

National Health and Medical Research Council

Whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice, for preventing and treating health conditions

Technical Report

18 September 2023

Authors

Fodero L, Stathis S, Soh N. Whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice, for preventing and treating health conditions. 2023

Acknowledgements:

Thanks to the members of the Department of Health and Aged Care's Natural Therapies Review Expert Advisory Panel (NTREAP) and the National Health and Medical Research Council's Natural Therapies Working Committee (NTWC) for their advice and comments throughout the creation of this document. PRACI data was provided by Dr Amie Steel, University of Technology (UTS), Sydney.

Membership and other details of the Panel and Committee can be found at:

<https://www.health.gov.au/committees-and-groups/natural-therapies-review-expert-advisory-panel>
<https://www.nhmrc.gov.au/about-us/leadership-and-governance/committees/natural-therapies-working-committee>

Copyright

© Commonwealth of Australia 2023

All material presented in this publication is provided under a Creative Commons Attribution 4.0 International licence (www.creativecommons.org.au), with the exception of the Commonwealth Coat of Arms, NHMRC logo and content identified as being owned by third parties. The details of the relevant licence conditions are available on the Creative Commons website (www.creativecommons.org.au), as is the full legal code for the CC BY 4.0 International licence.

Attribution

Creative Commons Attribution 4.0 International Licence is a standard form licence agreement that allows you to copy, distribute, transmit and adapt this publication provided that you attribute the work. The NHMRC preference is that you attribute this publication (and any material sourced from it) using the following wording:

Source: National Health and Medical Research Council.

Use of images

Unless otherwise stated, all images (including background images, icons and illustrations) are copyrighted by their original owners.

Contact

To obtain information regarding NHMRC publications or submit a copyright request, contact: communications@nhmrc.gov.au

Funding:

This review is funded by the Australian Government Department of Health and Aged Care via the NHMRC, under Official Order 2019-20P047.

Table of Contents

| | |
|--|-----|
| Appendix A: Searching, selection criteria and screening..... | 7 |
| Appendix B: Methods of data appraisal, extraction, analysis, and reporting for included studies | 26 |
| Appendix C: Excluded studies | 34 |
| Appendix D: Details of Included studies | 90 |
| Appendix E: Detailed study descriptions and outcomes as reported by the study authors..... | 151 |
| Appendix F: Characteristics of studies awaiting classification | 178 |
| Appendix G: Characteristics of ongoing studies..... | 182 |
| Appendix H: Differences between protocol and review | 230 |
| Appendix I: How comments from methodological review were addressed..... | 232 |
| Appendix J: References..... | 233 |

List of Tables

| | |
|--|----|
| Table 1: Medline via Ovid search strategy..... | 8 |
| Table 2: Embase via Ovid search strategy | 9 |
| Table 3: Cochrane CENTRAL search strategy | 11 |
| Table 4: CINAHL via EBSCO search strategy | 11 |
| Table 5: AMED via OVID search strategy..... | 13 |
| Table 6: Outcome prioritisation by condition..... | 22 |
| Table 7: From GRADE guidelines 26 (Santesso 2020) | 32 |
| Table 8: Full text exclusion wrong study type | 34 |
| Table 9: Full text exclusion wrong population | 35 |
| Table 10: Full text exclusion wrong intervention | 35 |
| Table 11: Full text exclusion wrong comparator | 37 |
| Table 12: Public Call for Evidence..... | 38 |
| Table 13: Excluded studies awaiting classification | 87 |

| | |
|--|------------|
| Table 14: Excluded ongoing studies trial protocols..... | 87 |
| Table 15: References to included studies – ordered by appearance in the main report..... | 90 |
| Table 16: Duplicates of included studies | 91 |
| Table 17: Full text errata..... | 92 |
| Table 18: Andersen 2018 | 92 |
| Table 19: Raghunath 2020 | 94 |
| Table 20: Braun 2013 | 96 |
| Table 21: Stier-Jarmer 2021 | 99 |
| Table 22: Bairy 2020 | 100 |
| Table 23: Arentz 2017 | 102 |
| Table 24: Ratnakumari 2018 | 105 |
| Table 25: Beer 2014 | 107 |
| Table 26: Bernhardt 2009..... | 110 |
| Table 27: Shinto 2008 | 113 |
| Table 28: Braun 2014 | 115 |
| Table 29: Mittman 1990..... | 118 |
| Table 30: Szczurko 2007..... | 119 |
| Table 31: Szczurko 2009..... | 121 |
| Table 32: Cramer 2003..... | 124 |
| Table 33: Seely 2013 | 126 |
| Table 34: Raghunath 2020 Risk of bias (RoB2) – FLIC, STAI, BDI | 130 |
| Table 35: Braun 2013 Risk of bias (ROBINS-I) – tumour progression..... | 131 |
| Table 36: Stier-Jarmer 2021 ROB | 133 |
| Table 37: Bairy 2020 ROB..... | 134 |
| Table 38: Arentz 2017 overall ROB | 135 |
| Table 39: Arentz 2017 ROB Oligomenorrhoea | 135 |
| Table 40: Arentz 2017 ROB PCOSQ | 136 |

| | |
|--|-----|
| Table 41: Arentz 2017 ROB subgroup – QUICKI | 136 |
| Table 42: Arentz 2017 ROB subgroup – Testosterone | 137 |
| Table 43: Ratnakumari 2018 ROB..... | 137 |
| Table 44: Beer 2004 ROB | 138 |
| Table 45: Bernhardt 2009 ROB | 139 |
| Table 46: Shinto 2008 ROB..... | 140 |
| Table 47: Shinto 2008 ROB QOL | 141 |
| Table 48: Shinto 2008 ROB function | 142 |
| Table 49: Braun 2014 ROB | 143 |
| Table 50: Mittman 1990 ROB | 144 |
| Table 51: Szczurko 2007 ROB | 145 |
| Table 52: Szczurko 2009 ROB | 146 |
| Table 53: Cramer 2003 ROB | 147 |
| Table 54: Seely 2013 ROB..... | 148 |
| Table 55: Raghunath 2020 colon cancer outcomes..... | 151 |
| Table 56: Braun 2013 prostate cancer outcomes | 153 |
| Table 57: Stier-Jarmer 2021 T2DM outcomes | 154 |
| Table 58: Bairy 2020 T2DM outcomes | 155 |
| Table 59: Arentz 2017 PCOS outcomes..... | 157 |
| Table 60: Beer 2014 overweight and obesity outcomes | 158 |
| Table 61: Bernhardt 2009 anxiety outcomes | 160 |
| Table 62: Shinto 2008 MS outcomes..... | 162 |
| Table 63: Braun 2014 CVD outcomes | 164 |
| Table 64: Mittman 1990 allergic rhinitis outcomes..... | 166 |
| Table 65: Szczurko 2007 LBP outcomes..... | 167 |
| Table 66: Szczurko 2009 rotator cuff tendinitis outcomes | 169 |
| Table 67: Cramer 2003 menopause outcomes..... | 172 |
| Table 68: Seely 2013 CVD risk outcomes | 175 |

| | |
|---|-----|
| Table 69: Aschenbrenner 2005 | 178 |
| Table 70: Bacharach-Buhles 2011 | 178 |
| Table 71: Chrubasik 1997 | 178 |
| Table 72: Hakimi 2012..... | 179 |
| Table 73: Kraft 2011 | 179 |
| Table 74: Rapp 2006..... | 179 |
| Table 75: Schimmel 2004..... | 180 |
| Table 76: Wiebelitz 2011 | 180 |
| Table 77: Wustrow 2005..... | 181 |
| Table 78: ACTRN12620001040954 (2020) | 182 |
| Table 79: ACTRN12620000928910 (2020) | 183 |
| Table 80: CTRI/2010/091/001169 (2010) | 185 |
| Table 81: CTRI/2010/091/001168 (2010) | 186 |
| Table 82: CTRI/2010/091/001171 (2010) | 188 |
| Table 83: CTRI/2011/03/001654 (2011) | 189 |
| Table 84: CTRI/2011/12/002286 (2011) | 190 |
| Table 85: CTRI/2011/12/002285 (2011) | 191 |
| Table 86: CTRI/2018/12/016550 (2018) | 192 |
| Table 87: CTRI/2018/10/015895 (2018) | 194 |
| Table 88: CTRI/2018/12/016512 (2018) | 195 |
| Table 89: CTRI/2019/01/016883 (2019) | 196 |
| Table 90: CTRI/2019/10/021775 (2019) | 198 |
| Table 91: CTRI/2020/12/029833 (2020) | 199 |
| Table 92: CTRI/2020/07/026734 (2020) | 200 |
| Table 93: DRKS00006343 (2014) | 201 |
| Table 94: DRKS00009884 (2016) | 203 |
| Table 95: ISRCTN61808774 (2003)..... | 205 |
| Table 96: NCT00010634 (2001)..... | 206 |

| | |
|--|-----|
| Table 97: NCT00169299 (2005)..... | 207 |
| Table 98: NCT00309439 (2006)..... | 208 |
| Table 99: NCT00334919 (2006)..... | 209 |
| Table 100: NCT00974506 (2009)..... | 210 |
| Table 101: NCT02396160 (2015)..... | 211 |
| Table 102: NCT02843724 (2016)..... | 212 |
| Table 103: NCT04120259 (2019)..... | 215 |
| Table 104: NCT04871412 (2021)..... | 216 |
| Table 105: CTRI/2020/09/028014 (2020)..... | 218 |
| Table 106: CTRI/2020/07/026842 (2020)..... | 219 |
| Table 107: CTRI/2020/06/025714 (2020)..... | 220 |
| Table 108: CTRI/2020/05/025320 (2020)..... | 221 |
| Table 109: ANZCTR347666 (2012)..... | 222 |
| Table 110: NCT00983502 (2009)..... | 224 |
| Table 111: NCT00409149 (2006)..... | 225 |
| Table 112: NCT00160901 (2005)..... | 226 |
| Table 113: Seely 2019..... | 227 |
| Table 114: Methods not implemented | 230 |
| Table 115: Changes from protocol | 231 |

List of Figures

| | |
|--|-----|
| Figure 1: PRISMA flowchart | 24 |
| Figure 2: Risk of bias for all included RCTs..... | 150 |
| Figure 3: Risk of bias for all included NRSIs..... | 150 |

Appendix A: Searching, selection criteria and screening

A.1. Search methods

A.1.1. Electronic database searches

Search strategies based on whole system naturopathy (including single and multi-modality interventions) were developed for each database and included search terms for the study types randomised controlled trials (RCTs) and/or non-randomised controlled trials (NRSIs) with contemporaneous control groups. The searches were designed so that they were restricted to humans but were not restricted by population, outcome, date, language, or geography.

Search strategies were designed for the following databases:

- Medline via OVID
- Embase
- Cochrane CENTRAL
- Allied and Complementary Medicine Database (AMED)
- Cumulative Index of Nursing and Allied Health Literature (CINAHL)

Databases in languages other than English were not searched.

The search strategies for each database are included in Section A.2 Database-specific terms for Medline, Embase, AMED, CINAHL, and Cochrane CENTRAL.

RCTs were primarily identified from Cochrane Central Register of Controlled Trials (CENTRAL). This is because Cochrane CENTRAL concurrently searches RCT and quasi-RCT (q-RCT) records from the PubMed/MEDLINE; Embase.com; CINAHL ClinicalTrials.gov and WHO ICTRP databases. NRSIs were identified from Medline via OVID and AMED databases. Embase.com and CINAHL included both RCT and NRSI search terms. The search strategies were designed to reduce the retrieval of duplicate citations.

A.1.2. Searching other sources

The reference lists of included articles were checked to find additional eligible studies (backward citation search).

Studies provided by the public and key stakeholders (via the Department of Health), NTREAP, and NTWC were screened for eligibility. Where these groups recommend particular systematic reviews, they were examined for eligible RCTs and NRSIs. The NHMRC also provided the 2015 evidence evaluation for whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice to HealthConsult reviewers to identify eligible primary studies within included systematic reviews. Systematic reviews not published in English were not translated but were examined to identify eligible RCTs and NRSIs.

The clinical trials registries International Clinical Trials Registry, Australian New Zealand Clinical Trials Registry and ClinicalTrials.gov were also searched.

Studies and publications that were identified for inclusion by full-text review were checked for retraction or errata within the databases. In Medline using the search terms 'retracted publication.pt. or retraction of publication.pt. or erratum.ti or errata.ti.' (refer to Section 3.9 of 4.S1

Technical Supplement to Chapter 4 of the Cochrane Handbook), as well as the 'erratum.tc. or exp published erratum/ or published erratum.pt.', together with the citations for the eligible studies. Articles that were indexed to Embase were checked using the terms 'erratum.pt. or retracted article/ or tombstone.pt or yes.nr'. As eligible studies were indexed in either Medline or Embase, errata and retractions were not further searched for in the Cochrane Library, CINAHL or AMED.

Retraction Watch using Zotero software was also used to check for retractions among the studies eligible for inclusion, there were none retracted.

A.2. Search strategy

A.2.1. Medline

The search terms for Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to July 02, 2021, conducted on 6 July 2022 to identify NRSIs are displayed in Table 1.

Table 1: Medline via Ovid search strategy

| # | Search terms | Results |
|-----|---|------------|
| #1 | exp cohort studies | 2,169,798 |
| #2 | exp Epidemiologic Studies | 2,716,327 |
| #3 | exp Clinical Trial | 529,622 |
| #4 | exp Evaluation Studies as Topic | 1,113,276 |
| #5 | exp Statistics as Topic | 2,866,176 |
| #6 | (control and (group* or study)).mp. | 2,236,124 |
| #7 | (time and factors).mp. | 1,657,237 |
| #8 | (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. | 5,257,060 |
| #9 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 | 10,026,819 |
| #10 | animals/ not humans | 4,822,396 |
| #11 | (Editorial or Comment or Letter or Newspaper article).pt. | 1,975,343 |
| #12 | hi.fs. or case report.mp. | 639,276 |
| #13 | #10 OR #11 OR #12 | 7,327,199 |
| #14 | exp Naturopathy | 1,012 |
| #15 | Naturopath*.tw. | 1,121 |
| #16 | Natural medicine.tw. | 527 |
| #17 | Natural therap*.tw. | 654 |
| #18 | Naturoceutical*.tw. | 4 |
| #19 | Naturopathic.tw. | 488 |
| #20 | Integrative Medicine | 1,685 |
| #21 | #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 | 4,350 |
| #22 | #9 AND #21 | 1,349 |

| # | Search terms | Results |
|-----|--------------------|--------------|
| #23 | #22 NOT #13 | 1,219 |

Abbreviations: ab, abstract; exp, explode MeSH term; fs, floating subject heading; MeSH, medical subject heading; mp, maps to keyword (mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms); pt, publication type; sh, MeSH heading subject; tw, text word

Note: integrative medicine included as proxy for complementary medicine

The search strategies were adapted from Myers (2019) and Cooley (2012)

In the search strategy for Medline (Table 1), sensitive search filters to identify RCTs from Section 3.6.1 of the Cochrane Handbook's Technical Supplement 4.S1 (2019) were applied.¹ Search strategies to identify NRSIs with control groups were based on Waffenschmidt (2020)², cited by the Information Specialists' Sub-Group (ISSG) Search Filter Resource.³

A.2.2. Embase

The search terms for Ovid Embase 1974 to 2022 February 01, conducted on 6 July 2021 to identify RCTs and NRSIs are displayed in Table 2.

Table 2: Embase via Ovid search strategy

| # | Search terms | Results |
|-----|---|-----------|
| #1 | Randomized controlled trial | 693,635 |
| #2 | Controlled clinical study | 464,897 |
| #3 | Random\$.ti,ab. | 1,749,870 |
| #4 | Randomization | 92,890 |
| #5 | Intermethod comparison | 27,9307 |
| #6 | Placebo.ti,ab. | 33,5731 |
| #7 | (compare or compared or comparison).ti. | 556,104 |
| #8 | ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. | 2,437,634 |
| #9 | (open adj label).ti,ab. | 94,218 |
| #10 | ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. | 252,798 |
| #11 | double blind procedure | 191,801 |
| #12 | parallel group\$1.ti,ab. | 28,792 |
| #13 | (crossover or cross over).ti,ab. | 114,565 |
| #14 | ((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. | 371,815 |
| #15 | (assigned or allocated).ti,ab. | 437,943 |
| #16 | (controlled adj7 (study or design or trial)).ti,ab. | 398,391 |
| #17 | (volunteer or volunteers).ti,ab. | 264,356 |
| #18 | human experiment | 564,206 |
| #19 | trial.ti. | 349,412 |
| #20 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 | 5,648,453 |

| # | Search terms | Results |
|-----|--|------------|
| #21 | (random\$ adj sampl\$ adj7 (cross section\$ or questionnaire\$1 or survey\$ or database\$1)).ti,ab. | 12,470 |
| #22 | comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab. | 9,441,736 |
| #23 | #21 NOT #22 | 8,847 |
| #24 | Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group\$1.ti,ab.) | 297,125 |
| #25 | ((case adj control\$) and random\$) not randomi?ed controlled).ti,ab. | 19,399 |
| #26 | (Systematic review not (trial or study)).ti. | 198,698 |
| #27 | (nonrandom\$ not random\$).ti,ab. | 17,536 |
| #28 | "Random field\$".ab,ti. | 2,639 |
| #29 | (random cluster adj3 sampl\$).ti,ab. | 1,405 |
| #30 | (review.ab. and review.pt.) not trial.ti. | 961,299 |
| #31 | we searched.ab. and (review.ti. or review.pt.) | 40,207 |
| #32 | update review.ab. | 119 |
| #33 | (databases adj4 searched).ab. | 48,159 |
| #34 | (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 | 1,136,764 |
| #35 | Animal experiment/ not (human experiment/ or human/) | 2,386,377 |
| #36 | #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 | 3,880,940 |
| #37 | #20 NOT #36 | 5,007,147 |
| #38 | Case control study/ or cohort analysis/ or controlled study/ or comparative study/ or intermethod comparison/ or major clinical study/ or outcomes research/ or population research/ or prospective study/ or retrospective study/ or treatment outcome/ | 12,730,004 |
| #39 | Clinical article/ or controlled study/ or major clinical study/ or prospective study/ or cohort.mp. or compared.mp. or groups.mp. or multivariate.mp. | 16,097,372 |
| #40 | #38 OR #39 | 17,118,426 |
| #41 | (Editorial or Comment or Letter or Newspaper article).pt. | 1,922,973 |
| #42 | Case report.mp. | 2,739,877 |
| #43 | #35 OR #41 OR #42 | 6,811,415 |
| #44 | #41 OR #42 | 4,434,170 |
| #45 | Naturopathy | 283 |
| #46 | Naturopath*.tw. | 1,780 |
| #47 | Natural medicine.tw. | 905 |
| #48 | Natural therap*.tw. | 999 |
| #49 | Naturoceutical*.tw. | 6 |
| #50 | Naturopathic.tw | 904 |
| #51 | Integrative medicine | 5,778 |

| # | Search terms | Results |
|-----|---|---------|
| #52 | #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 | 9,315 |
| #53 | #37 AND #52 | 1,638 |
| #54 | #40 AND #52 | 3,620 |
| #55 | #53 NOT #44 | 1,603 |
| #56 | #55 NOT #43 | 2,994 |

Abbreviations: ab, abstract; af, all fields; exp, explode; pt, publication type; sh, subject heading; ti, title; tw, text word

In the search strategy for Embase (Table 2), sensitive search filters to identify RCTs from Section 3.6.2 of the Cochrane Handbook's Technical Supplement 4.S1 (2019) were applied.¹ Search strategies to identify NRSIs with control groups were based on both Fixed Methods A and B from Furlan⁴ as cited by the ISSG Search Filter Resource.³ MeSH search terms for naturopathy and therapies were used to identify Emtree synonyms for inclusion in the search strategy

A.2.3. Cochrane CENTRAL

The search terms for Cochrane CENTRAL conducted on 6 July 2021 to identify are displayed in Table 3.

Table 3: Cochrane CENTRAL search strategy

| # | Search terms | Results |
|----|---|-------------|
| #1 | MeSH descriptor: [Naturopathy] | 21 |
| #2 | (naturopathy):ti,ab,kw | 94 |
| #3 | naturopathic | 132 |
| #4 | (natural medicine):ti,ab,kw | 894 |
| #5 | (natural NEXT therap*):ti,ab,kw | 51 |
| #6 | (naturoceutical):ti,ab,kw | 0 |
| #7 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 | 1112 |
| #8 | [LIMIT - Cochrane Library Central Register of Controlled Trials] | 1048 |

Abbreviations: ab, abstract; kw, keyword; MeSH, medical subject heading; ti, title

Specific search terms for RCTs and NRSIs were not implemented when searching the Cochrane Database, as it is not appropriate for a pre-filtered database (Cochrane Handbook Box C34).¹ As Cochrane uses MeSH terms, these were implemented according to the proposed Medline search strategy, using the Cochrane-specific suffixes for the field codes.

A.2.4. CINAHL

The search terms for CINAHL via EBSCOhost were conducted on 6 July 2022 to identify RCTs and NRSIs are displayed in Table 4.

Table 4: CINAHL via EBSCO search strategy

| # | Search terms | Results |
|----|---------------------------------|---------|
| #1 | MH randomized controlled trials | 116,109 |
| #2 | MH double-blind studies | 50,629 |
| #3 | MH single-blind studies | 14,912 |
| #4 | MH random assignment | 68,297 |
| #5 | MH pretest-posttest design | 46,558 |

| # | Search terms | Results |
|-----|--|-----------|
| #6 | MH cluster sample | 4,778 |
| #7 | TI randomised OR TI randomized | 116,846 |
| #8 | AB (random*) | 341,247 |
| #9 | TI (trial) | 151,135 |
| #10 | MH (sample size) AND AB (assigned OR allocated OR control) | 4,160 |
| #11 | MH (placebos) | 12,915 |
| #12 | PT (randomized controlled trial) | 129,671 |
| #13 | AB (control W5 group) | 121,887 |
| #14 | MH (crossover design) OR MH (comparative studies) | 391,791 |
| #15 | AB (cluster W3 RCT) | 390 |
| #16 | MH animals+ | 95,813 |
| #17 | MH (animal studies) | 136,235 |
| #18 | TI (animal model*) | 3,316 |
| #19 | S16 OR S17 OR S18 | 223,653 |
| #20 | MH (human) | 2,366,788 |
| #21 | S19 NOT S20 | 193,740 |
| #22 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 | 865,212 |
| #23 | S22 NOT S21 | 824,230 |
| #24 | (MH "Prospective Studies+") | 472,477 |
| #25 | (MH "Epidemiological Research+") | 30,309 |
| #26 | (MH "Clinical Trials+") | 318,627 |
| #27 | (MH "Evaluation Research+") | 285,497 |
| #28 | (MH "Statistics+") | 758,129 |
| #29 | TX control AND TX ((group* or study)) | 755,620 |
| #30 | TX (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*) | 1,792,668 |
| #31 | TX time AND TX factors | 397,450 |
| #32 | S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 | 2,857,227 |
| #33 | MH animals NOT TX human | 67,348 |
| #34 | PT Editorial OR PT Comment OR PT Letter OR PT Newspaper article | 683,318 |
| #35 | MW hi OR TX case report | 201,484 |
| #36 | S33 OR S34 OR S35 | 931,183 |
| #37 | S32 NOT S36 | 2,703,064 |
| #38 | (MH "Naturopathy") | 1,580 |
| #39 | TX naturopath* | 3,133 |
| #40 | TX natural medicine | 1,122 |

| # | Search terms | Results |
|-----|---|--------------|
| #41 | TX natural W1 therap* | 513 |
| #42 | TX naturoceutical* | 1 |
| #43 | (MH "Integrative Medicine") | 828 |
| #44 | TI naturopathic | 337 |
| #45 | S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 | 5,321 |
| #46 | S23 AND S45 | 499 |
| #47 | S37 AND S45 | 1,638 |

Abbreviations: +, explode search term; “ “, indicated key word search (used when MeSH term from Medline did not map to CINHAL subject heading); MH, exact CINAHL subject heading; MW, word in subject heading; PT, publication type; TI, title; TX, all text

Note the CINAHL subject heading for naturopathy, program evaluation, integrative medicine, or ‘Delivery of Health Care, Integrated’ could not be exploded.

In the search strategy for CINAHL (Table 4), sensitive search filters to identify RCTs from Section 3.6.3 of the Cochrane Handbook’s Technical Supplement 4.S1 (2019) were applied.⁵ A sensitive search filter for NRSIs was not identified for CINAHL and thus CINAHL subheadings and synonyms for the Medline version of the search filter were implemented. MeSH search terms for naturopathy and therapies were mapped to specific CINAHL subject headings and with appropriate field codes, where possible, for inclusion in the search. It should be noted that some MeSH terms, when translated to CINAHL subject headings, could not be exploded. MeSH terms for which there were no CINAHL subject headings were included as keywords.

A.2.5. AMED

The search terms for Ovid AMED (Allied and Complementary Medicine) 1985 to July 2021, conducted on 6 July 2021 to identify NRSIs are displayed in Table 5.

Table 5: AMED via OVID search strategy

| # | Search terms | Results |
|-----|---------------------------------|---------|
| #1 | randomized controlled trial.pt. | 5,253 |
| #2 | controlled clinical trial.pt. | 70 |
| #3 | randomized.ab. | 10,456 |
| #4 | placebo.ab. | 3,148 |
| #5 | drug therapy.sh. | 29,351 |
| #6 | randomly.ab. | 7,138 |
| #7 | trial.ab. | 9,543 |
| #8 | groups.ab. | 27,032 |
| #9 | or/1-8 | 65,964 |
| #10 | exp animals/ not humans.sh. | 13,697 |
| #11 | exp cohort studies/ | 1,569 |
| #12 | exp Epidemiology/ | 5,219 |
| #13 | epidemiologic studies.mp. | 194 |
| #14 | exp Clinical trials/ | 4,754 |
| #15 | Evaluation Studies.mp. | 54 |

| # | Search terms | Results |
|------------|---|------------|
| #16 | exp Statistics/ and topic.mp. | 31 |
| #17 | (control and (group* or study)).mp. | 20,784 |
| #18 | (time and factors).mp. | 3,752 |
| #19 | (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. | 40,190 |
| #20 | or/12-20 | 65,034 |
| #21 | animals/ not humans/ | 10,525 |
| #22 | (Editorial or Comment or Letter or Newspaper article).pt. | 15,299 |
| #23 | case report.mp. | 10,796 |
| #24 | #21 OR #22 OR #23 | 36,383 |
| #25 | #10 OR #22 OR #23 | 39,449 |
| #26 | exp Naturopathy/ | 1,135 |
| #27 | "naturopath*".ti,ab. | 524 |
| #28 | naturopathic.ti,ab. | 289 |
| #29 | natural medicine.ti,ab. | 114 |
| #30 | "natural therap*".ti,ab. | 141 |
| #31 | exp Integrative Medicine/ | 386 |
| #32 | #26 OR #27 OR #28 OR #29 OR #30 OR #31 | 1,917 |
| #33 | #9 AND #32 | 241 |
| #34 | #20 AND #32 | 217 |
| #35 | #33 NOT #25 | 224 |
| #36 | #34 NOT #24 | 213 |

Abbreviations: ab, abstract; af, all fields; mp, keyword; pt, publication type; sh, subject heading; ti, title

For the AMED strategy, no sensitive search filters for RCTs and NRSIs were identified. The search filters for Medline were adapted using AMED synonyms. MeSH search terms for naturopathy and therapies were mapped to specific AMED synonyms where possible for inclusion in the search. Floating subject heading and text word field codes are not available in AMED and were substituted with subject heading and title/abstract respectively instead. AMED does not have an additional limiter for 'humans'. However, a restriction to human studies is part of the RCT and NRSI search filters.

A.3. Literature search results

The search retrieved 7,600 citations, including 437 provided via stakeholder consultations. After removing duplicates, 5,887 unique citations were screened by title and abstract and 105 full-text citations were retrieved for screening by full text. Screening at full text identified 30 publications that were excluded for not matching inclusion criteria for study type, population, intervention, comparator, or outcomes (Section C.1). Studies awaiting classification included 9 in languages other than English (Section C.3) and 36 ongoing studies (registered trial protocols, Section C.4). Twenty-nine publications for 16 studies were included in this review (Appendix E: Detailed study descriptions and outcomes). Erratum were reviewed to confirm that the included studies were still eligible for inclusion in this review.

No studies provided by Office of the National Health and Medical Research Council (ONHMRC), NTREAP, NTWC, or other stakeholders that were unique to the searches of the electronic

databases and trial registries met inclusion criteria. One erratum for Shinto 2008 was identified in the literature search.

- Anonymous. Correction... "A randomized pilot study of naturopathic medicine in multiple sclerosis" (Volume 14, Number 5, 2008, pp. 489-496). *Journal of alternative and complementary medicine* (New York, NY). 2008;14(6):793.

An additional search for retractions or errata for the eligible studies resulted in the following article, a different report of the same study identified for cardiovascular risk (Seeley 2013):

- CMAJ September 06, 2016, 188 (12) 901; DOI: <https://doi.org/10.1503/cmaj.1150116>
 - For: Seely D, Szczurko O, Cooley K, Fritz H, Aberdour S, Herrington C, et al. Naturopathic medicine for the prevention of cardiovascular disease: a randomized clinical trial. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2013;185(9): E409-16.

The errata publications did not impact the eligibility of the studies.

A search using Zotero did not identify any retractions of the eligible studies.

A.4. Study selection criteria

A.4.1. Types of studies

To be eligible, studies had to be RCTs or NRSIs that examined the effectiveness of whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice (the intervention). The intervention group must be able to be compared to a contemporaneous control or another intervention group. There was no minimum sample size for studies. Only parallel RCTs were identified and included: no eligible cluster randomised trials, cross-over trials, or pseudorandomised controlled trials were identified.

Specific NRSI study designs were eligible to ensure evidence can be evaluated for a broad range of populations and outcomes. For example, where RCTs were not available for a particular population, or where available RCTs only provided findings of low certainty.

NRSIs were also eligible where they include the following features:

- Data were collected from an 'intervention' group and a comparison group (e.g. control/placebo/other intervention) contemporaneously.
- Allocation (to 'intervention', control/placebo, or another intervention) occurred by methods that were not random, including choice, availability, or non-random chance.

Consequently, the following types of NRSIs were eligible (assuming they have the two features listed above):

- **Non-randomised controlled studies:** Experimental studies in which people are allocated to whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice, or a control/placebo group and the outcomes compared.
- **Prospective cohort studies with contemporaneous comparator group:** Studies in which outcomes from a defined group of people (the cohort) are followed over time, with participants recruited before any intervention occurs. Outcomes are collected for both participants who are and are not exposed to whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice. The association between exposure and non-exposure with outcomes is examined.

- **Retrospective cohort studies with contemporaneous comparator group:** Studies in which outcomes from a defined group of people (the cohort) are examined after the intervention and outcomes occur. Outcomes are collected for both participants who are and are not exposed to whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice. The association between exposure and non-exposure with outcomes is examined.
- **Controlled before and after studies:** Studies that measure outcomes in an intervention group and control group before and after the implementation of an intervention. Outcomes for the intervention and control groups at the same time point are compared.

No eligible interrupted time series studies or case-control studies were identified.

The following types of studies are excluded:

- **Case series studies:** an uncontrolled observational study involving an intervention and outcome for more than one person.¹
- **Case reports:** an uncontrolled observational study involving an intervention and outcome for a single person (or other unit).¹
- **Cross-sectional studies:** studies that examine the relationship between diseases (or other health-related characteristics) and other variables of interest as they exist in a defined population at one particular time. The temporal sequence of cause and effect cannot necessarily be determined in a cross-sectional study.¹
- **Qualitative studies:** a research study that uses a qualitative method of data collection and analysis,² and
- **Single arm studies:** a sample of individuals are given the intervention and then followed over time to observe their response.³

Case reports, case series, and single arm studies do not include contemporaneous comparator groups and do not provide evidence of effectiveness of the intervention. Cross-sectional studies allow for assessment of an association between intervention and outcome but do not provide evidence of cause and effect. Qualitative studies do not quantify effectiveness of the intervention which is required to conduct meta-analyses.

The study type of a publication was confirmed by full-text review by assessing study design features (Section 24.1 of the Cochrane Handbook⁴). It is acknowledged that the study design/type stated by the authors may not accurately reflect the actual study features: for studies of effectiveness, caution was required when assessing NRSIs according to existing evidence hierarchies, as the study labels from such hierarchies were originally derived from aetiological research questions and may not apply to the broad range of effectiveness studies (Section 24.2.1 of the Cochrane Handbook⁴).

Critical risk of bias

If an NRSI is assessed as being at critical risk of bias in any one domain, its details were to be recorded in the characteristics of included studies tables and the reason for critical risk of bias rating documented, but it would not be further assessed and would not contribute to data synthesis.

As there were a limited number studies, no meta-analyses for data synthesis were conducted.

Publication date

There was no limitation to the publication date when the electronic searches for the systematic review were conducted. Studies provided to HealthConsult and the ONHMRC by the Natural Therapies Review Expert Advisory Panel (NTREAP), NTWC or other stakeholders were only

excluded based on publication date where they were published after the search date of the electronic searches for each systematic review literature search.

Trials that were ongoing, pending publication, or were completed but do not have results available, but otherwise meet inclusion criteria, are listed as 'ongoing studies' and are documented in a 'Studies awaiting classification' table (see Section C.4 Table 14). Such trials may have been published as conference abstracts.

Studies published in languages other than English

Databases in languages other than English were not searched. However, studies published in languages other than English were not excluded from the Review. Refer to Section A.5 for further details on how studies published in languages other than English were screened.

A.4.2. Types of participants

Study populations could have any injury, disease, medical condition, or pre-clinical condition and could be of any age. Studies with healthy but at-risk populations were also eligible. The NTWC agreed that for prevention studies to be eligible, they must provide evidence that an individual participant, not a population in general, has met a minimum threshold for being at risk (e.g. presenting with symptoms, or being assessed for symptoms of a condition, or a history of previous condition). For example, if a study is examining the effectiveness of naturopathy for prevention of burnout in nurses it is not enough for the individual participants to be considered at risk just because they are nurses. For studies where there was uncertainty about whether the minimum threshold had been met, NTWC reviewed the 'aim' of the study in question and decided on eligibility. One study with a geriatric population was excluded based on not meeting this definition of "at risk". There were no restrictions for study setting.

Studies that only included healthy populations seeking health improvement were excluded. However, where a study included both healthy populations (ineligible) and eligible populations and separate data was available for eligible populations, the study was eligible for inclusion.

Searches were limited to human studies, thus excluding animal and in vitro studies.

A.4.3. Types of interventions

Studies which met the definition of whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice were eligible. Both single and multi-modal interventions were eligible as long as they were described as naturopathy. To be eligible, the naturopathy intervention must include at least one of the following modalities that are central to naturopathic care in Australia:

- herbal medicine,
- complementary medicine prescription,
- dietary advice or
- lifestyle advice.

There were no restrictions on the setting in which the naturopathy intervention was delivered, for example in person, by telehealth or by another medium. However, the intervention had to be delivered in the context of naturopathic care, meaning at least one of the following criteria were met:

- (1) the study states the intervention was delivered by a naturopath
- (2) the study states the intervention was delivered in the context of naturopathic care

- (3) the intervention was described by the study as being a naturopathic intervention or by a naturopath.

Single and multi-modal interventions that met the definition of 'naturopathy' were to be synthesised together, but this was not possible as population groups did not have two or more eligible RCTs or two or more eligible NRSIs identified for inclusion. For the same reason, subgroup analyses within a population were not conducted, as there was insufficient evidence to do so.

Naturopathic interventions delivered as an adjunct to conventional care were eligible only if the comparator group also received conventional care.

Whole system, multi-modal naturopathy interventions

Included were naturopathic interventions in which multiple modal interventions were delivered, including at least one modality considered central to naturopathic care in Australia (as above). Additional modalities included (but were not limited to) yoga, meditation, exercise prescription, homeopathy, and manual therapies such as massage, shiatsu and kinesiology.

Whole system, single modal naturopathy interventions

Included were naturopathic interventions in which one of the four modalities considered central to naturopathic care in Australia was delivered (dietary advice, lifestyle advice, herbal medicine, or complementary medicine).

Exclusions

Studies were excluded where the 'naturopathic practice' intervention was combined with one or more other co-interventions unless the effect of the naturopathic practice alone could be determined.

Studies were excluded if the intervention was a whole system, multi-modal therapy that did not meet the definition of naturopathic practice (for example, other traditional medical systems such as Traditional Chinese Medicine and Ayurveda). Thus, studies where interventions that were not delivered by a naturopath or in the naturopathic context (e.g., were delivered by a conventional physician or by an Ayurvedic practitioner) were excluded. However, naturopathy interventions that included modalities derived from these systems (for example, yoga, acupuncture) were eligible for inclusion if the intervention met the definition of whole system, multi-modal 'naturopathy' as outlined above (i.e. included at least one of the modalities central to naturopathic care in Australia).

Modalities that were not central to naturopathic practice in Australia (for example, yoga, meditation, exercise prescription, homeopathy, and manual therapies such as massage, shiatsu, and kinesiology), were excluded as single modal naturopathy interventions. However, these interventions were eligible for inclusion when incorporated within a whole system, multi-modal naturopathy intervention that included one or more interventions central to naturopathic care in Australia (see above 'Whole system, multi-modal naturopathy interventions').

A.4.4. Types of comparators

The types of comparators used in studies were not restricted. Placebo/ sham, inactive control (i.e. inclusive of no intervention, wait-list, or usual care) and active comparators (i.e. inclusive of usual care or control if considered active) were eligible for inclusion.

Where naturopathy was administered as an adjunct (for example, naturopathy plus standard care vs standard care alone) this was classified as an inactive comparator.

Analyses were to be stratified by type of comparator, but there were insufficient eligible studies for each population group to be able to do so.

The Review aimed to assess the effectiveness of naturopathic practice and not different types of naturopathic practice. Thus, studies that compared groups receiving one form of whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice with groups receiving another type of naturopathic practice (analogous to a head-to-head trial) were not eligible for inclusion. Thus, studies comparing multi-modal naturopathic care to single modal naturopathic care, two or more groups each being treated by different types of single modal naturopathic care, or studies that compared two or more groups each treated with different combinations of modalities in their multi-modal care were excluded.

Comparisons

It was planned to compare studies if they compared naturopathic care (the intervention) with, (1) placebo/sham (if relevant), and (2) inactive control, with similar population groups and outcomes (see Section B.3), and that subgroup analyses were to be conducted for studies with multi-modal interventions and single modal interventions. Studies with active comparators were to be compared on the advice of the NTWC. These comparisons were not undertaken as there were insufficient numbers of eligible studies in each population group.

A.4.5. Types of outcome measures

Role of outcomes

Study eligibility was not restricted by the type of outcomes measured and outcomes were not used as an eligibility criterion. All included studies (regardless of their outcome measures or the time points of those outcome measures) were included in the 'Characteristics of included studies tables' (see Section 0). However, only certain outcomes were extracted and examined in the analysis, as indicated by the NTWC prioritisation process.

Outcome domains

Due to the broad nature of the review, it was not possible to pre-specify outcomes for prioritisation in the review. To prioritise outcomes for data extraction and synthesis, NTWC undertook a blinded prioritisation exercise.

Following the completion of screening, NTWC was provided with a list of conditions, outcome domains, and outcome measures to prioritise. The list was based on outcomes reported in the included studies as well as outcomes included within a relevant core outcome set (if available), identified using Core Outcome Measures in Effectiveness Trials (COMET)⁵ and other relevant or related Cochrane reviews. No additional information was provided that could enable NTWC to identify the included studies (e.g. names of authors, the study the country was conducted in), the results of the studies, or the number of studies examining each condition, outcome domain, or outcome measure.

Throughout the outcome prioritisation exercise, NTWC applied Grading of Recommendations Assessment, Development and Evaluation (GRADE)⁶ principles to identify up to seven critical and/or important (but not critical) outcomes for each population condition, for HealthConsult reviewers to extract and report on.

Outcome measures and timepoints of interest

NTWC focused on the relevance and validity of outcome measures. As the Review focuses on assessing the clinical effectiveness of therapies, the prioritised outcomes related to the potential benefits of whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice rather than potential harms. As stated under 'Outcome domains', NTWC's approach to outcome prioritisation was blinded. Outcome measures based on personal health care preferences, patient satisfaction, safety, quality, and economic outcomes (e.g. cost-effectiveness) were out of scope, as were adverse effects of treatment. However, effectiveness outcomes that

showed a harm through worsening of symptoms were eligible for inclusion. Timepoints were not pre specified during the outcome prioritisation exercise conducted by the NTWC. Prioritised outcomes are given in A.6.

A.5. Selection of studies

Following the database searches, duplicate citations were removed using Endnote software before screening. Screening of citations was conducted using Rayyan (<https://www.rayyan.ai/>). The studies were screened for eligibility by title and abstract and then by full text.

At the title and abstract stage, studies were screened for eligibility by a primary reviewer, with a secondary reviewer independently assessing an initial 20% of citations.⁷ The duplicate screening achieved 80% inter-annotator agreement between reviewers. Where there were discrepancies that the two reviewers could not agree on, a third reviewer's opinion was sought.

At the full-text stage, two independent reviewers screened the reports for eligibility: any disagreements were discussed between the primary and secondary reviewer, with a third reviewer consulted where the former were unable to reach an agreement.

Studies were excluded if they did not meet selection criteria (section A.4). For example, studies were excluded if the intervention was not delivered in a naturopathic context or by a naturopath and were instead delivered in a conventional health care context or by a conventional physician such as a GP.

A.5.1. Studies identified in the literature search

Eligible studies identified in the literature search included RCTs and NRSIs that examined the effectiveness of whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice (the intervention).

Refer to Section A.4.1 Types of studies for further details on studies identified in the literature search.

A.5.2. Evidence provided through the Department's public call for evidence

There were 437 citations provided by stakeholders 59 of which were identical. The 378 non-identical citations were all found in the electronic search. Details are provided at Appendix A.7.2 and C2.

For systematic reviews provided by stakeholders, the primary RCTs and NRSIs they included were cross-checked against the citations retrieved in the electronic searches.

A.5.3. Studies published in languages other than English

Studies published in languages other than English that were retrieved were managed using the following protocol:

- (1) Database searches were not restricted by language.
- (2) If the title and abstract were not available in English, they were translated using Google translator or an equivalent method (then proceeded to step 4).
- (3) If online translation did not facilitate an understanding of the title and abstract, the citations for these studies were listed as 'studies unable to be translated or interpreted at the title/abstract stage'. This step was unnecessary in this Review.
- (4) Translated titles and abstracts were screened and citations that were not eligible excluded. The number of these excluded citations published in languages other than English are

reported in the results of the search and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart.

- (5) If the translated citation indicates the study was likely to meet the criteria for considering studies for inclusion in the review (based on title and abstract screen), or if there were any uncertainty:
- The translated citation and available information was recorded in the 'Studies awaiting classification' table to inform readers of the Review of the availability of other possibly relevant reports. The information is reflected in the PRISMA flow diagram.
 - A copy of the finalised 'Studies awaiting classification' tables (see Section C.3) was provided to ONHMRC, noting that the Review was not expected to include any of these articles.
 - The potential risk of language bias and the implications in the Evidence Evaluation Report was appraised.
 - Appropriate qualifying statements are presented throughout the Evidence Evaluation Report that acknowledged only the evidence published in English was reviewed.
 - Potential limitations due to language bias and the potential impact on the certainty of evidence are presented in the Evidence Evaluation Report, noting that they may influence the conclusions of the Review.

A.5.4. Collation of studies

If multiple reports of the same study were identified, they were collated so that the study rather than each report was the unit of interest in the Review.⁸ This ensured that data from a study is included only once in the analyses and syntheses of evidence.

For citations of studies published in languages other than English that may be eligible for inclusion according to screening at the title and abstract stage (see below), full-text publications were not translated but the studies were documented in a 'Studies awaiting classification' table (see Section C.3 Table 13).

A PRISMA flowchart was generated to document the results of the searching and screening process (Figure 1, Section A.7). Studies excluded at the full-text stage were tabulated with a corresponding rationale for exclusion (Appendix C: Excluded studies).

A.6. Refining research question

A.6.1. Population prioritisation

As per the protocol, populations/conditions were not prioritised for this review because there was not an overwhelming number of studies rendering it necessary.

A.6.2. Outcome prioritisation

The outcome prioritisation process is described in Section A4.5. The outcome domains prioritised by the NTWC for each population group and for which eligible studies reported on are presented in Table 6. The NTWC excluded a particular study that did not meet the definition of at-risk (refer to Section A.4.2).

Table 6: Outcome prioritisation by condition

| Conditions ^a | Population | Prioritised outcome domain reported on by eligible studies |
|--|-----------------------------|---|
| Neoplasms | Breast cancer | <ul style="list-style-type: none"> Quality of life (assessed with SF-36) ^a |
| | Colon cancer | <ul style="list-style-type: none"> Quality of life (assessed with FLIC) Psychological function (assessed with STAI and BDI) |
| | Prostate cancer | <ul style="list-style-type: none"> Tumour progression with and without ablation |
| Endocrine, nutritional, or metabolic diseases | Type 2 diabetes mellitus | <ul style="list-style-type: none"> Glycaemic control (assessed with HbA1c) Bodyweight (kg) |
| | Polycystic ovarian syndrome | <ul style="list-style-type: none"> Menstrual regularity (no. of days between cycle) Quality of life (assessed with PCOSQ) Metabolic indices/outcomes (assessed with QUICKI) Reproductive hormonal profile (assessed with testosterone level) |
| | Overweight and obesity | <ul style="list-style-type: none"> Change in inpatient, rebound, and end of treatment weight Quality of life (non-standardised questionnaire) Change in physical activity (non-standardised questionnaire) |
| Mental, behavioural, or neurodevelopmental disorders | Anxiety | <ul style="list-style-type: none"> Change in anxiety (assessed with BAI) Quality of life (assessed with SF-36) Symptom burden/severity (assessed with VAS) |
| Diseases of the nervous system | Multiple sclerosis | <ul style="list-style-type: none"> Fatigue (assessed with MFIS) Quality of life (assessed with SF-36) Function/disability (assessed with EDSS) Function/disability (assessed with MSFC) Cognitive impairment (assessed with PASAT-3) |
| Diseases of the circulatory system | Cardiovascular disease | <ul style="list-style-type: none"> Non-fatal cardiac events (assessed with return to theatre incidence) Hospital length of stay (assessed with days) Arrhythmia (assessed with cases) |
| Diseases of the respiratory system | Allergic rhinitis | <ul style="list-style-type: none"> Symptom outcomes |
| Diseases of the digestive system | Ulcerative colitis | No measures prioritised by the NTWC were reported in eligible studies |
| Musculoskeletal system conditions | Back pain | <ul style="list-style-type: none"> Pain (assessed with VAS) Quality of life (assessed with SF-36) Function/disability (assessed with Oswestry disability questionnaire) |
| | Rotator cuff tendinitis | <ul style="list-style-type: none"> Pain (assessed with VAS) Quality of life (assessed with SF-36) Function (assessed with SPADI) Range of motion (assessed with Goniometer readings) Treatment success (assessed with MYMOP) |
| Genitourinary system conditions | Menopausal symptoms | <ul style="list-style-type: none"> Vasomotor menopausal symptoms Energy Menstrual changes Insomnia Anxiety Sleep |

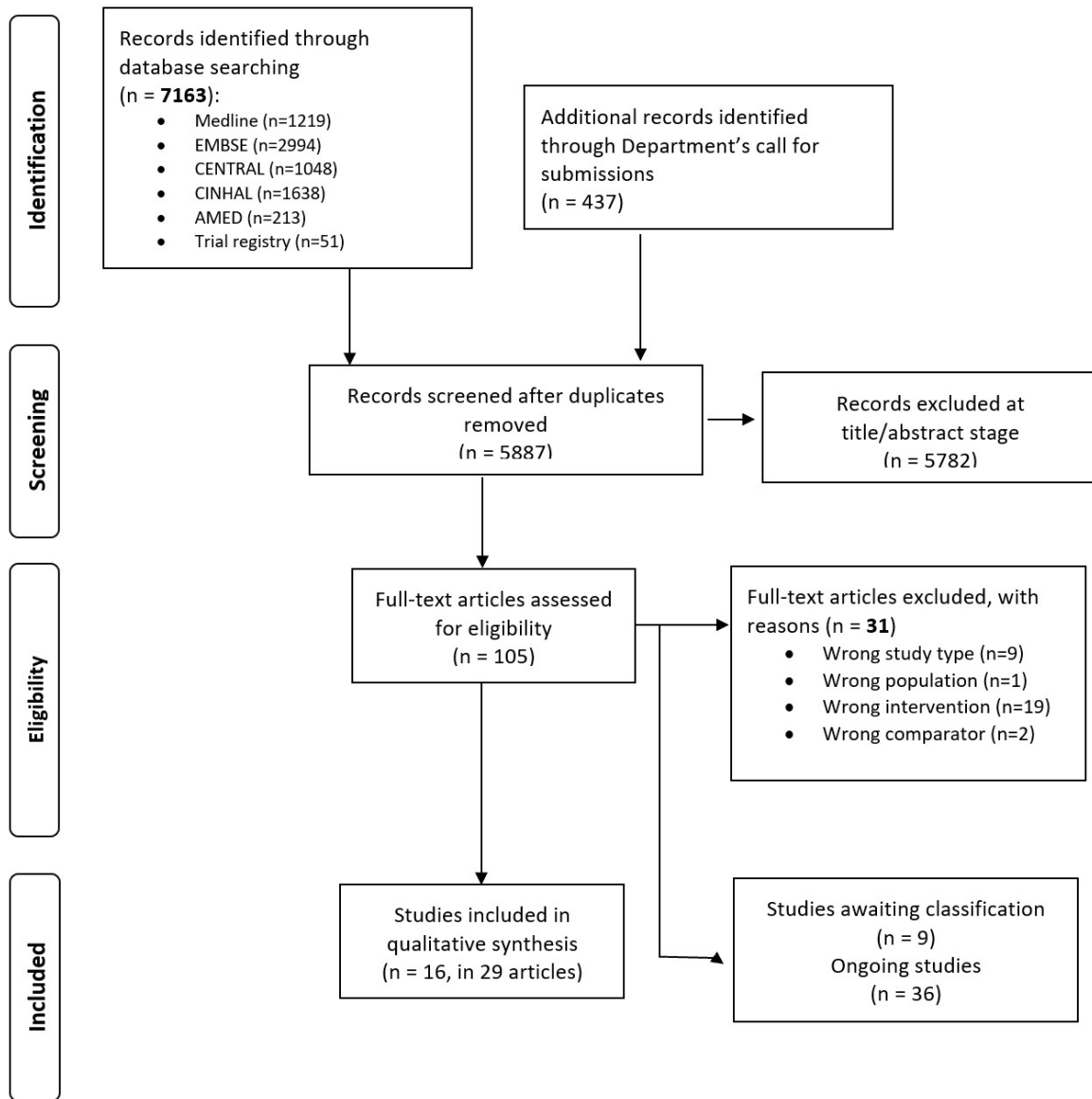
| Conditions ^a | Population | Prioritised outcome domain reported on by eligible studies |
|---|-----------------------------|---|
| Other: Prevention of disease, injury, or illness in at-risk populations | Cardiovascular disease risk | <ul style="list-style-type: none"> • Cardiovascular risk at 12 months • Cardiovascular risk at 10 years • LDL cholesterol • Prevalence of metabolic syndrome • T2DM severity (assessed with Hb1Ac) • Metabolic syndrome and metabolic syndrome risk factors |

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Index; EDSS, Expanded Disability Status Score; FLIC, Functional Living Index Cancer; HbA1c, haemoglobin A1c; kg, kilogram; LDL, low-density lipoprotein; MFIS, Modified Fatigue Impact Scale; MSFC, Multiple Sclerosis Functional Composite; MYMOP, Measure Yourself Medical Outcome Profile; PASAT-3, Paced Auditory Serial Addition Test 3; PCOSQ, Polycystic Ovary Syndrome Questionnaire; SPADI, Shoulder Pain and Disability Index; STAI, State Trait Anxiety Inventory; T2DM, type 2 diabetes mellitus; QUICKI, quantitative insulin-sensitivity check index; VAS, Visual Analogue Scale

A.7. Summary screening results

A.7.1. Summary search results

Figure 1: PRISMA flowchart



Abbreviations: AMED, Allied and Complementary Medicine Database; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature

Approximately 50% of citations were excluded at the title/abstract stage for wrong study type (e.g., single arm studies without a contemporaneous comparatory group) and about a third were excluded for wrong intervention (e.g., the intervention did not include one of the core modalities, was not delivered by a naturopath or in a naturopathic context).

A.7.2. Summary results for evidence provided through department

437 publication citations were provided by the department, of which 59 were identical duplicate citations. All 378 of the remaining citations had been found in the electronic search. Of the citations submitted by stakeholders 14 citations (corresponding to 7 studies) had already been found and included, 135 were wrong study type (more than half were systematic reviews and meta-analyses), 18 were the wrong population (healthy seeking wellness), 203 were the wrong intervention as defined in the eligibility criteria, 6 were the wrong comparator, and 2 the wrong outcome. The full details are provided in Appendix C2.

Appendix B: Methods of data appraisal, extraction, analysis, and reporting for included studies

B.1. Risk of Bias process

The risk of bias was assessed by two reviewers independently. Any disagreements were discussed between the two reviewers, with a third reviewer consulted where the former be unable to reach an agreement.

B.1.1. Tools used to assess Risk of Bias

The risk of bias tools used were Risk of Bias 2⁹ (ROB 2) and risk of bias in non-randomised studies of interventions (ROBINS-I).¹⁰ As no eligible case-control studies were identified, the SIGN-50 tool was not implemented.

B.1.2. Assessing Risk of Bias

Two independent reviewers responsible for data extraction completed the risk of bias assessments and the lead reviewer checked the completed assessments and discussed how differences could be resolved. This allowed for consistency in the risk of bias assessment process, including the management of differences in identifying potential confounders according to the ROBINS-I tool.

Where possible, the assessment was based on the primary outcome for that study (or that for which the study was powered). Two assessments were made to account for risk of bias associated with different (e.g., subjective and objective) outcome measures.

Risk of bias visual diagrams for ROB 2 and ROBINS-I were generated by robvis (<https://mcquinlu.shinyapps.io/robvis/>).

B.2. Data extraction processes

B.2.1. Data items

The data extracted from eligible studies were:¹¹

- Study citation
- Year of publication
- Study type: RCTs or NRSI with contemporaneous comparator (e.g. cohort or case-control studies)
- Study duration
- Country
- Population group, number of participants, setting, and demographic data (including gender, age, condition, and/or diagnosis), inclusion and exclusion criteria

Intervention:^{11,12}

1. Name and description of the intervention
2. Description of rationale, theory, or goal of the elements essential to the intervention

3. Materials used in the intervention
4. Procedures used in the intervention
5. Intervention provider
6. Modes of delivering the intervention
7. Location where the intervention occurred
8. Timepoints the intervention was delivered, time period, frequency/number of sessions, duration of the intervention session, intensity, and dosage
9. Tailoring of the intervention, if the intervention was personalised, titrated, or adapted, the rationale and method for doing so
10. Modifications to intervention, when they occurred, why and how
11. Strategies to maintain or improve adherence/fidelity to intervention, if assessed
12. Actual adherence or fidelity to intervention, if assessed.

Comparator:^{11,12}

1. Name and description of comparator
2. Description of rationale, theory, or goal of the elements essential to the comparator
3. Materials used in the comparator
4. Procedures used in the comparator
5. Comparator provider
6. Modes of delivering the comparator
7. Location where the comparator was administered
8. Timepoints the comparator was delivered, time period, frequency/number of sessions, duration of comparator session, intensity, and dosage
9. Tailoring of the comparator, if the comparator was personalised, titrated, or adapted, the rationale and method for doing so
10. Modifications to the comparator, when they occurred, why and how
11. Strategies to maintain or improve adherence/fidelity to the comparator, if assessed.
12. Actual adherence or fidelity to the comparator, if assessed.

Outcomes: The outcome results could be continuous or dichotomous (categorical) and included 'critical' and 'important but not critical' outcomes (up to seven) and the timepoints at which they were measured.

Outcomes:

1. Primary outcomes: Description, including measurement method
2. Secondary outcomes: Description, including measurement method
3. Whether there was evidence that the outcome domain was assessed (especially important if the outcome was assessed but the results not presented)
4. Measurement tool or instrument (including definition of clinical outcomes or endpoints); for a scale, name of the scale, upper and lower limits, and whether a high or low score was favourable, definitions of any thresholds if appropriate
5. Specific metric (e.g. post-intervention anxiety, or change in anxiety from baseline to a post-intervention time point, or post-intervention presence of anxiety (yes/no))
6. Method of aggregation (e.g. mean and standard deviation of anxiety scores in each group, or proportion of people with anxiety)
7. Timing/timepoints of outcome measurements (e.g. assessments at end of an eight-week intervention period, events occurring during the eight-week intervention period)
8. For each group, and for each outcome at each time point: number of participants randomly assigned and included in the analysis; and number of participants who withdrew, were lost to follow-up, or were excluded (with reasons for each).

Results data:

1. Intervention results: participant number, mean/proportion
2. Comparator (point estimate): participant number, mean/proportion
3. Point estimate: risk estimates and direction of effect. This includes estimates that are adjusted for confounders if reported by the study.

4. Measures of variation: such as standard deviation, standard error, and 95% confidence intervals.
- Other: funding sources, notable conflicts of interest of trial authors.

B.2.2. Requests for data

One author was contacted for a full publication (Stier-Jarmer 2021) but no response was received. One author (Seely 2019) was contacted regarding their published RCT protocol: the author confirmed that they were still collecting data and thus their study remains categorised as an 'ongoing study'. No other authors were contacted for missing data.

B.2.3. Transformations of data

Not applicable.

B.2.4. Missing outcome data

Published outcomes were relied on. Means were not imputed and there were insufficient data to do so. Where there were sufficient data, standard deviations or 95% confidence intervals of the means were imputed using the calculation methods in sections 6.5.2.2 and 6.5.2.3 of the Cochrane Handbook¹³.

Data was to be analysed on an intention to treat (ITT) basis where possible, including risk of bias assessment when considering bias arising from deviations from the intended intervention and bias arising from missing outcome data.

Sensitivity analyses (refer to Section B.3.9) were not performed to assess how sensitive the results are to reasonable changes in the assumptions made, as there were insufficient eligible studies to do so. Risk of bias due to missing outcome data was assessed as per Section B.1. The potential impact of missing data on the findings of this Review was addressed in the Discussion section (section 10.12, Cochrane Handbook¹⁴).

B.3. Data Analysis

B.3.1. Measures of treatment effect

Effect measures and clinical relevance

Measurement of treatment effect was by mean difference (MD)(preferred) or standardised mean differences (SMD) and 95% confidence intervals (continuous outcomes) and risk ratios (preferred) or odds ratios with 95% confidence intervals (dichotomous data) (refer to Sections 6.4 and 6.5 of the Cochrane Handbook 2019¹³). No eligible studies reported hazard ratios. To reduce the effects of confounding, summary statistics from NRSIs were reported as adjusted effect estimates where available. In instances where minimal clinically important differences (MCID) were unavailable, effect estimates were assessed using a threshold of (1) small mean difference (MD) <10% of the scale) (2) moderate (MD between 10% to 20% of the scale), or (3) large (MD more than 20% of the scale). If effect sizes could not be calculated or were not reported by studies, a relative risk increase of 25% or more was used as a default threshold for appreciable harm or benefit (GRADE Handbook section 5.2.4.2).

As there were insufficient numbers of eligible studies per population group, meta-analyses could not be conducted and thus standardised mean differences for continuous outcomes (Section 6.5.1.2 of the Cochrane Handbook¹³), where an outcome has been measured using different scales in different studies, were not calculated.

B.3.2. Unit of analysis issues

For eligible RCTs or NRSIs, the unit of analysis is the individual participant. As there were no eligible cross-over or cluster RCTs, unit of analysis concerns regarding under- or over-estimating precision (refer to Section 6.2, Cochrane Handbook 2019¹³) were not relevant to this Review.

Repeated observations

For studies that assess the same outcome several times over a long duration, it is acknowledged that results from more than one timepoint for each study cannot be combined in a standard meta-analysis without a unit of analysis error (Section 6.2.4 of the Cochrane Handbook¹³). Timepoints were not pre-specified during the outcome prioritisation exercise conducted by the NTWC. Ideally, the chosen timepoint would be a clinically important timepoint.¹³ It is acknowledged that choosing a timepoint that maximises the data available may lead to reporting biases.¹³ For this Review, observations for the first and last timepoints were extracted, as these were the timepoints studies reported numerical data for. The exceptions were type 2 diabetes and cardiovascular risk: for these two population groups, studies also reported outcome data at an intermediate timepoint, and this data were also extracted.

Naturopath practitioners treating multiple trial participants

A unit of analysis error could arise in an individually randomised trial where naturopath practitioners each treat multiple participants. Outcomes of participants of the same naturopath practitioner will be correlated, and if this correlation is not accounted for in the study analysis, the study's standard error may be incorrect which has implications for the meta-analysis.

Such intervention-related clustering was not identified in this Review.

Studies with more than two intervention groups

For eligible studies with more than two groups, results from treatment arms that do not meet the criteria for the intervention or comparator were excluded from the analyses (section 23.3.2, Cochrane Handbook 2019¹⁵). Where all groups were eligible or more than two groups are eligible, they were included in the analyses. As there were insufficient eligible studies within each population group, meta-analyses could not be undertaken and concerns that participants from one treatment arm were to be included only once were not relevant (section 23.3.4, Cochrane Handbook 2019¹⁵).

B.3.3. Risk of reporting bias across studies

The selective reporting or under-reporting of outcomes were assessed for individual RCTs and NRSIs as part of the risk of bias assessment (refer to Sections B.1).

The non-reporting of evidence refers to when evidence is not available. This includes studies that state in their methodology or trial protocol that they will assess certain outcomes, but then do not report the results of those outcomes or do not report the outcomes in a useable form for data synthesis (e.g., may only state there was no difference or that there was a significant difference but without presenting means or point estimates).

Studies that may exhibit non-reporting of evidence were identified when published reports were screened at the full-text stage, where studies report no useable results for the outcomes prioritised by the NTWC, and also when trial registries were searched (Section A.1.2, Chapter 13.2 of the Cochrane Handbook¹⁷). This will assist in reducing evidence gaps due to the non-reporting. Such studies are documented in the data extraction table unless the outcome results are missing. However if significance or direction of effect are reported, they are included.

As meta-analyses could not be conducted, appraising the risk of bias attributed to non-reporting of results guided by signalling questions 4.1, 4.2 and 4.4 of the preliminary Risk of Bias due to Missing Evidence tool (ROB-ME)¹⁸ and section 13.3 of the Cochrane Handbook¹⁷ was not performed.

As there were not at least 10 eligible RCTs with similar populations, interventions and outcome measures with which to conduct a meta-analysis, non-reporting bias as publication bias could not be assessed via regular funnel plots (Section 5.2.5, GRADE Handbook 2013⁶ Sections 13.3.5.2 and 13.3.5.5 of the Cochrane Handbook 2019¹⁷).

B.3.4. Data synthesis

Synthesis of RCTs

Meta-analyses using RevMan 5.3¹⁶ could not be performed as there were not at least two RCTs with similar outcome measures and population and which met the criteria for quantitative synthesis.

Synthesis of NRSIs

Meta-analyses using RevMan 5.3¹⁶ could not be performed as there were not at least two NRSIs of similar outcome measures and population and which meet the criteria for quantitative synthesis.

B.3.5. Quantitative synthesis

Both single and multi-modal interventions that met the definition of 'naturopathy' were to be synthesised together, with subgroup analyses conducted if there is sufficient evidence within a population to do so. See section 2.1.3 for definitions of whole system, multi-modal and whole system, single modal interventions. As there were insufficient number of eligible studies within each population group, meta-analyses and sensitive analyses to investigate the robustness of treatment effect could not be conducted.

Studies (including conference abstracts) with no useable results data were not included in any syntheses: this occurred when data was not presented in a useable form, for example, when study authors stated there is no difference in an outcome but do not provide point estimates that can be assessed. Studies that stated they collected data on an outcome but did not report on it were considered in the section on reporting bias (Section B.3.3). Hand searches were undertaken to locate eligible additional publications based on the same study that were not already identified.

B.3.6. Non-quantitative synthesis

As meta-analyses could not be conducted and there were at most one RCT and/or one NRSI eligible for inclusion for each population group, vote-counting also could not be conducted. Results of studies were synthesised narratively. Forest plots without summary diamonds were provided as a visual display of individual studies' summary statistics.

B.3.7. Subgroup analyses and investigations of heterogeneity

The limited number of studies meant that sub-group analysis could not be conducted.

Where there was only one study heterogeneity between studies could not be assessed. Where there were two studies, but meta-analyses could not be performed because one was an RCT and one an NRSI, I^2 could not be calculated, and heterogeneity was reported descriptively.

B.3.8. Addressing risk of bias

Refer to Section B.1.

Summary of findings tables were not presented for NRSI studies assessed as critical risk of bias.

B.3.9. Sensitivity analysis

As noted above sensitivity analysis could not be conducted due to the limited number of studies.

B.4. Evidence statements

B.4.1. Summary of findings and certainty of evidence

Certainty of the evidence

The certainty of evidence was assessed using the GRADE approach, which involved considering a range of factors that may decrease or increase certainty in the evidence to arrive at an overall 'certainty of the evidence' rating.⁶ The certainty was categorised as:

- **High:** We are very confident that the true effect is similar to that of the estimate of the effect.
- **Moderate:** The true effect is probably close to the estimated effect.
- **Low:** The true effect might be markedly different from the estimated effect.
- **Very low:** The true effect is probably markedly different from the estimated effect.

Certainty of the evidence was assessed for critical and important outcomes. RCTs and NRSIs were assessed separately. Assessment was by two independent reviewers: disagreements were resolved by discussion between the two reviewers, with a third reviewer consulted if the former could not reach an agreement.

