National Institute for Health and Care Excellence

Draft for consultation

Vitamin B12 deficiency in over 16s: diagnosis and management

[B] Evidence reviews for risk factors and symptoms and signs for vitamin B12 deficiency

NICE guideline <number>

Evidence reviews underpinning recommendations 1.2.1 to 1.2.7 and recommendations for research in the NICE guideline

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1. Risk factors for vitamin B12 deficiency

1.1. Review question

What are the risk factors for vitamin B12 deficiency?

1.1.1. Introduction

There are many possible risk factors for developing vitamin B12 deficiency. These can be broadly split into dietary and non-dietary factors and medicines. The extent to which these factors increase the risk of developing vitamin B12 deficiency is unclear.

There are a wide variety of possible symptoms and signs of vitamin B12 deficiency, but it is unclear which ones are most indicative and useful in the diagnostic process.

Better awareness regarding when to suspect and initiate testing for vitamin B12 deficiency would reduce delayed and missed diagnosis and help reduce complications associated with vitamin B12 deficiency. The following reviews seek to identify the most useful risk factors and symptoms and signs in raising suspicion of vitamin B12 deficiency.

1.1.2. Summary of the protocol

For full details see the review protocol in below.

Table 1: PICO characteristics of review question

Population	Adults
Prognostic variables under consideration	Dietary risk factors: • vegetarianism • veganism • restrictive diets including eating disorders • socioeconomic status (cannot afford enough food that is rich in vitamin B12) • learning difficulties Prescription medications: • metformin • proton pump inhibitors • colchicine • contraceptive pill • antibiotics (sulfonamides, tetracyclines, trimethoprim, minocycline, neomycin, co-trimoxazole, demeclocycline, fluoroquinolones, macrolides • h2 antagonists • anticonvulsants (valproic acid, phenobarbital (Donnatal®, Solfoton®), phenytoin) • nitrous oxide (prescription and recreational) Non-dietary risk factors: • gastric surgery (including bariatric) • terminal ileum resection • increasing age • family history of B12 deficiency/pernicious anaemia

	• history of another autoimmune disease (e.g., Sjögrens, vitiligo, diabetes type 1, autoimmune thyroid disease, multiple autoimmune disease) • documented gastric body-predominant gastritis • coeliac disease • abdominal/pelvic radiotherapy
Confounding factors	All exposure/risk factors listed above. Age and sex as a minimum.
Outcomes	Diagnosis of vitamin B12 deficiency at any time point reported in the study (adjusted hazard ratios, odds ratios or risk ratios).
Study design	Inclusion: • Prospective and retrospective cohort studies with multivariate analysis. • Case control studies with multivariate analysis. • Systematic reviews of the above. Exclusion: • Studies with univariate analysis only will be excluded.

1.1.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4. Prognostic evidence

1.1.4.1. Included studies

Seven studies were included in the review;[1-5, 7, 8] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 3, Table 4, Table 5, Table 6, Table 7 and Table 8).

- One randomised controlled trial, one prospective cohort study and one retrospective cohort study reported the predictive value of metformin use for vitamin B12 deficiency in people with type 2 diabetes or prediabetes.
- One case-control study reported the predictive value of proton pump inhibitor use for vitamin B12 deficiency.
- One case-control study reported the predictive value of H2 receptor antagonist use for vitamin B12 deficiency.
- Three retrospective cohort studies reported the predictive value of ileal resection for vitamin B12 deficiency in people with Crohn's disease.

Different confounders were considered in each study. All included studies adjusted/matched for age and gender as a minimum. Most of the studies used logistic regression analysis to adjust for confounders. A variety of different definitions of vitamin B12 deficiency were used in the studies.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2. Excluded studies

See the excluded studies list in below.

1.1.5. Summary of studies included in the prognostic evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Notes/Limitations
Aroda 2016[1] Secondary analysis of the Diabetes Prevention Program Outcomes Study (prospective cohort study)	n=1800 adults with impaired glucose tolerance (randomised to metformin, lifestyle intervention or placebo, followed up at mean 3.2 years, then participating in a follow up study in which those on metformin continued) USA	Logistic regression analysis	Metformin (risk per year of use)	Age, sex, BMI, use of prescription proton pump inhibitors or prescription H2 blockers, diabetes status, weight change during DPP/DPPOS, and treatment arm	Vitamin B12 deficiency (≤ 203 pg/mL)	Serious population indirectness: impaired glucose tolerance
Bermejo 2013[2] Retrospective cohort study	n=180 adults with Crohn's disease Spain	Logistic regression analysis	Ileal resection	CD location, disease activity and duration of CD (age and gender also considered in univariate analysis)	Vitamin B12 deficiency (<200 pg/ml) (n=28)	Serious population indirectness: Crohn's disease Those receiving supplemental B12 were excluded
De Jager 2010 [3] Randomised controlled trial	N=390 adults with insulin treated type two diabetes The Netherlands	-	Metformin	-	Vitamin B12 deficiency (< 150 pmol/L) (n=24)	Serious population indirectness: insulin treated type 2 diabetes Those with vitamin B-12 concentrations < 150 pmol/l at baseline, interim analysis, or

