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Coffee, vitamin K and physical limitations among older adults

DOCTORAL THESIS

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

ENRICA	Study on Nutrition and Cardiovascular Risk in Spain
HR	Hazard ratio
CI	Confidence interval
LASA	Longitudinal Aging Study Amsterdam
dp-ucMGP	Dephospho-uncarboxylated matrix Gla protein
FI	Frailty index
SD	Standard deviation
WHO	World Health Organization
ICF	International Classification of Functioning, Disability and Health
RDAs	Recommended Dietary Allowances
IADL	Instrumental Activities of Daily Living
ADL	Basic Activities of Daily Living
DASH	Dietary Approaches to Stop Hypertension
MIND	Mediterranea-DASH Intervention for Neurodegenerative Delay
MGP	Matrix ɤ-carboxyglutamate (Gla) protein
EPIC	European Investigation into Cancer and Nutrition
MEDAS	Mediterranean Diet Adherence Screener
TV	Television
SF-12	12-Item Short-Form Health Survey
SPPB	Short Physical Performance Battery
BMI	Body mass index
MMSE	Mini-Mental State Examination
MET	Metabolic equivalent
NHS	National Health Service
IPAQ	International Physical Activity Questionnaire
ELISA	Enzyme Linked Inmunosorbent Assay
CES-D	Center for Epidemiologic Studies depression scale
eGFR	Estimated glomerular filtration rate
GEE	Generalized estimating equations
ucOC	Non-carboxylated osteocalcin

1

SUMMARY

1

GENERAL SUMMARY

The aging population is a great challenge for modern societies, and therefore, ensuring healthy aging is essential to achieve a good quality of life in the elderly. Physical function impairment, frailty, disability and falls are major challenges facing the public health of the twenty-first century, as they compromise the quality of life of the elderly, increase the cost of the health system and increase the risk of adverse health outcomes. Lifestyles, such as diet and physical exercise, are modifiable factors that play an important role in the development of diseases, and therefore, knowing the dietary determinants that predispose to the public health problems mentioned above is important in order to design policies and strategies to prevent their development. This doctoral thesis aims to clarify the effect of habitual coffee consumption on the development of functional limitations, frailty and disability, as well as its effect on the risk of falls in elderly people, since coffee is the most consumed beverage in the world after water; therefore, any effect on health associated with this consumption have a high impact on the population. In addition, this thesis also analyzes the effect of vitamin K on frailty, measured with a plasma biomarker, which allows to take into account not only the intake, but also the biodisponibility of this vitamin. Therefore, this thesis covers two complementary approaches in Nutritional Epidemiology: the study of self-reported information on habitual diet and the study of biomarkers of nutients exposure.

Summary to Article 1

Background: Habitual coffee consumption has been associated with lower risk of type 2 diabetes and cardiovascular disease. Since these diseases are main determinants of functional limitations, we assess the hypothesis that coffee consumption was associated with lower risk of physical function impairment, frailty and disability in older adults. We focused on women and those with obesity, hypertension or type 2 diabetes because they are at higher risk of functional limitations.

Methods: Prospective study with 3,289 individuals ≥60 years from the Seniors-ENRICA cohort. In 2008-2010 coffee consumption was measured through a validated dietary history. Participants were followed-up until 2015 to ascertain incident impaired physical function, frailty and disability, assessed by both self-report and objective measures.

Results: Compared with non-drinking coffee, consumption of ≥2 cups of coffee/d was associated with lower risk of impaired agility in women (hazard ratio [HR]: 0.71, 95% confidence interval [CI]: 0.51-0.97, *P-trend*: 0.04) and in those with obesity (HR: 0.60; 95% CI: 0.40-0.90, *P-trend*: 0.04). Intake of ≥2 cups of coffee/d was also linked to reduced risk of impaired mobility in women (HR: 0.66; 95% CI: 0.46-0.95, *P-trend*: 0.02) and among individuals with hypertension (HR: 0.70, 95% CI 0.48-1.00, *P-trend*: 0.05). Moreover, among subjects with diabetes, those who consumed ≥2 cups/d had lower risk of disability in activities of daily living (HR: 0.30, 95% CI: 0.11-0.76, *P-trend*: 0.01).

Conclusions: In older people, habitual coffee consumption was not associated with increased risk of functional impairment, and it might even be beneficial in women and those with hypertension, obesity or diabetes.

Summary to Article 2

Background: Habitual coffee consumption has been associated with lower risk of type 2 diabetes, cardiovascular disease and sarcopenia, which are strong risk factors of falls. In addition, caffeine intake stimulates attention, vigilance and reaction time. Therefore, a protective effect of coffee on the risk of falling can be hypothesized.

Objective: To examine the association between habitual coffee consumption and the risk of ≥1 falls, injurious falls, and falls with fracture in older people.

Design: Data were taken from 2,964 participants ≥60 years from the Seniors-ENRICA cohort and 8,999 participants ≥60 years from the UK Biobank cohort. In the Seniors-ENRICA study, habitual coffee consumption was assessed with a validated diet history in 2008-10, and falls were ascertained up to 2015. In the UK Biobank study, coffee was measured with 3 to 5 multiple-pass 24-h food records starting in 2006, and falls were assessed up to 2016.

Results: A total of 793 individuals in Seniors-ENRICA and 199 in UK Biobank experienced ≥1 falls during follow-up. After multivariable adjustment for major lifestyle and dietary risk factors and compared with consumption of <1 cups/d of coffee, the pooled hazard ratio (HR) and 95% confidence interval of ≥1 falls was 0.75 (0.52, 1.07) for 1 cup/d of total coffee and 0.74 (0.62, 0.90) for ≥2 cups/d; p-trend: 0.001. Corresponding figures for caffeinated coffee were 0.67 (0.42, 1.07) and 0.70 (0.56, 0.87);

p-trend< 0.001. Decaffeinated coffee was not associated with risk of falling in the analyzed cohorts. In Seniors-ENRICA, there was a tendency to lower risk of injurious falls among those consuming caffeinated coffee [0.83, (0.68, 1.00) for 1 cup/d, 0.83 (0.64, 1.09) for ≥2 cups/d, p-trend: 0.09]. No association was observed between caffeinated or decaffeinated coffee consumption and risk of falls with fracture.

Conclusions: Habitual coffee consumption was associated with lower risk of falling in older adults in Spain and UK.

Summary to Article 3

Purpose: No previous study has evaluated the relationship between vitamin K and frailty. Thus, we assessed the relationship between vitamin K status and frailty over 13 years in the Longitudinal Aging Study Amsterdam (LASA).

Methods: Prospective cohort study with 644 community-dwelling adults ≥ 55 years from the LASA cohort. In 2002-2003, plasma desphospho-uncarboxylated matrix Gla protein (dp-ucMGP) was measured as marker of vitamin K status through a sandwich ELISA. Frailty was measured at baseline and in four follow-up examinations with the LASA Frailty Index (LASA-FI), which was used as both a continuous and a dichotomous measure (FI ≥ 0.25), as indicator of the degree of frailty and frailty risk, respectively. Statistical analyses were performed with multivariable generalized estimating equations using the lowest dp-ucMGP tertile, reflecting a high vitamin K status, as reference.

Results: The mean (SD) age was 59.9 (2.9) years, and 54% were female. Compared with the lowest tertile, the medium and highest dp-ucMGP tertile were associated with a higher degree of frailty [1.40, 95% confidence interval (0.01-2.81) and 1.62, (0.18-3.06), respectively. P-trend: 0.03]. Additionally, the medium and highest dp-ucMGP tertile had a higher odds ratio of frailty [1.75, (1.11-2.77) and 1.63, (1.04-2.57), respectively]. The degree of frailty increased over time, but the differences by dp-ucMGP tertiles existed since baseline and remained stable during follow-up.

Conclusions: Baseline plasma low vitamin K status was associated with a greater degree of frailty and frailty risk in this cohort of older adults, which highlights the importance of ensuring an optimal nutritional status of this vitamin in order to prevent frailty in later life.

RESUMEN GENERAL

El envejecimiento poblacional es un gran reto para las sociedades modernas, y por tanto, asegurar un envejecimiento saludable es esencial para alcanzar una buena calidad de vida en los ancianos. El deterioro de la función física, la fragilidad, la discapacidad y las caídas son grandes retos a los que tiene que hacer frente la salud pública del siglo XXI, ya que comprometen la calidad de vida de los mayores e incrementan los costes del sistema sanitario y el riesgo de resultados adversos sobre la salud. Los estilos de vida como la dieta y el ejercicio físico son factores modificables que juegan un papel importante en el desarrollo de enfermedades. Por tanto, conocer los determinantes nutricionales que predisponen a los problemas de salud pública mencionados anteriormente es importante con el fin de diseñar políticas y estrategias para prevenir su desarrollo. Esta tesis doctoral trata de esclarecer el efecto del consumo habitual de café sobre el desarrollo de las limitaciones funcionales, la fragilidad y la discapacidad, así como su efecto sobre el riesgo de caídas en ancianos, ya que esta bebida es la más consumida a nivel mundial y por ello, cualquier posible efecto en la salud tiene implicaciones importantes a nivel mundial. Además, esta tesis también analiza el efecto de la vitamina K sobre la fragilidad medida a través de un biomarcador plasmático, lo que permite tener en cuenta la ingesta y el metabolismo de esta vitamina. Por tanto, esta tesis cubre dos abordajes diferentes utilizados en Epidemiología Nutricional: el uso de información autorreportada sobre dieta habitual y el uso de biomarcadores de exposiciones nutricionales.

Resumen al artículo 1

Antecedentes: El consumo habitual de café se ha asociado con un menor riesgo de diabetes tipo 2 y enfermedad cardiovascular. Dado que estas enfermedades son las principales determinantes de las limitaciones funcionales, hemos comprobado la hipótesis de que el café se asocia con un menor riesgo de deterioro de la función física, fragilidad y discapacidad en adultos mayores. Nos centramos en mujeres y en participantes con obesidad, hipertensión o diabetes tipo 2 porque tienen un riesgo elevado de limitaciones funcionales.

Métodos: Se trata de un estudio prospectivo con 3,289 individuos mayores de 60 años de la cohorte Seniors-ENRICA. En 2008-2010 se midió el consumo de café a través de una historia dietética validada. Los participantes fueron seguidos hasta 2015 para determinar

los casos incidentes de deterioro de la función física, fragilidad y discapacidad, evaluados mediante medidas objetivas y autoreportadas.

Resultados: Comparado con los que no bebían café, el consumo de ≥2 tazas/día se asoció con un menor riesgo de deterioro de la agilidad en mujeres (hazard ratio [HR]: 0.71, intervalo de confianza del 95% [IC]: 0.51-0.97, P de tendencia: 0.04) y en aquellos que tenían obesidad (HR: 0.60; IC 95%: 0.40-0.90, P de tendencia: 0.04). La ingesta de ≥2 tazas/día de café también se relacionó con un menor riesgo de deterioro de la movilidad en mujeres (HR: 0.66; IC 95%: 0.46-0.95, P de tendencia: 0.02) y en individuos con hipertensión (HR: 0.70; IC 95%:0.48-1.00, P de tendencia: 0.05). Además, entre los sujetos con diabetes, los que consumieron ≥2 tazas/día de café tuvieron un menor riesgo de discapacidad en actividades básicas de la vida diaria (HR: 0.30; IC 95%: 0.11-0.76, P de tendencia: 0.01).

Conclusiones: En personas mayores, el consumo habitual de café no se asoció con un mayor riesgo de deterioro funcional, pudiendo ser incluso beneficioso en mujeres y en participantes con hipertension, obesidad o diabetes.

Resumen al artículo 2

Antecedentes: El consumo habitual de café se ha asociado con un menor riesgo de diabetes tipo 2, enfermedad cardiovascular y sarcopenia, que son fuertes factores de riesgo para las caídas. Además, la ingesta de cafeína estimula la atención, la vigilancia y el tiempo de reacción. Por tanto, se podría hipotetizar un efecto protector del café sobre el riesgo de caerse.

Objetivo: Examinar la asociación entre el consumo habitual de café y el riesgo de ≥1 caídas, caídas con consecuencias físicas leves, y caídas con fractura en personas mayores.

Diseño: Los datos fueron tomados de 2,964 participantes mayores de 60 años de la cohorte Seniors-ENRICA y de 8,999 participantes mayores de 60 años de la cohorte UK Biobank. En el estudio Seniors-ENRICA, el consumo habitual de café se evaluó en 2008-10 con una historia dietética validada y las caídas fueron evaluadas hasta 2015. En el estudio UK Biobank, el consumo de café se midió con 3-5 recordatorios 24-h de dieta comenzando en 2006 y las caídas fueron examinadas hasta 2016.

Resultados: Un total de 793 individuos en el estudio Seniors-ENRICA y 199 en el estudio UK Biobank experimentaron ≥1 caídas durante el seguimiento. Tras el ajuste multivariable por los principales factores de riesgo de estilos de vida y dietéticos y comparado con los que consumían <1 taza/día de café, el hazard ratio (HR) y el intervalo de confianza al 95% (IC) para los resultados agrupados de las 2 cohortes fueron 0.75 (0.52, 1.07) para los que consumieron 1 taza/día y 0.74 (0.62, 0.90) para los que consumieron ≥2 tazas/día; P de tendencia: 0.001. Los valores correspondientes para el café con cafeína fueron 0.67 (0.42, 1.07) y 0.70 (0.56, 0.87); P de tendencia: <0.001. El café descafeinado no se asoció con el riesgo de caerse en las cohortes analizadas. En el estudio Seniors-ENRICA, hubo una tendencia a un menor riesgo de caídas con consecuencias físicas leves entre los aprticipantes que consumieron café con cafeína [0.83, (0.68, 1.00) para 1 taza/día, 0.83 (0.64, 1.09) para ≥2 tazas/día, P de tendencia: 0.09]. No se observó ninguna asociación entre el consumo de café con cafeína o descafeinado y el riesgo de caídas con fractura.

Conclusión: El consumo habitual de café se asoció con un menor riesgo de caerse en adultos mayores de España y Reino Unido.

Resumen al artículo 3

Propósito: Ningún estudio previo ha evaluado la relación entre la vitamina K y la fragilidad. Por esto, analizamos la relación entre el estado de vitamina K en plasma y la fragilidad tras 13 años de seguimiento en el estudio Longitudinal Aging Study Amsterdam (LASA).

Métodos: Estudio de cohorte prospectivo con 644 adultos residentes en la comunidad y mayores de 55 años de la cohorte LASA. En 2002-2003, las proteínas plasmáticas de la matriz Gla desfosforiladas y decarboxiladas (dp-ucMGP) fueron medidas como marcador del estado de vitamina K a través de un sandwich ELISA. La fragilidad fue medida al inicio del estudio y en cuatro oleadas durante el seguimiento a través del Índice de Fragilidad de LASA (IF-LASA), que se usó como medida contínua y dicotómica (IF ≥ 0.25), como indicador del grado y del riesgo de fragilidad respectivamente. Los análisis estadísticos se realizaron con ecuaciones de estimación generalizadas utilizando el tercil más bajo de dp-ucMGP, lo que refleja un mayor estado de vitamina K, como referencia.

Resultados: La media (DE) de edad fue 59.9 (2.9) años y el 54% fueron mujeres. Comparado con el tercil más bajo, el tercil medio y más alto se asociaron con un mayor grado de fragilidad [1.40, intervalo de confianza al 95% (0.01-2.81) y 1.62, (0.18-3.06), respectivamente]. Adicionalmente, el tercil medio y alto de dp-ucMGP tuvieron un mayor odds ratio de fragilidad [1.75, (1.11-2.77) y 1.63, (1.04-2.57), respectivamente]. El grado de fragilidad se incrementó a lo largo del tiempo pero las diferencias entre los terciles de dp-ucMGP existían desde el inicio del estudio y permanecieron estables durante el seguimiento.

Conclusiones: Un bajo estado plásmatico de vitamina K al inicio del estudio se asoció con un mayor grado y riesgo de fragilidad en esta cohorte de adultos mayores, lo que destaca la importancia de garantizar un óptimo estado nutricional de esta vitamina con el fin de prevenir la fragilidad en la edad adulta.

2

GENERAL INTRODUCTION

INTRODUCTION

1.1 THE CHALLENGE OF POPULATION AGING

Numerous reports written by different organizations highlight the fact that the world population is aging (1-3). Population aging, understood as the increase in the proportion of the elderly in a population, is one of the most significant social transformations of the twenty-first century and one of the greatest challenges facing modern societies. Population aging also has implications for all sectors of society, so adapting to this new situation is essential to ensure healthy aging (1). The World Health Organization (WHO) defines healthy aging as "the process of promoting and maintaining functional capacity that allows well-being in old age" (2). One of the objectives to guarantee a healthy aging is that the settlements where older people live must be inclusive, safe, resilient and sustainable, and therefore, societies must provide an adequate environment for it (1).

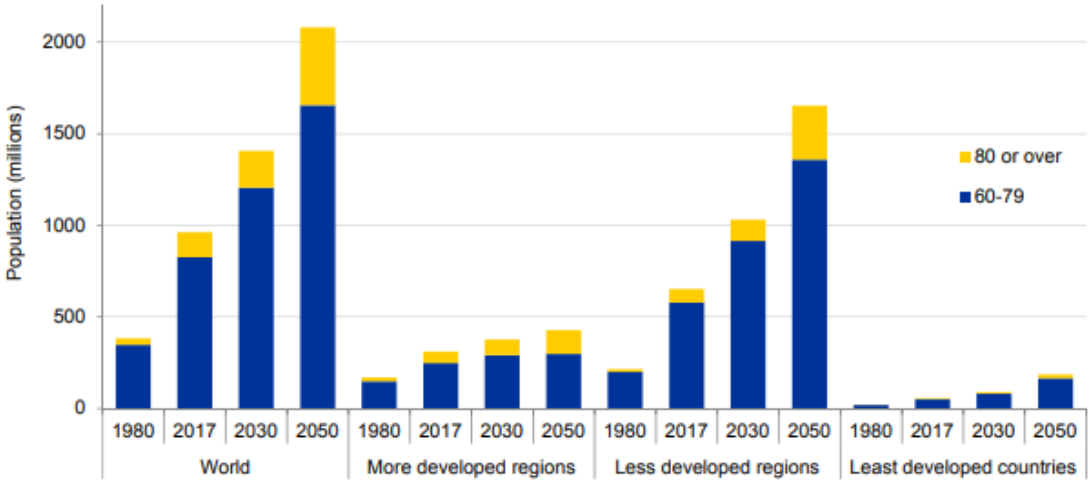


Figure 1. Number of persons aged 60-79 years and aged 80 or over for the world and development groups, 1980, 2017, 2030 and 2050 (1).

Globally, the main determinants of population aging are the decline in fertility and the increase in longevity. However, prospections for the future emphasize that international migrations could have different effects on population aging depending on the country or area (1). In 2017, there were 962 million people aged 60 or more around the world and projections indicate that these figures will more than double by 2050, reaching 2.1 billion (**Figure 1**). In addition, two thirds of the world's population of older people live in developing countries and their numbers will increase faster than in developed countries. In the same way, the proportion of people aged 80 and over increased notably between 1980 (9%) and 2017 (14%), however, projections indicate that it will remain relatively

stable until 2030. Subsequently, between 2030 and 2050 it is expected that the proportion of people aged 80 and over will increase by more than 20%, so guaranteeing healthy aging is essential (1).

Therefore, in order to develop health policies and strategies to ensure healthy aging, it is important to determine whether people who live longer are doing so in good health or if, on the contrary, years added to old age are not lived in a healthy way.

1.2 THE PROCESS OF DISABILITY IN THE ELDERLY

Different models and schemes have been developed to understand and explain the disabling process in the elderly (4-6). Nagi proposed a disability scheme formed by four central concepts (4). In this scheme, an active pathology interferes with the normal processes of the organism and could lead to an anatomical, physiological, mental or emotional loss or abnormality, known as impairment. This impairment would progress to a functional limitation, which is considered a limitation on performance at the level of the entire organism or person. Finally, functional limitations would result in disability, which is considered a limitation in the performance of socially defined roles and tasks within a sociocultural and physical environment.

Verbrugge et al. proposed in 1994 another disability scheme called "Disablement process" (5). In this scheme, the presence of a pathology could cause dysfunctions and significant structural abnormalities in specific body systems (cardiovascular, musculoskeletal, neurological, etc.), which is known as "impairment". The impairments could lead to "functional limitations", which are restrictions on basic physical and mental actions such as climbing stairs, and which could eventually lead to disability. Finally, disability is defined in this scheme as the difficulty to perform activities in any domain of life due to a physical or health problem. In addition, this scheme adds a series of factors, such as risk factors and individual factors, that could accentuate or attenuate the disabling process (**Figure 2**).

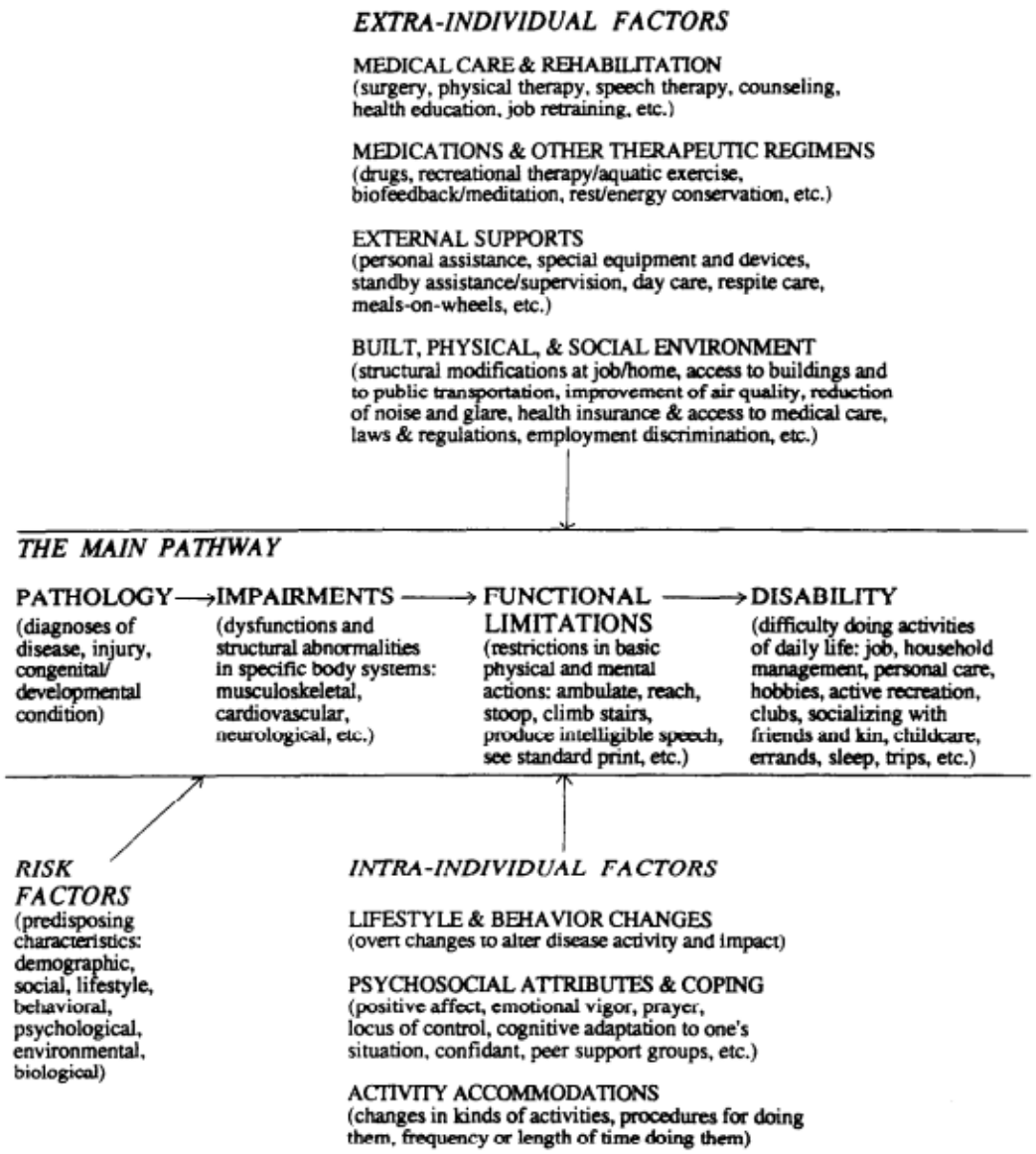


Figure 2. A model of The Disablement Process (5).

On the other hand, in 2001 the World Health Organization developed the International Classification of Functioning, Disability and Health (ICF) with the aim of establishing a common language to describe health and health status (6). In this classification, the elements are interrelated in both directions, so that it is not a causal scheme. In addition, each component has positive and negative aspects. The ICF is structured in two parts (**Table 1**): 1) Functioning and Disability: it is formed by two components; a) Body functions and structures: are the anatomical parts and physiological functions of the individual. Its positive aspect would be the integrity of the structure and the function and its negative aspect the deficiency. b) Activities and participation: activity is the realization of a task or action by an individual, so its negative aspect would be the limitation in the

activity that are the difficulties that a person can present in carrying out activities. Participation, however, is the act of getting involved in a vital situation, and therefore, its negative aspect would be the restriction on participation which are the problems that an individual may experience when engaging in life situations. 2) Contextual Factors: is formed in turn by Environmental Factors and Personal Factors. a) Environmental Factors: are those factors that constitute the physical and social environment in which people live. b) Personal factors: they represent the particular background of an individual's life and lifestyle.

Table 1. An overview of ICF (6).

<table>
<tr><td></td><td colspan="2">Part 1: Functioning and Disability</td><td colspan="2">Part 2: Contextual Factors</td></tr>
<tr><td>Components</td><td>Body Functions and Structures</td><td>Activities and Participation</td><td>Environmental Factors</td><td>Personal Factors</td></tr>
<tr><td>Domains</td><td>Body functions
Body structures</td><td>Life areas
(tasks, actions)</td><td>External influences on functioning and disability</td><td>Internal influences on functioning and disability</td></tr>
<tr><td>Constructs</td><td>Change in body functions (physiological)

Change in body structures (anatomical)</td><td>Capacity
Executing tasks in a standard environment

Performance
Executing tasks in the current environment</td><td>Facilitating or hindering impact of features of the physical, social, and attitudinal world</td><td>Impact of attributes of the person</td></tr>
<tr><td rowspan="2">Positive aspect</td><td>Functional and structural integrity</td><td>Activities
Participation</td><td rowspan="2">Facilitators</td><td rowspan="2">not applicable</td></tr>
<tr><td colspan="2">Functioning</td></tr>
<tr><td rowspan="2">Negative aspect</td><td>Impairment</td><td>Activity limitation
Participation restriction</td><td rowspan="2">Barriers / hindrances</td><td rowspan="2">not applicable</td></tr>
<tr><td colspan="2">Disability</td></tr>
</table>

This scheme considers functioning and disability as an interactive and evolutionary process, in which there is a dynamic interaction between its elements (**Figure 3**). Therefore, a given intervention would have the potential to modify one or more of the other elements. The ultimate objective of the ICF is not to classify people, but to describe the situation of each person within a set of health domains.

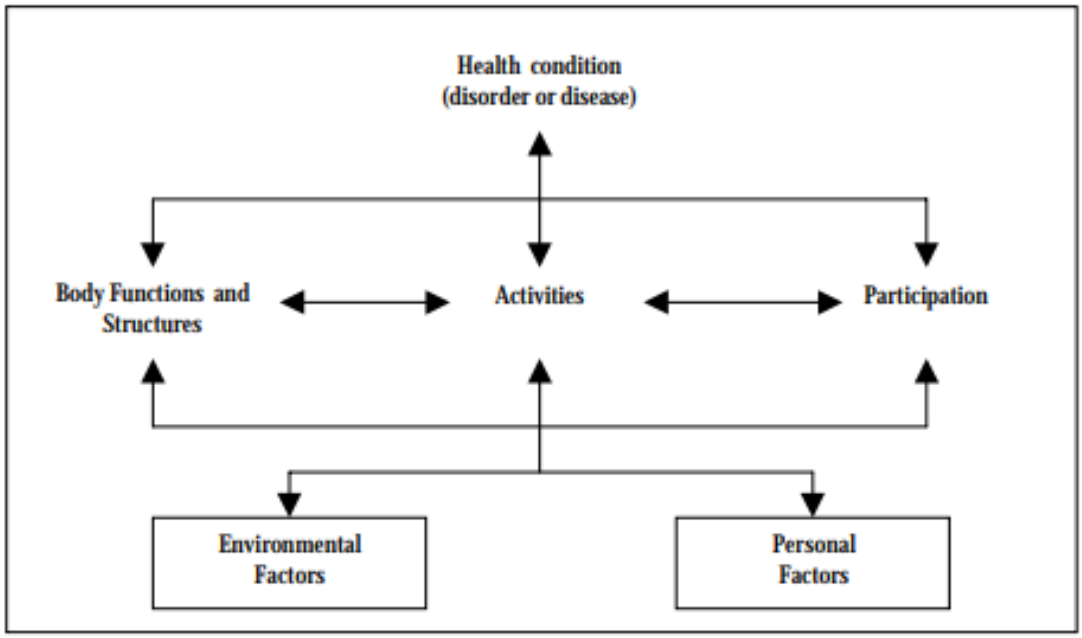


Figure 3. Interactions between the components of ICF (6).

1.3 IMPORTANCE OF DIETARY EXPOSURES IN THE DISABLING PROCESS

Dietary exposures are difficult to characterize and analyze, since food is often not consumed in isolation, but consumed as a whole and following patterns that adapt to our personal tastes and social and cultural factors (7). Therefore, the effect of an individual's diet on a given health outcome can be analyzed by adopting different approaches, either focusing on the quantity and quality of the nutrients consumed, on specific foods or food groups, or in function of the diet pattern adopted by the individual (7). In addition, diet is a fundamental component in the development and prevention of chronic diseases (8, 9) and, therefore, the process of disability. Knowing the nutritional factors, both risk and protective, that affect individuals is essential to establish recommendations and nutritional strategies focused on guaranteeing a healthy aging and a better quality of life for the elderly. However, the scientific evidence of the influence of diet on the development of disability is quite limited.

1.3.1 DIET AND PHYSICAL FUNCTION IMPAIRMENT

Functional limitations are frequent in the elderly, compromise their quality of life and predispose, to a large extent, to the appearance of disability. Mobility impairment is a very important aspect in the elderly since it is associated with an increased risk of mortality and functional disability [10,11]. Mobility is the ability of an individual to move

or walk taking into account the stimuli of the environment and being able to adapt to them. Furthermore, the mobility impairment depends on personal physical ability and environmental factors [12]. On the other hand, "agility" refers to the individual's ability to change the speed or direction of gait in response to a stimulus [13]. It is also possible to assess the overall physical function impairmtent or impairments in certain parts of the body using tests such as the Short Physical Performance Battery (SPPB). In this way, the impairment of mobility, agility or general physical function has been related to the ICF component "Impairments".

For all these reasons, studying dietary factors that influence the development of physical function impairment is important to ensure healthy aging and a better quality of life for the elderly. There are some studies that have found a beneficial effect of some foods such as fruits, vegetables (14,15) and dairy products (16,17) on physical function and the detrimental effect of foods processed at high temperatures (18) with the risk of physical function impairment. Our group has provided evidence on the beneficial effect of the Mediterranean diet pattern on physical function in the elderly (19) and the beneficial effect of nut consumption on impairment of mobility and agility in men and on overall physical function in women (20). In addition, it has been observed that a high consumption of processed meat was associated with an increased risk of agility impairment and limitation in the lower-extremity function (21).

1.3.2 DIET AND FRAILTY

Frailty is a state of great vulnerability to external stressors (infections, hospitalization, surgery, etc.) caused by the loss of abilities in multiple biological systems and that also increases the risk of adverse outcomes (22,23).

There are different tools that allow to measure the frailty, being the most used the frailty phenotype proposed by Fried et al. (24) and the frailty index proposed by Rockwood et al. (22). The scale proposed by Fried et al. (24) includes five phenotypic criteria: 1) unintentional weight loss, 2) low physical activity, 3) exhaustion, 4) weakness and 5) slow walking speed. According to this scale, a person is pre-frail when meets one or two phenotypic criteria, and is frail when meets three or more criteria. On the other hand, the frailty index proposed by Rockwood et al. (22) considers frailty as the accumulation of deficits, which may be symptoms, signs, disabilities and diseases. In this way, a greater

number of deficits correspond to a greater degree of frailty. Finally, a frailty score is calculated for each individual by dividing the number of deficits presented by the total number of deficits included in the scale. Overlap has been demonstrated in identifying frailty between the frailty phenotype and the defictis accumulation model (23).

In addition, frailty has been associated with different components of the ICF (25). In this way, in the phenotype proposed by Fried et al. (24) unintentional weight loss, exhaustion and low physical activity have been related to the ICF component "Body Functions", weakness has been related to the component "Activities and participation: Capacity" and finally, slow walking speed has been related to the component "Activities and participation: Performance". On the other hand, the items included in the 40-item frailty index proposed by Rockwood et al. (26) have been related to different components of the ICF such as "Body Functions", "Body Structures", "Activities and participation: Performance" and "Personal factors".