The GRADE approach commences by first assessing the following five factors and considering whether their certainty should be downgraded:⁶

- **Risk of bias:** as assessed by the risk of bias tools (Section B.1). The overall risk of bias across all studies contributing to each result and the extent to which high risk of bias studies influence the result (i.e. the weight these studies have in the meta-analysis) was considered.
- **Imprecision:** there is greater imprecision indicated by wide confidence intervals and small sample sizes. Further, imprecision is indicated when the confidence interval crosses the minimal clinically important threshold where the decision between recommending and not recommending a treatment is made and therefore encompasses both benefit and harm. MCID were sourced from published reports or guided by advice from the NTWC (see section B.3.1) If this was not available, a relative risk increase of 25% or more was used as a default threshold for appreciable harm or benefit (GRADE Handbook section 5.2.4.2). Imprecision could also be indicated by optimal information size (OIS). The OIS is calculated as the total number of participants included in the Review for a key outcome that is less than the number required for a sufficiently powered trial.¹⁹ In dichotomous outcomes, imprecision is indicated if the OIS is not met or when the OIS is met and the 95% confidence interval overlaps 'no effect'. An exception to rating down imprecision when the OIS is not met would be where the event rate was very low and the sample size was very large, with at least 2,000 participants (GRADE Handbook section 5.2.4.1). Similar criteria for rating down for imprecision apply to continuous outcomes, including when sample sizes are less than 400 (GRADE Handbook section 5.2.4.2).
- **Inconsistency:** reflected by the heterogeneity of the results. This involved visual inspection of the overlap in confidence intervals, in combination with cautious interpretation of heterogeneity statistics, and whether any observed inconsistency could be explained. In this Review, inconsistency for most outcomes in most population groups could not be assessed as there was only one included eligible study per group.

- **Indirectness:** reflected by how well the studies match all elements of the PICO criteria (see Section A.3). This included how applicable a study's population, intervention and outcomes were to that of the PICO criteria's and whether the outcome results were measured directly (a patient-important outcome) or by a surrogate endpoint (GRADE Handbook section 5.2.3).
- **Publication bias:** as described in Section B.3.3.

Following the assessment of the first five factors, if the evidence has not been downgraded except for confounding or selection bias, the certainty of evidence may be upgraded (i.e. certainty in the evidence may be increased) in the presence of:

- very large effect size
- a dose-response relationship
- increased effect despite having plausible confounders that should have reduced effect, or results show no effect despite plausible confounders that should have led to increased effect.

Upgrading did not apply in this report.

Incorporating recent advice from the GRADE Working Group regarding the use of ROBINS-I in evaluating risk of bias for NRSIs,^{20,21} the GRADE assessment process commenced at high certainty of evidence for both RCTs and NRSIs.

For each of the GRADE domains (risk of bias, imprecision, consistency, directness/indirectness, and publication and reporting bias), an assessment was made as to whether there are low or no concerns (no subtractions to the certainty of evidence rank), serious concerns (subtract 1) or very serious concerns (subtract 2). Following an assessment of the factors for downgrading certainty, consideration was given to whether there were any circumstances that warranted 'rating up' certainty in the evidence, based on the three factors outlined above and following GRADE guidance.⁶ The rationale for downgrading the certainty in the evidence has been provided as footnotes (see 'Summary of findings' tables).

'Summary of findings' tables

The findings from RCTs and NRSIs are presented separately within the Summary of Findings table. Findings are presented as point estimates (MDs and risk ratios) with 95% confidence intervals, for the key outcomes that were assessed. A Summary of Findings table was produced for each population/condition group.

The certainty of the evidence (GRADE) along with any reasons for downgrading is also presented in the tables. The tables were generated using GRADEPro software.

B.4.2. Development of evidence statements

Evidence statements were developed using the certainty of evidence assessed, and guided by the wording provided by GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions (Santesso 2020)²².

Table 7: From GRADE guidelines 26 (Santesso 2020)

| Size of the effect estimate | Suggested statements (replace X with intervention, replace 'reduce/increase' with direction of effect, replace 'outcome' with name of outcome, include 'when compared with Y' when needed) |
|---------------------------------------|--|
| HIGH Certainty of the evidence | |
| Large effect | X results in a large reduction/increase in outcome |

| Size of the effect estimate | Suggested statements (replace X with intervention, replace 'reduce/increase' with direction of effect, replace 'outcome' with name of outcome, include 'when compared with Y' when needed) |
|--|---|
| Moderate effect | X reduces/increases outcome X results in a reduction/increase in outcome |
| Small important effect | X reduces/increases outcome slightly X results in a slight reduction/increase in outcome |
| Trivial, small unimportant effect or no effect | X results in little to no difference in outcome X does not reduce/increase outcome |
| MODERATE Certainty of the evidence | |
| Large effect | X likely results in a large reduction/increase in outcome X probably results in a large reduction/increase in outcome |
| Moderate effect | X likely reduces/increases outcome X probably reduces/increases outcome X likely results in a reduction/increase in outcome X probably results in a reduction/increase in outcome |
| Small important effect | X probably reduces/increases outcome slightly X likely reduces/increases outcome slightly X probably results in a slight reduction/increase in outcome X likely results in a slight reduction/increase in outcome |
| Trivial, small unimportant effect or no effect | X likely results in little to no difference in outcome X probably results in little to no difference in outcome X likely does not reduce/increase outcome X probably does not reduce/increase outcome |
| LOW Certainty of the evidence | |
| Large effect | X may result in a large reduction/increase in outcome The evidence suggests X results in a large reduction/increase in outcome |
| Moderate effect | X may reduce/increase outcome The evidence suggests X reduces/increases outcome X may result in a reduction/increase in outcome The evidence suggests X results in a reduction/increase in outcome |
| Small important effect | X may reduce/increase outcome slightly The evidence suggests X reduces/increases outcome slightly X may result in a slight reduction/increase in outcome The evidence suggests X results in a slight reduction/increase in outcome |
| Trivial, small unimportant effect or no effect | X may result in little to no difference in outcome The evidence suggests that X results in little to no difference in outcome X may not reduce/increase outcome The evidence suggests that X does not reduce/increase outcome |
| VERY LOW Certainty of the evidence | |
| Any effect | The evidence is very uncertain about the effect of X on outcome X may reduce/increase/have little to no effect on outcome, but the evidence is very uncertain |

Appendix C: Excluded studies

C.1. Full text excluded studies

The following studies (n=30) were excluded at full-text review. Wrong study type (n=9), wrong population (n=1), wrong intervention (n=18), wrong comparator (n=2).

Citation details of studies awaiting classification (n=9) and ongoing studies or trial protocols (n=36) are located in Appendix C.4 and C.4 respectively.

C.1.1. Wrong study type

Table 8: Full text exclusion wrong study type

| # | Study | Reason for exclusion |
|---|---|---|
| 1 | Akumar B, Kadam A, Srikanth H, Rao R. Naturopathy and yoga based life style intervention for cardiovascular risk reduction in patients with cardiovascular risk factors: A pilot study. BMC Complementary and Alternative Medicine. 2012;12. | Insufficient details regarding naturopathy modalities (conference abstract) |
| 2 | Berman BM, Chiaramonte D, Kaiser A, Simone CB, McMath G, Regine WF. Integrative proton therapy: A novel, personalized strategy combining precision proton treatment with integrative medicine modalities to improve quality of life and outcomes for cancer patients. Global Advances in Health and Medicine. 2018;7:244. | Single-arm, no comparator |
| 3 | Breed C, Berezney C. Treatment of Depression and Anxiety by Naturopathic Physicians: An Observational Study of Naturopathic Medicine Within an Integrated Multidisciplinary Community Health Center. Journal of Alternative and Complementary Medicine. 2017;23(5):348-54. | Single-arm, no comparator |
| 4 | Desai SN, Deshmukh N. The effect of natural diet on Hb level of children age group 2-6 years: Positively link to global warming. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2013;4(1):1165-73. | Single-arm, no comparator |
| 5 | Jenefer Jerrin R, Manavalan N, Theebika S, Venkateswaran ST, Panneerselvam P, Maheshkumar K. Yoga and Naturopathy intervention for reducing anxiety and depression of Covid-19 patients - A pilot study. Clinical Epidemiology and Global Health. 2021;11:100800. | Single arm, no comparator |
| 6 | Milliman WB, Lamson DW, Brignall MS. Hepatitis C; a retrospective study, literature review, and naturopathic protocol. Alternative medicine review : a journal of clinical therapeutic. 2000;5(4):355-71. | Single arm, no comparator |
| 7 | Pooja MR, Pushpalatha MP. Cluster analysis to characterize the patterns of complementary and alternative medicines usage in asthma controls. Open Public Health Journal. 2020;13(1):227-31. | Prevalence study, not an intervention study |
| 8 | Smith F, Faydenko J. Use of cardiac risk biomarker testing in a naturopathic medicine teaching center: Lessons on standard of care. European Journal of Integrative Medicine. 2020;36:101135. | Observational study, not an intervention study |
| 9 | St, ish LJ, Dowd F, Sweet E, Dale L, Andersen MR. Do Women With Breast Cancer Who Choose Adjunctive Integrative Oncology Care Receive Different Standard Oncologic Treatment? Integrative cancer therapies. 2018;17(3):874-84 | Observational study |

C.1.2. Wrong population

One study, Teut 2013 (see Table 9) was excluded as wrong population. The study included a geriatric population, a healthy population, therefore it did not fit the 'at risk' population definition. This was confirmed by the NTWC.

Table 9: Full text exclusion wrong population

| # | Study | Reason for exclusion |
|---|---|---|
| 1 | Teut M, Schnabel K, Baur R, Kerckhoff A, Reese F, Pilgram N, et al. Effects and feasibility of an Integrative Medicine program for geriatric patients-a cluster-randomized pilot study. <i>Clinical interventions in aging</i> . 2013;8:953-61. | Study participants were enrolled regardless of their disease and health state Geriatric i.e. a healthy population is not an 'at risk' population; confirmation by NTWC |

Citation details of studies from non-priority populations are not applicable. Prioritisation was not required due to paucity of evidence.

C.1.3. Wrong intervention

Table 10: Full text exclusion wrong intervention

| # | Study | Reason for exclusion |
|---|--|--|
| 1 | Alaguraja K, Yoga P. Combination of naturopathy and yoga on Vo2 max among hypertensive patient. <i>Indian Journal of Public Health Research and Development</i> . 2020;11(4):131-4. | Naturopathy modalities not described and not known if any of the 4 core modalities are included |
| 2 | Andersen MR, Sweet E, Hager S, Gaul M, Dowd F, St, et al. Effects of Vitamin D Use on Health-Related Quality of Life of Breast Cancer Patients in Early Survivorship. <i>Integrative cancer therapies</i> . 2019;18:1534735418822056. | Intervention not necessarily administered in the 'naturopathic context' |
| 3 | Arankalle D, Wardle J, Nair PMK. Alternate hot and cold application in the management of heel pain: A pilot study. <i>Foot (Edinburgh, Scotland)</i> . 2016;29:25-8. | Not one of the 4 core naturopathic modalities |
| 4 | Balercia G, F.Regoli, T. Armeni, A.Koverech,F.Mantero, Boscaro M. Placebo-controlled double-blind randomized trial on the use of L-carnitine, L-acetylcarnitine, or combined L-carnitine and L-acetylcarnitine in men with idiopathic asthenozoospermia. <i>Fertility and sterility</i> . 2005;84(3):662-71. | No mention of naturopathy in the intervention |
| 5 | Balercia G BE, Vignini A, Tiano L, Paggi F, Amoroso S, Ricciardo-Lamonica G, Boscaro M, Lenzi A, Littarru, GP. Coenzyme Q10 treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial. <i>Fertility and Sterility</i> . 2009;91(5):1785-92. | No mention of naturopathy in the intervention |
| 6 | Chang Y-C, Tzu-hui AT, Chiu S-C. The Relation between Natural Therapy and Physiological at Diagnosis in Breast Cancer...5th Annual Worldwide Nursing Conference (WNC2017), 24th–25th July 2017, Singapore. <i>Annual Worldwide Nursing Conference</i> . 2017:237-9. | Intervention was 'walking in the park' and 'caring for potplants'. Not one of the 4 core modalities. |
| 7 | Jong M, Van De Vijver L, Busch M, Fritsma J, Seldenrijk R. Integrative primary care management improves quality of life in patients with chronic musculoskeletal pain: A randomized controlled comparative study. <i>Journal of Alternative and Complementary Medicine</i> . 2016;22(6):A5. | Some participants received acupuncture, which is not one of the core modalities, and they could not be removed from other participants' data |

| # | Study | Reason for exclusion |
|----|--|--|
| 8 | Kamat RV, hu R, Kamat V. Patient reported outcomes on biogetica formulations in trigeminal neuralgia. <i>International Journal of Research in Ayurveda and Pharmacy</i> . 2019;10(2):58-68. | Delivered in Ayurvedic context, not naturopathic context |
| 9 | Klafke N, Mahler C, Ehmann A, Bentner M, Uhlmann L, Von Hagens C, et al. Does a supportive nurse-led intervention including complementary and integrative medicine (CIM) help cancer patients undergoing chemotherapy and their family members to experience better quality of life? Results from the CONGO study. <i>Oncology Research and Treatment</i> . 2018;41:138. | Modalities of naturopathy not stated |
| 10 | Koch AK, Schols M, Zempel C, et al. There is more than pharmacology: Comprehensive lifestyle-modification in patients with ulcerative colitis - A randomized controlled trial. <i>Advances in Integrative Medicine</i> . 2019;6:S137. | Delivered by a physician not a naturopath and so not in the naturopathic context |
| 11 | Langhorst J, Koch AK, Schols M, Zempel T, Paul A, Cinar Z, et al. There is more than pharmacology: comprehensive lifestyle-modification in patients with ulcerative colitis - a randomized controlled trial. <i>Gastroenterology</i> . 2019;156(6):S-434. | Duplicate of Koch et al. |
| 12 | La Vallee R, Pierce G, Edel A, Rodriguez-Leyva D, Weighell W, Guzman R, et al. Flaxseed lignan metabolites elicit antihypertensive effects in pad patients in the flax-pad trial. <i>Annals of Nutrition and Metabolism</i> . 2013;63:1339. | Not stated intervention delivered in naturopathic context |
| 13 | Lenzi A, P. Sgro, P. Salacone, D. Paoli, B. Gilio, F. Lombardo, M. Santulli, A. Agarwal, G L, ini. A placebo-controlled double-blind randomized trial of the use of combined l-carnitine and l-acetyl-carnitine treatment in men with asthenozoospermia. <i>Fertility and sterility</i> . 2004;81(6):1578-84. | No mention of naturopathy |
| 14 | Salmond SJ GJ, Strasser SI, ., et al. Hep573 Study: A randomised, double-blind, placebo controlled trial of silymarin alone and combined with antioxidants to improve liver function and quality of life in people with chronic hepatitis C. <i>Aust Journal of Herbal & Naturopathic Medicine (AJHNM)</i> . 2018;30(2):64-76. | Delivered in conventional hospital and so not in the naturopathic context |
| 15 | Sarrell EM, elberg A, Cohen HA. Efficacy of naturopathic extracts in the management of ear pain associated with acute otitis media. <i>Archives of pediatrics & adolescent medicine</i> . 2001;155(7):796-9. | Intervention delivered by conventional clinicians and so not in the naturopathic context |
| 16 | Sarrell EM, Cohen HA, Kahan E. Naturopathic treatment for ear pain in children. <i>Pediatrics</i> . 2003;111(5):e574-9. | Delivered by conventional medical clinicians and so not in the naturopathic context |
| 17 | Scott R, A. MacPherson, R. Yates, B. Hussain, Dixon J. The effect of oral selenium supplementation on human sperm motility. <i>British journal of urology</i> . 1998;82(1):76-80. | No mention of naturopathy |
| 18 | Tulp O, Izunobi F, Einstein G. Effectiveness of synthetic medicine versus FI matrix natural therapy for autoimmune diseases and cancer. <i>FASEB Journal</i> . 2015;29(1). | No mention of naturopathy |
| 19 | Westphal LM, M. L. Polan, A. S. Trant, Mooney S. A nutritional supplement for improving fertility in women. <i>Journal of Reproductive Medicine</i> . 2004;49(4):289-93. | No mention of naturopathy and intervention delivered in a conventional medical setting, so not in the naturopathic context |

C.1.4. Wrong comparator

Table 11: Full text exclusion wrong comparator

| # | Study | Reason for exclusion |
|---|--|--|
| 1 | Koch AK, Schols M, Haller H, Anheyer D, Cinar Z, Eilert R, et al. Comprehensive lifestyle-modification including multi-modal stress management techniques in patients with ulcerative colitis - Results of the Trier Social Stress Test. <i>Advances in Integrative Medicine</i> . 2019;6:S79. | Compares two different naturopathic treatments (conference abstract) |
| 2 | Ritenbaugh C, Hammerschlag R, Calabrese C, Mist S, Aickin M, Sutherl, et al. A pilot whole systems clinical trial of traditional Chinese medicine and naturopathic medicine for the treatment of temporomandibular disorders. <i>Journal of alternative and complementary medicine (New York, NY)</i> . 2008;14(5):475-87. | Comparator is Traditional Chinese Medicine or usual care; mixed intervention |

C.2. Citation details of Studies provided through the Department's public call for evidence

There were 437 reports submitted through the Department's call for evidence. Of these 59 were exact duplicate citations. Citation details of the remaining 378 reports are displayed below in Table 12. There were 14 included reports which had already been found through the search (including duplicate reports of the same study, for a total of 7 studies), 135 wrong study type (e.g., systematic reports, case reports, narrative reviews, single arm studies), 18 wrong population (e.g., healthy population), 203 wrong intervention, 6 wrong comparator and 2 wrong outcome. There may be more than one reason for exclusion but only one is provided for each report. Note that the same submission pool will be considered for the companion review *Evidence on the clinical effectiveness of selected nutritional supplements prescribed in the context of naturopathic practice for preventing and/or treating injury, disease, medical conditions, or pre-clinical conditions: Overview of Reviews*, which will have different eligibility requirements. The table is sorted by included/excluded, then reason for exclusion, then alphabetically.

