UNIVERSITY OF THESSALY

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School of Health Sciences, Department of Medicine
International Interdepartmental Master of Science Programme in

LIFESTYLE MEDICINE

Impact of Mediterranean Nutrition Intervention on Oxidative Stress in Healthy Adults: A Systematic Review

by
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A Master Thesis submitted to the Faculty for the partial fulfilment
of the obligations in

order to obtain the postgraduate title of MSc in Lifestyle Medicine

of the University of Thessaly

2024

Author's Contribution Statement

I certify that I am the author of this thesis and that any assistance I have had in its preparation is fully acknowledged and referenced in the following text. I have also cited any sources from which I have used data, ideas or words, whether they are quoted exactly or paraphrased.

I also certify that this thesis was prepared by me personally specifically for the requirements of obtaining a Master's degree in Lifestyle Medicine by the University of Thessaly. I declare that I will respect co-authorship rights in any linked scientific publication and/or presentation stemming from this thesis, in accordance to my signed affirmation, and in respect of the principles of ethics in research. Likewise, I declare I will recognize any funding sources and will acknowledge my affiliation to the University of Thessaly during the preparation of this work in any future presentation.

EVGENIA LARSINOU

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Acknowledgments

This work would not have been possible had it not being for the helpful input and support from a number of people, to whom I would like to express my gratitude.

Firstly, my supervisors (Prof. Georgios Sakkas and Prof. Christina Kartatzaferi) for standing by me and offering their knowledge and support during the ‘dissertation challenge’.

I am also thankful of the wider University staff and the wonderful and friendly network of other students in the same boat as I. It would not have been possible to get to the end point without them.

Special thanks go to my friend Maria, who while she was a student at UCL-London, shared systematic reviews knowledge with me, and opened a new research world for me. She was also pivotal in helping me access the UCL Library Services – their input was invaluable.

Huge thanks should also go to my wonderful team at work, who were patient with me and able to keep things ticking over without my supervision, while I was immersed in notes, studies, analyses, and I was stressed on top of that.

Last but not least I offer my immense thanks to my family for supporting me throughout this challenge and keeping my spirits high during stressful times.

Huge THANKS to all

Evgenia (Malou) Larsinou

Abstract

Introduction: The benefits of Mediterranean Diet (MD) have been explored widely in the literature in connection to health conditions and benefits. The high intake of anti-oxidants found naturally in MD foods has been connected to improved oxidation stress status in adults with pre-existing conditions. The effects on healthy adults have not been fully explored to-date.

Aims: To identify, assess, and summarise the evidence of the effects of MD on people's health with emphasis on the association with levels of oxidative stress on healthy adults.

Methodology: A literature review explored the current evidence connecting MD and oxidation stress. This was followed by a systematic review using Cochrane's methodology. Two databases (Embase, Medline) and one Register (CENTRAL) were comprehensively searched (from conception to 25/4/2024). Randomised controlled trials in healthy populations, comparing MD to other diets were included and assessed for risk of bias in six domains.

Results: There were four studies identified (in 12 publications), relating to 218 participants. Due to heterogeneity of methods, populations, and outcome reporting, it was not possible to carry out meta-analysis. Results are reported as a narrative.
Three trials reported on the main outcome of oxidative stress and found that MD overall has a beneficial effect.
Two trials explored the effects of MD on cardiovascular markers, with conflicting evidence.
Two trials explored inflammation and found no significant effects of MD.
One trial explored cognitive outcomes and found no significant effects.
One trial explored other anthropogenic outcomes and found no significant effects.

Discussion: There is insufficient evidence to determine robustly the relationship between MD and oxidative stress. Despite the large heterogeneity the results are consistent pointing to a beneficial effect of MD on oxidative stress. However, the evidence is not generalisable to the wider healthy population, and more research and consistency of reporting is needed before results from this review can be confirmed.

[300 words]

Keywords: Mediterranean Diet, oxidative stress, healthy population, randomised controlled trials

Περίληψη

Εισαγωγή: Τα οφέλη της Μεσογειακής Διατροφής (ΜΔ) έχουν διερευνηθεί ευρέως στη βιβλιογραφία σε σχέση με την υγεία. Η υψηλή πρόσληψη αντιοξειδωτικών που βρίσκονται στα τρόφιμα της διατροφής ΜΔ έχει συνδεθεί με βελτιωμένη κατάσταση οξειδωτικού στρες σε ενήλικες με προϋπάρχουσες παθήσεις. Οι επιπτώσεις σε υγιείς ενήλικες δεν έχουν διερευνηθεί πλήρως μέχρι σήμερα.

Στόχοι: Να εντοπιστούν, να αξιολογηθούν και να συνοψιστούν τα στοιχεία των επιπτώσεων της ΜΔ στην υγεία των ανθρώπων με έμφαση στη συσχέτιση με τα επίπεδα οξειδωτικού στρες σε υγιείς ενήλικες.

Μεθοδολογία: Μια βιβλιογραφική ανασκόπηση διερεύνησε τα τρέχοντα στοιχεία που συνδέουν την ΜΔ και το οξειδωτικό στρες. Ακολούθησε μια συστηματική ανασκόπηση χρησιμοποιώντας τη μεθοδολογία του Cochrane. Έγινε διεξοδική αναζήτηση σε δύο βάσεις δεδομένων (Embase, Medline) και ένα Register (CENTRAL) (από τη σύλληψη έως τις 25/4/2024). Συμπεριλήφθηκαν τυχαιοποιημένες ελεγχόμενες δοκιμές σε υγιείς πληθυσμούς, συγκρίνοντας την ΜΔ με άλλες δίαιτες και αξιολογήθηκαν για τον κίνδυνο μεροληψίας σε έξι τομείς.

Αποτελέσματα: Εντοπίστηκαν τέσσερις μελέτες (σε 12 δημοσιεύσεις), που αφορούσαν 218 συμμετέχοντες. Λόγω της ετερογένειας των μεθόδων, των πληθυσμών, και της απεικόνησης αποτελεσμάτων, δεν ήταν δυνατή η διεξαγωγή μετα-ανάλυσης. Τα αποτελέσματα αναφέρονται περιφραστικά.
Τρεις μελέτες ανέλυσαν οξειδωτικό στρες και διαπίστωσαν ότι η ΜΔ συνολικά έχει ευεργετική επίδραση.
Δύο μελέτες ανέλυσαν τις επιδράσεις της ΜΔ στους καρδιαγγειακούς δείκτες, με αντικρουόμενα αποτελέσματα.
Δύο μελέτες ανέλυσαν τη φλεγμονή και δεν βρήκαν σημαντικές επιδράσεις της ΜΔ.
Μια μελέτη διερεύνησε γνωστικά πεδία και δεν βρήκε σημαντικά αποτελέσματα.
Μια μελέτη διερεύνησε άλλα ανθρωπογενή πεδία και δεν βρήκε σημαντικές επιδράσεις.

Συζήτηση: Δεν υπάρχουν επαρκή στοιχεία για να προσδιοριστεί με σαφήνεια η σχέση μεταξύ ΜΔ και οξειδωτικού στρες. Παρά τη μεγάλη ετερογένεια, τα αποτελέσματα είναι ομοιόμορφα στις συμπεριλαμβανόμενες μελέτες υποδεικνύοντας την ευεργετική επίδραση της ΜΔ στο οξειδωτικό στρες. Ωστόσο, τα αποτελέσματα δεν μπορούν να γενικευτούν στον ευρύτερο υγιή πληθυσμό και απαιτείται περισσότερη έρευνα και ομοιμορφία αναλύσεων οξειδωτικού στρες προτού επιβεβαιωθούν τα αποτελέσματα από αυτήν την ανασκόπηση.

List of Figures and Tables

List of abbreviations

Apo	Apolipoprotein
CAT	Catalase
CENTRAL	Cochrane Central Register of Randomised Trials
CI	Confidence Interval
GPx	Gluthatione peroxidase
HabDiet	Habitual Diet
HAD	High antioxidant diet
HDL-C	High-density lipoprotein-cholesterol
hs-CRP	High-sensitivity C-reactive protein
IL-	interleukin-
F2-IsoPs	F2-Isoprostanes
LDL-C	Low-density lipoprotein-cholesterol
LPO	Lipid peroxidation products
MDA	malondialdehyde
MD	Mediterranean Diet
NF-kappaB	Nuclear factor kappa B
OR/RR	Odds ratio / Risk Ratio
oxLDL	LDL oxidized
PC	Protein carbonyl
RCT	Randomised Controlled Trial
ROB	Risk of Bias (tool)
ROS	Reactive oxygen species
SCS	Seven Country Study
SOD	Superoxide dismutase
TAS	Total Antioxidant Status
TG	Triglycerides
TNF-alpha	Tumor necrosis factor alpha
WD	Western Diet

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1 Introduction

1.1 Mediterranean diet

The Mediterranean diet (MD) is a way of life for the populations around the Mediterranean sea (Southern Europe) and the Levant. At its core it has the high consumption of fruit and vegetables, moderate consumption of fish and poultry, low consumption of red meat and wine, and has olive oil as the main source of fat intake.

