

## Rationale of the association between Mediterranean diet and the risk of frailty in older adults and systematic review and meta-analysis

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### ABSTRACT

Frailty is a geriatric syndrome whose frequency is increasing in parallel with population aging and is of great interest due to its dire consequences: increased disability, hospitalizations, falls and fractures, institutionalization, and mortality. Frailty is multifactorial but nutritional factors, which are modifiable, play a crucial role in its pathogenesis. Epidemiologic evidence supports that high-quality dietary patterns can prevent, delay or even reverse the occurrence of frailty. In order to add new knowledge bridging the gap as the main purpose of the present article we performed a comprehensive review of the rationale behind the association of MedDiet with frailty and a systematic review and meta-analysis updating the latest ones published in 2018 specifically examining the relationship of Mediterranean diet (MedDiet) and incident frailty. Adding the updated information, our results confirmed a robust association of a higher adherence to MedDiet with reduced incident frailty. Key components of the MedDiet, i.e., abundant consumption of vegetables and fruit as well as the use of olive oil as the main source of fat, all of which have been associated with a lower incidence of frailty, may help explain the observed benefit. Future well-designed and sufficiently large intervention studies are needed to confirm the encouraging findings of the current observational evidence. Meanwhile, based on the existing evidence, the promotion of MedDiet, a high-quality dietary pattern, adapted to the conditions and traditions of each region, and considering lifelong and person-tailored strategies, is an open opportunity to reduced incident frailty. This could also help counteract the worrying trend towards the spread of unhealthy eating and lifestyle models such as those of Western diets that greatly contribute to the genesis of chronic non-communicable diseases and disability.

### 1. Introduction

Populations around the world continue to age remarkably. This phenomenon that has occurred incessantly during the last 150 years is unique in the history of humankind and entails drastic changes in all

aspects of society (Beard et al., 2016). The prediction is that aging of the population will continue, with recent data from 195 countries showing that the estimated global life expectancy will increase by 4.4 years for men and women by 2040 to a mean of 74.3 years and 79.7 years, respectively (Foreman et al., 2018). This triumph of humanity is

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overshadowed by the possibility of adding years of life with chronic non-communicable diseases (NCDs), which are now the primary cause of mortality, morbidity, and disability (Murray et al., 2015).

The aging process is complex involving the accumulation of effects of multiple health determinants (modifiable and non-modifiable) throughout life. Thus, everyone has his/her own individual aging rate and his/her own risk of chronic diseases and disabling conditions, such as frailty, which clearly mark the heterogeneity of the circumstances in which people age (Beard et al., 2016).

Frailty is a wide-ranging concept considered as a “geriatric giant syndrome” characterized by reduced strength and endurance and lessened physiological functioning, which increases the vulnerability to even minor internal and external stressors hindering the complete and prompt recovery from these events. Frailty entails multisystem impairments and results from various causes; it confers 2 to 3-fold higher risk of multimorbidity, falls, disability, delirium, repeated hospitalization, institutionalization, and death (Morley et al., 2013; Belloni and Cesari, 2019; Vermeiren et al., 2016; Clegg et al., 2013).

Recent analyses from sixty-two countries across the world reported a prevalence of frailty between 12 and 24 % of the population (O’Caoimh et al., 2021). Frailty is potentially preventable and reversible, which is why it arouses attention in order to develop strategies that may help prevent or delay it (Clegg et al., 2013; Merchant et al., 2022).

Malnutrition is one of the most frequent geriatric syndromes and a key determinant of frailty, especially in the very old (Morley et al., 2013; Merchant et al., 2022; Dominguez and Barbagallo, 2017; O’Shea et al., 2017). A multicenter study by O’Shea et al. reported that 63 % of people older than 70 years were malnourished or at risk of malnutrition according to the Mini-Nutritional Assessment-short form (O’Shea et al., 2017). Another multicenter European study including 4500 older adults in different geriatric settings showed that two thirds of the participants were malnourished or at risk of malnutrition (Kaiser et al., 2010). A systematic review of nineteen studies confirmed the relevance of quantitative (energy intake) and qualitative (nutrient quality source) nutritional characteristics in the development of frailty in old age (Lorenzo-Lopez et al., 2017). In fact, an inadequate diet, both quantitatively and qualitatively, is one of the crucial determinants for developing frailty. A poor nutritional status affects the five criteria in the most widely used definition of the frailty phenotype, including low physical activity, exhaustion, weak grip strength, slow speed, and unintentional weight loss (Bonney et al., 2015). A meta-analysis of fifteen cross-sectional and longitudinal studies reported that a higher conformance with a healthy eating pattern was significantly associated with a lower risk of frailty (Rashidi Pour Fard et al., 2019). Nevertheless, further good quality research is still needed to better understand the potential of nutritional strategies to prevent, postpone, or reverse frailty.

Among the high-quality dietary patterns studied for the prevention of frailty, the one with the greatest evidence and most promising results is the traditional Mediterranean dietary pattern. Indeed, prospective cohort studies conducted in Spain, Italy, Germany, and the USA have consistently reported that a greater adherence to this eating pattern is associated with a lower incidence of frailty (Leon-Munoz et al., 2014; Talegawkar et al., 2012; Veronese et al., 2018; Bollwein et al., 2013). Three previous meta-analysis published in 2018 found a robust association of MedDiet with the incidence of frailty (Kojima et al., 2018a; Silva et al., 2018; Wang et al., 2018).

The aim of the present article is to perform a comprehensive review of the rationale behind the association of MedDiet with frailty and to perform an updated systematic review and meta-analysis on longitudinal studies specifically examining adherence to the MedDiet in relation to the development of frailty.

## 2. Demographics of aging

A recent comprehensive study by Foreman et al. updated the previous incomplete present and future health scenarios of the population

aging (Foreman et al., 2018). This is of major relevance because it may help provide objective data from which policy options and potential health trajectories can be developed and implemented. The study (Foreman et al., 2018) analyzed life expectancy, all-cause mortality and cause of death forecasts as well as alternative future scenarios for 250 causes of death from 2016 to 2040 in 195 countries and territories. Globally, most independent determinants of health were estimated to improve by 2040, but for some contributing factors such as high body-mass index (BMI), their health burden will continue to rise if nothing is done to modify this scenario. Life expectancy is projected to increase by 4.4 years (95%UI 2.2 to 6.4) for men and 4.4 years (2.1 to 6.4) for women by 2040, with variations according to a better or worse health scenarios (Foreman et al., 2018). The fact that relevant determinants of health closely linked to nutritional and lifestyle parameters, such as increased BMI, continue to rise clearly validates the possibility that these factors might be included as a priority in strategies to promote healthy longevity.