Table 12: Public Call for Evidence

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|--|---------------|--------------|--------------------|---|
| Arentz S, Smith CA, Abbott J, et al | 2017 | Combined lifestyle and herbal medicine in overweight women with polycystic ovary syndrome (PCOS): a randomized controlled trial | Phytotherapy Research | 31(9) | 1330-40 | Included | Duplicate citation (already identified) |
| Cooley K, Szczurko O et al. | 2009 | Naturopathic Care for Anxiety: A randomised controlled study | PLoS One Journal | 4(8) | 1-Oct | Included | Duplicate citation (already identified) |
| Gunawan M, Braun L, Esmore D, et al | 2009 | Integrative wellness program for cardiac surgery patients: implementation and evaluation | Heart, Lung and Circulation | 18 | S259 | Included | Duplicate citation (already identified) |
| Herman PM, Szczurko O, Cooley K, et al | 2008 | Cost-effectiveness of naturopathic care for chronic low back pain | Alternative Therapies in Health & Medicine | 14 (2) | | Included | Duplicate citation (already identified) |
| Herman PM, Szczurko O, Cooley K, et al | 2014 | A naturopathic approach to the prevention of cardiovascular disease: cost-effectiveness analysis of a pragmatic multi-worksite randomized clinical trial | Journal of Occupational and Environmental Medicine | 56(2) | 171 | Included | Duplicate citation (already identified) |
| Herman PM, Szczurko O, Cooley K, Mills EJ | 2008 | Cost-effectiveness of naturopathic care for chronic low back pain | Alternative therapies in health and medicine | 14 (2) | 32-39 | Included | Duplicate citation (already identified) |
| Herman PM, Szczurko O, Cooley K, Seely D | 2014 | A naturopathic approach to the prevention of cardiovascular disease: cost-effectiveness analysis of a pragmatic multi-worksite randomized clinical trial | Journal of occupational and environmental medicine | 56 (2) | 171-176 | Included | Duplicate citation (already identified) |
| Ratnakumari ME, Manavalan N, Sathyanath D, et al | 2018 | Study to evaluate the changes in polycystic ovarian morphology after naturopathic and yogic interventions | International Journal of Yoga | 11(2) | 139-47 | Included | Duplicate citation (already identified) |
| Seely D, Szczurko O, Cooley K, et al | 2013 | Naturopathic medicine for the prevention of cardiovascular disease: a randomized clinical trial | Canadian Medical Association Journal | 185 (9) | E409-16 | Included | Duplicate citation (already identified) |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|---|--|---------------|--------------|--------------------|--|
| Seely D, Szczurko O, Kieran C, Fritz H, Herman P, Bradley R, Aberdour S, Herrington C, Rouchotas P, Lescheid D, Gignac T, Bernhardt B, Zhou Q, Guyatt G | 2012 | Naturopathic medicine for the prevention of cardiovascular disease: a pragmatic randomized clinical trial | BMC complementary and alternative medicine | 12 | | Included | Duplicate citation (already identified) |
| Shinto L, Calabrese C, Morris C, et al | 2008 | A randomized pilot study of naturopathic medicine in multiple sclerosis | Journal of Alternative & Complementary Medicine | 14(5) | 489-96 | Included | Duplicate citation (already identified) |
| Szczurko O, Cooley K, Bernhardt B, et al. | 2006 | Determining the impact of naturopathic treatment on Canadian postal workers with low back pain, a randomised controlled parallel group study | Focus on Alternative and Complementary Therapies | 11(Suppl 1) | 46 | Included | Duplicate citation (already identified) |
| Szczurko O, Cooley K, Busse JW, et al. | 2007 | Naturopathic care for chronic low back pain: a randomized trial | PLoS One | 2 (9)_ | E919 | Included | Duplicate citation (already identified) |
| Szczurko O, Cooley K, Mills EJ, et al | 2009 | Naturopathic treatment of rotator cuff tendinitis among Canadian postal workers: a randomized controlled trial | Arthritis Care & Research | 61(8) | 1037-45 | Included | Duplicate citation (already identified) |
| Calabrese C, Berman SH, Babish JG, et al. | 2000 | A phase I trial of andrographolide in HIV positive patients and normal volunteers. | Phytotherapy Research | 14(5) | 333-8 | Excluded | Duplicate (found in search) - Wrong comparator |
| Hawrelak JA, Myers SP | 2010 | Effects of two natural medicine formulations on irritable bowel syndrome symptoms: a pilot study | Journal of Alternative & Complementary Medicine | 16(10) | 1065-71 | Excluded | Duplicate (found in search) - Wrong Comparator |
| Joseph B, Nair PM, Nanda A | 2015 | Effects of naturopathy and yoga intervention on CD4 count of the individuals receiving antiretroviral therapy-report from a human immunodeficiency virus sanatorium, Pune | International Journal of Yoga | 8(2) | 122 | Excluded | Duplicate (found in search) - Wrong Comparator |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|---|---|---------------|--------------|--------------------|--|
| McEwen BJ, Morel-Kopp M-C, Chen W, et al | 2013 | Effects of omega-3 polyunsaturated fatty acids on platelet function in healthy subjects and subjects with cardiovascular disease | Semin Thromb Hemost | 39(01) | 25-32 | Excluded | Duplicate (found in search) - Wrong Comparator |
| McEwen BJ, Morel-Kopp M-C, Tofler GH, et al | 2015 | The effect of omega-3 polyunsaturated fatty acids on fibrin and thrombin generation in healthy subjects and subjects with cardiovascular disease | Semin Thromb Hemost | 41(3) | 315-22 | Excluded | Duplicate (found in search) - Wrong Comparator |
| Ritenbaugh C, Hammerschlag R, Calabrese C, et al. | 2008 | A pilot whole systems clinical trial of traditional Chinese medicine and naturopathic medicine for the treatment of temporomandibular disorders | Journal of Alternative & Complementary Medicine | 14(5) | 475-87 | Excluded | Duplicate (found in search) - Wrong Comparator |
| Adams JB, Baral M, Geis E, et al | 2009 | Safety and efficacy of oral DMSA therapy for children with autism spectrum disorders: Part B - Behavioral results | BMC Clinical Pharmacology | 9 | 17 | Excluded | Duplicate (found in search) - Wrong intervention |
| Alfaddagh A, Elajami TK, Ashfaq H, Saleh M, Bistran BR, Welty FK. | 2017 | Effect of eicosapentaenoic and docosahexaenoic acids added to statin therapy on coronary artery plaque in patients with coronary artery disease: a randomized clinical trial. | J Am Heart Assoc | 6(12) | 6981 | Excluded | Duplicate (found in search) - Wrong intervention |
| Ali A, Katz DL, Njike VY, et al | 2011 | Effect of fruit and vegetable concentrates on endothelial function in metabolic syndrome: a randomized controlled trial | Nutrition Journal | 10(1) | 72 | Excluded | Duplicate (found in search) - Wrong intervention |
| Ali A, Ma Y, Reynolds J, et al | 2011 | Chromium effects on glucose tolerance and insulin sensitivity in persons at risk for diabetes mellitus | Endocrine Practice | 17(1) | 16-25 | Excluded | Duplicate (found in search) - Wrong intervention |
| Ali A, Weiss TR, McKee D, et al | 2017 | Efficacy of individualised diets in patients with irritable bowel syndrome: a randomised controlled trial | BMJ Open Gastroenterology | 4(1) | E000164 | Excluded | Duplicate (found in search) - Wrong intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|---|---------------|--------------|--------------------|--|
| Allen J, Bradley RD | 2011 | Effects of oral glutathione supplementation on systemic oxidative stress biomarkers in human volunteers | Journal of Alternative & Complementary Medicine | 17(9) | 827-33 | Excluded | Duplicate (found in search) - Wrong intervention |
| Amini, L., Mojab, F., Jahanfar, S., Sepidarkish, M., Raoofi, Z., & Maleki-Hajiagha, A | 2020 | Efficacy of Salvia officinalis extract on the prevention of insulin resistance in euglycemic patients with polycystic ovary syndrome: A double-blinded placebo-controlled clinical trial. | Complementary Therapies in Medicine | 48 | 102245 | Excluded | Duplicate (found in search) - Wrong intervention |
| Arankalle D, Wardle J, Nair PM | 2016 | Alternate hot and cold application in the management of heel pain: a pilot study | The Foot | 29 | 25-Aug | Excluded | Duplicate (found in search) - Wrong intervention |
| Askari G, Nasiri M, Mozaffari-Khosravi H, Rezaie M, Bagheri-Bidakhvidi M, Sadeghi O. | 2017 | The effects of folic acid and pyridoxine supplementation on characteristics of migraine attacks in migraine patients with aura: A double-blind, randomized placebo-controlled, clinical trial. | Nutrition | 38 | 74-79 | Excluded | Duplicate (found in search) - Wrong intervention |
| Aucoin M, Cooley K, Anand L, et al. | 2018 | Adjunctive vitamin D in the treatment of non-remitted depression: lessons from a failed clinical trial | Complementary Therapies in Medicine | 36 | 38-45 | Excluded | Duplicate (found in search) - Wrong intervention |
| Aycinena AC, Valdovinos C, Crew KD, et al | 2017 | Barriers to recruitment and adherence in a randomized controlled diet and exercise weight loss intervention among minority breast cancer survivors | Journal of Immigrant and Minority Health | 19(1) | 120-9 | Excluded | Duplicate (found in search) - Wrong intervention |
| Balercia G, Buldreghini E, Vignini A, Tiano L, Paggi F, Amoroso S, Ricciardo-Lamonica G, Boscaro M, Lenzi A, Littarru, GP. | 2009 | Coenzyme Q10 treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial. | Fertility and Sterility. | 91(5) | 1785-92. | Excluded | Duplicate (found in search) - Wrong intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|--------------------------------------|---------------|--------------|--------------------|--|
| Balercia, G.,F.Regoli, T. Armeni, A.Koverech,F.Mantero and M. Boscaro | 2005 | Placebo-controlled double-blind randomized trial on the use of L-carnitine, L-acetylcarnitine, or combined L-carnitine and L-acetylcarnitine in men with idiopathic asthenozoospermia. | Fertility and sterility | 84(3) | 662-671 | Excluded | Duplicate (found in search) - Wrong intervention |
| Balfour L, Spaans JN, Fergusson D, et al | 2014 | Micronutrient deficiency and treatment adherence in a randomized controlled trial of micronutrient supplementation in ART-naïve persons with HIV | PloS One | 9(1) | e85607 | Excluded | Duplicate (found in search) - Wrong intervention |
| Banerjee B, Vadiraj H, Ram A, et al. | 2007 | Effects of an integrated yoga program in modulating psychological stress and radiation-induced genotoxic stress in breast cancer patients undergoing radiotherapy | Integrative Cancer Therapies | 6(3) | 242-50 | Excluded | Duplicate (found in search) - Wrong intervention |
| Bares JM, Berger J, Nelson JE, et al | 2008 | Silybin treatment is associated with reduction in serum ferritin in patients with chronic hepatitis C | Journal of Clinical Gastroenterology | 42(8) | 937-44 | Excluded | Duplicate (found in search) - Wrong intervention |
| Barrie SA, Wright JV, Pizzorno JE, et al | 1987 | Comparative absorption of zinc picolinate, zinc citrate and zinc gluconate in humans | Agents and actions | 21(1-2) | 223-8 | Excluded | Duplicate (found in search) - Wrong intervention |
| Bisgaard H, Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Schoos AM, et al. | 2016 | Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. | N Engl J Med | 5(26) | 2530-2539 | Excluded | Duplicate (found in search) - Wrong intervention |
| Bradbury J, Myers SP, Meyer B, et al | 2017 | Chronic psychological stress was not ameliorated by omega-3 eicosapentaenoic acid (EPA) | Frontiers in pharmacology | 8 | 551 | Excluded | Duplicate (found in search) - Wrong intervention |
| Bradbury J, Myers SP, Oliver C | 2004 | An adaptogenic role for omega-3 fatty acids in stress; a randomised placebo controlled double blind intervention study (pilot) [SRCTN22569553] | Nutrition Journal | 3(1) | 20 | Excluded | Duplicate (found in search) - Wrong intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|--|---|---------------|--------------|--------------------|--|
| Burr NE, Hull MA, Subramanian V. | 2017 | Folic acid supplementation may reduce colorectal cancer risk in patients with inflammatory bowel disease. | Journal of clinical gastroenterology | 51 (3) | 247-253 | Excluded | Duplicate (found in search) - Wrong intervention |
| Calabrese C, Gregory WL, Leo M, et al | 2008 | Effects of a standardized Bacopa monnieri extract on cognitive performance, anxiety, and depression in the elderly: a randomized, double-blind, placebo-controlled trial | Journal of Alternative & Complementary Medicine | 14(6) | 707-13 | Excluded | Duplicate (found in search) - Wrong intervention |
| Casanova MA, Medeiros F, Trindade M, Cohen C, Oigman W, Neves MF. | 2017 | Omega-3 fatty acids supplementation improves endothelial function and arterial stiffness in hypertensive patients with hypertriglyceridemia and high cardiovascular risk. | J Am Soc Hypertens | 11(1) | Oct-19 | Excluded | Duplicate (found in search) - Wrong intervention |
| Caudill MA, Strupp BJ, Muscalu L, Nevins JEH, Canfield RL. | 2018 | Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study. | FASEB J | 32 (4) | 2172-2180 | Excluded | Duplicate (found in search) - Wrong intervention |
| Chen AC, Martin AJ, Choy B, Fernández-Peñas P, Dalziel RA, McKenzie CA et al. | 2015 | A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. | N Engl J Med | 373 (17) | 1618-1626 | Excluded | Duplicate (found in search) - Wrong intervention |
| Chen H, Liu S, Ji L, Wu T, Ji Y, Zhou Y, et al. | 2016 | Folic acid supplementation mitigates Alzheimer's disease by reducing inflammation: a randomized controlled trial. | Mediators of Inflammation Epub | 5912146 | N/A | Excluded | Duplicate (found in search) - Wrong intervention |
| Cheraghi E, Mehranjeni MS, Shariatzadeh MA, Esfahani MH, Ebrahimi Z. | 2016 | N-Acetylcysteine improves oocyte and embryo quality in polycystic ovary syndrome patients undergoing intracytoplasmic sperm injection: an alternative to metformin. | Reprod Fertil Dev | 28(6) | 723-731 | Excluded | Duplicate (found in search) - Wrong intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|--|--|---------------|--------------|--------------------|--|
| Cheras PA, Myers SP, Paul-Brent PA, et al | 2010 | Randomized double-blind placebo-controlled trial on the potential modes of action of SheaFlex70 in osteoarthritis | Phytotherapy Research | 24 (8) | 1126-31 | Excluded | Duplicate (found in search) - Wrong intervention |
| Childs J, Higgins D, Parker S, et al | 2012 | Abstract OT3-1-02: Phase II randomized study of combination immunotherapy with or without Polysaccharide Krestin (PSK®) concurrently with a HER2 ICD peptide-based vaccine and trastuzumab in patients with stage IV breast cancer | Cancer Research | 72(4) | OT3-1-02 | Excluded | Duplicate (found in search) - Wrong intervention |
| Citronberg J, Bostick R, Ahearn T, et al | 2013 | Effects of ginger supplementation on cell-cycle biomarkers in the normal-appearing colonic mucosa of patients at increased risk for colorectal cancer: results from a pilot, randomized, and controlled trial | Cancer Prevention Research | 6(4) | 271 | Excluded | Duplicate (found in search) - Wrong intervention |
| Citronberg J, Bostick RM, Ruffin M, et al | 2012 | Ginger supplementation and the expression of BAX in the normal-appearing colorectal mucosa of sporadic colorectal adenoma patients: results from a pilot randomized, controlled trial | Pharm Biol | 50(5) | 629-30 | Excluded | Duplicate (found in search) - Wrong intervention |
| Cramer H, Lauche R, Hohmann C, et al. | 2013 | Randomized-controlled trial comparing yoga and home-based exercise for chronic neck pain. | Clin J Pain | 29(3) | 216-23 | Excluded | Duplicate (found in search) - Wrong intervention |
| Crew K, Ho K, Brown P, et al. | 2015 | Effects of a green tea extract, Polyphenon E, on systemic biomarkers of growth factor signalling in women with hormone receptor-negative breast cancer | Journal of Human Nutrition and Dietetics | 28(3) | 272-82 | Excluded | Duplicate (found in search) - Wrong intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|--|---|---------------|--------------|--------------------|--|
| Crew KD, Brown P, Greenlee H, et al. | 2012 | Phase IB randomized, double-blinded, placebo-controlled, dose escalation study of polyphenon E in women with hormone receptor-negative breast cancer | Cancer Prevention Research | 5(9) | 1144-54 | Excluded | Duplicate (found in search) - Wrong intervention |
| Crookes DM, Shelton RC, Tehranifar P, et al | 2016 | Social networks and social support for healthy eating among Latina breast cancer survivors: implications for social and behavioral interventions | Journal of Cancer Survivorship | 10(2) | 291-301 | Excluded | Duplicate (found in search) - Wrong intervention |
| de Bock, M, Derraik, JGB, Brennan, CM, Biggs, JB, Morgan, PE, Hodgkinson, SC, Hofman, PL and Cutfield, WS | 2013 | Olive (<i>Olea europaea</i> L.) leaf polyphenols improve insulin sensitivity in middle-aged overweight men: a randomized, placebo-controlled, crossover trial | PloS one | 8(3) | e57622 | Excluded | Duplicate (found in search) - Wrong intervention |
| Delgado-Cruzata L, Zhang W, McDonald JA, et al | 2015 | Dietary modifications, weight loss, and changes in metabolic markers affect global DNA methylation in Hispanic, African American, and Afro-Caribbean breast cancer survivors | The Journal of Nutrition | 145(4) | 783-90 | Excluded | Duplicate (found in search) - Wrong intervention |
| Dobos G, Overhamm T, Büssing A, et al. | 2014 | Effects of a mindfulness-based day-care clinic in cancer survivors | Journal of Alternative & Complementary Medicine | 20(5) | A53 | Excluded | Duplicate (found in search) - Wrong intervention |
| Ducrotté, P, Sawant, P, Jayanthi, V. | 2012 | Clinical trial: <i>Lactobacillus plantarum</i> 299v (DSM 9843) improves symptoms of irritable bowel syndrome | World Journal of Gastroenterology | 18 (30) | 4012-4018 | Excluded | Duplicate (found in search) - Wrong intervention |
| Dugoua J, Perri D, Seely D, et al. | 2012 | The anti-diabetic and cholesterol-lowering effects of common and cassia cinnamon (<i>Cinnamomum verum</i> and <i>C. aromaticum</i>): a randomized controlled trial | BMC Complementary and Alternative Medicine | 12(1) | P179 | Excluded | Duplicate (found in search) - Wrong intervention |
| Erdrich S, Bishop KS, Karunasinghe N, et al. | 2015 | A pilot study to investigate if New Zealand men with prostate cancer benefit from a Mediterranean-style diet. | PeerJ | 3 | E1080 | Excluded | Duplicate (found in search) - Wrong intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|---|---------------|--------------|--------------------|--|
| Fernandez-Pareja A, Hernandez-Blanco E, Perez-Maceda JM, Rubio VJ, Palazuelos JH, Dalmau JM. | 2007 | Prevention of Osteoporosis Four-Year Follow-Up of a Cohort of Postmenopausal Women Treated with an Ossein-Hydroxyapatite Compound. | Clin Drug Invest | 27(4) | 227-232 | Excluded | Duplicate (found in search) - Wrong intervention |
| Finnell J, Bradley R, Bulayeva N, et al | 2014 | Vitamin D sufficiency status may effect circulating levels of the anti-aging protein klotho. | Journal of Alternative & Complementary Medicine | 20(5) | A90-1 | Excluded | Duplicate (found in search) - Wrong intervention |
| Fruzzetti F, Perini D, Russo M, Bucci F, Gadducci A. | 2017 | Comparison of two insulin sensitizers, metformin and myo-inositol, in women with polycystic ovary syndrome (PCOS). | Gynecol Endocrinol | 33(1) | 39-42 | Excluded | Duplicate (found in search) - Wrong intervention |
| Galvez I, Torres-Piles S | 2018 | Balaneootherapy, Immune System, and Stress Response: A Hormetic Strategy? | International Journal of Molecular Science | 19(6) | 1687 | Excluded | Duplicate (found in search) - Wrong intervention |
| Govindaraj R, Naik S, Manjunath N, et al. | 2018 | Add-on yoga therapy for social cognition in schizophrenia: a pilot study | International Journal of Yoga | 11(3) | 242 | Excluded | Duplicate (found in search) - Wrong intervention |
| Greenlee H, Crew KD, Shao T, et al | 2013 | Phase II study of glucosamine with chondroitin on aromatase inhibitor-associated joint symptoms in women with breast cancer | Supportive Care in Cancer | 21(4) | 1077-87 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Greenlee H, Gaffney AO, Aycinena AC, et al | 2015 | ¡ Cocinar Para Su Salud!: randomized controlled trial of a culturally based dietary intervention among Hispanic breast cancer survivors. | Journal of the Academy of Nutrition and Dietetics | 115(5) | S42-56 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Greenlee H, Gaffney AO, Aycinena AC, et al. | 2016 | Long-term diet and biomarker changes after a short-term intervention among Hispanic breast cancer survivors: The ¡ Cocinar Para Su Salud! randomized controlled trial. | Cancer Epidemiol Biomarkers Prev | 25(11) | 1491-502 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|---|---|---------------|--------------|--------------------|--|
| Greenlee H, Molmenti CLS, Crew KD, et al. | 2016 | Survivorship care plans and adherence to lifestyle recommendations among breast cancer survivors | Journal of Cancer Survivorship | 10(6) | 956-63 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Greenlee HA, Crew KD, Mata JM, et al. | 2013 | A pilot randomized controlled trial of a commercial diet and exercise weight loss program in minority breast cancer survivors | Obesity | 21(1) | 65-76 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Guerrero-Romero, F et al. | 2014 | Oral Magnesium supplementation improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial. | Diabetes & Metabolism. | 30 (3) | 253–258 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Haghiac M, Yang XH, Presley L, Smith S, Dettelback S, Minium J, et al. | 2015 | Dietary omega-3 fatty acid supplementation reduces inflammation in obese pregnant women: a randomized double-blind controlled clinical trial. | PLoS One | 10(9) | e0137309 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Hansen S, Strøm M, Maslova E, Dahl R, Hoffmann HJ, Rytter D, et al. | 2017 | Fish oil supplementation during pregnancy and allergic respiratory disease in the adult offspring. | J Allergy Clin Immunol | 139(1) | 104-111 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Harnett J, Myers SP, Rolfe M | 2016 | Probiotics and the microbiome in celiac disease: a randomised controlled trial | Evidence-Based Complementary and Alternative Medicine | 2016 | Jan-16 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Hendren RL, James SJ, Widjaja F, Lawton B, Rosenblatt A, Bent S. | 2016 | Randomized, Placebo-Controlled Trial of Methyl B12 for Children with Autism. | J Child Adolesc Psychopharmacol | 26 (9) | 774-783 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Hershman DL, Unger JM, Crew KD, et al | 2013 | Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy | Journal of Clinical Oncology | 31(20) | 2627-33 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|---------------------------------|---------------|--------------|--------------------|--|
| Hershman DL, Unger JM, Crew KD, et al | 2015 | Randomized multicenter placebo-controlled trial of omega-3 fatty acids for the control of aromatase inhibitor–induced musculoskeletal pain: SWOG S0927 | Journal of Clinical Oncology | 33(17) | 1910-17 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Hershman DL, Unger JM, Crew KD, et al. | 2018 | Two-year trends of taxane-induced neuropathy in women enrolled in a randomized trial of acetyl-L-carnitine (SWOG S0715). | J Natl Cancer Inst | 110(6) | 669-76 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Jamilian M, Samimi M, Ebrahimi FA, Hashemi T, Taghizadeh M, Razavi M, et al. | 2017 | The effects of vitamin D and omega-3 fatty acid co-supplementation on glycemic control and lipid concentrations in patients with gestational diabetes. | J Clin Lipidol | 11(2) | 459-468 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Javanmanesh, Kashanian, Rahimi, Sheikhansari. | 2016 | A comparison between the effects of metformin and N-acetyl cysteine (NAC) on some metabolic and endocrine characteristics of women with polycystic ovary syndrome. | Gynecol Endocrinol | 32(4) | 285-289 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Jiang Y, Turgeon DK, Wright BD, et al | 2013 | Effect of ginger root on cyclooxygenase-1 and 15-hydroxyprostaglandin dehydrogenase expression in colonic mucosa of humans at normal and increased risk of colorectal cancer | Eur J Cancer Prev | 22(5) | 455 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Jung JY, Kwon HH, Hong JS, Yoon JY, Park MS, Jang MY et al. | 2014 | Effect of dietary supplementation with omega-3 fatty acid and gamma-linolenic acid on acne vulgaris: a randomised, double-blind, controlled trial. | Acta Derm Venereol | 94(5) | 521-525 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Kamenova P. | 2006 | Improvement of insulin sensitivity in patients with type 2 diabetes mellitus after oral administration of alpha-lipoic acid. | Hormones (Athens) | 5 | 251–258 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|---|----------------------------------|---------------|--------------|--------------------|--|
| Kastelein JJ, Maki KC, Susekov A, Ezhov M, Nordestgaard BG, Machielse BN, et al. | 2014 | Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the Epanova for Lowering Very high triglycerides (EVOLVE) trial. | J Clin Lipidol | 8(1) | 94-106 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Kazaks AG, Uriu-Adams JY, Albertson TE, Shenoy S, Stern JS | 2010 | Effect of Oral Magnesium Supplementation on Measures of Airway Resistance and Subjective Assessment of Asthma Control and Quality of Life in Men and Women with Mild to Moderate Asthma: A Randomized Placebo Controlled Trial. | Journal of Asthma | 47 (1) | 83-92 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Kean JD, Sarris J, Scholey A, et al | 2017 | Reduced inattention and hyperactivity and improved cognition after marine oil extract (PCSO-524®) supplementation in children and adolescents with clinical and subclinical symptoms of attention-deficit hyperactivity disorder (ADHD): a randomised, double-b | Psychopharmacology | 234(3) | 403-20 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Kennedy DA, Lewis E, Cooley K, et al. | 2014 | An exploratory comparative investigation of Food Allergy/Sensitivity Testing in IBS (The FAST Study): a comparison between various laboratory methods and an elimination diet | Advances in Integrative Medicine | 1(3) | 124-30 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Kessopoulou, E., H. J. Powers, K. K. Sharma, M. J. Pearson, J. M. Russell, I. D. Cooke and C. L. Barratt | 1995 | A double-blind randomized placebo cross-over controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. | Fertility and sterility | 64(4): | 825-831 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|---|---------------------------------|---------------|--------------|--------------------|--|
| Kim CH, Han KA, Yu J, Lee SH, Jeon HK, Kim SH, et al. | 2018 | Efficacy and safety of adding omega-3 fatty acids in statin-treated patients with residual hypertriglyceridemia: ROMANTIC (Rosuvastatin-OMAcor in residual hyperTriglyceridemia), a randomized, double-blind, and placebo-controlled trial. | Clin Ther | 40(1) | 83-94 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Kim LS, Hilli L, Orlowski J, et al | 2006 | Efficacy of probiotics and nutrients in functional gastrointestinal disorders: a preliminary clinical trial | Digestive Diseases and Sciences | 51(12) | 2134-44 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Kisan R, Sujan M, Adoor M, et al. | 2014 | Effect of yoga on migraine: A comprehensive study using clinical profile and cardiac autonomic functions. | International Journal of Yoga | 7(2) | 126 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Koutoubi S, Heiselmann PR, Murdoch S, et al | 2008 | Changes in consumer knowledge and behavioral intention toward genetically engineered (GE) foods | FASEB J | 22 (1Suppl) | 681.9-81.9 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Krishnamurthy MN, Telles S | 2007 | Assessing depression following two ancient Indian interventions: effects of yoga and ayurveda on older adults in a residential home | J Gerontol Nurs | 33(2) | 17-23 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Kristensen S, Schmidt EB, Schlemmer A, Rasmussen C, Johansen MB, Christensen JH. | 2018 | Beneficial effect of n-3 polyunsaturated fatty acids on inflammation and analgesic use in psoriatic arthritis: a randomized, double blind, placebo-controlled trial. | Scand J Rheumatol | 47(1) | 27-36 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Lauche R, Stumpe C, Fehr J, et al. | 2016 | The effects of tai chi and neck exercises in the treatment of chronic nonspecific neck pain: a randomized controlled trial | The Journal of Pain | 17(9) | 101-27 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Laviano A, Molfino A, Lacaria MT, Canelli A, De Leo S, Preziosa I, et al. | 2014 | Glutamine supplementation favors weight loss in nondieting obese female patients. A pilot study. | Eur J Clin Nutr | 68(11) | 1264-1266 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|---|----------------|--------------|--------------------|--|
| Leach MJ, Pincombe J, Foster G | 2006 | Clinical efficacy of horsechestnut seed extract in the treatment of venous ulceration | Journal of Wound Care | 15(4) | 159-67 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Lenzi, A., P. Sgro, P. Salacone, D. Paoli, B. Gilio, F. Lombardo, M. Santulli, A. Agarwal and L. Gandini | 2004 | A placebo-controlled double-blind randomized trial of the use of combined L-carnitine and L-acetyl-carnitine treatment in men with asthenozoospermia.. | Fertility and sterility | 81(6) | 1578-1584 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Leombruni P, Miniotti M, Colonna F, Sica C, Castelli L, Bruzzone M, et al. | 2015 | A randomised controlled trial comparing duloxetine and acetyl L-carnitine in fibromyalgic patients: preliminary data. | Clin Exp Rheumatol | 33(1 Suppl 88) | S82-85 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Li S, Chen X, Li Q, Du J, Liu Z, Peng Y, et al. | 2016 | Effects of acetyl-L-carnitine and methylcobalamin for diabetic peripheral neuropathy: A multicenter, randomized, double-blind, controlled trial. | J Diabetes Investig | 7(5) | 777-785 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Lubna Fatima, Arshiya S ultana | 2017 | Efficacy of Tribulus terrestris L. (fruits) in menopausal transition symptoms: A randomized placebo controlled study | Advances in Integrative Medicine | 4 (2) | 56-65 | Excluded | Duplicate (found in search) - Wrong Intervention |
| MacRedmond R, Singhera G, Attridge S, Bahzad M, Fava C, Lai Y, Hallstrand TS, Dorscheid DR. | 2010 | Conjugated linoleic acid improves airway hyper-reactivity in overweight mild asthmatics. | Clinical & Experimental Allergy | 40 | 1071–1078 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Magge S, Lembo A. | 2011 | Complementary and Alternative Medicine for the Irritable Bowel Syndrome | Gastroenterology Clinics | 40 (1) | 245–253 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Manjunath N, Telles S | 1999 | Factors influencing changes in tweezer dexterity scores following yoga training | Indian Journal of Physiology and Pharmacology | 43 | 225-9 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Manjunath N, Telles S | 2003 | Effects of sirsasana (headstand) practice on autonomic and respiratory variables | Indian Journal of Physiology and Pharmacology | 47(1) | 34-42 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|--|--|---------------|--------------|--------------------|--|
| Manjunath N, Telles S | 1999 | Improvement in visual perceptual sensitivity in children following yoga training | Journal of Indian Psychology | 17(2) | 41-5 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Marchioli R, Barzi F, Bomba E, et al. | 2002 | GISSI-Prevenzione Investigators. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. | Circulation | 105 | 1897–1903 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Maroon JC, Boost JW. | 2006 | Omega 3 (fish oil) fatty acids as an anti-inflammatory: an alternative to non-steroidal anti-inflammatory drugs for discogenic pain. | Surgical Neurology | 65 | 326-331 | Excluded | Duplicate (found in search) - Wrong Intervention |
| McCrary M, Roberts S, Gehrke M, et al | 2008 | Dietary variety increases ad-libitum energy intake more than does dietary fat: a 13-day randomized feeding trial | Obesity | 16 | S231-32 | Excluded | Duplicate (found in search) - Wrong Intervention |
| McDermott KA, Rao MR, Nagarathna R, et al. | 2014 | A yoga intervention for type 2 diabetes risk reduction: a pilot randomized controlled trial. | BMC Complementary and Alternative Medicine | 14(1) | 212 | Excluded | Duplicate (found in search) - Wrong Intervention |
| McDougall J, Thomas LE, McDougall C, et al | 2014 | Effects of 7 days on an ad libitum low-fat vegan diet: the McDougall Program cohort | Nutrition Journal | 13(1) | 99 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Menon R, Cribb L, Murphy J, et al | 2017 | Mitochondrial modifying nutrients in treating chronic fatigue syndrome: a 16-week open-label pilot study | Advances in Integrative Medicine | 4(3) | 109-14 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. | 2006 | Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. | Chest | 129 | 39-49 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|---|---------------------------------|---------------|--------------|--------------------|--|
| Mills E, Prousky J, Raskin G, et al | 2003 | The safety of over-the-counter niacin. A randomized placebo-controlled trial [ISRCTN18054903] | BMC Clinical Pharmacology | 3(1) | 4 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Mirmasoumi G, Fazilati M, Foroozanfard F, Vahedpoor Z, Mahmoodi S, Taghizadeh M, et al. | 2018 | The effects of flaxseed oil omega-3 fatty acids supplementation on metabolic status of patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. | Exp Clin Endocrinol Diabetes | 126(4) | 222-228 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Mischley LK, Conley KE, Shankland EG, et al | 2016 | Central nervous system uptake of intranasal glutathione in Parkinson's disease | NPJ Parkinson's Disease | 2 | 1-Jun | Excluded | Duplicate (found in search) - Wrong Intervention |
| Mischley LK, Lau RC, Shankland EG, et al | 2017 | Phase IIb study of intranasal glutathione in Parkinson's disease | Journal of Parkinson's Disease | 7(2) | 289-99 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Moran LJ, Tzagareli V, Noakes M, Norman R. | 2016 | Altered preconception fatty acid intake is associated with improved pregnancy rates in overweight and obese women undertaking in vitro fertilisation. | Nutrients | 8(1) | E10 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, Alehagen U, Steurer G, Littarru GP. Q-SYMBIO Study Investigators. | 2014 | The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. | JACC. Heart failure | 2 (6) | 641-649 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Myers SP, Mulder AM, Baker DG, et al. | 2016 | Effects of fucoidan from Fucus vesiculosus in reducing symptoms of osteoarthritis: a randomized placebo-controlled trial | Biologics : targets & therapy | 10 | 81-8 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Myers SP, O'Connor J, Fitton JH, et al | 2010 | A combined phase I and II open label study on the effects of a seaweed extract nutrient complex on osteoarthritis | Biologics : targets & therapy | 4 | 33-44 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|---|---|---------------|--------------|--------------------|--|
| Nagasukeerthi P, Mooventhan A, Manjunath N | 2017 | Short-term effect of add on bell pepper (<i>Capsicum annum var. grossum</i>) juice with integrated approach of yoga therapy on blood glucose levels and cardiovascular functions in patients with type 2 diabetes mellitus: a randomized controlled study | Complementary Therapies in Medicine | 34 | 42-5 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Nalgirkar SP, Vinchurkar SA, Saoji AA, et al. | 2018 | Yoga as a therapeutic intervention in the management of dysfunctional uterine bleeding: a controlled pilot study | Journal of Mid-Life Health | 9(1) | Aug-13 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Nandini B, Mooventhan A, Manjunath N. | 2018 | Add-on effect of hot sand fomentation to yoga on pain, disability, and quality of life in chronic neck pain patients. | Explore (New York, NY) | 14(5) | 373-8 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Naveen G, Rao M, Vishal V, et al. | 2013 | Development and feasibility of yoga therapy module for out-patients with depression in India | Indian Journal of Psychiatry | 55(Suppl 3) | S350 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Nesic J, Duka T. | 2014 | Effects of stress and dietary tryptophan enhancement on craving for alcohol in binge and non-binge heavy drinkers. | Behav Pharmacol | 25(5-6) | 503-517 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Neuendorf R, Corn J, Hanes D, et al | 2019 | Impact of food immunoglobulin G-based elimination diet on subsequent food immunoglobulin G and quality of life in overweight/obese adults | Journal of Alternative & Complementary Medicine | 25(2) | 241-8 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Newton KM, Reed SD, LaCroix AZ, et al | 2006 | Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial | Annals of Internal Medicine | 145 | 869-79 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Niedzielin K, Kordecki H, Birkenfeld B. | 2001 | A controlled, double-blind, randomized study on the efficacy of <i>Lactobacillus plantarum</i> 299V in patients with irritable bowel syndrome | Eur J Gastroenterol Hepatol | 13 | 1143-1147 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|---|---------------|--------------|--------------------|--|
| Nouri, K., K. Walch, A. Weghofer, M. Imhof, C. Egarter and J. Ott | 2017 | The impact of a standardized oral multivitamin supplementation on embryo quality in in vitro fertilization/intracytoplasmic sperm injection: a prospective randomized trial. | Gynecologic and obstetric investigation | 82(1) | 41852 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Papanikolopoulou A, Syrigos KN, Drakoulis N. | 2015 | The role of glutamine supplementation in thoracic and upper aerodigestive malignancies. | Nutr Cancer | 67(2) | 231-237 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Paydary K, Akamalo A, Ahmadipour A, Pishgar F, Emamzadehfard S, Akhondzadeh S. | 2016 | N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial. | J Clin Pharm Ther | 41(2) | 214-219 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Perlman AI, Lebow DG, Raphael K, et al | 2013 | A point-of-sale communications campaign to provide consumers safety information on drug–dietary supplement interactions: a pilot study | Health Communication | 28(7) | 729-39 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Quinn JF, Raman R, Thomas RG, et al | 2010 | Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial | JAMA | 304(17) | 1903-11 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Raghavendra R, Nagarathna R, Nagendra H, et al. | 2007 | Effects of an integrated yoga programme on chemotherapy-induced nausea and emesis in breast cancer patients | European Journal of Cancer Care | 16(6) | 462-74 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Raghavendra RM, Vadiraja H, Nagarathna R, et al | 2009 | Effects of a yoga program on cortisol rhythm and mood states in early breast cancer patients undergoing adjuvant radiotherapy: a randomized controlled trial | Integrative Cancer Therapies | 8(1) | 37-46 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|---|---|---------------|--------------|--------------------|--|
| Rajaei E, Mowla K, Ghorbani A, Bahadoram S, Bahadoram M, Dargahi-Malamir M. | 2015 | The effect of omega-3 fatty acids in patients with active rheumatoid arthritis receiving DMARDS therapy: double-blind randomized controlled trial. | Glob J Health Sci | 8(7) | 18-25 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Rao AV, Bested AC, Beaulne TM, et al. | 2009 | A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome | Gut Pathogens | 1(1) | 1-Jun | Excluded | Duplicate (found in search) - Wrong Intervention |
| Rao MR, Raghuram N, Nagendra H, et al | 2009 | Anxiolytic effects of a yoga program in early breast cancer patients undergoing conventional treatment: a randomized controlled trial | Complementary Therapies in Medicine | 17(1) | 1-Aug | Excluded | Duplicate (found in search) - Wrong Intervention |
| Rao RM, Raghuram N, Nagendra H, et al | 2017 | Effects of an integrated yoga program on self-reported depression scores in breast cancer patients undergoing conventional treatment: a randomized controlled trial | Indian Journal of Palliative Care | 21(2) | 174 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Rao RM, Raghuram N, Nagendra HR, et al. | 2017 | Effects of a yoga program on mood states, quality of life, and toxicity in breast cancer patients receiving conventional treatment: a randomized controlled trial | Indian Journal of Palliative Care | 23(3) | 247 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Rao RM, Vadiraja H, Nagaratna R, et al. | 2017 | Effect of yoga on sleep quality and neuroendocrine immune response in metastatic breast cancer patients | Indian Journal of Palliative Care | 23(3) | 253 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Richardson J, Lee H, Koch P, et al | 2013 | Mediators of dietary change among hispanic breast cancer survivors in a culturally-based dietary intervention | Journal of Nutrition Education and Behavior | 45(4) | S64 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Roffman JL, Petruzzij LJ, Tanner AS, Brown HE, Eryilmaz H, Ho NF, et al. | 2018 | Biochemical, physiological and clinical effects of L-methylfolate in schizophrenia: a randomized controlled trial. | Mol Psychiatry | 23 (2) | 316-322 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|---|---|---------------|--------------|--------------------|--|
| Ross C, Herman PM, Rocklin O, et al | 2008 | Evaluation of integrative medicine supplements for mitigation of chronic insomnia and constipation in an inpatient eating disorders setting | Explore: The Journal of Science and Healing | 4(5) | 315-20 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Ryan JJ, Hanes DA, Corroon J, et al | 2019 | Prospective safety evaluation of a cardiovascular health dietary supplement in adults with prehypertension and stage I hypertension | Journal of Alternative & Complementary Medicine | 25(2) | 249-256 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Salazar L, Higgins D, Childs J, et al | 2016 | Abstract P2-11-03: Phase I/II randomized study of combination immunotherapy with or without polysaccharide krestin (PSK) concurrently with a HER2 ICD peptide-based vaccine in patients with stage IV breast cancer receiving HER2-targeted monoclonal antibody therapy | Cancer Research | 76(4 Suppl) | P2-11-03 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Salmond SJ, George J, Strasser SI, et al. | 2019 | Hep573 Study: A randomised, double-blind, placebo controlled trial of silymarin alone and combined with antioxidants to improve liver function and quality of life in people with chronic hepatitis C. | Aust Journal of Herbal & Naturopathic Medicine (AJHNM) | 31 (2) | 64-76 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Salmond, S., et al | 2018 | Hep573 Study: A randomised, double-blind, placebo-controlled trial of silymarin alone and combined with antioxidants to improve liver function and quality of life in people with chronic hepatitis C | Australian Journal of Herbal and Naturopathic Medicine, Vol. 30, No. 1, 2018: 12-24 | 30, No. 1 | 45627 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Santamaria A, Di Benedetto A, Petrella E, Pintaudi B, Corrado F, D'Anna R, et al. | 2016 | Myo-inositol may prevent gestational diabetes onset in overweight women: a randomized, controlled trial. | J Matern Fetal Neonatal Med | 29 (19) | 3234-3237 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|--|---|---------------|--------------|--------------------|--|
| Saper RB, Lemaster C, Delitto A, et al. | 2017 | Yoga, physical therapy, or education for chronic low back pain: a randomized noninferiority trial | Annals of Internal Medicine | 167(2) | 85-94 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Sarris J, Byrne GJ, Bousman C, et al. | 2018 | Adjunctive S-adenosylmethionine (SAME) in treating non-remittent major depressive disorder: An 8-week double-blind, randomized, controlled trial | Neuropsychopharmacology | 28(10) | 1126-36 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Sarris J, Byrne GJ, Cribb L, et al. | 2018 | L-Theanine in the adjunctive treatment of generalised anxiety disorder: a double-blind, randomised, placebo-controlled trial | Journal of Psychiatric Research | 110 | 31-37 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Sarris J, Byrne GJ, Stough C, et al. | 2019 | Nutraceuticals for major depressive disorder- more is not merrier: an 8-week double-blind, randomised, controlled trial | Journal of Affective Disorders | 245 | 1007-15 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Sarris J, Fava M, Schweitzer I, et al. | 2012 | St John's wort (Hypericum perforatum) versus sertraline and placebo in major depressive disorder: continuation data from a 26-week RCT | Pharmacopsychiatry | 45(07) | 275-8 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Sarris J, Kavanagh D, Byrne G, et al. | 2009 | The Kava Anxiety Depression Spectrum Study (KADSS): a randomized, placebo-controlled crossover trial using an aqueous extract of Piper methysticum | Psychopharmacology | 205(3) | 399-407 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Sarris J, Kavanagh DJ, Adams J, et al. | 2009 | Kava Anxiety Depression Spectrum Study (KADSS): a mixed methods RCT using an aqueous extract of Piper methysticum | Complementary Therapies in Medicine | 17(3) | 176-8 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Sarris J, Kavanagh DJ, Deed G, et al | 2009 | St. John's wort and Kava in treating major depressive disorder with comorbid anxiety: a randomised double-blind placebo-controlled pilot trial | Human Psychopharmacology: Clinical and Experimental | 24(1) | 41-8 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|--|---|---------------|--------------|--------------------|--|
| Sarris J, Oliver G, Camfield DA, et al | 2016 | Participant characteristics as modifiers of response to N-acetyl cysteine (NAC) in obsessive-compulsive disorder | Clinical Psychological Science | 4(6) | 1104-11 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Sarris J, Papakostas GI, Vitolo O, et al | 2014 | S-adenosyl methionine (SAME) versus escitalopram and placebo in major depression RCT: efficacy and effects of histamine and carnitine as moderators of response | Journal of Affective Disorders | 164 | 76-81 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Sarris J, Scholey A, Schweitzer I, et al. | 2012 | The acute effects of kava and oxazepam on anxiety, mood, neurocognition; and genetic correlates: a randomized, placebo-controlled, double-blind study | Human Psychopharmacology: Clinical and Experimental | 27(3) | 262-9 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Sarris J, Stough C, Bousman CA, et al. | 2013 | Kava in the treatment of generalized anxiety disorder: a double-blind, randomized, placebo-controlled study | Journal of Clinical Psychopharmacology | 33(5) | 643-8 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Sarris J, Stough C, Teschke R, et al. | 2013 | Kava for the treatment of generalized anxiety disorder RCT: analysis of adverse reactions, liver function, addiction, and sexual effects | Phytotherapy Research | 27(11) | 1723-8 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Satish V, Rao RM, Manjunath NK, et al | 2018 | Yoga versus physical exercise for cardio-respiratory fitness in adolescent school children: a randomized controlled trial | International Journal of Adolescent Medicine and Health | | | Excluded | Duplicate (found in search) - Wrong Intervention |
| Saunders PR, Smith F, Schusky RW | 2007 | Echinacea purpurea L. in children: safety, tolerability, compliance, and clinical effectiveness in upper respiratory tract infections | Canadian Journal of Physiology and Pharmacology | 85(11) | 1195-9 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Schloss JM, Colosimo M, Airey C, et al | 2015 | Pilot trial assessing the efficacy and safety of a supplemental B vitamin complex to reduce the onset and severity of chemotherapy-induced peripheral neuropathy | Journal of Clinical Oncology | 33(15Sup pl) | 9604 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|---|---|---------------|--------------|--------------------|--|
| Schloss JM, Colosimo M, Airey C, et al | 2017 | A randomised, placebo-controlled trial assessing the efficacy of an oral B group vitamin in preventing the development of chemotherapy-induced peripheral neuropathy (CIPN) | Supportive Care in Cancer | 25(1) | 195-204 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Schmidt M, Thomsen M, Schmidt U | 2012 | Suitability of ivy extract for the treatment of paediatric cough | Phytotherapy Research | 26(12) | 1942-7 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Schoenthaler SJ, Bier ID | 2000 | The effect of vitamin-mineral supplementation on juvenile delinquency among American schoolchildren: a randomized, double-blind placebo-controlled trial | Journal of Alternative & Complementary Medicine | 6(1) | Jul-17 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Scholey A, Benson S, Gibbs A, et al. | 2017 | Exploring the effect of Lactium™ and Zizyphus Complex on sleep quality: a double-blind, randomized placebo-controlled trial | Nutrients | 9(2) | 154 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Schumann D, Langhorst J, Dobos G, et al. | 2018 | Randomised clinical trial: yoga vs a low-FODMAP diet in patients with irritable bowel syndrome | Alimentary Pharmacology & Therapeutics | 47(2) | 203-11 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Scott, R., A. MacPherson, R. Yates, B. Hussain and J. Dixon | 1998 | The effect of oral selenium supplementation on human sperm motility. | British journal of urology | 82(1) | 76-80 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Seely D, Singh R | 2007 | Adaptogenic potential of a polyherbal natural health product: report on a longitudinal clinical trial | Evidence-Based Complementary and Alternative Medicine | 4(3) | 375-80 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Selvakumar G, Shathirapathiy G, Jainraj R, et al. | 2017 | Immediate effect of bitter gourd, ash gourd, Knol-khol juices on blood sugar levels of patients with type 2 diabetes mellitus: a pilot study | Journal of Traditional and Complementary Medicine | 7(4) | 526-31 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|---|--|---------------|--------------|--------------------|--|
| Shi Z, Richardson JM, Aycinena AC, et al. | 2018 | Psychosocial mediators of dietary change among Hispanic/Latina breast cancer survivors in a culturally-tailored dietary intervention | Psycho-oncology | 27(9) | 2220-8 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Shim, Bongseok & Jeong, Hyewon & Lee, Sara & Hwang, Sehee & Moon, Byeongseok & Storni, Charlotte | 2014 | A randomized double-blind placebo-controlled clinical trial of a product containing pumpkin seed extract and soy germ extract to improve overactive bladder-related voiding dysfunction and quality of life | Journal of Functional Foods | 8 (1) | 111-117 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Shinto L, Marracci G, Baldauf-Wagner S, et al | 2009 | Omega-3 fatty acid supplementation decreases matrix metalloproteinase-9 production in relapsing-remitting multiple sclerosis. | Prostaglandins, Leukotrienes and Essential Fatty Acids | 80(2-3) | 131-6 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Shinto L, Quinn J, Montine T, et al | 2016 | A randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease | Journal of Alzheimer's Disease | 38(1) | 111-20 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Siegel AB, Narayan R, Rodriguez R, et al | 2014 | A phase I dose-finding study of silybin phosphatidylcholine (milk thistle) in patients with advanced hepatocellular carcinoma | Integrative Cancer Therapies | 13(1) | 46-53 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Smith DJ, Sarris J, Dowling N, et al | 2017 | Adjunctive low-dose docosahexaenoic acid (DHA) for major depression: an open-label pilot trial. | Nutritional Neuroscience | 21(3) | 224-8 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Sowmya M, Rao R, Sowjanya M, et al | 2018 | A comparative study on effect of lemon juice with lemon seeds vs. lemon juice alone on high sensitivity C-reactive protein in subjects with obesity undergoing calorie restriction--a pilot study | Journal of Evolution of Medical and Dental Sciences | 7(16) | | Excluded | Duplicate (found in search) - Wrong Intervention |
| Spence JD, Yi Q, Hankey GJ. | 2017 | B vitamins in stroke prevention: time to reconsider. | The Lancet Neurology | 16 (9) | 750-760 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|--|---|---------------|--------------|--------------------|--|
| Steels E, Steele M, Harold M, et al. | 2017 | Efficacy of a proprietary Trigonella foenum-graecum L. de-husked seed extract in reducing menopausal symptoms in otherwise healthy women: a double-blind, randomized, placebo-controlled study | Phytotherapy Research | 31(9) | 1316-22 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Stothers, L. | 2002 | A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women | Canadian Journal of Urology | 9 | 1558-1562 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Sun Q, Wang B, Li Y, Sun F, Li P, Xia W, et al. | 2016 | Taurine Supplementation Lowers Blood Pressure and Improves Vascular Function in Prehypertension: Randomized, Double-Blind, Placebo-Controlled Study. | Hypertension | 67(3) | 541-549 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Telles S, Narendran S, Raghuraj P, et al. | 1997 | Comparison of changes in autonomic and respiratory parameters of girls after yoga and games at a community home | Perceptual and Motor Skills | 84(1) | 251-7 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Telles S, Naveen K, Dash M, et al | 2006 | Effect of yoga on self-rated visual discomfort in computer users | Head & Face Medicine | 2(1) | 46 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Telles S, Naveen VK, Balkrishna A, et al. | 2009 | Short term health impact of a yoga and diet change program on obesity | Medical Science Monitor | 16(1) | CR35-40 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Tian T, Yang KQ, Cui JG, Zhou LL, Zhou XL. | 2017 | Folic acid supplementation for stroke prevention in patients with cardiovascular disease | The American journal of the medical sciences. | 354(4) | 379-387 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Torkelson CJ, Sweet E, Martzen MR, et al | 2012 | Phase 1 clinical trial of Trametes versicolor in women with breast cancer | ISRN Oncology | 2012 | 1-Jul | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|---|--|---------------|--------------|--------------------|--|
| Traub ML, Finnell JS, Bhandiwad A, et al | 2014 | Impact of vitamin D3 dietary supplement matrix on clinical response | The Journal of Clinical Endocrinology & Metabolism | 99(8) | 2720-8 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Usher C, Thompson A, Griebeler M, et al. | 2019 | Meals, mindfulness, & moving forward: a feasibility study to a multi-modal lifestyle approach in early psychosis | Early Intervention in Psychiatry | 13(1) | 147-50 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Vadiraja H, Rao MR, Nagarathna R, et al. | 2009 | Effects of yoga program on quality of life and affect in early breast cancer patients undergoing adjuvant radiotherapy: a randomized controlled trial | Complementary Therapies in Medicine | 17(5) | 274-80 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Vadiraja H, Rao RM, Nagarathna R, et al | 2017 | Effects of yoga in managing fatigue in breast cancer patients: a randomized controlled trial | Indian Journal of Palliative Care | 23(3) | 247 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Vadiraja SH, Rao MR, Nagendra RH, et al. | 2009 | Effects of yoga on symptom management in breast cancer patients: a randomized controlled trial | International Journal of Yoga | 2(2) | 73 | Excluded | Duplicate (found in search) - Wrong Intervention |
| van de Rest O, Bloemendaal M, de Heus R, Aarts E. | 2017 | Dose-dependent effects of oral tyrosine administration on plasma tyrosine levels and cognition in aging. | Nutrients | 9(12) | E1279 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Venugopal V, Rathi A, Raghuram N | 2017 | Effect of short-term yoga-based lifestyle intervention on plasma glucose levels in individuals with diabetes and pre-diabetes in the community | Diabetes Metab Syndr | 11(Suppl2) | S597-9 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Veselinovic M, Vasiljevic D, Vucic V, Arsic A, Petrovic S, Tomic-Lucic A, Savic M, Zivanovic S, Stojic V, Jakovljevic V. | 2017 | Clinical benefits of n-3 PUFA and α -linolenic acid in patients with rheumatoid arthritis. | Nutrients | 9(4) | 325 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|---|--|---------------|--------------|--------------------|--|
| Vinutha H, Raghavendra B, Manjunath N. | 2015 | Effect of integrated approach of yoga therapy on autonomic functions in patients with type 2 diabetes | Indian Journal of Endocrinology and Metabolism | 19(5) | 653 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Vishal AA, Mishra A, Raychaudhuri SP. | 2011 | A double blind, randomized, placebo controlled clinical study evaluates the early efficacy of aflapin in subjects with osteoarthritis of knee. | Int J Med Sci | 8 | 615–622 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Vitetta L, Coulson S, Beck SL, et al. | 2013 | The clinical efficacy of a bovine lactoferrin/whey protein Ig-rich fraction (Lf/IgF) for the common cold: a double blind randomized study | Complementary Therapies in Medicine | 7(4) | 526-31 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Vohra S, Johnston B, Laycock K, et al. | 2007 | Safety and tolerability of North American ginseng extract in the treatment of paediatric upper respiratory tract infection: a phase II randomised controlled trial of two dosing schedules. | Focus on Alternative and Complementary Therapies | 12(Suppl 1) | 52 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Watson CJ, Grando D, Fairley CK, et al. | 2014 | The effects of oral garlic on vaginal candida colony counts: a randomised placebo controlled double-blind trial | BJOG: An International Journal of Obstetrics & Gynaecology | 121(4) | 498-506 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Weber W, Taylor JA, Stoep AV, et al | 2005 | Echinacea purpurea for prevention of upper respiratory tract infections in children | Journal of Alternative & Complementary Medicine | 11(6) | 1021-6 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Weber W, Vander Stoep A, McCarty RL, et al | 2008 | Hypericum perforatum (St John's wort) for attention-deficit/hyperactivity disorder in children and adolescents: a randomized controlled trial | JAMA | 299(22) | 2633-41 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|--|--|---------------|--------------|--------------------|--|
| Westphal, L. M., M. L. Polan, A. S. Trant and S. Mooney | 2004 | A nutritional supplement for improving fertility in women. | Journal of Reproductive Medicine | 49(4) | 289-293 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Withee ED, Tippens KM, Dehen R, et al | 2015 | Effects of MSM on exercise-induced muscle and joint pain: a pilot study | Journal of the International Society of Sports Nutrition | 12(Suppl 1) | 8 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Withee ED, Tippens KM, Dehen R, et al | 2017 | Effects of Methylsulfonylmethane (MSM) on exercise-induced oxidative stress, muscle damage, and pain following a half-marathon: a double-blind, randomized, placebo-controlled trial | Journal of the International Society of Sports Nutrition | 14(1) | 24 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Withee ED, Tippens KM, Dehen R, et al. | 2016 | Methylsulfonylmethane supplementation as a nonpharmacological option for exercise-induced pain: a pilot study | Integrative Medicine | 25(1) | 44 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Witte AV, Kerti L, Hermannstädter HM, Fiebach JB, Schreiber SJ, Schuchardt JP, et al. | 2014 | Long-chain omega-3 fatty acids improve brain function and structure in older adults. | Cereb Cortex | 24(11) | 3059-3068 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Yazaki Y, Faridi Z, Ma Y, et al | 2010 | A pilot study of chromium picolinate for weight loss | Journal of Alternative & Complementary Medicine | 16(3) | 291-9 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Yu Y, Zick S, Li X, et al. | 2011 | Examination of the pharmacokinetics of active ingredients of ginger in humans | AAPS J | 13(3) | 417 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Zhou Q, Verne ML, Fields JZ, Lefante JJ, Basra S, Salameh H, et al. | 2019 | Randomised placebo-controlled trial of dietary glutamine supplements for postinfectious irritable bowel syndrome. | Gut | 68(6) | 996-1002 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|---|--|---------------|--------------|--------------------|--|
| Zick SM, Blume A, Normolle D, et al | 2005 | Challenges in herbal research: a randomized clinical trial to assess blinding with ginger | Complementary Therapies in Medicine | 13(2) | 101-6 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Zick SM, Colacino J, Cornellier M, et al. | 2017 | Fatigue reduction diet in breast cancer survivors: a pilot randomized clinical trial. | Breast Cancer Research and Treatment | 16(2) | 299-310 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Zick SM, Djuric Z, Ruffin MT, et al. | 2008 | Pharmacokinetics of 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol and conjugate metabolites in healthy human subjects | Cancer Epidemiology, Biomarkers & Prevention | 17(8) | 1930-6 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Zick SM, Gillespie B, Aaronson KD | 2008 | The effect of Crataegus oxycantha special extract WS 1442 on clinical progression in patients with mild to moderate symptoms of heart failure | European Journal of Heart Failure | 10(6) | 587-93 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Zick SM, Ruffin MT, Lee J, et al | 2009 | Phase II trial of encapsulated ginger as a treatment for chemotherapy-induced nausea and vomiting | Supportive Care in Cancer | 17(5) | 563-72 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Zick SM, Turgeon DK, Ren J, et al. | 2015 | Pilot clinical study of the effects of ginger root extract on eicosanoids in colonic mucosa of subjects at increased risk for colorectal cancer | Molecular Carcinogenesis | 54(9) | 908-15 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Zick SM, Turgeon DK, Vareed SK, et al. | 2011 | Phase II study of the effects of ginger root extract on eicosanoids in colon mucosa in people at normal risk for colorectal cancer | Cancer Prevention Research | 4(11) | 1929-37 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Zick SM, Vautaw BM, Gillespie B, et al | 2009 | Hawthorn extract randomized blinded chronic heart failure (HERB CHF) trial | European Journal of Heart Failure | 11(1) | 78 | Excluded | Duplicate (found in search) - Wrong Intervention |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|---|--|---------------|--------------|--------------------|--|
| Zick SM, Wright BD, Sen A, et al. | 2011 | Preliminary examination of the efficacy and safety of a standardized chamomile extract for chronic primary insomnia: a randomized placebo-controlled pilot study | BMC Complementary and Alternative Medicine | 11(1) | 78 | Excluded | Duplicate (found in search) - Wrong Intervention |
| Bayes J, Agrawal N, Schloss J. | 2019 | A pilot trial examining the absorption of oral forms of folate supplementation in a healthy population: a randomised control trial | Advances in Integrative Medicine | 6(2) | 51-57 | Excluded | Duplicate (found in search) - Wrong population |
| Berardi JM, Logan AC, Rao AV | 2008 | Plant based dietary supplement increases urinary pH | Journal of the International Society of Sports Nutrition | 5(1) | 20-Jul | Excluded | Duplicate (found in search) - Wrong population |
| Bertinato J, Simpson JR, Sherrard L, et al | 2013 | Zinc supplementation does not alter sensitive biomarkers of copper status in healthy boys | Journal of Nutrition | 143(3) | 284-9 | Excluded | Duplicate (found in search) - Wrong population |
| Calabrese C, Myer S, Munson S, et al | 1999 | A cross-over study of the effect of a single oral feeding of medium chain triglyceride oil vs. canola oil on post-ingestion plasma triglyceride levels in healthy men | Alternative Medicine Review | 4(1) | 23-Aug | Excluded | Duplicate (found in search) - Wrong population |
| Camfield DA, Wetherell MA, Scholey AB, et al | 2013 | The effects of multivitamin supplementation on diurnal cortisol secretion and perceived stress | Nutrients | 5(11) | 4429-50 | Excluded | Duplicate (found in search) - Wrong population |
| Faridi Z, Njike VY, Dutta S, et al | 2008 | Acute dark chocolate and cocoa ingestion and endothelial function: a randomized controlled crossover trial | The American Journal of Clinical Nutrition | 88(1) | 58-63 | Excluded | Duplicate (found in search) - Wrong population |
| Greenlee H, Atkinson C, Stanczyk FZ, et al. | 2007 | A pilot and feasibility study on the effects of naturopathic botanical and dietary interventions on sex steroid hormone metabolism in premenopausal women | Cancer Epidemiol Biomarkers Prev | 16(8) | 1601-9 | Excluded | Duplicate (found in search) - Wrong Population |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|---|---------------|--------------|--------------------|--|
| Hall,S.D, Wang, Zaiqi, Huang, Shiew-Mei, et al. | 2003 | The interaction between St John's wort and an oral contraceptive | Clinical Pharmacology & Therapeutics | 74(6) | 525-535 | Excluded | Duplicate (found in search) - Wrong Population |
| Harvey C, Schofield GM, Williden M, et al. | 2018 | The effect of medium chain triglycerides on time to nutritional ketosis and symptoms of keto-induction in healthy adults: a randomised controlled clinical trial | Journal of Nutrition and Metabolism | 2018 | 1-Sep | Excluded | Duplicate (found in search) - Wrong Population |
| Manjunath N, Telles S | 2001 | Improved performance in the Tower of London test following yoga | Indian Journal of Physiology and Pharmacology | 45(3) | 351-4 | Excluded | Duplicate (found in search) - Wrong Population |
| Myers SP, Stevenson L, Cheras PA, et al. | 2010 | A forced titration study of the antioxidant and immunomodulatory effects of Ambrotose AO supplement. | BMC Complementary and Alternative Medicine | 10 | 16 | Excluded | Duplicate (found in search) - Wrong Population |
| Nagashree RS, Manjunath N, Indu M, et al | 2017 | Effect of a diet enriched with fresh coconut saturated fats on plasma lipids and erythrocyte fatty acid composition in normal adults | Journal of the American College of Nutrition | 36(5) | 330-4 | Excluded | Duplicate (found in search) - Wrong Population |
| Oates L, Cohen M, Braun L, et al | 2014 | Reduction in urinary organophosphate pesticide metabolites in adults after a week-long organic diet | Environmental Research | 132 | 105-11 | Excluded | Duplicate (found in search) - Wrong Population |
| Pipingas A, Camfield D, Stough C, et al | 2013 | The effects of multivitamin supplementation on mood and general well-being in healthy young adults. A laboratory and at-home mobile phone assessment | Appetite | 69 | 123-36 | Excluded | Duplicate (found in search) - Wrong Population |
| Pipingas A, Camfield DA, Stough C, et al | 2014 | Effects of multivitamin, mineral and herbal supplement on cognition in younger adults and the contribution of B group vitamins | Human Psychopharmacology: Clinical and Experimental | 29(1) | 73-82 | Excluded | Duplicate (found in search) - Wrong Population |
| Sarris J, Laporte E, Scholey A, et al. | 2014 | Does a medicinal dose of kava impair driving? A randomized, placebo-controlled, double-blind study. | Human Psychopharmacology: Clinical and Experimental | 29(1) | 73-82 | Excluded | Duplicate (found in search) - Wrong Population |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|---|---------------|--------------|--------------------|--|
| Shetty P, Mooventhan A, Nagendra HR | 2016 | Does short-term lemon honey juice fasting have effect on lipid profile and body composition in healthy individuals? | Journal of Ayurveda and Integrative Medicine | 7(1) | 11-Mar | Excluded | Duplicate (found in search) - Wrong Population |
| Shetty S, Subramanya P, Moorthy VK. | 2018 | Effect of yoga on flexibility and psychomotor performance in college-going healthy individuals. | International Journal of Yoga-Philosophy, Psychology and Parapsychology | 6(1) | 51 | Excluded | Duplicate (found in search) - Wrong Population |
| Abdulrazaq M, Innes JK, Calder PC. | 2017 | Effect of ω -3 polyunsaturated fatty acids on arthritic pain: A systematic review. | Nutrition | 39 | 57-66 | Excluded | Duplicate (found in search) - Wrong study type |
| AbuMweis S, Jew S, Ttayem R, Agraib L. | 2018 | Eicosapentaenoic acid and docosahexaenoic acid containing supplements modulate risk factors for cardiovascular disease: a metaanalysis of randomised placebo-control human clinical trials. | Journal of human nutrition and dietetics | 31(1) | 67-84 | Excluded | Duplicate (found in search) - Wrong study type |
| Akbari M, Tabrizi R, Lankarani KB, Heydari ST, Karamali M, Kashanian M et al. | 2018 | The effects of folate supplementation on diabetes biomarkers among patients with metabolic diseases: a systematic review and meta-analysis of randomized controlled trials. | Horm Metab Res | 50(2) | 93-105 | Excluded | Duplicate (found in search) - Wrong study type |
| Akison LK, Kuo J, Reid N, Boyd RN, Moritz KM. | 2018 | Effect of choline supplementation on neurological, cognitive, and behavioral outcomes in offspring arising from alcohol exposure during development: a quantitative systematic review of clinical and preclinical studies. | Alcohol Clin Exp Res | 42(9) | 1591-1611 | Excluded | Duplicate (found in search) - Wrong study type |
| Apaydin, E. A., Maher, A. R., Shanman, R., Booth, M. S., Miles, J. N., Sorbero, M. E. and Hempel, S. | 2016 | A systematic review of St. John's wort for major depressive disorder | Systematic Reviews | 5(1) | 148 | Excluded | Duplicate (found in search) - Wrong study type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|---|---|-----------------|--------------|--------------------|--|
| Arentz S, Smith CA, Abbott J, Bensoussan A. | 2017 | Nutritional supplements and herbal medicines for women with polycystic ovary syndrome; a systematic review and meta-analysis. | BMC complementary and alternative medicine | 1.055555 556 | | Excluded | Duplicate (found in search) - Wrong study type |
| Asevedo E, Mendes AC, Berk M, Brietzke E. | 2014 | Systematic review of N-acetylcysteine in the treatment of addictions. | Braz J Psychiatry | 36(2) | 168-175 | Excluded | Duplicate (found in search) - Wrong study type |
| Sarris J, Cox KH, Camfield DA, et al | 2012 | Participant experiences from chronic administration of a multivitamin versus placebo on subjective health and wellbeing: a double-blind qualitative analysis of a randomised controlled trial | Nutrition Journal | 11(1) | 110 | Excluded | Duplicate (found in search) - Wrong Outcome |
| Taylor JA, Weber W, Standish L, et al | 2003 | Efficacy and safety of echinacea in treating upper respiratory tract infections in children: a randomized controlled trial | JAMA | 290(21) | 2824-30 | Excluded | Duplicate (found in search) - Wrong Outcome |
| Bae JH, Kim G. | 2018 | Systematic review and meta-analysis of omega-3-fatty acids in elderly patients with depression. | Nutrition Research | 1(50) | 1-Sep | Excluded | Duplicate (found in search) - Wrong Study Type |
| Barber GA, Weller CD, Gibson SJ. | 2018 | Effects and associations of nutrition in patients with venous leg ulcers: a systematic review. | Journal of advanced nursing | 74(4) | 774-787 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Barnes, L., Barclay, L., McCaffery, K., & Aslani, P | 2018 | Complementary medicine products used in pregnancy and lactation and an examination of the information sources accessed pertaining to maternal health literacy: a systematic review of qualitative studies | BMC-Complementary and alternative medicine | 18(1) | 229 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Bayes, J, Agrawal, N, Schloss, J | 2019 | The Bioavailability of Various Oral Forms of Folate Supplementation in Healthy Populations and Animal Models: A Systematic Review | Journal of Alternative and Complementary Medicine | 25(2) | 169-180 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|--|--|--------------------|-------------------|--------------------|--|
| Becic T, Studenik C. | 2018 | Effects of Omega-3 Supplementation on Adipocytokines in Prediabetes and Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis of Randomized Controlled Trials. | Diabetes & Metabolism Journal | 2 | 101 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Bishop SK, Erdrich S, Karunasinghe N, et al. | 2015 | An investigation into the association between DNA damage and dietary fatty acid in men with prostate cancer | Nutrients | 7(1) | 405-22 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Bolignano,D, Cernaro, V,Gembillo,G., Baggetta, R, Buemi, M, and D'Arrigo, G. | 2017 | Antioxidant agents for delaying diabetic kidney disease progression: A systematic review and meta-analysis | Plos One | 12(6) | e0178699-e0178699 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Bradley R, Sherman KJ, Catz S, et al | 2012 | Adjunctive naturopathic care for type 2 diabetes: patient-reported and clinical outcomes after one year | BMC Complementary and Alternative Medicine | 12(1) | 44 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Bradley, Ryan; Harnett, Joanna; Cooley, Kieran; McIntyre, Erica; Goldenberg, Joshua; Adams, Jon | 2019 | Naturopathy as a Model of Prevention-Oriented, Patient-Centered Primary Care: A Disruptive Innovation in Health Care | Medicina | 55(9) | | Excluded | Duplicate (found in search) - Wrong Study Type |
| Buhling, K. J., A. Schumacher, C. zu Eulenburg and E. Laakmann | 2019 | Influence of oral vitamin and mineral supplementation on male infertility: a meta-analysis and systematic review. | Reproductive biomedicine online. | Electronic journal | Electronic | Excluded | Duplicate (found in search) - Wrong Study Type |
| Canhada S, Castro K, Perry IS, Luft VC. | 2018 | Omega-3 fatty acids' supplementation in Alzheimer's disease: A systematic review. | Nutritional neuroscience | 21(8) | 529-538 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Cazzola M, Calzetta L, Page C, Jardim J, Chuchalin AG, Rogliani P et al. | 2015 | Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis. | Eur Respir Rev | 24(137) | 451-461 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|---|---|---------------|--------------|--------------------|--|
| Chandan, S., Mohan, B. P., Chandan, O. C., Ahmad, R., Challa, A., Tummala, H., and Adler, D. G. | 2020 | Curcumin use in ulcerative colitis: is it ready for prime time? A systematic review and meta-analysis of clinical trials. | Annals of Gastroenterology | 33(1) | 53 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Chang JP, Su KP, Mondelli V, Pariante CM. | 2018 | Omega-3 polyunsaturated fatty acids in youths with attention deficit hyperactivity disorder: a systematic review and meta-analysis of clinical trials and biological studies. | Neuropsychopharmacology | 43(3) | 534 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Chen LH, Wang YF, Xu QH, Chen SS. | 2018 | Omega-3 fatty acids as a treatment for non-alcoholic fatty liver disease in children: A systematic review and meta-analysis of randomized controlled trials. | Clinical Nutrition | 37(2) | 516-521 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Cheng YS, Tseng PT, Chen YW, Stubbs B, Yang WC, Chen TY, Wu CK, Lin PY. | 2017 | Supplementation of omega 3 fatty acids may improve hyperactivity, lethargy, and stereotypy in children with autism spectrum disorders: A meta-analysis of randomized controlled trials. | Neuropsychiatric disease and treatment | 13 | 2531 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Cohen AJ, Richardson CR, Heisler M, et al. | 2017 | Increasing use of a healthy food incentive: a waiting room intervention among low-income patients | American Journal of Preventive Medicine | 52(2) | 154-62 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Couto JP, Moreira R. | 2018 | Oral N-acetylcysteine in the treatment of obsessive-compulsive disorder: a systematic review of the clinical evidence. | Prog Neuropsychopharmacol Biol Psychiatry | 86 | 245-254 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Ding Y, Li Y, Wen A. | 2015 | Effect of niacin on lipids and glucose in patients with type 2 diabetes: a meta-analysis of randomized, controlled clinical trials. | Clinical Nutrition | 5 | 838 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Dinicola S, De Grazia S, Carlomagno G, Pintucci JP. | 2014 | N-acetylcysteine as powerful molecule to destroy bacterial biofilms. A systematic review. | Eur Rev Med Pharmacol Sci | 18(19) | 2942-2948 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|---|--|---------------|--------------|--------------------|--|
| Diudla PV, Dias SC, Obonye N, Johnson R, Louw J, Nkambule BB. | 2018 | A systematic review on the protective effect of N-acetyl cysteine against diabetes-associated cardiovascular complications. | American Journal of Cardiovascular Drugs | 18(4) | 283-298 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Diudla PV, Nkambule BB, Dias SC, Johnson R. | 2017 | Cardioprotective potential of N-acetyl cysteine against hyperglycaemia-induced oxidative damage: a protocol for a systematic review. | Syst Rev | 6(1) | 96 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Duailibi MS, Cordeiro Q, Brietzke E, Ribeiro M, LaRowe S, Berk M, Trevizol AP. | 2017 | N-acetylcysteine in the treatment of craving in substance use disorders: Systematic review and meta-analysis. | The American journal on addictions | 26(7) | 660-666 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Farimani AR, Hariri M, Azimi-Nezhad M, Borji A, Zarei S, Hooshmand E. | 2018 | The effect of n-3 PUFAs on circulating adiponectin and leptin in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. | Acta Diabetologica | 55(7) | 641–652 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Feathers A, Aycinena AC, Lovasi GS, et al | 2015 | Food environments are relevant to recruitment and adherence in dietary modification trials | Nutrition Research | 35(6) | 480-8 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Fen F, Zhang J, Wang Z, Wu Q, Zhou X. | 2019 | Efficacy and safety of N-acetylcysteine therapy for idiopathic pulmonary fibrosis: An updated systematic review and meta-analysis. | Experimental and Therapeutic Medicine | 18(1) | 802-816 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Fernandes BS, Dean OM, Dodd S, Malhi GS, Berk M. | 2016 | N-Acetylcysteine in depressive symptoms and functionality: a systematic review and meta-analysis. | J Clin Psychiatry | 77(4) | 457-466 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Firth J, Stubbs B, Sarris J, Rosenbaum S, Teasdale S, Berk M, Yung AR. | 2017 | The effects of vitamin and mineral supplementation on symptoms of schizophrenia: a systematic review and meta-analysis. | Psychological medicine | 47(9) | 1515-1527 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|---|---|---------------|--------------|--------------------|--|
| Fleming S, Gutknecht NC | 2010 | Naturopathic and Primary Care Practice | Primary Care | 37(1) | 119-36 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Fowdar K, Chen H, He Z, Zhang J, Zhong X, Zhang J, Li M, Bai J. | 2017 | The effect of N-acetylcysteine on exacerbations of chronic obstructive pulmonary disease: A meta-analysis and systematic review. | Heart & Lung | 46(2) | 120-128 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Gao H, Geng T, Huang T, Zhao Q. | 2017 | Fish oil supplementation and insulin sensitivity: a systematic review and meta-analysis. | Lipids in health and disease | 16(1) | 131 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Gao L, Lin L, Shan N, Ren C-Y, Long X, Sun Y-H, et al. | 2018 | The impact of omega-3 fatty acid supplementation on glycemic control in patients with gestational diabetes: a systematic review and meta-analysis of randomized controlled studies. | The Journal Of Maternal-Fetal & Neonatal Medicine | 29 | 1-7 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Goldenberg J, Ward L, Day A, and Coole K | 2019 | Naturopathic Approaches to Irritable Bowel Syndrome—A Delphi Study | The Journal of Alternative and Complementary Medicine | 25 (2) | 227-233 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Grace S, Barnes L, Reilly W, Vlass A, de Permentier P. | 2018 | An integrative review of dietetic and naturopathic approaches to functional bowel disorders. | Complementary Therapies in Medicine | 41 | 67-80 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Grosso G, Micek A, Marventano S, Castellano S, Mistretta A, Pajak A, Galvano F. | 2016 | Dietary n-3 PUFA, fish consumption and depression: A systematic review and meta-analysis of observational studies. | Journal of affective disorders | 15(205) | 269-281 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Grosso G, Pajak A, Marventano S, Castellano S, Galvano F, Bucolo C, Drago F, Caraci F. | 2014 | Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. | PloS One | 9(5) | 96905 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|---|---------------|--------------|--------------------|--|
| Guo X, Guo S, Miao Z, Li Z, Zhang H. | 2018 | Myo-inositol lowers the risk of developing gestational diabetic mellitus in pregnancies: A systematic review and meta-analysis of randomized controlled trials with trial sequential analysis. | J Diabetes Complications | 32(3) | 342-348 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Guo X-F, Li K-L, Li J-M, Li D. | 2019 | Effects of EPA and DHA on blood pressure and inflammatory factors: a meta-analysis of randomized controlled trials. | Critical Reviews In Food Science And Nutrition | 4 | 1–14 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Guo XF, Yang B, Tang J, Li D. | 2018 | Fatty acid and non-alcoholic fatty liver disease: meta-analyses of case-control and randomized controlled trials. | Clinical Nutrition | 37(1) | 113-122 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Hawrelak, J. A., Wohlmuth, H., Pattinson, M., Myers, S. P., Goldenberg, J. Z., Harnett, J., and Whitten, D. L. | 2019 | Western Herbal Medicines in the Treatment of Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. | Complementary Therapies in Medicine | 48 | | Excluded | Duplicate (found in search) - Wrong Study Type |
| Heron S, Yarnell E. | 2001 | The safety of low-dose Larrea tridentata (DC) Coville (creosote bush or chaparral): a retrospective clinical study | Journal of Alternative & Complementary Medicine | 7(2) | 175-85 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Houghton, Christine A | 2019 | Sulforaphane: Its “Coming of Age” as a Clinically Relevant Nutraceutical in the Prevention and Treatment of Chronic Disease | Oxidative Medicine and Cellular Longevity | 2019 | 46388 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Hsiao-Yean Chiu, Tu-Hsueh Yeh, Yin-Cheng Huang, Pin-Yuan Chen. | 2016 | Effects of Intravenous and Oral Magnesium on Reducing Migraine: A Meta-analysis of Randomized Controlled Trials. | Pain Physician | 19 | 97-112 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|--|---------------|--------------|--------------------|--|
| Hu, X. Y., Wu, R. H., Logue, M., Blondel, C., Lai, L. Y. W., Stuart, B., Flower, A., Fei, Y. T., Moore, M., Shepherd, J., Liu, J. P. and Lewith, G | 2017 | Andrographis paniculata for symptomatic relief of acute respiratory tract infections in adults and children: A systematic review and meta-analysis | PLoS One | 12(8) | e0181780 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Innes J, Calder P. | 2018 | The differential effects of eicosapentaenoic acid and docosahexaenoic acid on cardiometabolic risk factors: a systematic review. | International journal of molecular sciences | 19(2) | 532 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Irani M, Amirian M, Sadeghi R, Le Lez J, Roudsari RL. | 2017 | The effect of folate and folate plus zinc supplementation on endocrine parameters and sperm characteristics in sub-fertile men: a systematic review and meta-analysis. | Urology journal | 14(5) | 4069-4078 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Jang H, Park K. | 2019 | Omega-3 and omega-6 polyunsaturated fatty acids and metabolic syndrome: A systematic review and meta-analysis. | Clinical Nutrition | N/A | N/A | Excluded | Duplicate (found in search) - Wrong Study Type |
| Jayedi A, Zargar MS. | 2018 | Intake of vitamin B6, folate, and vitamin B12 and risk of coronary heart disease: A systematic review and dose-response meta-analysis of prospective cohort studies. | Critical reviews in food science and nutrition | 1 | 1 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Jiang DQ, Zhao SH, Li MX, Jiang LL, Wang Y, Wang Y. | 2018 | Prostaglandin E1 plus methylcobalamin combination therapy versus prostaglandin E1 monotherapy for patients with diabetic peripheral neuropathy: A meta-analysis of randomized controlled trials. | Medicine | 97(44) | N/A | Excluded | Duplicate (found in search) - Wrong Study Type |
| Jolfaie NR, Mirzaie S, Ghasvand R, Askari G, Miraghajani M. | 2015 | The effect of glutamine intake on complications of colorectal and colon cancer treatment: A systematic review. | J Res Med Sci | 20(9) | 910-918 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|--|---------------|--------------|--------------------|--|
| Kar S, Wong M, Rogozinska E, Thangaratinam S. | 2016 | Effects of omega-3 fatty acids in prevention of early preterm delivery: a systematic review and meta-analysis of randomized studies. | European Journal of Obstetrics & Gynecology and Reproductive Biology | 198 | 40-46 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Laganà AS, Vitagliano A, Noventa M, Ambrosini G, D'Anna R. | 2018 | Myo-inositol supplementation reduces the amount of gonadotropins and length of ovarian stimulation in women undergoing IVF: a systematic review and meta-analysis of randomized controlled trials. | Arch Gynecol Obstet | 298(4) | 675-684 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Lakhan, S. E., Ford, C. T. and Tepper, D | 2015 | Zingiberaceae extracts for pain: a systematic review and meta-analysis | Journal of Nutrition | 14 | 50 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Langhurst J, Musial F et al. | 2009 | Efficacy of Hydrotherapy in Fibromyalgia syndrome- a meta-analysis of randomized controlled clinical trials | Rheumatology (Oxford) | 48(9) | 1156-1159 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Leech, B, Schloss, J & Steel, A | 2018 | Investigation into complementary and integrative medicine practitioners' clinical experience of intestinal permeability: A cross-sectional survey. | Complementary therapies in clinical practice | 31 | 200-209 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Leslie MA, Cohen DJ, Liddle DM, Robinson LE, Ma DW. | 2015 | A review of the effect of omega-3 polyunsaturated fatty acids on blood triacylglycerol levels in normolipidemic and borderline hyperlipidemic individuals. | Lipids in health and disease | 14(1) | 53 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Leung HW, Chan AL. | 2016 | Glutamine in alleviation of radiation-induced severe oral mucositis: a meta-analysis. | Nutr Cancer | 68(5) | 734-742 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Li S, Li Q, Li Y, Li L, Tian H, Sun X. | 2015 | Acetyl-L-carnitine in the treatment of peripheral neuropathic pain: a systematic review and meta-analysis of randomized controlled trials. | PLoS One | 10(3) | 119479 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|---|--|---------------|--------------|--------------------|--|
| Lin PY, Chang CH, Chong MF, Chen H, Su KP. | 2017 | Polyunsaturated fatty acids in perinatal depression: a systematic review and meta-analysis. | Biological psychiatry | 82(8) | 560-569 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Liu Wei-Hong, Zhang Cheng-Gui, Gao Peng-Fei, Liu Heng, Yang Jian-Fang. | 2017 | Omega-3 Fatty acids as Monotherapy in Treating Depression in Pregnant Women: A Meta-Analysis of Randomized Controlled Trials. | Iranian Journal of Pharmaceutical Research | 16(4) | 1593–1599 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Maghsoumi-Norouzabad L, Mansoori A, Abed R, Shishehbor F. | 2018 | Effects of omega-3 fatty acids on the frequency, severity, and duration of migraine attacks: a systematic review and meta-analysis of randomized controlled trials. | Nutritional neuroscience | 21(9) | 614-623 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Mazahery H, Stonehouse W, Delshad M, Kruger M, Conlon C, Beck K, von Hurst P. | 2017 | Relationship between long chain n-3 polyunsaturated fatty acids and autism spectrum disorder: systematic review and meta-analysis of case-control and randomised controlled trials. | Nutrients | 9(2) | 155 | Excluded | Duplicate (found in search) - Wrong Study Type |
| McCabe D, Lisy K, Lockwood C, Colbeck M. | 2017 | The impact of essential fatty acid, B vitamins, vitamin C, magnesium and zinc supplementation on stress levels in women: a systematic review. | JB I Database System Rev Implement Rep | 15(2) | 402-453 | Excluded | Duplicate (found in search) - Wrong Study Type |
| McCrary MA, Gehrke MM, Eldridge GC, et al. | 2006 | Taste preferences: biobehavioural and nutrient correlates | FASEB J | 20(4) | A175-75 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Mehdi Bahreini, Amir-Hosseini Ramezani, Farideh Shishehbor, Anahita Mansoori. | 2018 | The effect of omega-3 on circulating adiponectin in adults with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. | Canadian Journal of Diabetes | 42(5) | 553–559 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|---|---------------|--------------|--------------------|--|
| Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. | 2018 | Omega-3 fatty acid addition during pregnancy. | Cochrane Database of Systematic Reviews | 11 | N/A | Excluded | Duplicate (found in search) - Wrong Study Type |
| Miller E, Van Elswyk M, Alexander D. | 2014 | Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta-analysis of randomized controlled trials. | American journal of hypertension | 27(7) | 885-896 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Milliman WB, Lamson DW, Brignall MS | 2000 | Hepatitis C: a retrospective study, literature review, and naturopathic protocol | Alternative Medicine Review | 5(4) | 355 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Miranti EH, Stolzenberg-Solomon R, Weinstein SJ, Selhub J, Mannisto S, Taylor PR, et al. | 2017 | Low vitamin B12 increases risk of gastric cancer: a prospective study of one-carbon metabolism nutrients and risk of upper gastrointestinal tract cancer. | Int J Cancer [Internet]. | 141 (6) | 1120-1129 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Mocking RJ, Harmsen I, Assies J, Koeter MW, Ruhé H, Schene AH. | 2016 | Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. | Translational psychiatry | 6(3) | 756 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Mozaffari H, Daneshzad E, Larijani B, Bellissimo N, Azadbakht L. | 2019 | Dietary intake of fish, n-3 polyunsaturated fatty acids, and risk of inflammatory bowel disease: a systematic review and meta-analysis of observational studies. | European Journal Of Nutrition | N/A | Jan-17 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Mukai T, Kishi T, Matsuda Y, Iwata N. | 2014 | A meta-analysis of inositol for depression and anxiety disorders. | Hum Psychopharmacol | 29(1) | 55-63 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Myers, S. P, Viga, V | 2019 | The State of the Evidence for Whole-System, Multi-Modality Naturopathic Medicine: A Systematic Scoping Review | Journal of Alternative and Complementary Medicine | 25(2) | 141-168 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|---|--|---------------|--------------|--------------------|--|
| Nandakumar B, Kadam A, Srikanth H, et al | 2012 | Naturopathy and yoga based life style intervention for cardiovascular risk reduction in patients with cardiovascular risk factors: a pilot study | BMC Complementary and Alternative Medicine | 12(Suppl 1) | P106 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Nocito Echevarria MA, Andrade Reis T, Ruffo Capatti G, Siciliano Soares V, da Silveira DX, Fidalgo TM. | 2017 | N-acetylcysteine for treating cocaine addiction - A systematic review. | Psychiatry Res | 251 | 197-203 | Excluded | Duplicate (found in search) - Wrong Study Type |
| O'Mahoney LL, Matu J, Price OJ, Birch KM, Ajjan RA, Farrar D, Tapp R, West DJ, Deighton K, Campbell MD. | 2018 | Omega-3 polyunsaturated fatty acids favourably modulate cardiometabolic biomarkers in type 2 diabetes: a meta-analysis and meta-regression of randomized controlled trials. | Cardiovascular diabetology | 17(1) | 98 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Oberg EB, Bradley et al. | 2015 | Estimated Effects of Whole System Naturopathic Medicine in Select Chronic Disease Conditions: A systematic review | Alternative and Integrative Medicine | Vol 4 | 192 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Oberg EB, Bradley RD, Allen J, et al | 2011 | Evaluation of a naturopathic nutrition program for type 2 diabetes | Complementary Therapies in Clinical Practice | 17(3) | 157-61 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Oliver G, Dean O, Camfield D, Blair- West S, Ng C, Berk M, Sarris J. | 2015 | N-acetyl cysteine in the treatment of obsessive compulsive and related disorders: a systematic review. | Clinical Psychopharmacology and Neuroscience | 13(1) | 12 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Özturan A, Arslan S, Kocaadam B, Elibol E, İmamoğlu İ, Karadağ MG. | 2019 | Effect of inositol and its derivatives on diabetes: a systematic review. | Crit Rev Food Sci Nutr | 59(7) | 1124-1136 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Pan Y, Liu Y, Guo H, Jabir MS, Liu X, Cui W, Li D. | 2017 | Associations between folate and vitamin B12 levels and inflammatory bowel disease: A meta-analysis | Nutrients | 9 (4) | 382 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|---|---|---------------|--------------|--------------------|--|
| Pundir J, Psaroudakis D, Savnur P, Bhide P, Sabatini L, Teede H et al. | 2018 | Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. | BJOG | 125(3) | 299-308 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Qiang Y, Li Q, Xin Y, Fang X, Tian Y, Ma J, Wang J, Wang Q, Zhang R, Wang J, Wang F. | 2018 | Intake of dietary one-carbon metabolism-related b vitamins and the risk of esophageal cancer: A dose-response meta-analysis. | Nutrients | 10(7) | 835 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Rangel-Huerta OD, Gil A. | 2018 | Omega 3 fatty acids in cardiovascular disease risk factors: an updated systematic review of randomised clinical trials. | Clinical Nutrition | 37(1) | 72-77 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Reid, R, Steel, A, Wardle, J. Adams, J | 2019 | Naturopathic Medicine for the Management of Endometriosis, Dysmenorrhea, and Menorrhagia: A Content Analysis | Journal of Alternative and Complementary Medicine | 25(2) | 202–226 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Romeyke T, Nöhammer E, Scheuer HC, Stummer H | 2017 | Integration of naturopathic medicine into acute inpatient care: An approach for patient-centred medicine under diagnosis-related groups | Complement Ther Clin Pract | 28 | 42979 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Sahebkar A, Reiner Ž, Simental-Mendía LE, Ferretti G, Cicero AFG. | 2016 | Effect of extended-release niacin on plasma lipoprotein(a) levels: a systematic review and meta-analysis of randomized placebo-controlled trials. | Metabolism | 65(11) | 1664-1678 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Sarris J, Adams J, Kavanagh DJ. | 2010 | An explorative qualitative analysis of participants' experience of using kava versus placebo in an RCT | Australian Journal of Medical Herbalism | 22(1) | 12-Jun | Excluded | Duplicate (found in search) - Wrong Study Type |
| Sarris J, Murphy J, Mischoulon D, Papakostas GI, Fava M, Berk M, Ng CH. | 2016 | Adjunctive nutraceuticals for depression: a systematic review and meta-analyses. | American Journal of Psychiatry | 173(6) | 575-587 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|---|---|---------------|---------------------------------|--------------------|--|
| Sayles C, Hickerson SC, Bhat RR, Hall J, Garey KW, Trivedi MV. | 2016 | Oral glutamine in preventing treatment-related mucositis in adult patients with cancer: a systematic review. | Nutr Clin Pract | 31(2) | 171-179 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Schloss J, McIntyre E, Steel A, et al. | 2019 | Lessons from Outside and Within: Exploring Advancements in Methodology for Naturopathic Medicine Clinical Research. | Journal of Alternative and Complementary Medicine | 25(2) | 135-140 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Senfleber N, Nielsen S, Andersen J et al. | 2017 | Marine oil supplements for arthritis pain: a systematic review and meta-analysis of randomized trials. | Nutrients | 9(1) | 42 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Showell, M. G., R. Mackenzie-Proctor, V. Jordan and R. J. Hart | 2017 | Antioxidants for female subfertility. | Cochrane Database of Systematic Reviews | (7). | Database Cochrane Collaboration | Excluded | Duplicate (found in search) - Wrong Study Type |
| Shuai Ben, Mulong Du, Gaoxiang Ma, Jianhua Qu, Liyang Zhu, Haiyan Chu, et al. | 2019 | Vitamin B2 intake reduces the risk for colorectal cancer: a dose-response analysis. | European Journal of Nutrition | 58(4) | 1591–1602 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Skvarc DR, Dean OM, Byrne LK, Gray L, Lane S, Lewis M, Fernandes BS, Berk M, Marriott A. | 2017 | The effect of N-acetylcysteine (NAC) on human cognition—A systematic review. | Neuroscience & Biobehavioral Reviews | 78 | 44-56 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Smits, RM, R. Mackenzie-Proctor, A. Yazdani, MT. Stankiewicz, V. Jordan and MG. Showell | 2019 | Antioxidants for male subfertility. | Cochrane Database of Systematic Reviews | -3 | Database Cochrane collaboration | Excluded | Duplicate (found in search) - Wrong Study Type |
| Steel, A, Foley, H et al | 2020 | Overview of international naturopathic practice and patient characteristics: results from a cross-sectional study in 14 countries | Biomed Central Journal | 20(59) | | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|--|--|---------------|--------------|--------------------|--|
| Steel, A. Bradley, R. Wardle, J. | 2019 | Naturopathic Research: Prevalent, Relevant, But Largely Hidden in Plain Sight | The Journal of Alternative Health and Complementary Medicine | 25(2) | 123-124 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Suskind DL, Wahbeh G, Burpee T, et al. | 2013 | Tolerability of curcumin in pediatric inflammatory bowel disease: a forced dose titration study. | 56(3) | 277 | | Excluded | Duplicate (found in search) - Wrong Study Type |
| Szczurko O, Shear N, Taddio A, et al. | 2011 | Ginkgo biloba for the treatment of Vitiligo vulgaris: an open label pilot clinical trial. | BMC Complementary and Alternative Medicine | 11(1) | 21 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Tabrizi R, Ostadmohammadi V, Lankarani KB, Peymani P, Akbari M, Kolahdooz F et al. | 2018 | The effects of inositol supplementation on lipid profiles among patients with metabolic diseases: a systematic review and meta-analysis of randomized controlled trials. | Lipids Health Dis | 17(1) | 123 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Talukdar R, Murthy HV, Reddy DN. | 2015 | Role of methionine containing antioxidant combination in the management of pain in chronic pancreatitis: a systematic review and meta-analysis. | Pancreatology | 15(2) | 136-144 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Thakker D, Raval A, Patel I, Walia R. | 2015 | N-acetylcysteine for polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled clinical trials. 2015. | Obstetrics and gynecology international | N/A | 2015 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Thompson DF, Saluja HS. | 2017 | Prophylaxis of migraine headaches with riboflavin: a systematic review. | J Clin Pharm Ther | 42(4) | 394–403 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Tippens KM, Erlandsen A, Hanes DA, et al. | 2019 | Impact of a short-term naturopathic whole-foods-based nutrition education intervention on dietary behavior and diabetes risk markers: a pilot study | Journal of Alternative & Complementary Medicine | 25(2) | 234-40 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|---|------------------|---|---|---------------|--------------|--------------------|--|
| Unfer V, Facchinetti F, Orrù B, Giordani B, Nestler J. | 2017 | Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials. | Endocrine connections | 6(8) | 647-658 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Veronese N, Stubbs B, Solmi M, Ajnakina O, Carvalho AF, Maggi S. | 2018 | Acetyl-L-carnitine supplementation and the treatment of depressive symptoms: A systematic review and meta-analysis. | Psychosomatic medicine | 80(2) | 154-159 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Vitagliano A, Saccone G, Cosmi E, Visentin S, Dessole F, Ambrosini G, et al. | 2019 | Inositol for the prevention of gestational diabetes: a systematic review and meta-analysis of randomized controlled trials. | Arch Gynecol Obstet | 299(1) | 55-68 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Waldron M, Patterson SD, Tallent J, Jeffries O. | 2018 | The effects of oral taurine on resting blood pressure in humans: a meta-analysis. | Curr Hypertens Rep | 20(9) | 81 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Wang JY, Wu YH, Liu SJ, Lin YS, Lu PH. | 2018 | Vitamin B12 for herpetic neuralgia: A meta-analysis of randomised controlled trials. | Complementary therapies in medicine | 41 | 277-282 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Wang WW, Wang XS, Zhang ZR, He JC, Xie CL. | 2017 | A meta-analysis of folic acid in combination with anti-hypertension drugs in patients with hypertension and hyperhomocysteinemia. | Frontiers in pharmacology | 8 | 585 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Wardle, J | 2016 | The Australian government review of natural therapies for private health insurance rebates: What does it say and what does it mean? | Advances in Integrative Medicine | 3 | 44107 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Wardle, J, Steel, A, Casteleijn, D, Bowman, D | 2019 | An evidence-based overview of naturopathic practice in Australia | Australian Journal of Herbal & Naturopathic Medicine | 31(1) | 41518 | Excluded | Duplicate (found in search) - Wrong Study Type |
| World Naturopathic federation | 2018 | Research Written by Naturopaths /Naturopathic Doctors | http://worldnaturopathicfederation.org/wp-content/uploads/2019/04/WNF_Research-Written-by-Naturopaths-Naturopathic-Doctors.pdf | | Jan-50 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|--|---|---------------|--------------|--------------------|--|
| World Naturopathic Federation | 2017 | WNF White Paper: Naturopathic Philosophies, Principals and Theories | http://worldnaturopathicfederation.org/wp-content/uploads/2019/11/WNF_White_Paper_June-2017.pdf | n/a | n/a | Excluded | Duplicate (found in search) - Wrong Study Type |
| Xin Fang, Hedong Han, Mei Li, Chun Liang, Zhongjie Fan, Aaseth Jan, Jia He, Montgomery Scott, Yang Cao. | 2016 | Dose-Response Relationship between Dietary Magnesium Intake and Risk of Type 2 Diabetes Mellitus: A Systematic Review and Meta Regression Analysis of Prospective Cohort Studies | Nutrients | 8(11) | 739 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Yadav V, Marracci G, Lovera J, et al | 2005 | Lipoic acid in multiple sclerosis: a pilot study | Multiple Sclerosis Journal | 11(2) | 159-65 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Yadav V, Marracci GH, Munar MY, et al. | 2010 | Pharmacokinetic study of lipoic acid in multiple sclerosis: comparing mice and human pharmacokinetic parameters | Mult Scler | 16(4) | 387-97 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Yan JH, Guan BJ, Gao HY, Peng XE. | 2018 | Omega-3 polyunsaturated fatty acid supplementation and non-alcoholic fatty liver disease A meta-analysis of randomized controlled trials. | Medicine | 97 | 37 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Yang J, Li JH, Deng BH, Wang QZ. | 2018 | Association of One-Carbon Metabolism-Related Vitamins (Folate, B6, B12), homocysteine and methionine with the risk of lung cancer: systematic review and meta-analysis | Frontiers in oncology | 8 | 493 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Yang K, Zeng L, Bao T, Ge J. | 2018 | Effectiveness of Omega-3 fatty acid for polycystic ovary syndrome: a systematic review and meta-analysis. | Reproductive Biology and Endocrinology | 16(1) | 27 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Yu L, Yuan M, Wang L. | 2017 | The effect of omega-3 unsaturated fatty acids on non-alcoholic fatty liver disease: A systematic review and meta-analysis of RCTs. | Pakistan journal of medical sciences | 33(4) | 1022-1028 | Excluded | Duplicate (found in search) - Wrong Study Type |

| Author/s | Publication year | Title of article | Name of journal or other source | Vol and issue | Page numbers | Included/ Excluded | Eligibility |
|--|------------------|---|---|---------------|--------------|--------------------|--|
| Yuhua Liao, Bo Xie, Huimin Zhang, Qian He, Lan Guo, M. Subramaniapillai, et al. | 2019 | Efficacy of omega-3 PUFAs in depression: A meta-analysis. | Translational Psychiatry | 1 | 1 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Zhang H, Lv Y, Li Z, Sun L, Guo W. | 2019 | The efficacy of myo-inositol supplementation to prevent gestational diabetes onset: a meta-analysis of randomized controlled trials. | The Journal Of Maternal-Fetal & Neonatal Medicine: The Official Journal Of The European Association Of Perinatal Medicine | 32(13) | 2249-2255 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Zhang YY, Liu W, Zhao TY, Tian HM. | 2017 | Efficacy of omega-3 polyunsaturated fatty acids supplementation in managing overweight and obesity: a meta-analysis of randomized clinical trials. | The journal of nutrition, health & aging | 21(2) | 187-192 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Zhao JV, Schooling CM, Zhao JX. | 2018 | The effects of folate supplementation on glucose metabolism and risk of type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. | Ann Epidemiol | 28(4) | 249-257 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Zheng W, Zhang QE, Cai DB, Yang XH, Qiu Y, Ungvari GS. | 2018 | N-acetylcysteine for major mental disorders: a systematic review and meta-analysis of randomized controlled trials. | Acta Psychiatr Scand | 137(5) | 391-400 | Excluded | Duplicate (found in search) - Wrong Study Type |
| Zhong N, Wang J. | 2019 | The efficacy of omega-3 fatty acid for gestational diabetes: a meta-analysis of randomized controlled trials. | Gynecological Endocrinolog | 35(1) | 4-9 | Excluded | Duplicate (found in search) - Wrong Study Type |

C.3. Citation details of Studies awaiting Classification

Studies awaiting classification included nine in languages other than English. Results are displayed in alphabetical order. See Table 13 below.

Table 13: Excluded studies awaiting classification

| | Citation |
|---|--|
| 1 | Aschenbrenner M, Heim ME. Wirkung und Vertraglichkeit eines eiweissangereicherten Molkegetrankes bei Mammakarzinompatientinnen. <i>Erfahrungsheilkunde</i> . 2005;54(8):508-14. |
| 2 | Bacharach-Buhles M, Beer A. [Naturopathy consultation. Acne]. <i>Sprechstunde Naturheilkunde Akne</i> . 2011;153(14):18. |
| 3 | Chrubasik S, Schmidt A, Junck H, Pfisterer M. Wirksamkeit und Wirtschaftlichkeit von Teufelskrallenwurzelextrakt bei Ruckenschmerzen: Erste Ergebnisse einer therapeutischen Kohortenstudie. <i>Forschende Komplementarmedizin und Klassische Naturheilkunde</i> . 1997;4(6):332-6. |
| 4 | Hakimi R. [Treatment of a questionable prostate carcinoma recurrence with oncolytic viruses, dendritic cells and heat shock proteins in established naturopathy practice]. <i>Versicherungsmedizin / herausgegeben von Verband der Lebensversicherungs-Unternehmen eV und Verband der Privaten Krankenversicherung eV</i> . 2012;64(2):87-8. |
| 5 | Kraft K. [Naturopathy consultation. Fatty liver and non-alcoholic steatohepatitis]. <i>Sprechstunde Naturheilkunde Fettleber und nicht alkoholische Steatohepatitis</i> . 2011;153(4):20. |
| 6 | Rapp A, er, Grohmann G, Oelzner P, Uehleke B, Uhlemann C. Does garlic influence rheologic properties and blood flow in progressive systemic sclerosis? <i>Forschende Komplementarmedizin</i> . 2006;13(3):141-6. |
| 7 | Schimmel KC. Assignments and possibilities to revitalize patients by naturopathic treatment and regulation therapy. <i>Arztezeitschrift fur Naturheilverfahren und Regulationsmedizin</i> . 2004;45(2):88-95. |
| 8 | Wiebelitz KR, Teske W, Henke T, Brach J, Beer AM. [Naturopathic and orthopaedic in-patient treatment of chronic back pain--a comparison study]. <i>Naturheilkundliche und orthopadische station are Behandlung bei chronischen Ruckenschmerzen: Eine Vergleichsstudie</i> . 2011;153:47-55. |
| 9 | Wustrow TPU. [Naturopathic therapy for acute otitis media. An alternative to the primary use of antibiotics]. <i>Naturheilkundliche Therapie der akuten Otitis media Eine Alternative zum primaren Antibiotikaeinsatz</i> . 2005;53(8):728-34. |

C.4. Citation details of Ongoing studies

Ongoing studies are registered trial protocols. Results are displayed in alphabetical order. See Table 14 below.

Table 14: Excluded ongoing studies trial protocols

| | Citation |
|---|---|
| 1 | Actrn. Investigating the effect of integrating complementary medicine therapies including acupuncture, naturopathy, yoga and massage therapy for military veterans with chronic pain. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12620001040954 . 2020. |
| 2 | Actrn. A practice based trial of a combination of nutritional interventions: probiotics, glutamine and fish oils in patients experiencing psychological distress. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12620000928910 . 2020. |
| 3 | Ctri. Effect of naturopathy interventions in bronchial asthma. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2010/091/001169 . 2010. |
| 4 | Ctri. Study to determine effect of naturopathy and yoga treatment in patients of osteoarthritis of knee. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2010/091/001168 . 2010. |
| 5 | Ctri. study to evaluate effect of naturopathy and yoga in modification of coronary risk factors. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2010/091/001171 . 2010. |
| 6 | Ctri. study on effect of naturopathy and yoga therapy on in improving psychological profile" in patients of metabolic syndrome. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2011/03/001654 . 2011. |

| | Citation |
|----|---|
| 7 | Ctri. Effect of Naturopathy and yoga Therapy on nervous control of heart in obese individuals. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2011/12/002286 . 2011. |
| 8 | Ctri. Effect of Naturopathy and yoga based lifestyle interventions on inflammation and utilization of insulin in patients with high risk of cardiovascular diseases. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2011/12/002285 . 2011. |
| 9 | Ctri. Yoga and Naturopathy strategy for Diabetes Mellitus. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2018/12/016550 . 2018. |
| 10 | Ctri. Effect of Yoga and Naturopathy on abnormally dilated veins of legs. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2018/10/015895 . 2018. |
| 11 | Ctri. To evaluate the effect of yoga and Naturopathy on obesity. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2018/12/016512 . 2018. |
| 12 | Ctri. Effect of yoga and Naturopathy on Hypertension. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2019/01/016883 . 2019. |
| 13 | Ctri. A clinical trial to study the Effects of Yoga and Nature cure treatments for Obese Patients. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2019/10/021775 . 2019. |
| 14 | Ctri. A comparative clinical study on the effect of naturopathy and yoga on rheumatoid arthritis. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2020/12/029833 . 2020. |
| 15 | Ctri. Effect of Yoga and Nature cure therapy on weight, heart status and mind of thyroid patients. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=43714 http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2020/07/026734 . 2020. |
| 16 | Drks. Controlled prospective study to evaluate the inpatient naturopathic fasting therapy in overweight and obese patients. http://www.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00006343 . 2014. |
| 17 | Drks. "AIM-Diabetes" (Anthroposophic/Naturopathic Integrative Medicine – Diabetes Intervention with Art-, Behavioral-, Exercise-Therapy and Education Study) A randomised, controlled, explorative, clinical study. http://www.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00009884 . 2016. |
| 18 | Isrctn. A randomised controlled trial of the effect on chronic low back pain of a naturopathic osteopathy intervention. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN61808774 . 2003. |
| 19 | Nct. Complementary Naturopathic Medicine for Periodontitis. https://clinicaltrials.gov/show/NCT00010634 . 2001. |
| 20 | Nct. Herbal Alternatives for Menopause Symptoms (HALT Study). https://clinicaltrials.gov/show/NCT00169299 . 2005. |
| 21 | Nct. ALA and Prostate Cancer. https://clinicaltrials.gov/show/NCT00309439 . 2006. |
| 22 | Nct. RCT of the Naturopathic Anti-Inflammatory Diet. https://clinicaltrials.gov/show/NCT00334919 . 2006. |
| 23 | Nct. Pilot Study: complementary Therapies in Geriatric Patients. https://clinicaltrials.gov/show/NCT00974506 . 2009. |
| 24 | Nct. The Effect of Urox™ in the Treatment of Overactive Bladder and Urinary Incontinence. https://clinicaltrials.gov/show/NCT02396160 . 2015. |
| 25 | Nct. Integrative Care for Type 2 Diabetes. https://clinicaltrials.gov/show/NCT02843724 . 2016. |
| 26 | Nct. Effect of Apple Cider Vinegar and Metformin Combination vs Metformin Alone in Type 2 Diabetics. https://clinicaltrials.gov/show/NCT04120259 . 2019. |
| 27 | NCT04871412. The Thoracic Peri-Operative Integrative Surgical Care Evaluation Trial - Stage II. https://ClinicalTrials.gov/show/NCT04871412 |
| 28 | CTRI/2020/09/028014. Study comparing raw vegetables and fruits on weight and blood cholesterol on fat individuals. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2020/09/028014 |
| 29 | CTRI/2020/07/026842. Effect of yoga and naturopathy therapies on nerves in sugar patients. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2020/07/026842 |
| 30 | CTRI/2020/06/025714. Holistic Health Management through Yoga and Naturopathy for Frontline COVID Health Care Providers?? The H2M trial. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2020/06/025714 |
| 31 | CTRI/2020/05/025320. Effect of Yoga & Naturopathy in patients with COVID-19. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2020/05/025320 |
| 32 | ANZCTR347666. The addition of naturopathic herbal medicine to a lifestyle intervention for women with polycystic ovary syndrome (PCOS), a randomised controlled trial. https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=347666&showOriginal=true&isReview=true |

| | Citation |
|----|---|
| 33 | NCT00983502. Pilot Study of Alternative Treatments of Unexplained Chronic Fatigue. https://ClinicalTrials.gov/show/NCT00983502 |
| 34 | NCT00409149. The Effect of a Complementary Multi Disciplinary Program on Blood Pressure in Hypertensive Patients. https://ClinicalTrials.gov/show/NCT00409149 |
| 35 | NCT00160901. Complementary Therapies for the Reduction of Side Effects During Chemotherapy for Breast Cancer. https://ClinicalTrials.gov/show/NCT00160901 |
| 36 | Seely D, Ennis JE, McDonell E, Fazekas A, Zhao L, Asmis T, et al. Intervention Development Process for a Pragmatic Randomized Controlled Trial: The Thoracic Peri-Operative Integrative Surgical Care Evaluation Trial. Journal of alternative and complementary medicine (New York, NY). 2019;25:S112-S23. |

Appendix D: Details of Included studies

There were 29 eligible publications for 16 studies included (9 RCTs, 7 NRSIs) which reported on outcome domains prioritised by the NTWC. These 16 studies spanned 14 populations: breast cancer, colon cancer, prostate cancer, T2DM, PCOS, overweight and obesity, anxiety, MS, CVD, allergic rhinitis, back pain, rotator cuff tendonitis, menopausal symptoms and CVD risk. Most of the population groups were represented by only one study except for T2DM and PCOS, both included one RCT and one NRSI each. The primary publications are in Table 15 below, with duplicate citations in Table 16, and an errata in Table 17.