Research on dietary determinants of frailty is relatively recent. So far, studies have suggested that low protein intake are linked to frailty (27). In addition, our group has provided some evidence of the beneficial effect of a Mediterranean diet pattern on frailty (28), the association of different types of dairy products with frailty (29), and the detrimental effect of added sugars (30). Furthermore, a low intake of vitamins B6, C, E and folate, as well as not meeting the vitamin Recommended Dietary Allowances (RDAs), were associated with an increased risk of frailty (31).

1.3.3 DIET AND FALLS

A fall is an event in which the person is lying on the ground or a lower level involuntarily (32). Falls are huge costs to the health system because they are one of the main causes of injury, disability and death in the elderly (33). Therefore, evaluating the factors that could increase the risk of falls in the elderly is very important in order to design strategies to prevent them. In addition, falls have been linked to several ICF domains such as "Body Functions", "Body Structures", "Activities and participation" and "Environmental factors" (34).

We have found in the literature some studies that evaluate the relationship between the consumption of certain nutrients and the risk of falls. However, studies that analyze the effect of specific foods or dietary patterns are quite scarce. It has been observed that

supplementation with some nutrients such as calcium (35) and vitamin D (36) was associated with a lower risk of falls in certain population subgroups, although more studies are still needed to clarify these relationships. On the other hand, in a study conducted with the Framingham cohort, no association was found between protein intake and risk of falls (37), and this was also observed in another study conducted on the Spanish population (38). In the same way, another study conducted with postmenopausal women did not find an association between protein and vitamin D intake and the risk of falls (39). Finally, a cross-sectional study observed that men who had a better diet quality were associated with a lower prevalence of falls (40), and similarly, in another cross-sectional study it was observed that as serum folate declines it increases the risk of falls (41).

1.3.4 DIET AND DISABILITY IN ACTIVITIES OF DAILY LIFE

Disability can be understood as the difficulty to perform activities of daily life, which limits individual capacity and compromises their quality of life (42,43). Due to the aging of the population and the increase in the prevalence of certain chronic diseases associated with disability, such as diabetes and cardiovascular diseases, the prevalence of disability is growing in developed countries (44). Graciani et al. (45) estimated that the prevalence in Spain of disability in Instrumental Activities of Daily Living (IADL) was 40.1%, while the prevalence of disability in Basic Activities of Daily Living (ADL) was 19.1%. The prevalence was much higher for mobility and agility impairment (51.6% and 59.1%, respectively) than for the disability itself. Furthermore, it has been observed that ADL disability is related to several ICF domains such as "Body structures", "Body functions" and "Personal factors" (46).

In relation to diet, a protective effect has been observed between the pattern of the Mediterranean diet and the disability in ADL and IADL in women (47). In addition, another study found a protective association between the Mediterranean diet pattern, the Dietary Approaches to Stop Hypertension (DASH) diet and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet and the risk of ADL disability (48). Finally, it has also been observed that some foods have a protective effect against disability, such as fruits and vegetables (16), legumes and soy products (49).

1.4 COFFEE

Coffee is the second most consumed beverage in the world after water and for this reason, the interest to know its effects on health has increased in recent years. In addition, the high consumption of coffee could have an important effect on public health, which has stimulated the interest of researchers around the world. However, the effect of coffee on chronic diseases has been debated due to the appearance of contradictory results (50).

Coffee is a brew prepared from the roasted seeds of a bush of the genus *Coffea* (50,51). The coffee beans, once ripened, are processed and dried. However, most countries have developed their own preferences when preparing and presenting it (50). Hundreds of substances are present in the coffee brew, many of them with biological action, and their composition depends on the type of coffee bean used, the roasting and the processing method (50,51). In addition, during the roasting process, complex reactions occur that give rise to small amounts of compounds with detrimental effects. However, the beneficial compounds are predominant (51). For all this, the coffee brew has a complex chemical composition that includes caffeine, diterpenes, magnesium, phenolic compounds, lignans, and trigonelline, among many others (51). In the same way, all the substances present in coffee contribute to its flavor and the bioactivity of the brew.

Caffeine is the compound present in coffee that has been most studied and is a natural alkaloid capable of stimulating the central nervous system by acting as an antagonist of adenosine receptors, promoting the release of different neurotransmitters at normal doses of consumption (51,52). However, its effects on health are controversial. On the one hand, caffeine is able to reduce reaction time and improve alertness, attention and vigilance, but it can also produce negative effects in sensitive individuals, such as anxiety, tachycardia and insomnia (51,53). However, it has been observed that habitual coffee drinkers develop a certain partial tolerance to the acute effects of caffeine due to metabolic adaptations (51,54).

Other components present in coffee, such as diterpenes, have shown antioxidant and anticarcinogenic properties (51,55). However, some studies have indicated a detrimental effect of these components by increasing the plasma levels of total cholesterol (56), triglycerides and some blood lipoproteins (57), so they could have a detrimental effect on cardiovascular disease (51). In addition, these components are present mainly in unfiltered coffee, since they are retained in paper filters (58,59).

Finally, habitual coffee consumption has been associated with a lower risk of type 2 diabetes (60), cardiovascular disease (61) and sarcopenia (62), which are major determinants of physical function. For these reasons it is important to evaluate the effect of coffee on the different components that are part of the disabling process in the elderly.

1.5 VITAMIN K

Vitamin K is a fat-soluble vitamin that can be found in different forms. Vitamin K_1 (phylloquinone) is mainly present in green leafy vegetables, algae and plant oils, and is the main source of vitamin K in our diet. On the other hand, vitamin K_2 (menaquinone) is found in animal foods such as meat, eggs, fermented dairy products (mainly cheese) and is also synthesized by intestinal bacteria from vitamin K_1 (63). Likewise, vitamin K_2 includes a wide range of forms of vitamin K that differs from vitamin K_1 in the length of its side chain and in the degree of saturation. In addition, vitamin K_2 has a longer half-life, as well as greater absorption and bioavailability than vitamin K_1 (64).

Vitamin K has an important role as it acts as a cofactor in the carboxylation of vitamin K-dependent proteins. The most well-known vitamin K-dependent proteins are involved in blood coagulation processes, but there are also others in extra-hepatic tissues, such as vascular and skeletal tissue, suggesting multiple effects of vitamin K on health and disease (65). Vitamin K-dependent proteins exert particular functions in the organism and constitute a family formed by 16 different proteins, such as Matrix Gla Protein, Osteocalcin, Gla-rich proteins and Gas-6 (66).

Vascular smooth cells and chondrocytes synthesize a small secretory protein called Matrix ɤ-carboxyglutamate (GLA) protein (MGP), which is also a potent inhibitor of vascular calcification. To be fully active, two posttranslational modifications are needed: ɤ-glutamate carboxylation dependent on vitamin K and serine phosphorylation (67). While Gla residues are considered a potent inhibitor of vascular calcification, phosphoserine residues have been linked to the secretion of MGP into the extracellular matrix (67). Vitamin K participates in the gamma-carboxylation process transforming the decarboxylated MGP into its active carboxylated forms. In addition, MGP activated by the action of vitamin K are able to bind calcium crystals thus preventing their deposition in the vascular wall (67). Another proposed mechanism is that carboxylated MGPs are capable of inhibiting the differentiation of vascular smooth cells into chondrocyte- and

osteoblast-like cells, binding bone growth factor BMP-2 and inhibiting its osteo-inductive properties (68,69). Therefore, vitamin K deficiency produces a greater synthesis of inactive (non-carboxylated) MGPs, which is also a risk factor for vascular calcification and cardiovascular disease (70).

Finally, there are different ways to measure vitamin K. Some observational studies measure the self-reported intake of vitamin K, while others measure the status of vitamin K in plasma. Plasma measurements are considered more objective since they reflect the intake and metabolism of vitamin K, in contrast to self-reported measures that only assess intake (71). The status of Vitamin K in plasma can be measured through the determination of the uncarboxylated fractions of certain vitamin K-dependent proteins such as osteocalcin (a marker of bone formation) or MGP. The levels of dephosphorylated uncarboxylated MGP (dp-ucMGP) are considered a functional marker of the bioactivity of vitamin K1 and K2. In this way, high levels of dp-ucMGP correspond to a low vitamin K status (72).

2 OBJECTIVES

OBJECTIVES

For all the above, the aims of this doctoral thesis are:

1. To evaluate the prospective association between habitual coffee consumption and risk of physical function impairment, frailty and disability in a cohort of older adults, paying special attention to subgroups of participants who have a high risk of disability such as women and those with obesity, hypertension and diabetes.
2. To assess the prospective association between habitual coffee consumption and risk of different falls-related outcomes in two populations of older adults in Spain and the United Kingdom: specifically, risk of ≥1 falls, injurious falls and, ≥1 falls with fracture. In addition, the effect of the coffee type consumed in the assessed relationship will be evaluated since it could be different between the two countries.
3. To examine the prospective association between vitamin K and frailty in older adults over 13 years of follow-up using data from the Longitudinal Aging Study Amsterdam (LASA).

The first objective is developed in Article 1, entitled "*Coffee consumption and risk of physical function impairment, frailty and disability in older adults*" and published in *European Journal of Nutrition* (Eur J Nutr 2018. doi: 0.1007/s00394-018-1664-7).

The second objective is developed in Article 2, entitled "*Habitual coffee consumption and risk of falls in 2 European cohorts of older adults*" and published in *The American Journal of Clinical Nutrition* (Am J Clin Nutr 2019. doi: 10.1093/ajcn/nqy369)

The third objective is developed in Article 3, entitled "*High dephospho-uncarboxylated matrix Gla protein concentrations, a plasma biomarker of vitamin K, in relation to frailty: the Longitudinal Aging Study Amsterdam* " and published in *European Journal of Nutrition (*Eur J Nutr 2019. doi: 10.1007/s00394-019-01984-9)

1

COFFEE CONSUMPTION AND RISK OF PHYSICAL FUNCTION IMPAIRMENT, FRAILTY AND DISABILITY IN OLDER ADULTS

INTRODUCTION

Aging entails a progressive functional deterioration of multiples biological systems due to the accumulation of molecular and cellular damages throughout life (73). Thus, older adults are at increased risk of functional impairment (74), frailty (24) and disability (75, 76). For instance, in a systematic review of studies across many countries, the prevalence of frailty was about 10% in those over the age of 60 and up to 25% in those aged 80 years and older (77). In addition, among people over 80 years in the US, 35% report mobility limitations, 50% disability in instrumental activities of daily living (IADLs), and 27% disability in basic activities of daily living (ADLs) (78). In Europe, figures are also very high with values around 30% for mobility limitation, 17% for IADLs disability, and 10% for ADLs disability (79). Accordingly, achieving healthy aging is a public health priority.

Evidence of the dietary factors that affect physical function, frailty and disability is rather limited, and corresponds to some nutrients (antioxidants and B-vitamins) (80-82), foods (fruit, vegetables and dairy) (16,17,29) and dietary patterns (83,19). Coffee is one of the most widely consumed beverages in the world, and has been linked to reduced risk of type 2 diabetes (60,84) and cardiovascular disease (61,85) which, in turn, are main determinant of impaired physical function (86,87). However, we are not aware of any investigation on the effect of coffee on physical functioning. Thus, in this study we tested the hypothesis that habitual coffee consumption is associated with lower risk of physical function impairment, frailty and disability in older adults; specifically we focused on individuals at higher disability risk, such as women (88) and those with obesity (89,90), hypertension (91) and diabetes (90), because in these subjects the effects of coffee could be more evident.

SUBJECT AND METHODS

Study design and participants

Data were taken from the Seniors-ENRICA cohort, whose methods have been reported elsewhere (19,92). The cohort was derived from the ENRICA study (Study on Nutrition and Cardiovascular Risk in Spain), an investigation conducted in 2008-2010 among 12,948 individuals representative of the non-institutionalized adult population of Spain. The study participants aged 60 years or older (n=3,289) comprised the Seniors-ENRICA cohort. At baseline, information on socio-demographic variables, lifestyle, health status and morbidity was collected through a phone interview; also, food consumption was obtained, and physical examination was performed by trained staff at the home of the participants. Two waves of data collection have been performed to update the information of the cohort, the first one in 2012 and a second one in 2015. Study participants gave their informed written consent. The Clinical Research Ethics Committee of 'La Paz' University Hospital in Madrid approved the study protocol.

Study variables

Coffee drinking and food consumption

Habitual consumption of coffee and food in the previous year was collected with a computerized diet history developed from the one used in the EPIC-Spain cohort study, which included 861 foods and beverages (93). Study participants reported the number of cups of coffee consumed per day, and its type (caffeinated or decaffeinated), method of preparation (filtered or unfiltered) and cup size. For data analyses, we standardized the ml of coffee consumed to a 70 ml-cup size for percolated and drip coffee and 50 ml-cup size for espresso coffee. Finally, three categories of coffee intake were considered: no consumption, 1 and ≥2 cups a day.

Caffeine intake was estimated using standard food composition tables (93). Thus, a cup of percolated caffeinated coffee (70 ml) was considered to provide 80 mg of caffeine, a cup of drip caffeinated coffee (70 ml) 115 mg of caffeine, and a cup of espresso caffeinated coffee (50 ml) 75 mg of caffeine. To calculate the total caffeine intake per day we included caffeine from coffee and also from tea (a bag contained 30 mg of caffeine), caffeinated soft drinks (a 200 ml glass contained 20 mg of caffeine, and a

333 ml bottle contained 33 mg) and from chocolate (150 ml of hot chocolate contained 4 mg of caffeine, and 28.34 g of solid chocolate contained 6 mg). Total caffeine intake was energy-adjusted by using the residual method (94). In addition, other nutrients and total energy intake (kcal/d) were also estimated. The adherence to Mediterranean diet was assessed with the Mediterranean Diet Adherence Screener (MEDAS) (95), as an indicator of diet quality.

The validity and reproducibility of the computerized diet history has been described in detail elsewhere (93). In the validation study, we obtained the follow correlations between consumption of coffee and caffeine estimated from the computerized diet history and consumption estimated from the mean of seven 24-hour recalls during one year (coffee, r=0.71; caffeine, r=0.47).

Physical function impairment

We assessed four different domains of physical function: self-reported agility, mobility and overall physical functioning, and an objective measure of lower extremity function. We considered that participants had impaired agility when they answered "a lot" to the following question from the Rosow and Breslau scale (96): "On an average day with your current health, would you be limited in bending and kneeling?", whose categories of response were "yes, a lot", "yes, a little" and "not at all". Likewise, impaired mobility was defined as responding "a lot" to any of the following questions also from the Rosow and Breslau scale (96): "On an average day with your current health, would you be limited in the following activities: 1) picking up or carrying a shopping bag?; 2) climbing one flight of stairs?; 3) walking several city blocks (a few hundred meters)?". Moreover, impaired overall physical functioning was defined as a ≥10-point decrease from baseline to follow-up in the physical component summary score of the 12-Item Short-Form Health Survey (SF-12) (97); we used this cut-off point because a 10-point lower score has been associated with adverse health outcomes (98). Lastly, limitation in the lower extremity function was assessed with the Short Physical Performance Battery (SPPB), which includes three measurements: gait speed across 2.44 meters, balance using three hierarchical tandem tests, and the ability to rise from a chair five times consecutively (99). Each component was scored on a 4-point scale, and the total score was the sum of the three components (range 0-12). A higher score indicates better physical performance.

Although the standard score for functional limitation is ≤9, we used a ≤6-point cut-off because the study participants were community-dwellers who were mostly independent.

Frailty

According to the phenotypic definition proposed by Fried et al (24), frailty was defined as meeting three or more of the following five criteria: 1) exhaustion: an affirmative response to any of two statements taken for the Center for Epidemiologic Studies Depression Scale: "I felt that everything I did was a big effort in the last week" or "I could not get going in the last week"; 2) weakness: the cohort-specific lowest quintile of grip strength adjusted for sex and body mass index (BMI); 3) weight loss: unintentional loss of ≥4.5 kg of body weight in the preceding year; 4) low physical activity: walking ≤2.5 hours/week in men and ≤2 hours/week in women; 5) slow walking speed: the cohort-specific lowest quintile of gait speed over 2.44 meters, adjusted for sex and height.

Disability

IADL was assessed with the Lawton and Brody Scale (100). It evaluates independent complex living skills, including the individual's ability to go shopping, use the telephone, prepare meals, do housework, do laundry, use different means of transportation, take medication and manage finances. This scale allows identifying mild disability. Due to cultural issues, questions about preparation of meals and housework were excluded in men (101). For these reasons, the range of the scale was 0-8 points for women and 0-5 for men, where 0 indicates low function/dependent and 8 or 5 indicates high function/independent. We considered that participants had disability when the score was ≤7 for women and ≤4 for men.

ADL was assessed with the Katz Scale (102). It measures more basic skills, including the ability to perform these activities: bathing, dressing, toileting, getting up, eating and continence. Thus, this scale captures more severe cases of disability. The scale range is 0-6 points. A total score of 6 indicates full function, and 0 indicates the maximum functional impairment. For our study, disability was defined when the score was ≤5 points.

Mortality

All-cause deaths were ascertained by a computerized search of the National Death Index, which contains information on the vital status of all residents in Spain (103). This information was available for 99.9% of the cohort. In total, we identified 177 (5.3%) deaths during follow-up.

Other variables

At baseline, we collected data on age and sex. Educational level was classified into primary, secondary and university studies. Smoking status was categorized as never smoker, former smoker, and current smoker. Individuals were classified according to their alcohol intake as abstainers (<0.1 g/d), moderate drinkers (0.1-39 g/d in men and 0.1-23 g/d in women), and heavy drinkers (≥40 g/d in men and ≥24 g/d in women). Physical activity during leisure time (metabolic equivalent hours/week) was ascertained with the EPIC-cohort questionnaire, validated in Spain (104). Sedentary behavior was approximated by the time (hours/week) spent watching TV. Weight and height were measured under standardized conditions. Body mass index (BMI) was calculated as weight (kg) divided by the square height (m), and obesity was defined as BMI ≥30 kg/m^2. Blood pressure (BP) was measured with a validated sphygmomanometer using standardized procedures, and hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or being under hypertensive drug treatment. Twelve-hour fasting serum glucose was centrally measured, and type 2 diabetes was defined as glucose ≥126 mg/dl or being on oral antidiabetic drugs or insulin. Cognitive function was assessed with the Mini-Mental State Examination (MMSE), and cognitive decline was defined as a MMSE score <23 (105). Finally, participants also reported the following physician-diagnosed diseases: osteomuscular disease (osteo-arthritis, arthritis, and hip fracture), cardiovascular disease (ischemic heart disease, stroke and heart failure), cancer, chronic lung disease (asthma and chronic bronchitis) and depression requiring treatment.

Statistical analysis

We excluded participants with missing data on coffee consumption, with energy intake outside the range of 800-5,000 kcal/d for men and 500-4,000 kcal/d for women, without information on each outcome at baseline, and with impaired physical function at baseline. Thus, this resulted in a different size for analyses on each outcome: 2,037 for impaired

agility (subsample 1); 2,062 for impaired mobility (subsample 2); 1,653 for overall physical functioning (subsample 3); 2,262 for impaired lower extremity function (subsample 4); 1,714 for frailty (subsample 5); 1,564 for IADL disability (subsample 6); and 1,756 for ADL disability (subsample 7) (**Figure 4**). Since we did not perform the SPPB at baseline, we excluded participants who had fatigue at baseline, as a proxy of overall limitation in physical functioning. Baseline fatigue was assessed by asking participants how much time during the past 4 weeks they felt tired; responses of "*all of the time*" or "*most of the time*" were considered positive (106,107); this resulted in 2,262 individuals (subsample 4).

Participants were classified according to levels of coffee consumption. Differences on sociodemographic characteristics, lifestyle and morbidity according to incident functional impairment, frailty and disability were assessed using the Student T-test or analysis of the variance, as appropriate.

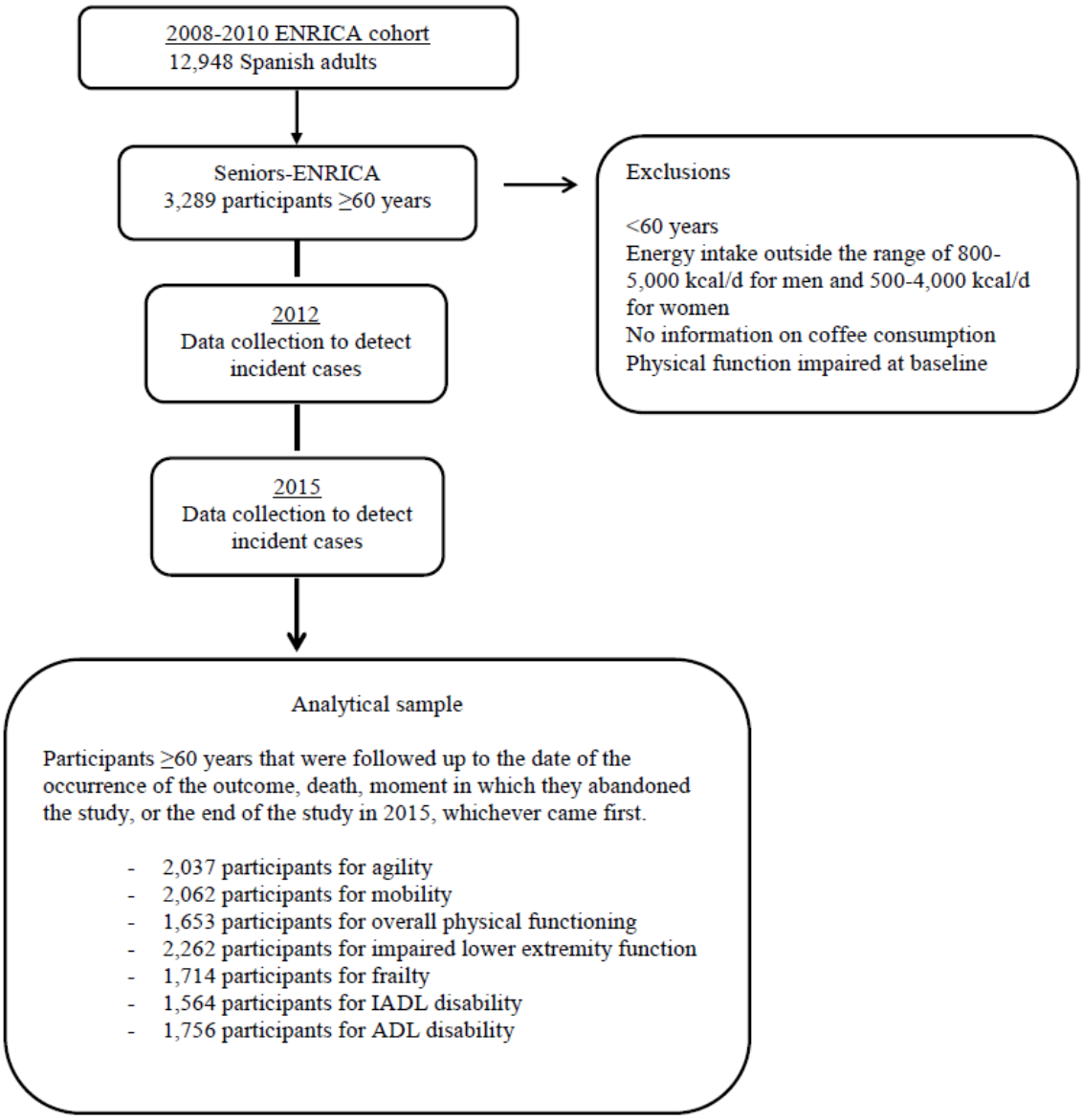
We assessed incident cases in the two waves of data collection, 2012 and 2015. Each wave of data collection lasted 9 months. Person-years of exposure were calculated from the date of the baseline questionnaire until the date of occurrence of the outcome, death, loss to follow-up, or the end of the study, whichever came first. For example, if a participant had an incident event detected in the 2012 wave, his/her follow-up was censored at 2012. In addition, if a participant abandoned the study, he/she was still included in the analyses, contributing to the total person-years of observation. Participants lost to follow-up were mostly women, had lower educational level and reported to suffer more diseases than those who remained in the study until the end; however, coffee consumption was similar in both groups [mean (SD): 1.40 (1.32) cups/d and 1.30 (1.24) cups/d, respectively].

Cox regression models were used to summarize the association between coffee consumption and incidence of the study outcomes. These models were adjusted for potential confounders, including age, sex, educational level, smoking status, heavy drinking, physical activity, time watching TV, energy intake, MEDAS score, BMI, and morbidity. We estimated the hazard ratio (HR) and its 95% confidence interval (CI) of each outcome, according to coffee consumption using non-coffee drinkers as reference. Also, to assess a linear dose-response relation, we modeled the categories of coffee consumption as a continuous variable.

To focus on subjects at higher risk of physical impairment, the main analyses were stratified by sex, hypertension, type 2 diabetes, and obesity. We assessed if results varied with the stratification variables using likelihood-ratio tests, which compared models with and without cross-product interaction terms. Analyses were replicated for different types of coffee (caffeinated, decaffeinated, filtered and unfiltered) and for total caffeine intake.

Statistical analyses were conducted using STATA (version 13.0; Stata Corp., College Station).

Figure 4. Flow diagram



RESULTS

Characteristics of the study participants according to incident functional impairment, frailty and disability are presented in **Table 2**. Those who developed any of the study outcomes were older, more frequently women, and with lower educational level. Moreover, they were less likely to be smokers and heavy drinkers, did less physical activity and spent more time watching TV. Also they had higher BMI, lower energy intake and MEDAS score, and higher frequency of osteomuscular disease, type 2 diabetes, cognitive impairment and depression. At baseline, study participants consumed a mean (SD) of 1.40 (1.32) cups /d of coffee. The mean (SD) consumption for caffeinated coffee was 0.88 (1.19) cups/d, and for decaffeinated coffee 0.53 (0.99) cups/d. Unfiltered coffee was the most consumed type of preparation (**Table 3**).

Over 7.2 years of follow-up, we documented 621 incident cases of impaired agility; 453 of impaired mobility; 554 cases of impairment in overall physical function; 418 of impaired lower extremity function; 198 incident cases of frailty; 158 of IADL disability; and 360 cases of ADL disability. In the total cohort, compared to non-drinkers of coffee, those who consumed ≥2 cups of coffee/d showed lower risk of impaired mobility (HR: 0.74, 95% CI: 0.54-1.00; *P*-trend: 0.04). However, we found no association between coffee consumption and most of the outcomes examined (**Table 4**).

When we focused on different subgroups of participants, consumption of ≥2 cups of coffee/d was associated with lower risk of impaired agility in women (HR: 0.71, 95% CI: 0.51-0.97, *P*-trend: 0.04) and in those with obesity (HR: 0.60; 95% CI: 0.40-0.90, *P*-trend: 0.04). Intake of ≥2 cups of coffee/d was also linked to reduced risk of impaired mobility in women (HR: 0.66; 95% CI: 0.46-0.95, *P*-trend: 0.02) and among individuals with hypertension (HR: 0.70, 95% CI 0.48-1.00, *P*-trend: 0.05). Moreover, among participants with diabetes, those who consumed ≥2 cups/d had lower risk of ADL disability (HR: 0.30, 95% CI: 0.11-0.76, *P*-trend: 0.01) (**Table 4**). Finally, no significant interaction for the subgroups considered was found (data not shown).

Table 5 shows the association of caffeinated, decaffeinated, filtered and unfiltered coffee intake with all the study outcomes. In general, we found no differences in the associations by type of coffee. Additional analyses to examine the association between caffeine intake and physical function showed a positive association between individuals who were on the second and third tertile of caffeine consumption and the risk of

Table 2. Participants' characteristics at baseline according to incident functional impairment, frailty and disability up to 2015.

	Impaired agility (Subsample 1)		Impaired mobility (Subsample 2)		Impaired overall physical function[1] (Subsample 3)		Impaired lower extremity function[2] (Subsample 4)		Frailty (Subsample 5)		IADL disability[3] (Subsample 6)		ADL disability[4] (Subsample 7)	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Participants, n	1416	621	1609	453	1099	554	1844	418	1516	198	1406	158	1396	360
Age, y	67.5 (5.8)	69.5 (6.2)^{c}	67.7 (5.8)	69.9 (6.1)^{c}	67.3 (5.5)	68.8 (6.1)^{c}	67.8 (5.7)	72.7 (6.9)^{c}	68.1 (6.1)	73.1 (7.1)^{c}	67.5 (5.5)	72.5 (7.4)^{c}	67.9 (6.1)	71.1 (6.5)^{c}
Men, %	56.1	34.6^{c}	54.5	28.9^{c}	50.1	44.8^{a}	49.6	38.3^{c}	50.1	29.8^{c}	50.1	37.9^{c}	52.5	28.1^{c}
Education, %														
≤ Primary	46	64	49	65	47	56	51	64	51	75	50	68	51	63
Secondary	28	20	27	21	27	25	26	19	26	14	27	17	24	23
University	26	16^{c}	24	14^{c}	26	19^{c}	23	17^{c}	23	11^{c}	23	15^{c}	25	14^{c}
Current smoker,%	13.1	10.2^{c}	12.1	11.3^{b}	11.6	12.8	12.5	7.6^{c}	12.1	7.1^{b}	11.7	11.4	12.5	7.3^{c}
Heavy drinker,[5] %	9.8	6.6^{c}	9.4	6.2^{c}	9.8	7.7^{b}	9.2	5.1^{c}	8.8	6.5^{c}	9.2	7.6^{c}	9.3	6.1^{c}
Physical activity, MET-h/week	24.1 (15.8)	19.3 (13.7)^{c}	23.7 (15.5)	18.4 (13.7)^{c}	23.2 (16.1)	20.2 (13.8)^{c}	23.1 (15.5)	17.8 (13.5)^{c}	22.4 (15.3)	13.8 (13.1)^{c}	22.6 (15.4)	18.1 (14.8)^{c}	22.6 (15.5)	17.1 (13.9)^{c}
TV watching , h/week	16.6 (10.4)	19.9 (11.8)^{c}	17.1 (10.6)	19.8 (11.5)^{c}	16.5 (9.8)	19.2 (12.6)^{c}	17.6 (10.8)	19.4 (12.1)^{b}	17.2 (10.6)	21.9 (16.8)^{c}	17.1 (10.4)	20.9 (14.1)^{c}	17.2 (10.6)	20.1 (12.4)^{c}
Energy intake, kcal/d	2085 (557)	1929 (574)^{c}	2089 (567)	1872 (541)^{c}	2066 (565)	2001 (584)^{a}	2042 (562)	1950 (584)^{b}	2049 (557)	1906 (637)^{c}	2058 (567)	1894 (555)^{c}	2058 (562)	1916 (580)^{c}
MEDAS, points	2.6 (1.6)	2.3 (1.5)^{c}	2.6 (1.6)	2.5 (1.5)	2.6 (1.6)	2.4 (1.6)^{a}	2.6 (1.6)	2.3 (1.5)^{c}	2.6 (1.6)	2.2 (1.5)^{b}	2.6 (1.6)	2.3 (1.5)^{b}	2.6 (1.6)	2.4 (1.6)
Body mass index, kg/m^{2}	27.5 (3.6)	29.6 (4.5)^{c}	27.9 (3.8)	29.5 (4.8)^{c}	28.1 (4.1)	29.3 (4.6)^{c}	28.2 (3.9)	29.1 (5.1)^{c}	28.2 (4.1)	31.5 (16.8)^{b}	28.3 (4.1)	28.6 (5.2)	28.2 (4.1)	29.7 (4.8)^{c}
Morbidity, %														
Hypertension	62	66	62	68^{a}	61	64	63	65	64	70	63	75^{b}	64	69
Diabetes	12	18^{b}	13	18^{b}	12	18^{b}	13	22^{c}	12	27^{c}	12	19^{a}	13	20^{c}
Cognitive impairment[6]	0.9	3^{c}	1	4^{c}	1	1	1	6^{c}	2	9^{c}	1	10^{c}	1	8^{c}
Osteomuscular disease	36	67^{c}	40	69^{c}	44	54^{c}	44	62^{c}	44	69^{c}	44	57^{b}	44	60^{c}
Cardiovascular disease	3	5	3	7^{c}	3	4	4	9^{c}	4	11^{c}	4	8	5	6
Cancer	1	2	1	2	1	1	1	3^{a}	1	2	1	1	2	1
Chronic lung disease	5	10^{c}	5	12^{c}	6	9	6	10^{a}	7	8	6	14^{b}	7	9
Depression	4	11^{c}	5	13^{c}	5	12^{c}	6	12^{c}	6	14^{c}	6	10^{a}	6	12^{c}

PCS: Physical component summary of the SF-12; SPPB: Short physical performance battery; MET: Metabolic equivalent. IADL: Instrumental activities of daily living; ADL: Basic activity of daily living · ^{a}p<0.05; ^{b}p<0.01;^{c}p<0.001

For continuous variables, the mean (standard deviation) is reported.

