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ΕΛΕΝΗ ΣΠΥΡΟΠΟΥΛΟΥ

Dietary patterns and food groups in relation to functionality: a systematic review and meta-analysis

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Η παρούσα διπλωματική εργασία εκπονήθηκε στο πλαίσιο των σπουδών για την απόκτηση του Μεταπτυχιακού Διπλώματος Ειδίκευσης στη

ΒΙΟΣΤΑΤΙΣΤΙΚΗ

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Περίληψη

Υπόβαθρο & Στόχος της έρευνας

Σημαντικά ερευνητικά δεδομένα αναδεικνύουν τον καθοριστικό ρόλο της διατροφής στην αιτιολογία πολλών χρόνιων νοσημάτων. Τα διατροφικά πρότυπα, δηλαδή οι συνδυασμοί και οι ποσότητες με τις οποίες καταναλώνονται τα τρόφιμα, εκφράζουν το σύνολο των χαρακτηριστικών της διατροφής που ακολουθεί ένα άτομο, και συνοψίζουν καλύτερα τη συνέργεια της δράσης των μεμονωμένων διατροφικών συστατικών ή ομάδων τροφίμων. Τα διατροφικά πρότυπα έχουν μελετηθεί διεξοδικά σε σχέση με πολλές νοσολογικές οντότητες όπως η κατάθλιψη και η γνωσιακή έκπτωση στους ηλικιωμένους, ο σακχαρώδης διαβήτης τύπου 2, ο καρκίνος και τα καρδιαγγειακά νοσήματα.

Ωστόσο, η βιβλιογραφία παραμένει περιορισμένη, όσον αφορά τις επιδράσεις της διατροφής στη λειτουργικότητα του ατόμου. Η λειτουργικότητα του ατόμου αφορά το επίπεδο της σωματικής του λειτουργίας ή απόδοσης που συνήθως εκτιμάται στις επιδημιολογικές μελέτες με δείκτες που μετρούν την επίδοση του ατόμου κατά την εκτέλεση απλών δραστηριοτήτων της καθημερινής ζωής, όπως το ντύσιμο και το πλύσιμο, ή πιο σύνθετων όπως η πληρωμή λογαριασμών ή οι οικιακές εργασίες. Το επίπεδο της σωματικής λειτουργίας και ευεξίας αποτελούν μία από τις κύριες διαστάσεις της ποιότητας ζωής ενός ατόμου και η διατήρησής της είναι σημαντική για την υγιή γήρανση ενός ατόμου.

Ο στόχος της συστηματικής αυτής ανασκόπησης και μετα-ανάλυσης είναι να συνοψίσει τα ευρήματα της υπάρχουσας βιβλιογραφίας σχετικά με τη τήρηση συγκεκριμένων a priori και a posteriori διατροφικών προτύπων ή κατανάλωση συγκεκριμένων ομάδων τροφίμων σε σχέση με την διατήρηση ή έκπτωση της λειτουργικότητας του ατόμου. Εξ’ όσων γνωρίζουμε, αυτή είναι η πρώτη συστηματική ανασκόπηση και μετα-ανάλυση που διερευνά αυτήν τη συγκεκριμένη ερευνητική υπόθεση τόσο ευρέως.

Μέθοδοι & Αποτελέσματα

Πραγματοποιήθηκε αναζήτηση της επιστημονικής βιβλιογραφίας ανεξάρτητα από το έτος δημοσίευσης της στην ηλεκτρονική σελίδα PubMed. Δεκαπέντε έρευνες συμπεριλήφθηκαν τελικά στη μετα-ανάλυση σύμφωνα με τα ακόλουθα κριτήρια: α) οι έρευνες έπρεπε να ήταν προοπτικές, ασθενών- μαρτύρων ή τυχαιοποιημένες-κλινικές δοκιμές. Ωστόσο όλες οι μελέτες που επιλέχθηκαν ήταν τελικά προοπτικές, β) Το ελάχιστο μέγεθος του πληθυσμού της μελέτης ήταν 100, γ) η διάρκεια παρακολούθησης στην περίπτωση προοπτικής μελέτης ήταν πάνω από έξι μήνες και δ) ο πληθυσμός της μελέτης έπρεπε να είναι ηλικίας 18+ και χωρίς συνοδά προβλήματα υγείας.

Τόσο στο μοντέλο σταθερών αποτελεσμάτων όσο και στο μοντέλο τυχαίων αποτελεσμάτων, παρατηρήθηκε μια προστατευτική επίδραση των υγιεινών διατροφικών προτύπων στη συνολική λειτουργικότητα. Η εκτίμηση σταθερών επιδράσεων ήταν 0,86 (95% Διάστημα εμπιστοσύνης (ΔΕ): 0,83 εως 0,89), ενώ η εκτίμηση τυχαίων επιδράσεων είναι 0,82 (95% ΔΕ 0,75, 0,90) για τη διαφορά στη συνολική έκπτωση της λειτουργικότητας μεταξύ της υψηλότερης έναντι της χαμηλότερης κατηγορίας στην κλίμακα αξιολόγησης της υιοθέτησης υγιεινών διατροφικών προτύπων. Όσον αφορά τη Μεσογειακή διατροφή, η εκτίμηση σταθερών επιδράσεων ήταν 0.86 (95% Διάστημα εμπιστοσύνης (ΔΕ): 0.78, 0.95) και των τυχαίων 0.84 (95% Διάστημα εμπιστοσύνης (ΔΕ): 0.73,0.95) για τη μείωση της συνολικής λειτουργικότητας σε άτομα που ακολουθούν σε μεγάλο βαθμό τη ΜΔ σε σύγκριση με άτομα που δεν την ακολουθούν.

Συμπεράσματα

Τα ευρήματα της μετα-ανάλυσης έδειξαν ότι τα άτομα που υιοθετούν σε μεγαλύτερο βαθμό ένα υγιεινό πρότυπο διατροφής σε σύγκριση με τα άτομα που το υιοθετούν σε μικρότερο βαθμό εμφανίζουν μικρότερη έκπτωση της λειτουργικότητας, λαμβάνοντας υπόψη το φύλο, την ηλικία και άλλους πιθανούς συγχυτικούς παράγοντες. Όσον αφορά τις ομάδες τροφίμων, τα αποτελέσματα δεν είναι σαφή.

Με βάση τα παραπάνω, φαίνεται ότι η προσήλωση στην μεσογειακή διατροφή καθώς και άλλα a priori διατροφικά πρότυπα, με κοινά χαρακτηριστικά, πιθανά να συμβάλλει στη μείωση της έκπτωσης της λειτουργικότητας. Δεδομένης της σημασίας διατήρησης της λειτουργικότητας κυρίως στις μεγάλες ηλικίες, υπάρχει ανάγκη για τη διενέργεια περαιτέρω ερευνών υψηλής ποιότητας για τη διερεύνηση της συγκεκριμένης ερευνητικής υπόθεσης.

Abstract

Background & Aim

Many lines of evidence have established the important role of diet in disease etiology and prevention. Dietary patterns, more specifically the combinations and quantities in which foods are consumed by the people, represent the totality of diet that most probably possesses synergistic and cumulative effects on health and disease, compared to individual foods and nutrients. Currently, the study of dietary patterns in relation to health has become a fundamental step in the process of formulating food-based dietary guidelines. Functionality is a broad term concerning the interactions between the physiological and anatomical structure of the body's system, the ability to accomplish a specific task in a standardized environment and the engagement in everyday life situations. Maintaining functional ability is an important component of the quality of life and healthy ageing.

Studies investigating the association between dietary patterns and/or food groups and functionality, measured through functional impairment, are limited. Therefore, the aim of this systematic review and meta- analysis was to summarize the available literature regarding adherence to a priori and a posteriori dietary patterns or specific food groups with domains of physical functioning impairment. To our knowledge, this is the first systematic review and meta-analysis investigating this relationship so broadly.

Methods & Results

A search of scientific literature was carried out in PubMed for studies without a limit in the year of their publication. Fifteen papers were finally included according to the following eligibility criteria: they had a prospective cohort or case-control design or they were randomized-clinical trials. The minimum size of the study population was 100 and the length of follow up in cohorts was over six months. Additionally, the study population had to be aged 18+ and to be presumably healthy.
Both at fixed effects and random effects model, a protective pooled effect estimate of adherence to ahealthy dietary pattern in overall functionality is observed. The pooled fixed effects estimate was 0.86 (95% C.I. 0.83, 0.89) while the random effects estimate was 0.82 (95% C.I. 0.75, 0.90) for overall functional decline comparing the highest vs the lowest compliance to healthy dietary patterns.

Conclusions

Our findings indicate that individuals with a higher adherence to healthy diets show a better functionality, in comparison to those with a lower adherence, irrespective of their sex, age and other possible confounders. Findings related to individual food groups are not consistent. Based on the above, and acknowledging the importance of maintaining functionality there is a need for further high-quality research in this area in the future.

Chapter 1. Introduction

1.1.Functionality

1.1.i. Definitions

Functioning or functionality is, according to the World Health Organization (WHO) and the International Classification of Functioning, Disability and Health(ICF), a broad term concerning the interactions between the physiological and anatomical structure of the body system, the ability to accomplish a specific task in a standardized environment and the engagement in everyday life situations. Functioning is affected not only by the individual's health, but also by other factors [1]. These factors could be related to the personal characteristics of the individual, such as self-esteem or related tothe environment of the individual, such as education or family support. These types of factors could contribute to the participation of a person in a society and in general can influence positively or negatively his actual performance. On the other hand, other factors that affect an individual's health are also related to his environment such as nutrition, climate or accessibility to health care [2]. Under this definition, functioning disability can be assessed through ICF model and three distinct areas (**Figure 1.**). The first area is the physiological impairment with a focus on individual organs or body systems, such as the musculoskeletal system. An impairment is a problem in body function or structure. Secondly, the functioning can be evaluated in terms of mobility limitation and performance-based measurement focusing on executing a specific activity, like sitting, standing or walking. Lastly, functioning could be evaluated by restrictions of an individual in performing basic and instrumental activities of daily living [1]. In cases when the environmental factors need to be assessed, functionality disability can be separated into: a) functional capacity, that indicates the ability of a person in a standardized environment, and b) functional performance, that indicates the ability of a person in a daily environment, all the factors influencing health included [2]. Physical functionality in a "standard environment" includes sectors such as physical strength, balance, durability, mobility limitation and agility. Mobility limitation includes problems on walking a specific small distance, such as the walking speed, up or downstairs or carrying a shopping bag. Agility is considered as having problems on bending or kneeling. Physical functionality in a "daily environment" consists of disabilities in activities of daily living (ADL) and in instrumental activities of daily living (IADL). Disability in ADL includes activities such as bathing, dressing, toileting, transferring from bed to chair and eating, while disability in IADL includes activities such as using telephone, managing medication or money, using public or private transport, doing shopping, laundry, housework or preparing meals.

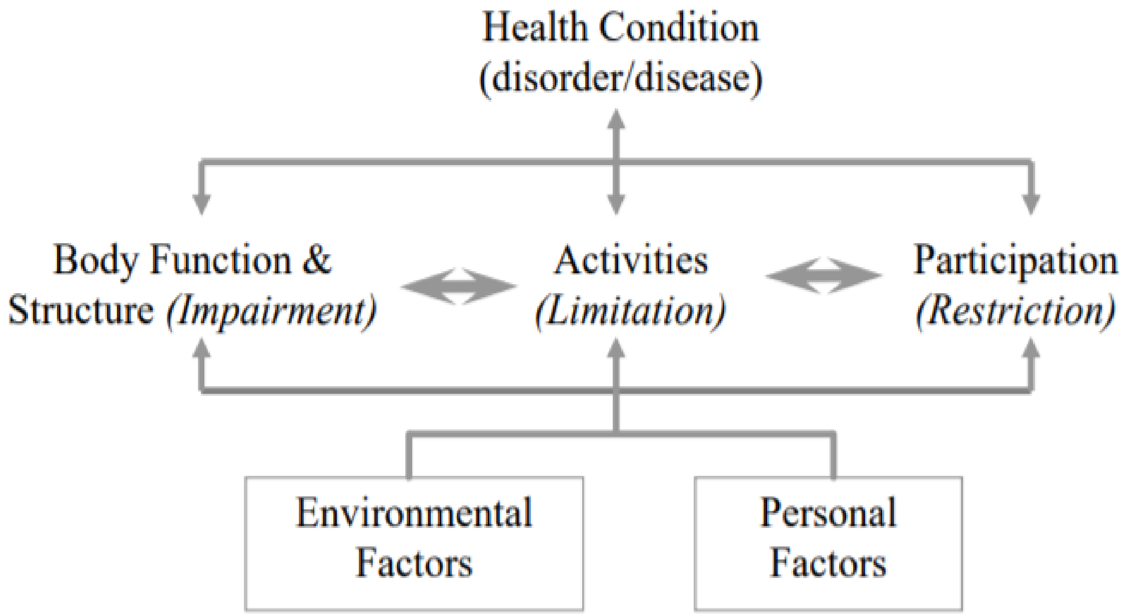

Figure 1. The ICF model. ICF: International Classification of Functioning, Disability and Health.

1.1.ii. Measurement of functionality in epidemiological studies

Functioning disability is a complex and challenging issue, as far as its measurement is concerned. To generalize people with disabilities can be misleading, while disability is diverse, heterogeneous and subjective in each of them. Impairments, limitations and restrictions can be visible or invisible and a lot of people with disabilities consider themselves healthy and not disabled at some level. There is a variance of approaches across countries to measuring functioning according to the purpose of the study, the question under study, the application of the data and their collection, reporting sources, the type of functionality examined and the personal or environmental factors that relate to the questioned disability. Having a whole picture of participants' functioning means the data should be on all aspects of disability and other factors. Data collected needs to be relevant at the national level and comparable globally. The possible approaches could be assessed through self – reported questionnaires or through objective measures.

The approaches via the self- reported questionnaires include self- identification as disabled [3]. In this approach, participants determine the level of this specific aspect of disability, usually having to decide whether the disability is none, mild, moderate, severe or extreme. Their answers are scored and a composite disability score is calculated in a continuous score range, where the lowest score means no disability and the highest means complete disability. A predetermined threshold value cut – off is important to be set in order to divide participants into "disabled" or "not disabled' [2]. Similar approaches are self- identification in conditions that can be diagnosed, where the participants read a list of conditions and decide if they have any of them and self- identification in participation, where the participant is asked if they have a condition that affects a specific social role, as being employed. In addition, there are the approaches that participants are asked if they can perform basic or instrumental activities of daily living. On the other hand, self- reported questionnaires have several limitations. First of all, “disability” gives a negative impression. Participants may feel ashamed or stigmatized by identifying themselves as “having a disability”. In addition, participants may not perceive their situation severe enough to identify themselves as disables, although they have mobility limitations. Under the same concept, people with diagnosable conditions, may not respond positively to these questions, although they have at least one diagnosable condition. For these reasons, approaches referring to activities of daily living serve as more representative screens [3]. In addition, the choice of both of the threshold cut-off point and of the questions in the questionnaire is crucial, especially in cases the results are desired to be internationally comparable. The World Health Organization has designed a set of Disability Assessment Schedules (known as the WHO-DAS) which have a long series of activity and participation based questions. Another source of questions comes from the UN Washington Group on Disability Statistics (WG) created by the United Nations Statistical Commission and fulfills the criteria for making meaningful comparisons of disability between nations [3].

As far as more objective measures of functionality is concerned, various tools have been developed to evaluate the functionality of individuals. A simple, standardized and objective tool is the Short Performance Battery (SPPB). SPPB is instant, simple to handle and in contrast with self-report measures is barely influenced by environmental and personal factors [4]. It can be used to measure lower extremity function and mobility disability and has high predictive ability in recognizing the adults, that are at high risk for hospitalization and incidence of disability. The SPPB represents the sum of results from three-component tests of functional relevance: standing balance, 4-meter gait speed and five-repetition sit-to-stand test. Other tools for evaluating functional decline include: sit-to- stand test, pick- up- weight test, half- turn test, six-meter walk and stair ascent- descent. Sit- to-stand test is used as a test for limb strength, functional mobility and balance, and participants are asked to rise from a chair five times in a row, as fast as possible, barefoot and with their arms at their chest. Pick – up – weight test evaluate the mobility through the ability to reach down and catch something from the floor. Another test for assessing the mobility and the balance is the half-turn test that evaluates the ability to turn around efficiently. In a six-meter walk in a normal or high speed, the slow gait speed is measured. Last but not least, the ability to use stairs in every- day life gives a meaningful impression for the individual’s functional decline and for this reason stair ascent and descent is measured [5]. Parallel, domains of functionality could be measured with the contribution of a calibrated dynamometer, such as knee or handgrip strength [6].

Estimates of prevalence of functional disability are derived from assessing it in multiple domains [2]. Each domain represents a different area of measurement and each category or element of classification within each domain represents a different area of operationalization of the domain concept.

As far as the domain of the physical functionality in a "standard" environment is concerned, the tools used to evaluate these issues were: gait speed and grip strength, with the contribution of a dynamometer and SPPB. Parallel, physical functionality in a "standard" environment is evaluated through specific scales, such as the Rosow-Breslau Index and the physical function scale of the medical Outcomes Short Form- 36 (SF 36,.

The SF-36 health scale is also known as the RAND-36 item general health survey or Health Status Questionnaire and covers health related qualities of life in both mental and physical domains. It consists of 36 items which are converted into eight subscales to describe the health state impacts on physical functioning, role limitations due to physical health, bodily pain, general health, energy, social functioning, role limitations due to emotional problems, emotional wellbeing. The physical factor domain of the SF-36 is a consistent and reliable predictor of morbidity and mortality in a variety of populations [54]. Except SF-36, there are, also, other scales, such as 12-Item Short-Form Health Survey (SF-12) and a physical functioning subscale of SF-36 (PF-10).

As far as the domain of physical functionality in a daily environment is concerned, it could be evaluated through: a) the activities of daily living (ADL) and b) the instrumental activities of daily living (IADL). For this category of functionality many standardized measures have been described, such as the Older Americans Resources and Services activities of daily living scale, performance ADL test, Katz Index of Activities of Daily living, Duke scale, Lawton-Brody scale. The Older Americans Resources and Services activities of daily living scale includes 14 items: seven items assess ADL and seven items assess IADL.

1.1. iii. The importance of studying functionality

There are many purposes of collecting data on functional disability and thus it has a great importance to study functionality. Firstly, it is important to monitor the level of functioning in a population. By doing this, we can understand the scope of potential concerns relating to disability, for example how high attention should we give in disability issues in a specific population. The more people exist in this population with functional disabilities, the higher priority it should be given in preventive interventions. Prevention of functional disability is thus very important and studies focusing on the identification of factors that are associated with functional disability are a priority. In parallel, through monitoring the level of functioning the interventions that are designed to prevent or minimize physical and cognitive limitations, activity limitations and participation restrictions are evaluated. For assessing the impact that preventive programs have on the population, it is important to know the picture of the functional ability of this population [3, 7]. Another reason is important to study functionality is to design and implement programs aimed at providing either general, but inclusive, either targeted services to people with disabilities. This purpose requires detailed information not only on individual's functioning levels but also on the available support people have within their family and their community and on environmental characteristics. For this reason, disability information gathered from censuses is not appropriate and it is better in this case to have a wide- ranging household survey or an administrative database [3, 7]. Lastly, another possible reason for studying functionality is for assessing the impact of having a disability or impairment on individuals and their families. The ultimate goal of broad development is to authorize all people to have equal opportunities within the economic and social lives of their communities as stated in the Convention on the rights of persons with disabilities [8]. The appropriate approach for looking at the equalization of opportunities and well-being is to focus on basic action/activity questions [3].

1.2 Dietary patterns

Diet contributes to the etiology of many chronic disease and thus is considered one of the main causes of disability and death worldwide. In the latest years, there has been a significant change in dietary habits and physical activity levels worldwide as a result of industrialization, urbanization and globalization, leading to an increase of diseases and conditions linked to an unhealthy diet including obesity, diabetes, coronary heart dieases and stroke. However, the measurement and the quantification of diet is demanding, because diet, by nature, is characterized by complexity, multidimensionality and strongly inter- correlated components. There are many ways of studying the relationship between diet and various diseases. An approach could be at a level of a single food, such as potatoes, or even at a level of a nutrient, such as carbohydrates. In addition, a dietary approach could be at a level of a food group, such as vegetables or even more holistically at a level of a combination of food groups that constitute a dietary pattern, such as the Mediterranean diet. Lastly, a biomarker could be used, such as a blood lipid profile, as a surrogate of diet in the investigation of nutrition with health [9]. Each approach has its advantages and disadvantages and the choice of the appropriate approach depends directly on the nature of the research question we are interested in.

Nevertheless, using the approach of dietary patterns, helps to overcome the problems that other approaches have. For instance, it is very difficult to isolate the effect of a single dietary component or nutrient because the consumption of them correlates strongly with the consumption of other food groups or nutrients. Therefore, it is better to evaluate the effect of a combination of food groups that people consume and form a specific pattern they may follow. The dietary patterns reflect also the nutritional status of an individual and are influenced by the culture and the tradition of the country people live in, the purchasing power, the availability of food components, the advertising, the ability of cooking and the public and individual information on health issues [9].

1.2. i. Definitions

Dietary patterns, as they already have described, are a combination of dietary components and the quantity and the frequency of them are taken into account. Their definition can be hypothesis oriented (a priori) or empirically derived (a posteriori). A priori dietary patterns may express the adherence to a traditional diet, such as the Mediterranean Diet or to a specific diet, such as the Vegetarian diet. In addition, a priori dietary patterns may express the level of compliance with formal dietary guidelines or/and recommendations that agree with the guidelines of the World Health Organisation (WHO), such as Dietary Approaches to Stop Hypertension (DASH diet) [10]. In both cases, the assessment is done through dietary indices [9]. Dietary indices or scores were the first methods used in epidemiology to assess how the combination of foods or nutrients based on predefined criteria was related to health outcomes. The a posteriori dietary patterns are defined by using statistical analysis once the dietary data have been collected. The statistical methods that are used in this type of dietary patterns are factor analysis, principal component analysis, cluster analysis and reduced rank regression. These methods identify combinations of groups of dietary variables [11]. The dietary patterns derived with a posteriori methods reflect the diets selected and consumed by individuals. Some of these dietary patterns may have similar characteristics compared to current dietary recommendations, but could simultaneously incorporate dietary components of less health value [13].

1.2. ii. A priori dietary patterns

To quantify a priori patterns usually a set of components is identified so that an aspect of the dietary recommendations is covered. Depending on the consumption level, individuals are scored on each component, and a summary score is computed for each individual, usually with specific cut-offs. This scoring system is set up to define the level of adherence to each component of the pattern. Higher scores reflect better adherence or compliance in the recommended diet [13]. The association of a priori dietary patterns with a type of functionality has been studied in a large number of studies. A usual a priori dietary pattern seen in such studies is the Mediterranean Diet pattern through the Mediterranean diet score. Mediterranean diet is a nutritional pattern inspired by the food traditions of the populations that live in countries bathed by the Mediterranean Sea [9]. Epidemiological studies conducted in different countries have shown that greater adherence in the Mediterranean diet has been associated with longer survival, reduced risk for cardiovascular and cancer mortality, lower cancer and Alzheimer's disease incidence and slower cognitive decline [12].

Other frequently used indices investigated in studies with types of functionality outcomes include: a)The Dietary Approaches to Stop Hypertension (DASH diet), b) MED-DASH Intervention Neurodegenerative Delay (MIND diet), c) Elderly Diet Indicator (EDI), d) Alternative Healthy Eating Index (AHEI), d) Healthy Diet Indicator (HDI), e) f) Recommended Food Diet score (RFS), g) Nordic Diet Score (NDS) and h) Dietary guideline diet index (DGI) as well as variations of the above. The DASH diet emphasizes in seven food groups and three dietary components. Epidemiological studies have subsequently shown that higher adherence to the DASH diet was associated with many favorable health outcomes, including a reduced risk of hypertension, cardiovascular disease and mortality [69]. In the MIND diet, the researchers combined two dietary plans—the Mediterranean and DASH diets —that have previously shown to lower the risk of hypertension, heart attack, and stroke. In addition, the MIND diet has been attributed to improved cognitive thinking and lowering the risk and slowing the progression of Alzheimer disease [14]. The MIND diet was developed based on the best scientific evidence of the foods and nutrients shown to be important for brain health and includes 10 brain-healthy food and 5 unhealthy food groups. EDI is based on Mediterranean-style dietary intake. EDI was previously shown to be associated with increased risk of both all-cause mortality and cardiovascular disease mortality [15]. AHEI was created in 2002 and was based on foods and nutrients predictive of chronic disease risk. Higher scores on the AHEI were strongly associated with a lower risk of major chronic disease as well as risk of CVD, diabetes, heart failure, colorectal and estrogen-receptor-negative breast cancer and total and cardiovascular mortality [16]. The Alternative Healthy Eating Index 2010 (AHEI-2010) was created as an update to the Alternative Healthy Eating Index and incorporates foods and nutrients that have been associated consistently with a lower risk of chronic disease in clinical and epidemiologic investigations, including information from the original AHEI [16]. Higher adherence to the AHEI-2010 has been associated with better lipid and inflammatory profile, decreased risk of clinical vascular disease and of developing impairments in physical function [17]. HDI is based on the World Health Organisation (WHO) dietary guidelines for the prevention of chronic disease and is designed for worldwide use and can make appropriate comparisons among different cultures [18]. HDI was developed > 20 years ago and was updated with the WHO's 2003 dietary recommendations using a score that consists of 8 components (seven nutrients and one food group). RFS is a food-based score that assesses the frequency of consumption of a range of foods considered to be consistent with existing dietary guidelines. Foods considered to be recommended in each recall were summed. The RFS is associated with biomarkers of dietary intake, chronic disease and mortality [19]. Nordic diet, which is also known as the Baltic

Sea diet, contains ten food groups. Nordic diet seems to be a valid tool to indicate a healthy diet and can be utilized to assess diet-disease relationships in public health surveys [20]. DGI reflects Australian guidelines for eating patterns which was shown to be a valid measure of diet quality. Indicators were identified for each dietary guideline with the development of cut-offs and food groupings guided by the Australian Guide to Healthy Eating (AGHE), which provides age- and sex-specific recommendations for the consumption of 5 core food groups and ‘‘extra foods’’. According to the AGHE, extra foods are defined as foods that are not essential to provide nutrient requirements and contain too much fat, sugar, and salt and include foods such as soft drinks, cordials, fruit juice drinks, mayonnaise and dressing, chips, jam and marmalade, confectionery, chocolate, hamburgers, hot chips, meat pies, pizza, cakes and muffins, pies and pastries, puddings, ice cream, cream, biscuits, and all alcoholic beverages. Diet quality was incorporated by the inclusion of items relating to whole-grain cereals, lean meat, reduced or low-fat dairy, and dietary variety [21]. Except of the above dietary patterns that reflect a positive health value on the individual, some patterns assess diets with less health value, such as the Inflammatory Diet Index, which provides a quantitative assessment of the inflammatory potential of a particular diet. In addition, it is also the Western-style diet, also called the meat-sweet diet or standard American diet, that is characterized by an over availability of food, with high intakes of high-fat foods, high-sugar desserts and drinks, as well as high intakes of red meat, refined grains, and high-fat dairy products and a lack of essential nutrients from complex grains, fruits and vegetables [22]. Details for the dietary a priori patterns and its components, including score's range, used in each study of the meta-analysis are in **Table 1a**.

1.2.iii. A posteriori dietary patterns

A posteriori (or data-driven) dietary patterns are formed based on a specific population and the available empirical data without prior assumptions through mathematical/statistical techniques (data-driven). Initially, a posteriori methods were developed for data reduction in statistical analysis in cases of problems with large data sets and many variables. However, they are now applied to data in nutritional epidemiology [13]. This approach aims to identify dietary profiles as they exist in a given community and they do not necessarily reflect dietary patterns with high health value. The main statistical methods for this approach are: factor analysis, principal component analysis, reduced rank regression and cluster analysis. Factor analysis aims to explain most of the variation in diet observed in the population through a few factors. Initially, the food components are grouped according to the correlation between them and constitute the factors of the analysis. A score is created for each factor and then its correlation with the disease of our interest is checked [23]. Principal component analysis has a lot in common with factor analysis. In nutritional epidemiology, the ultimate goal of this analysis is to explain the highest amount of variation in food intakes through the construction of linear combinations of them. A number of potentially related variables are converted to a smaller number of factors that they are not correlated and they are examined in a regression model. The first factor incorporates the maximum variability, while the second factor will maximally explain the remaining variance and that continues until the end of the existing factors [13]. The drawback of these methods is that the participants have scores for every factor and all the factors add up to a score for the overall diet. As a result, only one aspect of the diet is captured and a comprehensive picture of the food consumption is not provided. Therefore, in cases the aim is to describe the dietary pattern in the population, additional analysis is needed [13]. Reduced rank regression is similar to Principal Component Analysis with the difference that it works with two sets of variables. The first set is the predictor variables and the second set is the response variables. In the first set, the analysis purpose to find and describe linear combinations of the variables that belong to it, in a way that the proportion of the explained variation is maximized in the other set. In a second level, the procedure should identify the proper dietary patterns related to the disease, according to the response variables [13]. Cluster analysis sums participants into maximally separated clusters. These clusters are based on the Euclidean distances and through the Ward's method the variance within clusters is minimized. The K-means method is often used in nutritional epidemiology because it offers efficiency in handling a large number of variables. This method id non-hierarchical and iterative and it can create the most distance between clusters [13]. Details for the dietary a posteriori patterns and its components, including score's range, used in each study of the meta-analysis are in **Table 1b**.

1.2 iv. The role of dietary patterns in nutritional epidemiology

The aim of nutritional epidemiology is the study and the clarification of the role of nutrition in the etiology of diseases in the human population with the help of epidemiological methods. For this reason, it is crucial to the approach of diet used in an epidemiological study to reflect as well as possible the diet choices of the population. Individuals' diet is indeed complex, their diet components are varying in amounts and combinations and also diet is time-varying variable, with individual dietary habits and food composition changing over time [24]. Early efforts to understand diet-disease associations focused on the role of specific nutrients, but later on it became evident that in several instances dietary exposures may act synergistically. Therefore, isolating food and nutrients may not provide a representative picture of what people eat in combination with the impact these have on health. Not only, it is very possible, the cumulative and the interactive effects of multiple nutrients and food groups to not be taken into account when a single component is examined, but also our eating behavior may participate in interplay with other lifestyle factors, such as smoking [25]. On the other hand, in dietary pattern analysis, foods and nutrients are grouped, their collinearity is examined and that could be used as an advantage, as dietary patterns are constructed based on eating behavior. Therefore, studying dietary patterns concerning disease outcomes provides a practical way to evaluate the health effects of adherence to dietary guidelines by individuals. In addition, they enclose the totality of a diet and thus give more flexibility in achieving a healthy diet. It is easier for the public to interpret the scientific results into diets and eating behaviors and in this way provide guidance for nutrition intervention and education [23]. Thus, dietary patterns analysis is offered for informing public health recommendations and contributes to national food and nutrition policies [26].