Table 15: References to included studies – ordered by appearance in the main report

| | Study ID | Publication Details |
|----|------------------|--|
| 1 | Andersen 2018 | Andersen MR, Sweet E, Hager S, Gaul M, Dowd F, St, et al. Use of Integrative Oncology, Involvement in Decision-Making, and Breast Cancer Survivor Health-Related Quality of Life in the First 5 Years Postdiagnosis. <i>Integrative cancer therapies</i> . 2018;17(3):636-45. |
| 2 | Arentz 2017 | Arentz S, Smith CA, Abbott,J., Fahey,P., Cheema,BS., Bensoussan A. Combined lifestyle and herbal medicine in overweight women with polycystic ovary syndrome (PCOS): A randomized controlled trial. <i>Phytotherapy research</i> . 2017;31(9):1330-40. |
| 3 | Bairy 2020 | Bairy S, Rao MR, Edla SR, Manthena SR, Tatavarti NVGD. Effect of an Integrated Naturopathy and Yoga Program on Long-Term Glycemic Control in Type 2 Diabetes Mellitus Patients: A Prospective Cohort Study. <i>International journal of yoga</i> . 2020;13(1):42-9. |
| 4 | Beer 2014 | Beer A-M, Ismar LE, Wessely DK, Potschke T, Weidner B, Wiebelitz KR. Retrospective long-term comparison of naturopathic fasting therapy and weight reduction diet in overweight patients. <i>Evidence-based complementary and alternative medicine: eCAM</i> . 2014; 2014:453407. |
| 5 | Bernhardt 2009 | Bernhardt B, Seely D, Cooley K, Szczurko O, Perri D, Mills EJ, et al. Naturopathic care for anxiety: A randomized controlled trial <i>ISRCTN78958974</i> . <i>PLoS ONE</i> . 2009;4(8):e6628. |
| 6 | Braun 2013 | Braun DP, Gupta D, Birdsall TC, Sumner M, Staren ED. Effect of naturopathic and nutritional supplement treatment on tumor response, control, and recurrence in patients with prostate cancer treated with radiation therapy. <i>Journal of alternative and complementary medicine (New York, NY)</i> . 2013;19(3):198-203. |
| 7 | Cramer 2003 | Cramer EH, Jones P, Keenan NL, Thompson BL. Is naturopathy as effective as conventional therapy for treatment of menopausal symptoms? <i>Journal of alternative and complementary medicine (New York, NY)</i> . 2003;9(4):529-38. |
| 8 | Mittman 1990 | Mittman P. Randomized, double-blind study of freeze-dried <i>Urtica dioica</i> in the treatment of allergic rhinitis. <i>Planta medica</i> . 1990;56(1):44-7. |
| 9 | Raghunath 2020 | Raghunath K, Sumathi C, Rajappa SJ, Mohan MVTK, Kumar U, Shaik U, et al. Impact of naturopathy, yoga, and dietary interventions as adjuvant chemotherapy in the management of stage II and III adenocarcinoma of the colon. <i>International journal of colorectal disease</i> . 2020;35(12):2309-22. |
| 10 | Ratnakumari 2018 | Ratnakumari ME, Manavalan N, Sathyanath D, Ayda YR, Reka K. Study to Evaluate the Changes in Polycystic Ovarian Morphology after Naturopathic and Yogic Interventions. <i>International journal of yoga</i> . 2018;11(2):139-47. |
| 11 | Seely 2013 | Seely D, Szczurko O, Cooley K, Fritz H, Aberdour S, Herrington C, et al. Naturopathic medicine for the prevention of cardiovascular disease: a randomized clinical trial. <i>CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne</i> . 2013;185(9): E409-16. |

| | Study ID | Publication Details |
|----|-------------------|---|
| 12 | Shinto 2008 | Shinto L, Calabrese C, Morris C, Yadav V, Griffith D, Frank R, et al. A randomized pilot study of naturopathic medicine in multiple sclerosis. <i>Journal of alternative and complementary medicine (New York, NY)</i> . 2008;14(5):489-96. |
| 13 | Braun 2014 | Braun L, Stanguts C, Spitzer O, et al. A wellness program for cardiac surgery improves clinical outcomes. <i>Advances in Integrative Medicine</i> . 2014;1(1):32-37. |
| 14 | Stier-Jarmer 2021 | Stier-Jarmer M, Frisch D, Neuy S, Schuh A. A 3-Week Naturopathic Intervention Improves HbA1c, Weight, and Quality of Life Among Overweight and Obese Adults With Type 2 Diabetes: 6-Month Results From a Randomized Trial. <i>Alternative therapies in health and medicine</i> . 2021; 27: 61-71. |
| 15 | Szczurko 2007 | Szczurko O, Cooley K, Busse JW, Seely D, Bernhardt B, Guyatt GH, et al. Naturopathic care for chronic low back pain: a randomized trial. <i>PloS one</i> . 2007;2(9):e919. |
| 16 | Szczurko 2009 | Szczurko O, Cooley K, Mills EJ, Zhou Q, Perri D, Seely D. Naturopathic treatment of rotator cuff tendinitis among Canadian postal workers: a randomized controlled trial. <i>Arthritis and rheumatism</i> . 2009;61(8):1037-45. |

Table 16: Duplicates of included studies

| # | Publication details | Reason for exclusion |
|---|--|---|
| 1 | Smith C, Bensoussan A, Arentz S, Abbott J. Herbal medicine plus lifestyle for overweight women with polycystic ovary syndrome: A randomised control trial. <i>Australian Journal of Herbal and Naturopathic Medicine</i> . 2019;31(1):38. | Abstract only. Superseded by included study Arentz 2017 |
| 2 | Cooley K, Szczurko O, Perri D, et al. Naturopathic care for anxiety: a randomized controlled trial ISRCTN78958974. <i>PLoS One</i> . 2009;4(8):e6628. | Superseded by Bernhardt 2009 |
| 3 | Szczurko O, Cooley K, Mills E, Seely D, Bernhardt B, Guyatt GH, et al. Determining the effect of naturopathic treatments on anxiety outcomes of Canadian postal workers, randomised controlled parallel group study...13th Annual Symposium on Complementary Health Care, 12th-14th December, 2006, University of Exeter, UK. <i>Focus on Alternative & Complementary Therapies</i> . 2006;11:45-. | Abstract only. Superseded by Bernhardt 2009 |
| 4 | Birdsall TC, Cain L, Martin J, Birdsall SM, Wiersum L, Anderson K, et al. The effect of naturopathic and nutritional supplement treatment on tumor response, control, and survival in prostate cancer patients treated with radiation therapy. <i>Journal of Clinical Oncology</i> . 2009;27(15):e16088. | Abstract only. Superseded by included study Braun 2013 |
| 5 | Stanguts C, Gunawan M, Kwa L, Esmore D, Rosenfeldt F, Braun L, et al. A wellness program for cardiac surgery improves clinical outcomes. <i>Advances in Integrative Medicine</i> . 2014;1(1):32-7. | Duplicate of included study Braun 2014 |
| 6 | Herman PM, Szczurko O, Cooley K, Seely D. A naturopathic approach to the prevention of cardiovascular disease: cost-effectiveness analysis of a pragmatic multi-worksites randomized clinical trial. <i>Journal of occupational and environmental medicine</i> . 2014;56(2):171-6. | Duplicate of included study Seely 2013 |
| 7 | Nct. Naturopathic Treatment for the Prevention of Cardiovascular Disease. https://clinicaltrials.gov/show/NCT00718796 . 2008. | Abstract only. Full papers for this registered trial have been included (Herman 2014, Seely 2013) |
| 8 | Seely D, Szczurko O, Kieran C, Fritz H, Rouchotas P, Lescheid D, et al. Naturopathic medicine for the prevention of cardiovascular disease: A pragmatic randomized clinical trial. <i>BMC Complementary and Alternative Medicine</i> . 2012;12. | Oral presentation. Superseded by included study Seely 2013 |

| # | Publication details | Reason for exclusion |
|----|--|---|
| 9 | Szczurko O, Cooley K, Mills E, Seely D, Busse J, Bernhardt B, et al. Determining the impact of naturopathic treatment on Canadian postal workers with low back pain, a randomised controlled parallel group study...13th Annual Symposium on Complementary Health Care, 12th-14th December, 2006, University of Exeter, UK. Focus on Alternative & Complementary Therapies. 2006;11:46-. | Abstract only. Superseded by included study Szczurko 2007 |
| 10 | Szczurko O CK, Bernhardt B, ., et al. Determining the impact of naturopathic treatment on Canadian postal workers with low back pain, a randomised controlled parallel group study. Focus on Alternative and Complementary Therapies. 2006;11:46. | Abstract only. Superseded by included study Szczurko 2007 |
| 11 | Isrctn. Naturopathic Treatment of Rotator Cuff Tendinitis Amongst Postal Workers, a randomized controlled parallel group study. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN49884134 . 2007. | Abstract only. Full publication of this registered trial has been included (Szcurko 2009) |
| 12 | Isrctn. Naturopathic Care for Low Back Pain: a randomised controlled trial. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN41920953 . 2007. | Abstract only. Full paper for this registered trial has been included (Szczurko 2007) |

Table 17: Full text errata

| # | Study | Reason for exclusion |
|---|--|---|
| 1 | Anonymous. Correction... "A randomized pilot study of naturopathic medicine in multiple sclerosis" (Volume 14, Number 5, 2008, pp. 489-496). Journal of alternative and complementary medicine (new york, NY). 2008;14(6):793. | Erratum for Shinto 2008, an included study. |

D.1. Details of Included studies – characteristics of studies

Grouped by population

D.1.1. Breast cancer

Table 18: Andersen 2018

| Anderson 2018 | |
|-------------------------|--|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> 568 participants (Naturopathic oncology =193; Usual care = 375), mean age 54 y Breast cancer survivors who did and did not choose to supplement their breast cancer treatment with naturopathic oncology (NO) care within 2 years of diagnosis: mean age 53.3 y (SD 11.19) NO care patients were eligible if they spoke English fluently enough to complete surveys, were over 21 years old, and were diagnosed with breast cancer less than 2 years before visiting participating naturopathic doctor's clinic. Mean age 54.8 y (SD 10.30); enrolled median 4 months post-diagnosis. Comparator (usual care) patients were selected from the cancer registry based on their similarity to an enrolled NO patient. No statistical difference between intervention and comparator groups for any variables used for recruitment and matching. Enrolled median 9.7 months post-diagnosis, significantly later than the intervention group. Research centre setting |

Anderson 2018

| | |
|--|---|
| Study methods | <ul style="list-style-type: none"> • NCT01366248 • Matched longitudinal study • Number of recruiting centres not stated • Participants were recruited via naturopathic doctors' clinics (intervention) and cancer registries (comparators), US. • Comparator women were matched to NO care participants according to demographic characteristics and stage of cancer at the time of diagnosis • Unit of analysis: individual participant • Multivariate analyses: demographic variables and involvement in decision making score as predictors of SF-36 scores at enrolment and 6 months and also as predictors of the change in SF-36 score at 6 months from baseline • Multivariate analyses: demographic variables at enrolment as predictors of the decision-making score • Welsh 2-sample t-test to compare SF-36 scores between intervention and comparator groups • T-test to compare involvement in decision making score between intervention and comparator group at enrolment and 6 months • No method was stated for addressing missing data • There is a likelihood of reporting biases, as not all the data from the involvement in decision-making measure were presented. |
| Enrolment start/end dates Length of follow-up | <ul style="list-style-type: none"> • 12 months follow-up |
| Intervention | <ul style="list-style-type: none"> • 193 participants • Naturopathic oncology care was delivered by naturopathic doctors' clinics. No other details regarding frequency of visits, duration or the naturopathic components or modalities, or compliance, were provided. |
| Comparator | <ul style="list-style-type: none"> • 375 enrolled, 360 participants analysed • Usual care, with no visits to a naturopathic doctors' clinic. No other details of usual care provided |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: HRQOL assessed by SF-36 (at enrolment and 6 months) • Secondary outcomes: decision-making about cancer treatment assessed by 4-item measure (at enrolment and 6 months) • SF-36 results were reported for enrolment and at 6 months for both groups. The study reported decision-making and CAM usage at enrolment for intervention and comparator combined. Data was not shown for the 4-item measure at 6 months. • SF-36: higher scores are favourable. • 4-item measure: higher scores indicate greater involvement in decision making. |
| Funding source | <ul style="list-style-type: none"> • The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by the National Center for Complementary and Integrative Health (RO1 AT 5873, T32 AT815). |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: Fred Hutchinson Cancer Research Center, Seattle, WA, USA; University of Washington, Seattle, WA, USA; Bastyr University, Kenmore, WA, USA • The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article. |

Abbreviations: CAM, complementary and alternative medicine; HRQOL, health-related quality of life; NO, naturopathic oncology; SF-36, Short Form-36; y, year

D.1.2. Colon cancer

Table 19: Raghunath 2020

| Raghunath 2020 | |
|---------------------------|---|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> • 116 adult patients who underwent surgery for adenocarcinoma of the colon (stages II and III), aged 18-65 years, 21 days from surgery without radiation, with adequate renal and liver function, ECOG performance status 0, 1, or 2. • Exclusion criteria: not willing to sign an informed consent form; other than adenocarcinoma of the colon; positive for HIV/AIDs, recurrent case of colon cancer; ECOG performance status 3 or 4; stage IV colon cancer. • Intervention group: median age 47 y; male/female ratio 1.2:1; 13 stage II and 45 stage III patients. • Comparator group: median age 48 y, male/female ratio 0.7:1; 15 stage II and 43 stage III patients. • Setting: not stated • Hyderabad, India • Study eligibility criteria, including diagnostic criteria |
| Study methods | <ul style="list-style-type: none"> • RCT, investigators were blinded to the intervention • Single centre • Recruitment from outpatient and inpatient departments of Basavataarakam Indo-American Cancer Hospital, Hyderabad • 18 months • Details of random sequence generation, allocation sequence concealment, and masking for randomised trials, and methods used to prevent and control for confounding, selection biases, and information biases for non-randomised studies • Unit of analysis: individual participant • Per protocol analysis • Method to prevent/address missing data: not reported • Likelihood of reporting and other biases: high. E.g. 2 intervention participants were excluded to balance the dataset as 2 comparator participants developed recurrences; there appears to be selective reporting of psychological outcomes. |
| Enrolment start/end dates | 18 months |
| Length of follow-up | |
| Intervention | <ul style="list-style-type: none"> • 58 participants • Naturopathy, yoga and dietary interventions with adjuvant chemotherapy. Naturopathy and yoga intervention for 7 days following 1st cycle of chemotherapy. <ul style="list-style-type: none"> ➢ Morning naturopathy regimen was composed of a mudpack for 10 min. Partial manipulative therapy to limbs for 20 min on day 1; enema on days 1, 2, and 3; warm water bath on day 1; partial massage for 15 min on day 2 and 20 min on days 4 and 6; steam bath on day 2; neutral water bath on days 2, 3, 4, 5, 6 and 7; hot and cold hepato-gastric pack on days 4, 6 and 7; hot trunk pack for 15 min on day 3 with duration not stated for day 5. ➢ Evening naturopathy regimen composed of neutral hip bath (92-98°F) for 15 min on day 1, 15-20 min on day 2 and 10-15 min on day 3; neutral/hot foot bath 10 min at bedtime each day; cold hip bath (55-65°F) for 10-15 min on day 4; alternate hot and cold hip bath (55-65°F) on day 5 for 10-15 min; spinal jet bath (92-98°C) 10-15 min on day 6; neutral immersion bath for 15-20 min (92-98°C) on day 7. ➢ Yoga regimen: Sukshma vyayam for 10 min, pranayama for 15 min with emphasis on nadishuddi and bhrumari; 10 min of DRT in the morning. Special techniques which are proven in cancer care, viz., cyclic meditation |

| | <p>and yoga-based imagery and autosuggestion for 30 min, in the evening. [DRT was not defined]</p> <ul style="list-style-type: none"> For subsequent chemo cycles, 5-day in-house interventions followed by further follow-up interventions in months 9, 12, 15, and 18. <ul style="list-style-type: none"> Dietary intervention during follow-up visits (not clear whether this diet is only taken during the 5-day in-house follow-up visits). <table border="1" data-bbox="598 414 1420 795"> <thead> <tr> <th>Time</th> <th>Dietary intervention</th> </tr> </thead> <tbody> <tr> <td>6 AM</td> <td>Wake up take 1 or 2 glasses of water. Wheat grass juice 1 oz with tulasi (basil) juice and pudina (mint leaves)</td> </tr> <tr> <td>7 AM</td> <td>1 glass of vegetable juice (carrot, beetroot, tomato, bottle guard juice, ash guard juice), overnight soaked dry fruits ((badam (almonds), anjeer (figs), munakka (dried grapes), dry dates) 3-4 each)</td> </tr> <tr> <td>9 AM</td> <td>2 Idlis with green chutney, ragi porridge (little millet) with vegetables, fruits (orange, black grapes, pomegranate)</td> </tr> <tr> <td>12 noon</td> <td>Korralu (foxtail millet) or ragi or, 1 cup unpolished rice, boiled vegetable curry, dal (pulses) with green leafy vegetables, butter milk</td> </tr> <tr> <td>4 PM</td> <td>Fruit juice/ ragi malt (orange, black grapes, pomegranate)</td> </tr> <tr> <td>7 PM</td> <td>Dalia (broken what preparation)/unpolished rice/ ragi porridge, boiled vegetable curry</td> </tr> <tr> <td>9 PM</td> <td>1 cup of milk/ragi malt with buttermilk</td> </tr> </tbody> </table> <ul style="list-style-type: none"> Conventional chemotherapy treatment: 8 cycles of chemotherapy with Cape-Ox, which included injection of oxaliplatin 130 mg/m² and tablet capecitabine 1000 mg/m² twice a day for 14 days. Each cycle is repeated after a gap of 3 weeks. The rationale for how naturopathy, yoga, and diet interventions may assist with side effects caused by chemotherapy was not stated. Not stated who provided or delivered the intervention. The location not stated, but it is assumed it is the Basavatarakam Indo-American Cancer Hospital No mention of tailoring or modifying the intervention. No mention of compliance with the intervention | Time | Dietary intervention | 6 AM | Wake up take 1 or 2 glasses of water. Wheat grass juice 1 oz with tulasi (basil) juice and pudina (mint leaves) | 7 AM | 1 glass of vegetable juice (carrot, beetroot, tomato, bottle guard juice, ash guard juice), overnight soaked dry fruits ((badam (almonds), anjeer (figs), munakka (dried grapes), dry dates) 3-4 each) | 9 AM | 2 Idlis with green chutney, ragi porridge (little millet) with vegetables, fruits (orange, black grapes, pomegranate) | 12 noon | Korralu (foxtail millet) or ragi or, 1 cup unpolished rice, boiled vegetable curry, dal (pulses) with green leafy vegetables, butter milk | 4 PM | Fruit juice/ ragi malt (orange, black grapes, pomegranate) | 7 PM | Dalia (broken what preparation)/unpolished rice/ ragi porridge, boiled vegetable curry | 9 PM | 1 cup of milk/ragi malt with buttermilk |
|------------|---|------|----------------------|------|---|------|--|------|---|---------|---|------|--|------|--|------|---|
| Time | Dietary intervention | | | | | | | | | | | | | | | | |
| 6 AM | Wake up take 1 or 2 glasses of water. Wheat grass juice 1 oz with tulasi (basil) juice and pudina (mint leaves) | | | | | | | | | | | | | | | | |
| 7 AM | 1 glass of vegetable juice (carrot, beetroot, tomato, bottle guard juice, ash guard juice), overnight soaked dry fruits ((badam (almonds), anjeer (figs), munakka (dried grapes), dry dates) 3-4 each) | | | | | | | | | | | | | | | | |
| 9 AM | 2 Idlis with green chutney, ragi porridge (little millet) with vegetables, fruits (orange, black grapes, pomegranate) | | | | | | | | | | | | | | | | |
| 12 noon | Korralu (foxtail millet) or ragi or, 1 cup unpolished rice, boiled vegetable curry, dal (pulses) with green leafy vegetables, butter milk | | | | | | | | | | | | | | | | |
| 4 PM | Fruit juice/ ragi malt (orange, black grapes, pomegranate) | | | | | | | | | | | | | | | | |
| 7 PM | Dalia (broken what preparation)/unpolished rice/ ragi porridge, boiled vegetable curry | | | | | | | | | | | | | | | | |
| 9 PM | 1 cup of milk/ragi malt with buttermilk | | | | | | | | | | | | | | | | |
| Comparator | <ul style="list-style-type: none"> 58 participants Psychosocial counselling with adjuvant chemotherapy Psychosocial counselling was not defined Conventional chemotherapy treatment: 8 cycles of chemotherapy with Cape-Ox, which included injection of oxaliplatin 130 mg/m² and tablet capecitabine 1000 mg/m² twice a day for 14 days. Each cycle is repeated after the gap of 3 weeks No rationale as to how psychosocial counselling might work. Not stated who provided or delivered the comparator. Not stated how frequent, intense or long the psychosocial counselling sessions were. The location was not stated, but it is assumed it is the Basavatarakam Indo-American Cancer Hospital No mention of tailoring or modifying the comparator. No mention of compliance or adherence to treatment | | | | | | | | | | | | | | | | |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: haematological, biochemical and psychological evaluations <ul style="list-style-type: none"> Haemoglobin, leukocyte count, platelet count were assessed with an automated cell counter. Serum creatinine, serum carcinoembryonic antigen were measured by Olympus AU 400 clinical chemistry analyser. Serum bilirubin also measured (method not stated). Anxiety measured by STAI (4-point scale with 1 being less stress and 4 being high stress) | | | | | | | | | | | | | | | | |

| | |
|-----------------------|---|
| | <ul style="list-style-type: none"> ➤ Depression measured by BDI, composed of 21 categories of symptoms, with higher scores indicating greater severity. ➤ Distress and bothering were assessed to measure symptom severity from neutral to maximum. ➤ Functional Living Index, graded from none to very severe (0-4) • Comparison of outcomes between intervention and comparator groups at time points before and after chemotherapy (1-6 months and 9-18 months respectively), overall and by subgroups of gender and age: haemoglobin, leukocytes, platelet count, serum creatinine, serum bilirubin, and serum carcinoembryonic antigen. • Anxiety, depression, symptom severity, distress/bothering, and Functional Living Index before and after chemotherapy were presented graphically; comparisons between groups by t-test were presented but it is not clear if the comparison was at baseline or after the intervention. • Changes from baseline not assessed. • Mean and standard deviations were presented for outcomes; MDs were not presented in the t-tests but 95% CI and Cohen-d were reported. • Timepoints for assessment were not formally stated, only before and after chemotherapy. • 135 patients were originally screened with 15 dropping out for social reasons before randomisation. 120 were randomised: 2 comparator patients developed recurrences and were excluded; thus from the intervention group, 2 patients were also excluded to balance the dataset. |
| Funding source | <ul style="list-style-type: none"> • This work is supported by a grant from The Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha, Sowa Rigpa and Homeopathy (AYUSH). |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: Department of Academics, Basavatarakam Indo-American Cancer Hospital and Research Centre, Hyderabad, Telangana, India; Department of Naturopathy and Yoga – Addlife, Basavatarakam Indo-American Cancer Hospital and Research Centre, Hyderabad, Telangana, India; Department of Medical Oncology, Basavatarakam Indo-American Cancer Hospital and Research Centre, Hyderabad, Telangana, India; Indian Institute of Information Technology and Management Kerala, Affiliated to Cochin University, Cochin, India; Department of Indo American Cancer Research Foundation, Basavatarakam Indo-American Cancer Hospital and Research Centre, Hyderabad, Telangana, India • Authors' financial relationship: The study was undertaken by Dr. K. Kalpana Raghunath, Principal Investigator, with the support of the grant In-aid sanctioned to "Addlife Naturopathy Department" part of Basavatarakam Indo-American Cancer Hospital and Research Institute under EMR scheme of Ministry of AYUSH. • The authors declare that they have no conflict of interest. |

Abbreviations: BDI, Beck's Depression Inventory; ECOG, Eastern Cooperative Oncology Group; FLIC, Functional Living Index of Cancer; STAI, State Trait Anxiety Inventory

D.1.3. Prostate cancer

Table 20: Braun 2013

| Braun 2013 | |
|-------------------------|--|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> • 134 participants diagnosed with localised adenocarcinoma of the prostate between 2000 and 2004, who were treated with curative intent for limit-stage prostate cancer by radiation therapy • Intervention group: median age 62.0 y (range 46-81 y); tumour staging T1c (39%); T2a (44%); T2b (10%); T2c (5%) with 1 T3b tumour • Comparator group: median age 61.5 y (range 48-81 y); tumour staging T1b (3%); T1c (46%); T2a (32%); T2b (12%); T2c (5%) with 1 T3a tumour |

| | |
|---------------------------|--|
| | <ul style="list-style-type: none"> Setting: Midwestern and Southwestern Regional Medical Centers of Cancer Treatment Centers of America® |
| Study methods | <ul style="list-style-type: none"> Retrospective comparative cohort study Multicentre, number of recruiting centres not stated Patients self-selected to receive naturopathic and nutritional supplements (NNS). Patients were treated between 2000 and 2004 and were followed up for a minimum of 5 years after therapy. Method to control for confounding: patients were stratified according to pretreatment PSA level: low (4-10 ng), intermediate (10-20 ng), or high risk (>20 ng) No further details of methods to control for selection biases and information biases Unit of analysis: individual patient Statistical methods: differences between intervention and comparator groups compared with two-sample t-test and non-parametric Mann-Whitney U test. Chi-squared test was used for urinary and sexual performance assessments. Method to prevent/address missing data: none stated Likelihood of reporting and other biases: high, because of self-selection for intervention by participants. There was potential for reporting bias, as mean time to reach nadir and mean follow-up were not reported. |
| Enrolment start/end dates | Followed up for a minimum of 5 years post-completion of therapy unless lost to follow-up |
| Length of follow-up | |
| Intervention | <ul style="list-style-type: none"> 69 participants NNS as part of treatment and maintenance during an extended post-treatment interval of at least 2 years. <ul style="list-style-type: none"> At least 1 antioxidant supplement per day during 6-8 weeks of radiation therapy (mean 2.9 supplements/d (SD 1.7 supplements). Most frequent antioxidant naturopathic treatments included green tea extract (500–750mg twice per day, standardized to 80% catechins), melatonin (20mg daily at bedtime), vitamin C (500–1000mg 3 times per day), and vitamin E (200–400 IU twice per day) Radiation therapy and hormone ablation therapy: <ul style="list-style-type: none"> 94.2% received conformal external beam radiation therapy or tomotherapy (4500-5000 cGy) in conjunction with high dose rate brachytherapy (600-650cGy/fraction x 2-3 fractions) over 6-8 weeks The remainder received either high dose rate monotherapy, tomotherapy, or intensity-modulated radiation therapy with tomotherapy. 57% received hormone ablation therapy with oral bicalutamide (50mg/d) alone or in conjunction with leuprolide depot injection (generally 22.5 mg IM every 3 months) 39 received hormone therapy; 30 did not Patients were seen at regular intervals by both their attending radiation therapist and members of the naturopathic and nutrition teams during their radiation treatment and throughout their clinical follow-up. <ul style="list-style-type: none"> NNS prescribed by a naturopathic physician. How NNS might work: may ameliorate morbid effects of cancer and its treatment. As antioxidants they may reduce the oxidative modification of DNA, but may interfere with the reactive oxygen species-tumouricidal function of radiotherapy and may inhibit clinical tumour response to radiation therapy for prostate cancer. Location where NNS delivered not stated; radiotherapy and hormone ablation delivered at Midwestern and Southwestern Regional Medical Centers of Cancer Treatment Centers of America® |

| | |
|-----------------------|--|
| | <ul style="list-style-type: none"> No further details regarding tailoring or modification of intervention. Compliance: all patients were questioned concerning their use of NNS and this was monitored routinely for all patients by documenting that their prescriptions were filled as recommended. It was 'believed' that compliance with NNS recommendations was very high, but actual compliance was not measured. |
| Comparator | <ul style="list-style-type: none"> 65 participants Radiation therapy and hormone ablation therapy: <ul style="list-style-type: none"> 92.8% received conformal external beam radiation therapy or tomotherapy (4500-5000 cGy) in conjunction with high dose rate brachytherapy (600-650cGy/fraction x 2-3 fractions) over 6-8 weeks The remainder received either high dose rate monotherapy, tomotherapy or intensity-modulated radiation therapy with tomotherapy. 58% received hormone ablation therapy with oral bicalutamide (50mg/d) alone or in conjunction with leuprolide depot injection (generally 22.5 mg IM every 3 months) 38 received hormone therapy; 27 did not No further details regarding rationale for the comparator. Radiotherapy and hormone ablation delivered at Midwestern and Southwestern Regional Medical Centers of Cancer Treatment Centers of America® No further details were reported regarding tailoring or modification of comparator. No further details were reported regarding compliance with radiotherapy or hormone ablation therapy. |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: clinical tumour response measured by pre-treatment PSA, PSA nadir, and ≥ 24 months post-treatment PSA. Time to reach nadir, and time to last follow-up. <ul style="list-style-type: none"> Tumour progression declared as the time of biochemical failure as judged by a PSA level ≥ 2 ng/ml above the PSA nadir according to the Houston definition. Secondary outcomes: urinary and sexual function assessed by American Urological Association instrument querying urinary and sexual performance. Comparisons were between groups for each outcome but not changes from baseline. Primary outcomes were presented as means and medians for pretreatment PSA, PSA nadir, and post-treatment PSA, with medians only for time to reach nadir and follow-up duration, but no measures of precision (SDs, SEs or 95% CIs). Secondary outcomes were measured as percentages of participants. Timing/timepoints of outcome measurements (e.g. assessments at end of the eight-week intervention period, events occurring during the eight-week intervention period) 6 deaths during the 5 years of follow-up: 1 in the intervention group and 5 in the comparator group. 12 losses during follow-up where patients could not be contacted: 6 each for both groups. Subgroup analyses were not defined a priori: <ul style="list-style-type: none"> Results reported analyses according to whether or not hormone therapy was received and all outcomes were reported. Data were not reported for subgroup analyses according to risk based on pretreatment PSA levels and Gleason scores, only statistical significance. |
| Funding source | <ul style="list-style-type: none"> The study was funded by Cancer Treatment Centers of America® |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: Office of Clinical Research, Cancer Treatment Centers of America, Midwestern Regional Medical Center, US The authors declared there were no potential conflicts of interest. |

D.1.4. Type 2 diabetes mellitus

Table 21: Stier-Jarmer 2021

| Stier-Jarmer 2021 | |
|---------------------------|--|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> Number of participants: 98 Overweight or obese with type 2 diabetes. Mean age 61.5 years, 51% female Setting: Oberstaufen health resort, Bavaria, Germany |
| Study methods | <ul style="list-style-type: none"> RCT, 2 arms Single centre Recruitment and sampling procedures not stated Duration of study: 6 months (treatment for 3 weeks with follow-up) Details of random sequence generation, allocation sequence concealment, and masking for randomised trials, and methods used to prevent and control for confounding, selection biases, and information biases for non-randomised studies not stated Unit of analysis: individual participant Statistical methods: within group and between group comparisons, no further details Method to prevent/address missing data not stated Likelihood of reporting and other biases: 3 participants lost to follow-up, but not stated in abstract if analyses were intention to treat. |
| Enrolment start/end dates | 3 week interventions with follow-up to 6 months |
| Length of follow-up | |
| Intervention | <p>Number of participants 51</p> <ul style="list-style-type: none"> Oberstaufen Schrothkur, a traditional naturopathic treatment shown to lead to metabolic improvement in adults with type 2 diabetes Low calorie diet, daily changes between higher or lower fluid intake, daily alternation in physical activities, and daily application of cold and damp body packs. Conducted in Oberstaufen health resort, Bavaria, Germany <p>No further description of: rationale, theory, or goal of the elements essential to the intervention not stated; procedures used in the intervention; intervention provider; modes of delivering the intervention; timepoints the intervention was delivered, time period, frequency/number of sessions, duration of an intervention session, intensity, dosage; tailoring of the intervention; modifications to intervention; strategies to maintain or improve adherence/fidelity to intervention; or actual adherence or fidelity to the intervention</p> |
| Comparator | <p>Number of participants 47</p> <ul style="list-style-type: none"> Diabetes-friendly holiday, a holiday stay specifically tailored to diabetes No further details were presented regarding the comparator |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: HbA1c at baseline and 6 months Secondary outcomes: body weight, body mass index, blood pressure, levels of cholesterol and triglycerides, well-being (WHO-5), and general health status (EQ-5D and SF-36) |

| Stier-Jarmer 2021 | |
|-----------------------|--|
| | <ul style="list-style-type: none"> No further description of outcomes |
| Funding source | <ul style="list-style-type: none"> Not stated |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations were not stated Authors' financial relationship were not stated Other potential conflicts of interest not stated |

Abbreviations: EQ-5D, European Quality of Life Five Dimensions, SF-36, Short Form 36; WHO-5, World Health Organisation-Five Well-Being Index; y, year

Note: full text was not available, and characteristics were extracted from the study abstract only

Table 22: Bairy 2020

| Bairy 2020 | |
|-------------------------|---|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> 211 patients Patients with T2DM for at least 1 year attending outpatients clinics in endocrinology department of a tertiary medical teaching hospital. 18-06 y old, HbA1c >7%, dependent on oral or parenteral hypoglycaemic agents, and with Zubrod's performance status 0-2 Exclusion criteria: secondary complications of T2DM; history of recent myocardial infarction or transient ischemic attacks, hot water epilepsy, exercise-induced asthma, uncontrolled blood pressure (systolic blood pressure >160 mmHg and diastolic blood pressure >110 mmHg), anaemia (Hb <10g%), hyponatraemia (sodium <136 mg/dl), neutropenia, pancytopenia or thrombocytopenia, major depressive disorders, or psychiatric or neurological illness; participation in regular exercise, yoga, nutrition, or lifestyle modification program in the preceding six months; active infections or fever; have New York Heart Association Class III cardiac failure, or chronic obstructive pulmonary disease resulting in dyspnea or orthopnea. Intervention group: mean age 51 y (SD 8.1 y); mean duration diabetes 10.27 y (SD 6.6 y); 42.2% male; 67.7% have completed at least high school education; baseline HbA1c 9.6% (SD 1.8%), 27.5% had comorbid obesity, 45.1% had comorbid hypertension, 2.9% had comorbid coronary artery disease and 6.9% had comorbid Grade 1 nephropathy. Comparator group: mean age 48.8y (SD 8.1 y); mean duration diabetes 5.83 y (SD 5.7 y); 45.9% male; 42.2% have completed at least high school education; baseline HbA1c 9.0% (SD 1.7%), 33.9% had comorbid obesity, 43.1% had comorbid hypertension; 0% had comorbid coronary artery disease and 2.8% had comorbid Grade 1 nephropathy Setting: Naturopathy Centre, Manthena Satyanarayana Raju Arogyalayam in Vijayawada, India |
| Study methods | <ul style="list-style-type: none"> Prospective longitudinal open-label parallel two-arm cohort study Single centre Recruitment from outpatient clinics in the endocrinology department of a tertiary medical teaching hospital 3-month intervention with follow up to 12 months No methods were reported to prevent and control for confounding, selection biases, and information biases Unit of analysis: individual participant Statistical methods: repeated measures ANOVA with time and group being independent variables. The group-by-time interaction effects was computed using post hoc Bonferroni correction for four timepoints and two group measures. Both within- and between group effects were analysed using intention to treat analysis. |

| Bairy 2020 | |
|---------------------------|--|
| | <ul style="list-style-type: none"> • Changes from the baseline between groups were assessed using independent samples t-test • Missing data: imputed using the mean of the respective group for that assessment interval • Likelihood of reporting and other biases: low |
| Enrolment start/end dates | 12 months (3 months residential naturopathy treatment) |
| Length of follow-up | |
| Intervention | <ul style="list-style-type: none"> • 102 participants • Naturopathy and yoga-based lifestyle intervention, a 3-months residential naturopathy intervention program with diet, yoga, hydriatic treatments, massage, and didactic and interactive lectures on lifestyle modification and T2DM self-management. Patients underwent a structured routine that involved physical activity, a yoga program with asanas, pranayama, meditation and relaxation, calorie restriction, and salt-restricted diet. The diet prescribed was a low glycaemic index, low salt high-fibre plant-based diet, and short intermittent juice fasting with calorie restriction over 3-4 months. Hydriatic treatments involved a structured routine of hydriatic treatments such as hip bath, immersion bath, jets, sprays, douche, and mud and steam bath apart from partial and full-body Swedish massages. • How the intervention might work: raw diets, fasting, massage, yoga, physical exercise, and hot baths are independently known to confer weight reduction and glycaemic control. • The goal of the intervention was weight reduction if overweight, stress reduction, and dietary intervention to manage the glycaemic index. • During the 3 months of residential intervention, patients were supervised by doctors and diabetologists. • Oral antidiabetic medication was monitored and tapered based on blood glucose and HbA1c levels. • No other details were reported regarding frequency, dose, intensity, or duration of intervention sessions or modifications to intervention. • Compliance and adherence were only reported as the number that failed to adhere to diet and physical activity regimen in the intervention group during 3 months of treatment. |
| Comparator | <ul style="list-style-type: none"> • 109 participants • Conventional anti-diabetic treatment as per standard guidelines. Included oral hypoglycaemic agents, parenteral insulin, and other medicines to manage comorbid conditions, and supportive care. • Diabetes self-management program delivered by diabetes educator during participants' hospital visits • Diet and physical activity counselling were delivered by a clinical nutritionist • Dose escalation or tapering were done by a diabetologist based on HbA1c levels, blood glucose, and other biochemical tests. • No further details of frequency, dose, or duration reported. • Adherence or compliance not reported on. |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: HBA1c, measured by HPLC • Secondary outcomes: Fasting and post-prandial blood glucose measured by spectrophotometry; medication score calculated from oral hypoglycaemic agents and parenteral insulin using Diabetes Medical Satisfaction Tool, with higher scores indicating a more demanding regimen. <ul style="list-style-type: none"> ➢ Lipid profile, liver function tests, and renal function tests were conducted but were not identified as study outcomes. • All primary and secondary outcome domains were reported. |

| Bairy 2020 | |
|-----------------------|--|
| | <ul style="list-style-type: none"> Outcomes assessed at baseline, 6 and 12 months Means and standard deviations reported Intervention group: baseline n=102; 3 months n=102; 6 months n=78 (12 failed to adhere to diet and physical activity regimen, 9 lost to follow-up, 3 defaulted on tests and assessments); 12 months n=71 (5 lost to follow-up; 2 defaulted on tests) No subgroup analyses planned |
| Funding source | <ul style="list-style-type: none"> Nil |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: Manthena Satyanarayana Raju Arogyalayam, Guntur, Andhra Pradesh, India; HCG Cancer Centre, Bengaluru, Karnataka, India Authors declare nil financial support and sponsorship Authors declare they have no conflicts of interest |

Abbreviations: HbA1c, glycosylated haemoglobin; HPLC, high performance liquid chromatography

D.1.5. Polycystic ovary syndrome

Table 23: Arentz 2017

| Arentz 2017 | |
|-------------------------|--|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> 122 women, aged 18-44 y with a confirmed medical diagnosis of PCOS, BMI\geq24.5kg/m². Women were excluded if taking oestrogens and/or progestogens to regulate menstrual bleeding or antidepressants including selective serotonin reuptake inhibitors, selective noradrenergic reuptake inhibitors, tetracyclic antidepressants, noradrenergic and selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and melatonergic antidepressants. Baseline characteristics of intervention group: mean age 29.2 y (SD 5.6 y), mean weight 93.2 kg (SD 18.9 kg), mean waist to hip ratio 0.83 (SD 0.07), 66.7% Caucasian, 53/60 had tertiary qualifications; mean menstrual cycle length 106.0 days (SD 123.0 days) Baseline characteristics of comparator group: mean age 28.9 y (SD 5.6 y), mean weight 97.3 kg (SD 21.3 kg), mean waist to hip ratio 0.85 (SD 0.09), 69.4% Caucasian, 55/62 had tertiary qualifications; mean menstrual cycle length 109.5 days (SD 148.0 days) Setting: not clear – participants attended lifestyle coaches and a qualified naturopath Recruitment in New South Wales, Queensland, and Victoria, Australia |
| Study methods | <ul style="list-style-type: none"> ANZCTR 126 12000 122 853 Parallel RCT Multicentre, but not stated how many sites. Australia. Recruitment via Facebook, advertising and referrals from health providers and gynaecologists, and community settings including participants' homes and workplaces, gymnasiums, cafes, and parks The intervention ran for 3 months The randomized sequence was computer generated in permuted blocks of 50 by an external, independent organization. 3 levels of stratification by BMI: 24.5-29.9, 30-33, and >33 Unit of analysis: individual participant Intention to treat analyses |

| | |
|---------------------------|--|
| | <ul style="list-style-type: none"> Analysis of covariance to investigate differences between intervention and comparator groups at 3 months after controlling for baseline levels. Partial eta squared to estimate the effect size Chi-squared tests and relative risks to analyse differences between groups for secondary binary outcomes (pregnancy, miscarriage and live birth rates) Partial eta squared to investigate the effect of loss of body weight on primary outcome after controlling for baseline menstrual cycle variation and study group Results presented as adjusted MDs between groups at endpoint with 95% CI Missing endpoint data imputed with the last observation carried forward The likelihood of reporting and other biases appears low |
| Enrolment start/end dates | 3 months |
| Length of follow-up | |
| Intervention | <ul style="list-style-type: none"> 60 participants, lifestyle intervention, and herbal medicine Lifestyle intervention: evidence-based guidelines for the management of PCOS delivered by 2 trained lifestyle coaches (nutritionist and exercise physiologist), recommending a calorie-controlled diet within a healthy food choice setting and exercise for at least 150 min per week including 90min of aerobic activity (60-90% of maximum heart rate). Participants were contacted fortnightly, had access to the coaches throughout the trial, were invited to attend supervised exercise sessions, and helped to construct their personalised lifestyle plans. In the event of pregnancy, participants were advised to continue the lifestyle intervention without increasing the intensity of exercise until consultation with their obstetric carer. Two 30 min consultations with a qualified naturopath at trial weeks 4 and 8, where herbal tablets were administered. Two herbal tablets: <ul style="list-style-type: none"> Tablet 1: 750 mg each of <i>Glycyrrhiza glabra</i>, <i>Paeonia lactiflora</i>, <i>Cinnamomum verum</i> and <i>Hypericum perforatum</i>. Dose: 3 tablets/day. In the event of pregnancy, participants were advised to cease taking herbal medicine tablets Tablet 2: 13,500mg <i>Tribulus terrestris</i> extract. Dose: 3 tablets/day during follicular phase only (for 10 consecutive days starting on menstrual cycle day 5 for oligomenorrhoeic women and within 1 week of trial commencement for women with amenorrhoea) How the herbs might work: <ul style="list-style-type: none"> <i>G. glabra</i>: reduce androgens; digestive carminative properties; improve hepatic metabolism; anti-inflammatory actions; <i>P. lactiflora</i>: reduce androgens; digestive carminative properties; improve mood; improve cognition <i>C. verum</i>: improve insulin sensitivity; improve menstrual regularity <i>H. perforatum</i>: reduce depression; improve hepatic metabolism; anti-inflammatory actions; improve mood; improve cognition <i>T. terrestris</i>: potential mechanism not stated. Compliance with herbal tablets was assessed by the return of empty bottles and tablet count. Considered high, as all but 2 participants returned empty bottles Compliance to lifestyle intervention was assessed fortnightly and by interview at week 12, by self-reported exercise intensity (mild, moderate, or vigorous), number of minutes of exercise per week, the average number of self-reported servings of vegetables and fruits per day, and the number of high energy nutrient sparse meals per week. Compliance was not reported but the proportion of participants reporting improved lifestyle practices was presented. |
| Comparator | <ul style="list-style-type: none"> 62 participants, lifestyle intervention only Lifestyle intervention: evidence-based guidelines for the management of PCOS delivered by 2 trained lifestyle coaches (nutritionist and exercise physiologist), |

| | |
|---------|---|
| | <p>recommending a calorie-controlled diet within a healthy food choice setting and exercise for at least 150 min per week including 90min of aerobic activity (60-90% of maximum heart rate). Participants were contacted fortnightly, had access to the coaches throughout the trial, were invited to attend supervised exercise sessions, and helped to construct their personalised lifestyle plans. In the event of pregnancy, participants were advised to continue the lifestyle intervention without increasing the intensity of exercise until consultation with their obstetric carer.</p> <ul style="list-style-type: none"> Compliance to lifestyle intervention was assessed fortnightly and by interview at week 12, by self-reported exercise intensity (mild, moderate or vigorous), number of minutes of exercise per week, the average number of self-reported servings of vegetables and fruits per day, and number of high energy nutrient sparse meals per week. Compliance was not reported but the proportion of participants reporting improved lifestyle practices was presented. |
| Outcome | <ul style="list-style-type: none"> Assessments were conducted at the end of the 3-month intervention. Primary outcomes: oligomenorrhoea was defined as irregular menstruation or 35-179 days between menstrual periods measured as the mean number of days in the menstrual cycle. Assessed by self-report using printed menstrual charts or digital menstrual cycle tracking services. Secondary outcomes: <ul style="list-style-type: none"> serum concentration of reproductive hormones oestradiol, FSH, luteinizing hormone (LH), testosterone, sex hormone-binding globulin (SHBG) and free androgen index (FAI) were assessed by registered pathology companies. Blood was collected between 2 and 10 days of the menstrual cycle (non-amenorrhoeic) or within 1 week of trial commencement (amenorrhoeic) glucose and insulin sensitivity by insulin and glucose serum concentration following 8 h fasting with Quantitative Insulin Sensitivity Check Index anthropometric characteristics measured by BMI, waist and hip circumference, and waist to hip ratio HRQOL was assessed using Polycystic Ovary Syndrome Questionnaire. This study scored so that lower scores indicated better quality of life (not the conventional way of scoring this questionnaire). depression, anxiety, and stress assessed by DASS 21, with lower scores indicating a more favourable status. pregnancy and birth outcomes assessed by serum beta human chorionic gonadotropin following detection in urine, ultrasound reports, and post-natal reports provided by participants safety of herbal medicines assessed as blood pressure increments at weeks 4 and 8 and participants self-reporting adverse experiences, reactions, or events. Oligomenorrhoea, anthropometric characteristics, reproductive hormones, fasting glucose, fasting insulin, Quantitative Insulin Sensitivity Check Index, Polycystic Ovary Syndrome Questionnaire scores, DASS 21 scores, and blood pressure (as adverse events) presented as adjusted MDs between groups at the 3 months endpoint with 95% CI. Changes from baseline not assessed. For secondary binary outcomes (pregnancy, miscarriage, and live birth rates), percentages or proportions were presented. All outcome domains were reported. Reproductive hormone outcomes were available for 34 intervention and 37 comparator women. Insulin and glucose sensitivity only available for 26 intervention and 25 comparator women Intervention group: 8 lost to follow-up. Reasons were changes in personal circumstances (n=4), lost contact (n=2), and adverse effects (n=2). Comparator group: 6 lost to follow up. Reasons were changes in personal circumstances (n=1), lost contact (n=2), injury (n=2) and apprehension about exercise program (n=1) Two subgroups identified a priori: (1) women who participated in blood tests (n=71) and (2) women who self-identified at baseline that they wanted to conceive (n=70). |

| Arentz 2017 | |
|-----------------------|--|
| Funding source | <ul style="list-style-type: none"> This research project was funded by Western Sydney University as doctorate candidate project funding for S. A. with support from an Australian Postgraduate Award. Higher Degree Research training funds were used to fund analytical services of a retail pathology company. The herbal tablets were provided as an unconditional gift from MediHerb (Integria Healthcare (Australia) Pty Ltd) who also provided S. A. with a stipend between February and August 2014. The trial was conducted entirely independently of the company who had no role in the design, administration, data analyses, or interpretation of results. |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: National Institute of Complementary Medicine, Western Sydney University, Penrith, NSW, Australia; School of Women's and Children's Health, Women's Health Institute, Royal Hospital for Women, University of New South Wales, Randwick, NSW, Australia; School of Science and Health, Western Sydney University, Penrith, NSW, Australia There are no commercial affiliations between any of the authors and Integria Healthcare (Australia). Authors S. A. and J. A. are also engaged in clinical practice. |

Abbreviations: BMI, body mass index; DASS 21, Depression, Anxiety and Stress Short Form; HRQOL, health related quality of life; PCOS, polycystic ovarian syndrome

Table 24: Ratnakumari 2018

| Ratnakumari 2018 | |
|-------------------------|---|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> 50 female participants with PCOS 18-35 y old, who satisfied the three Rotterdam criteria: (1) oligo/amenorrhoea (absence of menstruation for ≥ 45 days and/or < 8 menses/y); (2) clinical hyperandrogenism (modified Ferriman and Gallwey score ≥ 6) or biochemical hyperandrogenism (serum testosterone level > 82 ng/dl) in the absence of other causes of hyperandrogenism; and (3) polycystic ovaries (presence of > 10 cysts, 2-8 mm diameter, usually combined with an increased ovarian volume of > 10 cm³ and an echo-dense stroma in the pelvic ultrasound scan. Exclusion criteria: use of oral contraceptives and intrauterine contraceptive devices or hormonal replacement treatments or insulin-sensitising agents within the previous 6 weeks; other metabolic disorders. Intervention group: mean age 23.77 y (SD 5.33); mean BMI 28.29 kg/m² (SD 5.25 kg/m²); mean waist-hip ratio 0.88 (SD 0.05) Comparator group: mean age 25.05 (SD 4.83); mean BMI 25.26 kg/m² (SD 6.61 kg/m²); mean waist-hip ratio 0.89 (SD 0.06) Setting: Government Yoga and Naturopathy Medical College and Hospital. Chennai, Tamil Nadu, India |
| Study methods | <ul style="list-style-type: none"> Single blinded prospective pre-post clinical trial Single centre Recruitment from patients of the Government Yoga and Naturopathy Medical College and Hospital. 12-week duration 54 patients satisfied the eligibility criteria, 50 were selected by convenience sampling. Unit of analysis: individual participant. Statistical methods: Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test for normal distribution. Mann-Whitney test was used to assess the change difference between intervention and comparator groups. Per protocol analyses (22 participants from each group). |

| Ratnakumari 2018 | |
|---------------------------|---|
| | <ul style="list-style-type: none"> • Method to prevent/address missing data: none stated. • Likelihood of reporting and other biases: high. |
| Enrolment start/end dates | 12 weeks |
| Length of follow-up | |
| Intervention | <ul style="list-style-type: none"> • 25 participants • Yoga and naturopathy <ul style="list-style-type: none"> ➢ Naturopathy included hydrotherapy, mud therapy, manipulative therapy, fasting, and natural diet therapy for 6 days every week for 12 weeks, excluding days of menstruation. ➢ Yoga comprised asanas (yoga postures), pranayama, relaxation techniques, and kriyas. Yoga practice was given for 20 min for 6 days, every week through the study period excluding days of menstruation. • How naturopathy might work: <ul style="list-style-type: none"> ➢ Hydrotherapy: cold hip bath for 15-20 min has pronounced effects on the pelvic circulation and tends to produce hyperemia of the pelvic viscera. The hot foot bath (10 min) dilates blood vessels in the feet and extends to the upper parts of the limbs and the vessels of the pelvic viscera, increasing the blood supply to the uterus and ovaries and restoring function to menstruation when suspended. The cold enema encourages the action of the liver and kidneys to cleanse the alimentary canal. ➢ Mud pack therapy: it is thought that absorption of peat substances occurs through hair follicles and apocrine glands. Mud pack therapy decreases the proinflammation factors IL-1, TNF-alpha, and radical-mediated peroxidations, nitric oxide, and myeloperoxidase. ➢ Massage: soft tissue manipulations decrease inappropriately elevated levels of cortisol and raise low levels of dopamine and serotonin. ➢ Juice fasting: diluted juices provide modest amounts of calories and stabilise blood glucose levels. ➢ Diet therapy: proposed specific dietary approaches in PCOS include high protein, low carbohydrate, and low glycaemic index/glycaemic load diets. This would reduce insulin secretion; insulin can promote the occurrence of PCOS. • How yoga might work: mainly improves reproductive functions by reducing stress and balancing the neurohormonal profile; it is a form of holistic mind-body medicine that is effective in reducing anxiety symptoms in PCOS patients. Yoga also reduces urinary excretion of catecholamines and aldosterone, decreases serum testosterone and LH levels, and increases cortisol excretion. It improves insulin secretion and sensitivity, blood pressure, lipid levels, oxidative stress, coagulation profile, and immune status. • Intervention provider and modes of delivery not stated. • The location was not stated, but it is assumed to be the Government Yoga and Naturopathy Medical College and Hospital. • No report of tailoring or modifications to the intervention. • 89% attendance, including absenteeism during menstruation. |
| Comparator | <ul style="list-style-type: none"> • 25 participants • Wait-list control • No further details regarding rationale or any treatments patients received while on the wait-list. |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: ovarian morphology at baseline and end of 12 weeks. Measurement was conducted by transabdominal 3D ultrasonogram of the pelvis and carried out by a certified postgraduate medical radiologist. • For both right and left ovaries, median and interquartile ranges for change from baseline to post measurement were reported for ovarian volume, ovarian size |

Ratnakumari 2018

| | |
|-----------------------|--|
| | <p>(length, width, thickness in cm); follicles antrum; largest follicle size (length, width in cm), and a 'total assessment'</p> <ul style="list-style-type: none"> • Secondary outcomes: body weight, BMI, chest circumference, waist circumference, hip circumference, mid-arm circumference, waist-hip ratio, and menstrual frequency at weeks 4, 8, and 12. Anthropometric measurements were recorded by trained internees of the Institute. It is not stated how the menstrual frequency was assessed. • For weight (kg), BMI (kg/m²), chest circumference (cm), waist circumference (cm), hip circumference (cm), mid-arm circumference (cm), and waist-hip ratio, changes from baseline to post measurement were reported as median and interquartile ranges. • Menstrual frequency was reported as the number of days between the last menstrual period and the first cycle, between the first cycle and second cycle, and between the second and third cycles. Reported as the median number of days with interquartile ranges. • In the intervention group, 3 participants dropped out (1 became pregnant, 1 could not continue with the intervention, 1 died in a road traffic accident) In the control group, 3 participants dropped out (2 relocated and could not participate in post-assessment scans and 1 withdrew). It was not stated at which assessment point the attrition occurred. • No subgroup analyses |
| Funding source | <ul style="list-style-type: none"> • This project was financially supported in part by the State Non-communicable Disease Cell, Tamil Nadu Health Systems Project, Chennai, Tamil Nadu, India. |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: Department of Naturopathy, Government Yoga and Naturopathy Medical College, Arumbakkam, Chennai, India; Department of Biostatistics, Christian Medical College, Vellore, Tamil Nadu, India • The authors state there are no conflicts of interest. |

Abbreviations: BMI, body mass index; IL-1, interleukin-1; LH, luteinising hormone; PCOS, polycystic ovarian syndrome

D.1.6. Overweight and obesity

Table 25: Beer 2014

| Beer 2014 | |
|-------------------------|--|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> • 275 participants randomised (200 intervention - fasting therapy and 75 weight reduction diet); 169 after exclusions (122 intervention, 47 weight reduction). • Patients aged 20 to 70 years who had undergone fasting therapy or a treatment with a weight reduction diet as part of the inpatient naturopathic complex treatment at the Blankenstein Clinic, Hattingen, from 1999 to 2002 and were overweight (BMI ≥ 25kg/m²) or obese (BMI ≥ 30kg/m²) at the time of treatment. • Exclusion criteria: patients who had at the time of inpatient therapy one of the following diagnoses: hepatic or renal failure, decompensated hyper- or hypothyroidism, diabetes mellitus type 1, malignant tumors, Crohn's disease or ulcerative colitis, dementia, eating disorders such as anorexia nervosa, bulimia, or binge eating disorder, drug addiction, or serious psychiatric disorders. Also excluded were pregnant or breastfeeding women and patients taking medications for overweight and obesity and patients after bariatric therapy. • Intervention group: 84% female; 31% completed at least secondary school; mean BMI 30.8 kg/m² (SD 4.6 kg/m²) at time of interview. Mean age on admission 55.7 y (SD 7.4 y) • Comparator group: 77% female; 26% completed at least secondary school; mean BMI 31.6 kg/m² (SD 4.7 kg/m²) at time of interview. The mean age on admission 54.5 y (SD 10.9 y). |

| | |
|---------------------------|--|
| | <ul style="list-style-type: none"> Setting: community (telephone interviews) Germany |
| Study methods | <ul style="list-style-type: none"> Comparative retrospective follow-up study Single centre Recruitment was done by record search to identify patients who had received weight reduction or fasting diets. Of the patients who met eligibility criteria, SPSS statistical software was used to select a random sample of 200 patients who had received fasting treatment; all 75 patients who received weight reduction diets were selected. Duration of study/dates of study (see also participant enrolment start/end dates and length of follow-up below) Unit of analysis: individual patients Statistical methods: <ul style="list-style-type: none"> parametric data: Student's <i>t</i>-test and the Mann-Whitney <i>U</i>-test. nominal and ordinal data: Pearson's chi-square test and Fisher's exact test descriptive ANCOVAs were performed for BMI and weight with the posttreatment, respectively, actual variable as the dependent variable, the group as fixed factors, and pretreatment score and other meaningful and influencing variables as covariates. Method to prevent/address missing data: not stated Likelihood of reporting and other biases: high, especially selection bias, assessor bias, and lack of standardised tools to measure outcomes. |
| Enrolment start/end dates | Telephone interviews were conducted on average 6.8 y after inpatient therapy (SD 1.1 y) |
| Length of follow-up | The mean inpatient treatment duration was 19.9 days (SD 1.9 days) for all study participants. |
| Intervention ^b | <ul style="list-style-type: none"> 122 participants Modified Buchinger fasting therapy: vegetable stocks and vegetable juices, tea, and water, but no fruit juices or solid foods, combined with regular defecation and exercise alternating with rest and was followed by a gradual return to solid food over 3 days. <ul style="list-style-type: none"> Mean duration of fasting therapy: 10.3 days (SD 1.8 days) Subsequent therapy: 87% received a weight reduction diet and 13% balanced basic diet) Weight reduction diet: diet with reduced caloric feed charge, well balanced, low fat and modified fat whole food basic diet with a daily energetic deficit of 500-800 kcal Balanced basic diet was not defined Rationale: fasting therapy may lead to long-term lifestyle modification in obese patients, sustained weight reduction, sustained changed diet, and lasting increase in physical activity and quality of life. Carried out in the context of inpatient naturopathic complex treatment; provided by Blankenstein Clinic, Hattingen, Germany. Mean duration of inpatient naturopathic complex treatment was 19.9 days (SD 1.9 days) for both intervention and comparator groups No other details were reported regarding frequency, duration, or intensity of treatment or the mode of delivery No details were reported regarding tailoring or modification of intervention Compliance and adherence not reported on |
| Comparator | <ul style="list-style-type: none"> 47 participants |

| | |
|-----------------------|---|
| | <ul style="list-style-type: none"> • Weight reduction diet: diet with reduced caloric feed charge, well balanced, low fat and modified fat whole food basic diet with a daily energetic deficit of 500-800 kcal • Rationale: how a weight reduction diet may work is not stated. • Carried out in the context of inpatient naturopathic complex treatment; provided by Blankenstein Clinic, Hattingen, Germany. • Mean duration of inpatient naturopathic complex treatment was 19.9 days (SD 1.9 days) for both intervention and comparator groups • No other details were reported regarding frequency, duration or intensity of treatment or the mode of delivery • No details were reported regarding tailoring or modification of intervention • Compliance and adherence not reported on |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: proportion of patients who, after fasting therapy or weight reduction diet, achieved a sustained weight loss of at least 5% of their initial weight. • Secondary outcomes: <ul style="list-style-type: none"> ➢ group differences regarding the ongoing absolute weight reduction compared to baseline body weight, the weight loss of more than 2.25 kg as a further criterion of success ➢ the weight development in post-stationary continued weight reduction and/or prolonged weight maintenance, ➢ the persistent change in diet taking account of the rules of nutrition therapy, ➢ the observing of specific inpatient trained nutritional aspects and the relationship between the number of observed aspects of nutrition and weight loss, ➢ the ongoing increase in physical activity in the form of basic, leisure and sports activities, ➢ post-hospital quality of life concerning body weight • All outcomes were measured through medical records and patient self-report through telephone interviews. No report of any particular tools or methods used to undertake assessments. • Means and standard deviations were presented. • Outcomes at admission, discharge and interview assessed. • Outcomes reported on: weight reduction; the proportion who reduced weight by $\geq 5\%$ between admission and discharge; weight at the time of interview and difference to admission weight; dietary changes 'up to this day'; the proportion who increased their leisure time activity; the proportion who reported quality of life improvements; descriptive ANCOVA for BMI. <ul style="list-style-type: none"> ➢ Overall, all outcomes stated in the introduction a priori were reported on. |
| Funding source | <ul style="list-style-type: none"> • Not stated |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: Department of Naturopathy, Blankenstein Hospital, Im Vogelsang 5-11, 45527 Hattingen, Germany; Department of Neurology, St. Johannes-Hospital, Springufer 7, 59755 Arnsberg, Germany; Clinic for Children and Adolescents, Prignitz Hospital, Dobberzinerstraße 112, 19348 Perleberg, Germany • Authors' financial relationships: not stated • The authors declare they have no conflicts of interest |

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index

D.1.7. Anxiety

Table 26: Bernhardt 2009

| Bernhardt 2009 | |
|---------------------------|---|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> 81 participants Employees of Canada Post who are members of the Canadian Union of Postal Workers, with moderate to severe anxiety for longer than 6 weeks. Screening for anxiety were undertaken by BAI. Exclusion criteria: unable to comply with study protocol; mild or no anxiety at the time of assessment (BAI score <10); concomitant mild to severe depression (BDI score <10); currently taking prescription medication that required daily doses of benzodiazepine class drugs; previously identified allergies or sensitivity to withanolides or <i>Withania somnifera</i>; abused substances such as alcohol or illegal drugs; severe concurrent illness; pregnant or breastfeeding. Intervention group: 26 female/15 male; mean age 52.02 y (SD 10.95 y); mean BMI 28.25 y (SD 3.70 y); 6 people using anxiety medication; mean BAI score 23.54 (SD 10.13); mean caffeine doses/wk 11.78^a Comparator group: 25 female/15 male; mean age 51.28 y (SD 8.18 y); mean BMI 29.02 (SD 5.08); 7 people using anxiety medications; mean BAI score 23.45 (SD 11.82); mean caffeine doses/wk 15.91^a Setting: workplace of the Canada Post Corporation Ontario, Canada |
| Study methods | <ul style="list-style-type: none"> ISRCTN78958974 Parallel RCT. Investigators and participants were blinded during randomisation and allocation, up to the point of treatment. 2 centres of the Canada Post Corporation, Ontario, Canada Recruitment through poster advertising; interested employees received an information package. The study ran from March to July 2006 Randomised with age and gender-matched stratification by an independent third party using a computer-generated randomisation sequence. Assignment to one of the two practitioners based on chronology and by alternating back and forth between practitioners at the time of enrolment. Unit of analysis: individual participant Statistical methods: paired t-tests to compare outcomes at week 12 to baseline within each group; independent t-tests to compare the difference of treatment effect between intervention and comparator groups. The statistician conducted analyses under blinded conditions. Intention to treat analysis based on participants available in week 8: 36 intervention and 39 comparator participants. Method to prevent/address missing data: if week 12 data was missing, week 8 values were used Likelihood of reporting and other biases: moderate, based on some intermediate outcome scores at weeks 4 and 8 not reported. Also, intention to treat analyses based on participants available in week 8, not at baseline: potential for selection bias. |
| Enrolment start/end dates | The study was conducted from March to July 2006. 12-week treatments |
| Length of follow-up | |
| Intervention | <ul style="list-style-type: none"> 41 participants Naturopathy care: dietary counselling, deep breathing relaxation techniques, standard multi-vitamin (dose not stated), and herbal medicine ashwagandha (<i>Withania somnifera</i>) (300mg twice/day) |

| | |
|------------|--|
| | <ul style="list-style-type: none"> ➤ <i>W. somnifera</i> standardised to 1.5% withanolides, prepared from the root • Clinical trials and animal research support the use of <i>W. somnifera</i> for anxiety, inflammation, Parkinson's disease, cognitive and neurological disorders, and as a useful adjunct for patients undergoing radiation and chemotherapy. Most studies on <i>W. somnifera</i>'s anxiolytic effects are based on animal studies. Withanolides, as hormone precursors, may be convertible into human physiologic hormones. <i>W. somnifera</i> may facilitate the ability to withstand stressors. <i>Withania</i> extract may exert anxiolytic effects through extracellular calcium antagonism in the central nervous system, counteracting the excitation in neurons. • 12-week duration • Delivered by a licensed naturopathic doctor with more than 4 years experience • Treatments delivered as 30 min sessions, once per week: <ul style="list-style-type: none"> ➤ Data on patients' lifestyle and diet were obtained; ➤ Diaphragmatic deep breathing exercises were performed; ➤ Lifestyle and nutritional counselling specific to the individual patient, with special emphasis on reducing intake of stimulants, eating small meals at regular intervals, and increasing consumption of fruit, fish, vegetables, nuts, and whole grains; ➤ Regular exercise encouraged ➤ Supplements provided • Location of intervention not stated. • The treatment protocol was 'generalised' and designed by a group of experienced naturopathic doctors for the trial. Treatments involving individualised recommendations were made at the discretion of the investigator providing study care. • Compliance was assessed through pill count in 30-day increments for the duration of the trial. The mean total missed supplements was 6.83 pills (94.3%) throughout 12 weeks of the trial. |
| Comparator | <ul style="list-style-type: none"> • 40 participants • Psychotherapy, matched deep breathing relaxation techniques, and placebo • No rationale was stated for how the comparator treatment might work. • Delivered by a practitioner with 5 years of training and experience in cognitive behavioural therapy. • Treatments: <ul style="list-style-type: none"> ➤ Psychotherapy consisting of patient-directed counselling and cognitive behavioural therapy for 30 min per week for 12 weeks. Participants received cognitive restructuring exercises for the symptoms of anxiety. ➤ Matched placebo pills of inert fibre (2 pills twice daily) ➤ Education on the importance of maintaining a healthy diet, reducing stimulants ➤ Participants were taught a deep breathing exercise at the start of the trial. ➤ To provide effective control measures, participants were asked about their dietary habits and stimulant use throughout the trial with no continued dietary or lifestyle counselling. Thus, participants were made aware of the importance of these issues without ongoing advice. • Treatments involving individualized recommendations were made at the discretion of the investigator providing study care. • Location not stated • Compliance was assessed through pill count in 30-day increments for the duration of the trial. The mean total missed supplements was 6.43 pills (94.6%) through the 12 weeks. |

| | |
|-----------------------|--|
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: Anxiety measured by BAI. Scores range from 0 to 63, with higher scores indicating greater anxiety. • Secondary outcomes: <ul style="list-style-type: none"> ➢ HRQOL measured by SF-36, which has 36 items in 8 domains and 2 summary scores Physical Function and Mental Health. Higher scores indicate better HRQOL; ➢ Physical and mental aspects of fatigue measured by FSI. 21 items each with 7 response options. Higher scores indicate higher levels of fatigue. ➢ Patient-centred outcomes measured by MY-MOP. Patients choose 2 personally relevant symptoms of greatest importance to their individual health and rate these on a 7-point VAS. Higher scores indicate a lower satisfaction level with health. • Assessments were conducted at baseline, 4, 8, and 12 weeks. • Additional outcomes were measured using 7-point VAS questions at 4, 8, and 12 weeks, with higher scores indicating greater positive subjective impressions (no baseline measure and week 4 was considered the baseline for analyses): <ul style="list-style-type: none"> ➢ Compliance with the treatment protocol; ➢ Benefit from the treatment; ➢ How well the study treatments met their expectations for treating their anxiety; ➢ Interest in pursuing treatments; and ability to cope with stress since starting study treatments. • Primary and secondary outcome data were presented, but 4 and 8-week data were not reported for SF-36 or FSI. 4 and 8-week data for BAI and MY-MOP were reported graphically. • For each group, changes from baseline to 12 weeks were presented for primary and secondary outcomes. Mean scores with SDs presented for each outcome at baseline and 12 weeks. Change at 12 weeks from baseline and difference between intervention and comparator groups in their change between baseline and 12 weeks were reported as means with 95% CI. • 87 participants randomised with a total of 17 patients withdrawing (8 from intervention and 9 from comparator groups). 6 dropped out by week 4, leaving 41 intervention and 40 comparator participants. At week 8, there were 36 intervention and 39 comparator participants. At week 12 there were 33 intervention and 31 comparator participants. Reasons for attrition: <ul style="list-style-type: none"> ➢ 6 lost on follow-up with no discernible reason given; ➢ 2 from the comparator group withdrew on advice from their medical doctor ➢ 1 withdrew due to a positive pregnancy test • No subgroup analyses were planned. |
| Funding source | <ul style="list-style-type: none"> • Swiss Herbals Inc. supplied study products free of charge. • Funded by National Joint Benefits Project of the Canada Post Corporation and Canadian Union of Postal Workers. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: Department of Research and Clinical Epidemiology, The Canadian College of Naturopathic Medicine, Toronto, Canada; Department of Social and Administrative Pharmacy, University of Toronto, Toronto, Canada; Department of Clinical Pharmacology and Toxicology, University of Toronto, Toronto, Canada; Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Canada; Institute of Medical Sciences, University of Toronto, Toronto, Canada • The authors have declared that no competing interests exist. |

