An empirical evaluation of the impact scenario of pooling bodies of evidence from randomized controlled trials and cohort studies in medical research

Nils Bröckelmann¹*, Julia Stadelmaier¹*, Louisa Harms¹, Charlotte Kubiak¹, Jessica Beyerbach¹, Martin Wolkewitz², Jörg J Meerpohl¹,²,³, Lukas Schwingshackl¹

¹ Institute for Evidence in Medicine, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany.

² Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center - University of Freiburg, Freiburg, Germany.

³ Cochrane Germany, Cochrane Germany Foundation, Freiburg, Germany.

* contributed equally

Corresponding author: Lukas Schwingshackl, PhD

Briesacher Straße 86, 79110 Freiburg, Germany

M: schwingshackl@ifem.uni-freiburg.de

P: +49 (0)761 203-96867

ORCID number: 0000-0003-3407-7594

Twitter: https://twitter.com/LSchwingshackl
Content Supplement

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| #1 | "lancet london england"[Journal] OR "JAMA"[Journal] OR "bmj clinical research ed"[Journal] OR "jama internal medicine"[Journal] OR "Annals of internal medicine"[Journal] OR "PLoS medicine"[Journal] OR "BMC medicine"[Journal] OR "The Cochrane database of systematic reviews"[Journal] OR "Mayo Clinic proceedings"[Journal] OR "Canadian Medical Association journal"[Journal] OR "Nat Rev Dis Primers"[Journal] OR "J Cachexia Sarcopenia Muscle"[Journal] OR "N Engl J Med"[Journal] |
| #2 | "systematic review"[Title/Abstract] OR "systematic literature review"[Title/Abstract] OR "systematic scoping review"[Title/Abstract] OR "systematic meta-review"[Title/Abstract] OR "systematic search"[Title/Abstract] OR "systematic review"[Publication Type] OR "meta analys*"[Title/Abstract] OR "meta analy*"[Publication Type] OR "cochrane database syst rev"[Journal] |
| #3 | "random*"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms:noexp] OR "trial"[Title] |
| #4 | "epidemiolog*"[Title/Abstract] OR "cohort stud*"[Title/Abstract] OR "observation*"[Title/Abstract] OR "non rct*"[Title/Abstract] OR "non random*"[Title/Abstract] |
| #5 | #1 AND #2 AND #3 AND #4 |
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**Table S1:** Explanation and definition for Population (P), Intervention/Exposure (I/E), Comparator (C), Outcome (O) similarity degree

| Rating | Population | Intervention/Exposure | Comparator | Outcome |
|--------|------------|-----------------------|------------|---------|
| 1 = “more or less identical” | Same health status and type of population | Same drug, invasive procedure, nutrition-intervention or vaccine | - Same drug or invasive procedure - Nutrition: Placebo vs. Nil or low intake; Low intake vs. Low intake | Same outcome |
| 2 = “similar but not identical” | Populations with mixed health status in RCTs and/or cohort studies | - Different drugs of the same class/ Any drug of the same class vs. Specific drug of the same class - Similar invasive procedure/ same invasive procedure with different co-interventions - Similar vaccines or identical vaccine with different route of administration - Supplementary or free food vs. Intake - Similar but not identical time frame of intervention | - Different drugs of the same class - Similar invasive procedures, drug, vaccine or diet - General dietary advice vs. High intake | - Similar outcome - Both with mixed similar outcomes |

*Example cases:*  
- Populations:  
  - Both BoE with either healthy population, general population or diseased population  
  - Same age category (both adults, both postmenopausal women)  
- Interventions/Exposures:  
  - Both Enoxaparin - Both PCI - Both high dairy-intake  
- Comparators:  
  - Both no Enoxaparin - Both UKA - Placebo vs. No intervention or low intake  
- Outcomes:  
  - Mortality in both BoE
| 3 = “broadly similar” | e.g. | e.g. | e.g. | e.g. |
|----------------------|------|------|------|------|
| Merged healthy and diseased population in one BoE vs. healthy population in the other BoE | -Both different SGAs | -Both similar regional anaesthetic nerve blocks | -Both different DDP-4 inhibitors | -Late stage only or all CRC vs. All CRC |
| Both BoE with merged healthy and diseased population | -Various pneumococcal vaccines (2,3,12,14,17 and 23-valent) versus 23-valent only | -“Best medical treatment” with Aspirin and additionally with various other drugs | -No vaccination or delayed vaccination versus no vaccination |
| Population with cardiovascular risk factors (without manifest disease) vs. Healthy population | -One or two doses of measles containing vaccines versus unclear number of doses | -Transfemoral vs. transapical TAVI | -Transfemoral versus no vaccination |
| | -Free non-caloric beverages vs. Low intake of SSBs | -General dietary advice vs. High red meat intake | -General dietary advice vs. Transfemoral TAVI |
| | -Early intervention with different time frame (first 14 vs. first 24 hours) | | -Early intervention with different time frame (first 14 vs. first 24 hours) |
| Different health status of populations in RCTs and cohort studies | Same drug for different indication | Active intervention (drug, invasive procedure, nutrient) vs. No intervention or placebo | | |
| Other substantial differences (e.g. Age-category, type of population) | -Enhanced treatment vs. Any treatment | -Different time frame/ early treatment vs. Any treatment | -Different time frame |
| | -Supplement vs. Status | | |
| Healthy population in one BoE vs. population with cardiovascular disease in the other BoE | e.g. | e.g. | e.g. | e.g. |
| Children/adolescents vs. Adults | Digoxin for HF vs. digoxin post-myocardial infarction without HF | Restrictive transfusion vs. No transfusion | Colorectal adenoma vs. Cancer |
| Travellers vs. Pregnant women | Dispatcher-assisted bystander CPR vs. unassisted bystander CPR | Placebo vs. Low selenium status | |
| | Enhanced training of birth attendants vs. Any support by birth attendant | -No vaccination of health care workers vs. Low share of vaccinated health care workers per facility | |
| | Selenium supplements vs. High selenium status | -Pregnant women with untreated bacteriuria vs. Pregnant without screening for bacteriuria | |
| | Early ART vs. Any ART | -Delayed ART vs. No ART | | |

ART: antiretroviral therapy; BoE: bodies of evidence; CRC: colorectal cancer; CPR: cardiopulmonary resuscitation; DDP-4: dipeptidyl peptidase 4; HF: heart failure; PCI: percutaneous coronary intervention; PI/ECO: population, intervention/ exposure, comparator, outcome; RCT: randomized controlled trial; SGA: second-generation antipsychotic; SSBs: sugar-sweetened beverages; TAVI: transcatheter aortic valve replacement; UKA: unicompartmental knee arthroplasty
Table S2: Ratings of Population (P), Intervention/Exposure (I/E), Comparator (C), Outcome (O) similarity degree for all identified body of evidence-pairs

