption of specific foods that might modulate inflammatory factors [11,12].

Several prospective cohort studies have investigated the associations between the potential inflammatory effects of diet and the incidence of self-reported diagnosis of depression [13,14] or depressive symptoms [15e19] throughout adulthood. However, only a few of these studies have examined this association specifically in older people [19] or stratified by older adult age subgroup [16,17]. Their findings showed a weak nonsignificant [16,17] or null [19] association between the highest versus the lowest inflammatory diet scores and the risk of depression in older adults from Australia, France and Italy [16,17,19]. However, in these studies, the analyses did not account for relevant confounders in the diet-depression relationship, such as loneliness [16,17,19], functional disability [16,17], or a wide range of chronic diseases [16,17,19]. To address these limitations, the present study assessed the association between the inflammatory potential of diet and the risk of depression, defined as a self-reported physician diagnosis of depression or mild-to-major depressive symptoms, adjusting for many risk factors for depression in older adults from Spain.

2. Materials & methods

2.1. Study design and participants

We used data from two cohorts of older adults with very similar designs and the same methods of data collection and variable measurement that have been published in detail elsewhere [20,21]. The first cohort was the Seniors-ENRICA-I (SE-I), established in 2008e2010 with 3289 individuals selected through stratified random sampling of the noninstitutionalized Spanish population aged ≥60 years [20,22]. Of these, 1627 individuals free of self-reported physician diagnosis of depression were followed-up during a mean time of 3.2 years. The second cohort was the Seniors-ENRICA-II (SE-II), established in 2015e2017 through stratified random sampling of all community-dwelling individuals aged ≥65 years holding a national healthcare card and living in Madrid (Spain) [21,23]. Of the 3273 individuals who completed the baseline interviews, we excluded 583 individuals who suffered from a self-reported physician diagnosis of depression or mild-to-major depressive symptoms. After a mean of 2.3 years, 1579 of these participants provided answers in the follow-up.

Both Seniors-ENRICA cohorts were registered on ClinicalTrials.gov (SE-I identifier: NCT02804672; SE-II identifier: NCT03541135) and approved by the Clinical Research Ethics Committee of the La Paz University Hospital in Madrid. Participants provided informed written consent.

2.2. Study variables

2.2.1. Exposure variable: dietary inflammatory index (DII)

The participant's regular diet in daily grams of food was assessed and estimated with a validated computer-based diet history, representing the average intake during a typical week of the previous year [24]. The questionnaire was administered by a trained interviewer and includes 880 foods that can be cooked in 29 different ways and 184 recipes for dishes commonly eaten in Spain or typical of each region. More details about the dietary information collection can be found elsewhere [24]. No missing values were observed because all data were checked for completeness during data collection, and if any data was lacking, a new visit was performed to the house of the participants to obtain the required information [20,21].

The inflammatory potential of the diet was estimated with the Dietary Inflammatory Index (DII) according to Shivappa's procedure [25]. The DII is a scoring algorithm based on a robust review of the literature published up to 2010, involving 1943 articles that analysed the effect of dietary components on inflammation [25]. A total of forty-five food parameters, including whole foods, nutrients and other bioactive compound components, were scored based on their effects on six inflammatory biomarkers (interleukin-1β, interleukin-4, interleukin-6, interleukin-10, tumour necrosis factor-α, and C-reactive protein) [25].

For the present analyses, 32 of the 45 original DII components (daily amounts of food or nutrients) were available in both Seniors-ENRICA cohorts and were used to calculate the DII by multiplying the overall inflammatory effect score for each component by its normalized intake using the global daily mean intakes and standard deviations provided by Shivappa et al. [25] and summing them (Table S1). A higher DII score (positive) indicates a proinflammatory diet, whereas a lower DII score (negative) indicates an anti-inflammatory diet. Participants in both cohorts were classified into quartiles of the DII scores.

2.2.2. Outcome variable: depression

For the SE-I, baseline depression was defined with a positive answer to the question 'Did a physician tell you if you currently have, or have had in the past year, depression (in need of treatment)?' For the SE-II, baseline depression was defined as in the SE-I, or additionally if the participant reported ≥3 depressive symptoms (which indicate mild-to-major depressive symptoms) [26] in the 10-item version of the Geriatric Depression Scale (GDS-10). All participants with depression at baseline according to these cohort-specific criteria were excluded from the analytical sample. In the follow-up, in both cohorts, data were collected on both self-reported physician diagnosis of depression and on depressive symptoms with the GDS-10. Therefore, incident cases of "self-reported physician diagnosis or mild-to-major depressive symptoms" were identified when at least one of the two criteria (i.e., self-reported physician diagnosis of depression and GDS-10 score ≥3) was met in the follow-up among individuals free of depression at baseline.

2.2.3. Covariates

Covariates were selected based on recent research on the potential determinants of depression and their associations with diet [27e32].

At baseline, for both SE-I and SE-II cohorts, self-reported information was obtained on sex (female *vs.* male), age (continuous, years), household economy (difficult *vs.* easy to make ends meet), education (no studies or primary studies *vs.* secondary or university studies), marital status (married *vs.* single, widowed or separated), smoking (never or former *vs.* current smoker), time watching TV (continuous, hours per week), night-time sleep duration (continuous, hours per night), and the number of physician-based diagnoses of the following chronic conditions: diabetes mellitus, cardiovascular disease (ischemic heart disease, stroke, or heart failure), hypertension, chronic respiratory disease (asthma or chronic bronchitis), cancer at any site, musculoskeletal disorder (osteoarthritis, rheumatoid arthritis, or hip fracture) and neurodegenerative disease (Parkinson's disease or dementia).

Physical activity in occupational, leisure and household domains was assessed with the validated EPIC-cohort questionnaire [33] and categorized into two groups: less active (inactive or moderately inactive) and more active (moderately active or active) [34]. Additionally, we assessed disability in activities of daily living with the Katz scale [35] and loneliness with a short 3-item scale [36] in the SE-II cohort. Moreover, body mass index (BMI) was calculated as weight divided by the square of the height (kg/m^2), both objectively measured under standardized conditions.

Finally, inflammatory biomarker levels, such as C-reactive protein, interleukin-6, growth differentiation factor-15, troponin T, and pro-brain natriuretic peptide, were obtained from biological blood samples to assess whether higher DII was associated with high-grade inflammation.

2.3. Statistical analysis

The following analyses were performed separately in each cohort's database. First, we described the baseline characteristics of cohort participants according to the quartiles of DII. Second, bivariate correlation coefficients were calculated to examine the baseline relationship between the DII scores and the following covariates: sex, age, household economy, education level, marital status, smoking, BMI, physical activity, time watching TV, night's sleep duration, chronic conditions, loneliness, and depressive symptoms. In addition, bivariate correlations were calculated to analyse the baseline association between DII scores and the level of some inflammatory biomarkers available in each database. Third, logistic binary regression models were used to estimate the odds ratio (OR) (as estimators of the relative risk) and the 95% confidence interval (95% CI) for the association between the overall baseline quartiles of the DII score and the incidence of self-reported physician diagnosis of depression or mild-to-major symptoms of depression over the follow-up period. We built three models: model 1, a crude model; model 2, adjusted for sex, age, household economy, education level, marital status, smoking status, BMI, physical activity, time watching TV and night-time sleep duration; and model 3, additionally adjusted for loneliness (only for the SE-II cohort), functional disability (only for the SE-II cohort), diabetes mellitus, cardiovascular disease, hypertension, chronic respiratory disease, cancer at any site, musculoskeletal disorder and neurodegenerative disease. To explore possible multicollinearity between independent variables such as physical activity, time spent watching TV, and BMI, bivariate correlations were computed. Potential multicollinearity involving two variables was considered if the correlation coefficient was >0.70 [37].

Stratified analyses were performed to identify potential modifiers of the study association, and *p* values were calculated using the log-likelihood ratio test to assess interactions between the main covariates (i.e., sex, age, physical activity, loneliness/poor social network, and morbidity) and DII scores on self-reported diagnosis or mild-to-major symptoms of depression. Additionally, to test the robustness of our results, sensitivity analyses were performed using an alternative cut-off value (≥5) in the GDS-10 score that specifies only major depressive symptoms [26] for the SE-II cohort. The KolmogoroveSmirnov test was applied to the GDS-10 score and confirmed that its distribution did not deviate from normality in the analytical sample (p ¼ 0.376). Furthermore, the relationship between the continuous DII score and the number of incident depressive symptoms (GDS-10 score) was summarized with b coefficients (95% CI) obtained from linear regression models for the SE-II cohort.

Finally, we combined the fully adjusted OR (95% CI) of each cohort to estimate the pooled OR with a DerSimonian and Laird random effects model [38]. Heterogeneity was measured using the I^2 statistic and was considered not important (I^2 < 40%), substantial (I^2: 30%e60%), important (I^2: 50%e90%), or considerable (I^2 > 75%) [39].

Statistical analyses were performed using STATA SE software, version 15 (StataCorp, College Station, TX, USA).

3. Results

A total of 1627 participants (mean age 71.5 ± 5.5, 53.1% female) from the SE-I cohort and 1579 participants (mean age 71.4 ± 4.2, 46.7% female) from the SE-II cohort were included in the analyses.

Slightly more than 55% of the individuals included had no studies or primary education level, 31% were single, widowed or separated, 66% were less physically active, and 49% had two or more chronic diseases. Tables 1, 2 and S1 present the main baseline characteristics of the study participants in the SE-I and SE-II cohorts, respectively. Bivariate correlations showed that the DII score was directly correlated with female sex, age, difficult household economy, education level (no studies or primary studies), marital status (single, widowed or separated), less physical activity and

Table 1
Baseline characteristics of the SE-I study sample by Dietary Inflammatory Index quartiles.

Baseline characteristics	Total (n ¼ 1627)	Quartiles of Dietary Inflammatory Index			
		Q1: anti-inflammatory diet (n ¼ 407)	Q2 (n ¼ 407)	Q3 (n ¼ 407)	Q4: proinflammatory diet (n ¼ 406)
Dietary Inflammatory Index, score	0.8 ± 1.9	−1.7 ± 0.8	0.1 ± 0.4	1.5 ± 0.4	3.2 ± 0.7
Female, *n* (%)	864 (53.1)	170 (41.8)	198 (48.6)	225 (55.3)	271 (66.7)
Age, years	71.5 ± 5.5	70.9 ± 5.2	71.2 ± 5.4	71.5 ± 5.4	72.2 ± 6.0
Difficult to make ends meet, *n* (%)	23 (1.5)	5 (1.3)	1 (0.3)	5 (1.4)	12 (3.2)
No studies/primary education, *n* (%)	934 (57.4)	213 (52.3)	228 (56.0)	231 (56.8)	262 (64.5)
Single/widowed/separated, *n* (%)	504 (31.4)	102 (25.3)	102 (25.1)	133 (33.1)	167 (42.2)
Current smoking status, *n* (%)	159 (9.8)	37 (9.1)	39 (9.6)	41 (10.1)	42 (10.3)
C-Reactive Protein, mg/L	3.8 ± 7.1	3.3 ± 4.9	3.6 ± 6.9	3.6 ± 4.7	4.8 ± 1.0
Body Mass Index, kg/m^2	28.6 ± 4.3	28.6 ± 4.6	28.5 ± 3.9	28.4 ± 4.2	29.1 ± 4.3
Less physical active, *n* (%)	1308 (80.4)	308 (75.7)	328 (80.6)	324 (79.6)	348 (85.7)
Time watching TV, h/wk	19.1 ± 11.6	18.0 ± 10.7	18.6 ± 6.5	19.1 ± 11.1	20.9 ± 13.6
Night's sleep duration, h/d	6.8 ± 1.4	6.9 ± 1.4	6.9 ± 1.3	6.8 ± 1.4	6.9 ± 1.5
One or more chronic conditions[a], *n* (%)	1486 (94.6)	372 (94.7)	378 (95.2)	371 (93.9)	365 (94.6)

Values are means ± standard deviations or *n* (%). Abbreviations: Q, quartile; SE, Seniors-ENRICA. The numbers of participants who were missing data were as follows: 137 for household economy, 20 for marital status, 1 for alcohol intake, 1 for total energy intake, 6 for C-reactive protein, 24 for body mass index, 21 for physical activity, 13 for time watching TV, 19 for night's sleep duration, 14 for diabetes, 8 for cardiovascular disease, 17 for hypertension, 3 for neurodegenerative disease, and 16 for musculoskeletal disorder.

[a] Chronic condition diagnosed by a physician includes diabetes mellitus, cardiovascular disease (ischemic heart disease, stroke, or heart failure), hypertension, chronic respiratory disease (asthma or chronic bronchitis), cancer at any site, musculoskeletal disorder (osteoarthritis, rheumatoid arthritis, or hip fracture), and neurodegenerative disease (Parkinson or dementia/Alzheimer).

Table 2
Baseline characteristics of the SE-II study sample by Dietary Inflammatory Index quartiles.

Baseline characteristics	Total (n ¼ 1579)	Quartiles of Dietary Inflammatory Index			
		Q1: anti-inflammatory diet (n ¼ 395)	Q2 (n ¼ 395)	Q3 (n ¼ 395)	Q4: proinflammatory diet (n ¼ 394)
Dietary Inflammatory Index, *score*	0.3 ± 1.6	�1.7 ± 0.7	�0.3 ± 0.3	0.9 ± 0.3	2.5 ± 0.7
Female, *n* (%)	738 (46.7)	153 (38.7)	164 (41.5)	201 (50.9)	220 (55.8)
Age, years	71.4 ± 4.2	70.8 ± 4.2	71.6 ± 4.2	71.1 ± 4.1	72.2 ± 4.4
Difficult to make ends meet, *n* (%)	181 (11.5)	34 (8.6)	46 (11.7)	45 (11.4)	56 (14.2)
No studies/primary education, *n* (%)	929 (58.9)	212 (53.7)	226 (57.2)	234 (59.2)	257 (65.4)
Single/widowed/separated, *n* (%)	485 (30.7)	115 (29.1)	110 (27.8)	108 (27.4)	152 (38.6)
Current smoking status, *n* (%)	138 (8.7)	27 (6.8)	28 (7.1)	37 (9.4)	46 (11.7)
Interleukin-6, pg/ml	3.3 ± 5.0	3.4 ± 7.4	3.0 ± 2.7	3.3 ± 4.4	3.5 ± 4.1
Growth Differentiation Factor-15, pg/ml	1336.4 ± 782.5	1236.8 ± 575.6	1307.3 ± 755.5	1324.2 ± 677.6	1481.5 ± 1036.7
Troponin T, pg/ml	10.49 ± 5.3	10.4 ± 4.7	10.4 ± 4.6	10.2 ± 5.0	10.9 ± 6.9
Pro-Brain Natriuretic Peptide, pg/ml	111.9 ± 138.9	112.0 ± 133.2	105.5 ± 140.8	107.4 ± 104.2	123.1 ± 170.2
Body Mass Index, kg/m^2	27.7 ± 4.3	28.0 ± 4.6	27.6 ± 4.2	27.6 ± 4.1	27.7 ± 4.3
Less physical active, n (%)	817 (52.4)	185 (47.3)	207 (52.8)	202 (52.1)	223 (57.6)
Time watching TV, h/wk	21.9 ± 10.5	20.7 ± 9.6	21.8 ± 10.2	22.6 ± 10.9	22.2 ± 11.2
Night's sleep duration, h/d	6.8 ± 1.3	6.9 ± 1.2	6.9 ± 1.2	6.8 ± 1.4	6.8 ± 1.3
One or more chronic conditions[a], *n* (%)	1221 (77.3)	299 (75.7)	320 (81.0)	292 (73.9)	310 (78.7)
Loneliness, scale score	3.4 ± 1.1	3.3 ± 0.9	3.4 ± 1.0	3.4 ± 1.0	3.6 ± 1.3
Depressive symptoms, GDS-10	0.3 ± 0.5	0.2 ± 0.5	0.3 ± 0.5	0.3 ± 0.6	0.4 ± 0.6

Values are means ± standard deviations or *n* (%). Abbreviations: Q, quartile; GDS-10, 10-item Geriatric Depression Scale; SE, Seniors-ENRICA. The numbers of participants who were missing data were as follows: 2 for household economy, 1 for education level, 1 for marital status, 3 for alcohol intake, 101 for interleukin-6, 100 for growth differentiation factor-15, troponin T and pro-brain natriuretic peptide, 6 for body mass index, 21 for physical activity, 9 for time watching TV, 2 for cardiovascular disease, 160 for hypertension, 1 for chronic respiratory disease, 43 for musculoskeletal disorder disease, 3 for functional disability, and 128 for depressive symptoms.

[a] Chronic condition diagnosed by a physician includes diabetes mellitus, cardiovascular disease (ischemic heart disease, stroke, or heart failure), hypertension, chronic respiratory disease (asthma or chronic bronchitis), cancer at any site, musculoskeletal disorder (osteoarthritis, rheumatoid arthritis, or hip fracture), neurodegenerative disease (Parkinson or dementia/Alzheimer), and functional disability (Katz scale).

time watching TV in the two baseline samples, and with current smoking status, loneliness and depressive symptoms in the SE-II sample. Moreover, the DII score was directly correlated with C-reactive protein (*r*¼0.080) in the SE-I sample and with growth differentiation factor-15 in the SE-II sample (r¼0.090). None of the covariates used in the logistic models had coefficient correlation with other independent variables higher than 0.2, meaning that there would be no multicollinearity in entering them simultaneously in the models.

The associations between DII and the incidence of self-reported physician diagnosis of depression and mild-to-major symptoms of depression are presented in Table 3. The overall incidence of self-reported diagnosed depression was 5.3% (n¼86) in the 3.2-year follow-up for SE-I. The overall incidence of self-reported diagnosis

Table 3
Prospective associations between a proinflammatory diet and the incidence of depression (diagnosed or �3 symptoms) in the SE-I and SE-II cohorts.

	Quartiles of Dietary Inflammatory Index				*p-for-trend*[a]
	Q1: anti-inflammatory diet	Q2	Q3	Q4: proinflammatory diet	
SE-I, *n*	407	407	407	406	
DII, score range	�4.562, �0.641	�0.629, 0.816	0.817, 2.231	2.233, 5.404	
Incidence of depression[b], *n* (%)	10 (0.6)	18 (1.1)	25 (1.5)	33 (2.0)	
Model 1 e crude model	1.00 (ref)	1.84 (0.84, 4.03)	2.60 (1.23, 5.48)*	3.51 (1.71, 7.23)*	<0.001
Model 2 e adjusted model	1.00 (ref)	1.22 (0.52, 2.83)	2.11 (0.97, 4.57)	2.27 (1.06, 4.84)*	0.015
Model 3 e adjusted model	1.00 (ref)	1.37 (0.57, 3.29)	2.24 (0.99, 5.08)	2.76 (1.25, 6.08)*	0.005
SE-II, *n*	395	395	395	394	
DII, score range	�4.403, �0.839	�0.838, 0.286	0.293, 1.501	1.503, 4.860	
Incidence of depression[c], *n* (%)	24 (6.1)	27 (6.8)	39 (9.9)	50 (12.7)	
Model 1 e crude model	1.00 (ref)	1.13 (0.64, 2.00)	1.69 (0.99, 2.87)	2.25 (1.35, 3.73)*	<0.001
Model 2 e adjusted model	1.00 (ref)	1.01 (0.55, 1.85)	1.58 (0.90, 2.75)	1.83 (1.06, 3.14)*	0.007
Model 3a e adjusted model	1.00 (ref)	0.95 (0.49, 1.87)	1.38 (0.74, 2.58)	1.90 (1.04, 3.40)*	0.005
Pooled cohorts					
Model 1 e crude model	1.00 (ref)	1.09 (0.45, 1.73)	1.84 (0.98, 2.70)	2.45 (1.35, 3.54)*	
Model 2 e adjusted model	1.00 (ref)	1.06 (0.49, 1.63)	1.69 (0.87, 2.51)	1.93 (1.02, 2.84)*	
Model 3 e adjusted model	1.00 (ref)	1.04 (0.42, 1.65)	1.52 (0.69, 2.36)	2.07 (1.01, 3.13)*	

Values are odds ratios (95% CI) for logistic regression models. * $p < 0.05$. Abbreviations: DII, Dietary Inflammatory Index; Q, quartile; SE, Seniors-ENRICA.

Model 2: adjusted for sex (female, male), age (y), household economy (difficult to make ends meet or easy to make ends meet), education level (no studies/primary or secondary/university), marital status (married or single/widowed/separated), smoking status (never/former or current), body mass index (kg/m^2), physical activity (less active or more active), time watching TV (h/wk), and night's sleep duration (h/d); Model 3: Model 2 adjusted for chronic conditions diagnosed by a physician, including diabetes mellitus (yes, no), cardiovascular disease (yes, no), hypertension (yes, no), chronic respiratory disease (yes, no), cancer at any site (yes, no), musculoskeletal disorder (yes, no), and neurodegenerative disease (yes, no). Model 3a: Model 3 adjusted for functional disability (yes, no) and loneliness (scale score). All covariates were from baseline.

[a] *p* value for linear association between the continuous score of the Dietary Inflammatory Index (main independent variable) and incidence of depression (dependent variable).

[b] Incident cases of depression were defined as those participants free of depression at baseline assessment and who self-reported physician-diagnosed depression during the 3.2-year follow-up.

[c] Incident cases of depression were defined as those participants free of depression at baseline assessment and who self-reported physician-diagnosed depression or �3 symptoms in the Geriatric Depression Scale-10 during the 2.3-year follow-up.

or mild/major symptoms of depression was 8.9% (n¼140) at the 2.3-year follow-up for SE-II. Of the 226 individuals who developed depression during follow-up in both cohorts, 72.6% (n¼164) were female. In crude regression models (model 1), direct associations between the highest versus the lowest quartile of DII and incidence of self-reported diagnosis or symptoms of depression were observed both in the SE-I (OR ¼3.51; 95% CI: 1.71e7.23, *p-for-trend* < 0.001) and in the SE-II (OR ¼2.25; 95% CI: 1.35e3.73, *p-for-trend* < 0.001). When covariates were added to the adjusted models, the association remained statistically significant (SE-I model 3, OR¼2.76; 95% CI: 1.25e6.08, *p-for-trend* ¼ 0.005; SE-II model 3, OR ¼1.90; 95% CI: 1.04e3.40, *p-for-trend* ¼0.005). Finally, when combining the results of both cohorts, the pooled fully adjusted OR for the association between the highest versus the lowest quartile of DII and incidence of self-reported diagnosis or symptoms of depression was 2.07 (95% CI: 1.01e3.13; I^2: 0%, *p*¼ 0.53) (Table 3). Additionally, in the pooled cohorts, the results were consistent across strata defined by sex, age, loneliness, and morbidity (all first-order interaction coefficients were *p* > 0.05) (Fig. S1).

Additionally, sensitivity analysis using �5 depressive symptoms as the cut-off value (major depressive symptomatology) on the GDS-10 score for the SE-II cohort showed similar results (4th quartile compared with 1st quartile, OR¼2.01; 95% CI: 1.03e3.93, *p-for-trend* ¼0.002) to the main analysis in the fully adjusted model (Table S2). Last, an increasing DII score was associated with an increasing number of incident depressive symptoms in the unadjusted and adjusted models for the SE-II cohort (Table S3).

4. Discussion

This study analysed the prospective association between the potential inflammatory effects of diet and the risk of self-reported diagnosis or symptoms of depression in national (SE-I) and regional (SE-II, region of Madrid) representative samples of Spanish older adults. The main finding was that in both cohorts, the individuals in the highest quartile of the DII score (indicating a high proinflammatory diet) at baseline had a greater incidence of self-reported diagnosis or symptoms of depression than those in the lowest quartile (indicating an anti-inflammatory diet) over a mean of 3.2- (SE-I) and 2.3-year (SE-II) follow-up. These associations remained significant after adjustment for several key confounders, such as socioeconomic factors, lifestyle habits and chronic diseases. The prospective results of both SE-I and SE-II cohorts were synthesized and confirmed in a pooled analysis. Specifically, older adults in the highest quartile of DII were twice as likely to develop self-reported diagnosis or symptoms of depression than those in the lowest quartile after two to three years of follow-up. Our results emphasize the key role of diet in the inflammatory pathway that may lead to depression in older adults.

Previous prospective cohort studies specifically in older adults [19] or analysing older population subgroups are scarce [16,17]. Of these, studies reporting the number of incident cases of depression showed similar (i.e., 8%) [16] or slightly higher (i.e., 13%) [17] results to ours; however, the number of incident cases of depressive symptoms was not reported specifically for older adults. In one study, French individuals �60 years in the highest quartile of DII did not have a significantly increased risk of developing depressive symptoms (OR: 1.22, 95% CI: 0.91 to 1.64) during ~5-year follow-up [16]. In another study with Australian participants �65 years, no significant association was observed across quartiles of DII and the risk of depressive symptoms during ~5-year follow-up [17]. Moreover, no significant association was found between higher inflammatory dietary patterns and depressive symptoms in Italian subjects �65 years over a period of nine years [19]. Conversely, the results from both the SE-I and SE-II cohorts showed that older adults consuming a highly inflammatory diet were more prone to develop self-reported diagnosis or symptoms of depression than those with the lowest inflammatory diet score. Several differences could be behind these apparently inconsistent findings. First, the other studies analysed changes in depressive symptoms. Our study used a more comprehensive definition of depression, including self-reported physician-diagnosed depression or many�(3 or�5) depressive symptoms. Second, the longitudinal studies were adjusted for socioeconomic and lifestyle factors, but their analyses did not consider the role of some relevant confounders, such as loneliness [16,17,19], functional disability [16,17] or a broad range of morbidities [16,17,19]. Last, our study adjusted for these main risk factors for depression and examined its influence on the association between the highest proinflammatory diet and the incidence of self-reported depression.

