**Supplementary file 1. PRISMA checklist 2020**

| **Section and Topic** | **Item #** | **Checklist item** | **Location where item is reported** |
| --- | --- | --- | --- |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review. | 1 |
| **ABSTRACT** | | |  |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | 2 |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | 4-5 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 5 |
| **METHODS** | | |  |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 6-7 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | 7 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | 7 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 7-8 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 8 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | 8 |
| 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Not reported |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 8 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | 8-9 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | 8 |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | 9 |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | 9 |
| 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | 9 |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | 9 |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Not reported |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 9 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Not reported |
| **RESULTS** | | |  |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | 10 |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Not reported |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Supplementary file 2 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Supplementary file 3 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Figure 2 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | 10 |
| 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | 10-11 |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | 11 |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Not reported |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | 11 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Not reported |
| **DISCUSSION** | | |  |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | 12 |
| 23b | Discuss any limitations of the evidence included in the review. | 13-14 |
| 23c | Discuss any limitations of the review processes used. | 14 |
| 23d | Discuss implications of the results for practice, policy, and future research. | 14-15 |
| **OTHER INFORMATION** | | |  |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | 3 |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | 3 |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Not applicable |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | 15 |
| Competing interests | 26 | Declare any competing interests of review authors. | 15 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | 15 |