[1]10-point decrease in Physical Component Summary of the SF-12; [2] Short Physical Performance Battery score ≤ 6; [3] Lawton-Brody score ≤ 4 (men) and ≤7 (women); [4] Katz score ≤ 5;

[5] Heavy drinker: ≥40 g/d of alcohol in men and ≥24 g/d in women; [6] Mini-Mental State Examination <23.

impaired lower extremity (adjusted HR: 1.32, 95% CI: 1.03-1.69, and HR: 1.39, 95% CI: 1.07-1.79, respectively; *P*-trend: 0.01), compared to those in the lowest tertile of consumption. However, we did not find an association between the consumption of caffeine and the other outcomes related to physical function, frailty or disability.

Table 3. Baseline information about coffee consumption by each subtype of coffee.

		Categories of coffee consumption, n (%)		
	Mean (SD) cups/d	0 cups/d	1 cups/d	≥ 2 cups/d
Overall coffee	1.40 (1.32)	379 (16.8)	1265 (55.9)	618 (27.3)
Caffeinated coffee	0.88 (1.19)	987 (43.6)	910 (40.2)	365 (16.2)
Decaffeinated coffee	0.53 (0.99)	1361 (60.2)	708 (31.3)	193 (8.5)
Filtered coffee	0.16 (0.59)	2007 (88.7)	192 (8.5)	63 (2.8)
Unfiltered coffee	1.24 (1.30)	543 (24.0)	1183 (52.3)	536 (23.7)

Table 4. Hazard ratios (95% confidence interval) for the association between coffee consumption and physical function impairment, frailty and disability during 7.2 year follow-up, by specific subgroups of older adults.

	Coffee consumption, cups/d			
	0	1	≥ 2	*P* for trend
Impaired agility				
Participants, n (N=2,037)	340	1134	563	
Person-years/ n cases	1881/107	6370/351	3191/163	
All[1]	1.00	0.83 (0.66-1.03)	0.80 (0.62-1.03)	0.11
Sex				
Men	1.00	0.94 (0.63-1.40)	1.01 (0.65-1.57)	0.86
Women	1.00	0.78 (0.59-1.03)	0.71 (0.51-0.97)	0.04
Hypertension				
No	1.00	0.88 (0.59-1.32)	0.67 (0.42-1.06)	0.07
Yes	1.00	0.84 (0.64-1.10)	0.92 (0.67-1.26)	0.76
Diabetes				
No	1.00	0.80 (0.63-1.03)	0.80 (0.61-1.06)	0.18
Yes	1.00	0.68 (0.35-1.31)	0.60 (0.29-1.21)	0.20
Obesity				
No	1.00	1.03 (0.77-1.37)	0.95 (0.67-1.33)	0.71
Yes	1.00	0.59 (0.41-0.85)	0.60 (0.40-0.90)	0.04
Impaired mobility				
Participants, n (N=2,062)	340	1152	570	
Person-years/ n cases	1944/79	6681/266	3332/108	
All	1.00	0.89 (0.68-1.15)	0.74 (0.54-1.00)	0.04
Sex				
Men	1.00	1.05 (0.63-1.75)	0.84 (0.46-1.52)	0.47
Women	1.00	0.83 (0.61-1.12)	0.66 (0.46-0.95)	0.02
Hypertension				
No	1.00	1.15 (0.68-1.94)	0.88 (0.48-1.59)	0.49
Yes	1.00	0.80 (0.59-1.09)	0.70 (0.48-1.00)	0.05
Diabetes				
No	1.00	0.84 (0.63-1.11)	0.74 (0.53-1.03)	0.08
Yes	1.00	0.72 (0.33-1.60)	0.56 (0.23-1.34)	0.19
Obesity				
No	1.00	0.89 (0.64-1.23)	0.72 (0.49-1.07)	0.10
Yes	1.00	0.80 (0.52-1.25)	0.70 (0.42-1.15)	0.17
Impaired overall physical function				
Participants, n (N=1,653)	272	906	475	
Person-years/ n cases	1535/87	5136/315	2725/152	
All	1.00	1.03 (0.81-1.32)	0.98 (0.75-1.29)	0.85
Sex				
Men	1.00	1.23 (0.84-1.80)	1.14 (0.75-1.74)	0.67
Women	1.00	0.91 (0.66-1.25)	0.90 (0.62-1.30)	0.62
Hypertension				
No	1.00	1.34 (0.86-2.08)	1.10 (0.67-1.80)	0.94
Yes	1.00	0.92 (0.69-1.24)	0.96 (0.69-1.35)	0.92
Diabetes				
No	1.00	0.99 (0.76-1.28)	1.03 (0.77-1.38)	0.77
Yes	1.00	1.23 (0.58-2.59)	0.85 (0.37-1.96)	0.45
Obesity				
No	1.00	1.14 (0.84-1.56)	1.04 (0.74-1.48)	0.93
Yes	1.00	0.91 (0.61-1.36)	0.92 (0.58-1.46)	0.78

Impaired lower extremity function				
Participants, n (N=2,262)	379	1265	618	
Person-years/ n cases	2164/68	7231/248	3598/102	
All	1.00	1.18 (0.90-1.56)	1.05 (0.77-1.45)	0.87
Sex				
Men	1.00	1.46 (0.89-2.40)	1.42 (0.82-2.48)	0.29
Women	1.00	1.04 (0.74-1.46)	0.88 (0.59-1.32)	0.49
Hypertension				
No	1.00	1.61 (0.95-2.73)	1.35 (0.73-2.49)	0.49
Yes	1.00	1.05 (0.75-1.46)	0.93 (0.63-1.37)	0.68
Diabetes				
No	1.00	1.20 (0.88-1.64)	1.22 (0.85-1.74)	0.31
Yes	1.00	0.77 (0.38-1.54)	0.51 (0.23-1.14)	0.08
Obesity				
No	1.00	1.19 (0.85-1.67)	1.06 (0.71-1.59)	0.80
Yes	1.00	1.18 (0.70-1.98)	1.13 (0.63-2.01)	0.77
Frailty				
Participants, n (N=1,714)	295	957	462	
Person-years/ n cases	1729/32	5662/117	2762/49	
All	1.00	1.12 (0.75-1.69)	1.13 (0.71-1.80)	0.61
Sex				
Men	1.00	2.07 (0.80-5.35)	2.16 (0.77-5.99)	0.19
Women	1.00	0.95 (0.60-1.52)	0.96 (0.56-1.66)	0.91
Hypertension				
No	1.00	1.42 (0.62-3.24)	1.69 (0.66-4.31)	0.27
Yes	1.00	0.94 (0.57-1.53)	0.94 (0.54-1.66)	0.87
Diabetes				
No	1.00	1.08 (0.68-1.72)	1.13 (0.66-1.92)	0.64
Yes	1.00	0.44 (0.15-1.25)	0.51 (0.16-1.59)	0.48
Obesity				
No	1.00	1.61 (0.91-2.96)	1.01 (0.48-2.12)	0.99
Yes	1.00	0.79 (0.44-1.42)	1.27 (0.67-2.38)	0.27
IADL disability				
Participants, n (N=1,564)	256	877	431	
Person-years/ n cases	1505/29	5257/85	2587/44	
All	1.00	0.89 (0.57-1.39)	1.03 (0.63-1.70)	0.78
Sex				
Men	1.00	0.62 (0.30-1.26)	0.62 (0.27-1.37)	0.30
Women	1.00	1.10 (0.61-1.98)	1.37 (0.70-2.65)	0.31
Hypertension				
No	1.00	0.97 (0.39-2.40)	1.15 (0.40-3.25)	0.77
Yes	1.00	0.78 (0.46-1.32)	0.94 (0.52-1.70)	0.96
Diabetes				
No	1.00	0.90 (0.55-1.47)	1.01 (0.57-1.78)	0.90
Yes	1.00	0.75 (0.15-3.54)	2.20 (0.42-11.4)	0.12
Obesity				
No	1.00	0.94 (0.54-1.61)	1.04 (0.56-1.93)	0.86
Yes	1.00	0.92 (0.40-2.14)	0.88 (0.35-2.21)	0.79
ADL disability				
Participants, n (N=1,756)	302	978	476	
Person-years/ n cases	1708/61	5635/199	2748/100	
All	1.00	0.92 (0.68-1.23)	1.14 (0.82-1.59)	0.30
Sex				
Men	1.00	0.89 (0.49-1.62)	1.64 (0.87-3.11)	0.06
Women	1.00	0.95 (0.67-1.35)	0.99 (0.66-1.48)	0.98
Hypertension				
No	1.00	1.31 (0.73-2.34)	1.42 (0.74-2.71)	0.30
Yes	1.00	0.77 (0.54-1.09)	1.05 (0.71-1.56)	0.52
Diabetes				
No	1.00	0.94 (0.67-1.30)	1.36 (0.94-1.96)	0.05
Yes	1.00	0.42 (0.19-0.92)	0.30 (0.11-0.76)	0.01
Obesity				
No	1.00	0.92 (0.63-1.34)	1.03 (0.67-1.59)	0.81
Yes	1.00	0.91 (0.55-1.49)	1.28 (0.74-2.20)	0.23

IADL: Instrumental activities of daily living; ADL: Basic activity of daily living

[1]Cox multivariable regression models adjusted for age, sex, education (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), alcohol consumption (none, moderate, heavy drinker), physical activity (MET-h/week), watching TV (quintiles of h/wk), energy intake (quintiles of kcal/d), MEDAS score (quintiles of score), body mass index, cognitive impairment, osteomuscular disease, cardiovascular disease, cancer, chronic lung disease and depression, except for the stratification variable.
Variables were defined as in Table 1.

Table 5. Hazard ratios (95% confidence interval) for the association between caffeinated, decaffeinated, filtered and unfiltered coffee consumption and physical function impairment, frailty and disability during 7.2 year follow-up.

	Coffee consumption, cups/d			
	0	1	≥ 2	*P* for trend
Impaired agility (N=2,037)				
Caffeinated coffee				
Person-years/ n cases	4878/296	4686/234	1877/91	
Multivariable model[1]	1.00	0.91 (0.77-1.09)	0.86 (0.67-1.10)	0.19
Decaffeinated coffee				
Person-years/ n cases	6886/354	3571/209	985/58	
Multivariable model	1.00	0.91 (0.76-1.08)	1.05 (0.79-1.41)	0.78
Filtered coffee				
Person-years/ n cases	10134/546	966/55	341/20	
Multivariable model	1.00	1.04 (0.78-1.37)	0.92 (0.58-1.45)	0.92
Unfiltered coffee				
Person-years/ n cases	2725/153	5969/331	2748/137	
Multivariable model	1.00	0.87 (0.71-1.06)	0.85 (0.67-1.08)	0.19
Impaired mobility (N=2,062)				
Caffeinated coffee				
Person-years/ n cases	5128/232	4889/157	1939/64	
Multivariable model	1.00	0.82 (0.66-1.01)	0.82 (0.61-1.09)	0.07
Decaffeinated coffee				
Person-years/ n cases	7213/250	3690/168	1053/35	
Multivariable model	1.00	1.08 (0.88-1.32)	0.87 (0.61-1.25)	0.93
Filtered coffee				
Person-years/ n cases	10635/406	983/34	339/13	
Multivariable model	1.00	0.95 (0.66-1.36)	1.10 (0.62-1.92)	0.92
Unfiltered coffee				
Person-years/ n cases	2810/108	6257/255	2889/90	
Multivariable model	1.00	0.97 (0.77-1.22)	0.75 (0.56-1.00)	0.05
Impaired overall physical function (N=1,653)				
Caffeinated coffee				
Person-years/ n cases	3953/242	3885/222	1558/90	
Multivariable model	1.00	0.98 (0.81-1.18)	1.03 (0.80-1.33)	0.88
Decaffeinated coffee				
Person-years/ n cases	5666/324	2811/179	919/51	
Multivariable model	1.00	1.03 (0.85-1.24)	0.93 (0.69-1.26)	0.86
Filtered coffee				
Person-years/ n cases	8328/485	755/46	314/23	
Multivariable model	1.00	1.14 (0.84-1.55)	1.40 (0.91-2.14)	0.08
Unfiltered coffee				
Person-years/ n cases	2441/130	4837/301	2319/123	
Multivariable model	1.00	1.01 (0.81-1.23)	0.89 (0.69-1.14)	0.38
Impaired lower extremity function (N=2,262)				
Caffeinated coffee				
Person-years/ n cases	5660/192	5208/168	2125/58	
Multivariable model	1.00	1.21 (0.97-1.50)	1.02 (0.75-1.38)	0.45
Decaffeinated coffee				
Person-years/ n cases	7820/237	4054/142	1120/39	
Multivariable model	1.00	0.99 (0.80-1.22)	1.12 (0.79-1.58)	0.66
Filtered coffee				
Person-years/ n cases	11522/380	1100/29	371/9	
Multivariable model	1.00	0.90 (0.61-1.32)	0.85 (0.43-1.66)	0.51
Unfiltered coffee				
Person-years/ n cases	3113/93	6768/233	3112/92	
Multivariable model	1.00	1.15 (0.90-1.47)	1.08 (0.80-1.46)	0.56
Frailty (N=1,714)				
Caffeinated coffee				
Person-years/ n cases	4354/92	4130/76	1668/30	
Multivariable model	1.00	1.16 (0.85-1.60)	1.23 (0.80-1.90)	0.25
Decaffeinated coffee				
Person-years/ n cases	6177/115	3093/67	882/16	
Multivariable model	1.00	0.89 (0.65-1.22)	0.87 (0.50-1.49)	0.45
Filtered coffee				
Person-years/ n cases	9005/176	840/16	307/6	
Multivariable model	1.00	1.23 (0.72-2.09)	1.14 (0.49-2.62)	0.48
Unfiltered coffee				
Person-years/ n cases	2493/45	5253/111	2406/42	
Multivariable model	1.00	1.05 (0.73-1.51)	1.05 (0.68-1.62)	0.81

IADL disability (N=1,564)				
Caffeinated coffee				
Person-years/ n cases	3854/81	3958/55	1536/22	
Multivariable model	1.00	0.79 (0.55-1.13)	0.93 (0.56-1.53)	0.46
Decaffeinated coffee				
Person-years/ n cases	5695/89	2811/52	843/17	
Multivariable model	1.00	1.06 (0.74-1.51)	1.17 (0.68-2.01)	0.53
Filtered coffee				
Person-years/ n cases	8278/141	796/13	275/4	
Multivariable model	1.00	1.12 (0.62-2.03)	0.96 (0.34-2.67)	0.85
Unfiltered coffee				
Person-years/ n cases	2192/42	4900/76	2256/40	
Multivariable model	1.00	0.80 (0.54-1.19)	1.05 (0.67-1.65)	0.82
ADL disability (N=1,756)				
Caffeinated coffee				
Person-years/ n cases	4318/180	4119/123	1654/57	
Multivariable model	1.00	0.78 (0.62-0.99)	1.07 (0.78-1.45)	0.66
Decaffeinated coffee				
Person-years/ n cases	6118/201	3092/120	881/39	
Multivariable model	1.00	1.02 (0.81-1.29)	1.29 (0.91-1.83)	0.24
Filtered coffee				
Person-years/ n cases	8929/328	847/25	315/7	
Multivariable model	1.00	0.87 (0.57-1.32)	0.73 (0.34-1.56)	0.31
Unfiltered coffee				
Person-years/ n cases	2474/83	5248/186	2369/91	
Multivariable model	1.00	0.95 (0.73-1.24)	1.25 (0.92-1.69)	0.15

IADL: Instrumental activities of daily living; ADL: Basic activity of daily living.
[1]Cox regression models adjusted for age, sex, education (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), alcohol consumption (none, moderate, heavy drinker), physical activity (MET-h/week), watching TV (quintiles of h/wk), energy intake (quintiles of kcal/d), MEDAS score (quintiles of score), body mass index, cognitive impairment, osteomuscular disease, cardiovascular disease, cancer, chronic lung disease and depression.
Variables were defined as in Table 1.

DISCUSSION

In the total study cohort, no association was observed between habitual coffee consumption and the risk of physical function impairment, frailty or disability in older adults; however, we did find a protective effect of coffee on physical function among women, hypertensive, diabetic and obese patients. Main results did not differ among the different types of coffee examined.

Several models and schemes have been elaborated to understand the disablement process (5,43,108). In one of these models (5), the presence of a disease can produce structural alterations or dysfunctions in specific body systems (musculoskeletal, cardiovascular, etc.), that are known as "impairments". This can lead to functional limitations, which are restrictions on physical and mental actions that could ultimately produce a disability. Disability can be understood as the difficulty to perform activities of daily living, which limits the capacity of the individual and could compromise their quality of life (43). There are different factors (psychosocial, behavioral, lifestyle) that could accentuate or attenuate the disablement process (5). For this reason, the different endpoints examined in our study allowed us to evaluate in detail different spheres of physical function framed within the process of disability and, therefore, allows us to understand the effect of coffee on each of them.

No other studies assessed this association yet in humans. However, several studies on animal models have examined the effect of coffee consumption on morphology and function of skeletal muscle, as well as its relationship with sarcopenia, which results in limitations in physical function, frailty (109) or disability (62). Guo et al. in a study *in vivo* on mice (110) concluded that coffee administration may reduce the progression of sarcopenia, by decreasing the serum inflammatory mediators and increasing the skeletal muscle weight, the grip strength and accelerating the regeneration of the injured muscle. In addition, in an *in vitro* study, the same authors concluded that coffee administration improved the proliferation rate and the DNA synthesis in the satellite cells of the muscle, which produces an increase in muscle mass and the maintenance of muscle integrity (110). These effects have been attributed to total coffee consumption but not to specific substances present in this beverage. Moreover, some components in coffee, mainly polyphenols, have been shown to induce autophagy in various tissues (liver, muscle and heart) in mice (111). Autophagy is an important process required for the renewal of

mitochondria and for prevention of mitochondrial damage during physical activity, in addition to improving and maintaining muscle mass and integrity (111). Moreover, coffee improves insulin sensitivity and increases glucose uptake into muscle, which allows better skeletal muscle function (62). Therefore, it is plausible that coffee could reduce indirectly the risk of physical function impairment, frailty or disability through slowed age-related sarcopenia and improved muscle integrity.

These same mechanisms can also contribute to the lower risk of type 2 diabetes associated with coffee consumption (60). In addition, type 2 diabetes is a major disabling disease in the old people because insulin resistance is associated with a decrease in muscle strength, due to an alteration in muscle glucose use, intracellular energy production and muscle contraction (112,113). The decreased risk of physical function impairment in coffee consumers observed in our study among participants at high risk of disability might simply reflect that coffee effects are more evident and relevant in those who already have decreased insulin sensitivity (because of obesity or type 2 diabetes), greater sarcopenia (e.g. women) or subclinical disease (older hypertensive), which are key components of the disablement process.

Unfiltered coffee is the most consumed type of coffee in Spain, in contrast with other countries such as the United States, where coffee is consumed mainly through filtering. The preparation method determines the concentration of substances on coffee. Thus, filtered coffee is free of the diterpenes cafestol and kahweol (58,114). By contrast, these diterpenes are found in unfiltered coffee, and have been found to increase plasma levels of total cholesterol (56,115), triglycerides (57) and blood lipoproteins (57); therefore, they could have a detrimental effect on cardiovascular disease, which is a main determinant of disability. Since we did not observe differences between filtered and unfiltered coffee on physical function impairment, diterpenes do not seem to be mediating this association. However, the association between caffeine intake and increased risk of impaired lower extremity function suggests that caffeine and coffee have different effects on health.

One of the strengths of this study was the estimation of coffee consumption through a validated diet history, which allowed detailed information on the type of coffee consumed and its preparation. Other strengths were the prospective design, the relative long follow-up period and the inclusion of physical performance tests as an objective measure of

physical performance. Another advantage was the large number of confounders that were considered in the analyses, including physical activity and comorbidity. Among the limitations, we did not account for variations in coffee consumption and other lifestyles that might have occurred during the follow-up, although it is presumable that long-term established habits, such as diet, have been maintained during the study period. Participants lost to follow-up were somewhat different from those who continued in the study; thus, although person-years of observation of these participants were included in the analyses, a certain degree of selection bias cannot be ruled out. Also, adjustment for a score of global diet quality might have not removed completely the effect of individual foods and nutrients on physical function. In addition, we performed these analyses in a cohort of community-dwelling old people, which only allowed examining the less severe cases of physical function impairment and disability in the population. Another limitation of the study was the lack of measurement of the lower extremity function at baseline; therefore, we eliminated those who reported fatigue as a proxy of prevalent cases of impaired physical function of the lower extremities. However, this was a conservative approach since individuals may feel fatigued by other causes unrelated to physical function. Finally, as in any observational study, some residual confounding may persist.

In conclusion, our results suggest that habitual coffee consumption does not pose a risk to physical functioning in the older people, and that it might be even beneficial in persons at higher risk of functional limitations, including women and those with hypertension, obesity or diabetes.

5

HABITUAL COFFEE CONSUMPTION AND RISK OF FALLS IN 2 EUROPEAN COHORTS OF OLDER ADULTS

INTRODUCTION

Falls in old people represent a major public health problem. About 28-35% of people aged over 65 years fall at least once a year and this figure is even higher in those over 75 years of age (116,33). Falling is also associated with adverse health outcomes (117,118) and poses a major cost to the health care systems (120,121). Specifically, falls are one of the main causes of injury (122), disability (123,124) and premature death in old people (125,126). Therefore, prevention of falls is essential to ensure the well-being of the older population.

Knowledge of dietary factors that affect the risk of falls is rather limited and mainly corresponds to certain nutrients, such as calcium (35,127), vitamin D (128,129) and protein intake (37,39), as well as some foods, such as alcohol beverages (129) or fruit and vegetables (130-132). A poor nutritional status has also been associated with increased risk of falls and fractures (133). One of the foods that merits attention in relation to risk of falling is coffee. Habitual coffee consumption has been associated with lower risk of type 2 diabetes (60,84), cardiovascular disease (61) and sarcopenia (62,110), which are strong risk factors of falls. Moreover, caffeine intake stimulates attention, vigilance and reaction time (53,134). Therefore, a protective effect of coffee on the risk of falling can be hypothesized.

The aim of this study was to assess the association between habitual coffee consumption and risk of several falls-related outcomes: ≥1 falls, injurious fall, and ≥1 falls with fracture. We examined this association in older adults from Spain and United Kingdom, to assess the generalizability of the results. Moreover, since the type of coffee consumed may differ between both countries, we could also assess its influence on falls risk.

SUBJECTS AND METHODS

Study design and participants

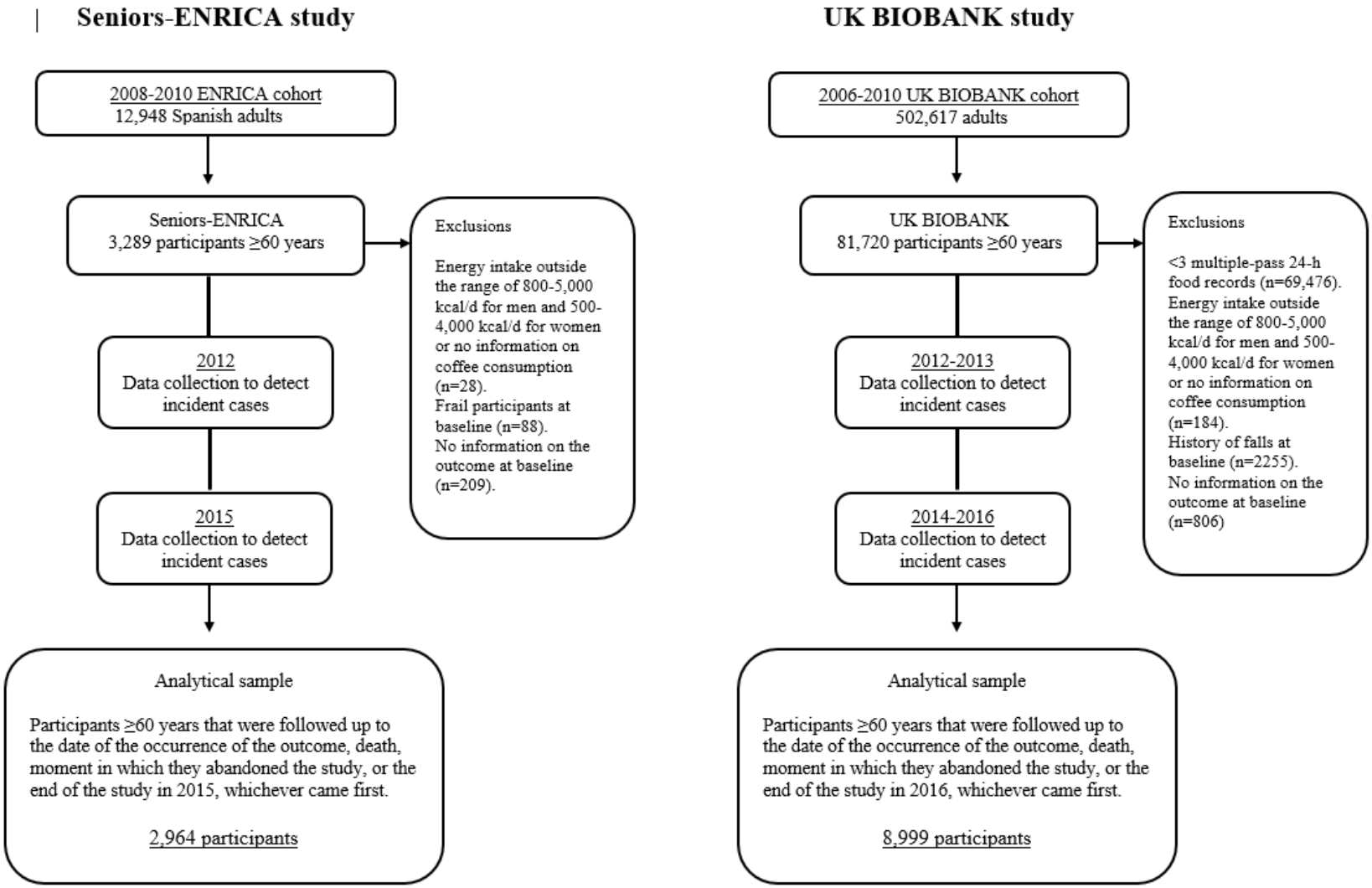
The Seniors-ENRICA study

We used data from the ENRICA study (Study on Nutrition and Cardiovascular Risk in Spain) (92). Briefly, this cohort was established in 2008-2010 when 12,948 individuals representative of the non-institutionalized adult population of Spain were selected. The study participants aged 60 years or older (n=3,289) comprised the Seniors-ENRICA cohort. At baseline, information on socio-demographic variables, lifestyle, health status and morbidity was collected through a phone interview. In two subsequent home visits, trained research staff collected dietary information and conducted a physical exam. Subsequently, two waves of data collection were performed in 2012 and 2015 to update information of the cohort (**Figure 5**). Study participants gave their informed written consent. The Clinical Research Ethics Committee of 'La Paz' University Hospital in Madrid approved the study protocol.

The UK Biobank Study

The UK Biobank is a large population-based cohort study that recruited more than 500,000 men and women between 40-69 years (81,720 were ≥60 y) in the 2006-2010 period throughout the United Kingdom (UK) (135). At baseline, in the assessment centers, the participants had to sign an informed consent, complete a touch-screen questionnaire, conduct a face-to-face interview and provide different anthropometric measurements and samples of blood, urine and saliva, as well as perform some physical tests. Subsequently, a subsample of participants was followed-up and provided updated information in 2012-13 and 2014-16. (**Figure 5**). This study was performed under generic ethical approval obtained by UK Biobank from the NHS National Research Ethics Service (ref 11/NW/0382, 17 June 2011).

Figure 5. Flow-chart



Study variables

Coffee and other dietary variables

In the Seniors-ENRICA, food consumption was collected with an electronic diet history developed from that used in the EPIC-Spain cohort study (93). This instrument included 860 foods and beverages, and took into account portion size, cooking methods, degree of food processing, and weekly and seasonal variations in food consumption. Coffee consumption was assessed in detail by asking participants whether they consumed caffeinated or decaffeinated coffee, the method of preparation [filtered (drip coffee), non-filtered (percolated, espresso), and instant], and cup size. For data analyses, we standardized the amount of coffee consumed to a 75 ml-cup size for percolated and drip coffee and 50 ml-cup size for espresso coffee. We considered an amount of 3.5 g of instant coffee per cup. Finally, three categories of coffee consumption were considered: <1, 1 and ≥2 cups/day.

Caffeine intake was estimated using standard food composition tables (93). Thus, a cup of percolated coffee, drip coffee, espresso and instant coffee was considered to provide 80, 115, 75 and 65 mg of caffeine, respectively. To calculate the total caffeine intake per day we included caffeine from coffee and also from tea (a bag provided 30 mg of caffeine), caffeinated soft drinks (a 200 ml glass provided 20 mg of caffeine, and a 333 ml can provided 33 mg) and from chocolate [150 ml of hot chocolate provided 4 mg of caffeine, and 28.34 g (1 ounce) of solid chocolate provided 6 mg]. Total caffeine intake was energy-adjusted by using the residual method (94). In addition, other nutrients and total energy intake (kcal/d) were also estimated (93).

The validity and reproducibility of the diet history has been reported in detail elsewhere (93). In the validation study, there was a moderate-to good correlation between consumption of coffee and caffeine estimated from the diet history and the mean of seven 24-hour recalls during one year (coffee, r=0.71; caffeine, r=0.47).

In the UK Biobank, dietary information was collected through five web-based 24-h recalls (Oxford WebQ) (136). The first one was administered at baseline in the assessment centers and the remaining four in the period of 2011-2012 with an estimated interval of 6 months, via e-mail. This took into account seasonal variations in food consumption. The Oxford WebQ included more than 200 individual foods frequently consumed in the UK.

For the present analyses, only participants who completed three or more 24-h recalls were selected, to reflect habitual diet. Coffee consumption was assessed in detail by asking participants whether they consumed caffeinated or decaffeinated coffee, and the method of preparation [instant, filtered, and non-filtered (cappuccino, latte, espresso)]. The possible recall responses were: none, 0.5, 1, 2, 3, 4, 5, and ≥6 cups per day. A value of 6 was used in our analyses for those reporting to consume "≥6 cups". Subsequently, the average consumption in cups/day was calculated between the 24-h recalls. Finally, three categories of coffee consumption were considered: <1, 1 and ≥2 cups/day. Total energy, and nutrients related to bone metabolism, muscle function and visual function (vitamin D, carotene, folate, calcium and protein intakes) were estimated with standard composition food tables in the UK (137).

Falls

In the Seniors-ENRICA study, falls were reported at the follow-up visits in wave 2 and 3. Trained interviewers asked participants: "How many times have you fallen down since the last interview?" Participants also reported if, as a result of the fall, they suffered an injury (contusion, bruise, sprain, superficial injury or deep wound) or fracture (hip, leg, shoulder or arm fracture). Therefore, we used the following outcomes in our analyses: a) ≥1 falls, b) injurious fall, ad c) ≥1 fall with fracture.

In the UK Biobank, falls were reported in wave 2 and 3 by asking the participants “In the last year have you had any falls?” The possible answers were “no falls”, “only one fall”, and “more than one fall”. We did not use data on falls with fractures in this cohort due to the very small number found (n= 19).

Mortality

In the Seniors-ENRICA study, all cause-mortality was ascertained by a computerized search of the National Death Index, which contains information on the vital status of all residents in Spain (103). This information was available for 99.9% of the cohort. In total, we found that 177 participant (5.3%) died during the follow-up. In the UK Biobank, all cause-mortality was obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland) (138).

Other variables

At baseline in the Seniors-ENRICA, we collected data on age, sex, educational level, smoking status and alcohol intake. Study participants were classified as abstainers (<0.1 g/d), moderate drinkers (0.1-39 g/d in men and 0.1-23 g/d in women) and heavy drinkers (≥40 g/d in men and ≥24 g/d in women). Weight and height were measured in each participant under standardized conditions. Body mass index (BMI) was calculated as weight (kg) divided by the square height (m), and obesity was defined as BMI ≥30 kg/m^2. Physical activity during leisure time (metabolic equivalent hours/week) was ascertained with the EPIC-cohort questionnaire, validated in Spain (104). Blood pressure (BP) was measured with a validated sphygmomanometer using standardized procedures, and hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or being under hypertensive drug treatment. Twelve-hour fasting serum glucose was centrally measured with standard techniques, and type 2 diabetes was defined as glucose ≥126 mg/dl or being treated with anti-diabetic drugs or insulin. Sleep duration as well as use of sleeping pills was self-reported. Finally, participants reported if they had received a diagnosis of osteomuscular disease (osteo-arthritis and arthritis).

In the UK Biobank study, most of the variables were collected and categorized as in Seniors-ENRICA study, except physical activity which was assessed with questions from the short International Physical Activity Questionnaire (IPAQ) (139), and the diagnosis of diabetes and hypertension, which were reported by the participants.