| Reference          | Intervention/Exposure (as defined by the authors) | Intervention/Exposure type | Outcome (as defined by the authors) | Outcome-category (e.g., cancer outcomes, cardiovascular disease, all-cause mortality) | Rating of PI/ECO-similarity degree | Included in the pooling scenario (Yes/No) |
|--------------------|---------------------------------------------------|-----------------------------|-------------------------------------|------------------------------------------------------------------------------------------|-----------------------------------|------------------------------------------|
| Abou-Setta 2011 (1)| Nerve block                                       | Invasive                    | Delirium                            | Neurological                                                                             | 2 2 2 1 2                        | No                                       |
| Abou-Setta 2011 (1)| Spinal anaesthesia                               | Invasive                    | All-cause mortality                 | All-cause mortality                                                                      | 2 1 1 1 2                        | No                                       |
| Aburto 2013 (2)    | Low sodium                                        | Nutrition                    | All-cause mortality                 | All-cause mortality                                                                      | 2 2 2 1 2                        | Yes                                      |
| Aburto 2013 (2)    | Low sodium                                        | Nutrition                    | Cardiovascular disease              | Cardiovascular disease                                                                   | 2 2 2 2 2                        | Yes                                      |
| Ahmad 2015 (3)     | Intra-aortic balloon pump                         | Invasive                    | All-cause mortality                 | All-cause mortality                                                                      | 1 1 1 1 1                        | Yes                                      |
| Alexander 2017 (4) | High DHA and EPA                                  | Nutrition                    | Coronary heart disease              | Cardiovascular disease                                                                   | 2 2 2 1 2                        | No                                       |
| Alexander 2017 (4) | High DHA and EPA                                  | Nutrition                    | Coronary heart disease mortality    | Cardiovascular disease                                                                   | 2 2 2 1 2                        | No                                       |
| Alexander 2017 (4) | High DHA and EPA                                  | Nutrition                    | Coronary heart disease incidence    | Cardiovascular disease                                                                   | 2 2 2 1 2                        | No                                       |
| Alipanah 2018 (5)  | Self-administered therapy                         | Drug                         | Treatment success                   | Infectiological                                                                         | 3 2 1 1 3                        | Yes                                      |
| Alipanah 2018 (5)  | Self-administered therapy                         | Drug                         | Treatment completion                | Drug safety                                                                              | 3 2 1 1 3                        | Yes                                      |
| Alipanah 2018 (5)  | Self-administered therapy                         | Drug                         | All-cause mortality                 | All-cause mortality                                                                      | 3 2 1 1 3                        | Yes                                      |
| Anglemyer 2013 (6) | Antiretroviral therapy                            | Drug                         | HIV infection                       | Infectiological                                                                         | 2 2 3 1 3                        | Yes                                      |
| Azad 2017 (7)      | Nonnutritive sweeteners                           | Nutrition                    | Body Mass Index                     | Metabolic                                                                                | 2 2 1 1 2                        | Yes                                      |
| Study                        | Intervention Description                                                                 | Type   | Primary Outcome                  | Barnard 2015 (8) | Barnard 2015 (8) | Barnard 2015 (8) | Bellemain-Appaix 2012 (9) | Bellemain-Appaix 2012 (9) | Bellemain-Appaix 2012 (9) | Bellemain-Appaix 2014 (10) | Bellemain-Appaix 2014 (10) | Bellemain-Appaix 2014 (10) | Bloomfield 2016 (11) |
|------------------------------|------------------------------------------------------------------------------------------|--------|----------------------------------|-----------------|-----------------|-----------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|------------------------|
| Barnard 2015 (8)             | Surgical abortion by mid-level providers                                                   | Invasive | Failure or incomplete abortion   | 2               | 2               | 1               | 1                         | 2                         | 2                         | 2                         | Yes                      |                        |
| Barnard 2015 (8)             | Surgical abortion by mid-level providers                                                   | Invasive | Complications                   | 2               | 2               | 1               | 1                         | 2                         | Yes                      |                          |                         |                        |
| Barnard 2015 (8)             | Surgical abortion by mid-level providers                                                   | Invasive | Abortion failure and complications | 2               | 2               | 1               | 1                         | 2                         | Yes                      |                          |                         |                        |
| Bellemain-Appaix 2012 (9)    | Clopidogrel pretreatment for percutaneous coronary intervention                           | Drug    | All-cause mortality              | 2               | 2               | 2               | 1                         | 2                         | Yes                      |                          |                         |                        |
| Bellemain-Appaix 2012 (9)    | Clopidogrel pretreatment for percutaneous coronary intervention                           | Drug    | Major bleeding                   | 2               | 2               | 2               | 1                         | 2                         | Yes                      |                          |                         |                        |
| Bellemain-Appaix 2012 (9)    | Clopidogrel pretreatment for percutaneous coronary intervention                           | Drug    | Coronary heart disease           | 2               | 2               | 2               | 1                         | 2                         | Yes                      |                          |                         |                        |
| Bellemain-Appaix 2014 (10)   | P2Y12 inhibitor pretreatment in non-ST elevation acute coronary syndrome                 | Drug    | All-cause mortality              | 2               | 2               | 2               | 1                         | 2                         | Yes                      |                          |                         |                        |
| Bellemain-Appaix 2014 (10)   | P2Y12 inhibitor pretreatment in non-ST elevation acute coronary syndrome                 | Drug    | Major bleeding                   | 2               | 2               | 2               | 1                         | 2                         | Yes                      |                          |                         |                        |
| Bellemain-Appaix 2014 (10)   | P2Y12 inhibitor pretreatment in non-ST elevation acute coronary syndrome                 | Drug    | Main composite ischemic endpoint | 2               | 2               | 2               | 1                         | 2                         | Yes                      |                          |                         |                        |
| Bloomfield 2016 (11)         | Mediterranean diet                                                                        | Nutrition | Breast cancer                   | 2               | 2               | 2               | 1                         | 2                         | Yes                      |                          |                         |                        |
| Authors          | Intervention & Process | Nutritional Component | Outcome | Disease Area        | Effect  |
|------------------|------------------------|-----------------------|---------|---------------------|---------|
| Bolland 2015 (12) | High calcium           | Nutrition             | All fractures | Orthopaedic         | 1 | 2 | 1 | 1 | 2 | Yes |
| Bolland 2015 (12) | High calcium           | Nutrition             | Vertebral fracture | Orthopaedic         | 1 | 2 | 1 | 1 | 2 | Yes |
| Bolland 2015 (12) | High calcium           | Nutrition             | Hip fracture     | Orthopaedic         | 1 | 2 | 1 | 1 | 2 | Yes |
| Brenner 2014 (13) | Sigmoidoscopy          | Invasive              | Colorectal cancer mortality | Oncological | 1 | 1 | 1 | 1 | 1 | Yes |
| Brenner 2014 (13) | Sigmoidoscopy          | Invasive              | Colorectal cancer incidence | Oncological | 1 | 1 | 1 | 2 | 2 | Yes |
| Chowdhury 2012 (14) | High omega-3          | Nutrition             | Cerebrovascular disease | Cardiovascular disease | 2 | 2 | 1 | 1 | 2 | Yes |
| Chowdhury 2014a (15) | High α-linolenic acid | Nutrition             | Coronary heart disease | Cardiovascular disease | 3 | 2 | 2 | 1 | 3 | Yes |
| Chowdhury 2014a (15) | High omega-3          | Nutrition             | Coronary heart disease | Cardiovascular disease | 3 | 2 | 2 | 1 | 3 | Yes |
| Chowdhury 2014a (15) | High omega-6          | Nutrition             | Coronary heart disease | Cardiovascular disease | 3 | 2 | 2 | 1 | 3 | Yes |
| Chowdhury 2014b (16) | High vitamin D       | Nutrition             | All-cause mortality | All-cause mortality | 2 | 3 | 3 | 1 | 3 | No |
| Chung 2011 (17)    | High vitamin D        | Nutrition             | Colorectal cancer | Oncological         | 2 | 3 | 3 | 1 | 3 | No |
| Chung 2011 (17)    | High vitamin D        | Nutrition             | Breast cancer    | Oncological         | 2 | 3 | 3 | 1 | 3 | No |
| Chung 2016 (18)    | High calcium          | Nutrition             | Cardiovascular mortality | Cardiovascular disease | 2 | 2 | 1 | 1 | 2 | Yes |
| Ding 2017 (19)     | High dairy            | Nutrition             | Systolic blood pressure | Cardiovascular disease | 2 | 1 | 1 | 1 | 2 | Yes |
| Fenton 2018 (20)   | Radiation therapy     | Invasive              | Erectile dysfunction | Urological          | 1 | 1 | 2 | 1 | 2 | Yes |
| Fenton 2018 (20)   | Radical Prostatectomy | Invasive              | Urinary incontinence | Urological          | 1 | 1 | 2 | 1 | 2 | Yes |
| Fenton 2018 (20)   | Radical Prostatectomy | Invasive              | Erectile dysfunction | Urological          | 1 | 1 | 2 | 1 | 2 | Yes |
| Filippini 2017 (21)| Disease-modifying drugs | Drug            | Conversion to clinically definite multiple sclerosis | Neurological       | 1 | 2 | 1 | 1 | 2 | Yes |
| Reference       | Intervention                                      | Type     | Endpoint                                      | Cause               | Score | Score | Score | Score | Score | Score | Score | Score | Score | Score | Yes  |
|----------------|---------------------------------------------------|----------|----------------------------------------------|---------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|------|
| Fluri 2010 (22) | Extracranial-intracranial arterial bypass         | Invasive | All-cause mortality                          | All-cause mortality | 2     | 1     | 2     | 1     | 2     | Yes  |
| Fluri 2010 (22) | Extracranial-intracranial arterial bypass         | Invasive | Stroke                                       | Cardiovascular disease | 2    | 1     | 2     | 1     | 2     | Yes  |
| Fluri 2010 (22) | Extracranial-intracranial arterial bypass         | Invasive | Stroke mortality or dependency               | Cardiovascular disease | 1    | 1     | 2     | 1     | 2     | Yes  |
| Gargiulo 2016 (23) | Transcatheter aortic valve implantation          | Invasive | Early all-cause mortality                    | All-cause mortality  | 2     | 2     | 1     | 1     | 2     | Yes  |
| Gargiulo 2016 (23) | Transcatheter aortic valve implantation          | Invasive | Mid-term all-cause mortality                 | All-cause mortality  | 2     | 2     | 1     | 1     | 2     | Yes  |
| Gargiulo 2016 (23) | Transcatheter aortic valve implantation          | Invasive | Long-term all-cause mortality                | All-cause mortality  | 2     | 1     | 1     | 1     | 2     | Yes  |
| Hartling 2013 (24) | Treating gestational diabetes mellitus            | Nutrition | High birth weight                            | Obstetrical         | 2     | 1     | 1     | 1     | 2     | Yes  |
| Hartling 2013 (24) | Treating gestational diabetes mellitus            | Nutrition | Large-for-gestational age neonate            | Obstetrical         | 2     | 1     | 1     | 1     | 2     | Yes  |
| Hartling 2013 (24) | Treating gestational diabetes mellitus            | Nutrition | Shoulder dystocia                            | Obstetrical         | 2     | 1     | 1     | 1     | 2     | Yes  |
| Henderson 2019 (25) | Treating asymptomatic bacteriuria                 | Drug     | Pyelonephritis                               | Infectiological     | 2     | 2     | 3     | 1     | 3     | Yes  |
| Higgins 2016 (26) | Bacillus Calmette-Guérin vaccination              | Vaccine  | All-cause mortality                          | All-cause mortality | 3     | 1     | 2     | 1     | 3     | Yes  |
| Higgins 2016 (26) | Measles containing vaccines                       | Vaccine  | All-cause mortality                          | All-cause mortality | 3     | 2     | 2     | 1     | 3     | Yes  |
| Hopley 2010 (27)  | Total hip arthroplasty                            | Invasive | Reoperation                                  | Orthopaedic         | 2     | 1     | 1     | 1     | 2     | Yes  |
| Hopley 2010 (27)  | Total hip arthroplasty                            | Invasive | Dislocation                                  | Orthopaedic         | 2     | 1     | 1     | 1     | 2     | Yes  |
| Hopley 2010 (27)  | Total hip arthroplasty                            | Invasive | Deep infection                               | Infectiological     | 2     | 2     | 1     | 1     | 2     | Yes  |
| Hüpf 2010 (28)    | Chest-compression-only cardiopulmonary            | Cardiopulmonary | Survival                                     | All-cause mortality | 1     | 3     | 3     | 1     | 3     | Yes  |
| Reference | Year | Intervention | Field | Outcome | Score 1 | Score 2 | Score 3 | Score 4 | Score 5 | Score 6 | Result |
|-----------|------|--------------|-------|---------|---------|---------|---------|---------|---------|---------|--------|
| Jamal 2013 (29) | 2013 | Non-calcium-based phosphate binders | Drug | All-cause mortality | All-cause mortality | 2 | 2 | 1 | 1 | 2 | Yes |
| Jefferson 2010 (30) | 2010 | Parenteral influenza vaccine | Vaccine | Influenza-like illness | Infectiological | 2 | 2 | 3 | 1 | 3 | Yes |
| Jefferson 2010 (30) | 2010 | Parenteral influenza vaccine | Vaccine | Influenza | Infectiological | 2 | 2 | 1 | 1 | 2 | Yes |
| Jefferson 2012 (31) | 2012 | Inactivated influenza vaccines | Vaccine | Influenza | Infectiological | 1 | 2 | 1 | 1 | 2 | Yes |
| Jefferson 2012 (31) | 2012 | Inactivated influenza vaccines | Vaccine | Influenza-like illness | Infectiological | 1 | 2 | 1 | 1 | 2 | Yes |
| Jin 2012 (32) | 2012 | High total flavonoids | Nutrition | Colorectal neoplasms | Oncological | 3 | 2 | 2 | 3 | 3 | Yes |
| Johnston 2019 (33) | 2019 | Red meat | Nutrition | All-cause mortality | All-cause mortality | 2 | 2 | 2 | 1 | 2 | No |
| Johnston 2019 (33) | 2019 | Red meat | Nutrition | Cardiovascular mortality | Cardiovascular disease | 2 | 2 | 2 | 1 | 2 | No |
| Johnston 2019 (33) | 2019 | Red meat | Nutrition | Cardiovascular disease | Cardiovascular disease | 2 | 2 | 2 | 1 | 2 | No |
| Kansagara 2013 (34) | 2013 | Transfusion | Transfusion | All-cause mortality | All-cause mortality | 2 | 3 | 3 | 2 | 3 | Yes |
| Keag 2018 (35) | 2018 | Caesarean section | Invasive | Urinary incontinence | Obstetrical | 3 | 2 | 2 | 1 | 3 | Yes |
| Keag 2018 (35) | 2018 | Caesarean section | Invasive | Fecal incontinence | Obstetrical | 3 | 2 | 2 | 1 | 3 | Yes |
| Kredo 2014 (36) | 2014 | Antiretroviral therapy by nurses | Drug | All-cause mortality | All-cause mortality | 2 | 3 | 1 | 1 | 3 | Yes |
| Kredo 2014 (36) | 2014 | Antiretroviral therapy by nurses | Drug | Attrition | Drug safety | 2 | 3 | 1 | 1 | 3 | Yes |
| Kredo 2014 (36) | 2014 | Nurses for maintenance of antiretroviral therapy | Drug | All-cause mortality | All-cause mortality | 2 | 3 | 2 | 1 | 3 | Yes |
| Li 2014 (37) | 2014 | Exenatide | Drug | Acute pancreatitis | Drug safety | 2 | 1 | 2 | 2 | 2 | Yes |
| Li 2016 (38) | 2016 | DDP-4 inhibitors | Drug | Heart failure | Drug safety | 2 | 2 | 2 | 1 | 2 | Yes |
| Reference       | Treatment                               | Indication                                      | Outcome Measure                      | Risk Factor | RR Ratio | 95% CI Low | 95% CI High | P Value | Safety Downstream Events |
|-----------------|-----------------------------------------|-------------------------------------------------|--------------------------------------|-------------|----------|------------|-------------|---------|--------------------------|
| Li 2016 (38)    | DDP-4 inhibitors                        | Drug admission for heart failure                | Drug safety                          | 2           | 2        | 2          | 1           | 2       | Yes                      |
| Matthews 2018 (39) | Tamoxifen                               | Drug Heart failure                             | Drug safety                          | 2           | 3        | 1          | 1           | 3       | Yes                      |
| Menne 2019 (40) | SGLT-2 inhibitors                       | Drug Acute kidney injury                       | Drug safety                          | 2           | 2        | 2          | 1           | 2       | Yes                      |
| Mesgarpour 2017 (41) | Erythropoiesis stimulating agents       | Drug Venous thromboembolism                    | Drug safety                          | 2           | 2        | 2          | 1           | 2       | Yes                      |
| Mesgarpour 2017 (41) | Erythropoiesis stimulating agents       | Drug All-cause mortality                       | All-cause mortality                  | 2           | 2        | 2          | 1           | 2       | Yes                      |
| Moherley 2013 (42) | Pneumococcal polysaccharide vaccines   | Vaccine Invasive pneumococcal disease           | Infectiological                      | 2           | 2        | 1          | 1           | 2       | Yes                      |
| Molnar 2015 (43) | Neoral (Cyclosporin)                    | Drug Acute rejection of kidney transplant      | Drug safety                          | 2           | 1        | 2          | 1           | 2       | Yes                      |
| Navarese 2013 (44) | Early intervention for NSTE-ACS         | Invasive All-cause mortality                    | All-cause mortality                  | 2           | 2        | 1          | 1           | 2       | Yes                      |
| Navarese 2013 (44) | Early intervention for NSTE-ACS         | Invasive Myocardial infarction                 | Cardiovascular disease               | 2           | 2        | 1          | 1           | 2       | Yes                      |
| Navarese 2013 (44) | Early intervention for NSTE-ACS         | Invasive Major bleeding                        | Drug safety                          | 2           | 2        | 1          | 1           | 2       | Yes                      |
| Nelson 2010 (45) | Caesarean section                       | Invasive Anal incontinence, feces             | Obstetrical                          | 3           | 2        | 2          | 1           | 3       | Yes                      |
| Nelson 2010 (45) | Caesarean section                       | Invasive Anal incontinence, flatus             | Obstetrical                          | 3           | 2        | 2          | 1           | 3       | Yes                      |
| Nieuwenhuijse 2014 (46) | Ceramic-on-ceramic bearings for total hip arthroplasty | Invasive Harris Hip Score                      | Orthopaedic                          | 2           | 1        | 1          | 1           | 2       | Yes                      |
| Nieuwenhuijse 2014 (46) | High-flexion total knee arthroplasty    | Invasive Flexion                             | Orthopaedic                          | 2           | 1        | 1          | 1           | 2       | Yes                      |
| Nieuwenhuijse 2014 (46) | Gender-specific total knee arthroplasty | Invasive Flexion-extension range              | Orthopaedic                          | 2           | 1        | 1          | 1           | 2       | Yes                      |
| Nikooie 2019 (47) | Second generation antipsychotics       | Drug Sedation                                 | Drug safety                          | 2           | 2        | 1          | 2           | 2       | Yes                      |
| Study (Year) | Intervention | Treatment Category | Outcomes | Level 1 | Level 2 | Level 3 | Level 4 | Yes/No |
|-------------|--------------|-------------------|----------|---------|---------|---------|---------|--------|
| Nikooie 2019 (47) | Second generation antipsychotics | Drug | Neurologic outcomes | Drug safety | 2 | 2 | 1 | 2 | 2 | Yes |
| Ochen 2019 (48) | Surgery for achilles tendon rupture | Invasive | Re-rupture | Orthopaedic | 1 | 2 | 2 | 1 | 2 | Yes |
| Ochen 2019 (48) | Surgery for achilles tendon rupture | Invasive | Complications | Orthopaedic | 1 | 2 | 2 | 1 | 2 | Yes |
| Pittas 2010 (49) | High vitamin D | Nutrition | Hypertension | Cardiovascular disease | 2 | 3 | 3 | 1 | 3 | Yes |
| Raman 2013 (50) | Carotid endarterectomy | Invasive | Ipsilateral stroke | Cardiovascular disease | 2 | 1 | 2 | 1 | 2 | Yes |
| Raman 2013 (50) | Carotid endarterectomy | Invasive | Stroke | Cardiovascular disease | 2 | 1 | 2 | 1 | 2 | Yes |
| Raman 2013 (50) | Carotid artery stenting | Invasive | Periprocedural stroke | Cardiovascular disease | 2 | 2 | 2 | 1 | 2 | Yes |
| Schweizer 2013 (51) | Nasal deconolization | Drug | Surgical site infection | Infectiological | 2 | 2 | 1 | 1 | 2 | Yes |
| Schweizer 2013 (51) | Glycopeptide prophylaxis | Drug | Surgical site infection | Infectiological | 2 | 2 | 2 | 1 | 2 | Yes |
| Silvain 2012 (52) | Enoxaparin | Drug | All-cause mortality | All-cause mortality | 2 | 1 | 2 | 1 | 2 | Yes |
| Silvain 2012 (52) | Enoxaparin | Drug | Major bleeding | Drug safety | 2 | 1 | 2 | 1 | 2 | Yes |
| Silvain 2012 (52) | Enoxaparin | Drug | All-cause mortality or myocardial infarction | Cardiovascular disease | 2 | 1 | 2 | 1 | 2 | Yes |
| Suthar 2012 (53) | Antiretroviral therapy | Drug | Tuberculosis infection | Infectiological | 2 | 3 | 3 | 1 | 3 | Yes |
| Te Morenga 2013 (54) | High sugar intake | Nutrition | Weight gain | Metabolic | 2 | 1 | 2 | 1 | 2 | Yes |
| Te Morenga 2013 (54) | High sugar intake | Nutrition | Body Mass Index | Metabolic | 2 | 2 | 2 | 1 | 2 | Yes |
| Thomas 2010 (55) | Influenza vaccines | Vaccine | Influenza-like illness | Infectiological | 2 | 3 | 3 | 1 | 3 | Yes |
| Tickell-Painter 2017 (56) | Mefloquine | Drug | Discontinuation due to adverse effects | Drug safety | 2 | 1 | 1 | 1 | 2 | Yes |
| Reference          | Treatment Type                                                                 | Endpoint Description                  | Field                  | Score | Grade | Absolute Mortality | Yes/No |
|-------------------|-------------------------------------------------------------------------------|---------------------------------------|------------------------|-------|-------|--------------------|--------|
| Tickell-Painter 2017 (56) | Mefloquine Drug                                                               | Serious adverse events or effects     | Drug safety            | 3     | 1     | 1                  | 2      | Yes               |
| Tickell-Painter 2017 (56) | Mefloquine Drug                                                               | Nausea                                | Drug safety            | 3     | 1     | 1                  | 1      | Yes               |
| Tricco 2018 (57)     | Live-attenuated zoster vaccines                                               | Suspected Herpes Zoster               | Infectiological        | 2     | 2     | 2                  | 1      | Yes               |
| Vinceti 2018 (58)    | High selenium Nutrition                                                       | Cancer                                | Oncological            | 2     | 3     | 3                  | 2      | Yes               |
| Vinceti 2018 (58)    | High selenium Nutrition                                                       | Cancer mortality                      | Oncological            | 2     | 3     | 3                  | 1      | Yes               |
| Vinceti 2018 (58)    | High selenium Nutrition                                                       | Colorectal cancer                     | Oncological            | 2     | 3     | 3                  | 1      | Yes               |
| Wilson 2011 (59)     | Training for traditional birth attendants/assistance by traditional birth attendants | Birth assistance                      | Perinatal mortality    | All-cause mortality   | 1     | 2     | 3                  | 1      | Yes               |
| Wilson 2011 (59)     | Training for traditional birth attendants/assistance by traditional birth attendants | Birth assistance                      | Neonatal mortality     | All-cause mortality   | 1     | 2     | 3                  | 1      | Yes               |
| Wilson 2019 (60)     | Unicompartmental knee arthroplasty                                             | Invasive Venous thromboembolism       | Orthopaedic            | 2     | 1     | 1                  | 1      | Yes               |
| Wilson 2019 (60)     | Unicompartmental knee arthroplasty                                             | Invasive Flexion-extension range      | Orthopaedic            | 2     | 1     | 1                  | 1      | Yes               |
| Wilson 2019 (60)     | Unicompartmental knee arthroplasty                                             | Invasive Operation duration           | Orthopaedic            | 2     | 1     | 1                  | 1      | Yes               |
| Yank 2011 (61)       | Recombinant factor VII Drug                                                   | All-cause mortality                   | All-cause mortality    | 2     | 2     | 1                  | 1      | Yes               |
| Yank 2011 (61)       | Recombinant factor VII Drug                                                   | Thromboembolism                       | Drug safety            | 2     | 2     | 1                  | 1      | Yes               |
| Zhang 2016 (62)      | Everolimus-eluting bioreabsorbable vascular scaffold                           | Invasive Stent thrombosis             | Cardiovascular disease | 2     | 1     | 1                  | 1      | Yes               |
| Author  | Year | Study Details                                                                 | Intervention | Outcomes | All-cause mortality | Cardiovascular disease | Drug safety | Drug | Outcome |
|---------|------|--------------------------------------------------------------------------------|--------------|----------|--------------------|------------------------|------------|------|---------|
| Zhang   | 2016 | Everolimus-eluting bioresorbable vascular scaffold                           | Invasive     | All-cause mortality | 2 | 1 | 1 | 1 | 2 | Yes |
| Zhang   | 2016 | Everolimus-eluting bioresorbable vascular scaffold                           | Invasive     | Coronary heart disease mortality | 2 | 1 | 1 | 1 | 2 | Yes |
| Zhang   | 2017 | Percutaneous coronary intervention                                            | Invasive     | All-cause mortality | 2 | 2 | 1 | 1 | 2 | Yes |
| Zhang   | 2017 | Percutaneous coronary intervention                                            | Invasive     | Cardiovascular mortality | 2 | 2 | 1 | 1 | 2 | Yes |
| Zhang   | 2017 | Percutaneous coronary intervention                                            | Invasive     | Myocardial infarction | 2 | 2 | 1 | 1 | 2 | Yes |
| Ziff    | 2015 | Digoxin                                                                         | Drug         | All-cause mortality | 3 | 1 | 1 | 1 | 3 | Yes |
| Ziff    | 2015 | Digoxin                                                                         | Drug         | Cardiovascular mortality | 3 | 1 | 1 | 1 | 3 | Yes |
| Ziff    | 2015 | Digoxin                                                                         | Drug         | Hospital admission | 2 | 1 | 1 | 1 | 2 | Yes |