**Supplementary file 2. Summary of the included studies**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Numbers of participants**  **(male: female)** | **Age of the participants (mean or median)** | **Population (condition)** | **Sham acupuncture type** | **Test Acupuncture type** | **Intervention period** | **Time point for outcome assessment** | **Accessed biomarkers** |
| Abdi 2012a [1] | A: 83  B: 86 (NR) | A: 38.7, 1.1  B: 37.3, 1.0 | Obesity | (a) | Ear acupuncture | 6 weeks | 6 weeks | FBG, TC, TG, HDL, LDL, CRP |
| Abdi 2012b [2] | A: 82  B: 79 (NR) | A: 37.41, 1.01  B: 36.88, 0.98 | Obesity | (b) | Electroacupuncture | 6 weeks | 6 weeks | FBG, TC, TG, HDL, LDL, CRP |
| Ahsin 2009 [3] | A: 20 (5:15)  B: 20 (7:13) | A: 51.45, 8.9  B: 51.05, 7.73 | Osteoarthritis of knee | (b) | Electroacupuncture | 10 days | 10 days | 𝛽-Endorphin, Cortisol |
| Arnetz 1995 [4] | A: 7  B: 13 | A: NR  B: NR | Environmental illness | (b) | Manual acupuncture | 5 weeks | 5 weeks | Cortisol, NPY |
| Aydoğmuş 2014 [5] | A: 24  B: 28 | A: NR  B: NR | Overactive bladder | (a) | Manual acupuncture | 4 weeks | 4 weeks | NR |
| Bao 2013 [6] | A: 24 (0:24)  B: 23 (0:23) | A: 61 (44-82)  B: 61 (45-85) | Musculoskeletal symptoms in breast cancer patients with aromatase inhibitor | (c) | Manual acupuncture | 8 weeks | 8 weeks | 𝛽-Endorphin, IFN-γ, IL-10, IL-12, IL-1, IL-6, IL-8, IL-17, TNF-α |
| Brustin 2017 [7] | A: 9  B: 11 | Median 40 year | Human papilloma virus-related warts | (a) | Manual acupuncture | 4 weeks | 4 weeks | IL-1, IL-6, IL-8, IL-10, IFN-γ, TNF-α |
| Chassot 2015 [8] | A: 18 (0:18)  B: 16 (0:18) | A: 41.44, 105  B: 39.11, 10.5 | Chronic tension type headache | (a) | Electroacupuncture | 5 weeks | 5 weeks | BDNF |
| Chen 2016 [9] | A: 46 (36:10)  B: 46 (32:14) | A: 56.93, 14.61  B: 55.8/15.75 | Postoperative pain | (a) | Electroacupuncture | 3 days | 3 days | 𝛽-Endorphin, Serotonin |
| Fitri 2019 [10] | A: 20 (2:18)  B: 20 (2:18) | A: 41.5 (20-57)  B: 47 (20-58) | Gastroesophageal reflux disease | (a) | Acupuncture point cat-gut | 15 days | 30 days | IL-6 |
| Haddad-Rodrigues [11] | A: 15 (0:15)  B: 14 (0:14) | A: 28, 33  B: 25, 29 | Anxiety of breast-feeding mothers | (a) | Ear acupuncture | NR | NR | NR |
| Han 2020 [12] | A: 70 (36:34)  B: 70 (37:33) | A: 62.4, 76.7  B: 61.9, 7.9 | Cancer pain | (c) | Electroacupuncture | 2 days | 2 days | Norepinephrine, Serotonin, 𝛽-Endorphin |
| Harbach 2007 [13] | A: 15 (15:0)  B: 15 (15:0) | A, B: 43.4, 11.4 | Chronic low back pain | (b) | Manual acupuncture | 1 day | 1 day | Cortisol, 𝛽-Endorphin |
| Huang 2017 [14] | A: 62 (40:22)  B: 61 (42:19) | A: 58, 10  B: 56, 11 | Asymptomatic hyperuricemia | (c) | Manual acupuncture | 10 days | 1 month | Creatinine, FBS, HbA1C, TC, TG, LDL, HDL |
| Ito 2015 [15] | A: 5 (0:5)  B: 5 (1:4) | A: 35.8, 7.85  B: 42.6, 2.41 | Healthy adults | (a) | Ear acupuncture | 4 weeks | 1 week | Insulin, ACTH, Leptin, Ghrelin, TP, LDL, HDL, FBS, C-peptide |
