INTRODUCTION

Review question / Objective: The aim of this study is to meta-analyze the associations between Mediterranean Diet and Osteoporosis. MD has been shown to have an effect on osteoporosis, but the results are inconsistent. Participant or population: Patients with osteoporosis. Intervention: Mediterranean diet. Comparator: Normal diet or None. Study designs to be included: Cross-sectional and prospective cohort studies. If high-quality RCTs are available, also consider.

Condition being studied: Osteoporosis is a chronic condition that can require long-term management, and the World Health Organization (WHO) describes it as a “progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture”. It has become a public health problem. The Mediterranean diet is characterized by a high intake of olive oil, moderate intake of fish, etc. Studies have shown that the Mediterranean diet has an effect on osteoporosis, but the results are not completely consistent. Therefore, in this present study we are going to explore the impact of the MD on osteoporosis by a meta-analysis of observational studies and randomized controlled trials (RCTs).

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 June 2022 and was last updated on 03 June 2022 (registration number INPLASY202260011).
Comparator: Normal diet or None. Study designs to be included: Crosssectional and prospective cohort studies. If high-quality RCTs are available, also consider.

**Condition being studied:** Osteoporosis is a chronic condition that can require long-term management, and the World Health Organization (WHO) describes it as a "progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture". It has become a public health problem. The Mediterranean diet is characterized by a high intake of olive oil, moderate intake of fish, etc. Studies have shown that the Mediterranean diet has an effect on osteoporosis, but the results are not completely consistent. Therefore, in this present study we are going to explore the impact of the MD on osteoporosis by a meta-analysis of observational studies and randomized controlled trials (RCTs).

**METHODS**

**Search strategy:** We have selected several databases such as PubMed, Cochrane Library, Web of Science and Embase, and searched in the form of Mesh subject terms + free words. Take the Mediterranean diet for example, the entry terms include "Diets, Mediterranean", "Mediterranean Diets" and "Diet, Mediterranean". As for the Mesh term "Osteoporosis", the entry terms include "Osteoporosis, Post-Traumatic", "Osteoporosis, Age-Related", "Bone Losses, Age-Related" and so on. The specific search strategy is as follows. (((((((((((((((Osteoporosis[Title/Abstract])) OR (Osteoporoses[Title/Abstract])) OR (Osteoporosis, Post-Traumatic[Title/Abstract])) OR (Osteoporosis, Post Traumatic[Title/Abstract])) OR (Post-Traumatic Osteoporoses[Title/Abstract])) OR (Post-Traumatic Osteoporosis[Title/Abstract])) OR (Osteoporosis, Senile[Title/Abstract])) OR (Osteoporosis, Senile[Title/Abstract])) OR (Senile Osteoporosis[Title/Abstract])) OR (Senile Osteoporosis[Title/Abstract])) OR (Osteoporosis, Age-Related[Title/Abstract])) OR (Osteoporosis, Age Related[Title/Abstract])) OR (Bone Loss, Age-Related[Title/Abstract])) OR (Age-Related Bone Loss[Title/Abstract])) OR (Age-Related Bone Losses[Title/Abstract])) OR (Bone Loss, Age Related[Title/Abstract])) OR (Bone Losses, Age Related[Title/Abstract])) OR (Age-Related Osteoporosis[Title/Abstract])) OR (Age Related Osteoporosis[Title/Abstract])) OR (Age-Related Osteoporoses[Title/Abstract])) OR (Osteoporoses, Age Related[Title/Abstract])) OR "Osteoporosis"[Mesh] AND "Diet, Mediterranean"[Mesh] OR (((Mediterranean Diet[Title/Abstract])) OR (Diet, Mediterranean[Title/Abstract])) OR (Diets, Mediterranean[Title/Abstract])) OR (Mediterranean Diets[Title/Abstract])) AND (prognosis[MeSH Major Topic] OR diagnosed[Title/Abstract] OR cohort*[Title/Abstract] OR cohort effect[MeSH Term] OR cohort studies[MeSH Major Topic] OR predictor*[Title/Abstract] OR death[Title/Abstract] OR "models, statistical"[MeSH Term]) OR risk[Title/Abstract] OR risk[MeSH Major Topic] OR mortality[Title/Abstract] OR mortality[MeSH Major Topic] OR cohort[Title/Abstract]).

**Participant or population:** Patients with Osteoporosis. we do not apply any restrictions in terms of age, gender and ethnicity.

**Intervention:** Mediterranean Diet.

**Comparator:** Normal Diet or None.

**Study designs to be included:** Crosssectional and prospective cohort studies. If high-quality RCTs are available, also consider.

**Eligibility criteria:** To meet the needs of meta-analyses, articles to be included must meet the following conditions: (1) participants: Generally healthy adults over the age of 18; (2) exposure: Mediterranean Diet measured using the MD adherence questionnaire or something similar; (3) outcomes analyzed: Article contains data on bone mineral density and...
other indicators related to osteoporosis; (4) study design: cross-sectional and prospective cohort studies, as well as high-quality RCTs; (5) language: Studies published in English.

**Information sources:** We systematically searched PUBMED, EMBASE, Web of Science and Cochrane Library four databases for articles (two independent authors). Searching was restricted to published articles in the English.

**Main outcome(s):** The main results were classified into categories as follows: (1) MD adherence level (by diet score or its related) (2) BMD (Bone Mineral Density).

**Quality assessment / Risk of bias analysis:** Risk of bias will be assessed using Quality Assessment Tool Observational cohort and cross-sectional studies. The checklist included 14 longitudinal study items, of which only 11 were available for cross-sectional studies. Each item of methodological quality will be classified as 'Yes', 'No' or 'Not reported'. For RCTs, we will use Cochrane Risk Assessment Tool. The first edition contains seven types of biases in six categories, and each bias is divided into three levels: high, low, and unknown.

**Strategy of data synthesis:** First, we will extract baseline data, so that the characteristics of the research subjects can be more accurately recognized. Reviewers will review and determine whether a meta-analysis is feasible. Data analysis were carried out using Review Manager 5.3 software. We will use the fixed-effect model if there is no evidence of heterogeneity, otherwise a random-effect model will be used. We will compare the SMD between MD and control diet with 95% CI. In the meantime, the drawing of forest plots and funnel plots is also essential for the interpretation of publication bias and other biases.

**Subgroup analysis:** If the source of heterogeneity can not be found after sensitivity analysis, we will perform further subgroup analysis. We will identified potential moderator variables a priori. The variables will be sex, age (elderly >70 years and elderly >= 60 years but <=70 years of mean age) and , by stratifying meta-analyses by each of these factors.

**Sensitivity analysis:** Sensitivity analysis will be performed to determine whether any single study with extreme findings had an undue influence on the overall results.

**Language:** English.

**Country(ies) involved:** China.

**Keywords:** Mediterranean Diet; Osteoporosis.

**Contributions of each author:**
- **Author 1 - Yue Huang** - Conceptualization, Original Draft. Email: huangyue202205@163.com
- **Author 2 - Huijie Cen** - Methodology, Review and Edit. Email: 1345440752@qq.com
- **Author 3 - Chenxi Ma** - Data Curation, Formal analysis. Email: 1325876686@qq.com
- **Author 4 - Mengfei Wang** - Validation. Email: 529844902@qq.com