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BMI, body mass index kg/m²; FSI, Fatigue Symptom Inventory; HRQOL, health-related quality of life; MY-MOP, Measure Yourself Medical Outcomes Profile; SF-36, Short Form 36; VAS, visual analogue scale; y, year

a 1.0 caffeine dose = 7 oz coffee, 1 serving cola, or 2 servings of tea

D.1.8. Multiple sclerosis

Table 27: Shinto 2008

| Shinto 2008 | |
|---------------------------|---|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> • 45 participants with MS defined by Poser criteria, relapsing-remitting course of MS, and EDSS≤6.0 indicating the ability to ambulate 100 m with mild-moderate neurologic impairment. • Exclusion criteria: if the participant had taken corticosteroids or had an MS relapse within 30 days of enrolment; a serious medical problem (e.g. cancer, uncontrolled diabetes mellitus, congestive heart failure, severe psychiatric disorder); pregnancy; recent visits to a CAM practitioner. • Mean age 43.5y (SD 9.2 y); 87% female; 96% white ethnicity; 47.8% with a college degree or greater; mean duration of MS 10.0 y (SD 7.6 y); mean number of relapses in the past 2 years 1.2 (SD 1.2); 84% had received disease-modifying therapy. • Setting: not stated • Portland, Oregon, US |
| Study methods | <ul style="list-style-type: none"> • 3-arm parallel RCT; neurologists and research assistants performing end of study assessments blinded • Single or multicentre study; if multicentre, number of recruiting centres • Recruitment from the general public, MS Society Oregon Chapter Newsletter, and the MS Center of Oregon at OHSU • 6 months trial • Randomisation method not stated. • Unit of analysis: individual participant • Statistical methods: ANOVA and chi-squared analyses assessed differences between groups at baseline. ANOVA was used to evaluate differences between groups in change from baseline for all outcomes. Tukey's highly significant difference was used to determine differences between any two groups. • Method to prevent/address missing data: not stated. • Likelihood of reporting and other biases: moderate as blinding not possible for participants. |
| Enrolment start/end dates | 6 months |
| Length of follow-up | |
| Intervention | <ul style="list-style-type: none"> • 15 participants • Naturopathic treatment plus usual care <ul style="list-style-type: none"> ➢ 8 visits with the naturopath following baseline assessments ➢ Daily supplementary with multivitamin/mineral without iron; vitamin C; vitamin E; fish oil; alpha-lipoic acid ➢ Intramuscular vitamin B12 once per week ➢ 4 diet levels, selected by naturopath on 2nd visit, on basis of 4-day diet recall: <ul style="list-style-type: none"> ▪ Level I limits trans fatty acids and decreases intake of artificial sweeteners, coffee, alcohol, and cigarettes, and increases intake of water to 6-8 cups/day ▪ Level II includes Level I and reduces intake of red meat to 2x4-6oz servings/ week and increases fresh fruit and vegetables to ≥6.5 cup servings/day |

| | |
|----------------|--|
| | <ul style="list-style-type: none"> ▪ Level III includes Level II plus no refined sugar, fried foods, processed/packaged foods, coffee or alcohol ▪ Level IV is a hypoallergenic diet (Brennamen's food elimination and challenge) ➢ Naturopath counselled participants at each subsequent visit and instructed them to follow chosen diet level guidelines. • Hypothesised that MS participants receiving naturopathic treatments plus conventional care would have improved QOL compared to those receiving comparator treatments. • The location where the intervention was delivered was not stated. • Tailoring and modification of intervention not reported on. • 4-day diet recall completed at baseline before randomisation, before each naturopathic study visit, and at the end of the study at 6 months. This allowed the naturopath and participant to track diet compliance. Compliance for oral supplements and intramuscular vitamin B12 was reported, but the method of assessment was not stated. |
| Comparator | <ul style="list-style-type: none"> • 15 participants usual care only: continued with standard medical care for 6 months. No information regarding duration, frequency, dosage or intensity of treatment. • 15 participants MS-focused educational visits plus usual care. In addition to usual care, participants received 8 visits with a nurse that specialised in MS care: <ul style="list-style-type: none"> ➢ At each visit, participants received an educational pamphlet published by the National MS Society, on 'Fatigue', 'Mood', 'Cognitive Problems', 'Bowel and Bladder Problems', 'Stress', 'Exercise', 'Nutrition', and 'Vitamins, Minerals, and Herbs'. ➢ The nurse instructed participants at each session that the focus was on the information contained in the pamphlets. If the participant had questions about other aspects of their care, the nurse instructed them to contact their physicians for answers. • For both arms, modifications or tailoring of the treatments were not reported. • Compliance and adherence not reported on. |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: QOL measured by SF-36 (higher scores indicate better QOL) and MSQLI (higher scores indicate poorer QOL). • Secondary outcomes: fatigue measured by Multidimensional Fatigue Inventory (higher scores indicate greater fatigue) and the Modified Fatigue Impact Scale of the MSQLI (higher scores indicate greater fatigue); depression measured by BDI; cognitive impairment measured by PASAT 3 (from MSFC, with higher scores indicating favourable status); neurological impairment measured by EDSS (higher scores indicate greater disability) and MSFC (calculated using z scores where +1 indicates 1 SD better than reference population). • Diet assessed by 4-day diet recall • Safety measured by a comprehensive metabolic panel, complete blood count with differential and adverse event reports. • All outcome domains were reported on; except for diet recall which was only assessed and reported on in the intervention group. • Outcomes were reported as mean changes at 6 months from baseline for each group, with SD. • Measurements at baseline and 6 months. • All participants completed the study and there were no withdrawals. • No subgroup analyses. |
| Funding source | <ul style="list-style-type: none"> • Funded by National Institutes of Health Grant P50 AT00066-01 and the Nancy Davis Center Without Walls. |

| Shinto 2008 | |
|-----------------------|--|
| | <ul style="list-style-type: none"> Pure Encapsulations provided oral supplements and Apothecure provided injectable vitamin B12 |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: Department of Neurology, Oregon Health & Science University, Portland, OR; Helfgott Research Institute, National College of Natural Medicine, Portland, OR; Departments of Medical Informatics and Clinical Epidemiology; and Neurology, Oregon Health & Science University, Portland, OR. No other conflicts of interest were declared. |

Abbreviations: ANOVA, analysis of variance; BDI, Beck Depression Inventory; CAM, complementary and alternative medicine; EDSS; Expanded Disability Status Score; MS, multiple sclerosis; MSFC, Multiple Sclerosis Functional Composite; MSQLI, Multiple Sclerosis Quality of Life Inventory; OHSU, Oregon Health & Science University; PASAT-3, Paced Auditory Serial Addition Test 3; QOL, quality of life; SF-36; Short Form 36; y, year

D.1.9. Cardiovascular disease

Table 28: Braun 2014

| Braun 2014 | |
|-------------------------|---|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> Number of participants: 922 Consecutive elective cardiothoracic surgical patients who attended preadmission clinics between September 2008 and August 2011. Inclusion criteria: elective surgery, able to give informed consent, and not allergic to any ingredients in the metabolic supplements. No exclusion criteria were stated. Intervention group: <ul style="list-style-type: none"> CABG: mean age 67 y (SD 10.5 y); 84% male; 90% with hypercholesterolemia; 37% with previous MI; 83% with HT; median NYHA class 1 (IQR 1-2); 30% with diabetes; 67% with smoking history; 9% with heart failure; 11% with left main disease; 11% used clopidogrel; 83% used aspirin; 62% had CAD history. Valve: mean age 68 y (SD 13 y); 59% male; 56% with hypercholesterolaemia; 6% with previous MI; 69% with HT; median NYHA class 2 (IQR 2-3); 16% with diabetes; 58% with smoking history; 35% with heart failure; 1% with left main disease; 3% used clopidogrel; 43% used aspirin; 24% had CAD history Comparator group: <ul style="list-style-type: none"> CABG: mean age 65 y (SD 11 y); 82% male; 84% with hypercholesterolemia; 45% with previous MI; 77% with HT; median NYHA class 1 (IQR 1-2); 31% with diabetes; 68% with smoking history; 35% with heart failure; 16% with left main disease; 9% used clopidogrel; 66% used aspirin; 37% had CAD history. Valve: mean age 68 y (SD 13 y); 64% male; 62% with hypercholesterolaemia; 19% with previous MI; 68% with HT; median NYHA class 2 (IQR 2-3); 19% with diabetes; 0% with smoking history; 73% with heart failure; 2% with left main disease; 2% used clopidogrel; 35% used aspirin; 23% had CAD history Setting: hospital Melbourne, Australia |
| Study methods | <ul style="list-style-type: none"> Clinical audit of pre-existing Integrative Cardiac Wellness Program Single centre, The Alfred Hospital Recruitment and sampling methods were not stated. Duration of study/dates of study (see also participant enrolment start/end dates and length of follow-up below) Methods to prevent and control for confounding, selection biases, and information biases were not stated, but multivariate analyses adjusted for confounders. |

| | |
|---|---|
| | <ul style="list-style-type: none"> • Unit of analysis: individual participant • Statistical methods: baseline comparisons using chi-squared tests for equal proportions. Continuous normally distributed outcomes compared using student t-tests. Non-parametrically distributed variables compared using Wilcoxon Rank Sum tests. Multivariate models were performed for binomial outcomes using logistic regression and adjusted for myocardial infarction, congestive heart failure, left main stenosis, Canadian cardiovascular society classification, number of diseased coronary systems, and number of distal anastomoses. • Not stated if analyses were intention to treat or per protocol, but total sample sizes were documented in tables presenting outcomes. • Method to prevent/address missing data: not stated. • Likelihood of reporting and other biases: comparator is not 'contemporaneous' to the intervention group but received their treatment just before the study period. |
| <p>Enrolment start/end dates</p> <p>Length of follow-up</p> | <p>Intervention patients who attended preadmission clinics between September 2008 and August 2011; comparator patients who attended from November 2005 to August 2008.</p> <p>The intervention program ran for 36 months; the comparator group care ran for 34 months</p> |
| <p>Intervention</p> | <ul style="list-style-type: none"> • 337 participants, 176 with CABG surgery and 161 with valve surgery. • Integrative Cardiac Wellness Program combining metabolic therapy with ward-based individualised health promotion delivered by naturopaths as an adjunct to standard pharmaceutical and surgical care: <ul style="list-style-type: none"> ➢ Oral metabolic therapy: 2 oral preparations, each at 1 capsule 3 times/day from day of enrolment until 4 weeks after surgery. Supplement 1 provided 225mg/d coenzyme Q10, 225mg/d R, S-alpha lipoic acid, 1500mg/d magnesium orotate (equivalent to 96mg magnesium) and 10.08 mg/d D-alpha-tocopherol. Supplement 2 provided 3000mg/d concentrated omega 3 triglycerides from fish (equivalent to 900mg EPA and 600mg/d DHA) ➢ Post-operative ward visits between days 3 and 6 post-surgery, for 10-20 min by a naturopath. The naturopath discussed health enhancement approaches relevant to the individual patient and their living situation, including modifying diet towards the Mediterranean diet and the importance of stress management, physical activity, and attendance at cardiac rehabilitation. Patients were asked about their emotional state and feelings about surgery, with discussion about personal meaning and wellbeing. ➢ Follow-up phone call 2 weeks after discharge, to check compliance with metabolic therapy and encourage and confirm attendance at cardiac rehabilitation sessions, and also to collect patient feedback about the Program. • Rationale for intervention: metabolic therapies' antioxidants, energy substrates and polyunsaturated fatty acids decrease the oxidative stress caused during surgical interventions, enhancing cellular energy production and enhancing recovery. Coenzyme Q10, alpha lipoic acid, selenium, magnesium orotate, and omega 3 fatty acids, in a previous RCT, reduced cardiac damage, shortened LOS, and showed a trend towards a reduction in the incidence of post-operative atrial fibrillation. • Tailoring of the intervention was undertaken by naturopaths individualising the approaches to the patient and their living situation. No mention of any modifications or titration of interventions. • Compliance with oral metabolic therapy was promoted by phone calls to participants 2 weeks after enrolment. |
| <p>Comparator</p> | <ul style="list-style-type: none"> • 585 participants, 354 with CABG surgery and 231 with valve surgery. • Usual care, historical comparator as patients received usual care from November 2005 to August 2008, the period immediately preceding the study. No further details regarding how the care was delivered or what it was comprised of. • Compliance with usual care not described. |

| | |
|---|---|
| Outcome | <ul style="list-style-type: none"> • Primary outcomes (post-surgery): 24 h serum troponin I, inotrope requirements, low output state, atrial fibrillation, hospital LOS, blood loss, total blood loss, the incidence of return to theatre due to bleeding, and blood transfusion requirements. • Secondary outcomes: none • Measurement tools or instruments not reported. Biochemical outcomes, recovery from surgery, and safety of the intervention were sourced from hospital records. • Metric was the comparison of outcomes between intervention and comparator participants within CABG and valve surgical groups. The outcomes were not measured at 'baseline'. • Method of aggregation: <ul style="list-style-type: none"> ➢ Atrial fibrillation, inotrope use, low output state 30-day mortality, blood transfusion requirement, and return to theatre due to haemorrhage reported as percentages of the study sample ➢ 24 h troponin I, LOS (days), blood drainage first 4 h (ml), and total blood loss (ml) were reported as means with 95% CI or medians with interquartile ranges. It is not clear which method of aggregation was used for which of these outcomes (table 3 of the study). ➢ Patient satisfaction was reported as percentages who rated the intervention as excellent/good (CSQ-8) and qualitative descriptive responses (3-4 months after intervention) • Attrition of participants not reported. • Analyses were done by CABG and valve surgery, with intervention and comparator patients compared within each surgical group. • A subgroup of patients (48 intervention patients) was assessed for patient satisfaction using CSQ-8 by a research assistant during the first 6 months. 12 intervention patients were interviewed 3-4 months after participating in the Program. • Increase in participant rates in intervention patients assessed by a random sample of patients 4-6 weeks before the introduction of the Program and comparing to the attendance rate during a 4-6 week period during the first 2 months of the Program. • All outcome domains were assessed and reported on, including attendance rates for a random sample of 65 patients. Odds ratios with 95% CI were assessed but not reported as such but as relative reduction (%) and significance for some outcomes only. |
| Funding source | <ul style="list-style-type: none"> • The Alfred Foundation received untied external funds to support the Integrative Cardiac Wellness Program. |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: Cardiac Surgical Research Unit, Department of Cardiothoracic Surgery, Alfred Hospital, Department of Surgery, Monash University, Australia; Pharmacy Department, The Alfred Hospital, Melbourne, Australia; Centre of Ethics in Medicine and Society, Monash University, Australia; Centre for Human Psychopharmacology, Swinburne University of Technology, Melbourne, Australia; Department of Epidemiology and Preventive medicine, Monash University, The Alfred Hospital, Melbourne, Australia • The authors declare that they have no competing interests. |
| Reasons for exclusion from data synthesis | <ul style="list-style-type: none"> • Not applicable |

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CSQ-8, Client Satisfaction Questionnaire 8; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HT, hypertension; IQR, interquartile range; LOS, length of stay; MI, myocardial infarction; NYHA, New York Heart Association; y, year

D.1.10. Allergic rhinitis

Table 29: Mittman 1990

| Mittman 1990 | |
|---------------------------|--|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> 98 volunteer participants, with at least 2 of the 3 following symptoms of allergic rhinitis, in at least moderate severity: rhinorrhea, sinus congestion, and excessive lacrimation. 32 participants had previously skin tested positive for environmental allergens. 69 participants completed the study. Intervention group: mean age 34.7 y (range 20-74 y); 20 men and 11 women; nasal smears positive for eosinophils in 19 participants. Comparator group: mean age 36.4 y (range 22-64 y); 15 men and 23 women; nasal smears positive for eosinophils in 24 participants. Setting: not stated. Portland metro area, Oregon, US |
| Study methods | <ul style="list-style-type: none"> Double-blind parallel RCT. The number of study centres was not stated. Recruitment of volunteers by newspaper advertisements, posters, and public service announcements. The study ran from May to early July, but the year was not stated. The randomisation method was not stated, but it was reported that the randomisation of men and women was moderately skewed, with a higher proportion of men in the intervention group. Unit of analysis: individual participant. Statistical methods: no statistical tests; descriptive statistics of outcomes as the number and percentage of participants. Not stated, but the analyses appear to be per protocol. Method to prevent/address missing data: not stated. Likelihood of reporting and other biases: high |
| Enrolment start/end dates | 1 week trial, from May to early July, the peak season for allergic rhinitis in Oregon's Willamette Valley. Year not stated. |
| Length of follow-up | |
| Intervention | <ul style="list-style-type: none"> 31 completed the study. Not stated how many were randomised to the intervention. 300mg freeze-dried <i>Urtica dioica</i> (stinging nettle) in a gelatine capsule, 2 capsules at the onset of symptoms. The number of doses taken during the week recorded. <i>U. dioica</i> stinging hairs contain histamine, betaine, choline, acetylcholine, serotonin, and formic acid. No other rationale was stated. Provider, mode of delivery, location, timepoints that the intervention was delivered, frequency, number of sessions, and tailoring or modification were not stated. Adherence and compliance were not reported, except that the mean number of doses taken during the trial period was 18.3. |
| Comparator | <ul style="list-style-type: none"> 38 participants completed the study. Not stated how many were randomised to the comparator. Placebo 300mg coloured lactose in a gelatine capsule, 2 capsules at the onset of symptoms. The number of doses taken during the week recorded. Rationale for placebo not stated. Provider, mode of delivery, location, timepoints that the comparator was delivered, frequency, number of sessions, and tailoring or modification not stated. |

| Mittman 1990 | |
|-----------------------|--|
| | <ul style="list-style-type: none"> Adherence and compliance were not reported, except that the mean number of doses taken during the trial period was 17.4. |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: response to medication reported in a patient diary as dramatic improvement, moderate improvement, no change or worse, within 1 h of taking medicine. This was further analysed as 'never', 'less than 50% of the time', and 'more than 50% of the time). Secondary outcomes: diary notes and global evaluation of the following questions: <ul style="list-style-type: none"> ➤ How did this medicine compare to medicines used in the past? (Less effective vs same/more effective) ➤ Did the effect of the medicine vary from dose to dose? ➤ Did you experience any side effects? (Side effects recorded) ➤ How would you rate the effectiveness of this medicine? (Ineffective vs moderately/highly effective) ➤ Would you buy this medicine? (Yes vs no) ➤ Did you think you had the placebo? The outcomes 'Did the effect of the medicine vary from dose to dose?' and 'Did you think you had the placebo?' were not reported. No standardised measurement tools were used. Outcomes were aggregated as the number and percentage of participants with a particular metric (eg percentage reporting dramatic improvement in symptoms). Timepoints for assessments not stated Overall, of the 98 participants included, 7 had a sharp decline in symptoms and had taken less than 5 doses and felt unable to evaluate the medicine (which treatment group not stated. 20 failed to return for follow-up (reasons not given; 13 intervention and 7 placebo participants), leaving 69 participants who finished (31 intervention and 38 comparator participants) No subgroup analyses |
| Funding source | <ul style="list-style-type: none"> Funding source not stated |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: National College of Naturopathic Medicine, Portland, Oregon US Other potential conflicts of interest were not stated. |

Abbreviations: RCT, randomised controlled trial; y, year

D.1.11. Low back pain

Table 30: Szczurko 2007

| Szczurko 2007 | |
|-------------------------|--|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> 75 participants, with low back pain of non-specific cause for the preceding 6 weeks. Exclusion criteria; unable to comply with study protocol; had mild or no pain at the time of assessment; history of back surgery; sciatica; systemic or visceral causes of pain; osteoporosis; vertebral fracture or dislocation; severe neurological signs; spondylolisthesis; coagulation disorders; severe concurrent illness; pregnancy; or involved in claiming for compensation or litigation because of back injury. Intervention group: mean age 45.3 y (SD 7.46 y); 56% women; mean weight 79.12 kg (SD 14.39 kg); BMI 28.70 kg/m² (SD 4.87 kg/m²); 48.7% day shift; 22 White, 3 Black, 11 South Asian, 2 East Asian, 1 Aboriginal; mean baseline Oswestry score 11.85 (SD 8.18); mean baseline SF Mental score -1.10 (SD 0.86), Physical score -0.27 (SD 1.15); median NSAID use 3 (range 0-49, n=21)). |

Szczurko 2007

| | |
|---------------------------|--|
| | <ul style="list-style-type: none"> • Comparator group: mean age 48.02 y (SD 8.27 y); 44% women; mean weight 78.66 kg (SD 18.13 kg); BMI 27.67 kg/m² (SD 3.68 kg/m²); 41.7% day shift; 17 White, 4 Black, 12 South Asian, 3 East Asian, 0 Aboriginal; mean baseline Oswestry score 11.08 (SD 7.83); mean baseline SF-36 Mental score -1.19 (SD 0.91), Physical score -0.06 (SD 1.18); median NSAID use 0 (range 0-15, n=19). • Mississauga, Ontario, Canada |
| Study methods | <ul style="list-style-type: none"> • ISRCTN41920953 • Parallel RCT; investigators and data analyses blinded to treatment allocation, but not patients or clinicians delivering care. • 1 main centre with a minority of participants recruited from other Canada Post facilities. • Recruitment through poster advertising at the Gateway Processing Plan of the Canada Post Corporation and local depots, of Canadian Union of Postal Workers members. • 12 weeks • Randomisation by 'coin-toss' • Unit of analysis: individual participant • Statistical methods: 5-point difference (10%) between groups established as the minimal clinically important difference (Owestry Low Back Pain Disability Questionnaire). The treatment effect was assessed as mean change scores between groups at week 12 and baseline. Change scores between groups compared with a 2-sample t-test. Construct validity of Owestry Low Back Pain Disability Questionnaire assessed by comparing with the Roland and Morris questionnaire using Pearson Correlation Coefficient at baseline and week 12 separately, • Intention-to-treat analysis • Method to prevent/address missing data: for any missing data at week 12, data at week 8 was carried forward. • Likelihood of reporting and other biases: moderate – selective reporting of outcomes, in that outcomes for weeks 4 and 8 were not reported. |
| Enrolment start/end dates | March to September 2005. |
| Length of follow-up | 12 weeks, with an option for the comparator group to receive naturopathic care at the end of week 12 for 4 weeks. |
| Intervention | <ul style="list-style-type: none"> • 39 participants • Naturopathic care: seen twice per week for specific acupuncture treatment for low back pain (total 24 treatments) which included diaphragmatic deep breathing exercises. Counselling to consume a diet high in omega-3 fatty acids, magnesium, and calcium. Encouraged to perform any kind of aerobic exercise for 30 min 3 times/week. • Delivered by licenced naturopathic physicians. • Rationale for intervention not stated. • Location: on-site (at participants' workplace) • Tailoring and modifications of intervention not reported • Compliance with dietary recommendations was measured by diet diaries and a checklist of questions about dietary intake at each visit. • Compliance was monitored on a semi-weekly basis using a percentage compliance scale; <70% adherence was considered non-compliant at each time point. |
| Comparator | <ul style="list-style-type: none"> • 36 participants • Standardised physiotherapy advice: participants received an educational booklet designed by the British Physiotherapy Association that has previously been validated to compare with active physiotherapy. The booklet provided information on causes of back pain, prognosis, appropriate use of imaging studies and |

Szczurko 2007

| | |
|---|---|
| | <p>specialists, and exercises for promoting recovery and preventing recurrences. Participants receiving the information booklet were instructed to follow the general advice to remain active, as specified in the booklet. At each subsequent visit, this group of participants received instruction on specific back stretching and strengthening exercises and were educated about relaxation exercises.</p> <ul style="list-style-type: none"> Delivered by licensed naturopathic physicians. Location: on-site No further details about the frequency or duration of visits to physicians or tailoring or modifications of comparator treatments were reported. Compliance was monitored on a semi-weekly basis using a percentage compliance scale; <70% adherence was considered non-compliant at each time point. |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: self-reported disability due to low back pain, measured by the Oswestry Low Back Pain Disability Questionnaire (higher scores indicate greater disability); QOL measured by SF-36 (higher scores indicate better QOL). Secondary outcomes: self-reported pain scale (10-point); Roland Morris Disability questionnaire (used to assess construct validity of primary outcome measure); forward lumbar flexion range of motion (cm); weight; BMI; use of NSAIDs; use of paramedical interventions. The intervention group asked about compliance, adverse events, and perceived benefit. All outcomes were measured at baseline and weeks 4, 8, and 12. 6 participants dropped out of the comparator group by week 2: 3 were dissatisfied with treatment and 3 were unable to commit to the time required. At week 8, 3 participants from the comparator group had dropped out; at week 12 3 from the intervention group and 4 from the comparator group had dropped out (reasons not stated). Data were available from 100% of the intervention group and 75% of the comparator group at week 8. Complete data were available on 92% of the intervention group and 63% of the comparator group at week 12. Median and interquartile ranges for outcomes at baseline and week 12 and change from baseline to 12 weeks were reported for Oswestry, Roland and Morris, Pain Scale and Spinal Flexion. Mean and SD and change from baseline to 12 weeks were reported for weight, BMI, and SF-36 scales. Week 4 and week 8 mean Oswestry scores and mean SF-36 Mental and Physical component aggregate scores were presented graphically. Other week 4 and week 8 outcomes were not reported. Construct validity of Oswestry questionnaire was reported. <p>No subgroup analyses were undertaken.</p> |
| Funding source | <ul style="list-style-type: none"> Funding was provided by the Canada Post Corporation and Canadian Union of Postal Workers. |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: Division of Clinical Epidemiology, Canadian College of Naturopathic Medicine, Toronto, Ontario, Canada; Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada The authors have declared that no competing interests exist. |
| Reasons for exclusion from data synthesis | <ul style="list-style-type: none"> Not applicable |

Abbreviations: BMI, body mass index; NSAIDs, non-steroidal anti-inflammatory drugs; SF-36, Short Form 36; RCT, randomised controlled trial

D.1.12. Rotator cuff tendinitis

Table 31: Szczurko 2009

| |
|------------------------|
| <h3>Szczurko 2009</h3> |
| Study Characteristics |

| | |
|---------------------------|--|
| Participant description | <ul style="list-style-type: none"> • 85 Canadian postal workers with rotator cuff tendinitis • Central processing plant, mail delivery depots • Day, evening, and night shift letter and package sorters; outdoor letter carriers and drivers. 18-65 y old. <ul style="list-style-type: none"> ➢ Intervention: mean age 50.7 y (SD 8.16 y), 58% female, 42% male ➢ Control: mean age 50.9 y (SD 7.86 y), 60% female, 40% male • Setting: workplace • Toronto, Ontario, Canada, with a minority from surrounding Toronto areas • Eligible if experiencing pain in at least 1 shoulder for ≥6 weeks and with symptoms consistent with rotator cuff tendinitis. • Exclusion: could not comply with the study protocol; no shoulder pain or range of motion limitations consistent with rotator cuff tendinitis at the time of assessment; previously identified allergies to any ingredients of Phlogenzym; receiving corticosteroid injection therapy; taking daily warfarin or antibiotics; abused substances such as alcohol or illegal drugs; severe concurrent illness; pregnant or breastfeeding. |
| Study methods | <ul style="list-style-type: none"> • ISRCTN: 49884134 • Pragmatic RCT • Single centre • Recruitment and sampling procedures were not stated, but were at the individual level and through the workplace • Duration of study: 12 weeks • Allocation concealment using central randomization was preserved up to the point of treatment and was maintained by the blinded coordinator performing range of motion and orthopaedic test assessments. Supplements and placebo were identical-looking. Intervention could not be masked from participants or clinicians delivering care. Randomisation was done by computer. • Unit of analysis: individual participant • Intention to treat analyses (baseline compared to week 12). Paired and independent t-tests. Mean changes from baseline in each group and mean changes between groups. • Data missing from week 12 was replaced with data from week 8 • Likelihood of reporting and other biases: low |
| Enrolment start/end dates | Intervention and control: 12 weeks |
| Length of follow-up | |
| Intervention | <p>43 participants</p> <ul style="list-style-type: none"> • Naturopathic care <ul style="list-style-type: none"> ➢ Acupuncture ➢ Dietary changes ➢ Supplement Phlogenzym (hydrolytic enzymes 90mg bromelain and 48 m trypsin, and 100mg bioflavonoid rutin per tablet), 2 tablets 3/day • Rationale: <ul style="list-style-type: none"> ➢ Acupuncture has been shown to be effective in musculoskeletal syndromes ➢ Anti-inflammatory diets high in omega-3 PUFAs from oily fish, soybeans, cherries, and plant flavonoids decrease inflammatory markers and decrease pain ➢ Oral hydrolytic enzymes are cited by European pharmacological and medical literature as fibrinolytic, anti edematous, anti-inflammatory, and analgesic. Activate macrophages and natural killer cells; degrades plasma proteins that invade interstitial space during acute inflammation; decreases fibrin deposits |

| | |
|------------|--|
| | <p>and restores microcirculation; rutin normalises pathologically increased vascular permeability; trypsin has antioxidant and anti-inflammatory properties; bromelain dissolves fibrin clots.</p> <ul style="list-style-type: none"> • Intervention provider: 2 licensed naturopathic doctors • Location: onsite • Timepoints: 1x/week for 30 min, for 12 weeks. Acupuncture at each visit, with needles inserted for ≥10 min. Supplements dispensed every 4 weeks • Tailoring of the intervention: dietary counselling specific to the individual • No modifications to intervention stated. • No strategies to maintain or improve adherence to intervention. • Compliance assessed through pill count every 4 weeks. Compliance to diet not assessed. |
| Comparator | <p>42 participants</p> <ul style="list-style-type: none"> • Standardised physical exercises, 12 weeks <ul style="list-style-type: none"> ➢ Passive, active-assisted, and active range of motion exercises ➢ Placebo supplement ➢ No dietary counselling • Rationale: physical exercise protocol has been shown to be effective for addressing pain consistent with workplace-related rotator cuff tendinitis • Comparator provider: not stated • Location: onsite • Timepoints: 1 x 30 min sessions for 12 weeks, physical exercises, and hands-on shoulder muscle and joint therapy. • Tailoring of the comparator: 'individualised treatment approach', not further defined • No modifications to comparator stated. • No strategies to maintain or improve adherence to comparator treatment. • Compliance was assessed through pill count every 4 weeks. |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: pain and disability associated with shoulder pathology measured by SPADI score • Secondary outcomes: Pain (VAS), HRQoL by SF-36, patient-centred outcomes by MYMOP, shoulder maximal range of motion by goniometer/inclinometer • Whether there is evidence that the outcome domain was assessed (especially important if the outcome was assessed but the results not presented) • SPADI: 0-50 for pain scale, 0-80 for disability scale and 0-130 for total score. Higher scores indicate greater pain and disability. • SF-36: 0-100; higher scores indicated better HRQoL • Shoulder maximal range of motion assessed flexion, extension, abduction, adduction, internal rotation, and external rotation. The assessor was blind to treatment • Pain VAS: 0-7; high scores indicate more severe pain • MYMOP: patients choose 2 personally relevant symptoms of greatest importance to their health and rate on a 7-point VAS. Higher scores indicate a worse level of health • Specific metric: mean change from baseline to end of 12 weeks of treatment, in pain and disability (SPADI score), pain (VAS), HRQoL (SF-36 score), range of motion, and MYMOP scores. • Method of aggregation: mean, SD, 95% CI |

| Szczurko 2009 | |
|-----------------------|--|
| | <ul style="list-style-type: none"> All outcomes measured at baseline and weeks 4, 8 and 12 Of the 89 eligible patients randomised, 4 withdrew before treatment commenced. 7 intervention and 10 comparator participants did not complete the 12-week trial: 1 broke her leg, 6 were unreachable, and 10 could not commit time or lost interest. <ul style="list-style-type: none"> Of the 43 intervention participants who started treatment, 41 completed week 8, and 36 completed week 12. Of the 42 comparator participants, 36 completed week 8 and 32 completed week 12 No subgroup analyses were reported. |
| Funding source | <ul style="list-style-type: none"> Supported by The Canadian Union of Postal Workers and the Canada Post Corporation, Joint Benefits Committee. Mucos Pharma, Puhonice, Czech Republic and Heel Canada, Anjou, Quebec, Canada supplied the study drug Chris Mazzuchin, BSc, PT, ND, for his physical therapy expertise and advice in the design of this study |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: Orest Szczurko, ND, Kieran Cooley, BSc, ND, Dugald Seely, ND, MSc: Canadian College of Naturopathic Medicine, Toronto, Ontario, Canada; Edward J. Mills, MSc, PhD, Qi Zhou, PhD, Dan Perri, BScPhm, MD, FRCPC: McMaster University, Hamilton, Ontario, Canada Authors' financial relationship: not stated No other conflicts of interest were stated. |

Abbreviations: HRQoL, health-related quality of life; MYMOP, Measure Yourself Medical Outcomes Profile; PUFA, polyunsaturated fatty acids, SF-36, Short Form 36; SPADI, Shoulder Pain and Disability Index; VAS, visual analogue scale; y, year

D.1.13. Menopausal symptoms

Table 32: Cramer 2003

| Cramer 2003 | |
|-------------------------|--|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> 239 participants Women aged ≥ 40 y with a diagnosis of menopausal symptoms documented by a naturopathic or conventional physician. ICD-9 criteria for menopausal and postmenopausal disorders codes 627.0-627.9 and by ICD-9 codes not primarily assigned to 627 but were commonly associated with code 627. Intervention group: mean age 51.7 y (SE 0.75 y); mean monthly income USD1,848 (SE USD209); 73.4% White ethnicity; 11.4% current smokers; 44.3% regular exercise program; 38.0% hysterectomy; 5.1% diabetes mellitus; 19.0% hypertension; 3.8% history of breast cancer; 13.9% family history of breast cancer; 77.2% anxiety; 41.8% decreased energy; 69.6% hot flushes; 57.0% insomnia; 44.3% menstrual changes; 29.1% urinary complaints; 16.5% vaginal dryness. Comparator group: mean age 50.7 y (SE 0.55 y); mean monthly income USD853.6 (SE USD54); 69.3% White ethnicity; 41.9% current smoker; 28.1% regular exercise program; 32.5% hysterectomy; 5.0% diabetes mellitus; 20.0% hypertension; 2.5% history of breast cancer; 14.4% family history of breast cancer; 55.0% anxiety; 24.4% decreased energy; 55.6% hot flushes; 33.1% insomnia; 51.9% menstrual changes; 32.5% urinary complaints; 18.1% vaginal dryness. Exclusion criteria: patients with only 1 visit for menopause-related symptoms or who were younger than 40 years. Setting: 1 natural medicine and 6 conventional medical clinics at Community Health Centers of King County, Washington, US |
| Study methods | <ul style="list-style-type: none"> Retrospective cohort study Multicentre – 1 natural medicine and 6 conventional medical clinics |

| | |
|--|--|
| | <ul style="list-style-type: none"> • Data abstracted from medical charts. • Recruitment by identifying ICD-9 diagnostic codes 627 and codes that were commonly associated with codes 627 using MarketScan Encounter Database™ for 1995 outpatient claims. Patients at the Community Health Centres of King County clinics and sampling procedures used (including at the level of individual participants and clusters/sites if relevant) • Eligible participants attended clinics from 1 Nov 1996 (the date that the naturopathic clinic opened) to 31 Jul 1998. No further details regarding follow-up time or study duration were stated: a patient's number of visits to her doctor was recorded but not the duration in between visits. • Data abstractors were blinded to the study question. No further details regarding methods to control for confounding or selection biases or information biases were reported. • Unit of analysis: individual participant • Statistical methods: comparison between intervention and comparator groups at baseline by 2-tailed t-test, chi-squared test, or Fisher's exact test. Multivariate analyses were performed using Generalised Estimating Equations to evaluate changes in menopausal symptoms. Repeated measures was used to analyse menopausal symptoms adjusted for age, weight, smoking status, regular exercise program, monthly income, and antihypertensive therapy. <ul style="list-style-type: none"> ➤ For each outcome (menopausal symptom), all visits to clinicians were included; if a patient had less than 2 visits for a particular symptom, they were excluded from the analyses for that symptom. • Method to prevent/address missing data: none stated • Likelihood of reporting and other biases: high likelihood. |
| Enrolment start/end dates Length of follow-up | Eligible naturopathic participants attended the naturopathic clinic from 1 Nov 1996 to 31 Jul 1998. No further details regarding follow-up time or study duration were stated. |
| Intervention | <ul style="list-style-type: none"> • 79 participants • 'Comprehensive aggregate system of naturopathic care', including patients treated with HRT who were seen by the naturopath. No further details of the treatment were reported. • Treated at a naturopathic clinic by licensed naturopaths, delivered by 3 naturopaths • No rationale for intervention reported • At least 2 visits for intervention; no other details regarding frequency, intensity or duration of intervention reported. • Location where the intervention occurred: natural medicine clinic • No information regarding tailoring or modification to intervention or compliance. |
| Comparator | <ul style="list-style-type: none"> • 160 participants • Conventional therapy, defined as an office consultation solely with a licensed physician during the study period. No further details regarding treatment reported • 6 conventional clinics, with 3 physicians at each providing care • No rationale for comparator reported • At least 2 visits for comparator; no other details regarding frequency, intensity, or duration of comparator reported. • Location: 1 of 6 conventional medical clinics • No information regarding tailoring or modification or comparator or compliance. |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: improvement in selected menopausal symptoms. Anxiety, decreased energy, hot flashes, insomnia, menstrual changes, urinary complaints, and vaginal dryness. Assessed by +patient report during visits to clinics, as 'new onset', 'improved', 'worse', 'resolved' or 'unchanged'. |

| Cramer 2003 | |
|-----------------------|---|
| | <ul style="list-style-type: none"> ➤ No specific or standardised measurement method was used to assess outcomes, but data abstraction forms were developed to standardise the abstraction of data from medical charts. Data abstractors were trained by the principal investigator and were blinded to the study question. • All outcome domains were reported on • Improvements in outcomes from baseline were reported (yes/no) with crude and adjusted odds ratios and 95% CI. • Outcomes were reported as the number of patients with improvements in symptoms as a fraction of the number of patients reporting symptoms, in each of the intervention and comparator groups. • Assessment timepoints were when patients visited their doctors. The duration between visits and duration of visits were not reported. • The number of visits to their doctors (timepoints) was not reported. The number of patients reporting a symptom was included if they had at least 2 visits to their doctors for the symptom. • No subgroup analyses. |
| Funding source | <ul style="list-style-type: none"> • 'This work was supported in part by the Office of Alternative Medicine, National Institutes of Health, Bethesda, MD.' |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: Vessel Sanitation Program, Centers for Disease Control and Prevention, Atlanta, GA; Epidemiology Program Office, Centers for Disease Control and Prevention, Atlanta, GA; National Center for Chronic Disease Prevention and Health Promotions, Centers for Disease Control and Prevention; Atlanta, GA. • No other conflicts of interest were declared. |

Abbreviations: HRT, hormone replacement therapy; y, year

D.1.14. Cardiovascular disease risk

Table 33: Seely 2013

| Seely 2013 | |
|-------------------------|---|
| Study Characteristics | |
| Participant description | <ul style="list-style-type: none"> • 246 participants randomised • Aged 25-65 years, under the care of a primary physician, able to answer self- and interviewer-administered questions in English. • Exclusion criteria: people with a history of myocardial infarction within the past 6 months; who had chronic kidney disease; with lower relative ratios of total cholesterol to HDL (<1.8); women who were pregnant or breastfeeding or who intended to become pregnant in the following year. • Participants were screened as having the highest risk of CVD based on the ratio of total cholesterol to HDL (mean 5.18, range 1.8-14.8). Gender profile and mean age not reported. • Intervention group: 55.1% had metabolic syndrome; 8.13% had cardiovascular risk; mean BMI 29.5 kg/m² (SD 7.0 kg/m²); mean waist hip ratio 0.93 (SD 0.06); mean total cholesterol/HDL ratio 5.27 (SD 1.57); mean glycosylated Hb 5.8% (SD 1.06%); mean systolic BP 125.5 mmHg (SD 16.4 mmHg); mean diastolic BP 81.9 mmHg (SD 10.9 mmHg); 11.3% current smokers; 44.0% consumed alcohol with mean number of drinks 6.67/week (SD 7 drinks/week); 85.3% used caffeine of which mean intake was 17.54 cups/week (SD 14.67 cups/week); mean low intensity exercise 14.67 min/week (SD 374.3 min/week); medium intensity exercise 15.9 min/week (SD 44.9 min/week) and high intensity exercise 8.4 min/week (SD 50.9 min/week) • Comparator group: 43.4% had metabolic syndrome; 9.54% had cardiovascular risk; mean BMI 28.3 kg/m² (SD 5.3 kg/m²); mean waist hip ratio 0.93 (SD 0.06); mean total cholesterol/HDL ratio 5 (SD 1.17); mean glycosylated Hb 5.7% (SD 0.97%); mean systolic BP 123.2 mmHg (SD 17.0 mmHg); mean diastolic BP 81.9 |

| | |
|---------------------------|--|
| | <p>mmHg (SD 10.9 mmHg); 15.8% current smokers; 43.9% consumed alcohol with mean number of drinks 6.44/week (SD 8.45 drinks/week); 92.9% used caffeine of which mean intake was 13.90 cups/week (SD 12.02 cups/week); mean low intensity exercise 153.2 min/week (SD 399.2 min/week); medium intensity exercise 3.7 min/week (SD 18.2 min/week) and high intensity exercise 3.5 min/week (SD 22.1 min/week).</p> <ul style="list-style-type: none"> • Setting: Canadian Union Postal Workers work sites. • Toronto, Canada |
| Study methods | <ul style="list-style-type: none"> • NCT00718796 • 2-arm parallel RCT. Statisticians were blinded to allocation. • 3 recruitment centres: Toronto, Vancouver, and Edmonton. • Recruitment from among Canadian Union Postal Workers by an unrestricted free screening of all Canada Post employees in Toronto, Vancouver, and Edmonton, Canada. 1125 were initial screened, with 879 excluded due to lack of interest, unable to contact, or having total cholesterol/HDL ratio<1.8, with 246 randomised. • 12-month study. • Randomisation was conducted centrally at the Canadian College of Naturopathic Medicine in blocks of 8 stratified by sex. • Unit of analysis: individual participant. • Statistical methods: repeated measures of mixed model for continuous outcomes and generalised estimating equations model for binary data. Baseline measures of the outcome variables were used as covariables. • Intention to treat analysis • Method to prevent/address missing data: multiple imputation method for primary outcomes metabolic syndrome and cardiovascular risk, using age, sex, exercise level, BMI, waist to hip ratio, smoking status, HDL, and ratio of total cholesterol to LDL. • Likelihood of reporting and other biases: low |
| Enrolment start/end dates | 2008 to 2010. |
| Length of follow-up | The study duration was 1 year. |
| Intervention | <ul style="list-style-type: none"> • 124 participants • Naturopathic care plus enhanced usual care <ul style="list-style-type: none"> ➢ Naturopathic care was received at 7 preset times over 12 months, with 1 h initial visit and subsequent 30 min visits. ➢ Naturopathic treatment recommendations were individualised from a predetermined menu of interventions based on which risk factors were present and patient preferences. ➢ Therapies included specific diet and lifestyle recommendations and prescription of selected natural health products: weight loss of about 2.3-4.6 kg through a combination of caloric restriction and regular physical activity; dietary recommendations were based on components of the Mediterranean and Portfolio dietary regimes; natural health products included omega-3 fatty acids EPA and DHA, soluble fibre, coenzyme Q10, and plant sterols. ➢ Participants were advised to continue seeing their family physician for routine care, without recommending changes in the frequency of visits. • Naturopathic care was delivered by licensed naturopathic doctors. • Rationale for naturopathic care not reported. • Location: worksite clinics • The authors stated frequency and composition of participant adherence to the intervention was not reported. |
| Comparator | <ul style="list-style-type: none"> • 122 participants |

| | |
|-----------------------|--|
| | <ul style="list-style-type: none"> • Enhanced usual care: <ul style="list-style-type: none"> ➢ Participants were advised to continue seeing their family physician for routine care, without recommending changes in the frequency of visits. ➢ Did not track or report recommendations made by participant's family physicians • Timepoints, duration, frequency, and number of sessions, and tailoring or modifications to the comparator treatment were not reported. • Compliance and adherence to comparator treatment were not reported. |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: prevalence of metabolic syndrome (%) defined as the presence of 3 of 5 risk factors (abdominal obesity ((1) waist circumference ≥ 102 cm for men and ≥ 88 cm for women); (2) TG ≥ 1.70 mmol/L or taking medication for elevated TG; (3) HDL < 1.03 mmol/L for men of < 1.3 mmol/L for women; (4) systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or taking antihypertensive medication; or (5) fasting blood glucose ≥ 5.6 mmol/L or taking medication for diabetes); 10-year cardiovascular risk (%) measured by changes in Framingham 10-year cardiovascular risk score. • Secondary outcomes: QOL measured by SF-36 and MYMOP questionnaire; adverse events; weight (kg); LDL (mmol/L); HDL (mmol/L); TG (mmol/L) total cholesterol/HDL ratio; glycated Hb (%); fasting blood glucose (mmol/L); systolic BP (mmHg); diastolic BP (mmHg) • Outcomes were reported at baseline and after 26 and 52 weeks, as % or means with standard deviations. Differences between groups were reported as % or means with 95% CI. All outcomes were reported for weeks 26 and 52; outcomes were measured at baseline, except for QOL and adverse events. • Whether there is evidence that the outcome domain was assessed (especially important if the outcome was assessed but the results not presented) • Comparisons were made between intervention and comparator groups at 26 and 52 weeks • Measurements made at 26 and 52 weeks • 39 participants dropped out (18 intervention and 21 comparator participants) with reasons obtained for 17 participants: 5 retired, were fired, or moved; 5 lost interest; 4 cited time commitment issues; 1 had a lack of mobility; 1 told to withdraw by a family physician; 1 cited personal reasons. It is not stated at which timepoint in the trial the attritions occurred. <ul style="list-style-type: none"> ➢ Baseline data was not available for every participant for every outcome (table 1 of the study), but it is not clear how many participants had missing data at weeks 26 and 52. • No subgroup analyses were reported. |
| Funding source | <ul style="list-style-type: none"> • Funded by the Joint Benefits Committee of the Canadian Union of Postal Workers and the Canada Post Corporation. • Seroyal International provided discounted natural health products to trial participants. • Kieran Cooley was supported by a SickKids Foundation Training Award in Complementary/Alternative Health Care. |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: From the Canadian College of Naturopathic Medicine (Seely, Szczurko, Cooley, Fritz, Aberdour, Herrington, Rouchotas, Lescheid, Gignac, Bernhardt), Toronto, Ont.; the Ottawa Hospital Research Institute (Seely), Ottawa, Ont.; the Ottawa Integrative Cancer Centre (Seely), Ottawa, Ont.; the Leslie Dan Faculty of Pharmacy, University of Toronto (Szczurko, Cooley), Toronto, Ont.; the Department of Psychology, University of Arizona (Herman), Tucson, Ariz.; Bastyr University (Bradley), Kenmore, Wash.; and the Department of Clinical Epidemiology and Biostatistics, McMaster University (Zhou, Guyatt), Hamilton, Ont. • Kieran Cooley has provided expert advisory commentary on microbiota for gastrointestinal health for Bayer. He holds grants from the Canadian Complementary and Alternative Medicine Research Fund, the Lotte and John Hecht Memorial Foundation, SickKids Foundation, HomeoNet Research Fund, the |

Seely 2013

| | |
|--|---|
| | <p>Interdisciplinary Network of Complementary and Alternative Medicine Research Fund and the First Nations Inuit Health Branch, Health Canada. Heidi Fritz has received payment for manuscript preparation from Integrative Healthcare Practitioners. Serenity Aberdour is scientific advisor for SISU, a distributor of natural health products. Patricia Herman has received consulting fees and payment for writing or reviewing manuscripts from the Canadian College of Naturopathic Medicine. Philip Rouchotas has served as a consultant for Nutritional Fundamentals of Health and is Editor-in-Chief of Integrated Healthcare Practitioners. Ryan Bradley has served as a consultant for Standard Process and has been employed by the Diabetes Action Research and Education Foundation. No competing interests declared for Dugald Seely, Orest Szczurko, Craig Herrington, David Lescheid, Tara Gignac, Bob Bernhardt, Qi Zhou and Gordon Guyatt.</p> |
|--|---|

Abbreviations: BP; blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; Hb, haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; QOL, quality of life; SF-36; Short Form 36; TG, triglyceride

D.2. Population grouping 1: Breast, colon, and prostate cancer

D.2.1. List of studies

| Study ID | Study type | Population | Citation |
|----------------|------------|-----------------|--|
| Andersen 2018 | NRSI | Breast cancer | Andersen MR, Sweet E, Hager S, Gaul M, Dowd F, St, et al. Use of Integrative Oncology, Involvement in Decision-Making, and Breast Cancer Survivor Health-Related Quality of Life in the First 5 Years Postdiagnosis. <i>Integrative cancer therapies</i> . 2018;17(3):636-45. |
| Raghunath 2020 | RCT | Colon cancer | Raghunath K, Sumathi C, Rajappa SJ, Mohan MVTK, Kumar U, Shaik U, et al. Impact of naturopathy, yoga, and dietary interventions as adjuvant chemotherapy in the management of stage II and III adenocarcinoma of the colon. <i>International journal of colorectal disease</i> . 2020;35(12):2309-22. |
| Braun 2013 | NRSI | Prostate cancer | Braun DP, Gupta D, Birdsall TC, Sumner M, Staren ED. Effect of naturopathic and nutritional supplement treatment on tumor response, control, and recurrence in patients with prostate cancer treated with radiation therapy. <i>Journal of alternative and complementary medicine (New York, NY)</i> . 2013;19(3):198-203. |

D.2.2. Risk of bias summary

Breast cancer

Anderson 2018 Risk of bias (ROBINS-I) - SF-36

| Andersen 2018 NRSI breast cancer | | |
|--|---------------|---|
| Domain | Judgement | Description |
| Bias due to confounding | Serious risk | There is no adjustment for confounding variables, mean scores are unadjusted |
| Bias in selection of participants into the study | Serious risk | Most of the intervention group participants were selected on the basis they had received naturopathic care and so the start of follow-up did not coincide with the start of the intervention. No adjustment techniques were used to correct for this. |
| Bias in classification of interventions | Moderate risk | The two treatment groups are well defined, and it is unlikely that the classification of the treatment group would be affected by knowledge of the |

| Andersen 2018 NRSI breast cancer | | |
|--|------------------------------|--|
| | | outcome (the SF-36 results). However, it is not reported how or when the classification of the groups was recorded. |
| Bias due to deviations from intended interventions | Low risk | The oncology treatments (surgery, chemotherapy, radiotherapy, endocrine therapy) were balanced between the two groups. Implementation of intervention in this study is whether or not participants visited a naturopathic oncologist, not whether they adhered to the naturopathic advice. |
| Bias due to missing data | Serious risk | Table 5 in the paper reports results from a multiple regression analysis which appears to adjust for potential confounding variables. However, the effect size appears only to be reported for 8 SF-36 domains for which there was a statistically significant association (in this case, one of 8 domains – general health, for with scores were 3.53 points lower in the usual care cohort [n=360] compared to the naturopathic oncology cohort [n=193]). Reporting of analyses in this paper is incomplete and ambiguous (e.g. there was data collected at 12 months, total participants included in the analyses were reported to be the same as available at 12 months, yet there is no mention of results at 12 months, only results at baseline and 6 months) |
| Bias in measurement of outcomes | Serious risk | The SF-36 is self-reported and thus the assessors (participants) were aware of their treatment allocation. There is no information in the paper about the scale range for each of the subscales or direction, so it is not possible to interpret the results without checking the SF-36 guidance. |
| Bias in selection of reported result | Serious risk | The study authors did not report a measure of precision (or data to calculate) or present unadjusted estimates (except for selected results, which appear to be those for which there was a statistically significant effect) |
| Overall risk of bias judgment | Critical risk of bias | All the outcome domains assessed were measured by the SF-36 and were the primary outcomes of the study. There was a high risk of bias overall, reflected by participants being selected after they had commenced treatment, a substantial proportion of intervention participants missing outcome data, and the self-report nature of the SF-36 tool when the participants were aware of their intervention treatment (with potential bias in favour of naturopathy). There were serious risks of bias due to confounding, missing and incomplete data with selective reporting of statistically significant results only. |

Colon Cancer

Table 34: Raghunath 2020 Risk of bias (RoB2) – FLIC, STAI, BDI

| Raghunath 2020 RCT colon cancer | | |
|--|---------------|--|
| Domain | Judgement | Description |
| Bias arising from the randomisation process | Low risk | Although the method of randomisation was not detailed, allocation used 'opaque envelopes with group assignments, which were opened sequentially in the order of assignment during recruitment with names and registration numbers written on their covers'. Demographic baseline data were not reported but the study states that the groups were well-balanced for age, gender, stage of disease, and performance status. |
| Bias due to deviations from intended interventions | Some concerns | Participants were not blinded to the intervention, although investigators were. No information regarding deviations from intended interventions in the trial context. Modified intention to treat analyses were appropriate |

| Raghunath 2020 RCT colon cancer | | |
|--|--------------------------------|--|
| Bias due to missing outcome data | Low risk | For both QoL and psychological functioning, 58/60 (97%) of participants in each group had outcome data. So nearly all participants had outcome data |
| Bias in measurement of the outcome | Some concerns | For both outcome domains, the methods for measuring outcome were standardised and appropriate, but as a self-reported measure, it is subject to influence by the knowledge of intervention received. Participants were not blinded. |
| Bias in selection of the reported result | Low risk | For both outcome domains, statistical methods were stated a priori, and the reported results aligned with the pre-specified plan. The outcome measures for each domain were reported. Effect sizes, though stated in the methodology, were not reported for these outcome domains for any of the measurement methods, and only the t-test results were. However, this does not appear to be selective as only one statistical test was used. (Effect sizes were reported for the study's haematological primary outcomes, which are not within scope for this Review). |
| OVERALL risk of bias | Some concerns (overall) | As participants were not blinded and the outcomes were measured by self-report methods, there were some concerns about the risk of bias due to deviations from intended interventions and in the measurement of the outcomes. The biases potentially favour naturopathy. There was low risk of bias for the other domains: allocation was concealed; outcome data were available for most participants; and there does not appear to be selective reporting of results from among multiple measurement methods. |

Abbreviations: BDI, Beck's Depression Inventory; FLIC, Functional Living Index Cancer; QoL, quality of life; STAI, State Trait Anxiety Inventory

Note: Outcome domains assessed, in order of NTWC prioritisation: QoL (FLIC); and psychological functioning (STAI, BDI). All were primary outcomes of the study.

Prostate Cancer

Table 35: Braun 2013 Risk of bias (ROBINS-I) – tumour progression

| Braun 2013 NRSI prostate cancer | | |
|--|----------------|---|
| Domain | Judgement | Description |
| Bias due to confounding | Serious risk | Results were stratified by whether or not participants received hormonal ablation. All outcome measurement methods were based on PSA levels, which age and baseline PSA levels will influence; neither of these confounding variables was controlled for and age was poorly reported. |
| Bias in selection of participants into the study | Low risk | Participants were selected based on attributes BEFORE the start of naturopathic interventions (ie selected because of cancer diagnosis). Follow-up commenced from the time of diagnosis. |
| Bias in classification of interventions | Low risk | Treatment groups were clearly defined, based on whether participants chose to take naturopathic supplements. It appears likely this information was recorded at the start of the intervention. |
| Bias due to deviations from intended interventions | No information | There was no information regarding any deviations from the intended intervention beyond what would be expected in usual practice. |
| Bias due to missing data | Low risk | Outcome data were available for all 134 included participants |
| Bias in measurement of outcomes | Low risk | All outcome measurement methods were based on PSA levels, an objective observation |

| Braun 2013 NRSI prostate cancer | | |
|--------------------------------------|--------------|---|
| Bias in selection of reported result | Serious risk | The statistical analysis methods were poorly presented. Both mean and median values for PSA (pre- and post-treatment) and PSA nadir were reported, analysed with t-tests for the means and Mann-Whitney U tests for the medians. Time to nadir was only presented as medians and analysed with Man Whitney U tests, suggesting selective reporting from multiple analyses |
| Overall risk of bias judgment | Serious risk | The overall serious risk of bias is attributed to confounding which was not adjusted for and the possibility of selective reporting from multiple analyses. There was no information regarding deviations from intended treatments. Other risk of bias domains were rated as low risk of bias: selection of participants; outcome data which was complete for participants; and the objectivity of the outcome measurement method. |

Abbreviations: N, no; PN, probably no; PSA, prostate-specific antigen; PY, probably yes; Y, yes

Tumour progression assessed by (in order of NTWC prioritisation) frequency of biochemical failure, PSA pre- and post-treatment, PSA nadir, and time to reach PSA nadir. All were primary outcomes of the study

D.3. Population grouping 2: T2DM, PCOS, overweight and obesity

D.3.1. List of studies

| Study ID | Study type | Population | Citation |
|-------------------|------------|------------------------|--|
| Stier-Jarmer 2021 | RCT | Type 2 diabetes | Stier-Jarmer M, Frisch D, Neuy S, Schuh A. A 3-Week Naturopathic Intervention Improves HbA1c, Weight, and Quality of Life Among Overweight and Obese Adults With Type 2 Diabetes: 6-Month Results From a Randomized Trial. <i>Alternative therapies in health and medicine.</i> 2021;27:61-71. |
| Bairy 2020 | NRSI | Type 2 diabetes | Bairy S, Rao MR, Edla SR, Manthena SR, Tatavarti NVGD. Effect of an Integrated Naturopathy and Yoga Program on Long-Term Glycemic Control in Type 2 Diabetes Mellitus Patients: A Prospective Cohort Study. <i>International journal of yoga.</i> 2020;13(1):42-9. |
| Arentz 2017 | RCT | PCOS | Arentz S, Smith CA, Abbott,J., Fahey,P., Cheema,BS., Bensoussan A. Combined lifestyle and herbal medicine in overweight women with polycystic ovary syndrome (PCOS): A randomized controlled trial. <i>Phytotherapy research.</i> 2017;31(9):1330-40. |
| Ratnakumari 2018 | NRSI | PCOS | Ratnakumari ME, Manavalan N, Sathyanath D, Ayda YR, Reka K. Study to Evaluate the Changes in Polycystic Ovarian Morphology after Naturopathic and Yogic Interventions. <i>International journal of yoga.</i> 2018;11(2):139-47. |
| Beer 2014 | NRSI | Overweight and obesity | Beer A-M, Ismar LE, Wessely DK, Potschke T, Weidner B, Wiebelitz KR. Retrospective long-term comparison of naturopathic fasting therapy and weight reduction diet in overweight patients. <i>Evidence-based complementary and alternative medicine : eCAM.</i> 2014;2014:453407. |

D.3.2. Risk of bias summary

Table 36: Stier-Jarmer 2021 ROB

| Stier-Jarmer 2021 RCT T2DM overall | | |
|--|----------------------------|--|
| Domain | Judgement | Description |
| Bias arising from the randomisation process | Some concerns | Randomisation process using permuted blocks is appropriate. There are concerns regarding randomisation due to differences in baseline biochemical and metabolic indices between intervention and comparator groups. Also, those in the intervention group were more likely to have received "Oberstufen Schrothkur" treatment before |
| Bias due to deviations from intended interventions | High risk | All participants were aware of their treatment and were not blinded. Participants from both groups were treated at the same health resort and could access similar facilities, with potential for participants to deviate from intended interventions and could have affected the outcome. The proportion participants that may have deviated from their intended treatments is not known. Modified intention to treat analyses were used, but did not include eligible participants who dropped out post-randomisation |
| Bias due to missing outcome data | Low risk | Outcome data were missing for more than 5% of participants. 1 participant was excluded post-randomisation as they had an occurrence that rendered them ineligible, while 7 eligible participants in the comparator group dropped out post-randomisation. 2 in the intervention group and 1 from the comparator group were lost to follow-up and their data were imputed. However, the loss of participants was probably unrelated to their health status or study outcomes |
| Bias in measurement of the outcome | Low risk | The measurement methods for outcome domains glycaemic control and body weight were appropriate and these were objective observations. Assessors were not blinded. It was not explicitly reported who collected the outcome data and how it was collected, but it would appear to be the same across both groups. Overall, it was unlikely that knowledge of the intervention (by participants or assessors) influenced the assessment of the outcomes. |
| Bias in selection of the reported result | High risk | Statistical analyses plans were not presented in the trial registration and the trial had been registered retrospectively. There was only one outcome measure for glycaemic control (HbA1c) but there was selective reporting for body weight outcomes, with more outcomes for BMI reported than for body weight. Data were collected at 3 months but not reported for HbA1c or body weight. |
| OVERALL risk of bias | High risk (overall) | Both outcome domains assessed were rated as having a high risk of bias due to potential deviations from intended interventions and because of selective reporting of results The randomisation process was appropriate, although there were some concerns due to differences at baseline. Participant attrition was unlikely to be due to their health status or study outcomes and it was unlikely that knowledge of the intervention by participants or assessors influenced the assessment of outcomes |

Abbreviations: BMI, body mass index; HbA1c, glycosylated haemoglobin; ITT, intention to treat

Outcome domains assessed, in order of NTWC prioritisation: glycaemic control (HbA1c, primary outcome of the study); and body weight (kg, secondary outcome)

Full text for this study was not available; data drawn from the study abstract.

Table 37: Bairy 2020 ROB

| Bairy 2020 NRSI T2DM | | |
|--|---------------------|--|
| Domain | Judgement | Description |
| Bias due to confounding | Serious risk | For both outcome domains (glycaemic control and body weight), age, comorbidities at baseline, and type of hypoglycaemic agent used are potential confounders. Multivariate analyses were mentioned but did not state which variables were adjusted for |
| Bias in selection of participants into the study | Low risk | Participants were recruited based on characteristics observed at the start of the study and follow-up commenced with the start of trial treatment. |
| Bias in classification of interventions | Low risk | Treatment groups were clearly defined and as the study was prospective, the classification of intervention status would not have been affected by knowledge of the outcome |
| Bias due to deviations from intended interventions | Low risk | From the flow of participants through the protocol, there were no deviations from the intended treatments |
| Bias due to missing data | Serious risk | At 12 months, 71/102 (70%) intervention and 81/109 (74%) participants had outcome data for analysis. These proportions are reasonably balanced between the two treatment groups. However, reasons for attrition were not balanced across groups. Analyses were not likely to have removed risk of bias from missing data |
| Bias in measurement of outcomes | Low risk | For the outcome domain glycaemic control , the measurement methods (HbA1c, fasting, and post-prandial blood glucose) are objective observations. |
| | No information | There was no information regarding how body weight was measured. If it were measured by assessors when participants attended clinics, the risk of bias would be low. If it were self-reported, it would be open to systematic errors in measurement. |
| Bias in selection of reported result | Moderate risk | For the outcome domain glycaemic control , a brief description of statistical method presented and results reported align with this. Analyses were reported for all 3 outcome measures |
| | Serious risk | For the outcome domain body weight , there is a strong possibility of selective reporting of measurement outcomes, as there was no reporting of weight at 12 months. Significant differences from baseline were presented, but not non-significant differences, and no means or standard deviations for any time point. |
| Overall risk of bias judgment | Serious risk | For both outcome domains, there is a serious risk of bias due to potential confounders which may not have been controlled for and missing data. Although the proportion of attrition was reasonably balanced across the groups, the reasons for attrition were not. Further, for body weight, there is a risk of selective reporting, as there was no reporting of weight at 12 months. Overall there were low risks of bias attributed to the selection of participants into the study, classification of treatment groups; and the unlikelihood of deviations from intended treatments. |

Abbreviations: HbA1c, glycosylated haemoglobin; N, no; PN, probably no; PY, probably yes; Y, yes

Outcome domains assessed, in order of NTWC prioritisation: glycaemic control (HbA1c, the study's primary outcome, and fasting blood glucose and post-prandial blood glucose which were secondary outcome); and body weight (study's secondary outcome)

Table 38: Arentz 2017 overall ROB

| Arentz 2017 RCT PCOS | | |
|--|----------------------------|---|
| Domain | Judgement | Description |
| Bias arising from the randomisation process | Low risk | Random sequence generation: computer-generated permuted blocks externally generated. Baseline differences were slightly increased in medicine plus lifestyle intervention towards those who were students (8% v 19%) and lifestyle intervention towards those already using herbal medicine (57% v 45%). |
| Bias due to deviations from intended interventions | Low risk | Allocation concealment: Participants and clinicians were not blinded. Blind to group allocation. Stratification by BMI to prevent similar BMI women in the intervention and control group. |
| Bias due to missing outcome data | Low risk | Even number of withdrawals during the study between intervention and control groups. Subgroup analysis presented for (i) women who participated in blood tests and (ii) women who wanted to conceive. |
| Bias in measurement of the outcome | High risk | The methods of measuring the outcomes for oligomenorrhoea, anthropometry, reproductive hormones, and metabolic hormones were appropriate although oligomenorrhoea could have used time to event analyses. QoL, was a self-reported questionnaire and participants (as outcome assessors) knew which treatment they were receiving. |
| Bias in selection of the reported result | High risk | A priori and registered with ANZCTR Jan 2012 and all outcomes in methods were all reported in the results. Primary outcome: Oligomenorrhoea (page 1333). The mean (\pm standard deviation) number of days in the menstrual cycle for women assigned to the herbal medicine plus lifestyle was 106.0 (\pm 123.0) days at base line and for women allocated to the lifestyle intervention only group 109.5 (\pm 148.0) days, ($p=0.889$). This is longer than the 3 months (90 days) in the trial suggesting selective reporting bias. Wide confidence intervals for adjusted MDs and measures of variation (i.e. standard deviations) not reported for mean values. |
| OVERALL risk of bias | High risk (overall) | No placebo group, the study design was of two active comparators (Herbal medicine plus lifestyle vs lifestyle intervention program). Placebo effect (of two motivational consultants) not controlled for. Primary outcome: Oligomenorrhoea. The mean (\pm standard deviation) number of days in the menstrual cycle for women assigned to the herbal medicine plus lifestyle was 106.0 (\pm 123.0) days at base line and for women allocated to the lifestyle intervention only group 109.5 (\pm 148.0) days, ($p=0.889$). This is longer than the 3 months (90 days) in the trial suggesting selective reporting bias. QoL, was a self-reported questionnaire and participants (as outcome assessors) knew which treatment they were receiving. |

Abbreviations: ANZCTR=Australia and New Zealand Clinical Trial Registry; QoL= quality of life

Outcomes assessed, in order of NTWC prioritisation: oligomenorrhoea (primary outcome of the study), QoL, anthropometry, reproductive hormones and metabolic hormones.