| Jeon 2015 [16] | A: 7 (0:7)  B: 7 (1:6) | A: 46.3  B: 42.3 | Radioactive iodine-induced anorexia in thyroid cancer patients | (c) | Manual acupuncture | 4 weeks | 4 weeks | ACTH, Cortisol |
| Joos 2004 [17] | A: 24 (7:17)  B: 27 (8:19) | A: 36.2, 8.8/ B: 39.9, 7.7 | Crohn’s disease | (b) | Manual acupuncture | 4 weeks | 4 weeks | A1-glycoprotein, CRP |
| Jubb 2008 [18] | A: 34 (8:26)  B: 34 (5:29) | A: 66.1, 1.9  B: 64.1, 1.6 | Knee osteoarthritis | (b) | Electroacupuncture | 5 weeks | 5 weeks | 𝛽-Endorphin |
| Karatay 2011 [19] | A: 17 (11:6)  B: 18 (12:6) | A: 21.29, 1.83  B: 22.39, 1.91 | Healthy young subject | (b) | Manual acupuncture | 2 weeks | 2 weeks | TNF-α, CRP |
| Karst 2003 [20] | A: 11 (5: 6)  B: 11 (5: 6) | A: 32.64, 8.77  B: 31.09, 8.34 | Healthy volunteers | (c) | Manual acupuncture | 4 weeks | 4 weeks | 𝛽-Endorphin, TNF-𝛽 |
| Kim 2021 [21] | A: 60 (0:60)  B: 60 (0:60) | A: 36.92, 7.93  B: 36.83, 8.79 | Premenopausal overweight and obese women | (b) | Electroacupuncture | 6 weeks | 6 weeks | TC, HDL, LDL. TG, FBS, Insulin, CRP |
| Kristen 2010 [22] | A: 8 (6:2)  B: 9 (5:4) | A: 58, 12  B: 60, 3 | Heart failure | (c) | Manual acupuncture | 5 weeks | 5 weeks | TNF-α |
| Kvorning 2010 [23] | A: 23  B: 22 | NR | Patients with scheduled surgery | (a) | Electroacupuncture | 1 day | 1 day | Adrenaline, Noradrenaline, ACTH, Cortisol |
| Lee 2015 [24] | A: 10  B: 10 | A+B 56.3, 10.5 | Cerebral infarction | (b) | Electroacupuncture | 1 day | 1 day | VEGF, IL-10 |
| Lee 2009 [25] | A: 12 (12:0)  B: 12 (12:0) | A: 36.4, 5.8  B: 23.5, 2.2 | Chronic prostatitis/Chronic pelvic pain syndrome | (b) | Electroacupuncture | 6 weeks | 6 weeks | NR |
| Leung 2011 [26] | A: 20 (8:12)  B: 20 (5:15) | A: 50.8, 5.8  B: 51.5, 4.6 | Healthy subject (Barostat-induced rectal distension) | (c) | Electroacupuncture | 1 day | 1 day | 𝛽-Endorphin |
| Li 2013 [27] | A: 19 (11:8)  B: 19 (10:9) | A: 39, 8  B: 42, 9 | Patients undergoing supratentorial craniotomy | (b) | Electroacupuncture | 1 day | 1 day | IL-10, IL-8 |
| Li 2017 [28] | A: 20 (12:8)  B: 20 (11:9) | A: 58, 12  B: 57, 11 | Acute pancreatitis | (b) | Electroacupuncture | 5 days | 5 days | TNF-α, IL-10 |
| Liang 2012 [29] | A: 50  B: 50 | NR | Severe multiple trauma patients | (b) | Manual acupuncture | 7 days | 7 days | NR |
| Lien 2012 [30] | A: 24 (0:24)  B: 24 (0:24) | A: 39.2, 11.6  B: 42.2, 12.4 | Obese women | (a) | Auricular acupuncture | 4 weeks | 4 weeks | Adiponectin, Insulin, Ghrelin, Leptin |
| Lu 2009 [31] | A: 9 (0:9)  B: 10 (0:10) | A: 50, 9.9  B: 50.8, 10.6 | Women undergoing chemotherapy due to ovarian cancer | (b) | Electroacupuncture | 3 weeks | 3 weeks | NR |
| Marie Lynning 2021 [32] | A: 21 (5:16)  B: 23 (8:15) | A: 46.8, 10.5  B: 46.5, 10.2 | Multiple sclerosis | (c) | Manual acupuncture | 4 weeks | 4 weeks | IFN-γ, IL-1, IL-12, IL-6, IL-8, TNF-α, IL-10 |
| McDonald 2016 [33] | A: 37  B: 36 | NR | Persistent allergic rhinitis | (b) | Manual acupuncture | 8 weeks | 12 weeks | IG-E |