In this regard, disability measured with disability-adjusted life years (DALYs) was mostly attributed to dietary risk factors in 2019: low consumption of whole grains and fruits and high sodium intake were significant factors increasing mortality and DALYs worldwide (Qiao et al., 2022). Moreover, nutritional determinants associated with a higher risk of NCDs, such as a greater global consumption of ultra-processed foods, have increased substantially in the past decades (Monteiro et al., 2013).

## 3. Heterogeneity of aging and definition of frailty

The complexity of the aging process and its multiple determinants make a conceptualization based only on the presence or absence of disease inadequate to define health as age increases. As proposed by the World Report on Ageing and Health, rather than the presence or absence of disease the most important consideration is likely to be its functionality (Beard et al., 2016). The comprehensive evaluation of functionality is also a better predictor of survival and risk of one or more diseases (Torisson et al., 2017; Zhao et al., 2021).

The heterogeneity of functional parameters also depends on the so-called intrinsic capacity, which tends to decrease with age. However, there are people with exceptional capacity who remain fully functional until very old age, while others experience significant losses even at younger ages. These dissimilar trajectories reveal how ‘diversity’ is the hallmark of aging and deconstruct stereotypes that are generally believed for an older person.

Thus, a well-accepted notion is that frailty among older adults is not necessarily a normal part of aging. Although there is general consensus on the importance of detecting frailty early in order to intervene preventively, the definition of frailty varies considerably. The concept of frailty is so complex and heterogeneous that various interpretations have been proposed. These comprise a definition that includes the presence of few biological and functional features conforming a specific phenotype (Fried et al., 2001); a progressive accumulation of deficits (Rockwood and Mitnitski, 2007); an integrated approach including physical, psychological, and social domains (Gobbens et al., 2010); a multidimensional concept where multiple domains aggregate together and interact (Sourial et al., 2010; Fulop et al., 2010; Doody et al., 2022), among others. Such a complex condition varies extensively among populations and among individuals within the same population; hence, it is not surprising that sometimes the results of studies that have frailty as an outcome are highly variable (Doody et al., 2022). Nevertheless, in epidemiological studies, the definitions that have been mostly used are the Fried’s phenotype (Fried et al., 2001) and the Rockwood frailty index (Rockwood et al., 2005), which with their advantages and limitations, make the results fairly comparable. Fried et al. identify frailty as the presence of three or more of five criteria: unintentional weight loss, weakness or poor handgrip strength; self-reported exhaustion; slow walking speed; and low physical activity (Fried et al., 2001). The frailty

index (Rockwood et al., 2005) operationalizes frailty as the fraction of deficits present in an individual (Searle et al., 2008). Both have demonstrated to be predictive of diverse health outcomes (Kojima et al., 2018b; Dent et al., 2016), although differences have also been found (O’Caoimh et al., 2021). Some authors have suggested that the two constructs should be considered complementary to one another rather than interchangeable (Cesari et al., 2014).

A recently published systematic revision and meta-analysis examined the prevalence of frailty at population level considering data from sixty-two countries from January 1998 to April 2020, including 1,755,497 participants aged  $\geq 50$  years from 240 studies, identifying frailty with different methods. Pooled prevalence in studies using physical frailty measures was 12 % (95 % CI 11–13 %;  $n = 178$ ), compared with 24 % (95 % CI 22–26 %;  $n = 71$ ) using the deficit accumulation model (frailty index). The prevalence of pre-frailty was similar: 46 % and 49 %, respectively. Both, physical frailty phenotype and the frailty index were more prevalent in women than in men with similar values for pre-frailty. Analyses of data considering only nationally representative studies gave a frailty prevalence of 7 % (95 % CI 5–9 %;  $n = 46$ ) for physical frailty and 24 % (95%CI: 22–26 %;  $n = 44$ ) for frailty index. Therefore, the prevalence of frailty at population levels was heterogeneous, particularly from nationally representative studies making the interpretation of differences by geographic region challenging (O’Caoimh et al., 2021).

#### 4. Nutritional components of frailty

Among the various factors that can contribute to the development of frailty, nutritional determinants are fundamental. On the one hand, malnutrition may contribute to the genesis of frailty and/or its worsening, and may also promote chronic diseases. On the other, the nutritional status of older persons is adversely affected by frailty. In fact, all five criteria of the definition by Fried et al. are related to a poor nutritional status (Bonnefoy et al., 2015). The notion of a vicious cycle, originally conceived as a spiral, in which reduced energy utilization is crucial to engender the frailty phenotype denotes clear links to

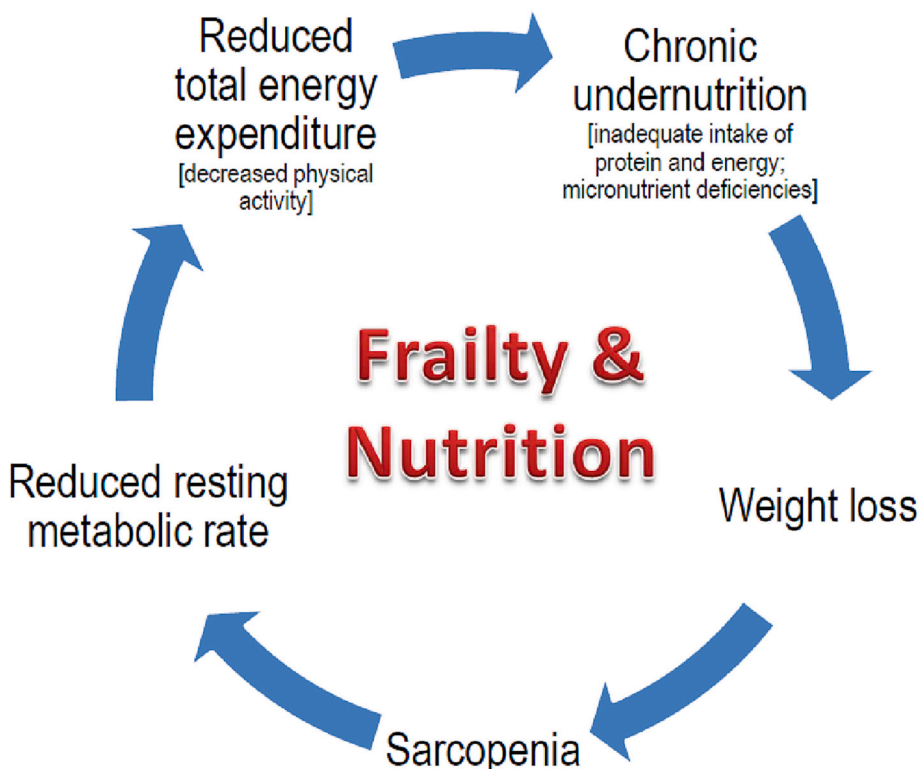
nutritional determinants (Fried et al., 2001) (Fig. 1). Also Rockwood’s Frailty Index (Mitnitski et al., 2002) and its clinical application (Rockwood et al., 2005) take nutritional status into account in its definition of frailty (Jayanama et al., 2018; Zupo et al., 2020).