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Notes/Limitations
						at both time points were supplemented at 16 weeks and, therefore, excluded from analyses after 16 weeks
Headstrom 2008[4] Retrospective cohort study	N=201 people with Crohn's disease USA	Logistic regression analysis	Ileal resection	Age, sex, race, duration of disease, disease location, and prior surgery	Vitamin B12 deficiency (Values from 180 – 223 pg/mL considered indeterminate and values <180 pg/mL considered deficient. For the primary analysis, B12 concentrations <224 pg/mL considered abnormal because practice to offer replacement at this concentration)	Serious population indirectness: Crohn's disease Those previously diagnosed with B12 deficiency or receiving supplemental B12 at the time of initial visit were excluded
Lam 2013[5] Case-control study	n=25956 B12 deficiency cases n=184199 matched controls identified from an electronic database covering the Kaiser Permanente Northern California integrated	Matched	Proton pump inhibitors H2 receptor antagonists	Matched by sex, region of home facility, race/ethnicity, year of birth, and membership duration. Additional potential confounders entered in the original model but not significant.	Vitamin B12 deficiency (1 of the following: first diagnostic code for vitamin B12 deficiency, or specific text diagnoses of vitamin B12 deficiency; an	

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Notes/Limitations
	healthcare system USA				abnormally low value for serum vitamin B12; a new and at least 6-month supply of injectable vitamin B12)	
Shivaprasad 2020[7] Retrospective cohort study	n=2887 adults with type 2 diabetes India	Logistic regression analysis	Metformin (metformin usage index) Age	Age, MUI, duration of diabetes, BMI, and HbA1c (gender also considered in univariate analysis)	Vitamin B12 deficiency (absolute deficiency <200 pg/ml and borderline deficiency 200–300 pg/ml)	Serious population indirectness: type 2 diabetes Age as a risk factor unclearly reported (units/polarity) Those receiving vitamin B12 supplementation over the last 6 months were excluded
Ward 2015[8] Retrospective cohort study	n=381 adults with Crohn's disease UK	Logistic regression analysis	Ileal resection	Age, gender, smoking status, disease phenotype, treatment with immunomodulators or anti–tumour necrosis factor agents, disease duration, ileal resection length, and disease activity were entered into the model and significant	Vitamin B12 deficiency (<25 pmol/L defined as deficiency, >50 pmol/L considered replete. Values 25-50 pmol/L underwent MMA analysis. MMA values >280 nmol/L confirmed B12 deficiency in patients <65 years	Serious population indirectness: Crohn's disease Unclear duration between prognostic factor and outcome Those receiving vitamin B12 replacement were excluded

Study	Population	Analysis	Prognostic variable(s)	Confounders	Outcomes	Notes/Limitations
				factors remained in the final model	old, or >360 nmol/L in patients >65 years old. Serum B12 measured using the ARCHITECT assay (Abbott Diagnostics). Patients with values <107 pmol/L were defined as B12 deficient as per local laboratory ranges. A separate analysis was performed using the National Health and Nutrition Evaluation Survey serum B12 cut-off for diagnosing B12 deficiency of <147 pmol/L)	

1 See Appendix D for full evidence tables.

2 1.1.6. Summary of the prognostic evidence

3 **Table 3: Clinical evidence summary: metformin (randomised controlled trials)**

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Metformin use for predicting vitamin B12 deficiency (<150 pmol/l)	390 (1)	VERY LOW[a,b]	HR: 5.5 (1.6 to 18.91)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
(insulin treated type 2 diabetes)	52 months	Due to risk of bias, indirectness	

(a) Downgraded by two increments due to very high risk of bias (those with vitamin B-12 concentrations < 150 pmol/l at baseline, interim analysis, or at both time points were excluded from analyses after 16 weeks; unclear measurement of adherence to metformin treatment; reported difference in age between groups, effects of which were investigated for B12 concentrations but not for deficiency outcome; high rate of missing outcome data at final visit)

(b) Downgraded by 1 increment due to serious population indirectness (applicability limited to those with insulin treated type 2 diabetes).

Table 4: Clinical evidence summary: metformin (prospective cohort studies)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Metformin use per year for predicting vitamin B12 deficiency (≤ 203 pg/mL) (impaired glucose tolerance)	1800 (1) 9 years	VERY LOW[a,b] Due to risk of bias, indirectness	Adjusted OR: 1.13 (1.06 to 1.2)

(c) Downgraded by two increments due to very high risk of bias (vitamin B12 status at baseline not reported; >10% last to follow up with no description of those missing from the analysis or attempts to follow up; measurement of metformin use included self-report; vitamin B12 deficiency based on serum level alone; not all confounders accounted for; model development strategy not reported)

(d) Downgraded by 1 increment due to serious population indirectness (applicability limited to those with impaired glucose tolerance).

