**Appendix 1: Database search strategies**

1. **General search themes & keywords**

|  |  |
| --- | --- |
| **Theme** | **Keywords** |
| 1. **Mediterranean diet**
 | Mediterranean diet, Mediterranean-style diet, Mediterranean-type diet, Mediterranean-like diet, Mediterranean food, Mediterranean nutrition, Mediterranean meal. |
| 1. **Inflamm-aging/ Inflammation**
 | Inflamm-aging, inflammation, inflammatory markers, inflammatory mediators, pro-inflammatory, anti-inflammatory, cytokines, chemokines, interleukins, interferons, lymphokines, monokines, transforming growth factor beta, tumor necrosis factor alpha, c-reactive protein, nuclear factor kappa b. |

1. **MEDLINE search strategy**

|  |  |
| --- | --- |
| **#** | **Query** |
| 1 | Diet, Mediterranean/ |
| 2 | (Mediterranean adj3 diet\*).ti,ab. |
| 3 | (Mediterranean adj3 meal\*).ti,ab. |
| 4 | (Mediterranean adj6 food\*).ti,ab. |
| 5 | (Mediterranean adj6 nutrition\*).ti,ab. |
| 6 | (Mediterranean adj6 eat\*).ti,ab. |
| 7 | MedDiet.ti,ab. |
| 8 | exp Inflammation/ |
| 9 | exp Inflammation Mediators/ |
| 10 | inflamm\*.ti,ab. |
| 11 | pro-inflamm\*.ti,ab. |
| 12 | proinflamm.ti,ab. |
| 13 | anti-inflamm\*.ti,ab. |
| 14 | antiinflam\*.ti,ab. |
| 15 | exp Cytokines/ |
| 16 | cytokine\*.ti,ab. |
| 17 | chemokine\*.ti,ab. |
| 18 | interleukin\*.ti,ab. |
| 19 | interferon\*.ti,ab. |
| 20 | lymphokine\*.ti,ab. |
| 21 | monokine\*.ti,ab. |
| 22 | transforming growth factor beta\*.ti,ab. |
| 23 | TGF.ti,ab. |
| 24 | tumor necrosis factor\*.ti,ab. |
| 25 | tumour necrosis factor\*.ti,ab. |
| 26 | TNF.ti,ab. |
| 27 | C-reactive protein/ |
| 28 | c-reactive protein.ti,ab. |
| 29 | exp NF-kappa B/ |
| 30 | NF-kappa B.ti,ab. |
| 31 | NF-kB.ti,ab. |
| 32 | NFkB.ti,ab. |
| 33 | 1 or 2 or 3 or 4 or 5 or 6 or 7 |
| 34 | 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 |
| 35 | 33 and 34 |
| 36 | limit 35 to english language |

1. **Web of Science search strategy**

|  |  |  |
| --- | --- | --- |
| **Mediterranean Diet** | **AND** | **Inflamm-aging/Inflammation** |
| TI=(Mediterranean NEAR/3 diet\*) OR TI=(Mediterranean NEAR/3 meal\*) OR TI=(Mediterranean NEAR/6 food\*) OR TI=(Mediterranean NEAR/6 nutrition\*) OR TI= (Mediterranean NEAR/6 eat\*) OR TI=(MedDiet) OR AB=(Mediterranean NEAR/3 diet\*) OR AB=(Mediterranean NEAR/3 meal\*) OR AB=(Mediterranean NEAR/6 food\*) OR AB=(Mediterranean NEAR/6 nutrition\*) OR AB= (Mediterranean NEAR/6 eat\*) OR AB=(MedDiet)  | AND | TI=(inflamm\*) OR TI=(pro-inflamm\*) OR TI= (proinflamm\*) OR TI=(anti-inflamm\*) OR TI= (antiinflamm\*) OR TI=(cytokine\*) OR TI=(chemokine\*) OR TI=(interleukin\*) OR TI=(interferon\*) OR TI= (lymphokine\*) OR TI=(monokine\*) OR TI=(transforming growth factor beta\*) OR TI=(TGF) OR TI=(tumor necrosis factor\*) OR TI=(TNF) OR TI=(tumour necrosis factor\*) OR TI=(c-reactive protein) OR TI=(NF-kappa B) OR TI=(NF-kB) OR TI=(NFkB) OR AB=(inflamm\*) OR AB=(pro-inflamm\*) OR AB= (proinflamm\*) OR AB=(anti-inflamm\*) OR AB= (antiinflamm\*) OR AB=(cytokine\*) OR AB=(chemokine\*) OR AB=(interleukin\*) OR AB=(interferon\*) OR AB= (lymphokine\*) OR AB=(monokine\*) OR AB=(transforming growth factor beta\*) OR AB=(TGF) OR AB=(tumor necrosis factor\*) OR AB=(TNF) OR AB=(tumour necrosis factor\*) OR AB=(c-reactive protein) OR AB=(NF-kappa B) OR AB= (NF-kB) OR AB=(NFkB)  |