An insufficient or inadequate dietary intake, in terms of both energy and nutrients, for proper body functioning, is a characteristic of frailty. Unintentional loss of body weight is by definition part of frailty (Fried et al., 2001; Rockwood and Mitnitski, 2007). Indeed, a high percentage of malnourished older adults are frail. Thus, malnutrition and frailty overlap and both are associated with an increased risk of repeated hospitalizations, increased length of stay, multiple medical visits, and progression to disability (Dominguez and Barbagallo, 2017; Morley, 2018). Another prevalent condition in old age that is interchanged with malnutrition is anorexia of aging (i.e., decreased appetite and/or food intake in old age), which is a precursor of drastic weight loss and significantly associated with incident frailty (Merchant et al., 2022). It should not be forgotten that over-nutrition with consequent overweight and obesity are also manifestations of malnutrition. Moreover, obesity also increases the probability of incident frailty (Crow et al., 2019). Considering changes in body composition, a greater adiposity accompanied by reduced muscle mass is as well significantly associated with frailty (Xu et al., 2020).

Besides considering under- or over-nutrition, the quality of dietary components that can influence the risk of frailty must also be taken into account. For example, there are nutritional factors that are pro-oxidant and pro-inflammatory and others, on the contrary, are antioxidant and anti-inflammatory, both aspects involved in the etiology of frailty (Lorenzo-Lopez et al., 2017; Soysal et al., 2017).

One of the most important aspects of nutritional factors as determinants of the development of frailty is that they are modifiable and, therefore, they represent optimal targets for the prevention and treatment of this debilitating condition.

Nutritional research has changed in recent decades. Previously, dietary recommendations were focused on nutrients or on individual healthy foods. Instead, in recent years there has been a shift considering the combination of foods and nutrients in dietary patterns with possible



**Fig. 1.** All Fried’s original criteria for the definition of frailty (unintentional weight loss; weakness or poor handgrip strength; self-reported exhaustion; slow walking speed; and low physical activity) have a close relationship with nutritional components. Hence, nutrition represents one of the most important mechanisms for either the risk of frailty when it is inadequate or its prevention when it is adequate. The figure illustrates the vicious cycle of frailty linked to nutritional determinants. (Modified from the original frailty spiral proposed by Fried et al. (2001).)

combined synergistic and eventual antagonistic effects (Jacobs and Orlich, 2014). As such, there is growing interest in the role of different types of dietary patterns and their quality in association with the risk of frailty. For example, a recent cross-sectional analysis of the Physicians' Health Study involving 9861 men aged over 60 years evaluated the presence of frailty (assessed with the frailty index) in relation to adherence to three high-quality dietary patterns: Alternative Healthy Eating Index, MedDiet, and Dietary Approaches to Stop Hypertension. Frailty was present in 18 % of participants, and prefrailty in 44 %. Logistic regression models adjusted for age, smoking status, and energy intake showed that the highest quintiles of adherence to the three high-quality dietary patterns were associated with lower odds of frailty and prefrailty (Ward et al., 2020). A meta-analysis of thirteen studies (including 9 cohort longitudinal and 4 cross-sectional studies) reported that a higher adherence to a healthy dietary pattern was associated with a lower risk of frailty (OR 0.69; 95 % CI 0.57–0.84) (Rashidi Pour Fard et al., 2019). Other recent studies have confirmed the association of high-quality dietary patterns and incident frailty and prefrailty in older adults from the Health ABC cohort (Hengeveld et al., 2019), women from the Nurses' Health Study (Struijk et al., 2020), and older men from the British Regional Heart Study (Parsons et al., 2019).

Thus, various dietary patterns have been associated with diverse health benefits, but the largest body of evidence in the medical literature is attributable to the traditional dietary habits and lifestyle followed by populations from the Mediterranean region.

## 5. The Mediterranean dietary pattern

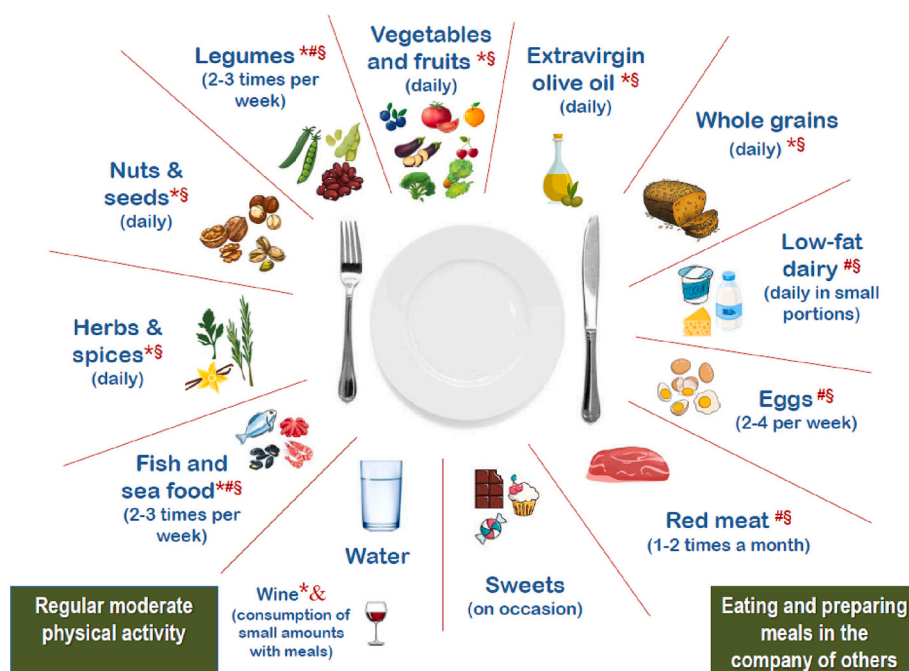
This dietary pattern comprises foods that are fresh or minimally processed including cold pressed extra-virgin olive oil consumed daily as the main source of dietary fat; the daily consumption of seasonal vegetables and fruits; nuts and seeds included in the traditional recipes or as snacks; legumes consumed several times per week; whole grains (pasta, bread) consumed daily instead of their refined versions; use of herbs and spices for flavoring; consumption of fish in moderate amounts at least two to three times weekly; daily consumption of small amounts of dairy products, preferably low-fat milk and yogurt, and occasionally small portions of cheese; consumption of two to four eggs weekly as sources of high-value proteins; and low consumption of cakes, cookies and sweets,

which is done only occasionally; low consumption of red and processed meat and only in small portions (once to twice per month); drinking water as the main beverage; wine consumption in small amounts ( $\leq 1$  drink/day for women and 1–2 drinks/day for men) always with meals and respecting beliefs of each community and former habits (Dominguez et al., 2021a) (Fig. 2). Although wine is a component of the traditional MedDiet, it does not necessarily have to be part of the MedDiet today, especially when it comes to the older adults for the prevention of frailty or other geriatrics syndromes (e.g., falls and fractures). In addition, wine is not currently part of the consumption habits of many people or of many countries. Older adults should know that the MedDiet can also reduce the risk of frailty even if wine or other alcoholic beverages are not consumed, either because they do not like them, are not used to them, or cannot consume alcohol due to their previous illnesses or medications, for which alcohol consumption is not appropriate. This represents a high percentage of all older adults.