Table 5: Clinical evidence summary: metformin (retrospective cohort studies)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Metformin (metformin usage index <5) for predicting vitamin B12 deficiency (<200 pg/ml or borderline deficiency 200–300 pg/ml) (type 2 diabetes)	2887 (1) unclear	VERY LOW[a,b,c] Due to risk of bias, indirectness, imprecision	Adjusted OR: 1.37 (0.88 to 2.13)
Metformin (metformin usage index >5) for predicting vitamin B12 deficiency (<200 pg/ml or borderline deficiency 200–300 pg/ml) (type 2 diabetes)	2887 (1) unclear	VERY LOW[a,b] Due to risk of bias, indirectness	Adjusted OR: 3.56 (2.29 to 5.53)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Metformin (metformin usage index >10) for predicting vitamin B12 deficiency (<200 pg/ml or borderline deficiency 200–300 pg/ml) (type 2 diabetes)	2887 (1) unclear	VERY LOW[a,b] Due to risk of bias, indirectness	Adjusted OR: 5.12 (3.12 to 8.4)
Metformin (metformin usage index >15) for predicting vitamin B12 deficiency (<200 pg/ml or borderline deficiency 200–300 pg/ml) (type 2 diabetes)	2887 (1) unclear	VERY LOW[a,b] Due to risk of bias, indirectness	Adjusted OR: 6.74 (4.39 to 10.35)

(a) Downgraded by two increments due to very high risk of bias (vitamin B12 status at baseline (prior to risk factors) not reported and those receiving supplements were excluded; unclear measurement of metformin use (based on clinical records - no further detail); no information on missing data; unclear whether borderline deficiency is included in deficiency outcome (appears so))
(b) Downgraded by one increment due to serious population indirectness (applicability limited to those with type 2 diabetes)
(c) Downgraded by one increment due to imprecision if the confidence interval crossed the null line

Table 6: Clinical evidence summary: proton pump inhibitors (case control studies)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Proton pump inhibitor (at least a 2-year supply prior to the index date) for predicting vitamin B12 deficiency (diagnostic code for deficiency/specific text diagnoses/low serum B12/new at least 6-month supply of injectable B12) (B12 deficiency cases and matched controls from an electronic database)	210155 (1) unclear	LOW[a] Due to risk of bias	OR: 1.65 (1.58 to 1.72)

(a) Downgraded by two increments due to very high risk of bias (unclear duration of follow up; medication duration <2 years and OTC medications not included in the analysis; not all key confounders considered/measurable due to study design; analytical strategy described, but results not fully reported)

Table 7: Clinical evidence summary: H2 receptor antagonists (case control studies)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
H2 receptor antagonists (at least a 2-year supply prior to the index date) for predicting vitamin B12 deficiency	210155 (1)	LOW[a] Due to risk of bias	OR: 1.25 (1.17 to 1.34)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
(diagnostic code for deficiency/specific text diagnoses/low serum B12/new at least 6-month supply of injectable B12) (B12 deficiency cases and matched controls from an electronic database)	unclear		

(a) Downgraded by two increments due to very high risk of bias (unclear duration of follow up; medication duration <2 years and OTC medications not included in the analysis; not all key confounders considered/measurable due to study design; analytical strategy described, but results not fully reported)

Table 8: Clinical evidence summary: Ileal resection (retrospective cohort studies)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Previous ileal or ileocolonic resection for predicting vitamin B12 deficiency (< 200 pg/ml) (Crohn's disease)	180 (1) unclear	VERY LOW[a,b] Due to risk of bias, indirectness	Adjusted OR: 2.7 (1.2 to 6.07)
Prior ileal resection 0-20cm for predicting vitamin B12 deficiency (<25 pmol/L Values 25-50 pmol/L underwent MMA analysis. See study details) (Crohn's disease)	381 (1) unclear	LOW[b,c] Due to risk of bias, indirectness	Adjusted OR: 3 (1.5 to 6)
Prior ileal resection >20cm for predicting vitamin B12 deficiency (<25 pmol/L Values 25-50 pmol/L underwent MMA analysis. See study details) (Crohn's disease)	381 (1) unclear	LOW[b,c] Due to risk of bias, indirectness	Adjusted OR: 6.7 (3 to 14.96)
Prior ileal resection for predicting vitamin B12 deficiency (<224 pg/mL) (Crohn's disease)	201 (1) unclear	VERY LOW[b,d] Due to risk of bias, indirectness	Adjusted OR: 7.22 (1.97 to 26.46)

(a) Downgraded by two increments due to very high risk of bias (B12 status at baseline (prior to/at the time of resection) not reported; those receiving B12 supplements excluded; not all confounders considered; no information on missing data; significant results only reported in text)
(b) Downgraded by one increment due to serious population indirectness (applicability limited to those with Crohn's disease)
(c) Downgraded by one increment due to high risk of bias (vitamin B12 status at baseline not reported, although history of diagnosed deficiency excluded; retrospective chart review with unclear duration between prognostic factor and outcome; not all key confounders measured/adjusted for)
(d) Downgraded by two increments due to very high risk of bias (unclear duration between prognostic factor and outcome; adjusted for some but not all key confounders; limited information on measurement of prognostic and confounding factors; definition of deficiency based on serum values only and includes indeterminate range)

See Appendix F for full GRADE tables.

1.1.7. Economic evidence

This is a prognostic risk factor review therefore economic evidence is not relevant to this review question.

1.2. Review question

What signs and symptoms are indicative of vitamin B12 deficiency?