DDP 4: Dipeptidylpeptidase-4; DHA and EPA: Docosahexaenoic acid and eicosapentaenoic acid; HIV: human immunodeficiency virus; NSTE-ACS: Non-ST-Segment Elevation Acute Coronary Syndromes; PI/ECO: population – intervention/exposure – comparator – outcome ; SGLT-2: Sodium dependent glucose transporter 2.
| Reference             | Intervention / Exposure (as defined by the authors) | Outcome (as defined by the authors) | RCTs Reported* RR/HR/OR or MD (95% CI) | Recalculated (RE and inverse-variance model) RR/HR/OR or MD (95% CI) | Cohort Studies Reported* RR/HR/OR or MD (95% CI) | Recalculated (RE and inverse-variance model) RR/HR/OR or MD (95% CI) |
|-----------------------|---------------------------------------------------|------------------------------------|---------------------------------------|-------------------------------------------------|-----------------------------------------------|-------------------------------------------------|
| Aburto 2013 (2)       | Low sodium                                        | Cardiovascular disease             | RR: 0.89 (0.75, 1.08)                | RR: 0.90 (0.75, 1.08)                           |                                               |
| Ahmad 2015 (3)        | Intra-aortic balloon pump                         | Mortality                          | RR: 0.81 (0.73, 0.89)                | RR: 0.81 (0.74, 0.88)                           | RR: 0.90 (0.67, 1.56)                        |
| Alipanah 2018 (5)     | Self-administered therapy                         | Treatment success                  | RR: 0.79 (0.56, 1.11)                | RR: 0.95 (0.87, 1.03)                           | RR: 1.00 (0.91, 1.33)                        |
| Alipanah 2018 (5)     | Self-administered therapy                         | Treatment completion               | RR: 1.10 (0.90, 1.35)                | RR: 1.10 (0.91, 1.33)                           | RR: 1.10 (0.91, 1.33)                        |
| Alipanah 2018 (5)     | Self-administered therapy                         | Mortality                          | RR: 1.35 (1.00, 1.84)                | RR: 1.35 (1.00, 1.83)                           |                                               |
| Anglemyer 2013 (6)    | Antiretroviral therapy                            | HIV Infection                      | RR: 0.11 (0.04, 0.32)                | RR: 0.11 (0.04, 0.30)                           | RR: 0.59 (0.36, 0.97)                        |
| Barnard 2015 (8)      | Surgical abortion by mid-level providers          | Failure or incomplete abortion     | RR: 2.97 (0.21, 41.82)               | RR: 2.84 (0.24, 32.97)                          | RR: 2.47 (1.44, 4.23)                        |
| Barnard 2015 (8)      | Surgical abortion by mid-level providers          | Complications                      | RR: 0.99 (0.17, 5.7)                | RR: 0.94 (0.14, 6.44)                           | RR: 1.30 (0.57, 2.96)                        |
| Barnard 2015 (8)      | Surgical abortion by mid-level providers          | Abortion failure and complications | RR: 2.93 (0.19, 44.15)               | RR: 3.07 (0.16, 59.08)                          | RR: 2.93 (0.19, 44.15)                       |
| Bellemain-Appaix 2012 (9) | Clopidogrel pretreatment for percutaneous coronary intervention | All-cause mortality | OR: 0.90 (0.80, 1.11)                | OR: 0.80 (0.75, 1.08)                           |                                               |
| Bellemain-Appaix 2012 (9) | Clopidogrel pretreatment for percutaneous coronary intervention | Major bleeding | OR: 0.79 (0.53, 1.18)                | OR: 0.79 (0.53, 1.18)                           |                                               |
| Study                                      | Intervention                                                                 | Endpoint                        | OR (95% CI)                  |
|-------------------------------------------|------------------------------------------------------------------------------|---------------------------------|------------------------------|
| Bellemain-Appaix 2012 (9)                 | Clopidogrel pretreatment for percutaneous coronary intervention              | Coronary heart disease          | -                            |
| Bellemain-Appaix 2014 (10)                | P2Y12 inhibitor pretreatment in non-ST elevation acute coronary syndrome      | All-cause mortality             | OR: 0.92 (0.43, 1.98)        |
| Bellemain-Appaix 2014 (10)                | P2Y12 inhibitor pretreatment in non-ST elevation acute coronary syndrome      | Major bleeding                  | OR: 1.45 (0.97, 2.15)        |
| Bellemain-Appaix 2014 (10)                | P2Y12 inhibitor pretreatment in non-ST elevation acute coronary syndrome      | Main composite ischemic endpoint| OR: 0.85 (0.67, 1.07)        |
| Bolland 2015 (12)                         | High-calcium                                                                 | All fractures                   | RR: 0.90 (0.83, 0.96)        |
| Bolland 2015 (12)                         | High-calcium                                                                 | Vertebral fracture              | -                            |
| Bolland 2015 (12)                         | High-calcium                                                                 | Hip fracture                    | -                            |
| Brenner 2014 (13)                         | Sigmoidoscopy                                                                | Colorectal cancer mortality     | -                            |
| Brenner 2014 (13)                         | Sigmoidoscopy                                                                | Colorectal cancer incidence     | RR: 0.82 (0.75, 0.89)        |
| Chowdhury 2012 (14)                       | High omega-3                                                                 | Cerebrovascular disease         | RR: 0.98 (0.89, 1.08)        |
| Chowdhury 2014a (15)                      | High α-linolenic acid                                                        | Coronary heart disease          | -                            |
| Chung 2016 (18)                           | High calcium                                                                 | Cardiovascular mortality        | RR: 1.05 (0.82, 1.33)        |
| Study (Year) | Intervention | Outcome | Odds Ratio (95% CI) |
|-------------|--------------|---------|--------------------|
| Fenton 2018 (20) | Radiation therapy | Erectile dysfunction | - | RR: 1.30 (1.19, 1.43)¹ |
| Fenton 2018 (20) | Radical Prostatectomy | Urinary incontinence | RR: 2.27 (1.82, 2.84) | RR: 2.25 (1.80, 2.82) | RR: 2.91 (1.80, 4.71)¹ |
| Fenton 2018 (20) | Radical Prostatectomy | Erectile dysfunction | RR: 1.60 (1.23, 2.07) | RR: 1.60 (1.24, 2.07) | RR: 1.49 (1.33, 1.66)¹ |
| Filippini 2017 (21) | Disease-modifying drugs | Conversion to clinically definite multiple sclerosis | HR: 0.52 (0.46, 0.60)⁴ | - | HR: 0.48 (0.30, 0.78)⁴ |
| Fluri 2010 (22) | Extracranial-intracranial arterial bypass | Mortality | - | - | OR: 0.97 (0.58, 1.62)¹,⁷ |
| Fluri 2010 (22) | Extracranial-intracranial arterial bypass | Any stroke | OR: 0.44 (0.06, 3.24)⁷ | - | OR: 0.76 (0.49, 1.17)¹,⁷ |
| Fluri 2010 (22) | Extracranial-intracranial arterial bypass | Death or dependency | - | - | OR: 0.80 (0.50, 1.29)⁷ | OR: 0.81 (0.50, 1.31)⁷ |
| Gargiulo 2016 (23) | Transcatheter aortic valve implantation | Early mortality | OR: 0.80 (0.51, 1.25) | OR: 0.80 (0.58, 1.11) | OR: 1.08 (0.84, 1.39)¹ |
| Gargiulo 2016 (23) | Transcatheter aortic valve implantation | Mid-term mortality | OR: 0.90 (0.64, 1.26) | OR: 0.90 (0.71, 1.13) | - |
| Gargiulo 2016 (23) | Transcatheter aortic valve implantation | Long-term mortality | OR: 1.03 (0.65, 1.62) | OR: 1.03 (0.77, 1.37) | OR: 1.70 (1.23, 2.35) | OR: 1.70 (1.31, 2.20) |
| Hartling 2013 (24) | Treating Gestational Diabetes Mellitus | Birth weight > 4000g | - | - | RR: 0.69 (0.31, 1.54)³ |
| Hartling 2013 (24) | Treating Gestational Diabetes Mellitus | Shoulder dystocia | - | - | RR: 0.38 (0.19, 0.78) | RR: 0.38 (0.18, 0.80) |
| Henderson 2019 (25) | Treating asymptomatic bacteriuria | Pyelonephritis | - | - | RR: 0.29 (0.15, 0.57)³ |
| Higgins 2016 (26) | Bacillus Calmette-Guérin vaccination | Mortality | - | RR: 0.67 (0.40, 1.14)¹ | - |
| Higgins 2016 (26) | Measles containing vaccines | Mortality | - | - | RR: 0.53 (0.40, 0.70)¹ |
| Hopley 2010 (27) | Total hip arthroplasty | Reoperation | - | - | RR: 0.45 (0.19, 1.08)¹ |
| Study (Year) | Intervention | Event | Outcome | RR (95% CI) | RR (95% CI) | OR (95% CI) | OR (95% CI) |
|-------------|--------------|-------|---------|-------------|-------------|-------------|-------------|
| Hopley 2010 (27) | Total hip arthroplasty | Dislocation | - | - | - | RR: 0.79 (0.27, 2.35) |
| Jamal 2013 (29) | Non-calcium-based phosphate binders | Mortality | RR: 0.78 (0.61, 0.98) | RR: 0.78 (0.62, 0.98) | - | - |
| Jefferson 2010 (30) | Parenteral influenza vaccine | Influenza-like illness | - | - | - | RR: 0.76 (0.66, 0.87) |
| Jefferson 2010 (30) | Parenteral influenza vaccine | Influenza | - | - | - | RR: 0.51 (0.27, 0.97) |
| Jefferson 2012 (31) | Inactivated influenza vaccines | Influenza | - | - | - | RR: 0.20 (0.10, 0.39) |
| Jefferson 2012 (31) | Inactivated influenza vaccines | Influenza-like illness | - | - | - | RR: 0.29 (0.07, 1.15) |
| Kansagara 2013 (34) | Transfusion | Mortality | RR: 0.94 (0.61, 1.42) | RR: 0.94 (0.62, 1.43) | - | RR: 2.49 (1.40, 4.43) |
| Keag 2018 (35) | Caesarean section | Urinary incontinence | - | - | - | OR: 0.56 (0.47, 0.66) |
| Keag 2018 (35) | Caesarean section | Fecal incontinence | OR: 3.07 (0.90, 10.49) | OR: 3.07 (0.90, 10.47) | - | - |
| Li 2014 (37) | Exenatide | Acute pancreatitis/Admission for acute pancreatitis | RR: 0.86 (0.22, 3.37) | RR: 0.86 (0.22, 3.39) | - | RR: 0.92 (0.69, 1.22) |
| Li 2016 (38) | DDP-4 Inhibitors | Heart failure | RR: 0.90 (0.61, 1.35) | RR: 0.95 (0.60, 1.50) | - | RR: 1.10 (1.04, 1.17) |
| Matthews 2018 (39) | Tamoxifen | Heart failure | RR: 0.52 (0.33, 0.71) | RR: 0.52 (0.33, 0.79) | RR: 0.84 (0.65, 1.07) | RR: 0.85 (0.66, 1.09) |
| Menne 2019 (40) | SGLT-2 inhibitors | Acute kidney injury | - | - | OR: 0.40 (0.33, 0.48) | OR: 0.40 (0.31, 0.52) |
| Mesgarpour 2017 (41) | Erythropoiesis stimulating agents | Venous thromboembolism | - | - | RR: 1.87 (0.59, 5.92) | RR: 1.92 (0.64, 5.76) |
| Mesgarpour 2017 (41) | Erythropoiesis stimulating agents | Mortality | RR: 0.81 (0.71, 0.93) | RR: 0.82 (0.71, 0.93) | RR: 1.07 (0.65, 1.77) | RR: 1.08 (0.66, 1.78) |
| Molnar 2015 (43) | Neoral (cyclosporine) | Acute rejection of kidney transplant | OR: 1.23 (0.64, 2.36) | OR: 1.25 (0.61, 2.56) | - | OR: 0.46 (0.25, 0.86) |
| Study        | Intervention/Procedure                                      | Outcome/Secondary Outcome | OR (95% CI) | CI (95% CI) | p-Value |
|--------------|-------------------------------------------------------------|----------------------------|-------------|------------|---------|
| Navarese 2013 (44) | Early intervention for NSTE-ACS                           | Myocardial infarction      | OR: 1.15 (0.65, 2.01) | OR: 1.16 (0.67, 2.00) | -       |
| Nelson 2010 (45)    | Caesarean section                                          | Anal incontinence, feces   | -           | -          | -       |
| Nelson 2010 (45)    | Caesarean section                                          | Anal incontinence, flatus  | -           | -          | -       |
| Nieuwenhuijse 2014 (46) | Ceramic-on-ceramic bearings for total hip arthroplasty | Harris Hip Score           | MD: -0.23 (-1.09, 0.63)^4 | - | MD: -0.50 (-2.09, 1.09)^4 |
| Nieuwenhuijse 2014 (46) | High-flexion total knee arthroplasty                      | Flexion (degrees)          | MD: 1.68 (0.28, 3.08)^4 | - | MD: 3.78 (1.64, 5.92)^4 |
| Nieuwenhuijse 2014 (46) | Gender-specific total knee arthroplasty                   | Flexion-extension range (degrees) | MD: 1.40 (-0.18, 2.99)^1,4 | - | MD: 3.15 (-0.03, 6.34)^1,4 |
| Nikooie 2019 (47)   | Second generation antipsychotics                          | Sedation                   | -           | -          | -       |
| Nikooie 2019 (47)   | Second generation antipsychotics                          | Neurologic outcomes        | -           | -          | -       |
| Ochen 2019 (48)     | Surgery for achilles tendon rupture                        | Re-rupture                 | -           | -          | RR: 0.42 (0.28, 0.64) |
| Ochen 2019 (48)     | Surgery for achilles tendon rupture                        | Complications              | RR: 3.26 (1.26, 8.41) | RR: 3.13 (1.33, 7.38) | -       |
| Raman 2013 (50)     | Carotid endarterectomy                                    | Ipsilateral stroke         | -           | -          | RR: 0.47 (0.05, 4.46)^1 |
| Raman 2013 (50)     | Carotid endarterectomy                                    | Any stroke                 | -           | -          | RR: 0.73 (0.43, 1.22)^1 |
| Raman 2013 (50)     | Carotid artery stenting                                   | Periprocedural stroke      | -           | RR: 1.75 (0.87, 3.52)^3 | -       |
| Schweizer 2013 (51) | Nasal deconolization                                     | Surgical site infection    | RR: 0.63 (0.63, 1.13) | RR: 0.63 (0.36, 1.12) | -       |
| Schweizer 2013 (51) | Glycopeptide prophylaxis                                  | Surgical site infection    | -           | -          | RR: 0.34 (0.11, 1.10) |
| Silvain 2012 (52)   | Enoxaparin                                                | Mortality                  | -           | RR: 0.88 (0.70, 1.10)^4 | -       |

^1 p < 0.05, ^3 p < 0.01, ^4 p < 0.001
| Study                          | Intervention                                                        | Outcome/Effect                                      | RR/HR (95% CI)                                    | MD (95% CI) |
|-------------------------------|---------------------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------|-------------|
| Silvain 2012 (52)             | Enoxaparin                                                         | Major bleeding                                      | RR: 0.88 (0.62, 1.24)                           |             |
|                               |                                                                     | Death or Myocardial infarction                      | RR: 0.86 (0.74, 0.99)                           |             |
| Suthar 2012 (53)              | Antiretroviral therapy                                             | Tuberculosis infection                              | HR: 0.50 (0.34, 0.75)                           |             |
| Te Morenga 2013 (54)          | High sugar intake                                                 | Weight gain (kg)                                   | MD: 0.75 (0.30, 1.19)                           | MD: 0.74 (0.30, 1.19) |
| Te Morenga 2013 (54)          | High sugar intake                                                 | Body Mass Index (kg/m²)                            | MD: -0.06 (-0.15, 0.04)                         |             |
| Tickell-Painter 2017 (56)     | Mefloquine                                                         | Discontinuation due to adverse effects             | RR: 0.70 (0.14, 3.53)                           | RR: 0.68 (0.11, 4.27) |
|                               |                                                                     | Serious adverse events or effects                   | RR: 0.70 (0.14, 3.53)                           | RR: 0.68 (0.11, 4.27) |
| Tickell-Painter 2017 (56)     | Mefloquine                                                         | Nausea                                             | RR: 1.35 (1.05, 1.73)                           | RR: 1.34 (1.04, 1.71) |
|                               |                                                                     |                                                     | RR: 1.85 (1.42, 2.43)                           | RR: 1.86 (1.42, 2.42) |
| Tricco 2018 (57)              | Live-attenuated zoster vaccines                                    | Suspected Herpes Zoster                            | RR: 0.61 (0.48, 0.93)                           | RR: 0.60 (0.54, 0.66) |
|                               |                                                                     |                                                     | RR: 0.48 (0.27, 0.84)                           | RR: 0.48 (0.27, 0.83) |
| Wilson 2011 (59)              | Training for traditional birth attendants/assistance by traditional birth attendants | Perinatal mortality                                | RR: 0.76 (0.64, 0.88)                           | RR: 0.77 (0.66, 0.89) |
| Wilson 2011 (59)              | Training for traditional birth attendants/assistance by traditional birth attendants | Neonatal mortality                                 | RR: 0.79 (0.69, 0.88)                           | RR: 0.80 (0.71, 0.90) |
| Wilson 2019 (60)              | Unilateral knee arthroplasty                                       | Venous thromboembolism                             | -                                                |             |
| Wilson 2019 (60)              | Unilateral knee arthroplasty                                       | Range of movement (degrees)                        | -                                                |             |
| Wilson 2019 (60)              | Unilateral knee arthroplasty                                       | Operation duration (minutes)                       | -                                                |             |

1. 1-sided 95% CI
2. 2-sided 95% CI
| Study Year | Treatment  | Event Type                          | RR (95% CI)          | OR (95% CI)          | HR (95% CI)          | CI: confidence interval; DDP 4: Dipeptidylpeptidase-4; HIV: human immunodeficiency virus; HR: hazard ratio; MD: mean difference; NSTE-ACS: Non–ST-Segment Elevation Acute Coronary Syndromes; OR: odds ratio; RCT: randomized controlled trial; RE: random effects; RR: risk ratio; SGLT-2: Sodium dependent glucose transporter 2. *some estimates were converted (detailed description is reported elsewhere (65)).  
1 Only re-calculated data is shown since we excluded some primary studies from the original estimate due to inappropriate study design.  
2 Pooled estimate includes observational analysis of randomized controlled trials.  
3 Primary studies were not pooled in the original paper.  
4 In the original paper cohort studies and randomized controlled trials were pooled together (sometimes without a subgroup).  
5 Re-analysis with unpublished data.  
6 Data converted (risk difference to risk ratio).  
7 In the original paper common effects were reported, we calculated estimates with random effects model.  |
| Systematic Review     | Intervention/Exposure                                      | Outcome                                          | Reason for exclusion                                      |
|-----------------------|------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------|
| Abou-Setta 2011 (1)   | Nerve block                                               | Delirium (OR)                                    | Forest plots not available                                |
| Abou-Setta 2011 (1)   | Spinal anaesthesia                                        | Mortality (OR)                                   | Forest plots not available                                |
| Alexander 2017 (4)    | High docosahexaenoic acid and eicosapentaenoic acid       | Any coronary heart disease event (RR)            | Forest plots not available                                |
| Alexander 2017 (4)    | High docosahexaenoic acid and eicosapentaenoic acid       | Fatal coronary heart disease events (RR)         | Forest plots not available                                |
| Alexander 2017 (4)    | High docosahexaenoic acid and eicosapentaenoic acid       | Non-fatal coronary heart disease events (RR)     | Forest plots not available                                |
| Chowdhury 2014b (16)  | High vitamin D                                            | Mortality (RR)                                   | Forest plot not available for RCTs                        |
| Chung 2011 (17)       | High vitamin D                                            | Colorectal cancer (RR)                           | Forest plots not available                                |
| Chung 2011 (17)       | High vitamin D                                            | Breast cancer (RR)                               | Forest plots not available                                |
| Johnston 2019 (33)    | Low red meat                                              | Mortality (HR)                                   | Forest plot not available for cohort studies              |
| Johnston 2019 (33)    | Low red meat                                              | Cardiovascular mortality (HR)                    | Forest plot not available for cohort studies              |
| Johnston 2019 (33)    | Low red meat                                              | Cardiovascular disease (HR)                      | Forest plot not available for cohort studies              |

HR: Hazard ratio; OR: Odds ratio; RCT: randomized controlled trial; RR: Risk ratio;
**Table S5:** Pooling results of bodies of evidence from cohort studies with RCTs based on random effects and common effect model, 95% prediction intervals, heterogeneity, test for subgroup difference, and Population (P), Intervention (I) / Exposure (E), Comparator (C) Outcome similarity degree.