1. **EMBASE search strategy**

|  |  |
| --- | --- |
| **#** | **Query** |
| 1 | Diet, Mediterranean/ |
| 2 | (Mediterranean adj3 diet\*).ti,ab. |
| 3 | (Mediterranean adj3 meal\*).ti,ab. |
| 4 | (Mediterranean adj6 food\*).ti,ab. |
| 5 | (Mediterranean adj6 nutrition\*).ti,ab. |
| 6 | (Mediterranean adj6 eat\*).ti,ab. |
| 7 | MedDiet.ti,ab. |
| 8 | exp Inflammation/ |
| 9 | exp Inflammation Mediators/ |
| 10 | Inflammaging/ |
| 11 | inflamm\*.ti,ab. |
| 12 | pro-inflamm\*.ti,ab. |
| 13 | proinflamm.ti,ab. |
| 14 | anti-inflamm\*.ti,ab. |
| 15 | antiinflam\*.ti,ab. |
| 16 | exp Cytokines/ |
| 17 | cytokine\*.ti,ab. |
| 18 | chemokine\*.ti,ab. |
| 19 | interleukin\*.ti,ab. |
| 20 | interferon\*.ti,ab. |
| 21 | lymphokine\*.ti,ab. |
| 22 | monokine\*.ti,ab. |
| 23 | transforming growth factor beta\*.ti,ab. |
| 24 | TGF.ti,ab. |
| 25 | tumor necrosis factor\*.ti,ab. |
| 26 | tumour necrosis factor\*.ti,ab. |
| 27 | TNF.ti,ab. |
| 28 | C-reactive protein/ |
| 29 | c-reactive protein.ti,ab. |
| 30 | exp NF-kappa B/ |
| 31 | NF-kappa B.ti,ab. |
| 32 | NF-kB.ti,ab. |
| 33 | NFkB.ti,ab. |
| 34 | 1 or 2 or 3 or 4 or 5 or 6 or 7 |
| 35 | 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 |
| 36 | 34 and 35 |
| 37 | limit 36 to english language |

1. **CINAHL search strategy**

|  |  |  |
| --- | --- | --- |
| **Search ID #** | **Search Terms** | **Search Options** |
| S1 | MH “Mediterranean Diet” OR TI Mediterranean N6 food\* OR TI Mediterranean N6 nutrition\* OR TI Mediterranean N6 eat\* OR TI MedDiet OR AB Mediterranean N3 diet\* OR AB Mediterranean N3 meal\* OR AB Mediterranean N6 food\* OR AB Mediterranean N6 nutrition\* OR AB Mediterranean N6 eat\* OR AB MedDiet | **Expanders** - Apply related words; Apply equivalent subjects **Search modes** - Boolean/Phrase  |
| S2 | MH “Inflammation+” OR MH “Inflammation Mediators+” OR TI inflamm\* OR TI pro-inflamm\* OR TI proinflamm\* OR TI anti-inflamm OR TI antiinflamm\* OR MH “Cytokines+” OR TI cytokine\* OR TI chemokine\* OR TI interleukin\* OR TI interferon\* OR TI lymphokine\* OR TI monokine\* OR TI transforming growth factor beta\* OR TI TGF OR TI tumor necrosis factor\* OR TI tumour necrosis factor\* OR TI TNF OR MH “C-Reactive Protein” OR TI C-reactive protein OR TI c-reactive protein OR SU NF-kappa B OR TI NF-kappa B OR TI NFkB OR AB inflamm\* OR AB pro-inflamm\* OR AB proinflamm\* OR AB anti-inflamm OR AB antiinflamm\* OR AB cytokine\* OR AB chemokine\* OR AB interleukin\* OR AB interferon\* OR AB lymphokine\* OR AB monokine\* OR AB transforming growth factor beta\* OR AB TGF OR AB tumor necrosis factor\* OR AB tumour necrosis factor\* OR AB TNF OR AB C-reactive protein OR AB c-reactive protein OR SU NF-kappa B OR AB NF-kappa B OR AB NFkB  | **Expanders** - Apply related words; Apply equivalent subjects **Search modes** - Boolean/Phrase  |
| S3 | S1 AND S2 | **Limiters** - English Language; Peer Reviewed **Expanders** - Apply related words; Apply equivalent subjects **Search modes** - Boolean/Phrase  |

**Appendix 2: Other Data Extraction and Quality Assessment**

1. **Study Characteristics**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Article** | **Acronym (Registration)** | **Crossover** | **Country** | **Centres** | **Setting** | **Arm length** | **Total sample size (n)** |
| 1. Ambring et al., 2006 (18) | NR (NR) | Yes | Sweden | Single | NR | 4 wk | 22 |
| 2. Camargo et al., 2012 (19) | NR (NR) | Yes | Spain | Single | Home | 4 wk | 20 |
| 3. Clements et al., 2017 (21) | NU-AGE (NCT01754012) | No | UK(Subset) | Single(Subset) | Home | 1 yr | 120 |
| 4. Davis et al., 2017 (16) | MedLey (ACTRN12613000602729) | No | Australia | Single | Home | 6 mo | 166 |
| 5. Djuric et al., 2009 (24) | N/A (NCT0012016) | No | USA | Multi | NR | 6 mo | 69 |
| 6. Jaacks et al., 2018 (26) | NR (NCT00166088) | No | USA | Single | Home | 8 wk | 20\* |
| 7. Konstantinidou et al., 2010 (23) | N/A (ISRCTN53283428) | No | Spain | Single | Home | 3 mo | 90 |
| 8. Lopez-Moreno et al., 2018 (14) | NR (NR)*(Same study as (15))* | Yes | Spain | Single | Home | 4 wk | 20 |
| 9. Maijo et al., 2018 (22) | NU-AGE(NCT01754012) | No | UK(Subset) | Single(Subset) | Home | 1 yr | 122 |
| 10. Meslier et al., 2020 (27) | DINAMIC(NCT03071718) | No | Italy | Single | NR | 8 wk | 82 |
| 11. Perez-Martinez et al., 2007 (20) | NR (NR) | Yes | Spain | Single | NR  | 4 wk | 16 |
| 12. Stendell-Hollis et al., 2013 (25) | N/A (NCT01459991) | No | USA | Single | NR  | 4 mo | 129 |
| 13. van Dijk et al., 2012 (28) | MARIS(NCT00405197) | No | Netherlands | Single | NR | 8 wk | 60 |
| 14. Yubero-Serrano et al., 2012 (15) | NR (NR)*(Same study as (14))* | Yes | Spain | Single | NR | 4 wk | 20 |

\*Note: The actual total sample size for the (26) study is n=27 because there is a second intervention arm (“Supplements diet”). This is NR for the present scoping review as it was not treated as a control compared to the MedDiet; therefore, the results of this diet do not help to answer the research question.