Several mechanisms underlying the potential damaging role of a proinflammatory diet in the risk of depression in older ages can be suggested, such as oxidative stress, alterations in brain immune and neuronal function, and the crosstalk between the gut microbiome and brain health [31,40e42]. Moreover, chronic inflammation in older adults is influenced by a complex process of cellular senescence, which is characterized by the detention of cell proliferation and the development of a multifaceted senescence-associated secretory phenotype [43]. This senescent phenotype turns senescent fibroblasts into proinflammatory cells (secretion of proinflammatory cytokines, chemokines and other proinflammatory molecules) [42,43], with its clinical consequences, including an increased risk of depression [44]. From the nonendogenous contributors, diet has been conceived as a major component in increasing inflammatory response system activation in older adults [45]. Evidence suggests that the activation of the innate immune system through proinflammatory nutrients releases proinflammatory cytokines, promoting depressive-like behaviours [46]. Furthermore, the impact of the highest proinflammatory diet on the risk of depression may be based on the synergistic combination of certain main risk factors for depression, including health conditions (obesity, chronic status) [32], poor social network (loneliness) [47], individual determinants (sex, age) [30], and lifestyle-related behaviours (physical activity) [48]. However, in this study, there were no consistent findings to establish which specific components significantly influenced this association. Further investigations assessing the multifactorial nature of the mechanisms by which diet-related inflammatory activity is associated with the risk of depression are needed for a deeper understanding.

The increased frequency of depression in older age and its clinical, economical, and socioemotional implications represent a crucial public health challenge. The results of this study, which include longitudinal prospective analyses of two cohorts of Spanish older adults and a pooled-analysis approach, have significant clinical and public health implications. A healthy diet aiming to disrupt the depressioneinflammation cycle should consider the favourable nutrient intake and the anti-inflammatory dietary components, such as high contents of polyunsaturated fatty acids, carotenoids, dietary fibre, vitamins, and minerals, mostly reported in this study with Spanish older adults. These nutrients and foods have been consistently associated with major pathophysiologic pathways of depression, such as oxidative stress, inflammation, and the gut microbiome [27,44]. Therefore, limiting a proinflammatory diet (e.g., lowering the intake of carbohydrates, cholesterol, total fat, saturated fat, and *trans*-fat) and promoting an anti-inflammatory diet (e.g., increasing the intake of fibre, *n*-3 fatty acids, *n*-6 fatty acids, vitamins A, B, C, D and E, and minerals such as selenium and zinc) should be considered among the preventive and non-pharmacological intervention approaches for depression in older adults.

Our study has some limitations that should be noted. First, dietary variables were collected through a questionnaire, which might have some degree of measurement errors due to recall and information biases. Second, although the DII score was calculated with a larger number of food parameters (32 of the 45 proposed), compared to previous studies [13e15,17,18], the unavailability of data on the remaining 13 food components may be a potential limitation. Third, due to the small number of participants in the prospective stratified analyses, we were unable to report consistent findings in the association between the proinflammatory diet and the risk of depressive disorder. Fourth, although individuals with depression at baseline were excluded, we cannot rule out the possibility that emerging depressive symptoms themselves could alter the food choices of participants. Previous studies [49,50] indicated that depressive symptoms may lead to increased inflammatory diet choices. Therefore, since a bidirectional association between DII and depressive symptoms may exist, well-designed, long-term clinical trials are needed to demonstrate consistent causal relationships. Fifth, this study did not assess depression as a structured clinical diagnostic interview conducted by a physician, which may affect prevalence and incidence estimates. Finally, unmeasured factors related to the association between diet and depression, such as xenobiotic exposure or early-life stress [42], might have led to potential residual confounding.

5. Conclusions

Our findings indicate that Spanish older adults consuming a high proinflammatory diet (i.e., a higher Dietary Inflammatory Index score) are more likely to develop self-reported diagnosis or symptoms of depression than those with an anti-inflammatory dietary pattern. Since diet is a modifiable lifestyle factor, future long-term clinical trials should test whether reducing the intake of proinflammatory foods (e.g., ultra-processed meat products or pastries) and nutrients (e.g., cholesterol or saturated fat) and encouraging an anti-inflammatory diet (rich in unsaturated fatty acids or dietary fibre) is an effective strategy to prevent depression in older ages. Moreover, additional prospective studies are needed to provide evidence on the biological and environmental mechanisms underlying the association between the potential inflammatory effect of diet and the risk of depression in older adults.

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Author contributions

B.B.-P.: Conceptualization, Formal analysis, Methodology, Visualization, Writing e original draft, Writing e review & editing. R.O.: Data curation, Methodology, Writing e review & editing. V.M.-V: Funding acquisition, Methodology, Writing e review & editing, Supervision. F.R.-A.: Data curation, Funding acquisition, Methodology, Writing e review & editing, Supervision. R.F.-R.: Formal analysis, Writing e review & editing. J.R. B.: Data curation, Funding acquisition, Writing e review & editing. E.L.-G.: Data curation, Methodology, Writing e review & editing. A.E.M.: Conceptualization, Formal analysis, Methodology, Visualization, Writing e original draft, Writing e review & editing, Supervision.

Data availability statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.10.007.

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MANUSCRIPT V

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Mediterranean Diet Interventions for Depressive Symptoms in Adults with Depressive Disorders: A Protocol for a Systematic Review and Meta-Analysis

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Abstract: The associations between Mediterranean diet (MD) adherence and depression levels have been synthesized from observational studies. However, a systematic review with meta-analysis including randomized controlled trials (RCTs) on this relationship in adults with depressive disorders remains lacking. This protocol was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols statement. MEDLINE (PubMed), Cochrane CENTRAL, PsycINFO, Scopus, and Web of Science databases will be systematically searched to identify studies published from database inception up to 30 September 2022. The inclusion criteria will comprise RCTs reporting pre-post changes in depression status (symptoms or remission) after a MD intervention compared to a control condition in adults over 18 years with depressive disorders. Pooled effect sizes and 95% confidence intervals will be calculated using the DerSimonian random-effects model. This study protocol determines the methodological approach for the systematic review and meta-analysis that will summarize the available evidence on the efficacy of MD interventions on depressive symptoms in adults with depressive disorders. The findings from this review may have implications for public mental health programs. The results will be disseminated through peer-reviewed publication, conference presentation, and infographics. No ethical approval will be required since only published data will be used. PROSPERO registration number: CRD42022341895.

Keywords: adulthood; healthy diet; Mediterranean foods; depression; study protocol; systematic review

1. Introduction

Depressive disorders ranked among the top 15 leading causes of burden worldwide in 2019 [1], affecting more than 270 million people [2]. The COVID-19 pandemic has created a high-risk scenario wherein some determinants (e.g., mobility or social interactions) of the cardinal features of all depression phenotypes (i.e., the presence of a sad, empty, or irritable mood and loss of interest or pleasure in life) have been affected [3]. In fact, the prevalence of major depressive disorder increased by 53.2 million additional cases in 2020 [4]. This calls for urgent mitigation strategies to promote mental wellbeing and reduce both the prevalence and burden of depressive disorders as well as their health-related consequences [5].

A complex interplay of genetic, biological, psychological, behavioral, and environmental determinants for depression has been proposed [6–8]. In particular, the role of diet in the etiology and course of depression has received more attention in recent years as a modifiable lifestyle factor that could contribute to the treatment of this mental disorder [9,10]. The pathways through which diet influences depression could be related to inflammation, oxidative stress, hypothalamic–pituitary–adrenal axis function, tryptophan–kynurenine metabolism, neurogenesis and brain-derived neurotrophic factor, epigenetics, mitochondrial function, and the gut microbiota [11]. Some evidence suggests that a healthy food matrix [11], such as that of the Mediterranean diet (MD), could influence some of these physiological pathways and, therefore, might potentially prevent the onset and relieve the symptomatology of depression [12–15]. The MD prototype (i.e., olive oil as the principal source of fat, high consumption of fruits, legumes, nuts, olives, seeds, spices, vegetables and whole-grain cereals, moderate consumption of eggs, fish or seafood, dairy products, red wine and white meat, and low consumption of red or processed meat and sweets) leads to a favorable nutrient intake (i.e., rich in dietary fiber, unsaturated fatty acids, prebiotics, vitamins, polyphenol compounds and carotenoids) associated with reduced oxidative stress [16] and proinflammatory cytokine expression [17] that drive important signaling events in the depression status [13].

The prospective cohort associations between MD adherence and depression in adults have been synthesized in several systematic reviews and meta-analyses of prospective observational studies, which showed mixed results [10,18–21]. While high MD adherence reduced the incidence of depression over time in some of these evidence syntheses [10,18,19], no significant association was observed in two other reviews [20,21]. Although observational studies provide relevant evidence, randomized controlled trials (RTCs) are known to provide a higher level of evidence for validating and judging the effects of an intervention (such as MD) on a health outcome (such as depressive symptomatology) [22]. Particularly, only RCTs can overcome the epistemological problems of dietary measurement error and form a sounder basis for informing dietary recommendations in human nutrition [23]. Previous systematic reviews of RCTs have analyzed the diet–depression association [24–26] but did not specifically examine MD as the exposure [25,26], did not consider adults with a diagnosis of depression [24,25], and did not perform a meta-analysis [24–26]. Moreover, in a preliminary search, new evidence from RCTs [27–29] was found, indicating that an update is required to help clinicians determine the extent to which MD should be recommended in the treatment of patients with depressive disorders. Therefore, the aim of this protocol is to provide a detailed plan to conduct a systematic review and meta-analysis synthesizing the available evidence from RCTs regarding the effectiveness of MD interventions on depression symptoms in adults with depressive disorders.

2. Materials and Methods

This protocol was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA-P) statement [30] (Table S1). The systematic review and meta-analysis will be conducted according to the PRISMA 2020 guidelines [31] and following the Cochrane Collaboration Handbook for Systematic Reviews of Interventions [32]. The overall content of the present protocol is registered in PROSPERO (CRD42022341895).

2.1. Eligibility Criteria

The rationale for the eligibility criteria was performed using the patient, intervention, comparison, outcome, and study design (PICOs) framework [32]. To be included, studies retrieved from the peer-reviewed literature must report the following: (i) population: adults over 18 years of age with a diagnosis of depressive disorder; (ii) intervention: experimental strategy that follows a Mediterranean dietary pattern, such as MD-related dietary advice or cooking workshops; (iii) comparator: control condition such as habitual diet, usual care, or 'social' groups; (iv) outcome: changes in depression status (i.e., number or severity of symptoms, or remission) for intervention and control groups separately; and (iv) study design: peer-reviewed RCTs.

Moreover, studies will be excluded if they report results in (i) population: individuals with different mental health disorders (e.g., depression, anxiety, bipolar disorder) without stratified data for those with only depression and participants under 18 years of age, even though the mean age of the study sample is over 18 years; (ii) intervention: diet in terms of intake of single nutrients, food items, and food groups; (ii) outcome: depressed mood and depression data that cannot be isolated and extracted (e.g., bipolar disorders, overall mood states, psychological stress); and (iii) data published as conference/meeting abstracts.

2.1.1. Population

We will consider the entire adult population (18 years or more) with a diagnosis of depressive disorders. For this study, RCTs that enrolled subjects with depressive disorders (i.e., major depressive disorder including major depressive episode, persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder) according to the fifth edition of the Diagnostic and Statistical Manual of Mental Health [3] will be included. Additionally, RCTs that determined the presence of a depressive disorder through trained professionals using a recognized diagnostic schedule, self-report of medical diagnosis or antidepressant treatment, or validated rating scale to specify high levels of depressive symptomology will be considered. No restrictions in terms of health status or sociodemographic characteristics will be imposed.

2.1.2. Intervention

The intervention under investigation will involve any type of face-to-face or virtual experimental treatment (e.g., dietary advice, cooking workshops, individual or group therapy sessions, provision of relevant Mediterranean foods) directly related to the MD; moreover, studies that implemented MD interventions along with a lifestyle or nutrient supplementation program will be included.

An important issue in nutrition research is the lack of detail and the great variability in the definitions of interventions [33]. The label MD is a concept widely used to describe the food prototype of the Mediterranean basin; however, its key determinants differ, even among experts [34]. Therefore, MD interventions will require at least two key items to reach a Mediterranean food matrix [35]. First, high consumption of plant-based foods, particularly, fruits, vegetables, and legumes; second, a high monounsaturated/saturated fat ratio (high consumption of food sources with high amounts of monounsaturated fat such as nuts, olive oil or whole grains and low consumption of food sources with high amounts of saturated fat such as butter, pastries, or processed meat). The rationale for this focus has two explanations. On the one hand, it is based on previous studies [36,37], which highlight the protective effects of MD. These benefits might be most attributable to specific food sources, such as fruits, legumes, nuts, olive oil, vegetables, and whole grains. Alternatively, it will cover the main MD components without neglecting the possible adaptations of this dietary pattern to the geographical location and sociocultural customs. Although the discrepancies in the MD definition could lead to inconsistencies and bias in the intervention-outcome relationship [33], this study will include RCTs from non-Mediterranean regions where this food system model (i.e., maintaining the abovementioned key components) can be adapted to country-specific agricultural resources and cultures and may have health benefits similar to those reported in Mediterranean regions [38].

2.1.3. Comparison

The review will include RCTs that present as comparators, control groups such as usual care, ‘social’ groups (e.g., befriending support sessions), standard diet, dietary advice unrelated to MD, or other diet regimens. All comparators will be recorded when randomization and the completion of outcomes are reported, as required for RCTs.

2.1.4. Outcome

Depression outcomes will be defined as changes in depressive symptoms according to validated [39] observer rating scales and self-rating scales (continuous data collected by screening instruments such as the Beck Depression Inventory, Hamilton Depression Rating Scale, Inventory of Depressive Symptomatology, Montgomery–Asberg Depression Rating Scale or Zung Self-Rating Depression Scale) and depression remission (dichotomous data defined by a prespecified threshold on a depression scale or no longer meeting clinical criteria for depression). Depressed mood and depression data that cannot be isolated and extracted (e.g., bipolar disorders, overall mood states, psychological stress) will not be included as depression outcomes.

2.1.5. Study Design

Only RCTs will be included because they provide (specifically high-quality RCTs) the most reliable evidence for healthcare intervention and clinical decision-making [22,23].

2.2. Search Methods for Study Identification

The systematic search will be conducted in MEDLINE (PubMed), Cochrane CENTRAL, PsycINFO, Scopus and Web of Science from database inception until 30 September 2022. Additional searches will be performed in the International Clinical Trials Registry Platform and the ClinicalTrials.gov websites to capture any study not covered by the main search. Further studies will be identified by screening the reference lists of the included studies and relevant reviews for potential relevance. The authors will be contacted in case of a lack of data. The electronic database searches will be limited to keywords, title, and abstract. The search strategy (Table 1) will involve a set of free text terms grouped from the PICO strategy. The search will first be carried out in MEDLINE and will subsequently be adapted to the other databases. No limits will be applied to the study language. In the case of non-English language articles, Google translate will be used to assess the eligibility of article abstracts, and those studies deemed eligible for full-text assessment will be translated by nonprofessional translators (i.e., volunteer researchers), by the University language department, or by professional translators who are native speakers of the language if necessary.

Table 1. Search strategy for the MEDLINE database.

PICO Component	Keywords
#1 Population	Adult* OR "young adult" OR "middle aged" OR aged OR elderly OR olde* OR patient
#2 Intervention	"Mediterranean diet" OR "Med-Diet" OR "Mediterranean-style diet" OR "Mediterranean food" OR "dietary pattern" OR "diet quality" OR "healthy diet" OR "diet intervention" OR "diet improvement" OR "food therapy"
#3 Outcome	Depress* OR dysthymi* OR "dysphoric disorder" OR "mood disorder" OR "affective disorder" OR "affective symptoms"
#4 Study design	(random* OR clinical OR controlled OR intervention* OR experimental) AND (trial OR study OR allocation)
Search Strategy	[(**#1**) AND (**#2**) AND (**#3**) AND (**#4**)]

Proximity operators (*) will be used to search for root words.

2.3. Data Collection and Analysis

2.3.1. Study Selection

All files of references from databases and other repositories will be imported into Mendeley Manager (v1.19.8; Elsevier, London, UK). Duplicate references will be identified using the in-built Mendeley function "check for duplicates". Following this step and based on inclusion/exclusion criteria, two researchers will first independently examine the titles and abstracts and then screen the full text of the studies identified, with consensus required for final inclusion. Discrepancies will be resolved by consulting a third reviewer. The results of searches in databases and other repositories and the selection process will be displayed using the PRISMA 2020 flow diagram (Figure 1).

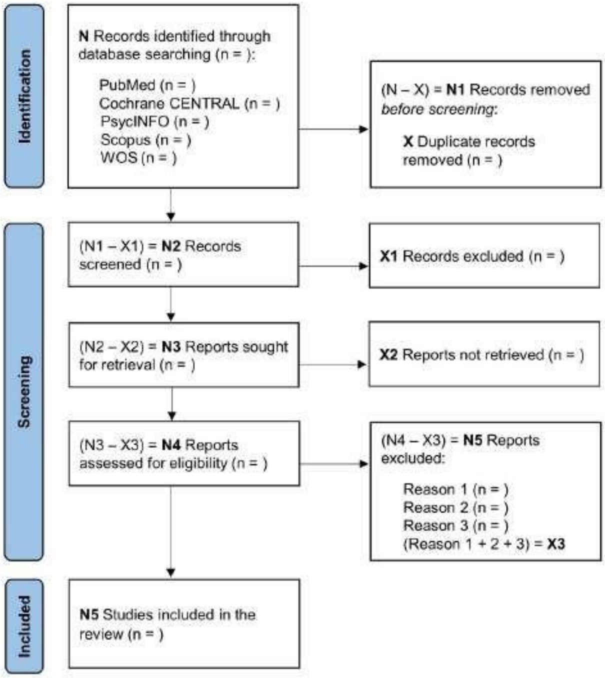

Figure 1. PRISMA flow diagram for identifying, screening, and determining the eligibility and inclusion of studies.

2.3.2. Data Collection Process

Two researchers will independently extract data extraction from the included studies on a standardized template, where the accuracy will be checked in case of discrepancies. If necessary, additional data will be requested from the corresponding authors via email.

The following study-specific data will be extracted: (1) name of the first author and year of publication; (2) country; (3) study design; (4) sample size; (5) characteristics of the participants (age, sex, type and duration of depressive disorder, medications); (6) MD intervention characteristics (type, duration, dietary components, adherence to the intervention according to follow-up measures, such as food diaries or monitoring face-to-face sessions, and pre-post adherence to MD according to diet quality measures, such as self-report questionnaires or spectrophotometer); (7) measures of depression; and (8) main findings. The information will be summarized in a "table of characteristics" (Table S2).

2.3.3. Risk of Bias

The risk of bias will be independently assessed by two researchers using the Cochrane Collaboration tool [40]. In cases of discrepancies, a third reviewer will be consulted.

2.3.4. Certainty of the Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to assess the evidence quality and to provide recommendations [41]. The GRADE method will be applied following five distinct steps: (1) assign an a priori ranking of 'high' to RCTs; (2) 'downgrade' or 'upgrade' the initial ranting; (3) assign final grade for the quality of evidence as 'high', 'moderate', 'low', or 'very low' for all critically important outcomes; (4) address other influencing factors that affect the recommendation strength of a course of action; (5) make a 'strong' or 'weak' recommendation [42].

2.4. Synthesis of Data

Once the primary data of the included studies had been extracted, pre vs. post MD interventions will be compared to control conditions for depression levels (i.e., symptoms or remission), and these data will be synthesized narratively. A meta-analysis will be conducted when we identify a minimum of five studies addressing the same outcome [43]. Continuous data (*n*, means, and standard deviations) will be collected from both the intervention and control groups at baseline and at the end of the follow-up period. When clinical trials report other descriptive (e.g., medians and interquartile ranges) or association (e.g., correlation or regression coefficients), these data will be extracted and subsequently converted into standardized measures (i.e., mean or standardized mean difference) that will allow comparison with the measures provided by the other studies [32]. The effect size (ES) and the 95% confidence interval (95% CI) will be calculated for each included study using Cohen's d index [44]. The pooled effect size (p-ES) for the effect of MD intervention vs. the control condition will be estimated for the RCTs using the DerSirmonian and Laird random-effects method [45,46]. The heterogeneity between the studies will be evaluated using the I^2 statistic, categorized as not important (0–30%), moderate (30–60%), substantial (60–75%), or considerable (75–100%) [32]. Additionally, the corresponding *p* values and 95% CIs for I^2 will be considered [47].

If there is available information, subgroup analyses will be performed based on characteristics of the population (age, sex, and type of depressive disorder), intervention (type, i.e., dietary treatment only vs. lifestyle program, and duration), comparison (type of control condition, i.e., active—such as befriending support sessions—vs. passive—such as usual diet), outcome (measures of depressive symptoms), and studies (methodological quality). Random-effects meta-regression models will be conducted to consider potential main factors of heterogeneity in the MD-depression association (e.g., age, sex, BMI, total energy intake, medications). To evaluate the robustness of the p-ESs and detect whether any specific study represents a large proportion of heterogeneity, sensitivity analyses will be performed by excluding the studies one by one. In addition, where possible, a sensitivity analysis according to the RCT data analysis method (i.e., completer, per-protocol, intent-to-treat, and modified intent-to-treat analyses) will be considered. Finally, publication bias will be evaluated through visual inspection of funnel plots and Egger's regression asymmetry test for assessing small study effects (*p* values < 0.05 implicates publication bias) [48].

We will conduct all statistical analyses in R software (version 4.2.1; R Foundation for Statistical Computing).

3. Ethics and Dissemination

Ethics committee approval and informed consent from patients will not be required. The planned systematic review and meta-analysis will have public health implications by providing updated evidence on the efficacy of MD interventions on depressive symptoms in adults with depressive disorders. The results of the systematic review and meta-analysis will be submitted to a peer-reviewed journal.

4. Discussion

This protocol describes the methodology that will be used for a systematic review and meta-analysis that will synthesize the efficacy of Mediterranean dietary interventions in improving levels of depression (i.e., symptoms or remission) in adults with depressive disorders. Moreover, the systematic review will intend to provide evidence of the main factors related to depression, such as age and sex.

Available evidence indicates that MD is one of the healthiest and most environmentally sustainable dietary matrix patterns [49], promoting a natural, simple, and feasible approach [34] with the potential to prevent the onset and reduce the symptomatology of depression [14,15]. Indeed, high MD adherence has been associated with a reduced risk of depression throughout adulthood in some meta-analyses of prospective cohort studies [10,18,19]. A previous systematic review of RCTs that specifically analyzed MD as a treatment for depressive symptoms in adults with depressive disorders showed both that this dietary pattern would provide a potential therapeutic intervention and the urgent need for more RCTs [24]. Since then, other intervention-controlled trials have been published [27–29] that may add important evidence to validate MD as an effective strategy to improve the symptoms of depression. To date, a meta-analysis has not been performed, highlighting the demand for MD recommendations based on the highest level of evidence.

A meta-analysis of multiple RCTs (preferably meticulous, large, and long-term) provides the best opportunity for reliable answers in human nutrition science [23,33], particularly to extrapolate the therapeutic potential of the MD on depression symptoms in adults with depressive disorder. To the best of our knowledge, an updated synthesis of RCTs with a meta-analytical approach is needed to answer the following question: does the available evidence support the efficacy of MD interventions in reducing levels of depression in adult patients with depressive disorder? Since both global dietary transitions [50] and the increasing trend of depression [4] have become growing challenges and public health issues, this study may have future implications for public mental health policies due to the urgent need for effective strategies for the treatment of depression.

The limitations of the review may include the usual shortcomings of systematic reviews and meta-analyses, such as publication bias, low methodological quality, and heterogeneity of the included studies. Differences regarding sample characteristics, dietary interventions, depressive symptoms assessment methods and methodological quality may limit the extrapolation of the findings.

5. Conclusions

This study facilitates the protocol methodology for a systematic review and the first meta-analysis of RCTs that will synthesize the efficacy of MD interventions on depressive symptoms in adults with depressive disorders. Specifically, this study will provide an update on the essential evidence regarding the role of MD as a potential nonpharmacological approach to improve the depression status of adult patients with depressive disorder. Findings from this systematic review and meta-analysis will be a key tool for evidence-based decision-making and will be useful for researchers and health professionals responsible for promoting healthy lifestyles and mental health care. The results obtained will be disseminated through peer-reviewed publications, national and international conferences, social networks, educational talks, and infographics.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph192114437/s1, Table S1: PRISMA-P 2015 checklist to address the systematic review protocol. *Adapted from Moher D et al. [30].; Table S2: Characteristics of studies included in the systematic review and meta-analysis. Abbreviations: MD, Mediterranean diet; RCT, randomized controlled trial.

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MANUSCRIPT VI

Title:
The impact of the Mediterranean diet on alleviating depressive symptoms in adults: a systematic review and meta-analysis of randomized controlled trials.