Statistical analyses

In the Seniors-ENRICA, we excluded participants with energy intake outside the range of 800-5,000 kcal/d for men and 500-4,000 kcal/d for women at baseline and with missing data on coffee consumption. In addition, we excluded those participants who were frail at baseline, because frailty is a strong predictor of falls and we had no information on falls at baseline (140). In the UK Biobank, among those ≥60 y, we excluded participants without a minimum of three web-based 24-h recall questionnaires, those with implausible high or low energy intake or missing on coffee consumption, and those who reported falls at baseline. This resulted in an analytical sample of 2,964 individuals in the Seniors-ENRICA and 8,999 in the UK Biobank Study.

Participants were classified according to baseline coffee consumption. Differences in sociodemographic characteristics, lifestyle and morbidity across categories of coffee intake were assessed with p values from linear or logistic regression using ordinal categories as predictors.

Person-years of follow-up were calculated from the date of the baseline questionnaire until the date of the outcome, death, loss to follow-up, or the end of the study, whichever came first. Cox models were used to investigate the association between coffee consumption and the incidence of falls. Several models were built. The first one was adjusted for age and sex. A second model was additionally adjusted for other potential confounders, including education, smoking, alcohol intake, BMI, physical activity, sleep duration, intake of energy, calcium, vitamin A, vitamin D and total protein, hypertension, diabetes, osteomuscular disease, and use of sleeping pills. Moreover, when we assessed the separate association of caffeinated and decaffeinated coffee, we built a third model additionally adjusted for the other type of coffee. We estimated a hazard ratio (HR) and its 95% confidence interval (CI) for each category of coffee consumption, compared with no consumption. To investigate the linear dose-response relation, we modeled the categories of coffee as a continuous variable. In the Seniors-ENRICA, these analyses were replicated using cumulative coffee consumption as the main exposure in order to account for changes in coffee consumption during follow-up.

Similar analyses were conducted to examine the association between total caffeine intake (mg/dl) and falls; this was performed in the Seniors-ENRICA, since caffeine intake was not available for UK Biobank participants. Finally, we tested if main results varied by categories of the following variables that are associated with different baseline risk of falls: age, sex, obesity, osteomuscular disease, protein intake, alcohol consumption, sleep duration and physical activity; to this end, we used likelihood-ratio tests that compared models with and without cross-product interaction terms. Analyses by age and osteomuscular disease were performed only in the Seniors-ENRICA, since there were no individuals aged >75 years in the UK Biobank and we did not have access to information about osteomuscular disease in this cohort.

The HRs from multivariable models for the risk of having ≥1 falls in each cohort were pooled to obtain a summary risk estimate with the use of an inverse variance-weighted meta-analysis by random-effects models, which allowed for between-study

heterogeneity. All analyses were conducted using Stata (version 13.0; Stata Corp., College Station).

RESULTS

Mean coffee consumption was 1.37 (standard deviation: 1.31) cups/d among participants in the Seniors-ENRICA, and 1.75 (1.38) cups/d among the UK Biobank participants. Caffeinated coffee accounted for most of this consumption in both populations. The mean (SD) intake of caffeinated and decaffeinated coffee in the Seniors-ENRICA was 0.87 (1.17) and 0.52 (0.96) cups/d, respectively, and in the UK Biobank 1.44 (1.37) and 0.31 (0.86) cups/d respectively. The method of preparation most frequent in the Spanish cohort was non-filtered coffee [1.22 (1.29) cups/d vs 0.16 (0.59) of filtered, and 0.24 (0.71) cups/d of instant]. Similarly, non-filtered coffee was the method preferred in the English cohort [1.28 (1.33) cups/d vs 0.48 (0.81) of filtered, and 1.10 (1.31) cups/d of instant]. In the Seniors-ENRICA, participants with higher consumption of coffee were younger and more likely to be current smokers, and reported higher intake of energy and vitamin D. In the UK Biobank, participants with higher coffee consumption had higher educational level, as well as higher intake of energy and retinol, and were more likely to be current smokers and heavy drinkers. (**Table 6**).

Over 7.2 years of follow-up in Seniors-ENRICA, 793 individuals reported ≥1 falls, 566 injurious falls, and 143 falls with fracture. In full adjusted analyses, compared with participants who consumed <1 cup/d of coffee, those who consumed 1 and ≥2 cups/d had a decreased risk of ≥1 falls [HR: 0.88 (95% CI: 0.73, 1.07) and 0.79 (0.63, 0.98), respectively; p-trend: 0.03]. Caffeinated coffee accounted for most of the association [HR: 0.84 (95% CI: 0.71, 0.99) for 1 cup/d and 0.76 (0.61, 0.96) for ≥2 cups/d, p-trend: 0.01].

In the UK Biobank, over 10.2 years of follow-up, 199 individuals reported ≥1 falls. Caffeinated coffee, but not decaffeinated coffee, was associated with lower risk of falling [HR: 0.52 (95% CI: 0.33, 0.83) for 1 cups/d and 0.60 (0.37, 0.96) for ≥2 cups/d, p-trend: 0.04]. (**Table 7**). The pooled HRs of falling across categories of total coffee consumption for the two cohorts were 1.0, 0.75 (0.52, 1.07), and 0.74 (0.62, 0.90); p-trend: 0.001. Corresponding figures for caffeinated coffee were 0.67 (0.42, 1.07) and 0.70 (0.56, 0.87); p-trend <0.001. Lastly, the pooled HRs across categories of decaffeinated coffee consumption were 1.0, 0.99 (0.84, 1.16), and 0.87 (0.69, 1.09); p-trend: 0.34.

Table 6. Participants' characteristics at baseline across the categories of coffee consumption.

	Seniors-ENRICA study (N=2,964)			UK Biobank study (N=8,999)		
	Total coffee consumption, cups/d			Total coffee consumption, cups/d		
	<1	1	≥ 2	<1	1	≥ 2
Participants, n	512	1670	782	1264	3831	3904
Age, y	70.1 (6.9)	69.2 (6.6)	68.0 (6.1)[5]	63.6 (2.7)	63.6 (2.7)	63.7 (2.7)
Men, %	46.5	45.4	51.0	52.5	52.1	54.5
Educational level, %						
≤ Primary	58.9	59.1	51.8	12.6	9.5	8.5
Secondary	22.7	22.8	25.8	32.3	30.4	27.7
University	18.4	18.1	22.4	55.1	60.1	63.8[5]
Current smoker, %	6.6	10.1	19.7[5]	3.6	3.9	6.4[5]
Heavy drinker[1], %	22.6	22.6	21.9	11.5	13.8	15.1[5]
BMI, kg/m [2]	27.7 (4.2)	28.7 (4.5)	28.7 (4.5)	26.6 (4.2)	26. (4.2)	26.8 (4.1)[5]
Physical activity, METs-h/week[2]	22.4 (16.1)	21.1 (14.9)	22.0 (14.9)	44.6 (54.6)	44.1 (48.2)	42.5 (48.4)
Sleep duration, h/d	6.9 (1.5)	6.9 (1.4)	6.9 (1.4)	7.3 (1.0)	7.3 (1.0)	7.3 (0.9)
Energy intake, kcal/d	1915 (583)	2020 (575)	2046 (578)[5]	2083 (560)	2093 (495)	2149 (489)[6]
Intake of vitamin D, µg/d	3.4 (2.9)	3.3 (2.9)	3.6 (3.3)[5]	3.0 (2.1)	3.1 (2.1)	3.1 (2.2)
Intake of vitamin A[3], µg/d	835 (626)	817 (504)	857 (625)	-	-	-
Intake of retinol, µg/d	-	-	-	319 (144)	330 (141)	350 (146)[6]
Intake of carotene, µg/d	-	-	-	3131 (2182)	3124 (1929)	3078 (1856)
Intake of calcium, mg/dL	873 (359)	877 (319)	889 (340)	988 (369)	982 (300)	991 (293)
Intake of protein, g/d	89.6 (30.8)	90.5 (25.4)	92.9 (25.7)	82.3 (20.7)	82.0 (19.0)	83.1 (19.3)[5]
Intake of caffeine, mg/d	17.3 (35.4)	46.4 (55.2)	151.6 (156.6)[6]	-	-	-
Diagnosed diseases, %						
Hypertension	64	65	62	37	35	32[5]
Diabetes	14	17	14	5	4	5
Osteomuscular disease[4]	48	49	47	-	-	-
Use of sleeping pills, %	17.5	13.8	13.9	0.4	0.6	0.4
Type of coffee, cup/d						
Caffeinted	0	0.61 (0.58)	1.97 (1.63)	0	0.87 (0.54)	2.48 (1.42)
Decaffeinated	0	0.39 (0.51)	1.11 (1.54)	0	0.17 (0.38)	0.56 (1.21)

MET: Metabolic equivalent. BMI: Body Mass Index.

For continuous variables, the mean (standard deviation) is reported.

[1] Heavy drinker: ≥40 g/d of alcohol in men and ≥24 g/d in women.

[2] In the UK Biobank study, physical activity was measured in METs-min/week.

[3] In the Seniors-ENRICA study, total intake of vitamin A corresponds to the sum of retinol (µg/d) and retinol equivalents (µg/d). In the UK Biobank study the amount of retinol (µg/d) and carotenes (µg/d; without transforming to retinol equivalents) was measured separately.

[4] Osteo-arthritis and arthritis.

[5]p<0.05; [6]p<0.001. P values were calculated from linear and logistic regressions using ordinal categories as predictors.

In addition, in the Seniors-ENRICA, we found some tendency to lower risk of injurious falls among those consuming caffeinated coffee [0.83, (0.68, 1.00) for 1 cup/d, and 0.83 (0.64, 1.09) for ≥2 cups/d, p-trend: 0.09]. No association was observed between caffeinated or decaffeinated coffee consumption and risk of falls with fracture (**Table 8**). Moreover, when cumulative coffee consumption was used, the results were similar (data not shown).

In **Table 9**, we presented the association between caffeine intake (mg/dl) and falls risk in the Seniors-ENRICA. Participants in the highest tertile of caffeine intake had lower risk of falls [HR: 0.80, 95% CI: 0.67, 0.96, p-trend: 0.02], compared with those in the lowest tertile. Also, the risk of injurious falls was reduced among participants in the highest tertile of intake: 0.78 (0.63, 0.97), p-trend: 0.03. No association was found for falls with fracture.

Finally, we examined the association between total coffee consumption and the risk of ≥1 fall in specific subgroups of participants in both cohorts. We found that the inverse association between coffee and risk of falling was rather consistent regardless of sex, obesity, protein intake, sleep duration, physical activity and alcohol consumption (all p for interaction >0.05).

Table 7. Hazard ratios (95% confidence interval) for the association between total, caffeinated and decaffeinated coffee consumption and the risk of ≥1 falls in the Seniors-ENRICA study (N=2,964) and in the UK Biobank study (N=8,999).

	Coffee consumption, cups/d			
	<1	1	≥ 2	*P* for trend
Seniors-ENRICA				
Total coffee				
Person-years/ cases	2501/146	8350/454	3987/193	
Age- and sex-adjusted model	1.00	0.89 (0.74, 1.07)	0.81 (0.65, 1.01)	0.06
Multivariable[1]	1.00	0.88 (0.73, 1.07)	0.79 (0.63, 0.98)	0.03
Caffeinated coffee				
Person-years/ cases	6485/384	5997/301	2356/108	
Age- and sex-adjusted model	1.00	0.85 (0.73, 0.99)	0.80 (0.73, 0.99)	0.01
Multivariable[1]	1.00	0.86 (0.73, 0.99)	0.76 (0.62, 0.96)	0.01
Multivariable[2]	1.00	0.84 (0.71, 0.99)	0.76 (0.61, 0.96)	0.01
Decaffeinated coffee				
Person-years/ cases	8999/458	4591/272	1248/63	
Age- and sex-adjusted model	1.00	1.10 (0.95, 1.28)	0.95 (0.73, 1.23)	0.68
Multivariable[1]	1.00	1.10 (0.95, 1.28)	0.95 (0.72, 1.24)	0.69
Multivariable[2]	1.00	1.01 (0.86, 1.20)	0.85 (0.64, 1.12)	0.47
UK Biobank				
Total coffee				
Person-years/ cases	4557/35	13728/85	14217/79	
Age- and sex-adjusted model	1.00	0.74 (0.50, 1.11)	0.70 (0.47, 1.04)	0.53
Multivariable[3]	1.00	0.61 (0.37, 0.98)	0.64 (0.39, 1.03)	0.13
Caffeinated coffee				
Person-years/ cases	8005/63	13046/69	11450/67	
Age- and sex-adjusted model	1.00	0.63 (0.44, 0.88)	0.72 (0.51, 1.01)	0.08
Multivariable[3]	1.00	0.51 (0.33, 0.79)	0.60 (0.38, 0.93)	0.02
Multivariable[4]	1.00	0.52 (0.33, 0.83)	0.60 (0.37, 0.96)	0.04
Decaffeinated coffee				
Person-years/ cases	26212/157	4077/29	2212/13	
Age- and sex-adjusted model	1.00	1.06 (0.71, 1.57)	1.07 (0.61, 1.89)	0.74
Multivariable[3]	1.00	0.91 (0.53, 1.58)	1.64 (0.86, 3.11)	0.30
Multivariable[4]	1.00	0.84 (0.48, 1.48)	1.14 (0.57, 2.27)	0.97
Pooled results				
Total coffee[5]	1.00	0.75 (0.52, 1.07)	0.74 (0.62, 0.90)	0.001
Caffeinated coffee[6]	1.00	0.67 (0.42,1.07)	0.70 (0.56, 0.87)	<0.001
Decaffeinated coffee[6]	1.00	0.99 (0.84, 1.16)	0.87 (0.69, 1.09)	0.34

[1] Cox model adjusted for age, sex, educational level (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), alcohol consumption (none, moderate, heavy drinker) , BMI (tertiles of kg/m^2), physical activity (tertiles of METs-h/week), sleep duration (tertiles of h/d), energy intake (tertiles of kcal/d), intake of vitamin D (tertiles of µg/d), intake of vitamin A (tertiles of µg/d), intake of calcium (tertiles of mg/d), protein intake (tertiles of g/d), and for hypertension, diabetes, osteomuscular disease, and use of sleeping pills at baseline.

[2] Model 1 additionally adjusted for the other type of coffee.

[3] Cox model adjusted for age, sex, educational level (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), alcohol consumption (none, moderate, heavy drinker) , BMI (tertiles of kg/m^2), physical activity (tertiles of METs-min/week), sleep duration (tertiles of h/d), energy intake (tertiles of kcal/d), intake of vitamin D (tertiles of µg/d), intake of retinol (tertiles of µg/d), intake of carotene (tertiles of µg/d), intake of calcium (tertiles of mg/d), protein intake (tertiles of g/d), and for hypertension, diabetes, and use of sleeping pills at baseline

[4] Model 3 additionally adjusted for the other type of coffee.

[5] From multivariable models 1 and 3 combined using random-effects model.

[6] From multivariable models 2 and 4 combined using random-effects model.

Table 8. Hazard ratios (95% confidence interval) for the association between total, caffeinated and decaffeinated coffee consumption and the risk of injurious falls and falls with fracture in the Seniors-ENRICA study (N=2,964).

	Coffee consumption, cups/d			
	<1	1	≥ 2	*P* for trend
Risk of injurious falls[1]				
Total coffee				
Person-years/ cases	2559/97	8492/329	4075/140	
Age- and sex-adjusted model	1.00	0.99 (0.79, 1.24)	0.88 (0.68, 1.15)	0.31
Multivariable[2]	1.00	0.99 (0.78, 1.25)	0.88 (0.67, 1.15)	0.29
Caffeinated coffee				
Person-years/ cases	6611/274	6110/210	2405/82	
Age- and sex-adjusted model	1.00	0.83 (0.69, 0.99)	0.84 (0.65, 1.07)	0.06
Multivariable[2]	1.00	0.83 (0.69, 1.00)	0.83 (0.65, 1.07)	0.06
Multivariable[3]	1.00	0.83 (0.68, 1.00)	0.83 (0.64, 1.09)	0.09
Decaffeinated coffee				
Person-years/ cases	9168/323	4678/199	1280/44	
Age- and sex-adjusted model	1.00	1.15 (0.96, 1.37)	0.93 (0.68, 1.28)	0.59
Multivariable[2]	1.00	1.14 (0.95, 1.37)	0.94 (0.68, 1.29)	0.61
Multivariable[3]	1.00	1.07 (0.88, 1.29)	0.85 (0.61, 1.19)	0.72
Risk of falls with fracture[4]				
Total coffee				
Person-years/ cases	2674/23	8889/83	4218/37	
Age- and sex-adjusted model	1.00	1.08 (0.68, 1.71)	1.06 (0.63, 1.79)	0.85
Multivariable[2]	1.00	1.12 (0.70, 1.81)	1.11 (0.66, 1.91)	0.72
Caffeinated coffee				
Person-years/ cases	6930/60	6362/62	2489/21	
Age- and sex-adjusted model	1.00	1.21 (0.84, 1.73)	1.07 (0.65, 1.77)	0.55
Multivariable[2]	1.00	1.27 (0.88, 1.83)	1.14 (0.68, 1.89)	0.39
Multivariable[3]	1.00	1.31 (0.88, 1.94)	1.18 (0.69, 2.03)	0.38
Decaffeinated coffee				
Person-years/ cases	9545/85	4910/46	1326/12	
Age- and sex-adjusted model	1.00	0.96 (0.67, 1.38)	0.99 (0.54, 1.81)	0.88
Multivariable[2]	1.00	0.97 (0.67, 1.40)	1.01 (0.55, 1.86)	0.94
Multivariable[3]	1.00	1.05 (0.71, 1.56)	1.14 (0.60, 2.18)	0.66

[1] Falls with contusion, bruise, sprain, superficial injury or deep wound.

[2] Cox model adjusted for age, sex, educational level (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), alcohol consumption (none, moderate, heavy drinker) , BMI (tertiles of kg/m^2), physical activity (tertiles of METs-h/week), sleep duration (tertiles of h/d), energy intake (tertiles of kcal/d), intake of vitamin D (tertiles of µg/d), intake of vitamin A (tertiles of µg/d), intake of calcium (tertiles of mg/d), protein intake (tertiles of g/d), and for hypertension, diabetes, osteomuscular disease, and use of sleeping pills at baseline.

[3] Multivariable model additionally adjusted for the other type of coffee.

[4] Falls with leg, hip, arm or shoulder fracture.

Table 9. Hazard ratios (95% confidence interval) for the association between tertiles of caffeine intake and risk of falls in the Seniors-ENRICA study (N=2,964).

	Total intake of caffeine, mg/d			
	Tertile 1 (lowest)	Tertile 2	Tertile 3 (highest)	*P* for trend
Incident risk of ≥1 falls				
Person-years/ cases	4941/276	4872/280	5026/237	
Age- and sex-adjusted model	1.00	0.93 (0.79, 1.11)	0.79 (0.67, 0.95)	0.01
Multivariable	1.00	0.98 (0.82, 1.16)	0.80 (0.67, 0.96)	0.02
Incident risk of injurious falls[1]				
Person-years/ cases	5020/200	4976/199	5130/167	
Age- and sex-adjusted model	1.00	0.91 (0.75, 1.12)	0.77 (0.62, 0.94)	0.01
Multivariable	1.00	0.95 (0.77, 1.17)	0.78 (0.63, 0.97)	0.03
Incident risk of falls with fracture[2]				
Person-years /cases	5258/38	5219/54	5304/51	
Age- and sex-adjusted model	1.00	1.18 (0.78, 1.79)	1.25 (0.81, 1.92)	0.31
Multivariable	1.00	1.24 (0.81, 1.91)	1.32 (0.85, 2.04)	0.22

Multivariable: Cox model adjusted for age, sex, educational level (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), alcohol consumption (none, moderate, heavy drinker) , BMI (tertiles of kg/m^2), physical activity (tertiles of MET-h/week), sleep duration (tertiles of h/d), energy intake (tertiles of kcal/d), intake of vitamin D (tertiles of µg/d), intake of vitamin A (tertiles of µg/d), intake of calcium (tertiles of mg/d), protein intake (tertiles of g/d), and for hypertension, diabetes, osteomuscular disease, and use of sleeping pills at baseline.
[1]Incident risk of falls with contusion, bruise, sprain, superficial injury or deep wound.
[2]Incident risk of falls with leg, hip, arm or shoulder fracture.

DISCUSSION

In this study, we found an inverse association between habitual coffee consumption and risk of falls. This was mainly observed for the consumption of caffeinated coffee. However since decaffeinated coffee consumption was lower in these populations, our data cannot discard a potential effect of this beverage. We also found some tendency to lower risk of injurious falls associated with coffee consumption.

We are not aware of previous studies that evaluated the relationship between coffee consumption and the risk of falls in older people. The protective association found in the present study might be due to the action of caffeine. Caffeine is an alkaloid present naturally in coffee and other foods, which also acts as an antagonist of adenosine A1 and A2 receptors promoting the release of different neurotransmitters at normal doses of consumption (52,53,141). Caffeine improves some aspects of cognitive function such as reaction time, attention and vigilance (53,134). Older people have less ability to react to external stimuli and barriers so this could lead to falling. Thus, the protective effect of caffeinated coffee and total caffeine in our study might be related to improved reaction time (142,143). Likewise, lower vigilance and lower level of attention have been associated with increased risk of falls (144), so our findings might also partially result from better caffeine-related vigilance and attention.

Age-associated poor functional status has been related to increased falls risk in older adults (145-147). Also, sarcopenia, which is a common syndrome in the older people, limits functional capacity and increases the risk of falls (148-150). *In vivo* and *in vitro* studies in mice have shown that coffee slows age-related sarcopenia by improving the structure and function of skeletal muscle through the induction of autophagy and decreased levels of inflammatory mediators (62,110). However, since these studies have been conducted with caffeinated coffee and not with other types of coffee, it cannot be ruled out that this effect is due, at least partially, to components of coffee other than caffeine. Therefore, coffee might also be able to lower the risk of falling by slowing down sarcopenia. In addition, numerous studies have shown a lower risk of clinical and subclinical cardiovascular disease among habitual coffee drinkers (61,151). We can speculate that the lower risk found in our study could be partly mediated by the reduction in the risk of cardiovascular disease in habitual coffee drinkers.

From a systematic review and meta-analysis of cohort and case-control studies, Lee et al. reported that coffee consumption was associated with a dose-dependent increased risk of fractures in women but, by contrast, men who consumed more coffee had lower risk of fractures (152). However, most reviewed studies did not assess caffeinated and decaffeinated coffee separately, and many of them did not fully account for important confounders, such as alcohol intake and smoking. Moreover, there is no clear biological basis for these gender-based differences in the coffee-fractures association. Thus, Lee et al. concluded that more prospective well-designed studies should be performed to confirm their findings. In our study, we did not find any statistically significant result for coffee associated with fractures risk, although the HR estimates found were always above 1. Studies in humans have suggested that caffeine intake could influence the metabolism of calcium by decreasing its absorption and increasing its excretion in urine. This would increase the risk of fractures, which highlights the findings of some observational studies. However, other studies indicate that some polyphenols present in coffee could have a beneficial effect on bone metabolism and, therefore, on the risk of fractures. However, more studies are needed to confirm the effect of the different compounds present in coffee on the risk of fractures (153,154).

Our study has several strengths, including the use of two distinct prospective cohorts from countries with different lifestyles and socioeconomic characteristics. This suggests that the protective association between coffee and falls risk is rather generalizable and, also, seems to be independent of the type of coffee preparation. Other strengths were that our analyses adjusted for many potential confounders, including diseases and drugs that may affect balance, and the consistency of the results among the various subgroups that presented different baseline risk of falls.

This study also has some limitations. In particular, coffee consumption in Seniors-ENRICA was assessed with a validated dietary history, and in the UK Biobank with several 24-h dietary records; thus, certain misreporting and misclassification of dietary intake cannot be ruled out, despite that we excluded participants with an implausible high or low energy intake level in both cohorts. Another limitation was the use of coffee consumption only measured at baseline since we tried to obtain comparable results between the cohorts and diet measurement in the UK Biobank study did not allow calculating cumulative consumptions. However, we were able to calculate cumulative consumption during follow-up in the Seniors-ENRICA and results were similar than

those obtained with baseline consumption. In addition, incident falls were self-reported and some events could have been missed because old people may not recall all falls they had during the follow-up. Also, some of the falls recorded might have been due to accidents rather than to health status, and we could not exclude them from the analyses because this information was lacking in the cohorts. Finally, as in any observational study, some residual confounding may persist.

In conclusion, habitual consumption of caffeinated coffee was associated with decreased risk of falling in older adults in Spain and UK. Future research should confirm these results in other populations and establish if caffeine or other coffee constituents account for the association observed.

6

HIGH DEPHOSPHO-UNCARBOXYLATED MATRIX GLA PROTEIN CONCENTRATIONS, A PLASMA, BIOMARKER OF VITAMIN K, IN RELATION TO FRAILTY: THE LONGITUDINAL AGING STUDY AMSTERDAM

INTRODUCTION

Recent findings highlight the importance of evaluating the role of vitamin K for human health (70). Vitamin K is a fat-soluble vitamin that exists in two different forms in our diet. Vitamin K_1 is the main source of vitamin K and is mainly present in green leafy vegetables, algae and plant oils. Vitamin K_2 is found in animal foods such as meat, eggs, fermented dairy products and is also synthesized by intestinal bacteria. In addition, vitamin K_2 has a longer half-life time and a greater absorption and bioavailability than vitamin K_1 (63,64).

Vitamin K acts as a cofactor in the carboxylation of vitamin K-dependent proteins. The most well-known vitamin K-dependent proteins are involved in blood coagulation processes, but other vitamin K-dependent proteins are involved in extra-hepatic tissue, such as bone and the vasculature. Matrix Gla protein (MGP) is a vitamin K-dependent protein present in the vascular wall, which inhibits vascular calcification by binding to Ca^{2+} ions (155). Likewise, osteocalcin is a vitamin K-dependent protein of bone matrix, which has a high affinity for calcium ions, and is involved in the synthesis and regulation of bone matrix (156). Therefore, a low status of vitamin K produces a lower calcium binding in the bones and greater calcium deposition in the vascular wall, which could lead to bone mass loss and vascular stiffness. Furthermore, multiple lines of research indicate that vitamin K is related to osteoarthritis, vascular stiffness and inflammation (157,158). In a previous analysis from our group, low vitamin K status was associated with lower handgrip strength and smaller calf circumference (159).

Frailty is a state of greater vulnerability to external stressors, caused by the loss of abilities in multiple domains of functioning (23). Furthermore, frailty is a reversible state and has been linked to various adverse health outcomes, such as falls, disability, hospitalization and death (27). So, it is of major importance to know the factors that influence frailty, in order to be able to develop public health strategies aimed at reducing or preventing frailty. Only limited evidence is available for a relationship between intake of certain nutrients and frailty. So far, prospective studies have suggested that low protein and micronutrient intake (such as B-vitamins, magnesium and selenium) increases frailty risk (27). Others have reported that adherence to a Mediterranean-style diet (28), and other healthy dietary patterns with well-balanced nutrient profile is related to lower risk of frailty (160). The relationship between vitamin K status and frailty has not been investigated to date.

Therefore, using data from the Longitudinal Aging Study Amsterdam (LASA), we examined the prospective association between vitamin K status and frailty in older adults over 13 years of follow-up.

SUBJECTS AND METHODS

Study population

LASA is a population-based cohort, which started in 1992 in order to determine consequences and predictors of aging focusing on physical, cognitive, mental, and social aspects. The sampling procedure and data collection have been described elsewhere (161,162). In summary, in 1992-1993 a representative sample of the Dutch population aged 55 to 85 years was invited to participate in the baseline study, which consisted of two rounds of interviews: a main interview to obtain demographic and lifestyle information, and a medical interview with physical measurements. Then, follow-up was performed approximately every 3 years to update baseline information. The medical ethics committee of the VU University medical center approved the study protocol and all participants gave written informed consent.

For the current study, we used data from the second cohort, which was added to LASA in 2002-2003 and consisted of 1,002 men and women aged 55 to 65 years. This new cohort was recruited from the same sampling frame as the first cohort in 1992-1993. Four follow-up waves have been performed, in 2005-2006, 2008-2009, 2011-2012, and 2015-2016. We excluded 358 participants from our analysis: 251 without blood sample, 49 without dp-ucMGP measurement, and 19 participants who were using vitamin K antagonists. Furthermore, 39 participants were excluded since no information on frailty during follow-up was available **(Figure 6)**. This resulted in a sample size of 644 LASA participants with at least 1 follow-up measurement.

Excluded participants were older (60 vs. 59 years), mostly male (51% vs 46%), had more often type 2 diabetes (10% vs. 6%), a greater frailty index (0.16 vs. 0.13) and a higher frailty prevalence at baseline (18% vs. 11%). Moreover, excluded participants had higher mean concentrations of dp-ucMGP, which corresponds to a lower status of vitamin K (557 nmol/L vs. 278 nmol/L).

Study variables

Vitamin K status

During the medical interview at baseline (2002-2003), trained personnel collected morning blood samples in a non-fasted state and samples were shipped to the VU

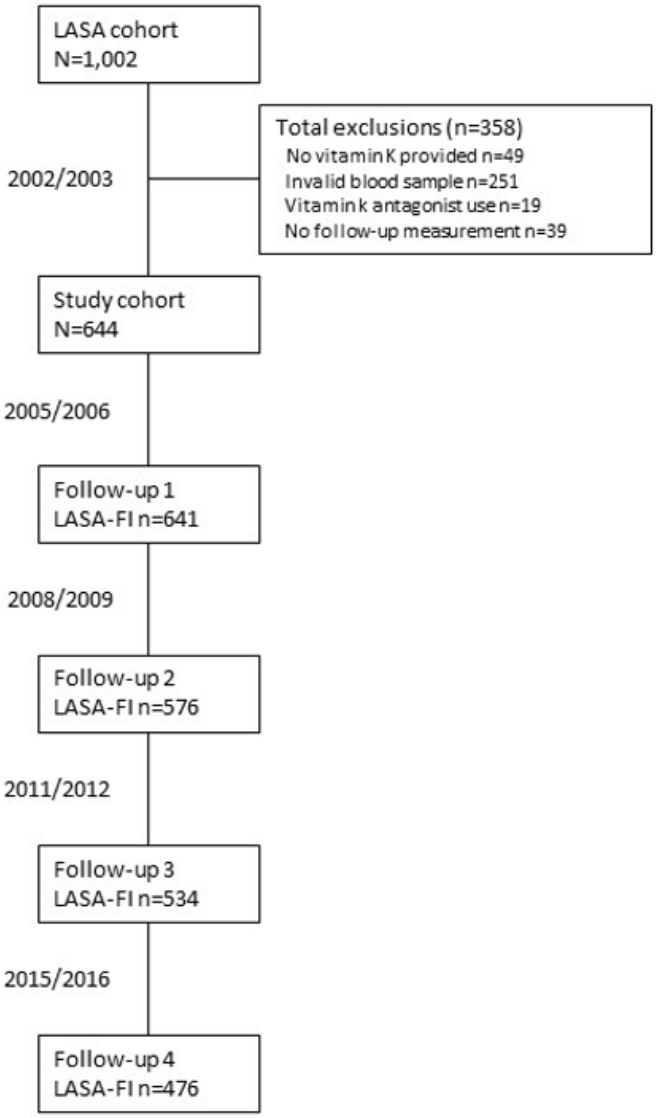


Figure 6. Flow diagram of LASA participants per frailty index outcome for each follow-up measurement between 2002 and 2016.

University Medical Center. Until analysis in 2010-2011, blood samples were stored at -80°C. For the assessment of vitamin K status, samples were shipped to the laboratory of VitaK, Maastricht to estimate dp-ucMGP concentrations. A sandwich (dual antibody) ELISA was used to measure plasma dp-ucMGP, with the capture antibody directed against the non-phosphorylated MGP sequence 3-15 and the detecting antibody directed against the uncarboxylated MGP sequence 35-49 (mAbucMGP; VitaK, Maastricht, the Netherlands). A low vitamin K status is reflected by high concentrations of dp-ucMGP. The reported intra- and inter-assay variation for plasma dp-ucMGP were 5.6 and 9.9%, respectively (72).

Frailty assessment

We used the frailty index, based on the deficit accumulation approach, to assess the degree of frailty (22). This is a widely accepted approach, and validated in several studies (163). The LASA frailty index (LASA-FI) was developed in 2017 and validated against risk of mortality **(Table 10)** (164). The fundamentals of the frailty index are that a greater number of health deficits correspond to a greater extent of frailty. The LASA-FI takes into account the accumulation of symptoms, signs, diseases, disability or any other deficiency in health with age (22). Health deficits had to meet a series of criteria to be included in the LASA-FI: a) were biologically meaningful in representing several organ systems, and b) not becoming too prevalent at younger age, and were accumulating with age, and c) did not contain a high number of missing values at item level (<6%), and d) were available in the main interview of LASA at different measurement waves. Thus, a 32-item frailty index was constructed, which included self-reported chronic conditions, functional limitations, self-rated health, 6 items from CES-D depression scale, self-reported memory complaints, 4 items from Mini-Mental State Examination (MMSE) and physical performance (164). Details of the items included in the LASA-FI and its validation have been published elsewhere (164). Finally, we calculated a frailty score for each participant by dividing the sum of the present health deficits score by the total number of health deficits. The resulted score ranged between 0 (no deficits) and 1 (all deficits) and accordingly higher values of the LASA-FI represent a larger degree of frailty. In addition to the continuous LASA-FI score, we used the LASA-FI also as a dichotomous outcome with a cutoff point of ≥0.25 to indicate frailty (164,165).

