**Supplemental file 3**

Cochrane risk of bias assessment of included studies.

# Dangour AD, Allen E, Clarke R, Elbourne D, Fletcher AE, Letley L, Richards M, Whyte K, Uauy R, Mills K. Effects of vitamin B-12 supplementation on neurologic and cognitive function in older people: a randomized controlled trial. Am J Clin Nutr 2015;102:639–47.

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| **Entry** | **Judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk. | Quote: “The study manager will telephone the central randomisation service to randomise the participant”  Comment: Probably done. |
| Allocation concealment (selection bias) | Low risk. | Quote: “The study manager will telephone the central randomisation service to randomise the participant”  Comment: Probably done. |
| Blinding of participants and personnel (performance bias) | Low risk. | Quote: “Following random allocation a trial number will be given to each study participant. This will also be used to identify the supply of dietary supplements to be prescribed for each participant.”  Comment: Probably done. |
| Blinding of outcome assessment (detection bias) (patient-reported outcomes) | NA | NA |
| Blinding of outcome assessment (detection bias) | NA | NA |
| Incomplete outcome data addressed (attrition bias) (Short-term outcomes  (2-6 weeks)) | NA | NA |
| Incomplete outcome data addressed (attrition bias) (Longer-term outcomes  (>6 weeks)) | Low risk | 12 months: 5/99 missing from intervention group; 5/102 missing from control group. Reasons withdrawal, death and no final data. |
| Selective reporting (reporting bias) | NA | NA |

Favrat B, Vaucher P, Herzig L et al. Oral vitamin B12 for patients suspected of subtle cobalamin deficiency: a multicentre pragmatic randomised controlled trial. *BMC Fam Pract.* 2011;122.

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| **Entry** | **Judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk. | Quote: ”An independent pharmacist delivered active or placebo pills according to a prior, simple computer-generated randomisation list.”  Comment: probably done |
| Allocation concealment (selection bias) | Low risk. | Quote: “An independent pharmacist delivered active or placebo pills according to a prior, simple computer-generated randomisation list. The active and placebo pills were similar in appearance and taste and were given in a similar container. Patients, caregivers, investigators, and the statistician were blinded to treatment until the end of the trial.”  Comment: probably done |
| Blinding of participants and personnel (performance bias) | Low risk. | Quote: “Patients, caregivers, investigators, and the statistician were blinded to treatment until the end of the trial.”  Comment: probably done |
| Blinding of outcome assessment (detection bias) (patient-reported outcomes) | NA | NA |
| Blinding of outcome assessment (detection bias) (mortality) | NA | NA |
| Incomplete outcome data addressed (attrition bias) (Short-term outcomes  (2-6 weeks)) | Low risk. | 1 month: 2/26 missing from intervention group; 2/24 missing from control group. Reasons: mishandling of blood samples and other missing data most completely at random. |
| Incomplete outcome data addressed (attrition bias) (Longer-term outcomes  (>6 weeks)) | Low risk. | 4 months: 7/26 missing from intervention group; 2/24 missing from control group. Reasons: mishandling of blood samples and other missing data most completely at random. |
| Selective reporting (reporting bias) | NA | NA |

# Hvas AM, Ellegaard J, Nexø E. Vitamin B12 Treatment Normalizes Metabolic Markers But Has Limited Clinical Effect: A Randomized Placebo-controlled Study. Clinical Chemistry 2001;47:8 1396–1404.

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| **Entry** | **Judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Quote: “the packets were delivered in two batches, each having an equal number of Betolvex and placebo packets, in random sequence”  Comment: probably done |
| Allocation concealment (selection bias) | Low risk | Quote: “the packets were delivered in two batches, each having an equal number of Betolvex and placebo packets, in random sequence. The code was kept by Dumex-Alpharma during the entire trial.”  Comment: probably done |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: “the packets were delivered in two batches, each having an equal number of Betolvex and placebo packets, in random sequence. The code was kept by Dumex-Alpharma during the entire trial.”  Comment: probably done |
| Blinding of outcome assessment (detection bias) (patient-reported outcomes) | NA | NA |
| Blinding of outcome assessment (detection bias) (mortality) | NA | NA |
| Incomplete outcome data addressed (attrition bias) (Short-term outcomes  (2-6 weeks)) | NA | NA |
| Incomplete outcome data addressed (attrition bias) (Longer-term outcomes  (>6 weeks)) | Low risk | 3 months: 3/70 missing from intervention group, no missing data in placebo group |
| Selective reporting (reporting bias) | NA | NA |

Seal EC, Metz J, Flicker L, Melny J. A randomized, double-blind, placebo-controlled study of oral vitamin B12 supplementation in older patients with subnormal or borderline serum vitamin B12 concentrations. *J Am Geriatr Soc.* 2002;50(1):146-151.