NR: Not Reported

N/A: Not Applicable

DINAMIC: Diet-induced Arrangement of the Gut Microbiome for Improvement of Cardiometabolic Health

MedLey: The MedDiet for Cardiovascular and Cognitive Health in the Elderly

NU-AGE: European Project on Nutrition in Elderly People

MARIS: Mediterranean Approach to Reduce Insulin-Resistance Study

1. **Molecular Changes**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Article** | **Molecular Change** | **Molecule** **or*****Gene*** | **Role** | **MD1** | **MD2** |
| **vs.****C1** | **vs.****C2** | **vs.****C1** | **vs.****C2** |
| 1. Ambring et al., 2006 (18) | Serum level | hs-CRP |  | NS |  |  |  |
| MCP-1 |  | NS |  |  |  |
| IL-6 |  | NS |  |  |  |
| 2. Camargo et al., 2012 (19) | Activation | NFκB |  | NS (0 hr PP)NS (4 hr PP) | NS (0 hr PP)NS (4 hr PP) |  |  |
| Expression | *p65* |  | ↓ (0 hr PP)↓ (2 hr PP)NS (4 hr PP) | NS (0 hr PP)↓ (2 hr PP)NS (4 hr PP) |  |  |
| *IκBα* |  | NS (0 hr PP)NS (2 hr PP)NS (4 hr PP) | NS (0 hr PP)NS (2 hr PP)NS (4 hr PP) |  |  |
| *MCP-1* | (+) | NS (0 hr PP)↓ (2 hr PP)NS (4 hr PP) | NS (0 hr PP)NS (2 hr PP)NS (4 hr PP) |  |  |
| *TNFα* |  | NS (0 hr PP)NS (2 hr PP)NS (4 hr PP) | NS (0 hr PP)NS (2 hr PP)NS (4 hr PP) |  |  |
| *IL-6* |  | NS (0 hr PP)NS (2 hr PP)NS (4 hr PP) | NS (0 hr PP)NS (2 hr PP)NS (4 hr PP) |  |  |
| *MIF-1* |  | NS (0 hr PP)NS (2 hr PP)NS (4 hr PP) | NS (0 hr PP)NS (2 hr PP)NS (4 hr PP) |  |  |
| *MMP-9* | (+) | NS (0 hr PP)↓ (2 hr PP)↓ (4 hr PP) | NS (0 hr PP)NS (2 hr PP)NS (4 hr PP) |  |  |
| Serum level | MCP-1 |  | NS (0 hr PP) NS (4 hr PP) | NS (0 hr PP)NS (4 hr PP) |  |  |
|  | TNFα |  | NS (0 hr PP)NS (4 hr PP) | NS (0 hr PP)NS (4 hr PP) |  |  |
| IL-6 |  | NS (0 hr PP)NS (4 hr PP) | NS (0 hr PP)NS (4 hr PP) |  |  |
| 3. Clements et al., 2017 (21) | Production by isolated PBMCs | MCP-1 | (+) | NS (↓Δ) |  |  |  |
| CXCL8 |  | NS |  |  |  |
| Resistin |  | NS |  |  |  |
| TNFα | (+) | NS (↓Δ) |  |  |  |
| 4. Davis et al., 2017 (16) | Serum level | hs-CRP |  | NS |  |  |  |
| 5. Djuric et al., 2009 (24) | Serum level | CRP |  | NS (T0.5)NS (T1) |  |  |  |
| 6. Jaack et al., 2018 (26) | Serum level | IL-6 |  | NS (T0.5)NS (T1) |  |  |  |
| IL-8 |  | NS (T0.5)NS (T1) |  |  |  |
| CRP |  | NS (T0.5)NS (T1) |  |  |  |
| Adiponectin |  | NS (T0.5)NS (T1) |  |  |  |
| 7. Konstantinidou et al., 2010 (23) | Serum level | IFNγ |  | NS |  | NS |  |
| MCP-1 |  | NS |  | NS |  |
| s-Ps |  | NS |  | NS |  |
| s-CD40L |  | NS |  | NS |  |
| hs-CRP | (+) | NS |  | NS (↓Δ) |  |
| Expression | *ARHGAP15* | (+) | NS |  | ↓ |  |
| *IFNγ* | (+) | NS |  | ↓ |  |
| *IL-7R* |  | NS |  | NS |  |
| 8. Lopez-Moreno et al., 2018 (14) | Serum level | dAGE | (+) | ↓ (0 hr PP)↓ (4 hr PP) |  | ↓ (0 hr PP)↓ (4 hr PP) |  |