Table 10. Variables included in the LASA frailty index.

Deficit
Self-reported chronic conditions
1. Cardiac disease
2. Peripheral arterial disease
3. Stroke
4. Diabetes
5. Lung disease
6. Cancer
7. Arthritis
8. Hypertension
9. Other chronic disease 1
10. other chronic disease 2
11. Incontinence
Functional limitations
12. Walk up/down staircase 15 steps without resting
13. Dess/undress self
14. Sit down/stand up from chair
15. Cut own toenails
16. Walk outside 5 min without stopping
17. Use of transportation
Self-rated health
18. How is your health in general?
19. How is your health compared to other people of your age
CES-D depression scale
20. Feel depressed
21. Feel everything is an effort
22. Feel happy
23. Feel lonely
24. Enjoy life
25. Could not get going
LASA physical activity questionnaire (LAPAQ)
26. Physical activity
Memory complaints
27. Self-reported memory complaints
Mini-Mental State Examination (MMSE)
28. Orientation time
29. Orientation place
30. Attention
31. Recall
Physical performance
32. Gait speed (6 m)

Baseline covariates

Information about educational level, smoking status, alcohol use and physical activity was obtained from a self-administered questionnaire. Educational level was classified into low (elementary school or less), medium (lower vocational or general intermediate education) and high (intermediate vocational education, general secondary school, higher vocational education, college or university). Smoking status was categorized as never, former and current smoker. Individuals were classified according to their alcohol intake as none, light (1-3 glasses/week), moderate (4-7 glasses/week), excessive (≥8 glasses/week) according to the Garretsen index (166). Body mass index (BMI) was calculated as measured weight (kg) divided by the square height (m^2).

In addition, glomerular filtration rate (eGFR) was estimated from serum creatinine using the Chronic Kidney Disease Epidemiology 2009 equation, as indicator of kidney function. To determine vitamin D status, the concentrations of serum 25-hydroxyvitamin D were estimated using a radioimmunoassay (DiaSorin, Stillwater, Minnesota, USA). The inter-assay coefficient of variation was 10.0%. The Endocrine Laboratory of the VU University Medical Center Amsterdam performed all biochemical analyses (162).

Statistical analyses

We categorized dp-ucMGP concentrations into tertiles as no validated clinical cut-off values are established yet. We used the first tertile as reference for all analyses since it corresponds to a higher vitamin K status. Differences in sociodemographic characteristics, lifestyle and morbidity according to tertiles of dp-ucMGP were reported as mean and standard deviation for normally distributed variables and skewed variables were reported as median and interquartile range. Categorical variables are presented as number and percentage.

The frailty index was used as a continuous variable and multiplied by 100 for easier interpretation of the regression coefficients.

To assess the longitudinal relationship between the dp-ucMGP tertiles and frailty, we used generalized estimating equation (GEE) analysis to estimate regression coefficients for the continuous score frailty index and logistic GEE analysis to estimate odds ratios with 95% confidence intervals for the dichotomous frailty outcome. Due to the close

correlation between follow-up measures within participants, we used an exchangeable correlation structure (167). To assess the linear dose-response relation, we modeled the medians of the tertiles of dp-ucMGP as a continuous variable.

We used two nested models: 1) adjusted for baseline age and sex, and follow-up time (years), 2) additionally adjusted for education (low/ intermediate/high), BMI (kg/m^2), smoking status (never/former/current), alcohol consumption (non /light /moderate /excessive), vitamin D (nmol/L) and eGFR (ml/ min/1.73 m^2). Sensitivity analyses were conducted by adjusting model 2 for changes over time in smoking, alcohol consumption and BMI. Sex and BMI were tested as potential effect modifiers in adjusted models by including interaction terms (dp-ucMGP*sex) and (dp-ucMGP*BMI) to the regression models, because BMI was associated with frailty in previous studies. Interaction was tested with the Wald test and results were stratified in case of significant interaction, $P<0.10$.

To measure the rate of frailty increase by dp-ucMGP tertiles during follow-up, we added an interaction term (dp-ucMGP*time) to the model. All analyses were conducted using Stata (version 15.0; Stata Corp., College Station).

RESULTS

Study population

Over 13 years of follow-up, among the study sample of 644 people, 462 participants provided data at all five measurements waves, 72 at four waves, 51 at three waves and 59 at two waves. Of the 644 participants in the study, the mean age was 59.9±2.9 years, 46% were men (n=297) and 19% had lower education level. Furthermore, 26% were current smokers and mean BMI was 27.3±4.2 kg/m^2.

Vitamin K

Mean plasma dp-ucMGP was 376±232 pmol/L, and was slightly skewed to the right. Plasma dp-ucMGP was divided into tertiles: low: <267 pmol/L, medium: 268-408 pmol/L and high: >409 pmol/L **(Table 11)**. These dp-ucMGP concentrations are in line with previous values reported in similarly aged cohorts with values between ≤181 pmol/L and ≥647 pmol/L (168,169) (CITA). Participants in the highest tertile of dp-ucMGP had a greater BMI, a lower eGFR and higher prevalence of frailty.

Associations with the extent of frailty

At baseline, the mean frailty score was 0.13 and increased to 0.17 after 13 years of follow-up. The frailty index increased across all vitamin K tertiles over 13 years of follow-up **(Figure 7)**. The frailty index showed a good correlation over 5 follow-up exams (Pearson correlation coefficient r>0.71).

In the crude model, the medium and highest tertile of dp-ucMGP were associated with a higher frailty index score: regression coefficient 2.09 (95% confidence interval: 0.59, 3.58) and 2.37 (0.82, 3.92), respectively **(Table 12)**. In the fully adjusted model, the relationship between dp-ucMGP tertiles and frailty attenuated, but was still statistically significant: 1.40 (0.01, 2.81) for the medium tertile and 1.62 (0.18, 3.06) for the highest tertile, P-trend=0.03 (Table 2). The frailty index score gradually increased across all groups of dp-ucMGP over 13 years follow-up (*P*-time<0.001). However, in none of these models the interaction between dp-ucMGP and time was statistically significant (*P*-interaction >0.05), indicating that differences in frailty index scores across tertiles of dp-ucMGP existed since baseline and remained stable during follow-up. Furthermore, additional adjustment for changes in smoking, alcohol consumption and BMI over time

Table 11. Participants'characteristics at baseline stratified by plasma dp-ucMGP tertiles (N=644)

	Dephosphorylated uncarboxylated matrix gla protein		
	Low ≤ 267 pmol/L	Medium 268-408 pmol/L	High ≥ 409 pmol/L
	N=216	N=214	N=214
Demographic			
Age (years)	59.6 ± 2.9	59.7 ± 2.9	60.2 ± 3.0[a]
Women	115 (53%)	108 (50%)	124 (58%)
Education			
Low	38 (17%)	51 (24%)	35 (16%)
Intermediate	127 (59%)	122 (57%)	134 (63%)
High	51 (24%)	41 (19%)	45 (21%)
Lifestyle			
Physical activity (min/day)	135 (84-228)	159 (92-228)	150 (96-217)
BMI (kg/m^2)	25.8 (23.6-28.5)	26.8 (24.1-28.9)	27.9 (25.5-31.4)[c]
Smoking status			
Never	125 (58%)	114 (53%)	125 (58%)
Former	33 (15%)	38 (18%)	42 (20%)
Current	58 (27%)	62 (29%)	47 (22%)
Alcohol consumption			
Non-drinker	3 (1%)	8 (4%)	6 (3%)
Light drinker	116 (54%)	98 (46%)	107 (50%)
Moderate drinker	76 (35%)	84 (39%)	78 (36%)
Excessive drinker	21 (10%)	24 (11%)	23 (11%)
Disease state			
Hypertension	39 (18%)	47 (22%)	59 (28%)
Type 2 diabetes	11 (5%)	9 (4%)	18 (8%)
Metabolic			
25-hydroxyvitamin D (nmol/L)	56.5 (43.5-67.3)	52.3 (41.1-66.3)	57.1 (42.6-69.6)
eGFR (ml/min/1.73m^2)	71.1 (63.5-80.0)	68.6 (61.9-79.1)	65.3 (60.1-74.6)[c]
Frailty			
Frailty index	0.12 ± 0.07	0.14 ± 0.1	0.14 ± 0.1
Frailty prevalence (FI ≥0.25)	17 (8%)	24 (11%)	31 (14%)

Note: Values are mean ± SD or median and interquartile range. Abbreviations: dp-ucMGP: dephosphorylated uncarboxylated Matrix Gla protein, eGFR: estimated glomerular filtration rate.
[a]p<0.05; [b]p<0.01;[c]p<0.001

did not change the association. In the fully adjusted model, participants who were in the highest tertile of dp-ucMGP had a higher frailty index score in the sensitivity analyses compared who were in the lowest tertile: 2.03 (0.58, 3.49), P-trend=0.006 (data not shown).

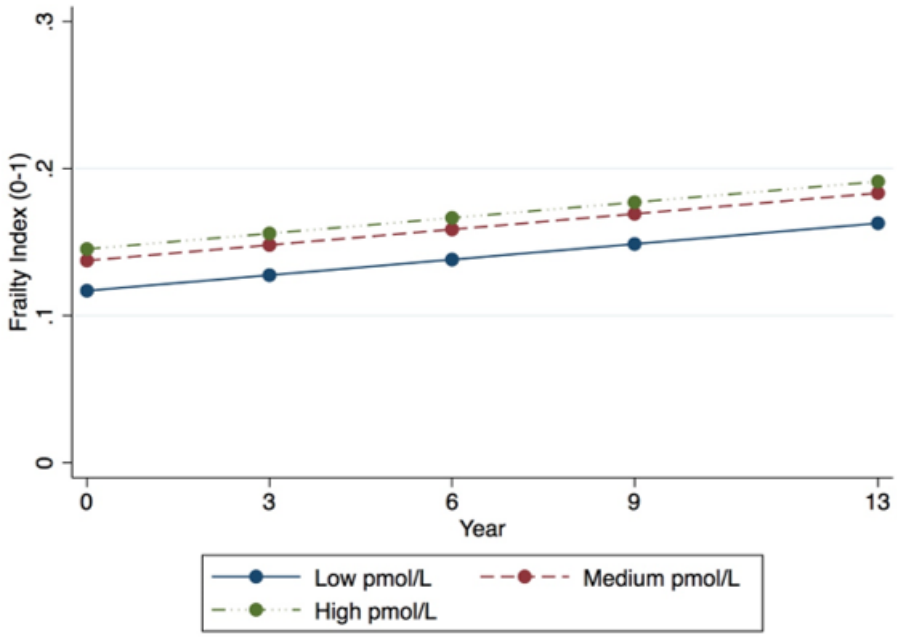


Figure 7. Mean values of frailty index by dp-ucMGP tertiles. Data are presented as means adjusted for time (years), age (years), sex, education (low/intermediate/high), BMI (tertiles of kg/m^2), smoking status (never/former/current), alcohol consumption (non/light/moderate/excessive), vitamin D (nmol/l) and eGFR (ml/min/1.73 m^2).

Table 12. Longitudinal associations between baseline plasma dp-ucMGP tertiles and frailty index in 644 LASA partcipants over 13 years follow-up.

	Dephosphorylated uncarboxylated matrix gla protein				
	Low	Medium	High	*P*-trend	*P*-time
	≤ 267 pmol/L	268-408 pmol/L	≥ 409 pmol/L		
Frailty Index score (0-100)		Beta (95% CI)	Beta (95% CI)		
Model 1	ref.	2.09 (0.59-3.58)	2.37 (0.82-3.92)	0.003	<0.001
Model 2	ref.	1.40 (0.01-2.81)	1.62 (0.18-3.06)	0.03	<0.001

Dp-ucMGP: dephosphorylated uncarboxylated matrix gla protein.
Model 1: adjusted for time (years), age (years) and sex.
Model 2: additionally adjusted for education (low/intermediate/high), BMI (tertiles of kg/m^2), smoking status (never/former/current), alcohol consumption (non/light/moderate/excessive), vitamin D (nmol/l) and eGFR (ml/min/1.73 m^2).

Risk of frailty

We observed similar associations for vitamin K and frailty risk. The medium and highest tertile were associated with a greater risk of frailty (FI ≥ 0.25) compared with the dp-ucMGP lowest tertile odds ratio: 1.75 (95% confidence interval: 1.11, 2.77) and 1.63 (1.04, 2.57), respectively **(Table 13)**. Similarly, a gradual increase in the risk of frailty across tertiles of dp-ucMGP was observed over 13 years follow-up (*P*-time<0.001), but the differences in the risk of frailty existed since baseline and remained stable during follow-up (*P*-interaction >0.05).

Sex and BMI did not modify the relationship between both dp-ucMGP with the degree of frailty and frailty risk (*P*-interaction> 0.13).

Table 13. Association between baseline plasma dp-ucMGP tertiles and frailty risk over 13 years follow-up.

	Dephosphorylated uncarboxylated matrix gla protein				
	Low	Medium	High	*P*-trend	*P*-time
	≤ 267 pmol/L	268-408 pmol/L	≥ 409 pmol/L		
Frailty (FI ≥ 0.25)		OR (95% CI)	OR (95% CI)		
Model 1	ref.	1.99 (1.28-3.08)	1.90 (1.22-2.94)	0.01	<0.001
Model 2	ref.	1.75 (1.11-2.77)	1.63 (1.04-2.57)	0.04	<0.001

Dp-ucMGP: dephosphorylated uncarboxylated matrix gla protein.
Model 1: adjusted for time (years), age (years) and sex.
Model 2: additionally adjusted for education (low/intermediate/high), BMI (tertiles of kg/m^2), smoking status (never/former/current), alcohol consumption (non/light/moderate/excessive), vitamin D (nmol/l) and eGFR (ml/min/1.73 m^2).

DISCUSSION

We assessed the relationship between vitamin K status as measured by plasma dp-ucMGP and the frailty index in the LASA cohort over a period of 13 years. Our results indicate that higher concentrations of dp-ucMGP, reflecting a lower vitamin K status, were associated with higher frailty index scores in older adults. The degree of frailty increased over time, but the rate of increase did not differ between the dp-ucMGP tertiles. Similarly, our results were consistent for frailty as a dichotomous outcome, using a relevant cut-off to indicate frailty.

To our knowledge, no previous study has evaluated the relationship between vitamin K and frailty so we only have other indirect studies to compare our results with. In line with our results, high levels of dp-ucMGP have been associated with increased cardiovascular risk (70), a worse prognosis of chronic heart failure (170) and a high mortality (171). In a cross-sectional study, frail participants presented a greater arterial calcification than their non-frail counterparts (172). In addition, in the LASA cohort of older adults with cardiovascular disease, only patients with heart failure had a greater frailty risk after 17 year follow-up (173). Therefore, it is plausible that low vitamin K status increase the risk of vascular calcification and cardiovascular disease and thus increase the extent of frailty in older adults, as observed in our results.

The physical component is an essential part of frailty and frail adults often have a compromised locomotor system. Osteocalcin is a vitamin K-dependent protein that promotes mineralization of bone, so that a low vitamin K status has been associated with higher levels of non-carboxylated osteocalcin (ucOC)) (156). In addition, vitamin K_2 has been linked to a lower urinary calcium excretion and an inhibitory effect of bone resorption in *in vitro* and *in vivo* studies (174). All this suggests that vitamin K plays an important role in bone metabolism. Furthermore, arthritis is part of the LASA-FI. Vitamin K deficiency has been associated with knee osteoarthritis in cross-sectional and longitudinal studies (157,175). A longitudinal study using data from six European cohorts, including LASA, observed a higher odds of frailty among patients with osteoarthritis (176). Additionally, low calf circumference has been associated with frailty (177) and low grip strength is considered part of frailty in the phenotypic definition (24). In a previous analysis in the LASA cohort, a lower status of vitamin K was longitudinally associated with lower grip strength and calf circumference over 13 year follow-up (159).

All this highlights the importance of the physical component in the development of frailty and points out the complexity to establish direct mechanisms between vitamin K and frailty.

Likewise, aging is associated with chronic inflammation in certain tissues due to the imbalance between pro-inflammatory and anti-inflammatory cytokines. In a cross-sectional study with 4735 participants aged 65 years and older, those who were frail had higher levels of C-reactive protein compared with non-frail individuals (178). In another cross-sectional study with 110 patients aged over 75 years, an association between inflammatory markers and different frailty measures was observed, which indicates that the association seems consistent for different frailty measures (179). In addition, inflammation could be a precursor of frailty in older adults (180), as the increase in pro-inflammatory factors has been associated with age-related declines in physical function and muscle weakness in men and women aged 70-79 years (181). In animal studies, rats treated with vitamin K_1 had lower levels of inflammation due to the decrease in the concentration of pro-inflammatory cytokines (158). Furthermore, in a cross-sectional study on the association between serum vitamin K_1 and inflammatory biomarkers, serum phylloquinone was inversely associated with several inflammatory biomarkers (182). From another perspective, cognition is an important aspect of the frailty index and, therefore, of frailty. Rats deficient in vitamin K had a 25% lower locomotor activity in the brain than controls (183). Furthermore, another cross-sectional study observed that participants with higher vitamin K intake had better cognitive state (184). However, the results of this previous study should be interpreted with caution, since causal relationships cannot be established due to the cross-sectional design. Similarly, a cross-sectional study observed a relationship between higher intakes of vitamin K and less severe subjective memory complaints (185). Therefore, vitamin K could have an effect in different health deficits interrelated which are part of the FI.

Although a low vitamin K status was associated with frailty, we did not find differences in the rate of increase in frailty between the different tertiles of dp-ucMGP over time. Older people often reduce their food intake due to different factors such as loss of appetite, dental problems or chronic diseases. For this reason, some of them have an inadequate intake of energy and other micronutrients, which makes it difficult to meet the nutritional recommendations and results in a worse nutritional status (186). In the same way, vitamin K deficiency is often accompanied by a worse nutritional status as well as

the deficiency in other micronutrients (186). Therefore, our results may thus reflect the association of a low nutritional status with frailty although due to the lack of dietary information in this cohort we have not been able to test this hypothesis. Some longitudinal studies have evaluated the relationship between diet quality measured by different indexes and the risk of frailty, finding that participants who had a higher diet quality had a lower frailty risk (160,187). In addition, a low diet quality is related to a worse nutritional status. Optimal levels of vitamin K can be achieved with an adequate diet and therefore, foods rich in vitamin K should be part of a balanced diet offered to older adults in order to ensure an adequate status of vitamin K in this population.

Thus, our findings are novel, and are a first step to understand the effect that nutritional status and specifically vitamin K could have on frailty. This is also one of the great challenges of public health because it is a reversible situation in older adults and it has been related to adverse health outcomes. More research is needed in order to elucidate if the different forms of vitamin K influence frailty in a different way.

Our study has several strengths, including the prospective design, the long follow-up period and control for potential confounders, such as BMI, vitamin D status and eGFR. Another strength is the use of a validated frailty index to measure the extent of frailty, which is useful to monitor changes in frailty over time in longitudinal studies. Another one was the large number of respondents with available data for all waves (72%). Furthermore, we used plasma dp-ucMGP as a measure of vitamin K status, which is a reliable marker because it takes absorption and metabolism into account in contrast to other methods that only reflect intake (71).

This study also has some limitations. Vitamin K status, was only measured at baseline and changes in vitamin K intake that may have occurred during follow-up could not be taken into account. Furthermore, excluded participants had a higher frailty index and a higher frailty prevalence at baseline, in addition to higher concentrations of dp-ucMGP, which corresponds to a lower vitamin K status. For these reasons, the observed associations might have been underestimated due to exclusion of the most frail participants. Another limitation of the study was the use of only one plasma biomarker to estimate vitamin K concentrations, although levels of dp-ucMGP are considered a reliable biomarker of this vitamin (72). However, the samples were stored at -80°C after collection for 12 years and no data is available whether potential sample degradation

could have affected our results. In addition, the lack of dietary information in this cohort did not allow us to adjust our analyses for dietary variables such as energy intake, as well as to test the effect of vitamin K intake or a worse nutritional status on frailty. Finally, some residual confounding may persist because of the observational design.

Conclusion

Higher concentrations of dp-ucMGP, which corresponds with a lower vitamin K status, was associated with a higher frailty index score. However, the differences in frailty between the tertiles of vitamin K exist from baseline and remain the same during follow-up over a period of 13 years. This highlights the importance of ensuring adequate nutritional status of this vitamin in older adults in order to reach optimal levels by promoting the consumption of foods rich in vitamin K, such as green leafy vegetables and fermented dairy products, which could slow down the development of frailty in this population.

7

CONCLUSIONS

CONCLUSIONS

Conclusion to objective 1

No association was observed between habitual coffee consumption and the risk of physical function impairment, frailty or disability in the total cohort; however, we found a protective effect of coffee on physical function in women and in hypertensive, diabetic and obese patients. Therefore, our results suggest that habitual coffee consumption does not pose a risk to physical functioning in older people, and could even be beneficial in people at higher risk of functional limitations.

Conclusion to objective 2

Habitual consumption of coffee was associated with a lower risk of falls in older adults in Spain and the United Kingdom and this was observed mainly with the consumption of caffeinated coffee. Likewise, the association seems to be independent of the type of coffee preparation. In addition, we also find a certain tendency that coffee decreases the risk of injurious falls. Future research should establish if caffeine or other coffee constituents account for the association observed.

Conclusion to objective 3

Higher concentrations of dp-ucMGP, which corresponds with a lower vitamin K status, was associated with a higher frailty index score. However, the differences in frailty between the tertiles of vitamin K exist from baseline and remain the same during follow-up over a period of 13 years. This highlights the importance of ensuring adequate nutritional status of this vitamin in older adults in order to reach optimal levels by promoting the consumption of foods rich in vitamin K, such as green leafy vegetables and fermented dairy products, which could slow down the development of frailty in this population.

CONCLUSIONES

Conclusión al objetivo 1

No se observó ninguna asociación entre el consumo habitual de café y el riesgo de deterioro de la función física, fragilidad o discapacidad en la totalidad de la cohorte. Sin embargo, encontramos un efecto protector del café sobre la función física en mujeres y en pacientes hipertensos, diabéticos u obesos. Por tanto, nuestros resultados sugieren que el consumo habitual de café no supone un riesgo para el funcionamiento físico de las personas mayores, pudiendo ser incluso beneficioso en personas con un elevado riesgo de limitaciones funcionales.

Conclusión al objetivo 2

El consumo habitual de café se asoció con un menor riesgo de caídas en adultos mayores de España y Reino Unido y esto se observó principalmente con el consumo de café con cafeína. De la misma forma, la asociación parece ser independiente del tipo de preparación. Además, encontramos una cierta tendencia que indica que el café redujo el riesgo de caídas con consecuencias físicas leves. Las investigaciones futuras deben establecer si la cafeína u otros componentes del café son los responsables de la asociación observada.

Conclusión al objetivo 3

Altas concentraciones de proteínas de la matriz Gla desfosforiladas y descarboxiladas, lo que corresponde a un bajo estatus de vitamina K, se asociaron con una mayor puntuación del índice de fragilidad, así como con un mayor riesgo. Sin embargo, las diferencias en la fragilidad entre los terciles de vitamina K existen desde el inicio del estudio y permanecen estables durante el seguimiento superior a 13 años. Esto destaca la importancia de asegurar un adecuado estado nutricional de esta vitamina en las personas mayores con el fin de alcanzar unos niveles óptimos mediante la promoción del consumo de alimentos ricos en vitamina K como vegetales de hoja verde y productos lácteos fermentados, lo que podría ralentizar el desarrollo de la fragilidad en esta población.

8

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9

ANNEXES

PUBLICATION 1

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ORIGINAL CONTRIBUTION

Coffee consumption and risk of physical function impairment, frailty and disability in older adults

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Abstract

Purpose Habitual coffee consumption has been associated with lower risk of type 2 diabetes and cardiovascular disease. Since these diseases are main determinants of functional limitations, we have tested the hypothesis that coffee intake is associated with lower risk of physical function impairment, frailty and disability in older adults. We focused on women and those with obesity, hypertension or type 2 diabetes because they are at higher risk of functional limitations.

Methods Prospective study with 3289 individuals ≥ 60 years from the Seniors-ENRICA cohort. In 2008–2010 coffee consumption was measured through a validated dietary history. Participants were followed up until 2015 to ascertain incident impaired physical function, frailty and disability, assessed by both self-report and objective measures.

Results Compared with non-drinking coffee, consumption of ≥ 2 cups of coffee/day was associated with lower risk of impaired agility in women (hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.51–0.97, *P* trend 0.04) and in those with obesity (HR 0.60; 95% CI 0.40–0.90, *P* trend 0.04). Intake of ≥ 2 cups of coffee/day was also linked to reduced risk of impaired mobility in women (HR 0.66; 95% CI 0.46–0.95, *P* trend 0.02) and among individuals with hypertension (HR 0.70, 95% CI 0.48–1.00, *P* trend 0.05). Moreover, among subjects with diabetes, those who consumed ≥ 2 cups/day had lower risk of disability in activities of daily living (HR 0.30, 95% CI 0.11–0.76, *P* trend 0.01).

Conclusions In older people, habitual coffee consumption was not associated with increased risk of functional impairment, and it might even be beneficial in women and those with hypertension, obesity or diabetes.

Keywords Coffee · Mobility · Agility · Frailty · Disability

Abbreviations

IADLs	Instrumental activities of daily living
ADLs	Basic activities of daily living
MEDAS	Mediterranean diet adherence screener
SF-12	12-Item short-form health survey
SPPB	Short Physical Performance Battery
BMI	Body mass index
MMSE	Mini-mental state examination
HR	Hazard ratio
CI	Confidence interval

Introduction

Aging entails a progressive functional deterioration of multiples biological systems due to the accumulation of molecular and cellular damages throughout life [1]. Thus, older adults are at increased risk of functional impairment [2], frailty [3] and disability [4, 5]. For instance, in

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a systematic review of studies across many countries, the prevalence of frailty was about 10% in those over the age of 60 and up to 25% in those aged 80 years and older [6]. In addition, among people over 80 years in the US, 35% report mobility limitations, 50% disability in instrumental activities of daily living (IADLs), and 27% disability in basic ADLs [7]. In Europe, figures are also very high with values around 30% for mobility limitation, 17% for IADLs disability, and 10% for ADLs disability [8]. Accordingly, achieving healthy aging is a public health priority.

Evidence of the dietary factors that affect physical function, frailty and disability is rather limited, and corresponds to some nutrients (antioxidants and B-vitamins) [9–11], foods (fruit, vegetables and dairy) [12–14] and dietary patterns [15, 16]. Coffee is one of the most widely consumed beverages in the world, and has been linked to reduced risk of type 2 diabetes [17, 18] and cardiovascular disease [19, 20] which, in turn, are main determinant of impaired physical function [21, 22]. However, we are not aware of any investigation on the effect of coffee on physical functioning. Thus, in this study we tested the hypothesis that habitual coffee consumption is associated with lower risk of physical function impairment, frailty and disability in older adults; specifically we focused on individuals at higher disability risk, such as women [23] and those with obesity [24, 25], hypertension [26] and diabetes [25], because in these subjects the effects of coffee could be more evident.

Subject and methods

Study design and participants

Data were taken from the Seniors-ENRICA cohort, whose methods have been reported elsewhere [16, 27]. The cohort was derived from the ENRICA study (Study on Nutrition and Cardiovascular Risk in Spain), an investigation conducted in 2008–2010 among 12,948 individuals representative of the non-institutionalized adult population of Spain. The study participants aged 60 years or older ($n = 3289$) comprised the Seniors-ENRICA cohort. At baseline, information on socio-demographic variables, lifestyle, health status and morbidity was collected through a phone interview; also, food consumption was obtained, and physical examination was performed by trained staff at the home of the participants. Two waves of data collection have been performed to update the information of the cohort, the first one in 2012 and a second one in 2015. Study participants gave their informed written consent. The Clinical Research Ethics Committee of 'La Paz' University Hospital in Madrid approved the study protocol.

Study variables

Coffee drinking and food consumption

Habitual consumption of coffee and food in the previous year was collected with a computerized diet history developed from the one used in the EPIC-Spain cohort study, which included 861 foods and beverages [28]. Study participants reported the number of cups of coffee consumed per day, and its type (caffeinated or decaffeinated), method of preparation (filtered or unfiltered) and cup size. For data analyses, we standardized the ml of coffee consumed to a 70 ml-cup size for percolated and drip coffee and 50 ml-cup size for espresso coffee. Finally, three categories of coffee intake were considered: no consumption, 1 and ≥ 2 cups a day.

Caffeine intake was estimated using standard food composition tables [28]. Thus, a cup of percolated caffeinated coffee (70 ml) was considered to provide 80 mg of caffeine, a cup of drip caffeinated coffee (70 ml) 115 mg of caffeine, and a cup of espresso caffeinated coffee (50 ml) 75 mg of caffeine. To calculate the total caffeine intake per day we included caffeine from coffee and also from tea (a bag contained 30 mg of caffeine), caffeinated soft drinks (a 200 ml glass contained 20 mg of caffeine, and a 333 ml bottle contained 33 mg) and from chocolate (150 ml of hot chocolate contained 4 mg of caffeine, and 28.34 g of solid chocolate contained 6 mg). Total caffeine intake was energy-adjusted by using the residual method [29]. In addition, other nutrients and total energy intake (kcal/day) were also estimated. The adherence to Mediterranean diet was assessed with the Mediterranean diet adherence screener (MEDAS) [30], as an indicator of diet quality.

The validity and reproducibility of the computerized diet history has been described in detail elsewhere [28]. In the validation study, we obtained the following correlations between consumption of coffee and caffeine estimated from the computerized diet history and consumption estimated from the mean of seven 24-h recalls during 1 year (coffee, $r = 0.71$; caffeine, $r = 0.47$).

Physical function impairment

We assessed four different domains of physical function: self-reported agility, mobility and overall physical functioning, and an objective measure of lower extremity function. We considered that participants had impaired agility when they answered "a lot" to the following question from the Rosow and Breslau scale [31]: "On an average day with your current health, would you be limited in bending and kneeling?", whose categories of response

were "yes, a lot", "yes, a little" and "not at all". Likewise, impaired mobility was defined as responding "a lot" to any of the following questions also from the Rosow and Breslau scale [31]: "On an average day with your current health, would you be limited in the following activities: (1) picking up or carrying a shopping bag?; (2) climbing one flight of stairs?; (3) walking several city blocks (a few 100 m)?". Moreover, impaired overall physical functioning was defined as ≥ 10-point decrease from baseline to follow-up in the physical component summary score of the 12-item short-form health survey (SF-12) [32]; we used this cut-off point because a ten-point lower score has been associated with adverse health outcomes [33]. Lastly, limitation in the lower extremity function was assessed with the Short Physical Performance Battery (SPPB), which includes three measurements: gait speed across 2.44 m, balance using three hierarchical tandem tests, and the ability to rise from a chair five times consecutively [34]. Each component was scored on a four-point scale, and the total score was the sum of the three components (range 0–12). A higher score indicates better physical performance. Although the standard score for functional limitation is ≤ 9, we used a ≤ 6-point cut-off because the study participants were community-dwellers who were mostly independent.

Frailty

According to the phenotypic definition proposed by Fried et al. [3], frailty was defined as meeting three or more of the following five criteria: (1) exhaustion: an affirmative response to any of two statements taken for the center for epidemiologic studies depression scale: "I felt that everything I did was a big effort in the last week" or "I could not get going in the last week"; (2) weakness: the cohort-specific lowest quintile of grip strength adjusted for sex and body mass index (BMI); (3) weight loss: unintentional loss of ≥ 4.5 kg of body weight in the preceding year; (4) low physical activity: walking ≤ 2.5 h/week in men and ≤ 2 h/week in women; (5) slow walking speed: the cohort-specific lowest quintile of gait speed over 2.44 m, adjusted for sex and height.

Disability

IADL was assessed with the Lawton and Brody Scale [35]. It evaluates independent complex living skills, including the individual's ability to go shopping, use the telephone, prepare meals, do housework, do laundry, use different means of transportation, take medication and manage finances. This scale allows identifying mild disability. Due to cultural issues, questions about preparation of meals and housework were excluded in men [36]. For these reasons, the range of the scale was 0–8 points for women and 0–5 for men, where 0 indicates low function/dependent and 8 or 5 indicates high function/independent. We considered that participants had disability when the score was ≤ 7 for women and ≤ 4 for men.