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| **Entry** | **Judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Quote: “After baseline testing, patients were randomized in a double-blind manner to receive either placebo or vitamin B12 10 ug or 50 ug daily for 4 weeks.  Comment: probably done |
| Allocation concealment (selection bias) | Low risk | Quote: “After baseline testing, patients were randomized in a double-blind manner to receive either placebo or vitamin B12 10 ug or 50 ug daily for 4 weeks.  Comment: probably done |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: “After baseline testing, patients were randomized in a double-blind manner to receive either placebo or vitamin B12 10 ug or 50 ug daily for 4 weeks.  Comment: probably done |
| Blinding of outcome assessment (detection bias) (patient-reported outcomes) | NA | NA |
| Blinding of outcome assessment (detection bias) (mortality) | NA | NA |
| Incomplete outcome data addressed (attrition bias) (Short-term outcomes  (2-6 weeks)) | Low risk | 4 weeks: no missings |
| Incomplete outcome data addressed (attrition bias) (Longer-term outcomes  (>6 weeks)) | NA | NA |
| Selective reporting (reporting bias) | NA | NA |

Durga J, Bots ML, Schouten EG, Grobbee DE, Kok FJ, Verhoef P. Effect of 3 y of folic acid supplementation on the progression of carotid intima-media thickness and carotid arterial stiffness in older adults. *Am J Clin Nutr.* 2011;93(5):941-949.

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| **Entry** | **Judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk. | Quote: “The sequence of entry into the study was allocated to either treatment by using permuted blocks with block sizes of 4 and 6, which varied randomly”  Comment: Probably done. |
| Allocation concealment (selection bias) | Low risk. | Quote: “The sequence of entry into the study was allocated to either treatment by using permuted blocks with block sizes of 4 and 6, which varied randomly”  Comment: Probably done. |
| Blinding of participants and personnel (performance bias) | Low risk. | Quote: “Specialized personnel not involved in the study allocated and labelled the capsule boxes with the subjects’ unique sequence number. Members of the same household received the same treatment. Folic acid and placebo capsules, produced by Swiss-Caps Benelux (Heerhugowaard, Netherlands), were indistinguishable in appearance (yellow coating and content).”  Comment: Probably done. |
| Blinding of outcome assessment (detection bias) (patient-reported outcomes) | NA | NA |
| Blinding of outcome assessment (detection bias) (mortality) | NA | NA |
| Incomplete outcome data addressed (attrition bias) (Short-term outcomes  (2-6 weeks)) | NA | NA |
| Incomplete outcome data addressed (attrition bias) (Longer-term outcomes  (>6 weeks)) | Low risk | 3 years: 13/406 missing from intervention group; 6/413 missing from control group. Reasons: mainly because of death. |
| Selective reporting (reporting bias) | NA | NA |

Pathansali R, Mangoni AA, Creagh-Brown B et al. Effects of folic acid supplementation on psychomotor performance and hemorheology in healthy elderly subjects. *Arch Gerontol Geriatr.* 2006;43(1):127-137.

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| **Entry** | **Judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Quote: ”The allocation sequence was generated by software located in the Pharmacy Department”  Comment: Probably done. |
| Allocation concealment (selection bias) | Low risk | Quote: ”randomized, double-blind, parallel-group study”  Comment: Probably done. |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: ”randomized, double-blind, parallel-group study”  Comment: Probably done. |
| Blinding of outcome assessment (detection bias) (patient-reported outcomes) | NA | NA |
| Blinding of outcome assessment (detection bias) (mortality) | NA | NA |
| Incomplete outcome data addressed (attrition bias) (Short-term outcomes  (2-6 weeks)) | Low risk | 4 weeks: no missing data |
| Incomplete outcome data addressed (attrition bias) (Longer-term outcomes  (>6 weeks)) | NA | NA |
| Selective reporting (reporting bias) | NA | NA |

Ntaios G, Savopoulos C, Karamitsos D et al. The effect of folic acid supplementation on carotid intima-media thickness in patients with cardiovascular risk: a randomized, placebo-controlled trial. *Int J Cardiol.* 2010;143(1):16-19.

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| **Entry** | **Judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Quote: “The patients were randomized to receive  either a daily dose of 5 mg folic acid (group I, n=53) or placebo  (group II, n=50) for 18 months. ”  Comment: Probably done. |
| Allocation concealment (selection bias) | Low risk | Quote: “The patients were randomized to receive  either a daily dose of 5 mg folic acid (group I, n=53) or placebo  (group II, n=50) for 18 months. ”  Comment: Probably done. |
| Blinding of participants and personnel (performance bias) | Low risk | Quote: “The patients were randomized to receive  either a daily dose of 5 mg folic acid (group I, n=53) or placebo  (group II, n=50) for 18 months. ”  Comment: Probably done. |
| Blinding of outcome assessment (detection bias) (patient-reported outcomes) | NA | NA |
| Blinding of outcome assessment (detection bias) (mortality) | NA | NA |
| Incomplete outcome data addressed (attrition bias) (Short-term outcomes  (2-6 weeks)) | NA | NA |
| Incomplete outcome data addressed (attrition bias) (Longer-term outcomes  (>6 weeks)) | Low risk | No missing data |
| Selective reporting (reporting bias) | NA | NA |