1.2.v. Measurement of diet in epidemiological studies

To measure dietary intake for assessing the eating habits of a specific population is not an easy task. There are several ways of assessing dietary intake (**Figure 2**.). In the following paragraphs the self – reported methods of dietary assessment and biomarkers will be in focus. The criteria for selecting the appropriate dietary measurement method consist of the purpose of the research, the characteristics of the population under study, the desired financial burden of the participants, the available time and budget of the research as well as the time of the research at the level of season, day or even time of day.

The self- reported methods can be divided into the methods of memorandum recall and the methods of real-time recording. Methods of recall of occasional or usual dietary intake consist of single or multiple daily (24-hour food record) or more rarely weekly (7- day food record) recalls and food frequency questionnaires (FFQs) [25]. In both ways, data collection can be through a personal interview with the help of a specially trained interviewer or self- administered. In the FFQ method the participant is usually asked, also, to define the frequency of consumption through predetermined options [25]. In a 24- hour food record, the participants are asked for an accurate recall of food and drinks that they consumed during a specific 24 hour period, preferably the day before. It is important to emphasize that their answers refer to the absolute, as much as possible, nutritional intake and not to their perception of their food consumption. The use of technology contributes to the recording of the type and quantity, as well as the way of preparation, ingredients and the trade names of food consumed. The ways of calculating the quantities are through household units, physical sizes, photos, 3D models, etc. [25]. The advantages of this method are that it could be conducted relatively in a short period, is cheap and practically easy. In addition, it does not require the long term memory nor does it interfere with eating behavior. It collects detailed information as it exists flexibility in food recording and recipes and it can be applied to populations with low educational levels or/and with different nutritional habits. On the other hand, it demands accuracy in recall of type and quantity and that may not be feasible as it is based on good short-term memory. In addition, one day may not be representative of the usual diet. So, the variation of diet is not taken into account at a level of day or season. For this reason, studies employing this assessment method should be carefully designed to include multiple administrations and cover both seasonal and weekly variations in intake [25]. As far as the method of the FFQ is concerned, it focuses on the recording of food and beverages frequency by each participant over a long period, most frequently a year. The FFQ consists of a list of food and recipes, in which there is the opportunity of frequencies and quantities of food groups. They are listed either collectively or individually. The information on quantities is often collected with the use of photographs of various portions and household or standard units. The FFQ may include questions on the usual quantity consumed (semi-quantitative, quantitative FFQs) or not (non-quantitative FFQs). In this method, is easier the memorandum recall of the usual diet, is relatively easy and cheap, especially in cases of self – administration. In addition, FFQs provide information regarding seasonal variations and through FFQ is possible for the participants to be assorted into groups of different size of intakes (e.g. low, medium, high). However, misclassification problems could be arisen, for example in populations with unusual types of dietary intakes, as well as if there are errors in its design, then they are not random but systematic. Both methods tend to have recall bias, especially the FFQ method, due to the retrospective design in a prolonged time. Parallel, in both methods, participants could misreport intentionally the information of their food consumption due to their characteristics, such as age, gender or weight [25].

Real-time recording methods consist of food diaries and the duplicate portion method. In the first case, the participants are obliged to list every food or beverage they consume during a short period in real time. When food diaries include, also, weighing, they must record the actual quantities consumed, too. In the duplicate portion method, the participants weigh and put aside a duplicate portion of all the foods they have eaten. One is consumed by the individual, and in the second a chemical analysis is performed for its content. On the one hand, in real-time recording methods it is not required the memorandum recall of the food consumption and provides detailed quantitative information. In addition, the methods are open-ended and give flexibility in data collection and analysis. On the other hand, there is a risk of modifying the eating behavior and the probability of errors due to incomplete description or quantification. Parallel the participants must have an above-average level of education and they usually need personal initiatives to accomplish the task of recording. Real-time recording methods are less often used in large-scale epidemiologic investigations of diet-disease associations, due to their cost and complexity. The error sources are these related to coding of food components and their quantities [25].
As far as biomarkers or biochemical indicators of nutritional intake are concerned, is often recommended to overcome the errors of self-reported dietary intake and the bias introduced by the use of food composition tables. They are indicators of the intake of specific nutrients or the nutritional status of an individual. Their advantages include their objectivity, their availability retrospectively and the fact that through biomarkers the measurement of some ingredients, whose food content varies considerably, is achieved. On the other hand, biomarkers are expensive and may only exist for a few components, while they are not, also, detectable after

a certain period. They can be distinguished in two categories, the recovery dietary biomarkers and the concentration and replacement dietary biomarkers. The first category is based on the assumption that there is a metabolic balance between the intake and elimination of a nutritional trait over a while can provide a dose-response relationship with intake. The levels of elimination of nutrients are significantly related to their levels of intake. Usually this category of biomarkers is used to measure the reliability of a non-objective measure of nutritional intake. The replacement dietary biomarkers reflect the nutritional intake. The concentration of these biochemical markers also depends on the physical characteristics, lifestyle and metabolism of the individual. They are commonly used to find relationships between diet and various diseases [25].

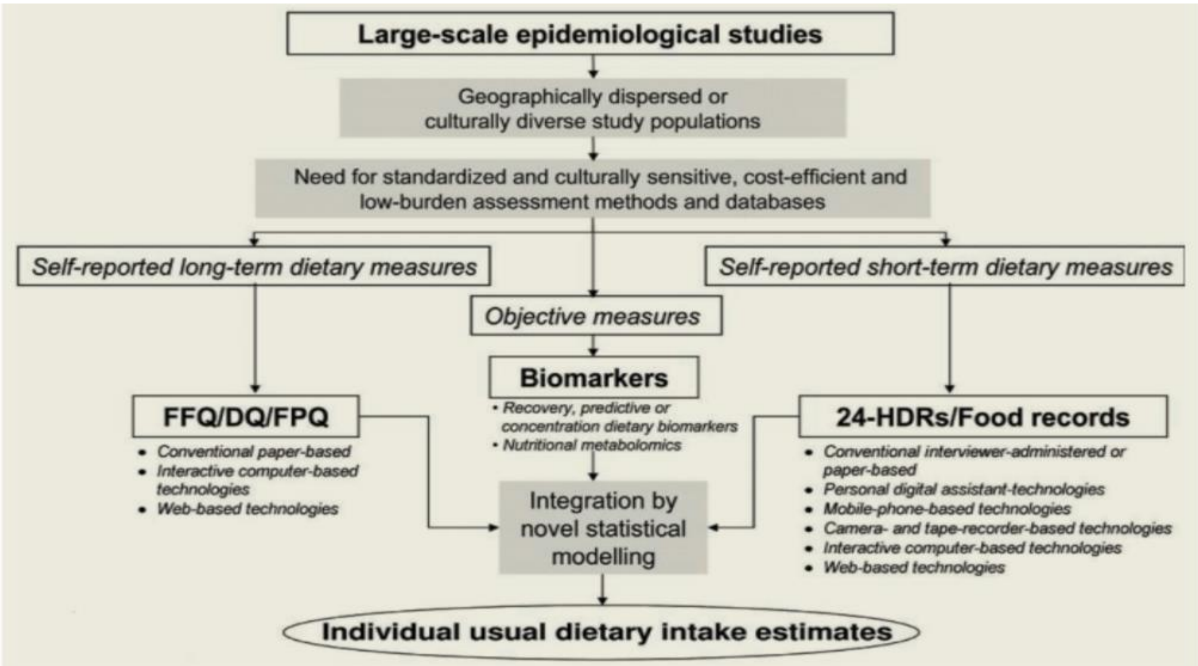

Figure 2. Integrative approaches for measuring diet in large-scale epidemiological studies. 24- HDRs: 24 hours dietary recalls, DQ: Dietary Questionnaire, FFQ: Food Frequency Questionnaire, FPQ: Food Propensity Questionnaire (non- quantitative FFQ). Source: World Cancer Report, 2014

1.3. Systematic reviews and Meta-analysis

1.3.i. Introduction

Meta-Analysis is a quantitative, formal study design and refers to the statistical synthesis of analysis results from a set of individual studies. The purpose of this synthesis is to understand the results of any individual study in the context of the rest of the studies, to integrate the findings and to derive conclusions about a specific research question. While the statistical procedures used in a meta-analysis can be applied to any set of data, it will be meaningful only if the studies have been collected and analyzed systematically. Systematic methods are used to minimize bias and therefore to provide more reliable findings from which more robust conclusions can be drawn comparing to traditional review methods. Systematic reviews need not contain necessarily a meta-analysis, although the majority of them contain meta-analyses. Therefore, the meta- analysis is a subset of the systematic review [27, 28].

The core features of a systematic review include a clearly stated set of objectives with pre-defined eligibility criteria for studies determining which will be included in or excluded from the analysis, a specific and reproducible methodology, a systematic search that aims to identify all studies that meet the eligibility criteria, an assessment of the validity of the findings of the included studies, such as through the assessment of risk of bias. This systematic search leads to the presentation and the synthesis of the characteristics and findings from the studies included. If the pooled effect size is consistent across the studies, this procedure allows us to report that the effect is robust across the kinds of populations included in the synthesis, and also to estimate the magnitude of the effect more accurately than we could with any of the studies alone. On the other hand, if the effect size varies substantially from study to study, it enables us to report on the range of effects, to quantify the extent of the variance and maybe to identify factors associated with the magnitude of the effect size [27]. Identifying sources of variation is one of the most important tasks in meta- analysis, as examining the heterogeneity of the studies and the generalizability of responses can lead to more effective modifications of management or treatments, in case of epidemiological studies [68]. It is important to note that since there is an element of subjectivity in setting these eligibility criteria, as well as in the conclusions drawn from the meta-analysis, we cannot say that the systematic review is entirely objective [27].

In medicine and in epidemiology, systematic review and meta-analysis can ensure that medical treatments are based on the best available empirical data. In addition, they are also used to examine either the performance of diagnostics tests either the potential epidemiological associations between exposure and disease prevalence, among other topics. Moreover, although their most common use is to synthesize the available data in order to inform policy, systematic reviews and meta- analyses can also play an important role in other parts of the research process, such as in designing new research (**Figure 3.**). For this reason, various government agencies, including institutes of health in numerous countries, have been encouraging researchers to conduct a meta-analysis of existing research prior to undertaking new funded studies. Naturally, examples of these procedures are, also, cited from social science, business, ecology, criminology, education and other fields, too [27].

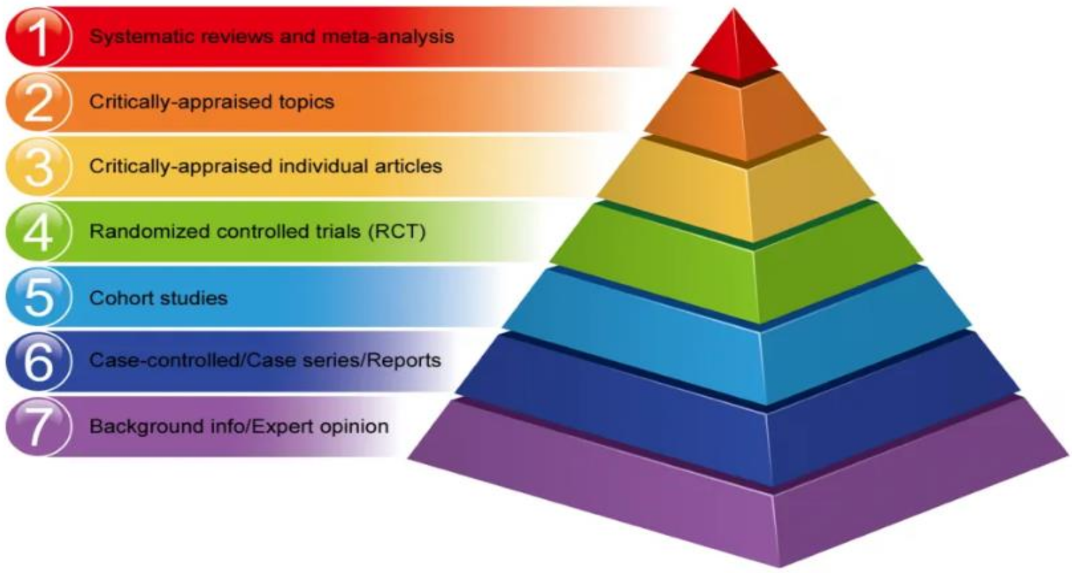

Figure 3. Hierarchy of evidence

1.3. ii. Effect Measures

Effect measures are statistics that provide a standardized measure of the mean change in the dependent variable in each study [31]. The effect size or the treatment effect, as often is mentioned to the meta-analyses in medicine are assumed to be odds ratios, risk ratios or risk differences. Both the terms "effect size" and "treatment effect" refer to any of these indices and the distinction between these terms lies mostly in the nature of the study. The term "effect size" is appropriate, in cases the index is for quantifying the relationship between two variables or a difference between two groups. The term "treatment effect" is appropriate for an index is used to quantify the impact of a purposeful intervention [27].

As far as the choice of the appropriate effect size index is concerned, three major criteria should be taken into account. Firstly, the effect sizes from the different studies should be substantively interpretable and comparable to one another in the sense that the same relationship is approximately measured in all of them.

Therefore, the effect size should not depend on aspects of study design that may are distinguished from study to study, such as sample size or whether covariates are used. Secondly, the estimates of the effect size should be computable from the information that is reported in published research reports. Thus, the re-analysis of the raw data should not be required, unless these are known to be available. Thirdly, the effect size should have good technical characteristics. For example, its sampling distribution should be known in order to be able the variances and the confidence intervals to be computed [27].

All of the effect size measures can be calculated from reported means, variances, SEs, correlation coefficients and frequencies. If these are not available then effect sizes can be calculated from reported t, F or Chi-squared statistics or from P-values. The exact formulas for calculating effect sizes from these data differ depending on the nature of the statistical tests and experimental designs from which they were taken [31]. Additionally, there are formulas for converting the measures of effect size into others. It is important, also, to note that sometimes a systematic review will include studies that have different designs. On the one hand, from a statistical perspective the effect size has the same meaning regardless of the study design, but there may be a concern that studies which used different designs might vary in substantial ways [27].

In practice, the kind of data used in the primary studies will usually lead to a pool of two or three effect sizes that meet the criteria outlined, which makes the process of selecting an effect size relatively straightforward [27]. A meaningful measure of effect size depend on the nature of the data being considered, as the 'best' measure of effect size must be judged based on its compatibility with the available raw data and its ease of interpretation. The choice falls mostly into one of the following three categories.

Effect measures based on means

In the first category, if the summary data reported by the primary study are continuous or ordinal data from two or more groups and are presented using means and standard deviations in the groups, the appropriate effect size is selected between the raw difference in the group means, the standardized difference in the group means and the response ratio. In cases, the out come is reported on a scale, that all primary studies use, the meta-analysis can be performed directly on the raw mean difference. The formula of the raw mean difference (D) is: $D = \overline{X_1} - \overline{X_2}$, where $\overline{X_1}, \overline{X_2}$ are the sample means of two independent groups. Assuming that the two population standard deviations are the same, the variance of D (V_D) is: $V_D = \frac{n_1 + n_2}{n_1 n_2} S^2_{pooled}$, where

$S_{pooled} = \sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}}$, n_1, n_2 are the sample sizes in two groups, S_1, S_2 are the sample standard deviations of the two groups. Otherwise, the variance of D (V_D) is: $V_D = \frac{S_1^2}{n_1} + \frac{S_2^2}{n_2}$.

In each case, the standard deviation of D is: $SE_D = \sqrt{V_D}$. The main advantage of the raw difference in means is its instinctive meaning [27, 31]. However, the raw mean difference is recommended if all the studies in the meta-analysis use the same scale and the measure is well known. If different studies have applied different instruments to assess the outcome, then the scale of measurement will differ from study to study and it would not be meaningful to combine raw mean differences. In such cases, the standardized mean difference, the mean difference in each study divided by its study standard deviation, would be a comparable measure across studies. Two commonly used measures of standardized mean difference are Cohen's d and Hedge's g when studies report different scales. Their difference lies to the method used for calculating the pooled standard deviation [31]. The exact formulas are:

For Cohen's d is:

d= $\frac{\overline{X_1}-\overline{X_2}}{S_{within}}$, where $S_{within}=\sqrt{\frac{(n_1-1)S_1{}^2+(n_2-1)S_2{}^2}{n_1+n_2-2}}$. The variance of d is:

$V_d=\frac{n_1+n_2}{n_1 n_2}+\frac{d^2}{2(n_1+n_2)}$ and its standard deviation is: $SE_d=\sqrt{V_d}$.

For Hedge's g is:

g= $J\cdot d$, where $J=1-\frac{3}{4df-1}$. The variance of g is $V_g=J^2\times V_d$ and its standard deviation is: $SE_g=\sqrt{V_g}$.

Parallel, in research domains where the outcome is measured on a physical scale, such as the length or area and is unlikely to be zero, the ratio of the means in the two groups might serve as the effect size index. This effect size index is called the response ratio, measures the ratio of the mean change in one group to the mean change in the other and is only meaningful when the outcome is measured on a true ratio scale [27]. The response ratio is computed as: $R=\frac{\overline{X_1}}{\overline{X_2}}$. The response ratio is log-transformed prior to meta-analysis for linearizing and normalizing the raw ratios [31]. In other words, $\ln R=\ln(\overline{X_1})-\ln(\overline{X_2})$. The variance of the approximate log response ratio is:

$V_{\ln R}=S_{pooled}^2\left(\frac{1}{n_1(\overline{X_1})^2}+\frac{1}{n_2(\overline{X_2})^2}\right)$, where S_{pooled} is the pooled standard deviation and the standard error is approximately: $SE_{\ln R}=\sqrt{V_{\ln R}}$.

Effect measures based on binary data

In the second category lie the summary data that are based on a binary yes/no outcome such as events and non-events in two groups and are generally analysed using logistic regression or a chi-squared test. In this case, the appropriate effect size is usually selected between the risk ratio, the odds ratio and the risk difference. The risk ratio has the advantage of being intuitive and its computational formula is: $RiskRatio = \frac{Events_{treated} \cdot n_{control}}{Events_{control} \cdot n_{treated}}$. For risk ratios, computations are carried out on a log scale. In other words, $LogRiskRatio = \ln(RiskRatio)$. Its variance approximately is: $V_{LogRiskRatio} = \frac{1}{Events_{treated}} - \frac{1}{n_1} + \frac{1}{Events_{control}} - \frac{1}{n_2}$. Its approximate standard error is: $SE_{LogRiskRatio} = \sqrt{V_{LogRiskRatio}}$. In contrary, although the odds ratio is considered less intuitive, it has such statistical properties that makes it in many cases the best choice. The computational formula for odds ratio is: $OddsRatio = \frac{Events_{treated} \cdot Non\_Events_{control}}{Non\_Events_{treated} \cdot Events_{control}}$, while computations also for odds ratios are carried out on a log scale. Its variance approximately is:

$V_{LogRiskRatio} = \frac{1}{Events_{treated}} + \frac{1}{Non\_Events_{control}} + \frac{1}{Events_{control}} + \frac{1}{Non\_Events_{treated}}$ and the approximate standard error is $SE_{LogOddsRatio} = \sqrt{V_{LogOddsRatio}}$. When the risk of the event is low, the odds ratio is approximately similar to the risk ratio. Although, computations for both risk ratio and odds ratio are carried out on a log scale, computations for risk differences are carried out in raw units rather than log units [27]. Taken together, the risk ratio and odds ratio are relative measures and therefore tend to be relatively insensitive to differences in baseline events. By contrast, the risk difference is an absolute measure and as such is very sensitive to the baseline risk. Its formula is:

$RiskDifference = (\frac{Events_{treated}}{n_{treated}}) - (\frac{Events_{control}}{n_{control}})$. The variance is

$V_{RiskDiff} = \frac{Events_{treated} \cdot Non\_Events_{treated}}{n_1^3} + \frac{Events_{control} \cdot Non\_Events_{control}}{n_2^3}$ and the approximate standard error is $SE_{RiskDiff} = \sqrt{V_{RiskDiff}}$. 7Because the ratios are less sensitive to baseline risk while the risk difference is sometimes more clinically meaningful, it is suggested to use the risk ratio or odds ratio to perform the meta-analysis and compute a summary risk or odds ratio [27].

Effect measures based on correlations

In the third category, the primary studies use a continuous or ordinal variable as a response to a continuous or ordinal independent variable and their aim is to report a correlation between these two continuous variables. In this case, the correlation coefficient itself can be used as a measure of the effect size index [27, 31]. When a study reports the results of statistical tests that include also other variables, the partial correlation coefficient is potential to be used. Irrespective of the type of correlation coefficient is used, Fisher's z transformation is generally applied in order to balance the variance among coefficients prior to meta-analysis [31]. In other words, the transformation from sample correlation r to Fisher's z is given by: $z = 0.5 \cdot \ln(\frac{1+r}{1-r})$. The variance of z is approximately $V_z = \frac{1}{n-3}$ and the standard error is $SE_z = \sqrt{V_z}$. In case of using Fisher's z, it is not used the variance of the correlation. The Fisher's z score and its variance are used in the analysis, yielding a summary effect, confidence limits in this metric and then these values are converting to correlation units. The formula of transformation is $r = \frac{e^{2z}-1}{e^{2z}+1}$.

1.3. iii. Fixed- Effects and Random- Effects Models

A meta-analysis combines the effect estimates of the included studies by weighting these estimates according to the different amounts of information in each study. There are two major statistical models for a meta-analysis: the fixed- effects model and the random- effects model. In both models, each study are weighted by the inverse of its variance. In other words,

$W_i = \frac{1}{V_{y_i}*}$, where $V_{y_i}*$ is the variance for study i

The two models diverge in their characterizations and underlying assumptions about the underlying association and source of variability in the population parameters. Under the fixed-effects model, it is assumed that all studies in the meta-analysis estimate one true and identical effect size. The observed variation among studies is due to random within study variation. So,

$V_{y_i}* = V_{y_i}$, where V_{y_i} is the within-study variance

It follows that the information in the smaller studies is given less weight, given that there is more precise information in the larger studies. The summary effect is the estimate of this common effect size and the confidence intervals depict the uncertainty around this estimate [27, 30, 32]. Tests which are analogous to analysis of variance (anova) and weighted regression can then be applied to the population of effect sizes to identify dependent variables that explain a significant amount of variation between studies [31]. By contrast, the random-effects model assumes that different studies indicate substantial diversity and the true effect size may vary from study to study.

Thus, $V_{y_i}* = V_{y_i} + T^2$, where V_{y_i} is the within-study variance and T^2 is the between-study variance. Differences in the characteristics of the sample populations and in the definition or the measurement of the outcomes together with other reasons, such as geographical variation, lead to assume that studies will not share a common effect size. The true effect sizes are distributed about some mean and considered a random sample from a distribution, which is usually Gaussian [30]. Therefore, the studies included in the analysis represent a random sample of effect sizes that could have been observed. The goal in this model is not to estimate one true effect, but to estimate the mean of a distribution of effects. Consequently, the summary effect is the estimate of the mean of these effects and the confidence intervals depict the uncertainty around this estimate, including the component of heterogeneity [27, 30, 32]. To conclude, the weighted mean in each case is computed through the formula: $M = \frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i}$.

In summary, in the fixed effect model, the source of uncertainty is intra-study sampling or estimation errors, while the random effect model assesses not only this source of uncertainty, but also the inter-study variance. Thus, this double source of variability (within and between- study variance) leads to wider variance, standard error and confidence intervals for the summary effect compared to the fixed- effect one. As far as the weights of the studies are concerned, both in the fixed- and in the random- effects analysis, each study was weighted by the inverse of its variance. The difference between the two models is that in the random-effects model the variance consists of the within-studies variance and the between-studies variance, on the contrary to the fixed-effects model that the variance is considered the within-studies variance. Therefore the weights are more balanced under the random- effects model than under the fixed- effects model, in the presence of heterogeneity, as random-effects methods add a common component of variance to each study weight to account for between study variability in effect size. Large studies are assigned less relative weight and small studies are assigned more relative weight as compared with the fixed- effect model [27, 30, 32].

The question that arises is which model should be chosen and under which criteria should this choice be taken. The selection of the meta- analysis model depends on the belief about the effect size and whether this is common in the studies included. In other words, the choice of the model should be based on the presence or absence of heterogeneity [27, 30]. In cases that it is believed that all the studies included are functionally identical and the study groups are homogeneous, the fixed- effects model could be an appropriate model [27, 30]. However, the data collected derive mostly from a group of studies that had been performed independently and are gathered from the published literature. Therefore, the possibility all the studies to be functionally equivalent is low and a common effect size cannot be assumed. In these cases, the between- studies variance is substantial and the choice of the random- effects model is considered as the better one [27]. Parallel, the goal in performing the analysis should be also taken into account to the choice of the appropriate model. In cases, the goal is a common effect size for the identified population to be computed and the results not to be extrapolated to other populations, the fixed- effects model can be used. Otherwise, the random- effects model could be a better choice, as the goal of this type of analysis is usually to generalize to a range of scenarios and its service is broader [27, 30].

It is also important to note that even if the study groups are homogeneous both random-effects model and fixed- effects model estimate similar results. For this reason and in combination with the restrictions fixed- effects model have, many studies suggested that the random- effects model is generally a more plausible approach [27, 32, 33].

1.3.iv. Heterogeneity

An important step in a meta- analysis is the assessment of the heterogeneity among studies, as the goal of this synthesis is not only to compute a summary effect, but also to interpret the pattern of effects. In other words, whether the effect size is consistent or not across the literature, the proper implications are needed to be considered [27]. In addition, given the fact that in most cases the assumption of the same true effect size across studies and thus the absence of heterogeneity is implausible, the quantification and further investigation of patterns driving the heterogeneity is considered as fundamental. The observed variation in the estimated effect sizes is partly counterfeit, while it includes both true variation in effect sizes and also random error. Meta-analysis heterogeneity is called the degree of dissimilarities in the individual study results and depicts the true differences in effect sizes related to underlying factors of the studies included in the meta-analysis [27, 30, 32]. As it has already been stated, the assumption on whether heterogeneity is present or absent among the studies is a crucial point when conducting a meta-analysis as it leads to different statistical methods (fixed- effects or random- effects model) for summarizing data and also to the different interpretation of results.

Taken together, it is very essential to identify and quantify the heterogeneity. To the quantification of the heterogeneity, the partition the observed variation into its two components, true variation and random error, is needed and then to focus on the former. The mechanism used to isolate the true variance is to compare the observed dispersion with the amount it would be expected if all studies shared a common effect size. The excess portion is assumed to reflect real differences among studies. This portion of the variance is then used to create several measures of heterogeneity [27]. Five statistics are computed for these purposes. They have different meanings and give interdependent information, providing various perspectives on the dispersion. In summary, Q statistic and the results of a statistical test based on the X^2 distribution (P-value) confirm whether effect sizes are homogeneous, I^2 expresses the proportion of variability due to heterogeneity over the total observed variation and the between- studies variance (T^2) or the between-studies standard deviation (T) estimate the amount of heterogeneity. A sixth statistic describing the effects of heterogeneity could be the random-effects estimator of the pooled effect size [27, 32].

Specifically, the Q statistic test, also known as Cochrane's Q test, and its P-value are used to determine whether there are substantial differences between the primary studies if the observed variation is random. Cochran's Q-value is calculated by summing the squared deviations of the estimate of each study from the overall estimate and is a measure of the total dispersion of the estimated effect sizes. In other words,

$Q = \sum_{i=1}^{k} W_i (Y_i - M)^2$, where k is the number of studies, W_i is the study weight, Y_i is the study effect size and M is the summary effect. The same formula can be written as: $Q = \sum_{i=1}^{k} (\frac{Y_i - M}{S_i})^2$.

Q is a standardized value, which means that it is not affected by the metric of the effect size [27]. Thus, it is not a measure of dispersion on the same scale of the effect size. In addition, while Q reflects the total dispersion, the difference of degrees of freedom from Q-value (Q- df) depicts the differences in the true effects, as degrees of freedom represent the within- study error. Q- df is also a standardized measure, where df= k-1. Test for assumption of homogeneity is based on Q statistics and tests the null hypothesis that all studies share a common effect size. The Q-value is compared with the chi-square distribution with k–1 degrees of freedom, where k is the number of studies [27, 30, 32]. However, the Q statistic and the homogeneity test cannot be employed as an estimate of the amount of heterogeneity, and it simply tests the null hypothesis that all effect sizes are consistent. In addition, to be noted that the Q test performs badly, in cases the number of studies in the meta- analysis is small. The results are sensitive to the excess of dispersion, the number of studies included as increase of dispersion moves towards significance and an increased number of studies strengthen the evidence of the test. Thus, due to the low statistical strength and its insensitivity, the threshold of the heterogeneity test is 0.10 and not 0.05 for indicating the presence of heterogeneity [27, 30, 32]. A method that overcomes the problem of the small sample setting and is commonly used for testing heterogeneity is the I^2 value. I^2 value quantifies the effect of heterogeneity and is not affected by the number of studies included in the meta-analysis or the type of outcome data. I^2 is computed as: $I^2 = (\frac{Q-df}{Q}) \cdot 100$

While I^2 value is calculated based on Q-value, it is a descriptive statistic and not an estimate [30, 32]. It represents the proportion, as its values range from 0% to 100%, of inter-study variability that can be attributed to true dispersion and not to chance being the ratio between the excess of dispersion and total dispersion. If the I^2 value is around 25% or 50% is considered as low or moderate heterogeneity, respectively, while if it is almost 100% is considered as high heterogeneity [27].

Parallel, for estimating the variance and the standard deviation of the true effects, derived from the observed effects, the between- studies variance estimate, T^2, and between-studies standard deviation estimate, T, can be used, respectively. They are expressed in the same metric (squared) as the effects themselves [27, 32]. The formula of T^2 is: $T^2 = \frac{Q-df}{C}$, where C = $C = \sum_{i=1}^{k} W_i - \frac{\sum_{i=1}^{k} W_i^2}{\sum_{i=1}^{k} W_i}$

C is a quantity that not only puts the measure back into its original metric, but also makes this measure average. T^2 represents the amount of true dispersion of the effect sizes. It can be used to estimate the distribution of true effects and consider the substantive implications of this distribution [27]. T is the square root of T^2 ($T = \sqrt{T^2}$) and represents the estimate of standard deviation of the distribution of the true effect sizes. A useful assumption for describing the distribution of the effects around their mean and calculating the 95% CI of the summary effect could be that this distribution is normal [32]. However, the most commonly used method in order to estimate the between-studies variance is the Der Simonian- Laird estimator, which is based on the method of moments, although recent studies indicate that it underestimates the between –studies variability in some settings [32].