1.2.1. Introduction

See section 1.1.1

1.2.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 9: PICO characteristics of review question

Population	Adults who have symptoms compatible with vitamin B12 deficiency but who do not have a diagnosis. Strata: • Older adults (65 and over)
Target condition	Vitamin B12 deficiency
Signs and symptoms	General symptoms: • Unexplained fatigue • Unexplained chronic headache/migraine Haematological manifestations: • Anaemia • Macrocytosis Neurological manifestations: • Peripheral neuropathy • Gait disorders • Falls • Altered cognition (including delirium) • Dementia • Paraesthesia (pins and needles) • Ataxia/diminished proprioception/vibration sensation Mental health manifestations: • Depression • Anxiety • Psychosis Other: • Glossitis • Optic nerve atrophy/dysfunction/blurred vision
Reference standard	Reference standard:

	• clinical diagnosis of vitamin B12 deficiency
Statistical measures	Diagnostic association of signs and symptoms with a confirmed diagnosis of vitamin B12 deficiency. Measured by: Diagnostic accuracy data • Sensitivity (prioritised), specificity, PPV, NPV Association data • Adjusted RR or OR.
Study design	• Prospective and retrospective cohort studies with multivariate analysis • Cross-sectional studies • Systematic reviews of the above

1.2.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.2.4. Diagnostic evidence

1.2.4.1. Included studies

No relevant diagnostic accuracy or association studies of symptoms and signs in people under investigation for vitamin B12 deficiency were identified.

See also the study selection flow chart in Appendix C.

1.2.4.2. Excluded studies

See the excluded studies list in Appendix J.

1.2.5. Summary of studies included in the diagnostic evidence

No evidence identified.

1.2.6. Summary of the diagnostic evidence

No evidence identified.

1.2.7. Economic evidence

This is a diagnostic review therefore economic evidence is not relevant to the review question.

1.3. The committee's discussion and interpretation of the evidence

The committee discussion of the review on symptoms and signs is included in the discussion of the review on risk factors.

1.3.1. The outcomes that matter most

The outcome of interest for the review of risk factors was diagnosis of vitamin B12 deficiency. There is wide variation and lack of agreement on the definition of vitamin B12 deficiency, therefore any definition reported in the studies was included. The predictive values of each potential risk factor were reported as adjusted odds ratios, hazard ratios or risk ratios.

Diagnostic accuracy for diagnosis of vitamin B12 deficiency as defined by the studies was the most important outcome for the review of symptoms and signs. The committee prioritised sensitivity over specificity because and symptoms and signs would be used to help select those suspected of having a deficiency, in whom further investigation may be required. Supplementary diagnostic association data, reported as adjusted odds ratios or risk ratios were also included, as it was anticipated that there may be little diagnostic accuracy data available.

1.3.2. The quality of the evidence

Risk factors

One randomised controlled trial, one prospective cohort study and one retrospective cohort study reported the predictive value of metformin use for vitamin B12 deficiency in people with type 2 diabetes or prediabetes. Evidence was of very low quality, mainly due to risk of bias and population indirectness. Studies were based on adults with diabetes or prediabetes and evidence was therefore not applicable to the wider adult population.

One case-control study reported the predictive value of proton pump inhibitor and H2 receptor antagonist use for vitamin B12 deficiency. Evidence was of low quality due to risk of bias. Main sources of potential bias were an unclear duration of follow up; exposure to medicines for less than two years and over-the-counter medicines being excluded from the analysis; lack of consideration of all key confounding factors; and incomplete reporting of results.

Three retrospective cohort studies reported the predictive value of ileal resection for vitamin B12 deficiency in people with Crohn's disease. Evidence was of low to very low quality due to risk of bias and population indirectness. Studies were based on adults with Crohn's disease and evidence was therefore not applicable to the wider adult population. However, the committee agreed that the evidence is applicable to all other indications for ileal resection, such as ileal neuroendocrine tumours and to gastric resections and total gastrectomy. See section 1.3.3 for further explanation on gastrointestinal surgery as a risk factor.

Different confounding factors were considered and there were a variety of definitions of vitamin B12 deficiency used in the studies. Therefore, no meta-analysis was carried out. The committee considered that although the evidence identified was of low to very low quality, the results of the review were in line with their expectations and clinical experience.

No evidence was identified for any dietary risk factors, including vegetarianism, veganism, restrictive diets, socioeconomic status, or learning difficulties. No evidence was identified for the non-dietary risk factors of gastric surgery, increasing age, family history of pernicious anaemia, history of another autoimmune disease, documented gastric body-predominant gastritis, coeliac disease, or abdominal or pelvic radiotherapy. No evidence was identified for the prescription medicines colchicine, contraceptive pill, antibiotics, anticonvulsants, or nitrous oxide with air (gas and air).

Symptoms and signs

No studies were identified that assessed the accuracy of symptoms and signs in diagnosing vitamin B12 deficiency. No studies that assessed the association of symptoms and signs with a diagnosis of vitamin B12 deficiency were identified.

1.3.3. Benefits and harms

Risk factors

Medicines and recreational nitrous oxide with air (gas and air) use

Evidence suggested that metformin use is a risk factor for vitamin B12 deficiency. Despite the very low quality of the evidence, the committee noted that the increased risk in this group is generally accepted in current clinical practice. The Medicines and Healthcare products Regulatory Agency advise that vitamin B12 deficiency is a common side effect experienced by patients on metformin treatment, especially in those receiving a higher dose or longer treatment duration and in those with existing risk factors. They advise that those who are being treated with metformin and who have symptoms suggestive of vitamin B12 deficiency have their serum B12 levels checked and that those with risk factors for deficiency should be considered for periodic monitoring. The committee therefore agreed to recommend suspicion of vitamin B12 deficiency in people taking metformin and awareness that people who receive a higher dose of metformin, are on longer term treatment, or have other risk factors are at higher risk of developing vitamin B12 deficiency. The committee also cross-referred to the existing MHRA advice.