The Med Diet was considered as one of the healthiest dietary patterns in the 2015–2020 Dietary Guidelines for Americans (Tagtow et al., 2016). Accumulating evidence has shown that a high adherence to the Med Diet was associated with a reduced risk of total and cause-specific mortality (Bonaccio et al., 2018; Eleftheriou et al., 2018), and a lower incidence of numerous age-associated NCDs (Dominguez et al., 2021a) including CVD (Martinez-Gonzalez et al., 2019), cognitive decline, dementia, depression (Singh et al., 2014; Dominguez et al., 2021b), colorectal, breast, gastric, respiratory, bladder, liver, and head and neck cancer (Morze et al., 2021), type 2 diabetes (Schwingshackl et al., 2015), chronic obstructive respiratory disease (Fischer et al., 2019), fragility fractures (Byberg et al., 2016; Haring et al., 2016), and frailty (Rashidi Pour Fard et al., 2019; Kojima et al., 2018a; Silva et al., 2018; Wang et al., 2018; Struijk et al., 2020; Tanaka et al., 2021), as will be discussed in the next section.

A hallmark of the MedDiet is the being rich in unprocessed foods, which are full of healthy nutrients, as opposed to Western dietary patterns, characterized by ultra-processed foods, which are full of calories and additives but usually poor in nutrients ("empty calories"), linked to an excess risk of overweight and obesity (Mendonca et al., 2016). The Med Diet is also tasty and highly palatable, which can enable adherence for a longer time (Polak et al., 2018).

In summary, the Med Diet is considered a paradigm of a high-quality



**Fig. 2.** The components of Mediterranean dietary and lifestyle pattern, mainly vegetables, fruits and extra-virgin olive oil, are rich in phytochemicals with antioxidant and anti-inflammatory properties, as well as minerals, and vitamins, especially when consumed in combination. This may help explain its benefit on the prevention of incident frailty. In addition, limiting ultra-processed foods as part of this high-quality dietary pattern may also reduce the risk of frailty, along with the other non-dietary components of this healthy lifestyle.

\*Contain antioxidants and anti-inflammatory compounds; #source of proteins; \*source of vitamins and minerals. &The consumption of small amounts of wine with meals would only be appropriate for people who like it or are used to consume it. Wine is not recommended for older adults with some chronic diseases (e.g. atrial fibrillation, cognitive impairment or dementia, depression, fatty liver disease, breast or colon cancer survivors, etc.), and/or those taking medications that may interact with alcohol. In general, the less alcohol, the better.

dietary pattern with the largest evidence for healthy effects.

## 6. Systematic review and meta-analysis on the association between MedDiet diet and frailty

We performed a systematic review and meta-analysis in order to update previous meta-analyses published in 2018 (Kojima et al., 2018a; Silva et al., 2018; Wang et al., 2018) (Table 1). The systematic review of literature on the association of the adherence to the MedDiet and incident frailty was performed using the Clarivate (Web of Science/Medline) and the PubMed databases. The search was based on “Mediterranean diet” and “frailty” as descriptors. We could not include any RCTs because there are still none with adequate dietary intervention and frailty as a specific outcome. There were no case-control studies and we excluded cross-sectional studies. Only prospective studies were considered. We did not make exclusions by age, sex or by the different definitions of adherence to the MedDiet or frailty.

As shown in Fig. 3, from 357 studies initially identified, 95 records were removed because they were duplicates. A total of 262 remaining studies were screened. Further 58 records were excluded because they were reviews or not original studies and 183 were excluded because they had a different outcome or exposure. Among the remaining 21 records, one record was excluded due to duplicate information of the same study, 7 were excluded because they had cross-sectional design, and 2 were excluded due to other designs (e.g., cluster analysis). After exclusions, 11 cohort studies were identified (Leon-Munoz et al., 2014; Talegawkar

et al., 2012; Veronese et al., 2018; Struijk et al., 2020; Parsons et al., 2019; Jayanama et al., 2021; Rahi et al., 2018; Millar et al., 2022; Ntanasi et al., 2022; Chan et al., 2015; Gangler et al., 2022) with 103,615 participants and included in the present systematic review (Table 2). A meta-analysis was performed including cohort studies with comparable information (Leon-Munoz et al., 2014; Talegawkar et al., 2012; Veronese et al., 2018; Struijk et al., 2020; Parsons et al., 2019; Rahi et al., 2018; Millar et al., 2022; Ntanasi et al., 2022).

The pooled odds ratio for the risk of incident frailty was 0.55 (0.44–0.70) when extreme categories of the adherence to the MedDiet were compared (Fig. 4). To calculate the pooled odds ratio, a random-effect model was used due to the presence of heterogeneity ( $I^2$ : 72 %) although, in all studies a higher adherence to the MedDiet was associated with a lower risk of frailty.

In order to assess sources of heterogeneity a meta-regression was performed. The results of these analyses showed that having <1000 participants in the included study partially explained the variability of the estimates ( $p = 0.05$ ). Thus, studies with fewer number of participants derived in more extreme estimators.

## 7. Discussion

In the present systematic review and meta-analysis, we found a strong association between adherence to the MedDiet and lower incidence of frailty. These results, which update previous meta-analyses from 2018, confirm the key role that MedDiet may play on the

**Table 1**

Summary of results from previous systematic reviews and meta-analyses of cohort studies/cross sectional studies on the association of Mediterranean diet and frailty.