Authors:
Bruno Bizzozero-Peroni, Vicente Martínez-Vizcaíno, Rubén Fernández-Rodríguez, Estela Jiménez-López, Sergio Núñez de Arenas-Arroyo, Alicia Saz-Lara, Valentina Díaz-Goñi, Arthur Eumann Mesas.

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Meta-analysis

The impact of the Mediterranean diet on alleviating depressive symptoms in adults: a systematic review and meta-analysis of randomized controlled trials

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Original article

Nut consumption is associated with a lower risk of depression in adults: A prospective analysis with data from the UK Biobank cohort

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S U M M A R Y

Background & aims: Evidence on the association between nut consumption and depression is mainly based on cross-sectional studies. This study aims to analyse whether nut consumption is prospectively associated with the risk of depression in adults.
Methods: This study was conducted using the United Kingdom (UK) Biobank resource. Data from middle-aged and older UK adults who participated in this cohort between 2007e2012 (baseline) and 2013e2020 (follow-up) were analysed. Baseline information on nut consumption was obtained with the Oxford WebQ 24-h questionnaire. Depression, defined as a self-reported physician diagnosis of depression or antidepressant use, was assessed at baseline and follow-up. Hazard regression models estimating the predictive ability of nut consumption for the risk of developing depression were adjusted for sociodemographic, lifestyle, and health confounders.
Results: A total of 13,504 participants (mean age 57.5 ± 7.2 years, 50.7% female) free of depression at baseline were included in the analyses. After a mean follow-up of 5.3 ± 2.4 years, 1122 (8.3%) incident cases of depression were identified. Compared with no nut consumption, the daily consumption of >0 to 1 serving of 30 g of nuts was associated with a lower risk of depression (hazard ratio, HR ¼ 0.83; 95% confidence interval, CI: 0.71e0.97) regardless of all potential confounders considered. In stratified analyses, a decreased risk of depression was more clearly observed in UK adults with adequate weight control, a healthy lifestyle, and better health status than in their counterparts ($p < 0.05$).
Conclusions: Low-to-moderate nut consumption (>0 to 1 serving of 30 g/day) was associated with a 17% lower risk of depression during a 5.3-year follow-up compared with no nut consumption in a large sample of middle-aged and older UK adults. This protective association is enhanced in the absence of other known risk factors for depression.

1. Introduction

Depression is among the most common mental disorders, affecting 279.6 million people worldwide in 2019, with a lifetime prevalence ranging from 3.4 to 4.2% [1]. These are probably conservative estimates since the complex clinical picture of depression leads to a high proportion of undiagnosed cases [2]. Although treatments based on antidepressant use may mitigate depressive symptoms [3], not all patients with depression can sustain symptom remission with antidepressant use alone [4,5]. This could be explained because depression pathophysiology involves psychosocial, behavioral, and environmental factors, in addition to genetic and biological interactions [6]. In this sense, complementary lifestyle-oriented approaches have shown

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PART II – CHAPTER 3

MANUSCRIPT VIII

Title:
Daily step count and depression in the general adult population: a systematic review and meta-analysis of observational studies.

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Daily steps and depression in the general adult population.

Authors

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CONCLUSIONS

The main conclusions of this doctoral dissertation related to the aims are as follows:

PART I – Chapter 1

Manuscript I

Objective 1: To provide the methodology for a systematic review and meta-analysis to update the evidence on the associations between adherence to the Mediterranean diet and physical fitness in young, middle-aged, and older adults.

- A clear and structured procedure is facilitated to maximize the extraction of relevant data and to provide summary information on the associations between adherence to the Mediterranean diet and physical fitness in young, middle-aged, and older adults.

Manuscript II

Objective 2: To synthesize the associations of high (vs. low) adherence to the Mediterranean diet and its specific foods with physical fitness levels, including each of its components (cardiorespiratory, motor, and musculoskeletal), in adulthood.

- Our findings extend knowledge by providing a comprehensive picture of the available evidence, pointing out significant positive cross-sectional and longitudinal (3–12-year follow-up) associations between high (vs. low) Mediterranean diet adherence and higher physical fitness levels in adults of all ages. According to each fitness indicator, high (vs. low) adherence to the Mediterranean diet was associated with improved cardiorespiratory (cross-sectional association), musculoskeletal (cross-sectional and longitudinal associations), and motor (cross-sectional association in populations from Mediterranean countries) fitness levels. Sex, age, body mass index, health status, current smoking status, and total energy intake did not influence the study associations. In addition, our data showed inconsistent results regarding specific Mediterranean foods. Clinical trials and cohort studies are needed to provide evidence on the biological and environmental mechanisms underlying the study associations and to determine the role of each specific Mediterranean food.

Manuscript III

Objective 3: To analyze the associations between the consumption of different types of meat and muscle strength in Spanish young adults and to determine whether these relationships are mediated by total protein intake and percentage of lean mass.

- In conclusion, the relationship between regular meat consumption and muscle strength, although still lacking confirmation from cohorts and experimental studies, reinforces the importance of this food group as an essential item in a healthy diet, especially in young adults. With respect to the benefits for muscle strength, our data suggest that a higher daily consumption of white and fish meat contributes in the same way as red meat through the mediation of total protein intake and lean mass percentage. Thus, our findings agree with dietary guidelines of healthy diets such as the Mediterranean diet, which recommends the preferential consumption of white and fish meat over the consumption of red or processed meat.

PART II – Chapter 2

Manuscript IV

Objective 4: To examine the associations between a proinflammatory dietary pattern and the incidence of depression in community-dwelling older adults in Spain.

- In summary, our findings demonstrated that a proinflammatory dietary pattern is associated with depression risk. Specifically, older adults in the highest quartile of the Dietary Inflammatory Index were twice as likely to develop depression than those in the lowest quartile after 2 to 3 years of follow-up. The associations remained significant after adjustment for several key confounders, such as socioeconomic factors, lifestyle habits and chronic diseases. Future clinical research should evaluate whether reducing the inflammatory component of diet leads to reduced depressive symptoms in this population.

Manuscript V

Objective 5: To determine the methodological approach for a systematic review and meta-analysis that will summarize the available evidence on the efficacy of Mediterranean diet interventions on depressive symptoms in adults with depressive disorders.

- A detailed and structured plan is facilitated to maximize the extraction of relevant data and to provide summary information on the effects of Mediterranean diet interventions on depressive symptoms in adults with depressive disorders.

Manuscript VI

Objective 6: To synthesize the effects of Mediterranean diet-based interventions on the severity of depressive symptoms in adults with depression or mild to severe depressive symptoms.

- In conclusion, our results suggest that Mediterranean diet interventions (6 to 48 weeks of duration) can be effective in reducing depressive symptoms among young and middle-aged adults with mild or major depression, achieving moderate significant relief compared to control conditions. This synthesis of randomized controlled trials provides the highest level of evidence to consider Mediterranean diet-based interventions as a potential component of health care for depression management. However, our data showed only low-certainty evidence for the proposed association and should be interpreted with caution, highlighting the demand for more large-scale, long-term randomized controlled trials to provide consistent conclusions.

Manuscript VII

Objective 7: To estimate the associations between nut consumption and the risk of depression in middle-aged and older UK adults and to determine whether these relationships are affected by other risk factors for depression related to lifestyle and health status.

- In summary, our findings indicate that regular low to moderate consumption of nuts (>0 to 1 serving of 30 g/day) is associated with a 17% lower risk of depression in middle-aged and older adults compared to no nut consumption after a 5.3-year follow-up, regardless of relevant sociodemographic, lifestyle, and health confounders. In addition, our results highlight the potential role of nut consumption as a healthy dietary behavior to prevent depression in those free of other known risk factors for depression, such as obesity, unhealthy lifestyle behaviors (smoking, frequent alcohol consumption, low intake of fruits and vegetables, insufficiently active, and inadequate sleep duration), loneliness, and medical conditions such as cardiovascular, metabolic, or mental comorbidities. Since diet is a modifiable lifestyle factor, future long-term clinical trials should evaluate whether nut consumption is an effective strategy to prevent depression during adulthood.

PART II – Chapter 3

Manuscript VIII

Objective 8: To synthesize the associations between objectively measured daily steps and both depression and depressive symptoms from observational studies in the general adult population.

- In summary, our findings indicate that a greater number of daily steps could help reduce both depression and depressive symptoms in the general adult population. Even modest increments in the number of daily steps were associated with fewer depressive symptoms. In addition, compared to <5000 steps/day, reaching ≥5000 steps/day may provide a lower prevalence of depression or fewer depressive symptoms. In turn, adults taking more than 7000 steps/day were less likely to develop depression or depressive symptoms after 2–5 years of follow-up. Cohort studies are needed that, in addition to providing a better understanding of step-based physical activity goals for depression prevention, provide crucial evidence to identify specific daily step requirements according to depression phenotype and associated factors such as age or sex.

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CONCLUSIONES

Las principales conclusiones de esta disertación doctoral en relación con los objetivos son las siguientes:

PARTE I – Capítulo 1

Manuscrito I

Objetivo 1: Proporcionar la metodología para una revisión sistemática y metaanálisis para actualizar la evidencia sobre las asociaciones entre la adherencia a la dieta Mediterránea y la condición física en adultos jóvenes, de mediana edad y mayores.

- Se facilita un procedimiento claro y estructurado para maximizar la extracción de datos relevantes y proporcionar información resumida sobre las asociaciones entre la adherencia a la dieta Mediterránea y la condición física en adultos jóvenes, de mediana edad y mayores.

Manuscrito II

Objetivo 2: Sintetizar las asociaciones de la adherencia alta (frente a la baja) a la dieta Mediterránea y sus alimentos específicos con los niveles de condición física, incluyendo cada uno de sus componentes (cardiorrespiratorio, motor y musculoesquelético), en la edad adulta.

- Nuestros hallazgos amplían el conocimiento al proporcionar una imagen completa de la evidencia disponible, señalando asociaciones positivas significativas transversales y longitudinales (3–12 años de seguimiento) entre una adherencia alta (frente a la baja) a la dieta Mediterránea y mayores niveles de condición física en adultos de todas las edades. Considerando cada indicador de condición física, la adherencia alta (frente a la baja) a la dieta Mediterránea se asoció con mejores niveles de condición física cardiorrespiratoria (asociación transversal), musculoesquelética (asociaciones transversales y longitudinales) y motora (asociación transversal en poblaciones de países Mediterráneos). El sexo, la edad, el índice de masa corporal, el estado de salud, el hábito de fumar y la ingesta energética total no influyeron las asociaciones de estudio propuestas. Además, nuestros datos mostraron resultados inconsistentes en relación con alimentos Mediterráneos específicos. Son necesarios ensayos clínicos y estudios de cohortes para aportar evidencias sobre los mecanismos biológicos y ambientales subyacentes a las asociaciones de estudio, así como para determinar el papel de cada alimento Mediterráneo especifico.

Manuscrito III

Objetivo 3: Analizar las asociaciones entre el consumo de diferentes tipos de carne y la fuerza muscular en adultos jóvenes españoles y determinar si estas relaciones están mediadas por la ingesta total de proteínas y el porcentaje de masa magra.

- En conclusión, la relación entre el consumo habitual de carne y la fuerza muscular, aunque aún no se ha confirmado en estudios cohortes y experimentales, refuerza la importancia de este grupo de alimentos como elemento esencial de una dieta saludable, especialmente en adultos jóvenes. Con respecto a los beneficios para la fuerza muscular, nuestros datos sugieren que un mayor consumo diario de carne blanca y de pescado contribuye de la misma manera que la carne roja a través de la mediación de la ingesta total de proteínas y el porcentaje de masa magra. Así, nuestros hallazgos concuerdan con las directrices dietéticas de dietas saludables como la dieta Mediterránea, que recomiendan el consumo preferente de carne blanca y de pescado sobre el consumo de carne roja o procesada.

PARTE II – Capítulo 2

Manuscrito IV

Objetivo 5: Examinar las asociaciones entre un patrón dietético proinflamatorio y la incidencia de depresión en adultos mayores residentes en la comunidad en España.

- En resumen, nuestros hallazgos demostraron que un patrón dietético proinflamatorio está asociado con el riesgo de depresión en adultos mayores. En concreto, los adultos mayores en el cuartil más alto del Índice Dietético Inflamatorio tenían el doble de probabilidades de desarrollar depresión que aquellos en el cuartil más bajo después de 2 a 3 años de seguimiento. Las asociaciones siguieron siendo significativas tras ajustar por varios factores de confusión clave, como factores socioeconómicos, hábitos del estilo de vida y enfermedades crónicas. Futuras investigaciones clínicas deberían evaluar si la reducción del componente inflamatorio de la dieta conduce a una reducción de los síntomas depresivos en esta población.

Manuscrito V

Objetivo 6: Determinar el enfoque metodológico para una revisión sistemática y metaanálisis que resumirá la evidencia disponible sobre la eficacia de las intervenciones con dieta Mediterránea sobre los síntomas depresivos en adultos con trastornos depresivos.

- Se facilita un plan detallado y estructurado para maximizar la extracción de datos relevantes y proporcionar información resumida sobre los efectos de las intervenciones con dieta Mediterránea sobre los síntomas depresivos en adultos con trastornos depresivos.

Manuscrito VI

Objetivo 7: Sintetizar los efectos de las intervenciones basadas en la dieta Mediterránea sobre la gravedad de los síntomas depresivos en adultos con depresión o síntomas depresivos de leves a graves.

- En conclusión, nuestros resultados sugieren que las intervenciones basadas en la dieta Mediterránea (6 a 48 semanas de duración) pueden ser eficaces para reducir los síntomas depresivos entre adultos jóvenes y de mediana edad con depresión leve o grave, logrando un alivio significativo moderado en comparación con las condiciones de control. Esta síntesis de ensayos controlados aleatorios proporciona el mayor nivel de evidencia para considerar las intervenciones basadas en la dieta Mediterránea como un componente potencial de la atención sanitaria para el tratamiento de la depresión. Sin embargo, nuestros datos sólo mostraron evidencia de baja certeza para la asociación propuesta y deben interpretarse con cautela, lo que pone de relieve la demanda de más ensayos controlados aleatorios a gran escala y a largo plazo para proporcionar conclusiones consistentes.

Manuscrito VII

Objetivo 8: Estimar las asociaciones entre el consumo de frutos secos y el riesgo de depresión en adultos de mediana edad y mayores del Reino Unido y determinar si estas relaciones se ven afectadas por otros factores de riesgo de depresión relacionados con el estilo de vida y el estado de salud.

- En resumen, nuestros hallazgos indican que el consumo regular bajo a moderado de frutos secos (>0 a 1 ración de 30 g/día) se asocia con un riesgo 17% menor de depresión en adultos de mediana edad y mayores en comparación con la ausencia de consumo de frutos secos después de un seguimiento de 5,3 años, independientemente de factores relevantes de confusión sociodemográficos, de estilo de vida y de salud. Además, nuestros resultados ponen de relieve el papel potencial del consumo de frutos secos como comportamiento dietético saludable para prevenir la depresión en aquellas personas libres de otros factores de riesgo conocidos para la depresión, como la obesidad, los comportamientos de estilo de vida poco saludables (tabaquismo, consumo frecuente de alcohol, baja ingesta de frutas y verduras, actividad física insuficiente y duración inadecuada del sueño), la soledad y afecciones médicas como comorbilidades cardiovasculares, metabólicas o mentales. Dado que la dieta es un factor modificable del estilo de vida, futuros ensayos clínicos deberían evaluar si el consumo de frutos secos es una estrategia eficaz para prevenir la depresión durante la edad adulta.

PARTE II – Capítulo 3

Manuscrito VIII

Objetivo 9: Sintetizar las asociaciones entre los pasos diarios medidos objetivamente y tanto la depresión como los síntomas depresivos a partir de estudios observacionales en la población adulta general.

- En resumen, nuestros hallazgos indican que un mayor número de pasos diarios podría ayudar a reducir tanto la depresión como los síntomas depresivos en la población adulta general. Incluso incrementos modestos en el número de pasos diarios se asociaron con menos síntomas depresivos. Además, en comparación con <5000 pasos/día, alcanzar ≥5000 pasos/día puede proporcionar una menor prevalencia de depresión o menos síntomas depresivos. A su vez, los adultos que daban más de 7000 pasos/día eran menos propensos a desarrollar depresión o síntomas depresivos tras un seguimiento de 2 a 5 años. Se necesitan estudios de cohorte que, además de proporcionar una mejor comprensión de los objetivos de actividad física basados en pasos para la prevención de la depresión, aporten evidencias cruciales para identificar los requisitos específicos de pasos diarios según el fenotipo de depresión y los factores asociados, como la edad o el sexo.

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FUTURE RESEARCH LINES

Future research lines will be focused on some of the study proposals detailed below:

Outcome: physical fitness

- The associations between daily step counts and physical fitness in older adults: a systematic review and meta-analysis of observational studies.
- Nut consumption and physical fitness in university students: the mediating role of diet quality and micronutrients.

Outcome: depression

- Effectiveness of dietary interventions to reduce depressive symptoms in adults with depression: a network meta-analysis.
- The effect of multicomponent lifestyle interventions on depressive symptoms in adults of all ages: a systematic review with meta-analysis of randomized controlled trials.
- Associations between nut consumption and depressive symptoms in young adults: cross-sectional analyses from the Nuts4Brain-Z study.
- Associations of physical fitness parameters with risk of depression in adults: an overview of reviews.

Outcome: physical fitness-related variable

- Effectiveness of daily step interventions to increase physical activity levels in adults with depression: a systematic review and meta-analysis.
- The associations between a proinflammatory diet and daily living functioning in middle-aged and older adults: a meta-analysis.

Outcome: mental health-related variable

- The associations between Mediterranean diet-based interventions and cognitive function in adulthood: a systematic review with meta-analysis.
- The associations between Mediterranean diet adherence and risk of anxiety in adults: a meta-analysis of prospective cohort studies.
- Associations between nut consumption and risk of dementia in middle-aged and older adults from the UK Biobank cohort.
- Associations between nut consumption and quality of life in university students: the Nuts4Brain-Z cross-sectional study.

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APPENDIX

APPENDIX I. PROSPERO PROTOCOL MANUSCRIPTS I–II

Manuscript I: The associations between adherence to the Mediterranean diet and physical fitness in young, middle-aged, and older adults: A protocol for a systematic review and meta-analysis.

Manuscript II: High Adherence to the Mediterranean Diet is Associated with Higher Physical Fitness in Adults: a Systematic Review and Meta-Analysis.

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UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

A list of fields that can be edited in an update can be found here

1. * Review title.

Give the title of the review in English

The associations between adherence to the Mediterranean Diet and physical fitness in young, middle-aged, and older adults: a systematic review and meta-analysis.

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

01/02/2022

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/12/2022

5. * Stage of review at time of this submission.
[1 change]

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

The review has not yet started: No

Review stage	**Started**	**Completed**
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Bruno Bizzozero Peroni

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Mr Bruno Bizzozero Peroni

7. * Named contact email.

Give the electronic email address of the named contact.

bruno.bizzozero@uclm.es

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

C\ Santa Teresa Jornet, s\/n, 16071, Cuenca, Spain

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Universidad de Castilla-La Mancha, Health and Social Research Center, Cuenca, Spain. Instituto Superior de Educación Física, Universidad de la República, Rivera, Uruguay. Faculty of Medicine, Universidad Autónoma de Chile, Talca, Chile.

Organisation web address:

https://www.uclm.es/

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Mr Bruno Bizzozero Peroni. Health and Social Research Center, Universidad de Castilla-La Mancha, Cuenca 16071, Spain. Instituto Superior de Educación Física, Universidad de la República, Rivera 40000, Uruguay. Grupo de Investigación en Análisis del Rendimiento Humano, Universidad de la República, Rivera 40000, Uruguay.
Dr Javier Brazo Sayavera. Department of Sports and Computer Science, Universidad Pablo de Olavide, Sevilla 41013, Spain. Grupo de Investigación en Análisis del Rendimiento Humano, Universidad de la República, Rivera 40000, Uruguay.
Dr Arthur E Mesas. Health and Social Research Center. Universidad de Castilla-La Mancha, Cuenca 16071, Spain. Post-graduate Program in Public Health, Universidade Estadual de Londrina, Londrina, Paraná 86057–970, Brazil.
Dr Vicente Martínez Vizcaíno. Health and Social Research Center. Universidad de Castilla-La Mancha, Cuenca 16071, Spain. Faculty of Medicine, Universidad Autónoma de Chile, Talca 1101, Chile.

12. * Funding sources/sponsors.
[1 change]

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

Universidad de Castilla-La Mancha, Fondo Social Europeo.

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person,**

unless you are amending a published record.

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Does the available evidence support a relationship between adherence to the Mediterranean Diet and health-related physical fitness levels throughout adulthood (young adults, middle-aged adults, and elderly)? Which individual dietary components are associated with each physical fitness component?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

This systematic review will be conducted according to the PRISMA statement (Page et al., 2020, BMJ), the MOOSE recommendations for observational studies (Stroup et al., 2000, JAMA), and the Cochrane

Collaboration Handbook (Higgins et al., 2021, Cochrane). A systematic search will be conducted on MEDLINE (PubMed), Scopus, Web of Science, SPORTDiscus and Cochrane CENTRAL from database inception up to 31st January, 2022. We will use keywords related to both Mediterranean diet and physical fitness issues, in addition to terms related to the adulthood. These search terms will be combined with Boolean operators adapted for each database.

In addition, the search will be supplemented by additional searches where reference lists of included studies and relevant systematic reviews will be screened for potential relevance. In case of lack of data, experts will

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

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Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Adherence to overall Mediterranean Diet and specific Mediterranean foods, physical fitness, adults aged 18+

years. Healthy diet and high physical fitness may be part of an overall healthy lifestyle. The relationship between adherence to the Mediterranean Diet and physical fitness levels has been analyzed in several studies. However, no studies have synthesized the evidence on this relationship throughout adulthood. Additionally, there is a lack of synthesis on the associations of individual components of the Mediterranean diet, in addition to the overall Mediterranean dietary pattern, with physical fitness indicators.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

We will include studies recruiting adults aged 18+ years. Exclusion: adolescents and children (under 18 years of age).

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

The adherence of the Mediterranean Diet according to overall score of scales and to specific components (foods and nutrients) of these scales.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Lower levels of the adherence to the Mediterranean Diet or its specific components.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Observational studies (cross-sectional, case-control, prospective/retrospective cohort and longitudinal) and randomized controlled trials analyzing the association between the Mediterranean Diet and physical fitness in adults aged 18+ years.To be included, studies must report:

(a) Exposure analyzed: Mediterranean Diet measured by Mediterranean diet adherence indices (e.g., Mediterranean Diet Score, Mediterranean Diet Adherence Screener, etc.);

(b) Healthy and unhealthy adult population aged 18+ years; and

(c) Outcome analyzed: components of health-related physical fitness (i.e., cardiorespiratory fitness, musculoskeletal fitness, and motor fitness).

Studies will be excluded if they report:

(a) Duplicate data published in another included study;

(b) Diet in terms of intake of single nutrients, food items, and food groups;

(c) Special interest groups data (e.g., elite athletes or firefighters);

(d) Data published as conference/meeting abstracts or in peer-reviewed, refereed, non-predatory journals;

(e) Qualitative data; or

(f) Physical fitness measured by self-report.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

Studies of the association between the adherence to the overall Mediterranean Diet (and specific Mediterranean foods) and physical fitness in the general healthy or unhealthy adult population aged 18+ years.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Physical fitness (cardiorespiratory fitness, musculoskeletal fitness, and motor fitness) by using standardized battery test. Standardized tests provide valid means to assess physical fitness in adults of all ages (e.g., 20-m shuttle run test, 1.5-mile run/walk test, 12 min run/walk test, handgrip strength test with TKK dynamometer, sit-and-reach test, etc.).Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Higher vs lower Mediterranean diet exposures were compared for each fitness outcome, and these data will be synthesized narratively, sub-grouped by age, sex, health status, and individual dietary components of the

Mediterranean Diet where possible. Once the main characteristics of the included studies have been extracted, we will determine whether a metaanalysis is possible. Effect sizes (ES) and their 95% confidence intervals (95% CIs) will be calculated for each study.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

None.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Not applicable.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

The procedures will be divided in steps:

First step: Title and abstract screening

Firstly, two independent reviewers (BBP and JBS) will screen the titles for potential inclusion. Then, both reviewers will continue with the abstracts of the selected articles. In case of disagreement, in title and in abstract inclusion, a third reviewer (AEM) will decide. In cases where a decision for exclusion or potential inclusion cannot be made by the title/abstract, the full text will be retrieved.

Second step: Full-text screening

The two independent reviewers will review the full texts of the previously included articles and will decide the inclusion or exclusion based on the selected criteria (inclusion and exclusion) by the completion of a checklist. A third reviewer will decide on the inclusion or exclusion if there is no consensus between reviewers.

Third step: Data extraction

The extraction will include bibliographic information (authors and year of publication); study design; participant's characteristics (place, age, % male/female), diet assessment, Mediterranean Diet adherence, dietetic individual components analyzed, and fitness outcomes. One reviewer (BBP) will extract the information from the selected studies and another reviewer (JBS) will check it out. In case of discrepancies, a third reviewer (AEM) will act to solve the disagreements.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

The included studies will be assessed for methodological quality as their full published versions independently by two researchers (BBP and JBS). In case of discrepancies, a third reviewer (AEM) will act to solve the disagreements.
The tools to evaluate the risk of bias will be the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Heart, Lung, and Blood Institute, 2022) and the Cochrane Collaboration's tool for assessing risk of bias (RoB2) (Sterne et al., 2019, BMJ).