| Mehta 2014 [34] | A: 52 (37: 15)  B: 47 (32: 15) | A: 63, 11  B: 64.9, 11 | Stable ischemic heart disease | (a) | Manual acupuncture | 12 weeks | 12 weeks | NR |
| Painovich 2012 [35] | A: 12 (0:12)  B: 12 (0:12) | A: 56.8, 6.5  B: 57.2, 5.2 | Menopause | (a) | Manual acupuncture | 12 weeks | 12 weeks | Cortisol |
| Swanson 2015 [36] | A: 13 (9:4)  B: 12 (8:4) | A: 47.69, 4.8  B: 47.33, 9.1 | HIV-infected adults | (c) | Manual acupuncture | 8 weeks | 8 weeks | CRP, TC, HDL, LDL, TG |
| Takahashi 2021 [37] | A: 3 (3:0)  B: 3 (3:0) | 20.1, 0.4 | Healthy male adult | (a) | Electroacupuncture | 2 weeks | 2 weeks | Aldosterone, Epinephrine, Norepinephrine |
| Wang 2008 [38] | A: 10 (8:2)  B: 9 (8:1) | A: 57.1, 9.9  B: 57.7, 7.4 | Gastroparesis | (b) | Electroacupuncture | 2 weeks | 2 weeks | FBS, PP2, Gastrin, Motilin |
| Wang 2016 [39] | A: 19 (9:10)  B: 20 (11:9) | A: 27.11, 1.16  B: 28, 1.10 | Healthy adults | (b) | Manual acupuncture | 1 day | 1 day | SP, VIP, NPY |
| Wang 2019 [40] | A: 15 (0:15)  B: 21 (0:21) | NR | polycystic ovarian syndrome | (b) | Electroacupuncture | 16 weeks | 16 weeks | Adrenaline, Noradrenaline, Serotonin, GABA |
| Xi 2021 [41] | A: 29 (13:16)  B: 29 (12:17) | A: 41, 12  B: 44, 12 | Chronic insomnia | (b) | Electroacupuncture | 4 weeks | 4 weeks | GABA |
| Xie 2017 [42] | A; 30 (5:25)  B: 30 (6:24) | A: 34, 7  B: 33, 6 | Obese patients | (b) | Manual acupuncture | 8 weeks | 8 weeks | Leptin |
| Xu 2015 [43] | A: 30 (11:19)  B: 30 (12:18) | A: 53.2, 12.1  B: 52.73, 14.7 | Functional constipation | (b) | Electroacupuncture | 8 weeks | 8 weeks | Serotonin |
| Yiiu 2016 [44] | A: 8  B: 9 | NR | Phonotraumatic vocal pathologies | (c) | Manual acupuncture | 1 day | 1 day | NR |
| Yu 2014 [45] | A: 20 (14:6)  B: 20 (12:8) | A: 56, 15  B: 56, 17 | Patients under surgery with etomidate anesthesia | (b) | Electroacupuncture | 1 day | 1 day | NR |
| Zhang 2013a [46] | A: 30 (0:30)  B: 30 (0:30) | A: 32, 3  B: 31, 5 | in vitro fertilization-embryo transfer (IVF-ET) transvaginal oocyte retrieval | (c) | Manual acupuncture | 1 day | 1 day | NR |
| Zhang 2020 [47] | A: 54 (36:18)  B: 81 (50:31) | NR | Gastric cancer | (b) | Manual acupuncture | 3 sessions | 4 weeks | IFN-γ, IL-4, IL-6, CRP |
| Zhang 2013b [48] | A: 34 (1:33)  B: 36 (11:25) | A: 48.2, 9.8  B: 46.3, 9.9 | Depression | (c) | Electroacupuncture | 3 weeks | 2 weeks | Serotonin |
| Zhao 2020 [49] | A: 33 (13:20)  B: 34 (11:23) | A: 45.16, 11.39  B: 43.87, 10.51 | Depression and insomnia | (c) | Manual acupuncture | 8 weeks | 8 weeks | NPY, Substance-p |
| Zhao 2018 [50] | A: 30 (14:16)  B: 30 (12:18) | A: 66.7, 3.84  B: 65.23, 4.03 | Patients under knee replacement surgery | (c) | Electroacupuncture | 1 day | 1 day | IL-1, TNF-α |
| Zuppa 2015 [51] | A: 24 (5:19)  B: 24 (5:19) | A: 65.75, 3.8  B: 67.13, 4.9 | Healthy aged adult | (b) | Manual acupuncture | 5 weeks | 5 weeks | BDNF |