| mRNA level | *MG* | (+) | ↓ (0 hr PP)↓ (4 hr PP) |  | ↓ (0 hr PP)↓ (4 hr PP) |  |
| *CML* | (+) | ↓ (0 hr PP)↓ (4 hr PP) |  | ↓ (0 hr PP)↓ (4 hr PP) |  |
| *AGER1* | (+) | ↑ (0 hr PP)↑ (4 hr PP) |  | ↑ (0 hr PP)↑ (4 hr PP) |  |
| *RAGE* | (+) | ↓ (0 hr PP)↓ (4 hr PP) |  | ↓ (0 hr PP)↓ (4 hr PP) |  |
| *GloxI* | (-) | ↑ (0 hr PP)↑ (4 hr PP) |  | ↑ (0 hr PP)↑ (4 hr PP) |  |
| *ERɑ* | (-) | NS (0 hr PP)↑ (4 hr PP) |  | NS (0 hr PP)↑ (4 hr PP) |  |
| 9. Maijo et al., 2018 (22) | Production by isolated PBMCs | IFNα |  | NS |  |  |  |
| IFNβ |  | NS |  |  |  |
| IFNγ |  | NS |  |  |  |
| IL-12p40 |  | NS |  |  |  |
| IL-12p70 |  | NS |  |  |  |
| IL-12Rβ1 |  | NS |  |  |  |
| IL-12Rβ2 |  | NS |  |  |  |
| SOCS3 |  | NS |  |  |  |
| 10. Meslier et al., 2020 (27) | Serum level | hs-CRP |  | NSΔ (T0.5)NSΔ (T1) |  |  |  |
| 11. Perez-Martinez et al., 2007 (20) | Activation in PBMCs | NFκB | (+) | ↓ | NS |  |  |
| Serum level | VCAM-1 | (+) | ↓ | NS |  |  |
| ICAM-1 |  | NS | NS |  |  |
| MCP-1 |  | NS | NS |  |  |
| IL-6 |  | NS | NS |  |  |
| TNFα |  | NS | NS |  |  |
| 12. Stendell-Hollis et al., 2013 (25) | Serum level | IL-6 |  | NSΔ |  |  |  |
| TNFα |  | NSΔ |  |  |  |
| 13. van Dijk et al., 2012 (28) | Serum level | IL-1β |  | NSΔ | NSΔ |  |  |
| Factor VII |  | NSΔ | NSΔ |  |  |
| MIP-1α |  | NSΔ | NSΔ |  |  |
| SAP |  | NSΔ | NSΔ |  |  |
| TP |  | NSΔ | NSΔ |  |  |
| VEGF |  | NSΔ | NSΔ |  |  |
| IL-12p70 |  | NSΔ | NSΔ |  |  |
| CRP |  | NSΔ | NSΔ |  |  |
| IL-10 |  | NSΔ | NSΔ |  |  |
| IL-11 |  | NSΔ | NSΔ |  |  |
| IL-13 |  | NSΔ | NSΔ |  |  |
| IL-15 |  | NSΔ | NSΔ |  |  |
| IL-16 |  | NSΔ | NSΔ |  |  |
| IL-17 |  | NSΔ | NSΔ |  |  |
| IL-18 |  | NSΔ | NSΔ |  |  |
| IL-23 |  | NSΔ | NSΔ |  |  |
| IL-3 |  | NSΔ | NSΔ |  |  |
| IL-4 |  | NSΔ | NSΔ |  |  |
| IL-5 |  | NSΔ | NSΔ |  |  |
| IL-6 |  | NSΔ | NSΔ |  |  |
| IL-7 |  | NSΔ | NSΔ |  |  |
| IL-8 |  | NSΔ | NSΔ |  |  |
| IL-1RA |  | NSΔ | NSΔ |  |  |
| MCP-1 |  | NSΔ | NSΔ |  |  |
| MCSF |  | NSΔ | NSΔ |  |  |
| MDC |  | NSΔ | NSΔ |  |  |
| MIP-1β |  | NSΔ | NSΔ |  |  |
| TNFα-RTII |  | NSΔ | NSΔ |  |  |
| VCAM-1 |  | NSΔ | NSΔ |  |  |
| 14. Yubero-Serrano et al., 2012 (15) | mRNA level | *p65* | (+) | NS (0 hr PP)↓ (2 hr PP)↓ (4 hr PP) |  | NS (0 hr PP)↓ (2 hr PP)↓ (4 hr PP) |  |
| *IKKβ* | (+) | NS (0 hr PP)↓ (2 hr PP)↓ (4 hr PP) |  | NS (0 hr PP)↓ (2 hr PP)↓ (4 hr PP) |  |
| *IκBα* | (-) | NS (0 hr PP)↑ (2 hr PP)NS (4 hr PP) |  | NS (0 hr PP)↑ (2 hr PP)↑ (4 hr PP) |  |
| *MMP9* | (+) | NS (0 hr PP)↓ (2 hr PP)↓ (4 hr PP) |  | ↓ (0 hr PP)↓ (2 hr PP)↓ (4 hr PP) |  |
| *IL-1β* | (+) | NS (0 hr PP)↓ (2 hr PP)↓ (4 hr PP) |  | NS (0 hr PP)↓ (2 hr PP)↓ (4 hr PP) |  |
| *JNK1* | (+) | NS (0 hr PP)↓ (2 hr PP)↓ (4 hr PP) |  | NS (0 hr PP)↓ (2 hr PP)↓ (4 hr PP) |  |