To conclude, there are several ways of detecting and quantifying the heterogeneity in a set of studies included in a meta-analysis. Each of these methods contributes in a different perspective to understand and to interpret the pattern of the effects observed in the primary studies and they serve a role either in determining whether there is heterogeneity or not either in reflecting the amount of true dispersion over the total one. Taken together, Q statistic and its p-value serve as a test of significance, T^2 and T serve as the between-studies variance and the standard deviation of the true effects, respectively. I^2 reflects the proportion of the true variation in observed effects [27].

1.3. v. Types of bias

Two levels are involved in the major areas of bias which appear in meta-analysis. These are: (a) finding or retrieval of all studies and (b) selection of retrieved studies [29].

At the first level of capturing all studies specific on the research question of our interest, bias can occur in any stage of the procedure. The most common bias at this point is the publication bias. The publication bias refers to the fact that studies showing positive effects tend to be published more frequently than those that do not, and studies showing no significant results tend to remain unpublished. That has as a result the actual effect degree to be probably overestimated, particularly if studies have relatively small sizes [30]. The most commonly used graphic test to evaluate publication bias is the funnel plot **(Figure 4.)**. The funnel plot is a scatterplot of the effect estimate from each study in the meta-analysis against the measure of its variance, standard error or sample size. The effect estimates of small studies will scatter at the bottom of the graph, while the spread of larger studies will be narrower. If there was no publication bias, the funnel plot would resemble a symmetrical inverted funnel with a wide dispersion of results among studies. Otherwise, if an asymmetrical inverted funnel was generated, the presence of publication bias is being suggested (**Figure 4.).**

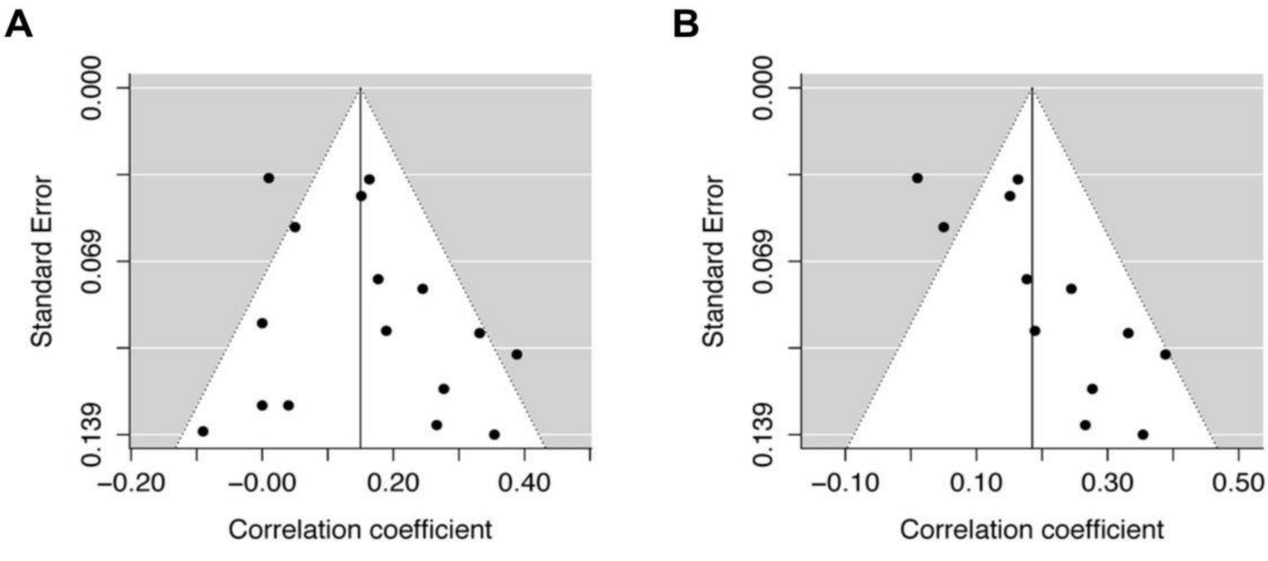

Figure 4. Example of a symmetrical funnel plot (A) and of an asymmetrical funnel plot (B), indicating the presence or not of publication bias

Although the funnel plot is a simple method, it is difficult to interpret when the number of studies is small and can be misleading [30]. In an attempt to avoid this kind of limitations, publication bias can be evaluated using other methods, such as Egger's linear regression test, which measures funnel plot asymmetry using a natural logarithm scale of odds ratios. Egger et al. suggested a regression test, regressing the standardized effect sizes ($\frac{y_i}{s_i}$) on the corresponding precisions ($\frac{1}{s_i}$). That is,

$$\frac{y_i}{s_i} = a + \mu \cdot \frac{1}{s_i} + \varepsilon_i \, .$$

There are, also, other sources that can lead to an upward bias in effect size and are included under the umbrella of publication. For instance, one such bias is the language bias, while English-language databases and journals are more often searched, which leads to an oversampling of statistically significant studies. In addition, regarding the detection of studies, there are availability bias and cost bias, in which the researcher selects the studies that are more easily accessible or the studies that are free or at low cost to access, respectively. Lastly, studies with statistically significant results tend to be published more than once and it is more likely to be cited by others. That leads to duplication bias or/and citation bias [27].

Parallel, even among published studies, many articles are not discovered after an expert search. The meta-analyst should choose a systematic strategy in their approach by entering a search database and choosing the appropriate index terms. However, either in the expert search either in the casual database search, it is possible to miss a substantial percentage of studies. Even with the onset of electronic searching, it is likely that some studies which meet our criteria will escape our search and not be included in the analysis. This may result in search bias, another type of sampling bias which is a bias in captured studies resulting from an inadequate or incomplete search. If the missing studies are a random subset of all relevant studies, the failure to include these studies will result in less information, wider confidence intervals and less powerful tests, but will have no systematic impact on the effect size. However, if the missing studies are systematically different than the ones we were able to locate, then our sample will be biased. Search bias can be prevented by a careful, informed search strategy [27, 29].

At a second level, once studies are captured by the search procedure, a meta- analyst then chooses among studies retrieved for the meta- analysis. In selection bias, although inclusion criteria have been set, they may not be so specific as to dictate which studies are included or excluded from the meta-analysis. This leaves the meta-analyst free to choose studies, a choice which is susceptible to bias. At a third level, another type of misinformation is recording error bias which is when the actual study results and the recorded results in the published paper differ [29].

Chapter 2. Aim/Objective

2.1. Current status of knowledge on functionality and diet

Studies investigating the association between dietary patterns and/or food groups and functionality are limited. Furthermore, researchers have focused more on the relationships between dietary patterns and health in older people in relation to depression and cognitive impairment, as well as, chronic diseases such as cardiovascular diseases, diabetes and cancer [34]. Overall, there is growing scientific evidence indicating that diets rich in fruits and vegetables, such as Mediterranean diet, play a beneficial role in preventing those diseases and in promoting quality of life and overall survival. Consumption of dairy products and meat require further investigation [35]. Also, there is evidence regarding the association of protein intake and parameters of functionality, such as slow walking speed, poor balance, lower muscle strength and overall physical functioning but it not consistent.

As far as our hypothesis is concerned, a potential relationship between healthier dietary patterns and better outcomes in older people either in overall functionality or in a domain of overall functionality is suggested by a small number of observational studies. The most commonly assessed healthy dietary pattern is the Mediterranean diet [36]. Among cross- sectional studies, participants with higher adherence to Mediterranean diet showed a significantly higher walking speed, higher scores in the physical component of tests and lower likelihood of experiencing limitations in physical function [37]. Moreover, not only a US cross-sectional study showed an inverse association between the Health Eating Index, an *a priori* dietary pattern, and the risk of developing limitations in IADL, but also a Brazilian cross- sectional study found similar results, that is a positive effect of the nutritional status in disabilities in ADL, IADL [38, 39]. Also, cross- sectional data show evidence that nutrition and better diet quality can impact physical health, especially in populations with osteoarthritis [40].

Prior reviews conducted have similar results with the above mentioned cross- sectional studies. In general, there is increasing interest to examine dietary patterns rather than single nutrients. Intervention that aims at improving overall diet quality may prove to have better success than single nutrient intervention. Although, most reviews focused on domains or states of health that include physical functioning, such as sarcopenia [36, 41], healthy aging [34] or frailty [42], all of them encourage the beneficial role of the “healthier” diets on physical performance and levels of physical activity in older age. Parallel, similar results are observed in reviews regarding either the Mediterranean diet or micronutrients related to the Mediterranean diet [43, 44]. To our knowledge there are no published reviews in specific domains of functionality, such as mobility disability. Additionally, there are no reviews investigating the relationship between *a posteriori* dietary patterns and functionality. Among cross- sectional designs, the prudent dietary pattern has shown to be associated to a higher grip strength and a better physical performance mainly in women [45, 46].

Experimental studies, such as trials showed that nutritional interventions based on Mediterranean-style diet significantly reduced the levels of inflammatory markers, which are part of the hypothesized pathway that leads to loss of muscle strength, reduced physical function and disability [43].

In contrast, there is a sizeable body of longitudinal evidence providing a link between healthier diets and smaller declines in physical performance. Overall, the current observational evidence for a positive relationship between diet quality and physical performance is strong.

Additionally, some of the evidence suggest possible differences between men and women in terms of the effects of diet quality and dietary indices on physical performance, although these findings were inconsistent and the overall message on differences by gender was not clear.

In conclusion, prior studies, although few, support the protective effects of healthy dietary patterns, mainly the Mediterranean diet, with better physical functioning, including lower body function and mobility observed across the studies. The differences on the results by gender are not strongly suggested.

Lastly, although not the subject of this investigation, there are some frequent aspect of nutrition-related conditions that have been examined broadly in relation to functionality. There are malnutrition, dysphagia and sarcopenia. In summary, both cross-sectional and prospective cohort studies have shown that malnutrition is associated strongly with functional impairment in ADL, especially in populations with chronic conditions or diseases, such as peritoneal dialysis or hemodialysis and chronic obstructive pulmonary disease. Malnutrition affects negatively the functionality of the individuals in all the possible phases of their life, from maternal malnutrion during pregnancy to the adult and the later years. In addition, improved nutritional status produces improvements in several functional outcomes, including muscle strength and walking endurance [8, 47-51]. In relation to sarcopenia, there are few cross-sectional studies pointing to a possible association between healthier diets and lower likelihood of sarcopenia in older people. However, there is a lack of longitudinal evidence for this relationship.

2.2. Aim of the Study

The present systematic review and meta- analysis was conducted with the aim to investigate the relationship between dietary patterns, food groups and functionality impairment. To our knowledge, this is the first systematic review investigating this relationship so thoroughly and broadly.

Ultimately, our findings could contribute to a knowledge base for the development of interventions for optimal healthy aging and may inform nutritional public policy aimed to its promotion.

Chapter 3. Materials and methods

This systematic literature review was performed following the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines [52, 53]. Methods of the analysis and inclusion criteria were specified in advance and documented in a protocol.

3.1. Search Strategy

The literature search was carried out using the electronic database PubMed up to 30/6/2019. The search did not include editorials, letters, comments, conference letters and it was limited to English articles. In addition, it was not restricted by publication year. The search string consisted of keywords describing nutritional status, dietary patterns, specific food groups and functionality, such as diet, nutrition, dietary pattern, vegetables, fruits, sugar, functional ability, activities of daily living, and mobility disability. The full search terms are shown in Appendix.

3.2. Study selection

Inclusion and Exclusion Criteria

Studies were eligible for inclusion: i) if they had a prospective cohort or case-control design or if they were randomized-clinical trials, ii) the minimum size of the study population was 100. For case-control studies, each cases and controls were over 100, iii) the length of the follow-up in cohorts range was over 6 months, iv) the study population consisted of people aged 18+ years who were presumably healthy, v) Provided a measure of association such as Hazard Ratios (HRs) and the corresponding 95% confidence intervals (CIs) or sufficient information for their calculation. Following the literature search, potential eligible studies were screened, re-evaluated and the non- relevant were excluded: cross-sectional studies, systematic reviews or meta- analyses. In addition, studies in which the functionality as an outcome was referred to cognitive functionality instead of physical performance or capacity, were excluded. Lastly, in cases where the functionality was given in an evaluation scale or an index that included a part of cognitive functionality, such as frailty or healthy aging, were also excluded. Overall, a total of 20 publications were identified for data extraction.

3.3. Measurement of the outcome under study

We focused on physical functionality and performance (as described in chapter 1.1.i) and not on cognitive function to the extent that these types of functionality could be separated.

In particular, in this meta-analysis for a standard environment eight studies assessed physical functioning in the scale SF-36 (3 studies) [17, 54, 56] or SF-12 (2 studies) [37, 57] or PF-10 a subscale of SF-36 (1 multi-center study that is considered as 3 studies) [58]. Three studies assessed physical functioning through SPPB [59, 60, 61]. The one of them assess the lower extremity function, but the description of the outcome matches in physical functioning [61]. Three studies assessed mobility disability through Rosow –Breslau scale [37, 57, 62] one study assessed mobility disability through a questionnaire that had questions related in walking, upstairs or downstairs [15]. One study assessed mobility disability through a specific subscale of SF-36 scale in combination to a Senior Fitness Test [63]. Three studies assessed agility through Rosow-Breslau scale [37, 57, 61]. For a daily environment, one study assessed ADL through Katz scale [62]. One study assessed ADL through the Older American Resources and services [38]. One study assessed difficulties in performing self-care activities such as bathing or dressing through a subscale of SF-36 scale [63]. The latter was considered as ADL assessment. Also, one study assessed ADL through LTCI system in Japan [11]. One study assessed IADL through Lawton- Brody scale [60], one study assessed IADL through Duke scale [62] and one study assessed IADL through the Older American Resources and services [38]. Lastly, one study assessed B-IADL that refers to both ADL and IADL through Lawton-Brody, Katz scales [12].

3.4. Data Extraction

For each study, data were extracted on first author, publication year, study name, country, study design, duration of follow-up or mean duration of follow- up where relevant, enrolment period, sample size in overall and by sex, sex distribution, age range of the study population or mean age if reported, type of dietary pattern or food group studied and dietary assessment method used (e.g. Food Frequency Questionnaire (FFQ)), adherence scale to the specific type of diet and diet score, type of functionality and evaluation methods, increment, assessment and categories of diet used for comparison (e.g. values from tertiles/quartiles/quintiles used to define higher categories and the lowest category taken as reference), whether the dietary pattern derived from a priori index or a posteriori analysis, type of results (e.g. Cox model), estimates of the effects (e.g. hazard rate (HR)) and their corresponding 95% confidence intervals (CI) and covariates/confounders adjusted for in the analysis. Values were extracted as values for total groups when available. If an overall value of the total group was not provided in the study publication, data of subgroups were converted into a calculated weighted average for the total group [12, 57, 58]. From each study we selected the effect estimate adjusted for the largest number of potential confounders and extracted the estimates regarding the highest vs the lowest level of the categories of diet assessment that was used in each study (tertile /quartile/ quintile). In cases that more than one MedDiet indices were used to measure the adherence to the Mediterranean Diet, we selected the one more closely resembling the most commonly MedDiet index [37].

3.5. Assessment of Risk of Bias

Study quality was assessed using the Newcastle-Ottawa Scale (NOS) a risk of bias assessment tool for observational studies. The NOS assigns up to a maximum of nine points for the studies with the least risk of bias in three domains: 1) selection of participants and study design (four points), 2) comparability of groups (two points) and 3) ascertainment of exposure and outcomes (three points). Scores for low (0-3), moderate (4-6) and high quality studies (7-9) were assigned and a star was awarded for high quality in each domain [64].

3.6. Statistical Analysis

The pooled estimate for the association of diet, in particular dietary patterns or food groups with each of the outcomes of interest was evaluated by combining the study-specific effect estimates with fixed or random effects models in the presence of heterogeneity, using the Inverse Variation Method. The between studies variance component was estimated using the Der Simonian and Laird approach. To explore heterogeneity between the studies the I^2 and the chi square statistic for heterogeneity were estimated. When I^2 was > 0.50% the statistical heterogeneity was considered substantial [65]. If studies reported RR or HR instead of OR, it was treated the same as OR for comparing highest compliance to lowest in studies specific categories. Publication bias was assessed by funnel plots and the Egger's tests to investigate the asymmetry among the study estimates. Based on the available data of the eligible studies, we considered six different categorizations of functionality based on its type: a) physical functioning, b) mobility disability, c) agility, d) IADL, e) ADL and f) B-IADL. Physical functioning, mobility disability and agility refer to functionality in a standard environment, while IADL, ADL and B-IADL refer to functionality in a daily environment. Sensitivity analysis was conducted to determine whether differences in sex affected study conclusions. Furthermore, we performed sensitivity analysis by omitting the Nurse's Health study and assessing its effect on the overall summary HRs as estimated before and after the exclusion of this specific study [17]. We decided to omit this study, because its weight in each meta-analysis is much greater than the rest of studies and it seems to affect crucial the pooled effect estimate. All analyses were conducted using STATA statistical package (version 13.1.).

Chapter 4.RESULTS

4.1 Search Results

The flow diagram of the study selection procedure is provided in **Figure 5**. After exclusion of non-relevant studies in the initial search and through a secondary hand search, 81 studies remained. Following further exclusion of studies that did not met the eligibility criteria 20 studies remained for a qualitative analysis. Due to the limited number of publications found reporting results given in dietary clusters or publications assessing coffee, green tea and dairy, four publications were excluded from the analysis. In addition, one publication was excluded because the results compared the lowest category vs the highest instead of the opposite. Finally, 15 prospective cohort studies published between 2010 and 2019 were included in the analysis. Detailed characteristics of the selected studies are shown in **Table 1a, Table 1b, Table 1c.**

Generally, from the 15 studies, nine studies were related to a priori dietary patterns, two studies were related to a priori and a posteriori dietary patterns and one study was related to a posteriori dietary patterns exclusively. Four were related both to food groups and dietary patterns and two studies were related only to food groups. The vast majority of studies refer to a priori healthy dietary patterns (13 of 14 studies, 92.86%). In general, the healthy dietary pattern is characterized by high intakes of vegetables, fruits, whole grains, olive oil, fish, soy, poultry and low fat dairy. For this reason, one study that referred to unhealthy dietary pattern was excluded from the meta-analysis for a priori dietary patterns and was included in the meta-analysis for a posteriori dietary patterns [60]. Three studies were conducted in the United States [17, 54, 62], two in Australia [28, 56], four in Spain (Seniors ENRICA cohort) [37, 57, 60, 61] and one study was conducted for each of the countries England [15], France [12], Italy [59], Japan [11], Norway [63]. In addition, one study was multi-centered including data from three European countries, Czech Republic, Poland and Russia [58]. Most of studies (12 of 15 studies; 80%) derived from the general population of both sexes, except from one (1 of 15 studies; 6.67%) which included nurses women only [17] and two (2 of 15 studies; 13.33%) which included men only [15, 54]. The dataset comprised 118.900 participants. The follow up time ranged from 2 to 18 years and the mean baseline age ranged from 55.71 to 80.7 years. All studies used the following covariates as possible risk factors/confounders: age, smoking status and sex in cases studies were not only in one sex or had separate results for both sexes. Most studies used, also, education, physical activity, energy intake, body mass index (BMI), depression, cognitive impairment and diseases, such as cancer or cardiovascular disease, or chronic diseases, such as diabetes, hypertension or cholesterol as possible confounders. Few studies examined, also, alcohol, time spent in TV, marital status and monthly income/economic activity.

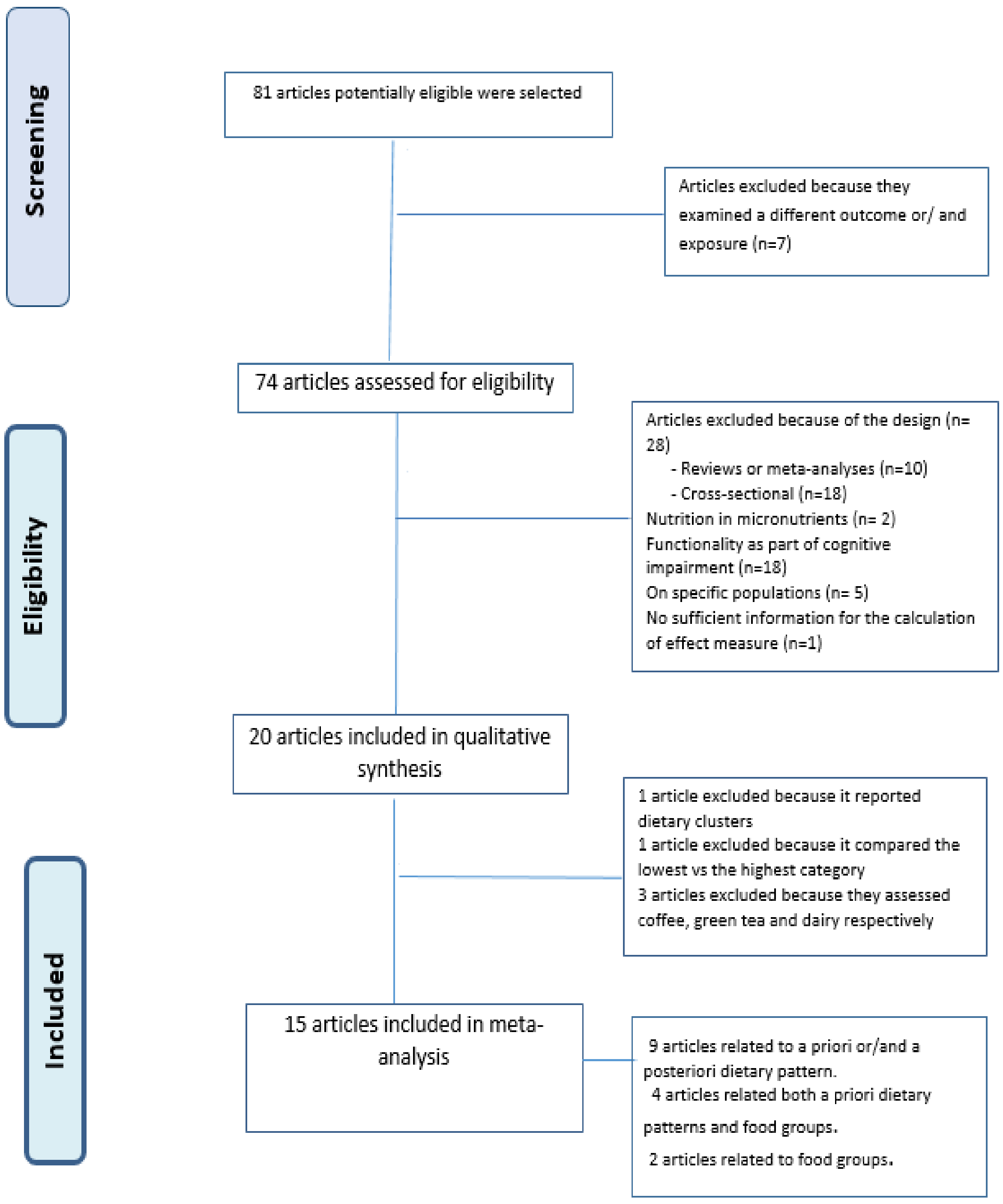

Figure 5. Flowchart of the study selection process.

Table 1a. Characteristics of the 11 studies included in the meta-analysis investigating a priori dietary patterns and functionality.

id	Study reference/cohort name/ location	Enrollment/ follow up	Dietary pattern	Dietary Pattern construction	Mean Age at baseline /N (N by sex)	Dietary assessment method	Outcomes	Covariates controlled	Effect estimate and Multivariate adjusted results
1	Féart et al. -2011- 3C study- France	2001-2002 / 4.1 years	Mediterranean diet(MDS)	**MDS** components: 9 ↑ vegetables, fruits, legumes, cereal, fish, MUFA-to-SFA ratio ↓ meat, dairy products, alcohol Cut-off: sex-specific median intakes MDS score range: 0-9	75.7 years / 1179 (470 men and 709 women)	Not semi-quantitative FFQ and 24H recall	Incident disability in B-IADL in Lawton Brody scale, Katz scale scores	Age, education, monthly income, marital status, physical exercise, BMI, Hypertension, Diabetes, smoking, MMSE, stroke, energy intake	HR : 0.70 (0.42,1.19) Tertile 3 vs tertile 1 linear : 0.95 (0.86, 1.06) 1 point increase
2	Milte et al. -2015 - WELL study- Australia	2010 / 2 years	Mediterranean Diet (MDS) Dietary guideline index (DGI)(based on Australian guidelines) Recommended Food score index (RFS)	**MDS** components: 8 ↑ vegetables, cereal, legumes, fruits and nuts, fish and seafood ↔ alcohol ↓ meat , dairy products Cut-off: sex-specific median intakes MDS score range: 0-8 **DGI** Components: 13 Vegetables, fruits, grains, meat and alternatives, dairy, fluids and discretionary foods,	59.9 years/ 2457 (1150 men and 1307 women)	111-item FFQ over the last 6 months	1) Physical functioning in RAND-36-item score 2) PCS in RAND-36-item score	Age, BMI, physical activity, region, smoking, country of birth, marital status, education, menopausal status	**MDS** OR(**Physical functioning**): 1.26 (1.00,1.60) OR(**PCS**): 1.02(0.81,1.29) **DGI** OR(**Physical functioning**) : 1.56 (1.22,1.99) OR(**PCS**): 1.46(1.15,1.86) **RFS**

				lean protein, unsaturated fat Each component scored 0-10 according to fully meeting the recommendation or not Cut-offs: age and sex-specific scoring DGI score range: 0-130 **RFS** Components: 49 Dietary guidelines : fruits, vegetables, whole grains, lean meat and alternatives, low fat dairy products Each component scored 0 or 1 according to consuming more than once a week or not Cut-offs: age and sex-specific scoring RFS score range: 0-49					OR(**Physical functioning**) : 1.43 (1.13,1.82) OR(**PCS**): 1.0.8 (0.85,1.37) Quartile 4 vs Quartile 1
3	Agarwal et al. -2018 - MAP study-Chicago	2004/ 5 years	Mediterranean Diet (MDS) Mediterranean-DASH intervention for Neurodegenerative Delay (MIND) pattern DASH diet	**MDS** Components: 11 each scored 0-5 Comparison metric: serving quantities MDS score range: 0-55 **MIND** Components: 15 ↑ green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil, wine	80.7 years/ 809 (210 men and 599 women)	144- item semi-quantitative FFQ over the last 12 months	1) ADL 2)IADL 3) incident mobility disability in Katz, Duke, Rosow-Breslau scale scores	Age, sex, education, smoking, physical activity weekly, BMI, depression, energy, Global cognitive score, diabetes, hypertension, myocardial infarctions, stroke	**MDS** HR (**ADL**) : 0.73 (0.56,0.95) HR (**IADL**): 0.86(0.63,1.18) HR (**Incident Mobility Disability**) : 0.82 (0.62,1.08) **MIND** HR (**ADL**) : 0.65 (0.51,0.84)

				↓ red meats, butter and stick margarine, cheese, pastries and sweets, fried/fast food Each component were scored from 0 (low adherence to recommended servings) to 1 (high adherence to recommended servings) MIND score range: 0-15 **DASH** Components: 7 food groups and 3 dietary components ↑ fruit, vegetables, nuts and legumes, low-fat dairy products, whole grains ↓ red/processed meats, sweets, sodium, saturated fat, total fat Each component scored 0, 0.5 or 1 DASH score range : 0-10					HR (**IADL**): 0.81 (0.61,1.07) HR (**Incident Mobility Disability**) : 0.80 (0.61,1.05) **DASH** HR (**ADL**) : 0.77 (0.60,0.98) HR (**IADL**): 0.86 (0.66,1.12) HR (**Incident Mobility Disability)** : 0.76 (0.58,0.99) Tertile 3 vs Tertile 1
4	Milaneschi et al. - 2010 - InCHIANTI study – Italy	1998-1999 / 9 years	Mediterranean Diet (MDS)	**MDS** components: 9 ↑ vegetables, fish, legumes, fruits, cereal, ratio of monounsaturated to saturated fats ↔ ethanol ↓ meat, dairy products	74.1 years / 684 (304 men and 380 women)	FFQ	1) Physical performance in SPPB score 2) incident mobility disability	Age, sex, education, smoking, MMSE,BMI, physical activity, depression, no medications, no chronic diseases, no IADL, ADL disabilities, SPPB score, energy intake, knee strength	OR(**physical performance**): 0.73 (0.41,1.28) HR (**incident mobility disability**) : 0.71 (0.51,0.98) Tertile 3 vs Tertile 1 Linear(**physical performance**):

				Cut-off: sex specific median intakes MDS score range: 0-9					0.92 (0.73,1.17) Linear(**incident mobility disability**): 0.86 (0.74,0.99) 2 points increase
5	Struijk et al. -2016 - Seniors-ENRICA cohort- Spain	2008-2010/ 3.5 years	Mediterranean Diet (MDS)	**MDS** components: 9 ↑ vegetables, legumes, fruits and nuts, grains, fish and seafood, ratio of unsaturated to saturated fatty acids ↔ alcohol ↓ dairy, meat and poultry products Cut-off: sex-specific median intakes MDS score range: 0-9	68.1 years/ 1630 men and women	Validated computer-assisted face-to-face diet history	1) Agility in Rosow-Breslau score 2) mobility in Rosow-Breslau score 3) physical functioning in SF-12 score	Age, sex, education, smoking, leisure-time physical activity, time spent watching TV, energy intake, BMI, hypertension, diabetes, cognitive impairment, osteomuscular disease, cardiovascular disease, cancer, chronic lung disease, depression	OR(**Agility**): 0.94 (0.67,1.31) OR(**Mobility**): 0.85 (0.58,1.26) OR(**Physical functioning**): 0.79 (0.59,1.06) Tertile 3 vs Tertile 1 Linear (**Agility**) : 0.95 (0.8,1.12) Linear (**Mobility**): 0.91 (0.75,1.1) Linear (**Physical functioning**): 0.87 (0.75,1) 2 points increase
6	Stefler et al. -2018 - HAPIEE study - Czech Republic, Poland, Russia federation	2002-2005/ 10 years	Mediterranean Diet (MDS)	**MDS** components: 9 ↑ vegetables, fish, legumes, fruits and nuts, cereals, olive oil ↔ alcohol ↓ meat and dairy products Cut-off: pre-defined absolute values based on review of food intake in previous studies	58 years/ 7215 Czechs, 9042 Russians 9247 Polish men and women	Semi-quantative FFQ (136 Czech, 147 Russian, 148 Polish food and drink items)	Physical functioning in PF-10 score	Age, sex, marital status, education, ownership of household items, economic activity, spine/joint problems, smoking	Slope (**Czech Republic**): 0.04 (-0.18 , 0.26) Slope (**Russia**): -0.04 (-0.36, 0.28) Slope (**Poland**): -0.235 (-0.51 , 0.04) Tertile 3 vs Tertile 1 Slope (difference in the mean PF score with the reference category and linear)