ADL was assessed with the Katz Scale [37]. It measures more basic skills, including the ability to perform these activities: bathing, dressing, toileting, getting up, eating and continence. Thus, this scale captures more severe cases of disability. The scale range is 0–6 points. A total score of 6 indicates full function, and 0 indicates the maximum functional impairment. For our study, disability was defined when the score was ≤ 5 points.

Mortality

All-cause deaths were ascertained by a computerized search of the National Death Index, which contains information on the vital status of all residents in Spain [38]. This information was available for 99.9% of the cohort. In total, we identified 177 (5.3%) deaths during follow-up.

Other variables

At baseline, we collected data on age and sex. Educational level was classified into primary, secondary and university studies. Smoking status was categorized as never smoker, former smoker, and current smoker. Individuals were classified according to their alcohol intake as abstainers (< 0.1 g/day), moderate drinkers (0.1–39 g/day in men and 0.1–23 g/day in women), and heavy drinkers (≥ 40 g/day in men and ≥ 24 g/day in women). Physical activity during leisure time (metabolic equivalent h/week) was ascertained with the EPIC-cohort questionnaire, validated in Spain [39]. Sedentary behavior was approximated by the time (h/week) spent watching TV. Weight and height were measured under standardized conditions. Body mass index (BMI) was calculated as weight (kg) divided by the square height (m), and obesity was defined as BMI ≥ 30 kg/m^2. Blood pressure (BP) was measured with a validated sphygmomanometer using standardized procedures, and hypertension was defined as systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or being under hypertensive drug treatment. 12-h fasting serum glucose was centrally measured, and type 2 diabetes was defined as glucose ≥ 126 mg/dl or being on oral antidiabetic drugs or insulin. Cognitive function was assessed with the mini-mental state examination (MMSE), and cognitive decline was defined as a MMSE score < 23 [40]. Finally, participants also reported the following physician-diagnosed diseases: osteomuscular disease (osteo-arthritis, arthritis, and hip fracture), cardiovascular disease (ischemic heart disease, stroke and heart failure), cancer, chronic lung disease (asthma and chronic bronchitis) and depression requiring treatment.

Statistical analysis

We excluded participants with missing data on coffee consumption, with energy intake outside the range of 800–5000 kcal/day for men and 500–4000 kcal/day for women, without information on each outcome at baseline, and with impaired physical function at baseline. Thus, this resulted in a different size for analyses on each outcome: 2037 for impaired agility (subsample 1); 2062 for impaired mobility (subsample 2); 1653 for overall physical functioning (subsample 3); 2262 for impaired lower extremity function (subsample 4); 1714 for frailty (subsample 5); 1564 for IADL disability (subsample 6); and 1756 for ADL disability (subsample 7) (Supplemental Fig. 1). Of note, since we did not perform the SPPB at baseline, we excluded participants who had fatigue at baseline, as a proxy of overall limitation in physical functioning. Baseline fatigue was assessed by asking participants how much time during the past 4 weeks they felt tired; responses of "all of the time" or "most of the time" were considered positive [41, 42].

Participants were classified according to levels of coffee consumption. Differences on socio-demographic characteristics, lifestyle and morbidity according to incident functional impairment, frailty and disability were assessed using the Student's *T* test or analysis of the variance, as appropriate.

We assessed incident cases in the two waves of data collection, 2012 and 2015. Each wave of data collection lasted 9 months. Person-years of exposure were calculated from the date of the baseline questionnaire until the date of occurrence of the outcome, death, loss to follow-up, or the end of the study, whichever came first. For example, if a participant had an incident event detected in the 2012 wave, his/her follow-up was censored at 2012. In addition, if a participant abandoned the study, he/she was still included in the analyses, contributing to the total person-years of observation. Participants lost to follow-up were mostly women, had lower educational level and reported to suffer more diseases than those who remained in the study until the end; however, coffee consumption was similar in both groups [mean (SD) 1.40 (1.32) and 1.30 (1.24) cups/day, respectively].

Cox regression models were used to summarize the association between coffee consumption and incidence of the study outcomes. These models were adjusted for potential confounders, including age, sex, educational level, smoking status, heavy drinking, physical activity, time watching TV, energy intake, MEDAS score, BMI, and morbidity. We estimated the hazard ratio (HR) and its 95% confidence interval (CI) of each outcome, according to coffee consumption using non-coffee drinkers as reference. Also, to assess a linear dose–response relation, we modeled the categories of coffee consumption as a continuous variable.

To focus on subjects at higher risk of physical impairment, the main analyses were stratified by sex, hypertension, type 2 diabetes, and obesity. We assessed if results varied with the stratification variables using likelihood-ratio tests, which compared models with and without cross-product interaction terms. Analyses were replicated for different types of coffee (caffeinated, decaffeinated, filtered and unfiltered) and for total caffeine intake.

Statistical analyses were conducted using STATA (version 13.0; Stata Corp., College Station).

Results

Characteristics of the study participants according to incident functional impairment, frailty and disability are presented in Table 1. Those who developed any of the study outcomes were older, more frequently women, and with lower educational level. Moreover, they were less likely to be smokers and heavy drinkers, did less physical activity and spent more time watching TV. Also they had higher BMI, lower energy intake and MEDAS score, and higher frequency of osteomuscular disease, type 2 diabetes, cognitive impairment and depression. At baseline, study participants consumed a mean (SD) of 1.40 (1.32) cups/day of coffee. The mean (SD) consumption for caffeinated coffee was 0.88 (1.19) cups/day, and for decaffeinated coffee 0.53 (0.99) cups/day. Unfiltered coffee was the most consumed type of preparation (Table 2).

Over 7.2 years of follow-up, we documented 621 incident cases of impaired agility; 453 of impaired mobility; 554 cases of impairment in overall physical function; 418 of impaired lower extremity function; 198 incident cases of frailty; 158 of IADL disability; and 360 cases of ADL disability. In the total cohort, compared to non-drinkers of coffee, those who consumed ≥ 2 cups of coffee/day showed lower risk of impaired mobility (HR 0.74, 95% CI 0.54–1.00; *P* trend 0.04). However, we found no association between coffee consumption and most of the outcomes examined (Table 3).

When we focused on different subgroups of participants, consumption of ≥ 2 cups of coffee/day was associated with lower risk of impaired agility in women (HR 0.71, 95% CI 0.51–0.97, *P* trend 0.04) and in those with obesity (HR 0.60; 95% CI 0.40–0.90, *P* trend 0.04). Intake of ≥ 2 cups of coffee/day was also linked to reduced risk of impaired mobility in women (HR 0.66; 95% CI 0.46–0.95, *P* trend 0.02) and among individuals with hypertension (HR 0.70, 95% CI 0.48–1.00, *P* trend 0.05). Moreover, among participants with diabetes, those who consumed ≥ 2 cups/day had lower risk of ADL disability (HR 0.30, 95% CI 0.11–0.76, *P* trend 0.01) (Table 3). Finally, no significant interaction for the subgroups considered was found (data not shown).

Table 1 Participants' characteristics at baseline according to incident functional impairment, frailty and disability up to 2015

	Impaired agility (Subsample 1)		Impaired mobility (Subsample 2)		Impaired overall physical function[d] (Subsample 3)		Impaired lower extremity function[e] (Subsample 4)		Frailty (Subsample 5)		IADL disability[f] (Subsample 6)		ADL disability[g] (Subsample 7)	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Participants, *n*	1416	621	1609	453	1099	554	1844	418	1516	198	1406	158	1396	360
Age, year	67.5 (5.8)	69.5 (6.2)[c]	67.7 (5.8)	69.9 (6.1)[c]	67.3 (5.5)	68.8 (6.1)[c]	67.8 (5.7)	72.7 (6.9)[c]	68.1 (6.1)	73.1 (7.1)[c]	67.5 (5.5)	72.5 (7.4)[c]	67.9 (6.1)	71.1 (6.5)[c]
Men, %	56.1	34.6[c]	54.5	28.9[c]	50.1	44.8[a]	49.6	38.3[c]	50.1	29.8[c]	50.1	37.9[c]	52.5	28.1[c]
Education, %														
≤ Primary	46	64	49	65	47	56	51	64	51	75	50	68	51	63
Secondary	28	20	27	21	27	25	26	19	26	14	27	17	24	23
University	26	16[c]	24	14[c]	26	19[c]	23	17[c]	23	11[c]	23	15[c]	25	14[c]
Current smoker, %	13.1	10.2[c]	12.1	11.3[b]	11.6	12.8	12.5	7.6[c]	12.1	7.1[b]	11.7	11.4	12.5	7.3[c]
Heavy drinker[h], %	9.8	6.6[c]	9.4	6.2[c]	9.8	7.7[b]	9.2	5.1[c]	8.8	6.5[c]	9.2	7.6[c]	9.3	6.1[c]
Physical activity, MET-h/week	24.1 (15.8)	19.3 (13.7)[c]	23.7 (15.5)	18.4 (13.7)[c]	23.2 (16.1)	20.2 (13.8)[c]	23.1 (15.5)	17.8 (13.5)[c]	22.4 (15.3)	13.8 (13.1)[c]	22.6 (15.4)	18.1 (14.8)[c]	22.6 (15.5)	17.1 (13.9)[c]
TV watching, h/week	16.6 (10.4)	19.9 (11.8)[c]	17.1 (10.6)	19.8 (11.5)[c]	16.5 (9.8)	19.2 (12.6)[c]	17.6 (10.8)	19.4 (12.1)[b]	17.2 (10.6)	21.9 (16.8)[c]	17.1 (10.4)	20.9 (14.1)[c]	17.2 (10.6)	20.1 (12.4)[c]
Energy intake, kcal/day	2085 (557)	1929 (574)[c]	2089 (567)	1872 (541)[c]	2066 (565)	2001 (584)[a]	2042 (562)	1950 (584)[b]	2049 (557)	1906 (637)[c]	2058 (567)	1894 (555)[c]	2058 (562)	1916 (580)[c]
MEDAS, points	2.6 (1.6)	2.3 (1.5)[c]	2.6 (1.6)	2.5 (1.5)	2.6 (1.6)	2.4 (1.6)[a]	2.6 (1.6)	2.3 (1.5)[c]	2.6 (1.6)	2.2 (1.5)[b]	2.6 (1.6)	2.3 (1.5)[b]	2.6 (1.6)	2.4 (1.6)
Body mass index, kg/m^2	27.5 (3.6)	29.6 (4.5)[c]	27.9 (3.8)	29.5 (4.8)[c]	28.1 (4.1)	29.3 (4.6)[c]	28.2 (3.9)	29.1 (5.1)[c]	28.2 (4.1)	31.5 (16.8)[b]	28.3 (4.1)	28.6 (5.2)	28.2 (4.1)	29.7 (4.8)[c]
Morbidity, %														
Hypertension	62	66	62	68[a]	61	64	63	65	64	70	63	75[b]	64	69
Diabetes	12	18[b]	13	18[b]	12	18[b]	13	22[c]	12	27[c]	12	19[a]	13	20[c]
Cognitive impairment[i]	0.9	3[c]	1	4[c]	1	1	1	6[c]	2	9[c]	1	10[c]	1	8[c]
Osteomuscular disease	36	67[c]	40	69[c]	44	54[c]	44	62[c]	44	69[c]	44	57[b]	44	60[c]
Cardiovascular disease	3	5	3	7[c]	3	4	4	9[c]	4	11[c]	4	8	5	6
Cancer	1	2	1	2	1	1	1	3[a]	1	2	1	1	2	1
Chronic lung disease	5	10[c]	5	12[c]	6	9	6	10[a]	7	8	6	14[b]	7	9
Depression	4	11[c]	5	13[c]	5	12[c]	6	12[c]	6	14[c]	6	10[a]	6	12[c]

For continuous variables, the mean (standard deviation) is reported

PCS physical component summary of the SF-12, *SPPB* Short Physical Performance Battery, *MET* metabolic equivalent, *IADL* instrumental activities of daily living, *ADL* basic activity of daily living

[a]$p < 0.05$; [b]$p < 0.01$; [c]$p < 0.001$

[d]10-point decrease in Physical Component Summary of the SF-12

[e]Short Physical Performance Battery score ≤ 6

[f]Lawton–Brody score ≤ 4 (men) and ≤ 7 (women)

[g]Katz score ≤ 5

[h]Heavy drinker: ≥ 40 g/day of alcohol in men and ≥ 24 g/day in women

[i]Mini-Mental State Examination < 23

Table 2 Baseline information about coffee consumption, by each subtype of coffee

	Mean (SD) cups/day	Categories of coffee consumption, *n* (%)		
		0 cups/day	1 cups/day	≥ 2 cups/d
Overall coffee	1.40 (1.32)	379 (16.8)	1265 (55.9)	618 (27.3)
Caffeinated coffee	0.88 (1.19)	987 (43.6)	910 (40.2)	365 (16.2)
Decaffeinated coffee	0.53 (0.99)	1361 (60.2)	708 (31.3)	193 (8.5)
Filtered coffee	0.16 (0.59)	2007 (88.7)	192 (8.5)	63 (2.8)
Unfiltered coffee	1.24 (1.30)	543 (24.0)	1183 (52.3)	536 (23.7)

Table 4 shows the association of caffeinated, decaffeinated, filtered and unfiltered coffee intake with all the study outcomes. In general, we found no differences in the associations by type of coffee. Additional analyses to examine the association between caffeine intake and physical function showed a positive association between individuals who were on the second and third tertile of caffeine consumption and the risk of impaired lower extremity (adjusted HR 1.32, 95% CI 1.03–1.69, and HR 1.39, 95% CI 1.07–1.79, respectively; *P* trend 0.01), compared to those in the lowest tertile of consumption. However, we did not find an association between the consumption of caffeine and the other outcomes related to physical function, frailty or disability.

Discussion

In the total study cohort, no association was observed between habitual coffee consumption and the risk of physical function impairment, frailty or disability in older adults; however, we did find a protective effect of coffee on physical function among women, hypertensive, diabetic and obese patients. Main results did not differ among the different types of coffee examined.

Several models and schemes have been elaborated to understand the disablement process [43–45]. In one of these models [45], the presence of a disease can produce structural alterations or dysfunctions in specific body systems (musculoskeletal, cardiovascular, etc.), that are known as "impairments". This can lead to functional limitations, which are restrictions on physical and mental actions that could ultimately produce a disability. Disability can be understood as the difficulty to perform activities of daily living, which limits the capacity of the individual and could compromise their quality of life [43]. There are different factors (psychosocial, behavioral, lifestyle) that could accentuate or attenuate the disablement process [45]. For this reason, the different endpoints examined in our study allowed us to evaluate in detail different spheres of physical function framed within the process of disability and, therefore, allows us to understand the effect of coffee on each of them.

No other studies assessed this association yet in humans. However, several studies on animal models have examined the effect of coffee consumption on morphology and function of skeletal muscle, as well as its relationship with sarcopenia, which results in limitations in physical function, frailty [46] or disability [47]. Guo et al. in a study in vivo on mice [48] concluded that coffee administration may reduce the progression of sarcopenia, by decreasing the serum inflammatory mediators and increasing the skeletal muscle weight, the grip strength and accelerating the regeneration of the injured muscle. In addition, in an in vitro study, the same authors concluded that coffee administration improved the proliferation rate and the DNA synthesis in the satellite cells of the muscle, which produces an increase in muscle mass and the maintenance of muscle integrity [48]. These effects have been attributed to total coffee consumption but not to specific substances present in this beverage. Moreover, some components in coffee, mainly polyphenols, have been shown to induce autophagy in various tissues (liver, muscle and heart) in mice [49]. Autophagy is an important process required for the renewal of mitochondria and for prevention of mitochondrial damage during physical activity, in addition to improving and maintaining muscle mass and integrity [49]. Moreover, coffee improves insulin sensitivity and increases glucose uptake into muscle, which allows better skeletal muscle function [47]. Therefore, it is plausible that coffee could reduce indirectly the risk of physical function impairment, frailty or disability through slowed age-related sarcopenia and improved muscle integrity.

These same mechanisms can also contribute to the lower risk of type 2 diabetes associated with coffee consumption [17]. In addition, type 2 diabetes is a major disabling disease in the old people because insulin resistance is associated with a decrease in muscle strength, due to an alteration in muscle glucose use, intracellular energy production and muscle contraction [50, 51]. The decreased risk of physical function impairment in coffee consumers observed in our study among participants at high risk of disability might simply reflect that coffee effects are more evident and relevant in those who already have decreased insulin sensitivity (because of obesity or type 2 diabetes), greater sarcopenia

Table 3 HRs (95% CI) for the association between coffee consumption and physical function impairment, frailty and disability during 7.2-year follow-up, by specific subgroups of older adults

	Coffee consumption, cups/day			*P* for trend
	0	1	≥2	
Impaired agility				
Participants, *n* (*N*=2037)	340	1134	563	
Person-years/*n* cases	1881/107	6370/351	3191/163	
All[a]	1.00	0.83 (0.66–1.03)	0.80 (0.62–1.03)	0.11
Sex				
Men	1.00	0.94 (0.63–1.40)	1.01 (0.65–1.57)	0.86
Women	1.00	0.78 (0.59–1.03)	0.71 (0.51–0.97)	0.04
Hypertension				
No	1.00	0.88 (0.59–1.32)	0.67 (0.42–1.06)	0.07
Yes	1.00	0.84 (0.64–1.10)	0.92 (0.67–1.26)	0.76
Diabetes				
No	1.00	0.80 (0.63–1.03)	0.80 (0.61–1.06)	0.18
Yes	1.00	0.68 (0.35–1.31)	0.60 (0.29–1.21)	0.20
Obesity				
No	1.00	1.03 (0.77–1.37)	0.95 (0.67–1.33)	0.71
Yes	1.00	0.59 (0.41–0.85)	0.60 (0.40–0.90)	0.04
Impaired mobility				
Participants, *n* (*N*=2062)	340	1152	570	
Person-years/*n* cases	1944/79	6681/266	3332/108	
All	1.00	0.89 (0.68–1.15)	0.74 (0.54–1.00)	0.04
Sex				
Men	1.00	1.05 (0.63–1.75)	0.84 (0.46–1.52)	0.47
Women	1.00	0.83 (0.61–1.12)	0.66 (0.46–0.95)	0.02
Hypertension				
No	1.00	1.15 (0.68–1.94)	0.88 (0.48–1.59)	0.49
Yes	1.00	0.80 (0.59–1.09)	0.70 (0.48–1.00)	0.05
Diabetes				
No	1.00	0.84 (0.63–1.11)	0.74 (0.53–1.03)	0.08
Yes	1.00	0.72 (0.33–1.60)	0.56 (0.23–1.34)	0.19
Obesity				
No	1.00	0.89 (0.64–1.23)	0.72 (0.49–1.07)	0.10
Yes	1.00	0.80 (0.52–1.25)	0.70 (0.42–1.15)	0.17
Impaired overall physical function				
Participants, *n* (*N*=1653)	272	906	475	
Person-years/*n* cases	1535/87	5136/315	2725/152	
All	1.00	1.03 (0.81–1.32)	0.98 (0.75–1.29)	0.85
Sex				
Men	1.00	1.23 (0.84–1.80)	1.14 (0.75–1.74)	0.67
Women	1.00	0.91 (0.66–1.25)	0.90 (0.62–1.30)	0.62
Hypertension				
No	1.00	1.34 (0.86–2.08)	1.10 (0.67–1.80)	0.94
Yes	1.00	0.92 (0.69–1.24)	0.96 (0.69–1.35)	0.92
Diabetes				
No	1.00	0.99 (0.76–1.28)	1.03 (0.77–1.38)	0.77
Yes	1.00	1.23 (0.58–2.59)	0.85 (0.37–1.96)	0.45
Obesity				
No	1.00	1.14 (0.84–1.56)	1.04 (0.74–1.48)	0.93
Yes	1.00	0.91 (0.61–1.36)	0.92 (0.58–1.46)	0.78

Table 3 (continued)

	Coffee consumption, cups/day			*P* for trend
	0	1	≥2	
Impaired lower extremity function				
Participants, *n* (*N*=2262)	379	1265	618	
Person-years/*n* cases	2164/68	7231/248	3598/102	
All	1.00	1.18 (0.90–1.56)	1.05 (0.77–1.45)	0.87
Sex				
Men	1.00	1.46 (0.89–2.40)	1.42 (0.82–2.48)	0.29
Women	1.00	1.04 (0.74–1.46)	0.88 (0.59–1.32)	0.49
Hypertension				
No	1.00	1.61 (0.95–2.73)	1.35 (0.73–2.49)	0.49
Yes	1.00	1.05 (0.75–1.46)	0.93 (0.63–1.37)	0.68
Diabetes				
No	1.00	1.20 (0.88–1.64)	1.22 (0.85–1.74)	0.31
Yes	1.00	0.77 (0.38–1.54)	0.51 (0.23–1.14)	0.08
Obesity				
No	1.00	1.19 (0.85–1.67)	1.06 (0.71–1.59)	0.80
Yes	1.00	1.18 (0.70–1.98)	1.13 (0.63–2.01)	0.77
Frailty				
Participants, *n* (*N*=1714)	295	957	462	
Person-years/*n* cases	1729/32	5662/117	2762/49	
All	1.00	1.12 (0.75–1.69)	1.13 (0.71–1.80)	0.61
Sex				
Men	1.00	2.07 (0.80–5.35)	2.16 (0.77–5.99)	0.19
Women	1.00	0.95 (0.60–1.52)	0.96 (0.56–1.66)	0.91
Hypertension				
No	1.00	1.42 (0.62–3.24)	1.69 (0.66–4.31)	0.27
Yes	1.00	0.94 (0.57–1.53)	0.94 (0.54–1.66)	0.87
Diabetes				
No	1.00	1.08 (0.68–1.72)	1.13 (0.66–1.92)	0.64
Yes	1.00	0.44 (0.15–1.25)	0.51 (0.16–1.59)	0.48
Obesity				
No	1.00	1.61 (0.91–2.96)	1.01 (0.48–2.12)	0.99
Yes	1.00	0.79 (0.44–1.42)	1.27 (0.67–2.38)	0.27
IADL disability				
Participants, *n* (*N*=1564)	256	877	431	
Person-years/*n* cases	1505/29	5257/85	2587/44	
All	1.00	0.89 (0.57–1.39)	1.03 (0.63–1.70)	0.78
Sex				
Men	1.00	0.62 (0.30–1.26)	0.62 (0.27–1.37)	0.30
Women	1.00	1.10 (0.61–1.98)	1.37 (0.70–2.65)	0.31
Hypertension				
No	1.00	0.97 (0.39–2.40)	1.15 (0.40–3.25)	0.77
Yes	1.00	0.78 (0.46–1.32)	0.94 (0.52–1.70)	0.96
Diabetes				
No	1.00	0.90 (0.55–1.47)	1.01 (0.57–1.78)	0.90
Yes	1.00	0.75 (0.15–3.54)	2.20 (0.42–11.4)	0.12
Obesity				
No	1.00	0.94 (0.54–1.61)	1.04 (0.56–1.93)	0.86
Yes	1.00	0.92 (0.40–2.14)	0.88 (0.35–2.21)	0.79

Table 3 (continued)

	Coffee consumption, cups/day			*P* for trend
	0	1	≥2	
ADL disability				
Participants, *n* (*N*=1756)	302	978	476	
Person-years/*n* cases	1708/61	5635/199	2748/100	
All	1.00	0.92 (0.68–1.23)	1.14 (0.82–1.59)	0.30
Sex				
Men	1.00	0.89 (0.49–1.62)	1.64 (0.87–3.11)	0.06
Women	1.00	0.95 (0.67–1.35)	0.99 (0.66–1.48)	0.98
Hypertension				
No	1.00	1.31 (0.73–2.34)	1.42 (0.74–2.71)	0.30
Yes	1.00	0.77 (0.54–1.09)	1.05 (0.71–1.56)	0.52
Diabetes				
No	1.00	0.94 (0.67–1.30)	1.36 (0.94–1.96)	0.05
Yes	1.00	0.42 (0.19–0.92)	0.30 (0.11–0.76)	0.01
Obesity				
No	1.00	0.92 (0.63–1.34)	1.03 (0.67–1.59)	0.81
Yes	1.00	0.91 (0.55–1.49)	1.28 (0.74–2.20)	0.23

Variables are defined as in Table 1

IADL instrumental activities of daily living, *ADL* basic activity of daily living

[a]Cox multivariable regression models adjusted for age, sex, education (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), alcohol consumption (none, moderate, heavy drinker), physical activity (MET-h/week), watching TV (quintiles of h/week), energy intake (quintiles of kcal/day), MEDAS score (quintiles of score), body mass index, cognitive impairment, osteomuscular disease, cardiovascular disease, cancer, chronic lung disease and depression, except for the stratification variable

(e.g., women) or subclinical disease (older hypertensive), which are key components of the disablement process.

Unfiltered coffee is the most consumed type of coffee in Spain, in contrast with other countries such as the United States, where coffee is consumed mainly through filtering. The preparation method determines the concentration of substances on coffee. Thus, filtered coffee is free of the diterpenes cafestol and kahweol [52, 53]. By contrast, these diterpenes are found in unfiltered coffee, and have been found to increase plasma levels of total cholesterol [54, 55], triglycerides [56] and blood lipoproteins [56]; therefore, they could have a detrimental effect on cardiovascular disease, which is a main determinant of disability. Since we did not observe differences between filtered and unfiltered coffee on physical function impairment, diterpenes do not seem to be mediating this association. However, the association between caffeine intake and increased risk of impaired lower extremity function suggests that caffeine and coffee have different effects on health.

One of the strengths of this study was the estimation of coffee consumption through a validated diet history, which allowed detailed information on the type of coffee consumed and its preparation. Other strengths were the prospective design, the relative long follow-up period and the inclusion of physical performance tests as an objective measure of physical performance. Another advantage was the large number of confounders that were considered in the analyses, including physical activity and comorbidity. Among the limitations, we did not account for variations in coffee consumption and other lifestyles that might have occurred during the follow-up, although it is presumable that long-term established habits, such as diet, have been maintained during the study period. Participants lost to follow-up were somewhat different from those who continued in the study; thus, although person-years of observation of these participants were included in the analyses, a certain degree of selection bias cannot be ruled out. Also, adjustment for a score of global diet quality might have not removed completely the effect of individual foods and nutrients on physical function. In addition, we performed these analyses in a cohort of community-dwelling old people, which only allowed examining the less severe cases of physical function impairment and disability in the population. Another limitation of the study was the lack of measurement of the lower extremity function at baseline; therefore, we eliminated those who reported fatigue as a proxy of prevalent cases of impaired physical function of the lower extremities. However, this was a conservative approach since individuals may feel fatigued by other causes unrelated to physical function. Finally, as in any observational study, some residual confounding may persist.

Table 4 HRs (95% CI) for the association between caffeinated, decaffeinated, filtered and unfiltered coffee consumption and physical function impairment, frailty and disability during 7.2-year follow-up

	Coffee consumption, cups/day			*P* for trend
	0	1	≥2	
Impaired agility (*N* = 2037)				
Caffeinated coffee				
Person-years/*n* cases	4878/296	4686/234	1877/91	
Multivariable model[a]	1.00	0.91 (0.77–1.09)	0.86 (0.67–1.10)	0.19
Decaffeinated coffee				
Person-years/*n* cases	6886/354	3571/209	985/58	
Multivariable model	1.00	0.91 (0.76–1.08)	1.05 (0.79–1.41)	0.78
Filtered coffee				
Person-years/*n* cases	10,134/546	966/55	341/20	
Multivariable model	1.00	1.04 (0.78–1.37)	0.92 (0.58–1.45)	0.92
Unfiltered coffee				
Person-years/*n* cases	2725/153	5969/331	2748/137	
Multivariable model	1.00	0.87 (0.71–1.06)	0.85 (0.67–1.08)	0.19
Impaired mobility (*N* = 2062)				
Caffeinated coffee				
Person-years/*n* cases	5128/232	4889/157	1939/64	
Multivariable model	1.00	0.82 (0.66–1.01)	0.82 (0.61–1.09)	0.07
Decaffeinated coffee				
Person-years/*n* cases	7213/250	3690/168	1053/35	
Multivariable model	1.00	1.08 (0.88–1.32)	0.87 (0.61–1.25)	0.93
Filtered coffee				
Person-years/*n* cases	10,635/406	983/34	339/13	
Multivariable model	1.00	0.95 (0.66–1.36)	1.10 (0.62–1.92)	0.92
Unfiltered coffee				
Person-years/*n* cases	2810/108	6257/255	2889/90	
Multivariable model	1.00	0.97 (0.77–1.22)	0.75 (0.56–1.00)	0.05
Impaired overall physical function (*N* = 1653)				
Caffeinated coffee				
Person-years/*n* cases	3953/242	3885/222	1558/90	
Multivariable model	1.00	0.98 (0.81–1.18)	1.03 (0.80–1.33)	0.88
Decaffeinated coffee				
Person-years/*n* cases	5666/324	2811/179	919/51	
Multivariable model	1.00	1.03 (0.85–1.24)	0.93 (0.69–1.26)	0.86
Filtered coffee				
Person-years/*n* cases	8328/485	755/46	314/23	
Multivariable model	1.00	1.14 (0.84–1.55)	1.40 (0.91–2.14)	0.08
Unfiltered coffee				
Person-years/*n* cases	2441/130	4837/301	2319/123	
Multivariable model	1.00	1.01 (0.81–1.23)	0.89 (0.69–1.14)	0.38
Impaired lower extremity function (*N* = 2262)				
Caffeinated coffee				
Person-years/*n* cases	5660/192	5208/168	2125/58	
Multivariable model	1.00	1.21 (0.97–1.50)	1.02 (0.75–1.38)	0.45
Decaffeinated coffee				
Person-years/*n* cases	7820/237	4054/142	1120/39	
Multivariable model	1.00	0.99 (0.80–1.22)	1.12 (0.79–1.58)	0.66
Filtered coffee				
Person-years/*n* cases	11,522/380	1100/29	371/9	

Table 4 (continued)

	Coffee consumption, cups/day			*P* for trend
	0	1	≥2	
Multivariable model	1.00	0.90 (0.61–1.32)	0.85 (0.43–1.66)	0.51
Unfiltered coffee				
Person-years/*n* cases	3113/93	6768/233	3112/92	
Multivariable model	1.00	1.15 (0.90–1.47)	1.08 (0.80–1.46)	0.56
Frailty (*N* = 1714)				
Caffeinated coffee				
Person-years/*n* cases	4354/92	4130/76	1668/30	
Multivariable model	1.00	1.16 (0.85–1.60)	1.23 (0.80–1.90)	0.25
Decaffeinated coffee				
Person-years/*n* cases	6177/115	3093/67	882/16	
Multivariable model	1.00	0.89 (0.65–1.22)	0.87 (0.50–1.49)	0.45
Filtered coffee				
Person-years/*n* cases	9005/176	840/16	307/6	
Multivariable model	1.00	1.23 (0.72–2.09)	1.14 (0.49–2.62)	0.48
Unfiltered coffee				
Person-years/*n* cases	2493/45	5253/111	2406/42	
Multivariable model	1.00	1.05 (0.73–1.51)	1.05 (0.68–1.62)	0.81
IADL disability (*N* = 1564)				
Caffeinated coffee				
Person-years/*n* cases	3854/81	3958/55	1536/22	
Multivariable model	1.00	0.79 (0.55–1.13)	0.93 (0.56–1.53)	0.46
Decaffeinated coffee				
Person-years/*n* cases	5695/89	2811/52	843/17	
Multivariable model	1.00	1.06 (0.74–1.51)	1.17 (0.68–2.01)	0.53
Filtered coffee				
Person-years/*n* cases	8278/141	796/13	275/4	
Multivariable model	1.00	1.12 (0.62–2.03)	0.96 (0.34–2.67)	0.85
Unfiltered coffee				
Person-years/*n* cases	2192/42	4900/76	2256/40	
Multivariable model	1.00	0.80 (0.54–1.19)	1.05 (0.67–1.65)	0.82
ADL disability (*N* = 1756)				
Caffeinated coffee				
Person-years/*n* cases	4318/180	4119/123	1654/57	
Multivariable model	1.00	0.78 (0.62–0.99)	1.07 (0.78–1.45)	0.66
Decaffeinated coffee				
Person-years/*n* cases	6118/201	3092/120	881/39	
Multivariable model	1.00	1.02 (0.81–1.29)	1.29 (0.91–1.83)	0.24
Filtered coffee				
Person-years/*n* cases	8929/328	847/25	315/7	
Multivariable model	1.00	0.87 (0.57–1.32)	0.73 (0.34–1.56)	0.31
Unfiltered coffee				
Person-years/*n* cases	2474/83	5248/186	2369/91	
Multivariable model	1.00	0.95 (0.73–1.24)	1.25 (0.92–1.69)	0.15

Variables are defined as in Table 1

IADL instrumental activities of daily living, *ADL* basic activity of daily living

[a]Cox regression models adjusted for age, sex, education (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), alcohol consumption (none, moderate, heavy drinker), physical activity (MET-h/week), watching TV (quintiles of h/week), energy intake (quintiles of kcal/day), MEDAS score (quintiles of score), body mass index, cognitive impairment, osteomuscular disease, cardiovascular disease, cancer, chronic lung disease and depression

In conclusion, our results suggest that habitual coffee consumption does not pose a risk to physical functioning in the older people, and that it might be even beneficial in persons at higher risk of functional limitations, including women and those with hypertension, obesity or diabetes.