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

The potential for conducting a meta-analysis will be assessed based on the data which has been extracted. Stata 14 software will be used to combine the pooled mean differences with 95% CIs. A fixed effect model will be used if there is no evidence of heterogeneity, otherwise, a random-effects model will be used. Study heterogeneity will be assessed using the I^2 statistic, in which usually, I^2 values of 25%, 25-50% and 50% represent small, medium, and large levels of heterogeneity, respectively.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

If there is available information we will divide the information by sex, age groups, health status, and individual dietary components of the Mediterranean Diet or individual components of physical fitness.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness

No

Diagnostic

No

Epidemiologic

No

Individual patient data (IPD) meta-analysis

No

Intervention

No

Living systematic review

No

Meta-analysis

Yes

Methodology

No

Narrative synthesis

No

Network meta-analysis

No

Pre-clinical

No

Prevention

No

Prognostic

No

Prospective meta-analysis (PMA)

No

Review of reviews

No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

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National Institute for Health Research

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Spain
Uruguay

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Refer nce and/or URL for published protocol.
[3 changes]

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Bizzozero-Peroni B, Brazo-Sayavera J, Martínez-Vizcaíno V, Núñez de Arenas-Arroyo S, Lucerón-Lucas-Torres M, Díaz-Goñi V, et al. (2022) The associations between adherence to the Mediterranean diet and physical fitness in young, middle-aged, and older adults: A protocol for a systematic review and meta analysis. PLoS ONE 17(7): e0271254. https://doi.org/10.1371/journal.pone.0271254

Add web link to the published protocol.

https://doi.org/10.1371/journal.pone.0271254

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Adulthood

Healthy diet

Diet, Mediterranean

Mediterranean foods

Physical fitness

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

None.

38. * Current review status.
[2 changes]

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review_Completed_published

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.
[2 changes]

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

https://doi.org/10.1093/advances/nmac104

APPENDIX II. PROSPERO PROTOCOL MANUSCRIPTS V–VI

Manuscript V: Mediterranean Diet Interventions for Depressive Symptoms in Adults with Depressive Disorders: A Protocol for a Systematic Review and Meta-Analysis.

Manuscript VI: The impact of the Mediterranean diet on alleviating depressive symptoms in adults: a systematic review and meta-analysis of randomized controlled trials.

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UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

A list of fields that can be edited in an update can be found here

1. * Review title.
[1 change]

Give the title of the review in English

Mediterranean diet interventions for depressive symptoms in adults with depressive disorders: a systematic

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.
[1 change]

Give the date the systematic review started or is expected to start.

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/01/2023

5. * Stage of review at time of this submission.
[2 changes]

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Bruno Bizzozero Peroni

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

MSc Bizzozero Peroni Peroni

7. * Named contact email.

Give the electronic email address of the named contact.

bruno.bizzozero@uclm.es

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

C\/ Santa Teresa Jornet, s\/n, 16071, Cuenca, Spain

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+34 969179100

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be

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completed as 'None' if the review is not affiliated to any organisation.

Health and Social Research Center, Universidad de Castilla-La Mancha, Cuenca, Spain.

Organisation web address:

https://www.uclm.es/

1 . * Review team members and their organisational affiliations. [**1** change]

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Mr BRUNO BIZZOZERO PERONI. Health and Social Research Center. Universidad de Castilla-La Mancha, Cuenca 16071, Spain. Instituto Superior de Educación Física, Universidad de la República, Rivera 40000, Uruguay.
Dr Vicente Martínez-Vizcaino. Universidad de Castilla-La Mancha
Dr Arthur E Mesas. Health and Social Research Center, Universidad de Castilla-La Mancha, Cuenca, Spain. Postgraduate Program in Public Health, Universidade Estadual de Londrina, Londrina, Paraná, Brazil.

12. * Funding sources/sponsors. [1 change]

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

Universidad de Castilla-La Mancha, Fondo Social Europeo.

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Does the available evidence support the effectiveness of Mediterranean diet interventions in reducing levels of depression in patients with depressive disorders throughout adulthood?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

This systematic review will be conducted according to the PRISMA statement (Page et al., 2020, BMJ) and the Cochrane Collaboration Handbook (Higgins et al., 2021, Cochrane).

A systematic search will be conducted on MEDLINE (PubMed), Web of Science, Cochrane CENTRAL and PsycINFO from database inception. We will use keywords related to both Mediterranean diet and depression issues, in addition to terms related to the adulthood. These search terms will be combined with Boolean operators adapted for each database.

In addition, the search will be supplemented by additional searches where reference lists of included studies and relevant systematic reviews will be screened for potential relevance. In case of lack of data, experts will be contacted to provide information about other possible data.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Depressive symptoms in adults aged 18+ years with depressive disorders.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

We will include studies recruiting adults aged 18+ years with depressive disorders.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Any type of intervention (e.g., counseling, face-to-face sessions) that follow a Mediterranean diet.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

No restriction (e.g., habitual diet, usual care).

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Randomized controlled trials analyzing the association between Mediterranean diet interventions and depressive symptoms in adults aged 18+ years with depressive disorders.To be included, studies must report:

(a) Population: adults aged 18+ years with depressive disorders;

(b) Intervention: Mediterranean diet treatment (e.g., counseling, face-to-face sessions);

(c) Outcome: depression symptoms according to validated rating scales.

Studies will be excluded if they report:

(a) Diet in terms of intake of single nutrients, food items, and food groups;

(b) Depressed mood and depression data that cannot be isolated and extracted (e.g., bipolar disorders);

(c) Data published as conference/meeting abstracts.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

Studies of the association between Mediterranean diet interventions and depressive symptoms in the entire adult population aged 18+ years with depressive disorders.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Depression outcomes will be defined as changes in depressive symptoms according to validated observer rating scales and self-rating scales.

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Pre vs. post changes in depression levels will be compared between MD interventions and control conditions, and these data will be synthesized narratively, sub-grouped by age and sex where possible. For the meta-analysis, effect sizes (ES) and their 95% confidence intervals (95% CIs) will be calculated for each study using Cohen’s d index.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

None

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

The procedures will be divided in steps:
First step: Title and abstract screening

Firstly, two independent reviewers will screen the titles for potential inclusion. Then, both reviewers will continue with the abstracts of the selected articles. In case of disagreement, in title and in abstract inclusion, a third reviewer will decide. In cases where a decision for exclusion or potential inclusion cannot be made by the title/abstract, the full text will be retrieved.

Second step: Full-text screening

The two independent reviewers will review the full texts of the previously included articles and will decide the inclusion or exclusion based on the selected criteria (inclusion and exclusion) by the completion of a checklist. A third reviewer will decide on the inclusion or exclusion if there is no consensus between reviewers.

Third step: Data extraction

The extraction will include bibliographic information (authors and year of publication); study design characteristics; participant's characteristics (region, age, % female, medication), Mediterranean diet intervention characteristics (dietary components, duration, type), depression outcomes (measures), and main findings. One reviewer will extract the information from the selected studies and another reviewer will check it out. In case of discrepancies, a third reviewer will act to solve the disagreements.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

The included studies will be assessed for methodological quality as their full published versions independently by two researchers. In case of discrepancies, a third reviewer will act to solve the disagreements. The tool to evaluate the risk of bias will be the Cochrane Collaboration's tool for assessing risk of bias (Sterne et al., 2019, BMJ).

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If metaanalysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

The potential for conducting a meta-analysis will be assessed based on the data which has been extracted. Stata 15 software will be used to combine the pooled mean differences with 95% CIs. A a random-effects model will be used. Study heterogeneity will be assessed using the I^2 statistic, categorized as not important (0% - 30%), moderate (30% - 60%), substantial (60% - 75%), or considerable (75 - 100%).

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

If there is available information we will divide the information by sex, age groups, type of depressive disorder, duration of intervention, type of control condition and measures of depressive symptoms.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
Yes

Living systematic review
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

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National Institute for Health Research

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
Yes

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
Yes

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine

No

Urological

No

Wounds, injuries and accidents

No

Violence and abuse

No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Chile

Spain

Uruguay

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Refer nce and/or URL for published protocol. [1 change]

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Bizzozero-Peroni, B.; Godoy-Cumillaf, A.; Fernández-Rodríguez, R.; Rodríguez-Gutiérrez, E.; Jiménez-

López, E.; Giakoni-Ramírez, F.; Duclos-Bastías, D.; Mesas, A.E. Mediterranean Diet Interventions for

Depressive Symptoms in Adults with Depressive Disorders: A Protocol for a Systematic Review and Meta-

Analysis. Int. J. Environ. Res. Public Health 2022, 19, 14437. https://doi.org/10.3390/ijerph192114437

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

No

Give brief details of plans for communicating review findings.?

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Adulthood, healthy diet, Mediterranean foods, depressive disorder

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.
[1 change]

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review_Completed_not_published

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

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National Institute for
Health Research

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Give the link to the published review or preprint.

APPENDIX III. PROSPERO PROTOCOL MANUSCRIPT VIII

Manuscript VIII: Daily step count and depression in the general adult population: a systematic review and meta-analysis of observational studies.

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National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

A list of fields that can be edited in an update can be found here

1. * Review title.

Give the title of the review in English

Physical activity and depression: a systematic review with meta-analysis

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

03/03/2023

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/07/2023

5. * Stage of review at time of this submission.

[4 changes]

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Bruno Bizzozero Peroni

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Mr Bizzozero Peroni

7. * Named contact email.

Give the electronic email address of the named contact.

bruno.bizzozero@uclm.es

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

C\/ Santa Teresa Jornet, s\/n, 16071, Cuenca, Spain

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+34 969179100

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Health and Social Research Center, Universidad de Castilla-La Mancha, Cuenca, Spain.

Instituto Superior de Educación Física, Universidad de la República, Rivera 40000, Uruguay.

Organisation web address:

https://www.uclm.es/

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Mr Bruno Bizzozero Peroni. Health and Social Research Center, Universidad de Castilla-La Mancha, Cuenca, Spain. Instituto Superior de Educación Física, Universidad de la República, Rivera 40000, Uruguay.
Dr Vicente Martínez Vizcaíno. Health and Social Research Center, Universidad de Castilla-La Mancha, Cuenca, Spain.
Arthur E. Mesas. Health and Social Research Center, Universidad de Castilla-La Mancha, Cuenca, Spain.

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

Universidad de Castilla-La Mancha, Fondo Social Europeo.

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Does the available evidence support a relationship between daily steps and depression throughout adulthood?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

This systematic review will be conducted according to the PRISMA statement (Page et al., 2020, BMJ), the MOOSE recommendations for observational studies (Stroup et al., 2000, JAMA), and the Cochrane Collaboration Handbook (Higgins et al., 2021, Cochrane).

A systematic se rch will be conducted on MEDLINE (PubMed), Scopus, Web of Science, SPORTDiscus, PsycINFO, and Cochrane CENTRAL from database inception up to March, 2023. We will use keywords related to both steps and depression, in addition to terms related to the adult population. These search terms will be combined with Boolean operators adapted for each database.

In addition, the search will be supplemented by additional searches where reference lists of included studies and relevant systematic reviews will be screened for potential relevance. In case of lack of data, experts will be contacted to provide information about other possible data.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

General adult population (over 18 years of age, with or without pathological processes). Daily steps (continuous or categorical) as exposure. Depression as outcome (clinical diagnosis, self-reported diagnosis, depressive symptoms).

19. * Participants/population.

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Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

We will include studies recruiting adults aged 18+ years. Exclusion: adolescents and children (under 18 years of age).

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Daily steps based on objective measures of physical activity (e.g., accelerometer, pedometer).

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

For observational studies, lower levels of daily steps. For intervention studies, control groups as non-active control conditions.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Cross-sectional, prospective cohort, RCTs, non-RCTs, pre-post studies.

To be included, studies must report:

(a) Healthy and unhealthy adult population over 18 years of age;

(b) Daily step count by objective measures (e.g., accelerometers, pedometers);and

(c) Depression outcomes (e.g., clinical diagnosis, depressive symptoms).

Studies will be excluded if they report:

(a) Duplicate data published in another included study;

(b) Mental disorder other than depression;

(c) Walking or ligth-intensity physical activity as exposure or intervention, withouth step count;

(d) Multi-component interventions;

(e) Active control groups;

(f) Specific types of depression (i.e., perinatal or postnatal depression);

(g) Depressed mood and depression data that cannot be isolated and extracted (e.g., bipolar disorders);

(h) Data published as conference/meeting abstracts or in peer-reviewed, refereed, non-predatory journals; or

(i) Qualitative data.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

Studies of the association between daily step count and depression outcomes in the entire adult population over 18 years of age.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Depression outcomes will be defined as changes in depressive symptoms according to validated observer rating scales and self-rating scales. Moreover, incidence depression as clinical diagnosis or self-reported diagnosis will be included as ouctome.

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Once the main characteristics of the included studies have been extracted, we will determine whether a meta-analysis is possible. We consider effect sizes (ES) and their 95% confidence intervals (95% CIs) will be calculated for each study using Cohen's d index. Higher vs lower daily step count (or pre-post changes) will be compared for depression outcomes, and these data will be synthesized narratively, sub-grouped by age, sex, and health status where possible.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

None.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Not applicable.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

The procedures will be divided in steps:

First step: Title and abstract screening

Firstly, two independent reviewers will screen the titles for potential inclusion. Then, both reviewers will continue with the abstracts of the selected articles. In case of disagreement, in title and in abstract inclusion, a third reviewer will decide. In cases where a decision for exclusion or potential inclusion cannot be made by the title/abstract, the full text will be retrieved.

Second step: Full-text screening

The two independent reviewers will evaluate the full texts of the previously included articles and will decide the inclusion or exclusion based on the selected criteria (inclusion and exclusion) by the completion of a checklist. A third reviewer will decide on the inclusion or exclusion if there is no consensus between reviewers.

Third step: Data extraction

The extraction will include bibliographic information (authors and year of publication); study design; participant's characteristics (e.g., site, age, % women, health status), steps assessment (e.g., accelerometer, pedometer), measures of daily step count (continuous or categorical), depression outcomes (clinical diagnosis, self-reported diagnosis, depressive symptoms), and measures of depression (e.g., self-report scales). One reviewer will extract the information from the selected studies and another reviewer check it out. In case of discrepancies, a third reviewer will act to solve the disagreements.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

The included studies will be assessed independently by two researchers. In case of discrepancies, a third reviewer will act to solve the disagreements.

The tools to evaluate the risk of bias will be the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Heart, Lung, and Blood Institute, 2022), the Cochrane Collaboration's tool for assessing risk of bias (RoB2) (Sterne et al., 2019, BMJ), and the the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool (Sterne et al., 2016, BMJ).

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

The potential for conducting a meta-analysis will be assessed based on the data which has been extracted. R software will be used to combine the pooled mean differences with 95% CIs. A random-effects model will be used. Study heterogeneity will be assessed using the I^2 statistic.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

If there is available information we will divide the information by sex, age groups, and health status. In addition, we will consider the risk of bias of the studies, the objective measures used to report daily step counts, and the scales used to assess depressive symptoms.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness

No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Living systematic review
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other

No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics

No

Health inequalities/health equity

No

Infections and infestations

No

International development

No

Mental health and behavioural conditions

Yes

Musculoskeletal

No

Neurological

No

Nursing

No

Obstetrics and gynaecology

No

Oral health

No

Palliative care

No

Perioperative care

No

Physiotherapy

No

Pregnancy and childbirth

No

Public health (including social determinants of health)

No

Rehabilitation

No

Respiratory disorders

No

Service delivery

No

Skin disorders

No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Spain
Uruguay

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Adulthood

Physical activity

Walking

Depressive disorder

Depression symptoms

Mental health

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.
[1 change]

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review_Completed_not_published

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

APPENDIX IV. SUPPLEMENTARY MATERIAL MANUSCRIPT I

Supplementary material: The associations between adherence to the Mediterranean diet and physical fitness in young, middle-aged, and older adults: A protocol for a systematic review and meta-analysis.

The associations between adherence to the Mediterranean diet and physical fitness in young, middle-aged, and older adults: A protocol for a systematic review and meta-analysis

Online Supplemental Material

S1 Table. PRISMA-P 2015 checklist to address the systematic review protocol.

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number inthe Abstract	☒	☐	50
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	5 to 19 and forms submission
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	20 to 23 and forms submission
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Forms submissions
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	NA – no funding
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	NA – no funding
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	54 to 82

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	82 to 85
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	96 to 112
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	114 to 119
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	120 to 125
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	129 and 130
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	130 to 139
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	142 to 144
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	145 to 149
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	154 to 160
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	162 to 165
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	178 and 179

Bizzozero-Peroni et al. The associations between adherence to the Mediterranean diet and physical fitness in young, middle-aged, and older adults: A protocol for a systematic review and meta-analysis — Online Supplemental Material

Section/topic	#	Checklist item	Information reported Yes	Information reported No	Line number(s)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	180 to 186
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	187 to 196
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	176 to 178
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	197 to 198
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	167 to 174

Adapted from Table 3 in Moher et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1.

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S2 Table. Characteristics of the studies to be included in the systematic review and meta-analysis.

Studies				**Participants**			**Intervention/exposure**		**Outcomes**		
Reference	**Country**	**Study Design**	**Sample size**	**Sex**	**Age**	**Adult age group**	**MD Index**	**MD foods**	**CRF**	**MSF**	**MF**
Author information and year of publication	Country	Design of the study	Number of participants for total	Number of participants for sex	Range or means ± SD (years)	Young, middle-aged, or older	MD scoring systems assessed	Specific MD foods analyzed	Fitness component measured	Fitness component measured	Fitness component measured

Abbreviations: ACR: cardiorespiratory fitness; DM: Mediterranean diet; MFA: motor fitness; MMA: musculoskeletal fitness.

APPENDIX V. SUPPLEMENTARY MATERIAL MANUSCRIPT II

Supplementary material: High Adherence to the Mediterranean Diet is Associated with Higher Physical Fitness in Adults: a Systematic Review and Meta-Analysis.

High adherence to the Mediterranean diet is associated with higher physical fitness in adults: a systematic review and meta-analysis

Online Supplementary Material

Bizzozero-Peroni et al. High adherence to the Mediterranean diet is associated with higher physical fitness in adults: a systematic review and meta-analysis — Online Supplementary Material

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Supplementary Table 1. Search strategy detailed information.

Source	Search terms
PubMed	(adult* OR "young adult" OR "middle aged" OR aged OR elderly OR olde*) AND ("Mediterranean index" OR adherence OR "Mediterranean score" OR "Mediterranean diet" OR MedDiet OR "Mediterranean-style diet" OR "Mediterranean eat" OR "Mediterranean food" OR "dietary pattern" OR "diet quality") AND (fitness OR "fitness level" OR "physical fitness" OR "physical performance" OR "functional fitness" OR "physical function" OR "functional capacity" OR "frailty" OR "sarcopenia" OR "muscle strength" OR "muscular power" OR "muscular fitness" OR "muscle endurance" OR "explosive strength" OR flexibility OR "musculoskeletal fitness" balance OR coordination OR agility OR speed OR "motor fitness" OR "aerobic fitness" OR "aerobic capacity" OR "cardiorespiratory fitness" OR "cardiorespiratory endurance" OR "aerobic endurance")
Cochrane CENTRAL, Scopus	(adult* OR "young adult" OR "middle aged" OR aged OR elderly OR olde*) AND ("Mediterranean index" OR "Mediterranean score" OR "Mediterranean diet" OR MedDiet OR "Mediterranean-style diet" OR "Mediterranean eat" OR "Mediterranean food" OR "dietary pattern" OR "diet quality") AND (fitness OR "fitness level" OR "physical fitness" OR "physical performance" OR "functional fitness" OR "physical function" OR "muscle strength" OR "muscular power" OR "muscular fitness" OR "muscle endurance" OR "explosive strength" OR flexibility OR "musculoskeletal fitness" OR balance OR coordination OR agility OR speed OR "motor fitness" OR "aerobic fitness" OR "aerobic capacity" OR "cardiorespiratory fitness" OR "cardiorespiratory endurance" OR "aerobic endurance")
SPORTDiscus	(adult* OR "young adult" OR "middle aged" OR aged OR elderly OR olde*) AND ("Mediterranean index" OR adherence OR "Mediterranean score" OR "Mediterranean diet" OR MedDiet OR "Mediterranean-style diet" OR "Mediterranean eat" OR "Mediterranean food" OR "dietary pattern" OR "diet quality") AND (fitness OR "fitness level" OR "physical fitness" OR "physical performance" OR "functional fitness" OR "physical function" OR "muscle strength" OR "muscular power" OR "muscular fitness" OR "muscle endurance" OR "explosive strength" OR flexibility OR "musculoskeletal fitness" OR balance OR coordination OR agility OR speed OR "motor fitness" OR "aerobic fitness" OR "aerobic capacity" OR "cardiorespiratory fitness" OR "cardiorespiratory endurance" OR "aerobic endurance")

Web of Science	(adult OR "young adult" OR "middle aged" OR aged OR elderly OR older) AND ("Mediterranean dietary pattern" OR "Mediterranean index" OR "Mediterranean adherence" OR "Mediterranean score" OR "Mediterranean questionnaire" OR "Mediterranean screener" OR MedDiet OR "Mediterranean Diet" OR "healthy dietary pattern" OR "diet quality") AND (fitness OR "fitness level" OR "physical fitness" OR "physical performance" OR "muscle strength" OR "muscular power" OR "muscular fitness" OR "muscular endurance" OR "explosive strength" OR "motor fitness" OR "musculoskeletal fitness" OR coordination OR speed OR balance OR flexibility OR agility OR "aerobic fitness" OR "aerobic capacity" OR "cardiorespiratory fitness" OR "cardiorespiratory endurance")

Bizzozero-Peroni et al. High adherence to the Mediterranean diet is associated with higher physical fitness in adults: a systematic review and meta-analysis — Online Supplementary Material

Supplementary Table 2. List of the studies fully assessed for eligibility and excluded.