Authors/country	Year	n. of studies and characteristics	n. of participants	MedDiet adherence assessment method	Frailty assessment method	Mean age or range in years	Range or mean of follow-up duration (years)	Summary of results
Wang et al. (2018), China	2018	5 prospective cohorts + 1 cross-sectional	10,210	5 MDS + 1 aMED	4 Fried criteria; 1 FRAIL scale; 1 SOF index	73.1 (61.2 to 83)	2 to 8	Highest adherence to MedDiet was significantly associated with lower incident frailty (RR = 0.56, 95 % CI = 0.36–0.89, $p = 0.015$ ). The pooled estimates from 4 studies from western countries (European and North American) showed that higher adherence to MedDiet was associated with a 52 % reduced risk of frailty (RR = 0.48, 95 % CI = 0.32–0.72, $p < 0.001$ ). One study showed no association between MedDiet and frailty among Asian elders (RR = 1.06, 95 % CI = 0.83–1.36, $p = 0.638$ ).
Kojima et al. (2018a), UK	2018	4 prospective cohorts	5789	4 MDS; 1 plus MEDAS	3 mCHS; 1 FRAIL scale	75.5	3.9	Greater adherence to a MedDiet was associated with significantly lower incident frailty risk (pooled OR = 0.62, 95 % CI = 0.47–0.82, $p = 0.001$ for MDS 4–5; pooled OR = 0.44, 95 % CI = 0.31–0.64, $p < 0.001$ for MDS 6–9) than poorer adherence (MDS 0–3). Neither significant heterogeneity ( $I^2 = 0–16$ %, $p = 0.30$ ) nor evidence of publication bias was observed.
Silva et al. (2018), Brazil	2018	8 prospective cohorts + 4 cross-sectional	20,518	MDS, modified MDS, the alternative Mediterranean Diet Score and the MeDi Score	Frailty phenotype, modified versions of the frailty phenotype, and FRAIL Scale	68 to 84	3.5 to 9	A higher adherence to Med Diet was inversely associated with incident frailty (OR 0.42, 95 % CI: 0.28–0.65) and functional disability (OR 0.75, 95 % CI: 0.61–0.93). Highly different study characteristics prevented the performance of a meta-analysis for sarcopenia.

MDS: Mediterranean diet score (MDS) developed by Trichopoulou et al.; aMED: Mediterranean diet proposed by Panagiotakos et al.; MEDAS: Mediterranean diet adherence screener; MedDiet: Mediterranean diet; mCHS: Modified Cardiovascular Health Study frailty criteria; SOF: Study of Osteoporotic Fractures; SMD: standard mean differences; WS: walking speed.

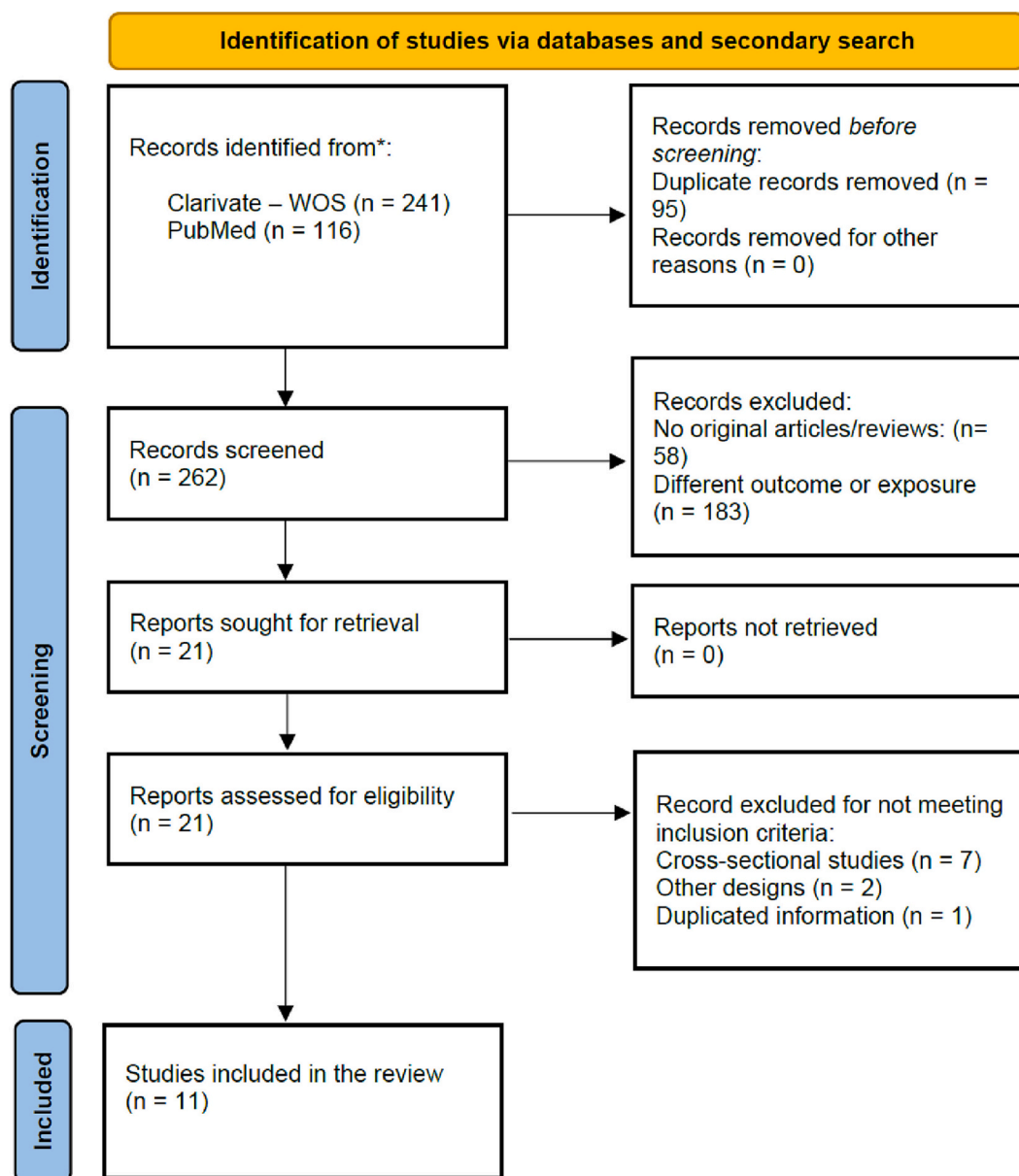


Fig. 3. Flow diagram of the literature search and study selection (date of the search: January 29, 2023).

prevention of frailty and entails an opportunity to help preventing this growing geriatric condition.