Sham acupuncture: A/ Test acupuncture: B

Sham acupuncture types: three groups including skin stimulation with acupuncture needles or without acupuncture needles such as cocktail stick or tooth picks (a), superficial needling on acupuncture points or non-acupuncture points (b), sham device without penetration-Park, Streitburger, Takakura sham device (c).

BDNF: brain derived neurotrophic factor; CRP: C-reactive protein; FBS: fasting blood glucose; GABA: γ-aminobutyric acid; HDL: high- density lipoprotein cholesterol; IFN-γ: Interferon gamma; IL: interleukin; LDL: low-density lipoprotein cholesterol; NGF: nerve growth factor; NPY: Neuropeptide Y; NR: not reported; PP2: 2-hr postprandial blood glucose; SP: substance-P; TC: total cholesterol; TG: Triglycerides; TNF-α: tumor necrosis factor-α; VIP: vasoactive intestinal peptide

**Supplementary 3. References of the included studies**

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**Supplementary file 4. Risk of bias assessment**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Sequence generation** | **Allocation concealment** | **Blinding of participants** | **Blinding of outcome assessor** | **Incomplete outcome data** | **Selective outcome reporting** | **Other bias** | **Overall risk of bias** |
| Abdi 2012a [1] | U | U | L | U | H | L | L | H |
| Abdi 2012b [2] | U | U | L | U | H | L | L | H |
| Ahsin 2009 [3] | H | H | L | L | H | L | L | H |
| Arnetz 1995 [4] | U | U | L | U | H | L | L | H |
| Aydoğmuş 2014 [5] | U | U | L | U | H | L | L | H |
| Bao 2013 [6] | L | U | L | L | L | L | L | L |
| Brustin 2017 [7] | U | U | L | U | L | L | L | H |
| Chassot 2015 [8] | L | L | L | L | L | L | L | L |
| Chen 2016 [9] | L | L | L | U | L | L | L | L |
| Fitri 2019 [10] | L | L | L | U | L | L | L | L |
| Haddad-Rodrigues [11] | L | L | L | L | H | L | L | H |
| Han 2020 [12] | L | L | L | U | L | L | L | L |
| Harbach 2007 [13] | L | L | L | L | L | L | L | L |
| Huang 2017 [14] | L | L | L | L | H | L | L | H |
| Ito 2015 [15] | L | L | L | L | L | L | L | L |
| Jeon 2015 [16] | L | L | L | L | L | L | L | L |
| Joos 2004 [17] | U | U | L | L | H | L | L | H |
| Jubb 2008 [18] | U | U | L | U | L | L | L | H |
| Karatay 2011 [19] | U | U | L | L | L | L | L | L |
| Karst 2003 [20] | U | U | L | L | L | L | L | L |
| Kim 2021 [21] | L | L | L | L | L | L | L | L |
| Kristen 2010 [22] | L | L | L | L | H | L | L | H |
| Kvorning 2010 [23] | U | U | L | L | L | L | L | L |
| Lee 2015 [24] | U | U | L | U | L | L | L | H |
| Lee 2009 [25] | L | U | L | L | L | L | L | L |
| Leung 2011 [26] | L | L | L | L | L | L | L | L |
| Li 2013 [27] | U | U | L | U | L | L | L | H |
| Li 2017 [28] | L | U | L | U | U | L | L | H |
| Liang 2012 [29] | U | U | L | U | U | L | L | H |
| Lien 2012 [30] | L | U | L | U | U | L | L | H |
| Lu 2009 [31] | L | U | L | L | H | L | L | H |
| Marie Lynning 2021 [32] | L | U | L | L | H | L | L | H |
| McDonald 2016 [33] | L | U | L | L | H | L | L | H |
| Mehta 2014 [34] | U | U | L | L | H | L | L | H |
| Painovich 2012 [35] | L | U | L | L | U | L | L | H |
| Swanson 2015 [36] | L | U | L | L | L | L | L | L |
| Takahashi 2021 [37] | U | U | L | L | L | L | L | H |
| Wang 2008 [38] | U | U | L | L | H | L | L | H |
| Wang 2016 [39] | L | L | L | L | L | L | L | L |
| Wang 2019 [40] | L | L | L | L | H | L | L | H |
| Xi 2021 [41] | U | U | L | L | L | L | L | H |
| Xie 2017 [42] | L | U | L | L | L | L | L | L |
| Xu 2015 [43] | U | U | L | L | L | L | L | H |
| Yiiu 2016 [44] | U | U | L | L | L | L | L | H |
| Yu 2014 [45] | L | U | L | L | L | L | L | L |
| Zhang 2013a [46] | U | U | L | L | L | L | L | H |
| Zhang 2020 [47] | L | L | L | L | H | L | L | H |
| Zhang 2013b [48] | U | U | L | L | H | L | L | H |
| Zhao 2020 [49] | L | U | L | L | L | L | L | L |
| Zhao 2018 [50] | L | L | L | L | L | L | L | L |
| Zuppa 2015 [51] | L | L | L | L | L | L | L | L |

L: low risk of bias; H: high risk of bias; U: unclear bias

**Supplementary file 5. Funnel plot**