No Mediterranean diet analysis	
1.	Arias-Fernandez L, Struijk EA, Rodriguez-Artalejo F, Lopez-Garcia E, Lana A. Habitual dietary fat intake and risk of muscle weakness and lower-extremity functional impairment in older adults: A prospective cohort study. *Clin Nutr*. 2020;39(12):3663–70. doi: 10.1016/j.clnu.2020.03.018
2.	Buteau-Poulin D, Poirier P, Despres J-P, Almeras N. Assessing nutritional quality as a “vital sign” of cardiometabolic health. *Br J Nutr*. 2019;122(2):195–205. doi: 10.1017/S0007114519001016
3.	Grace-Farfaglia P. Self-Reported Diet and Health Outcomes of Participants of the CCSVI-Tracking Survey Study. *Nutrients*. 2021;13(6):1891. doi: 10.3390/nu13061891
4.	Granic A, Jagger C, Davies K, Adamson A, Kirkwood T, Hill TR, et al. Effect of Dietary Patterns on Muscle Strength and Physical Performance in the Very Old: Findings from the Newcastle 85+Study. *PLoS One*. 2016;11(3). doi: 10.1371/journal.pone.0149699
5.	Granic A, Mendonca N, Sayer AA, Hill TR, Davies K, Siervo M, et al. Effects of dietary patterns and low protein intake on sarcopenia risk in the very old: The Newcastle 85+study. *Clin Nutr*. 2020;39(1):166–73. doi: 10.1016/j.clnu.2019.01.009
6.	Honório S, Batista M, Paulo R, Mendes P, Serrano J, Petrica J, et al. Functional ftness and nutritional status of institutionalized elderly. *Med dello Sport*. 2017;70(2):200–11. doi: 10.23736/S0025-7826.17.03050-2
7.	Kenzik KM, Morey MC, Cohen HJ, Sloane R, Demark-Wahnefried W. Symptoms, weight loss, and physical function in a lifestyle intervention study of older cancer survivors. *J Geriatr Oncol*. 2015;6(6):424-432. doi: 10.1016/j.jgo.2015.08.004
8.	Mohammadpour S, Ghanbari M, Shahinfar H, Gholami F, Djafarian K, Shab-Bidar S. The association between healthy lifestyle score with cardiorespiratory fitness and muscle strength. *Int J Clin Pract*. 2020;74(12):e13640. doi: 10.1111/IJCP.13640
9.	Pilleron S, Ajana S, Jutand M-A, Helmer C, Dartigues J-F, Samieri C, et al. Dietary Patterns and 12-Year Risk of Frailty: Results From the Three-City Bordeaux Study. *J Am Med Dir Assoc*. 2017;18(2):169–75. doi: 10.1016/j.jamda.2016.09.014
10.	Rempe HM, Calvani R, Marzetti E, Picca A, Sieber CC, Freiberger E, et al. Are Health Behaviors and Self-Rated Health Related to Cardiovascular Health and Functional Performance? Results from the Lookup 7+Cross-Sectional Survey Among Persons Aged 65+. *J Nutr Health Aging*. 2020;24(4):379–87. doi: 10.1007/s12603-020-1342-3

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11. Robinson SM, Jameson KA, Syddall HE, Dennison EM, Cooper C, Aihie Sayer A. Clustering of lifestyle risk factors and poor physical function in older adults: The hertfordshire cohort study. *J Am Geriatr Soc*. 2013;61(10):1684–91. doi: 10.1111/JGS.12457

12. Robinson SM, Westbury LD, Cooper R, Kuh D, Ward K, Syddall HE, et al. Adult Lifetime Diet Quality and Physical Performance in Older Age: Findings From a British Birth Cohort. *Journals Gerontol Ser A*. 2018;73(11):1532–7. doi: 10.1093/gerona/glx179

13. Robinson SM, Westbury LD, Ward K, Syddall H, Cooper R, Cooper C, et al. Is lifestyle change around retirement associated with better physical performance in older age?: insights from a longitudinal cohort. *Eur J Ageing*. 2021;18(4):513–21. doi: 10.1007/S10433-021-00607-9

14. Shahinfar H, Djafari F, Babaei N, Davarzani S, Ebaditabar M, Clark CCT, et al. Cardiorespiratory fitness is positively associated with both healthy and western dietary pattern in Iranian middle-aged. *Int J Vitam Nutr Res*. 2020; doi: 10.1024/0300-9831/A000685

15. Shahinfar H, Ghanbari M, Jalilpiran Y, Payande N, Shahavandi M, Babaei N, et al. Interaction between major dietary patterns and cardiorespiratory fitness on metabolic syndrome in Iranian adults: a cross-sectional study. *Nutr J*. 2021;20(1). doi: 10.1186/s12937-021-00695-4

16. Shahinfar H, Safabakhsh M, Babaei N, Ebaditabar M, Davarzani S, Amini MR, et al. Association of major dietary patterns with muscle strength and muscle mass index in middle-aged men and women: Results from a cross-sectional study. *Clin Nutr ESPEN*. 2020;39:215–21. doi: 10.1016/j.clnesp.2020.06.010

17. Shikany JM, Jacobs DR, Lewis CE, Steffen LM, Sternfeld B, Carnethon MR, et al. Associations between food groups, dietary patterns, and cardiorespiratory fitness in the coronary artery risk development in young adults study 1-3. *Am J Clin Nutr*. 2013;98(6):1402–9. doi: 10.3945/AJCN.113.058826

18. Zhang X, Gu Y, Cheng J, Meng G, Zhang Q, Liu L, et al. The relationship between dietary patterns and grip strength in the general population: the TCLSIH cohort study. *Eur J Nutr*. 2020;5:2409–21. doi: 10.1007/s00394-020-02385-z

No analysis of the association between Mediterranean diet adherence and physical fitness

1. Alvarez-Bustos A, de Pedro CG, Romero-Elias M, Ramos J, Osorio P, Cantos B, et al. Prevalence and correlates of cancer-related fatigue in breast cancer survivors. *Support*

Care Cancer. 2021;29(11):6523–34. doi: 10.1007/s00520-021-06218-5

2. Arias-Fernandez L, Machado-Fragua MD, Graciani A, Guallar-Castillon P, Banegas JR, Rodriguez-Artalejo F, et al. Prospective Association Between Nut Consumption and Physical Function in Older Men and Women. *Journals Gerontol Ser A*. 2019;74(7):1091–7. doi: 10.1093/gerona/gly171

3. Bantle AE, Chow LS, Steffen LM, Wang Q, Hughes J, Durant NH, et al. Association of Mediterranean diet and cardiorespiratory fitness with the development of pre-diabetes and diabetes: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *BMJ Open Diabetes Res Care*. 2016;4(1). doi: 10.1136/bmjdrc-2016-000229

4. Buglio AL, Bellanti F, Capurso C, Paglia A, Vendemiale G. Adherence to mediterranean diet, malnutrition, length of stay and mortality in elderly patients hospitalized in internal medicine wards. *Nutrients*. 2019;11(4). doi: 10.3390/nu11040790

5. Delgado M, Gutierrez A, Cano MD, Castillo MJ. Elimination of meat, fish, and derived products from the Spanish-Mediterranean diet: Effect on the plasma lipid profile. *Ann Nutr Metab*. 1996;40(4):202–11. doi: 10.1159/000177915

6. Demark-Wahnefried W, Morey MC, Sloane R, Snyder DC, Miller PE, Hartman TJ, et al. Reach out to enhance wellness home-based diet-exercise intervention promotes reproducible and sustainable long-term improvements in health behaviors, body weight, and physical functioning in older, overweight/obese cancer survivors. *J Clin Oncol*. 2012;30(19):2354-2361. doi: 10.1200/JCO.2011.40.0895

7. Demark-Wahnefried W, Clipp EC, Morey MC, Pieper CF, Sloane R, Clutter Snyder D, et al. Lifestyle intervention development study to improve physical function in older adults with cancer: Outcomes from Project LEAD. *J Clin Oncol*. 2006;24(21):3465–73. doi: 10.1200/JCO.2006.05.7224

8. Fares JE-H, Al-Hayek S, Jaafar J, Djabrayan N, Farhat AG. Factors affecting body composition of Lebanese university students. *Nutr Food Sci*. 2018;48(2):228–44. doi: 10.1108/NFS-08-2017-0172

9. Jeong EH, Kim E, Hong CH, Moon SY, Park HK, Jeong JH, et al. Practicability of Six Weeks of Korean-Style Mediterranean Diet for Elderly Koreans with High Risk for Dementia. *J Korean Diet Assoc*. 2019;25(4):237–56. doi: 10.14373/JKDA.2019.25.4.237

10. Marcos-Forniol E, Meco JF, Corbella E, Formiga F, Pinto X. Secondary prevention programme of ischaemic heart disease in the elderly: A randomised clinical trial. *Eur J Prev Cardiol*. 2018;25(3):278–86. doi: 10.1177/2047487317742998

11. Maroto-Rodriguez J, Delgado-Velandia M, Ortolá R, García-Esquinas E, Martinez-Gomez D, Struijk EA, et al. A Mediterranean lifestyle and frailty incidence in older adults: the Seniors-ENRICA-1 cohort. *Journals Gerontol Ser A*. 2021; doi: 10.1093/GERONA/GLAB292

12. Mertens E, Clarys P, Mullie P, Lefevre J, Charlier R, Knaeps S, et al. Stability of physical activity, fitness components and diet quality indices. *Eur J Clin Nutr*. 2017;71(4):519–24. doi: 10.1038/EJCN.2016.172

13. Moral-Garcia J, Al Nayf Mantas M, Lopez-Garcia S, Maneiro R, Amatria M. Nutritional status and physical condition in active vs. sedentary elderly perople. *Rev Int Med y Ciencias la Act Física y del Deport*. 2019;19(76):685–98. doi: 10.15366/rimcafd2019.76.003

14. O'Connell ML, Coppinger T, Lacey S, Walton J, Arsenic T, McCarthy AL. Associations between Food Group Intake and Physical Frailty in Irish Community-Dwelling Older Adults. *Nutr Metab Insights*. 2021;14. doi: 10.1177/11786388211006447

15. Ramirez-Velez R, Enrique Correa-Bautista J, Liliana Ojeda-Pardo M, Sandoval-Cuellar C, Garcia-Hermoso A, Alejandro Carrillo H, et al. Optimal Adherence to a Mediterranean Diet and High Muscular Fitness Are Associated with a Healthier Cardiometabolic Profile in Collegiate Students. *Nutrients*. 2018;10(4). doi: 10.3390/nu10040511

16. Rebollo-Ramos M, Velázquez-Díaz D, Corral-Pérez J, Barany-Ruiz A, Pérez-Bey A, Fernández-Ponce C, et al. Aerobic fitness, Mediterranean diet and cardiometabolic risk factors in adults. *Endocrinol Diabetes y Nutr*. 2020;67(2):113–21. doi: 10.1016/J.ENDINU.2019.04.004

17. Rizka A, Indrarespati A, Dwimartutie N, Muhadi M. Frailty among older adults living in nursing homes in indonesia: Prevalence and associated factors. *Ann Geriatr Med Res*. 2021;25(2):93–7. doi: 10.4235/AGMR.21.0033

18. Santi-Cano MJ, Pedro Novalbos-Ruiz J, Angeles Bernal-Jimenez M, del Mar Bibiloni M, Tur JA, Rodriguez Martin A, et al. Association of Adherence to Specific Mediterranean Diet Components and Cardiorespiratory Fitness in Young Adults. *Nutrients*. 2020;12(3). doi: 10.3390/nu12030776

No physical fitness analysis

1. Alaghehband FR, Erkkilä AT, Rikkonen T, Sirola J, Kröger H, Isanejad M, et al. Association of Baltic Sea and Mediterranean diets with frailty phenotype in older women, Kuopio OSTPRE-FPS study. *Eur J Nutr*. 2021;60(2):821–31. doi: 10.1007/s00394-020-

02290-5

2. Buglio AL, Bellanti F, Capurso C, Paglia A, Vendemiale G. Adherence to Mediterranean diet, malnutrition, length of stay and mortality in elderly patients hospitalized in internal medicine wards. *Nutrients*. 2019;11(4). doi: 10.3390/nu11040790

3. Chan R, Leung J, Woo J. A Prospective Cohort Study to Examine the Association Between Dietary Patterns and Sarcopenia in Chinese Community-Dwelling Older People in Hong Kong. J Am Med Dir Assoc. 2016;17(4):336–42. doi: 10.1016/j.jamda.2015.12.004

4. Iturriaga T, Barcelo O, Diez-Vega I, Cordero J, Pulgar S, Fernandez-Luna A, et al. Effects of a short workplace exercise program on body composition in women: A randomized controlled trial. *Heal Care Women Int*. 2020;41(2):133–46. doi: 10.1080/07399332.2019.1679813

5. León-Muñoz LM, Guallar-Castillón P, López-García E, Rodríguez-Artalejo F, Leon-Munoz LM, Guallar-Castillon P, et al. Mediterranean Diet and Risk of Frailty in Community-Dwelling Older Adults. *J Am Med Dir Assoc*. 2014;15(12):899–903. doi: 10.1016/j.jamda.2014.06.013

6. Ortola R, Garcia-Esquinas E, Galan I, Guallar-Castillon P, Lopez-Garcia E, Banegas JR, et al. Patterns of alcohol consumption and risk of falls in older adults: a prospective cohort study. *Osteoporos Int*. 2017;28(11):3143–52. doi: 10.1007/s00198-017-4157-2

7. Parsons TJ, Papachristou E, Atkins JL, Papacosta O, Ash S, Lennon LT, et al. Physical frailty in older men: Prospective associations with diet quality and patterns. *Age Ageing*. 2019;48(3):355–60. doi: 10.1093/AGEING/AFY216

Qualitative data

1. Lopez-Garcia E, Hagan KA, Fung TT, Hu FB, Rodríguez-Artalejo F. Mediterranean diet and risk of frailty syndrome among women with type 2 diabetes. *Am J Clin Nutr*. 2018;107(5):763–71. doi: 10.1093/AJCN/NQY026

2. Porciello G, Montagnese C, Crispo A, Grimaldi M, Libra M, Vitale S, et al. Mediterranean diet and quality of life in women treated for breast cancer: a baseline analysis of DEDiCa multicentre trial. *PLoS One*. 2020;15(10). doi: 10.1371/journal.pone.0239803

3. Rahi B, Ajana S, Tabue-Teguo M, Dartigues J-F, Peres K, Feart C. High adherence to a Mediterranean diet and lower risk of frailty among French older adults community-dwellers: Results from the Three-City-Bordeaux Study. *Clin Nutr*. 2017;37(4):1293–8. doi: 10.1016/j.clnu.2017.05.020

4. Sköldstam L, Hagfors L, Johansson G. An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. *Ann Rheum Dis*. 2003;62(3):208-214. doi: 10.1136/ard.62.3.208

5. Stefler D, Hu Y, Malyutina S, Pajak A, Kubinova R, Peasey A, et al. Mediterranean diet and physical functioning trajectories in Eastern Europe: Findings from the HAPIEE study. *PLoS One*. 2018;13(7). doi: 10.1371/journal.pone.0200460

6. Struijk EA, Guallar-Castillón P, Rodríguez-Artalejo F, López-García E. Mediterranean Dietary Patterns and Impaired Physical Function in Older Adults. *Journals Gerontol Ser A*. 2018;73(3):333–9. doi: 10.1093/GERONA/GLW208

7. Struijk EA, Hagan KA, Fung TT, Hu FB, Rodríguez-Artalejo F, Lopez-Garcia E. Diet quality and risk of frailty among older women in the Nurses' Health Study. *Am J Clin Nutr*. 2020;111(4):877–83. doi: 10.1093/AJCN/NQAA028

Supplementary Table 3. List of models, effect sizes and covariates used in the meta-analyses of the included studies.

Reference	Method	Effect size	Adjustment
Barrea et al. (2019) (67)	Bivariate correlation	r (*p*-value)	BMI
Bibiloni et al. (2017) (46)	Analysis of covariance	Mean (95% CI)	Age
Bollwein et al. (2013) (45)	Logistic regression	OR (95% CI)	Age, sex, energy intake, comorbidity, and educational level
Buchanan and Villani. (2021) (44)	Logistic regression	β (95% CI)	Age, gender, appendicular lean mass index, BMI, fat mass, percent body fat, and physical function measures
Cobo-Cuenca et al. (2019) (43)	Analysis of covariance	Mean (SD)	Age, sex, smoking habits, alcohol habits, and type of housing
Cuenca-García et al. (2014) (42)	Analysis of covariance	Mean (SE)	Age, sex, and examination year
Fougère et al. (2016) (41)	Logistic regression	β (SE)	Age, sex, BMI, Cumulative Illness Rating Scale, current smoking, depression, education, functional disability, Mini Mental State Examination score
Huang et al. (2020) (62)	GEE	B (95% CI)	Age, sex, BMI, educational level, economic status, Charlson Comorbidity Index, Baecke Physical Activity Questionnaire, Mini-Nutritional Assessment, total daily energy, and daily protein intake
Isanejad et al. (2018) (61)	Analysis of covariance	Mean (SD)	Age, energy intake, smoking, total physical activity, hormone therapy, osteoporosis, rheumatoid arthritis, coronary heart disease, income per month, and fat mass percentage

Jin et al. (2017) (60)	GEE	OR (95% CI)	Age, years of education, impaired cognition, depressed mood, and presence of chronic disease
Kelaiditi et al. (2016) (40)	Analysis of covariance	Mean (SE)	Age, physical activity, smoking status, energy intake, misreporting, menopausal status, use of hormone replacement therapy, protein intake, and height
Kim and Kwon. (2019) (56)	Logistic regression	OR (95% CI)	Age, BMI, education, smoking, alcohol drinking, number of physician-diagnosed chronic conditions, energy intake, physical activity, and age at menarche
Marcos-Pardo et al. (2020) (48)	Bivariate correlation	r (*p*-value)	-
Marcos-Pardo et al. (2021) (55)	Logistic regression	OR (*p*-value)	Age and sex
Martin-Espinosa et al. (2020) (54)	Bivariate correlation	r (*p*-value)	-
McClure and Villani. (2019) (53)	Logistic regression	β (95% CI)	Age, physical activity, and time since type 2 diabetes mellitus diagnosis
Milaneschi et al. (2011) (59)	Analysis of variance	Mean (SD)	-
	GEE	β (SE)	Age, sex, energy intake, BMI, Mini Mental State Examination score, physical activity, functional disability, depressed mood, and number of chronic diseases
Mohseni et al. (2017) (52)	Logistic regression	OR (95% CI)	Age, BMI, menopause duration, physical activity, hypothyroidism, hormone replacement therapy, angiotensin converting enzyme inhibitor use, statin use, and vitamin D use

Payandeh et al. (2021) (51)	Analysis of covariance	Mean (SD)	Age, sex, BMI, smoking, marital status, physical activity, and energy intake
Saadeh et al. (2021) (58)	LMM	β (95% CI)	Age, sex, education level, civil status, number chronic diseases at baseline, dietary supplements, and death/dropouts
Shahar et al. (2012) (66)	Analysis of variance	Mean (SD)	-
Stanton et al. (2019) (49)	Logistic regression	OR (95% CI)	Age, sex, education level, civil status, number chronic diseases at baseline, dietary supplements, death/dropouts, physical activity, and social support
Talegawkar et al. (2012) (57)	Logistic regression	OR (95% CI)	Age, sex, energy intake, status of frailty at previous examinations, BMI, education, Mini Mental State Examination score, current smoker, and presence of chronic diseases
Tepper et al. (2018) (39)	Analysis of variance GLM	Mean (SD) B (SE)	- Age, sex, BMI, and physical activity score
Zbeida et al. (2014) (38)	Analysis of variance Logistic regression	Mean (SD) OR (95% CI)	- Age, sex, BMI, education, physical activity, number of chronic diseases, and cognitive function

β, standardized beta coefficient; B, unstandardized beta coefficient; GEE, generalized estimating equations; GLM, generalized linear model; LMM, linear mixed models.

Supplementary Methods: Risk of bias appendix

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (24) was used to evaluate the risk of bias in observational studies. This tool evaluates 14 items for prospective cohort studies and 11 items for cross-sectional studies (24). Each criterion could be scored as “yes” when the study achieves the criterion, “no” when the study does not achieve the criterion, and “not reported” when the studies do not clearly report the required information (24). Following this risk of bias tool, studies could be rated good (i.e., at least 11 criteria for prospective cohort studies and 8 criteria for cross-sectional studies were met), fair (i.e., from 6–10 criteria for prospective cohort studies and 4–7 criteria for cross-sectional studies were met), or poor (i.e., from 1–5 criteria for prospective cohort studies and 1–3 criteria for cross-sectional studies were met) (24).

The Cochrane risk-of-bias tool for crossover trials (25) was used to evaluate the risk of bias of the included crossover randomized controlled trial (RCT). The following domains were assessed: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results (25). Each of the five domains was graded as “low risk of bias”, “some concerns”, or “high risk of bias” (25). Finally, the overall risk of bias for each RCT was classified as “low risk of bias” when a low risk of bias was determined for all domains; “some concerns” when at least one domain was evaluated as raising some concerns, but no single domain was assessed as having a high risk of bias; or “high risk of bias” when a high risk of bias was identified for at least one domain or when there were some concerns for multiple domains (25).

Supplementary Table 4. Risk of bias of cross-sectional and prospective cohort studies. [1]

Reference	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Score	Quality
Cross-Sectional																
Barrea et al. (2018) (47)	Y	Y	Y	Y	Y	NA	NA	Y	Y	N	Y	N	NA	N	8	Good
Bibiloni et al. (2017) (46)	Y	Y	NR	Y	N	NA	NA	Y	N	N	N	NR	NA	N	5	Fair
Bollwein et al. (2013) (45)	Y	Y	Y	Y	N	NA	NA	Y	Y	N	N	NR	NA	Y	8	Good
Buchanan and Villani. (2021) (44)	Y	Y	NR	Y	N	NA	NA	N	Y	N	N	NR	NA	Y	5	Fair
Cobo-Cuenca et al. (2019) (43)	Y	Y	Y	Y	Y	NA	NA	Y	Y	N	Y	NR	NA	N	8	Good
Cuenca-García et al. (2014) (42)	Y	Y	Y	Y	N	NA	NA	Y	Y	N	Y	NR	NA	Y	8	Good
Fougère et al. (2016) (41)	Y	Y	N	Y	Y	NA	NA	N	Y	N	N	NR	NA	Y	6	Fair
Kelaiditi et al. (2016) (40)	Y	Y	Y	Y	N	NA	NA	Y	Y	N	Y	NR	NA	Y	8	Good
Kim and Kwon. (2019) (56)	Y	Y	Y	Y	N	NA	NA	Y	Y	N	Y	NR	NA	Y	8	Good
Marcos-Pardo et al. (2020) (48)	Y	Y	NR	Y	Y	NA	NA	N	Y	N	Y	N	NA	N	6	Fair
Marcos-Pardo et al. (2021) (55)	Y	Y	Y	Y	Y	NA	NA	Y	Y	N	N	N	NA	N	7	Fair
Martin-Espinosa et al. (2020) (54)	Y	Y	Y	Y	Y	NA	NA	N	Y	N	Y	NR	NA	N	7	Fair
McClure and Villani. (2019) (53)	Y	Y	NR	Y	Y	NA	NA	N	Y	N	N	N	NA	N	5	Fair
Mohseni et al. (2017) (52)	Y	Y	NR	Y	N	NA	NA	Y	N	N	N	NR	NA	Y	5	Fair
Payandeh et al. (2021) (51)	Y	Y	NR	Y	N	NA	NA	N	Y	N	Y	NR	NA	Y	6	Fair

Ryu et al. (2021) (50)	Y	Y	Y	Y	N	NA	NA	N	Y	N	Y	NR	NA	N	6	Fair
Stanton et al. (2019) (49)	Y	Y	Y	Y	Y	NA	NA	Y	Y	N	N	NR	NA	N	7	Fair
Tepper et al. (2018) (39)	Y	Y	NR	Y	Y	NA	NA	Y	Y	N	Y	NR	NA	Y	8	Good
Zbeida et al. (2014) (38)	Y	Y	N	Y	Y	NA	NA	Y	Y	N	N	NR	NA	Y	7	Fair
Prospective cohort																
Cervo et al. (2021) (65)	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	NR	N	Y	9	Fair
Chan et al. (2019) (64)	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	NR	N	Y	9	Fair
Gallucci et al. (2019) (63)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	NR	N	N	9	Fair
Huang et al. (2020) (62)	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	NR	N	Y	9	Fair
Isanejad et al. (2018) (61)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	NR	N	Y	11	Good
Jin et al. (2017) (60)	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	NR	N	Y	9	Fair
Milaneschi et al. (2011) (59)	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	NR	N	Y	9	Fair
Saadeh et al. (2021) (58)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	NR	N	Y	10	Fair
Shahar et al. (2012) (66)	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	NR	N	Y	9	Fair
Talegawkar et al. (2012) (57)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	NR	Y	Y	11	Good

[1] Numbers represent the questions included in the ¨The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies¨.
N, no; NA, not applied; NR, not reported; Y, yes.

Supplementary Table 5. Associations between Mediterranean diet adherence and physical fitness in adults of all ages from studies included only in the systematic review. [1]

Reference	Effect Size	CRF	MF	MSF
Prospective cohort [2]				
Cervo et al. (2021) (65)	β (95% CI)	.	▲►	▼►
Chan et al. (2019) (64)	β (SE)	▲►	-	-
Gallucci et al. (2019) (63)	SCM	-	▲	▲
RCT [3]				
Baker et al. (2019) (67)	Means (SE)	▲	-	◄►

[1] Upward arrow ▲ = positive significant associations between higher MD scores and higher physical fitness levels; upward and sideway arrows ▲► = positive nonsignificant associations; downward and sideway arrows ▼► = negative nonsignificant associations; sideways arrow ◄► = mixed associations. [2] Participants of the studies included were only older adults. [3] Participants of the studies included were young, middle-aged, and older adults.
β, standardized beta coefficient; CRF, cardiorespiratory fitness; MF, motor fitness; MSF, musculoskeletal fitness; RCT, randomized controlled trial; SCM, semantic connectivity map.

Supplementary Table 6. Subgroup analysis of the association between Mediterranean diet adherence and physical fitness in adults of all ages by geographical location. [1]

	CRF			MF [3]			MSF [4]			PF		
	n	**OR (95% CI)**	**I^2 (%)**	**n**	**OR (95% CI)**	**I^2 (%)**	**n**	**OR (95% CI)**	**I^2 (%)**	**n**	**OR (95% CI)**	**I^2 (%)**
Cross-sectional data [2]												
Med region	2	**1.96 (1.19, 2.72)**	0.0	4	**1.41 (1.03, 1.79)**	0.0	5	**1.32 (1.00, 1.64)**	56.4	7	**1.47 (1.29, 1.66)**	0.0
Non-Med region	2	**2.21 (1.78, 2.65)**	26.2	5	1.36 (0.75, 1.97)	70.7 *	7	**1.33 (1.04, 1.62)**	56.9 *	9	**1.63 (1.17, 2.09)**	92.6 *
Prospective cohort data [3]												
Med region		NA		3	**1.70 (1.21, 2.20)**	0.0		NA		3	**1.58 (1.16, 2.00)**	0.0
Non-Med region				4	1.05 (0.91, 1.19)	0.0				4	1.09 (0.96, 1.23)	0.0

[1] Studies that included adult populations from Mediterranean and non-Mediterranean regions and that did not report results stratified by geographic location were not included in the subgroup analysis. Bold font indicates statistical significative effects size. I^2 informed heterogeneity (*statistically significant at $p < 0.05$). n represents number of studies included in the subgroup analysis.
[2] Participants of the studies included were young, middle-aged, and older adults. [3] Participants of the studies included were only older adults. [4] One study analyzed data from two different samples.
CRF, cardiorespiratory fitness; Med, Mediterranean; MF, motor fitness; MSF, musculoskeletal fitness; NA, not applicable; PF, overall physical fitness.