Molecule “Role” is provided only for molecules with statistically significant results, to allow for interpretation of the change as pro- or anti-inflammatory. Greyed out cells are irrelevant or not applicable.

\*For Clements et al., 2017, non-significance was determined by overlap of error bars. For all other studies, it was determined using reported p-values.

For full names of molecule acronyms, please see **Appendix 2F**. Citations of “Role” for molecules is provided in **Appendix 2G**.

NS: Not significant difference (absolute value for MD vs. C at T1, unless otherwise specified)

↑: MD significantly higher than C (absolute value for MD vs. C at T1, unless otherwise specified)

↓: MD significantly lower than C (absolute value for MD vs. C at T1, unless otherwise specified)

NSΔ: Not significant difference (change from baseline for MD vs. C at T1, unless otherwise specified)

↑Δ: MD significantly higher than C (change from baseline for MD vs. C at T1, unless otherwise specified)

↓Δ: MD significantly lower than C (change from baseline for MD vs. C at T1, unless otherwise specified)

PP: Postprandial

(+): Molecule is pro-inflammatory and/or marker of inflammation

(-): Molecule is anti-inflammatory and/or higher levels indicate less inflammation

T0.5: Study midpoint

T1: Study endpoint

1. **Baseline Population Characteristics**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Article** | **Mean Age** **(yrs ± SD/SEM)** | **Age Range (yrs)** | **Baseline BMI** | **% Female** | **Unique population** | **Clinically diagnosed chronic disease**  | **Baseline diet** | **SES** | **Race** |
| 1. Ambring et al., 2006 (18) | 43 ± 1 | 36-51 | Overweight (mean) | 45% | N/A | No - described as "healthy" (p. 575) | NR | NR | NR |
| 2. Camargo et al., 2012 (19) | 67.1 ± 4.52  | NR | Obese (mean) | 50% | N/A | No - described as "healthy" (p. 503) except 6 cases of HTN, 2 HLD, 3 DM.  | NR | NR | NR |
| 3. Clements et al., 2017 (21) | 70.33 ± 4.16 | 65-79 | Overweight (mean) | 61% | N/A | No - excluded individuals with chronic disease in past 2 or 3 years (according to trial registry and publication, respectively)  | NR | NR | NR |
| 4. Davis et al., 2017 (16) | MD1: 71.0 ± 4.9C1: 70.8 ± 4.9 | NR (Inclusion: ≥65) | Overweight (mean) | MD1: 58%C1: 54% | N/A | No - excluded individuals with chronic disease | NR | NR | NR |
| 5. Djuric et al., 2009 (24) | 44 ± NR | 25-59 | Normal (mean) | 100% | N/A | No - described as "healthy" (p. 156) | Inclusion criteria (7d):Fat: ≥23%MUFA: ≤48%Fruit: <5.5 s/dSupplements: ≤150% RDA | College graduates: 91%  | White: 86%  |
| 6. Jaacks et al., 2018 (26) | 51.4 ± NR | NR | Overweight to obese (inclusion) | 73% | N/A | No - excluded individuals with chronic disease | Inclusion:TFA: >10% (24 hr)Cholesterol: >300mg/d (24 hr)No antioxidants, vitamins, or minerals (4 wk)Reported (3d): MD1 group (Mean)Fat: 40%SFA: 13%CHO: 47%Protein: 14%Fibre: 20gCholesterol: 362mgMUFA: 17gOmega-3 FAs: 0.8gOmega-6 FAs: 7.1gC1 group (Mean)Fat: 40%SFA: 13%CHO: 44%Protein: 17%Fibre: 18g/dCholesterol: 292mg/dMUFA: 23gOmega-3 FAs: 0.8g/dOmega-6 FAs:7.6g/d | NR | NR |
| 7. Konstantinidou et al., 2010 (23) | MD1: 44 ± 10MD2: 45 ± 10C1: 43 ± 13 | 20-50 | Overweight (mean) | MD1: 73% MD2: 77% C1: 66% | N/A | Likely No - excluded individuals with HCE, DM, HTN, intestinal diseases, other diseases which could affect study adherence | Inclusion: No antioxidants | NR | NR |
| 8. Lopez-Moreno et al., 2018 (14) | NR(Inclusion: ≥65) | NR (Inclusion: ≥65) | Normal to extremely obese (inclusion) | NR(Both sexes) | N/A | No - excluded individuals with chronic disease | Inclusion:No FA supplements (including fish oil)No “high doses” (p. 341) of antioxidant vitamins (A, C, E, β-carotene) | NR | NR |
| 9. Maijo et al., 2018 (22) | 70.27 ± 4.02  | NR (Inclusion: 65-79) | Overweight (mean) | 60% | N/A | No - excluded individuals with chronic disease in past 2 years | NRExcluded those already enrolled in another dietary intervention study | NR | NR |
| 10. Meslier et al., 2020 (27) | 43 ± 12 | NR(Inclusion: 20-65) | Obese (mean) | 52% | N/A | No - excluded individuals with chronic disease in past 3 months | Run-in (2 weeks): HabDietInclusion:No probiotics, functional foods, or supplements Whole foods and/or fibre-enriched: ≤2s/dFruits/vegetables: ≤3s/d | NR | NR |
| 11. Perez-Martinez et al., 2007 (20) | NR | NR | NR | 0% | Medical students | No - described as "healthy" (p. e141) | NR | NR | NR |
| 12. Stendell-Hollis et al., 2013 (25) | 29.7 ± 4.6 | NR (Inclusion: 18-40) | Overweight (mean) | 100% | Postpartum breastfeeding women | No - described as being in "general good health" (p. 49) | Run-in (1 week): 6oz orange juice + 1oz cheese (2x/d)Washout (4 weeks): No nuts + ≥5 servings/d of fruits/vegetables | College graduates: 69.0% | White: 75.2%Hispanic: 24.8% |
| 13. van Dijk et al., 2012 (28) | MD1: 55.6 ± 6.5C1: 52.2 ± 6.9C2: 58.4 ± 5.3  | 45-60 | Overweight (mean) | MD1: 60%C1: 53%C2: 53% | N/A | No - described as "healthy" (p. 1220) | Run-in (2 weeks): 35-40% fat [19% SFA] | NR | NR |
| 14. Yubero-Serrano et al., 2012 (15) | NR | NR (Inclusion: ≥65) | Normal to extremely obese (inclusion) | NR(Both sexes) | N/A | No - excluded individuals with chronic disease | Inclusion:No FA supplements (including fish oil)No “high doses” (p. 341) of antioxidant vitamins (A, C, E, β-carotene) | NR | NR |

NR: Not Reported

N/A: Not Applicable

BMI: Body Mass Index

CHO: Carbohydrate

DM: Diabetes mellitus

HabDiet: Habitual diet

HCE: Hypercholesterolemia

HLD: Hyperlipidemia

HTN: Hypertension

MUFA: Monounsaturated fatty acid

RDA: Recommended daily allowance

SES: Socioeconomic status (includes income, education, and occupation, as per (40))

SFA: Saturated fatty acid

TFA: Trans fatty acid

See **Appendix 2D** for specific information on MD1, MD2, C1, C2 (where applicable).