Evidence suggested that proton pump inhibitor (PPI) and H2 receptor antagonist use are risk factors for vitamin B12 deficiency. The committee considered that the apparent increased risk of taking these medicines may be confounded by the indication for their use. For example, people taking proton pump inhibitors are more likely to have a diagnosed or underlying gastritis, which causes deficiency. Despite this limitation and the low quality of the evidence, the committee agreed that it is still important to be aware that people using PPIs and H2 receptor antagonists might be at an increased risk of vitamin B12 deficiency. The committee were also aware of evidence that colchicine and antiseizure medicines including phenobarbital, pregabalin, primidone and topiramate reduce the level of circulating vitamin B12. This evidence did not meet inclusion criteria for the evidence review as it is unclear whether the reduction in circulating vitamin B12 is reflective of true vitamin B12 deficiency. However, the committee agreed that awareness should still be raised. The committee considered whether carbamazepine, valproate or phenytoin should be included in the list of antiseizure medicines to be aware of when assessing an individual's risk of vitamin B12 deficiency. However, the committee concluded that based on their knowledge, the evidence did not show as strong an association between use of these medicines and vitamin B12 deficiency.

The committee considered that it may be particularly useful to review what medicines a person is taking if they experience symptoms or signs of vitamin B12 deficiency, or if they have a diagnosed deficiency of unknown cause. In some circumstances, it may be appropriate to make a shared decision on whether to continue use of the medicine.

The committee were particularly concerned at the lack of evidence for nitrous oxide with air (gas and air) given that recreational use is a significant public health issue. They noted the difficulties in undertaking prospective studies in this area but agreed that research on the effects of nitrous oxide with air (gas and air) use, particularly of large amounts as well as chronic use, is greatly needed. Therefore, the committee included nitrous oxide with air (gas and air) within the research recommendation on what medicines increase the risk of vitamin B12 deficiency. This research recommendation includes prescription as well as recreational use and dose and duration of exposure.

The committee discussed whether there are any potential risks of nitrous oxide with air (gas and air) use within the clinical context, such as dental procedures and during labour. No evidence was identified in the review although the committee were aware of the MHRA statement that nitrous oxide with air (gas and air) has a very good safety profile in normal use under the supervision of a healthcare professional. This also notes that prolonged use may lead in rare cases to megaloblastic anaemia and neurological toxic effects (myelopathy) due to inactivation of vitamin B12. Therefore, nitrous oxide with air (gas and air) should not be given continuously for more than 24 hours, or more frequently than every 4 days, without close clinical supervision and haematological monitoring. However, the committee agreed that given its good safety profile in normal use and the MHRA statement there was no need to include medicinal nitrous oxide with air (gas and air) as a risk factor in the guideline.

The committee considered the mechanism of action of nitrous oxide with air (gas and air) on vitamin B12, inactivating vitamin B12, leading to dissociation from methionine synthase and inactivation of apo-Methionine synthase. Vitamin B12 concentrations as measured by the serum B12 test in nitrous oxide with air (gas and air) users may remain within the reference range. Homocysteine should be measured instead in this clinical context. The committee agreed that this should be highlighted to health care professionals, to reduce the risk of missed diagnoses. See recommendations on diagnosing vitamin B12 deficiency. The committee also noted that there is information and guidance available for health care professionals on TOXBASE, the primary clinical toxicology database of the National Poisons Information Service, including how nitrous oxide with air (gas and air) toxicity should be managed.

Medicines listed in the review protocol for which no evidence was identified included nitrous oxide with air (gas and air), colchicine, the contraceptive pill, antibiotics, and anticonvulsants. The committee considered that there are plausible mechanisms by which these medicines cause or may cause a deficiency of vitamin B12. However, for some, evidence would be needed to support recommendations. Therefore, the committee made a recommendation for further research to understand the association between use of these medicines and vitamin B12 deficiency.

Gastrointestinal surgery

Evidence suggested that ileal resection is a risk factor for vitamin B12 deficiency. The committee agreed that this evidence could be extended to gastric resections, total gastrectomy and many bariatric operations. Gastrectomy and major gastric resection lead to lack of intrinsic factor, preventing absorption of vitamin B12 and people will usually develop a deficiency after these types of surgery if they do not receive vitamin B12 replacement.

Therefore, the committee made a recommendation to be aware of this. Terminal ileal resection and bariatric operations such as Roux-en-Y gastric bypass and sleeve gastrectomy can increase risk of developing vitamin B12 deficiency as they lead to loss of the receptors that absorb the intrinsic factor-vitamin B12 complex. Therefore, the committee made a recommendation to be aware that these procedures increase the risk of vitamin B12 deficiency. The need for vitamin B12 replacement is usually planned for at the time of the operation. However, the committee agreed it was important to highlight that some people may stop taking or receiving vitamin B12 replacement or may have problems accessing ongoing treatment (for example, if they move GP practice or lived abroad when they had the surgery).