| Author, year, and reference | Intervention/ Exposure | Outcome | BoE CSs, n | Effect estimate (95% CI) | $I^2$ (%) / tau² | Pooled effect estimate (95%) RE (95% prediction interval) | $I^2$ (%) / tau² | Weight CS (%) | CS conclusion modified | Pooled effect estimate (95%) CE | Degree of PI/ECO similarity* |
|-----------------------------|------------------------|---------|------------|--------------------------|-----------------|----------------------------------------------------------|-----------------|---------------|----------------------|---------------------------------|-----------------------------|
| Aburto 2013 (2)             | Low sodium             | Mortality | 7          | RR: 0.94 (0.83, 1.06)    | 61/ 0.02        | RR: 0.93 (0.83, 1.04) / (0.68, 1.26)                     | 47/ 0.02        | 95.0          | No                   | RR: 0.94 (0.88, 1.00)            | 2                           |
| Aburto 2013 (2)             | Low sodium             | Cardiovascular disease | 9          | RR: 0.90 (0.75, 1.08)    | 78/ 0.07        | RR: 0.89 (0.75, 1.06) / (0.49, 1.62)                     | 74/ 0.07        | 91.3          | No                   | RR: 0.86 (0.80, 0.93)            | 2                           |
| Ahmad 2015 (3)              | Intra-aortic balloon pump | Mortality | 14         | OR: 1.02 (0.57, 1.82)   | 97/ 1.03        | OR: 1.02 (0.67, 1.56) / (0.14, 7.32)                    | 95/ 0.86        | 62.2          | No                   | OR: 0.76 (0.72, 0.82)            | 1                           |
| Alipanah 2018 (5)           | Self-administered therapy | Treatment success | 16         | RR: 0.81 (0.74, 0.88)   | 91/ 0.02        | RR: 0.84 (0.78, 0.90) / (0.62, 1.14)                    | 89/ 0.02        | 80.9          | No                   | RR: 0.92 (0.90, 0.94)            | 3                           |
| Alipanah 2018 (5)           | Self-administered therapy | Treatment completion | 14         | RR: 1.10 (0.91, 1.33)   | 86/ 0.07        | RR: 1.02 (0.84, 1.23) / (0.51, 2.02)                    | 88/0.10        | 75.6          | No                   | RR: 1.12 (1.07, 1.17)            | 3                           |
| Alipanah 2018 (5)           | Self-administered therapy | Mortality | 23         | RR: 1.35 (1.00, 1.83)   | 90/ 0.34        | RR: 1.26 (0.95, 1.67) / (0.37, 4.28)                    | 88/ 0.33        | 90.2          | No                   | RR: 1.26 (1.18, 1.34)            | 3                           |
| Anglemyer 2013 (6)          | Antiretroviral therapy  | HIV infection | 9          | RR: 0.59 (0.36, 0.97)   | 63/ 0.25        | RR: 0.45 (0.26, 0.78) / (0.09, 2.31)                    | 75/ 0.42        | 88.2          | No                   | RR: 0.72 (0.64, 0.82)            | 3                           |
| Azad 2017 (7)               | Non-nutritive sweeteners | BMI      | 1          | MD: 0.77 (0.47, 1.07)   | NA              | MD: 0.23 (-0.77, 1.23) / (-3.88, 4.34)                  | 79/ 0.65        | 38.6          | Yes                  | MD: 0.53 (0.26, 0.80)            | 2                           |
| Barnard 2015 (8)            | Surgical abortion by mid-level providers | Failure or incomplete abortion | 2          | RR: 2.47 (1.44, 4.23)   | 0/ 0.00        | RR: 2.23 (1.15, 4.32) / (0.24, 20.54)                   | 33/ 0.15        | 65.5          | No                   | RR: 2.14 (1.35, 3.39)            | 2                           |
| Barnard 2015 (8)            | Surgical abortion by mid-level providers | Complications | 2          | RR: 1.30 (0.57, 2.96)   | 70/ 0.26        | RR: 1.31 (0.70, 2.42) / (0.17, 10.11)                   | 32/ 0.13        | 90.3          | No                   | RR: 1.51 (1.05, 2.17)            | 2                           |
| Study Year | Group 1 | Group 2 | Outcome | RR 95% CI | P Value | Effect Size | RR 95% CI | P Value | RR 95% CI | P Value |
|------------|---------|---------|---------|-----------|---------|-------------|-----------|---------|-----------|---------|
| Barnard 2015 (8) | Surgical abortion by mid-level providers | Abortion failure and complications | 3 | RR: 1.33 (0.78, 2.27) | 74/0.16 | 65/0.17 | 80.5 | No | RR: 1.43 (1.12, 1.82) | 2 |
| Bellemain-Appaix 2012 (9) | Clopidogrel pretreatment for percutaneous coronary intervention | Mortality | 8 | OR: 0.79 (0.53, 1.18) | 79/0.23 | 66/0.17 | 69.3 | No | OR: 0.65 (0.57, 0.75) | 2 |
| Bellemain-Appaix 2012 (9) | Clopidogrel pretreatment for percutaneous coronary intervention | Major bleeding | 8 | OR: 1.03 (0.69, 1.53) | 64/0.16 | 46/0.08 | 59.6 | No | OR: 1.07 (0.92, 1.24) | 2 |
| Bellemain-Appaix 2012 (9) | Clopidogrel pretreatment for percutaneous coronary intervention | Major coronary event | 8 | OR: 0.76 (0.60, 0.95) | 82/0.08 | 69/0.05 | 64.0 | No | OR: 0.78 (0.73, 0.85) | 2 |
| Bellemain-Appaix 2014 (10) | P2Y12 inhibitor pretreatment in non-ST elevation acute coronary syndrome | Mortality | 4 | OR: 0.69 (0.35, 1.32) | 35/0.17 | 10/0.01 | 33.2 | No | OR: 0.91 (0.80, 1.04) | 2 |
| Bellemain-Appaix 2014 (10) | P2Y12 inhibitor pretreatment in non-ST elevation acute coronary syndrome | Major bleeding | 4 | OR: 1.13 (0.92, 1.39) | 0/0.00 | 0/0.00 | 50.3 | No | OR: 1.27 (1.10, 1.47) | 2 |
| Bellemain-Appaix 2014 (10) | P2Y12 inhibitor pretreatment in non-ST elevation acute coronary syndrome | Main composite ischemic endpoint | 4 | OR: 0.78 (0.56, 1.08) | 65/0.07 | 52/0.02 | 45.0 | Yes | OR: 0.85 (0.78, 0.93) | 2 |
| Bloomfield 2016 (11) | Mediterranean diet | Breast cancer | 13 | RR: 0.96 (0.90, 1.03) | 52/0.01 | 57/0.01 | 99.1 | No | RR: 0.98 (0.95, 1.02) | 2 |
| Bolland 2015 (12) | High calcium | All fractures | 5 | RR: 1.02 (0.93, 1.12) | 68/0.01 | 50/0.01 | 42.0 | No | RR: 0.99 (0.96, 1.02) | 2 |
| Bolland 2015 (12) | High calcium | Vertebral fracture | 1 | RR: 1.40 (1.10, 1.78) | NA | 22/0.02 | 23.3 | Yes | RR: 0.98 (0.87, 1.11) | 2 |
| Bolland 2015 (12) | High calcium | Hip fracture | 6 | RR: 1.09 (0.91, 1.30) | 50/0.03 | 46/0.04 | 57.2 | No | RR: 0.98 (0.91, 1.07) | 2 |
| Study (Year) | Intervention | Outcome | RR (95% CI) | N | Mortality Rate | RR (95% CI) | N | Mortality Rate |
|-------------|--------------|---------|-------------|---|---------------|-------------|---|---------------|
| Brenner 2014 (13) | Sigmoidoscopy, screening for CRC | Colorectal cancer mortality | 1 | RR: 0.59 (0.45, 0.77) | NA | RR: 0.70 (0.64, 0.77) | 0/0.00 | 12.7 | No | RR: 0.70 (0.64, 0.77) | 1 |
| Brenner 2014 (13) | Sigmoidoscopy, screening for CRC | Colorectal cancer incidence | 2 | RR: 0.50 (0.37, 0.69) | 0/0.00 | RR: 0.78 (0.69, 0.89) | 65/0.01 | 11.0 | No | RR: 0.79 (0.74, 0.84) | 2 |
| Chowdhury 2012 (14) | High omega-3-fatty acids | Cerebrovascular disease | 10 | RR: 0.89 (0.80, 0.99) | 17/0.01 | RR: 0.93 (0.85, 1.01) | 21/0.00 | 59.3 | Yes | RR: 0.95 (0.89, 1.01) | 2 |
| Chowdhury 2014a (15) | High α-linolenic acid | Coronary event | 7 | RR: 0.99 (0.88, 1.11) | 61/0.02 | RR: 0.99 (0.88, 1.11) | 54/0.02 | 78.6 | No | RR: 1.01 (0.95, 1.08) | 3 |
| Chowdhury 2014a (15) | High omega-3-fatty acids | Coronary event | 16 | RR: 0.87 (0.78, 0.97) | 76/0.03 | RR: 0.90 (0.83, 0.97) | 61/0.02 | 61.9 | No | RR: 0.93 (0.89, 0.97) | 3 |
| Chowdhury 2014a (15) | High omega-6-fatty acids | Coronary event | 8 | RR: 0.98 (0.90, 1.06) | 54/0.01 | RR: 0.94 (0.87, 1.03) | 56/0.01 | 70.0 | No | RR: 0.96 (0.94, 1.01) | 3 |
| Chung 2016 (18) | High calcium | Cardiovascular disease mortality | 6 | RR: 0.97 (0.86, 1.09) | 37/0.01 | RR: 0.99 (0.92, 1.07) | 11/0.00 | 89.9 | No | RR: 1.01 (0.95, 1.07) | 2 |
| Ding 2017 (19) | High dairy | Systolic blood pressure | 27 | MD: -0.11 (-0.20, -0.02) | 30/0.01 | MD: -0.11 (-0.20, -0.03) | 24/0.01 | 98.8 | No | MD: -0.16 (-0.21, -0.11) | 2 |
| Fenton 2018 (20) | Radiation therapy | Erectile dysfunction | 7 | RR: 1.30 (1.19, 1.43) | 31/0.00 | RR: 1.24 (1.09, 1.41) | 70/0.02 | 85.7 | No | RR: 1.23 (1.15, 1.32) | 2 |
| Fenton 2018 (20) | Radical Prostatectomy | Urinary incontinence | 5 | RR: 2.91 (1.80, 4.71) | 67/0.18 | RR: 2.54 (1.97, 3.27) | 51/0.06 | 52.1 | No | RR: 2.46 (2.08, 2.90) | 2 |
| Fenton 2018 (20) | Radical Prostatectomy | Erectile dysfunction | 6 | RR: 1.49 (1.33, 1.66) | 63/0.01 | RR: 1.53 (1.37, 1.70) | 75/0.02 | 65.1 | No | RR: 1.50 (1.42, 1.58) | 2 |
| Filippini 2017 (21) | Disease-modifying drugs | Conversion to clinically definite multiple sclerosis | 2 | HR: 0.48 (0.30, 0.78) | 62/0.08 | HR: 0.53 (0.47, 0.59) | 0/0.00 | 70.0 | No | HR: 0.53 (0.47, 0.59) | 2 |
| Fluri 2010 (22) | Extracranial-intracranial arterial bypass | Mortality | 11 | OR: 0.97 (0.58, 1.62) | 0/0.00 | OR: 0.84 (0.66, 1.06) | 0/0.00 | 20.3 | No | OR: 0.84 (0.66, 1.06) | 2 |
| Study (Year) | Intervention | Outcome | Event Rate | RR/95% CI | Event Rate | RR/95% CI | p-value | RR/95% CI |
|-------------|--------------|---------|------------|-----------|------------|-----------|---------|-----------|
| Fluri 2010 (22) | Extracranial-intracranial arterial bypass | Any stroke | 15 | OR: 0.76 (0.49, 1.17) | 2/ 0.02 | OR: 0.77 (0.50, 1.17) | 29/ 0.17 | 67.5 | No | OR: 0.95 (0.78, 1.16) | 2 |
| Fluri 2010 (22) | Extracranial-intracranial arterial bypass | Death or dependency | 8 | OR: 0.81 (0.50, 1.31) | 0/ 0.00 | OR: 0.91 (0.73, 1.14) | 0/ 0.00 | 20.6 | No | OR: 0.91 (0.73, 1.14) | 2 |
| Gargiulo 2016 (23) | Transcatheter aortic valve implantation | Early mortality | 29 | OR: 1.08 (0.84, 1.39) | 41/ 0.16 | OR: 1.01 (0.81, 1.26) | 39/ 0.13 | 81.6 | No | OR: 1.02 (0.88, 1.19) | 2 |
| Gargiulo 2016 (23) | Transcatheter aortic valve implantation | Mid-term mortality | 18 | OR: 1.00 (0.81, 1.24) | 46/ 0.08 | OR: 0.96 (0.82, 1.13) | 40/ 0.05 | 71.0 | No | OR: 0.93 (0.83, 1.04) | 2 |
| Gargiulo 2016 (23) | Transcatheter aortic valve implantation | Long-term mortality | 6 | OR: 1.70 (1.31, 2.20) | 0/ 0.00 | OR: 1.28 (1.00, 1.65) | 62/ 0.08 | 46.7 | Yes | OR: 1.18 (1.03, 1.35) | 2 |
| Hartling 2013 (24) | Treating Gestational Diabetes Mellitus | Birth weight > 4000g | 6 | RR: 0.69 (0.31, 1.54) | 88/ 0.64 | RR: 0.58 (0.40, 0.86) | 79/ 0.25 | 48.3 | Yes | RR: 0.54 (0.46, 0.63) | 2 |
| Hartling 2013 (24) | Treating Gestational Diabetes Mellitus | Large-for-gestational age neonate | 4 | RR: 0.43 (0.27, 0.70) | 58/ 0.13 | RR: 0.47 (0.36, 0.62) | 60/ 0.07 | 49.8 | No | RR: 0.45 (0.39, 0.52) | 2 |
| Hartling 2013 (24) | Treating Gestational Diabetes Mellitus | Shoulder dystocia | 4 | RR: 0.38 (0.19, 0.75) | 16/ 0.09 | RR: 0.39 (0.26, 0.60) | 0/ 0.00 | 50.1 | No | RR: 0.39 (0.26, 0.60) | 2 |
| Henderson 2019 (25) | Treating asymptomatic bacteriuria | Pyelonephritis | 2 | RR: 0.29 (0.15, 0.57) | 0/ 0.00 | RR: 0.25 (0.16, 0.39) | 48/ 0.28 | 15.1 | No | RR: 0.30 (0.23, 0.40) | 3 |
| Higgins 2016 (26) | BCG | Mortality | 8 | RR: 0.46 (0.30, 0.69) | 63/ 0.19 | RR: 0.51 (0.36, 0.72) | 67/ 0.19 | 70.1 | No | RR: 0.57 (0.48, 0.68) | 3 |
| Higgins 2016 (26) | Measles containing vaccines | Mortality | 13 | RR: 0.53 (0.40, 0.70) | 67/ 0.14 | RR: 0.57 (0.45, 0.72) | 58/ 0.11 | 80.4 | No | RR: 0.65 (0.57, 0.74) | 3 |
| Hopley 2010 (27) | Total hip arthroplasty | Reoperation | 6 | RR: 0.45 (0.19, 1.08) | 23/ 0.28 | RR: 0.66 (0.33, 1.32) | 34/ 0.39 | 56.1 | No | RR: 0.72 (0.43, 1.20) | 2 |
| Hopley 2010 (27) | Total hip arthroplasty | Dislocation | 5 | RR: 0.79 (0.27, 2.35) | 18/ 0.28 | RR: 1.20 (0.52, 2.76) | 12/ 0.17 | 63.7 | No | RR: 1.16 (0.54, 2.52) | 2 |
| Study (Year) | Intervention | Outcome | RR with 95% CI | OR with 95% CI | P-value | Risk Difference | Comment |
|-------------|--------------|---------|----------------|----------------|---------|----------------|---------|
| Hopley 2010 (27) | Total hip arthroplasty | Deep infection | 4 | RR: 0.91 (0.25, 3.28) | 0/ 0.00 | RR: 1.37 (0.64, 2.94) | 0/ 0.00 | 35.9 | No | RR: 1.37 (0.64, 2.94) |
| Hüpf 2010 (28) | Chest-compression-only cardio-pulmonary resuscitation | Survival | 7 | RR: 0.96 (0.83, 1.11) | 0/ 0.00 | RR: 1.04 (0.92, 1.19) | 0/ 0.00 | 13/ 0.01 | 61.9 | No | RR: 1.05 (0.93, 1.18) |
| Jamal 2013 (29) | Non-calcium-based phosphate binders | Mortality | 3 | RR: 0.89 (0.78, 1.00) | 0/ 0.00 | RR: 0.87 (0.77, 0.97) | 28/ 0.01 | 49.1 | Yes | RR: 0.89 (0.82, 0.96) |
| Jefferson 2010 (30) | Parenteral influenza vaccine | Influenza-like illness | 30 | RR: 0.76 (0.66, 0.87) | 57/ 0.07 | RR: 0.73 (0.64, 0.82) | 54/ 0.06 | 85.6 | No | RR: 0.70 (0.65, 0.75) |
| Jefferson 2010 (30) | Parenteral influenza vaccine | Influenza | 10 | RR: 0.51 (0.27, 0.97) | 64/ 0.52 | RR: 0.51 (0.32, 0.80) | 59/ 0.34 | 68.7 | No | RR: 0.60 (0.47, 0.78) |
| Jefferson 2012 (31) | Inactivated influenza vaccines | Influenza | 1 | RR: 0.20 (0.10, 0.39) | NA | RR: 0.37 (0.26, 0.53) | 44/ 0.11 | 15.2 | No | RR: 0.34 (0.27, 0.43) |
| Jefferson 2012 (31) | Inactivated influenza vaccines | Influenza-like illness | 2 | RR: 0.29 (0.07, 1.15) | 95/ 1.43 | RR: 0.56 (0.46, 0.68) | 87/ 0.04 | 34.8 | Yes | RR: 0.74 (0.71, 0.77) |
| Jin 2012 (32) | High total flavonoids | Colorectal neoplasms | 3 | RR: 1.00 (0.80, 1.25) | 66/ 0.02 | RR: 1.03 (0.88, 1.20) | 56/ 0.01 | 69.6 | No | RR: 1.02 (0.93, 1.13) |
| Kansagara 2013 (34) | Transfusion | Mortality | 11 | RR: 2.49 (1.40, 4.43) | 97/ 0.94 | RR: 1.84 (1.10, 3.07) | 96/ 1.00 | 74.4 | No | RR: 3.32 (3.03, 3.65) |
| Keag 2018 (35) | Caesarean section | Urinary incontinence | 8 | OR: 0.56 (0.48, 0.66) | 70/ 0.04 | OR: 0.58 (0.50, 0.68) | 68/ 0.04 | 90.0 | No | OR: 0.62 (0.57, 0.67) |
| Keag 2018 (35) | Caesarean section | Fecal incontinence | 5 | OR: 1.04 (0.73, 1.48) | 72/ 0.10 | OR: 1.11 (0.78, 1.58) | 71/ 0.12 | 93.6 | No | OR: 1.11 (0.94, 1.31) |
| Kredo 2014 (36) | Antiretroviral therapy by nurses | Mortality | 2 | RR: 1.23 (1.14, 1.33) | 0/ 0.00 | RR: 1.13 (0.94, 1.36) | 76/ 0.02 | 64.7 | Yes | RR: 1.17 (1.10, 1.26) |
| Reference          | Intervention                                                                 | Outcome                  | RR  | 95% CI           | OR  | 95% CI           | Events | Event Rate | Outcome  | RR  | 95% CI            |
|-------------------|-------------------------------------------------------------------------------|--------------------------|-----|------------------|-----|------------------|--------|------------|-----------|-----|------------------|
| Kredo 2014 (36)   | Antiretroviral therapy by nurses                                              | Attrition                | 2   | RR: 0.30 (0.05, 1.94) | 98/ 1.77 | 65.6 | Yes | RR: 0.75 (0.71, 0.79) | 3   |
| Kredo 2014 (36)   | Nurses for maintenance of antiretroviral therapy                             | Mortality                | 1   | RR: 0.19 (0.05, 0.78) | NA | RR: 0.61 (0.28, 1.35) | 56/ 0.28 | 20.2 | Yes | RR: 0.79 (0.54, 1.16) | 3   |
| Li 2014 (37)      | Exenatide                                                                     | Acute pancreatitis/ Admission for acute pancreatitis | 2   | RR: 0.92 (0.69, 1.22) | 0/0.00 | RR: 0.92 (0.69, 1.22) | 0/0.00 | 96.0 | No | RR: 0.92 (0.69, 1.21) | 2   |
| Li 2016 (38)      | DDP-4 Inhibitors                                                             | Heart failure            | 4   | RR: 1.10 (1.04, 1.17) | 0/0.00 | RR: 1.10 (1.04, 1.17) | 0/0.00 | 98.4 | No | RR: 1.10 (1.04, 1.17) | 2   |
| Li 2016 (38)      | DDP-4 Inhibitors                                                             | Hospital admission for heart failure | 6   | OR: 0.85 (0.74, 0.97) | 33/0.01 | OR: 0.74 (0.83, 1.08) | 55/0.02 | 58.1 | Yes | OR: 0.97 (0.90, 1.05) | 2   |
| Matthews 2018 (39)| Tamoxifen                                                                     | Heart failure            | 2   | RR: 0.85 (0.66, 1.09) | 10/0.00 | RR: 0.74 (0.53, 1.04) | 59/0.05 | 70.5 | No | RR: 0.75 (0.61, 0.92) | 3   |
| Menne 2019 (40)   | SGLT-2 inhibitors                                                            | Acute kidney injury      | 5   | OR: 0.40 (0.31, 0.52) | 39/0.03 | OR: 0.58 (0.49, 0.69) | 27/0.05 | 36.9 | No | OR: 0.62 (0.56, 0.68) | 2   |
| Mesgarpour 2017 (41)| Erythropoiesis stimulating agents                                           | Venous thromboembolism  | 5   | RR: 1.92 (0.64, 5.76) | 75/1.03 | RR: 1.26 (0.76, 2.10) | 84/0.70 | 28.4 | No | RR: 1.71 (1.45, 2.01) | 2   |
| Mesgarpour 2017 (41)| Erythropoiesis stimulating agents                                           | Mortality                | 7   | RR: 1.08 (0.66, 1.78) | 91/0.35 | RR: 0.88 (0.64, 1.21) | 92/0.46 | 33.5 | No | RR: 2.20 (2.15, 2.25) | 2   |
| Moberley 2013 (42)| Pneumococcal polysaccharide vaccines                                        | Invasive pneumococcal disease | 2   | OR: 0.57 (0.36, 0.89) | 0/0.00 | OR: 0.40 (0.26, 0.61) | 12/0.07 | 51.9 | No | OR: 0.42 (0.29, 0.59) | 2   |
| Molnar 2015 (43)  | Neoral (cyclosporine)                                                        | Acute rejection of kidney transplant | 2   | OR: 0.46 (0.25, 0.86) | 5/0.02 | OR: 0.74 (0.36, 1.54) | 56/0.29 | 50.4 | Yes | OR: 0.71 (0.46, 1.10) | 2   |
| Navarese 2013 (44)| Early intervention for NSTE-ACS                                              | Mortality                | 4   | OR: 0.80 (0.63, 1.02) | 78/0.04 | OR: 0.82 (0.69, 0.97) | 45/0.03 | 74.8 | Yes | OR: 0.86 (0.80, 0.94) | 2   |
| Navarese 2013 (44)| Early intervention for NSTE-ACS                                              | Myocardial infarction    | 3   | OR: 0.86 (0.69, 1.08) | 86/0.03 | OR: 0.97 (0.77, 1.22) | 81/0.08 | 49.4 | No | OR: 0.90 (0.83, 0.97) | 2   |
| Study                          | Category                          | Outcome                  | No. | RR (95% CI) | MD (95% CI) | OR (95% CI) | OR (95% CI) | Outcome |
|-------------------------------|-----------------------------------|--------------------------|-----|-------------|-------------|-------------|-------------|----------|
| Navarese 2013 (44)            | Early intervention for NSTE-ACS   | Major bleeding           | 3   | OR: 1.12    |             | OR: 0.92    |             | 92/0.17  |
|                               |                                   |                          |     | (0.69, 1.82)|             | (0.68, 1.24)|             | 70/0.11  |
|                               |                                   |                          |     |             |             | (0.39, 2.15)|             | 56.3     |
|                               |                                   |                          |     |             |             |             |             | No       |
|                               |                                   |                          |     |             |             |             |             | OR: 1.00 |
|                               |                                   |                          |     |             |             |             |             | (0.88, 1.13)|         |
| Nelson 2010 (45)              | Caesarean section                 | Anal incontinence, feces| 12  | OR: 0.91    |             | OR: 0.92    |             | 0/0.00   |
|                               |                                   |                          |     | (0.72, 1.16)|             | (0.74, 1.16)|             | 90.0     |
|                               |                                   |                          |     |             |             | (0.72, 1.19)|             | No       |
|                               |                                   |                          |     |             |             |             |             | OR: 0.92 |
|                               |                                   |                          |     |             |             |             |             | (0.74, 1.16)|         |
| Nelson 2010 (45)              | Caesarean section                 | Anal incontinence, flatus| 4   | OR: 1.02    |             | OR: 1.00    |             | 0/0.00   |
|                               |                                   |                          |     | (0.87, 1.20)|             | (0.86, 1.16)|             | 90.3     |
|                               |                                   |                          |     |             |             | (0.78, 1.28)|             | No       |
|                               |                                   |                          |     |             |             |             |             | OR: 1.00 |
|                               |                                   |                          |     |             |             |             |             | (0.86, 1.16)|         |
| Nieuwenhuijse 2014 (46)       | Ceramic-on-ceramic bearings for total hip arthroplasty | Harris Hip Score | 3   | MD: -0.50   | 62/ 1.08    | MD: -0.29   | 32/ 0.31    | 40.7     |
|                               |                                   |                          |     | (-2.09, 1.09)|             | (-0.96, 0.38)|             | No       |
|                               |                                   |                          |     |             |             | (-1.81, 1.22)|             | MD: -0.20 |
|                               |                                   |                          |     |             |             |             |             | (-0.66, 0.26)|         |
| Nieuwenhuijse 2014 (46)       | High-flexion total knee arthroplasty | Flexion (degrees) | 26  | MD: 3.78    | 78/ 19.12  | MD: 2.91    | 73/ 12.7    | 53.2     |
|                               |                                   |                          |     | (1.64, 5.92)|             | (1.56, 4.27)|             | No       |
|                               |                                   |                          |     |             |             | (-4.42, 10.25)|             | MD: 2.49  |
|                               |                                   |                          |     |             |             |             |             | (1.84, 3.14)|         |
| Nieuwenhuijse 2014 (46)       | Gender-specific total knee arthroplasty | Flexion-extension range (degrees) | 2   | MD: 3.15    | 29/ 1.58    | MD: 1.80    | 9/ 0.40     | 25.6     |
|                               |                                   |                          |     | (-0.03, 6.34)|             | (0.40, 3.21)|             | Yes      |
|                               |                                   |                          |     |             |             | (-0.53, 4.14)|             | MD: 1.85  |
|                               |                                   |                          |     |             |             |             |             | (0.54, 3.16)|         |
| Nikooie 2019 (47)             | Second generation antipsychotics | Sedation                | 3   | RR: 1.84    | 34/ 0.84    | RR: 1.29    | 0/0.00      | 6.0      |
|                               |                                   |                          |     | (0.40, 8.54)|             | (0.95, 1.74)|             | No       |
|                               |                                   |                          |     |             |             | (0.91, 1.83)|             | RR: 1.29  |
|                               |                                   |                          |     |             |             |             |             | (0.95, 1.74)|         |
| Nikooie 2019 (47)             | Second generation antipsychotics | Neurologic outcomes      | 5   | RR: 0.76    | 0/0.00      | RR: 0.73    | 0/0.00      | 91.0     |
|                               |                                   |                          |     | (0.59, 0.99)|             | (0.57, 0.93)|             | No       |
|                               |                                   |                          |     |             |             | (0.56, 0.95)|             | RR: 0.73  |
|                               |                                   |                          |     |             |             |             |             | (0.57, 0.93)|         |
| Ochen 2019 (48)               | Surgery for achilles tendon rupture | Re-rupture              | 18  | RR: 0.42    | 30/0.19     | RR: 0.43    | 21/0.12     | 69.6     |
|                               |                                   |                          |     | (0.28, 0.65)|             | (0.31, 0.60)|             | No       |
|                               |                                   |                          |     |             |             | (0.20, 0.96)|             | RR: 0.65  |
|                               |                                   |                          |     |             |             |             |             | (0.54, 0.79)|         |
| Ochen 2019 (48)               | Surgery for achilles tendon rupture | Complications            | 15  | RR: 2.93    | 0/0.00      | RR: 2.72    | 41/0.28     | 57.8     |
|                               |                                   |                          |     | (2.28, 3.75)|             | (1.84, 4.02)|             | No       |
|                               |                                   |                          |     |             |             | (0.84, 8.82)|             | RR: 2.63  |
|                               |                                   |                          |     |             |             |             |             | (2.13, 3.27)|         |
| Pittas 2010 (49)              | High vitamin D                    | Hypertension             | 3   | RR: 0.57    | 0/0.00      | RR: 0.68    | 77/0.14     | 61.8     |
|                               |                                   |                          |     | (0.41, 0.79)|             | (0.43, 1.07)|             | Yes      |
|                               |                                   |                          |     |             |             | (0.10, 4.51)|             | RR: 1.00  |
|                               |                                   |                          |     |             |             |             |             | (0.95, 1.05)|         |
| Raman 2013 (50)               | Carotid endarterectomy            | Ipsilateral stroke       | 2   | RR: 0.47    | 83/2.19     | RR: 0.70    | 38/0.05     | 11.9     |
|                               |                                   |                          |     | (0.05, 4.46)|             | (0.51, 0.97)|             | Yes      |
|                               |                                   |                          |     |             |             | (0.29, 1.69)|             | RR: 0.72  |
|                               |                                   |                          |     |             |             |             |             | (0.58, 0.89)|         |
| Raman 2013 (50)               | Carotid endarterectomy            | Any stroke               | 3   | RR: 0.73    | 0/0.00      | RR: 0.67    | 0/0.00      | 9.7      |
|                               |                                   |                          |     | (0.43, 1.22)|             | (0.57, 0.79)|             | Yes      |
|                               |                                   |                          |     |             |             | (0.53, 0.84)|             | RR: 0.67  |
|                               |                                   |                          |     |             |             |             |             | (0.57, 0.79)|         |
| Author          | Year  | Study Intervention | Outcomes                  | RR (CI)                  | p-value | Odds Ratio (CI) | p-value | Event Rate   | Outcome   | Note (RR) (CI) |
|-----------------|-------|--------------------|---------------------------|--------------------------|---------|----------------|---------|--------------|-----------|---------------|
| Raman 2013      | 50    | Carotid artery stenting | Periprocedural stroke    | RR: 1.91 (1.72, 2.11)    | 7/0.00  | 98.2 | No | RR: 1.91 (1.74, 2.10) | 2   |
| Schweizer 2013  | 51    | Nasal deconolization | Surgical site infection  | RR: 0.40 (0.28, 0.57)    | 0/0.00  | 44/0.15 | No | RR: 0.54 (0.42, 0.69) | 2   |
| Schweizer 2013  | 51    | Glycopeptide prophylaxis | Surgical site infection  | RR: 0.35 (0.12, 1.03)    | 80/1.44 | 62/0.25 | No | RR: 1.04 (0.66, 1.24) | 2   |
| Silvain 2012    | 52    | Enoxaparin         | Mortality                | RR: 0.50 (0.40, 0.62)    | 0/0.00  | 46/0.08 | No | RR: 0.66 (0.56, 0.77) | 2   |
| Silvain 2012    | 52    | Enoxaparin         | Major bleeding           | RR: 0.72 (0.56, 0.93)    | 0/0.00  | 30/0.05 | Yes | RR: 0.84 (0.72, 0.98) | 2   |
| Silvain 2012    | 52    | Enoxaparin         | Death or Myocardial infarction | RR: 0.44 (0.35, 0.55)  | 0/0.00  | 58/0.07 | No | RR: 0.77 (0.71, 0.85) | 2   |
| Suthar 2012     | 53    | Antiretroviral therapy | Tuberculosis infection   | HR: 0.32 (0.23, 0.41)   | 27/0.03 | 26/0.03 | No | HR: 0.37 (0.31, 0.44) | 3   |
| Te Morenga 2013 | 54    | High sugar intake  | Weight gain (kg)         | MD: 0.31 (-0.07, 0.68)   | 99/0.14 | NA   | Yes | MD: 0.59 (0.58, 0.60) | 2   |
| Te Morenga 2013 | 54    | High sugar intake  | BMI (kg/m²)              | MD: -0.02 (-0.05, 0.00)  | 74/0.00 | 58/0.00 | No | MD: -0.01 (-0.03, -0.00) | 2   |
| Thomas 2010     | 55    | Influenza vaccines | Influenza-like illness   | RR: 0.31 (0.26, 0.36)    | NA      | 94/0.28 | 24.5 | No | RR: 0.48 (0.43, 0.53) | 3   |
| Tickell-Painter 2017 | 56 | Mefloquine        | Discontinuation due to adverse effects | RR: 2.73 (1.84, 4.06) | 31/0.11 | 15/0.04 | 79.2 | No | RR: 2.85 (2.19, 3.71) | 2   |
| Tickell-Painter 2017 | 56 | Mefloquine        | Serious adverse events or effects | RR: 3.09 (0.38, 24.95) | 0/0.00 | 0/0.00 | 43.7 | No | RR: 1.31 (0.33, 5.23) | 3   |
| Tickell-Painter 2017 | 56 | Mefloquine        | Nausea                    | RR: 1.86 (1.42, 2.42)    | 0/0.00  | 0/0.00 | 46.3 | No | RR: 1.56 (1.30, 1.87) | 3   |
| Study          | Intervention                                | Outcome                  | RR (95% CI) | P value | RR (95% CI) | P value | RR (95% CI) | P value | RR (95% CI) | P value | RR (95% CI) | P value |
|---------------|---------------------------------------------|--------------------------|-------------|---------|-------------|---------|-------------|---------|-------------|---------|-------------|---------|
| Tricco 2018   | Live-attenuated zoster vaccines             | Suspected Herpes Zoster  | 3           | 0.48 (0.27, 0.83) | 99/ 0.24 | 0.55 (0.40, 0.77) | 97/ 0.14 | 0.72 (0.70, 0.74) | 2       |
| Vinceti 2018  | Selenium                                    | Any cancer               | 7           | 0.72 (0.55, 0.93) | 46/ 0.06 | 0.86 (0.73, 1.01) | 64/ 0.04 | 0.94 (0.88, 1.01) | 3       |
| Vinceti 2018  | Selenium                                    | Cancer mortality         | 7           | 0.76 (0.59, 0.97) | 66/ 0.07 | 0.78 (0.64, 0.95) | 65/ 0.05 | 0.88 (0.80, 0.96) | 3       |
| Vinceti 2018  | Selenium                                    | Colorectal cancer        | 6           | 0.82 (0.72, 0.94) | 0/ 0.00  | 0.83 (0.74, 0.94) | 0/ 0.00  | 0.83 (0.74, 0.94) | 3       |
| Wilson 2011   | Training for traditional birth attendants   | Perinatal mortality      | 1           | 0.82 (0.38, 1.78) | NA       | 0.77 (0.67, 0.89) | 52/ 0.01 | 0.79 (0.73, 0.86) | 3       |
| Wilson 2011   | Training for traditional birth attendants   | Neonatal mortality       | 2           | 0.80 (0.47, 1.37) | 0/ 0.00  | 0.80 (0.67, 0.95) | 14.0/ 0.00 | 0.80 (0.74, 0.87) | 3       |
| Wilson 2019   | Unilateral knee arthroplasty                | Venous thromboembolism   | 8           | 0.42 (0.30, 0.57) | 24/ 0.04 | 0.43 (0.33, 0.55) | 8/ 0.01  | 0.45 (0.37, 0.54) | 2       |
| Wilson 2019   | Unilateral knee arthroplasty                | Range of movement        | 11          | -8.43 (-10.15, -6.71) | 86/ 6.20 | -7.60 (-9.27, -5.93) | 91/ 7.85 | -8.29 (-8.63, -7.95) | 2       |
| Wilson 2019   | Unilateral knee arthroplasty                | Operation duration       | 8           | -23.80 (-40.43, -7.17) | 99/ 491.19 | -17.07 (-29.11, -5.04) | 98/ 365.45 | -11.25 (-12.71, -9.97) | 2       |
| Yank 2011     | Recombinant factor VII                      | Mortality                | 2           | 0.91 (0.39, 2.12) | 0/ 0.00  | 1.08 (0.56, 2.09) | 0/ 0.00  | 1.08 (0.56, 2.09) | 2       |
| Yank 2011     | Recombinant factor VII                      | Thromboembolic events    | 2           | 1.81 (0.67, 4.87) | 0/ 0.00  | 1.88 (0.85, 4.16) | 0/ 0.00  | 1.88 (0.85, 4.16) | 2       |
| Study (Year) | Drug/Treatment                          | Outcome                  | Effect Size | CI         | p Value | Evidence | RR          | CI         | p Value | Evidence |
|-------------|-----------------------------------------|---------------------------|-------------|------------|---------|----------|-------------|------------|---------|----------|
| Zhang 2016 (62) | Everolimus-eluting bioresorbable vascular scaffold | Stent thrombosis         | 3           | OR: 2.22  (1.00, 4.93) | 0/ 0.00 | Yes      | OR: 2.09  (1.20, 3.64) | 0/ 0.00 | 48.9 | Yes      |
| Zhang 2016 (62) | Everolimus-eluting bioresorbable vascular scaffold | Mortality                | 4           | OR: 0.63  (0.24, 1.63) | 0/ 0.00 | Yes      | OR: 0.73  (0.34, 1.57) | 15/ 0.20 | 48.3 | No       |
| Zhang 2016 (62) | Everolimus-eluting bioresorbable vascular scaffold | Cardiac death            | 4           | OR: 0.94  (0.43, 2.06) | 0/ 0.00 | Yes      | OR: 1.05  (0.53, 2.12) | 0/ 0.00 | 78.6 | No       |
| Zhang 2017 (63) | Percutaneous coronary intervention       | Mortality                | 17          | HR: 1.07  (0.92, 1.26) | 37/ 0.03 | No       | HR: 1.05  (0.93, 1.20) | 32/ 0.03 | 74.4 | No       |
| Zhang 2017 (63) | Percutaneous coronary intervention       | Cardiovascular mortality  | 5            | HR: 1.08  (0.51, 2.28) | 78/ 0.49 | No       | HR: 1.05  (0.69, 1.59) | 72/ 0.25 | 48.8 | No       |
| Zhang 2017 (63) | Percutaneous coronary intervention       | Myocardial infarction     | 5            | HR: 2.00  (1.65, 2.44) | 0/ 0.00 | No       | HR: 1.69  (1.22, 2.33) | 57/ 0.12 | 46.3 | No       |
| Ziff 2015 (64)  | Digoxin                                 | Mortality                | 8            | RR: 1.60  (1.31, 1.96) | 63/ 0.05 | No       | RR: 1.38  (1.15, 1.66) | 75/ 0.06 | 69.8 | No       |
| Ziff 2015 (64)  | Digoxin                                 | Cardiovascular mortality  | 3            | RR: 2.53  (1.12, 5.70) | 96/ 0.48 | No       | RR: 1.71  (1.04, 2.80) | 96/ 0.29 | 58.1 | No       |
| Ziff 2015 (64)  | Digoxin                                 | Hospital admission        | 4            | RR: 0.92  (0.85, 0.99) | 64/ 0.00 | No       | RR: 0.93  (0.88, 0.98) | 61/ 0.00 | 62.2 | No       |