BMI was categorized according to the following ranges, as per (41):

Underweight: <18.5 kg/m2

Normal: 18.5-24.9 kg/m2

Overweight: 25-29.9 kg/m2

Obese: 30-34.9 kg/m2

Extremely obese: >35 kg/m2

1. **Dietary Intervention Characteristics**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Article** | **Name (Label)** | **Sample size** | **Description**  | **Caloric state** | **Frequency** |
| 1. Ambring et al., 2006 (18) | Med-inspired Diet (MD1) | 22 | Protein: 16%CHO: 48%Fat: ~40.5%[SFA: 7.5%, MUFA: 5%, n-6 PUFA: ~15%, n-3 PUFA: ~2-3%]Alcohol: 2%Glycemic index: ↓ 30%+ Sterol esters in margarine (2g/d)Fibre: 34gAntioxidants: 3-4x (vs. C1) | NR | NR |
| Ordinary Swedish Diet (C1) | 22 | Protein: 16%CHO: 48%Fat: 34%[SFA: 15%, MUFA: 13%, n-6 PUFA: 5%, n-3 PUFA: 1%]Alcohol: 2%Cholesterol: 321gFibre: 17g | NR | NR |
| 2. Camargo et al., 2012 (19) | MedDiet + VOO (MD1) | 20 | Protein: 15%CHO: 47%Fat: 38% [SFA: <10%, MUFA: 24%, PUFA: 4% (ɑ-linolenic acid: 0.4%)]Cholesterol: <300mg/d | NR | NR |
| SFA diet (C1) | 20 | Protein: 15%CHO: 47%Fat: 38%[SFA: 22%, MUFA: 12%, PUFA: 4% (ɑ-linolenic acid: 0.4%)]Cholesterol: <300mg/d | NR | NR |
| CHO-PUFA diet (C2) | 20 | Protein: 15%CHO: 55%Fat: 30%[SFA: <10%, MUFA: 12%, PUFA: 8% (ɑ-linolenic acid: 2%)]Cholesterol: <300mg/d | NR | NR |
| 3. Clements et al., 2017 (21) | MedDiet (MD1) | 65 | Whole grains: 6sFruits: 2sVegetables: 330g (Legumes: 200g/wk)Dairy: 500 mL (30g cheese)Seafood: 2s/wkMeat/poultry: 4s/wkNuts: 2s/wkStarch: 150g (80g whole grain rice or pasta: 2s/wk)Eggs: 2-4s/wkOil/fat: 20g/d oil + 30g/d margarine (rich in MUFA + PUFA)Alcohol: ≤2s/d men, ≤1s/d women (preferably red wine)Fluid: 1.5L/dSalt: ReduceSugar: Reduce | NR | NR |
| HabDiet (C1) | 57 | Maintain habitual dietProvided healthy living leaflet | NR | NR |
| 4. Davis et al., 2017 (16) | Australianized MedDiet (MD1) | 73 (3 months), 70 (6 months) | Dependent on energy levelProtein: 17-18%CHO: NRFat: 38-40%[SFA: 7-8%, MUFA: 21-23%, PUFA: 18-21%] | Isocaloric | NR |
| HabDiet (C1) | 68 (3 months), 67 (6 months) | Maintain habitual diet | Isocaloric  | NR |
| 5. Djuric et al., 2009 (24) | Modified MedDiet (MD1) | 35 (baseline), 27 (3 and 6 months) | Goal: PUFA:SFA:MUFA = 1:2:5↑ Vegetables to 7-9s | NR | NR |
| HabDiet (C1) | 34 (baseline, 3 mo), 33 (6 mo) | Maintain habitual dietCorrect any nutritional deficiencies <67% RDA | NR | NR |
| 6. Jaack et al., 2018. (26) | MedDiet (MD1) | 11 | Protein: 0.8g/kdSFA & TFA: <7%Cholesterol: <200mg/d | NR | 3 meals + beverages2 snacks |
| HabDiet, high fat American-type (C1) | 9 | Maintain habitual dietNo supplements allowedNo dietary advice provided*(See Baseline Diet,* ***Appendix 2C****)* | NR | NR |
| 7. Konstantinidou et al., 2010 (23) | MedDiet + WOO (MD1) | 30 (serum concentration), 16 (gene expression) | Individualized advice from dietitian to increase MedDiet score+ Use of WOO (polyphenols: 55mg/kg; otherwise, same characteristics as VOO) | NR | NR |
| MedDiet + VOO (MD2) | 30 (serum concentration), 20 (gene expression) | Individualized advice from dietitian to increase MedDiet score+ Use of VOO (polyphenols: 328mg/kg; otherwise, same characteristics as WOO) | NR | NR |
| HabDiet (C1) | 29 (serum concentration), 20 (gene expression) | NR (Maintain habitual diet) | NR | NR |
| 8. Lopez-Moreno et al., 2018 (14) | MedDiet + CoQ (MD1) | 20 | Protein: 15%CHO: 47%Fat: 38%[SFA: 10%, MUFA: 24%, PUFA: 4%]+ 200mg CoQ capsule | Isocaloric | NR |
| MedDiet + placebo (MD2) | 20 | Protein: 15%CHO: 47%Fat: 38%[SFA: 10%, MUFA: 24%, PUFA: 4%]+ placebo capsule | Isocaloric | NR |
| Western SFA diet (C1) | 20 | Protein: 15%CHO: 47%Fat: 38%[SFA: 22%, MUFA: 12%, PUFA: 4%] | Isocaloric | NR |
| 9. Maijo et al., 2018 (22) | MedDiet + Vit D (MD1) | NR | Protein: 15-20%CHO: NRFat: ~31-51% [SFA: <10%, TF: <1%, MUFA: 8-28%, PUFA: <12%]Vitamin D: 15μg/dRecommended:Fibre: 30-40g/dSodium: 2g/dPotassium: 1.3g/dIron: 10mg/dFolate: 400μg/dVitamin B12: 5μg/d |  |  |
| HabDiet (C1) | 61 | Maintain habitual dietProvided national dietary guidelines leaflet | NR | NR |
| 10. Meslier et al., 2020 (27) | MedDiet (MD1) | 43 | Personalized based on following principles:Fruit/vegetables: ≥5s/d (~500g/d)Nuts: 30g/dRefined → Wholegrain cereal products: ≥2s/d (~200g/d)Meat/Eggs/Dairy → Fish/Legumes[Fish ≥2s/wk (~300g/wk), Legumes: ≥3s/wk (~300g/wk)]Butter/margarine → EVOO | NR | NR |
| HabDiet (C1) | 39 | Maintain habitual diet*(See Baseline Diet,* ***Appendix 2C****)*  | NR | NR |
| 11. Perez-Martinez et al., 2007 (20) | MedDiet + VOO (MD1) | 16 | Protein: 15%CHO: 47%Fat: 38%[SFA: <10%, MUFA: 24%, PUFA: 4% (ɑ-linolenic acid: 0.4%)]Cholesterol: <300mg/d | NR | 3 meals1 snack |
| Western SFA Diet (C1) | 16 | Protein: 15%CHO: 47%Fat: 38%[SFA: 22%, MUFA: 12%, PUFA: 4% (ɑ-linolenic acid: 0.4%)]Cholesterol: <300mg/d | NR | 3 meals1 snack |
| High-CHO + vegetal n-3 FAs Diet (C2) | 16 | Protein: 15%CHO: 55%Fat: <30%[SFA: <10%, MUFA: 12%, PUFA: 8% (ɑ-linolenic acid: 2%)]Cholesterol: <300mg/d | NR | 3 meals1 snack |
| 12. Stendell-Hollis et al., 2013 (25) | Med-style Diet (MD1) | 65 | Walnuts: 28g/dOlive oil: 1-2 tbp (refined or virgin)Fruits/vegetables: ≥7s/d+ Prenatal vitaminRecommended:Whole grains: ≥6s/dFish: ≥2s/wk↑ Legumes↓ Whole fat dairy, red meat, processed foods, desserts, fat (except olive oil) | NR | NR |
| MyPyramid Diet (C1) | 64 | USDA MyPyramid Diet for Pregnancy and Breastfeeding (NR in article; information obtained from (42)):Depends on if breastfeeding only vs. breastfeeding + formula:Fruits: 2 cups/dVegetables: 3 cups/dGrains: 7-8 oz/dMeat & Beans: 6-6.5 oz/dMilk: 3 cups/dUse of olive oil and fruits/vegetables “deemphasized” (p. 51) to distinguish from MD1.  | NR | NR |
| 13. van Dijk et al., 2012 (28) | MedDiet (MD1) | 15 | MUFA: 21% | NR | 3 meals+ snacks |
| Western-type SFA diet (C1) | 17 | Fat: 35-40%[SFA: 19%](Same as run-in diet) | NR | 3 meals+ snacks |
| Western-type MUFA diet (C2) | 17 | MUFA: 20% | NR | 3 meals + snacks |
| 14. Yubero-Serrano et al., 2012 (15) | MedDiet + CoQ (MD1) | 20 | Protein: 15%CHO: 47%Fat: 38%[SFA: 10%, MUFA: 24%, PUFA: 4%]+ 200mg CoQ capsule | Isocaloric | NR |
| MedDiet + placebo (MD2) | 20 | Protein: 15%CHO: 47%Fat: 38%[SFA: 10%, MUFA: 24%, PUFA: 4%]+ placebo capsule | Isocaloric | NR |
| Western SFA diet (C1) | 20 | Protein: 15%CHO: 47%Fat: 38%[SFA: 22%, MUFA: 12%, PUFA: 4%] | Isocaloric | NR |