Table 39: Arentz 2017 ROB Oligomenorrhoea

| Arentz 2017 RCT Oligomenorrhoea | | |
|---|-----------|-------------|
| Domain | Judgement | Description |
| Bias arising from the randomisation process | Low risk | As above |

| Arentz 2017 RCT Oligomenorrhoea | | |
|--|------------------------------------|---|
| Bias due to deviations from intended interventions | Low risk | As above |
| Bias due to missing outcome data | Low risk | As above |
| Bias in measurement of the outcome | High risk | As above |
| Bias in selection of the reported result | High risk | Primary outcome: Oligomenorrhoea (page 1333). The mean (\pm standard deviation) number of days in the menstrual cycle for women assigned to the herbal medicine plus lifestyle was 106.0 (\pm 123.0) days at base line and for women allocated to the lifestyle intervention only group 109.5 (\pm 148.0) days, ($p = 0.889$). This is longer than the 3 months (90 days) in the trial suggesting selective reporting bias. |
| OVERALL risk of bias | High risk (primary outcome) | Primary outcome: Oligomenorrhoea (page 1333). The mean (\pm standard deviation) number of days in the menstrual cycle for women assigned to the herbal medicine plus lifestyle was 106.0 (\pm 123.0) days at base line and for women allocated to the lifestyle intervention only group 109.5 (\pm 148.0) days, ($p = 0.889$). This is longer than the 3 months (90 days) in the trial suggesting selective reporting bias. Wide confidence intervals for adjusted MDs and measures of variation (i.e. standard deviations) not reported for mean values. |

Note: Oligomenorrhoea is the primary outcome

Table 40: Arentz 2017 ROB PCOSQ

| Arentz 2017 RCT PCOSQ | | |
|--|------------------------|---|
| Domain | Judgement | Description |
| Bias arising from the randomisation process | Low risk | As above |
| Bias due to deviations from intended interventions | Low risk | As above |
| Bias due to missing outcome data | Low risk | As above |
| Bias in measurement of the outcome | High risk | QoL was a self-reported questionnaire and participants (as outcome assessors) knew which treatment they were receiving. |
| Bias in selection of the reported result | Low risk | A priori and registered with ANZCTR Jan 2012 and all outcomes in methods were all reported in the results. |
| OVERALL risk of bias | High risk (QoL) | QoL was rated as high risk of bias because of being assessed by self-report and participants being aware of which treatment they received. |

Table 41: Arentz 2017 ROB subgroup – QUICKI

| Arentz 2017 RCT QUICKI | | |
|---|---------------|--|
| Domain | Judgement | Description |
| Bias arising from the randomisation process | Some concerns | The subgroup of women wanting to conceive included participants who self-identified during baseline data collection. |

| Arentz 2017 RCT QUICKI | | |
|--|--------------------------------|---|
| Bias due to deviations from intended interventions | Low risk | Allocation concealment: Participants and clinicians were not blinded. Blind to group allocation. Stratification by BMI to prevent similar BMI women in the intervention and control group. |
| Bias due to missing outcome data | Some concerns | Subgroup analysis only presented for women who wanted to conceive (n=51 out of 122). |
| Bias in measurement of the outcome | Low risk | The methods of measuring the outcomes for oligomenorrhoea, anthropometry, reproductive hormones, and metabolic hormones were appropriate. |
| Bias in selection of the reported result | Low risk | A priori and registered with ANZCTR Jan 2012 and all outcomes in methods were all reported in the results. |
| OVERALL risk of bias | Some concerns (overall) | Overall the outcome QUICKI was assessed as some concerns. Participants 'self-reported' wanting to conceive and were allocated to receive metabolic hormone concentration blood tests including QUICKI. |

Abbreviations: ANZCTR=Australia and New Zealand Clinical Trial Registry; BMI= body mQOL= quality of life; QUICKI= Quantitative Insulin Sensitivity Check Index

Table 42: Arentz 2017 ROB subgroup – Testosterone

| Arentz 2017 RCT Testosterone | | |
|--|--------------------------------|---|
| Domain | Judgement | Description |
| Bias arising from the randomisation process | Some concerns | The subgroup of women who participated in blood tests included women with oligomenorrhoea, selected in the order of recruitment and limited by the funding available for the doctoral study. |
| Bias due to deviations from intended interventions | Low risk | Allocation concealment: Participants and clinicians were not blinded. Blind to group allocation. Stratification by BMI to prevent similar BMI women in the intervention and control group. |
| Bias due to missing outcome data | Some concerns | Subgroup analysis presented for women who participated in reproductive hormones assessment (Oligomenorrhoea defined as menstrual cycle days 35-179 days) (n=71 out of 122). |
| Bias in measurement of the outcome | Low risk | The methods of measuring the outcomes for oligomenorrhoea, anthropometry, reproductive hormones, and metabolic hormones were appropriate. |
| Bias in selection of the reported result | Low risk | A priori and registered with ANZCTR Jan 2012 and all outcomes in methods were all reported in the results. |
| OVERALL risk of bias | Some concerns (overall) | Overall the outcome testosterone was assessed as some concerns. Participants who participated in blood tests (eg testosterone) included women with oligomenorrhoea, selected in the order of recruitment and limited by the funding available for this doctoral study. |

Abbreviations: ANZCTR=Australia and New Zealand Clinical Trial Registry

Table 43: Ratnakumari 2018 ROB

| Ratnakumari 2018 NRSI PCOS | | |
|----------------------------|--------------|---|
| Domain | Judgement | Description |
| Bias due to confounding | Serious risk | Weight, BMI, and waist and hip circumferences (potential confounders) were markedly greater in the intervention group compared to the comparator group at baseline, although it was not reported if they were statistically different. No mention if participants were using hormonal contraceptives. |

| Ratnakumari 2018 NRSI PCOS | | |
|--|----------------------|--|
| | | Menstrual regularity outcomes were not adjusted for any of these potential confounders |
| Bias in selection of participants into the study | Low risk | Participants were selected based on characteristics observed BEFORE the start of the intervention. Follow-up commenced with the start of the intervention. |
| Bias in classification of interventions | Low risk | Treatment groups were clearly defined; the classification of intervention status was known before outcomes were measured and so could not be affected by knowledge of outcomes. |
| Bias due to deviations from intended interventions | Moderate risk | There was no information presented regarding any deviations from the intended intervention. For example, it is not known if wait-list control participants decided to undertake yoga or naturopathy while 'waiting'. |
| Bias due to missing data | Low risk | Outcome data were reasonably complete and were available for 22/25 (88%) intervention and 22/25 (88%) control participants. |
| Bias in measurement of outcomes | Low risk | Although participants were aware of their intervention status, menstrual regularity is an objective observation. |
| Bias in selection of reported result | Critical risk | IQR is a not a measure of precision (it gives information about the distribution of effects, not confidence in the estimate). There are no CIs. The OIS, sample size is small |
| Overall risk of bias judgment | Critical risk | <p>The outcome domain assessed (menstrual regularity) is at serious risk of bias as potential confounding variables were not adjusted for. There was no information regarding any deviations from intended treatments.</p> <p>Other risk of bias domains were assessed as having low risk: the outcome data were reasonably complete; the outcome was an objective observation; treatment groups were clearly defined from the start of the intervention; and follow-up commenced with the start of the intervention.</p> <p>There was critical risk in selection of reported results due to imprecision. IQR is a not a measure of precision (it given information about the distribution of effects, not confidence in the estimate). There are no CIs. The OIS, sample size is small</p> |

Abbreviations: N, no; PN, probably no; PY, probably yes; Y, yes

Menstrual regularity was the outcome prioritised by NTWC. This was a secondary outcome of the study and was assessed by 3 methods: Last Menstrual Period to first cycle, first to second cycle, and second to third cycle durations.

Table 44: Beer 2004 ROB

| Beer 2004 NRSI Overweight and obesity | | |
|--|--------------|--|
| Domain | Judgement | Description |
| Bias due to confounding | Serious risk | Potential confounders are age, metabolic comorbidities such as type 2 diabetes and hyperlipidaemia, and type 2 diabetes medications (note that type 1 diabetes was an exclusion criterion). Of these, only age was measured and reported. No adjustments for confounders in the analyses |
| Bias in selection of participants into the study | Serious risk | The selection of participants partly relied on characteristics that developed AFTER the start of treatment, in that participants were excluded if they developed certain conditions. Eating disorders was one condition that may be related to the intervention (fasting therapy). No adjustments were made in the analyses. |

| Beer 2004 NRSI Overweight and obesity | | |
|--|----------------|---|
| Bias in classification of interventions | Low risk | The study clearly defined which therapy the participant groups would receive, being documented when the participants were admitted. This data was extracted from medical files by the researchers. |
| Bias due to deviations from intended interventions | Low risk | This was a retrospective study with no deviations from intended treatments reported. |
| Bias due to missing data | Low risk | No participants were excluded based on not having outcome data. |
| Bias in measurement of outcomes | Serious risk | Apart from weight at admission and at end of inpatient treatment, all other outcome measurements (including weight at telephone interview) were self-reported and subject to recall bias. |
| Bias in selection of reported result | Serious risk | For the outcome domain of weight/weight loss, the a priori statistical plan was poorly described. Bodyweight was reported in detail, but not BMI which was reported only at baseline, suggesting a risk of selective reporting of outcomes |
| | No information | For the outcome domains quality of life and changes in physical activity, both were assessed with one outcome method each, but there was a lack of information regarding multiple analyses. |
| Overall risk of bias judgment | Serious risk | Overall, the outcome domains assessed had a serious risk of bias, reflected by the potential confounding variables that were not measured or adjusted for, that participants were selected based on characteristics after the start of treatment, and that most of the outcome measurements were self-reported at the time of the telephone interview, being subject to recall bias. In addition, there may be selective reporting of weight and weight loss results where BMI was documented at baseline but not reported at other timepoints. There were low risks of bias for other domains in the tool: outcome data were reasonably complete; the treatment groups were clearly defined, and no participants were excluded based on having no outcome data. |

Abbreviations: N, no; PN, probably no; PY, probably yes; Y, yes

Outcome domains assessed, in order of NTWC prioritisation: weight/weight loss (body weight and body mass index); quality of life; and changes to physical activity. All are secondary outcomes of the study.

D.4. Anxiety

D.4.1. List of studies

| Study ID | Study type | Population | Citation |
|----------------|------------|------------|---|
| Bernhardt 2009 | RCT | Anxiety | Bernhardt B, Seely D, Cooley K, Szczurko O, Perri D, Mills EJ, et al. Naturopathic care for anxiety: A randomized controlled trial ISRCTN78958974. PLoS ONE. 2009;4(8):e6628. |

D.4.2. Risk of bias summary

Table 45: Bernhardt 2009 ROB

| Bernhardt 2009 RCT Anxiety | | |
|----------------------------|-----------|-------------|
| Domain | Judgement | Description |

| Bernhardt 2009 RCT Anxiety | | |
|--|--|---|
| Bias arising from the randomisation process | Low risk | For all outcomes assessed, there was centralised randomisation with concealment. Participants were blinded to treatment allocation and supplements were in opaque capsules, but participants could not be blinded to other aspects of treatment. No statistical difference between groups for baseline data. |
| Bias due to deviations from intended interventions | Low risk | For all outcomes assessed, participants were aware of whether they were receiving naturopathic care or psychotherapy. Thus, it is likely that carers would also know. Those providing the intervention would also be aware. It is stated in the discussion that there was 'no contamination' of either group (ie in terms of intervention) and so there were no deviations from intended interventions. Intention to treat analyses were conducted and were appropriate to estimate the effect of assignment to intervention. |
| Bias due to missing outcome data | Low risk | Anxiety symptoms: Outcome data available for 33/41 intervention and 31/40 comparator participants at 12 weeks. QoL: Outcome data for SF-36 and MYMOP subscales available for at least 34/40 intervention and 38/41 comparator participants at 12 weeks. Symptom burden: Outcome data for Fatigue Questionnaire and VAS Stress available for at least 36/40 intervention and 38/41 comparator participants at 12 weeks. For each outcome domain, data were available for nearly all participants, and reasons for attrition appear unrelated to study outcomes. |
| Bias in measurement of the outcome | High risk | For all three outcome domains, the measurement methods were appropriate but were self-reported. Thus, the assessors were the participants, who were aware of which treatment they were receiving. There may be strong beliefs about naturopathic care, which could influence the assessment of outcomes in favour of naturopathy. |
| Bias in selection of the reported result | Low risk | Outcome data were analysed according to a pre-specified protocol. Anxiety was assessed by only one measure; QoL and symptom burden each had 2 measurement methods and data from each measurement method were presented. Only one analysis method was used. No selective reporting of results for these outcomes. |
| OVERALL risk of bias | High risk (all assessed outcomes) | Anxiety symptoms, QoL, and symptom burden were at high risk of bias, as they were assessed by self-report measures and the participants could not be blinded. This potentially favours the intervention group. There was a low risk of bias for all other domains assessed: randomisation process was sound; outcome data were available for most participants; intention to treat analyses were appropriate; and results were not selectively reported where there were multiple outcome measurement methods. |

Abbreviations: MYMOP, Measure Yourself Medical Outcomes Profile; SF-36, Short Form 36; VAS, Visual Analog Scale

Outcome domains assessed, in order of NTWC prioritisation: anxiety (BAI, the study's primary outcome), QoL (SF-36, MYMOP), and symptom burden (Fatigue questionnaire and VAS)

D.5. Multiple sclerosis

D.5.1. List of studies

| Study ID | Study type | Population | Citation |
|-------------|------------|--------------------|---|
| Shinto 2008 | RCT | Multiple sclerosis | Shinto L, Calabrese C, Morris C, Yadav V, Griffith D, Frank R, et al. A randomized pilot study of naturopathic medicine in multiple sclerosis. <i>Journal of alternative and complementary medicine (New York, NY)</i> . 2008;14(5):489-96. |

D.5.2. Risk of bias summary

Table 46: Shinto 2008 ROB

| Shinto 2008 RCT MS | | |
|--------------------|-----------|-------------|
| Domain | Judgement | Description |

| Shinto 2008 RCT MS | | |
|--|----------------------------|---|
| Bias arising from the randomisation process | Some concerns | No information regarding randomisation process or concealment of allocation sequence. Baseline differences were not statistically significant and suggest no problem with randomisation process. |
| Bias due to deviations from intended interventions | Some concerns | Participants were not blinded to the intervention. There was no information regarding any deviations from intended interventions. All randomised participants completed the trial. |
| Bias due to missing outcome data | Low risk | All participants completed the trial |
| Bias in measurement of the outcome | Low risk | The outcome domains function/disability and cognitive impairment were assessed by neurologists who were blinded to treatment assignment (retention of blinding was 93%). The assessment tools were appropriate |
| Bias in selection of the reported result | Low risk | All measurement tools and the statistical methods were specified a priori; the results presented aligned with this. There were multiple eligible outcome measures for fatigue and function/disability, and all were presented. Only one analysis was conducted for each outcome measure. There was no evidence of selective reporting of results. |
| OVERALL risk of bias | High risk (overall) | The primary outcome of the study was QoL as assessed by the SF-36 and as a self-reported outcome, is at high risk of bias and potentially favours naturopathy. Overall, there were some concerns reflected in the lack of information of the randomisation process. There was a low risk of bias regarding the completeness of data and there was no evidence of selective reporting of results. |

Abbreviations: MS, Multiple Sclerosis

Table 47: Shinto 2008 ROB QOL

| Shinto 2008 RCT QOL | | |
|--|---------------|--|
| Domain | Judgement | Description |
| Bias arising from the randomisation process | Some concerns | As above |
| Bias due to deviations from intended interventions | Some concerns | As above |
| Bias due to missing outcome data | Low risk | As above |
| Bias in measurement of the outcome | High risk | The outcome domains fatigue and QoL were assessed by self-report using standardised questionnaires and the assessors (participants) were not blinded. There is potential for bias in favour of naturopathy |
| Bias in selection of the reported result | Low risk | As above |

| Shinto 2008 RCT QOL | | |
|-----------------------------|---------------------------------|---|
| OVERALL risk of bias | High risk (fatigue, QoL) | The outcome domains fatigue and QoL were rated as having a high risk of bias as they were assessed by self-report and the assessors (participants) were not blinded. This potentially favours naturopathy. |

Table 48: Shinto 2008 ROB function

| Shinto 2008 RCT Function | | |
|--|--|---|
| Domain | Judgement | Description |
| Bias arising from the randomisation process | Some concerns | As above |
| Bias due to deviations from intended interventions | Some concerns | As above |
| Bias due to missing outcome data | Low risk | As above |
| Bias in measurement of the outcome | Low risk | As above (overall) |
| Bias in selection of the reported result | Low risk | As above |
| OVERALL risk of bias | Some concerns (function/disability, cognitive impairment) | The outcome domains function/disability and cognitive impairment were rated as having some concerns regarding risk of bias, reflecting the lack of information around the randomisation process. |

Abbreviations: EDSS, Expanded Disability Status Score; MS, multiple sclerosis; MSFC, Multiple Sclerosis Functional Composite; MSQLI, Multiple Sclerosis Quality of Life Inventory; PASAT 3, Paced Auditory Serial Addition Test 3

Outcome domains assessed, in order of NTCW prioritisation: fatigue (Modified Fatigue Impact Scale (part of the MSQLI, secondary outcome) and the Multidimensional Fatigue Inventory (secondary outcome)); QoL (primary outcomes SF-36 physical and mental aggregate scales and the General Health scale); function/disability (secondary outcomes EDSS and MSFC); and cognitive impairment (secondary outcomes PASAT 3 and Stroop)

D.6. CVD

D.6.1. List of studies

| Study ID | Study type | Population | Citation |
|------------|------------|------------------------|---|
| Braun 2014 | NRSI | Cardiovascular disease | Braun L, Stanguts C, Spitzer O, et al. A wellness program for cardiac surgery improves clinical outcomes. <i>Advances in Integrative Medicine</i> . 2014;1(1):32-37 |

D.6.2. Risk of bias summary

Table 49: Braun 2014 ROB

| Braun 2014 NRSI CHD | | |
|--|---------------------|--|
| Domain | Judgement | Outcome |
| Domain 1: Bias due to confounding | Serious risk | There were confounding variables. Variables that were not balanced between intervention and comparator groups were controlled for in the multivariate analyses. Outcomes were stratified by the cardiac surgery type (CABG vs valve surgery). |
| Domain 2: Bias in selection of participants into the study | Low risk | For the intervention group, it is clear that follow-up commenced with the start of the integrative wellness treatment post-surgery. There is no information regarding the start of follow-up for the historical comparator group |
| Domain 3: Bias in classification of interventions | Low risk | The intervention and comparator groups are clearly defined and because the comparator group comprises historical controls, the groups are also separated by time. It is unlikely that the classification of treatment status could be affected by knowledge of any of the outcome domains. However, it is not stated whether the information used to define the comparator (usual care) group was recorded at the start of treatment. |
| Domain 4: Bias due to deviations from intended interventions | No information | The study acknowledges in the discussion that they did not assess for compliance with the intervention. There were no dropouts reported in the study and thus no reasons for dropping out were provided. |
| Domain 5: Bias due to missing data | Low risk | Data for the three outcome domains assessed were complete; there is no evidence to suggest participants were excluded due to missing data for confounding variables that were adjusted for in multivariate analyses |
| Domain 6: Bias in measurement of outcomes | Low risk | Although the study was open-label, the outcome domains were assessed using objective observations. |
| Domain 7: Bias in selection of reported result | Serious risk | A brief description of the statistical methods and the outcomes measurement methods were presented, and the results aligned with them. However, no a priori plan was found. Multiple outcome domains (for non-fatal cardiovascular events) and both univariate and multivariate analyses were presented. The study did not assess compliance with the intervention. |
| Overall risk of bias judgment | Serious risk | The risk of bias for this study overall is serious. There was no information regarding the start of follow-up for the historical comparator group and the study did not assess compliance with the intervention. Concerning other domains, there was a moderate risk of bias associated with confounding, and the statistical analysis method was only briefly described. There was low risk of bias associated with the classification of intervention status, the completeness of the data, and the objective nature of the outcome measurement method. |

Abbreviations: CABG, coronary artery bypass graft; CHD, coronary heart disease; N, no; PN, probably no; PY, probably yes; Y, yes

Outcome domains assessed, in order of NTWC prioritisation: non-fatal cardiovascular events (incidence of return to theatre due to bleeding and blood transfusion requirements; blood loss in 1st 4h post-surgery; and total blood loss post-surgery; hospital length of stay; and arrhythmias requiring treatment. All were primary outcomes of the study.

D.7. Allergic rhinitis

D.7.1. List of studies

| Study ID | Study type | Population | Citation |
|--------------|------------|-------------------|---|
| Mittman 1990 | RCT | Allergic rhinitis | Mittman P. Randomized, double-blind study of freeze-dried <i>Urtica dioica</i> in the treatment of allergic rhinitis. <i>Planta medica</i> . 1990;56(1):44-7. |

D.7.2. Risk of bias summary

Table 50: Mittman 1990 ROB

| Mittman 1990 RCT Allergic rhinitis | | |
|--|----------------------------|--|
| Domain | Judgement | Description |
| Bias arising from the randomisation process | Low risk | It was stated that the allocation was randomised but the method of randomisation was not stated. The allocation sequence had to be concealed, as the study was double-blind, and placebo controlled. Baseline data was not presented, and it is not known if there were differences between groups at baseline. |
| Bias due to deviations from intended interventions | Low risk | The trial was double-blind, and placebo controlled. There was no evidence of participants 'swapping' between treatment groups. Modified intention to treat analyses were appropriate (i.e. only participants with outcome data were analysed). |
| Bias due to missing outcome data | Low risk | All participants had outcome data. |
| Bias in measurement of the outcome | High risk | Although the trial was double-blind and placebo-controlled, the method for measuring outcomes was by patient diary without any mention of a standardised reporting method. This could be highly subjective and there was no information as to whether the recording method varied greatly between participants or between treatment groups. |
| Bias in selection of the reported result | Some concerns | There was no pre-specified protocol and the methodology presented was brief. Analyses were descriptive statistics and as there was only one analysis method and one method for measuring outcomes, there was no evidence of selective reporting of results although it was noted there were 29 were drop outs. There were two withdrawals in the nettle group that were not included in analysis. |
| OVERALL risk of bias | High risk (overall) | Efficacy outcomes were rated as high risk of bias, in light of the measurement method being highly subjective and non-standardised. It is not sufficient information to determine whether this would favour naturopathy or placebo treatments. All other risk of bias domains were rated as low risk: the study was double-blind and placebo-controlled; outcome data were available for all participants; no evidence of selective reporting of outcomes; and modified intention to treat analyses were appropriate. |

Abbreviations: ITT, intention to treat

Outcome domains assessed, in order of NTWC prioritisation: efficacy outcomes (% of whether there was a dramatic improvement, down to worse symptoms). This was the study's primary outcome.

D.8. Population grouping 3: LBP and rotator cuff

D.8.1. List of studies

| Study ID | Study type | Population | Citation |
|---------------|------------|-------------------------|---|
| Szczurko 2007 | RCT | Low back pain | Szczurko O, Cooley K, Busse JW, Seely D, Bernhardt B, Guyatt GH, et al. Naturopathic care for chronic low back pain: a randomized trial. PloS one. 2007;2(9): e919. |
| Szczurko 2009 | RCT | Rotator cuff tendinitis | Szczurko O, Cooley K, Mills EJ, Zhou Q, Perri D, Seely D. Naturopathic treatment of rotator cuff tendinitis among Canadian postal workers: a randomized controlled trial. Arthritis and rheumatism. 2009;61(8):1037-45. |

D.8.2. Risk of bias summary

Table 51: Szczurko 2007 ROB

| Szczurko 2007 RCT LBP | | |
|--|----------------------------|--|
| Domain | Judgement | Description |
| Bias arising from the randomisation process | Some concerns | No information regarding allocation sequence concealment. The baseline data suggests there is no problem with the randomisation process. |
| Bias due to deviations from intended interventions | Low risk | The trial was open-label. There was no mention of deviations from intended treatments arising from the trial context. Intention-to-treat analyses were appropriate. |
| Bias due to missing outcome data | High risk | Outcome data at end of treatment were available for 36/39 (92%) intervention and 23/30 (77%) comparator participants. This is not balanced between groups. 3 participants reported dropping out due to dissatisfaction with (comparator) treatment, which is likely to be associated with the 'true value' of the outcome. |
| Bias in measurement of the outcome | High risk | All outcome domains were assessed with self-report measures and the assessors (participants) were aware of their group allocation. There is a high risk of bias in favour of the naturopathy intervention. The self-report tools were mostly standardised and appropriate for the outcomes they assessed. |
| Bias in selection of the reported result | Low risk | Statistical analyses were detailed a priori in the methods and the trial protocol. The presentation of the results aligned with this. The statistician was blinded. One measurement method was used for the outcome domain pain; 2 methods were used each for outcome domains QoL (2 subscales of the one tool) and function/disability. All results were reported. There was only one analysis method used. There is no evidence of selective reporting of results. |
| OVERALL risk of bias | High risk (overall) | <p>All three outcome domains assessed were at high risk of bias due to the open-label design of the study, the attrition rates being substantially greater in the comparator group than the intervention group, and the self-reported measurement methods. The bias is likely to favour naturopathic treatment.</p> <p>There were some concerns regarding the concealment of the allocation process, but baseline data suggests no problems with the randomisation process. All other risk of bias domains were rated as low risk: there was no evidence of selective reporting of results and intention to treat analyses were appropriate.</p> |

Abbreviations: LBP, low back pain; QoL, quality of life; SF-36, Short Form 36; VAS, Visual Analogue Scale

Outcome domains assessed, in order of NTCW prioritisation: pain (secondary outcome VAS); QoL (primary outcome SF-36 (physical and mental aggregate scales)) and disability/physical functioning (primary outcome Oswestry disability questionnaire and secondary outcome Roland Morris Disability Questionnaire)

Table 52: Szczurko 2009 ROB

| Szczurko 2009 RCT Rotator cuff tendinitis | | |
|--|----------------------------|--|
| Domain | Judgement | Description |
| Bias arising from the randomisation process | Low risk | Randomisation was computerised and centralised, with allocation concealment preserved up to the point of treatment. Baseline characteristics showed no suggestion of a problem with the randomisation process. |
| Bias due to deviations from intended interventions | Some concerns | No information was reported regarding any deviations from intended interventions. Participants and those delivering the interventions are aware of treatment allocation. Modified ITT analyses were appropriate analyses, based on participants who had week 8 data. |
| Bias due to missing outcome data | High risk | 36/43 (84%) intervention participants and 32/42 (76%) comparator participants completed week 12 of the trial. It is not reported whether the participants who remained at week 12 had complete data for all outcomes. The proportion of participants who dropped out is not similar between the treatment groups, suggesting missing outcome data depended on the outcome value. No sensitivity analyses or other techniques were applied to correct for bias due to missing data. |
| Bias in measurement of the outcome | High risk | Pain, QoL, and treatment success were assessed by self-report. While the assessment tools were standardised, the participants were aware of their treatment allocation and there is a high risk of bias in favour of the naturopathy intervention. |
| | Low risk | The outcome domains function and range of motion were measured by assessors who were blinded to the participants' treatment. The assessment methods were appropriate. |
| Bias in selection of the reported result | Low risk | Statistical methods were pre-specified, and the results aligned with the method, comparing baseline to week 12. Statistical methods did not say they would compare weeks 4 or 8 data. Only one analysis method was applied to each outcome (paired t-tests). For the outcome domains pain, QoL, function, and treatment success, there was only 1 outcome measurement method for each. Only baseline and week 12 data were reported numerically; week 4 and week 8 were only reported graphically for total SPADI (function) and VAS (pain) outcomes. For range of motion, internal and external rotation were NOT reported despite being mentioned in the methodology; adduction, abduction, flexion, and extension were reported at baseline and 12 weeks. It does not appear likely that the omission of interim results (weeks 4 and 8) for QoL or the SPADI subscales, or internal/external rotation, were due to selective reporting of numerical results. |
| OVERALL risk of bias | High risk (overall) | All outcome domains were assessed as having a high risk of bias due to a higher proportion of participants dropping out of the comparator group compared to the intervention group. Reasons for dropping out were not available for all the participants. In addition, the outcome domains pain, QoL, and treatment success were measured by self-report, with the potential for bias in favour of the naturopathy intervention. There were some concerns for all the outcomes assessed as participant blinding could not be maintained when treatment started |

Szczurko 2009 RCT Rotator cuff tendinitis

and there was no information about deviations from intended treatments. Other risk of bias domains were assessed as low risk: the randomisation process was sound; and there did not appear to be selective reporting of results.

Abbreviations: ITT, intention to treat; MYMOP, Measure Yourself Medical Outcomes Profile; QoL, quality of life; SF-36, Short form 36; SPADI, Shoulder Pain and Disability Index; VAS, Visual Analogue Scale

Outcome domains assessed in order of NTWC prioritisation: pain (VAS); QoL (SF-36); function (SPADI - this was the trial's primary outcome); range of motion (maximal range of motion goniometer readings: flexion, extension, abduction, and adduction); and treatment success (MYMOP, 2 symptoms)

D.9. Menopausal symptoms

D.9.1. List of studies

| Study ID | Study type | Population | Citation |
|-------------|------------|---------------------|--|
| Cramer 2003 | NRSI | Menopausal symptoms | Cramer EH, Jones P, Keenan NL, Thompson BL. Is naturopathy as effective as conventional therapy for treatment of menopausal symptoms? Journal of alternative and complementary medicine (New York, NY). 2003;9(4):529-38 |

D.9.2. Risk of bias summary

Table 53: Cramer 2003 ROB

| Cramer 2003 NRSI Menopause | | |
|--|----------------|---|
| Domain | Judgement | Description |
| Bias due to confounding | Serious risk | Only age was adjusted for. Other potential confounders were HRT use, antidepressant use (may influence anxiety outcomes as well as vasomotor symptoms and sleep), and pre-existing mental illness (not assessed and may influence anxiety outcomes) |
| Bias in selection of participants into the study | Low risk | Participants were selected based on being diagnosed with menopausal symptoms and being over 40 years old. These are characteristics observed BEFORE the start of the intervention. It is likely that treatments did not start until after diagnosis for menopausal symptoms (start of follow-up) and therefore the start of follow-up and the start of intervention coincides for most participants. |
| Bias in classification of interventions | Low risk | Intervention groups clearly defined: had attended naturopathic clinic vs had not, using medical and billing records |
| Bias due to deviations from intended interventions | Low risk | The intervention was that a participant was treated by a naturopath, not whether they complied with or adhered to the treatment prescribed |
| Bias due to missing data | No information | All participants had data on intervention status. Participants were excluded from analyses of a particular outcome if there were not at least 2 visits to the naturopathy/ conventional care clinician for that symptom: there was no information as to how many participants this applied to. |
| Bias in measurement of outcomes | Serious risk | Although the assessors extracting data from medical and billing records were trained to standardise the process, they and the clinicians who recorded the outcome data were aware of the intervention received. The outcomes were not assessed using standardised tools; if self-reported by the participants for clinicians to record, this adds to the bias as participants are also aware of the intervention they received. Different clinicians also |

| Cramer 2003 NRSI Menopause | | |
|--------------------------------------|---------------|--|
| | | recorded the outcomes, which may also mean measurement processes between the two groups were different. |
| Bias in selection of reported result | Moderate risk | The statistical analysis plan was described briefly and the results appear aligned with it. Both unadjusted and adjusted odds ratios were presented for all outcome measures for all outcome domains, including for VMS. Subgroup analyses were conducted but not reported; this does not appear to be based on the results |
| Overall risk of bias judgment | Serious risk | <p>There was a serious overall risk of bias for all outcomes domains assessed from this study, stemming from confounding variables not being adjusted for in the analyses, the assessors not being blinded, and the lack of information on how the outcomes were measured when recorded by clinicians.</p> <p>There was no information regarding the number of participants excluded due to missing data (had less than 2 visits to clinicians for an outcome domain) and a moderate risk of bias reflected in the brevity of the a priori statistical analysis plan reported. There was a low risk of bias associated with the selection of participants into the study; the classification of treatment groups; and any deviations from intended treatments.</p> |

Abbreviations HRT, hormone replacement therapy; N, no; PN, probably no; PY, probably yes; VMS, vasomotor menopausal symptoms; Y, yes

Outcome domains assessed, in order of NTWC prioritisation: frequency of intensity of VMS (proportion of participants with hot flashes and improvements in decreased energy, vaginal dryness, and urinary complaints); menstrual changes; sleep; and anxiety. All were primary outcomes of the study.

D.10. Cardiovascular disease risk

D.10.1. List of studies

| Study ID | Study type | Population | Citation |
|------------|------------|-----------------------------|--|
| Seely 2013 | RCT | Cardiovascular disease risk | Seely D, Szczurko O, Cooley K, Fritz H, Aberdour S, Herrington C, et al. Naturopathic medicine for the prevention of cardiovascular disease: a randomized clinical trial. CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne. 2013;185(9): E409-16. |

D.10.2. Risk of bias summary

Table 54: Seely 2013 ROB

| Seely 2013 RCT CVD risk | | |
|--|---------------|--|
| Domain | Judgement | Description |
| Bias arising from the randomisation process | Low risk | For all outcome domains assessed, the process of randomisation was centralised, so it is likely the allocation sequence was concealed until participants were enrolled and assigned to interventions. From baseline characteristics, there does not appear to be a problem with the randomisation process. |
| Bias due to deviations from intended interventions | Some concerns | Participants and those delivering the intervention were aware of the assigned treatment (statisticians were not). There was no mention of any deviations from intended treatments arising from the trial context. The intention-to-treat analyses were appropriate. |

| Seely 2013 RCT CVD risk | | |
|--|---|--|
| Bias due to missing outcome data | Low risk | At 52 weeks only 82/124 (66.1%) of the intervention and 87/122 (71.3%) of comparator participants had outcome data. But the reasons for attrition were balanced across the groups and do not appear to depend on the trial's 'true value'. |
| Bias in measurement of the outcome | Low risk | For all outcome domains, assessors were aware of group allocations, but outcome measures were objective observations. |
| Bias in selection of the reported result | High risk of bias | <p>No <i>a priori</i> plan for the statistical methods were identified.</p> <p>Compared with the registry record, the paper reporting results of the trial reports:</p> <ul style="list-style-type: none"> • an additional time point for the primary outcomes (26 weeks) • additional secondary outcomes not in the registry record (Weight, Cholesterol (various), Blood pressure, BMI, Waist/hip measurements, Alcohol, caffeine, exercise, smoking, MYMOP). Some of the secondary outcomes were statistically significant and reported as such. • one outcome, quality of life, was meant to be measured by SF-36, but the MYMOP was also reported in the paper, and it was pointed out that there was statistical significance (but not with SF-36). <p>Only one statistical analysis was undertaken for each measurement method. So there is no evidence of selective reporting from multiple measurements or multiple analyses.</p> |
| OVERALL risk of bias | <p>Some concerns (overall)</p> <p>(POTENTIALLY HIGH RISK if any of the time points in the trial registry would have been reported in the SR if available)</p> | <p>There were some concerns about the risk of bias for all outcome domains assessed, due to participants not being blinded to their treatment allocation. However, outcome measurement methods were objective observations.</p> <p>Other domains were rated as being at low risk of bias: there does not appear to be a problem with the randomisation process; although the outcome data was not complete the reasons for attrition were balanced across the groups and did not appear related to the treatments; and there was no evidence of selective reporting of results.</p> <p>Selection of reported results was rated as high risk of bias. There was no <i>a priori</i> plan identified, compared to the trial registry there was an additional time point for primary outcomes at 26 weeks; additional secondary outcomes (Weight, Cholesterol, blood pressure, BMI, Waist/hip measurements, Alcohol, caffeine, exercise, smoking, MYMOP) were reported that were not in trial registry and QOL was meant to be SF-36 but MYMOP was also reported in the main paper.</p> |

Abbreviations: CVD, cardiovascular disease; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides

Outcome domains assessed, in order of NTWC prioritisation: CVD modifiable risk factors (Framingham 10-year cardiovascular risk score (primary outcome)); total and LDL cholesterol (secondary outcomes LDL and TC: HDL ratio); metabolic syndrome markers (prevalence of metabolic syndrome (primary outcome), waist circumference (part of assessing for metabolic syndrome), TG, HDL, SBP, DBP, FBG (secondary outcomes); and type 2 diabetes (secondary outcome HbA1c).

D.11. Overall summary of risk of bias for RCTs and NRSIs

Risk of bias for all included RCT

Figure 2: Risk of bias for all included RCTs

| Study | Risk of bias domains | | | | | Overall |
|-------------------|----------------------|----|----|----|----|---------|
| | D1 | D2 | D3 | D4 | D5 | |
| Arentz 2017 | - | + | - | ⊗ | ⊗ | ⊗ |
| Bernhardt 2009 | + | + | + | ⊗ | + | ⊗ |
| Mittman 1990 | + | + | + | ⊗ | - | ⊗ |
| Raghunath 2020 | + | - | + | - | + | - |
| Seely 2013 | + | - | + | + | ⊗ | ⊗ |
| Shinto 2008 | - | - | + | ⊗ | ⊗ | ⊗ |
| Szczurko 2007 | - | + | ⊗ | ⊗ | + | ⊗ |
| Szczurko 2009 | + | - | ⊗ | ⊗ | ⊗ | ⊗ |
| Stier-Jarmer 2021 | - | ⊗ | + | + | ⊗ | ⊗ |

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
⊗ High
- Some concerns
+ Low

Source: Risk of bias visual graphic performed in McGuinness, LA, Higgins, JPT. Risk of bias VISualization (robvis): An R package and Shiny web app for visualizing risk of bias assessments. Res Syn Meth. 2020; 1- 7. <https://doi.org/10.1002/jrsm.1411>

Risk of bias for all included NRSIs

Figure 3: Risk of bias for all included NRSIs

| Study | Risk of bias domains | | | | | | | Overall |
|------------------|----------------------|----|----|----|----|----|----|---------|
| | D1 | D2 | D3 | D4 | D5 | D6 | D7 | |
| Andersen 2018 | ⊗ | ⊗ | - | + | ⊗ | ⊗ | ⊗ | ⊗ |
| Bairy 2020 | ⊗ | + | + | + | ⊗ | ? | ⊗ | ⊗ |
| Beer 2004 | ⊗ | ⊗ | + | + | + | ⊗ | ⊗ | ⊗ |
| Braun 2013 | ⊗ | + | + | ? | + | + | ⊗ | ⊗ |
| Braun 2014 | ⊗ | + | + | ? | + | + | ⊗ | ⊗ |
| Cramer 2003 | ⊗ | + | + | ? | ? | ⊗ | - | ⊗ |
| Ratnakumari 2018 | ⊗ | + | + | - | + | + | ⊗ | ⊗ |

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
⊗ Critical
⊗ Serious
- Moderate
+ Low
? No information

Source: Risk of bias visual graphic performed in McGuinness, LA, Higgins, JPT. Risk of bias VISualization (robvis): An R package and Shiny web app for visualizing risk of bias assessments. Res Syn Meth. 2020; 1- 7. <https://doi.org/10.1002/jrsm.1411>

Appendix E: Detailed study descriptions and outcomes as reported by the study authors

Only prioritised outcomes are reported. These are the main outcomes of relevance to the review question, are essential outcomes for decision-making, and are those that form the basis of a 'Summary of findings' table.

E.1. Breast, colon, and prostate cancer

E.1.1. Breast cancer - NRSI

Data not included as the study was at critical risk of bias.

E.1.2. Colon cancer - RCT

Table 55: Raghunath 2020 colon cancer outcomes

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), | P-value reported by authors Direction of effect | Certainty of evidence |
|--|---|---|-----------------|--|---|---|---|--|--|-----------------------|
| Raghunath (2020) Study design: RCT N=116 | Adult patients who underwent surgery for adenocarcinoma of the colon (stages II and III), aged 18-65 years, 21 days from surgery without radiation, with adequate renal and liver function, ECOG performance status 0, 1, or 2. | Naturopathy, yoga and dietary interventions with adjuvant chemotherapy vs psychosocial counselling with adjuvant chemotherapy | Quality of life | Functional Living Index Cancer Higher total scores mean better QoL ^a | 18 months from 1 st cycle chemotherapy ('overall data') ^b | N=58 Mean = 90.159 | N=58 Mean = 82.54 | MD NR, SD = 3.66 | p<0.0001 Favours naturopathy | Very low |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NR, not reported

a Some subscales of the Functional Living Index Cancer are scored so that higher scores indicate worse symptoms or severity.

b Outcomes for this study were measured at baseline, 3 times during chemotherapy, and then at 9-, 12-, 15-, and 18-months follow-up from the first cycle of chemotherapy.

E.1.3. Prostate cancer – NRSI

Table 56: Braun 2013 prostate cancer outcomes

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI) | p-value reported by authors Direction of effect | Certainty of evidence |
|--|---|--|--------------------|---|---|---|---|---|--|--------------------------|
| Braun (2013) Study design: NRSI, retrospective N=134 | Men diagnosed with localised adenocarcinoma of the prostate between 2000 and 2004, who were treated with curative intent for limit-stage prostate cancer by radiation therapy (median age 62.0 y (range 46-81 y) intervention; 61.5 y (range 48-81 y) comparator) | Naturopathic and nutritional supplements + radiation therapy and hormone ablation therapy vs radiation therapy and hormone ablation therapy only | Tumour progression | Tumor progression (biochemical failure PSA>2ng/ml above PSA nadir) n participants (months follow-up) | N/A (Had received hormonal ablation) | N=39 n=2 (15 and 45) | N=38 n=2 (14 and 59) | N/A | NR | Very low |
| | | | | | N/A (Had not received hormonal ablation) | N=30 n=1 (29) | N=27 n=0 | N/A | NR | Very low |

Abbreviations: MD, mean difference; N/A, not applicable; NR, not reported; PSA, prostate-specific antigen

a <https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/prostate-cancer-testing>

E.2. T2DM, PCOS, overweight and obesity

E.2.1. T2DM – RCT

Table 57: Stier-Jarmer 2021 T2DM outcomes

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI) | p-value reported by authors Direction of effect | Certainty of evidence |
|--|--|--|----------------------|--|--|---|---|---|---|--------------------------|
| Stier-Jarmer (2021) Study design: RCT N=98 | Overweight or obese with type 2 diabetes. Mean age 61.5 y | Naturopathic treatment + diet vs diabetes- friendly holiday | Glycaemic control | HbA1c (%) Higher value means poorer glycaemic control Reference range 3.5% to 6.0% ^b | Change at 6 months from baseline | N=51 ^a MD = -0.67% SD = NR | N=47 ^a MD = -0.55% SD = NR | NR | Between groups: p=NR | Very low |
| | | | Body weight | Body weight (kg (%)) | Change at 6 months from baseline | N=51 ^a MD = -4.71 (- 4.65%) SD = NR | N=47 ^a MD = -3.95 (- 3.91%) SD = NR | NR | Between groups: p=not significant | Very low |

Abbreviations: HbA1c, glycosylated haemoglobin; MD, mean difference; NR, not reported

^a Three participants were lost to follow-up, but it is not reported how many were lost from intervention or comparator groups.

^b Royal College of Pathologists Australasia <https://www.rcpa.edu.au/Manuals/RCPA-Manual/Pathology-Tests>

E.2.2. T2DM – NRSI

Table 58: Bairy 2020 T2DM outcomes

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI) | P-value reported by authors Direction of effect | Certainty of evidence |
|---|--|--|-------------------|---|---|---|---|---|--|-----------------------|
| Bairy (2020) Study design: NRSI, prospective cohort N=211 | Adults aged 18-60 y old (mean age 51 y (SD 8.1 y) intervention; 48.8y (SD 8.1 y) comparator) with T2DM > 1 year attending outpatients clinics in the endocrinology department of a tertiary medical teaching hospital, HbA1c >7%, dependent on oral or parenteral hypoglycaemic agents, and with Zubrod's performance status 0-2 | Naturopathy and yoga-based lifestyle intervention vs conventional antidiabetic treatment | Glycaemic control | HbA1c% Lower values indicate benefit | Baseline | N=102 Mean = 9.6 SD = 1.8 | N=109 Mean = 9.0 SD = 1.7 | MD: NP | p=NP No analysis | Very low |
| | | | | | At end of intervention (3 months from baseline) | N=102 Mean = 7.5 SD = 1.8 | N=92 Mean = 8.2 SD = 1.2 | MD: NP | p<0.001 Favours naturopathy | |
| | | | | | At follow-up (6 months from baseline) | N=78 Mean = 7.9 SD = 1.5 | N=83 Mean = 8.4 SD = 1.6 | MD: NP | p=0.035 Favours naturopathy | |
| | | | | | At follow-up (12 months from baseline) | N=71 Mean = 8.5 SD = 1.7 | N=81 Mean = 8.4 SD = 1.7 | MD: NP | p=NS Groups similar | |
| | | | Body weight | Body weight (kg) Weight loss indicates benefit | Baseline | N=102 Mean = NP SD = NP | N=109 Mean = NP SD = NP | MD NP | p=NP No analysis | Very low |
| | | | | | At end of intervention (3 months from baseline) | N=102 Mean = NP SD = NP | N=92 Mean = NP SD = NP | MD: NP | p<0.01 Favours: NP | |

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI) | P-value reported by authors Direction of effect | Certainty of evidence |
|---|--------------------------|------------|-------------------|--|--|---|---|---|---|--------------------------|
| | | | | | At follow-up (6 months from baseline) | N=78 Mean = NP SD = NP | N=83 Mean = NP SD = NP | MD: NP | p<0.01 Favours: NP | |
| | | | | | At follow-up (12 months from baseline) | N=71 Mean = NP SD = NP | N=81 Mean = NP SD = NP | MD: NP | p=NS Favours: NP | |

Abbreviations: NP, not presented; NS, not significant

a Post hoc Bonferroni corrected tests

ITT analyses

E.2.3. PCOS - RCT

Table 59: Arentz 2017 PCOS outcomes

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI) | P-value reported by authors Direction of effect | Certainty of evidence |
|---|---|---|--------------------------|---|---|---|---|--|---|--------------------------|
| Arentz (2017) Study design: Parallel RCT N=122 | 122 women, aged 18-44 y with a confirmed medical diagnosis of PCOS, BMI≥24.5kg/m ² | Lifestyle intervention + naturopathic consultations + herbal tablets vs lifestyle intervention only | Menstrual regularity | Number of days in the menstrual cycle Oligomenorrhoe a defined as irregular menstruation or 35-179 days between menstrual periods | Baseline | N=60 Mean = 106.0 SD = 123.01 | N=62 Mean = 109.5 SD = 148.0 | MD 3.5, (95% CI NP) | p=0.889 Groups similar | Low |
| | | | | | At end of intervention (3 months) | N=60 Mean = 63.7 SD = NP | N=62 Mean = 106.6 SD = NP | MD ^b -42.9 (-64.8, -21.1) Effect size $\eta^2_p=0.11$ | p<0.01 (for MD) Favours naturopathy | |
| | | | Quality of Life | PCOSQ (25- 182) Higher score means poorer QoL ^a | At end of intervention (3 months) | N=60 Mean = 81.5 SD = NP | N=62 Mean = 109.3 SD = NP | MD ^b -31.1 (-41.4, -20.7) Effect size $\eta^2_p=0.3$ | p<0.01 (for MD) Favours naturopathy | Low |
| | | | Metabolic indices | QUICKI Lower scores indicate greater insulin resistance | At end of intervention (3 months) | N=26 Mean = 0.32 SD = NP | N=25 Mean = 0.35 SD = NP | MD ^b 0.002 (-0.06, 0.12) Effect size $\eta^2_p=0.03$ | p=0.24 (for MD) Groups similar | Very low |
| | | | Reproductive hormones | Testosterone nmol/L Reference range 0.3-1.8nmol/L ^c | At end of intervention (3 months) | N=34 Mean = 1.63 SD = NP | N=37 Mean = 1.59 SD = NP | MD ^b -0.04 (-0.33, 0.25) Effect size $\eta^2_p<0.01$ | p=0.79 (for MD) Groups similar | Very low |

Abbreviations: NP, not presented; PCOS, polycystic ovarian syndrome; PCOSQ, Polycystic Ovarian Syndrome Questionnaire; QoL, quality of life; QUICKI, Quantitative Insulin Sensitivity Check Index

η^2_p value of 0.01 was interpreted as a small effect size, 0.02 to 0.06 as medium and 0.07 to 0.14 as a large effect size

a For this study, higher score means poorer QoL; normally the PCOSQ is scored such that higher score means better QoL

b Adjusted for baseline values using ANCOVA

c <https://www.clinicallabs.com.au/about-us/doctor-media-releases/minor-changes-to-androgen-reference-ranges/>

E.2.4. Overweight and obesity - NRSI

Table 60: Beer 2014 overweight and obesity outcomes

| Study ID Type No. participants | Population / condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI) | p-value reported by authors Direction of effect | Certainty of evidence |
|--|--|---|--------------------|---|--|---|---|---|--|-----------------------|
| Beer (2014) Study design: NRSI, retrospective follow-up N=275 randomised, 169 included | Adults aged 20 to 70 years; overweight (BMI ≥ 25kg/m ²) or obese (BMI ≥ 30kg/m ²) at the time of treatment | Modified Buchinger fasting therapy vs weight reduction diet | Weight/Weight loss | Weight reduction kg | At admission | N=122 Mean = 86.0 SD = 14.1 | N=47 Mean = 89.7 SD = 14.3 | MD NP | P = NP | N/A |
| | | | | | At telephone interview | N = 122 Mean = 86.5 SD = 15.6 | N=47 Mean = 87.1 SD 16.8 | MD NP | P = NP | N/A |
| | | | | | Change from admission to interview | | | MP NP | P = NP | Very low |
| | | | Quality of Life | Improvement in quality of life | Sustained improvement from enrolment, % participants | N = 122 16% | N = 47 28% | MD NP | Between groups: p=0.008 Direction of effect unclear | Very low |
| | | | | | Improvement for some time, % participants | N = 122 44% | N = 47 19% | | | |
| | | | | | | | | | | |

| Study ID Type No. participant s | Population / condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI) | p-value reported by authors Direction of effect | Certainty of evidence |
|---------------------------------|------------------------|------------|------------------------------|--|--------------------------------|---|---|---|--|-----------------------|
| | | | | | No improvement, % participants | N = 122 40% | N = 47 53% | | P = NP Direction of effect unclear | |
| | | | Changes to physical activity | Persistent increase in leisure time activity, % participants | From enrolment to interview | N = 122 21% | N = 47 40% | MD NP | Difference in increase between groups: p=0.041 Direction of effect unclear | Very low |
| | | | | Increase in activity for some time, % participants | From enrolment to interview | N=122 7% | N=47 4% | | P = NP Direction of effect unclear | |
| | | | | No increase in activity % participants | From enrolment to interview | N=122 71% | N=47 55% | | P= NP Direction of effect unclear | |

Abbreviations: NP, not presented

E.3. Anxiety

E.3.1. RCTs

Table 61: Bernhardt 2009 anxiety outcomes

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI) | p-value reported by authors Direction of effect | Certainty of evidence |
|---|---|--|-------------------|--|--|---|---|--|---|--------------------------|
| Bernhardt 2009 RCT N = 81 | Adults with moderate to severe anxiety for longer than 6 weeks (mean age 52.02 y (SD 10.95 y) intervention; age 51.28 y (SD 8.18 y) comparator) | Naturopathy care (dietary counselling + deep breathing relaxation techniques + standard multi-vitamin + herbal medicine) vs psychotherapy + matched deep breathing relaxation techniques + placebo | Anxiety symptoms | BAI (0-63) Higher scores mean greater anxiety | Baseline | N=41 Mean = 23.54 SD = 10.13 | N=40 Mean = 23.45 SD = 11.2 | Difference of changes between groups: -6.16 (-10.24, -2.08) | p=0.0036 Favours naturopathy | Very low |
| | | | | | At end of intervention (week 12 from baseline) | N=36 Mean = 10.89 SD = 11.69 | N=39 Mean = 16.28 SD = 10.89 | | | |
| | | | Quality of Life | SF-36 -aggregate physical component higher score means better QoL | Baseline | N=36 Mean = 46.23 SD = 7.99 | N=39 Mean = 45.51 SD = 8.82 | Difference of changes between groups: 3.26 (-0.15, 6.66) | p=0.0608 Groups similar | Very low |
| | | | | | At end of intervention (week 12 from baseline) | N=34 Mean = 49.83 SD = 7.24 | N=38 Mean = 46.59 SD = 7.98 | | | |
| | | | | SF-36 -aggregate mental component higher score means better QoL | Baseline | N=36 Mean = 38.97 SD = 9.81 | N=39 Mean = 39.03 SD = 9.95 | Difference of changes between groups: | p=0.0001 Favours naturopathy | Very low |

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI) | p-value reported by authors Direction of effect | Certainty of evidence |
|---|--------------------------|------------|--|---|---|---|---|--|---|--------------------------|
| | | | | | <i>At end of intervention (week 12 from baseline)</i> | <i>N=34 Mean = 50.92 SD = 7.29</i> | <i>N=38 Mean = 41.54 SD = 10.61</i> | <i>10.34 (5.21, 15.46)</i> | | |
| | | | <i>Symptom burden/sever- ity</i> | <i>Ability to cope with stress since start of treatment, VAS Higher scores indicate more positive subjective impressions</i> | <i>Baseline</i> | <i>N = 40 Mean = 5.00 SD = 1.26</i> | <i>N = 39 Mean = 4.41 SD = 1.23</i> | <i>Difference of changes between groups: 0.81 (0.24, 1.37)</i> | <i>p=0.0055 Favours naturopathy</i> | <i>Very low</i> |
| | | | | | <i>At end of intervention (week 12 from baseline)</i> | <i>N = 36 Mean = 5.83 SD = 0.85</i> | <i>N = 38 Mean = 4.45 SD = 1.11</i> | | | |

Abbreviations: BAI, Beck Anxiety Inventory; MYMOP, Measure Yourself Medical Outcomes Profile; SF-36, Short Form 36; VAS, Visual Analog Scale

E.4. Multiple sclerosis

E.4.1. RCTs

Table 62: Shinto 2008 MS outcomes

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | | p-value reporter by authors Direction of effect | Certainty of evidence |
|--|---|---|-------------------|---|-----------|---|--|---|---|-----------------------------|
| Shinto (2008) Study design: RCT, 3 arms =45 | Individuals with MS defined by Poser criteria, relapsing- remitting course of MS, and EDSS≤6.0, mean age 43.5y (SD 9.2 y) | Naturopathic treatment + usual care vs usual care only vs focused education visits + usual care | Fatigue | Modified Fatigue Impact Scale (part of MSQLI) Change from baseline Higher scores mean greater fatigue | 6 months | N = 15 Mean change = 0.93 SD = 3.0 | N = 15 Mean change = -0.20 SD = 4.2 | N = 15 Mean change = 0.29 SD = 3.0 | P = 0.68 Groups similar | Very low |
| | | | Quality of life | SF-36 ^a – aggregate physical component Change from baseline Higher scores mean better QoL | 6 months | N = 15 Mean change = 1.5 SD = 5.9 | N = 15 Mean change = -0.30 SD = 6.4 | N = 15 Mean change = 1.5 SD = 5.0 | P=0.64 Groups similar | Very low |
| | | | | SF-36 ^a – aggregate mental component Change from baseline Higher scores mean better QoL | 6 months | N = 15 Mean change = 0.10 SD = 6.5 | N = 15 Mean change = -1.2 SD = 9.0 | N = 15 Mean change = 0.40 SD = 9.7 | P=0.85 Groups similar | Very low |

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | | p-value reporter by authors Direction of effect | Certainty of evidence |
|---|--------------------------|------------|-------------------------|--|-----------|---|---|--|---|-----------------------------|
| | | | | SF-36 ^a – general health Change from baseline Higher scores mean better QoL | 6 months | N = 15 Mean change = 7.9 SD = 10.6 | N = 15 Mean change = -3.1 SD = 18.1 | N = 15 Mean change = 4.8 SD = 13.2 | P=0.11 Groups similar | Very low |
| | | | Function/ disability | EDSS Change from baseline Higher scores mean greater disability | 6 months | N = 15 Mean change = 0.20 SD = 0.4 | N = 15 Mean change = -0.33 SD = 0.6 | N = 15 Mean change = - 0.07 SD = 0.8 | P=0.07 Groups similar | Very low |
| | | | | Multiple Sclerosis Functional Composite (MSFC) Change from baseline z-score change: +1 means 1 SD better than reference population | 6 months | N = 15 Mean change = 0.09 SD = 0.39 | N = 15 Mean change = 0.09 SD = 0.37 | N = 15 Mean change = - 0.14 SD = 0.53 | P=0.24 Groups similar | Very low |
| | | | Cognitive impairment | PASAT 3 Change from baseline Higher scores mean favourable status | 6 months | N = 15 Mean change = 0.18 SD = 0.44 | N = 15 Mean change = 0.15 SD = 0.31 | N = 15 Mean change = 0.32 SD = 0.38 | P=0.45 Groups similar | Low |

Abbreviations: EDSS, Expanded Disability Status Score; MS, multiple sclerosis; MSQLI, Multiple Sclerosis Quality of Life Inventory; PASAT 3, Paced Auditory Serial Addition Test 3
a The MSQLI incorporates the SF-36 scale to measure quality of life, supplemented with nine symptom-specific measures, including fatigue.

E.5. Cardiovascular disease

E.5.1. NRSI

Table 63: Braun 2014 CVD outcomes

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | p-value reported by authors Direction of effect | Certainty of evidence |
|---|--|---|----------------------------------|---|--------------|--|--|---|-----------------------|
| Braun (2014) Study design: NRSI, clinical audit N=922 | Elective cardiothoracic surgical patients, mean age 65-68 y (SD 10.5-13 y) | Integrative Cardiac Wellness Program including treatment by naturopaths vs usual care | Non- fatal cardiovascular events | Incidence of return to theatre due to bleeding and blood transfusion requirements, n(%) | Post-surgery | CABG: N=176 n = 5 (2%) Valve: N = 161 n = 6 (4%) | CABG: N = 354 n = 11 (3%) Valve: N = 231 n = 6 (4%) | CABG: P (univariate) = 0.34 P (multivariate) ^a = 0.71 Groups similar Valve: P (univariate) = 0.93 P (multivariate) ^a = 0.76 Groups similar | Very low |
| | | | Hospitalisation length of stay | Length of stay (days) | Post-surgery | CABG: N=176 Median = 6.5 IQR = 6-8 Valve: N = 161 Median = 8 IQR = 7-12 | CABG: N = 354 Median = 6 IQR = 5-8 Valve: N = 231 Median = 8 IQR = 6-13 | CABG: P (univariate) =0.17 P (multivariate) ^a =0.09 Groups similar Valve: P (univariate) = 0.12 P (multivariate) ^a = 0.13 Groups similar | Very low |

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | p-value reported by authors Direction of effect | Certainty of evidence |
|--------------------------------|-----------------------|------------|--------------------------------|---|--------------|---|--|--|-----------------------|
| | | | Arrhythmia requiring treatment | Atrial fibrillation prevalence n (%) | Post-surgery | CABG: N=176 n = 46 (26%) Valve: N = 161 34%, SD=4% | CABG: N = 354 n = 126 (36%) Valve: N = 231 36%, SD = 3% | CABG: <i>P (univariate) = 0.029</i> <i>P (multivariate)^a = 0.56</i> Groups similar Valve: <i>P (univariate) = 0.56</i> <i>P (multivariate)^a = 0.25</i> Groups similar | Very low |

Abbreviations: CABG, coronary artery bypass graft; IQR, interquartile range

^a Multivariate analysis adjusted for myocardial infarction, congestive heart failure, left main stenosis, Canadian cardiovascular society classification, number of diseased coronary systems and number of distal anastomoses.

E.6. Allergic rhinitis

E.6.1. RCTs

Table 64: Mittman 1990 allergic rhinitis outcomes

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), p- value reported by authors Direction of effect | Certainty of evidence |
|--|--|--|-------------------|--|--------------------------|---|--|--|-----------------------------|
| Mittman (1990) Study design: RCT N=98 | Volunteers with at least 2 of the following symptoms of allergic rhinitis, in at least moderate severity: rhinorrhea, sinus congestion, excessive lacrimation (mean age 34.7 y (range 20-74 y) intervention; | Urtica dioica (stinging nettle) vs placebo | Efficacy outcomes | Effectiveness ratings of the medicines within 1 h of intake Dramatic improvement n(%) | At end of trial (1 week) | N=31 Never: 21 (68%) <50% of time: 5 (16%) >50% of time: 5 (16%) | N=38 Never: 32 (84%) <50% of time: 5 (13%) >50% of time: 1 (3%) | NR | Very low |
| | | | | Moderate improvement n(%) | | Never: 5 (16%) <50% of time: 11 (36%) >50% of time: 15 (48%) | Never: 11 (29%) <50% of time: 15 (39%) >50% of time: 12 (32%) | NR | Very low |
| | | | | No change n(%) | | Never: 8 (26%) <50% of time: 4 (13%) >50% of time: 19 (1%) | Never: 2 (5%*) <50% of time: 9 (24%*) >50% of time: 27 (71%)5 | NR | Very low |

| Study ID Type No. participants | Population/condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), p-value reported by authors Direction of effect | Certainty of evidence |
|--------------------------------|----------------------|------------|----------------|---|-----------|---|--|---|-----------------------|
| | | | | Worse n(%) | | Never: 21 (68%) <50% of time: 10 (32%) >50% of time: 0 (0%) | Never: 25 (66%) <50% of time: 12 (31%*) >50% of time: 1 (3%) | NR | Very low |

Abbreviations: NR, not reported

* denotes percentage rounding error in Millman 1989 corrected by evaluators

E.7. LBP and rotator cuff

E.7.1. LBP- RCT

Table 65: Szczurko 2007 LBP outcomes

| Study ID Type No. participants | Population/condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), | P-value reported by authors Direction of effect | Certainty of evidence |
|--------------------------------|---|-----------------------------------|----------------|---|-----------|---|---|--|--|-----------------------|
| Szczurko (2007) | Adults with low back pain of non-specific cause for preceding 6 | Naturopathic care vs standardised | Pain | Self-reported pain scale (10 points) | Baseline | N = 39 Median = 2 IQR = 1, 3 | N = 30 Median = 2 IQR = 1, 2 | Point estimate: NP | Between groups: p<0.0001 | Very low |

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), | P-value reported by authors Direction of effect | Certainty of evidence |
|--------------------------------|--|----------------------|----------------------------------|--|---|---|---|--|---|-----------------------|
| Study design: RCT N=75 | weeks (mean age 45.3 y (SD 7.46 y) intervention, 48.02 y (SD 8.27 y) comparator) | physiotherapy advice | | | End of treatment (12 weeks from randomisation) | N = 39 Median = 1 IQR = 0, 1.5 | N = 27 Median = 2 IQR = 1, 2 | | Favours naturopathy | |
| | | | Quality of Life | SF-36 – aggregate mental component Higher score means better QoL | Baseline | N = 39 Mean = 47.30 SD = 11.46 | N = 30 Mean = 51.57 SD = 8.05 | MD of changes between groups: 7.00 (2.25, 11.75) | p= 0.0045 Favours naturopathy | Very low |
| | | | | | End of treatment (12 weeks from randomisation) | N = 39 Mean = 49.15 SD = 11.18 | N = 27 Mean = 47.57 SD = 10.03 | | | |
| | | | Disability/ physical functioning | Oswestry disability questionnaire Higher scores mean greater disability | Baseline | N = 39 Median = 10 IQR = 5, 16 | N = 30 Median = 9 IQR = 4, 6 | Point estimate: NP | Between groups: p<0.0001 Favours naturopathy | Very low |
| | | | | | End of treatment (12 weeks from randomisation) | N = 39 Median = 4 IQR = 1, 9 | N = 27 Median = 12 IQR = 4, 16 | | | |

Abbreviations: IQR, interquartile range; NP, not presented; QoL, quality of life

At week 12, there were 36 intervention and 23 comparator participants remaining. Intention to treat analyses were undertaken based on participants remaining at week 8 (39 intervention and 27 comparator). Missing data at week 12 were imputed from week 8 data.

E.7.2. Rotator cuff - RCT

Table 66: Szczurko 2009 rotator cuff tendinitis outcomes

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measuremen t details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), p- value direction of effect | P-value reported by authors Direction of effect | Certainty of the evidence |
|--|--|--|-------------------|--|--------------------------------------|---|---|--|---|------------------------------|
| Szczurko (2009) Study design: RCT N=85 | Postal workers with rotator cuff tendinitis (18-65 y old) | Naturopathic care vs standardised physical exercises | Pain | VAS Higher score means more pain | Baseline | N=43 Mean = 5.09 SD = 1.52 | N=42 Mean = 4.85 SD = 1.48 | MD between groups: -1.67 (-2.47, -0.88) | p=0.0001 Favours naturopathy | Very low |
| | | | | | At end of treatment (12 weeks) | N=41 Mean = 2.75 SD = 1.77 | N=36 Mean = 4.05 SD = 1.69 | | | |
| | | | Quality of Life | SF-36 – aggregate mental component Higher score means better QoL | Baseline | N=43 Mean = 44.22 SD = 11.66 | N=42 Mean = 50.13 SD = 11.38 | MD between groups: 5.73 (1.37, 10.09) | p=0.0107 Favours naturopathy | Very low |
| | | | | | At end of treatment (12 weeks) | N=41 Mean = 46.19 SD = 8.88 | N=36 Mean = 50.05 SD = 10.40 | | | |
| | | | Function | Shoulder Pain and Disability Index (SPADI) – total | Baseline | N=43 Mean = 77.64 SD = 29.38 | N=42 Mean = 69.61 SD = 24.11 | MD between groups: -29.66 | p<0.0001 Favours naturopathy | Very low |

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), p-value direction of effect | P-value reported by authors Direction of effect | Certainty of the evidence |
|--------------------------------|-----------------------|------------|--|---|--------------------------------|---|---|--|---|---------------------------|
| | | | | Higher score means more pain and disability | At end of treatment (12 weeks) | N=41 Mean = 35.30 SD = 31.57 | N=36 Mean = 56.24 SD = 36.57 | (-42.35, -16.98) | | |
| | | | Range of motion - Shoulder maximal range of motion | Abduction - maximal range of motion goniometer readings | Baseline | N=43 Mean = 101.17 SD = 44.24 | N=42 Mean = 104.47 SD = 44.73 | MD between groups: 46.57 (31.21, 61.94), | p<0.0001 Favours naturopathy | Very low |
| | | | | Higher values mean greater range of motion | At end of treatment (12 weeks) | N=41 Mean = 148.63 SD = 34.73 | N=36 Mean = 105.36 SD = 45.05 | | | |
| | | | Treatment success | Measure Yourself Medical Outcomes Profile (MYMOP) symptom 1 Higher scores mean worse level of health | Baseline | N=43 Mean = 5.62 SD = 1.21 | N=42 Mean = 5.48 SD = 1.31 | MD between groups: -0.91 (-1.68, -0.13) | p=0.0225 Favours naturopathy | Very low |
| | | | | | At end of treatment (12 weeks) | N=41 Mean = 3.59 SD = 1.72 | N=36 Mean = 4.08 SD = 1.76 | | | |
| | | | | Measure Yourself Medical Outcomes | Baseline | N=43 Mean = 5.36 | N=42 Mean = 3.03 | MD between groups: -1.86 | p=0.0001 | Very low |

| Study ID Type No. participants | Population/condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), p-value direction of effect | P-value reported by authors Direction of effect | Certainty of the evidence |
|--------------------------------|----------------------|------------|----------------|---|---------------------------------------|---|---|---|--|---------------------------|
| | | | | <i>Profile (MYMOP) symptom 2</i> <i>Higher scores mean worse level of health</i> | | <i>SD = 1.36</i> | <i>SD = 1.58</i> | <i>(-2.73, -1.00)</i> | <i>Favours naturopathy</i> | |
| | | | | | <i>At end of treatment (12 weeks)</i> | <i>N=41</i> <i>Mean = 3.03</i> <i>SD = 1.58</i> | <i>N=36</i> <i>Mean = 4.38</i> <i>SD = 1.68</i> | | | |

Abbreviations: QoL, quality of life; VAS, visual analog scale

Intention to treat analyses were based on participants with available data at week 8. At week 12, 36 intervention and 32 comparator participants remained. Missing data at week 12 were imputed from week 8 data.