				MDS score range: 1-16					
7	Gopinath et al. - 2014 - BMES study- Sydney (Australia)	1992-1994/ 5 years	Total diet score (TDS) based on Australian guidelines	**TDS** Components: 10 ↑ vegetables, fruits, whole grain cereal and breads, lean red meat, fish, poultry, reduced-fat dairy ↓ sodium, alcohol, sugar and extra food intakes Each component was scored from 0 to 2 according to adherence to guidelines TDS score range: 0-20	71.55 years/ 895 (374 men, 521 women)	145-item semi-quantitative FFQ	1) ADL 2) IADL in The Older American Resources and Services scale scores	Age, sex, lives alone, poor self-rated health, smoking, walking disability, cognitive impairment, diabetes, hypertension, admission to hospital during the past 12 months	OR(**ADL**): 1.33 (0.70,2.51) OR(**IADL**): 0.50 (0.28,0.87) Quartile 4 vs Quartile 1
8	Parsons et al. - 2018 - The British Regional Heart Study - England	1998-2000/ 15 years	Healthy Diet Indicator (HDI) Elderly Dietary Index (EDI)	**HDI** Components: 8 (7 nutrients and 1 food group) Saturated fatty acids, poly-unsaturated fatty acids, protein, carbohydrates, . sugar, fibre, cholesterol, fruit/vegetables Each component was scored 0 or 1 according to if it was in the guideline or not HDI: 0-8 **EDI** Components: 9 Meat, fish and seafood, legumes, fruits, vegetables,	66 years/ 1158 men	86-item FFQ over frequency of items	Mobility limitation in yes/no question	age, manual social class, smoking, physical activity, alcohol, energy intake, BMI, CRP	**HDI** OR: 0.49 (0.31,0.78) **EDI** OR: 0.53 (0.35,0.82) Quartile 4 vs Quartile 1

				cereal, bread, olive oil, dairy Each component was scored from 1 to 4 according to optimal frequency EDI score range: 9-36					
9	Hagan et al. - 2016 - The Nurses' Health study - USA	1976/ 18 years	Alternative Health Eating Index (AHEI-2010)	**AHEI-2010** Components : 11 ↑ vegetables, fruits, whole grains, nuts and legumes, LCFA n-3, PUFAs, ↓ sugar-sweetened beverages and fruit juice, red and processed meat, sodium, trans fats ↔ alcohol AHEI-2010 score range: 0-110	55.71 years/ 54762 Women	FFQ and average frequency of food consumption the last year	Physical functioning in a score	age, BMI, physical activity, Mental Health Index, smoking, alcohol intake, education, hypertension, cholesterol, myocardial infarction, stroke, diabetes, energy intake	HR: 0.87 (0.84, 0.90) Quintile 5 vs Quintile 1
12	Hagan et al.- 2019- HPF study - USA	2008/ 4 years	Alterntive Health Eating Index (AHEI)	**AHEI** components: 11 ↑ vegetables, fruits, whole grains, nuts and legumes, long chain omega-3 fatty acids, polyunsaturated fatty acids ↔ alcohol ↓ sugar sweetened beverages and fruit juice, red and processed meat, trans fatty acids, sodium AHEI score range: 0-110	69.9 years/ 12658 men	FFQ over the frequency during the previous year based on units or portion sizes	Physical functioning in SF-36 score	Age, total energy intake, BMI, physical activity, smoking, depression, cancer, myocardial infarction, stroke, diabetes, hypertension, cholesterol	OR : 0.74 (0.63, 0.86) Quintile 5 vs quintile 1 Linear: 0.90 (0.86,0.95) 10 points increase

15	Perálâ et al. -2018 – Helsinki Birth Cohort study - Helsinski	2001-2004/ 10 years	Mediterranean Diet (MDS) Nordic Diet score (NDS)	**MDS** Components: 9 ↑ Vegetables (excluding potatoes), fruits and nuts, cereals, legumes, fish and fish products, ratio of polyunsaturated to saturated fat ↔ alcohol ↓ meat and dairy products Cut-off: sex specific median intakes MDS score range: 0-9 **NDS** components: 9 ↑ nordic vegetables (excluding potatoes), nordic fruits, nordic cereals, fish, ratio of polyunsaturated fatty acids to saturated fatty acids and trans- fatty acids , low fat milk ↔ alcohol ↓ red and processed meat, intake of total fat Cut-off: sex specific quartile ranks NDS score range: 0-25	61.6 years / 962 (439 men and 523 women)	Validated 128-item FFQ over frequency the previous year	1) moblitiy limitation in RAND 36-item score 2) self-care activities (ADL) in RAND 36-item score	Sex, age, BMI, smoking, education, physical activity, energy intake, chronic diseases, depression, impaired cognition, self-care dependence	**MDS** OR (**mobility limitation**): 0.61 (0.28, 1.30) OR (**self-care activities**) : 0.45 (0.17, 1.21) **NDS** OR (**mobility limitation**): 0.42 (0.21, 0.84) OR (**self-care activities**) : 0.45 (0.17, 1.16) Tertile 3 vs tertile 1

Table 1b. Characteristics of the 3 studies included in the meta-analysis investigating a posteriori dietary patterns and functionality

id	Study reference/cohort name	Location	Enrollment/ follow up	Dietary patterns	Dietary pattern construction	Mean Age /sex	Dietary assessment method	Outcome	Covariates controlled	Effect estimate and Multivariate adjusted results
8	Parsons et al. - 2018 - The British Regional Heart Study	England (24 British towns)	1998-2000/ 15 years	High-fat/low fibre pattern, Prudent pattern, High-sugar pattern	**High-fat/low fibre pattern**: ↑ red meat, meat products, fried potato, white bread, eggs and beer, ↓ low intake of wholemeal bread **Prudent:** ↑ fruits, vegetables, wholemeal bread, poultry, fish, legumes, pasta and rice, eggs, sauces, soups, olive oil **High-sugar pattern**: ↑ breakfast cereals, full fat	66 years/ 1158 men	86-item FFQ over frequency of items	Mobility limitation in yes/no question	age, manual social class, smoking, physical activity, alcohol, energy intake, BMI, CRP	OR(**High-fat/low fibre pattern**): 2.74 (1.65, 4.54) OR(**prudent**): 0.94 (0.59, 1.50) OR(**High sugar pattern**) : 0.71 (0.42, 1.20) Quartile 4 vs Quartile 1

					cheese, biscuits, puddings, chocolates , sweets and sweet spreads, ↓ low consumption of beer Score range: PCA					
10	Tomata et al. - 2013 - Ohsaki study	Ohsaki city (Japan)	2006/ 5 years	Japanese pattern , Animal food pattern, High dairy pattern	**Japanese pattern:** ↑ rice, miso soup, seaweeds, pickles, green and yellow vegetables, fish, green tea ↓ beef and pork, coffee cut-offs: sex specific medians **Animal food pattern:** NA	73.9 years/ 14260 (6388 men, 7872 women)	39-item FFQ	Incident Functional Disability of LTCI system	age, sex, education, smoking, alcohol, BMI, psychological distress, time spent walking, motor function, energy, protein	HR(**Japanese pattern**): 0.77 (0.68, 0.88) HR(**Animal food pattern**): 1.16 (1.02, 1.31) HR(**High dairy pattern**) : 1.11 (0.99, 1.26) Quartile 4 vs Quartile 1

					High dairy pattern: NA Score range: PCA					
11	Laclaustra et al. - 2019-Seniors ENRICA study	Spain	2008-2010/ 3 years	Empirical Dietary Inflammatory Index (EDII)	**EDII** 18 food groups ascertained as daily portions. Daily intake of food were summed, converted in standardized score	68.4 years/ 1948 (945 men and 1003 women)	A computer based diet history of the regular diet	1) IADL in Lawton Brody scale 2) physical performance in SPPB score	Sex, age, education, BMI, energy intake, time spent watching TV, leisure time physical activity, MEDAS, smoking status, diagnosed diseases	**EDII** OR (**IADL**): 1.10 (0.59, 2.05) OR (**physical performance**): 1.18 (0.90, 1.55) Tertile 3 vs Tertile 1

Table 1c. Characteristics of the 2 studies included in the meta-analysis investigating food groups and functionality

id	Study reference/cohort name	Location	Enrollment/ follow up	Food group	Mean Age /sex	Food group assessment method	Outcome	Covariates controlled	Effect estimate and multivariate adjusted results
13	Struijk et. al.– 2018- Seniors ENRICA cohort	Spain	2008/ 2 years	**Red meat** Beef, lamb, pork **Processed Meat** Bacon, salami, sausages **Poultry** Several types of fowl and rabbit Organ meat has not been taken into account due to its low intake	68.8 years/ 2982 (1387 men and 1595 women)	Validated computer-assisted face-to-face diet history	1) agility in Rosow-Breslau score 2) lower extremity function in SPPB score	Age, sex, educational level, smoking status, leisure time physical activity, watching TV, energy intake, alcohol intake, BMI, cancer, osteomuscular disease, cognitive impairment, cardiovascular disease, chronic lung disease, depression	**Red meat** HR (**agility**): 1.14 (0.92, 1.41) HR (**lower extremity function**): 0.86 (0.67, 1.12) **Processed Meat** HR (**agility**): 1.33 (1.08, 1.64) HR (**lower extremity function**): 1.31 (1.02, 1.68) **Poultry** HR (**agility**): 1.07 (0.88, 1.32) HR (**lower extremity function**): 1.08 (0.85, 1.38) Tertile 3 vs Tertile 1
14	Lucia Arias-Fernandez- 2018- Seniors ENRICA cohort	Spain	2008-2010/ 7.2 years	**Nut consumption** 20 types of nuts		Validated computerized diet history over a year recall	1) agility 2) mobility in Rosow Breslau score 3)grip strength in measurements from a Jamar dynamometer, 4) gait speed 5) overall function in SF-12 score	Age, education, smoking, alcohol intake, leisure time physical activity, time in TV, energy intake, diet score, PUFA intake, MUFA intake, BMI, hypertension, diabetes, cardiovascular, lung disease, musculoskeletal, cancer, depression,	HR (**agility**): 0.78 (0.56, 1.10) HR (**mobility**): 0.9 (0.57, 1.28) HR (**grip strength**): 0.82 (0.54, 1.24) HR (**gait speed**): 1.16 (0.79, 1.71) HR (**overall physical function**): 0.78 (0.57, 1.07) Tertile 3 vs Tertile 1

								cognitive decline, falls	

4.2. Meta-Analysis by Type of Functionality

Different meta-analyses for the association between a priori dietary patterns and overall functionality by type of functionality were conducted. In cases where studies assessed more than one dietary pattern, we followed a specific strategy. When Mediterranean diet was one of the dietary patterns, this was the one that was included in meta-analysis [12, 37, 56, 58, 59, 62, 63]. When Mediterranean diet was not one of the dietary patterns, the next option was a diet that reflects a positive impact on adults health and not specifically on elderly (Total diet [38], alternative healthy eating [17, 54], healthy diet [15]). **Figure. 6.** and **Figure. 7.** present the results of the meta-analysis for dietary patterns with each type of functionality among participants using the fixed and random effects model, respectively, as well as the results of the meta-analysis for dietary patterns with overall functionality.

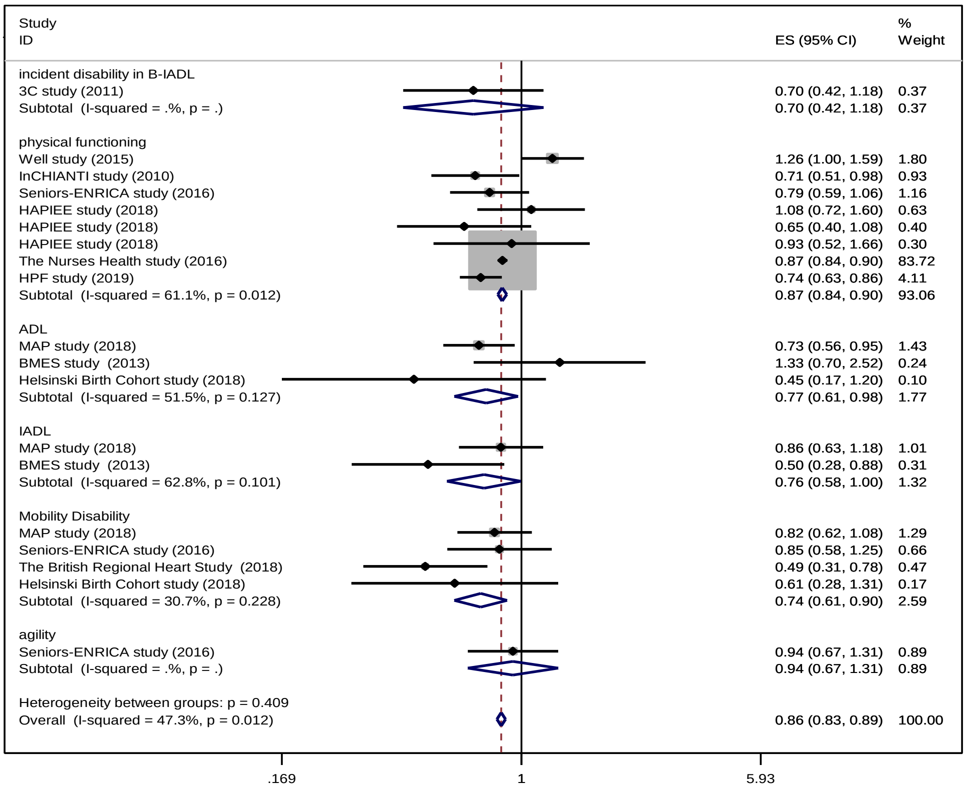

Figure. 6. Forest plot for the association between Dietary patterns and Functionality. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate, ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, B-IADL: Basic and Instrumental Activities of Daily Living.

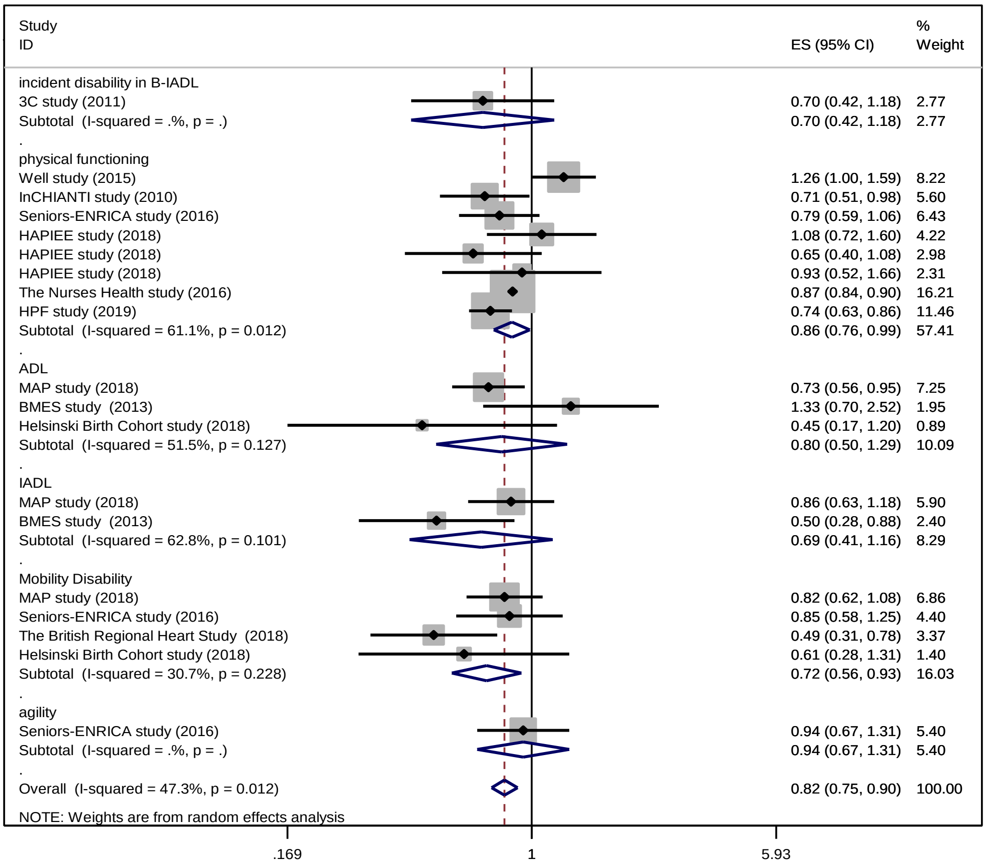

Figure. 7. Forest plot for the association between Dietary patterns and Functionality. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate, ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, B-IADL: Basic and Instrumental Activities of Daily Living.

4.2.i. Dietary patterns and physical functioning

Physical functioning was the most frequently reported type of functionality that was presented in 15 studies. In this analysis 8 studies were included with 97,695 participants. The median mean age of the participants was 58.95 years. Six studies assessed Mediterranean diet in physical functioning and two studies assessed Alternative Healthy eating index in physical functioning. The majority of studies were in both sexes, (6 of 8 studies, 75%), while one study was only in men (1 of 8 studies, 12.5%) [54] and one study only in women (1 of 8 studies, 12.5%) [17]. Two studies were in USA, one study was in Spain, one study was in Australia, one study was in Italy and one multi-centered study that was in Czech Republic, in Poland and in Russia [58]. The minimum years of follow up was 2 years [56], while the maximum was 18 years [17]. Six out of eight studies reported a protective effect of healthy dietary patterns in physical functioning [17, 37, 54, 58, 59] and three of them were statistically significant [17, 54, 59]. This is also observed in our results, both at fixed effects and random effects model, where a protective statistical significant pooled effect estimate of dietary patterns in physical functioning is observed. The pooled fixed effects estimate was 0.87, (95 % C.I. 0.84, 0.90) (**Figure. 6.)**

while the random effects estimate was 0.86, (95 % C.I. 0.76, 0.99) (**Figure. 7.**) comparing physical functioning decline between participants having the highest vs the lowest compliance to a healthy dietary pattern. There was significant heterogeneity observed (I^2 =61.1 % and chi square p=0.012). The funnel plot (**Supplementary Figure. 1**.) and the Egger's test p= 0.924 do not support evidence of small studies effects.

4.2.ii. Dietary patterns and ADL

In this analysis 3 studies were included with 2,666 participants [38, 62, 63]. The median age of the participants was 71.55 years. Two studies assessed Mediterranean Diet with ADL and one study assessed Total Diet- ADL. Total Diet assess the adherence to the dietary guidelines for Australian adults. All studies included both sexes, (3 of 3 studies, 100%). One study was in Chicago, one study was in Sydney, Australia and one study was in Helsinski. The minimum years of follow up was 5 years [38], while the maximum was 10 years [63]. Two out of three studies showed a protective effect of healthy dietary patterns in ADL [62, 63] and one of them was statistically significant [62]. A protective pooled effect estimate of dietary patterns in relation to ADL decline is observed, in both models The pooled fixed effects estimate was 0.77 (95% C.I. 0.61, 0.98) (**Figure 6.),** while the random effects estimate was 0.80 (95% C.I. 0.50, 1.29) (**Figure 7.**) for comparing ADL decline between participants having the highest vs lowest compliance to a healthy dietary pattern. A significant heterogeneity (I^2 =51.5 % and chi square p=0.127) was observed. The funnel plot (**Supplementary Figure 3**.) and the Egger's test p=0.928 do not support evidence of small studies effects.

4.2.iii. Dietary patterns and mobility disability

In this analysis 4 studies were included with 4,234 participants. The median age of the participants was 67 years. Three studies assessed Mediterranean diet in relation to mobility limitation [37, 62, 63] and one study assessed healthy diet in relation to mobility limitation [15]. The majority of studies included both sexes (3 of 4 studies, 75%), while one study only in men (1 of 4 studies, 25%). One study was conducted in Chicago, one study in Spain, one study was in England and one study was in Helsinski. The minimum years of follow up was 3.5 years [37], while the maximum was 15 years [15]. All studies reported a protective effect of healthy dietary patterns in mobility disability [15, 37, 62, 63]. However, only in one of them the results were statistically significant [15]. Both at fixed effects model and random effects model, a protective pooled effect estimate of dietary patterns in relation to mobility disability is observed. The pooled fixed effects estimate was 0.74 (95% C.I. 0.61, 0.90) (**Figure 6.)** while the random effects estimate was 0.72 (95% C.I. 0.56, 0.93) (**Figure 7.**) for mobility disability comparing participants with the highest vs lowest compliance to a healthy dietary pattern. Significant heterogeneity (I^2 =30.7 % and chi square p=0.228) was also observed. The funnel plot (**Supplementary Figure 5**.) and the Egger's test p=0.398 do not support evidence of small studies effects.

4.2.iv. Dietary Patterns and other types of functionality

Studies have evaluated also other types of functionality scores. One study assessed agility [37], two studies assessed IADL [38, 62] and one study assessed B-IADL [12].

4.3. Meta-Analysis by Dietary pattern

The results of the meta-analysis by type of dietary pattern used in relation to overall functionality and individual components of functionality are presented below.

4.3.i. Mediterranean diet and functionality

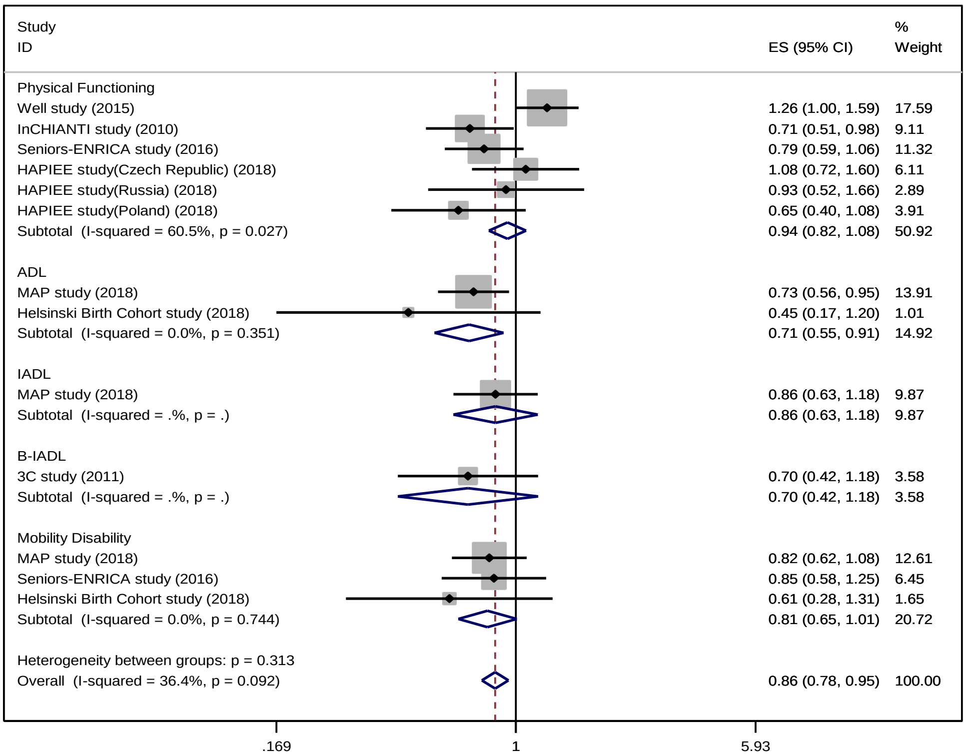

Figure 8. Forest plot for the association between Mediterranean Diet and Functionality. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate, ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, B-IADL: Basic and Instrumental Activities of Daily Living.

Seven studies investigated adherence to the Mediterranean diet and the association with a type of functionality in different populations – five in Europe, one of them is multi-centered [12, 37, 58, 59, 63] and two studies in non-European populations [56, 62]. Vegetables, fruits and nuts, legumes, cereals, fish and seafood, meat and dairy products were always part of the Mediterranean diet indices. In European population olive oil or monounsaturated to saturated fat ratio is also included in the diet index. Mild to Moderate alcohol consumption, a characteristic of the MD was rated always higher than High alcohol consumption. In one study is not specified the exact method that the Mediterranean diet score was constructed, it reported to have 11 dietary components of the traditional Greek Mediterranean diet and each scored 0 to 5 and then summed for a total score ranging 0 to 55 [62]. As far as the rest of studies concerned, four out of six studies had a score ranging from 0 to 9 [12, 37, 59, 63], one study had a score ranging from 0 to 8 [56] and one study had a score ranging from 1 to 16 [58]. In total, 5 of 6 studies and in multi-centered study, 2 of 3 studies observed a protective effect of Mediterranean diet in any type of functionality, but most of them were not statistically significant.

Both at fixed effects model and random effects model, a statistically significant protective pooled effect estimate of Mediterranean diet with overall functionality is observed. The pooled fixed effects estimate was 0.86 (95% C.I. 0.78, 0.95) (**Figure 8.**) while the random effects estimate was 0.84 (95% C.I. 0.73,0.95) (**Figure 9.**) for overall functionality decline comparing participants with the highest vs lowest compliance to Mediterranean diet. There was medium heterogeneity among all studies (I^2 =36.4 % and Q p=0.092).

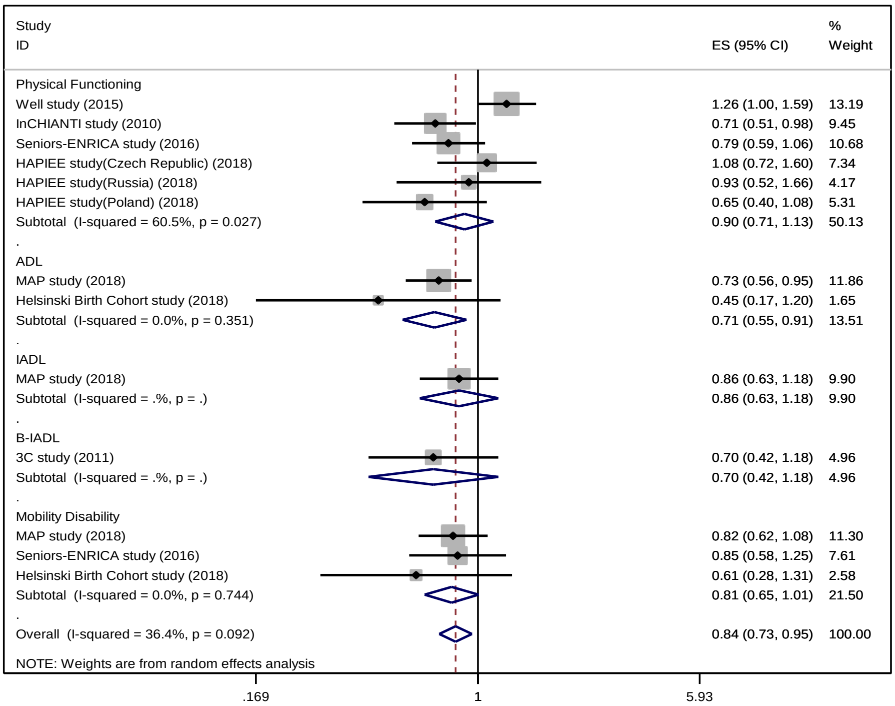

Figure 9. Forest plot for the association between Mediterranean Diet and Functionality. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate, ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, B-IADL: Basic and Instrumental Activities of Daily Living.

Mediterranean Diet and physical functioning

In this analysis 6 studies were included with 30,275 participants. The median mean age of the participants was 58.5 years. All studies were in both sexes (6 of 6 studies, 100%). One study was in Australia [56], one study was in Spain [37], one study was in Italy [59] and one multi-centered study that was in Czech Republic, in Poland

and in Russia [58]. The minimum years of follow up was 2 years (Well study), while the maximum was 10 years (HAPIEE study). Four out of six studies showed a protective effect of Mediterranean diet in physical functioning and only in one of them the result is statistically significant. Both at fixed effects model and random effects model, a protective pooled effect estimate of Mediterranean diet in relation to physical functioning decline is observed. The pooled fixed effects estimate was 0.94 (95% C.I. 0.72, 1.08) (**Figure 8.**) while the random effects estimate was 0.90 (95% C.I. 0.71, 1.13) (**Figure 9.**) for the difference in physical functioning between highest vs lowest compliance to Mediterranean diet. There was significant heterogeneity (I^2 =60.5 % and chi square p=0.027). The funnel plot (**Supplementary Figure 7**.) and the Egger's test p= 0.339 do not support evidence of small studies effects.

Mediterranean Diet and IADL, ADL or both

With respect to MD and ADL or IADL activities, insufficient number of studies was found to enable the meta-analysis. Two studies were found in relation to ADL decline with a total of 1,771 participants [62, 63] and only one study was found with a total of 515 participants in relation to IADL decline [62]. In addition, one study assessed both types of activities (B-IADL) with a total of 1,179 participants [12].

Mediterranean Diet and mobility disability

In this analysis 3 studies were included with 3,107 participants. The median mean age of the participants was 68.1 years. All studies were in both sexes (3 of 3 studies, 100%). One study was in Chicago [62], one study was in Spain [37] and one study was in Helsinki [63]. The minimum years of follow up was 3.5 years [37], while the maximum was 10 years [63]. All studies showed a protective association of Mediterranean diet in relation to mobility disability and none of them is statistically significant. Both at fixed effects model and random effects model, a protective pooled effect estimate of Mediterranean diet in physical functioning is observed. The pooled fixed effects estimate was 0.81 (95% C.I. 0.65, 1.01) (**Figure 8.**) while the random effects estimate was 0.81 (95% C.I. 0.65, 1.01) (**Figure 9.**) for the difference in mobility disability between highest vs lowest compliance to Mediterranean diet. There was not significant heterogeneity (I^2 =0 % and chi square p=0.744). The funnel plot (**Supplementary Figure 9**.) and the Egger's test p= 0.370 do not support evidence of small studies effects.

4.3.ii. Other *a priori patterns* and functionality

Apart from the Mediterranean diet, the other dietary patterns included in this meta-analysis were as follows: One study referred to Dietary Approaches Stop Hypertension (DASH diet) and to MED-DASH Intervention Neurodegenerative Delay (MIND diet) [62], one study referred to dietary guideline diet score and to recommended food diet score [56], one study referred to Nordic diet [63], two studies referred to alternative healthy eating [17, 54], one study referred to total diet score [38] and one study referred to healthy diet and to elderly diet [15]. Total Diet score reflects the extent to the adherence to Australian dietary guidelines. The construction rule of dietary patterns for each study are shown in **Table 1a**.