NR: Not reported

CHO: Carbohydrate

CoQ: Coenzyme Q

EVOO: Extra virgin olive oil

HabDiet: Habitual diet

MUFA: Monounsaturated fatty acid

PUFA: Polyunsaturated fatty acid

RDA: Recommended daily allowance

SFA: Saturated fatty acid

USDA: United States Department of Agriculture

VOO: Virgin olive oil

WOO: Washed olive oil

1. **Quality Assessment**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Article** | **Q1****Question** | **Q2****Rand.** | **Q3****Follow-up** | **Q4a****Participant blinding** | **Q4b****Investigator blinding** | **Q4c****Assessor blinding** | **Q5****Baseline** | **Q6****Treatment** | **Q7****Data** | **Q8****Precision** | **Q9****Benefits** | **Q10****Application** | **Q11****Value** | **Total Score (/11)** | **Overall Quality** |
| 1. Ambring et al., 2006 (18) | Y | C | Y | N | C | C | Y | Y | Y | Y | Y | Y | Y | 9 | HIGH |
| 2. Camargo et al., 2012 (19) | Y | C | Y | N | N | Y | Y | Y | Y | Y | Y | Y | Y | 9 1/3 | HIGH |
| 3. Clements et al., 2017 (21) | Y | Y | Y | N | C | C | Y | N | Y | Y | Y | Y | Y | 9 | HIGH |
| 4. Davis et al., 2017 (16) | Y | Y | Y | N | N | C | Y | N | Y | Y | Y | Y | Y | 9 | HIGH |
| 5. Djuric et al., 2009 (24) | Y | C | Y | N | C | C | Y | N | Y | Y | Y | N | Y | 7 | MOD |
| 6. Jaacks et al., 2018 (26) | Y | C | Y | N | N | Y | C | N | Y | Y | Y | Y | Y | 7 1/3 | MOD |
| 7. Konstantinidou et al., 2010 (23) | Y | Y | Y | N | C | C | N | N | Y | Y | Y | Y | Y | 8 | MOD |
| 8. Lopez-Moreno et al., 2018 (14) | Y | C | Y | C | C | C | C | Y | Y | Y | Y | Y | Y | 8 | MOD |
| 9. Maijo et al., 2018 (22) | Y | Y | Y | N | N | Y | Y | N | Y | Y | Y | Y | Y | 9 1/3 | HIGH |
| 10. Meslier et al., 2020 (27) | Y | Y | Y | Y | C | Y | Y | Y | Y | Y | Y | Y | Y | 10 2/3 | HIGH |
| 11. Perez-Martinez et al., 2007 (20) | Y | C | C | N | C | C | C | Y | Y | Y | Y | N | Y | 6 | MOD |
| 12. Stendell-Hollis et al., 2013 (25) | Y | Y | Y | N | N | Y | Y | N | Y | Y | Y | N | Y | 8 1/3 | MOD |
| 13. van Dijk et al., 2012 (28) | Y | Y | Y | Y | N | C | C | Y | Y | Y | Y | Y | Y | 9 1/3 | HIGH |
| 14. Yubero-Serrano et al., 2012 (15) | Y | C | Y | C | C | C | C | Y | Y | Y | Y | Y | Y | 8 | MOD |
| **Total Yes (/14)** | 14 | 7 | 13 | 2 | 0 | 5 | 8 | 7 | 14 | 14 | 14 | 11 | 14 |  |  |