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Author contributions MMF and ELG designed and conducted research; MMF and EAS analyzed data; MMF and ELG wrote the paper; MMF and ELG had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed the manuscript for important intellectual content and approved the final version.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Study participants gave their informed written consent. The Clinical Research Ethics Committee of 'La Paz' University Hospital in Madrid approved the study protocol.

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PUBLICATION 2

Habitual coffee consumption and risk of falls in 2 European cohorts of older adults

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ABSTRACT

Background: Habitual coffee consumption has been associated with lower risk of type 2 diabetes, cardiovascular disease, and sarcopenia, which are strong risk factors of falls. In addition, caffeine intake stimulates attention and vigilance, and reduces reaction time. Therefore, a protective effect of coffee on the risk of falling can be hypothesized.

Objectives: The aim of this study was to examine the association between habitual coffee consumption and the risk of ≥1 falls, injurious falls, and falls with fracture in older people.

Methods: Data were taken from 2964 participants aged ≥60 y from the Seniors-ENRICA (Study on Nutrition and Cardiovascular Risk in Spain) cohort and 8999 participants aged ≥60 y from the UK Biobank cohort. In the Seniors-ENRICA study, habitual coffee consumption was assessed with a validated diet history in 2008–2010, and falls were ascertained up to 2015. In the UK Biobank study, coffee was measured with 3–5 multiple-pass 24-h food records starting in 2006, and falls were assessed up to 2016.

Results: A total of 793 individuals in Seniors-ENRICA and 199 in UK Biobank experienced ≥1 fall during follow-up. After multivariable adjustment for major lifestyle and dietary risk factors and compared with daily consumption of <1 cup of coffee, the pooled HR for ≥1 fall was 0.75 (95% CI: 0.52, 1.07) for total coffee consumption of 1 cup/d and 0.74 (95% CI: 0.62, 0.90) for ≥2 cups/d (P-trend = 0.001). The corresponding figures for caffeinated coffee were 0.67 (95% CI: 0.42, 1.07) and 0.70 (95% CI: 0.56, 0.87) (P-trend < 0.001). Decaffeinated coffee was not associated with risk of falling in the analyzed cohorts. In Seniors-ENRICA, there was a tendency to lower risk of injurious falls among those consuming caffeinated coffee (HR: 0.83; 95% CI: 0.68, 1.00 for 1 cup/d; HR: 0.83; 95% CI: 0.64, 1.09 for ≥2 cups/d; P-trend = 0.09). No association was observed between caffeinated or decaffeinated coffee consumption and risk of falls with fracture.

Conclusions: Habitual coffee consumption was associated with lower risk of falling in older adults in Spain and the United Kingdom. *Am J Clin Nutr* 2019;0:1–8.

Keywords: coffee, cohort study, falls, older population, Seniors-ENRICA, UK Biobank

Introduction

Falls in old people represent a major public health problem. About 28–35% of people aged >65 y fall at least once a year and this figure is even higher in those >75 y of age (1, 2). Falling is also associated with adverse health outcomes (3, 4) and poses a major cost to health care systems (5, 6). Specifically, falls are one of the main causes of injury (7), disability (8, 9), and premature death in old people (10, 11). Therefore, prevention of falls is essential to ensure the well-being of the older population.

Knowledge of dietary factors that affect the risk of falls is rather limited and mainly corresponds to certain nutrients, such as calcium (12, 13), vitamin D (14, 15), and protein intake (16, 17), as well as some foods, such as alcoholic beverages (18) or fruit and vegetables (19–21). A poor nutritional status has also been associated with increased risk of falls and fractures (22). One of the foods that merits attention in relation to risk of falling is coffee. Habitual coffee consumption has been associated with lower risk of type 2 diabetes (23, 24), cardiovascular disease (25), and sarcopenia (26, 27), which are strong risk factors of

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Supplemental Figure 1 and Supplemental Table 1 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/ajcn/.

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falls. Moreover, caffeine intake stimulates attention, vigilance, and reaction time (28, 29). Therefore, a protective effect of coffee on the risk of falling can be hypothesized.

The aim of this study was to assess the association between habitual coffee consumption and risk of several falls-related outcomes: ≥1 fall, injurious fall, and ≥1 fall with fracture. We examined this association in older adults from Spain and the United Kingdom in order to assess the generalizability of the results. Moreover, since the type of coffee consumed may differ between both countries, we could also assess its influence on the risk of falls.

Methods

Study design and participants

The Seniors-ENRICA study.

We used data from the ENRICA study (Study on Nutrition and Cardiovascular Risk in Spain) (30). Briefly, this cohort was established in 2008–2010 when 12,948 individuals representative of the noninstitutionalized adult population of Spain were selected. Study participants aged ≥60 y at baseline ($n = 3289$) comprise the Seniors-ENRICA cohort. At baseline, information on sociodemographic variables, lifestyle, health status, and morbidity was collected through a telephone interview. In 2 subsequent home visits, trained research staff collected dietary information and conducted a physical examination. Subsequently, 2 waves of data collection were performed in 2012 and 2015 to update information about the cohort (**Supplemental Figure 1**). Study participants gave their informed written consent. The Clinical Research Ethics Committee of "La Paz" University Hospital in Madrid approved the study protocol.

The UK Biobank Study.

The UK Biobank is a large population-based cohort study that recruited >500,000 men and women aged 40–69 y (81,720 were ≥60 y) in the 2006–2010 period throughout the United Kingdom (31). At baseline, in the assessment centers, the participants had to sign an informed consent, complete a touchscreen questionnaire, conduct a face-to-face interview, and provide various anthropometric measurements and samples of blood, urine, and saliva, as well as perform some physical tests. Subsequently, a subsample of participants was followed-up and provided updated information in 2012–2013 and 2014–2016 (Supplemental Figure 1). This study was performed under generic ethical approval obtained by UK Biobank from the National Health Service National Research Ethics Service (ref 11/NW/0382, 17 June 2011).

Study variables

Coffee and other dietary variables.

In the Seniors-ENRICA cohort, food consumption was collected with an electronic diet history developed from that used in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Spain study (32). This instrument included 860 foods and beverages, and took into account portion size, cooking methods, degree of food processing, and weekly and seasonal variations in food consumption. Coffee consumption was assessed in detail by asking participants whether they consumed caffeinated or decaffeinated coffee, the method of preparation [filtered (drip coffee), nonfiltered (percolated, espresso), and instant], and cup size. For data analyses, we standardized the amount of coffee consumed to a 75-mL cup size for percolated and drip coffee and a 50-mL cup size for espresso coffee. We considered an amount of 3.5 g of instant coffee to equal 1 cup. Finally, 3 categories of coffee consumption were considered: <1, 1 and ≥2 cups/d.

Caffeine intake was estimated with the use of standard food composition tables (32). Thus, a cup of percolated coffee, drip coffee, espresso, and instant coffee was considered to provide 80, 115, 75, and 65 mg of caffeine, respectively. To calculate the total caffeine intake per day we included caffeine from coffee and also from tea (a bag provided 30 mg of caffeine), caffeinated soft drinks (a 200-mL glass provided 20 mg of caffeine, and a 333-mL can provided 33 mg), and from chocolate [150 mL of hot chocolate provided 4 mg of caffeine, and 28.34 g (1 oz) of solid chocolate provided 6 mg]. Total caffeine intake was energy-adjusted by the residual method (33). In addition, other nutrients and total energy intake (kcal/d) were also estimated (32).

The validity and reproducibility of the diet history has been reported in detail elsewhere (32). In the validation study, there was a moderate to good correlation between consumption of coffee and caffeine estimated from the diet history and the mean of seven 24-h recalls during 1 y (coffee, $r = 0.71$; caffeine, $r = 0.47$).

In the UK Biobank, dietary information was collected through 5 web-based 24-h recalls (Oxford WebQ) (34). The first one was administered at baseline in the assessment centers and the remaining 4 in the period 2011–2012 at estimated intervals of 6 mo, via e-mail. This took into account seasonal variations in food consumption. The Oxford WebQ included >200 individual foods frequently consumed in the United Kingdom. For the present analyses, only participants who completed 3 or more 24-h recalls were selected, to reflect habitual diet. Coffee consumption was assessed in detail by asking participants whether they consumed caffeinated or decaffeinated coffee, and the method of preparation [instant, filtered, and nonfiltered (cappuccino, latte, espresso)]. The possible recall responses were: none, 0.5, 1, 2, 3, 4, 5, and ≥6 cups/d. A value of 6 was used in our analyses for those reporting to consume "≥6 cups." Subsequently, the average consumption in cups/day was calculated between the 24-h recalls. Finally, 3 categories of coffee consumption were considered: <1, 1 and ≥2 cups/d. Total energy, and nutrients related to bone metabolism, muscle function, and visual function (vitamin D, carotene, folate, calcium, and protein intakes) were estimated with standard composition food tables in the United Kingdom (35).

Falls.

In the Seniors-ENRICA study, falls were reported at the follow-up visits in waves 2 and 3. Trained interviewers asked participants: "How many times have you fallen down since the last interview?" Participants also reported if, as a result of the fall, they had suffered an injury (contusion, bruise, sprain, superficial injury, or deep wound) or fracture (hip, leg, shoulder or arm fracture). Therefore, we used the following outcomes in our analyses: ≥1 fall, injurious fall, and ≥1 fall with fracture.

In the UK Biobank, falls were reported in waves 2 and 3 by asking the participants "In the last year have you had any falls?" The possible answers were "no falls," "only one fall," and "more than one fall." We did not use data on falls with fractures in this cohort due to the very small number reported ($n = 19$).

Mortality.

In the Seniors-ENRICA study, all cause-mortality was ascertained by a computerized search of the National Death Index, which contains information on the vital status of all residents in Spain (36). This information was available for 99.9% of the cohort. In total, we found that 177 participant (5.3%) died during the follow-up. In the UK Biobank, all cause-mortality was obtained from death certificates held by the National Health Service Information Centre (England and Wales) and the National Health Service Central Register Scotland (Scotland) (37).

Other variables.

At baseline in the Seniors-ENRICA, we collected data on age, sex, educational level, smoking status, and alcohol intake. Study participants were classified as abstainers (<0.1 g/d), moderate drinkers (0.1–39 g/d in men and 0.1–23 g/d in women), and heavy drinkers (≥40 g/d in men and ≥24 g/d in women). Weight and height were measured in each participant under standardized conditions. BMI was calculated as weight (kg) divided by height (m) squared, and obesity was defined as BMI ≥30 kg/m^2. Physical activity during leisure time (metabolic equivalent hours/week) was ascertained with the EPIC-cohort questionnaire, validated in Spain (38). Blood pressure (BP) was measured with a validated sphygmomanometer according to standardized procedures, and hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or being under hypertensive drug treatment. Twelve-hour fasting serum glucose was centrally measured with standard techniques, and type 2 diabetes was defined as glucose ≥126 mg/dL or being treated with antidiabetic drugs or insulin. Sleep duration as well as use of sleeping pills was self-reported. Finally, participants reported if they had received a diagnosis of osteomuscular disease (osteoarthritis or arthritis).

In the UK Biobank study, most of the variables were collected and categorized as in the Seniors-ENRICA study, except physical activity which was assessed with questions from the short International Physical Activity Questionnaire (39), and diagnoses of diabetes, and hypertension, which were reported by the participants.

Statistical analyses

In the Seniors-ENRICA group, we excluded participants with energy intake outside the range of 800–5000 kcal/d for men and 500–4000 kcal/d for women at baseline and with missing data on coffee consumption. In addition, we excluded those participants who were frail at baseline, because frailty is a strong predictor of falls and we had no information on falls at baseline (40). In the UK Biobank, among those aged ≥60 y, we excluded participants without a minimum of 3 web-based 24-h recall questionnaires, those with implausibly high or low energy intake, or missing coffee consumption data, and those who reported falls at baseline. This resulted in an analytic sample of 2964 individuals from the Seniors-ENRICA group and 8999 from the UK Biobank.

Participants were classified according to baseline coffee consumption. Differences in sociodemographic characteristics, lifestyle, and morbidity across categories of coffee intake were assessed with *P* values from linear or logistic regression based on the use of ordinal categories as predictors.

Person-years of follow-up were calculated from the date of the baseline questionnaire until the date of the outcome, death, loss to follow-up, or the end of the study, whichever came first. Cox models were used to investigate the association between coffee consumption and the incidence of falls. Several models were built. The first one was adjusted for age and sex. A second model was additionally adjusted for other potential confounders, including education, smoking, alcohol intake, BMI, physical activity, sleep duration, intake of energy, calcium, vitamin A, vitamin D, and total protein, as well as hypertension, diabetes, osteomuscular disease, and use of sleeping pills. Moreover, when we assessed the separate association of caffeinated and decaffeinated coffee, we built a third model additionally adjusted for the other type of coffee. We estimated the HR and its 95% CI for each category of coffee consumption, compared with no consumption. To investigate the linear dose-response relation, we modeled the categories of coffee as a continuous variable. In the Seniors-ENRICA group, these analyses were replicated based on cumulative coffee consumption as the main exposure in order to account for changes in coffee consumption during follow-up.

Similar analyses were conducted to examine the association between total caffeine intake (mg/dL) and falls; this was performed in the Seniors-ENRICA group, since caffeine intake was not available for UK Biobank participants. Finally, we tested if main results varied by categories of the following variables that are associated with different baseline risk of falls: age, sex, obesity, osteomuscular disease, protein intake, alcohol consumption, sleep duration, and physical activity; to this end, we used likelihood-ratio tests that compared models with and without cross-product interaction terms. Analyses by age and osteomuscular disease were performed only in the Seniors-ENRICA group, since there were no individuals aged >75 y in the UK Biobank and we did not have access to information about osteomuscular disease in this cohort.

The HRs from multivariable models for the risk of having ≥1 fall in each cohort were pooled to obtain a summary risk estimate with the use of an inverse variance-weighted meta-analysis by random-effects models, which allowed for between-study heterogeneity. All analyses were conducted with Stata version 15.0 (Stata Corp.).

Results

Mean ± SD coffee consumption was 1.37 ± 1.31 cups/d among participants in the Seniors-ENRICA, and 1.75 ± 1.38 cups/d among the UK Biobank participants. Caffeinated coffee accounted for most of this consumption in both populations. The mean ± SD intake of caffeinated and decaffeinated coffee in the Seniors-ENRICA group was 0.87 ± 1.17 and 0.52 ± 0.96 cups/d, respectively, and in the UK Biobank group 1.44 ± 1.37 and

TABLE 1 Participants' characteristics at baseline across the categories of coffee consumption[1]

	Total coffee consumption, cups/d					
	Seniors-ENRICA study ($n = 2964$)			UK Biobank study ($n = 8999$)		
	<1	1	≥2	<1	1	≥2
Participants, *n*	512	1670	782	1264	3831	3904
Age, y	70.1 ± 6.9	69.2 ± 6.6	68.0 ± 6.1*	63.6 ± 2.7	63.6 ± 2.7	63.7 ± 2.7
Men, %	46.5	45.4	51.0	52.5	52.1	54.5
Educational level, %						
≤Primary	58.9	59.1	51.8	12.6	9.5	8.5
Secondary	22.7	22.8	25.8	32.3	30.4	27.7
University	18.4	18.1	22.4	55.1	60.1	63.8*
Current smoker, %	6.6	10.1	19.7*	3.6	3.9	6.4*
Heavy drinker,[2] %	22.6	22.6	21.9	11.5	13.8	15.1*
BMI, kg/m^2	27.7 ± 4.2	28.7 ± 4.5	28.7 ± 4.5	26.6 ± 4.2	26. ± 4.2	26.8 ± 4.1*
Physical activity,[3]	22.4 ± 16.1	21.1 ± 14.9	22.0 ± 14.9	44.6 ± 54.6	44.1 ± 48.2	42.5 ± 48.4
METs-h/week						
Sleep duration, h/d	6.9 ± 1.5	6.9 ± 1.4	6.9 ± 1.4	7.3 ± 1.0	7.3 ± 1.0	7.3 ± 0.9
Energy intake, kcal/d	1915 ± 583	2020 ± 575	2046 ± 578*	2083 ± 560	2093 ± 495	2149 ± 489**
Intake of vitamin D, μg/d	3.4 ± 2.9	3.3 ± 2.9	3.6 ± 3.3*	3.0 ± 2.1	3.1 ± 2.1	3.1 ± 2.2
Intake of vitamin A,[4] μg/d	835 ± 626	817 ± 504	857 ± 625	—	—	—
Intake of retinol, μg/d	—	—	—	319 ± 144	330 ± 141	350 ± 146**
Intake of carotene, μg/d	—	—	—	3131 ± 2182	3124 ± 1929	3078 ± 1856
Intake of calcium, mg/dL	873 ± 359	877 ± 319	889 ± 340	988 ± 369	982 ± 300	991 ± 293
Intake of protein, g/d	89.6 ± 30.8	90.5 ± 25.4	92.9 ± 25.7	82.3 ± 20.7	82.0 ± 19.0	83.1 ± 19.3*
Intake of caffeine, mg/d	17.3 ± 35.4	46.4 ± 55.2	151.6 ± 156.6**	—	—	—
Diagnosed diseases, %						
Hypertension	64	65	62	37	35	32*
Diabetes	14	17	14	5	4	5
Osteomuscular disease[5]	48	49	47	—	—	—
Use of sleeping pills, %	17.5	13.8	13.9	0.4	0.6	0.4
Type of coffee, cups/d						
Caffeinated	0	0.61 ± 0.58	1.97 ± 1.63	0	0.87 ± 0.54	2.48 ± 1.42
Decaffeinated	0	0.39 ± 0.51	1.11 ± 1.54	0	0.17 ± 0.38	0.56 ± 1.21

[1]Continuous variables are given as means ± SDs. *P* values were calculated from linear and logistic regressions based on the use of ordinal categories as predictors: *$P < 0.05$; **$P < 0.001$. MET, metabolic equivalent.

[2]Heavy drinker: ≥40 g/d of alcohol in men and ≥24 g/d in women.

[3]In the UK Biobank study, physical activity was measured in METs-min/wk.

[4]In the Seniors-ENRICA study, total intake of vitamin A corresponds to the sum of retinol (μg/d) and retinol equivalents (μg/d). In the UK Biobank study the amount of retinol (μg/d) and carotenes (μg/d; without transforming to retinol equivalents) was measured separately.

[5]Osteoarthritis and arthritis.

0.31 ± 0.86 cups/d respectively. The method of preparation most frequent in the Spanish cohort was nonfiltered coffee (1.22 ± 1.29 cups/d compared with 0.16 ± 0.59 cups filtered/d and 0.24 ± 0.71 cups instant/d). Similarly, nonfiltered coffee was the method preferred in the English cohort (1.28 ± 1.33 cups/d compared with 0.48 ± 0.81 cups filtered/d and 1.10 ± 1.31 cups instant/d). In the Seniors-ENRICA group, participants consuming more coffee were younger and more likely to be current smokers, and reported higher intakes of energy and vitamin D. In the UK Biobank, participants consuming more coffee had higher educational levels, as well as higher intakes of energy and retinol, and were more likely to be current smokers and heavy drinkers (**Table 1**).

Over 7.2 y of follow-up of the Seniors-ENRICA group, 793 individuals reported ≥1 fall, 566 injurious falls, and 143 falls with fracture. In full adjusted analyses, compared with participants who consumed <1 cup coffee/d, those who consumed 1 and ≥2 cups/d had a decreased risk of ≥1 fall (HR: 0.88; 95% CI: 0.73, 1.07 and HR: 0.79; 95% CI: 0.63, 0.98, respectively; *P*-trend = 0.03). Caffeinated coffee accounted for most of the association (HR: 0.84; 95% CI: 0.71, 0.99 for 1 cup/d and HR: 0.76; 95% CI: 0.61, 0.96 for ≥2 cups/d; *P*-trend = 0.01). In the UK Biobank group, over 10.2 y of follow-up, 199 individuals reported ≥1 fall. Caffeinated coffee, but not decaffeinated coffee, was associated with lower risk of falling (HR: 0.52; 95% CI: 0.33, 0.83 for 1 cup/d and HR: 0.60; 95% CI: 0.37, 0.96 for ≥2 cups/d; *P*-trend = 0.04) (**Table 2**). The pooled HRs of falling across categories of total coffee consumption for the 2 cohorts were 1.0, 0.75 (95% CI: 0.52, 1.07), and 0.74 (95% CI: 0.62, 0.90) (*P*-trend = 0.001). Corresponding figures for caffeinated coffee were 1.0, 0.67 (95% CI: 0.42, 1.07) and 0.70 (95% CI: 0.56, 0.87) (*P*-trend < 0.001). Lastly, the pooled HRs across categories of decaffeinated coffee consumption were 1.0, 0.99 (95% CI: 0.84, 1.16), and 0.87 (95% CI: 0.69, 1.09) (*P*-trend = 0.34).

TABLE 2 Hazard ratios (95% CIs) for the association between total, caffeinated and decaffeinated coffee consumption and the risk of ≥1 fall in the Seniors-ENRICA study ($n = 2964$) and in the UK Biobank study ($n = 8999$)[1]

	Coffee consumption, cups/d			
	<1	1	≥2	*P*-trend
Seniors-ENRICA				
Total coffee				
Person-y/cases	2501/146	8350/454	3987/193	
Age- and sex-adjusted model	1.00	0.89 (0.74, 1.07)	0.81 (0.65, 1.01)	0.06
Multivariable[2]	1.00	0.88 (0.73, 1.07)	0.79 (0.63, 0.98)	0.03
Caffeinated coffee				
Person-y/cases	6485/384	5997/301	2356/108	
Age- and sex-adjusted model	1.00	0.85 (0.73, 0.99)	0.80 (0.73, 0.99)	0.01
Multivariable[2]	1.00	0.86 (0.73, 0.99)	0.76 (0.62, 0.96)	0.01
Multivariable[3]	1.00	0.84 (0.71, 0.99)	0.76 (0.61, 0.96)	0.01
Decaffeinated coffee				
Person-y/cases	8999/458	4591/272	1248/63	
Age- and sex-adjusted model	1.00	1.10 (0.95, 1.28)	0.95 (0.73, 1.23)	0.68
Multivariable[2]	1.00	1.10 (0.95, 1.28)	0.95 (0.72, 1.24)	0.69
Multivariable[3]	1.00	1.01 (0.86, 1.20)	0.85 (0.64, 1.12)	0.47
UK Biobank				
Total coffee				
Person-y/cases	4557/35	13,728/85	14,217/79	
Age- and sex-adjusted model	1.00	0.74 (0.50, 1.11)	0.70 (0.47, 1.04)	0.53
Multivariable[4]	1.00	0.61 (0.37, 0.98)	0.64 (0.39, 1.03)	0.13
Caffeinated coffee				
Person-y/cases	8005/63	13,046/69	11,450/67	
Age- and sex-adjusted model	1.00	0.63 (0.44, 0.88)	0.72 (0.51, 1.01)	0.08
Multivariable[4]	1.00	0.51 (0.33, 0.79)	0.60 (0.38, 0.93)	0.02
Multivariable[5]	1.00	0.52 (0.33, 0.83)	0.60 (0.37, 0.96)	0.04
Decaffeinated coffee				
Person-y/cases	26,212/157	4077/29	2212/13	
Age- and sex-adjusted model	1.00	1.06 (0.71, 1.57)	1.07 (0.61, 1.89)	0.74
Multivariable[4]	1.00	0.91 (0.53, 1.58)	1.64 (0.86, 3.11)	0.30
Multivariable[5]	1.00	0.84 (0.48, 1.48)	1.14 (0.57, 2.27)	0.97
Pooled results				
Total coffee[6]	1.00	0.75 (0.52, 1.07)	0.74 (0.62, 0.90)	0.001
Caffeinated coffee[7]	1.00	0.67 (0.42,1.07)	0.70 (0.56, 0.87)	<0.001
Decaffeinated coffee[7]	1.00	0.99 (0.84, 1.16)	0.87 (0.69, 1.09)	0.34

[1]MET, metabolic equivalent.

[2]Cox model adjusted for age, sex, educational level (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), alcohol consumption (none, moderate, heavy drinker), BMI (tertiles of kg/m^2), physical activity (tertiles of MET-h/wk), sleep duration (tertiles of h/d), energy intake (tertiles of kcal/d), intake of vitamin D (tertiles of μg/d), intake of vitamin A (tertiles of μg/d), intake of calcium (tertiles of mg/d), protein intake (tertiles of g/d), and for hypertension, diabetes, osteomuscular disease, and use of sleeping pills at baseline.

[3]Model 1 additionally adjusted for the other type of coffee.

[4]Cox model adjusted for age, sex, educational level (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), alcohol consumption (none, moderate, heavy drinker) , BMI (tertiles of kg/m^2), physical activity (tertiles of MET-min/wk), sleep duration (tertiles of h/d), energy intake (tertiles of kcal/d), intake of vitamin D (tertiles of μg/d), intake of retinol (tertiles of μg/d), intake of carotene (tertiles of μg/d), intake of calcium (tertiles of mg/d), protein intake (tertiles of g/d), and for hypertension, diabetes, and use of sleeping pills at baseline

[5]Model 3 additionally adjusted for the other type of coffee.

[6]From multivariable models 1 and 3 combined with the use of a random-effects model.

[7]From multivariable models 2 and 4 combined with the use of a random-effects model.

In addition, in the Seniors-ENRICA group, we found some tendency to lower risk of injurious falls among those consuming caffeinated coffee (HR: 0.83; 95% CI: 0.68, 1.00 for 1 cup/d, and HR: 0.83; 95% CI: 0.64, 1.09 for ≥2 cups/d; *P*-trend = 0.09). No association was observed between caffeinated or decaffeinated coffee consumption and risk of falls with fracture (**Table 3**). Moreover, when cumulative coffee consumption was used, the results were similar (data not shown).

In **Supplemental Table 1**, we present the association between caffeine intake (mg/dL) and falls risk in the Seniors-ENRICA group. Participants in the highest tertile of caffeine intake had a lower risk of falls (HR: 0.80; 95% CI: 0.67, 0.96; *P*-trend = 0.02) than those in the lowest tertile. Also, the risk of injurious falls was reduced among participants in the highest tertile of intake (HR: 0.78; 95% CI: 0.63, 0.97; *P*-trend = 0.03). No association was found for falls with fracture.

TABLE 3 Hazard ratios (95% CIs) for the association between total, caffeinated, and decaffeinated coffee consumption and the risk of injurious falls and falls with fracture in the Seniors-ENRICA study ($n = 2964$)[1]

	Coffee consumption, cups/d			
	<1	1	≥2	*P*-trend
Risk of injurious falls[2]				
Total coffee				
Person-y/cases	2559/97	8492/329	4075/140	
Age- and sex-adjusted model	1.00	0.99 (0.79, 1.24)	0.88 (0.68, 1.15)	0.31
Multivariable[3]	1.00	0.99 (0.78, 1.25)	0.88 (0.67, 1.15)	0.29
Caffeinated coffee				
Person-y/cases	6611/274	6110/210	2405/82	
Age- and sex-adjusted model	1.00	0.83 (0.69, 0.99)	0.84 (0.65, 1.07)	0.06
Multivariable[3]	1.00	0.83 (0.69, 1.00)	0.83 (0.65, 1.07)	0.06
Multivariable[4]	1.00	0.83 (0.68, 1.00)	0.83 (0.64, 1.09)	0.09
Decaffeinated coffee				
Person-y/cases	9168/323	4678/199	1280/44	
Age- and sex-adjusted model	1.00	1.15 (0.96, 1.37)	0.93 (0.68, 1.28)	0.59
Multivariable[3]	1.00	1.14 (0.95, 1.37)	0.94 (0.68, 1.29)	0.61
Multivariable[4]	1.00	1.07 (0.88, 1.29)	0.85 (0.61, 1.19)	0.72
Risk of falls with fracture[5]				
Total coffee				
Person-y/cases	2674/23	8889/83	4218/37	
Age- and sex-adjusted model	1.00	1.08 (0.68, 1.71)	1.06 (0.63, 1.79)	0.85
Multivariable[3]	1.00	1.12 (0.70, 1.81)	1.11 (0.66, 1.91)	0.72
Caffeinated coffee				
Person-y/cases	6930/60	6362/62	2489/21	
Age- and sex-adjusted model	1.00	1.21 (0.84, 1.73)	1.07 (0.65, 1.77)	0.55
Multivariable[3]	1.00	1.27 (0.88, 1.83)	1.14 (0.68, 1.89)	0.39
Multivariable[4]	1.00	1.31 (0.88, 1.94)	1.18 (0.69, 2.03)	0.38
Decaffeinated coffee				
Person-y/cases	9545/85	4910/46	1326/12	
Age- and sex-adjusted model	1.00	0.96 (0.67, 1.38)	0.99 (0.54, 1.81)	0.88
Multivariable[3]	1.00	0.97 (0.67, 1.40)	1.01 (0.55, 1.86)	0.94
Multivariable[4]	1.00	1.05 (0.71, 1.56)	1.14 (0.60, 2.18)	0.66

[1]MET, metabolic equivalent.

[2]Falls with contusion, bruise, sprain, superficial injury, or deep wound.

[3]Cox model adjusted for age, sex, educational level (≤primary, secondary, university), smoking status (never smoker, former smoker, current smoker), alcohol consumption (none, moderate, heavy drinker), BMI (tertiles of kg/m^2), physical activity (tertiles of MET-h/wk), sleep duration (tertiles of h/d), energy intake (tertiles of kcal/d), intake of vitamin D (tertiles of μg/d), intake of vitamin A (tertiles of μg/d), intake of calcium (tertiles of mg/d), protein intake (tertiles of g/d), and for hypertension, diabetes, osteomuscular disease, and use of sleeping pills at baseline.

[4]Multivariable model additionally adjusted for the other type of coffee.

[5]Falls with leg, hip, arm, or shoulder fracture.

Finally, we examined the association between total coffee consumption and the risk of ≥1 fall in specific subgroups of participants in both cohorts. We found that the inverse association between coffee and risk of falling was rather consistent regardless of sex, obesity, protein intake, sleep duration, physical activity, and alcohol consumption (all *P*-interaction > 0.05).

Discussion

In this study, we found an inverse association between habitual coffee consumption and the risk of falls. This effect was mainly observed for the consumption of caffeinated coffee. However, since decaffeinated coffee consumption was lower in these populations, our data cannot discount a potential effect of this beverage. We also found some tendency for a lower risk of injurious falls to be associated with coffee consumption.

We are not aware of previous studies evaluating the relationship between coffee consumption and the risk of falls in older people. The protective association found in the present study might be due to the action of caffeine. Caffeine is an alkaloid present naturally in coffee and other foods that also acts as an antagonist of adenosine A1 and A2 receptors, promoting the release of different neurotransmitters at normal doses of consumption (28, 41, 42). Caffeine improves some aspects of cognitive function such as reaction time, attention, and vigilance (28, 29). Older people have a reduced ability to react to external stimuli and barriers, which is a deficit that can lead to falling. Thus, the protective effect of caffeinated coffee and total caffeine in our study might be related to improved reaction time (43, 44). Likewise, lower vigilance and a lower level of attention have been associated with increased risk of falls (45), and therefore our findings might also partially result from caffeine-enhanced vigilance and attention.

Age-associated poor functional status has been related to an increased risk of falls in older adults (46–48). In addition, sarcopenia, which is a common syndrome in older people, limits

functional capacity and increases the risk of falls (49–51). In vivo and in vitro studies in mice have shown that coffee slows age-related sarcopenia by improving the structure and function of skeletal muscle through the induction of autophagy and decreased levels of inflammatory mediators (26, 27). However, since these studies have been conducted with caffeinated coffee and not with other types of coffee, it cannot be ruled out that this effect is due, at least partially, to components of coffee other than caffeine. Therefore, coffee might also be able to lower the risk of falling by slowing down sarcopenia. In addition, numerous studies have shown a lower risk of clinical and subclinical cardiovascular disease among habitual coffee drinkers (25, 52). We can speculate that the lower risk found in our study could be partly mediated by the reduction in the risk of cardiovascular disease in habitual coffee drinkers.

From a systematic review and meta-analysis of cohort and case-control studies, Lee et al. (53) reported that coffee consumption was associated with a dose-dependent increased risk of fractures in women but, by contrast, men who consumed more coffee had a lower risk of fractures. However, most reviewed studies did not assess caffeinated and decaffeinated coffee separately, and many of them did not fully account for important confounders, such as alcohol intake and smoking. Moreover, there is no clear biological basis for these gender-based differences in the coffee-fracture association. Thus, Lee et al. concluded that more prospective well-designed studies should be performed to confirm their findings. In our analysis, we did not find any statistically significant result for coffee associated with fracture risk, although the HR estimates found were always >1. Studies in humans have suggested that caffeine intake could influence the metabolism of calcium by decreasing its absorption and increasing its excretion in urine. This would increase the risk of fractures, in line with the findings of some observational studies. However, other studies indicate that some polyphenols present in coffee could have a beneficial effect on bone metabolism and, therefore, on the risk of fractures. However, more studies are needed to confirm the effect of the different compounds present in coffee on the risk of fractures (54, 55).