Diet

Although no evidence was identified for dietary factors, the committee agreed based on consensus that it was important to highlight certain factors that can cause a deficiency. Anyone not getting enough B12 in their body can get a deficiency. The committee agreed the key groups of people to highlight are those that follow diets that exclude or are low in animal source foods (such as a vegetarian or vegan diet). The committee discussed that this could include vegetarians, vegans or people following a strict diet based on religious or personal belief. However, they agreed that for these groups there is no evidence that they were at increased risk of a deficiency and that most people effectively manage a balanced diet. Other people at risk include those who do not follow a varied diet or limit their food intake, where vitamin B12 may not form part of their regular diet, including those with eating disorders such as anorexia. Finally, the committee agreed that a deficiency could be a risk factor for people who have a restricted ability or energy to buy or prepare food. For example, in older people with a disability, people who have dementia or advanced frailty, those with mental health conditions or people who misuse substances.

Other risk factors

No evidence was identified for the other non-dietary risk factors listed in the review protocol, however the committee considered that there was enough biological plausibility for each factor to make a consensus-based recommendation to be aware that they may be associated with deficiency. Abdominal/pelvic radiotherapy can have consequences of bacterial overgrowth and an acute toxic effect or chronic scarring of the terminal ileum, which can lead to an impaired ability to absorb nutrients including vitamin B12. Gastric body predominant atrophic gastritis is a risk factor for vitamin B12 deficiency because intrinsic factor is made in the gastric body, therefore atrophy causes impairment of vitamin B12 absorption. Coeliac disease can cause malabsorption of nutrients including vitamin B12, that can lead to a deficiency. Presence of other tissue-specific autoimmune conditions, which often occur together because of underlying genetic predisposition, such as thyroid disease, Sjögren's disease or type 1 diabetes, increases the risk of vitamin B12 deficiency because of the association with autoimmune gastritis. Due to the hereditary nature of the tendency to develop autoimmune conditions, a family history of such conditions can also increase the likelihood of having vitamin B12 deficiency. There are several reasons why increasing age is a risk factor for deficiency because of physiological changes in the gastrointestinal system that impact on the quality and quantity of the diet as well as cobalamin malabsorption from food. Older people are also at a higher risk of mental health problems such as cognitive impairment and dementia, which can affect dietary intake.

Symptoms and signs

Symptoms and signs listed in the review protocol were included because they are known to be associated with vitamin B12 deficiency. However, no evidence was identified to indicate the strength of the associations. The committee considered that despite not having the evidence to show which symptoms and signs are most useful in suspecting and diagnosing deficiency, it was important to raise awareness of the most common symptoms and signs. The committee agreed not to include unexplained chronic headache/migraine within the list of the most common symptoms and signs because although it is a common symptom among people with vitamin B12 deficiency, there are many other possible causes. Some causes of chronic headache/migraine can be serious and should be investigated and ruled out before investigating vitamin B12 deficiency. The committee made a recommendation not to rule out a diagnosis of vitamin B12 deficiency based solely on the absence of anaemia or macrocytosis because although anaemia and macrocytosis are associated with vitamin B12 deficiency, people with vitamin B12 deficiency do not always have anaemia and macrocytosis, as this is a common misconception.

The committee also made a recommendation to highlight the important caveat that clinical presentations of vitamin B12 deficiency are highly variable and other less common symptoms and signs may occur alone or in combination with any of the listed symptoms.

Based on expert witness advice, the committee agreed that the same symptoms, signs and risk factors would apply in pregnancy and breastfeeding. However, they also agreed that a poor response to iron treatment is also a sign of vitamin B12 deficiency in women and people who are pregnant or breastfeeding so included this in the list of symptoms and signs.

Overall

The committee hoped that by raising awareness of the most common risk factors and symptoms and signs, delayed and missed diagnosis of vitamin B12 deficiency could be reduced, which would also help to reduce complications associated with vitamin B12 deficiency.

1.3.4. Cost effectiveness and resource use

There were no economic evaluations identified as this was a prognostic (for risk factors) and diagnostic (for symptoms and signs) review. Increased awareness of the risk factors, symptoms and signs of vitamin B12 deficiency can aid clinicians in suspecting the diagnosis. This is thought to have a resource impact due to more people being offered testing and treatment. However, this will be offset by people with B12 deficiency being diagnosed and managed earlier, with less risk of complications. This can increase QALYs and reduce unnecessary referrals and investigations of the symptoms associated with B12 deficiency.

1.3.5. Other factors the committee took into account

The committee noted that the development of a validated symptom assessment questionnaire would be extremely useful in the diagnosis of vitamin B12 deficiency. It would also provide a measure by which change in symptoms could be monitored, which could inform treatment decisions. The committee considered the practical challenges in developing such a tool. Clinical presentations of vitamin B12 deficiency are highly variable, many symptoms overlap with other conditions and some less common symptoms can occur alone or in combination with more common ones. The first step in developing a symptom questionnaire would be to determine the diagnostic value of individual symptoms and signs, but no such evidence was identified.

1.3.6. Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.1 to 1.2.7 and the recommendations for research on what medicines increase the risk of vitamin B12 deficiency and what dietary factors increase the risk of vitamin B12 deficiency.