The many benefits have become increasingly evident through extensive research connecting the diet to a number of health conditions. MD's importance and popularity took off after results from the 'Seven Country Study (SCS)'[1, 2] started to emerge. The study's (SCS) first measurements in 1958 linked diet with cardiovascular disease through a long follow-up of originally healthy populations with contrasting diets and lifestyles. Since that time numerous publications followed with more detailed analysis of the dietary ingredients of MD and their effect on a number of health areas and conditions.

1.2 Oxidative stress

Evolution of the research on the DM properties that help improve health outcomes has led to the exploration of oxidative stress as an important factor.

Oxidation is a normal process in the human body and involves the release of free radicals as metabolic process by-products[3]. Low or moderate levels of free radicals are essential for human health. Oxidative stress, however, occurs when there is an imbalance in the formation of excess free radicals and the body's capability of clearing them[3], partially due to lack of endogenous anti-oxidants. Exogenous anti-oxidants found in nutrition can help the body to restore the balance, and hence have a protective effect.

There is extensive evidence in the scientific literature on the harmful effects of oxidative stress in the body in relation to several conditions, such as cardiovascular disease[4], cancer[5], and neurological diseases[6] among others.

1.3 Thesis outline

By nature, the choice of foods in MD contains known anti-oxidants; the beneficial effects of MD in relation to oxidative stress, is the working hypothesis of this work.

A literature review sets the scene by bringing together evidence of the effects of: a) MD on health outcomes, and b) oxidative stress in relation to a number of health conditions.

A systematic review, following the Cochrane methodology, will then investigate the impact of MD on oxidative stress in healthy adults only.

2 Aims and Objectives

To identify, assess, and summarise the evidence of the effects of Mediterranean diet on people's health and consequently on their lives with emphasis on the association with levels of oxidative stress.

More specifically, the relationship between MD and oxidative stress is explored on healthy populations.

2.1 Types of outcome measures

The systematic review will investigate oxidative stress outcomes in populations free of comorbidities, especially those with a known clinical association to oxidative stress (for example, cardiovascular and neurological co-morbidities, among others).

The caveat of 'healthy population' narrows the available published literature, and hence a broader range of outcomes and measurements is considered here.

2.1.1 Primary outcomes

The primary outcome of this review is the effect of MD in the levels of oxidative stress.

However, there is no known agreed way in the scientific community for the way oxidative stress should be measured and reported. Instead, there is a host of known biological markers connected to oxidative stress and anti-oxidant activities that can be used either alone or in combination to report on the oxidative status in the body.

Consequently, a variety of reporting ways is expected for this outcome.

All assessment methods and time points as they are reported in the included studies will be considered but reported separately in this review. If there are more than one study reporting the same oxidative stress marker, then pooling of results will be attempted.

2.1.2 Secondary outcomes

A number of secondary outcomes will also be explored:

Inflammation measurements as expressed in the included studies, at any follow-up point are considered. It is expected that a variety of inflammation markers may be reported; they will be considered separately, combining data only from similar markers and time points.

Cardiovascular markers, such as cholesterol and triglycerides and including glucose and insulin levels are considered. All measurements as expressed in the included studies and at any time point are considered, but only similar data are analysed together.

Other antropometric outcomes as reported in the included studies aree considered. These include (but not exclusively) cognitive and psychological outcomes, as well as outcomes related to body image, and eating attitudes.

3 Literature Review

This literature review describes oxidative stress and the related mechanisms of action in the body, reports on evidence of health benefits of Mediterranean diet (MD), and explores the possible pathways of linking MD with oxidative stress.

3.1 Description of oxidative stress status

Oxidation is a biological process naturally occurring in the body, involving the production of reactive oxygen species (ROS) through metabolic processes[3]. ROS can act as free radicals or may eventually produce free radicals[7]. ROS are involved in normal cell functions and the production and presence inside cells (particularly the mitochondria) should ideally be kept at low levels. At that (low) level concentrations they have a vital role in the defence against pathogens[8]. In contrast, excessive amounts of ROS are detrimental to the body.

Under normal circumstances the body can regulate ROS production and neutralisation, through the use of endogenous antioxidants naturally produced in the body, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase[9].

Sustained over-production of ROS results in oxidative stress, a state that can lead to harmful effects. At a physiological level oxidative stress can affect all cellular components[10], thereby linking it to corresponding health conditions[11];

- *DNA damage*[12, 13] - Chronic oxidative stress activates inflammatory pathways that can lead to DNA mutations and transformation of a normal cell to tumor cell
- *Lipid (related to triglycerides and cholesterol) peroxidation*[14] – ROS/free radicals can affect lipids, especially polyunsaturated fatty acids (PUFAs) resulting in the formation of malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE)

- *Protein Oxidation*[15] - ROS can modify proteins leading to loss of function and degradation, hence disrupting cellular functions (this can be related to aging).

Some pathological conditions – such as inflammation and infection - may (temporarily) affect the ROS balance and lead to oxidation stress[16, 17]. External factors also contribute to dysregulation of ROS in the body. These include environmental influences (including aging[16]), smoking[18], and poor diet[19].

3.1.1 Measuring oxidative stress

Oxidative stress is a concept[20] and a state of many facets, and hence measuring oxidative stress is pausing a challenge to the scientific community.

As Sies[8] mentions in his editorial "the field of oxidative stress research embraces chemistry, biochemistry, cell biology, physiology and pathophysiology, all the way to medicine and health and disease research", hence the very term 'oxidative stress' has gone through an evolution of definitions since it was first used/introduced.

There is no single agreed way of measuring oxidative stress. Instead, a host of biomarkers are used to express the excess ROS[21, 22] that may well be different depending on which health condition are related to[23].

3.1.2 Dealing with oxidative stress

Clearly dysregulation of oxidation stress levels is linked to a multitude of health problems[11]. An obvious way to deal with oxidation stress is to attempt to regulate it with increased exogenous antioxidant intake in order to promote well-being. This can be in the form of lifestyle changes[24] (eg. avoiding smoking, taking regular exercise, etc.), pharmacological interventions[25], or diet modification[26, 27] (and possibly including antioxidant supplements[28, 29]).

A better understanding of the oxidative stress mechanisms has also led to research for developing therapeutic strategies[30] such as genotoxic therapy for cancer[31, 32].

3.2 Description of the Mediterranean Diet

The Mediterranean diet (MD) since becoming a popular nutritional choice and scientific research area in the 60's through the seven countries study[1, 2] has remained largely unaltered. It emphasises the consumption of nutrient-dense foods, and is characterized by high intake of fruits, vegetables, whole grains, legumes, nuts, and olive oil, along with low to moderate intake of fish, poultry, and red wine[33].

Over the years researchers have used the core definition of MD with occasionally minor alternations to either allow for geographical individualities and/or offer advice on the 'right' quantity to consume. A review of MD variations used found that although there may be differences of quantities of foods the nutrient profile remains the same[34].

The body of evidence exalting MD continues to accumulate rapidly and expands to a variety of clinical specialties. Systematic reviews summarising this evidence suggest adherence to MD for (indicative list) prevention and/or improvement of cardiovascular disease[35, 36], reduction of cancer risk[37, 38], control of levels and/or prevalence of type-2 diabetes[39-41] or other metabolic risk factors[42-44], control of body weight[45, 46], improvement and/or prevention of cognitive function issues (including dementia)[47-49], inflammation[50], all-cause mortality and chronic diseases[51], psychiatric conditions[52], and quality of life[53].

3.3 How could the Mediterranean diet affect oxidation stress

Nutritionally, MD is low in saturated fats and animal protein. At the same time it is rich in bioactive compounds and high in antioxidants, fiber and monounsaturated fats (including, polyphenols, and omega-3 fatty acids, which are known for their anti-inflammatory and neuroprotective properties)[54].