Our study has several strengths, including the use of 2 distinct prospective cohorts from countries with different lifestyles and socioeconomic characteristics. This suggests that the protective association between coffee and the risk of falls is rather generalizable, and also seems to be independent of the type of coffee preparation. Other strengths were that our analyses adjusted for many potential confounders, including diseases and drugs that may affect balance, and the consistency of the results among the various subgroups that presented different baseline risks of falls.

This study also has some limitations. In particular, coffee consumption in Seniors-ENRICA was assessed with a validated dietary history, and in the UK Biobank with several 24-h dietary records; thus, a degree of misreporting and misclassification of dietary intake cannot be ruled out, even though we excluded participants with an implausibly high or low energy intakes in both cohorts. Another limitation was the use of coffee consumption only measured at baseline since the dietary information in the UK Biobank study did not allow cumulative consumptions to be calculated and we intended to use comparable exposures between the cohorts. However, we were able to calculate cumulative consumption during follow-up in the Seniors-ENRICA and results were similar to those obtained with baseline consumption. In addition, incident falls were self-reported and some events could have been missed because old people may not recall all falls they had during the follow-up. Also, some of the falls recorded might have been due to accidents rather than to health status, and we could not exclude them from the analyses because this information was lacking in the cohorts. Finally, as in any observational study, some residual confounding may persist.

In conclusion, habitual consumption of caffeinated coffee was associated with a decreased risk of falling in older adults in Spain and the United Kingdom. Future research should confirm these results in other populations and establish if caffeine or other coffee constituents account for the association observed.

This research has been conducted with the use of the UK Biobank Resource under application number 29009. UK Biobank is an open access resource. Bona fide researchers can apply to use the UK Biobank data by registering and applying (http://www.ukbiobank.ac.uk/register-apply/).

The authors' contributions were as follows—MMF and ELG: designed the research; MMF and ELG: performed the statistical analyses; all authors: contributed to interpretation of the results; MMF and ELG: drafted the manuscript; ELG: supervised the conduct of research and had primary responsibility for final content; and all authors: reviewed the manuscript for important intellectual content, and read and approved the final manuscript. None of the authors has a conflict of interest related to this work.

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ORIGINAL CONTRIBUTION

High dephospho-uncarboxylated matrix Gla protein concentrations, a plasma biomarker of vitamin K, in relation to frailty: the Longitudinal Aging Study Amsterdam

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Abstract

Purpose No previous study has evaluated the relationship between vitamin K and frailty. Thus, we assessed the relationship between vitamin K status and frailty over 13 years in the Longitudinal Aging Study Amsterdam (LASA).

Methods Prospective cohort study with 644 community-dwelling adults ≥ 55 years from the LASA cohort. In 2002–2003, plasma desphospho-uncarboxylated matrix Gla protein (dp-ucMGP) was measured as marker of vitamin K status through a sandwich ELISA. Frailty was measured at baseline and in four follow-up examinations with the LASA Frailty Index (LASA-FI), which was used as both a continuous and a dichotomous measure (FI ≥ 0.25), as indicator of the degree of frailty and frailty risk, respectively. Statistical analyses were performed with multivariable generalized estimating equations using the lowest dp-ucMGP tertile, reflecting a high vitamin K status, as reference.

Results The mean (SD) age was 59.9 (2.9) years, and 54% were female. Compared with the lowest tertile, the medium and highest dp-ucMGP tertile were associated with a higher degree of frailty [1.40, 95% confidence interval (0.01–2.81) and 1.62, (0.18–3.06), respectively. *P* trend: 0.03]. Additionally, the medium and highest dp-ucMGP tertile had a higher odds ratio of frailty [1.75 (1.11–2.77) and 1.63 (1.04–2.57), respectively]. The degree of frailty increased over time, but the differences by dp-ucMGP tertiles existed since baseline and remained stable during follow-up.

Conclusions Baseline plasma low vitamin K status was associated with a greater degree of frailty and frailty risk in this cohort of older adults, which highlights the importance of ensuring an optimal nutritional status of this vitamin to prevent frailty in later life.

Keywords Matrix Gla protein · Frailty index · Epidemiology · Vitamin k · Frailty · Older adults

Introduction

Recent findings highlight the importance of evaluating the role of vitamin K for human health [1]. Vitamin K is a fat-soluble vitamin that exists in two different forms in our diet. Vitamin K_1 is the main source of vitamin K and is mainly present in green leafy vegetables, algae, and plant oils.

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Vitamin K_2 is found in animal foods such as meat, eggs, fermented dairy products and is also synthesized by intestinal bacteria. In addition, vitamin K_2 has a longer half-life time and a greater absorption and bioavailability than vitamin K_1 [2, 3].

Vitamin K acts as a cofactor in the carboxylation of vitamin K-dependent proteins. The most well-known vitamin K-dependent proteins are involved in blood coagulation processes, but other vitamin K-dependent proteins are involved in extra-hepatic tissue, such as bone and the vasculature. Matrix Gla protein (MGP) is a vitamin K-dependent protein present in the vascular wall, which inhibits vascular calcification by binding to Ca^{2+} ions [4]. Likewise, osteocalcin is a vitamin K-dependent protein of bone matrix, which has a high affinity for calcium ions, and is involved in the synthesis and regulation of bone matrix [5]. Therefore, a low status of vitamin K produces a lower calcium binding in the bones and greater calcium deposition in the vascular wall, which could lead to bone mass loss and vascular stiffness. Furthermore, multiple lines of research indicate that vitamin K is related to osteoarthritis, vascular stiffness and inflammation [6, 7]. In a previous analysis from our group, low vitamin K status was associated with lower handgrip strength and smaller calf circumference [8].

Frailty is a state of greater vulnerability to external stressors, caused by the loss of abilities in multiple domains of functioning [9]. Furthermore, frailty is a reversible state and has been linked to various adverse health outcomes, such as falls, disability, hospitalization and death [10]. So, it is of major importance to know the factors that influence frailty, to be able to develop public health strategies aimed at reducing or preventing frailty. Only limited evidence is available for a relationship between intake of certain nutrients and frailty. So far, prospective studies have suggested that low protein and micronutrient intake (such as B-vitamins, magnesium, and selenium) increases frailty risk [10]. Others have reported that adherence to a Mediterranean-style diet [11], and other healthy dietary patterns with well-balanced nutrient profile is related to lower risk of frailty [12]. The relationship between vitamin K status and frailty has not been investigated to date.

Therefore, using data from the Longitudinal Aging Study Amsterdam (LASA), we examined the prospective association between vitamin K status and frailty in older adults over 13 years of follow-up.

Subjects and methods

Study population

LASA is a population-based cohort, which started in 1992 to determine consequences and predictors of aging focusing on physical, cognitive, mental, and social aspects. The sampling procedure and data collection have been described elsewhere [13, 14]. In summary, in 1992–1993 a representative sample of the Dutch population aged 55–85 years was invited to participate in the baseline study, which consisted of two rounds of interviews: a main interview to obtain demographic and lifestyle information, and a medical interview with physical measurements. Then, follow-up was performed approximately every 3 years to update baseline information. The medical ethics committee of the VU University medical center approved the study protocol and all participants gave written informed consent.

For the current study, we used data from the second cohort, which were added to LASA in 2002–2003 and consisted of 1002 men and women aged 55–65 years. This new cohort was recruited from the same sampling frame as the first cohort in 1992–1993. Four follow-up waves have been performed, in 2005–2006, 2008–2009, 2011–2012, and 2015–2016. We excluded 358 participants from our analysis: 251 without blood sample, 49 without dp-ucMGP measurement, and 19 participants who were using vitamin K antagonists. Furthermore, 39 participants were excluded since no information on frailty during follow-up was available (Fig. 1). This resulted in a sample size of 644 LASA participants with at least one follow-up measurement.

Excluded participants were older (60 vs. 59 years), mostly male (51% vs. 46%), had more often type 2 diabetes (10% vs. 6%), a greater frailty index (0.16 vs. 0.13) and a higher frailty prevalence at baseline (18% vs. 11%). Moreover,

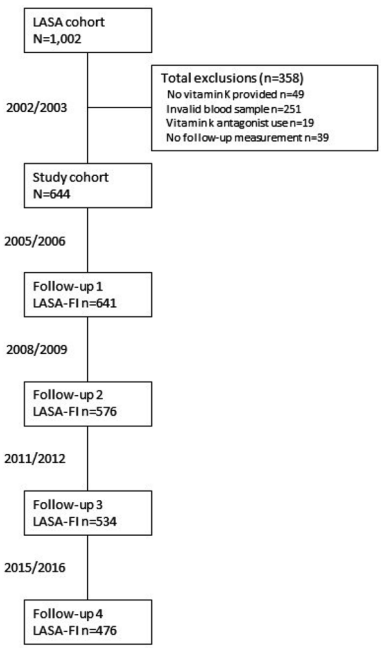

Fig. 1 Flow diagram of LASA participants per frailty index outcome for each follow-up measurement between 2002 and 2016

excluded participants had higher mean concentrations of dp-ucMGP, which correspond to a lower status of vitamin K (557 nmol/L vs. 278 nmol/L).

Study variables

Vitamin K status

During the medical interview at baseline (2002–2003), trained personnel collected morning blood samples in a non-fasted state and samples were shipped to the VU University Medical Center. Until analysis in 2010–2011, blood samples were stored at − 80 °C. For the assessment of vitamin K status, samples were shipped to the laboratory of VitaK, Maastricht to estimate dp-ucMGP concentrations. A sandwich (dual antibody) ELISA was used to measure plasma dp-ucMGP, with the capture antibody directed against the non-phosphorylated MGP sequence 3–15 and the detecting antibody directed against the uncarboxylated MGP sequence 35–49 (mAbucMGP; VitaK, Maastricht, the Netherlands). A low vitamin K status is reflected by high concentrations of dp-ucMGP. The reported intra- and inter-assay variation for plasma dp-ucMGP were 5.6 and 9.9%, respectively [15].

Frailty assessment

We used the frailty index, based on the deficit accumulation approach, to assess the degree of frailty [16]. This is a widely accepted approach, and validated in several studies [17]. The LASA frailty index (LASA-FI) was developed in 2017 and validated against risk of mortality (See supplemental Table 1 for an overview) [18]. The fundamentals of the frailty index are that a greater number of health deficits correspond to a greater extent of frailty. The LASA-FI takes into account the accumulation of symptoms, signs, diseases, disability or any other deficiency in health with age [16]. Health deficits had to meet a series of criteria to be included in the LASA-FI: (a) were biologically meaningful in representing several organ systems, and (b) not becoming too prevalent at younger age, and were accumulating with age, and (c) did not contain a high number of missing values at item level (< 6%), and (d) were available in the main interview of LASA at different measurement waves. Thus, a 32-item frailty index was constructed, which included self-reported chronic conditions, functional limitations, self-rated health, six items from CES-D depression scale, self-reported memory complaints, four items from Mini-Mental State Examination (MMSE) and physical performance [18]. Details of the items included in the LASA-FI and its validation has been published elsewhere [18]. Finally, we calculated a frailty score for each participant by dividing the sum of the present health deficits score by the total number of health deficits. The resulted score ranged between 0 (no deficits) and 1 (all deficits) and accordingly higher values of the LASA-FI represent a larger degree of frailty. In addition to the continuous LASA-FI score, we used the LASA-FI also as a dichotomous outcome with a cutoff point of ≥ 0.25 to indicate frailty [18, 19].

Baseline covariates

Information about educational level, smoking status, alcohol use and physical activity was obtained from a self-administered questionnaire. Educational level was classified into low (elementary school or less), medium (lower vocational or general intermediate education) and high (intermediate vocational education, general secondary school, higher vocational education, college or university). Smoking status was categorized as never, former and current smoker. Individuals were classified according to their alcohol intake as none, light (1–3 glasses/week), moderate (4–7 glasses/week), excessive (≥ 8 glasses/week) according to the Garretsen index [20]. Body mass index (BMI) was calculated as measured weight (kg) divided by the square height (m^2).

In addition, glomerular filtration rate (eGFR) was estimated from serum creatinine using the Chronic Kidney Disease Epidemiology 2009 equation, as indicator of kidney function. To determine vitamin D status, the concentrations of serum 25-hydroxyvitamin D were estimated using a radioimmunoassay (DiaSorin, Stillwater, Minnesota, USA). The inter-assay coefficient of variation was 10.0%. The Endocrine Laboratory of the VU University Medical Center Amsterdam performed all biochemical analyses [14].

Statistical analyses

We categorized dp-ucMGP concentrations into tertiles as no validated clinical cutoff values are established yet. We used the first tertile as reference for all analyses since it corresponds to a higher vitamin K status. Differences in sociodemographic characteristics, lifestyle and morbidity according to tertiles of dp-ucMGP were reported as mean and standard deviation for normally distributed variables and skewed variables were reported as median and interquartile range. Categorical variables are presented as number and percentage.

The frailty index was used as a continuous variable and multiplied by 100 for easier interpretation of the regression coefficients.

To assess the longitudinal relationship between the dp-ucMGP tertiles and frailty, we used generalized estimating equation (GEE) analysis to estimate regression coefficients for the continuous score frailty index and logistic GEE analysis to estimate odds ratios with 95% confidence intervals for the dichotomous frailty outcome. Due to the close correlation between follow-up measures within participants, we used an exchangeable correlation structure [21]. To assess

the linear dose–response relation, we modeled the medians of the tertiles of dp-ucMGP as a continuous variable.

We used two nested models: (1) adjusted for baseline age and sex, and follow-up time (years), (2) additionally adjusted for education (low/intermediate/high), BMI (kg/m^2), smoking status (never/former/current), alcohol consumption (non/light/moderate/excessive), vitamin D (nmol/L) and eGFR (mL/min/1.73 m^2). Sensitivity analyses were conducted by adjusting model 2 for changes over time in smoking, alcohol consumption and BMI. Sex and BMI were tested as potential effect modifiers in adjusted models by including interaction terms (dp-ucMGP × sex) and (dp-ucMGP × BMI) to the regression models, because BMI was associated with frailty in previous studies. Interaction was tested with the Wald test and results were stratified in case of significant interaction, $P < 0.10$.

To measure the rate of frailty increase by dp-ucMGP tertiles during follow-up, we added an interaction term (dp-ucMGP × time) to the model. All analyses were conducted using Stata (version 15.0; Stata Corp., College Station).

Results

Study population

Over 13 years of follow-up, among the study sample of 644 people, 462 participants provided data at all five measurements waves, 72 at four waves, 51 at three waves and 59 at two waves. Of the 644 participants in the study, the mean age was 59.9 ± 2.9 years, 46% were men ($n = 297$) and 19% had lower education level. Furthermore, 26% were current smokers and mean BMI was 27.3 ± 4.2 kg/m^2.

Vitamin K

Mean plasma dp-ucMGP was 376 ± 232 pmol/L, and was slightly skewed to the right. Plasma dp-ucMGP was divided into tertiles: low: < 267 pmol/L, medium: 268–408 pmol/L and high: > 409 pmol/L (Table 1). These dp-ucMGP concentrations are in line with previous values reported in similarly aged cohorts with values between ≤ 181 and ≥ 647 pmol/L [22, 23]. Participants in the highest tertile of dp-ucMGP had a greater BMI, a lower eGFR and higher prevalence of frailty.

Associations with the extent of frailty

At baseline, the mean frailty score was 0.13 and increased to 0.17 after 13 years of follow-up. The frailty index increased across all vitamin K tertiles over 13 years of follow-up (Fig. 2). The frailty index showed a good correlation over five follow-up exams (Pearson correlation coefficient $r > 0.71$).

In the crude model, the medium and highest tertile of dp-ucMGP were associated with a higher frailty index score: regression coefficient 2.09 (95% confidence interval 0.59, 3.58) and 2.37 (0.82, 3.92), respectively (Table 2). In the fully adjusted model, the relationship between dp-ucMGP tertiles and frailty attenuated, but was still statistically significant: 1.40 (0.01, 2.81) for the medium tertile and 1.62 (0.18, 3.06) for the highest tertile, P trend = 0.03 (Table 2). The frailty index score gradually increased across all groups of dp-ucMGP over 13 years follow-up (P time < 0.001). However, in none of these models the interaction between dp-ucMGP and time was statistically significant (P interaction > 0.05), indicating that differences in frailty index scores across tertiles of dp-ucMGP existed since baseline and remained stable during follow-up. Furthermore, additional adjustment for changes in smoking, alcohol consumption and BMI over time did not change the association. In the fully adjusted model, participants who were in the highest tertile of dp-ucMGP had a higher frailty index score in the sensitivity analyses compared with who were in the lowest tertile: 2.03 (0.58, 3.49), P trend = 0.006 (data not shown).

Risk of frailty

We observed similar associations for vitamin K and frailty risk. The medium and highest tertile were associated with a greater risk of frailty (FI ≥ 0.25) compared with the dp-ucMGP lowest tertile odds ratio: 1.75 (95% confidence interval 1.11, 2.77) and 1.63 (1.04, 2.57), respectively (Table 3). Similarly, a gradual increase in the risk of frailty across tertiles of dp-ucMGP was observed over 13 years follow-up (P time < 0.001), but the differences in the risk of frailty existed since baseline and remained stable during follow-up (P interaction > 0.05).

Sex and BMI did not modify the relationship between both dp-ucMGP with the degree of frailty and frailty risk (P interaction > 0.13).

Discussion

We assessed the relationship between vitamin K status as measured by plasma dp-ucMGP and the frailty index in the LASA cohort over a period of 13 years. Our results indicate that higher concentrations of dp-ucMGP, reflecting a lower vitamin K status, were associated with higher frailty index scores in older adults. The degree of frailty increased over time, but the rate of increase did not differ between the dp-ucMGP tertiles. Similarly, our results were consistent for frailty as a dichotomous outcome, using a relevant cutoff to indicate frailty.

Table 1 Participants' characteristics at baseline stratified by plasma dp-ucMGP tertiles ($N=644$)

	Dephosphorylated uncarboxylated matrix Gla protein		
	Low ≤267 pmol/L $N=216$	Medium 268–408 pmol/L $N=214$	High ≥409 pmol/L $N=214$
Demographic			
Age (years)	59.6 ± 2.9	59.7 ± 2.9	60.2 ± 3.0[a]
Women	115 (53%)	108 (50%)	124 (58%)
Education			
Low	38 (17%)	51 (24%)	35 (16%)
Intermediate	127 (59%)	122 (57%)	134 (63%)
High	51 (24%)	41 (19%)	45 (21%)
Lifestyle			
Physical activity (min/day)	135 (84–228)	159 (92–228)	150 (96–217)
BMI (kg/m^2)	25.8 (23.6–28.5)	26.8 (24.1–28.9)	27.9 (25.5–31.4)[c]
Smoking status			
Never	125 (58%)	114 (53%)	125 (58%)
Former	33 (15%)	38 (18%)	42 (20%)
Current	58 (27%)	62 (29%)	47 (22%)
Alcohol consumption			
Non-drinker	3 (1%)	8 (4%)	6 (3%)
Light drinker	116 (54%)	98 (46%)	107 (50%)
Moderate drinker	76 (35%)	84 (39%)	78 (36%)
Excessive drinker	21 (10%)	24 (11%)	23 (11%)
Disease state			
Hypertension	39 (18%)	47 (22%)	59 (28%)
Type 2 diabetes	11 (5%)	9 (4%)	18 (8%)
Metabolic			
25-Hydroxyvitamin D (nmol/L)	56.5 (43.5–67.3)	52.3 (41.1–66.3)	57.1 (42.6–69.6)
eGFR (mL/min/1.73 m^2)	71.1 (63.5–80.0)	68.6 (61.9–79.1)	65.3 (60.1–74.6)[c]
Frailty			
Frailty index	0.12 ± 0.07	0.14 ± 0.1	0.14 ± 0.1
Frailty prevalence (FI ≥ 0.25)	17 (8%)	24 (11%)	31 (14%)

Values are mean ± SD or median and interquartile range

dp-ucMGP dephosphorylated uncarboxylated Matrix Gla protein, *eGFR* estimated glomerular filtration rate

[a]$p<0.05$; [b]$p<0.01$; [c]$p<0.001$

To our knowledge, no previous study has evaluated the relationship between vitamin K and frailty so we only have other indirect studies to compare our results with. In line with our results, high levels of dp-ucMGP have been associated with increased cardiovascular risk [1], a worse prognosis of chronic heart failure [24] and a high mortality [25]. In a cross-sectional study, frail participants presented a greater arterial calcification than their non-frail counterparts [26]. In addition, in the LASA cohort of older adults with cardiovascular disease, only patients with heart failure had a greater frailty risk after 17 year follow-up [27]. Therefore, it is plausible that low vitamin K status increases the risk of vascular calcification and cardiovascular disease and thus increases the extent of frailty in older adults, as observed in our results.

The physical component is an essential part of frailty and frail adults often have a compromised locomotor system. Osteocalcin is a vitamin K-dependent protein that promotes mineralization of bone, so that a low vitamin K status has been associated with higher levels of non-carboxylated osteocalcin (ucOC) [5]. In addition, vitamin K_2 has been linked to a lower urinary calcium excretion and an inhibitory effect of bone resorption in in vitro and in vivo studies [28]. All this suggests that vitamin K plays an important role in bone metabolism. Furthermore, arthritis is part of the LASA-FI. Vitamin K deficiency has been associated with knee osteoarthritis in cross-sectional and longitudinal studies [6, 29]. A longitudinal study using data from six European cohorts, including LASA, observed a higher odds of frailty among patients with osteoarthritis [30]. Additionally, low calf

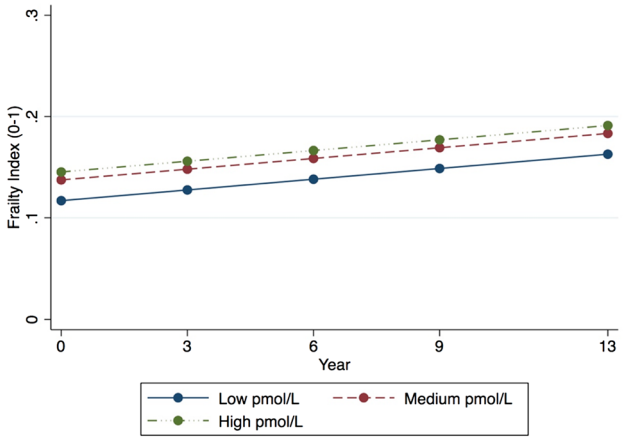

Fig. 2 Mean values of frailty index by dp-ucMGP tertiles. Data are presented as mean values adjusted for time (years), age (years), sex, education (low/intermediate/high), BMI (tertiles of kg/m^2), smoking status (never/former/current), alcohol consumption (non/light/moderate/excessive), vitamin D (nmol/L) and eGFR (mL/min/1.73 m^2)

circumference has been associated with frailty [31] and low grip strength is considered part of frailty in the phenotypic definition [32]. In a previous analysis in the LASA cohort, a lower status of vitamin K was longitudinally associated with lower grip strength and calf circumference over 13 year follow-up [8]. All this highlights the importance of the physical component in the development of frailty and points out the complexity to establish direct mechanisms between vitamin K and frailty.

Likewise, aging is associated with chronic inflammation in certain tissues due to the imbalance between pro-inflammatory and anti-inflammatory cytokines. In a cross-sectional study with 4735 participants aged 65 years and older, those who were frail had higher levels of C-reactive protein compared with non-frail individuals [33]. In another cross-sectional study with 110 patients aged over 75 years, an association between inflammatory markers and different frailty measures was observed, which indicates that the association seems consistent for different frailty measures [34]. In addition, inflammation could be a precursor of frailty in older adults [35], as the increase in pro-inflammatory factors has been associated with age-related declines in physical function and muscle weakness in men and women aged 70–79 years [36]. In animal studies, rats treated with vitamin K_1 had lower levels of inflammation due to the decrease in the concentration of pro-inflammatory cytokines [7]. Furthermore, in a cross-sectional study on the association between serum vitamin K_1 and inflammatory biomarkers,

Table 2 Longitudinal associations between baseline plasma dp-ucMGP tertiles and frailty index in 644 LASA partcipants over 13 years follow-up

	Dephosphorylated uncarboxylated matrix Gla protein			*P* trend	*P* time
	Low ≤267 pmol/L	Medium 268–408 pmol/L	High ≥409 pmol/L		
Frailty index score (0–100)		Beta (95% CI)	Beta (95% CI)		
Model 1	Ref.	2.09 (0.59–3.58)	2.37 (0.82–3.92)	0.003	< 0.001
Model 2	Ref.	1.40 (0.01–2.81)	1.62 (0.18–3.06)	0.03	< 0.001

Model 1: adjusted for time (years), age (years) and sex

Model 2: additionally adjusted for education (low/intermediate/high), BMI (tertiles of kg/m^2), smoking status (never/former/current), alcohol consumption (non/light/moderate/excessive), vitamin D (nmol/L) and eGFR (mL/min/1.73 m^2)

dp-ucMGP dephosphorylated uncarboxylated matrix Gla protein

Table 3 Association between baseline plasma dp-ucMGP tertiles and frailty risk over 13 years follow-up

	Dephosphorylated uncarboxylated matrix Gla protein			*P* trend	*P* time
	Low ≤267 pmol/L	Medium 268–408 pmol/L	High ≥409 pmol/L		
Frailty (FI ≥ 0.25)		OR (95% CI)	OR (95% CI)		
Model 1	Ref.	1.99 (1.28–3.08)	1.90 (1.22–2.94)	0.01	< 0.001
Model 2	Ref.	1.75 (1.11–2.77)	1.63 (1.04–2.57)	0.04	< 0.001

Model 1: adjusted for time (years), age (years) and sex

Model 2: additionally adjusted for education (low/intermediate/high), BMI (tertiles of kg/m^2), smoking status (never/former/current), alcohol consumption (non/light/moderate/excessive), vitamin D (nmol/L) and eGFR (mL/min/1.73 m^2)

dp-ucMGP dephosphorylated uncarboxylated matrix Gla protein

serum phylloquinone was inversely associated with several inflammatory biomarkers [37]. From another perspective, cognition is an important aspect of the frailty index and, therefore, of frailty. Rats deficient in vitamin K had a 25% lower locomotor activity in the brain than controls [38]. Furthermore, another cross-sectional study observed that participants with higher vitamin K intake had better cognitive state [39]. However, the results of this previous study should be interpreted with caution, since causal relationships cannot be established due to the cross-sectional design. Similarly, a cross-sectional study observed a relationship between higher intakes of vitamin K and less severe subjective memory complaints [40]. Therefore, vitamin K could have an effect in different health deficits interrelated which are part of the FI.

Although a low vitamin K status was associated with frailty, we did not find differences in the rate of increase in frailty between the different tertiles of dp-ucMGP over time. Older people often reduce their food intake due to different factors such as loss of appetite, dental problems or chronic diseases. For this reason, some of them have an inadequate intake of energy and other micronutrients, which makes it difficult to meet the nutritional recommendations and results in a worse nutritional status [41]. In the same way, vitamin K deficiency is often accompanied by a worse nutritional status as well as the deficiency in other micronutrients [41]. Therefore, our results may thus reflect the association of a low nutritional status with frailty although due to the lack of dietary information in this cohort we have not been able to test this hypothesis. Some longitudinal studies have evaluated the relationship between diet quality measured by different indexes and the risk of frailty, finding that participants who had a higher diet quality had a lower frailty risk [12, 42]. In addition, a low diet quality is related to a worse nutritional status. Optimal levels of vitamin K can be achieved with an adequate diet and therefore, foods rich in vitamin K should be part of a balanced diet offered to older adults to ensure an adequate status of vitamin K in this population.

Thus, our findings are novel, and are a first step to understand the effect that nutritional status and specifically vitamin K could have on frailty. This is also one of the great challenges of public health because it is a reversible situation in older adults and it has been related to adverse health outcomes. More research is needed to elucidate if the different forms of vitamin K influence frailty in a different way.

Our study has several strengths, including the prospective design, the long follow-up period and control for potential confounders, such as BMI, vitamin D status and eGFR. Another strength is the use of a validated frailty index to measure the extent of frailty, which is useful to monitor changes in frailty over time in longitudinal studies. Another one was the large number of respondents with available data for all waves (72%). Furthermore, we used plasma dp-ucMGP as a measure of vitamin K status, which is a reliable marker because it takes absorption and metabolism into account in contrast to other methods that only reflect intake [43].

This study also has some limitations. Vitamin K status was only measured at baseline and changes in vitamin K intake that may have occurred during follow-up could not be taken into account. Furthermore, excluded participants had a higher frailty index and a higher frailty prevalence at baseline, in addition to higher concentrations of dp-ucMGP, which corresponds to a lower vitamin K status. For these reasons, the observed associations might have been underestimated due to exclusion of the most frail participants. Another limitation of the study was the use of only one plasma biomarker to estimate vitamin K concentrations, although levels of dp-ucMGP are considered a reliable biomarker of this vitamin [15]. However, the samples were stored at − 80 °C after collection for 12 years and no data are available whether potential sample degradation could have affected our results. In addition, the lack of dietary information in this cohort did not allow us to adjust our analyses for dietary variables such as energy intake, as well as to test the effect of vitamin K intake or a worse nutritional status on frailty. Finally, some residual confounding may persist because of the observational design.

Conclusion

Higher concentrations of dp-ucMGP, which correspond with a lower vitamin K status, were associated with a higher frailty index score. However, the differences in frailty between the tertiles of vitamin K exist from baseline and remain the same during follow-up over a period of 13 years. This highlights the importance of ensuring adequate nutritional status of this vitamin in older adults to reach optimal levels by promoting the consumption of foods rich in vitamin K, such as green leafy vegetables and fermented dairy products, which could slow down the development of frailty in this population.

Authors' contributions MMF and AJB designed and conducted research, analyzed data and wrote the paper; MMF and AJB had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. All authors reviewed the manuscript for important intellectual content and approved the final version.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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CONGRESS PRESENTATIONS & ACTIVITIES

CONGRESS PRESENTATIONS

- Oral communication "Coffee consumption aned risk of physical function impairment, frailty and disability in older adults" presented at "XXI Jornadas de Nutrición Práctica" and "XI Congreso Internacional de Nutrición, Alimentación y Dietética" (Madrid, April 2017). ***Machado-Fragua MD**, Struijk EA, Graciani A, Guallar-Castillon P, Rodriguez-Artalejo F, Lopez-Garcia E. Coffee consumption and risk of physical function impairment, frailty and disability in older adults.*
- Oral communication "Habitual coffee consumption and risk of falls in 2 European cohorts of older adults" presented at "XXXVI Reunión Annual de la Sociedad Española de Epidemiología (SEE)" and "XIII Congresso da Associação Portuguesa de Epidemiologia (APE)" (Lisboa, September 2018). ***Machado-Fragua MD**, Struijk EA, Ballesteros JM, Ortolá R, Rodriguez-Artalejo F, Lopez-Garcia E.*
- Electronic poster "Low vitamin K status is associated with frailty in older adults: the Longitudinal Aging Study Amsterdam" presented at "XXIII Jornadas de Nutrición Práctica" and "XIII Congreso Internacional de Nutrición Alimentación y Dietética" (Madrid, April 2019). ***Machado-Fragua MD**, Hoogendijk EO, Struijk EA, Rodriguez-Artalejo F, Beulens JW, van Ballegooijen AJ.*

ACTIVITIES

- Epidemiology seminars at Centro Nacional de Epidemiología (Instituto de Salud Carlos III, Madrid. 2017, 2018 and 2019).
- Course in genetic epidemiology techniques (Granada, November 2017).
- Course "Workshop on Eppi Reviewer 4: a tool to assist in the management of systematic reviews" (Hospital Ramón y Cajal, Madrid. November 2017).
- Predoctoral research stay at VU University Amsterdam (From August to November 2018. Amsterdam, the Netherlands).

CURRICULUM VITAE

CURRICULUM VITAE

The author of this thesis, Marcos Daniel Machado Fragua, born on the 5th of April 1992 in Madrid (Spain), attended high School at Centro Cultural Elfo in Madrid. From 2010 on he studied Nutrition and Dietetics at Universidad Autónoma de Madrid, completing his BDc in 2014 with a thesis about binge drinking in a young population in Madrid.

Subsequently Marcos studied a Master Degree in Treatment and Prevention of the Obesity at Universidad Nacional de Estudios a Distancia (UNED). Marcos also estudied a Master Degree in Quantitative Methods for Epidemiological Research at the School of Medicine (Universidad Autónoma de Madrid) and obtained his MSc in 2016. As a part of this study he conducted a research project about the benefits of coffee consumption.

In 2017 he started his PhD research described in this thesis at the Department of Preventive Medicine and Public Health, and Microbiology (Universidad Autónoma de Madrid). He worked under the supervision of Dr. Esther López García and Dr. Ellen A. Struijk. During his PhD, Marcos moved to Vrije Universiteit Amsterdam in order to complete a research stay.