4. 4. Meta-Analysis of a priori Dietary patterns and Functionality overall

Overall, a protective effect estimate is observed irrespective of the type of functionality. Both at fixed effects model and random effects model, a protective pooled effect estimate of healthy dietary patterns in relation to overall functionality is observed. The pooled fixed effects estimate was 0.86 (95% C.I. 0.83, 0.89) (**Figure 6.**) while the random effects estimate was 0.82 (95% C.I. 0.75, 0.90) (**Figure 7.**) for overall functionality comparing participant with the highest vs lowest compliance to healthy dietary patterns.

4.5. *A posteriori* patterns and functionality

From the search three studies were found that assessed a posteriori patterns with 17,342 participants. The median mean age of the participants was 68.4 years. Two studies were in both sexes (2 of 3 studies, 66,7%) [11, 60] and one study was only in men (1 of 3 studies, 33.3%) [15]. One study was in Japan [11], one study was in Spain [60] and one study was in England 15]. The minimum years of follow up was 3 years [60], while the maximum was 15 years [15]. The first study assessed High-fat / low fiber pattern, prudent pattern, high-sugar pattern in relation to mobility limitation [15]. The second study assessed Japanese pattern, animal food pattern, high dairy pattern in relation to incident functional disability through LTCI certification [11]. A community-based study has shown that levels of LTCI certification are well correlated with ability to perform activities of daily living (ADL) [66]. So, we concluded that this study assess the ADL ability. The third study concerned empirical inflammatory diet pattern through Empirical Inflammatory Diet Index (EDII) in relation to physical functioning [60]. We decided that meta-analyses could be conducted investigating the potential association of an “unhealthy” dietary pattern with functionality. We conducted several meta-analyses in order to make all the possible combinations of the dietary patterns of the three studies and data that referred to prudent pattern and Japanese pattern were excluded. As regards to outcomes, we followed a specific strategy. In cases, where the outcome was one that referred to physical functioning, this was the one that was included in meta-analysis. Otherwise, priority was given to outcomes that referred to mobility disability and in third place priority is given to functionality in a daily environment. All outcomes were considered as overall functionality.

4.5.i. High fat/low fibre - Animal food- empirical inflammatory diet

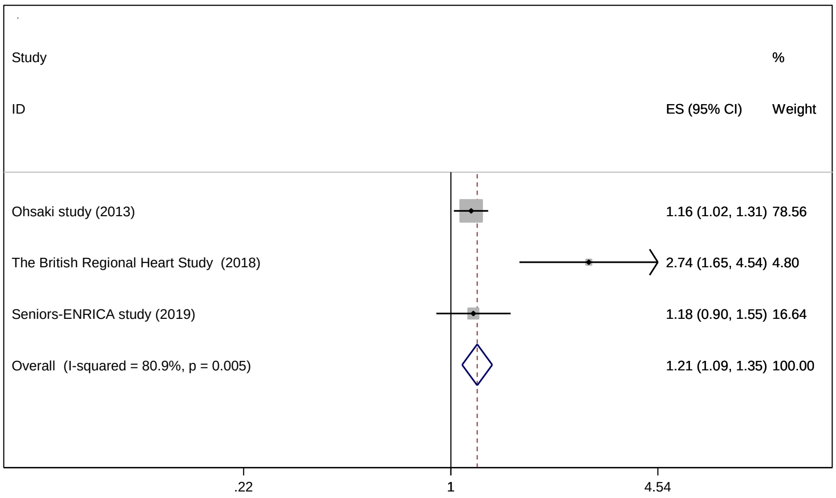

Figure 10. Forest plot for the association between A posteriori Dietary patterns (High fat/low fibre, animal food, empirical inflammatory diet) and Functionality. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate**.**

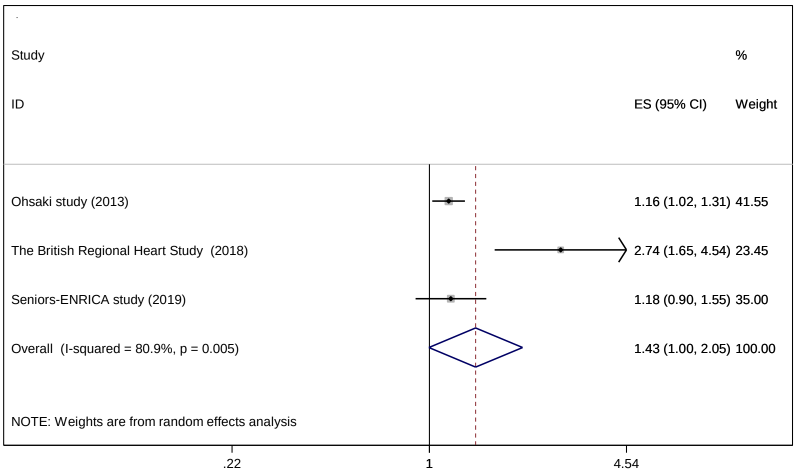

Figure 11. Forest plot for the association between A posteriori Dietary patterns (High fat/low fibre, animal food, empirical inflammatory diet) and Functionality. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate.

In this analysis, one study assessed high fat pattern in mobility disability, one study assessed animal food pattern in ADL and one study assessed empirical inflammatory diet in physical functioning. Both at fixed effects model and random effects model, a non protective pooled effect estimate of the a posteriori dietary patterns in functionality is observed. The pooled fixed effects estimate was 1.21 (95% C.I. 1.09, 1.35) (**Figure 10.)** while the random effects estimate was 1.43 (95% C.I. 1.00, 2.05)

(**Figure 11.**) for the difference in functionality between highest vs lowest compliance to an unhealthy diet. There was significant heterogeneity (I^2 =80.9 % and chi square p=0.005).

4.5.ii. High dairy- high fat/low fibre –empirical inflammatory diet

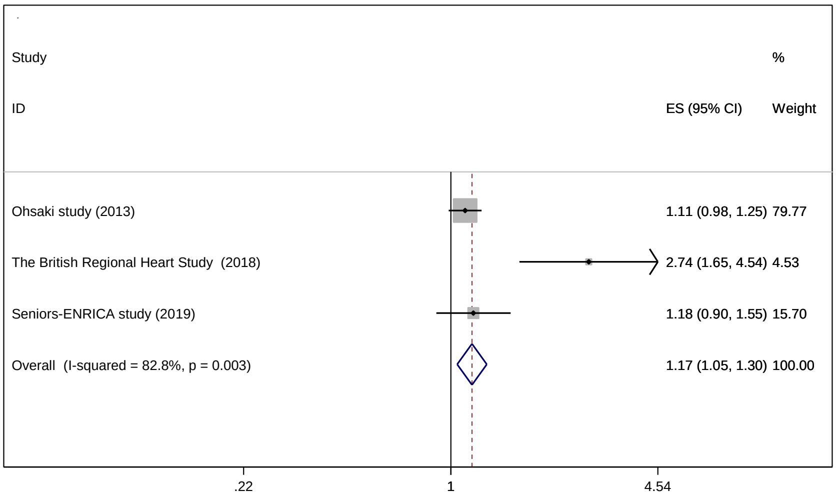

Figure 12. Forest plot for the association between A posteriori Dietary patterns (High dairy, High fat/low fibre, empirical inflammatory diet) and Functionality. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate.

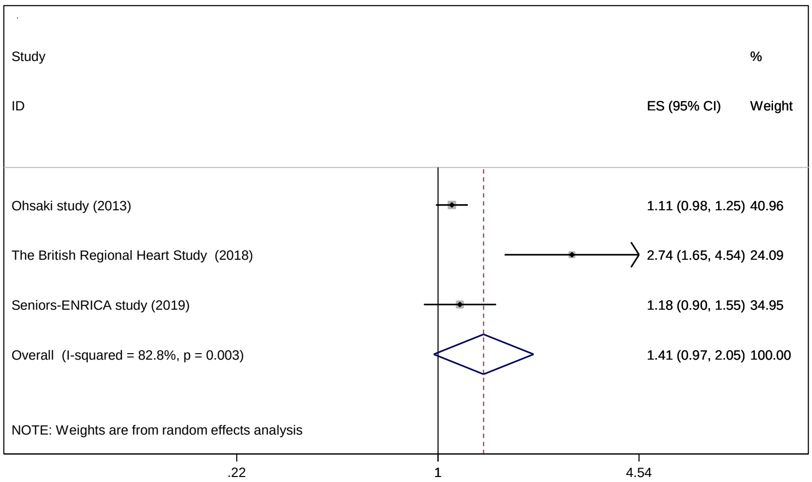

Figure 13. Forest plot for the association between A posteriori Dietary patterns (High dairy, High fat/low fibre, empirical inflammatory diet) and Functionality. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate.

In this analysis, one study assessed high fat pattern in mobility disability, one study assessed high dairy pattern in ADL and one study assessed empirical inflammatory diet in physical functioning. Both at fixed effects model and random effects model, a non protective pooled effect estimate of the a posteriori dietary patterns in functionality is observed. The pooled fixed effects estimate was 1.17 (95% C.I. 1.05, 1.30) (**Figure 12.)** while the random effects estimate was 1.41 (95% C.I. 0.97, 2.05) (**Figure 13.**) for the difference in functionality between highest vs lowest compliance to an unhealthy diet. There was significant heterogeneity (I^2 =80.9 % and chi square p=0.005).

4.5.iii. Animal food-High sugar – empirical inflammatory diet

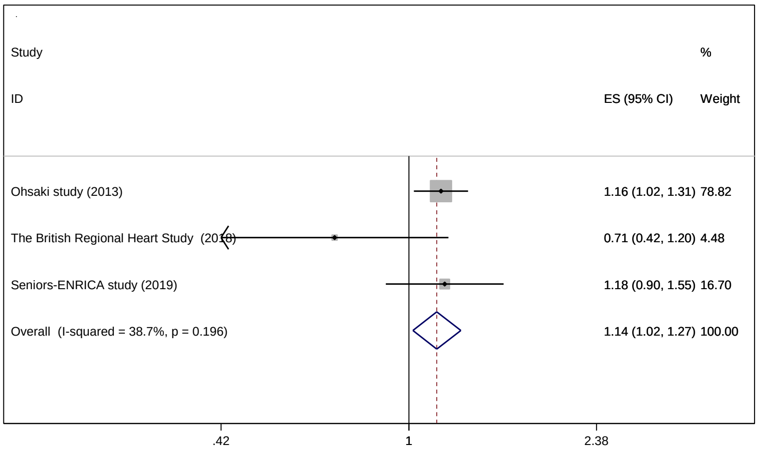

Figure 14. Forest plot for the association between A posteriori Dietary patterns (Animal food, High sugar, empirical inflammatory diet) and Functionality. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate.

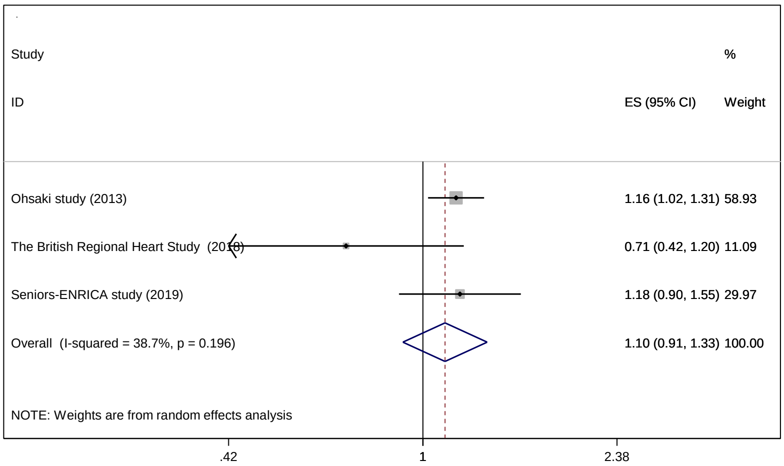

Figure 15. Forest plot for the association between A posteriori Dietary patterns (Animal food, High sugar, empirical inflammatory diet) and Functionality. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate**.**

In this analysis, one study assessed high sugar pattern in mobility disability, one study assessed animal food pattern in ADL and one study assessed empirical inflammatory diet in physical functioning. Both at fixed effects model and random effects model, a non protective pooled effect estimate of the a posteriori dietary patterns in functionality is observed. The pooled fixed effects estimate was 1.14 (95% C.I. 1.02, 1.27) (**Figure 14.)** while the random effects estimate was 1.10 (95% C.I. 0.91, 1.33) (**Figure 15.**) for the difference in functionality between highest vs lowest compliance to an unhealthy diet. There was not significant heterogeneity (I^2 =38.7 % and chi square p=0.196).

4.5.iv. High dairy – high sugar – empirical inflammatory diet

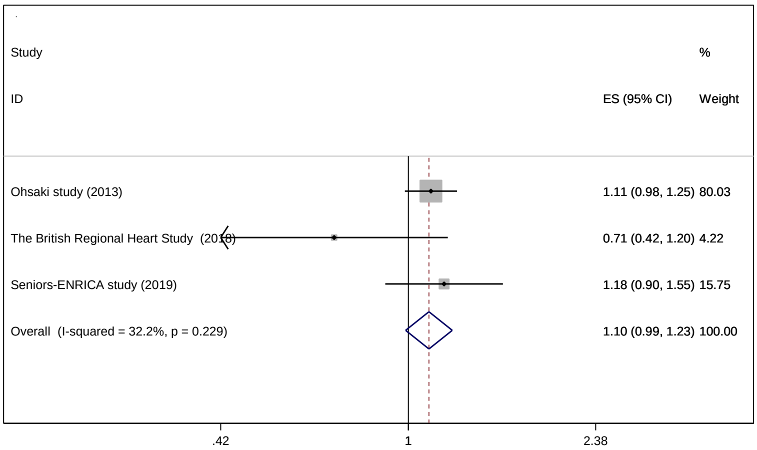

Figure 16. Forest plot for the association between A posteriori Dietary patterns (High dairy, High sugar, empirical inflammatory diet) and Functionality. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate.

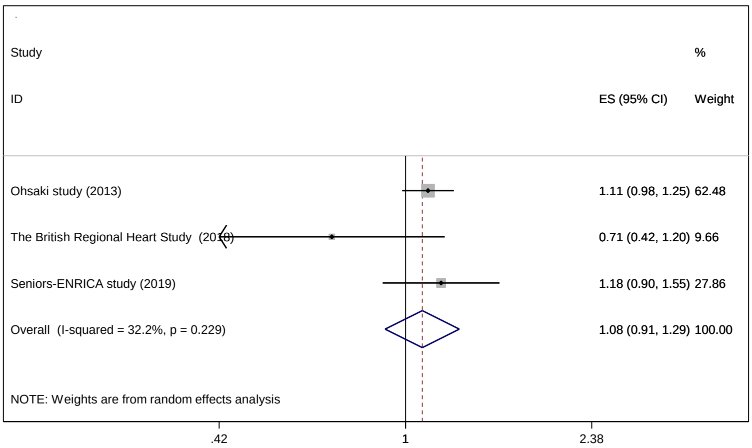

Figure 17. Forest plot for the association between A posteriori Dietary patterns (High dairy, High sugar, empirical inflammatory diet) and Functionality. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate.

In this analysis, one study assessed high sugar pattern in mobility disability, one study assessed high dairy pattern in ADL and one study assessed empirical inflammatory diet in physical functioning. Both at fixed effects model and random effects model, a non protective pooled effect estimate of the a posteriori dietary patterns in functionality is observed. The pooled fixed effects estimate was 1.10 (95% C.I. 0.99, 1.29) (**Figure 16.)** while the random effects estimate was 1.08 (95% C.I. 0.91, 1.29) (**Figure 17.**) for the difference in functionality between highest vs lowest compliance to an unhealthy diet. There was not significant heterogeneity (I^2 =32.2 % and chi square p=0.229).

4.6. Meta-Analysis of Food Groups and Functionality

In the analyses: i) vegetables and functionality, ii) fruits and functionality and iii) alcohol and functionality, 4 studies were included with 70,012 participants. Three studies assess the exposure of interest in physical functioning [17, 37, 54] and one study assess the exposure of interest in mobility limitation [63]. The outcomes were considered as overall functionality. The mean age of the participants was 58.64 years, while the median mean age was 64.6 years. Two studies were in both sexes (2 of 4 studies, 50%) [37, 63], one study was only in men (1 of 4 studies, 25%) [54] and one study was only in women (1 of 4 studies, 25%) [17]. Two studies were conducted in USA [17, 54], one study in Spain [37] and one study in Norway [63]. The minimum years of follow up was 3.5 years [37], while the maximum years of follow up was 18 years [17].

4.6.i. Vegetables and functionality

Both at fixed effects model and random effects model, a protective pooled effect estimate of vegetables in overall functionality is observed. The pooled fixed effects estimate was 0.95 (95% C.I. 0.91, 0.99) (**Figure 18.**) while the random effects estimate was 0.94 (95% C.I. 0.88, 1.01) (**Figure 19.**) for the difference in overall functionality comparing individuals consuming the highest vs lowest category of vegetable consumption. There was not significant heterogeneity (I^2 =13.2 % and chi square p=0.326). The funnel plot (**Supplementary. Figure 19**.)

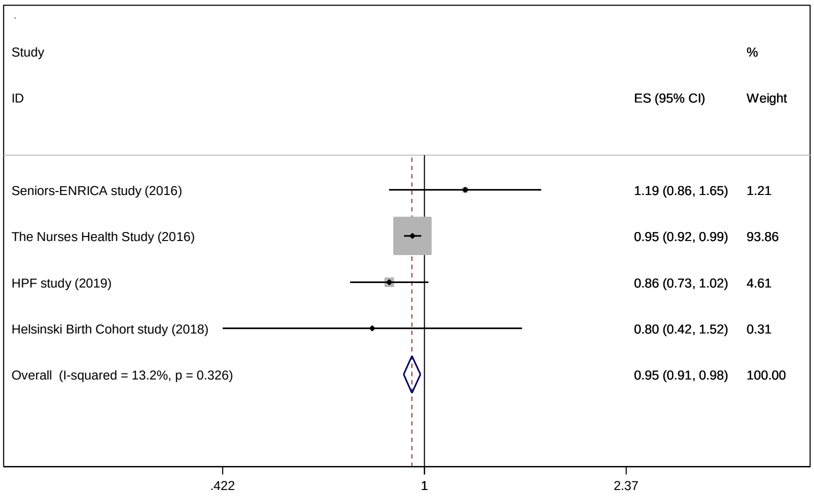

Figure 18. Forest plot for the association between Vegetables and Functionality. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate.

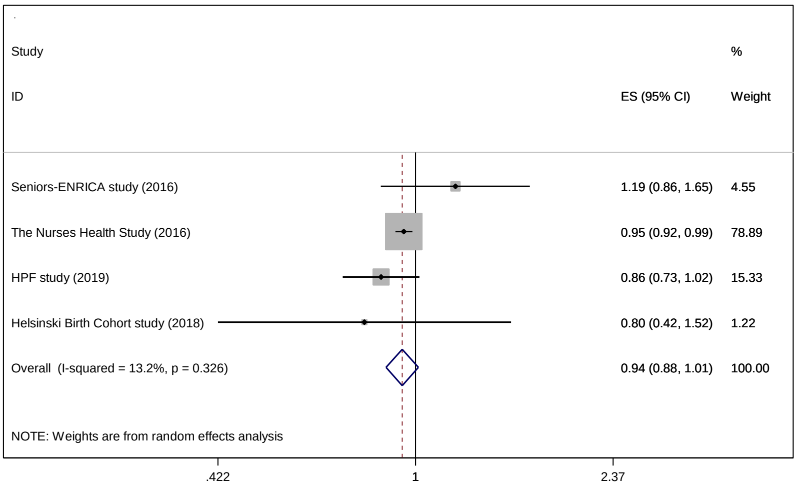

Figure 19. Forest plot for the association between Vegetables and Functionality. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate.

4.6.ii. Fruits and functionality

Three out of four studies assess the association of fruits in relation to physical functioning and one study assessed the association of fruits and nuts in relation to mobility limitation. Both exposures were considered as fruit. Both at fixed effects model and random effects model, a protective pooled effect estimate of fruits in overall functionality was observed. The pooled fixed effects estimate was 0.93 (95% C.I. 0.90, 0.97) (**Figure 20.**) while the random effects estimate was 0.85 (95% C.I. 0.71, 1.03) (**Figure 21.**) for the difference in overall functionality between highest vs lowest consumption to fruits. There was significant heterogeneity (I^2 =65.6 % and chi square p=0.033).

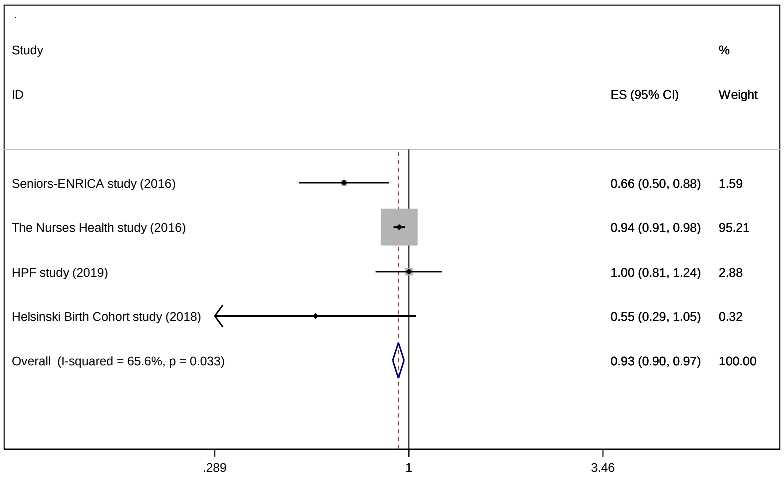

Figure 20. Forest plot for the association between Fruits and Functionality. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate.

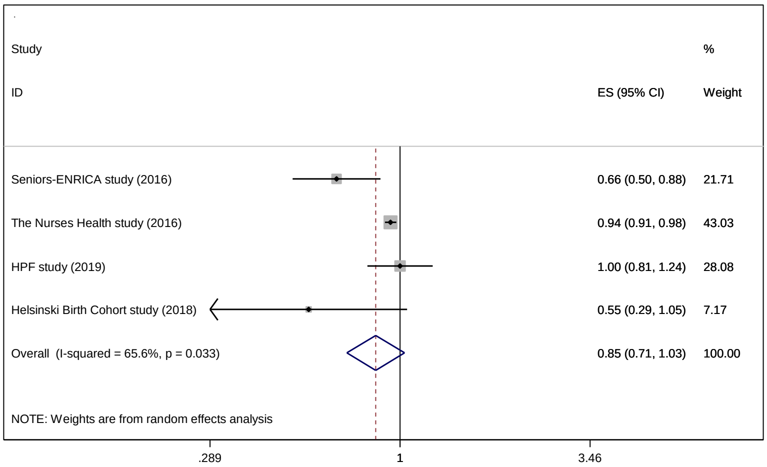

Figure. 21. Forest plot for the association between Fruits and Functionality. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate.

4. 6. iii. Alcohol – functionality

Two out of four studies assessed the association of alcohol in relation to physical functioning, one study assess the association of wine in physical functioning and one study assess the association of alcohol in mobility limitation. All exposures were considered as alcohol. Both at fixed effects model and random effects model, a protective pooled effect estimate of alcohol in overall functionality is observed. The pooled fixed effects estimate was 0.92 (95% C.I. 0.89, 0.95) (**Figure 22.**) while the random effects estimate was 0.89 (95% C.I. 0.77, 1.02) (**Figure 23.**) for the difference in overall functionality between highest vs lowest consumption of alcohol. There was not significant heterogeneity (I^2 =42.0 % and chi square p=0.160).

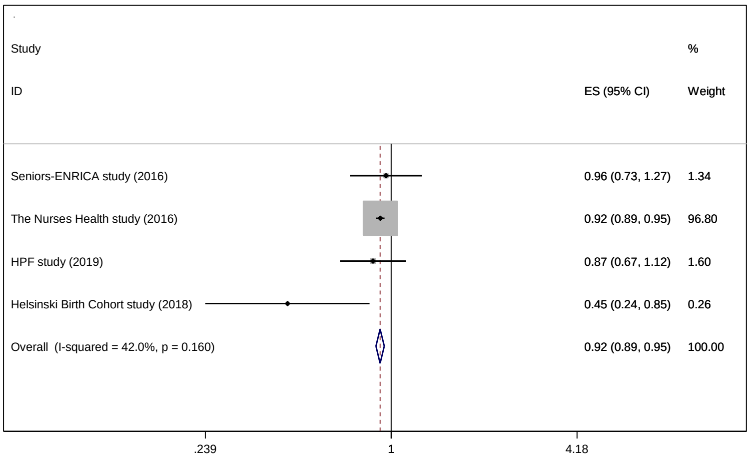

Figure. 22. Forest plot for the association between Alcohol and Functionality. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate.

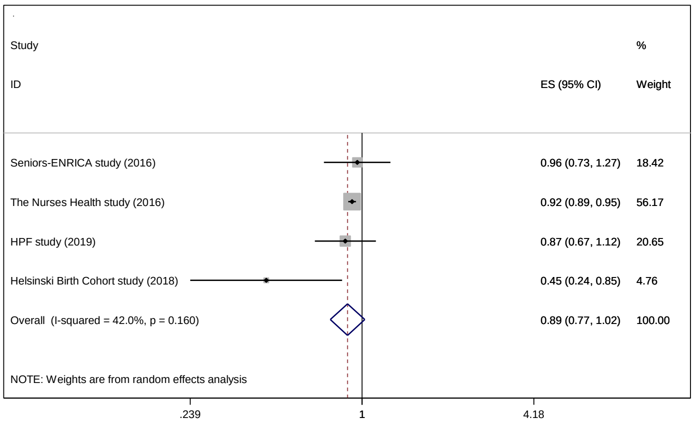

Figure. 23. Forest plot for the association between Alcohol and Functionality. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate.

4.6.iv. Sugar-sweetened beverages and Functionality

In this analysis 3 studies were included with 69,050 participants. The median mean age of participants was 68.1 years. One study assess the association of sugar-sweetened or carbonated beverages in physical functioning [37], one study assess the effect of sugar-sweetened beverages in physical functioning [17] and one study assess the association of sugar sweetened beverages or fruit juice in physical functioning [54]. The outcomes were considered as physical functioning while the exposures are considered as sugar-sweetened beverages. One study was in both sexes (1 of 3 studies , 33.33%) [37], one study was only in men (1 of 3 studies, 33.33%) [54] and one study was only in women (1 of 3 studies, 33.33%) [17]. Two studies were conducted in USA [17, 54] and one study in Spain [37]. The minimum years of follow up was 3.5 years [37], while the maximum years of follow up was 18 years [17]. Both fixed and random effects model did not found any association between sugar sweetened beverages and physical functioning. The pooled fixed effects estimate was 1.07 (95% C.I. 1.03, 1.10) (**Figure 24.**), while the random effects estimate was 0.93 (95% C.I. 0.72, 1.19) (**Figure 25.**) for the difference in physical functioning between highest vs lowest compliance to sugar sweetened beverages. There was significant heterogeneity (I^2 =82.8 % and chi square p=0.003).

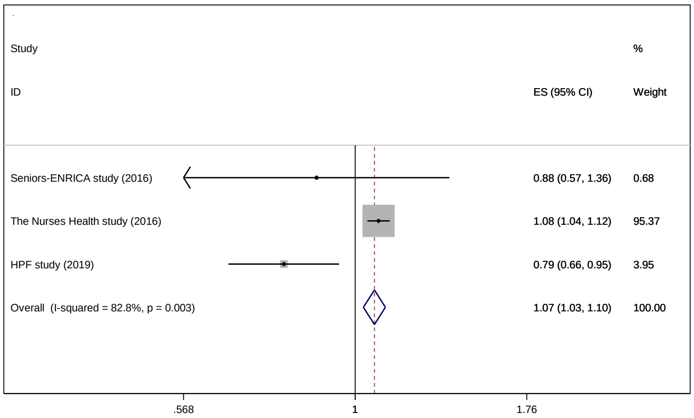

Figure. 24. Forest plot for the association between Sugar sweetened beverages and Functionality. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate.

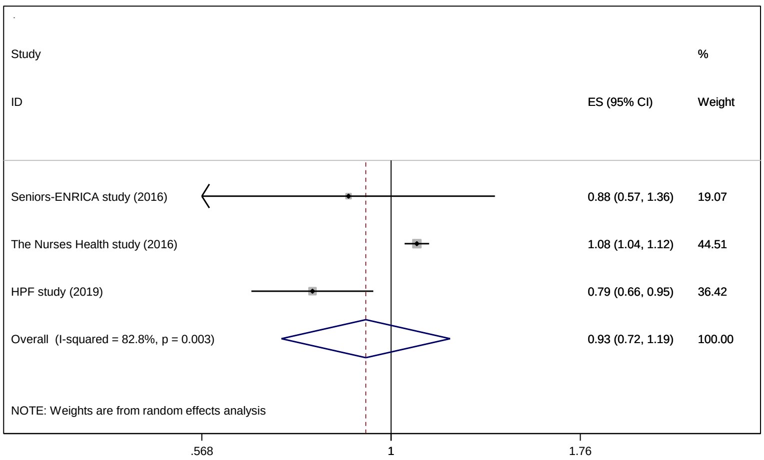

Figure. 25. Forest plot for the association between Sugar sweetened beverages and Functionality. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate.

4. 6. v. Red and processed meat and Functionality

In this analysis 5 studies were included with 72,994 participants. The median mean age of participants was 68.1 years. One study assess the effect of red meat, hamburger or sausage in physical functioning [37], two studies assess the effect of red and processed meat in physical functioning [17, 54], one study assess the association of total meat (of all kinds) in relation to mobility limitation [63] and one study assess the association of red meat in lower-extremity function [61]. The outcomes are considered as overall functionality while the exposures are considered as red and processed meat. Three studies were in both sexes (3 of 5 studies, 60%) [37, 61, 63], one study was only in men (1 of 5 studies, 20%) [54] and one study was only in women (1 of 5 studies, 20%) [17]. Two studies were conducted in USA [17,54], two studies in Spain [61] and one study in Norway [63]. The minimum years of follow up was 3.5 years [37], while the maximum years of follow up was 18 years [17]. Both at fixed effects and random effects model a protective pooled effect estimate of red and processed meat in overall functionality is observed. The pooled fixed effects estimate was 0.97 (95% C.I. 0.94, 0.99) (**Figure. 26.**), while the random effects estimate was 0.97 (95% C.I. 0.94, 0.99) (**Figure. 27.**) for the difference in overall functionality between highest vs lowest compliance to red and processed meat. There was not significant heterogeneity (I^2 =0 % and chi square p=0.629). The funnel plot (**Supplementary Figure 27**.) and the Egger's test p= 0.373 do not support evidence of small studies effects.