It is potentially the micronutrients and antioxidants provided by MD that offer the protective effect, as numerous epidemiological studies have concluded[55, 56]. Incorporating the key components of MD with its antioxidant-rich foods[57, 58] and anti-inflammatory properties[56, 59], would bring a protective effect against various oxidative stress-related diseases[60-62], by improving lipid profiles[63] and reducing levels of oxidative stress[64, 65].

3.4 Why it is important to do a systematic review

The is an abundance of evidence relating MD adherence with improvement of oxidative stress in populations with specific pre-existing health conditions, both at primary study level and systematic reviews.[36, 40, 66-70].

For healthy populations there is evidence at primary study level, for observational studies (cohorts, case-controls) and randomised trials but has not yet been summarised into a systematic review.

By synthesizing existing evidence through a systematic review, this work will aim to fill this current research gap, investigating the effects of MD oxidative stress levels in healthy adults.

4 Methodology

The systematic review was conducted using Cochrane methodology[71] and elements and flow chart from the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist[72, 73].

4.1 Criteria for considering studies – inclusion and exclusion criteria

The inclusion and exclusion criteria have been drawn up using the PICOS principle;

P = population criteria,

I/C = criteria for the intervention and comparison interventions,

O=list of outcomes explored (in section 2.1 – page 3), and

S=types of study design considered.

4.1.1 Types of studies

Randomised controlled trials (RCTs) investigating the effect of Mediterranean diet and oxidative stress were considered. All types of RCT design, such as cross-over and cluster trials, are included. Case series, case reports, and any other type of observational investigation, as well as conference abstracts, and study protocols were excluded. Intervention studies, animal studies, as well as studies of children and those dealing with pregnancy and maternal health were also excluded.

4.1.2 Types of participants

We include studies of human adults of all ages (18 years and above) who are generally healthy. Studies dealing with specific sub-populations based on any type of morbidity (including overweight populations) were excluded. For example participants with depression or anxiety disorder were not considered as anxiety disorder is linked to oxidative stress levels. Similarly for other conditions, such as (list is not exhaustive) diabetes, rheumatoid arthritis, cancer, and fatty liver disease.

Additionally, studies of children and babies, pregnant women, and any peri-or neonatal conditions were also excluded.

4.1.3 Types of interventions

Studies comparing Mediterranean diet (MD) as intervention compared with non-specific diets and/or any other recognised diet scheme intervention were included.

4.2 Materials and Search methods

Comprehensive searches were conducted with input from a librarian. Searches were limited to humans but were not restricted by date, language, or publication status.

4.2.1 Electronic searches

The databases, Embase, Medline, and the Cochrane Central Register of Randomised Trials (CENTRAL). In the first instance conference abstracts and trial registrations were included, with the view to possibly identify manually further publications.

The following search terms “Mediterranean diet,” “MedDiet” “MediDiet,” “Cretan diet” were included. The results from this initial search were then combined with a separate search using the terms “cortisol”, “cortisol levels”, “stress marker”, “corticosteroid” or “hydrocortisone” to retrieve relevant studies for screening. Medical subject headings (MeSH) or equivalent and text word terms were also used to capture studies evaluating the effects of MedDiet adherence on cortisol levels.

4.2.2 Searching other resources

Reference lists of identified trials and systematic reviews were also searched to identify any further literature.

4.3 Data collection and analysis methods

The data collection and analysis methods follow the broad Cochrane Methodology of Systematic Reviews[71].

4.3.1 Selection of studies

The search results were exported into EndNote software (version X20, Thomson Reuters, Philadelphia, PA, USA) and duplicates were removed. Titles and abstracts were screened using the online free software service of Rayyan[74], and the full-text of those eligible at this stage were screened, based on the *a priori* selection criteria for the review.

4.3.2 Data extraction and management

Data extraction was performed by the lead reviewer under supervision, and was based on a electronic data collection form. Information on the following fields was extracted: author, study design and methods, participant characteristics (number of subjects randomised, age, gender, criteria for cortisol levels), intervention and control group characteristics, main findings, study quality and bias assessment, and any additional notes.

4.3.3 Assessment of risk of bias in included studies

The risk of bias in the included studies was assessed using the Cochrane's risk of bias tool (version 1) for randomised trials[75], which was accessed and used within RevMan v5.4, the free Cochrane software for systematic reviews and meta-analysis.

The tool assesses studies for possible risk of bias using information from the study's text on the design, conduct, analysis, and reporting. The evaluation, devised by Cochrane methodology[75], uses a 3-point scale (low, high, unclear bias) for the following domains:

- Selection bias (random sequence generation and allocation concealment)
- Performance bias (blinding of participants and personnel)
- Detection bias (blinding of outcome assessment)
- Attrition bias (incomplete outcome data)
- Reporting bias (selective reporting)
- Other bias

A risk of bias table for each study was created alongside summary bias graphs.

4.3.4 Measures of treatment effect

For dichotomous outcomes, the odds ratios (ORs) or risk ratios (RR) alongside the corresponding 95% confidence interval (CI) would be used if a meta-analysis was possible. For cross-over trials, the results from paired analysis are considered when available. For continuous outcome measures, the mean difference and corresponding standard deviation are considered, if measurements used the same scales. If different scales are used then the standardised mean differences (SMDs) would be used if meta-analysis was possible, and where feasible the resulting SMDs would be re-expressed as units of a familiar scale.

While a pooled analysis was not possible, the numerical results from individual studies were considered and summarised in a table and as a narrative.

4.3.5 Unit of analysis issues

For the parallel trials the unit of randomisation was the patient. For cross-over trials, however, each patient received more than one treatment. Where data from both periods were available, the risk of carry-over effect was considered, and where adequate, both periods of the trials were included as a matched pair analysis[76].

For studies with more than 2 comparison groups, either the merging of the non-MD groups was planned, where feasible, or instead the method of splitting the control group participants was considered.

As meta-analysis was not possible in this review, all data are presented as a narrative.

4.3.6 Dealing with missing data

All analyses were performed on an intention-to-treat basis. There was no need for imputations for missing data to be undertaken, as missing data in all included trials was not observed.

4.3.7 Assessment of heterogeneity

We intended to use the I^2 statistic to estimate statistical heterogeneity between studies. However, a meta-analysis was not possible mainly due to varied reporting, but also due to the small number of included studies. Any synthesis of the evidence was hence reported as a narrative, and clinical diversity as a source of heterogeneity was particularly considered.

4.3.8 Assessment of reporting biases

There were under 10 studies included in this review. Had there been at least 10 studies we would have explored the risk of publication bias through a funnel plot. Such exploration may be carried out in a future update of this review.

4.3.9 Data synthesis and subgroup analysis

Aggregate data as available in the included studies are used for all analyses. If sufficient studies were to be included meta-analysis was planned; for continuous outcomes the inverse variance method would have been used to allow for the paired analysis of cross-over trials and/or the multiple comparison groups and for dichotomous outcomes, where feasible, the Mantel-Haenszel method or Peto method as necessary (ie. for small sample sizes fulfilling additionally the Peto method criteria.

As heterogeneity of methods was expected all analyses were planned using the random-effects model. However, since only a small number of studies are included it was not possible to carry out any meta-analysis and all data are presented as a narrative.

4.3.10 Subgroup analysis and sensitivity analysis

As part of the investigation for heterogeneity relevant sub-group analyses were also planned, to allow for different age groups, and different comparison groups of interventions.

Similarly sensitivity analysis was planned, in the form of considering temporarily only the low risk of bias trials as assessed using ROB1.

However, as meta-analysis was not possible in this review, all data were presented as a narrative.

4.3.11 Assessing the quality of the evidence

The quality of the evidence was going to be explored using the GRADE approach[77], and rating the evidence from numerical results as 'high', 'moderate', 'low', or 'very low' using the five GRADE considerations for: Risk of Bias, Inconsistency, Indirectness, Imprecision, and Publication bias.

As meta-analysis was not possible in this review, any assessment of the quality of the evidence was attempted as a narrative.