E.8. Menopausal symptoms

E.8.1. NRSI

Table 67: Cramer 2003 menopause outcomes

| Study ID Type No. participants | Population/ condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), p-value reported by authors direction of effect | Certainty of the evidence |
|---|--|---|---|--|---|---|--|---|------------------------------|
| Cramer (2003) Study design: NRSI, retrospective cohort N=239 | Women aged ≥40 y with a diagnosis of menopausal symptoms | Comprehensive aggregate system of naturopathic care vs conventional therapy | Frequency or intensity of vasomotor menopausal symptoms (VMS) | Hot flashes | Baseline (proportion with symptoms) | N = 79 n/N = 55/79 (69.6%) | N = 160 n/N = 89/160 (55.6%) | P = 0.038 Favours conventional therapy | Very low |
| | | | | | N/A) | n/N = 25/55 (36.4%) | n/N=27/89 (30.3%) | P=0.110 OR = 1.50 (0.90, 2.51), p=0.119 Adj OR = 1.40 (0.68, 2.88), p=0.359 Groups similar | |
| | | | | Menopause symptoms | Baseline | N=79 n/N = 33/79 (41.8%) | N=160 n/N = 39/160 (24.4%) | P=0.006 Favours conventional therapy | |
| | | | Decreased energy (proportion improved) | N/A | n/N=12/33 (36.4%) | n/N=6/39 (15.4%) | P=0.039 OR = 2.46 (0.86, 7.03), p=0.093 Adj OR = 6.55 (0.96, 44.74), p=0.056 | Very low | |

| Study ID Type No. participants | Population/condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), p-value reported by authors direction of effect | Certainty of the evidence |
|--------------------------------|----------------------|------------|--------------------------|--|-----------------|---|---|--|---------------------------|
| | | | | | | | | <i>Groups similar</i> | |
| | | | <i>Menstrual changes</i> | <i>Menstrual changes (proportion with symptoms)</i> | <i>Baseline</i> | <i>N=79 n/N = 35/79 (44.3%)</i> | <i>N=160 n/N = 83/160 (51.9%)</i> | <i>P=0.271 Groups similar</i> | <i>Very low</i> |
| | | | | <i>Menstrual changes (proportion improved over time)</i> | <i>N/A</i> | <i>n/N=9/35 (25.7%)</i> | <i>n/N=28/83 (33.7%)</i> | <i>P=0.373 OR = 0.74 (0.34, 1.58), p=0.431 Adj OR = 0.98 (0.43, 2.24), p=0.973 Groups similar</i> | |
| | | | <i>Sleep</i> | <i>Insomnia (proportion with symptoms)</i> | <i>Baseline</i> | <i>N=79 n/N = 45/79 (57.0%)</i> | <i>N=160 n/N = 53/160 (33.1%)</i> | <i>P=0.001 Favours naturopathy</i> | <i>Very low</i> |
| | | | | <i>Insomnia (proportion improved)</i> | <i>N/A</i> | <i>n/N=17/45 (37.8%)</i> | <i>n/N=9/53 (17.0%)</i> | <i>P=0.019 OR = 2.18 (1.92, 2.47), p= 0.119 Adj OR = 6.77 (1.71, 26.63), p=0.006 Favours naturopathy</i> | |

| Study ID Type No. participants | Population/condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), p-value reported by authors direction of effect | Certainty of the evidence |
|--------------------------------|----------------------|------------|----------------|---|-----------|---|---|---|---------------------------|
| | | | Anxiety | Anxiety (proportion with symptoms) | Baseline | N=79 n/N = 61/79 (77.2%) | N=160 n/N = 88/160 (55.0%) | P=0.100 Groups similar | Very low |
| | | | | Anxiety (proportion improved) | N/A | n/N=28/61 (45.5%) | n/N=29/88 (32.9%) | P=0.110 OR = 1.41 (0.89, 2.25), p=0.129 Adj OR = 1.27 (0.63, 2.56), p=0.500 Groups similar | |

Abbreviations: Adj OR, adjusted odds ratio; N/A, not applicable; OR, odds ratio

Adjusted OR: adjusted for age, weight, smoking status, monthly income, regular exercise program, antihypertensive therapy

E.9. Cardiovascular disease risk

E.9.1. RCTs

Table 68: Seely 2013 CVD risk outcomes

| Study ID Type No. participants | Population / condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), p-value direction of effect | P-value reported by authors Direction of effect | Certainty of evidence |
|--|--|---|-----------------------------|--|-----------|---|---|---|--|-----------------------|
| Seely (2013) Study design: RCT N=246 | Adults aged 25-65 years who were screened as having the highest risk of CVD based on the ratio of total cholesterol to HDL | Naturopathic care + enhanced usual care vs enhanced usual care only | CVD modifiable risk factors | 10-year cardiovascular risk (Framingham 10-year cardiovascular risk score, %) Higher score means greater risk of CVD in the next 10 years | Baseline | N=107 Mean = 10.73 SD = 8.13 | N=114 Mean = 9.54 SD = 6.88 | MD NR | P = NR | N/A |
| | | | | | 26 weeks | N = 124 Mean = 8.99 SE = 0.44 | N = 122 Mean = 11.35 SE = 0.47 | MD (risk reduction) -2.36 (-3.66, -1.09) | P = NR | N/A |
| | | | | | 52 weeks | N = 124 Mean = 7.74 SE = 0.46 | N = 122 Mean = 10.81 SE = 0.47 | MD (risk reduction) -3.07 (-4.35 to -1.78) | p<0.001 Favours naturopathy | Low |
| | | | Total and LDL cholesterol | LDL (mmol/L) Therapeutic target < 2.5 mmol/L ^a | Baseline | N = 98 Mean = 3.49 SD = 0.98 | N = 108 Mean = 3.3 SD = 0.98 | MD NR | P = NR | N/A |
| | | | | | 26 weeks | N = 122 Mean = 3.54 SE = 0.10 | N = 124 Mean = 3.71 SE = 0.10 | MD -0.17 (-0.44, -0.11), p=NR | P = NR | N/A |
| | | | | | | | | | | |

| Study ID Type No. participants | Population / condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), p-value direction of effect | P-value reported by authors Direction of effect | Certainty of evidence |
|--------------------------------|------------------------|------------|-------------------------------------|--|-----------|---|---|---|--|-----------------------|
| | | | | | 52 weeks | N = 124 Mean = 3.49 SE = 0.10 | N = 122 Mean = 3.50 SE = 0.09 | MD -0.01 (-0.28, 0.25) | P = NR | Low |
| | | | Metabolic syndrome and risk factors | Metabolic syndrome prevalence n (%) ^b | Baseline | N = 107 n = 59 (55.1%) SD = NR | N = 113 N = 49 (43.4%) SD = NR | MD NR | P = NR | N/A |
| | | | | | 26 weeks | N = 124 38.11% SE = 0.04% | N = 122 53.05% SE = 0.04% | MD (risk reduction) - 14.94% (-26.49%, -3.39%) | P = NR | N/A |
| | | | | | 52 weeks | N = 124 31.58% SE = 0.04% | N = 122 48.48% SE = 0.05% | MD (risk reduction) - 16.90% (-29.55%, -4.25%) | p=0.002 Favours naturopathy | Low |
| | | | Type 2 diabetes | HbA1c (%) Higher value means poorer glycaemic control | Baseline | N = 109 Mean = 5.81 SD = 1.06 | N = 113 Mean = 5.7 SD = 0.97 | MD NR | P = NR | N/A |
| | | | | Reference range 3.5% to 6.0% ^a | 26 weeks | N = 124 Mean = 5.69 SE = 0.04 | N = 122 Mean = 5.77 SE = 0.05 | MD -0.08 (-0.21, 0.04) | P = NR | N/A |

| Study ID Type No. participants | Population / condition | Comparison | Outcome domain | Outcome measure and measurement details | Timepoint | Intervention Results N n/N (%) or mean (SD) | Comparator results N n/N (%) or mean (SD) | Point estimate (RR, OR, MD, SMD) (95% CI), p-value direction of effect | P-value reported by authors Direction of effect | Certainty of evidence |
|--------------------------------|------------------------|------------|----------------|---|-----------|---|---|---|--|-----------------------|
| | | | | | 52 weeks | N = 124 Mean = 5.64 SE = 0.05 | N = 122 Mean = 5.78 SE = 0.05 | MD -0.14 (-0.29, 0) | P = NR | Low |

Abbreviations: BP, blood pressure; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NR, not reported; TG, triglycerides

a Royal College of Pathologists Australasia <https://www.rcpa.edu.au/Manuals/RCPA-Manual/Pathology-Tests>

b Metabolic syndrome is defined as the presence of 3 of 5 risk factors (abdominal obesity ((1) waist circumference ≥ 102 cm for men and ≥ 88 cm for women); (2) TG ≥ 1.70 mmol/L or taking medication for elevated TG; (3) HDL < 1.03 mmol/L for men or < 1.3 mmol/L for women; (4) systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or taking antihypertensive medication; or (5) fasting blood glucose ≥ 5.6 mmol/L or taking medication for diabetes)

Appendix F: Characteristics of studies awaiting classification

Table 69: Aschenbrenner 2005

| Study ID (year) | Aschenbrenner (2005) |
|-------------------------|---|
| Participant description | <ul style="list-style-type: none"> Women with breast cancer |
| Study methods | <ul style="list-style-type: none"> NRSI, before-after design. Number of centres not stated Study 1: 5 days. Study 2: 2 weeks Individual patients Statistical methods not stated |
| Intervention | <ul style="list-style-type: none"> Study 1: 21 women after breast cancer treatment. Whey as part of a modified fasting cure for 5 days; dosage, method of dosage and frequency not stated. Who delivered the intervention not stated. Study 2: 20 breast cancer patients substituted [supplemented?] with protein-supplemented whey while eating their normal diet, over 2 weeks. Dosage and frequency not stated. Who delivered the intervention not stated. |
| Comparator | <ul style="list-style-type: none"> Study 1: 32 women with breast cancer after primary therapy as control group. No other details provided. Study 2: Not stated. |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: decrease in median body weight; decrease in fat mass as percentage of body weight. Secondary outcomes: Serum cholesterol, lymphocyte count |
| Funding source | Not stated |
| Conflicts of interest | Not stated |
| Comments | Reason this study is awaiting classification: not in the English language. |

Table 70: Bacharach-Buhles 2011

| Study ID (year) | Bacharach-Buhles (2011) |
|-----------------|---|
| | No abstract available |
| Comments | Reason this study is awaiting classification: not in the English language |

Table 71: Chrubasik 1997

| Study ID (year) | Chrubasik (1997) |
|-------------------------|--|
| Participant description | <ul style="list-style-type: none"> 102 patients suffering acute local (non-pseudoradiating) low back pain for more than 6 months, that was not attributable to identifiable causes. |
| Study methods | <ul style="list-style-type: none"> Open prospective study Number of centres not stated 6 weeks |

| Study ID (year) | Chrubasik (1997) |
|-----------------------|--|
| | <ul style="list-style-type: none"> Individual patients analysed Statistical methods not stated |
| Intervention | <ul style="list-style-type: none"> 51 patients; older, multimorbid, and suffered longer from low back pain than comparator patients. 1,800 mg Harpagophytum extract with 30 mg harpagoside per day as single or co-treatment Delivered by naturopathically orientated physicians Duration of treatment not stated. |
| Comparator | <ul style="list-style-type: none"> 51 patients Conventional treatment: mostly oral nonsteroidal anti-inflammatory drugs, physical exercises, or paravertebral injections |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: Arhus low back pain index before treatment and at 4 and 6 weeks after treatment Secondary outcome: Relative costs of treatment |
| Funding source | Not stated |
| Conflicts of interest | <p>Authors' affiliations: Institut für Pharmazeutische Biologie, Universität Heidelberg; Orthopädische Klinik, Caritas-Krankenhaus, Bad Mergentheim; Klinik für Anästhesiologie. Heidelberg</p> <p>No other conflicts of interest were stated.</p> |
| Comments | Reason this study is awaiting classification: not in the English language |

Table 72: Hakimi 2012

| Study ID (year) | Hakimi (2012) |
|-----------------|---|
| | Abstract not available |
| Comments | Reason this study is awaiting classification: not in the English language |

Table 73: Kraft 2011

| Study ID (year) | Kraft (2011) |
|-----------------|---|
| | Abstract not available |
| Comments | Reason this study is awaiting classification: not in the English language |

Table 74: Rapp 2006

| Study ID (year) | Rapp (2006) |
|-------------------------|---|
| Participant description | <ul style="list-style-type: none"> 20 female inpatients with systemic sclerosis |
| Study methods | <ul style="list-style-type: none"> Randomised double-blind pilot Number of centres not stated 7 days Individual patients analysed Statistical methods not stated |
| Intervention | <ul style="list-style-type: none"> Number of intervention patients not stated |

| Study ID (year) | Rapp (2006) |
|-----------------------|--|
| | <ul style="list-style-type: none"> 900 mg dried garlic powder as add-on therapy. Frequency not stated. Who delivered the intervention not stated. |
| Comparator | <ul style="list-style-type: none"> Number of placebo patients not stated |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: <ul style="list-style-type: none"> Rheologic properties (erythrocyte aggregation, ADP-induced thrombocyte aggregation, plasma viscosity, fibrinogenous plasma level, blood sedimentation rate) were measured initially and on days 1 and 7 Vasomotor function evaluated by near-infrared photoplethysmography Acral skin temperature |
| Funding source | Not stated |
| Conflicts of interest | <p>Authors' affiliations: Kompetenzzentrum Naturheilverfahren, Klinik für Innere Medizin II, Friedrich-Schiller-Universität Jena, Deutschland.</p> <p>No other conflicts of interest stated.</p> |
| Comments | Reason this study is awaiting classification: not in the English language |

Table 75: Schimmel 2004

| Study ID (year) | Schimmel (2004) |
|-----------------|---|
| | Abstract not available |
| Comments | Reason this study is awaiting classification: not in the English language |

Table 76: Wiebelitz 2011

| Study ID (year) | Wiebelitz (2011) |
|-------------------------|--|
| Participant description | <ul style="list-style-type: none"> 187 conservatively treatment patients of an orthopaedic clinic and 161 patients of a clinic for naturopathy Patients needed inpatient treatment because of chronic back pain |
| Study methods | <ul style="list-style-type: none"> Controlled prospective cohort study 2 centres 6 months Individual patients analysed, before treatment, after 3 months, and after 6 months Statistical methods not stated |
| Intervention | <ul style="list-style-type: none"> 161 naturopathic patients No further description of intervention |
| Comparator | <ul style="list-style-type: none"> 187 orthopaedic clinic patients No further description of comparator treatment |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: Oswestry Score for orthopaedic symptoms; SF-36 for life quality before treatment, after 3 months, and after 6 months Secondary outcomes: SES ('Schmerzempfindungsskala', pain perception scale) for pain intensity and pain quality before treatment, at discharge, after 3 months, and after 6 months. |

| Study ID (year) | Wiebelitz (2011) |
|-----------------------|---|
| Funding source | Not stated |
| Conflicts of interest | Authors' affiliations: Abteilung for Naturheilkunde, Klinik Blankenstein, Hattingen. ruediger.wiebelitz@gmx.de No other conflicts of interest stated. |
| Comments | Reason this study is awaiting classification: not in the English language |

Table 77: Wustrow 2005

| Study ID (year) | Wustrow (2005) |
|-------------------------|--|
| Participant description | <ul style="list-style-type: none"> 390 children aged 1-10 years old with uncomplicated acute otitis media |
| Study methods | <ul style="list-style-type: none"> Prospective open controlled study Number of centres not stated Duration of study not stated Individual patients analysed Statistical methods not stated |
| Intervention | <ul style="list-style-type: none"> Number of participants not stated Otoovowen supplemented by conventional medications when considered necessary Dosage, frequency, and who delivered the treatment were not stated. |
| Comparator | <ul style="list-style-type: none"> Number of participants not stated Conventional treatment: free combinations of decongestant nose drops, mucolytics, analgesics, and antibiotics. Dosage, frequency, and who delivered the treatment were not stated. |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: quantity of antibiotics taken; time to recovery; number of days absent from school or preschool; pain resolution |
| Funding source | Including 'other material support' for study |
| Conflicts of interest | Author affiliations: HNO-Gemeinschaftspraxis, München. wustrowt@gmx.de No other conflicts of interest stated. |
| Comments | Reason this study is awaiting classification: not in the English language |

Appendix G: Characteristics of ongoing studies

Table 78: ACTRN12620001040954 (2020)

| ACTRN12620001040954 (2020) | Adjunct Professor Jon Wardle (primary sponsor) |
|----------------------------|--|
| Participant description | <ul style="list-style-type: none"> • Number of participants: 56 • Ex-military personnel who are eligible for treatment of a chronic musculoskeletal pain condition (lasting 6 months or more) through the Department of Veterans Affairs (White Card or Gold Card system), and who consent to involvement in the study, will be included in the study • 18 years and older; male and female • Setting: GP clinic; yoga provided at a community centre • Exclusion criteria: Individuals who are already receiving care through the clinic or who are not eligible for a General Practice Management Plan will be excluded, as pre-existing treatment may be a confounder |
| Study methods | <ul style="list-style-type: none"> • Pilot parallel open-label RCT • Number of study centres not stated • Duration 26 weeks • Unit of analysis: individual • Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>Description of intervention, including modalities, dose, method of administration, frequency of administration, who delivered the intervention</p> <p>Intervention includes:</p> <ul style="list-style-type: none"> • Standard care was described in the control (comparator treatment was not reported) • Referrals to CM therapists that have a demonstrable evidence base for pain or musculoskeletal conditions in general or military or veteran populations. Referrals will be determined by a GP in collaboration with other health professionals where appropriate, based on the identified need of the patient • CM practices in this study include acupuncture/Chinese medicine, massage therapy, naturopathic medicine, or yoga. • All practitioners will need to be eligible for private health insurance rebates under current rules. The acupuncturist, massage therapist, and naturopath will provide services at the same clinical location as the GP while the yoga classes will be delivered in a nearby community centre. • No specified maximum number of consultations or consultation frequency was specified for each intervention. The frequency and number of consultations will be dictated by the individual practitioner. The only exception is yoga which will be conducted as a weekly group session. |
| Comparator | <p>The number of participants was not stated.</p> <p>Comparator (control) treatment not reported.</p> |

| ACTRN12620001040954 (2020) | Adjunct Professor Jon Wardle (primary sponsor) |
|----------------------------|--|
| | Specific referrals for each individual will be determined by the General Practitioner, in collaboration with the other health professionals where appropriate, based on the identified need of the patient |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: Pain intensity measured by BPI, at recruitment, Week 8, Week 12 and Week 26. • Secondary outcomes: <ul style="list-style-type: none"> ➤ Feasibility assessed post Week 26 by examining the study-specific participant case report form, participant medical file and instrument results. ➤ Healthcare behaviours, assessed by examining the participant medical file and case report form, at recruitment, Week 8, Week 12, and Week 26. Includes questions about current smoking behaviours, use of illicit substances, diet, and exercise ➤ Healthcare utilisation, assessed by examining the participant medical file and case report form: out-of-pocket healthcare costs are also asked at Week 8, Week 12, and Week 26. Includes questions on current medication, current complementary medicine, health services used in the past, and ever having out-of-pocket healthcare costs. ➤ Incremental cost-effectiveness ratio, assessed by EQ-5D instrument at recruitment, Week 8, Week 12, and Week 26. Also by asking participants to note any out-of-pocket health expenses that were incurred in the last 3 months to recruitment as well as before Week 8, Week 12, and Week 26 throughout the trial. ➤ Pain self-efficacy, assessed by the PSEQ instrument at recruitment and Week 26. ➤ Predicted risk of long-term disability, assessed by OMSQ instrument conducted at recruitment and Week 26 ➤ Quality of life, assessed by SF-12 and EQ-5D conducted at recruitment, Week 8, Week 12, and Week 26 ➤ Safety, assessed by examining participant medical files for safety issues identified by the participant or health practitioners, throughout the 26 weeks |
| Funding source | Defence of Health Foundation |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: University of Technology Sydney • Authors' financial relationships not stated • No other conflicts of interest stated |
| Status | Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: BPI, Brief Pain Inventory; CM, complementary medicine; EQ-5D, 5-Item European Quality of Life; OMSQ, Orebro Musculoskeletal Screening Questionnaire; PSEQ, Pain Self-Efficacy Questionnaire; SF-12, Short Form 12

Table 79: ACTRN12620000928910 (2020)

| ACTRN12620000928910 (2020) | Southern Cross University (primary sponsor) |
|----------------------------|--|
| Participant description | <ul style="list-style-type: none"> • Number of participants: 10 • Eligibility: score of greater than or equal to 16 and less than 30 on the K-10 scale; symptoms of mild gut dysfunction (e.g. abdominal cramps or sharp pains, recurrent diarrhoea or constipation, excessive wind, |

| ACTRN12620000928910 (2020) | Southern Cross University (primary sponsor) |
|----------------------------|--|
| | <p>abdominal bloating); agree to comply with the study protocols; willing to have blood taken on two occasions during the study</p> <ul style="list-style-type: none"> Exclusion: taking immunosuppressive medication, Warfarin, or other anticoagulant medication; major surgery within the last 6 months; diagnosed with chronic mental health conditions and taking prescribed medication for same (unless their condition has been stable for a minimum of 12 months); diabetes; BMI \geq 35; unexplained weight loss; females who are lactating, pregnant or planning to become pregnant Age 18-65 years; males and females Setting not stated |
| Study methods | <ul style="list-style-type: none"> Phase 2 RCT, blinded, 3 arms: <ul style="list-style-type: none"> Group 1: 6 weeks of placebos followed by 12 weeks of verum supplements Group 2: 8 weeks of placebos followed by 10 weeks of verum supplements Group 3 took placebo for 12 weeks and then 6 weeks of verum supplements. Each participant took two doses of each supplement/placebo supplement each day of the trial. The dosage form and contents of the verum supplements are detailed below per dose. Number of study centres not stated Duration of study: 18 weeks Unit of analysis: individual Statistical methods: not stated |
| Intervention | <p>Number of participants not stated</p> <p>3 nutritionally based supplements (verum):</p> <ul style="list-style-type: none"> Metagenics Ultra Flora Intensive Care (ARTG 286746) 600mg maroon (00 size Vcap with cream coloured powder) clear capsule for oral consumption containing Lactobacillus rhamnosus (LGG®) (10 x 109CFU), Saccharomyces cerevisiae (boulardii) (7.5 x 109 CFU) and Bifidobacterium animalis ssp lactis (BB-12®) (5 x 109 CFU). Participants swallowed one capsule of this probiotic supplement morning and evening. Metagenics Glutagenics (ARTG 213315) Powder for oral consumption after dissolving in water. Each 4.33g dose contains: Aloe vera 3.25mg/g (equiv. fresh herb 649.35mg/g); Boswellia serrata 19.48mg/g (equiv. fresh herb 194.8mg/g); Cholecalciferol 1.6233mcg/g; Glutamine 285.71mg/g; Larix arabinogalactan 259.74mg/g; Retinol palmitate 178.57mcg/g; Zinc amino acid chelate 9.74mg/g. Participants took one dose: 7.7g (two scoops - scoop included) of this oral powder supplement in 200ml water morning and evening. [3rd supplement was not stated] <p>All practitioner-researchers were qualified naturopathic practitioners, apart from one who was a qualified nutritionist. It was beyond the scope of this practitioner-researcher to prescribe herbal medicines</p> |
| Comparator | <p>Number of participants not stated</p> <p>Placebos matched to intervention supplements</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: risk of severe mental disorder, assessed by K-10. Change in the total score as an estimate of the change in risk of mental |

| ACTRN1262000928910 (2020) | Southern Cross University (primary sponsor) |
|---------------------------|--|
| | <p>disorder. 7 timepoints: initial screening clinic (week -2) and 6 subsequent clinics (week 0, week 4, week 8, week 12, week 16, and week 18).</p> <ul style="list-style-type: none"> Secondary outcomes: <ul style="list-style-type: none"> Mood disturbance measured by Abbreviated POMS Short Form, at week 0 and week 18 Inflammation measured by CRP mg/L serum assay, week 0 and week 18 Change in GIT function measured with CDSA to assess levels of faecal calprotectin ug/g, faecal zonulin ng/g, short chain fatty acids in umol/g, numbers of CFU of Lactobacillus spp, Bifidobacterium spp., Enterococcus spp, and E. coli at week 0 and week 18 Common symptoms of gastrointestinal disorders measured by GSRS at weeks 0, 4, 8, 12, 16, and 18. Patient perspectives on patient outcomes, assessed by a one-on-one interview between the patient and the practitioner within 9 months after week 18. Perceived stress measured by PSS-10 at weeks 0, 4, 8, 12, 16 and 18 |
| Funding source | Australian Traditional Medicine Society |
| Conflicts of interest | <ul style="list-style-type: none"> Contact person's affiliations: Prof Sandra Grace and Prof Joanne Bradbury, N-of-1 Clinical Trials Group School of Health and Human Sciences Southern Cross University. Contact person's financial relationship: not stated No other conflicts of interest stated. |
| Status | Complete, data not available |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: CDSA, Complete Digestive Stool Analysis; CFU, colony forming units; CRP, C-reactive protein; GSRS, Gastrointestinal Symptom Rating Scale; K-10, Kessler-10; PSS-10, Perceived Stress Scale-10; POMS, Profile of Mood States

Table 80: CTRI/2010/091/001169 (2010)

| CTRI/2010/091/001169 (2010) | INYS-medical research society.Bangalore.Karnataka (primary sponsor) |
|-----------------------------|---|
| Participant description | <ul style="list-style-type: none"> Number of participants: 60 Inclusion criteria: mild to moderate persistent asthma; FEV1 Pred 60-80% after 6 hrs of withholding inhalers; 12% increase in FEV1 after inhalers; non-smokers/stopped smoking 6 months back 18-65 years; gender not specified Exclusion criteria: asthmatics with severe airflow limitation or more (FEV1 <60% predicted) comorbid conditions such as: a) patients with uncontrolled hypertension systolic BP >200mm Hg or diastolic BP >100mmHg, or b) a history of cerebrovascular events, or ischemic cardiac events in last 6 months or having known aortic aneurysms, or c) Patients who are pregnant/lactating mothers, and or d) patients who are on cholinergic medication (Myasthenia Gravis). Inability to ambulate >50% of the time. History of recurrent or chronic respiratory infections such as pulmonary tuberculosis and autoimmune lung diseases, ARDS, cancer Major psychiatric illnesses. As these subjects may not be able to follow the instructions and study procedures and fill up questionnaires. Practicing yoga for the last six months. |

| CTRI/2010/091/001169 (2010) | INYS-medical research society.Bangalore.Karnataka (primary sponsor) |
|-----------------------------|---|
| Study methods | <ul style="list-style-type: none"> RCT, open-label Number of study centres not stated Duration of study: 21 days Unit of analysis: individual Statistical methods: not stated |
| Intervention | <p>Number of participants not stated</p> <ul style="list-style-type: none"> Naturopathy and yoga interventions. Dose, method of administration, frequency of administration, and who delivered the intervention were not stated |
| Comparator | <p>Number of participants not stated</p> <p>Waitlist controls</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: Nyugen asthma severity index; Juniper asthma quality of life; Asthma control score. Secondary outcomes: <ul style="list-style-type: none"> Lung function: FEV1, FVC, FEV 1/FVC, PEFr baseline and after salbutamol, FEV Variability, Exercise-induced maximum percent fall in Fev1 (max FEv1%) and area under the curve (AUC-0-30) relative to pre-exercise FEv 1 up to 30 minutes following exercise challenge. (10 min ex challenge/ up to exhaustion) Perceived control of asthma questionnaire Asthma Diary, every day. Epworth daytime sleepiness scale. AEC, CBC Assessments at baseline, 10 days, 21 days. |
| Funding source | INYS-medical research society, Bangalore, Karnataka. |
| Conflicts of interest | <ul style="list-style-type: none"> Contact person's affiliations: SN Murthy, INYS-Medical Research Society, India Contact person's financial relationship: not stated Other conflicts of interest not stated |
| Status | Open to Recruitment |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviation: AEC, absolute eosinophil count; BP, blood pressure; CBC, complete blood count; FEV, forced expiratory volume; FVC, forced vital capacity; PEFr, peak expiratory flow rate; Pred, predicted

Table 81: CTRI/2010/091/001168 (2010)

| CTRI/2010/091/001168 (2010) | INYS-medical research society.Bangalore.Karnataka (primary sponsor) |
|-----------------------------|---|
| Participant description | <ul style="list-style-type: none"> Number of participants: 132 Eligibility criteria: documented radiographic changes of osteoarthritis (Kellgren-Lawrence grade > 2) at the time of rheumatologic screening; palpable synovial swelling on clinical examination; pre-randomization |

| CTRI/2010/091/001168 (2010) | INYS-medical research society.Bangalore.Karnataka (primary sponsor) |
|-----------------------------|---|
| | <p>pain VAS score between 4 and 9; must be taking analgesic or non-steroidal anti-inflammatory agents for control of pain</p> <ul style="list-style-type: none"> • Exclusion criteria: rheumatoid arthritis, fibromyalgia, recurrent or active pseudo-gout, cancer, or other serious medical condition; history of kidney or liver failure; oral steroids within the last four weeks; intra-articular knee depo-corticosteroids within the previous 3 months; intra-articular hyaluronate within the previous 6 months; arthroscopy of the knee within the previous year; significant injury to the knee within the previous 6 months; rash or open wound over the knee; structured exercise more than once per week for 20 minutes or longer during the 3 months before study entry; anticipates moving from the area within 18 months of study entry; anorexiant or other medications known to affect metabolism; current or planned pregnancy. • 30 years and older, gender not stated • Setting not stated |
| Study methods | <ul style="list-style-type: none"> • RCT. Participant, Investigator, Outcome Assessor, and Data-entry Operator blinded • Number of study centres not stated • Duration of study: 21 days • Unit of analysis: individual participant • Statistical methods: not stated |
| Intervention | <p>Number of participants not stated</p> <p>Naturopathy and yoga interventions. Dose, method of administration, frequency of administration, and who delivered the intervention were not stated</p> |
| Comparator | <p>Number of participants not stated</p> <p>Waitlist controls</p> |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: Walking Pain measured by VAS; Patient Global Assessment measured by WOMAC • Secondary outcomes: <ul style="list-style-type: none"> ➤ Knee Circumference. ➤ General Health Status (SF-36) ➤ Patient Global Assessment (100mm VAS) ➤ Medication use: Requirement of pain medication before the intervention, during, and after ➤ Physical performance: 50 feet walk time; time to climb stairs; time to get downstairs. ➤ Weight in kgs • Measurements at baseline, 10 days and 21days |
| Funding source | INYS-medical research society, Bangalore, Karnataka. |
| Conflicts of interest | <ul style="list-style-type: none"> • Contact person's affiliations: Dr.Babina Nandkumar, INYS-medical research society, India • Contact person's financial relationship: not stated • Other conflicts of interest not stated |
| Status | Open to Recruitment |

| | |
|------------------------------------|--|
| CTRI/2010/091/001168 (2010) | INYS-medical research society.Bangalore.Karnataka (primary sponsor) |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: VAS, visual analogue score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

Table 82: CTRI/2010/091/001171 (2010)

| CTRI/2010/091/001171 (2010) | INYS medical research society, Bangalore, Karnataka (primary sponsor) |
|------------------------------------|---|
| Participant description | <ul style="list-style-type: none"> Number of participants: 72 Inclusion criteria: [high] BP, obesity, type II DM, prediabetes, and dyslipidemia Exclusion criteria: history of CAD, Angina, TMT positive for inducible ischemia; uncontrolled hypertension (SBP>200mm Hg, DBP>100); receiving parental insulin or statins; receiving other therapies such as homeopathy / Ayurveda; pregnancy/lactation; hypothyroidism, Cushing's syndrome, pheochromocytoma; steroids / HRT use; ambulatory <50% of the time; practicing yoga for last 6 months; major psychiatric illness; COPD, congenital heart defects, aortic aneurysm, DVT. 18-65 years old, male and female Setting not stated |
| Study methods | <ul style="list-style-type: none"> RCT, double-blinded Number of study centres not stated Duration of study: 21 days Unit of analysis: individual participant Statistical methods: not stated |
| Intervention | <p>Number of participants not stated</p> <p>Naturopathy and yoga treatment</p> <p>No further descriptions of modalities, dose, method of administration, frequency of administration, or who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <p>Wait-list controls with education about lifestyle modification.</p> <p>No further descriptions of modalities, dose, method of administration, frequency of administration, or who delivered the comparator</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: resting blood pressure, mean arterial pressure; FBG/ PPBG with 75gm glucose (2hr); BMI, skinfold thickness and anthropometry, body fat percentage.; lipid profile: VLDL, LDL, HDL, total cholesterol (by serum electrophoresis / direct enzymatic method, Triglycerides); Framingham cardiac risk score Secondary outcomes: HADS Questionnaire, SCL 90 Somatization component, General Health Perceptions questionnaire Assessments at baseline and days 10 and 21 |
| Funding source | INYS-medical research society, Bangalore, Karnataka, India |
| Conflicts of interest | <ul style="list-style-type: none"> Contact person's affiliations: SN Murthy, INYS-Medical Research Society, India Contact person's financial relationship: not stated No other potential conflicts of interest were stated. |

| CTRI/2010/091/001171 (2010) | INYS medical research society, Bangalore, Karnataka (primary sponsor) |
|-----------------------------|--|
| Status | Complete, data not available |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; FBG, fasting blood glucose; ADS, Hamilton Anxiety and Depression; HDL, high-density lipoprotein; HRT, hormone replacement therapy; INYS, Institute of Naturopathy and Yogic Sciences; LDL, low-density lipoprotein; PPBG, postprandial blood glucose; SBP, systolic blood pressure; SCL 90, Symptom Checklist 90; TMT, treadmill test; VLDL, very low-density lipoprotein

Table 83: CTRI/2011/03/001654 (2011)

| CTRI/2011/03/001654 (2011) | INYSMRS (primary sponsor) |
|----------------------------|--|
| Participant description | <ul style="list-style-type: none"> Number of participants: 30 Inclusion criteria: diagnosed with metabolic syndrome as per ATPIII criteria; willing to take residential treatment for minimum of 21 days. Exclusion criteria: not willing to give consent; history of CAD, Angina, TMT positive for inducible ischemia; renal calculi or history of renal calculi in the past with oxalate or phytate calculi; uncontrolled hypertension (SBP200mmHg, DBP100 mmHg); uncontrolled diabetes with or without diabetic nephropathy or microalbuminuria; taking parental insulin, statins; taking other therapies such as homeopathy / Ayurveda, etc, which can have a direct or indirect effect on study variables; abnormal RFT as defined by BUN [value not stated], Serum Creatinine 1.2, Serum Uric Acid [value not stated]; pregnancy/lactation; hypothyroidism, Cushing's syndrome, pheochromocytoma; taking steroids / HRT; regularly practicing yoga for last 3 months; major psychiatric illness with cognitive impairments; known COPD or congenital heart defects. 18-70 years old; male and female Setting: residential treatment |
| Study methods | <ul style="list-style-type: none"> 3-arm parallel RCT, blinding not stated Number of study centres not stated Duration of study: 21 days Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <ul style="list-style-type: none"> Intervention 1: Yoga and Nature-cure interventions: 21 days Inpatient Naturopathy and yoga-based lifestyle intervention Intervention 2: Nature cure and yoga intervention along with glutathione rich diet in form of tomato juice/salads: add-on of glutathione rich diet Dose, method of administration, frequency of administration, and who delivers intervention were not stated |
| Comparator | <p>Number of participants not stated</p> <p>Waitlist controls (21 days) will receive advice regarding a healthy lifestyle and will continue taking their medications</p> <ul style="list-style-type: none"> Dose, method of administration, frequency of administration, and who delivers comparator were not stated |

| CTRI/2011/03/001654 (2011) | INYSMRS (primary sponsor) |
|----------------------------|--|
| Outcome | <ul style="list-style-type: none"> Primary outcomes: reduction in Alexithymia measured by Toronto Alexythymia Scale; reductions in anger, hostility, anxiety, and depression in SCL90 Secondary outcomes: fasting lipid profile (TC, LDL-C, HDL-C, VLDL, Triglycerides); SBP and DBP; fasting and postprandial blood glucose; waist circumference, hip circumference, waist-hip ratio, BMI; body composition analysis [method not stated]; serum insulin; CRP; platelet aggregation factor; glutathione peroxides, glutathione synthase, glutathione reductase; Framingham risk reduction. Assessment at baseline and 21 days |
| Funding source | INYS Medical Research Society |
| Conflicts of interest | <ul style="list-style-type: none"> Contact person's affiliations: INYS Medical Research Society, India Contact person's financial relationship: not stated No other conflicts of interest were stated. |
| Status | Open to Recruitment |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: ATPIII, Adult Treatment Panel III; BUN, blood urea nitrogen; CAD, coronary artery disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HRT, hormone replacement therapy; LDL-C, low-density lipoprotein cholesterol; RFT, renal function test; SBP, systolic blood pressure; SCL90, Symptom Checklist-90; TC, total cholesterol; TMT, treadmill test; VLDL, very low-density lipoprotein

Table 84: CTRI/2011/12/002286 (2011)

| CTRI/2011/12/002286 (2011) | Institute of Naturopathy and Yogic Sciences Medical Research Society INYSMRS (primary sponsor) |
|----------------------------|---|
| Participant description | <ul style="list-style-type: none"> Number of participants: 60 Inclusion criteria: BMI > 25 Exclusion criteria: uncontrolled hypertension, hypercholesterolemia, type two diabetes mellitus, drug-induced obesity (e.g. corticosteroid) or endocrine disorders (e.g., hypothyroidism, polycystic ovarian syndrome), BMI >40, physical disability such as osteoarthritis which could influence their balance and stability. Age and gender were not stated Setting: Jindal Nature Cure Institute |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, allocation not concealed, blinding not stated Single centre study Duration of study: 3 weeks Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <ul style="list-style-type: none"> Naturopathy and Yoga based Lifestyle interventions 3 weeks of inpatient Nature Cure and yoga therapies in Jindal Nature Cure Institute. |
| Comparator | <p>Number of participants not stated</p> <ul style="list-style-type: none"> Waitlist controls (later to undergo intervention after waitlist period) |

| CTRI/2011/12/002286 (2011) | Institute of Naturopathy and Yogic Sciences Medical Research Society INYSMRS (primary sponsor) |
|----------------------------|--|
| Outcome | <ul style="list-style-type: none"> Primary outcomes: BMI, waist circumference, hip circumference, fasting plasma glucose, postprandial plasma glucose, insulin, and insulin resistance (HOMA - IR), Cardiac Autonomic Function Test. Secondary outcomes: Self-Esteem Inventory, lipid profile Assessments at baseline, day 10, and day 21 |
| Funding source | Room NO 14. Research Department. Institute of Naturopathy and Yogic Sciences Medical Research Society (INYSMRS) |
| Conflicts of interest | <ul style="list-style-type: none"> Contact person's affiliations: Dr Avinash Kadam, Institute of Naturopathy and Yogic Sciences Medical Research Society (INYSMRS) Contact person's financial relationship: not stated No other conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Table 85: CTRI/2011/12/002285 (2011)

| CTRI/2011/12/002285 (2011) | Institute of Naturopathy and Yogic Sciences Medical Research Society INYSMRS (primary sponsor) |
|----------------------------|---|
| Participant description | <ul style="list-style-type: none"> Number of participants: 60 Inclusion criteria: high blood pressure (DBP > 90 mm/Hg SBP >140mm/Hg or on antihypertensive medications); BMI >25; pre-diabetes (FBS-110 to 125 mg/dL/ PPBS 140 to 199 mg/dL); type II diabetes (FBS >126 mg/dL/PPBS > 200 mg/dl); and dyslipidemia (NCEP ATP III criteria) Exclusion criteria: history of CAD, angina, or TMT positive for inducible ischemia; uncontrolled hypertension (SBP >200mmHg, DBP >100); on parental insulin or statins; receiving other therapies such as homeopathy / Ayurveda to treat the above conditions; pregnancy/lactation; hypothyroidism, Cushing's syndrome or pheochromocytoma; using steroids / HRT/non-steroidal anti-inflammatory drugs (other than low-dose aspirin < 150mg/day); practicing yoga for last 6 months; major psychiatric illness; COPD, congenital heart defects, aortic aneurysm or DVT; active infection, systemic inflammatory disease, autoimmune disorders, SLE or RA; any other condition which places the participant at increased risk or will influence the outcome of the study. 18-65 years, males and females Setting: Jindal Nature Cure Institute |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, blinding not stated Single centre study Duration of study: 21 days Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>Naturopathy and Yoga based lifestyle interventions:</p> <ul style="list-style-type: none"> Calorie restriction, various packs [not defined] Water treatments |

| CTRI/2011/12/002285 (2011) | Institute of Naturopathy and Yogic Sciences Medical Research Society INYSMRS (primary sponsor) |
|----------------------------|---|
| | <ul style="list-style-type: none"> • Massages • Physical Activity, Yoga, Meditation • Treatments delivered in an inpatient setting in Jindal Nature Cure Institute, Bangalore, India. <p>No further descriptions of dose, method of administration, frequency of administration, or who delivered the intervention.</p> |
| Comparator | <p>Number of participants not stated</p> <p>Waitlist controls (for 21 days); given advice about lifestyle modification; continue with their ongoing conventional care. After the wait-list period, they will receive intervention treatment.</p> |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: high sensitivity C reactive protein; serum fasting insulin; FBG/ PPBG with 75gm glucose (2hr); HOMA-IR • Secondary outcomes: resting blood pressure; mean arterial pressure; autonomic function test (deep breathing test, handgrip test, Valsalva manoeuvre, heart rate variability); BMI, body fat percentage, waist, and hip circumference; lipid profile (VLDL, LDL, HDL, total cholesterol and triglycerides by serum Electrophoresis / direct enzymatic method) • Assessments at baseline, day 10, and day 21 |
| Funding source | Institute of Naturopathy and Yogic Sciences Medical Research Society (INYSMRS) |
| Conflicts of interest | <ul style="list-style-type: none"> • Contact person's affiliations: Dr Avinash Kadam, Institute of Naturopathy and Yogic sciences Medical Research Society, India • Contact person's financial relationship not stated • No other conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HRT, hormone replacement therapy; LDL, low-density lipoprotein; NCEP ATP III, US National Cholesterol Education Programme Adult Treatment Panel III; PPBS, postprandial blood sugar; RA, Rheumatoid Arthritis; SBP, systolic blood pressure; SLE, systemic lupus erythematosus; VLDL, very low-density lipoprotein

Table 86: CTRI/2018/12/016550 (2018)

| CTRI/2018/12/016550 (2018) | Ministry of AYUSH (primary sponsor) |
|----------------------------|--|
| Participant description | <ul style="list-style-type: none"> • Number of participants: 200 • Inclusion criteria: clinical diagnosis of diabetes mellitus according to ADA criteria; diabetes duration since diagnosis < 12 months; written informed consent <ul style="list-style-type: none"> ➤ Control cohort: proven normal glucose tolerance according to ADA criteria • Exclusion criteria: diabetes mellitus category 3 B-H (ADA criteria); pregnancy; severe renal, liver, or heart disease; malignant cancer; severe psychiatric illness or addiction; participation in intervention trial; other major morbidities that can affect the diabetic status; patient consuming multivitamin/ multimineral supplements. • Age and gender were not stated |

| CTRI/2018/12/016550 (2018) | Ministry of AYUSH (primary sponsor) |
|----------------------------|---|
| | <ul style="list-style-type: none"> Setting not stated |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, investigator-blinded [note that this does not align with a trial including a control cohort with normal glucose tolerance] Number of study centres not stated Duration of study: 9 months Unit of analysis: individual participant Statistical methods: not stated |
| Intervention | <p>Number of participants not stated</p> <ul style="list-style-type: none"> Yoga therapy 2 hours Yoga session/day: practices including Asana, Pranayama, and Meditation adopted from Yoga for Hypertension and Heart disease by Dr. H R Nagendra, Dr. R. Nagarathna, SVYP Publications 45 minutes Yoga for minimum 5 days/ week: Module based on Yoga for Hypertension and Heart disease by Dr. H R Nagendra, Dr. R. Nagarathna, SVYP Publications Diet Therapy Low calorie, Low salt Naturopathy diet including calorie restriction (Fasting Therapy) prescribed as per individual subject's needs. Low calorie, Low salt Naturopathy diet including calorie restriction. Physical activity. Subjects will be encouraged to involve in moderate aerobic exercises like walking for 45 min/ day Subjects will be encouraged to involve in moderate aerobic exercises like walking for 45 min/ day/ 5 days a week. Hydrotherapy steam bath Sauna bath Under-water massage Spinal bath Hip bath Neutral chest pack Mud Therapy Manipulative therapy <p>No further descriptions of frequency or intensity of treatment, or who will deliver the treatment</p> |
| Comparator | <p>Number of participants not stated</p> <ul style="list-style-type: none"> Physical activity- Subjects will be encouraged to involve in moderate aerobic exercises like walking for 45 min/ day Subjects will be encouraged to involve in moderate aerobic exercises like walking for 45 min/ day/ 5 days a week. Diet restrictions [not further described] <p>No further descriptions of dose, method of administration, frequency of administration, or who delivered the comparator.</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: fasting BG (mg%); postprandial BG (mg%); HbA1c% Secondary outcomes: <ul style="list-style-type: none"> Clinical parameters diabetic patients: Height (cm); Weight (kg); BMI (kg/m²); Waist circumference (cm); Hip circumference (cm); Waist-hip ratio; Systolic BP; Diastolic BP; HRV Biochemical parameters of diabetic patients; Total cholesterol (mg%); Triglyceride (mg%); LDL (mg%); HDL (mg%); VLDL (mg%); |

| CTRI/2018/12/016550 (2018) | Ministry of AYUSH (primary sponsor) |
|----------------------------|---|
| | <p>C- Reactive protein; Salivary Cortisol; Calcium and Serum Electrolyte</p> <ul style="list-style-type: none"> Assessments at baseline and at 1, 3, 6 and 9 months, except for calcium and serum electrolytes assessed at baseline, 3 and 9 months. |
| Funding source | Ministry of AYUSH, AYUSH Bhawan, B Block,GPO complex, INA, New Delhi-110023 |
| Conflicts of interest | <ul style="list-style-type: none"> Contact person's affiliations: Dr Honnegowda TM, Sri Dharmasthala Manjunatheswara College for Naturopathy and Yoga Science, India Contact person's financial relationship: not stated No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: ADA, American Diabetes Association; BG, blood glucose; BP, blood pressure; HbA1c, glycosylated haemoglobin; HDL, high density lipoprotein; HRV, heart rate variability; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

Table 87: CTRI/2018/10/015895 (2018)

| CTRI/2018/10/015895 (2018) | Balwantrai Mehta Arogya Bhavan (primary sponsor) |
|----------------------------|---|
| Participant description | <ul style="list-style-type: none"> Number of participants: 52 Inclusion criteria: clinically diagnosed with varicose veins based upon symptoms C2 and C3 according to criteria proposed in CEAP classification Exclusion criteria: pregnant or lactating women; any complications related to varicose veins like venous ulcers deep vein thrombosis bleeding varicose eczema lipodermatosclerosis thrombophlebitis chronic lower limb ischemia skin infections lymphangitis; C4 to C6 criteria in CEAP classification; renal failure; malignancy, chronic obstructive lung disease heart failure, or any other psychiatric illness or dementia; patients who have undergone surgeries for varicose veins; above or below age limit [note these limits were not stated]; not clinically fit for performing prescribed yoga intervention; not willing to undergo the treatment program Age and gender were not stated Setting not stated |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, double-blinded Number of study centres not stated Duration of study: 1 month Unit of analysis: individual participant Statistical methods: not stated |
| Intervention | <p>Number of participants not stated</p> <p>Yoga and Naturopathy Interventions</p> <p>No further descriptions of dose, method of administration, frequency of administration, who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <p>Passive exercises and stretching</p> |

| CTRI/2018/10/015895 (2018) | Balwantrai Mehta Arogya Bhavan (primary sponsor) |
|----------------------------|---|
| | No further description of dose, method of administration, frequency of administration, who delivered the comparator |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: pain, leg swelling, skin colour change, and daily activity by Aberdeen varicose veins questionnaire; mobility, self-care, usual activity pain or discomfort anxiety or depression by EQ5D5L; haemodynamic changes by Laser Doppler Flowmetry Secondary outcomes: stress by PSS; vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health by SF-36 Assessments at 1 month [not stated if assessments will be made at baseline] |
| Funding source | Balwantrai Mehta Arogya Bhavan Next to Keshav Garden Water Tank Road Karelibaug Vadodara Gujarat 390018 |
| Conflicts of interest | <ul style="list-style-type: none"> Contact person's affiliations: Dr Sanjib Kumar Patra, Anveshana Research Lab, India; Shweta Chauhan, Doctors Cabine number 11 Balwantrai Mehta Arogya Bhavan Next to Keshav Garden Karelibaug Vadodara Gujarat 560105, India Contact person's financial relationship: not stated No other conflicts of interest stated |
| Status | Complete, data not available |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: CEAP, Clinical Etiology Anatomy Pathophysiology; PSS, Perceived Stress Scale; SF36, Short Form 36

Table 88: CTRI/2018/12/016512 (2018)

| CTRI/2018/12/016512 (2018) | Ministry of AYUSH (primary sponsor) |
|----------------------------|---|
| Participant description | <ul style="list-style-type: none"> Number of participants: 200 Inclusion criteria: no regular physical exercise; waist circumference = 88cm; BMI = 25; willingness to participate in 10 days of treatment, follow up and practice at home for 9 months Exclusion criteria: physical impairments that preclude participation in easy yoga exercises; regular physical activity or yoga practice within the preceding 3 months; currently following a weight-loss diet or planning to start such a diet within the following 24 weeks; diagnosed psychosis that is being treated with psychopharmaceutical drugs; malignant hypertension (diastolic blood pressure >120 mm Hg); diabetes mellitus type 1 or type 2 diabetes requiring insulin; manifest coronary heart disease, myocardial infarction, pulmonary artery embolism, or apoplexy; current participation in other clinical studies or planning to enter into a study within the following 24 weeks; pregnancy or breastfeeding period Age and gender were not stated Setting not stated |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, double-blinded Number of study centres not stated Duration of study: 9 months Unit of analysis: individual participant Statistical methods: not stated |

| CTRI/2018/12/016512 (2018) | Ministry of AYUSH (primary sponsor) |
|----------------------------|---|
| Intervention | <p>Number of participants not stated</p> <ul style="list-style-type: none"> Yoga therapy 2 hours Yoga session/day: practices including Asana, Pranayama, and Meditation adopted from Yoga for Hypertension and Heart disease by Dr. H R Nagendra, Dr. R. Nagarathna, SVYP Publications 45 minutes Yoga for minimum 5 days/ week: Module based on Yoga for Hypertension and Heart disease by Dr. H R Nagendra, Dr. R. Nagarathna, SVYP Publications Diet Therapy Low calorie, Low salt Naturopathy diet including calorie restriction (Fasting Therapy) prescribed as per individual subject's needs. Low calorie, Low salt Naturopathy diet including calorie restriction. Physical activity Subjects will be encouraged to involve in moderate aerobic exercises like walking for 45 min/ day Subjects will be encouraged to involve in moderate aerobic exercises like walking for 45 min/ day/ 5 days a week. Hydrotherapy steam bath sauna bath under-water massage Spinal bath hip bath Neutral chest pack Mud Therapy Manipulative therapy <p>No further description of dose, method of administration, frequency of administration, who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <ul style="list-style-type: none"> Standard care: Physical activity- Subjects will be encouraged to involve in moderate aerobic exercises like walking for 45 min/ day Subjects will be encouraged to involve in moderate aerobic exercises like walking for 45 min/ day/ 5 days a week. Diet restrictions [not further described] <p>No further description of dose, method of administration, frequency of administration, who delivered the comparator</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: height (cm); weight (kg); BMI (kg/m²); waist circumference (cm); hip circumference (cm); waist-hip ratio; arterial BP; HRV; salivary cortisol; quality of life style questionnaire-Farrans and power. Secondary outcomes: total cholesterol (mg%); triglyceride (mg%); LDL (mg%); HDL (mg%); C- Reactive protein; Salivary Cortisol; Calcium and Serum [word missing] Assessments at baseline and 1, 3, 6, and 9 months |
| Funding source | Ministry of AYUSH |
| Conflicts of interest | <ul style="list-style-type: none"> Contact person's affiliations: Dr Honnegowda TM, Sri Dharmasthala Manjunatheswara College For Naturopathy And Yoga Sciences, India Contact person's financial relationship: not stated No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: Registered trial |

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; HRV, heart rate variability; LDL, low-density lipoprotein

Table 89: CTRI/2019/01/016883 (2019)

| CTRI/2019/01/016883 (2019) | Ministry of AYUSH |
|----------------------------|---|
| Participant description | <ul style="list-style-type: none"> Number of participants: 200 |

| CTRI/2019/01/016883 (2019) | Ministry of AYUSH |
|----------------------------|--|
| | <ul style="list-style-type: none"> Inclusion criteria: with at least one elevated blood pressure measurement (as defined by the study) identified by clinic-based screening; any clinic-based blood pressure measurement confirmed by another clinic-based, home, or ambulatory blood pressure measurement; first-degree relatives of hypertensive patients (father, mother, brothers or sisters, sons or daughters); overweight (BMI \geq 25); dyslipidaemia Exclusion criteria: known secondary cause of hypertension that causes concern regarding the safety of the protocol; arm circumference too large or small to allow accurate blood pressure measurement with available devices; cardiovascular event or procedure or hospitalization for unstable angina within last 3 months; medical condition likely to limit survival to less than 3 years or a malignancy other than non-melanoma skin cancer within the last 2 years; any factors judged by the clinic team to be likely to limit adherence to interventions; failure to obtain informed consent from participant; any organ transplant; pregnancy, currently trying to become pregnant, or of childbearing potential and not using birth control 18-65 years old, gender not stated Setting not stated |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, double-blinded Number of study centres not stated Duration of study: 9 months Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>Yoga, Naturopathy treatment, and diet restrictions:</p> <ul style="list-style-type: none"> Yoga therapy 2 hours Yoga session/day: practices including Asana, Pranayama, and Meditation adopted from Yoga for Hypertension and Heart disease by Dr. H R Nagendra, Dr. R. Nagarathna, SVYP Publications. 45 minutes of Yoga for minimum 5 days/ week: Module based on Yoga for Hypertension and Heart disease by Dr. H R Nagendra, Dr. R. Nagarathna, SVYP Publications Diet Therapy Low calorie, Low salt Naturopathy diet including calorie restriction (Fasting Therapy) prescribed as per individual subject's needs. Low calorie, Low salt Naturopathy diet including calorie restriction. Physical activity Subjects will be encouraged to involve in moderate aerobic exercises like walking for 45 min/ day Subjects will be encouraged to involve in moderate aerobic exercises like walking for 45 min/ day/ 5 days a week. Hydrotherapy steam bath sauna bath under-water massage Spinal bath hip bath Neutral chest pack Mud Therapy Manipulative therapy <p>No further description of dose, method of administration, frequency of administration, who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <p>Standard care:</p> <ul style="list-style-type: none"> Physical activity- Subjects will be encouraged to involve in moderate aerobic exercises like walking for 45 min/ day Subjects will be |

| CTRI/2019/01/016883 (2019) | Ministry of AYUSH |
|----------------------------|--|
| | <p>encouraged to involve in moderate aerobic exercises like walking for 45 min/ day/ 5 days a week.</p> <ul style="list-style-type: none"> Diet restrictions [not further described] <p>No further descriptions of dose, method of administration, frequency of administration, or who delivered the comparator</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: arterial BP; HRV; 10-year cardiac risk assessment by Framingham's risk equation; salivary cortisol; quality of lifestyle questionnaire-Farrans and power cardiac version Secondary outcomes: total cholesterol (mg%); triglyceride (mg%); LDL (mg%); HDL (mg%); C- Reactive protein Assessments at baseline and months 1, 3, 6 and 9 |
| Funding source | Ministry of AYUSH, India |
| Conflicts of interest | <ul style="list-style-type: none"> Contact person's affiliations: Dr Honnegowda TM, Sri Dharmasthala Manjunatheshwara College of Naturopathy and Yogic Sciences Dept. of Yoga and Naturopathy, India Contact person's financial relationship: not stated No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: AYUSH, Ayurveda, Yoga, Naturopathy, Unani, Siddha, and Homeopathy; BP, blood pressure; HDL, high-density lipoprotein; HRV, heart rate variability; LDL, low-density lipoprotein

Table 90: CTRI/2019/10/021775 (2019)

| CTRI/2019/10/021775 (2019) | Dr Buvanavar M |
|----------------------------|--|
| Participant description | <ul style="list-style-type: none"> Number of participants: 60 Inclusion criteria: overweight and obese patients with BMI 25 kg/m² - 40 kg/m² Exclusion criteria: fever; pregnant and lactating women; menstruating; open wounds; cardiac disorders; hypertensive individuals; physical/mental impairment [that does not allow participant] to participate in the study Age and gender not stated Setting not stated |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, blinding not stated Number of study centres not stated Duration of study: 10 days Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>Yoga practices, naturopathy treatments, diet plan</p> <p>No further description of modalities, dose, method of administration, frequency of administration, who delivered the intervention</p> |
| Comparator | Number of participants not stated |

| CTRI/2019/10/021775 (2019) | Dr Buvanavar M |
|----------------------------|--|
| | No specific treatment No further description of modalities, dose, method of administration, frequency of administration, who delivered the comparator |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: heart rate variability and stress questionnaire Secondary outcomes: nil Assessment at 10 days [not stated if assessments taken at baseline] |
| Funding source | Nil |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: Pathanjali Mens Hostel, SDM College of Naturopathy, India Authors' financial relationship: not stated No other potential conflicts of interest stated |
| Status | Complete, data not available |
| Comments | Reason this study is awaiting classification: registered trial |

Table 91: CTRI/2020/12/029833 (2020)

| CTRI/2020/12/029833 (2020) | Dr Geetha Kumari V |
|----------------------------|--|
| Participant description | <ul style="list-style-type: none"> Number of participants: 160 Inclusion criteria: diagnosis of rheumatoid arthritis according to the revised 1987 ACR criteria for at least 6 months; disease activity, as defined using a 28 joint count by ≥ 5 tender joints, ≥ 5 swollen joints, and one of the following: Erythrocyte Sedimentation Rate (ESR) ≥ 28 mm/hour, CRP ≥ 1.5 mg/dL, duration of a.m. stiffness ≥ 45 minutes Exclusion criteria: history of drug, alcohol, or chemical abuse within 6 months before screening; intra-articular steroid injections within 4 weeks of screening; inability to comply with study and follow-up procedures; any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion that might affect the interpretation of the results; currently pregnant or lactating; begun any new treatment for rheumatoid arthritis during the previous 4 weeks (except analgesic treatment with paracetamol or NSAIDs) 25-60 years old, males and females Setting not stated |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, multi-arm, phase 3, assessor blinded Number of study centres not stated Duration of study: 3 months Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <ul style="list-style-type: none"> Group 1: Naturopathy intervention with Enema, Sauna bath, Partial and full body massage, Alternate hot and cold-water compress, hot mud application joint range of movements, and naturopathy diet Group 2: One hour of yoga session per day between 6.30 am to 8 am for 3 months weekly minimum of 6 sessions which consists of Sukhasana and Prarthana Universal Prayer for a minute, Sukshma vyayama movements of all the joints with slow and deep breathing for 9 minutes, |

| CTRI/2020/12/029833 (2020) | Dr Geetha Kumari V |
|----------------------------|--|
| | <p>25 minutes Asanas including Standing series, tadasana, triyak tadasana, katichakrasana, trikonasana, Sitting series, Ardhapadmāsana, Vajrasana, Sukasana, Supine series, Uttana padasana, Merudandasana, Mathsyasana, Prone series, Bhujangasana, ardha shalabasana, Savasana and deep relaxation technique, Sectional yogic breathing, Kapalabhati, Nadisodhana pranayama, and Bhramari, for 15 minutes and Meditation for 10 minutes</p> <ul style="list-style-type: none"> Group 3: combined naturopathy and yoga intervention <p>No further description of dose, method of administration, frequency of administration, who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <p>3 control groups, each instructed to continue their normal day-to-day physical activities along with their ongoing medical care.</p> <p>No further description of modalities, dose, method of administration, frequency of administration, or who delivered the comparator</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: disease activity assessed by DAS-28; pain intensity assessed by Visual Analogue Scale Secondary outcomes: handgrip strength; depression, anxiety and stress scale by DASS 21 questionnaire; QoL by SF-36 questionnaire; inflammatory markers, CRP, ESR, rheumatoid arthritis factor Assessments at 3 months [not stated if assessments will be conducted at baseline] |
| Funding source | SDM College of Naturopathy & Yogic Sciences College and Hospital, Ujire |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: Shri Dharmasthala Manjunatheshwara College of Naturopathy and Yogic Sciences, India Authors' financial relationship: not stated No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: ACR, American College of Rheumatology; CRP, C-reactive protein; DAS-28, Disease Activity Score-28 (for rheumatoid arthritis); DASS-21, Depression Anxiety Stress Scale 21; ESR, erythrocyte sedimentation rate; NSAID, non-steroidal anti-inflammatory drug; QoL, quality of life; SF-36, Short Form 36

Table 92: CTRI/2020/07/026734 (2020)

| CTRI/2020/07/026734 (2020) | Dr Sharada Shetty P S |
|----------------------------|--|
| Participant description | <ul style="list-style-type: none"> Number of participants: 60 Inclusion criteria: known hypothyroidism and under medication Exclusion criteria: history of substance dependence; psychotic disorders; pregnant or breastfeeding; major medical disorders; and who are unable to perform yoga and physical activity Age and gender not stated Setting not stated |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, blinding not stated Number of study centres not stated Duration of study: 10 days |

| CTRI/2020/07/026734 (2020) | Dr Sharada Shetty P S |
|----------------------------|--|
| | <ul style="list-style-type: none"> Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>Yoga and Naturopathy treatment adjunct with conventional treatment:</p> <ul style="list-style-type: none"> Yoga therapy Diet therapy Massage therapy Hydrotherapy Mud therapy Exercise therapy Acupuncture <p>No further descriptions of dose, method of administration, frequency of administration, or who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <p>Conventional therapy alone as prescribed by the family physician without interruption; oral thyroid medications for hypothyroidism</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: heart rate variability Secondary outcomes: body composition; mental health Assessment at baseline and 10 days <p>No further descriptions of assessment methods</p> |
| Funding source | SDM Yoga and Naturecure Hospital, India |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: Ragiv Gandhi University of Health Sciences Authors' financial relationship: not stated No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Table 93: DRKS00006343 (2014)

| DRKS00006343 (2014) | Abt. für Naturheilkunde, Klinik Blankenstein (primary sponsor) |
|-------------------------|---|
| Participant description | <ul style="list-style-type: none"> Number of participants: 68 Inclusion criteria: overweight (BMI 25-29.9 kg / m²) or obese (BMI = 30 kg / m²); wished to reduce body weight; and who were prescribed fasting therapy or a weight reduction diet as a form of nutritional therapy. Exclusion criteria: pregnant and lactating women; patients who participated in another study simultaneously or in an organized weight reduction program or took a medicament against obesity; extensive bowel resection or bariatric treatment; inflammatory bowel disease; malignant neoplastic disease; postoperative nutritional deficit; hepatic or renal failure; insulin-dependent diabetes mellitus; not compensated hypothyroidism or hyperthyroidism; coronary heart disease or acute or chronic cardiac arrhythmia; eating disorders like anorexia nervosa, bulimia or binge eating disorder; severe psychiatric disorders; addictive disorders and dementia. |

| DRKS00006343 (2014) | Abt. für Naturheilkunde, Klinik Blankenstein (primary sponsor) |
|---------------------|--|
| | <ul style="list-style-type: none"> • 18-75 years old, male and female • Setting not stated |
| Study methods | <ul style="list-style-type: none"> • NRSI, parallel with comparator group, open-label • Single centre study, naturopathic department of Blankenstein hospital, Germany • Duration of study: 6 months • Unit of analysis: individual participant • Statistical methods: not stated |
| Intervention | <p>Number of participants: 43</p> <ul style="list-style-type: none"> • Modified Buchinger fasting therapy, including vegetable stocks and vegetable juices, teas, and water, but no fruit juices. <ul style="list-style-type: none"> ➤ Fasting duration is 7 to 10 days, followed by a gradual return to solid food over 3 to 4 days and then a balanced basic diet. ➤ Fasting is accompanied by individually prescribed therapies within the scope of naturopathic complex treatment. Starting with a balanced basic diet alimentation is changed with a portion of fruit in the evening of the priming [?] day. ➤ During the fasting period, the patients receive 250 ml of vegetable stock in the morning, at noon, and in the evening, additional 150 ml of vegetable juices made of celery, carrots, beet, tomatoes, or sauerkraut, containing a total energetic load of 150kcal/d. Additional fluid is provided by mineral water, herbal teas, and fasting tea containing licorice root, nettle herb, and hawthorn leaves. The targeted daily fluid intake is 3 to 4 L. ➤ On the fasting days, the patients receive additionally a warm liver package after noon. Purgation of the bowels is accomplished initially using Glauber salt (sodium sulfate) or FX passage SL (magnesium sulfate), followed by enemas every 2 to 3 days. ➤ Patients attend focus groups three times a week. • Participants receive information about fasting and planned change of diet after fasting from scientifically trained ecotrophologists. • For clinical surveillance, periodic laboratory measurements, ECGs and daily blood pressure measurements are performed. • Breaking of the fasting is accomplished by eating a ground apple or apple sauce. Further buildup is carried out with soups, vegetables, curd, natural yoghurt, potatoes, fruit, and finally raw foods and wholemeal products. • Energy intake is raised to 1000 kcal/d. The number of buildup days is designated individually, normally 3 days after a seven-day-fasting, and 4 days after 10 days of fasting |
| Comparator | <p>Number of participants: 43</p> <p>Active control: Weight reduction diet</p> <ul style="list-style-type: none"> • Reduced caloric feed charge. Patients receive a well-balanced low-fat and modified fat wholefood basic diet with a daily energetic deficit of 500-800 kcal. • The food contains ~50% carbohydrates, ~30% fat, and ~20% proteins. Fat reduction is primarily achieved by restriction of animal fat leading to saturated fatty acids contributing less than 7% to the daily energetic supply. |

| DRKS00006343 (2014) | Abt. für Naturheilkunde, Klinik Blankenstein (primary sponsor) |
|-----------------------|--|
| | <ul style="list-style-type: none"> • A high proportion of dietary fibre and complex carbohydrates ensure a prolonged feeling of satiety. • The weight reduction diet patients continued their diet throughout the entire inpatient stay. • The patients are expected to continue this diet after discharge |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: weight loss after 6 months of patients who received in-patient fasting treatment in comparison to those receiving a weight reduction diet. A MD of 3 kg between the treatment groups was considered clinically significant: A permanent reduction of 5% of the starting weight is considered a success and a general goal of therapy in both German and the U.S. American guidelines. • Secondary outcomes: <ul style="list-style-type: none"> ➢ Which percentage of the patients achieve a weight loss of = 5% of the initial weight after fasting therapy or a weight reduction diet? ➢ SBP and DBP ➢ Serum concentrations of total, LDL- and HDL-cholesterol, triglycerides, and glucose ➢ Changes in eating behaviour: in the dimensions cognitive control, distractibility, and hunger feelings [FEV] ➢ Changes in physical activity, measured by duration of activity in basic, leisure time, and sport [FFKA] ➢ Relation between possible raised physical activity and loss of weight after 6 months ➢ Changes in QoL [SF-12] ➢ Relation between possible increased QoL and loss of weight after 6 months • Assessment at 3 and 6 months [not clear if assessments will be made at baseline] |
| Funding source | Abt. für Naturheilkunde, Klinik Blankenstein, Germany |
| Conflicts of interest | <ul style="list-style-type: none"> • Contact person's affiliations: André-Michael Beer, Abt. f. Naturheilkunde, Klinik Blankenstein, Germany • Contact person's financial relationship: not stated • No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial; language other than English |