BCG: Bacillus Calmette-Guérin; BMI: Body Mass Index; BoE: Bodies of Evidence; CE: Common Effects; CI: Confidence Interval; CRC: Colorectal Cancer; CS: Cohort Studies; DDP 4: Dipeptidylpeptidase-4; HIV: Human Immunodeficiency Virus; HR: Hazard Ratio; MD: Mean Difference; NA: Not Applicable; NSTE-ACS: Non–ST-Segment Elevation Acute Coronary Syndromes; OR: Odds Ratio; PI/ECO: Population – Intervention/Exposure – Comparator – Outcome; RCT: Randomized Controlled Trial; RE: Random Effects; RR: Risk Ratio; SGLT-2: Sodium Dependent Glucose Transporter 2;
**Figure S1**: Aburto 2013; Intervention/Exposure: Low sodium; Outcome: All-cause mortality
Figure S2: Aburto 2013; Intervention/Exposure: Low-sodium; Outcome: Cardiovascular disease
Figure S3: Ahmad 2015; Intervention/ Exposure: Intra-aortic balloon pump; Outcome: All-cause mortality
### Figure S4: Alipanah 2018

**Intervention/Exposure:** Self-administered therapy  
**Outcome:** Treatment success (Risk Ratio >1 indicates a favorable effect)**

| Study or Subgroup | Weight | IV, Random, 95% CI | Risk Ratio | Weight | IV, Random, 95% CI |
|-------------------|--------|---------------------|------------|--------|---------------------|
| **6.1.1 RCTs**    |        |                     |            |        |                     |
| Kamolratnarakul   | 6.6%   | 0.90 [0.84, 0.97]   |            |        |                     |
| Valleroy 2001a    | 5.8%   | 1.01 [0.89, 1.15]   |            |        |                     |
| Zwarenesen 1998   | 2.9%   | 1.19 [0.85, 1.66]   |            |        |                     |
| Zwarenesen 2000   | 3.5%   | 0.91 [0.68, 1.20]   |            |        |                     |
| **Subtotal (95% CI)** | 19.1% | 0.95 [0.87, 1.03]   |            |        |                     |
| **Heterogeneity** | Tau² = 0.00; Chi² = 3.58; df = 3 (p = 0.26); I² = 25% |            | Test for overall effect: Z = 1.22 (p = 0.22) |

| **6.1.2 Cohort studies** |        |                     |            |        |                     |
| Akkari 1999          | 5.8%   | 0.83 [0.73, 0.94]   |            |        |                     |
| Ar suwadontrisksale 2008 | 7.0%   | 0.78 [0.74, 0.83]   |            |        |                     |
| Covercante 2007      | 7.0%   | 0.96 [0.82, 1.10]   |            |        |                     |
| Chung 2007           | 5.5%   | 0.70 [0.50, 1.02]   |            |        |                     |
| Daniel 2006          | 5.0%   | 0.67 [0.55, 0.81]   |            |        |                     |
| Das 2014             | 1.0%   | 0.77 [0.47, 1.24]   |            |        |                     |
| Erohova 2014         | 11.0%  | 0.69 [0.35, 1.31]   |            |        |                     |
| Jyuan 2006           | 11.0%  | 0.36 [0.28, 0.45]   |            |        |                     |
| Mathema 2001         | 6.6%   | 0.66 [0.62, 0.70]   |            |        |                     |
| Mohr 2017            | 4.7%   | 1.02 [0.83, 1.25]   |            |        |                     |
| Nirmala 2005         | 4.3%   | 0.96 [0.77, 1.19]   |            |        |                     |
| Olle-Goerg 2001      | 5.5%   | 0.67 [0.47, 0.93]   |            |        |                     |
| Szczesniak 2009      | 5.3%   | 0.77 [0.65, 0.93]   |            |        |                     |
| Tsuchida 2003        | 4.1%   | 0.70 [0.62, 1.00]   |            |        |                     |
| Xu 2006              | 8.0%   | 0.64 [0.59, 0.71]   |            |        |                     |
| Yan 2013             | 7.1%   | 1.04 [0.81, 1.34]   |            |        |                     |
| **Subtotal (95% CI)** | 80.9% | 0.81 [0.74, 0.88]   |            |        |                     |
| **Heterogeneity**    | Tau² = 0.02; Chi² = 170.26; df = 16 (p < 0.00001); I² = 91% |            | Test for overall effect: Z = 4.73 (p < 0.00001) |