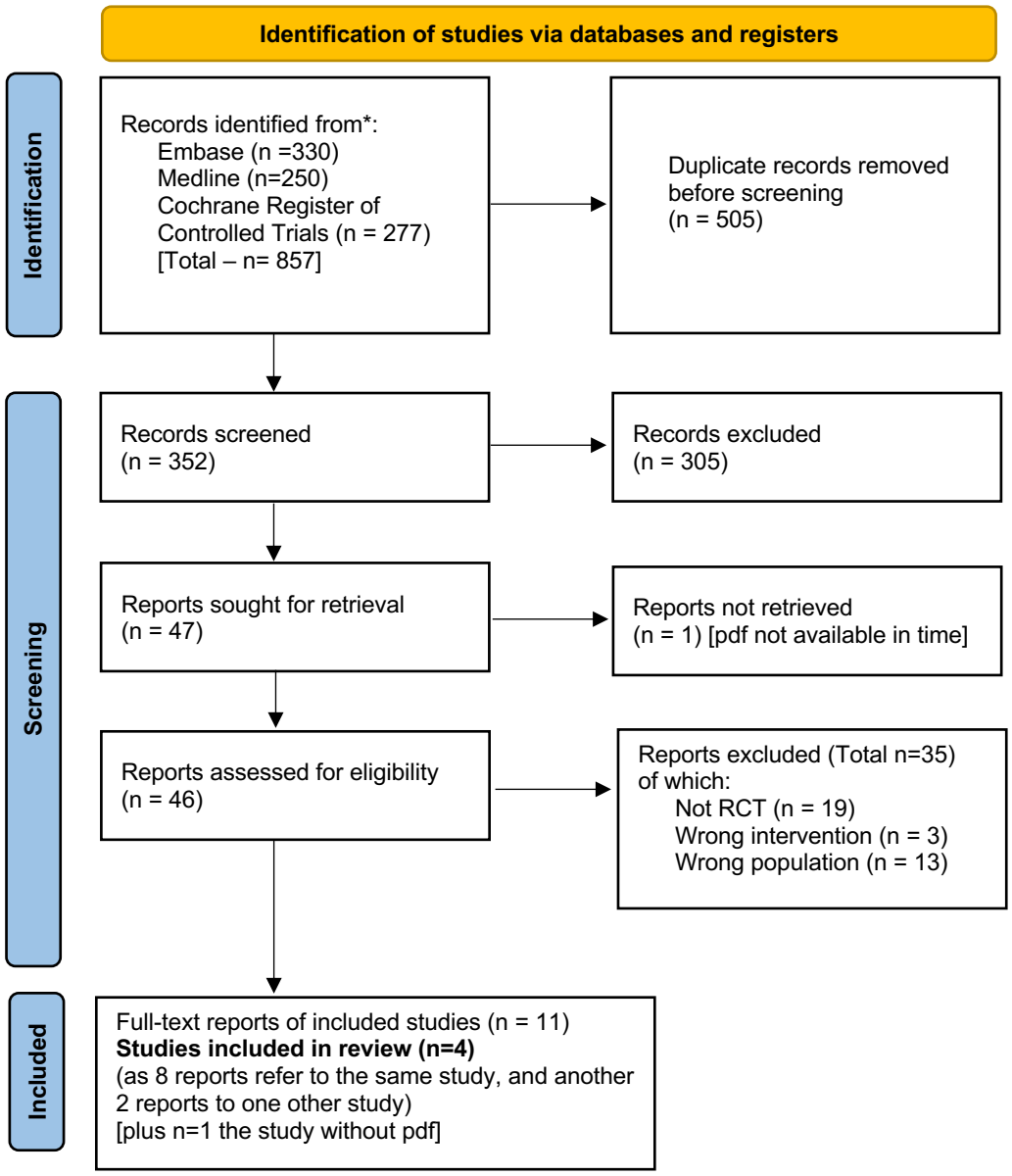
5 Results

5.1 Results of the search

The databases, Embase, Medline, and CENTRAL were comprehensively searched from inception to 25th April 2024, yielding 857 records of which 505 were duplicates and were removed.

All search strategies used for the different databases can be found in Appendix A1, while the number of records involved at each stage is shown in the PRISMA flow diagram as per the PRISMA 2020 statement[72, 73] (Figure 1).

Figure 1: PRISMA flow diagram



The 352 unique records were screened at the title and abstract level, of which 305 were irrelevant, and for the remaining 47 records the full text publication was sought for further screening.

Of those, one study's full text was not available in time for this work[78] and was not assessed at full text, but any information available from the abstract was considered. All remaining 46 records were assessed at full text.

5.2 Description of studies

Tables with characteristics of individuals included and excluded studies can be found in Tables 2 and 3 in Appendix A2.

5.2.1 Excluded studies

There were 13 records[28, 53, 59, 60, 65, 79-86] which although were RCTs, the population baseline had a pre-existing condition, hence were excluded as they considered the wrong population.

Other exclusions were due to wrong study design (ie. not RCTs – 19 records)[87-105], or wrong intervention (3 records)[106-108].

A table of the excluded studies with brief information on the reason for exclusion can be found in Appendix A2 – Table 3.

5.2.2 Included studies

There were 11 reports fulfilling the eligibility criteria and they are included in the review. One study[78] for which the full text was not available is not included in the count of these 11 reports assessed at full text, but as it fulfils the criteria it is considered as an included study.

Of these 11 reports, eight refer to the same study population[109-116] and were considered together as one study, so that inclusion of duplicate data is avoided. The record published earlier than the others is considered as the primary study of this group of eight, and will be referred to as Yubero-Serrano 2011[111] but in terms of information extracted, all other records were considered as needed.

Similarly, another two of the nine reports refer to the same study, one report being the protocol with information on the trial procedures[117] and the other containing data from part of the study[118]. The report containing data was considered as the primary publication, and will be referred to as Davis 2017[118], albeit any information on procedures may also be obtained from the (merged) publication of the protocol (Knight 2015)[117].

The remaining 1 report referred to a unique study[119].

Along with the record available only in abstract format, there are four included studies in this review (details of the studies and the merging of reports can be found in Appendix A2 – Table 2):

- Tuccar 2023[78] (abstract only),
- Davis 2017[118] (which includes Knight 2015[117]),
- Miralles-Amoros 2023[119], and
- Yubero-Serrano 2011[111] (which includes the records of Yubero-Serrano 2013[112], Lopez-Moreno 2016[110] and 2018[109], Goutierrez-Mariscal 2012[115] and 2014[116], Meza-Miranda 2014[114], and Marin 2012[113]).

***Trial Design and follow-up time*:** There were two parallel trials[118, 119] and two cross-over designs[78, 111]. The follow-up duration ranged from immediate (postprandrial) measurement to a max of 6 months (see table of characteristics of included studies Table 2 - Appendix A2). No two of the four trials had the same duration, which was one of several reasons why a pooled numerical analysis was not possible in this review.

***Trial size and participants*:** The four trials referred to a total of 218 participants. The largest study has 166 participants[118], and the other 3 had only small samples ranging from 11 to 21 in total of all comparisons groups within the trials.

All participants were considered ‘healthy’ as per the inclusion criteria, albeit the age ranges were from healthy, younger, handball players[119] to elderly populations over 65 years of age but free of any chronic diseases[118], with their health status being confirmed through tests before entering the trial.

Two of the trials only included female participants[78, 119], and the remaining two trials included mixed-gender populations.

***Settings*:** One trial was conducted at a hospital setting[111], and two had a University/academic base[118, 119], with the participants of all three trials presumably visiting for assessments. It has not been possible to establish the setting for the trial by Tuccar et al[78] as only the abstract was available but didn't mention information on the setting.

***Interventions and Outcomes*:** All trials included Mediterranean diet (MD) as one of their comparison groups as per the review's inclusion criteria. There was variation in the comparison groups though, which was one of several reasons why a numerical pooled analysis was not possible in this review (see Table of Characteristics of included studies, Appendices A2 - Table 2).

- Tuccar *et al*[78] (only abstract available) randomised participants (a cross-over design) to either a MD or Western diet (WD) meal, both isocaloric, with any outcome blood sample measurements taking place at 2, 3, and 4 hrs after the meal, and compared with the base line measurements. Outcome measurements included factors for oxidative stress [total antioxidant status (TAS), total oxidant status (TOS), total thiol, native thiol, malondialdehyde (MDA)] and inflammation [high sensitivity C-reactive protein (hs-CRP), interleukin (IL)-6, IL-17, IL-23, tumor necrosis factor alpha (TNF-alpha) and nuclear factor kappa B (NF-kappaB)].