Supplementary Table 7. Meta-regressions of high Mediterranean diet adherence and physical fitness in adults of all ages by mean of age, BMI and total energy intake, and percentage of women, one or more chronic diseases and current smokers. [1]

	Women			Age			BMI			Diseases			Smoker			TEI		
	n	**ß**	***p***	**n**	**ß**	***p***	**n**	**ß**	***p***	**n**	**ß**	***p***	**n**	**ß**	***p***	**n**	**ß**	***p***
CRF [2]																		
Cross-sectional data	4	-0.128	0.288	4	0.023	0.284	3	0.242	0.399	4	0.008	0.165	3	-0.212	0.346	3	-0.001	0.371
MF [3]																		
Cross-sectional data	10	0.019	0.416		NA		9	-0.065	0.148	8	-0.005	0.303	5	-0.020	0.516	4	0.001	0.725
Prospective cohort data	7	0.024	0.465		NA		6	0.102	0.383	5	0.006	0.486	5	0.119	0.084	6	0.001	0.726
MSF																		
Cross-sectional data [2,4]	13	0.001	0.899	13	0.002	0.804	12	-0.028	0.517	9	0.002	0.699	8	-0.044	0.093	7	-0.001	0.774
Prospective cohort data [3]	4	0.003	0.790		NA		3	0.069	0.636	3	0.005	0.690		NR		3	-0.001	0.953
PF																		
Cross-sectional data [2,4]	17	-0.007	0.230	17	-0.002	0.799	16	-0.056	0.282	12	-0.001	0.907	12	-0.004	0.899	10	0.001	0.865
Prospective cohort data [3]	7	0.009	0.561		NA		6	0.070	0.357	5	0.006	0.338	5	0.076	0.132	6	0.001	0.838

[1] n represents number of studies included in each meta-regression analysis. [2] Participants of the studies included were young, middle-aged, and older adults. [3] Participants of the studies included were only older adults.
[4] One study analyzed data from two different samples.
CRF, cardiorespiratory fitness; MF, motor fitness; MSF, musculoskeletal fitness; NA, not applicable; NR, not reported; PF, overall physical fitness; TEI, total energy intake.

Supplementary Table 8. Sensitivity analysis by removing studies one by one from the pooled cross-sectional analysis in adults of all ages. [1]

Cardiorespiratory fitness [2]			
Reference removed	**OR**	***LL***	***UL***
All studies	2.26	2.06	2.47
Bibiloni et al. (2017) (46)	2.13	1.72	2.54
Cobo-Cuenca et al. (2019) (43)	2.29	2.08	2.50
Cuenca-García et al. (2014) (42)	1.87	1.26	2.47
Payandeh et al. (2021) (51)	2.29	2.08	2.50
Motor fitness [3]			
Reference removed	**OR**	***LL***	***UL***
All studies	1.27	0.96	1.58
Bibiloni et al. (2017) (46)	1.24	0.93	1.54
Bollwein et al. (2013) (45)	1.26	0.95	1.57
Fougère et al. (2016) (41)	1.25	0.95	1.56
Isanjejad et al. (2017) (61)	1.24	0.94	1.54
Marcos-Pardo et al. (2021) (55)	1.38	1.00	1.76
Milaneschi et al. (2011) (59)	1.27	0.93	1.61
Mohseni et al. (2017) (52)	1.26	0.96	1.57
Shahar et al. (2012) (66)	1.15	0.86	1.44
Stanton et al. (2019) (49)	1.37	1.08	1.66
Zbeida et al. (2014) (38)	1.28	0.91	1.65
Musculoskeletal fitness [2]			
Reference removed	**OR**	***LL***	***UL***
All studies	1.26	1.05	1.47
Bibiloni et al. (2017) (46)	1.31	1.08	1.53
Bollwein et al. (2013) (45)	1.25	1.04	1.47
Cobo-Cuenca et al. (2019 (43)	1.26	1.03	1.49
Isanjejad et al. (2017) (61)	1.26	1.04	1.47
Kelaiditi et al. (2016) (40)	1.23	1.01	1.46
Kelaiditi et al. (2016b) (40)	1.31	1.08	1.54
Kim and Kwon. (2019) (56)	1.21	1.01	1.42
Marcos-Pardo et al. (2021) (55)	1.31	1.12	1.52
Milaneschi et al. (2011) (59)	1.21	1.01	1.43
Mohseni et al. (2017) (52)	1.24	1.04	1.45

Stanton et al. (2019) (49)	1.30	1.05	1.54
Tepper et al. (2018) (39)	1.26	1.04	1.47
Zbeida et al. (2014) (38)	1.24	1.01	1.47
	Overall Physical Fitness [2]		
Reference removed	**OR**	***LL***	***UL***
All studies	1.44	1.20	1.68
Bibiloni et al. (2017) (46)	1.52	1.21	1.83
Bollwein et al. (2013) (45)	1.51	1.20	1.81
Cobo-Cuenca et al. (2019) (43)	1.54	1.22	1.86
Cuenca-García et al. (2014) (42)	1.36	1.16	1.56
Isanjejad et al. (2017) (61)	1.51	1.21	1.82
Kelaiditi et al. (2016) (40)	1.54	1.21	1.87
Kelaiditi et al. (2016b) (40)	1.58	1.26	1.90
Kim and Kwon. (2019) (56)	1.50	1.19	1.81
Marcos-Pardo et al. (2021) (55)	1.59	1.28	1.90
Milaneschi et al. (2011) (59)	1.52	1.20	1.84
Mohseni et al. (2017) (52)	1.50	1.20	1.80
Shahar et al. (2012) (66)	1.53	1.20	1.85
Stanton et al. (2019) (49)	1.58	1.26	1.89
Tepper et al. (2018) (39)	1.52	1.22	1.83
Zbeida et al. (2014) (38)	1.54	1.21	1.87

[1] The ORs and 95% CI represents the pooled estimations after excluding from the analysis the corresponding reference. [2] Participants of the studies included were young, middle-aged, and older adults. [3] Participants of the studies included were only older adults.

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Supplementary Table 9. Sensitivity analysis by removing studies one by one from the pooled prospective analysis in older adults. [1]

	Motor fitness		
Reference removed	**OR**	***LL***	***UL***
All studies	1.17	0.95	1.38
Huang et al. (2020) (62)	1.21	0.94	1.49
Isanjejad et al. (2017) (61)	1.15	0.95	1.35
Jin et al. (2017) (60)	1.09	0.91	1.27
Milaneschi et al. (2011) (59)	1.15	0.94	1.36
Saadeh et al. (2021) (58)	1.30	0.97	1.63
Shahar et al. (2012) (66)	1.29	0.94	1.65
Talegawkar et al. (2012) (57)	1.13	0.93	1.32
	Musculoskeletal fitness		
Reference removed	**ES**	***LL***	***UL***
All studies	1.20	1.01	1.38
Huang et al. (2020) (62)	1.24	1.03	1.45
Isanjejad et al. (2017) (61)	1.19	1.00	1.38
Saadeh et al. (2021) (58)	1.11	0.79	1.43
Talegawkar et al. (2012) (57)	1.20	1.00	1.39
	Overall Physical Fitness		
Reference removed	**ES**	***LL***	***UL***
All studies	1.14	1.02	1.26
Huang et al. (2020) (62)	1.18	1.01	1.35
Isanjejad et al. (2017) (61)	1.14	1.00	1.29
Jin et al. (2017) (60)	1.11	0.98	1.25
Milaneschi et al. (2011) (59)	1.14	1.00	1.27
Saadeh et al. (2021) (58)	1.18	0.98	1.39
Shahar et al. (2012) (66)	1.19	1.01	1.37
Talegawkar et al. (2012) (57)	1.13	0.99	1.26

[1] The ORs and 95% CI represents the pooled estimations after excluding from the analysis the corresponding reference. Participants of the studies included were only older adults.

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Supplementary Table 10. Meta-bias for the association between high Mediterranean diet adherence and physical fitness.

	Coefficient	***p***
Cross-sectional		
Motor fitness	1.444	0.008
Musculoskeletal fitness	1.373	0.127
Overall physical fitness	1.182	0.328

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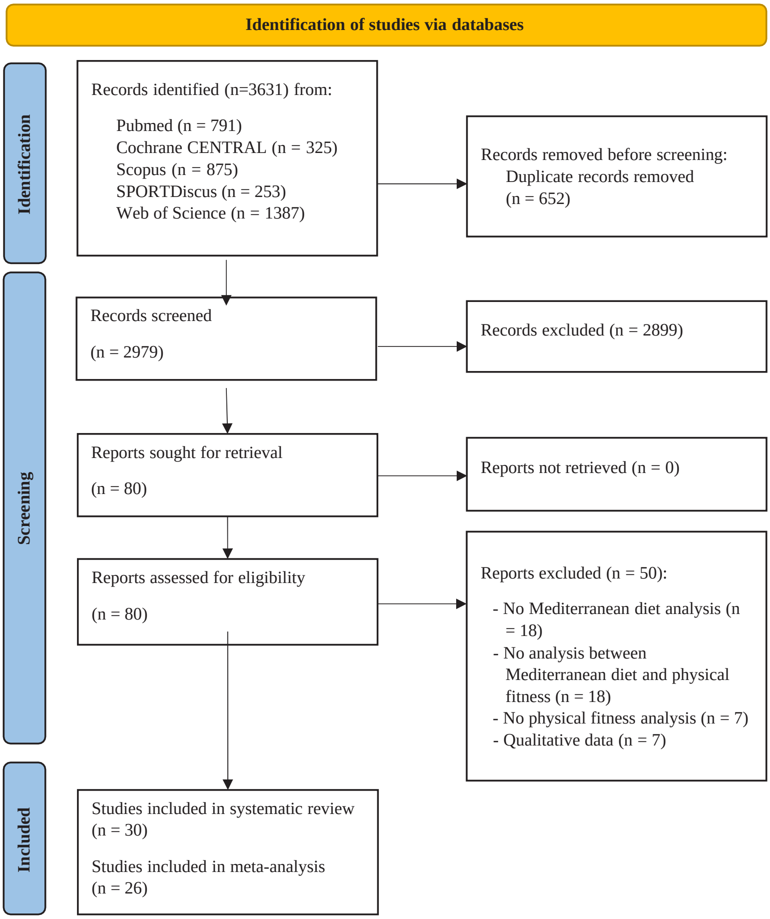

Supplementary Figure 1. PRISMA flow diagram for identifying, screening, and determining the eligibility and inclusion of studies.

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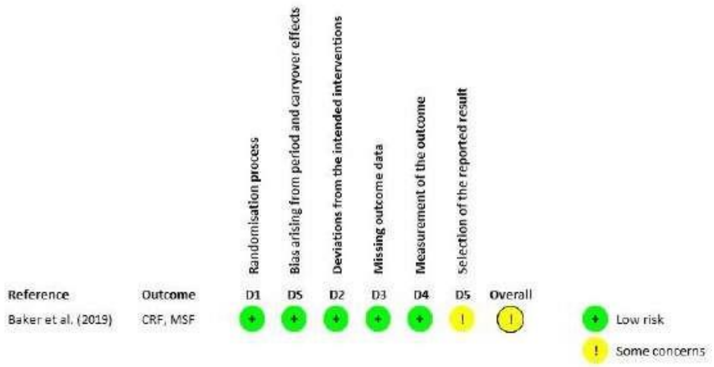

Supplementary Figure 2. Quality assessment using the Cochrane Collaboration's tool for assessing risk of bias in randomized controlled trials.

CRF, cardiorespiratory fitness; MD, Mediterranean diet; MSF, musculoskeletal fitness.

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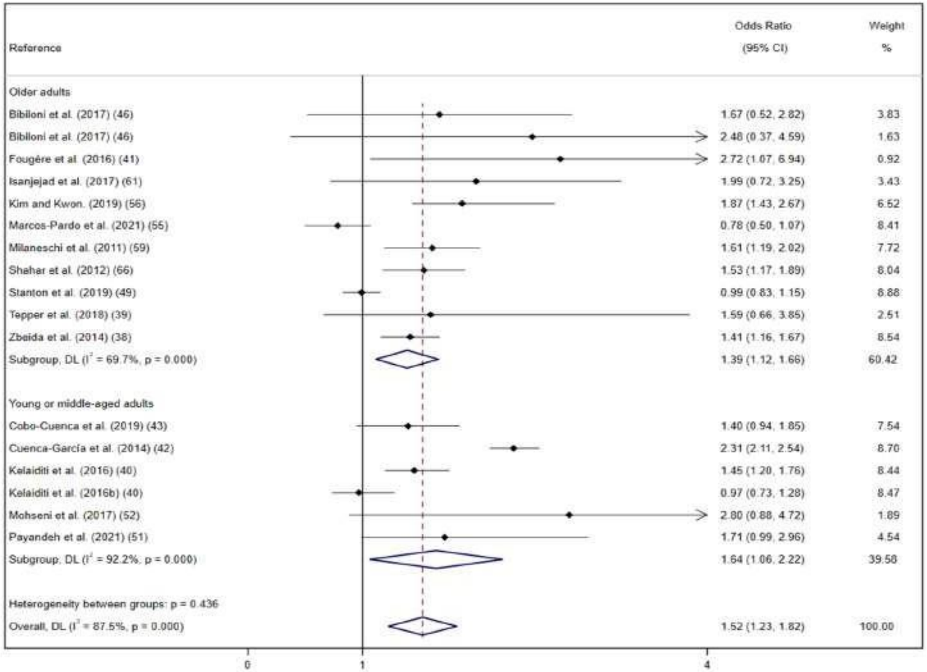
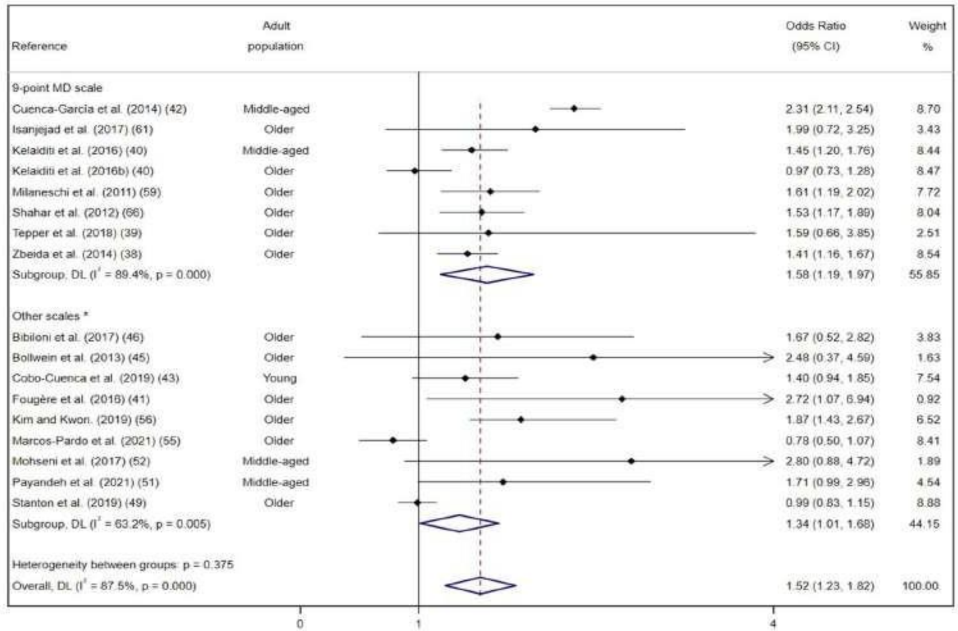
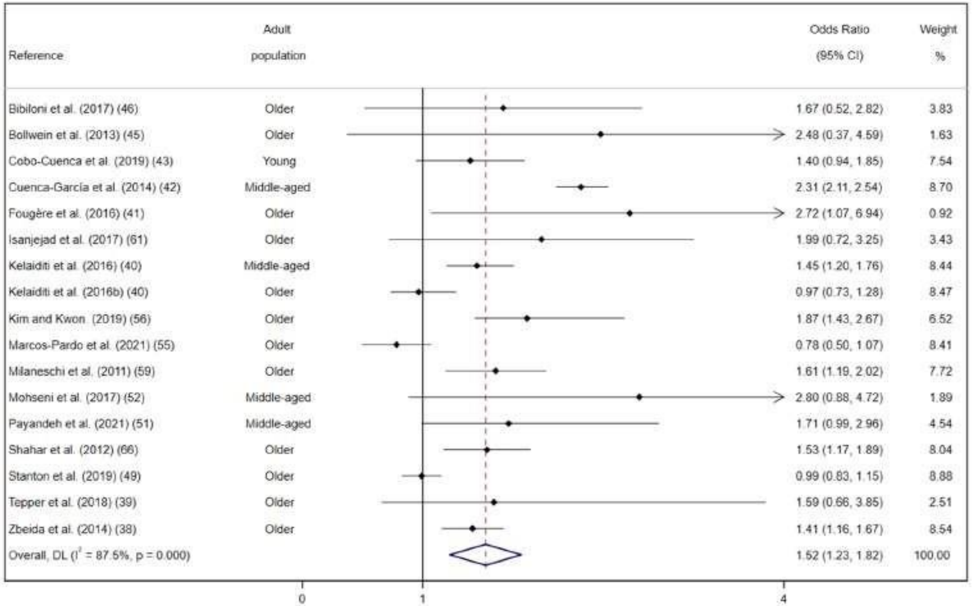


Supplementary Figure 3. Forest plot for the cross-sectional association between high Mediterranean diet adherence and overall physical fitness by adult age groups.

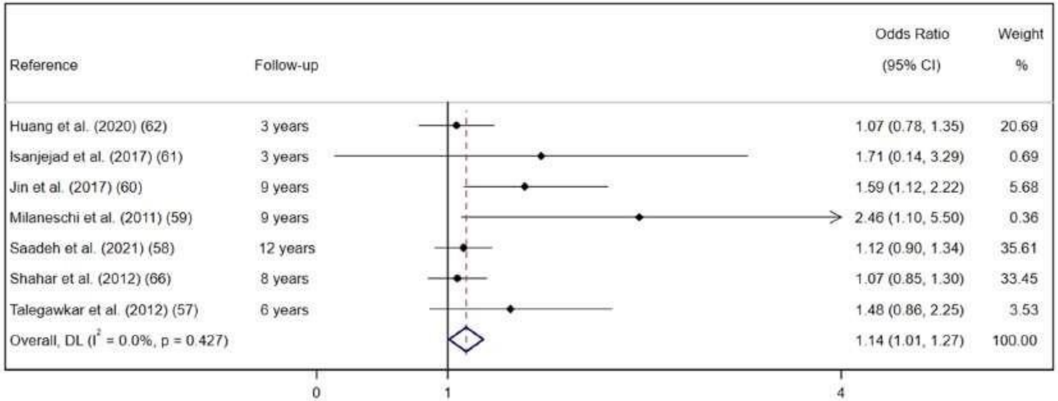


Supplementary Figure 4. Forest plot for the cross-sectional association between high Mediterranean diet adherence and overall physical fitness by Mediterranean diet adherence indices in adults of all ages.

* Alternate MD scale, MD quality index, 14-point MD scale, Mediterranean Pattern score, Mediterranean-Style Dietary Pattern Score.



Supplementary Figure 5. Forest plot for the cross-sectional association between high Mediterranean diet adherence and overall physical fitness in adults of all ages.



Supplementary Figure 6. Forest plot for the prospective association between high Mediterranean diet adherence and overall physical fitness in older adults.

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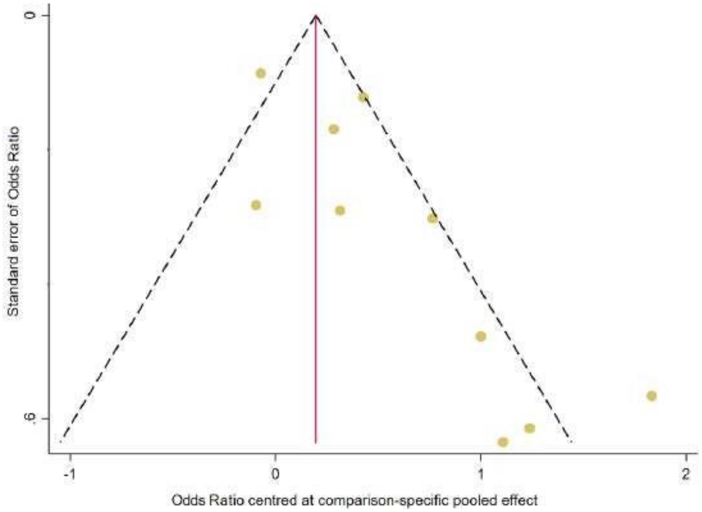
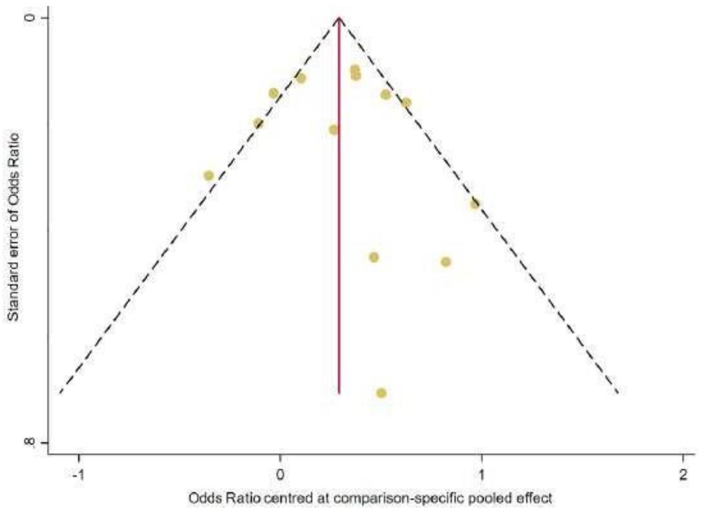


Supplementary Figure 7. Funnel plot for comparison-specific cross-sectional pooled odds ratios for motor fitness.



Supplementary Figure 8. Funnel plot for comparison-specific cross-sectional pooled odds ratios for musculoskeletal fitness.

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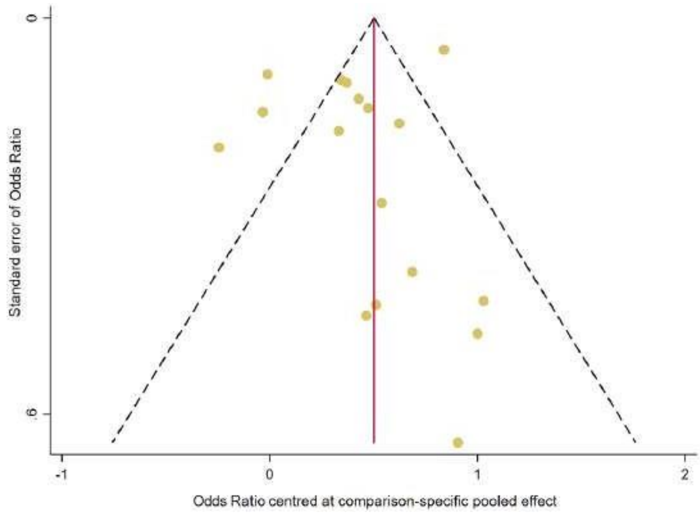

Supplementary Figure 9. Funnel plot for comparison-specific cross-sectional pooled odds ratios for overall physical fitness.

APPENDIX VI. SUPPLEMENTARY MATERIAL MANUSCRIPT III

Supplementary material: The association between meat consumption and muscle strength index in young adults: the mediating role of total protein intake and lean mass percentage.

The association between meat consumption and muscle strength index in young adults: the mediating role of total protein intake and lean mass percentage

European Journal of Nutrition

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Table S1 "A Guideline for Reporting Mediation Analyses" checklist for the reporting of mediation analyses of observational studies.

Section/Topic	Item Number	Item Description	Reported on page No
Title and abstract			
Title	1	Identify that the study uses mediation analysis	0
Abstract	2	Provide a structured summary of the objectives, methods, results, and conclusions specific to mediation analyses	1
Introduction			
Background and rationale	3	Describe the study background and theoretical rationale for investigating the mechanisms of interest. Include supporting evidence or theoretical rationale for why the intervention or exposure might have a causal relationship with the proposed mediators. Include supporting evidence or theoretical rationale for why the mediators might have a causal relationship with the outcomes	2-3
Objectives	4	State the objectives of the study specific to the mechanisms of interest. The objectives should specify whether the study aims to test or estimate the mechanistic effects	3
Methods			
Study registration	5	If applicable, provide references to any protocols or study registrations specific to the mediation analysis, and highlight any deviations from the planned protocol	NA (authors' statement on page 7)
Study design and source of data	6	Specify the design of the original study that was used in mediation analyses and where the details can be accessed, supported by a reference. If applicable, describe study design features that are relevant to mediation analyses	3-7
Participants	7	Describe the target population, eligibility criteria specific to mediation analyses, study locations, and study dates (start of participant enrollment and end of follow-up)	3
Sample Size	8	State whether a sample size calculation was conducted for mediation analyses. If so, explain how it was calculated	3
Effects of interest	9	Specify the effects of interest	6-7
Assumed causal model	10	Include a graphic representation of the assumed causal model including the exposure, mediator, outcome, and possible confounders	6-7 and Figure S1
Causal assumptions	11	Specify assumptions about the causal model	6-7
Measurement	12	Clearly describe the interventions or exposures, mediators, outcomes, confounders, and moderators that were used in the analyses. Specify how and when they were measured, the measurement properties, and whether blinded assessment was used	3-7

Measurement levels	13	If relevant, describe the levels at which the exposure, mediator, and outcome were measured	NA
Statistical methods	14	Describe the statistical methods used to estimate the causal relationships of interest. This description should specify analytical strategies used to reduce confounding, model building procedures, justification for the inclusion or exclusion of possible interaction terms, modelling assumptions, and methods used to handle missing data. Provide a reference to the statistical software and package used	6-7
Sensitivity analyses	15	Describe any sensitivity analyses that were used to explore causal or statistical assumptions and the influence of missing data	7
Ethical approval	16	Name the institutional research board or ethics committee that approved the study. Provide a description of participant informed consent or ethics committee waiver of informed consent	3
Results			
Participants	17	Describe baseline characteristics of participants included in mediation analyses. Report the total sample size and number of participants lost during follow-up or with missing data	7-8
Outcomes and estimates	18	Report point estimates and uncertainty estimates for the exposure-mediator and mediator-outcome relationships. If inference concerning the causal relationship of interest is considered feasible given the causal assumptions, report the point estimate and uncertainty estimate	7-8
Sensitivity parameters	19	Report the results from any sensitivity analyses used to assess robustness of the causal or statistical assumptions, and the influence of missing data	8
Discussion			
Limitations	20	Discuss the limitations of the study including potential sources of bias	11-12
Interpretation	21	Interpret the estimated effects considering the study's magnitude and uncertainty, plausibility of the causal assumptions, limitations, generalizability of the findings, and results from relevant studies	8-11
Implications	22	Discuss the implications of the overall results for clinical practice, policy, and science	8-12
Other information			
Funding and role of sponsor	23	List all sources of funding or sponsorship for the mediation analysis and the role of the funders/sponsors in the conduct of the study, writing of the manuscript, and decision to submit for publication.	12-13
Conflicts of interest and financial disclosures	24	State any conflicts of interest and financial disclosures for all authors	13
Data and code	25	Authors are encouraged to provide a statement for sharing data and code for the mediation analysis	13

List of Figures

Fig. S1 Panel A represents the directed acyclic graph (DAG) for the causal structure of the relationship between meat consumption (exposure, green circle) and muscle strength index (outcome, orange circle). The yellow circles represent the possible "causal" mediators considered (M1: total protein intake; M2: lean mass %). Pink circles indicate ancestor variables of both the exposure and the outcome (sex, age, and socioeconomic level). Blue circles indicate ancestor variables of the outcome (tobacco, alcohol intake, physical activity, cardiorespiratory fitness, and total energy intake). Green arrows indicate "causal" paths, and pink arrows indicate biasing paths.