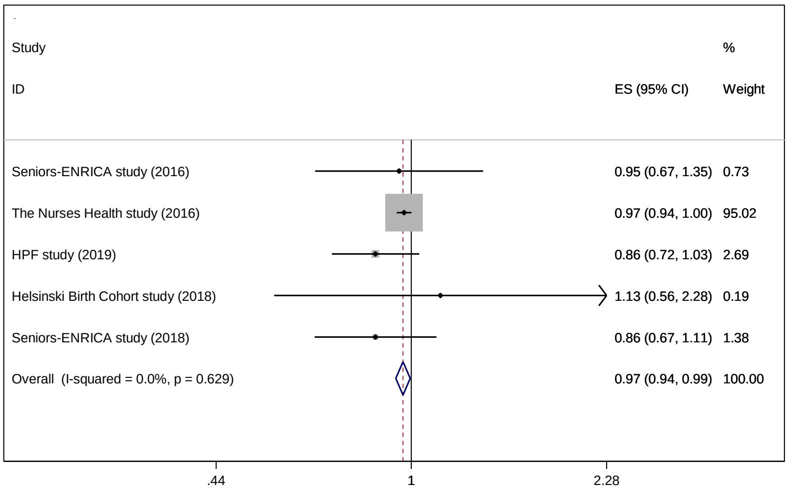

Figure. 26. Forest plot for the association between Red and Processed meat and Functionality. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate.

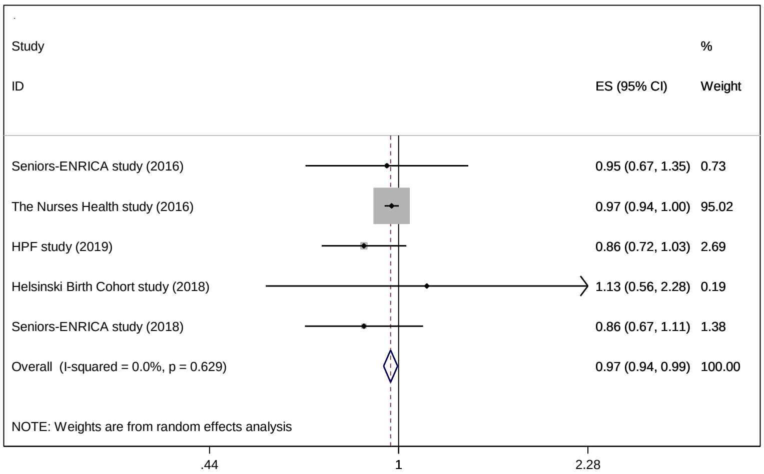

Figure 27. Forest plot for the association between Red and Processed meat and Functionality. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate.

4.6.vi. Nuts and Physical functioning

In this analysis 4 studies were included with 70,015 participants. The median mean age of participants was 68.5 years. Two studies assess the effect of nuts in physical functioning [37, 57] and two studies assess the effect of nuts and legumes in physical functioning [17, 54]. The exposures are considered as nuts. Two studies were in both sexes (2 of 4 studies, 50%) [37, 57], one study was only in men (1 of 4 studies, 25%) [54] and one study was only in women (1 of 4 studies, 25%) [17]. Two studies were conducted in USA [17, 54] and two studies in Spain [37, 57]. The minimum years of follow up was 3.5 years [37], while the maximum years of follow up was 18 years [17]. At fixed effects model a non protective pooled effect estimate of nuts in physical functioning is observed, while at random effects model a protective pooled effect estimate of nuts in physical functioning is observed. The pooled fixed effects estimate was 1.04 (95% C.I. 1.00, 1.08) (**Figure. 28.**), while the random effects estimate was 0.87 (95% C.I. 0.71, 1.07) (**Figure. 29.**) for the difference in physical functioning between highest vs lowest compliance to nuts. There was significant heterogeneity (I^2 =78.9 % and chi square p=0.003). The funnel plot (**Supplementary Figure 29**.) and the Egger's test p= 0.012 do not support evidence of small studies effects.

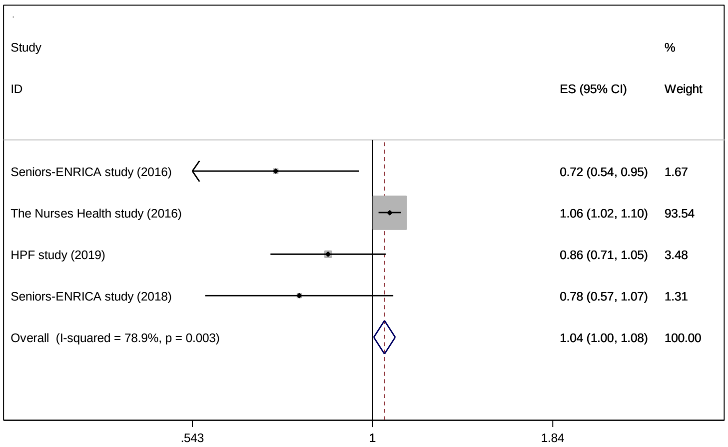

Figure 28. Forest plot for the association between Nuts and Physical Functioning. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate.

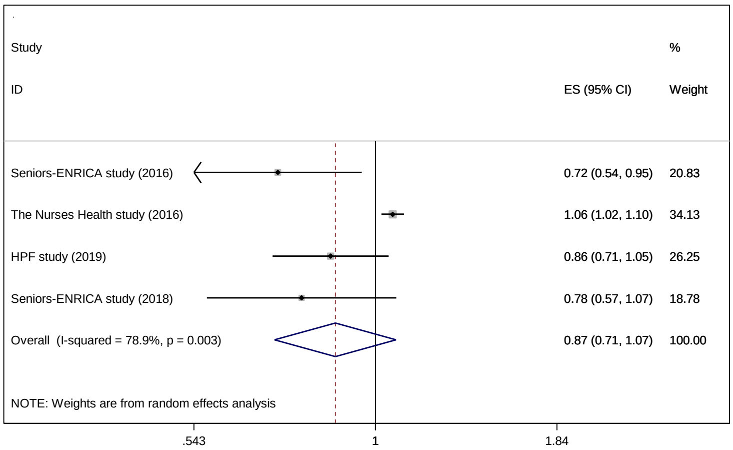

Figure. 29. Forest plot for the association between Nuts and Physical Functioning. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate.

4.6.vii. Other food groups and functionality

One study that assessed the coffee consumption, one study that assessed green tea consumption and one study that assessed dairy were excluded. As the studies included in the analyses concerned, two studies had as outcome of interest fish or seafood or whole grains.

4.7. Subgroup analysis

4.7.i. By sex

The sensitivity analysis revealed that differences in sex had not a significant impact on the associations between healthy dietary patterns and functionality. Not only both at fixed effects model and random effects model, but also both in men and women, a protective pooled effect estimate of healthy dietary patterns in functionality is observed. We can observe that men have lower risk on having a disability in functionality than women. The pooled fixed effects estimate for men was 0.79 (95% C.I. 0.70, 0.89) while for women was 0.87 (95% C.I. 0.84, 0.90) **(Figure 30.)** At random effects model, the pooled estimate for men was 0.81 (95% C.I. 0.64, 1.02) while for women was 0.90 (95% C.I. 0.71, 1.14) (**Figure 31.**) but were not statistically significant different (P>0.10)

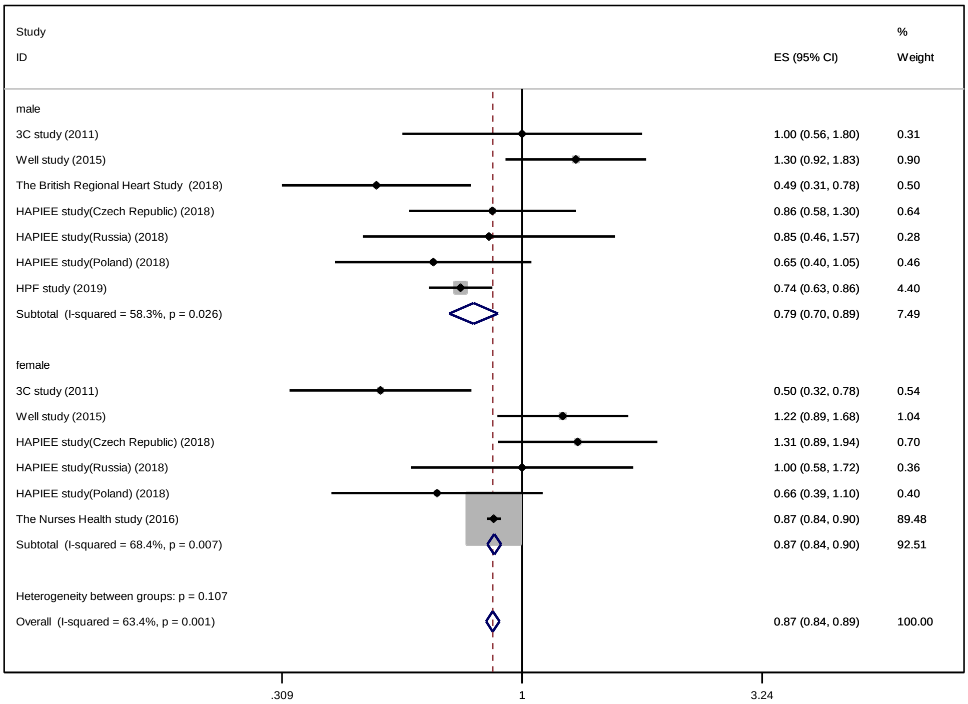

Figure. 30. Forest plot for showing the differences in sexes for the association between a priori healthy dietary patterns and functionality. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate.

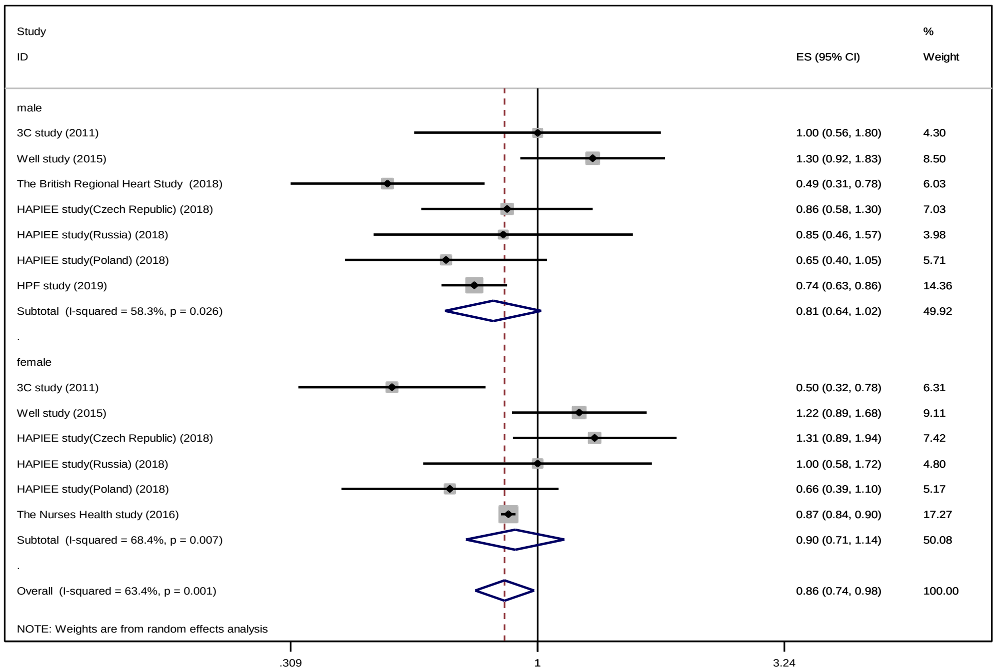

Figure 31. Forest plot for showing the differences in sexes for the association between a priori healthy dietary patterns and functionality. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate.

4.8.ii. Sensitivity analysis the Nurses' Health Study excluded

The Nurses' Health Study began in 1976 and the study population is 54762 female registered nurses in the age from 30 to 55. The nurses completed a mailed questionnaire on their health and lifestyle. In this study evaluated the effect of diet, through AHEI-2010 score in physical functioning. Physical functioning was assessed via the SF-36 questionnaire. The follow up was 18 years [17]. The size of the study sample in combination with the large follow up time range have as a result this study have much bigger weight in all analyses was included than the rest of the studies. For this reason we conducted a sensitivity analysis excluding The Nurses' Health Study.

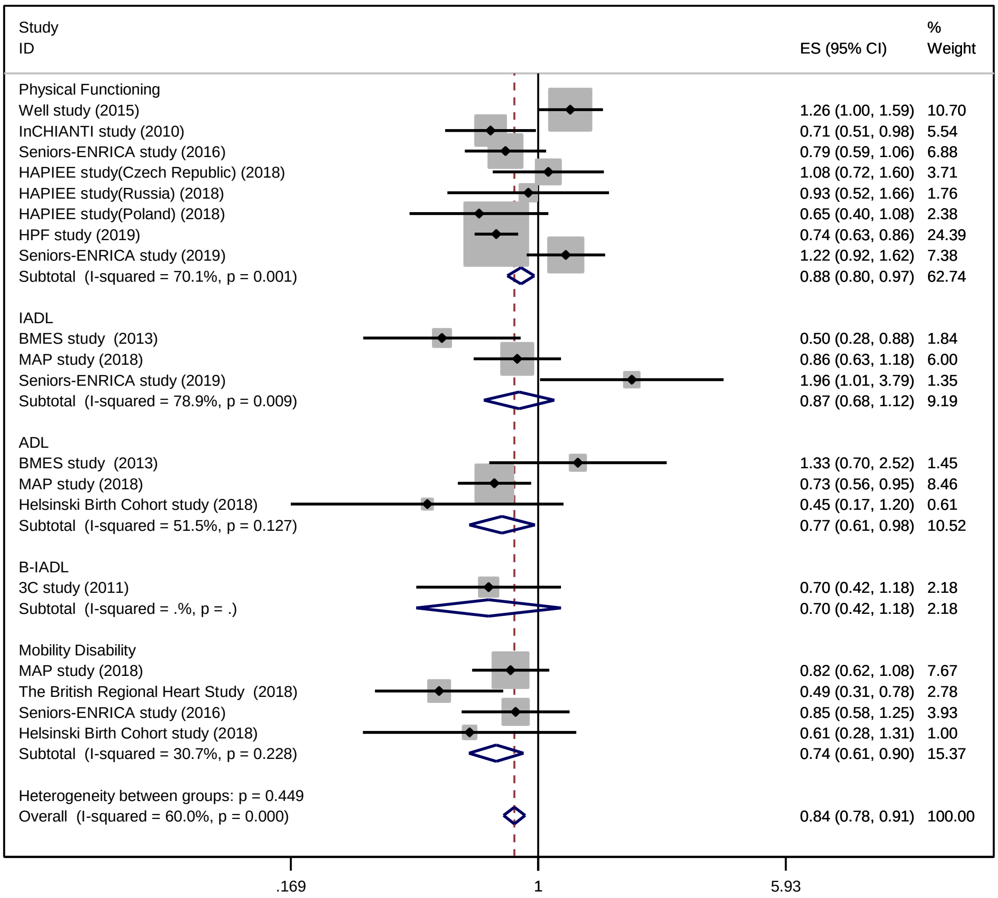

Figure. 32. Forest plot for the association between a priori healthy dietary patterns and functionality, Nurses' Health Study excluded. Results from fixed effects models. CI: Confidence Interval, ES: Effect Estimate, ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, B-IADL: Basic and Instrumental Activities of Daily Living.

The sensitivity analysis revealed that excluding The Nurses' Health Study had not a tremendous impact on the associations between healthy dietary patterns and physical functioning. The pooled fixed effects estimate is 0.88, (95 % C.I. 0.80, 0.97, I^2=70.1%) (**Figure. 32.**) for the difference in physical functioning between highest vs lowest compliance to a healthy diet**,** while the former was 0.87, (95 % C.I. 0.84, 0.90) (**Figure. 6.**) The Nurses' Health Study included. At random effects model, the estimate was 0.91, (95 % C.I. 0.74, 1.10, I^2=70.1%) (**Figure. 33.**) for the difference in physical functioning between highest vs lowest compliance to a healthy diet, while the former was 0.86, (95 % C.I. 0.76, 0.99, I^2=61.1%) (**Figure. 7.**) the Nurses' Health Study included. In addition, as the overall functionality concerned, the pooled fixed effects estimate is 0.84, (95 % C.I. 0.78, 0.91, I^2=60%) (**Figure. 32.**) for the difference in functionality between highest vs lowest compliance to a healthy diet**,** while the former was 0.86, (95 % C.I. 0.83, 0.89, I^2=47.3%) (**Figure. 6.**) the Nurses' Health Study included. At random effects model, the estimate was 0.84, (95 % C.I. 0.73, 0.96, I^2=60%) (**Figure. 33.**) for the difference in functionality between highest vs lowest compliance to a healthy diet, while the former was 0.82, (95 % C.I.

0.75, 0.90, I^2=47.3%) (**Figure. 7.**) The Nurses' Health Study included. We conclude, that despite the weight of The Nurses' Health Study on the analyses, the pooled HRs are not modified.

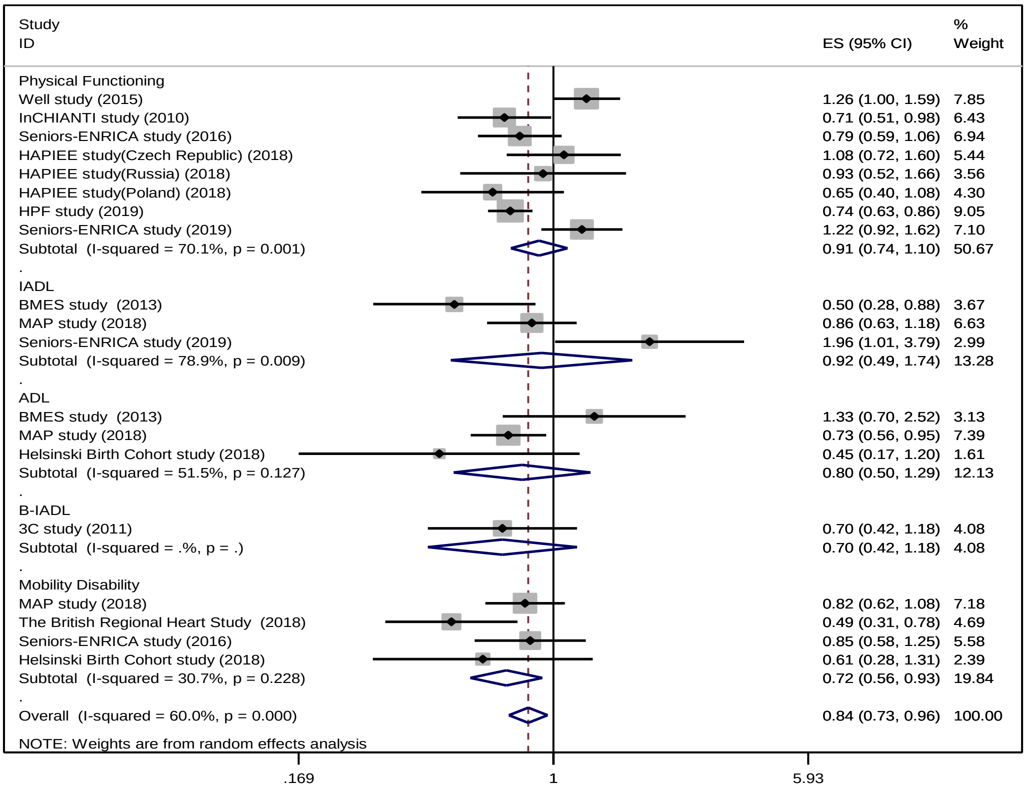

Figure. 33. Forest plot for the association between a priori healthy dietary patterns and functionality, Nurses' Health Study excluded. Results from random effects models. CI: Confidence Interval, ES: Effect Estimate, ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, B-IADL: Basic and Instrumental Activities of Daily Living.

4.9. Risk of Bias on Selected Studies

The quality scores ranged from 4 to 6, indicating a moderate quality of studies. However, given the complex nature of the nutrition as exposure and regarding the domain of selection of participants, we consider that 14 out of 15 studies, ranging from 5 to 6, fulfill the criteria of low risk of bias. One study is considered as a study of moderate quality. Taken together, all studies were deemed satisfactory. The sum score of the quality assessment is shown in **Supplementary Table 1**.

Chapter 5. Discussion

5.1. Interpretation of findings

We have summarized the available evidence regarding the association of dietary patterns and food groups with functionality in adults. The findings of this analysis indicate that individuals with a higher adherence to healthy dietary patterns show better functionality, in comparison to those with a lower adherence, irrespective of their sex. The results are consistent, even in the case of examining only the Mediterranean diet, as an exposure. As far as food groups are concerned, vegetables, fruits, alcohol, red and processed meat were associated with better overall functionality. No association was found for sugar-sweetened beverages in relation to functionality. To date, reviews investigating relationships between dietary patterns and health in older people have focussed on mortality and chronic disease outcomes such as cardiovascular disease and diabetes [34]. In our review, we decided to study functionality impairment, an outcome not as extensively studied so far. To our knowledge, this is the first systematic review of dietary patterns and food groups with any type of functionality.

Overall, there is a small body of mainly cross-sectional studies suggesting a possible relationship between healthier diets and better overall functionality or a specific domain of functionality in older people, although, on the whole, the current evidence is fairly weak. Most of them are referring to the Mediterranean diet. In general, "healthier" diets are characterized by greater fruit and vegetable consumption, greater consumption of wholemeal cereals and oily fish, which indicate higher intakes of a range of nutrients and dietary constituents that have been associated with lower risk of chronic disease and better survival [36].

Referring to mobility disability, this review provides support for a relationship between dietary patterns and outcomes referred to mobility longitudinally. There have been no published reviews of the literature on dietary patterns and mobility disability to date. Among cross-sectional analyses, participants from the US NHANES showed that the Mediterranean diet was associated with significantly higher walking speed, a sensitive marker of mobility [37]. Previous longitudinal analyses suggested that higher adherence to the Mediterranean diet leads to a slower decline in walking speed and lower body mobility significantly [37]. There were four out of fifteen studies in our study that reported a protective relationship between a priori indices of adherence to a particular diet and better mobility using report- based measures. Tessa J. Parsons et al. found that among individuals with high-quality diet scores as predefined dietary quality scores, a lower risk of mobility limitation was seen in terms of difficulty walking 400 yards or going up- or downstairs 15 years later [15]. Two studies prospectively examining this relationship through multiple dietary indices found positive associations using Mediterranean diet score (MDS), healthy Nordic diet score (NDS), Dietary Approaches to Stop Hypertension score(DASH) and Mediterranean- DASH Intervention for Neurodegenerative Delay score (MIND) [62, 63]. Parallel, one study investigated the particular association between a posteriori dietary pattern and mobility disability and this should be investigated more in future studies [15].

Of the studies in this current review, physical functioning was the most commonly assessed outcome. There were six out of eight studies relevant in this outcome that reported an inverse association of healthier diets and physical functioning. Regarding to AHEI diet pattern, two studies in our review indicated a strong association of this pattern with the physical function [17, 54]. Focusing on the most usually examined dietary pattern, a higher adherence to the Mediterranean diet is shown to be associated protectively with a better quality of life, including physical functioning and a lower likelihood of impairment in overall physical functioning [37, 38, 56, 62]. In Australia, people of both sexes with better quality diets (RFS, DGI, MDS) report better physical functioning [56]. The results are consistent, concerning the reviews that investigated this relationship [34, 36, 43, 44]. Most reviews focused on domains or states of health that include physical functioning, such as sarcopenia [36, 41], healthy aging [34] or frailty [42]. Each of them supports the beneficial role of the "healthier" diets on physical performance and levels of physical activity. Moreover, similar results are observed in reviews engaged either in the Mediterranean diet either in micronutrients related to the Mediterranean diet as exposures [43, 44]. Among cross-sectional analyses, in the Nurses' Health study, a higher concordance to the Mediterranean diet was related to a lower likelihood of limitations in physical function, measured based on mobility questions from SF-36. In the Spanish population, higher adherence in the Mediterranean diet was associated with higher scores in the physical component of the SF-12 in men, but not in women. Taken together, prior studies support the protective effects of the Mediterranean diet, with better physical functioning, including lower body function and mobility observed across the studies, suggesting that higher adherence to a high quality diet may be 'myoprotective' in older adults. However, the literature remains limited.

As far as disabilities in a daily environment are concerned, the risk of developing ADL and IADL disabilities is lower in individuals following a high-quality diet. Our results indicate that healthy dietary patterns, such as MIND, DASH, Mediterranean diet and Nordic diet were associated with a lower likelihood of developing self- reported domains of disability [38, 62, 63]. A prospective study conducted in French elderly showed an inverse association between adherence to Mediterranean diet and risk of B-IADL in women and no association in men [12]. Our results are consistent with prior studies. A US cross-sectional study showed an association between Health Eating Index and IADL [38].

Two out of 15 studies investigated the relationship of empirically derived dietary patterns and any type of functionality. Greater adherence to the high-fat/ low-fibre pattern was associated with a higher risk of mobility limitation [15]. On the other hand, the Japanese pattern was associated with a decreased risk of incident functional disability [11]. No associations were seen for the prudent dietary pattern, the high- sugar pattern, the animal food pattern or the high dairy pattern [11, 15]. The Japanese pattern, as reported, has some similarities with healthy a priori dietary patterns, such as the Mediterranean diet and Healthy Eating Index, although there are some differences, mainly in the energy intake, too [11]. To our knowledge, there are no reviews related to data-driven dietary patterns and functionality. Among cross-sectional designs, although we have not found results regarding the grip strength, a prudent pattern of eating was associated with higher grip strength [45] and that is partially explained because the prudent pattern includes fish consumption and fish consumption is associated with grip strength [45]. Helen Martin et al. found that there is an association of the prudent pattern with physical performance in women but not in men [46]. The prudent pattern has many similarities with healthy eating recommendations that are included in a priori dietary patterns, while it is characterized by high consumption of fruit, vegetables, whole-grain cereals and oily fish, but low consumption of white bread, chips, sugar and full-fat dairy products. Our results suggest that there is an association between the unhealthy a posteriori dietary patterns (high fat/low fibre, high dairy/high sugar, empirical inflammatory diet and animal food dietary pattern) and the mobility limitation. However, it is important to underline the heterogeneity of these dietary patterns, as there are many differences between them.

In terms of food components, our review provides support that fruit and vegetable consumption has a protective association with functionality. Given the fact that fruits and vegetables are the basis of the healthy dietary patterns included in the meta-analysis, their positive impact on functionality agrees with the respective results of dietary patterns. In addition, the results are consistent with prior studies. Among prospective studies, higher intake of fruits and vegetables was associated with a lower risk of disability in B-IADL over time, mainly in women [12]. Parallel, nuts are shown to be associated with an increased risk of physical impairment. That is partially consistent with the literature, as Lucia Fernandez et al. suggested that nut consumption in the Spanish population was associated with a lower risk of physical function impairment [57]. This inconsistency may be partially explained by the heterogeneity of populations and the complexity of the functionality as an outcome. The Health Professional Follow- up Study (HPFS) and K.A. Hagan support that greater intake of vegetables, nuts and legumes were considered with lower odds of physical function impairment and better physical function [54]. In our review, a higher habitual consumption of red and processed meat is associated with a lower risk of functional disability. That is not consistent with prior studies. A prospective study conducted in a Spanish population suggested that processed meat is associated with increased risk of impaired agility and lower extremity function and no significant associations between red meat or poultry and physical function were found [61]. However, these inconsistencies can be partially explained by the fact that red meat has been strongly associated with increased mortality. For this reason, it is possible that the actual consumption of red and processed meat not to be reflected enough to reveal a strong impact on physical functioning [61]. To our knowledge, there are no reviews regarding the association of specific food groups and functionality.

It is suggested that the whole diet is a stronger predictor of disability in old age than single foods or nutrients [63]. For instance, the AHEI diet pattern was shown to be more strongly associated with physical functioning than the individual_components or individual foods, although greater intake of vegetables and fruits, moderate alcohol consumption, lower intake of sugar-sweetened beverages, trans fats and sodium were all significantly associated with lower risk of physical impairment [17, 54].

Our results indicate that several potential biological factors may play a role in functionality. Firstly, dietary patterns and dietary guidelines in this review, including the Mediterranean diet and Alternative Healthy Eating, are diets rich in vitamins and other antioxidants. Berries, fruits, nuts, chocolate, vegetables, legumes and whole grains are good dietary sources of antioxidants. Vitamins and antioxidants are reported to be associated with disability. Higher plasma carotenoid levels were found to be protective against the decline in walking speed, the development of walking disability and poor muscle strength. As far as carotenoids are concerned, the six major dietary carotenoids are α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene and constitute an important component of the antioxidant defense system in humans, too. Parallel, higher serum levels of vitamin E, which are included mainly in vegetables, nuts and whole grains, were associated with lower risk of frailty, which affects multiple domains of human functioning, including mobility and muscle strength. Moreover, homocysteine, which is a sensitive marker for a shortage in B vitamins, such as folic acid, is independently related to physical function. Thus, B vitamins may influence physical function through homocysteine levels. Overall, higher intake and plasma levels of antioxidants are correlated protectively with various measures of physical performance and muscle strength [15, 37, 43, 57, 59, 62].

Secondly, aging is known to be related to higher levels of oxidants and free radicals, which lead to oxidative stress. If the amount of free radicals generated outpaces the antioxidant plausible capacity, this imbalance may cause oxidative damage to DNA, proteins and lipids in skeletal muscle, leading to atrophy and loss of muscle tissues. Parallel, oxidative stress is damaging and may foster inflammation. Oxidative stress and inflammation cause also muscle damages and the worsening of degenerative diseases that lead to mobility impairments and difficulties in performing basic and instrumental activities of daily living. Antioxidants contribute to balance the increase in oxidative stress through the shattering of hydroxyl radical and reduction in lipid peroxidation. For this reason, higher adherence to dietary patterns or guidelines that include several antioxidants is associated with lower oxidative stress and a better lipid and inflammatory profile, with lower levels of inflammatory markers. Both of them lead to a reduction in oxidative damage and therefore to a deceleration in the onset of functional limitations [12, 15, 17, 37, 38, 43, 59]. Moreover, a reduction in the accumulation of oxidative damage is associated with a decreased risk of oxidative- related chronic diseases, such as clinical vascular disease or cardiovascular disease. Oxidative- related chronic diseases are strongly related to physical function limitations [17, 54].