- Davis *et al*[118] was the longest (6 months follow-up time) and largest of the included studies with 166 participants, all free of chronic disease and at least 65yrs of age. The two groups were assigned to either MD or habitual diet (HabDiet). The study took place in Australia and hence the MD version included some modifications to allow for the locally available foods (eg. tropical fruit, canned fish, etc). The study was part of the MedLey trial (The MedDiet for cardiovascular and cognitive health in the elderly)[117] and the primary outcome explored cognitive function. The secondary outcomes explored inflammation and oxidative stress, through biochemistry measurements of high-sensitivity C-reactive protein (hs-

CRP), and F2-Isoprostanes (F2-IsoPs). The following cardiovascular risk biomarkers were also measured; total plasma lipids, LDL, and HDL cholesterol, triglycerides (TGs), and total-to-HDL-cholesterol ratio.

- **Miralles-Amoros *et al*[119]** explores primarily psychosomatic effects of either MD or free diet or high antioxidant diet (HAD), in young female handball players, and links these with papers supporting the arguments of oxidative stress and psychiatric disorders[52, 120]. The participants were given personalised dietary plans and nutritional advice and were contacted each week (of the 12 week duration) to improve compliance. The method of measurement is a questionnaire where participants indicate their attitudes towards eating, hence the link of oxidative stress is by proxy as no biochemical results are available. Only the secondary outcomes of anthropogenic measurements were available from this study.

- **Yubero-Serrano *et al*[111]** along with the other 7 reports referring to the same population compare three groups (using cross-over design) of either MD or MD supplemented with Q10 enzyme (MD+Q10) or saturated fatty acid-rich diet (western diet – WD), over a 4-week period for each intervention. After the intervention period (of 4 weeks) a test meal was given to all participants and measurements were taken at baseline, 2hrs, and 4hrs. The postpandrial outcomes, measured biochemically, included metabolic and cardiovascular parameter levels, antioxidant enzyme activities, and biomarkers of oxidative stress.

5.3 Risk of bias in included studies

Cochrane's risk of bias tool (ROB1)[75] was used to assess all studies for risks of bias. Judgements and supporting information (extracted for study's text) for each study is available in Appendices A3. Figures 2 and 3 offer visual representation of the risk of bias judgements for each trial/domain and as a summary.

None of the four trials was assessed as high risk of bias in any of the domains of selection bias, performance bias, detection bias, and attrition bias. For the selective reporting bias domain one trial (Tuccar 2023 - only available in abstract) was

judged as high risk because only statistically significant results were reported; all other three trials were free of bias in that domain.

All trials were assessed as low risk of bias for the randomisation's sequence generation (selection bias). However, two trials[78, 111] were assessed to be of unclear risk of bias for the allocation concealment, and the blinding of participants and outcomes, as there was no adequate reporting provided in the text. One trial[78] (only available as an abstract) did not provide information on whether there was any loss of participants at follow-up and was judged as unclear risk of attrition bias.

Figure 2: Risk of bias judgements about each domain for included studies

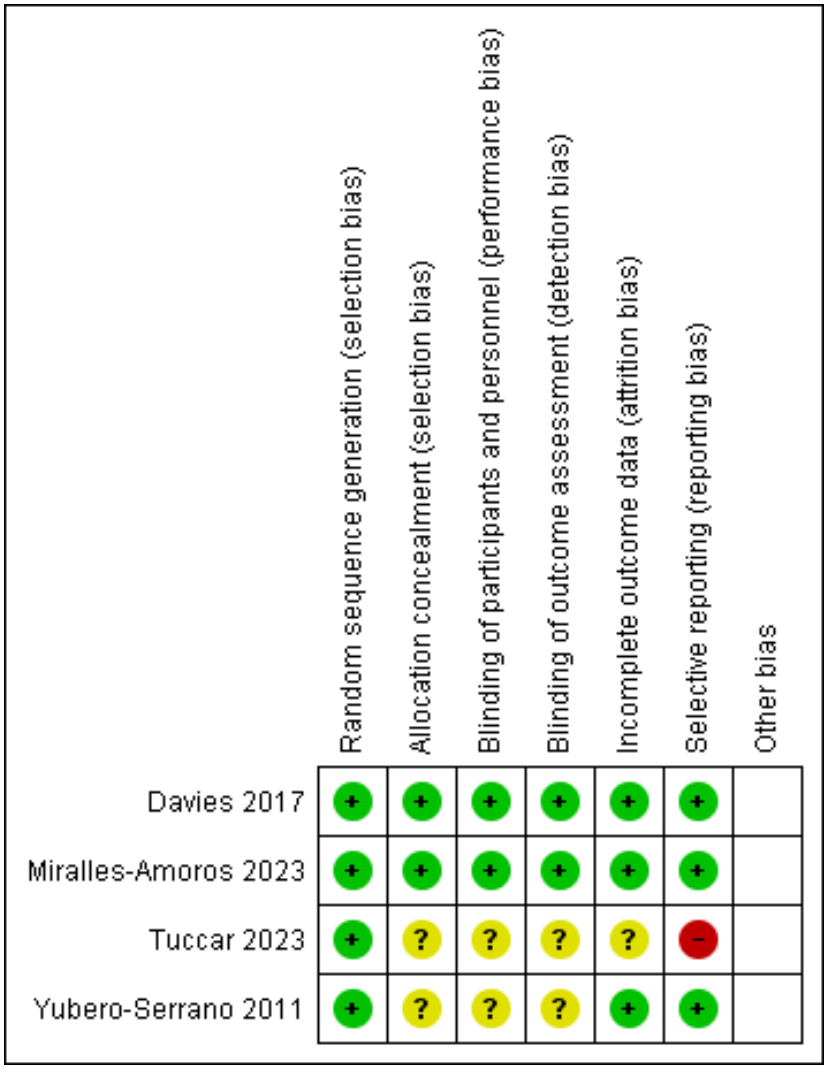
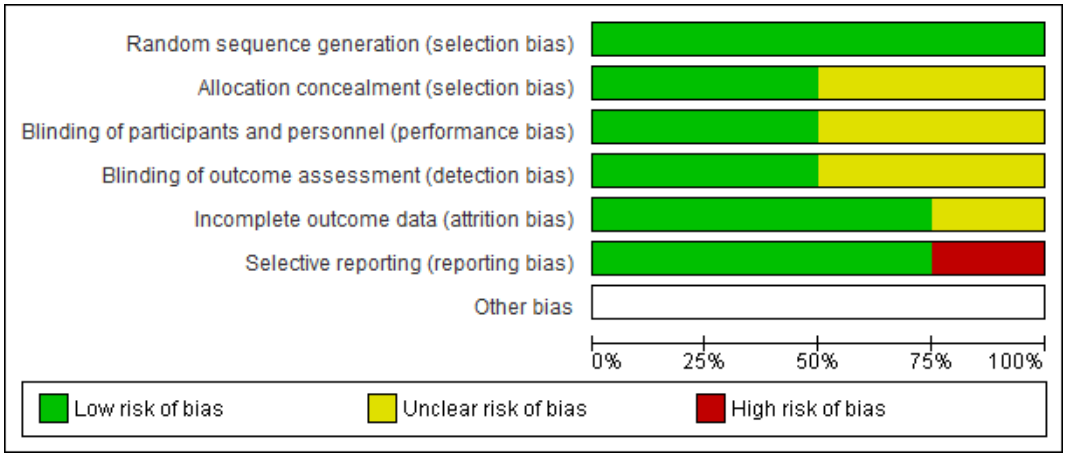


Figure 3: Summary judgements about each risk of bias domain
(as % across all studies)



5.4 Effects of interventions

All 4 included studies had varied follow-up durations, comparison groups, and outcomes expressing the primary and secondary outcomes oxidative stress, hence it was not possible to carry out a numerical pooled analysis.

Instead, results are reported as a narrative and results from each trial are presented in Table 1 (statistically significant results highlighted in bold blue colour).

5.4.1 Primary outcomes – Oxidative stress and anti-oxidant activities

Three of the four studies (Tuccar 2023[78], Davis 2017[118], and Yubero-Serrano 2011[111]) reported results on oxidative stress, referring to a total of 197 participants. As expected, there is a variety in the way oxidative stress is expressed and measured within the included studies.

Tuccar et al.[78] (11 female participants) reported on five markers of oxidative stress (Table 1), all of which showed statistically significant differences at 2hrs after the intervention meal was taken. The abstract mentions measurements taken at other times (3hrs and 4hrs postprandial) but these results are not reported.

Davis et al.[118] (166 elderly participants) explored one marker of oxidative stress and found significantly lower levels of F2-IsoPs for the MD groups at 3 and 6 months.