**Total (95% CI)**   | 100.0% | 0.84 [0.78, 0.90]   |            |        |                     |
| **Heterogeneity**    | Tau² = 0.02; Chi² = 180.41; df = 19 (p < 0.00001); I² = 99% |            | Test for overall effect: Z = 5.60 (p < 0.00001) |
| **Test for subgroup differences** | Chi² = 6.33; df = 1 (p = 0.01); I² = 84.2% |            |
Figure S5: Alipanah 2018; Intervention/ Exposure: Self-administered therapy; Outcome: Treatment completion (Risk Ratio >1 indicates a favorable effect)
Figure S6: Alipanah 2018; Intervention/Exposure: Self-administered therapy; Outcome: All-cause mortality
Figure S7: Anglemyer 2013; Intervention/Exposure: Antiretroviral therapy; Outcome: HIV infection
### Figure S8: Azad 2017; Intervention/Exposure: Nonnutritive sweeteners; Outcome: Body Mass Index
**Figure S9:** Barnard 2015; Intervention/Exposure: Surgical abortion by mid-level providers; Outcome: Failure or incomplete abortion
Figure S10: Barnard 2015; Intervention/Exposure: Surgical abortion by mid-level providers; Outcome: Complications
**Figure S11:** Barnard 2015; Intervention/Exposure: Surgical abortion by mid-level providers; Outcome: Abortion failure and complications
**Figure S12**: Bellemain-Appaix 2012; Intervention/ Exposure: Clopidogrel pretreatment for percutaneous coronary intervention; Outcome: All-cause mortality
**Figure S13:** Bellemain-Appaix 2012; Intervention/Exposure: Clopidogrel pretreatment for percutaneous coronary intervention; Outcome: Major bleeding
**Figure S14**: Bellemain-Appaix 2012; Intervention/Exposure: Clopidogrel pretreatment for percutaneous coronary intervention; Outcome: Coronary heart disease
Figure S15: Bellemain-Appaix 2014; Intervention/ Exposure: P2Y12 inhibitor pretreatment in non-ST elevation acute coronary syndrome; Outcome: All-cause mortality
**Figure S16**: Bellemain-Appaix 2014; Intervention/Exposure: P2Y12 inhibitor pretreatment in non-ST elevation acute coronary syndrome; Outcome: Major bleeding
Figure S17: Bellemain-Appaix 2014; Intervention/Exposure: P2Y12 inhibitor pretreatment in non-ST elevation acute coronary syndrome; Outcome: Main composite ischemic endpoint
| Study or Subgroup | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|-------------------|--------|-------------------------------|-------------------------------|
| **12.1.1 RCTs**   |        |                               |                               |
| Toledo 2015 FREDI MED | 0.9%   | 0.43 [0.21, 0.88]             |                               |
| Subtotal (95% CI) | 0.9%   | 0.43 [0.21, 0.88]             |                               |
| **Heterogeneity:** Not applicable |        |                               |                               |
| Test for overall effect: $Z = 2.31$ ($P = 0.02$) |        |                               |                               |
|                      |        |                               |                               |
| **12.1.2 Cohort studies** |        |                               |                               |
| Adeyemo et al. 2005 | 4.5%   | 0.90 [0.68, 1.19]             |                               |
| Aguas-Collins 2009 | 5.7%   | 0.86 [0.68, 1.09]             |                               |
| Bueckmann 2013      | 14.0%  | 0.94 [0.88, 1.00]             |                               |
| Cade 2011           | 3.7%   | 0.96 [0.70, 1.32]             |                               |
| Calgary 2015        | 5.0%   | 0.73 [0.55, 0.92]             |                               |
| Coulo 2013          | 13.9%  | 1.08 [1.00, 1.17]             |                               |
| Dufour 2006         | 12.0%  | 0.99 [0.88, 1.09]             |                               |
| Lack 2013           | 12.2%  | 1.12 [1.01, 1.24]             |                               |
| Mannisto 2005       | 4.1%   | 0.90 [0.67, 1.21]             |                               |
| NBBS                | 5.1%   | 0.84 [0.65, 1.09]             |                               |
| ORDET               | 0.9%   | 0.72 [0.55, 1.14]             |                               |
| Terry 2001          | 7.4%   | 0.92 [0.75, 1.11]             |                               |
| Vello 2005          | 0.0%   | 1.03 [0.88, 1.21]             |                               |
| **Subtotal (95% CI)** | 99.1%  | 0.98 [0.90, 1.03]             |                               |
| **Heterogeneity:** $Tau^2 = 0.01$, Ch $P = 25.21$, df = 12 ($P = 0.01$); $I^2 = 52\%$ |        |                               |                               |
| Test for overall effect: $Z = 1.09$ ($P = 0.28$) |        |                               |                               |
|                      |        |                               |                               |
| **Total (95% CI)**  | 100.0% | 0.05 [0.89, 1.62]             |                               |
| **Heterogeneity:** $Tau^2 = 0.01$, Ch $P = 30.86$, df = 13 ($P = 0.004$); $I^2 = 57\%$ |        |                               |                               |
| Test for overall effect: $Z = 1.34$ ($P = 0.18$) |        |                               |                               |
| Test for subgroup differences: Ch $P = 4.85$, df = 1 ($P = 0.030$); $I^2 = 79.4\%$ |        |                               |                               |

**Figure S18:** Bloomfield 2016; Intervention/Exposure: Mediterranean diet; Outcome: Breast cancer
Figure S19: Bolland 2015; Intervention/ Exposure: High calcium; Outcome: All fractures
| Study or Subgroup | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|-------------------|--------|-------------------------------|-------------------------------|
| Chevalley 1994    | 2.0%   | 0.75 [0.53, 1.08]             |                               |
| Fujita 2004       | 1.0%   | 0.76 [0.54, 1.09]             |                               |
| Grant 2005        | 1.4%   | 0.61 [0.43, 0.85]             |                               |
| Hansson 1987      | 0.4%   | 1.03 [0.67, 1.58]             |                               |
| Jackson 2006      | 27.0%  | 0.92 [0.75, 1.12]             |                               |
| Peacock 2000      | 3.8%   | 0.56 [0.24, 1.30]             |                               |
| Prince 2006       | 11.6%  | 0.97 [0.63, 1.50]             |                               |
| Recknor 1986      | 12.2%  | 0.86 [0.59, 1.26]             |                               |
| Reid 1983         | 0.5%   | 0.33 [0.01, 1.28]             |                               |
| Reid 2006         | 10.0%  | 0.72 [0.44, 1.16]             |                               |
| Riggs 1998        | 3.3%   | 0.87 [0.35, 2.19]             |                               |
| Salvyaza 2010     | 3.8%   | 0.69 [0.30, 1.61]             |                               |

**Subtotal (95% CI):** 76.7% [0.74, 1.00]

**Heterogeneity:** Test $I^2 = 0.00$; $Chi^2 = 3.86$, df = 11 ($P = 0.97$); $I^2 = 0$

Test for overall effect: $Z = 2.02$ ($P = 0.04$)

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### 13.4.2 Cohort studies

| Study or Subgroup | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|-------------------|--------|-------------------------------|-------------------------------|
| Cumming 1997      | 23.3%  | 1.40 [1.10, 1.78]             |                               |
| Subtotal (95% CI) | 23.3%  | 1.40 [1.10, 1.78]             |                               |

**Heterogeneity:** Not applicable

Test for overall effect: $Z = 2.74$ ($P = 0.006$)

**Total (95% CI):** 100.0% [0.79, 1.11]

**Heterogeneity:** Test $I^2 = 0.24$; $Chi^2 = 15.42$, df = 12 ($P = 0.22$); $I^2 = 22$

Test for overall effect: $Z = 0.75$ ($P = 0.40$)

Test for subgroup differences: $Chi^2 = 11.47$, df = 1 ($P = 0.0007$); $I^2 = 91.3$

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**Figure S20:** Bolland 2015; Intervention/Exposure: High calcium; Outcome: Vertebral fracture
Figure S21: Bolland 2015; Intervention/ Exposure: High calcium; Outcome: Hip fracture
Table: Risk Ratio

| Study or Subgroup | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|-------------------|--------|-------------------------------|-------------------------------|
| **14.2.1 RCTs**   |        |                               |                               |
| Atkin 2010        | 36.0%  | 0.89 [0.59, 0.81]             |                               |
| Hoff 2009         | 4.8%   | 0.73 [0.47, 1.11]             |                               |
| Schoen 2012       | 36.0%  | 0.74 [0.33, 0.87]             |                               |
| Segnan 2011       | 8.5%   | 0.78 [0.56, 1.09]             |                               |
| Subtotal (95% CI) | 87.3%  | 0.72 [0.65, 0.80]             |                               |
| **Heterogeneity: Tau^2 = 0.00, Ch^2 = 3 (P = 0.89), I^2 = 0%** | | | |
| Test for overall effect Z = 0.21 (P = 0.89201) | | | |

| **14.2.2 Cohort studies** | | | |
| Mihara 2013         | 12.7%  | 0.59 [0.45, 0.77]             |                               |
| Subtotal (95% CI)   | 12.7%  | 0.59 [0.45, 0.77]             |                               |
| **Heterogeneity: Not applicable** | | | |
| Test for overall effect Z = 3.02 (P = 0.0001) | | | |

| Total (95% CI)      | 100.0% | 0.70 [0.64, 0.77]             |                               |
| Heterogeneity: Tau^2 = 0.00, Ch^2 = 7.16 (P = 0.0061), I^2 = 0% | | | |
| Test for overall effect Z = 3.02 (P = 0.0001) | | | |
| Test for subgroun differences: Ch^2 = 1.84, df= 1 (P = 0.18), I^2 = 45.5% | | | |

**Figure S22:** Brenner 2014; Intervention/Exposure: Sigmoidoscopy; Outcome: Colorectal cancer mortality
Figure S23: Brenner 2014; Intervention/ Exposure: Sigmoidoscopy; Outcome: Colorectal cancer incidence
Figure S24: Chowdhury 2012; Intervention/ Exposure: High omega-3; Outcome: Cerebrovascular disease
Figure S25: Chowdhury 2014a; Intervention/Exposure: High α-linolenic acid; Outcome: Coronary heart disease
Figure S26: Chowdhury 2014a; Intervention/Exposure: High omega-3; Outcome: Coronary heart disease
| Study or Subgroup | Weight | IV. Random, 95% CI | Study or Subgroup | Weight | IV. Random, 95% CI |
|------------------|--------|-------------------|------------------|--------|-------------------|
| DART             | 6.3%   | 0.91 [0.72, 1.15] | ATBC             | 11.4%  | 1.05 [0.92, 1.19] |
| FMHS             | 2.7%   | 0.59 [0.37, 0.93] | Group 5          | 5.2%   | 0.93 [0.68, 1.28] |
| LA Veteran       | 4.6%   | 0.74 [0.53, 1.03] | HPFS             | 14.3%  | 0.97 [0.93, 1.02] |
| MCH              | 5.7%   | 1.19 [0.98, 1.48] | KHD              | 8.3%   | 1.13 [0.98, 1.48] |
| MRC              | 4.2%   | 0.88 [0.61, 1.22] | MALMO            | 10.3%  | 1.09 [0.93, 1.29] |
| OSLO             | 2.3%   | 0.66 [0.33, 0.94] | MOROEN           | 5.7%   | 0.95 [0.72, 1.28] |
| SDHS             | 2.3%   | 1.74 [1.04, 2.92] | MRFIT            | 4.5%   | 0.70 [0.50, 0.98] |
| STARS            | 0.3%   | 0.41 [0.03, 1.49] | NHS              | 9.7%   | 0.82 [0.63, 1.06] |
| **Subtotal (95% CI)** | 30.8%  | 0.86 [0.69, 1.07] | **Subtotal (95% CI)** | 79.6%  | 0.8 [0.63, 1.07] |

Heterogeneity: Tau² = 0.05, Chi² = 17.72, df = 7 (P = 0.02), I² = 59%
Test for overall effect: Z = 1.37 (P = 0.17)

**Figure S27:** Chowdhury 2014a; Intervention/ Exposure: Omega-6; Outcome: Coronary heart disease
**Figure S28:** Chung 2016; Intervention/Exposure: High calcium; Outcome: Cardiovascular mortality
Figure S29: Ding 2017; Intervention/Exposure: High dairy; Outcome: Systolic blood pressure
Figure S30: Fenton 2018; Intervention/Exposure: Radiation therapy; Outcome: Erectile dysfunction
### Figure S31: Fenton 2018; Intervention/Exposure: Radical prostatectomy; Outcome: Urinary incontinence

| Study or Subgroup   | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|---------------------|--------|--------------------------------|--------------------------------|
| Donovan 2016        | 17.2%  | 2.07 [1.44, 2.98]              |                                |
| Johansson 2011      | 13.9%  | 2.25 [1.60, 3.16]              |                                |
| Will 2012           | 12.7%  | 2.69 [1.91, 4.01]              |                                |
| **Subtotal (95% CI)** | 47.9%  | 2.25 [1.80, 2.82]              |                                |

Heterogeneity: $I^2 = 0.00$, $Q = 0.07$, df = 2 ($P = 0.71$), $I^2 = 0%$
Test for overall effect: $Z = 7.11$ ($P < 0.000001$)

### 24.5.2 Cohort studies

| Study or Subgroup   | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|---------------------|--------|--------------------------------|--------------------------------|
| Barocas 2017        | 14.8%  | 2.34 [1.49, 3.85]              |                                |
| Chen 2017           | 13.9%  | 1.58 [0.99, 2.53]              |                                |
| Hoffman 2003        | 14.8%  | 4.27 [2.76, 6.80]              |                                |
| Schapira 2001       | 1.6%   | 11.11 [5.57, 23.47]            |                                |
| Smith 2009          | 7.2%   | 3.77 [1.98, 8.46]              |                                |
| **Subtotal (95% CI)** | 52.1%  | 2.01 [1.80, 4.71]              |                                |

Heterogeneity: $I^2 = 0.18$, $Q = 12.30$, df = 4 ($P = 0.02$), $I^2 = 87%$
Test for overall effect: $Z = 4.36$ ($P < 0.0001$)

Total (95% CI) 100.0% 2.54 [1.97, 3.27]

Heterogeneity: $I^2 = 0.08$, $Q = 14.20$, df = 7 ($P = 0.05$), $I^2 = 51%$
Test for overall effect: $Z = 7.25$ ($P < 0.00001$)
Test for subgroups differences: $Q = 0.90$, df = 1 ($P = 0.34$), $I^2 = 0%$
### Figure S32: Fenton 2018; Intervention/ Exposure: Radical Prostatectomy; Outcome: Erectile dysfunction

#### 24.4.1 RCTs

| Study or Subgroup | Weight |
|-------------------|--------|
| Donovan 2018      | 12.1%  |
| Johansson 2011    | 10.6%  |
| Witt 2012         | 12.2%  |
| Subtotal (95% CI) | 34.9%  |

Heterogeneity: $\tau^2 = 0.05; \chi^2 = 16.80, df = 2 (P = 0.0004); I^2 = 87\%$

Test for overall effect $Z = 3.57 (P = 0.0004)$

#### 24.4.2 cohort studies

| Study or Subgroup | Weight |
|-------------------|--------|
| Schapira 2001     | 7.3%   |
| Chen 2017         | 12.6%  |
| Barocas 2017      | 13.5%  |
| Siegel 2001       | 10.4%  |
| Smith 2009        | 11.8%  |
| Hoffman 2003      | 9.4%   |
| Subtotal (95% CI) | 65.1%  |

Heterogeneity: $\tau^2 = 0.01; \chi^2 = 13.51, df = 5 (P = 0.02); I^2 = 63\%$

Test for overall effect $Z = 5.89 (P < 0.00001)$

#### Total (95% CI)

| Weight |
|--------|
| 100.0% |

Heterogeneity: $\tau^2 = 0.02; \chi^2 = 31.41, df = 8 (P = 0.0001); I^2 = 75\%$

Test for overall effect $Z = 7.89 (P < 0.00001)$

Test for subgroup differences: $\chi^2 = 0.25, df = 1 (P = 0.62); I^2 = 0\%$
**Figure S33**: Filippini 2017; Intervention/Exposure: Disease-modifying drugs; Outcome: Conversion to clinically definite multiple sclerosis

| Study or Subgroup | Weight | IV, Random, 95% CI | Hazard Ratio |
|-------------------|--------|--------------------|--------------|
| **22.1.1 RCTs**   |        |                    |              |
| BENEFIT 2006      | 12.8%  | 0.60 [0.36, 0.66]  |              |
| CHAMPS 2000       | 9.2%   | 0.68 [0.38, 0.83]  |              |
| CHAMPS 2000       | 0.5%   | 0.14 [0.02, 1.12]  |              |
| ETOMUS 2001       | 10.3%  | 0.65 [0.45, 0.94]  |              |
| ORACLE 2014       | 7.8%   | 0.39 [0.25, 0.59]  |              |
| PREDICT 2009      | 13.7%  | 0.55 [0.40, 0.77]  |              |
| REFLEX 2012       | 7.3%   | 0.49 [0.31, 0.74]  |              |
| TOPIC 2014        | 8.4%   | 0.57 [0.38, 0.86]  |              |
| **Subtotal (95% CI)** | 70.0%  | 0.52 [0.46, 0.60]  |              |

Heterogeneity, Tau² = 0.00, Chi² = 5.74, df = 7 (P = 0.57), I² = 0%
Test for overall effect: Z = 0.98 (P < 0.00001)

| **22.1.2 Cohort studies** |        |                    |              |
|--------------------------|--------|--------------------|--------------|
| ACIBS 2010               | 4.7%   | 0.35 [0.19, 0.62]  |              |
| MEGASIS 2016             | 26.0%  | 0.59 [0.46, 0.73]  |              |
| **Subtotal (95% CI)**    | 30.0%  | 0.48 [0.30, 0.78]  |              |

Heterogeneity, Tau² = 0.08, Chi² = 2.64, df = 1 (P = 0.10), I² = 82%
Test for overall effect: Z = 2.95 (P = 0.003)

**Total (95% CI)**

100.0% 0.53 [0.47, 0.59]

Heterogeneity, Tau² = 0.00, Chi² = 8.43, df = 9 (P = 0.49), I² = 0%
Test for overall effect: Z = 10.59 (P < 0.00001)
Test for subgroup difference: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%

Favours disease-modifying drugs  Favours control

0.01  0.1  1  10  100
Figure S34: Fluri 2010; Intervention/Exposure: Extracranial-intracranial arterial bypass; Outcome: All-cause mortality
Figure S35: Fluri 2010; Intervention/Exposure: Extracranial-intracranial arterial bypass; Outcome: Stroke
Figure S36: Fluri 2010; Intervention/Exposure: Extracranial-intracranial arterial bypass; Outcome: Stroke mortality or dependency.
Figure S37: Gargiulo 2016; Intervention/ Exposure: Transcatheter aortic valve implantation; Outcome: Early all-cause mortality
Figure S38: Gargiulo 2016; Intervention/ Exposure: Transcatheter aortic valve implantation; Outcome: Mid-term all-cause mortality
### Figure S39: Gargiulo 2016; Intervention/ Exposure: Transcatheter aortic valve implantation; Outcome: Long-term all-cause mortality

| Study or Subgroup | Odds Ratio (IV, Random, 95% CI) | Weight |
|-------------------|---------------------------------|--------|
| **21.3.1 RCTs**   |                                 |        |
| NOTION            | 0.81 [0.35, 1.87]                | 6.1%   |
| PARTNER           | 1.49 [1.10, 2.02]                | 15.2%  |
| PARTNER 2A        | 0.96 [0.78, 1.24]                | 16.7%  |
| U.S. CoreValve    | 0.01 [0.00, 1.09]                | 15.3%  |
| **Subtotal (95% CI)** | 1.03 [0.77, 1.37]                   | 53.3%  |