As far as other nutrients are concerned, saturated and trans fat, which are in a considerable amount in meat and especially in processed meat, have previously been shown to increase inflammation, which may subsequently reduce physical functioning. Trials showed that nutritional interventions based on the Mediterranean diet significantly reduced the levels of inflammatory markers such as interleukin- 6 and C reactive protein [59, 61].

In our review, we found a significant association with functionality in certain studies and no significant association in other studies. There may be several explanations for this. Firstly, each study has a distinct study population with distinct characteristics that may explain why an association is present or not. Most importantly, the number of years of follow-up and the specific tool of functionality assessment that was applied, may explain why there are differences regarding the results between studies. More research in varied large populations, using the same design and measurement tools, is needed to confirm the presence or absence of associations where we have varying results so far.

Moreover, most studies included in this review used a priori indices, rather than a posteriori or empirical approaches. The reasons that a priori indices are more popular may be explained partially not only due to the variety of the available scores for use but also with the fact that they are relatively easy to use and to interpret, compared to a posteriori approaches. The main advantage of a priori approach lead to the comparability of the findings across study samples, while in an a priori approach is examined whether a sample population is meeting a pre-defined diet according to healthy eating recommendations and in an a posteriori approach the current dietary profiles within a specific sample are reflected, although considerable reproducibility across populations has been indicated [52]. Of the three studies that included an a posteriori approach to diet assessment, all studies derived patterns using a PCA or factor analysis and not cluster analysis, which reflects previous reviews. Ultimately, both approaches can provide valuable information on the relationship between dietary intake and health outcomes [34].

Our results suggest that there is not a difference in the associations under investigation by sex. While overall a significant inverse relationship between the healthy dietary patterns and the functionality is observed, a more protective impact on functionality was observed in men. Overall, our results are partially consistent with prior studies, while there are studies that support a significant protective relationship only in women [12, 45, 46], or they do not support a statistically significant association between the dietary patterns and functionality at all [56, 58]. Moreover, the differences in this association according to gender may be explained by several factors. Some chronic and acute conditions vary on men and women and that may influence the disablement process. Although this is not consistent with our findings, men tend to have a higher incidence of cardiovascular disease that leads to death without prior disability. Therefore, in men the protective effect of a healthy dietary pattern, Mediterranean diet included, may be captured more on mortality than on disability [12].

5.2. Strengths and limitations

This review has several limitations that should be mentioned. Firstly, given the fact that our analysis consists of observational studies, the possibility of residual confounding by other unknown risk or protective factors cannot be ruled out. Particularly, because diet could be a proxy marker for other healthful lifestyle parameters that could influence the quality of life and activities of daily living. Therefore, the results should be interpreted with caution. However, the fact that the associations were adjusted for a wide range of confounders related to the lifestyle characteristics, such as physical activity and body mass index, in all studies significantly reduced the room for potential confounding.

Secondly, in the present analysis, a substantial heterogeneity was observed among the studies. The studies were diverse in terms of the analyzed population size, follow-up duration, baseline age, assessment of diet, dietary indices and scoring approaches, outcome measurements, as well as confounding factors adjusted for in the statistical models. These dissimilarities could potentially contribute to some of the heterogeneity in the results. Although we tried to explore heterogeneity among the studies performing the analysis with random effects, the investigations did not offer sufficient details about the samples. This variation between included studies may have affected the comparability of results. However, as far as the variation between dietary indices and scoring approaches is concerned, the main assumptions of these measures are similar since the "healthiness" of diets is generally characterized by similar foods and intakes, such as high intake of fruits and low intake of dairy products. Also, different dietary assessment methods have been shown to define dietary patterns comparably [66]. Another important limitation was the indication of small study effects such as publication bias.

Lastly, there is potential for measurement error and recall bias in both the dietary assessment and the outcome assessment. Dietary information of all the included studies derives from food frequency questionnaires which represent a subjective approximation of past dietary behaviors rather than an assessment of absolute intakes. It is well known that a general finding in dietary studies is under-reporting of energy intake, and it has been found in both adults and elderly populations. Under-reporting in women is associated with fear of negative evaluation, weight loss history, percentage of energy from fat, or variability in the number of meals per day. Under-reporters usually tend to be less physically active, and they are more likely to dieting [67]. In any case, our results may underestimate true associations. In addition, dietary intakes were measured mostly at baseline and no information was gathered of changes in dietary habits that may have occurred over time. Repeated nutritional assessments could strengthen the results in future studies. Parallel, the vast majority of the studies made use of self-reported information as a proxy for each type of functionality instead of objective measures. Although, most of these questionnaires have been widely used in clinical practice and population studies, these measures might be subject to recall bias and may cause misclassification of disability status. Moreover, given the fact that some studies divided the follow-up duration into two or three waves, functional impairment was evaluated either at the end of the follow up either at the end of each wave of the follow-up. Thus, the temporality and development of impairments during the interval period could not be fully confirmed. For instance, it is a general finding that women usually experience longer disability before death than men. Therefore, more new cases of disability may have been missed in men who have passed away in a disable state between two waves of follow up and never detected.

Despite these limitations, the present study has several strengths. Our major strength is that to our knowledge this is the first systematic review to the topic on whether the diet is associated with the functionality in presumably healthy populations. Another strength is that this review provides evidence for the benefits of healthy diet patterns on outcomes regarding to functionality especially in older people, adding to the existing evidence base that links overall diet quality with health outcomes in later life, including all-cause mortality and chronic disease. No restrictions were placed on the exposure, the outcome and the year of publication. As a result, both the exposure and the outcome have been thoroughly investigated. Regarding to the diet, a priori and a posteriori dietary patterns, dietary guidelines and food groups are examined. As far as functionality is concerned, physical functioning and impairment, mobility limitation and performance-based measurement and disabilities in performing basic and instrumental activities of daily living were taken into account. Moreover, the vast majority of the included studies used widely used, validated FFQs for diet assessment and either validated questionnaires either standardized, objective measures for the assessment of functionality.

Lastly, our analysis consists only of observational prospective studies. This design provided the opportunity to investigate long- term influences of diet on disability and is considered to be the most suited design for nutritional studies regarding long- term health, despite its drawbacks. Although randomized trials of hard endpoints are considered the gold standard of scientific evidence in medicine, it is often impossible to be executed for nutritional questions owing to practical and ethical considerations. Nutritional research examines the effect of a complex, dynamic, and interactive set of exposures, as it is the human diet, on disease endpoints. Especially, when the outcome of interest has, also, a long etiologic period, as it is the functionality, the nutritional comparison would be practically infeasible in an interventional setting, as it is often followed with a considerable noncompliance and drop out. To that point, observational studies can be a valuable resource. Particularly, long-term prospective cohort studies are the strongest observational study design, as their prospective nature makes them less susceptible to reverse causation, recall bias, and selection bias, commonly found in retrospective or cross-sectional studies [68].

5.3. Conclusions

Taken together, this systematic review attempts to address a gap in the available literature related to dietary patterns and food groups and their association with each type of functionality impairment and more broadly with the overall physical functioning. The findings of this meta-analysis indicate that individuals with a higher adherence to healthy diets, such as Mediterranean diet, show a better functionality, in comparison to those with the lower adherence. In particular, all "healthy" dietary patterns had some common characteristics, such as high amount of fruit, vegetables and fish, moderate alcohol and small amounts of meat and dairy products. Despite the fact that the whole diet is a stronger predictor of disability in old age than single foods or nutrients, better results in terms of functionality also occur when specific food groups, such as fruits or vegetables, are consumed. No differences were found between the sexes. Our results are consistent with prior studies. To our knowledge, this is the first systematic review regarding this hypothesis. .

5.4. Further recommendations

Due to the limited relevant literature, more prospective cohort studies in older adults are needed to further explore the potential role of diet, in the form of a healthy dietary pattern, in the prevention, delay or reversal of functionality impairment. Given this promising findings, there is a need for further high-quality research in this area in the future.

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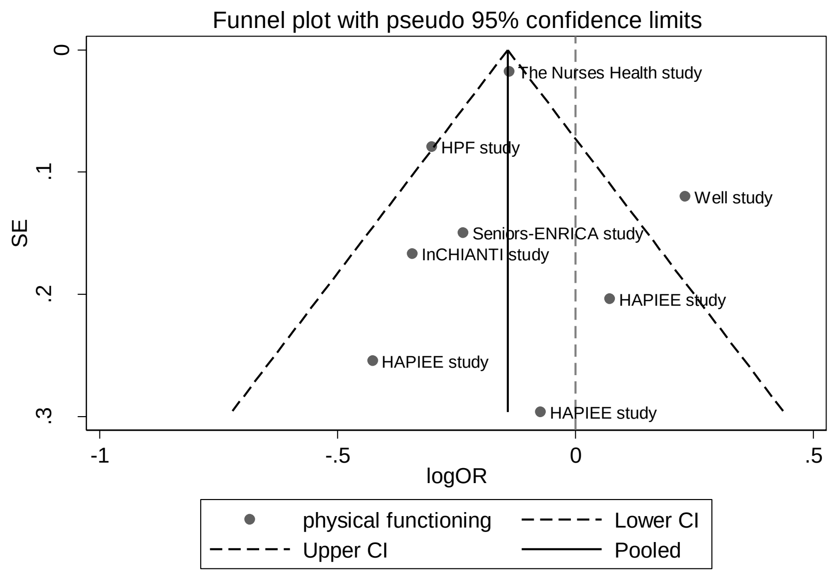
7. APPENDIX

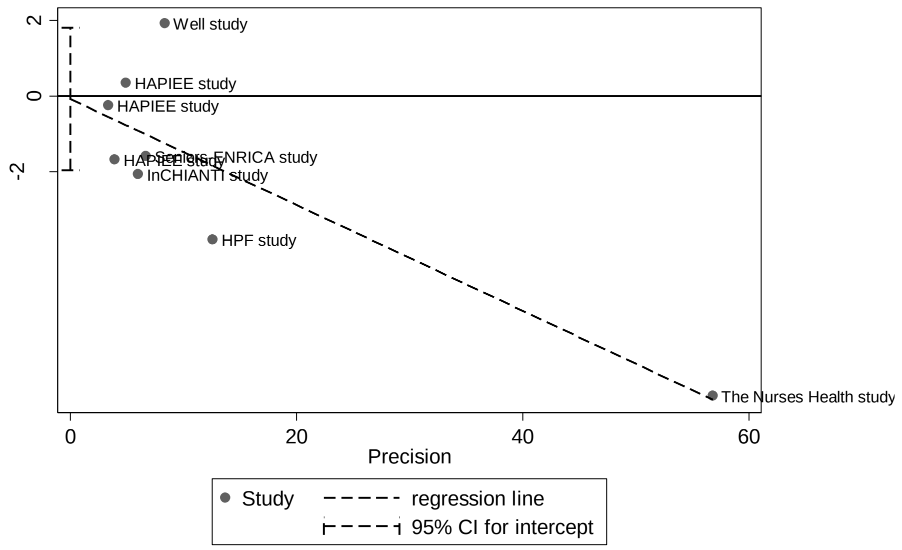
7.1. Search Strategy

The keywords were: ("Mediterranean diet" OR diet OR nutrition OR food OR "dietary habits" OR "dietary pattern" OR "western pattern" OR "food habits" OR "vegetarian diet" OR "prudent pattern" OR "traditional pattern" OR "DASH diet" OR "diet index" OR "whole grain" OR "refined grain" OR cereal OR pasta OR rice OR potato OR vegetable OR fruit OR legumes OR nut OR egg OR dairy OR dairies OR milk OR yogurt OR cheese OR fish OR seafood OR meat OR "processed meat" OR sugar OR sweets OR "sugar sweetened beverages" OR "food groups") AND ("functional ability" OR "functional status" OR "functional capacity" OR "physical function" OR "physical capacity" OR "physical function impairment" OR "physical capacity" OR "activities of daily living" OR "instrumental activities of daily living" OR mobility OR "mobility decline" OR disability).

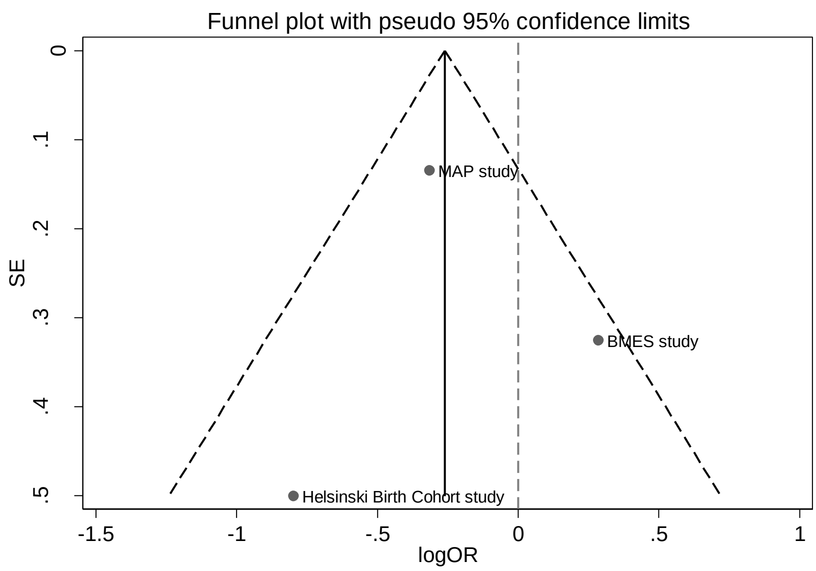
7.2. Supplementary figures



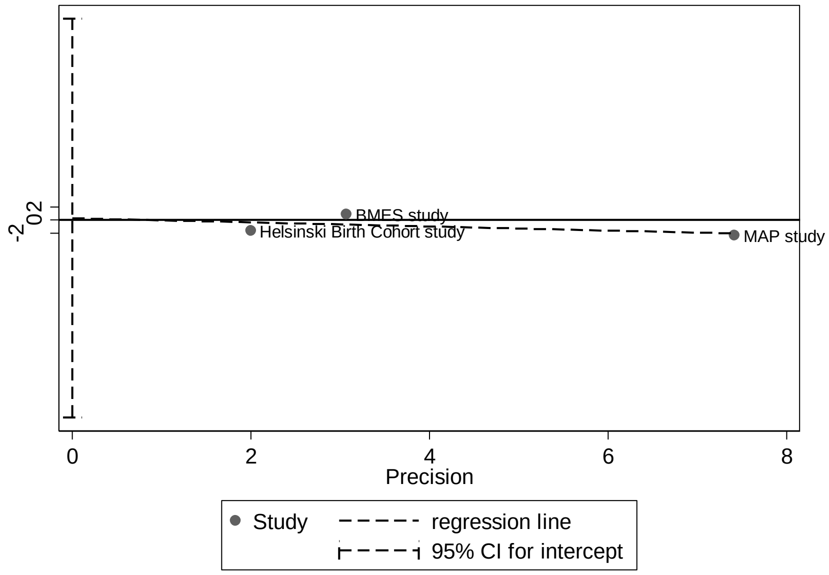
Suppl. Fig. 1. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of physical functioning in association with the highest v. the lowest level of dietary patterns score (P for Egger test 0.924). Dashed diagonal lines indicate 95 % CI.



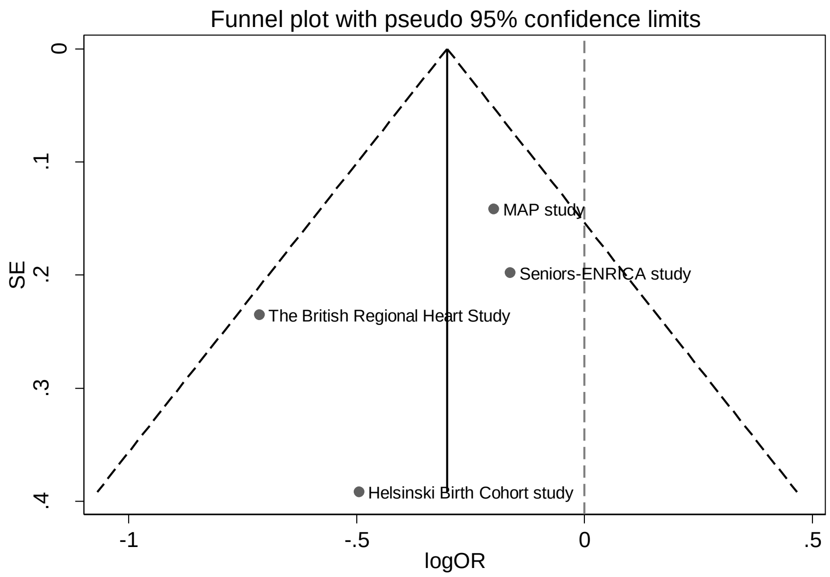
Suppl. Fig. 2. Metabias for assessing the relationship between dietary patterns and physical functioning.



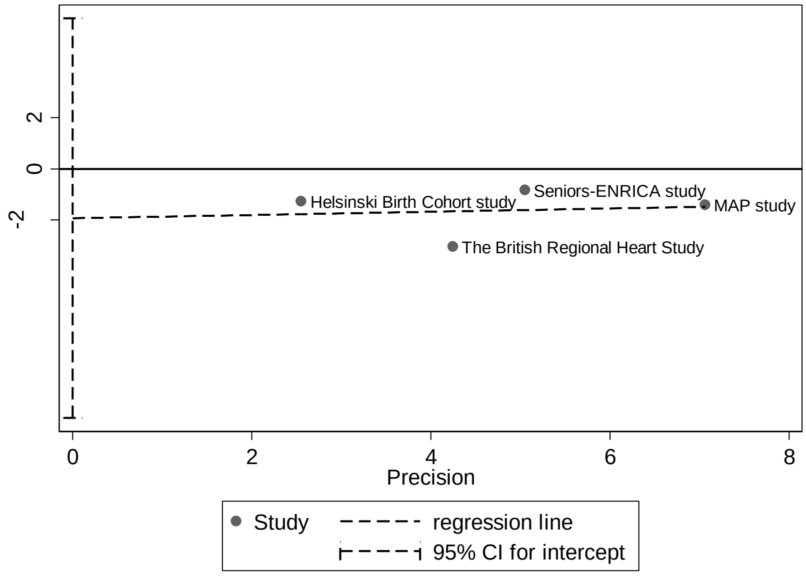
Suppl. Fig. 3. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of ADL in association with the highest v. the lowest level of dietary patterns score (P for Egger test 0.928). Dashed diagonal lines indicate 95 % CI. ADL: Activities of Daily Living.



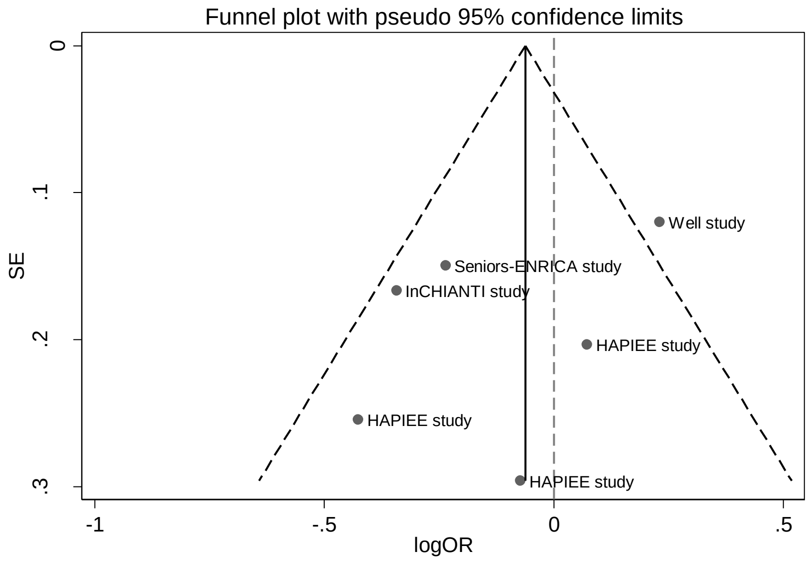
Suppl. Fig. 4. Metabias for assessing the relationship between dietary patterns and ADL.



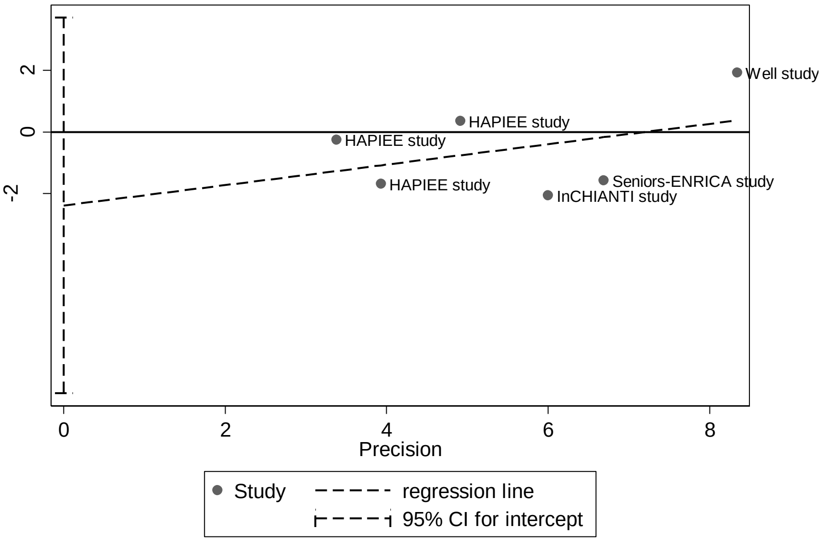
Suppl. Fig. 5. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of mobility disability in association with the highest v. the lowest level of dietary patterns score (P for Egger test 0.228). Dashed diagonal lines indicate 95 % CI.



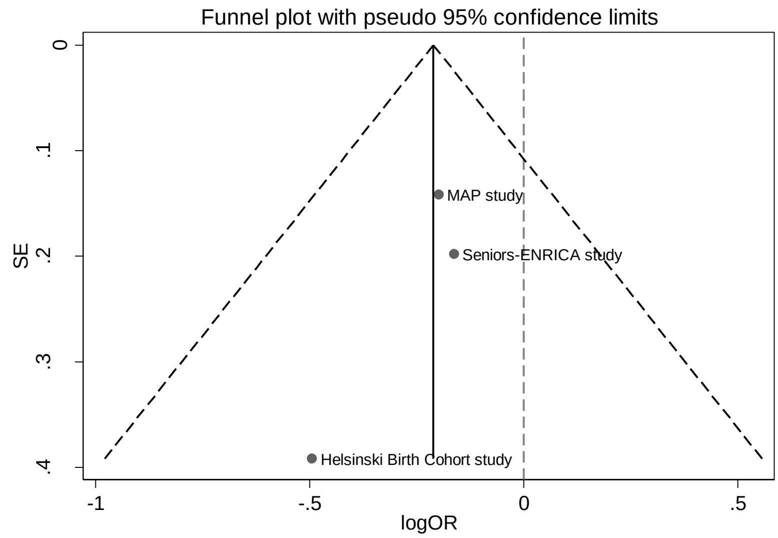
Suppl. Fig. 6. Metabias for assessing the relationship between dietary patterns and mobility disability.



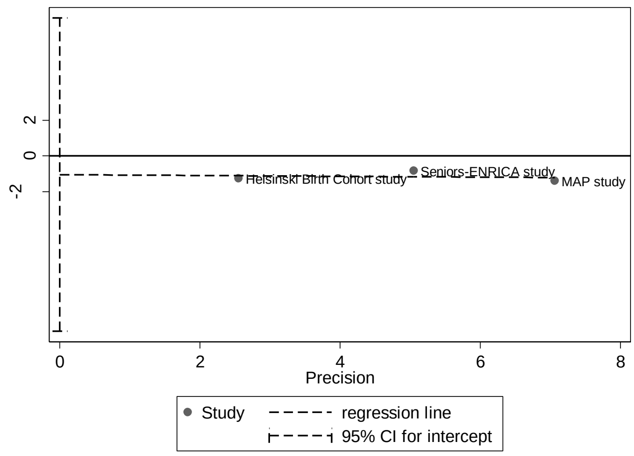
Suppl. Fig. 7. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of physical functioning in association with the highest v. the lowest level of Mediterranean diet score (P for Egger test 0.339). Dashed diagonal lines indicate 95 % CI.



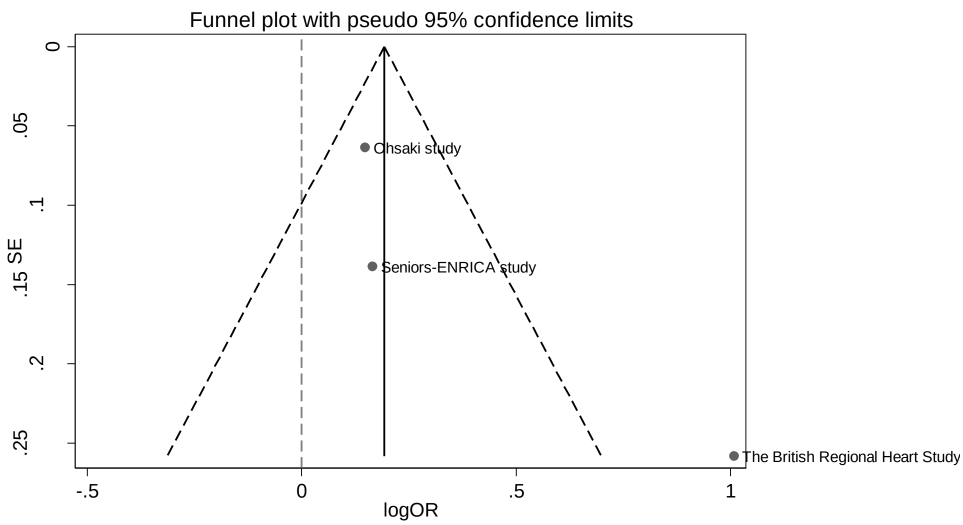
Suppl. Fig. 8. Metabias for assessing the relationship between Mediterranean diet and physical functioning.



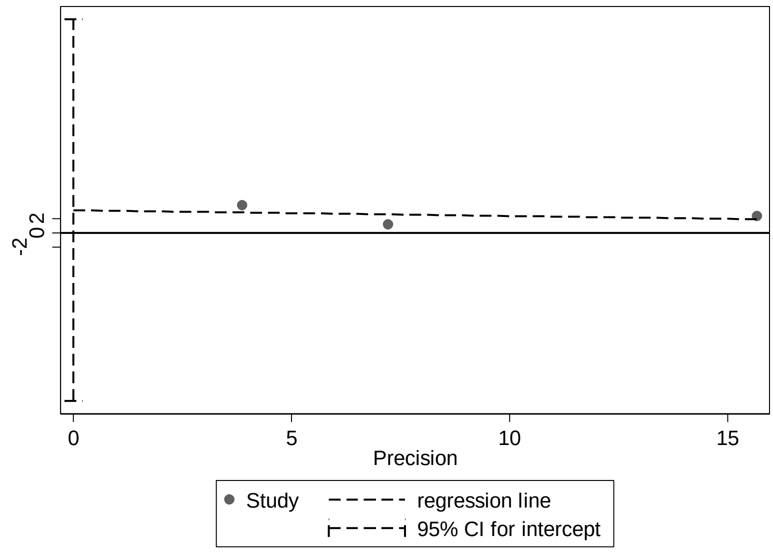
Suppl. Fig. 9. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of mobility disability in association with the highest v. the lowest level of Mediterranean diet score (P for Egger test 0.370). Dashed diagonal lines indicate 95 % CI.



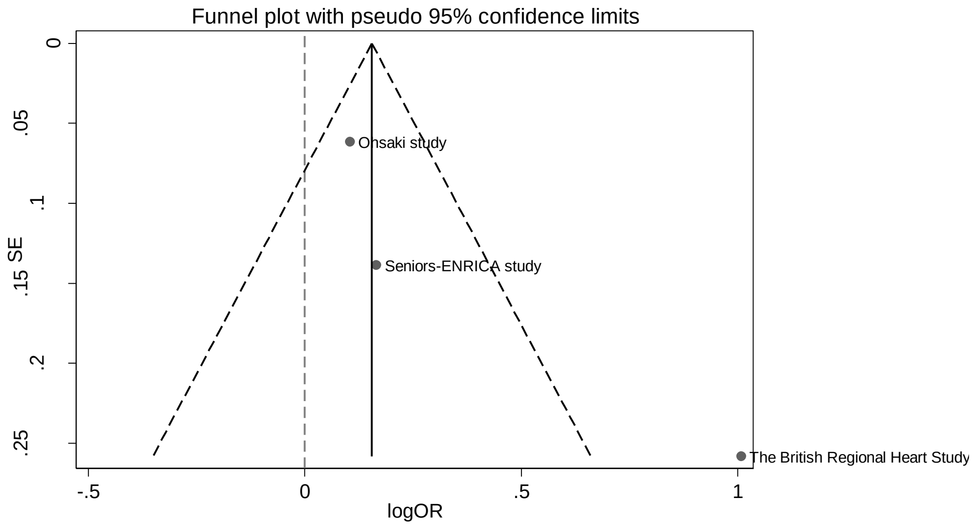
Suppl. Fig. 10. Metabias for assessing the relationship between Mediterranean diet and mobility disability.



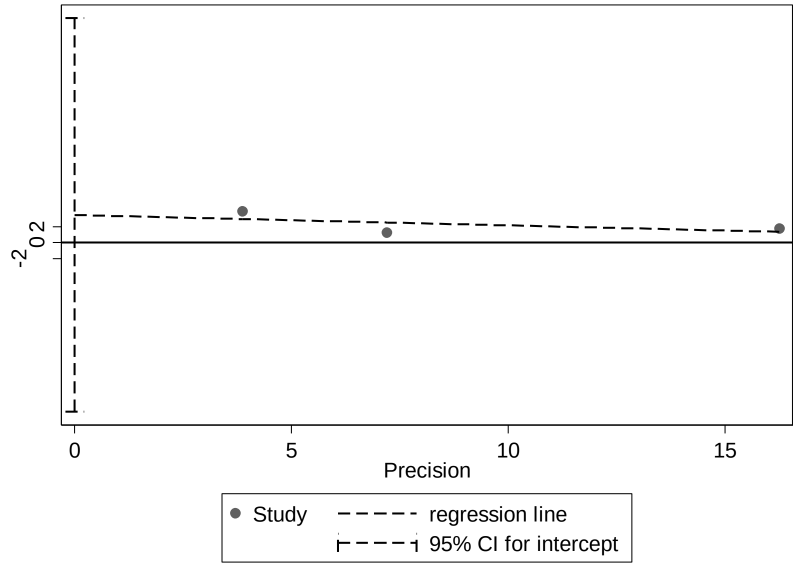
Suppl. Fig. 11. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of functionality in association with the highest v. the lowest level of the posteriori dietary patterns score (High fat/low fibre - Animal food- empirical inflammatory diet) (P for Egger test 0.373). Dashed diagonal lines indicate 95 % CI.