Abbreviations: FEV, German version of the Three-Factor Eating Questionnaire; FFKA, Freiburger Questionnaire for Physical Activity; HDL, high-density lipoprotein; LDL, low-density lipoprotein; QoL, quality of life; SF-12, Short Form 12

Table 94: DRKS00009884 (2016)

| DRKS00009884 (2016) | Forschungsinstitut Havelhöhe (FIH) (primary sponsor) |
|-------------------------|---|
| Participant description | <ul style="list-style-type: none"> • Number of participants: 50 • Inclusion criteria: diabetes mellitus Type 2, first diagnosis = 8 years; HbA1c = 6.5%; BMI = 25 – 40; able to take part in activity exercise therapy and in the other planned interventions |

| DRKS00009884 (2016) | Forschungsinstitut Havelhöhe (FIH) (primary sponsor) |
|---------------------|---|
| | <ul style="list-style-type: none"> Exclusion criteria: insulin therapy; myocardial infarction, pulmonary artery embolism, or stroke in the last 6 months; unstable angina pectoris; heart insufficiency= NYHA 3; COPD = GOLD grade 3; peripheral artery disease = Fontaine stage 2a; known high-grade renal insufficiency; manifest major depression: VAS Depression = 60; other high-grade organic or psychological disease that requires treatment; pregnancy and lactation 18-75 years old, male and female |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, open-label Duration of study: 15 weeks |
| Intervention | <p>Number of participants not stated</p> <p>Group-therapeutical offer (15 weekly dates): Exercise therapy, stress management and education, eurythmy, modelling, nutritional/dietary treatment, and sleep education.</p> <p>No further descriptions of dose, method of administration, frequency of administration, who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <p>Active control: additional recommendations to lifestyle optimisation besides the standard supply in Diabetes mellitus Type 2 by diabetologist or general practitioner.</p> <p>No further descriptions of dose, method of administration, frequency of administration, or who delivered the comparator</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: improvement of the metabolic state, QoL, sleep quality, autonomic regulation, rest/activity regulation, and self-regulation. <ul style="list-style-type: none"> Metabolic state: HbA1c on day of study inclusion, after 9 weeks of interventions, and at the end of the interventions (at the end of the study) S-insulin, S-glucose (HOMA index), adiponectin, LDL-C, HDL-C, Non-HDL-C, TG, total cholesterol, blood pressure, heart rate, and actigraphy) on day of study inclusion and after the interventions (at the end of the study). Sleep quality: PSQI Life quality SF-12 at day of study inclusion, as baseline at the first day of the study (before the start of interventions), and after the interventions (at the end of the study). Autonomic regulation and the rest-/activity regulation: 18-item Trait autonomic Regulation questionnaire on day of study inclusion and as baseline on the first day of the study (before the start of interventions), after nine weeks of interventions, and after the interventions (at the end of the study). Self-regulation: 16-item self-regulation questionnaire on day of study inclusion and as baseline on the first day of the study (before the start of interventions), after nine weeks of interventions, and after the interventions (at the end of the study). Secondary outcomes: validation of Inner Congruence with the Modelling Therapy questionnaire |
| Funding source | Damus-Donata e.V. Dr. Hauschka Stiftung; Mahle-Stiftung |

| DRKS00009884 (2016) | Forschungsinstitut Havelhöhe (FIH) (primary sponsor) |
|-----------------------|---|
| Conflicts of interest | <ul style="list-style-type: none"> Contact person's affiliations: Roland Zerm and Danilo Pranga Gemeinschaftskrankenhaus Havelhöhe und Forschungsinstitut Havelhöhe (FIH), Germany Contact person's financial relationship: not stated No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial; language other than English |

Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HDL, high-density lipoprotein; HOMA index, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; NYHA, New York Heart Association; PSQI, Pittsburgh Sleep Quality Index; SF-12, Short Form 12; TG, triglyceride; VAS, visual analogue scale

Table 95: ISRCTN61808774 (2003)

| ISRCTN61808774 (2003) | Department of Health (UK) (primary sponsor) |
|-------------------------|--|
| Participant description | <ul style="list-style-type: none"> Number of participants: 240 Inclusion criteria: people presenting at ten general practices in Brent in the summer of 2000 with low back pain of over three months duration. Exclusion criteria: does not match inclusion criteria 20-65 years old, male and female Setting: British College of Naturopathy and Osteopathy |
| Study methods | <ul style="list-style-type: none"> Parallel RCT Single centre study Duration of study/dates of study Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>Treatment at the British College of Naturopathy and Osteopathy by third/fourth-year students under the supervision of experienced trainer practitioners:</p> <ul style="list-style-type: none"> Naturopathic osteopathy and include patient diaries. Up to 7 treatments, expecting an average of 5 weekly treatments. <p>No further descriptions of dose, method of administration, frequency of administration, or who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <p>Usual care [not further described]</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: disability (Roland Morris Score); self-competence (Perceived Pain Management Competence Scale); beliefs (Back Beliefs Questionnaire); pain (Von Korff questionnaire); well-being (SF12) Secondary outcomes: nil Assessments at 3, 6, and 12 months and at 5 years [not stated if assessments will be made at baseline] |
| Funding source | The West London Research Network (WeLReN) (UK) |

| ISRCTN61808774 (2003) | Department of Health (UK) (primary sponsor) |
|-----------------------|---|
| Conflicts of interest | <ul style="list-style-type: none"> Contact person's affiliations: Paul Thomas, Kilburn Park Medical Centre, UK Contact person's financial relationship: not stated Other potential conflicts of interest, including those declared by the researchers not stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: SF12, Short Form 12

Table 96: NCT00010634 (2001)

| NCT00010634 (2001) | Therese Madden |
|-------------------------|---|
| Participant description | <ul style="list-style-type: none"> Number of participants not stated 35 years and older, with periodontitis, males and females, Kaiser Permanente patients Setting: The Oregon Health Sciences University (OHSU), Portland, Oregon, United States |
| Study methods | <ul style="list-style-type: none"> RCT, phase 2, 4 arms Single centre Duration of study not stated Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants: not stated</p> <ul style="list-style-type: none"> Group 1: glutamine Group 2: Connective Tissue Nutrient Formula: vitamins A, C, and D, glucosamine sulfate, oligoproanthocyanindins, copper, zinc, manganese, boron, silicon, magnesium, and calcium Group 3: adaptogenic herbs: Panax ginseng, Withania somnifera and Eleutherococcus senticosus <p>No further descriptions of dose, method of administration, frequency of administration, or who delivered the intervention</p> |
| Comparator | <p>Number of participants: not stated</p> <ul style="list-style-type: none"> Standard treatment <p>No further descriptions of modalities, dose, method of administration, frequency of administration, who delivered the comparator</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: <ul style="list-style-type: none"> Clinical outcomes: attachment loss, pocket depths, indicators of inflammation, plaque composition, need for periodontal surgery, acute periodontal problems, tooth loss Stress, coping, quality of life, assessed with self-report measures Secondary outcomes: nil Study subjects will provide samples of blood, saliva, gingival cervical fluid, and bacterial dental plaque. |
| Funding source | National Center for Complementary and Integrative Health (NCCIH), sponsor |

| NCT00010634 (2001) | Therese Madden |
|-----------------------|--|
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: Center for Health Research, Kaiser Foundation Hospitals • Authors' financial relationship: not stated • No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Table 97: NCT00169299 (2005)

| NCT00169299 (2005) | Katherine M Newton |
|-------------------------|--|
| Participant description | <ul style="list-style-type: none"> • Number of participants: 351 • Inclusion criteria: female, 45-55 years old, peri- or post-menopausal, moderate to severe vasomotor symptoms, normal thyroid-stimulating hormone, proof of normal mammogram within past 2 years • Exclusion criteria: use of hormone therapy or oral contraceptives within the past 3 months, use of herbs or alternative or complementary medicines for vasomotor symptoms within the past 1 month; a medical history of contraindications to hormone therapy; bone mineral density greater than 2 standard deviations below age-specific mean; bilateral oophorectomy; current use of tamoxifen, raloxifene, bisphosphonates, cholesterol-lowering medications, prescription blood-thinners, or oral steroids; pregnant or planning to become pregnant; allergy to soybeans or soy protein; unable to swallow pills; current participation in another investigational drug trial; intention to move out of area in the next 12 months; non-compliance with procedures involved in screening and run-in trial • Setting: Group Health Cooperative, Center for Health Studies, Seattle, Washington, United States |
| Study methods | <ul style="list-style-type: none"> • Parallel RCT, double-blinded, 5-arms • Single centre study • Duration of study: 12 months, with follow-up to 4 years • Unit of analysis: individual participant • Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <ul style="list-style-type: none"> • Group 1: conjugated equine estrogen with or without medroxyprogesterone acetate in women with or without an intact uterus respectively • Group 2: a single herbal product, black cohosh • Group 3: multi botanical preparation • Group 4: combination regimen that includes the same multi botanical preparation plus soy diet counselling <p>No further descriptions of dose, method of administration, frequency of administration, who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <ul style="list-style-type: none"> • Placebo <p>No further descriptions of dose, method of administration, frequency of administration, or who delivered the comparator</p> |

| NCT00169299 (2005) | Katherine M Newton |
|-----------------------|--|
| Outcome | <ul style="list-style-type: none"> Primary outcomes: self-report daily diary of frequency and intensity of vasomotor symptoms; Wiklund Menopause Symptom Checklist Secondary outcomes: vaginal cytology (vaginal maturation index); serum lipids (total cholesterol, HDL and LDL cholesterol, triglycerides); bone mineral density (hip and spine dual-energy x-ray absorptiometry scan); glucose metabolism (insulin, fasting blood glucose); coagulation factors (fibrinogen, PAI-1) Assessments at baseline and 3, 6 and 12 months |
| Funding source | Sponsors: Kaiser Permanente; National Institute on Aging (NIA); and National Center for Complementary and Integrative Health (NCCIH) |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: Group Health Cooperative, Center for Health Studies Authors' financial relationship: not stated No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial. Published study from this trial does not have 'whole-systems naturopathy' as the intervention |

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor-1

Table 98: NCT00309439 (2006)

| NCT00309439 (2006) | David JA Jenkins |
|-------------------------|--|
| Participant description | <ul style="list-style-type: none"> Number of participants not stated 18 to 77 years old All genders [error? Trial measures 'prostate cancer'] Inclusion criteria: blood samples available from Bordeaux Exclusion criteria: blood samples not available from Bordeaux Setting not stated |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, single blinding Number of study centres not stated Duration of study not stated Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>ALA-rich diet</p> <p>No further descriptions of modalities, dose, method of administration, frequency of administration, or who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <p>Comparator treatment not stated</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: atrial fibrillation, prostate cancer [methods of assessment not stated] Secondary outcomes: nil |
| Funding source | Not stated |

| NCT00309439 (2006) | David JA Jenkins |
|-----------------------|--|
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: University of Toronto • Authors' financial relationship: not stated • No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: ALA, alpha-linolenic acid

Table 99: NCT00334919 (2006)

| NCT00334919 (2006) | Patricia Elmer |
|-------------------------|---|
| Participant description | <ul style="list-style-type: none"> • Number of participants: 30 • Inclusion criteria: BMI: 25-45 kg/m²; diagnosed with type 2 diabetes or pre-diabetes; at risk for type 2 diabetes; fasting blood glucose of 100-200 mg/dL; must meet 2 of the following 3 criteria: <ul style="list-style-type: none"> ➢ BMI 30-45 kg/m² ➢ age 50 or older, and/or ➢ family history of type 2 diabetes • Exclusion criteria: current major debilitating mental or physical illness that would interfere with participation (as determined by the participant's medical history); taking diabetic medication other than sulfonylurea; taking <i>Gymnema silvestra</i>; taking medications that have anti-inflammatory effects (lipid-lowering agents, NSAIDs, COX 2 inhibitors, aspirin, HRT, oral contraceptives, testosterone, seizure medications) taking weight loss medications; severe renal, hepatic, or heart disease; triglycerides >500 mg/dL; bulimia; pregnancy or lactation; current excessive use of alcohol; current/recent chronic use of recreational drugs; smoker; > 4 hours/week of aerobic exercise; gained or lost more than 15 pounds during previous 6 months; planning on moving out of the area in the next 4 months; participating in another medical research study; following a weight loss diet; unwilling to accept random assignment of the experimental diets; food preferences and/or allergies that will interfere with consumption of experimental diet • Age 18-75 years, males and females • Setting: Oregon Health & Science University General Clinical Research Center, Portland, Oregon, US |
| Study methods | <ul style="list-style-type: none"> • RCT, open-label • Number of study centres not stated • Duration of study: 6 weeks treatment with follow-up to 13 weeks • Unit of analysis: individual participant • Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>Anti-inflammatory diet</p> <p>No further description of the intervention</p> |
| Comparator | <p>Number of participants Not stated</p> <p>Standard ADA diet</p> <p>No further description of the comparator</p> |

| NCT00334919 (2006) | Patricia Elmer |
|-----------------------|--|
| Outcome | <ul style="list-style-type: none"> Primary outcomes: cytokines Secondary outcomes: glucose; weight; lipids |
| Funding source | Sponsors: National University of Natural Medicine; National Center for Complementary and Integrative Health (NCCIH) |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: National College of Naturopathic Medicine Authors' financial relationship: not stated No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: ADA, American Diabetic Association

Table 100: NCT00974506 (2009)

| NCT00974506 (2009) | Claudia M Witt |
|-------------------------|---|
| Participant description | <ul style="list-style-type: none"> Number of participants: 50 Inclusion criteria: living in shared flat/residential community informed consent of the patient or authorised representative Exclusion criteria: participation in another study within the last 6 months; acute or chronic disease condition that does not allow participation; actual use of complementary therapies 70 years and older, males and females Setting: Institute for Social Medicine, Epidemiology, and Health Economics, Charité University Medical Center, Berlin, Germany |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, open-label Single or multicentre study; if multicentre, number of recruiting centres Duration of study/dates of study Unit of analysis (e.g. individual participant, clinic, village, body part) Statistical methods |
| Intervention | <p>Number of participants not stated</p> <p>A complex intervention containing exercise therapy, nutritional advice, homeopathy, and naturopathy in addition to routine therapy by the general practitioner</p> <p>No further description of modalities, dose, method of administration, frequency of administration, who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <p>Routine care by a general practitioner</p> <p>No further descriptions of modalities, dose, method of administration, frequency of administration, or who delivered the comparator</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: activities of daily living (AMPS, Barthel Index, Nosger); quality of life (Qualidem, Profile of Wellbeing); risk of falls (Tinetti); falls; cognition (Minimental Status Test); hospital admissions; medication use. <ul style="list-style-type: none"> ➤ Frequency of assessments not stated Secondary outcomes: |

| NCT00974506 (2009) | Claudia M Witt |
|-----------------------|---|
| | <ul style="list-style-type: none"> ➤ At 3, 6 and 12 months: assessment of motor and process skills (AMPS); Qualidem; Barthel Index; Nurses Observation Scale for Geriatric Patients; Tinetti Test; Profile of Wellbeing; Medication use and Potentially Inappropriate Medication Use (Beers Criteria 2003) ➤ At 12 months: Minimental Status Test; Falls (Esslinger Sturzprotokoll); hospital admissions; adverse effects; interviews with health care team and relatives |
| Funding source | Sponsors: Charite University, Berlin, Germany; Homöopathie Stiftung; omeoeon e.V. |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: Institute for Social Medicine, Epidemiology, and Health Economics, Charité University Medical Center, Berlin, Germany • Authors' financial relationship not stated • No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Table 101: NCT02396160 (2015)

| NCT02396160 (2015) | Niikee Schoendorfer |
|-------------------------|---|
| Participant description | <ul style="list-style-type: none"> • Number of participants: 150 • Inclusion criteria: symptoms of urinary frequency (at least 10 times per day) and/or incontinence (at least nine episodes per week), provided they have experienced symptoms of OAB for at least 6 months. • Exclusion criteria: recent surgery particularly hysterectomy or prolapse repair (within the last 12 months); recently undergone childbirth (within the last 12 months), or currently pregnant; use of any natural therapies for bladder symptoms in the last month; concomitant health conditions such as uncontrolled diabetes mellitus, heart disease, pancreatic, hepatic or renal disease, recurrent urinary tract infections, and chronic inflammatory conditions, which may otherwise affect outcomes; currently being treated for mental health issues or psychiatric disturbances; presently taking prescribed medication for incontinence or OAB. • 18 years and older; males and females • Setting: clinics and college campus |
| Study methods | <ul style="list-style-type: none"> • Parallel RCT, quadruple-blinded • Multicentre study, 3 locations: Brisbane campus of the Endeavour College of Natural Medicine Naturopathic clinic or at Kelvin Grove Natural Medicine clinic, Brisbane • Duration of study: 8 weeks • Unit of analysis: individual participant • Statistical methods: intention to treat |
| Intervention | <p>Number of participants not stated</p> <p>2 capsules per day of the herbal formula (Urox®) with each capsule containing 420mg of a concentrated proprietary blend of extracts of <i>Crateva nurvala</i> stem bark, <i>Equisetum arvense</i> stem, and <i>Lindera aggregata</i> root</p> <p>No further description method of administration, who delivered the intervention</p> |
| Comparator | Number of participants not stated |

| NCT02396160 (2015) | Niikee Schoendorfer |
|-----------------------|---|
| | Placebo vegetarian capsule containing colour-matched cellulose No further description of the method of administration, frequency of administration, or who delivered the comparator |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes, recorded in a validated urinary diary: <ul style="list-style-type: none"> ➤ Day Urinary Frequency: number of voluntary diurnal micturition's per day ➤ Nocturia Frequency: number of voluntary nocturnal micturitions per day • Secondary outcomes, recorded in a validated urinary diary: <ul style="list-style-type: none"> ➤ Urinary Urgency Frequency: number of urgency episodes per day ➤ Urge Incontinence Frequency: number of incontinence episodes per day resulting from urinary urgency ➤ Stress Incontinence Frequency: number of episodes of incontinence per day related to stress |
| Funding source | Sponsor: The University of Queensland Collaborators: University of Tasmania; Seipel Group Pty Ltd; Endeavour College of Natural Health |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: University of Queensland • Authors' financial relationship: not stated • No other potential conflicts of interest stated |
| Status | Results available |
| Comments | Reason this study is awaiting classification: registered trial; published study not in scope (Schoendorfer N, Sharp N, Seipel T, Schauss AG, Ahuja KDK. Urox containing concentrated extracts of Crataeva nurvala stem bark, Equisetum arvense stem and Lindera aggregata root, in the treatment of symptoms of overactive bladder and urinary incontinence: a phase 2, randomised, double-blind placebo controlled trial. BMC Complement Altern Med. 2018 Jan 31;18(1):42. doi: 10.1186/s12906-018-2101-4.) |

Abbreviations: OAB, overactive bladder

Table 102: NCT02843724 (2016)

| NCT02843724 (2016) | Ellen Wong |
|-------------------------|---|
| Participant description | <ul style="list-style-type: none"> • Number of participants: 148 • Inclusion criteria: <ul style="list-style-type: none"> ➤ enrolled as a patient with WE-FHT ➤ type 2 diabetes and not adequately controlled (HbA1c > 7.0mmol/L) ➤ currently seeking care with a medical doctor, nurse practitioner, and/or physician assistant ➤ willing to adhere to randomized treatment with availability for follow-up ➤ ability to answer self- and interviewer-administered questions in English or have an English-speaking caregiver who can aid in answering self- and interviewer-administered questions ➤ ability to provide written informed consent or give informed consent through a substitute decision-maker |

| NCT02843724 (2016) | Ellen Wong |
|--------------------|--|
| | <ul style="list-style-type: none"> ➤ capacity to maintain a diary and log of treatments and recommendations given during the study • Exclusion criteria: <ul style="list-style-type: none"> ➤ Lacking capacity for consent ➤ Pregnancy or an intention to become pregnant in the following two years ➤ Breastfeeding ➤ History of myocardial infarction within the past 6 months ➤ Chronic kidney (eGFR <30 mL/min) or liver disease ➤ Actively receiving care from a complex care diabetes clinic ➤ History of severe hypoglycemia in the last year resulting in hospital emergency care [where hypoglycemia is defined to be: 1) development of autonomic or neuroglycopenic symptoms, 2) low plasma glucose level (<4.0mmol/L for patients treated with insulin or an insulin secretagogue) and 3) symptoms responding to the administration of carbohydrate] or hypoglycemia unawareness ➤ Current bolus or pre-mixed insulin treatment ➤ Limited life expectancy (< 6 months) ➤ High level of functional dependency (inability to perform common activities of daily living) ➤ In participants aged 65 years to 75 years, the following also serve as exclusion criteria: <ul style="list-style-type: none"> ▪ Recent MI or stroke (within the last 6 months) ▪ NYHA CHF Functional Capacity Stage III or above ▪ NYHA CHF Objective Assessment Stage C or greater ▪ Planned revascularization procedure (PCI or coronary artery bypass graft) or coronary angiogram within 90 days after screening or randomization • Age 21-75 years, males and females • Setting: Brampton Naturopathic Teaching Clinic • Study eligibility criteria, including diagnostic criteria |
| Study methods | <ul style="list-style-type: none"> • Parallel RCT, open-label • Single centre study • Duration of study: 1 year • Unit of analysis (e.g. individual participant, clinic, village, body part) • Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>In addition to conventional care:</p> <ul style="list-style-type: none"> • Free naturopathic care at Brampton Naturopathic Teaching Clinic (located within the Brampton Civic Hospital) • Senior student clinicians will provide care under the direct supervision of licensed naturopathic doctors. • A naturopathic menu of treatment options has been designed to reflect naturopathic practice and vetted by 3 licensed naturopathic doctors and experts in the field. |

| NCT02843724 (2016) | Ellen Wong |
|-----------------------|--|
| | <ul style="list-style-type: none"> Participants' other health concerns will be addressed as per naturopathic doctors' discretion. Naturopathic diabetes care will be selected from a pre-approved menu. <p>Frequency of naturopathic visits were not described</p> |
| Comparator | <p>Number of participants not stated</p> <ul style="list-style-type: none"> Treatment of Type 2 Diabetes according to the Canadian Diabetes Association guidelines. Participants' other health concerns to be addressed as per usual care by practitioners at Wise-Elephant Family Health Team 2016 Canadian Diabetes Clinical Practice Guidelines (self-management, blood-glucose-lowering, vascular protection, pharmacotherapy) will be implemented <p>Frequency of practitioner visits were not described</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: HbA1c over 1 year Secondary outcomes, over 2 years: <ul style="list-style-type: none"> Incidence of metabolic syndrome Weight, height (as part of BMI) Waist circumference (as part of metabolic syndrome) Fasting blood glucose, HbA1c, biomarkers associated with diabetes Blood pressure, systolic and diastolic blood pressure, seated, resting Total cholesterol, HDL, LDL, triglycerides: biomarkers associated with cholesterol & cardiovascular risk High-sensitivity C-reactive protein, a biomarker associated with cardiovascular risk Incidence of smoking, modifiable risk factors for cardiovascular disease Incidence of obesity, modifiable risk factors for cardiovascular disease, BMI equal to or greater than 30.0 kg/m² Incidence of depression (PHQ-9) Impact on stress, anxiety, quality of life: ADDQoL Impact on anxiety, GAD 7 Impact on quality of life: DES, SF-12 Compliance/adherence with treatment prescriptions including changes in lifestyle, diet, exercise, and nutraceutical supplementation, assessed by diet and physical activity tracker Compliance/adherence with pharmaceutical prescriptions using a medication adherence questionnaire Adverse Events |
| Funding source | Sponsor: The Canadian College of Naturopathic Medicine |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: The Canadian College of Naturopathic Medicine Authors' financial relationship: not stated No other potential conflicts of interest stated |
| Status | Not Recruiting |

| NCT02843724 (2016) | Ellen Wong |
|--------------------|--|
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: ADDQoL, Audit of Diabetes Dependent Quality of Life; DES, Dissociative Experiences Scale GAD-7, General Anxiety Disorder-7; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; NYHA, New York Heart Association; SF-12, Short Form 12; WE-FHT, Wise Elephant Family Health Team

Table 103: NCT04120259 (2019)

| NCT04120259 (2019) | Dr Momina Abid |
|-------------------------|---|
| Participant description | <ul style="list-style-type: none"> Number of participants: 126 Inclusion criteria: recently diagnosed Type 2 diabetic patients taking metformin 750 mg daily as the oral antidiabetic agent; HbA1c 6.5 to 7.5% Exclusion criteria: all newly diagnosed diabetic patients requiring a dosage other than 750 mg per day; on insulin therapy or any drugs for diabetes other than Metformin; pregnant and lactating women; food allergies to either apple or any source of vinegar; unable to communicate efficiently/mentally challenged; Type 2 diabetes with any of the complications of long-standing uncontrolled diabetes 18-65 years old, males and females Setting not stated |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, open-label Number of study centres not stated Duration of study: 12 weeks Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>Metformin 750 mg oral plus 2 tablespoons of apple cider vinegar/day</p> <p>No further description of the method of administration, or who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <p>Metformin Tablet oral 750 mg /day</p> <p>No further description of the method of administration, or who delivered the comparator</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes (over 12 weeks): BMI, HbA1c, fasting blood glucose Secondary outcomes: nil No description of frequency measurement |
| Funding source | Sponsor: Ziauddin University, Pakistan |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: Ziauddin University, Pakistan Authors' financial relationship not stated No other potential conflicts of interest stated |
| Status | Complete, data not available |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: BMI, body mass index; HbA1c, glycosylated haemoglobin

Table 104: NCT04871412 (2021)

| NCT04871412 (2021) | Andrew Seely |
|-------------------------|--|
| Participant description | <ul style="list-style-type: none"> • Number of participants: 40 • Inclusion criteria: adults eligible for complete resection of lung, gastric or oesophageal cancer • Exclusion criteria: small cell, carcinoid, or gastrointestinal stromal; tumours; any wedge resections of lung cancer; history of cancer with active treatment in the last 3 years (not including superficial bladder cancer or non-melanoma skin cancer); currently receiving care guided by an ND or who have previously seen an ND in the last 3 months; pregnant or breastfeeding women; any reason which, in the opinion of the Principal Investigator (or delegate), would prevent the subject from participating in the study; use of an investigational drug or participation in an investigational study within 30 days before starting the study • 18 years and older, males and females • Setting: Ottawa Hospital and Centre for Health Innovation • Study eligibility criteria, including diagnostic criteria |
| Study methods | <ul style="list-style-type: none"> • Parallel RCT, open-label, Phase 3 • Single centre • Duration of study: at least 2 years • Unit of analysis: individual participant • Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>Standard surgical and oncologic care at The Ottawa Hospital plus complementary care guided by a naturopathic doctor at The Centre for Health Innovation:</p> <ul style="list-style-type: none"> • Dietary supplements: vitamin D3 drops 1,000-10,000 units/day based on serum levels throughout the study; Coriolus Versicolor 1.5g twice/day throughout the study; Trident SAP 66.:33 Lemon (fish oil) 3g/day throughout study; Probiotic Pro12 12 billion colony forming units/day during the perioperative period; Provitlix Pure Whey Protein (protein powder) 22g/day during peri-operative period and any adjuvant chemotherapy and radiation treatments; Theracurmin 2X (curcumin) 1.2g twice/day after the peri-operative period and during adjuvant chemotherapy and radiation; green tea extract 700mg twice/day after the peri-operative period (not during adjuvant radiation or chemotherapy treatment) • Nutrition recommendations based on the Mediterranean diet and lower glycaemic index foods • Physical activity recommendations: 150min moderate intensity aerobic exercise/week and resistance exercise program 2 days/week • Psychological recommendations: activities with the intention to actively improve participants' mental and emotional health |
| Comparator | <p>Number of participants not stated</p> <p>Standard surgical and oncologic care at The Ottawa Hospital</p> <p>No further description of modalities, dose, method of administration, frequency of administration, who delivered the comparator</p> |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: |

| NCT04871412 (2021) | Andrew Seely |
|-----------------------|---|
| | <ul style="list-style-type: none"> ➤ Participant Recruitment Rates at end of recruitment (estimated 1 year) ➤ Participant Retention Rates at 2 years ➤ Cross-over and contamination in the control arm - Supplement usage at 1 year: the number of participants in the control arm who use the integrative interventions outlined in the protocol independent of a naturopathic doctor. Information on the number of supplements used and the length of use will be collected at each standard of care visit ➤ Cross-over and contamination in the control arm - Mediterranean Diet Scores at 1 year: number of participants in the control arm who use the integrative interventions outlined in the protocol independent of a naturopathic doctor. Mediterranean diet scores (scale of 0-9) will be calculated in the control group using the Harvard Food Frequency Questionnaire to assess for changes over the 1-year follow-up period. ➤ Cross-over and contamination in the control arm - Physical Activity levels at 1 year: changes in physical activity will be monitored using the International Physical Activity Questionnaire, which is used to calculate total metabolic equivalent task (MET) minutes. ➤ Cross-over and contamination in the control arm - Psychological Health Activities at 1 year: number of participants in the control arm who perform activities in which the goal of the activity was to improve mental and emotional health. • Secondary outcomes: <ul style="list-style-type: none"> ➤ Communication at 2 years: type and frequency of communications between research staff at The Ottawa Hospital and the Centre for Health Innovation, as well as within both institutions through the number of emails, phone calls, meetings (in-person or virtual), or any other communication method. ➤ Natural Killer Cell Function at enrolment, 2-3 days pre-op, and 6 months and 12 months post-surgery: by serum Interferon Gamma Levels ➤ Qualitative Experience at 2 years: qualitative experience of care of participants in both arms through semi-structured interviews ➤ Inflammatory Response at enrolment, 2-3 days pre-op, and 1 day, 3-4 weeks, 6 months, and 12 months post-surgery: by serum C-Reactive Protein Levels ➤ Neutrophil to Lymphocyte Ratio at enrolment, 2-3 days pre-op, and 6 months and 12 months post-surgery: complete blood count with differential and comparing neutrophil and lymphocyte levels |
| Funding source | Sponsors and collaborators: Ottawa Hospital Research Institute; The Canadian College of Naturopathic Medicine; Lotte & John Hecht Memorial Foundation The Centre for Health Innovation; University of Ottawa |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: Andrew Seely, Ottawa Hospital Research Institute; Dugald Seely, The Canadian College of Naturopathic Medicine • Authors' financial relationship: not stated • No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: ND, naturopathic doctor

Table 105: CTRI/2020/09/028014 (2020)

| CTRI/2020/09/028014 (2020) | Dr Sahana Bhandary M |
|----------------------------|--|
| Participant description | <ul style="list-style-type: none"> • Number of participants: 60 • Inclusion criteria: under BMI 27kg/m²; not diagnosed with diabetes, hypercholesterolemia, or mental disorder. • Exclusion criteria: major illnesses; diabetes mellitus; heavy alcohol consumption; recent acute or chronic disease; changing medications that affect weight; weight loss >5 kg in the last 3 months; fluctuating exercise patterns; strenuous exercise >1 h per day; dietary limitations, and dislike of vegetables; cardiovascular, kidney, liver, thyroid or renal diseases; endocrine disorders; cancer or AIDS; use of medications that could influence lipid or carbohydrate metabolism (thiazides, β-blockers, glucocorticoids, weight-loss medications, thyroid hormone, or hypolipidemic drugs); pregnancy or lactation • Age and gender not stated • Setting not stated |
| Study methods | <ul style="list-style-type: none"> • Parallel RCT, blinding not stated. 3 arms • Number of study centres not stated • Duration of study: 10 days • Unit of analysis (e.g. individual participant, clinic, village, body part) • Statistical methods |
| Intervention | <p>Number of participants not stated</p> <ul style="list-style-type: none"> • Group 1: diet with yoga and naturopathic treatment for 10 days: <ul style="list-style-type: none"> ➤ Raw vegetable diet, raw fruit diet ➤ Yoga therapy, ➤ Massage therapy, hydrotherapy, mud therapy • Group 2: fruit diet with yoga and naturopathy treatment: <ul style="list-style-type: none"> ➤ Fruit diet ➤ Yoga therapy ➤ Naturopathy treatments: hydrotherapy, massage therapy, mud therapy <p>No further description of dose, method of administration, frequency of administration, who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <ul style="list-style-type: none"> • Raw vegetable diet with yoga therapy and naturopathy treatments <ul style="list-style-type: none"> ➤ Raw vegetable diet ➤ Yoga therapy ➤ Naturopathy treatments: hydrotherapy, mud therapy, massage therapy <p>No further description of dose, method of administration, frequency of administration, who delivered the comparator</p> |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: body fat water percentage; BMI; LDL; total cholesterol triglyceride • Secondary outcomes: total body weight • Assessment on days 1 and 10 |

| CTRI/2020/09/028014 (2020) | Dr Sahana Bhandary M |
|----------------------------|---|
| Funding source | SDM Yoga and Nature Cure Hospital, South India |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: Rajiv Gandhi University Of Health Sciences • Authors' financial relationship: not stated • No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: BMI, body mass index; LDL, low-density lipoprotein

Table 106: CTRI/2020/07/026842 (2020)

| CTRI/2020/07/026842 (2020) | Dr Somisetty Koushik Gupta |
|----------------------------|---|
| Participant description | <ul style="list-style-type: none"> • Number of participants: 76 • Inclusion criteria: T2DM meeting the American Diabetic Association diagnostic criteria and those who are on oral antidiabetic therapy • Exclusion criteria: T2DM with hypertension; history of kidney or liver failure; rash or open wounds on the limbs; underweight; morbid obesity; T2DM with autoimmune or established CAD or any organic vascular disease; history of neurological thyroid disorders; nutritional disorders; any other acute illness • Age and gender not stated • Setting not stated |
| Study methods | <ul style="list-style-type: none"> • NRSI: prospective matched controlled trial • Number of study centres not stated • Duration of study: 10 days • Unit of analysis: individual participant • Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>Yoga and naturopathy treatments in adjunct with conventional therapy: hydrotherapy; diet therapy; yoga therapy; exercise therapy; massage therapy; mud therapy; acupuncture</p> <p>No further description of dose, method of administration, frequency of administration, who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <p>Conventional therapy alone: routine oral anti-diabetic medications as prescribed by their regular consultant physician</p> |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: motor and sensory nerve conduction velocity • Secondary outcomes: insulin resistance; fasting blood glucose • Assessment at baseline and 10 days <p>No further description of assessment methods</p> |
| Funding source | SDM Yoga and Nature Cure Hospital, South India |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: Rajiv Gandhi University Of Health Sciences • Authors' financial relationship not stated |

| | |
|-----------------------------------|---|
| CTRI/2020/07/026842 (2020) | Dr Somisetty Koushik Gupta |
| | <ul style="list-style-type: none"> No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: CAD, coronary artery disease

Table 107: CTRI/2020/06/025714 (2020)

| CTRI/2020/06/025714 (2020) | Government Yoga And Naturopathy Medical College and Hospital Chennai (primary sponsor) |
|-----------------------------------|--|
| Participant description | <ul style="list-style-type: none"> Number of participants: 1,200 Inclusion criteria: doctors and healthcare workers of all ages irrespective of gender willing to participate Exclusion criteria: confirmed diagnosis of COVID-19; explicit non-willingness to participate Setting not stated |
| Study methods | <ul style="list-style-type: none"> NRSI with active control, Phase 3,4 Number of study centres not stated Duration of study: 4 weeks Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>Yoga & Naturopathy:</p> <ul style="list-style-type: none"> Prevalidated scientific yoga module comprising asanas, pranayama, relaxation, and meditation would be administered by a Government Yoga and Naturopathy physician 6 days a week for 4 weeks as a recorded video 5 simple lifestyle modification tips: <ul style="list-style-type: none"> Drinking 1.5-2 litres of water every day Practising mental silence for 10 minutes every day Diet to include sprouts, greens, and vegetables daily and making one meal a complete fruit diet at least once a week Hot water with salt and turmeric gargling once a day Including natural immune-boosting fresh juice (made of Indian Gooseberry, Ginger, Turmeric, tulsi, and lemon) and natural immune-boosting hot drink (made of ginger, tulsi, pepper, licorice, turmeric) once a day |
| Comparator | <p>Number of participants not stated</p> <p>Usual care, no intervention</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: Perseverative Thinking Questionnaire; GAD 7 Questionnaire; Pittsburg Sleep Quality Index; Freiburg Mindfulness Inventory; qualitative assessments for subjective perception of Stress and Yoga Secondary outcomes: nil Assessments at 15 days and 4 weeks |

| CTRI/2020/06/025714 (2020) | Government Yoga And Naturopathy Medical College and Hospital Chennai (primary sponsor) |
|----------------------------|--|
| | <ul style="list-style-type: none"> Only assessment methods and tools were reported; outcomes they were measuring were not further reported |
| Funding source | Indian Naturopathy And Yoga Graduates Medical Association |
| Conflicts of interest | <ul style="list-style-type: none"> Contact person's affiliations: Dr Manavalan Narayanaswamy, Government Yoga AND Naturopathy Medical College Contact person's financial relationship: not stated No other potential conflicts of interest stated |
| Status | Not Recruiting |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: GAD 7, General Anxiety Disorder 7

Table 108: CTRI/2020/05/025320 (2020)

| CTRI/2020/05/025320 (2020) | Government Yoga And Naturopathy Medical College Chennai (primary sponsor) |
|----------------------------|--|
| Participant description | <ul style="list-style-type: none"> Number of participants: 658 Inclusion criteria: informed consent; laboratory-confirmed SARS-CoV-2 infection as determined by PCR in naso/oropharyngeal swabs or any other relevant specimen; asymptomatic/uncomplicated illness / mild pneumonia COVID-19 as defined by ICMR Exclusion criteria: explicit non-willingness to be a part of the research study; moderate/severe stages of COVID19; participation in any other clinical trials Age 18-75 years old, males and females Setting not stated |
| Study methods | <ul style="list-style-type: none"> NRSI, with active control Number of study centres not stated Duration of study: up to 28 days Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <ul style="list-style-type: none"> Yoga & Naturopathy immune boosting and stress management protocol: <ul style="list-style-type: none"> ➤ Morning: Natural immune boosting fresh juice: Indian Gooseberry juice 50ml, Basil Juice 50ml; Ginger Juice 10ml, Fresh Lime juice 5ml, turmeric powder ¼ tsp, water 150 ml ➤ Evening: Natural immune-boosting hot drink: Peeled Crushed Ginger 5 gm, Tulsi (Basil) leaves 10 gms, Pepper powder ¼ tsp, Crushed Adhimaduram 5 gms (licorice root), turmeric powder ¼ tsp and drinking water 250 ml ➤ Yoga: Vajrasana, Bhastrika, Brahmari, Quick relaxation technique, Deep relaxation technique, Jala Neti (twice/thrice a day) Care as indicated by Yoga and Naturopathy physician: <ul style="list-style-type: none"> ➤ Hot water gargling: 30-50 ml of water and whirl it around the pharynx & oral cavity. |

| CTRI/2020/05/025320 (2020) | Government Yoga And Naturopathy Medical College Chennai (primary sponsor) |
|----------------------------|--|
| | <ul style="list-style-type: none"> ➤ Steam inhalation: Inhalation of steam with or without essential oils for 5-10 minutes. ➤ Sun bath: Sun exposure (10 minutes) in the morning and in the evening ➤ Aromatherapy (Eucalyptus/peppermint/thyme/lavender/basil): 1-2 drops in tissue paper or mix with gingely oil & apply over nose and neck. <p>These treatments will be given from enrolment till 14 days post-confirmation of infection</p> |
| Comparator | <p>Number of participants not stated</p> <p>Standard care as per local protocol</p> |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: time to progress to next stage of severity i.e., from asymptomatic/uncomplicated/mild pneumonia to moderate/severe stages, at 15 days • Secondary outcomes: <ul style="list-style-type: none"> ➤ Clinical endpoints: time to all-cause mortality at discharge; all-cause mortality at 28 days ➤ Measures of morbidity: number of days lived with infection; the number of days lived with intensive care if the disease has progressed to severe infection from asymptomatic, mild, and moderate stages; measuring the symptoms using standard scores ➤ Patient-reported outcomes: QoL assessed by WHO-QoL BREF; anxiety as assessed by GAD scale • Safety outcomes at discharge |
| Funding source | Not stated |
| Conflicts of interest | <ul style="list-style-type: none"> • Contact person's affiliations: Manavalan Narayanaswamy, Government Yoga AND Naturopathy Medical College • Contact person's financial relationship: not stated • No other potential conflicts of interest stated |
| Status | Open to Recruitment |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: GAD, General Anxiety Disorder; ICMR, Indian Council of Medical Research; PCR, polymerase chain reaction; QoL, quality of life; WHO-QoL BREF, abbreviated World Health Organization Quality of Life scale

Table 109: ANZCTR347666 (2012)

| ANZCTR347666 (2012) | Douglas Hanly Moir (primary sponsor) |
|-------------------------|--|
| Participant description | <ul style="list-style-type: none"> • Number of participants: 152 • Inclusion criteria: diagnosis of PCOS according to ESHRE diagnostic criteria detailed at Rotterdam in 2004; BMI > 25 kg/m²; basic level of literacy; availability for about 30 minutes to complete questionnaires at the beginning and after the trial; physical ability and time availability to exercise three times per week for 40-60 minutes; willingness to attend a pathology clinic and to provide a specimen of blood for analysis; ability to swallow 3-4 tablets per day time to attend a naturopathic consultation for 30 minutes every 4 weeks for 12 weeks. |

| ANZCTR347666 (2012) | Douglas Hanly Moir (primary sponsor) |
|---------------------|---|
| | <ul style="list-style-type: none"> Exclusion criteria: women with PCOS and a BMI \leq24; women with conditions characterised by similar reproductive symptoms to PCOS; insufficient English literacy; pregnancy; people highly dependent on medical care 18–44-year-old females Setting not stated |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, open-label, Phase 1,2 Number of study centres not stated Duration of study: 12 weeks Unit of analysis: individual participants Statistical methods not stated |
| Intervention | <p>Number of participants (N)</p> <ul style="list-style-type: none"> Lifestyle intervention: structured exercises supervised by an exercise physiologist once per week for 60 minutes, and home-based exercises (unsupervised) 2-3 times per week (either twice for 45 minutes or three times for 30 minutes). The structured exercise will be developed according to individual capability and capacity, with adjustment following weekly review. Exercises will include aerobic components and resistance-based exercises. Home-based exercise will be monitored using a pedometer. Education about healthy food choices, irrespective of diet composition, which is in alignment with the Evidence Based Guideline for PCOS, at trial entry. Herbal medicine tablets, 3 tablets per day + 3 during the pre-ovulation phase. The formula contains herbs that are commonly used by naturopaths and herbalists to treat PCOS. <ul style="list-style-type: none"> Each tablet contains a total of 5.4 grams of herbal medicine, which is constructed from 4 different herbal medicines The additional 3 tablets taken during the pre-ovulation phase of the menstrual cycle (days 5 to 17) contain Tribulus terrestris 1.8 grams. 3 consultations (0.5 hour each) with a naturopath will take place over the trial period every 4 weeks. Consultations will have a participant-centred format and address individual needs, answer questions, refresh educational components of the trial such as menstrual cycle tracking, or revising dietary intake. The naturopathic consultation reflects the usual practice of naturopathy, one of the complementary therapies. |
| Comparator | <p>Number of participants not stated</p> <p>Active control: standard care comprising structured diet and exercise advice according to evidence-based guideline</p> |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: time to menstruation (reduced oligomenorrhoea) Secondary outcomes: hormone and endocrine markers assessed by blood tests; ovulation urine tests by menstrual diary; anthropometric features; QoL questionnaire; anxiety and depression by depression and anxiety scale questionnaire <ul style="list-style-type: none"> A subset of 30 oligomenorrhoeic women to be blood-tested for FSH, LH, oestradiol, progesterone; testosterone, free androgen index, insulin, SHBG, and glucose Assessments at baseline and at 12 weeks |

| ANZCTR347666 (2012) | Douglas Hanly Moir (primary sponsor) |
|-----------------------|--|
| Funding source | Funding source: University of Western Sydney; Mediherb Australia (owned by Integria Healthcare Australia Pty Ltd) Sponsors: Douglas Hanly Moir; University of Western Sydney; |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: no contact person or primary investigator reported • Authors' financial relationship: not reported • Other potential conflicts of interest not reported |
| Status | Complete, Data not available? |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: ESHRE, European Society of Hormone and Reproductive Endocrinology; FSH, follicle-stimulating hormone; LH, luteinising hormone; PCOS, polycystic ovarian syndrome; SHBG, sex hormone-binding globulin

Table 110: NCT00983502 (2009)

| NCT00983502 (2009) | Arthur J Hartz |
|-------------------------|--|
| Participant description | <ul style="list-style-type: none"> • Number of participants: 240 • Inclusion criteria: severe debilitating fatigue that substantially reduces the quality of life; does not have any organic, psychological, or lifestyle problems that are the primary disorder and are likely to be the cause of this fatigue; the severe, unexplained fatigue has persisted for at least 6 months; has not been previously treated by a current physician for chronic fatigue; can speak and read English; not pregnant or planning to become pregnant within 6 months; has a telephone. • Exclusion criteria: no known history of bipolar disorder, psychosis, major depressive disorder, sleep disorder, anaemia, thyroid disease, rheumatoid arthritis, systemic lupus, cancer, heart disease, or liver disease • 18-65 years, males and females • Setting: outpatient clinic |
| Study methods | <ul style="list-style-type: none"> • Observational prospective cohort study, pilot • Multicentre, at least 4 recruiting sites • Duration of study: 6 months • Unit of analysis: individual participant • Statistical methods not stated |
| Intervention | <p>Number of participants: 60 in each group</p> <p>Participants are patients of:</p> <ul style="list-style-type: none"> • medical doctors trained in CAM • practitioners who are not medical doctors who are trained in naturopathic medicine • medical doctors specialising in treating chronic fatigue and related conditions |
| Comparator | <p>Number of participants: 60</p> <p>Control participants are patients treated by primary care medical doctors in practice-based research networks</p> |

| NCT00983502 (2009) | Arthur J Hartz |
|-----------------------|--|
| Outcome | <ul style="list-style-type: none"> Primary outcomes: differences among four groups of clinicians concerning patient treatment outcomes [no further description of outcomes] Secondary outcomes: nil |
| Funding source | Sponsors and collaborators: University of Utah; National Institutes of Health (NIH); National Center for Complementary and Integrative Health (NCCIH) |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: Huntsman Cancer Institute/ University of Utah Authors' financial relationship not stated No other potential conflicts of interest |
| Status | Trial Terminated |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: CAM, complementary and alternative medicine

Table 111: NCT00409149 (2006)

| NCT00409149 (2006) | Shai Efrati |
|-------------------------|--|
| Participant description | <ul style="list-style-type: none"> Number of participants: 120 (113 enrolled) Inclusion criteria: using antihypertensive medications with mean SBP of 120-180 mm Hg and/or mean DBP of 70-100 mm Hg as determined by a 24-hour Holter test; not using antihypertensive medications with mean SBP of 130-180 mm Hg and or DBP of 80-100 mmHg Exclusion criteria: cardiovascular event within the past 6 months; inability to walk independently for 15 minutes or less; poorly controlled insulin-dependent diabetes mellitus with HbA1c measurements > 7.5; inflammatory bowel disorders; acute malignancy with life expectancy of less than 5 years; pregnancy or lactation; BMI> 35; > 20 alcoholic beverages per week; change in antihypertensive medications within the last 3 months; planning to change smoking habits Aged 18 years and older, males and females Setting not stated |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, Phase 3, participant blinded Number of study centres not stated Duration of study not stated Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <p>CALM program for reducing blood pressure: dietary approach, education on cooking and food consumption choices, walking physical exercise, Qi Gong - a form of Chinese slow movement exercise combined with relaxation breathing and imagery and group therapy coaching in stress management techniques and mind-body balancing technique</p> <p>No further description of dose, method of administration, frequency of administration, who delivered the intervention</p> |
| Comparator | <p>Number of participants not stated</p> <p>Standard DASH diet and lifestyle modification counselling</p> |

| NCT00409149 (2006) | Shai Efrati |
|-----------------------|---|
| | No further description of dose, method of administration, frequency of administration, who delivered the comparator |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: change in blood pressure Secondary outcomes: use of BP medications; weight loss; lab test and pulse wave analysis Assessments at beginning and end of the trial |
| Funding source | Sponsor: Assaf-Harofeh Medical Center, Israel |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: Assaf-Harofeh Medical Center, Israel Authors' financial relationship not stated No other potential conflicts of interest stated |
| Status | Completed, data not available |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: CALM, Complementary Approaches to Lower Mean arterial pressure; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; SBP, systolic blood pressure

Table 112: NCT00160901 (2005)

| NCT00160901 (2005) | Cornelia U. von Hagen |
|-------------------------|--|
| Participant description | <ul style="list-style-type: none"> Number of participants: 150 Inclusion criteria: indication for chemotherapy for breast cancer for at least 3 cycles Exclusion criteria: prior chemotherapy within 12 months; use of herbal or nutritional supplements or other complementary or alternative medications ≥ 7 days before the start of chemotherapy and during the trial; allergy to study medication; selenium intoxication; current use of coumarins or other medication influencing the coagulation system; oedema in case of impaired cardiac or renal function; other severe medical condition; psychiatric or central neurological disorders; regular fluid intake < 2000 ml per day 18–75-year-old females Setting not stated |
| Study methods | <ul style="list-style-type: none"> Parallel RCT, open-label, phase 4, 3 arms Number of study centres not stated Duration of study: dependent on treatment cycles – up to 5 weeks after 3rd treatment cycle Unit of analysis: individual participant Statistical methods not stated |
| Intervention | <p>Number of participants not stated</p> <ul style="list-style-type: none"> Group 1: Individual nutrition consultation with recommendations for physical activity before or on the first day of chemotherapy together with daily oral medication consisting of selenium (sodium-selenit 100 μg/d), milk thistle (226ilybin 280 mg/d), goldenrod (solidago 1,680g/d) and pineapple enzyme (bromelaine 3.000 F.I.P. units/d) during the first three cycles till 3-5 weeks later Group 2: individual nutrition consultation with recommendations for physical activity only |

| NCT00160901 (2005) | Cornelia U. von Hagen |
|-----------------------|---|
| | No further descriptions of the frequency of administration, or who delivered the intervention |
| Comparator | Number of participants not stated '5-a-day' leaflet |
| Outcome | <ul style="list-style-type: none"> Primary outcomes: difference in the sum score of the most common side effects of a chemotherapy (fatigue, nausea, loss of appetite, constipation, diarrhea) measured by the EORTC QLQ C30 3-5 weeks after and before 3 cycles of chemotherapy. Secondary outcomes: difference in general EORTC QOL 3-5 weeks after and before three cycles of chemotherapy; difference in anxiety and depression measured by HADS-D 3-5 weeks after and before three cycles of chemotherapy; sensitivities measured by the perimed sensitivity questionnaire; creatinine; ALAT; coagulation time; selenium |
| Funding source | Sponsors and collaborators: Heidelberg University; Hector-Stiftung; Cefak KG, Kempten; Ursapharm, Saarbrücken; Schwabe-Wenex International Ltd |
| Conflicts of interest | <ul style="list-style-type: none"> Authors' affiliations: Department of Complementary and Integrative Medicine Women's Hospital, University of Heidelberg Authors' financial relationship not stated No other potential conflicts of interest stated |
| Status | Completed, data not available |
| Comments | Reason this study is awaiting classification: registered trial |

Abbreviations: ALAT, alanine aminotransferase; EORTC QLQ, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; HADS-D, Hospital Anxiety and Depression Scale – Depression;

Table 113: Seely 2019

| Seely (2019) | Seely (2019) |
|-------------------------|--|
| Participant description | <ul style="list-style-type: none"> 22 patients in pilot single arm feasibility study; 440 participants for the parallel RCT. Thoracic cancer patients: patients with resectable lung, gastric and oesophageal cancers. Patients are eligible for curative-intent surgery. Exclusion criteria: individuals under 18 y old; pregnant and breastfeeding women; small cell, carcinoid, or gastrointestinal stromal tumours; history of cancer in the last 3 years; already seeing a naturopathic doctor or involved in an integrative program of care in the last 3 months that includes complementary medicine. Setting: hospital and cancer care centres, Ottawa, Ontario, Canada |
| Study methods | <ul style="list-style-type: none"> NCT02845479 Thoracic POISE trial Pilot study to evaluate feasibility of intervention: single arm, open-label. Eventually to culminate in a multicentre two-arm parallel RCT with a planned enrolment of 440 participants 2 centres: Ottawa General Hospital and Ottawa Integrative Cancer Centre Timeframe: enrolment to 1 y post-surgery. Pilot study commenced Dec 2018 and was completed Dec 2020. Unit of analysis: individual participant Statistical methods: not stated |
| Intervention | <ul style="list-style-type: none"> Integrating care provided by naturopathic doctors alongside usual care. A broad-based multi-agent integrative care program delivered by naturopathic doctors in conjunction with standard surgical and oncological care. Standardised |

| Seely (2019) | Seely (2019) |
|-----------------------|--|
| | <p>supplemental/natural health product, physical, nutritional and mental/emotional recommendations based on the phases of standard care (neo-adjuvant, perioperative, adjuvant, and long-term maintenance).</p> <ul style="list-style-type: none"> ➤ Vitamin D; melatonin; coriolus versicolor; fish oil; probiotics; L-arginine; whey protein; curcumin; green tea extract; L-glutamine; ginseng panax; ginger ➤ Nutritional counselling; exercise prescription; mind-body medicine audio recordings with psychoeducation, visualisation, breathing exercises, mindfulness, gentle movement and mediation. <ul style="list-style-type: none"> • 22 participants in single arm feasibility study • Frequency of administration and dose not stated |
| Comparator | <ul style="list-style-type: none"> • NA for feasibility pilot study; not stated for RCT • Description of comparator: NA for feasibility pilot study; not stated for RCT. |
| Outcome | <ul style="list-style-type: none"> • Primary outcomes: QOL measured over 1st year of recovery, measured by Functional Assessment Cancer Therapy – General Score • Secondary outcomes: intra- and postoperative adverse events by collection of adverse events related to surgery, adjuvant therapy, and the interventions; overall survival; cost-effectiveness. • Additional outcomes: determining biological impact of interventions on immune and inflammatory function; evaluation of qualitative outcomes within a rigorous mixed-methods approach. <ul style="list-style-type: none"> ➤ Cancer-related symptoms measured by Edmonton Symptom Assessment Scale ➤ Anxiety and Depression measured by HADS ➤ Fatigue measured by Multidimensional Fatigue Inventory ➤ Functional exercise capacity measured by 6 min walk test ➤ NK cell activation measured by NKVue™. ➤ Communication between practitioners measured by the number of communications between integrative and standard care practitioners per participant. ➤ Qualitative experience of care and study protocol measured by semi-structured interviews and thematic analysis ➤ Feasibility of recruitment to be measured by percentage of participants recruited out of potentially eligible patients invited. • Compliance with nutritional intervention measured by the Mediterranean diet score calculated by FFQ • Compliance assessed by patient diary: <ul style="list-style-type: none"> ➤ Supplements: count of missed doses ➤ Physical intervention: extent of adherence to physical recommendations ➤ Mental/emotional domain: number of days audio-recordings • The feasibility of the study protocol was a primary outcome according to the trial registration and assessed by the percentage of participants who complete all assessments and integrative care appointments. |
| Funding source | <ul style="list-style-type: none"> • Funding source not stated |
| Conflicts of interest | <ul style="list-style-type: none"> • Authors' affiliations: Ottawa Integrative Cancer Centre; Canadian College of Naturopathic Medicine, Toronto, Canada; Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Canada; Ottawa Hospital, Ottawa, Canada; Paradigm Naturopathic Medicine, Vernon, Canada; The Royal Melbourne Hospital, Melbourne, Australia • Conflicts of interest not stated. |

| Seely (2019) | Seely (2019) |
|--------------|--|
| Status | Complete |
| Comments | Reason this study is awaiting classification: registered trial protocol without reported outcomes. |

Abbreviations: HADS, Hospital Anxiety and Depression Scale; POISE, Peri-Operative Integrative Surgical Care Evaluation; QOL, quality of life

Appendix H: Differences between protocol and review

H.1. Methods not implemented

Several methods described in the protocol could not be implemented. These are presented in Table 116.

Table 114: Methods not implemented

| Method not implemented | Comment |
|--|--|
| SIGN-50 risk of bias analysis for case-control studies | No cluster randomised trials, cross-over trials, or pseudorandomised controlled trials were identified as eligible. Among NRSIs, no interrupted time series studies or case-control studies were identified as eligible. |
| Addressing unit-of-analyses concerns for cluster and cross-over RCTs | |
| Synthesising single and multi-modal interventions that met the definition of naturopathy together, and subgroup analyses within a population. | At most, only one RCT and/or one NRSI were eligible for inclusion in each population group |
| Stratifying analyses by type of comparator (placebo/sham, inactive control, or active comparators). | |
| Meta-analyses and associated subgroup analyses, sensitivity analyses, and statistical heterogeneity analyses (I^2 statistics). | |
| <ul style="list-style-type: none"> • Intention to treat analyses • Sensitivity analyses where missing outcome data were imputed • Standardised mean differences (for continuous outcomes) • In studies with more than two treatment arms, ensuring that participants from one treatment arm were included only once in meta-analyses. • Appraising the risk of bias attributed to non-reporting of results guided by the preliminary Risk of Bias due to Missing Evidence (ROB-ME) tool and section 13.3 of the Cochrane Handbook, by comparing studies that did not report results with studies that were included in a meta-analysis for a particular comparison and outcome. | |
| Vote-counting. | |
| Non-reporting bias assessment by regular funnel plot. | |
| Assessment of inconsistency during the GRADE assessment process, where the outcome was represented by only one eligible study. | |
| Potential unit of analysis errors associated with intervention-related clustering arising from naturopath practitioners treating multiple trial participants was not identified in this Review. As meta-analyses could not be | |

| Method not implemented | Comment |
|--|--|
| undertaken, the impact of clustering on meta-analyses was not relevant. | |
| Summary of findings tables present point estimates and measures of variation for outcomes for individual studies, as meta-analyses and vote-counting could not be conducted. | |
| NTWC were not consulted as to whether a study met the definition of whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice. | It was clear in the screening process whether studies met the definition for whole system, multi-modal or single modal interventions delivered in the context of naturopathic practice. |
| For citations in languages other than English, 'Step (3)' of the protocol was not applied. | This protocol step for managing citations proved unnecessary, as online translations were sufficient to facilitate an understanding of titles and abstracts. |
| Outcome data from studies with repeated observations to be extracted from clinically important timepoints, pre-specified by the NTWC in their outcome prioritisation process. | For this Review, most studies only reported numerical data for the first and last (end of treatment) timepoints, which were extracted. The exceptions were studies for the population groups type 2 diabetes and cardiovascular risk. Cardiovascular risk was extracted for 12 month and 10 years, type 2 diabetes presented data for 3 weeks and 6 months although only the 6 month data was extracted. |

H.2. Changes from protocol

There were several changes from the registered protocol. These are presented in Table 117.

Table 115: Changes from protocol

| Protocol item | Change |
|---|---|
| Minimally clinically important differences (MCIDs) as a measure of appreciable harm or benefit. | MCIDs were sourced from published reports and change scores were calculated to assess if the clinical importance was met. If effect sizes were not published or could not be calculated, an estimate of effect based on a 25% or greater increase or decrease of the intervention group compared to the comparator group's measure was used as a default threshold for appreciable harm or benefit, as per the protocol. |

Appendix I: How comments from methodological review were addressed

The authors have addressed the concerns raised by the methodological reviewers and updated the systematic literature review carefully addressing all issues. The methodological reviewer key points that were addressed and updated are displayed below.

- **Search methods.** Efforts have been made to increase transparency in how randomised trial records were identified and handled within the review. *'RCTs were primarily identified from Cochrane Central Register of Controlled Trials (CENTRAL). This is because Cochrane CENTRAL concurrently searches RCT and quasi-RCT (q-RCT) records from the PubMed/MEDLINE; Embase.com; CINAHL ClinicalTrials.gov and WHO ICTRP databases. NRSIs were identified from Medline via OVID and AMED databases. Embase.com and CINAHL included both RCT and NRSI search terms. The search strategies were designed to reduce the retrieval of duplicate citations.'*
- **Risk of bias assessments.** Review and update of risk of bias assessments with further interrogation of the data have been performed. We note that the majority of studies are at high risk of bias and particular attention has been paid to NRSIs especially in circumstances where unadjusted effect estimates are reported.
- **Effect measures.** Effect measures for continuous outcomes have been updated to MD and expressed in the units of the original measure used for outcome assessment. No changes have been made to dichotomous outcomes presented with relative risk which was addressed in the methods.
- **Reporting of results.** Slight adjustments have been made to the result text to improve the readability and allow for a more balanced interpretation of the evidence.
- **Interpretation of results.** We have provided explanation on effect estimates to ensure consistent and transparent interpretation of the effect size and to verify judgements for rating imprecision when applying GRADE. This appears in the footnotes of the SoF table. We have stated MCIDs from the literature and calculated out change scores and applied the following interpretation *'effect estimates were considered on three levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale)'* to thresholds.
- **Summary of findings tables.** Revisions have been made to the Summary of Findings (SoF) tables to improve the reporting of results and provide information needed to interpret the results. This includes calculating confidence intervals for the absolute risk with intervention; reporting scale range, direction and threshold for an important difference and addressing concerns about GRADE judgements.
- **Certainty of the evidence.** We have considered imprecision when a confidence interval could not be calculated. We have revised GRADE ratings, where appropriate.
- **Evidence statements.** Where revisions to GRADE rating of an outcome have been revised, we have subsequently updated the wording of the overall conclusions, plain language summaries, the executive summary and the evidence statements to reflect the result.

Appendix J: References

1. Ryan R, Hill S, Broclain D, Horey D, Oliver S, Prictor M. Cochrane Consumers and Communication Review Group. Study Design Guide. Cochrane. <http://cccrq.cochrane.org/author-resources>. Published 2013. Updated June 2013. Accessed 14 September 2020, 2020.
2. Noyes J, Booth A, Cargo M, et al. Chapter 21: Qualitative evidence. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*: Cochrane; 2019.
3. Evans SR. Clinical trial structures. *Journal of experimental stroke & translational medicine*. 2010;3(1):8.
4. Reeves BC, Deeks JJ, Higgins JPT, Shea B, Tugwell P, Wells GA. Chapter 24: Including non-randomized studies on intervention effects. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*: Cochrane; 2019.
5. COMET Initiative. Core Outcome Measures in Effectiveness Trials (COMET). <http://www.comet-initiative.org/>. Accessed 26 August 2020, 2020.
6. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. In: Schünemann H, Brożek J, Guyatt G, Oxman A, eds. 2013: <https://gdt.gradeapro.org/app/handbook/handbook.html#h.svwngs6pm0f2>. Accessed 6 July 2020.
7. Higgins JPT, Lasserson T, Chandler J, et al. Standards for the conduct of new Cochrane Intervention Reviews. In: Higgins JPT, Lasserson T, Chandler J, et al., eds. *Methodological Expectations of Cochrane Intervention Reviews*. London: Cochrane; 2020.
8. Lefebvre C, Glanville J, Briscoe S, et al. Chapter 4: Searching for and selecting studies Cochrane, 2019. In: Higgins JP, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*: Cochrane; 2019.
9. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *bmj*. 2019;366.
10. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *bmj*. 2016;355.
11. Li T, Higgins JPT, Deeks JJ. Chapter 5: Collecting data. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*: Cochrane; 2019.
12. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *Bmj*. 2014;348:g1687.
13. Higgins JPT, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*: Cochrane; 2019.
14. Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*: Cochrane; 2019.
15. Higgins JPT, Eldridge S, Li T. Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*: Cochrane; 2019.
16. *Review Manager (RevMan) [computer program] Version 5.3 [computer program]*. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
17. Page MJ, Higgins JPT, Sterne JAC. Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6 (updated July 2019)*: Cochrane; 2019.
18. ROB-ME Development Group. Risk of Bias due to Missing Evidence (ROB-ME): a new tool for assessing risk of non-reporting biases in evidence syntheses. Cochrane Collaboration.

<https://sites.google.com/site/riskofbiastool/welcome/rob-me-tool>. Published 2020. Updated 24 October 2020. Accessed 5 March 2021, 2021.

19. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. *Journal of clinical epidemiology*. 2011;64(12):1283-1293.
20. Schünemann HJ, Cuello C, Akl EA, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *Journal of Clinical Epidemiology*. 2019;111:105-114.
21. Schünemann HJ, Higgins JPT, Vist GE, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*: Cochrane; 2019.
22. Santesso N, Glenton C, Dahm P, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *Journal of Clinical Epidemiology*. 2020;119:126-135.