Heterogeneity: $\text{I}^2 = 0.05; \text{Ch}^2 = 0.48; df = 3 (P = 0.04); P = 0.86$

Tests for overall effect $Z = 0.18 (P = 0.86)$

| **21.3.2 Cohort studies** | Odds Ratio (IV, Random, 95% CI) | Weight |
|---------------------------|---------------------------------|--------|
| Hotzley                   | 1.74 [1.12, 2.73]                | 12.2%  |
| Munarotto                 | 2.66 [1.49, 4.76]                | 9.6%   |
| Papasopoulou              | 0.86 [0.32, 2.39]                | 4.8%   |
| Santoro                   | 1.74 [0.61, 4.98]                | 4.4%   |
| Schymik                   | 1.43 [0.89, 2.38]                | 10.9%  |
| Zweng                     | 1.30 [0.49, 3.53]                | 4.6%   |

**Subtotal (95% CI)**: 1.70 [1.31, 2.20]

Heterogeneity: $\text{I}^2 = 0.00; \text{Ch}^2 = 4.56; df = 5 (P = 0.47); P = 0.83$

Test for overall effect $Z = 4.01 (P < 0.0001)$

**Total (95% CI)**: 1.28 [1.00, 1.65]

Heterogeneity: $\text{I}^2 = 0.06; \text{Ch}^2 = 23.63; df = 9 (P = 0.006); P = 62%$

Test for overall effect $Z = 1.92 (P = 0.05)$

Test for subgroup differences: $\text{Ch}^2 = 6.45; df = 1 (P = 0.01); P = 64.5%$
| Study or Subgroup | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|------------------|--------|-------------------------------|-------------------------------|
| Beizer 1999      | 3.0%   | 0.11 [0.02, 0.64]             |                               |
| Landon 2009      | 13.1%  | 0.41 [0.27, 0.63]             |                               |
| Crowther 2005    | 14.1%  | 0.46 [0.34, 0.63]             |                               |
| Eronero 1997     | 9.2%   | 0.50 [0.22, 1.13]             |                               |
| Garber 1987      | 12.4%  | 0.86 [0.53, 1.42]             |                               |
| Subtotal (95% CI)| 51.7%  | 0.50 [0.36, 0.71]             |                               |

Heterogeneity: $\text{I}^2 = 79\%$, $\text{Chi}^2 = 21.9$, df = 4 ($P = 0.003$); $I^2 = 79\%$

Test for overall effect: $Z = 2.74$ ($P = 0.006$)

Test for sub-group differences: $\text{Chi}^2 = 41.87$, df = 8 ($P < 0.00001$); $I^2 = 79\%$

**Figure S40:** Hartling 2013; Intervention/Exposure: Treating gestational diabetes mellitus; Outcome: High birth weight
**Figure S41**: Hartling 2013; Intervention/ Exposure: Treating gestational diabetes mellitus; Outcome: Large-for-gestational age neonate
**Figure S42:** Hartling 2013; Intervention/ Exposure: Treating gestational diabetes mellitus; Outcome: Shoulder dystocia
Figure S4: Henderson 2019; Intervention/Exposure: Treating asymptomatic bacteriuria; Outcome: Pyelonephritis
**Figure S44:** Higgins 2016; Intervention/Exposure: Bacillus Calmette-Guérin vaccination; Outcome: All-cause mortality
**Figure S45:** Higgins 2016; Intervention/Exposure: Measles containing vaccines; Outcome: All-cause mortality
Figure S46: Hopley 2010; Intervention/Exposure: Total hip arthroplasty; Outcome: Reoperation
| Study or Subgroup | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|------------------|--------|-------------------------------|-------------------------------|
| 28.5.1 RCTs      |        |                               |                               |
| Baker 2005       | 7.5%   | 7.17 [0.38, 134.62]           |                               |
| Keating 2008     | 22.2%  | 1.61 [0.33, 7.75]             |                               |
| Macaulay 2008    | 6.6%   | 4.00 [0.17, 92.57]            |                               |
| Subtotal (95% CI)| 36.3%  | 2.47 [0.69, 8.76]             |                               |
|                  |        |                               |                               |
| 28.5.2 Cohort studies |    |                               |                               |
| Byssel 1994      | 19.8%  | 0.35 [0.07, 1.90]             |                               |
| Gebhard 1992     | 13.8%  | 0.46 [0.06, 3.73]             |                               |
| Narayan 2005     | 7.5%   | 7.70 [0.41, 142.01]           |                               |
| Squires 1999     | 11.2%  | 2.59 [0.25, 23.38]            |                               |
| Xu 2002          | 11.5%  | 0.36 [0.04, 3.90]             |                               |
| Subtotal (95% CI)| 63.7%  | 0.79 [0.27, 2.35]             |                               |
|                  |        |                               |                               |
| Total (95% CI)   | 100.0% | 1.20 [0.52, 2.70]            |                               |

Heterogeneity: $\tau^2 = 0.07$, $I^2 = 45\%$, $p = 0.34$; $I^2 = 12\%$
Test for overall effect: $Z = 0.43$, $p = 0.67$

Test for subgroup differences: $\chi^2 = 7.91$, $df = 7$, $p = 0.34$; $I^2 = 12\%$

**Figure S47**: Hopley 2010; Intervention/Exposure: Total hip arthroplasty; Outcome: Dislocation
Figure S48: Hopley 2010; Intervention/ Exposure: Total hip arthroplasty; Outcome: Deep infection
Figure S49: Hüpfl 2010; Intervention/Exposure: Chest-compression-only cardiopulmonary resuscitation; Outcome: Survival (Risk Ratio > 1 indicates a favorable effect)
| Study or Subgroup | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|------------------|--------|-------------------------------|-------------------------------|
| Barreto 2008     | 0.3%   | 0.12 [0.02, 0.81]             |                               |
| Block 2007       | 3.2%   | 0.83 [0.28, 1.00]             |                               |
| Chertow 2002     | 1.0%   | 1.22 [0.39, 3.88]             |                               |
| Di Iorio 2012    | 3.0%   | 0.54 [0.28, 1.03]             |                               |
| Quindi 2008      | 0.8%   | 0.44 [0.12, 1.68]             |                               |
| Sadik 2003       | 0.3%   | 0.33 [0.04, 2.23]             |                               |
| Suki 2008        | 24.5%  | 0.97 [0.84, 1.12]             |                               |
| Wilson 2009      | 17.9%  | 0.95 [0.70, 1.05]             |                               |
| **Subtotal (95% CI)** | 50.9% | **0.78 [0.62, 0.98]** |                               |

Heterogeneity: Tau² = 0.03, Ch² = 12.27, df = 7 (P = 0.08), I² = 43%
Test for overall effect: Z = 2.09 (P = 0.04)

| Study or Subgroup | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|------------------|--------|-------------------------------|-------------------------------|
| Borzechski 2007  | 20.6%  | 0.82 [0.69, 0.98]             |                               |
| Jean 2011        | 12.7%  | 0.89 [0.78, 1.02]             |                               |
| Pancheri 2010    | 15.9%  | 0.83 [0.74, 1.18]             |                               |
| **Subtotal (95% CI)** | 49.1% | **0.89 [0.78, 1.00]** |                               |

Heterogeneity: Tau² = 0.00, Ch² = 1.57, df = 2 (P = 0.46), I² = 0%
Test for overall effect: Z = 1.90 (P = 0.06)

**Total (95% CI)**

| Risk Ratio IV, Random, 95% CI |
|------------------------------|
| 0.87 [0.77, 0.97]            |

Heterogeneity: Tau² = 0.01, Ch² = 13.83, df = 10 (P = 0.18), I² = 28%
Test for overall effect: Z = 2.40 (P = 0.02)
Test for subgroup differences: Ch² = 0.91, df = 1 (P = 0.34), I² = 0%

**Figure S50:** Jamal 2013; Intervention/Exposure: Non-calcium-based phosphat binders; Outcome: All-cause mortality
**Figure S51**: Jefferson 2010; Intervention/ Exposure: Parenteral influenza vaccine; Outcome: Influenza-like illness
### 31.4.1 RCTs

| Study or Subgroup     | Weight | IV, Random, 95% CI       |
|-----------------------|--------|--------------------------|
| Edmondsdon 1971       | 8.4%   | 0.36 [0.12, 1.06]        |
| Ouwae 1984            | 13.0%  | 0.41 [0.23, 0.74]        |
| Rudenko 2001          | 9.9%   | 0.50 [0.20, 1.25]        |
| **Subtotal (95% CI)** | 31.3%  | **0.42 [0.27, 0.66]**   |

Heterogeneity: *I^2* = 0.00; *Chi^2* = 0.25, df = 2 (*P* = 0.66); *P* = 0%
Test for overall effect: *Z* = 3.79 (*P* = 0.0002)

### 31.4.2 Cohort studies

| Study or Subgroup     | Weight | IV, Random, 95% CI       |
|-----------------------|--------|--------------------------|
| Cuneo Devani 1980     | 3.7%   | 0.21 [0.03, 1.74]        |
| Feary 1976            | 12.6%  | 0.16 [0.01, 1.92]        |
| Gross 1986            | 3.7%   | 0.11 [0.01, 0.94]        |
| Howarth 1967a         | 5.2%   | 0.21 [0.04, 1.14]        |
| Howarth 1967b         | 1.9%   | 0.33 [0.01, 3.00]        |
| Morena 1985           | 2.5%   | 1.41 [0.10, 20.60]       |
| Nicholson 1988        | 4.0%   | 0.05 [0.01, 0.37]        |
| Ruben 1974            | 10.5%  | 0.54 [0.23, 1.25]        |
| Taylor 1992           | 11.7%  | 2.05 [1.01, 4.19]        |
| Voordouw 2003         | 12.6%  | 0.50 [0.27, 0.91]        |
| **Subtotal (95% CI)** | 68.7%  | **0.51 [0.27, 0.97]**   |

Heterogeneity: *I^2* = 0.52; *Chi^2* = 25.28, df = 9 (*P* = 0.003); *P* = 64%
Test for overall effect: *Z* = 2.07 (*P* = 0.04)

**Total (95% CI)**: 100.0% 0.51 [0.32, 0.80]

Heterogeneity: *I^2* = 0.34; *Chi^2* = 23.15, df = 12 (*P* = 0.004); *P* = 59%
Test for overall effect: *Z* = 2.80 (*P* = 0.004)
Test for subgroup differences: *Chi^2* = 0.24, df = 1 (*P* = 0.62), *P* = 0%

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**Figure S52**: Jefferson 2010; Intervention/ Exposure: Parenteral influenza vaccine; Outcome: Influenza
Figure S53: Jefferson 2012; Intervention/ Exposure: Inactivated influenza vaccines; Outcome: Influenza
**Figure S54**: Jefferson 2012; Intervention/Exposure: Inactivated influenza vaccines; Outcome: Influenza-like illness
Figure S55: Jin 2012; Intervention/Exposure: High total flavonoids; Outcome: Colorectal neoplasms
| Study or Subgroup | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|------------------|--------|-------------------------------|-------------------------------|
| Bush 1997        | 4.6%   | 1.02 [0.97, 1.07]             |                               |
| Carson 1998      | 2.3%   | 1.00 [0.90, 1.11]             |                               |
| Carson 2011      | 5.2%   | 1.44 [0.91, 2.25]             |                               |
| Carson 2013      | 5.2%   | 0.14 [0.02, 1.10]             |                               |
| Cooper 2011      | 2.6%   | 0.57 [0.30, 1.06]             |                               |
| Hébert 2001      | 6.4%   | 0.81 [0.53, 1.26]             |                               |
| **Subtotal (95% CI)** | 25.6% | 0.84 [0.62, 1.14]             |                               |

Heterogeneity: Tau² = 0.05, Chi² = 6.00, df = 5 (P = 0.31); η² = 17%
Test for overall effect: Z = 0.30 (P = 0.76)

35.1.2 Cohort studies - Converted RR

| Study | Weight | Risk Ratio IV, Random, 95% CI |
|-------|--------|-------------------------------|
| Boulé 2009 | 4.7%   | 5.38 [1.45, 20.01]         |
| Carson 1998 | 5.6%   | 1.06 [0.78, 1.48]          |
| Chase 2003  | 6.7%   | 3.21 [2.64, 3.89]           |
| Doyle 2008  | 6.6%   | 8.90 [6.30, 12.68]          |
| Doyle 2008  | 6.6%   | 10.10 [13.59, 23.97]        |
| Garty 2009  | 5.8%   | 0.31 [0.14, 0.66]           |
| Malvanada 2009 | 0.2%   | 1.40 [0.90, 2.45]           |
| Nikolsky 2009 | 5.6%   | 4.71 [1.97, 11.26]          |
| Rao 2004    | 6.7%   | 3.94 [3.26, 4.75]           |
| Shishibor 2009 | 0.5%   | 3.89 [2.66, 5.68]           |
| Singla 2007 | 6.3%   | 2.26 [1.36, 3.80]           |
| Wu 2001     | 6.0%   | 0.23 [0.12, 0.46]           |
| **Subtotal (95% CI)** | 74.4% | 2.49 [1.40, 4.43]           |

Heterogeneity: Tau² = 0.04, Chi² = 23.19, df = 11 (P < 0.0001); η² = 97%
Test for overall effect: Z = 3.12 (P = 0.002)

**Figure S56:** Kansagara 2013; Intervention/Exposure: Transfusion; Outcome: All-cause mortality
**Figure S57**: Keag 2018; Intervention/Exposure: Caesarean section; Outcome: Urinary incontinence
Figure S58: Keag 2018; Intervention/ Exposure: Caesarean section; Outcome: Fecal incontinence
Figure S59: Kredo 2014; Intervention/ Exposure: Antiretroviral therapy by nurses; Outcome: All-cause mortality
Figure S60: Kredo 2014; Intervention/ Exposure: Antiretroviral therapy by nurses; Outcome: Attrition
**Figure S61:** Kredo 2014; Intervention/Exposure: Nurses for maintenance of antiretroviral therapy; Outcome: All-cause mortality
Figure S62: Li 2014; Intervention/Exposure: Exenatide; Outcome: Acute pancreatitis
Figure S63: Li 2016; Intervention/Exposure: DDP-4 inhibitors; Outcome: Heart failure
Figure S64: Li 2016; Intervention/ Exposure: DDP-4 inhibitors; Outcome: Hospital admission for heart failure
Heterogeneity: Not applicable
Test for overall effect: Z = 3.02 (P = 0.003)

Heterogeneity: Tau^2 = 0.03, Ch^2 = 1.11, df = 1 (P = 0.29), I^2 = 10%
Test for overall effect: Z = 1.29 (P = 0.20)

Heterogeneity: Tau^2 = 0.05, Ch^2 = 4.93, df = 2 (P = 0.08), I^2 = 59%
Test for overall effect: Z = 1.72 (P = 0.08)
Test for subgroup differences: Ch^2 = 3.78, df = 1 (P = 0.05), I^2 = 73.5%

**Figure S65:** Matthews 2018; Intervention/ Exposure: Tamoxifen; Outcome: Heart failure
**Figure S66**: Menne 2019; Intervention/Exposure: SGLT-2 inhibitors; Outcome: Acute kidney injury
### Figure S67: Mesgarpour 2017; Intervention/Exposure: Erythropoiesis stimulating agents; Outcome: Venous thromboembolism
Figure S68: Mesgarpour 2017; Intervention/Exposure: Erythropoiesis stimulating agents; Outcome: All-cause mortality
Figure S69: Moberley 2013; Intervention/Exposure: Pneumococcal polysaccharide vaccines; Outcome: Invasive pneumococcal disease
Figure S70: Molnar 2015; Intervention/Exposure: Neoral (Cyclosporin); Outcome: Acute rejection of kidney transplant
**Figure S71:** Navarese 2013; Intervention/Exposure: Early intervention for NSTE-ACS; Outcome: All-cause mortality
**Figure S72**: Navarese 2013; Intervention/Exposure: Early intervention for NSTE-ACS; Outcome: Myocardial infarction

| Study or Subgroup | Weight | Odds Ratio IV, Random, 95% CI | Odds Ratio IV, Random, 95% CI |
|-------------------|--------|-------------------------------|-------------------------------|
| ABOARD            | 4.9%   | 2.13 [0.89, 5.10]             |                               |
| ELISA             | 3.4%   | 1.20 [0.39, 3.70]             |                               |
| ISAR-COOL         | 6.2%   | 0.56 [0.27, 1.16]             |                               |
| LIPSIA-NSTEMI     | 7.0%   | 2.84 [1.45, 5.68]             |                               |
| OPTIMA            | 7.0%   | 2.36 [1.20, 4.63]             |                               |
| TIMACS            | 13.1%  | 0.63 [0.50, 1.14]             |                               |
| Zhang et al. 2010 | 9.0%   | 0.45 [0.26, 0.70]             |                               |
| Subtotal (95% CI) | 50.6%  | 1.16 [0.67, 2.00]             |                               |

Heterogeneity: Tau² = 0.41; Chi² = 30.88, df = 6 (P < 0.0001); I² = 81%
Test for overall effect: Z = 0.54 (P = 0.59)

**45.2.2 Cohort studies**

| Study           | Weight | Odds Ratio IV, Random, 95% CI | Odds Ratio IV, Random, 95% CI |
|-----------------|--------|-------------------------------|-------------------------------|
| ACUITY          | 16.3%  | 0.70 [0.60, 0.82]             |                               |
| CRUSADE         | 16.0%  | 1.04 [0.91, 1.17]             |                               |
| SYNERGY         | 16.4%  | 0.87 [0.75, 1.00]             |                               |
| Subtotal (95% CI)| 49.4%  | 0.85 [0.69, 1.00]             |                               |

Heterogeneity: Tau² = 0.03; Chi² = 14.64, df = 2 (P = 0.0007); I² = 86%
Test for overall effect: Z = 1.32 (P = 0.19)

**Total (95% CI)**

| Weight | Odds Ratio IV, Random, 95% CI | Odds Ratio IV, Random, 95% CI |
|--------|-------------------------------|-------------------------------|
| 100.0% | 0.97 [0.77, 1.22]             |                               |

Heterogeneity: Tau² = 0.08; Chi² = 48.30, df = 9 (P < 0.00001); I² = 81%
Test for overall effect: Z = 0.29 (P = 0.78)