1.4. References

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6. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated January 2022]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

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8. Ward MG, Kariyawasam VC, Mogan SB, Patel KV, Pantelidou M, Sobczynska-Malefora A et al. Prevalence and risk factors for functional vitamin B12 deficiency in patients with Crohn's disease. Inflammatory Bowel Diseases. 2015; 21(12):2839-2847

Appendices

Appendix A Review protocols

A.1 Review protocol for risk factors for vitamin B12 deficiency

ID	Field	Content
0.	PROSPERO registration number	CRD42022360738
1.	Review title	What are the risk factors for vitamin B12 deficiency?
2.	Review question	What are the risk factors for vitamin B12 deficiency?
3.	Objective	To identify the risk factors and comorbidities associated with vitamin B12 deficiency to aid in the initial identification and assessment of vitamin B12 deficiency.
4.	Searches	The following databases (from inception) will be searched: • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews

		The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Vitamin B12 deficiency
6.	Population	Inclusion: adults.
7.	Exposure	Dietary risk factors: • vegetarianism • veganism • restrictive diets including eating disorders • socioeconomic status • learning difficulties Prescription medications: • metformin • proton pump inhibitors • colchicine • contraceptive pill • antibiotics (sulfonamides, tetracyclines, trimethoprim, minocycline, neomycin, co-trimoxazole, demeclocycline, fluoroquinolones, macrolides • h2 antagonists • anticonvulsants (valproic acid, phenobarbital (Donnatal®, Solfoton®), phenytoin) • nitrous oxide (prescription and recreational) Non-dietary risk factors:

		• gastric surgery (including bariatric) • terminal ileum resection • increasing age • family history of B12 deficiency/pernicious anaemia • history of another autoimmune disease (e.g., Sjögrens, vitiligo, diabetes type 1, autoimmune thyroid disease, multiple autoimmune disease) • documented gastric body-predominant gastritis • coeliac disease • abdominal/pelvic radiotherapy
8.	Confounding factors	All exposure/risk factors listed above. Age and sex as a minimum.
9.	Types of study to be included	Inclusion: • Prospective and retrospective cohort studies with multivariate analysis. • Case control studies with multivariate analysis. • Systematic reviews of the above. Exclusion: • Studies with univariate analysis only will be excluded.
10.	Other exclusion criteria	• Studies that do not adjust for at least age and sex. • Non-English language studies. • Conference abstracts.
11.	Context	In clinical practice a number of risk factors may be associated with vitamin B12 deficiency. An understanding of these risk factors would improve awareness regarding when to suspect vitamin B12 deficiency, which can facilitate further diagnostic investigations to confirm diagnosis and guide treatment.
12.	Primary outcomes (critical outcomes)	Diagnosis of vitamin B12 deficiency at any time point reported in the study.
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.

		10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. The QUIPs checklist will be used to assess risk of bias for each individual study. PROBAST checklist for studies with external validation performed to evaluate discrimination and coherence.
15.	Strategy for data synthesis	• Where data allows, pairwise meta-analysis will be performed using Cochrane Review manager (RevMan5) software. A fixed-effect meta-analysis, with hazard ratios, odds ratios or risk ratios (as appropriate), and 95% confidence intervals will be calculated for each outcome. • Data from the meta-analysis will be presented and quality assessed in adapted GRADE tables taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each risk factor. Publication or other bias will only be taken into consideration in the quality assessment if it is apparent.

		• Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. We will conduct sensitivity analyses based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. • If meta-analysis is not possible or appropriate, results will be reported individually per outcome in adapted GRADE tables.		
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Duration since procedure (for gastric surgery, terminal ileum resection or radiotherapy only)		
17.	Type and method of review	☐	Intervention	
		☐	Diagnostic	
		☒	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date	14/09/2022		
21.	Anticipated completion date	01/11/2023		
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐

		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail PerniciousAnaemia@nice.nhs.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
24.	Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Maria Smyth [Senior systematic reviewer] Toby Sands [Systematic reviewer] Aamer Jawed [Health economist]		

		Stephen Deed [Information specialist] Katie Tuddenham [Project manager]
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Project documents | Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management | Guidance | NICE
28.	Other registration details	
29.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022360738
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
31.	Keywords	

32.	Details of existing review of same topic by same authors		
33.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information		
35.	Details of final publication	www.nice.org.uk	

A.2 Review protocol for symptoms and signs of vitamin B12 deficiency

Field	Content
PROSPERO registration number	CRD42022360745
Review title	What signs and symptoms are indicative of vitamin B12 deficiency?
Review question	What signs and symptoms are indicative of vitamin B12 deficiency?
Objective	To identify the signs and symptoms that are indicative of vitamin B12 deficiency to aid in the initial identification and assessment of vitamin B12 deficiency.
Searches	The following databases (from inception) will be searched: • Embase • MEDLINE

	Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
Condition or domain being studied	Vitamin B12 deficiency
Population	Adults who have symptoms compatible with vitamin B12 deficiency but who do not have a diagnosis Strata: • Older adults (65 and over)
Signs and symptoms	General symptoms: • Unexplained fatigue • Unexplained chronic headache/migraine Haematological manifestations: • Anaemia

	• Macrocytosis Neurological manifestations: • Peripheral neuropathy • Gait disorders • Falls • Altered cognition (including delirium) • Dementia • Paraesthesia (pins and needles) • Ataxia/diminished proprioception/vibration sensation Mental health manifestations: • Depression • Anxiety • Psychosis Other: • Glossitis • Optic nerve atrophy/dysfunction/blurred vision
Reference standard	Reference standard: • clinical diagnosis of vitamin B12 deficiency
Types of study to be included	• Prospective and retrospective cohort studies with multivariate analysis • Cross-sectional studies • Systematic reviews of the above
Other exclusion criteria	Exclusions: • Non-English language studies

	• Conference abstracts
Context	In clinical practice a number of signs and symptoms might indicate that a person has a vitamin B12 deficiency. An understanding of which signs and symptoms better indicate a vitamin B12 deficiency can facilitate further diagnostic investigations to confirm diagnosis and guide treatment.