Yubero-Serrano et al.[111] (20 participants) measured oxidative stress parameters and anti-oxidant activities at the end of the 4 week intervention. After this time a test meal was given to all participants and measurements were taken again at 2hrs (results not reported here) and 4hrs post-prandial. They found that overall for the majority of the parameters measured, MD+Q10 shows the most improvement in oxidative stress and anti-oxidant activities both at the end of the 4-week intervention and at 4hrs after the meal, while WD showed the least benefit.

5.4.2 Secondary outcomes

Inflammation

Two of the four studies (Tuccar 2023[78], Davis 2017[118]) explored inflammatory markers.

Tuccar et al[78] (11 female participants) explored 6 markers of inflammation in relation to diet, and found that there were significant differences in the IL postpandrial levels, while for the other markers there were no differences between MD and WD.

Davis et al.[118] (166 elderly participants) found no significant differences between the two intervention groups for the hs-CRP marker at the 6 month follow-up.

Cardiovascular markers

Two studies (Davis 2017[118] and Yubero-Serrano 2011[111])

Davis et al.[118] (166 elderly participants) found that the MD-group participants had significantly better TG levels at the 6 month follow-up, but there were no significant differences in all other cardiovascular markers explored (including insulin and glucose levels).

Yubero-Serrano et al.[111] (20 participants) measured a host of cardiovascular parameters (including glucose and insulin) at the end of the 4-week intervention, and found that MD (or MD+Q10) showed the most benefit for total cholesterol,

LDL-C, ApoA-I, and ApoB, while there was no difference between the diets for the other parameters (HDL-C, TGs, glucose and insulin).

Cognitive function

One study only (Davis 2017[118]) explored cognitive function in association with the choice of diet. The results for this outcome were published in a different report to the one included in this review[121]. This report was not in the included studies as it only concentrates on cognitive function and doesn't mention oxidative stress, hence doesn't fulfil the inclusion criteria of this review. However, reporting of the cognitive function as a secondary outcome of the same population is of interest. The results from 137 participants found no significant differences in the cognitive function between the two intervention groups.

Other anthropometric measurements

Only one study (Miralles-Amoros 2023 [119] – 21 young female participants) explored outcomes related to eating attitudes, body image, mood, anger, and depression. They used specific scales and questionnaires for the measurements and found that for the MD group the body image scores were significantly decreased compared to the other two group interventions. No other differences were observed for the other parameters explored.

Table 1: Results and outcomes (primary and secondary)

Study and summary characteristics	Participants /interventions	Outcomes	Results	Significance /p-values
Tuccar 2023 [78] [Abstract only] Cross-over trial Duration: immediate (postprandial, measured at 2, 3, and 4 hrs after meal)	11 women MD meal - 11 WD meal - 11	**Primary (oxidative stress) (at 2 hrs)**		
		total antioxidant status (TAS)	**0.05+/-0.02 mmol/L**	**p=0.017**
		total thiol	**23.00+/-7.69 mumol/L**	**p=0.013**
		native thiol	**12.82+/-4.94 mumol/L**	**p=0.027**
		malondialdehyde (MDA)	**-0.17+/-0.06 nmol/L**	**p=0.022**
		Secondary (inflammatory factors) at 4 hrs		
		high sensitivity C-reactive protein (hs-CRP)	No differences	p≥0.05
		interleukin (IL)-6	**1.39+/-0.49 pg/mL**	**p=0.017**
		IL-17	**4.30+/-1.50 pg/mL**	**p=0.017**
		IL-23	**8.38+/-3.51 pg/mL**	**p=0.038**
		tumor necrosis factor alpha (TNF-alpha)	No differences	p≥0.05
		nuclear factor kappa B (NF-kappaB)	No differences	p≥0.05
Davis 2017 [118] [includes Knight 2015 [117]] Parallel trial	166 participants MD – HabDiet -	**Primary (oxidative stress)**		
		F2-IsoPs (3 months and 6 months)	**Significantly lower for MD**	**p<0.05**
		Secondary (inflammation, cognitive, and cardiovascular markers - at 3, 6 months)		
		Total plasma lipids	No differences	p≥0.05

Study and summary characteristics	Participants /interventions	Outcomes	Results	Significance /p-values
Duration: 6 months		LDL cholesterol	No differences	p≥0.05
		HDL cholesterol	No differences	p≥0.05
		Triglycerides (TGs)	**Significantly lower for MD**	**p<0.05**
		Total-to-HDL-cholesterol ratio	No differences	p≥0.05
		Glucose	No differences	p≥0.05
		Insulin	No differences	p≥0.05
		hs-CRP	No differences	p≥0.05
		Cognitive function (reported elsewhere[121])	No differences	p≥0.05
Miralles-Amoros 2023 [119] Parallel trial Duration: 12 weeks	Total 21 participants MD – 7 women FD – 7 women HAD – 7 women	**Primary (oxidative stress) -** Not available in this study		
		Secondary (anthropometric measurements)		
		Eating attitude (EAT-26 questionnaire)	No differences between the 3 groups	p≥0.05
		Body image (BSQ questionnaire)	**Score decreased for the MD group for pre and post measurements**	**p=0.049**
		Tension (POMS scale)	No differences between the 3 groups	p≥0.05
		Vigour (POMS)	No differences between the 3 groups	p≥0.05
		Anger (POMS)	No differences between the 3 groups	p≥0.05
		Depression (POMS)	Differences over time in each group but no differences between groups	p≥0.05
		Fatigue (POMS)	No differences between the 3 groups	p≥0.05
Yubero-Serrano 2011[111] (original)		**Primary (oxidative stress biomarkers)**		

Study and summary characteristics	Participants /interventions	Outcomes	Results	Significance /p-values
[Other records referring to the same population and considered as the same study: Lopez-Moreno 2016[110], 2018[109], Gutierrez-Mariscal 2012[115], 2014[116] Marin 2012[113], Meza-Miranda 2014 [114] Yubero-Serrano 2013[112]] Cross-over trial Duration: 4 weeks interventions, after which, measurements were taken and then a test meal was given and measurements were taken again at 2 and 4hrs	20 men and women MD MD+Q10 suppl WD	LDL oxidized (oxLDL) (U/L)	**At end of intervention - MD+Q10 most benefit**	**p<0.001**
			4hrs postprandial – No difference in groups	p≥0.05
		Protein carbonyl levels (PC)	**At end of intervention - MD+Q10 most benefit**	**p=0.022**
			4hrs postprandial - MD+Q10 most benefit	**p=0.013**
		Lipid peroxidation products (LPO)	**At end of intervention – MD(+Q10) most benefit**	**p<0.05**
			4hrs postprandial - MD+Q10 most benefit	**p=0.003**
		Nitrotyrosine (nmol/L)	**At end of intervention - MD+Q10 most benefit**	**p<0.05**
			4hrs postprandial - MD+Q10 most benefit	**p=0.041**
		Primary (anti-oxidant enzyme activities)		
		Superoxide dismutase (SOD) activity (U/mL)	**At end of intervention - MD+Q10 most benefit**	**p<0.05**
			4hrs postprandial – MD+Q10 most benefit	**p<0.001**
		Catalase (CAT) activity (U/dLx10)	**At end of intervention - MD+Q10 most benefit**	**p<0.05**
			4hrs postprandial - MD+Q10 most benefit	**p<0.002**
		Gluthatione peroxidase(GPx) activity (nmol/mL/min)	At end of intervention – No difference in groups	p≥0.05
			4hrs postprandial - MD+Q10 most benefit	**p<0.042**
		Secondary (cardiovascular markers - at the end of intervention period of 4 weeks**)**		

Study and summary characteristics	Participants /interventions	Outcomes	Results	Significance /p-values
		Total cholesterol	**WD showed least benefit**	**p<0.001**
		LDL cholesterol	**WD showed least benefit**	**p=0.013**
		HDL cholesterol	No difference in groups	p=0.069
		Triglycerides (TGs)	No difference in groups	p=0.675
		Apolipoprotein A-I (ApoA-I)	**WD showed least benefit**	**p=0.002**
		Apolipoprotein B (Apo B)	**WD showed least benefit**	**p=0.017**
		Glucose	No difference in groups	p=0.440
		Insulin	No difference in groups	p=0.470

NB1: Statistically significant results are highlighted in bold blue colour
NB2: Explanations of the abbreviations in this table can be found in the List of Abbreviations (page viii)

6 Discussion

The observed results are summarised and discussed here, separately per outcome.

6.1 Oxidative stress

Three of the four included trials (Tuccar 2023[78], Davis 2017[118], and Yubero-Serrano 2011[111]) reported outcomes related to oxidative stress. Across these there were 12 different biomarkers reported of either oxidative stress or anti-oxidant activities. No two trials reported the same biomarker, rendering meta-analysis impossible.