Test for subgroup differences: Chi² = 1.00, df = 1 (P = 0.32); I² = 0%
**Figure S73:** Navarese 2013; Intervention/Exposure: Early intervention for NSTE-ACS; Outcome: Major bleeding
Figure S74: Nelson 2010; Intervention/Exposure: Caesarean section; Outcome: Anal incontinence, feces
**Figure S75:** Nelson 2010; Intervention/Exposure: Caesarean section; Outcome: Anal incontinence, flatus
Figure S76: Nieuwenhuijse 2014; Intervention/ Exposure: Ceramic-on-ceramic bearings for total hip arthroplasty; Outcome: Harris Hip Score
Figure S77: Nieuwenhuijse 2014; Intervention/Exposure: High-flexion total knee arthroplasty; Outcome: Flexion in degrees
Figure S78: Nieuwenhuijse 2014; Intervention/ Exposure: Gender-specific total knee arthroplasty; Outcome: Flexion-extension range
**Figure S79**: Nikooie 2019; Intervention/Exposure: Second generation antipsychotics; Outcome: Sedation
**Figure S80:** Nikooie 2019; Intervention/Exposure: Second generation antipsychotics; Outcome: Neurologic outcomes
Figure S81: Ochen 2019; Intervention/Exposure: Surgery for achilles tendon rupture; Outcome: Re-rupture
**Figure S82:** Ochen 2019; Intervention/ Exposure: Surgery for achilles tendon rupture; Outcome: Complications
Figure S83: Pittas 2010; Intervention/Exposure: High vitamin D; Outcome: Hypertension
**Figure S84**: Raman 2013; Intervention/ Exposure: Carotid endarterectomy; Outcome: Ipsilateral stroke

| Study or Subgroup | Weight (%) | Risk Ratio 4, Random, 95% CI | Risk Ratio 4, Random, 95% CI |
|-------------------|------------|-----------------------------|-----------------------------|
| 51.1.1 RCTs       |            |                             |                             |
| ACAS 1995         | 20.8%      | 0.84 [0.42, 0.98]           |                             |
| ACST 2010         | 39.4%      | 0.76 [0.57, 1.01]           |                             |
| VA 1993           | 10.9%      | 0.76 [0.42, 1.35]           |                             |
| **Subtotal (95% CI)** | 88.1%      | 0.72 [0.58, 0.90]           |                             |
| Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.42$, df = 2 ($P = 0.81$); $I^2 = 0\%$
| Test for overall effect: $Z = 2.88$ ($P = 0.004$) |

| 51.1.2 Cohort studies |            |                             |                             |
|-----------------------|------------|-----------------------------|-----------------------------|
| Caracci 1996          | 4.5%       | 0.14 [0.03, 0.62]           |                             |
| Lubman 1994           | 7.4%       | 1.41 [0.48, 4.31]           |                             |
| **Subtotal (95% CI)** | 11.9%      | 0.47 [0.05, 4.46]           |                             |
| Heterogeneity: $\tau^2 = 2.19$; $\chi^2 = 6.93$, df = 1 ($P = 0.01$); $I^2 = 83\%$
| Test for overall effect: $Z = 0.65$ ($P = 0.51$) |

| Total (95% CI)        | 100.0%     | 0.70 [0.51, 0.97]           |                             |
| Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 6.48$, df = 4 ($P = 0.17$); $I^2 = 33\%$
| Test for overall effect: $Z = 2.15$ ($P = 0.03$) |
| Test for suborco differences: $\chi^2 = 0.14$, df = 1 ($P = 0.71$), $P = 9\%$ |

0.01 0.1 1 10 100
Favours carotid EE  Favours control

Favours carotid EE  Favours control
| Study or Subgroup | Weight | IV, Random, 95% CI | Study or Subgroup | Weight | IV, Random, 95% CI |
|------------------|--------|--------------------|------------------|--------|--------------------|
| ACAS 1996        | 26.1%  | 0.71 [0.61, 0.87]  |                  |        |                    |
| ACST 2010        | 63.7%  | 0.81 [0.49, 0.76]  |                  |        |                    |
| VA 1993          | 10.6%  | 0.92 [0.56, 1.51]  |                  |        |                    |
| **Total (95% CI)** | **100.0%** | **0.67 [0.57, 0.75]** | **Total (95% CI)** | **100.0%** | **0.67 [0.57, 0.75]** |

Heterogeneity: Tau² = 0.00; Ch² = 2.78, df = 5 (P = 0.73), I² = 0%
Test for overall effect: Z = 4.85 (P < 0.00001)
Test for subcategory differences: Ch² = 0.07, df = 1 (P = 0.79), P = 0%

**Figure S85**: Raman 2013; Intervention/ Exposure: Carotid endarterectomy; Outcome: Stroke
Figure S86: Raman 2013; Intervention/ Exposure: Carotid artery stenting; Outcome: Periprocedural stroke
Figure S87: Schweizer 2013; Intervention/ Exposure: Nasal deconolization; Outcome: Surgical site infection
**Figure S88**: Schweizer 2013; Intervention/Exposure: Glycopeptide prophylaxis; Outcome: Surgical site infection
### Figure S89

Silvain 2012; Intervention/Exposure: Enoxaparin; Outcome: All-cause mortality

| Study or Subgroup | Risk Ratio IV, Random, 95% CI | Weight | Heterogeneity, Tau² = 0.00, Ch² = 5.00, df = 5 (P = 0.50), I² = 0% |
|-------------------|--------------------------------|--------|---------------------------------------------------------------------|
| **ASSENT-3 2003** | 8.3% 0.93 [0.47, 1.85]        | 8.3%   | Test for overall effect: Z = 1.13 (P = 0.26)                         |
| **ATOLL 2011**    | 10.0% 0.60 [0.33, 1.06]        | 10.0%  |                                                                     |
| **EXTRACT-TIMI 25 2007** | 15.8% 0.98 [0.71, 1.37]   | 15.8%  |                                                                     |
| Galeote et al 2002 | 0.8% 2.94 [0.12, 70.49]        | 0.8%   |                                                                     |
| **STEEPLE 2008**  | 4.7% 1.30 [0.50, 3.80]         | 4.7%   |                                                                     |
| **SYNERGY 2006**  | 11.5% 0.75 [0.45, 1.23]        | 11.5%  |                                                                     |
| **Subtotal (95% CI)** | 51.1% 0.88 [0.70, 1.16] | 51.1%  |                                                                     |

**Total (95% CI)** | 100.0% 0.61 [0.49, 0.82] | 100.0% | Heterogeneity, Tau² = 0.09, Ch² = 4.33, df = 12 (P = 0.46), I² = 0% |

Test for overall effect: Z = 6.19 (P < 0.00001)

Test for subgroup differences: Ch² = 12.37, df = 12 (P = 0.0084), I² = 51.9%
Figure S90: Silvain 2012; Intervention/ Exposure: Enoxaparin; Outcome: Major bleeding
| Study or Subgroup | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|-------------------|--------|-----------------------------|-----------------------------|
| **53.3.3 RCTs**   |        |                             |                             |
| ACTION 2005       | 4.0%   | 0.57 [0.25, 1.00]           |                             |
| ATOLL 2011        | 7.7%   | 0.96 [0.59, 1.55]           |                             |
| CRUGGE 2003       | 4.1%   | 1.13 [0.80, 2.56]           |                             |
| Drozdz et al 2001 | 0.4%   | 0.20 [0.01, 4.06]           |                             |
| Dudek et al 2000a | 3.2%   | 0.39 [0.15, 1.02]           |                             |
| Dudek et al 2000b | 5.6%   | 1.25 [0.00, 3.10]           |                             |
| ExTRACT-TIMI 25 2007 | 13.2% | 0.77 [0.46, 1.30]           |                             |
| Gisle et al 2002  | 1.0%   | 1.63 [0.41, 6.47]           |                             |
| Her et al 2006    | 0.6%   | 0.52 [0.05, 5.63]           |                             |
| Rabah et al 1999  | 0.4%   | 0.33 [0.01, 7.87]           |                             |
| STEEPLE 2006      | 11.1%  | 1.06 [0.80, 1.39]           |                             |
| SYNERGY 2006      | 13.2%  | 0.91 [0.78, 1.06]           |                             |
| ZELUS 2000        | 2.6%   | 0.29 [0.00, 0.02]           |                             |
| **Subtotal (95% CI)** | 65.7% | 0.98 [0.23, 0.99]           |                             |

Heterogeneity Tau² = 0.01; CH² = 15.18, df= 12 (P = 0.23); I² = 21%  
Test for overall effect: Z = 2.07 (P = 0.04)  

| **53.3.4 Cohort studies** | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|---------------------------|--------|-----------------------------|-----------------------------|
| Bieger et al 2011         | 5.8%   | 0.44 [0.24, 0.83]           |                             |
| Drez et al 2009           | 5.3%   | 0.50 [0.25, 0.98]           |                             |
| Gisle et al 2008          | 0.7%   | 0.37 [0.04, 3.46]           |                             |
| Krompas et al 2008        | 1.6%   | 0.95 [0.00, 20.35]          |                             |
| Li et al 2010             | 10.2%  | 0.46 [0.03, 0.63]           |                             |
| Zeyner et al 2005         | 3.9%   | 0.97 [0.18, 0.87]           |                             |
| Zeyner et al 2008         | 6.7%   | 0.36 [0.21, 0.63]           |                             |
| **Subtotal (95% CI)**     | 34.3%  | 0.44 [0.35, 0.55]           |                             |

Heterogeneity Tau² = 0.00; CH² = 1.62, df= 6 (P = 0.95); I² = 0%  
Test for overall effect: Z = 7.06 (P = 0.00001)  

**Total (95% CI)** 100.0% 0.67 [0.55, 0.81]  
Heterogeneity Tau² = 0.07; CH² = 44.04, df= 19 (P = 0.0007); I² = 58%  
Test for overall effect: Z = 4.04 (P = 0.0001)  
Test for subgroup differences: CH² = 23.73, df= 1 (P = 0.000001), I² = 95.8%  

**Figure S91:** Silvain 2012; Intervention/ Exposure: Enoxaparin; Outcome: All-cause mortality or myocardial infarction
Figure S92: Suthar 2012; Intervention/Exposure: Antiretroviral therapy; Outcome: Tuberculosis infection
Figure S93: Te Morenga 2013; Intervention/Exposure: High sugar intake; Outcome: Weight gain
Figure S94: Te Morenga 2013; Intervention/ Exposure: High sugar intake; Outcome: Body Mass Index
**Figure S95:** Thomas 2010; Intervention/ Exposure: Influenza vaccines; Outcome: Influenza-like illness
Figure S96: Tickell-Painter 2017; Intervention/ Exposure: Mefloquine; Outcome: Discontinuation due to adverse effects
Figure S97: Tickell-Painter 2017; Intervention/ Exposure: Mefloquine; Outcome: Serious adverse events or effects
Figure S98: Tickell-Painter 2017; Intervention/Exposure: Mefloquine; Outcome: Nausea
Figure S99: Tricco 2018; Intervention/ Exposure: Live-attenuated zoster vaccines; Outcome: Suspected Herpes Zoster
Figure S100: Vinceti 2018; Intervention/Exposure: High selenium; Outcome: Cancer
Figure S101: Vinceti 2018; Intervention/Exposure: High selenium; Outcome: Cancer mortality
Figure S102: Vinceti 2018; Intervention/Exposure: High selenium; Outcome: Colorectal cancer
Figure S103: Wilson 2011; Intervention/ Exposure: Training for traditional birth attendants/ assistance by traditional birth attendants; Outcome: Perinatal mortality
**Figure S104**: Wilson 2011; Intervention/Exposure: Training for traditional birth attendants/assistance by traditional birth attendants; Outcome: Neonatal mortality
Figure S105: Wilson 2019; Intervention/Exposure: Unicompartmental knee arthroplasty; Outcome: Venous thromboembolism
Figure S106: Wilson 2019; Intervention/ Exposure: Unicompartmental knee arthroplasty; Outcome: Flexion-extension range
### Study or Subgroup

| Study or Subgroup | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|------------------|--------|-----------------------------------|-----------------------------------|
| 61.6.1 RCTs      |        |                                   |                                   |
| Beaud 2017       | 10.2%  | -1.00 [-4.43, 2.43]               |                                   |
| Kunsche 2017     | 9.8%   | 0.00 [1.49, 16.51]                |                                   |
| Sun 2011         | 10.0%  | -1.20 [-19.01, -6.39]             |                                   |
| **Subtotal (95% CI)** | 30.2% | -1.72 [-11.86, 8.45]             |                                   |
| **Heterogeneity:** τ² = 71.80, Chi² = 18.81, df = 2 (P = 0.0301); I² = 90% |
| Test for overall effect: Z = 0.33 (P = 0.74) |

| 61.6.3 Cohort studies |        |                                   |                                   |
|-----------------------|--------|-----------------------------------|-----------------------------------|
| Courtoy 2019          | 10.1%  | -6.20 [-12.32, 0.07]              |                                   |
| Duchmann 2014         | 10.3%  | -1.20 [-3.81, -3.09]              |                                   |
| Lombarst 2009         | 10.1%  | -5.00 [-10.06, 0.08]              |                                   |
| Lum 2010              |        | Not estimable                     |                                   |
| Manzotti 2007         | 10.1%  | -6.50 [-12.05, -6.06]             |                                   |
| Schwab 2015           | 10.1%  | -21.00 [-25.59, -16.51]           |                                   |
| Sihak 2018            | 8.0%   | -30.80 [-45.01, -16.59]           |                                   |
| Siman 2017            | 10.1%  | -45.50 [-35.12, -53.99]           |                                   |
| **Subtotal (95% CI)** | 58.8% | -23.20 [-40.43, -7.71]           |                                   |
| **Heterogeneity:** τ² = 49.19, Chi² = 464.14, df = 6 (P < 0.00001); I² = 99% |
| Test for overall effect: Z = 2.80 (P = 0.005) |

| **Total (95% CI)** | 100.0% | -17.07 [-29.11, -5.04] |                                   |
| **Heterogeneity:** τ² = 38.45, Chi² = 542.69, df = 9 (P < 0.00001); I² = 98% |
| Test for overall effect: Z = 2.78 (P = 0.005) |
| Test for subgroup differences: Chi² = 4.83, df = 1 (P = 0.03), I² = 79.7% |

**Figure S107:** Wilson 2019; Intervention/Exposure: Unicompartmental knee arthroplasty; Outcome: Operation duration
Figure S108: Yank 2011; Intervention/Exposure: Recombinant factor VII; Outcome: All-cause mortality
Figure S109: Yank 2011; Intervention/ Exposure: Recombinant factor VII; Outcome: Thromboembolism
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Figure S110: Zhang 2016; Intervention/Exposure: Everolimus-eluting bioresorbable vascular scaffold; Outcome: Stent thrombosis
Figure S111: Zhang 2016: Intervention/ Exposure: Everolimus-eluting bioresorbable vascular scaffold; Outcome: All-cause mortality
**Figure S112**: Zhang 2016; Intervention/Exposure: Everolimus-eluting bioresorbable vascular scaffold; Outcome: Coronary heart disease mortality

| Study of Subgroup | Odds Ratio | Weight IV, Random, 95% CI | Odds Ratio | Weight IV, Random, 95% CI |
|-------------------|------------|---------------------------|------------|---------------------------|
| **63.3.1 RCTs**   |            |                           |            |                           |
| ABSORB China, 2015| 5.3%       | 0.14 [0.01, 2.73]         |            |                           |
| ABSORB III, 2015  | 10.6%      | 0.02 [0.52, 0.20]         |            |                           |
| EVERBIO II, 2015  | 3.5%       | 0.12 [0.13, 7.66]         |            |                           |
| **Subtotal (95% CI)** | 20.7% | 1.40 [0.17, 11.23] | 20.7% | 1.40 [0.17, 11.23] |
| **63.3.2 Cohort study** | 33.1% | 1.20 [0.37, 3.65] | 33.1% | 1.20 [0.37, 3.65] |
| Abizaid, 2015     | 35.9%      | 1.00 [0.32, 3.14]         |            |                           |
| Costopoulus, 2015 | 4.5%       | 0.33 [0.01, 0.20]         |            |                           |
| **Subtotal (95% CI)** | 79.3% | 0.91 [0.42, 1.97] | 79.3% | 0.91 [0.42, 1.97] |

Heterogeneity: Tau² = 1.49, Chi² = 5.65, df = 2 (P = 0.17), P = 44%
Test for overall effect: Z = 0.31 (P = 0.75)

Total (95% CI) 100.0% 1.63 [0.52, 2.04]

Heterogeneity: Tau² = 0.00, Chi² = 4.7, df = 3 (P = 0.09), P = 9%
Test for overall effect: Z = 0.23 (P = 0.82)
Test for substantial differences: Chi² = 0.14, df = 1 (P = 0.71), P = 0%
Figure S113: Zhang 2017; Intervention/Exposure: Percutaneous coronary intervention; Outcome: All-cause mortality
Figure S114: Zhang 2017; Intervention/ Exposure: Percutaneous coronary intervention; Outcome: Cardiovascular mortality
### Figure S115: Zhang 2017; Intervention/ Exposure: Percutaneous coronary intervention; Outcome: Myocardial infarction

| Study or Subgroup | Hazard Ratio IV, Random, 95% CI | Weight |
|-------------------|--------------------------------|--------|
| **64.3.1 RCTs**   |                                |        |
| EKCEL 2016        | 0.93 [0.67, 1.29]              | 19.1%  |
| LE MANS 2016      | 0.88 [0.24, 3.23]              | 4.9%   |
| NOBLE 2016        | 2.88 [1.43, 5.92]              | 10.6%  |
| PRECOMET 2015     | 1.20 [0.37, 3.93]              | 5.8%   |
| SYNTAX 2014       | 1.67 [0.91, 3.06]              | 13.0%  |
| **Subtotal (95% CI)** | 1.39 [0.86, 2.28] | 53.7% |

Heterogeneity: Tau² = 0.16; Chi² = 9.34, df = 4 (P = 0.05); I² = 57%

Test for overall effect: Z = 1.33 (P = 0.19)

| **64.3.2 Cohort studies** | Hazard Ratio IV, Random, 95% CI | Weight |
|---------------------------|--------------------------------|--------|
| CREDO-Kyoto 2 2012        | 2.47 [0.81, 7.53]              | 6.2%   |
| CUSTOMIZE registry 2011   | 4.80 [1.30, 17.90]             | 1.3%   |
| Jeong 2013                | 4.73 [0.99, 22.60]             | 3.6%   |
| Yu 2016                   | 1.86 [0.94, 2.93]              | 13.7%  |
| Zheng 2016                | 2.00 [1.61, 2.48]              | 21.5%  |
| **Subtotal (95% CI)**     | 2.00 [1.65, 2.44]              | 46.3%  |

Heterogeneity: Tau² = 0.00; Chi² = 2.10, df = 4 (P = 0.72); I² = 0%

Test for overall effect: Z = 6.81 (P < 0.0001)

Total (95% CI): 1.50 [1.22, 1.88]

Heterogeneity: Tau² = 0.12; Chi² = 21.05, df = 9 (P = 0.01); I² = 67%

Test for overall effect: Z = 3.17 (P < 0.002)

Test for subgroup differences: Chi² = 1.58, df = 1 (P = 0.17); I² = 46.8%
Figure S116: Ziff 2015; Intervention/Exposure: Digoxin; Outcome: All-cause mortality
**Figure S117**: Ziff 2015; Intervention/Exposure: Digoxin; Outcome: Cardiovascular mortality
**Figure S118:** Ziff 2015; Intervention/Exposure: Digoxin; Outcome: Hospital admission

| Study or Subgroup | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|-------------------|--------|------------------------------|------------------------------|
| **65.3.1 RCTs**   |        |                              |                              |
| Ahmed 2006        | 15.4%  | 1.01 [0.92, 1.11]            |                              |
| DIG 1997          | 22.4%  | 0.92 [0.97, 0.97]            |                              |
| Subtotal (95% CI)| 37.8%  | 0.96 [0.87, 1.05]            |                              |

Heterogeneity: $I^2 = 0.00, \chi^2 = 3.83, df = 1 (P = 0.06)$; $I^2 = 65$

Test for overall effect: $Z = 0.97 (P = 0.33)$

| **65.3.2 Cohort studies** |        |                              |                              |
|----------------------------|--------|------------------------------|------------------------------|
| Ahmed 2014                 | 21.9%  | 0.68 [0.93, 0.93]            |                              |
| Banerjee 1998              | 16.5%  | 0.68 [0.82, 0.94]            |                              |
| Ghali 2004                 | 2.3%   | 1.30 [0.93, 1.82]            |                              |
| Khazraie 2013              | 16.5%  | 0.66 [0.89, 1.04]            |                              |
| Subtotal (95% CI)          | 62.2%  | 0.92 [0.85, 0.99]            |                              |

Heterogeneity: $I^2 = 0.00, \chi^2 = 8.3, df = 3 (P = 0.04)$; $I^2 = 84$

Test for overall effect: $Z = 2.28 (P = 0.02)$

**Total (95% CI)**

100.0% 0.93 [0.88, 0.98]

Heterogeneity: $I^2 = 0.00, \chi^2 = 12.93, df = 6 (P = 0.02)$; $I^2 = 61$

Test for overall effect: $Z = 2.06 (P = 0.04)$

Test for sub-group differences: $\chi^2 = 0.47, df = 1 (P = 0.49), P = 0.00$
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