Besides the benefits in various health outcomes, MedDiet was formerly also significantly associated with decreased risk of frailty. In a previous meta-analysis by Rashidi et al. regarding the association of a high-quality diet with frailty, the dietary pattern with the greatest effect was the MedDiet (Rashidi Pour Fard et al., 2019). Three previous meta-analyses published in 2018 that specifically examined this association (Kojima et al., 2018a; Silva et al., 2018; Wang et al., 2018) across longitudinal and cross-sectional studies confirmed the significant association of a greater adherence to MedDiet with a lower risk of frailty, even after adjusting for multiple confounders. In the first meta-analysis by Wang et al., including six studies (five prospective and one cross-sectional) participants with the highest vs. the lowest adherence had a 44 % significantly lower risk of frailty. Studies conducted in European and North American countries showed an even higher reduction in the risk of frailty (–52 %). One study among Asian older adults showed no association between MedDiet and frailty, confirming that there are relevant geographical differences with benefits being more obvious

among elders from western countries (Wang et al., 2018). A second systematic review and meta-analysis by Kojima et al., including community-dwelling adults older than sixty years found that participants with greater adherence to a MedDiet had a significantly lower incident frailty (–38 % for MedDiet Score 4–5; –56 % for MDS 6–9) vs. poorer adherence (MDS 0–3) (Kojima et al., 2018a). Similarly, a third systematic review and meta-analysis by Silva et al. found that a higher adherence to a MedDiet was inversely associated with frailty (OR 0.42, 95 % CI 0.28–0.65) and functional disability (OR 0.75, 95 % CI 0.61–0.93) (Silva et al., 2018).

A systematic review and meta-analysis of cross-sectional and longitudinal studies published recently by Coelho et al. did not examine the whole concept of frailty but single parameters that are related to frailty, such as walking speed, knee extensor muscle strength, isometric hand-grip strength and mobility considering only cross-sectional studies. A high adherence to MedDiet was cross-sectionally associated with higher walking speed and knee muscle strength speed, separately. In longitudinal studies the results indicated no significant associations between MedDiet and mobility problems. The authors warned about the presence

**Table 2**

Included studies in the present updated systematic review on the association of Mediterranean diet and incident frailty (n = 11).

Authors/country	Year	Design, follow-up duration in years	n. of participants	MedDiet adherence assessment method	Frailty assessment method	Mean age or age in years	Summary of results
Talegawkar et al. (2012), Italy	2012	Cohort, 6 years	690	MDS developed by Trichopoulou (range 0–9 points)	Based on 4 Fried criteria: exhaustion, weakness, low physical activity, slow walking speed	73	A higher score for the adherence to a MedDiet (MDS $\geq$ 6) was associated with a lower risk of developing frailty OR: 0.30 (95 % CI: 0.14–0.66) when compared with those with a low adherence (MDS $\leq$ 3)
Leon-Munoz et al. (2014), Spain	2014	Cohort, 3.5 years	1815	MDS developed by Trichopoulou (range 0–9 points); MEDAS (0–14 points)	Based on 5 Fried criteria: exhaustion, weakness, low physical activity, slow walking speed, weight loss	71	Being in the highest tertile of adherence to the MDS was associated with a lower risk of developing frailty OR 0.48 (95 % CI: 0.30–0.77) p-trend 0.002 when compared with those in the lowest tertile. The association was OR 0.65 (95 % IC 0.40–1.04) p-trend 0.07 when extreme tertiles of the MEDAS score were compared
Chan et al. (2015), China <sup>a</sup>	2015	Cohort, 4 years	2724	MDS developed by Trichopoulou (range 0–9 points)	Based on 5 FRAIL criteria: fatigue, resistance, ambulation, having more than five diseases, weight loss	72	1 point-increase in the adherence to the MDS was not associated with the risk of developing frailty OR 1.06 (95 % CI: 0.83–1.36) p-trend 0.638
Rahi et al. (2018), France	2018	Cohort, 2 years	560	MDS developed by Trichopoulou modified (range 0–9 points)	Based on 5 mCHS criteria: exhaustion, weakness, low physical activity, ability to walk, weight loss	81	A higher score for the adherence to a MedDiet (MDS $\geq$ 6) was associated with a lower risk of developing frailty OR: 0.32 (95 % CI: 0.14–0.72) when compared with those with a low adherence (MDS $\leq$ 3)
Veronese et al. (2018), USA	2018	Cohort, 8 years	4421	aMED: adherence to MedDiet proposed by Panagiotakos (range 0–55 points)	Based on 3 SOF criteria: inability to rise from a chair, poor energy, weight loss	61	A higher score for the adherence to a MedDiet (aMED $>$ 32) was associated with a lower risk of developing frailty OR: 0.71 (95 % CI: 0.50–0.99) when compared with those with a low adherence (aMED $<$ 24)
Parsons et al. (2019), UK	2019	Cohort, 3 years	945	EDI: Elderly Dietary Index as a proxy for MedDiet (range 9–36 points)	Based on 5 Fried criteria: exhaustion, weakness, low physical activity, slow walking speed, weight loss	80	A higher score for the adherence to a MedDiet (EDI 27–28) was associated with a lower risk of developing frailty OR: 0.51 (95 % CI: 0.30–0.86) when compared with those with a low adherence (EDI 9–22)
Struijk et al. (2020), USA	2020	Cohort, 22 years	71,941	AMED: Alternative MEDiet (range 0–9 points)	Based on 5 FRAIL criteria: fatigue, reduced resistance, reduced aerobic capacity, $\geq$ 5 illnesses, weight loss	$\geq$ 60	A higher score for the adherence to a MedDiet (AMED 6–9) was associated with a lower risk of developing frailty RR: 0.78 (95 % CI: 0.74–0.83) p-trend $<$ 0.001 when compared with those with a low adherence (AMED 0–2). RR for 1-SD RR: 0.87 (95 % CI: 0.85–0.90)
Millar et al. (2022), USA	2022	Cohort, 11 years	2384	MSDPS: Mediterranean-style dietary pattern score (range: 0–100 after standardization)	Based on 5 Fried criteria: exhaustion, weakness, low physical activity, slow walking speed, weight loss	60	Being in the highest tertile of adherence to the MSDPS was associated with a lower risk of developing frailty OR 0.62 (95 % CI: 0.47–0.82) when compared with those in the lowest tertile. OR for 1-unit MSDPS increase was 0.97 (95 % CI: 0.96–0.99). Among those aged $\geq$ 60 the OR for 1-unit MSDPS increase was: 0.98 (95 % CI: 0.97–1.00)
Jayanama et al. (2021), USA <sup>a</sup>	2021	Cohort, 8 years	15,249	MDS developed by Trichopoulou (range 0–10 points)	Based on the proportion of 36 accumulated deficits	47	1-point increase in the MDS was associated with a decrease in the development of frailty risk with a beta-coefficient of $-0.003$ (95 % CI $-0.004$ to $-0.002$ )
Ntanasi et al. (2022), Greece	2022	Cohort, 3 years	1075	aMED: adherence to MedDiet proposed by Panagiotakos (range 0–55 points)	1) Based on the Rockwood index and defined as a proportion of 61 accumulated deficits. 2) Based on 12 Tilburg Frailty Indicator criteria	$\geq$ 65	1) Rockwood: Being in the highest tertile of adherence to the aMED was associated with a lower risk of developing frailty OR 0.60 (95 % CI: 0.39–0.93) p-trend 0.02 when compared with those in the lowest tertile. 2) Tilburg: Being in the highest tertile of adherence to the aMED