Even if meta-analysis were possible in terms of similarity of biomarker reported, there were heterogeneity issues that would have likely prevented reporting of pooled results. This was due to the small trial samples, the differences in trial design (parallel and cross-over), the baseline differences of the population, and the comparison interventions used as the alternative to MD.

Despite the heterogeneous study designs, samples sizes, and reported biomarkers, there is overall consistency on the apparently statistically significant superiority of the MD diet on the improvement of oxidative stress status. Davis et al.[118] offered the largest sample size, and the one oxidative stress biomarker reported showed a significant result.

6.2 Secondary outcomes

Similar situation was observed for the secondary outcomes of inflammation markers, cognitive effects, and anthropometric measures.

Cardiovasucal biomarkers: Two studies reported a good set of similar biomarkers that could potentially be used to carry out meta-analysis. However, the trial designs were different (one parallel one cross-over) and there was insufficient information to extract the necessary data for meta-analysis. In particular, Davis 2017[118] is a parallel trial but the numbers of participants in each comparison group

was not reported in the study text. Yubero-Serrano 2011[111] is a cross-over trial of three intervention groups, but the reporting is per intervention group separately, making meta-analysis impossible (a paired analysis would have been needed for meta-analysis). More importantly, the comparison groups to the MD intervention are not the same in the two trials. Hence, again meta-analysis was not possible.

The largest study's (Davis 2017[118]) results show a significant difference in triglycerides (with the benefit coming for the MD) while the smaller study (Yubero-Serrano 2011[111]) doesn't show report significance for this marker. Similar inconsistency is observed for the other cardiovascular markers, with the results from the largest study not showing a significant difference between the groups on the major cardiovascular markers.

Both studies agree that there is no difference between the groups for the glucose and insulin levels.

Inflammation: Both studies (Davis 2017[118] and Tuccar 2023[78]) agree that there was no significant difference between the diet intervention groups on the inflammation marker of creatinine (hs-CRP). The conclusion here is that MD doesn't affect inflammation (when this is expressed as creatinine levels) in the body. Although there is consistency in both included studies, the sample size and heterogenous designs of the trials are serious considerations.

Cognitive function and anthropometric measures: There is only one study reporting on each of these outcomes; there are no comparison observations to discuss. The limited available evidence on these outcomes points to no differences due to diet choices on the cognitive function and anthropometric measures, except possibly the body image (as reported in Miralles-Amoros 2023[119]).

7 Conclusions

7.1 Overall completeness and applicability of evidence

Despite the comprehensive systematic search, the evidence based on RCTs on the effects of MD on the oxidative stress status of healthy adults is rather limited. Lower-level evidence from observational studies (cohorts, case-controls, and sectional studies) was not considered in the systematic review.

There is a body of literature exploring the effects of MD on oxidative stress for populations with specific pre-existing conditions, but these studies were excluded from the review, as the emphasis was on healthy populations.

The significant, albeit limited, evidence found in this systematic review is however encouraging as it is consistent among the included studies.

7.2 Implications for research and practice

In order to make inferences for the wider healthy population, more concrete evidence is needed.

Hence the question on whether MD has an effect on the oxidative stress status cannot be answered robustly without further evidence on larger populations and improved consistency and reporting among studies.

While the consistent results in the, mainly small, included studies in this work, are encouraging, the practice of following the MD diet with the sole purpose of improving oxidative stress status cannot be recommended on the basis of this review.

8 Strengths and Weaknesses of this work

The literature review part includes a comprehensive but not systematic exploration of the published works, hence some evidence may be missing.

The systematic review however, includes a comprehensive and systematic search of the literature of 2 databases (Embase and Medline) and a register (CENTRAL); this is considered a strength.

These databases have an emphasis on English language, hence there may be material published in other languages/databases that is not considered here.

The processes followed for the systematic review are those suggested by Cochrane, known to provide systematic reviews of very high quality, and this is another strength of this work.

8.1 Potential biases in the review process

For the systematic review part, the relevance and eligibility of identified studies were assessed carefully, however for one study it was not possible to obtain the full text paper in time for this work to be completed, hence there may be details that are missed which may contribute to biases being introduced in the process.

Furthermore, it was not possible to conduct an assessment of publication bias (through a funnel plot) as there were less that the minimum requirement of 10 studies included.

8.2 Reporting of oxidative stress

There is currently no agreed biomarker, or set of biomarkers, within the scientific community that should be reported for oxidative stress, and neither is there a suggested time-scale within which measurements should be taken. Consequently, researchers feel free to choose how and when oxidative stress should be measured and reported in their published works.

This not only introduces a currently insurmountable source of heterogeneity among studies but may also be a source of reporting and/or selective reporting bias, as researchers could potentially choose to report only the choice of oxidative stress biomarkers that show a significant result. Prospective trial registration records would help to detect and assess this source of bias, but of the three trials included in this review only one (Davis et al.[118]) provided a trial registration number.

8.3 Quality of the evidence

The overall quality of the evidence is considered low due to the very small number of participants involved in the included studies. The small samples in three of the four studies, means that the data were not normally distributed and hence their numerical results were obtained using non-parametric statistical techniques. This weakness is likely affecting the robustness and accuracy of the resulting measurements. Consequently, the applicability of the evidence in the wider population is affected.

Nevertheless, the consistently statistically significant results observed within the trials, are encouraging, but further research is needed before they can be confirmed.

Appendices

A1. Search strategies

The following search strategies were used to the corresponding databases – searches carried out on 25th April 2024.

A1.1 Medline

Line	Command	Yield
1	Diet, Mediterranean/	5600
2	(((mediterranean or med or medi or md or mind or cretan or hellenic) adj3 diet*) or meddiet*).ti,ab,kf.	9499
3	1 or 2	10218
4	Hydrocortisone/an, bl [Analysis, Blood]	35922
5	Stress, Psychological/ or Stress, Physiological/	216476
6	(cortisol or ((corti* or hydrocorti*) adj5 (blood? or serum or sera or plasma or analys* or level? or test*))).ti,ab,kf.	120067
7	stress*.ti,ab,kf.	1158236
8	4 or 5 or 6 or 7	1315075
9	exp randomized controlled trial/	612834
10	controlled clinical trial.pt.	95525
11	randomized.ab.	643414
12	placebo.ab.	247760
13	drug therapy.fs.	2686446
14	randomly.ab.	432247
15	trial.ab.	695207
16	groups.ab.	2669730
17	or/9-16	5941455
18	exp animals/ not humans/	5213998
19	17 not 18	5197512
20	3 and 8 and 19	**250**

A1.2 Embase

Line	Command	Yield
1	exp Mediterranean diet/	13646
2	(((mediterranean or med or medi or md or mind or cretan or hellenic) adj3 diet*) or meddiet*).ti,ab,kf.	13119
3	1 or 2	16964
4	hydrocortisone blood level/	27292
5	exp physiological stress/	368801
6	(cortisol or ((corti* or hydrocorti*) adj5 (blood? or serum or sera or plasma or analys* or level? or test*))).ti,ab,kf.	153064
7	stress*.ti,ab,kf.	1437290
8	4 or 5 or 6 or 7	1689942
9	exp randomized controlled trial/	820744
10	Controlled clinical trial/	472977
11	random$.ti,ab.	2060097
12	randomization/	99186
13	intermethod comparison/	306120
14	placebo.ti,ab.	376020
15	(compare or compared or comparison).ti.	623219
16	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	2907788
17	(open adj label).ti,ab.	114887
18	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	281653
19	double blind procedure/	218262
20	parallel group$1.ti,ab.	33425
21	(crossover or cross over).ti,ab.	127955
22	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	431455
23	(assigned or allocated).ti,ab.	509889
24	(controlled adj7 (study or design or trial)).ti,ab.	469651
25	(volunteer or volunteers).ti,ab.	288749
26	human experiment/	658935
27	trial.ti.	421759
28	or/9-27	6571151
29	(random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)	9937
30	Cross-sectional study/ not (exp randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)	388709

Line	Command	Yield
31	(((case adj control$) and random$) not randomi?ed controlled).ti,ab.	22283
32	Systematic review.ti,ab. not (trial or study).ti.	352405
33	(nonrandom$ not random$).ti,ab.	19432
34	random field$.ti,ab.	3071
35	(random cluster adj3 sampl$).ti,ab.	1645
36	(review.ab. and review.pt.) not trial.ti.	1189910
37	we searched.ab. and (review.ti. or review.pt.)	52496
38	update review.ab.	140
39	(databases adj4 searched).ab.	67572
40	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	1249320
41	Animal experiment/ not (human experiment/ or human/)	2627131
42	or/29-41	4554130
43	28 not 42	5773087
44	3 and 8 and 43	**330**