Y: Yes

N: No

C: Can’t tell

CASP RCT Questionnaire (43):

1. Did the study address a clearly focused research question?
2. Was the assignment of participants to interventions randomized?
3. Were all participants who entered the study accounted for at its conclusion?
4. *Multi-part question, see below:*
	1. Were the participants ‘blind’ to intervention they were given?
	2. Were the investigators ‘blind’ to the intervention they were giving to participants?
	3. Were the people assessing/analysing outcome/s ‘blinded’?
5. Were the study groups similar at the start of the randomised controlled trial?
6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?
7. Were the effects of intervention reported comprehensively?
8. Was the precision of the estimate of the intervention or treatment effect reported?
9. Do the benefits of the experimental intervention outweigh its harms and costs?
10. Can the results be applied to your local population/in your context?
11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?
12. **Alphabetical Summary List of Molecules**

|  |  |
| --- | --- |
| **Molecule or Gene** | **Full name** |
| Adiponectin | N/A |
| AGER1 | AGE receptor 1 (AGE=Advanced Glycation End product) |
| ARHGAP15 | Rho GTPase activating protein 15 |
| CML | N-carboxylmethyllysine (AGE) |
| CRP | C-reactive protein |
| hs-CRP | high sensitivity CRP |
| CXCL8 | C-X-C motif chemokine ligand 8 |
| dAGE | dietary AGE |
| ERɑ | Estrogen receptor alpha |
| Factor VII | N/A |
| GloxI | Glyoxylase I |
| ICAM-1 | Intercellular adhesion molecule 1 |
| IFNα | Interferon alpha |
| IFNβ | Interferon beta |
| IFNγ | Interferon gamma |
| IKKβ | Inhibitor of nuclear factor kappa-B kinase subunit beta |
| IL-10 | Interleukin 10 |
| IL-11 | Interleukin 11 |
| IL-12p40 | Interleukin 12 subunit p40 (also known as Interleukin 12 subunit beta) |
| IL-12p70 | Interleukin 12 subunit p70 (also known as Interleukin 12 subunit alpha) |
| IL-12Rβ1 | Interleukin 12 receptor beta 1 subunit |
| IL-12Rβ2 | Interleukin 12 receptor beta 2 subunit |
| IL-13 | Interleukin 13 |
| IL-15 | Interleukin 15 |
| IL-16 | Interleukin 16 |
| IL-17 | Interleukin 17 |
| IL-18 | Interleukin 18 |
| IL-1RA | Interleukin 1 receptor agonist |
| IL-1β | *See IL-12p40* |
| IL-23 | Interleukin 23 |
| IL-3 | Interleukin 3 |
| IL-4 | Interleukin 4 |
| IL-5 | Interleukin 5 |
| IL-6 | Interleukin 6 |
| IL-7 | Interleukin 7 |
| IL-7R | Interleukin 7 receptor |
| IL-8 | Interleukin 8 |
| IκBα | Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha |
| JNK1 | c-Jun N-terminal kinase 1 |
| MCP-1 | Monocyte chemoattractant protein 1 |
| MCSF | Macrophage colony-stimulating factor |
| MDC | Macrophage-derived chemokine |
| MG | Methylglyoxyl (AGE) |
| MIF-1 | Melanocyte-inhibiting factor |
| MIP-1α | Macrophage inflammatory protein 1 alpha |
| MIP-1β | Macrophage inflammatory protein 1 beta |
| MMP-9 | Matrix metallopeptidase 9 |
| NFκB | Nuclear factor kappa B |
| p65 | p65 subunit (of NFκB) |
| RAGE | Receptor for AGE |
| Resistin | N/A |
| s-CD40L | Soluble CD40 ligand |
| s-Ps | Soluble P-selectin |
| SAP | Serum amyloid P |
| SOCS3 | Suppressor of cytokine signalling 3 |
| TNFα | Tumour necrosis factor alpha |
| TNFα-RTII | TNFα receptor type II |
| TP | Thrombopoietin |
| VCAM-1 | Vascular cell adhesion molecule 1 |
| VEGF | Vascular endothelial growth factor |

1. **References for Molecule Roles**

|  |  |
| --- | --- |
| **Molecule or Gene** | **Reference for Role** |
| AGER1 | *See associated primary article* |
| ARHGAP15 | (44) |
| CML | *See associated primary article* |
| hs-CRP | *See associated primary article* |
| dAGE | *See associated primary article* |
| ERɑ | (45) |
| GloxI | *See associated primary article* |
| IFNγ | (46) |
| IKKβ | (47) |
| IL-12p40 | *See associated primary article* |
| IL-12p70 | *See associated primary article* |
| IL-1β | *See associated primary article* |
| IL-7R | (48) |
| IκBα | (49) |
| JNK1 | (50) |
| MCP-1 | *See associated primary article* |
| MG | *See associated primary article* |
| MMP-9 | (51) |
| NFκB | *See associated primary article* |
| p65 | *See associated primary article* |
| RAGE | *See associated primary article* |
| TNFα | (52) |
| VCAM-1 | (53) |