(continued on next page)

Table 2 (continued)

Authors/country	Year	Design, follow-up duration in years	n. of participants	MedDiet adherence assessment method	Frailty assessment method	Mean age or age in years	Summary of results
Gangler et al. (2022), Switzerland, Austria, Germany, France, and Portugal <sup>a</sup>	2022	Cohort, 3 years	1811	aMED: adherence to MedDiet proposed by Panagiotakos (range 0–55 points)	Based on 5 Fried criteria: fatigue, weakness, low physical activity, slow walking speed, weight loss	75	was associated with a lower risk of developing frailty OR 0.43 (95 % CI: 0.26–0.70) p-trend <0.001 when compared with those in the lowest tertile. 5-point increase in the aMED was associated with a decrease in the development of pre-frailty risk OR 0.77 (95 % CI 0.68–0.88) and frail OR 0.77 (95 % CI 0.64–0.92).

AMED: Alternative Mediterranean Diet; aMED: Mediterranean diet proposed by Panagiotakos et al.; EDI: Elderly Dietary Index; mCHS = modified Cardiovascular Health Study frailty criteria; MDS: Mediterranean diet score developed by Trichopoulou et al.; MEDAS: Mediterranean diet screener; MedDiet: Mediterranean diet; MSDPS: Mediterranean-style dietary pattern score; OR: odds ratio; RR: relative risk; SD: standard deviation; SOF: Study of Osteoporotic Fractures.

<sup>a</sup> Not included in the meta-analysis due to heterogeneity in the reporting of results.

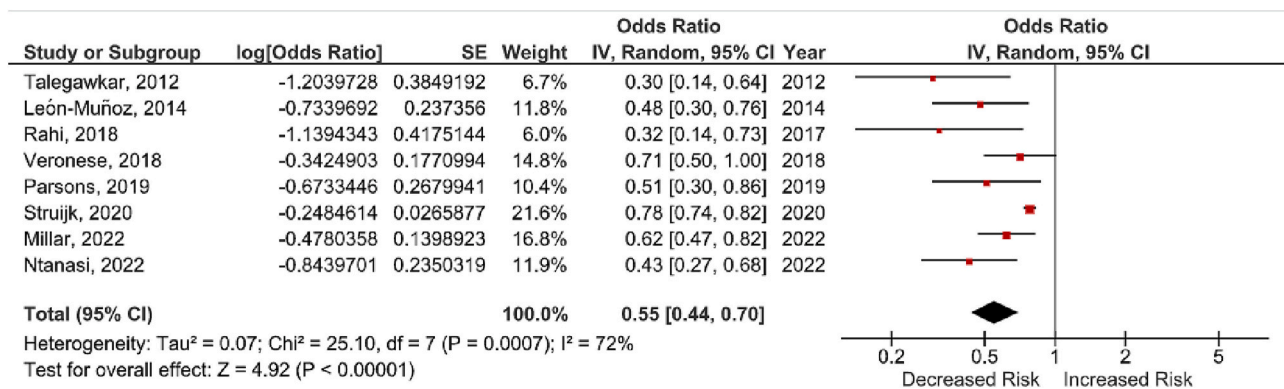


Fig. 4. Forrest plot of association between Mediterranean diet and incident frailty.

of heterogeneity and publication bias in the studies included in the analyses, which consequently should be carefully interpreted (Coelho-Junior et al., 2021).

In our updated meta-analysis specifically examining adherence to MedDiet and frailty, we included also other longitudinal studies published after the previous meta-analyses (Table 2 and Fig. 4). All studies included confirmed the benefits of the MedDiet with greater adherence to this healthy dietary pattern being associated with reduced incident frailty. Five of the articles were part of those already included in previous meta-analyses (Leon-Munoz et al., 2014; Talegawkar et al., 2012; Veronese et al., 2018; Rahi et al., 2018; Chan et al., 2015), while six new quality longitudinal studies included were published in the last two years (Struijk et al., 2020; Parsons et al., 2019; Jayanama et al., 2021; Millar et al., 2022; Ntanasi et al., 2022; Gangler et al., 2022). The study by Parson et al. among 945 men from the British Regional Heart Study with mean age of 80 years, found that those with a higher MedDiet adherence score had a significantly lower risk (–49 %) of developing frailty vs. participants with low adherence (Parsons et al., 2019). The study by Struijk et al. including over 70,000 participants of the Nurses' Health Study aged over 60 years found a reduction in the risk of incident frailty (–22 %) for a higher vs. a lower adherence to MedDiet (Struijk et al., 2020). Millar et al. included 2384 nonfrail adults from the Framingham Offspring Study and found that those in the highest tertile of adherence to a MedDiet score had a 38 % lower risk of developing frailty vs. those in the lowest tertile (Millar et al., 2022). Ntanasi et al. analyzed data from over 1000 Greek community-dwelling older adults from the Hellenic Longitudinal Investigation of Aging and Diet. They found that the highest tertile of adherence to MedDiet was associated with a significantly lower risk of frailty assessed with two methods: Rockwood's frailty index (–40 % of incident frailty) and Tilburg frailty

indicator (–57 % of incident frailty) (Ntanasi et al., 2022). Gängler et al. used data from the DO-HEALTH trial coming from different European countries. The results of this analysis showed that a 5-point increase in the MedDiet adherence score was associated with a 23 % decrease in the risk of developing pre-frailty and frailty (Gangler et al., 2022). Only one of the studies included in the systematic review by Jayanama et al. (2021) had an average age of 47 years compared to the mean age of all the other studies, which as from 60 to 80 years. Interestingly, even in this younger population the inverse association between adhering to MedDiet and incident frailty was similarly significant as it was for studies that included older populations. Unfortunately, we could not include this study in the meta-analysis due to heterogeneity in the reporting of its results.

Interpretation of dietary exposures related to MedDiet in different context may be particularly challenging across studies (Abdelhamid et al., 2020). Hence, the results of a study from analysis of the Framingham Offspring Study in the USA with adapted scores evaluating adherence to MedDiet (Millar et al., 2022), which was included in our meta-analysis, is of great value. Likewise, recent results from post-doc analyses based on previously prospectively collected data from the multicenter European DO-HEALTH RCT with participants from non-Mediterranean countries (Switzerland, Austria, Germany, France, and Portugal), investigated whether the degree of adherence to the MedDiet at baseline, or changes in adherence over time, were associated with the incidence of pre-frailty or frailty in generally healthy older adults. The authors found that a 5-point increase in the MedDiet score over three years was associated with lower odds of becoming pre-frail and frail (–23 % for both) (Gangler et al., 2022).