A1.3 Cochrane

Line	Command	Yield
#1	MeSH descriptor: [Diet, Mediterranean] explode all trees	945
#2	((((mediterranean or med or medi or md or mind or cretan or hellenic) NEAR/3 diet*) or meddiet*)):ti,ab,kw	2701
#3	#1 or #2	2701
#4	MeSH descriptor: [Hydrocortisone] explode all trees and with qualifier(s): [analysis - AN, blood - BL]	4393
#5	MeSH descriptor: [Stress, Psychological] explode all trees	8877
#6	MeSH descriptor: [Stress, Physiological] this term only	1701
#7	((cortisol or ((corti* or hydrocorti*) NEAR/5 (blood? or serum or sera or plasma or analys* or level? or test*)))):ti,ab,kw	17210
#8	(stress*):ti,ab,kw	84928
#9	#4 or #5 or #6 or #7 or #8	96572
#10	#3 and #9 in Trials	**277**

A2. Characteristics of studies

Table 2: Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes
Tuccar 2023 [78]	Randomised cross-over Follow-up time: Immediately after food.	11 healthy women, aged 19-45 yrs BMI: 20.0-24.9 kg/m2	two different isocaloric meals: MD diet and western diet (WD)	Postprandial oxidative and inflammatory responses at 2, 3, and 4hrs after the meal. (oxidative [total antioxidant status (TAS), total oxidant status (TOS), total thiol, native thiol, malondialdehyde (MDA)] and inflammatory [high sensitivity C-reactive protein (hs-CRP), interleukin (IL)-6, IL-17, IL-23, tumor necrosis factor alpha (TNF-alpha) and nuclear factor kappa B (NF-kappaB)] markers)	Not able to obtain pdf
Davis 2017 [118] [includes Knight 2015 [117]]	Randomised parallel (MedLey) Intervention period – 6 months	166 adults ≥65 yrs, nonsmokers and free of chronic disease Australian population	MedDiet (MD) habitual diet (HabDiet)	outcomes: cognitive function (reported elsewhere[121]), cardiovascular risk including inflammation biochemistry results measured at 3 and 6 months (comparisons between these 2 time points)	
Miralles-Amoros 2023 [119]	Randomised parallel – block design in 3 arms 12 weeks duration	21 female handball players, age 22 ± 4 yrs 172.0 ± 5.4 cm and 68.4 ± 6.7 kg	three groups: FD (free diet) MD (Mediterranean diet) HAD (High antioxidant diet)	Outcomes: Body image, psychological variables (associated with oxidative stress) Measured pre, during, and post intervention (only pre and post considered here)	
Yubero-Serrano 2011[111] (original) [Other records referring to the same population and considered as the same study: Lopez-Moreno 2016[110], 2018[109], Gutierrez-Mariscal 2012[115], 2014[116] Marin 2012 [113], Meza-Miranda 2014 [114]	Randomised cross-over 4-week duration each branch, after which a test meal was given	20 Elderly men and women	Three branches: MD diet MD+Q10 supplement Western diet	Outcomes (measured after the test meal following 4 weeks of intervention) postpandrial oxidative status (includes biochemical analysis), cardiovascular markers (including insulin and glucose)	

Yubero-Serrano, 2013[112]]					

References to included studies

78. Tuccar TB, Akbulut G. Mediterranean meal favorably effects postprandial oxidative stress response compared with a Western meal in healthy women: A randomized crossover trial. International Journal for Vitamin and Nutrition Research. 2023;93(4):319-28

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Table 3: Characteristics of excluded studies

Study	Reason for exclusion
Al-Aubaidy 2021[79]	RCT but wrong population (type II diabetes)
Arcan 2024 [80]	RCT but wrong population (post-traumatic stress disorder)
Barona 2012 [81]	RCT but wrong population (women only with metabolic syndrome)
Georgoulis 202 [82]	RCT but wrong population (obstructive sleep apnea)
Hagfors 2003 [28]	RCT but wrong population (rheumatoid arthritis)
Monserrat-Mesquida 2022a [59]	RCT but wrong population (non-alcoholic fatty liver disease)
Monserrat-Mesquida 2022b [65]	RCT but wrong population (non-alcoholic fatty liver disease)
Parletta 2019 [83]	RCT but wrong population (depression)
Quetglas-Llabres 2023 [60]	RCT but wrong population (non-alcoholic fatty liver disease)
Radkhah 2023 [84]	RCT but wrong population (depression)
Stachowska 2005 [85]	RCT but wrong population (kidney graft patients)
Toobert 2002 [86]	RCT but wrong population (type II diabetes)
Toobert 2003 [53]	RCT but wrong population (type II diabetes)
Angelico 2012 [102]	Not RCT (consecutive cohort)
Athanassopoulou 2018 [104]	Not RCT (randomly selected sub-cohort from an RCT-intervention group)
Barkhordari 2022 [87]	Not RCT (cross-sectional)
Bekkouche 2014 [88]	Not RCT (case-control)
Biasini 2021 [89]	Not RCT (survey)
D'Amico 2021 [90]	Not RCT (cross-sectional)
Davinelli 2019 [91]	Not RCT (review)
Garcia-Prieto 2007 [92]	Not RCT (cohort)
Jang 2024 [93]	Not RCT (cohort)
Kaluza 2023 [94]	Not RCT (cohort)
Kim 2011 [95]	Not RCT (cohort)
Luisi 2019 [105]	Not RCT (2 groups where subjects were divided in two arms according to their BMI)
Mahmoudzadeh 2023 [96]	Not RCT (cohort)
Marendic 2024 [97]	Not RCT (survey)
Mohajeri 2023 [98]	Not RCT (cross-sectional)
Morales 2023 [103]	Not RCT (cross-sectional)
Ojeda-Rodriguez 2021 [99]	Not RCT (cohort)
Ruiz-Saavedra 2020 [100]	Not RCT (cross-sectional)
Ulker 2024 [101]	Not RCT (case-control)

Study	Reason for exclusion
Abenavoli 2017 [106]	Wrong intervention (antioxidant intake as part of intervention)
Urquiaga 2010 [108]	Wrong intervention (not Med diet)
Urquiaga 2017 [107]	Wrong intervention (ready-made diet with red wine)

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A3. Risk of Bias tables for each study

Davis 2017[118]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent holder of the randomisation schedule performed treatment allocation without contact with the volunteers (information from the trial registration record: ACTRN12613000602729}
Allocation concealment (selection bias)	Low risk	An independent holder of the randomisation schedule performed treatment allocation without contact with the volunteers.
Blinding of participants and personnel (performance bias)	Low risk	An independent holder of the randomisation schedule performed treatment allocation without contact with the volunteers.
Blinding of outcome assessment (detection bias)	Low risk	An independent holder of the randomisation schedule performed treatment allocation without contact with the volunteers
Incomplete outcome data (attrition bias)	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All oputcomes reported
Other bias	Unclear risk	

Miralles-Amoros 2023[119]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	an online computer software was used to electronically randomise subjects using a block design in three arms (one control and two experimental)
Allocation concealment (selection bias)	Low risk	A researcher external to this study was in charge of preparing these envelopes.
Blinding of participants and personnel (performance bias)	Low risk	A researcher external to this study was in charge of preparing these envelopes.
Blinding of outcome assessment (detection bias)	Low risk	A researcher external to this study was in charge of preparing these envelopes.
Incomplete outcome data (attrition bias)	Low risk	All participants were included in the analysis (Figure 1)
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Unclear risk	

Tuccar 2023[78]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomised cross-over design
Allocation concealment (selection bias)	Unclear risk	No information in abstract
Blinding of participants and personnel (performance bias)	Unclear risk	No information in abstract
Blinding of outcome assessment (detection bias)	Unclear risk	No information in abstract
Incomplete outcome data (attrition bias)	Unclear risk	No information in abstract
Selective reporting (reporting bias)	High risk	Only significant results are reported numerically
Other bias	Unclear risk	

Yubero-Serrano 2011[111]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned in acrossover design.
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias)	Unclear risk	No information
Blinding of outcome assessment (detection bias)	Unclear risk	No information
Incomplete outcome data (attrition bias)	Low risk	All participants included in the analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	

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