Panel B represents the DAG after adjusting for the minimum sufficient adjustment set for the total effect (i.e., age, sex, and socioeconomic level, now represented with white circles). Note that the biasing paths were completely closed (pink arrows became black arrows, suggesting the correct control for the relevant confounders) and that only the "causal" paths remained opened (both the direct path and the indirect paths, i.e., through mediators).

Observation: As explained in the Methods section, body mass was not included as a possible adjustment covariate because its potential biasing effect was controlled intrinsically in the definition of the study's main variables.

Fig. S2 Additional mediation analyses of the association between meat consumption (g/kg BM/d) and muscle strength index. Serial multiple mediation models were used with total protein intake (g/kg BM/d) and lean mass (%) as mediators, controlled for age (y), sex (female, male), socioeconomic level (level of parental education), alcohol intake (alcoholic beverages drinker, nondrinker), tobacco smoking (current smoker, nonsmoker), physical activity (mean minutes per day of moderate and vigorous physical activity), cardiorespiratory fitness (VO_2 max estimate, mL/kg/min), and total energy intake (kcal/d). Values for the a_1, a_2, b_1, b_2, d, c, and c′ paths are expressed as the unstandardized regression coefficient (standard error). IE_1, IE_2, and IE_3 are expressed as unstandardized regression coefficients (95% confidence intervals). Continuous lines (pathways) and bold values (IEs) indicate a statistically significant effect. * $p < 0.05$, ** $p < 0.01$. Abbreviations: IE, indirect effect; LM%, lean mass percentage; MSI, muscle strength index; PMC, processed meat consumption; RMC, red meat consumption; TMC, total meat consumption; TPI, total protein intake; WFMC, white and fish meat consumption.

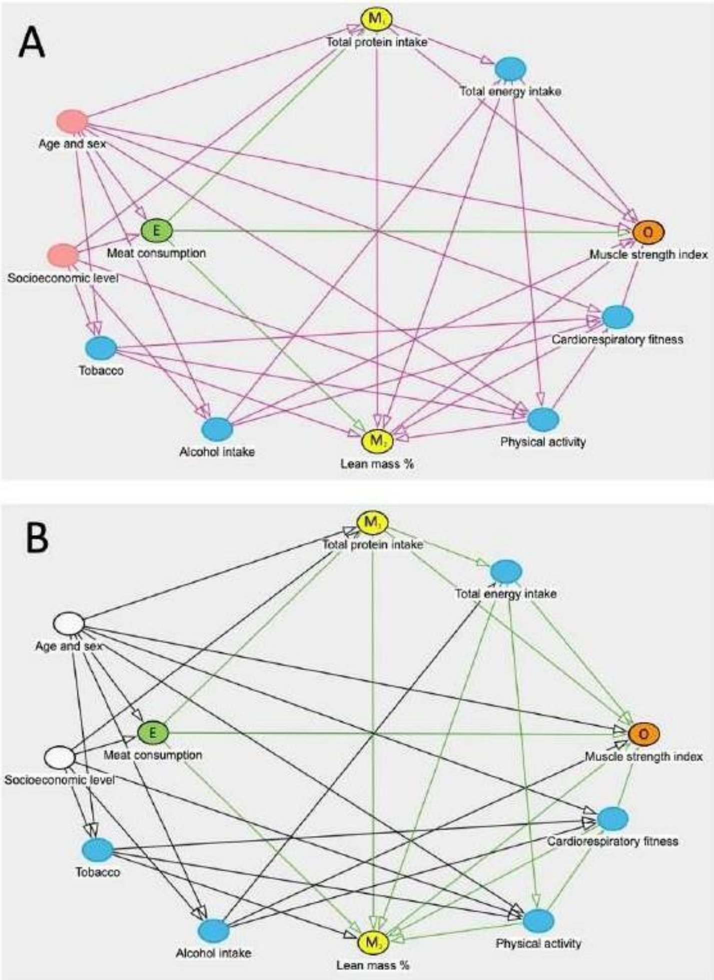

A
Total protein intake
Total energy intake
Age and sex
Meat consumption
Socioeconomic level
Muscle strength index
Cardiorespiratory fitness
Tobacco
Physical activity
Alcohol intake
Lean mass %
B
Total protein intake
Total energy intake
Age and sex
Meat consumption
Socioeconomic level
Muscle strength index
Cardiorespiratory fitness
Tobacco
Physical activity
Alcohol intake
Lean mass %

Fig. S1

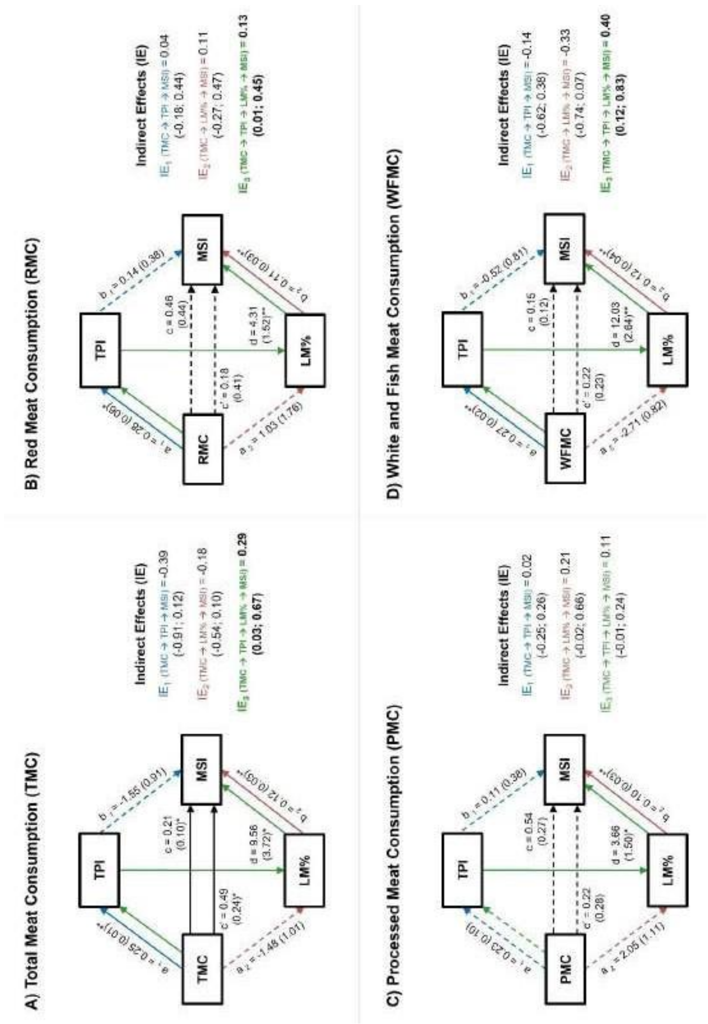

A) Total Meat Consumption (TMC)
TPI
MSI
TMC
LM%
a_1 = 0.25 (0.01)**
b_1 = -1.55 (0.91)
c = 0.21 (0.10)*
c' = 0.49 (0.24)*
d = 9.56 (3.72)*
a_2 = -1.48 (1.01)
b_2 = 0.12 (0.05)*
Indirect Effects (IE)
IE_1 (TMC → TPI → MSI) = -0.39 (-0.91; 0.12)
IE_2 (TMC → LM% → MSI) = -0.18 (-0.54; 0.10)
IE_3 (TMC → TPI → LM% → MSI) = 0.29 (0.03; 0.67)
B) Red Meat Consumption (RMC)
TPI
MSI
RMC
LM%
a_1 = 0.28 (0.09)*
b_1 = 0.14 (0.38)
c = 0.46 (0.44)
c' = 0.18 (0.41)
d = 4.31 (1.52)**
a_2 = 1.03 (1.76)
b_2 = 0.11 (0.03)**
Indirect Effects (IE)
IE_1 (TMC → TPI → MSI) = 0.04 (-0.18; 0.44)
IE_2 (TMC → LM% → MSI) = 0.11 (-0.27; 0.47)
IE_3 (TMC → TPI → LM% → MSI) = 0.13 (0.01; 0.45)
C) Processed Meat Consumption (PMC)
TPI
MSI
PMC
LM%
a_1 = 0.23 (0.10)
b_1 = 0.11 (0.38)
c = 0.54 (0.27)
c' = 0.22 (0.28)
d = 3.66 (1.50)*
a_2 = 2.05 (1.11)
b_2 = 0.10 (0.03)**
Indirect Effects (IE)
IE_1 (TMC → TPI → MSI) = 0.02 (-0.25; 0.26)
IE_2 (TMC → LM% → MSI) = 0.21 (-0.02; 0.66)
IE_3 (TMC → TPI → LM% → MSI) = 0.11 (-0.01; 0.24)
D) White and Fish Meat Consumption (WFMC)
TPI
MSI
WFMC
LM%
a_1 = 0.27 (0.02)**
b_1 = -0.52 (0.81)
c = 0.15 (0.12)
c' = 0.22 (0.23)
d = 12.03 (2.64)**
a_2 = -2.71 (0.82)
b_2 = 0.12 (0.04)**
Indirect Effects (IE)
IE_1 (TMC → TPI → MSI) = -0.14 (-0.62; 0.38)
IE_2 (TMC → LM% → MSI) = -0.33 (-0.74; 0.07)
IE_3 (TMC → TPI → LM% → MSI) = 0.40 (0.12; 0.83)

Fig. S2

APPENDIX VII. SUPPLEMENTARY MATERIAL MANUSCRIPT IV

Supplementary material: Proinflammatory dietary pattern and depression risk in older adults: Prospective analyses from the Seniors-ENRICA studies.

Supplementary data

Table S1. Baseline study sample daily intakes, global daily intakes and inflammatory effect scores for the food parameters included in the SE-cohorts dietary inflammatory index.

Dietary Parameter	Daily mean-intake (SD) for SE-I	Daily mean-intake (SD) for SE-II	Global daily mean-intake (SD) [a]	Overall inflammatory effect score [b]
Carbohydrate (g)	207.54 ± 62.46	203.12 ± 39.63	272.20 ± 40.00	0.097
Cholesterol (mg)	304.65 ± 137.37	285.52 ± 90.48	279.40 ± 51.20	0.110
Energy (kcal)	1991.58 ± 654.41	1975.58 ± 354.68	2056.00 ± 338.00	0.180
Iron (mg)	12.85 ± 3.89	12.88 ± 2.44	13.35 ± 3.71	0.032
Protein (g)	89.79 ± 25.76	90.40 ± 16.95	79.40 ± 13.90	0.021
Saturated fat (g)	23.89 ± 10.92	22.96 ± 7.69	28.60 ± 8.00	0.373
Total fat (g)	79.50 ± 29.96	80.77 ± 20.58	71.40 ± 19.40	0.298
Trans fat (g)	1.64 ± 1.28	1.39 ± 0.96	3.15 ± 3.75	0.229
Vitamin B_{12} (µg)	6.17 ± 3.88	5.49 ± 2.44	5.15 ± 2.70	0.106
Alcohol (g)	9.87 ± 17.20	10.00 ± 14.10	13.98 ± 3.72	-0.278
β-Carotene (µg)	3312.23 ± 2403.50	3146.30 ± 1900.28	3718.00 ± 1720.00	-0.584
Caffeine (g)	0.06 ± 0.11	0.08 ± 0.11	8.05 ± 6.66	-0.110
Fiber (g)	23.79 ± 8.23	23.79 ± 5.95	18.80 ± 4.90	-0.663
Folic acid (µg)	317.64 ± 110.38	323.25 ± 87.75	273.00 ± 70.70	-0.190
Garlic (g)	0.87 ± 1.71	0.82 ± 1.61	4.35 ± 2.90	-0.412
Green/black tea (g)	0.97 ± 7.97	1.32 ± 9.27	1.69 ± 1.53	-0.536
Magnesium (mg)	315.15 ± 95.15	331.08 ± 75.61	310.10 ± 139.40	-0.484
MUFA (g)	34.88 ± 13.98	35.49 ± 2.44	27.00 ± 6.10	-0.009
Niacin (mg)	20.19 ± 6.71	20.91 ± 4.78	25.90 ± 11.77	-0.246
ω-3 fatty acids (g)	2.04 ± 1.26	2.06 ± 0.95	1.06 ± 1.06	-0.436
ω-6 fatty acids (g)	11.38 ± 6.31	12.44 ± 5.30	10.80 ± 7.50	-0.159
Onion (g)	11.73 ± 12.88	11.94 ± 12.16	35.90 ± 18.40	-0.301
PUFA (g)	13.56 ± 7.03	15.49 ± 2.44	13.88 ± 3.76	-0.337
Riboflavin (mg)	1.60 ± 0.48	1.55 ± 0.37	1.70 ± 0.79	-0.068
Selenium (µg)	139.46 ± 54.98	137.34 ± 35.55	67.00 ± 25.10	-0.191
Thiamin (mg)	1.31 ± 0.46	1.37 ± 41.08	1.70 ± 0.66	-0.098
Vitamin A (RE)	835.94 ± 576.17	782.43 ± 457.43	983.90 ± 518.60	-0.401

1

Vitamin B_6 (mg)	1.97 ± 0.60	2.01 ± 0.46	1.47 ± 0.74	-0.365
Vitamin C (mg)	136.98 ± 71.72	153.50 ± 72.68	118.20 ± 43.46	-0.424
Vitamin D (µg)	3.38 ± 3.13	3.13 ± 2.01	6.26 ± 2.21	-0.446
Vitamin E (mg)	9.74 ± 4.91	10.40 ± 4.41	8.73 ± 1.49	-0.419
Zinc (mg)	8.92 ± 2.66	8.75 ± 1.79	9.84 ± 2.19	-0.313

Abbreviations: **MUFA**, monounsaturated fatty acids; **PUFA**, polyunsaturated fatty acids; **RE**, retinol equivalents; **SE**, Seniors-ENRICA.

[a] From the world composite database (25).

[b] A positive value indicates proinflammatory effects, and a negative value indicates anti-inflammatory effects (25).

Table S2. Prospective associations between a proinflammatory diet and the incidence of self-reported diagnosis or ≥5 symptoms of depression in the SE-II cohort.

	Quartiles of Dietary Inflammatory Index				
	Q1: anti-inflammatory diet	**Q2**	**Q3**	**Q4: proinflammatory diet**	***p-for-trend*** [a]
SE-II, *n (%)*	395	395	395	394	
DII, *score range*	-4.403, -0.839	-0.838, 0.286	0.293, 1.501	1.503, 4.860	
Incidence of depression [b], *n (%)*	17 (1.0)	20 (1.2)	26 (1.6)	39 (2.3)	
Model 1 – crude model	1.00 (ref)	1.17 (0.60, 2.26)	1.54 (0.82, 2.89)	2.34 (1.30, 4.21) *****	**<0.001**
Model 2 – adjusted model	1.00 (ref)	1.06 (0.53, 2.12)	1.37 (0.71, 2.63)	1.87 (1.01, 3.46) *****	**0.007**
Model 3 – adjusted model	1.00 (ref)	0.95 (0.44, 2.04)	1.29 (0.63, 2.62)	2.01 (1.03, 3.93) *****	**0.002**

Values are ORs (95% CI) for logistic regression models. * $p < 0.05$. Abbreviations: **DII**, Dietary Inflammatory Index; **Q**, quartile; **SE**, Seniors-ENRICA.

[a] *p* value for linear association between the continuous score of the Dietary Inflammatory Index (main independent variable) and incidence of self-reported diagnosis or ≥5 symptoms of depression (dependent variable).

[b] Incident cases of depression were defined as those participants free of self-reported diagnosis or ≥5 symptoms of depression at baseline assessment and who self-reported physician-diagnosed depression or ≥5 symptoms in the Geriatric Depression Scale-10 during the 2.3-year follow-up.

Model 2: adjusted for sex (female, male), age (y), household economy (difficult to make ends meet or easy to make ends meet), education level (no studies/primary or secondary/university), marital status (married or single/widowed/separated), smoking status (never/former or current), body mass index (kg/m^2), physical activity (less active or more active), time watching TV (h/wk), and night's sleep duration (h/d); Model 3: Model 2 adjusted for functional disability (yes, no), loneliness (scale score) and chronic conditions diagnosed by a physician, including diabetes mellitus (yes, no), cardiovascular disease (yes, no), hypertension (yes, no), chronic respiratory disease (yes, no), cancer at any site (yes, no), musculoskeletal disorder (yes, no), and neurodegenerative disease (yes, no). All covariates were from baseline.

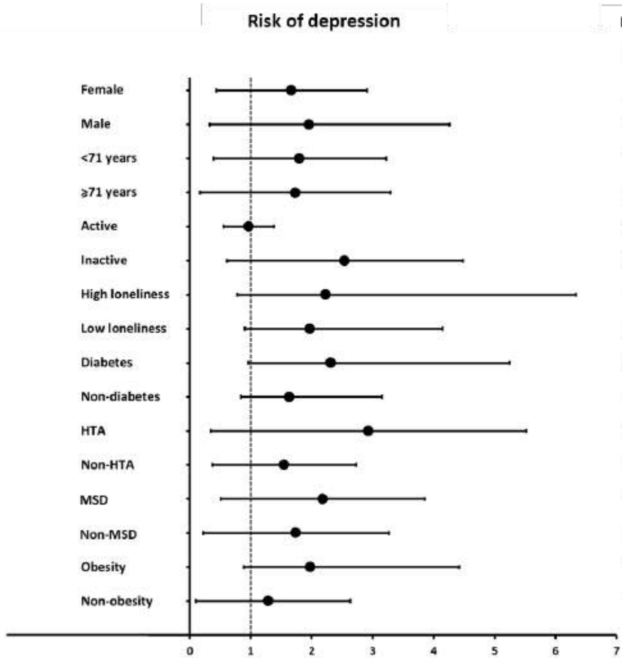
Table S3. Prospective associations between a proinflammatory diet and the number of incident depressive symptoms in the SE-II cohort.

	β	Lower limit	Upper limit	p value
Number of incident depressive symptoms [a]				
Model 1 – crude model	0.09	0.04	0.14	**<0.001**
Model 2 – adjusted model	0.06	0.01	0.11	**0.012**
Model 3 – adjusted model	0.07	0.01	0.12	**0.037**

Values are standardized β coefficients (95% CI) between the continuous score of DII and the incidence of depressive symptoms. Abbreviations: **SE**, Seniors-ENRICA.

[a] Incident cases of depression were defined as those participants free of self-reported diagnosis or mild-to-major symptoms of depression at baseline assessment and who self-reported depressive symptoms in the Geriatric Depression Scale-10 during the 2.3-year follow-up.

Model 2: adjusted for sex (female, male), age (y), household economy (difficulty in making end meet or ease in making end meet), education level (no studies/primary or secondary/university), marital status (married or single/widowed/separated), smoking status (never/former or current), body mass index (kg/m^2), physical activity (less active or more active), time watching TV (h/wk), and night's sleep duration (h/d); Model 3: Model 2 adjusted for functional disability (yes, no), loneliness (scale score) and chronic conditions diagnosed by a physician, including diabetes mellitus (yes, no), cardiovascular disease (yes, no), hypertension (yes, no), chronic respiratory disease (yes, no), cancer at any site (yes, no), musculoskeletal disorder (yes, no), and neurodegenerative disease (yes, no). All covariates were from baseline.



Pooled cohorts (Q4 vs Q1 DII)			p-interaction	
OR	LL	UL	SE-I	SE-II
1.67	0.44	2.91	0.253	0.905
1.96	0.33	4.26		
1.80	0.39	3.22	0.131	0.468
1.73	0.17	3.29		
0.97	0.56	1.38	0.070	0.945
2.54	0.61	4.48		
2.23	0.78	6.33	NA	0.710
1.97	0.90	4.14		
2.31	0.96	5.25	0.432	0.082
1.63	0.84	3.15		
2.93	0.34	5.52	0.624	0.872
1.55	0.37	2.73		
2.18	0.51	3.85	0.287	0.866
1.74	0.22	3.26		
1.98	0.89	4.42	0.663	0.111
1.29	0.10	2.63		

Fig. S1. Risk of self-reported diagnosis or mild-to-major symptoms of depression for the highest quartile *vs.* the lowest quartile of the Dietary Inflammatory Index in the pooled cohorts, stratified by sex, age, physical activity, loneliness, and chronic conditions. Values are pooled ORs (95% CI) of the fully adjusted ORs (95% CI) of each cohort. Abbreviations: **HTA**, hypertension; **LL**, lower limit; **NA**, not applicable; **MSD**, musculoskeletal disorder; **SE**, Seniors-ENRICA; **UL**, upper limit.

APPENDIX VIII. SUPPLEMENTARY MATERIAL MANUSCRIPT V

Supplementary material: Mediterranean Diet Interventions for Depressive Symptoms in Adults with Depressive Disorders: A Protocol for a Systematic Review and Meta-Analysis.

Table S1. PRISMA-P 2015 checklist to address the systematic review protocol*.

Section/topic	#	Checklist item	Information reported Yes	Information reported No	Line number(s)
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registrationnumber in the Abstract	☒	☐	47
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors;provide physical mailing address of corresponding author	☒	☐	4 to 19
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	476 to 480
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	481 to 484
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	NA – no sponsor
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing theprotocol	☐	☒	NA – no role
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	61 to 102

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with referenceto participants, interventions, comparators, and outcomes (PICO)	☒	☐	102 to 105
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be usedas criteria for eligibility for the review	☒	☐	115 to 183
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates ofcoverage	☒	☐	182 to 187
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	187 to 191
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughoutthe review	☒	☐	194 to 196
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusionin meta-analysis)	☒	☐	196 to 203
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	209 to 211
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	212 to 217

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization ofmain and additional outcomes, with rationale	☒	☐	168 to 177
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, includingwhether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	218 to 220
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	232 and 233
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies,including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	233 to 242
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses,meta-regression)	☒	☐	243 to 251
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	230 to 232
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	251 to 252
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	221 to 228

*Adapted from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1.

Table S2. Characteristics of studies included in the systematic review and meta-analysis.

Studies			**Participants**				**Intervention/Comparator**		**Outcome**	
Reference	**Country**	**Study Design**	**Sample size**	**Sex**	**Age**	**Depressive disorder**	**MD intervention**	**Control condition**	**Measure**	**Main findings**
Author information and year of publication	Country	Specific characteristics of RCTs	Number of participants for total	Number of participants for sex	Range or means ± SD (years)	Type of depressive disorder	Number of participants Diet intervention characteristics	Number of participants Control group characteristics	Details of depression outcomes	Results on depression levels (i.e., symptoms or remission)

15

OTHER SCIENTIFIC CONTRIBUTIONS

15.1 ACADEMIC TRAINING

- 2017–2018. University Master's degree in Physical Activity and Health. Faculty of Education Sciences, University of Cádiz, Cádiz, Spain.
- 2013–2016. Graduate degree in Physical Education. Higher Institute of Physical Education, University of the Republic, Maldonado, Uruguay.
- 2008–2011. Superior degree in Social Education. Social Educators Training Center, Uruguayan Institute for Children and Adolescents, Montevideo, Uruguay.