Bearing in mind the possibility of extending the benefits of the MedDiet in countries with diverse food and culinary traditions, it is



crucial to recognize that the MedDiet is mainly a plant-based diet. Recent analyses of the relationship of plant-based diets and frailty are very encouraging (Maroto-Rodriguez et al., 2022a) and could help to apply the principles of MedDiet in different geographical areas and contexts, adapting them to each local products and conditions.

The consumption of vegetables and fruits, of which the MedDiet is rich, may help partly explain the benefit regarding frailty. In addition to their nutrient content, fresh vegetables and fruits are sources of phytochemicals with antioxidant and anti-inflammatory actions (Blumfield et al., 2022; Slavin and Lloyd, 2012). Another hallmark of the MedDiet also linked to antioxidant (Yubero-Serrano et al., 2019; Farr et al., 2012) and anti-inflammatory actions (Beauchamp et al., 2005; Lucas et al., 2011) is the consumption of cold-pressed extravirgin olive oil as the main (an almost only) source of dietary fat. These effects are mainly exerted by its content in minor bioactive compounds (Visioli et al., 2020). There is evidence of the independent association of olive oil consumption with the incidence of frailty (Donat-Vargas et al., 2022).

Frailty has been associated with deficiency of various individual nutrients, for example proteins (Coelho-Junior et al., 2018; Isanejad et al., 2020; Beasley et al., 2010), folate, vitamin D, E, C, B6 or combinations of them (Bartali et al., 2006; Semba et al., 2006; Moradell et al., 2021; Balboa-Castillo et al., 2018). The Mediterranean dietary pattern has among its components optimal sources of all these nutrients (Fig. 2), which may help to explain its benefit.

Avoiding processed and ultra-processed foods is also part of adherence to the MedDiet. This type of foods have been shown to exert pro-inflammatory effects on the gut microbiota (Monteiro et al., 2019) that could be important in the pathophysiology of frailty. Analyses of data from the prospective cohort Seniors-ENRICA-1 showed that participants with the highest consumption of ultra-processed food had a 3-fold increased risk of incident frailty over 3.5 years, when compared to those with low consumption, even after adjustments for multiple relevant confounders (Sandoval-Insausti et al., 2020).

The word diet in Greek '*diata*' goes beyond the specific nutritional aspects to include also lifestyles. The Mediterranean lifestyle is not only a combination of healthy foods but it also comprises other aspects of behavior, such as physical activity, adequate rest or social engagement. Recent analyses from the prospective Seniors-ENRICA-1 cohort examined the association between a Mediterranean lifestyle (diet, customs, and traditions) and frailty incidence in older adults. Adherence to the Mediterranean lifestyle was assessed at baseline with the 27-item MEDLIFE index (higher scores representing better adherence), divided into 3 blocks: (1) Mediterranean food consumption, (2) Mediterranean dietary habits (practices around meals), and (3) Physical activity, rest, social habits and conviviality. After a 3.3-year follow-up, participants in the highest tertile of the MEDLIFE score had a significantly lower risk of frailty (OR 95 % CI 0.38; 0.21–0.69) vs. the lowest tertile (Maroto-Rodriguez et al., 2022b).

Strengths of the present review comprise the possibility of updating previous publications, allowing to include in the systematic review and meta-analysis six new quality studies published in the past two years. Another strength is the inclusion of a comprehensive review on the rationale behind the association of MedDiet and frailty to better understand possible explanations for this robust relationship repeatedly demonstrated by the available studies. Indeed, all the estimators were significant (below 1) and in the same direction despite heterogeneity. It should be noted that among the articles the one by Struijk et al. (Struijk et al., 2020) stands out due to the number of participants, the high-quality design and the statistical power.

The findings of the present meta-analysis should be also interpreted with its limitations. First, the number of studies with enough information and quality to be included in the meta-analysis according to PRISMA recommendations is not high. We could not include any RCTs because there are still none with adequate dietary intervention and frailty as a specific outcome. However, the overall number of participants is substantial (over 100,000), which allowed us to perform the

analyses. Furthermore, as mentioned, in the last two years six new quality studies have been published, which were included in the present review. Another limitation is that the studies used different methods for the definition and assessment of both, adherence to MedDiet and frailty, which may have contributed to the large heterogeneity we observed in the results of the meta-analysis ( $I^2 > 50\%$ ).

## 8. Conclusions

The Mediterranean dietary pattern has characteristics that make it a high-quality healthy diet. A high accrual of epidemiologic evidence has confirmed that a better conformity with this dietary model is associated with reductions in mortality and incidence of various NCDs (Dominguez et al., 2021a) indicating that the traditional MedDiet may have promising value in promoting a healthy longevity. Frailty is another of the conditions that does not necessarily accompany aging, but when it occurs, it determines important disabling and costly consequences from the financial, human, familial, and social point of view. Nutritional determinants, along with other factors, are significantly involved in the development of frailty. Indeed, a poor quality diet is currently a primary modifiable cause of mortality and disability worldwide.

Thus, there is already evidence that a greater adherence to the MedDiet is associated with a lower presence and incidence of frailty. The components of MedDiet, mainly vegetables, fruits and extra-virgin olive oil, rich in phytochemicals with antioxidant and anti-inflammatory properties, as well as minerals, vitamins, especially when consumed in combination in this dietary pattern, may help explain its benefit on the prevention of incident frailty. In addition, limiting ultra-processed foods as part of this high-quality dietary pattern may also reduce the risk of frailty, along with the other non-dietary components of this healthy lifestyle.

The currently available studies reporting these beneficial associations are observational. There is still no evidence from randomized controlled trials that are certainly the next path to take. Nevertheless, the existing evidence is unequivocal about the associations of following the MedDiet and its main components with the reduction of frailty. These findings are so compelling in spite of the difficulties in defining frailty with different methods, using diverse scores to assess the adherence to MedDiet, and studies being conducted in populations with diverse cultural, food and culinary traditions.

Well-designed and sufficiently large intervention studies are needed to confirm whether the associations observed so far are truly causal. Meanwhile, with hitherto existent evidence of its multiple benefits, it would be worth to initiate international actions that can reach the general public to disseminate the concepts of how to follow the MedDiet according to the traditions of food and lifestyle of each region, while considering lifelong and person-tailored strategies. This also may contribute to reverse the worrying current trend of spreading unhealthy Western diets and high consumption of ultra-processed foods, contrary to the principles of MedDiet, and which contribute greatly to the genesis of NCDs and disability.

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## CRedit authorship contribution statement

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## Declaration of competing interest

The authors declare no conflict of interest.

## Data availability

No data was used for the research described in the article.

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