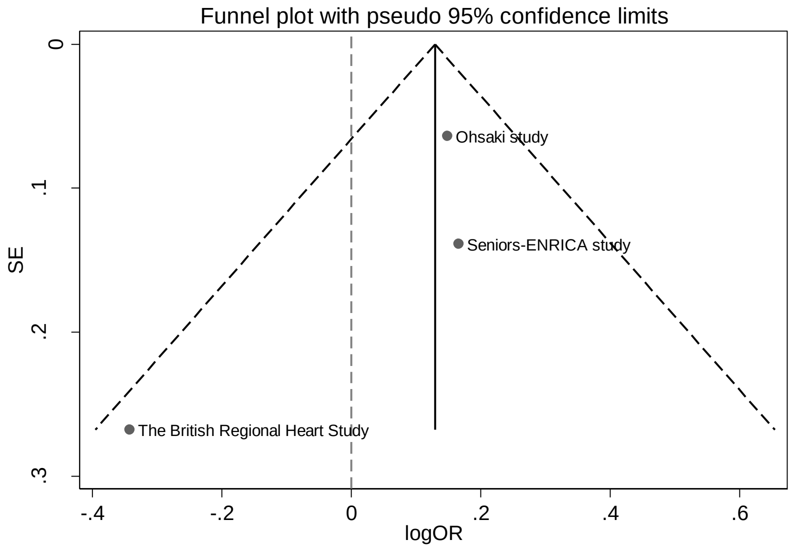
Suppl. Fig. 12. Metabias for assessing the relationship between the a posteriori dietary patterns (High fat/low fibre - Animal food- empirical inflammatory diet) and functionality.



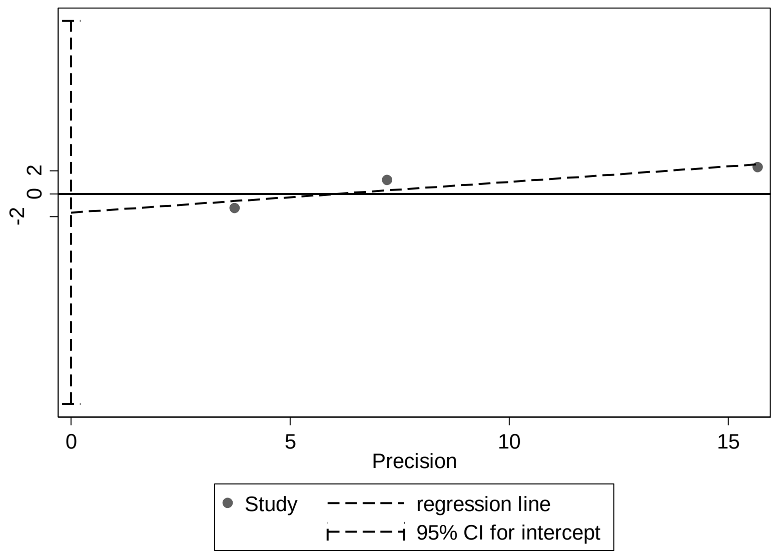
Suppl. Fig. 13. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of functionality in association with the highest v. the lowest level of a posteriori dietary patterns score (High dairy- high fat/low fibre –empirical inflammatory diet) (P for Egger test 0.326). Dashed diagonal lines indicate 95 % CI.



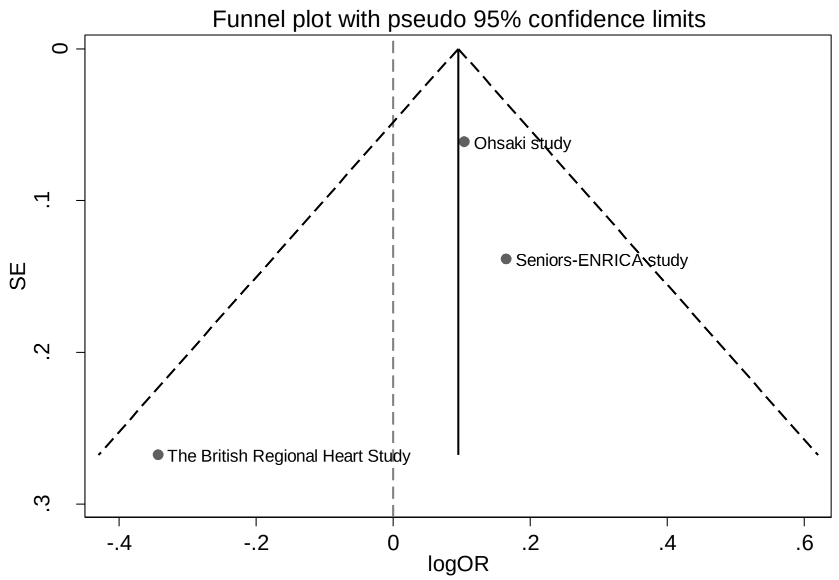
Suppl. Fig. 14. Metabias for assessing the relationship between the a posteriori dietary patterns (High dairy-high fat/low fibre –empirical inflammatory diet) and functionality.



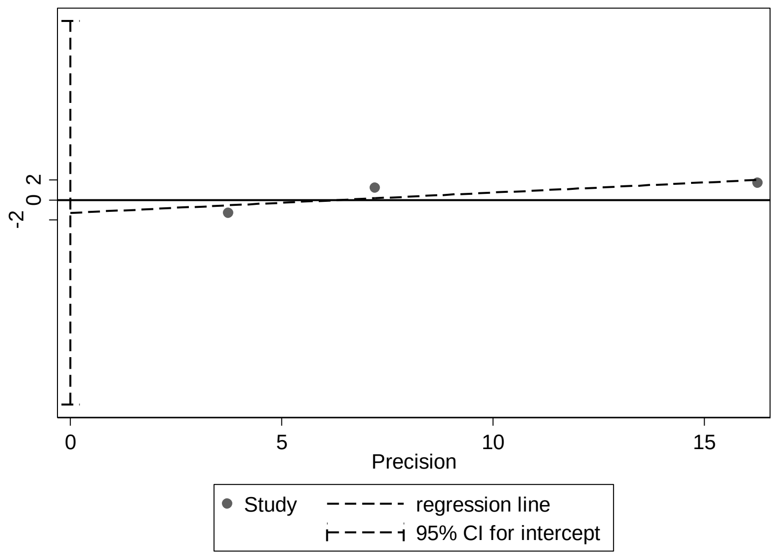
Suppl. Fig. 15. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of functionality in association with the highest v. the lowest level of a posteriori dietary patterns score (Animal food- High sugar – empirical inflammatory diet) (P for Egger test 0.430). Dashed diagonal lines indicate 95 % CI.



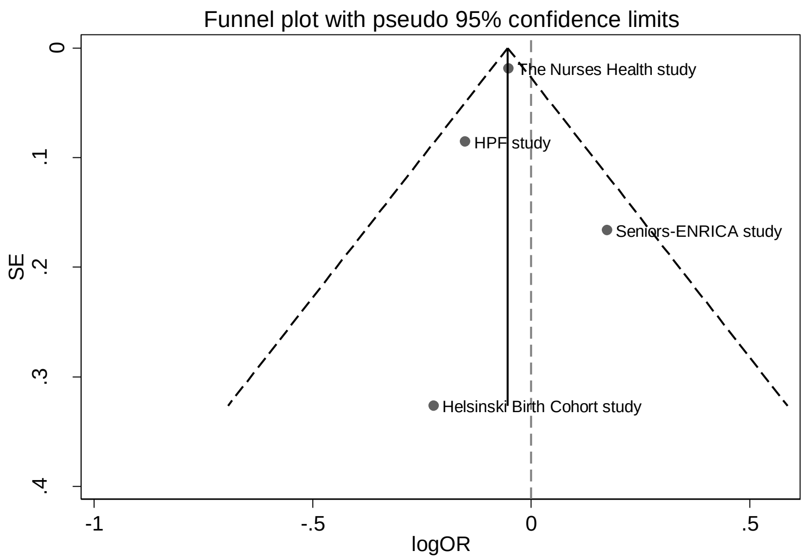
Suppl. Fig. 16. Metabias for assessing the relationship between the a posteriori dietary patterns (Animal food- High sugar – empirical inflammatory diet) and functionality.



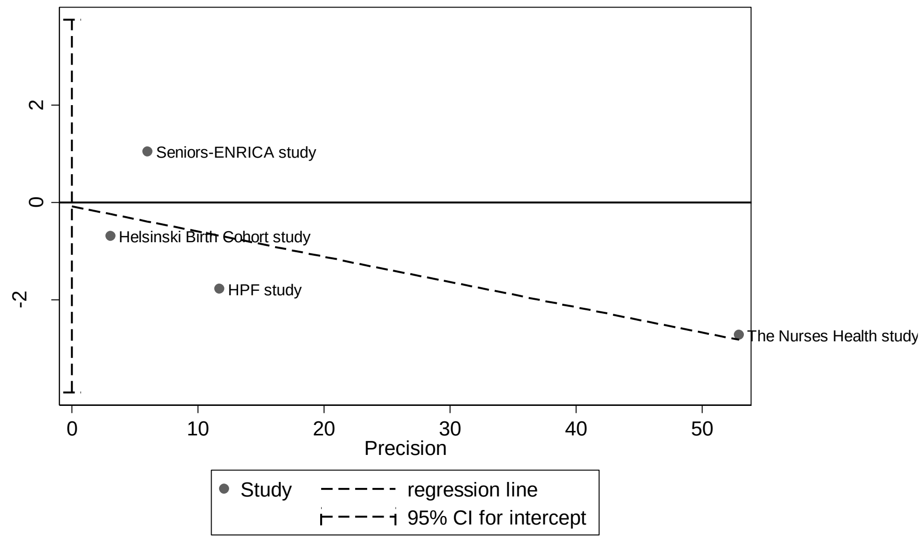
Suppl. Fig. 17. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of functionality in association with the highest v. the lowest level of a posteriori dietary patterns score (High dairy – high sugar – empirical inflammatory diet) (P for Egger test 0.548). Dashed diagonal lines indicate 95 % CI.



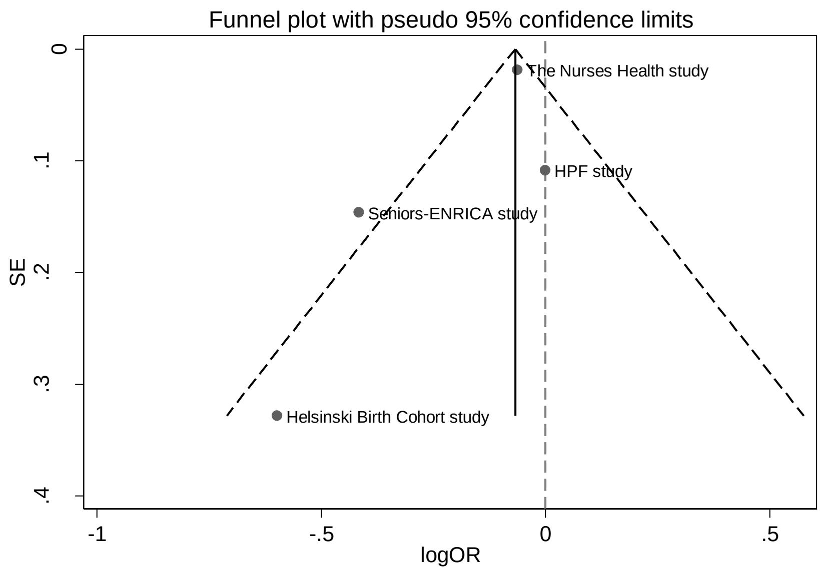
Suppl. Fig. 18. Metabias for assessing the relationship between the a posteriori dietary patterns (High dairy – high sugar – empirical inflammatory diet) and functionality



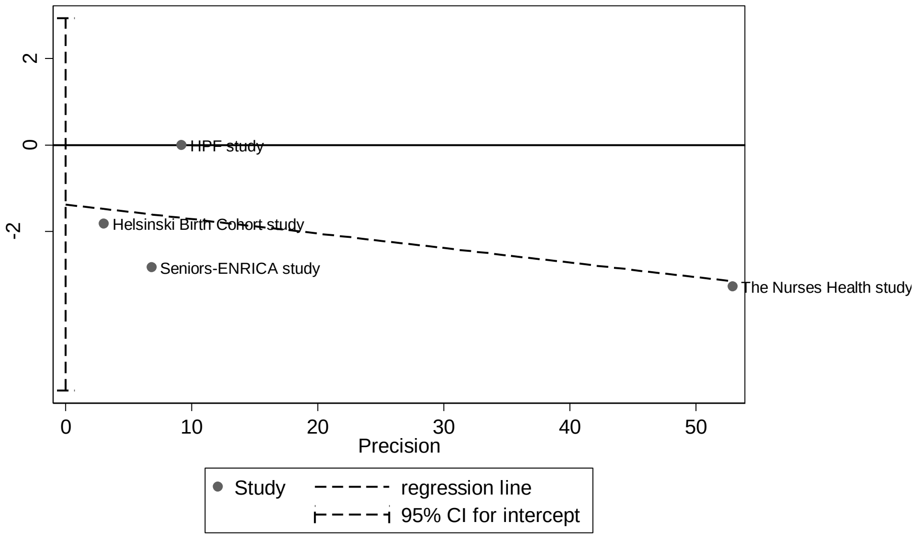
Suppl. Fig. 19. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of functionality in association with the highest v. the lowest level of vegetables consumption (P for Egger test 0.941). Dashed diagonal lines indicate 95 % CI.



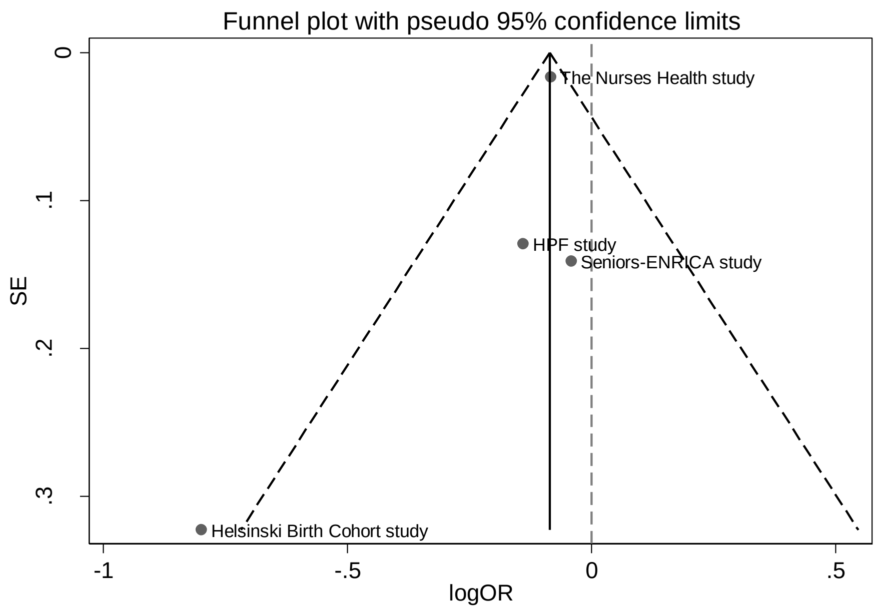
Suppl. Fig. 20. Metabias for assessing the relationship between vegetables and functionality



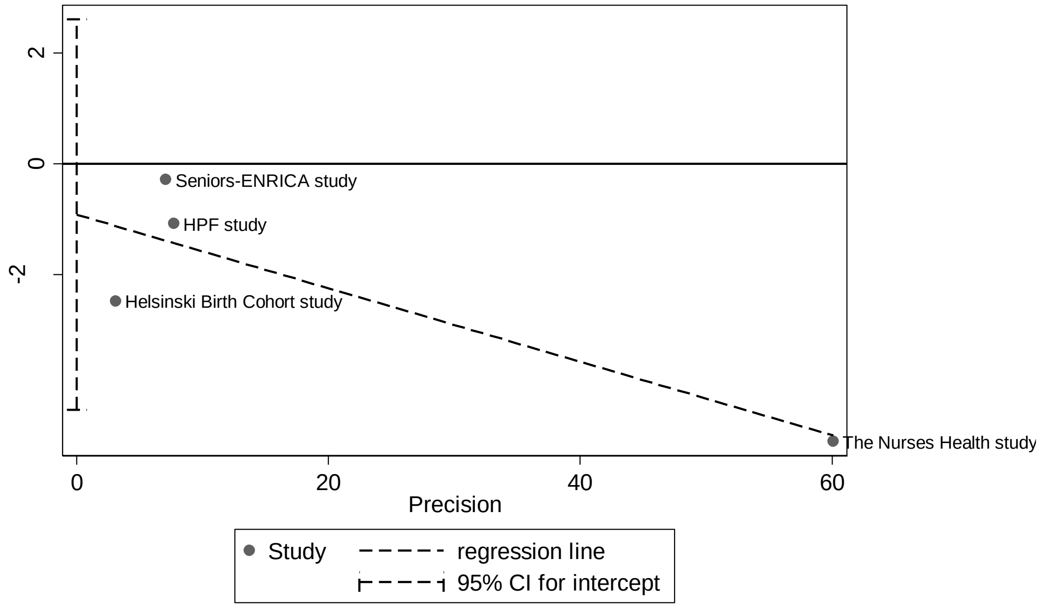
Suppl. Fig. 21. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of functionality in association with the highest v. the lowest level of fruits consumption (P for Egger test 0.303). Dashed diagonal lines indicate 95 % CI.



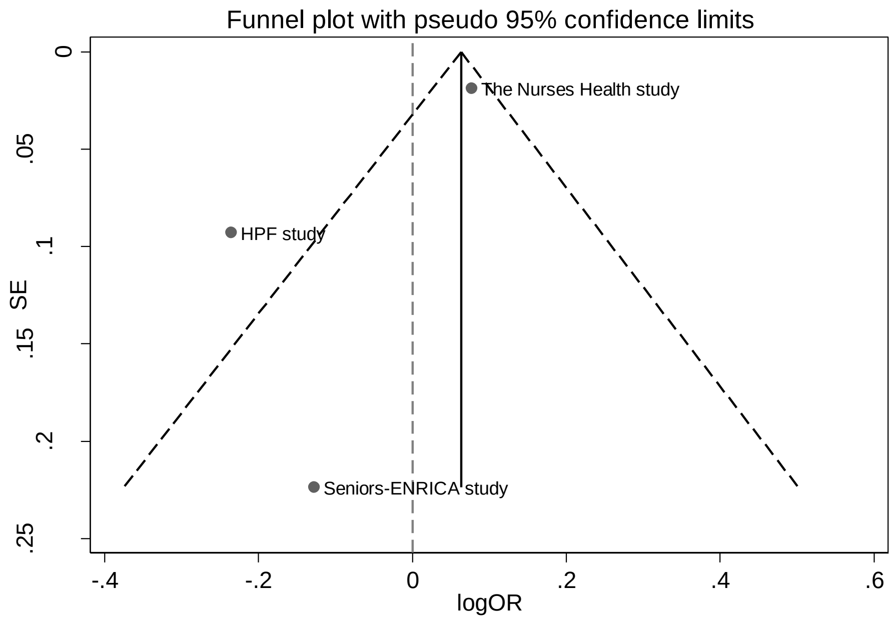
Suppl. Fig. 22. Metabias for assessing the relationship between fruits and functionality



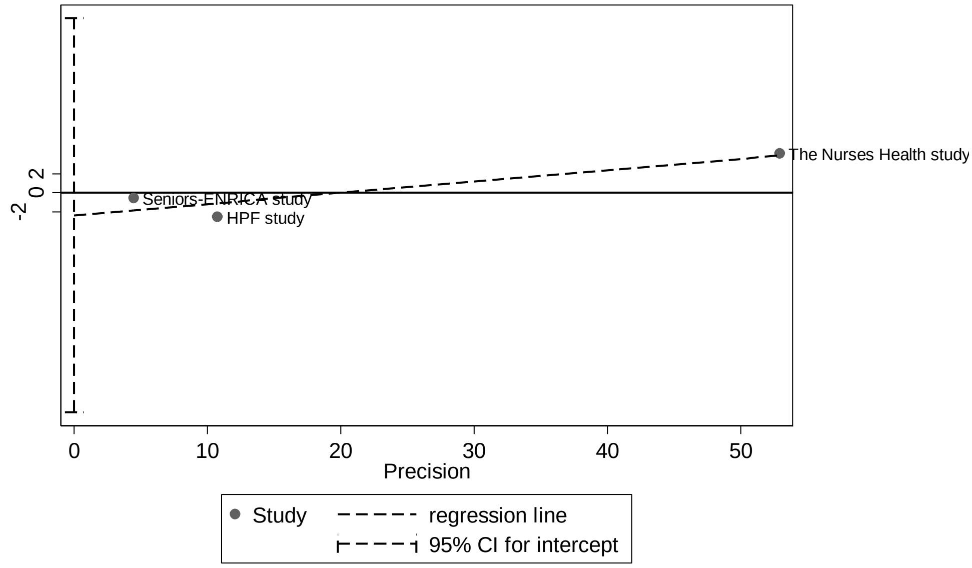
Suppl. Fig. 23. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of functionality in association with the highest v. the lowest level of alcohol consumption (P for Egger test 0.378). Dashed diagonal lines indicate 95 % CI.



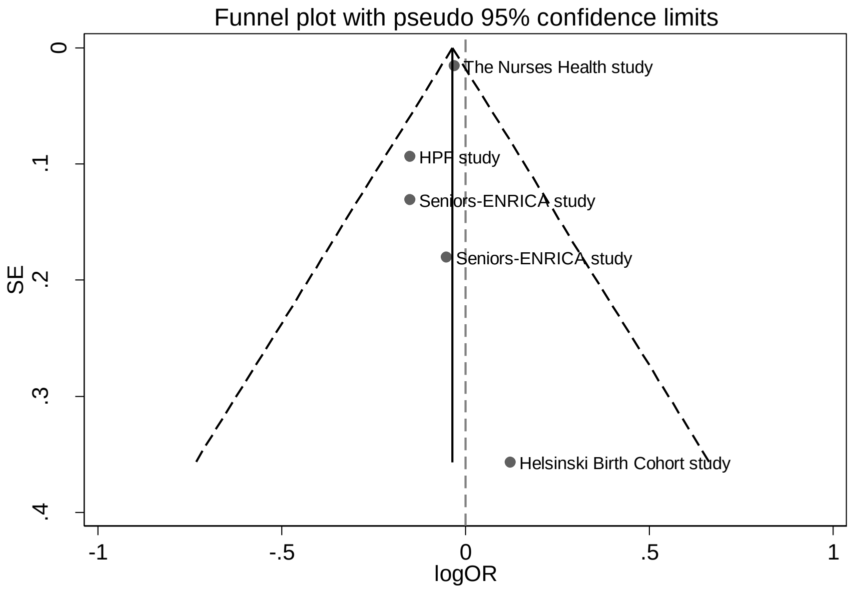
Suppl. Fig. 24. Metabias for assessing the relationship between alcohol and functionality



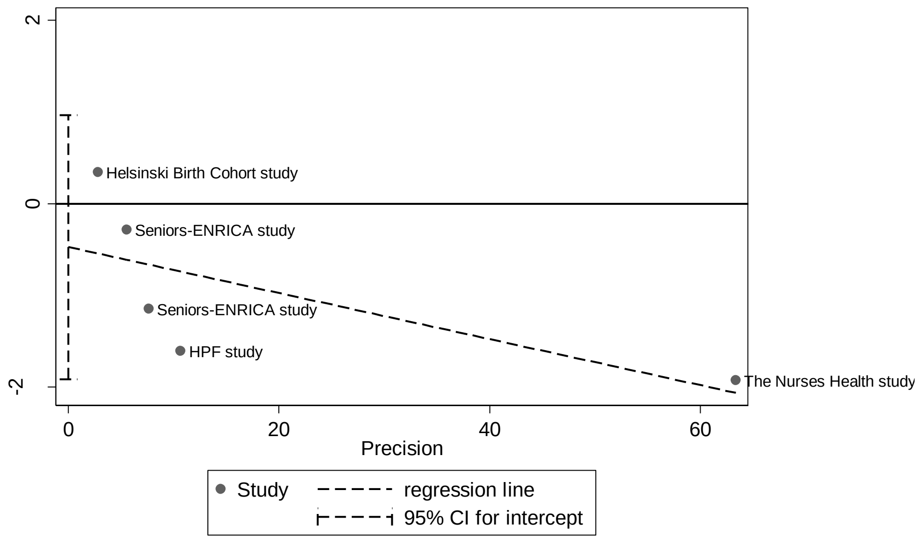
Suppl. Fig. 25. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of functionality in association with the highest v. the lowest level of sugar sweetened beverages consumption (P for Egger test 0.378). Dashed diagonal lines indicate 95 % CI.



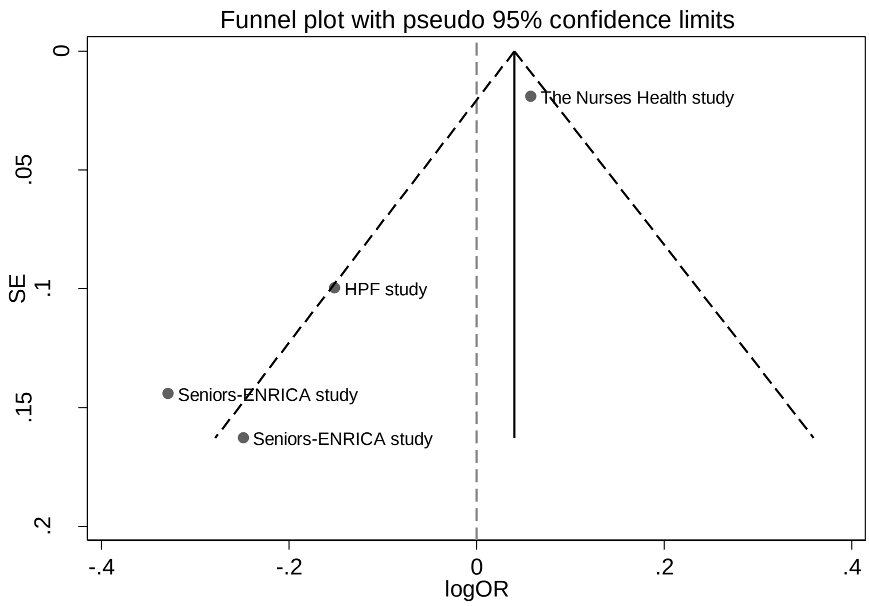
Suppl. Fig. 26. Metabias for assessing the relationship between sugar-sweetened beverages and functionality



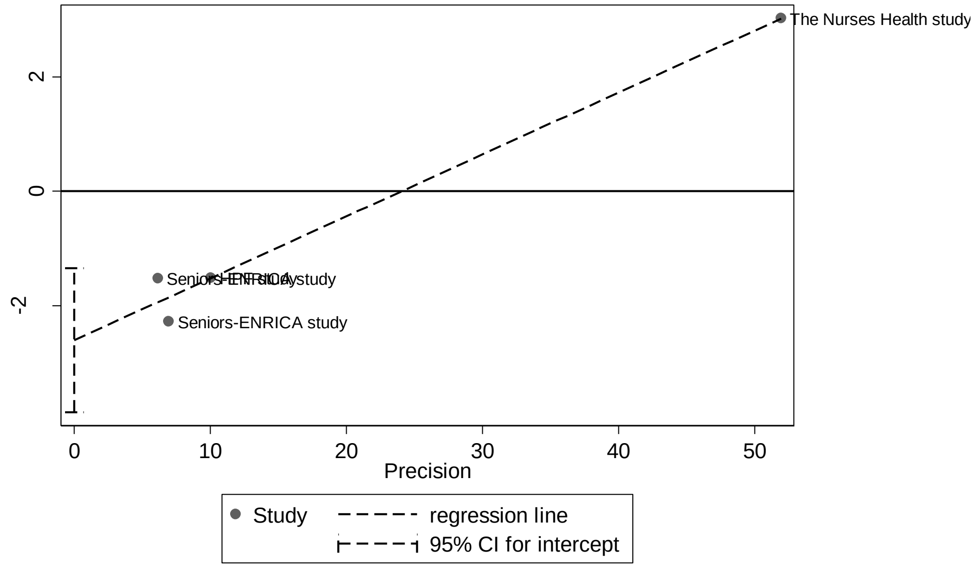
Suppl. Fig. 27. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of functionality in association with the highest v. the lowest level of red and processed meat consumption (P for Egger test 0.378). Dashed diagonal lines indicate 95 % CI.



Suppl. Fig. 28. Metabias for assessing the relationship between red and processed meat and functionality



Suppl. Fig. 29. Funnel plot for the assessment of publication bias in the studies included in the meta-analysis of physical functioning in association with the highest v. the lowest level of nuts consumption (P for Egger test 0.378). Dashed diagonal lines indicate 95 % CI.



Suppl. Fig. 30. Metabias for assessing the relationship between nuts consumption and functionality

7.3. Supplementary table 1. Risk of bias summary for each included study using the Newcastle - Ottava Scale.

	SELECTION				COMPARABILITY	OUTCOME			
Study	**Representativeness of the exposed participants**	**Representativeness of the non-exposed participants**	**Ascertainment of the dietary supplementation**	**Demonstration that outcomes were not present at start of study**	**Comparability of the exposed groups on the basis of the design or analysis**	**Assessment of outcomes**	**Was follow up long enough for outcomes to occur**	**Adequancy of follow up of exposure groups**	**Star Total**
Fe´art, 2011	1	0	0	1	1	1	0	1	5
Milte, 2015	1	0	0	0	1	1	0	1	5
Agarwal, 2018	1	0	0	1	1	1	1	1	6
Milaneschi, 2010	1	0	0	1	1	1	1	1	6
Struijk, 2016	1	0	0	1	1	1	0	1	5
Stefler, 2018	1	0	0	0	1	1	1	1	5
Gopinath, 2013	1	0	0	0	1	1	1	1	5
Parsons, 2018	1	0	0	1	1	1	1	1	6
Hagan, 2016	1	0	0	0	1	1	1	1	5
Laclaustra, 2019	1	0	0	1	1	1	0	1	5
Hagan, 2019	1	0	0	0	1	1	0	1	4
Perälä, 2018	1	0	0	1	1	1	1	1	6
Struijk, 2018	1	0	0	1	1	1	1	1	6
Tomata, 2013	1	0	0	0	1	1	1	1	5
Arias – Ferna’ndez, 2018	1	0	0	0	1	1	1	1	5