15.2 GRANTS AND SCHOLARSHIPS

- 2022. Grants for stays in universities and research centers abroad year 2022 by the University of Castilla–La Mancha co-financed by the FEDER Funds.
- 2021. Grant for training course, IE Best Practices in Digital Education for Teachers. IE Foundation–Banco Santander.
- 2021. Predoctoral scholarship from the University of Castilla-La Mancha co-financed by the European Social Fund under *Beatriz Galindo* Grant (2020-PREDUCLM-16746).
- 2020. Grants for presentation of research advances at international conferences from the University of the Republic (Sectorial Commission for Scientific Research, grant MIA220/48).
- 2019. Grants for stays in universities and research centers abroad year 2019 by the University of the Republic (Sectorial Commission for Scientific Research, grant MIA419/226).
- 2019. Grants for presentation of research advances at international conferences from the University of the Republic (Department of Regional Relations and Integration, International Relations Service).
- 2017. Master's degree scholarship from the Ibero-American Graduate University Association.

15.3 RESEARCH STAYS

- 2022. Stay with a duration of three months at the Human Performance Analysis Research Group – PDU EFISAL (*Polo de Desarrollo Universitario Educación Física y Salud*), University of the Republic, Rivera, Uruguay.
- 2019. Stay with a duration of one month at the GALENO Research Group, University of Cádiz, Spain.

15.4 AWARDS AND RECOGNITIONS

- 2023. Elsevier Research Selection (e-newsletter for science journalists and reporters) of the article “Nut consumption is associated with a lower risk of depression in adults: a prospective analysis with data from the UK Biobank cohort” published in Clinical Nutrition.
- 2021. Associate Researcher at the initial level, National System of Researchers, National Agency for Research and Innovation, Uruguay.

15.5 OTHER PEER REVIEW PUBLICATIONS

15.5.1 Published

- Sequí-Dominguez, I, Cavero-Redondo I, Rodríguez-Gutiérrez E, **Bizzozero-Peroni B**, Martinez-Madrid V, Prada de Medio E, Martínez-García I, Martínez-Vizcaíno V. Association of daily steps on lipid and glycaemic profiles in children: The mediator role of cardiorespiratory fitness. *Acta Paediatrica*. 2023;1-7.
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- *Validity of an accelerated vascular aging model as an index of cardiovascular risk in healthy adults: confirmatory factor analysis. EvasCu study.* IP: Alicia Saz-Lara. Comillas Pontifical University. 21/04/2022–21/04/2024.
- *A school-based, family involved e-health program to improve adiposity, cardiometabolic risk, cognition by enhancing schoolchildren's diet and movement behavior: The e-Movi Intervention.* IP: Vicente Martínez Vizcaíno. Carlos III Health Institute (PI19/01126). 01/02/2021–31/12/2023.
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- *Global Matrix 4.0: Report Card on physical activity indicators in children and adolescents in Uruguay*. IP: Javier Brazo Sayavera. University of the Republic–Active Healthy Kids Global Alliance. 01/11/2020–21/12/2022.

15.7 RESEARCH DISSEMINATION PROJECT PARTICIPATION

- *Concurso fotográfico y evento divulgativo científico coordinado: Nutre-Activa tu Mente*. IP: Arthur Eumann Mesas. University of Castilla-La Mancha. IV Dissemination Plan "UCLMdivulga". 2022/2023.
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- **Bizzozero-Peroni B**, MJ, Fernández-Giménez S, Pintos-Toledo E, Souza-Marabotto F, Brazo-Sayavera J. Active and motorized transportation time in schoolchildren as a function of perceived safety: a pilot study. *1st Latin American Congress on Physical Activity and Health Research*. Mexico, 2021.
- Brazo-Sayavera J, Pintos-Toledo E, Fernández-Giménez S, Corvos CA, **Bizzozero-Peroni B**. Entren-arte: Proposal of exercises to perform at home. *III Academic Conference on Extension and Integrality of the School of Medicine*. Uruguay, 2021.
- **Bizzozero-Peroni B**, Díaz-Goñi V. Effects of interval training vs. continuous training on left ventricular ejection fraction in patients with heart failure: a review of systematic reviews. *47th Argentine Congress of Cardiology*. Argentina, 2021.
- **Bizzozero-Peroni B**, Díaz-Goñi V. Physical exercise programs for people with coronary artery disease. *47th Argentine Congress of Cardiology*. Argentina, 2021.

15.9 DISSEMINATION OF THE RESEARCH FINDINGS

15.9.1 Popular science articles and interviews

- *Eating One Serving of Nuts Each Day Might Help Lower Your Risk of Depression*. Health website, Dotdash Meredith Mediaroom, USA. 2023. Accessible at: https://www.health.com/nuts-decrease-depression-risk-7852708
- *Handful of nuts a day 'associated with 17% lower risk of depression'*. The Independent journal, UK. 2023. Accessible at: https://www.independent.co.uk/%20news/science/data-uk-biobank-britons-brazil-spain-b2389577.html
- *High adherence to the Mediterranean diet is associated with higher physical fitness*. Science & Mediterranean Diet blog, Portugal. 2023. Accessible at: https://www.ciencia-e-vinho.com/2023/01/29/high-adherence-to-the-mediterranean-diet-is-associated-with-higher-physical-fitness/

- *Experts' opinion: Physical activity for rehabilitation and health*. Radio program: Integrated Conversations. National University of La Matanza, Argentina. 2023. Accessible at: https://www.youtube.com/watch?v=tzvMjwPcBoQ&t=1399s
- *Mediterranean diet and physical fitness in adults*. Science & Mediterranean Diet blog, Portugal. 2022. Accessible at: https://www.ciencia-e-vinho.com/2022/07/17/mediterranean-diet-and-physical-and-fitness-ans-adults/
- *Does the type of meat consumed influence muscle mass?* Science Communication Center, Autonomous University of Chile. 2022. Accessible at: https://ciencias.uautonoma.cl/noticias/carne/

15.9.2 Impact on social networks

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LATEST ARTICLES

Can a Mediterranean Diet Improve Physical Fitness?

January 5, 2023 by Eric Graber

Review published in Advances in Nutrition *finds high adherence to the Mediterranean diet associated with higher levels of physical fitness*

The Centers for Disease Control and Prevention (CDC) reports that "regular physical activity is one of the most important things you can do for your health." Being physically fit can "improve your brain health, help manage weight, reduce the risk of disease, strengthen bones and muscles, and improve your ability to do everyday activities." Fortunately, most adults at any age have the ability to improve their physical fitness. In fact, higher physical fitness has been associated with improved health and reduced mortality in all phases of the lifespan, from youth to old age.

Published in *Advances in Nutrition*, the international review journal of the American Society for Nutrition, High Adherence to the Mediterranean Diet is Associated with Higher Physical Fitness in Adults: A Systematic Review and Meta-Analysis examines the link between the Mediterranean diet and general physical fitness as well as specific components of fitness such as cardiorespiratory, motor, and musculoskeletal fitness. The authors believe that their study represents the first systematic review and meta-analysis to provide a comprehensive picture of the associations between high and low adherence to the Mediterranean diet and physical fitness in adulthood.

Science & Wine

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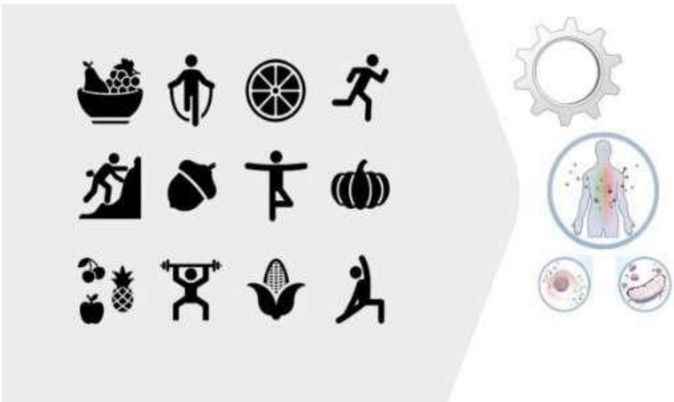
High adherence to the Mediterranean diet is associated with higher physical fitness

By Bruno Bizzozero-Peroni, Javier Brazo-Sayavera, Vicente Martínez-Vizcaíno, Rubén Fernández-Rodríguez, José Francisco López-Gil, Valentina Díaz-Goñi, Iván Cavero-Redondo, Arthur Eumann Mesas



After analyzing the scientific literature comprising 30 studies conducted with 36,807 adult participants, some conclusions were drawn. First, a significant positive association was found between high adherence to the Mediterranean diet (compared to low adherence) and higher fitness levels in both cross-sectional and longitudinal observational studies. Second, according to each fitness indicator, the Mediterranean diet was associated with improved cardiorespiratory fitness (cross-sectional association), musculoskeletal fitness (cross-sectional and longitudinal association), and motor fitness (cross-sectional association in populations from Mediterranean countries).

Centro de Comunicación
de las Ciencias
Universidad Autónoma de Chile

¿El tipo de carne que se consume influye en la masa muscular?

Publicado : **24 octubre 2022**

Estudio analizó la relación entre el consumo de diferentes tipos de carne (total, roja, procesada, y blanca o pescado) y el índice de fuerza muscular, examinando si estas asociaciones estaban mediadas por la ingesta total de proteínas y el porcentaje de masa magra.

Por último, la complejidad y diversidad de las asociaciones entre el consumo de carne y la salud, marcadas por diferentes elementos como las características/requerimientos fisiológicos de los individuos, dificultan establecer límites saludables para el consumo de carne y proteínas.

«Teniendo en cuenta la evidencia previa, se recomienda una ingesta de proteínas de alta calidad que oscile entre 0.8 y 3.5 gramos/día kg de peso para adultos sanos. Sin embargo, son necesarios más estudios que analicen los efectos del consumo de carne y proteínas en esta población para llegar a conclusiones consistentes sobre las cantidades de ingesta óptimas para la salud general, y para la composición corporal y fuerza muscular en particular» concluye el especialista.

Bizzozero-Peroni, B., Martínez-Vizcaíno, V., Garrido-Miguel, M., Fernández-Rodríguez, R., Torres-Costoso, A., Ferri-Morales, A., Martín-Espinosa, N. M., & Mesas, A. E. (2022). **The association between meat consumption and muscle strength index in young adults: the mediating role of total protein intake and lean mass percentage.** European journal of nutrition, 10.1007/s00394-022-03014-7. Advance online publication. https://doi.org/10.1007/s00394-022-03014-7

INDEPENDENT

News > Science

Handful of nuts a day 'associated with 17% lower risk of depression'

Researchers speculate that anti-inflammatory and antioxidant properties of nuts may have a protective effect.

Nilima Marshall • Tuesday 08 August 2023 15:18 BST

Consuming nuts may lower risk of depression, scientists say (Victoria Jones/PA) *(PA Archive)*

For the study, published in the journal Clinical Nutrition, the researchers looked at data from more than 13,000 people aged 37-73, between 2007 to 2020.

These people did not report having depression at the start of the study.

Questionnaires were used to assess nut consumption and over the course of the study, self-reported doctor's diagnosis of depression or antidepressant use were recorded.

> *This provides an even stronger rationale for people to become enthusiastic about consuming nuts*
>
> *Bruno Bizzozero-Peroni*

health

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NEWS

Eating One Serving of Nuts Each Day Might Help Lower Your Risk of Depression

By Lauren Manaker MS, RDN, LD • Published on September 7, 2023

Fact checked by Sarah Scott

GETTY IMAGES / AZMANJAKA

How Eating Nuts May Help Lower Your Risk of Depression

There aren't many foods as nutritious as nuts. Some of these nutritional aspects may play into why eating nuts supports mental health.

"The main components of the nutritional profile of nuts (e.g., dietary fiber, omega-3 fatty acids, phenols, polyphenols, and vitamin E) include a large spectrum of anti-inflammatory and antioxidant qualities that may contribute to protection against depression," said Bruno Bizzozero Peroni,

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Feeling depressed? Just a handful of nuts could help

Just a few cashews or peanuts could cut the risk of depression by almost a fifth, study finds

Scientists believe the fats, amino acids and proteins in nuts can reduce stress inside the body, boosting the link with the brain | CREDIT: STONE RF/DAVID MALAN

Eating a handful of nuts each day cuts the risk of depression by almost a fifth, a study has found.

NEW YORK POST

OCTOBER 14, 2023

The study found that low to moderate nut consumption was linked to a 17% decrease in the risk of depression compared to the participants who did not eat nuts

Getty Images

All nut consumption was recorded, including unsalted nuts, such as almonds, cashews and pistachios, salted nuts, roasted nuts and peanuts.

"This study analyzed the prospective association between nut consumption and the risk of depression in a large sample of middle-aged and older adults in the UK," the authors wrote in the journal.

Researchers examined participants' data over the course of five years, and 8% of the subjects were diagnosed with depression during that time.

MailOnline

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Eating 30g of nuts each day may help you ward off depression, study claims

- **Eating nuts is linked to a 17 per cent lower risk of depression, scientists say**
- **Just a 30g daily potion of nuts is enough to reap the anti-inflammatory benefits**

By XANTHA LEATHAM DEPUTY SCIENCE EDITOR

PUBLISHED: 12:11 BST, 8 August 2023 | **UPDATED:** 12:39 BST, 8 August 2023

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Whether it's peanuts in the pub, walnuts in a salad or simply a tasty trail mix, most of us like nuts in some shape or form.

Now there's an even better excuse to go nutty for them – as they could provide an unexpected mental health benefit.

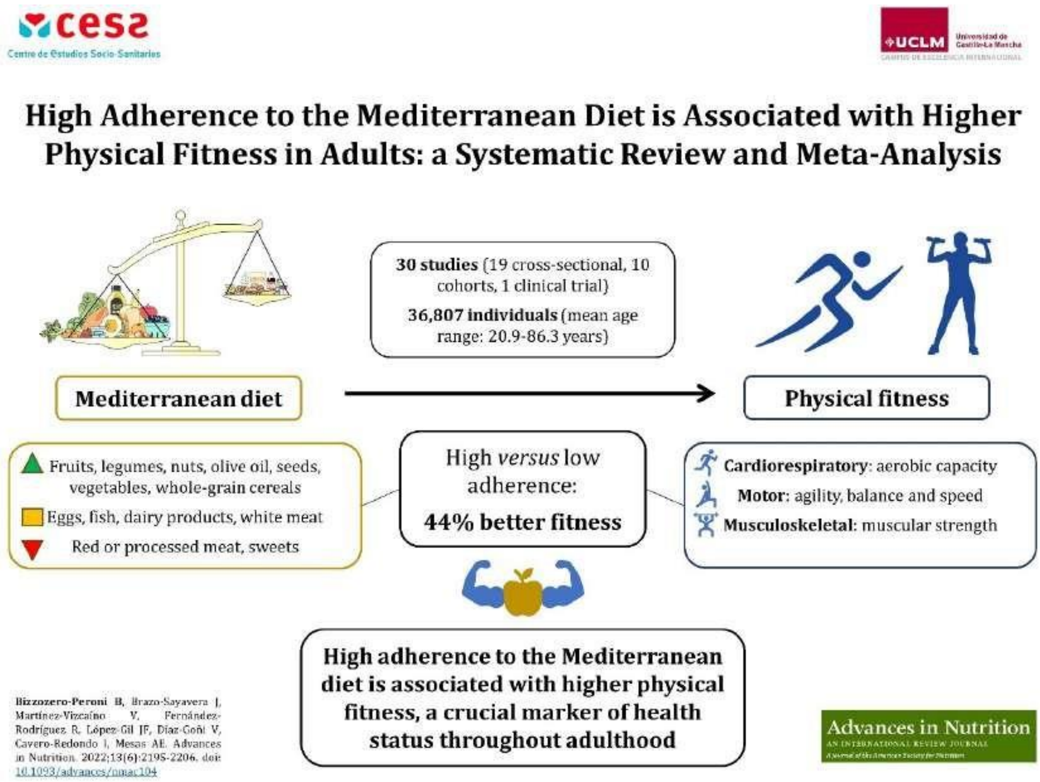
Researchers examined data on more than 13,500 people in the UK aged 37 to 73, who did not have **depression** at the start of the study.

Scientists say that nuts' anti-inflammatory and antioxidant effects on the brain may be the reason for the results

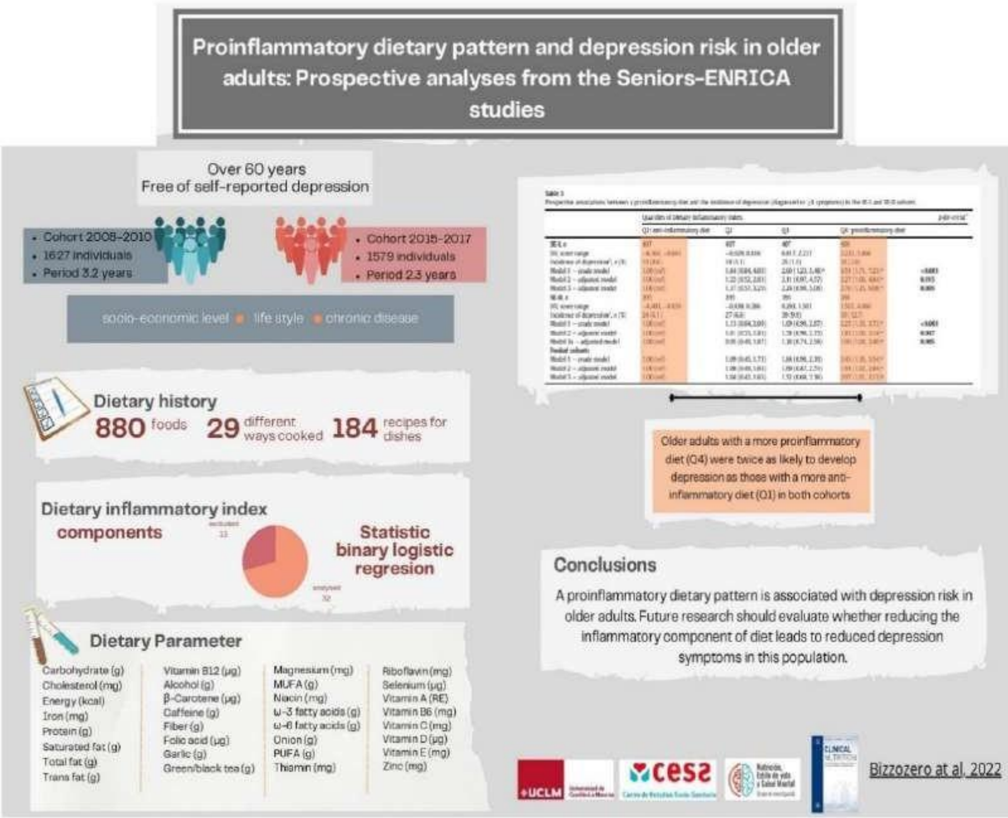
Lead author Bruno Bizzozero-Peroni, from the University of Castilla-La Mancha, in Spain, said: 'Our findings highlight yet another benefit of consuming nuts, with a 17 per cent decrease in depression associated with nut consumption.

15.9.3 Infographic for social media

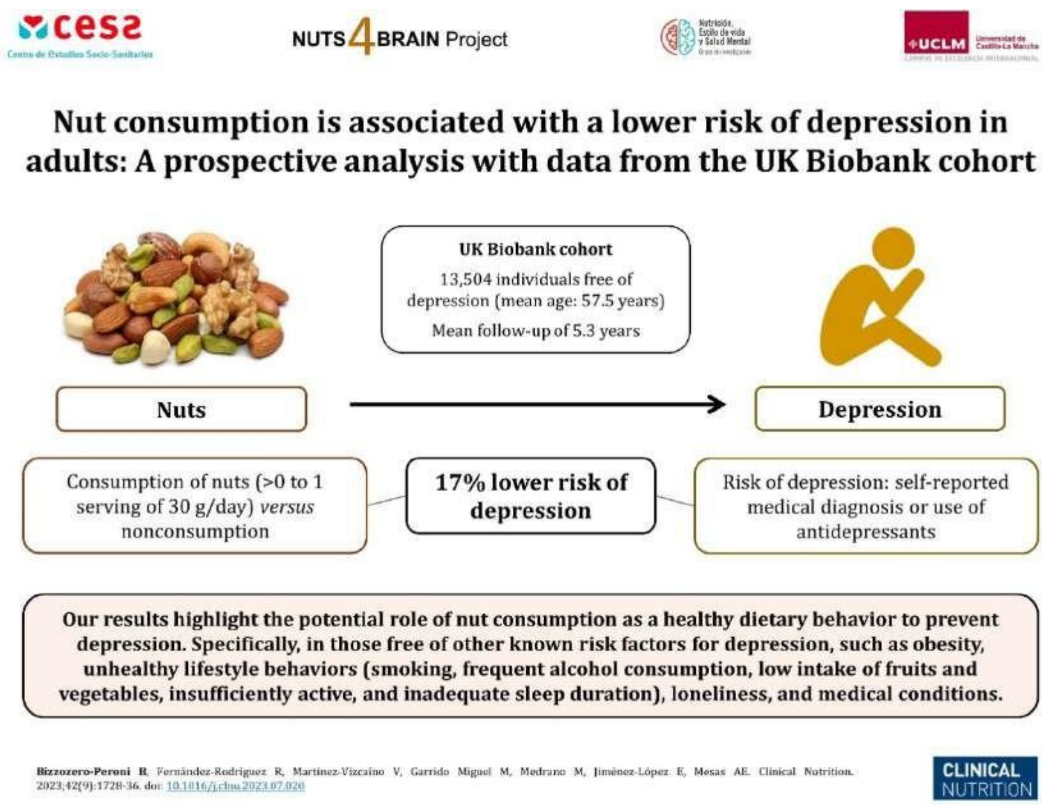
Manuscript II



Manuscript IV



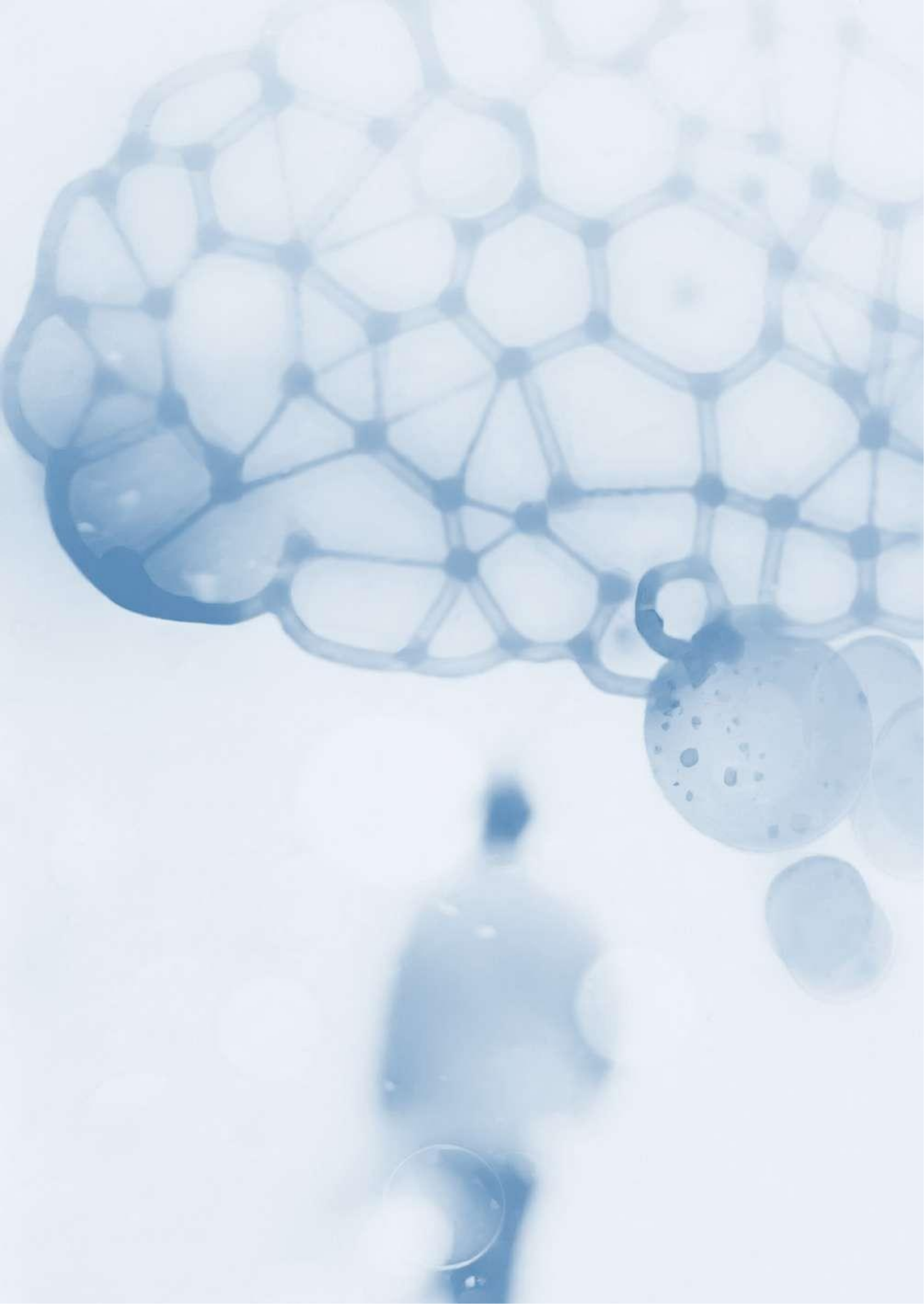
Manuscript VII



“We must give thanks to life. To succeed in life is not to win,
to succeed in life is to get up and start again
every time you fall.”

*“Hay que darle gracias a la vida. Triunfar en la vida no es ganar,
triunfar en la vida es levantarse y volver a empezar
cada vez que uno cae.”*

José Mujica



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