Primary outcomes (critical outcomes)	Diagnostic association of signs and symptoms with a confirmed diagnosis of vitamin B12 deficiency.
	Measured by:
	• Diagnostic accuracy data
	  ○ Sensitivity (prioritised), specificity, PPV, NPV
	• Association data
	  ○ Adjusted RR or OR.

Data extraction (selection and coding)	Or use following text if using EPPI: All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions

	• correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. QUADAS will be used to assess diagnostic association reviews.
Strategy for data synthesis	Aggregate data on diagnostic association of signs and symptoms will be collected and synthesized in a quantitative data analysis. If more than one study covered the same combination of population, sign/symptom and outcome then meta-analysis will be used to pool results. Meta-analysis will be carried out using the generic inverse variance function on Review Manager using fixed effect model. Data synthesis will be completed by two reviewers, with any disagreements resolved by discussion, or if necessary a third independent reviewer. Data from the meta-analysis will be presented and quality assessed in adapted GRADE tables taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each sign/symptom. Publication or other bias will only be taken into consideration in the quality assessment if it is apparent. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. We will conduct sensitivity analyses based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random effects. If meta-analysis is not possible or appropriate, results will be reported individually per outcome in adapted GRADE tables. Endnote will be used for bibliography, citations, sifting and reference management.

Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Religion • Sex • Other autoimmune disease			
Type and method of review	☐	Intervention		
	☒	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	14/09/2022			
Anticipated completion date	01/11/2023			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☐	☐
	Piloting of the study selection process		☐	☐
	Formal screening of search results against eligibility criteria		☐	☐

	Data extraction	☐	☐
	Risk of bias (quality) assessment	☐	☐
	Data analysis	☐	☐
Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail PerniciousAnaemia@nice.nhs.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Maria Smyth [Senior systematic reviewer] Toby Sands [Systematic reviewer] Aamer Jawed [Health economist] Stephen Deed [Information specialist] Katie Tuddenham [Project manager]		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared		

	publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Project documents | Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management | Guidance | NICE	
Other registration details		
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022360745	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords		
Details of existing review of same topic by same authors		
Current review status	☐	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated

	☐	Discontinued
Additional information		
Details of final publication	www.nice.org.uk	

1 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[6] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

	The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2006 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B Literature search strategies

The literature searches for these reviews are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[6]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 What are the risk factors for vitamin B12 deficiency?

B.1.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 10: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 14 December 2022	Observational studies Systematic review studies Risk Prognostic Diagnosis Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 14 December 2022	Observational studies Systematic review studies Risk Prognostic Diagnosis Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language

Medline (Ovid) search terms

1.	exp Vitamin B 12 Deficiency/

2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp Macrocytic Anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	Intrinsic Factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	exp Vegetarians/
29.	(vegetarian* or vegan*).ti,ab,kf.
30.	Malnutrition/
31.	(malnutrition or malnourish*).ti,ab,kf.
32.	((poor or restrict* or lack* or deficien*) adj3 (diet* or nutrit* or food* or intake)).ti,ab,kf.
33.	((picky or fussy) adj2 (eater* or eating)).ti,ab,kf.
34.	exp "Feeding and Eating Disorders"/
35.	(bulimia or anorexia).ti,ab,kf.
36.	((eating or feeding or appetite or diet or food) adj3 (disorder* or aversion* or avoid* or selectiv*)).ti,ab,kf.
37.	Social Class/
38.	((socioeconomic* or socio economic*) adj2 (level* or class* or context* or factor* or status*)).ti,ab,kf.
39.	Learning Disabilities/ or Intellectual Disability/
40.	((learning or intellectual) adj2 (difficult* or disabilit* or impairment* or disorder*)).ti,ab,kf.

41.	exp Metformin/
42.	metformin*.ti,ab,kf.
43.	exp Proton Pump Inhibitors/
44.	proton pump inhibitor*.ti,ab,kf.
45.	(dexlansoprazole or omeprazole or lansoprazole or esomeprazole or pantoprazole or rabeprazole).ti,ab,kf.
46.	PPI*.ti,ab,kf.
47.	exp Colchicine/
48.	colchicine*.ti,ab,kf.
49.	exp Contraceptive Agents/
50.	((contraceptive* or combined) adj2 (agent* or pill* or oral or hormonal)).ti,ab,kf.
51.	(Microgynon or Marvelon or Yasmin or Logynon).ti,ab,kf.
52.	Anti-bacterial agents/
53.	(antibacterial* or anti bacterial* or antibiotic* or anti biotic*).ti,ab,kf.
54.	exp Sulfonamides/ or exp Trimethoprim/ or Demeclocycline/ or Fluoroquinolones/ or Minocycline/ or Neomycin/ or Tetracycline/ or exp Macrolides/
55.	(sulfonamide* or tetracycline* or trimethoprim* or minocycline* or neomycin* or co-trimoxazole* or cotrimoxazole* or demeclocycline* or fluoroquinolone* or macrolide*).ti,ab,kf.
56.	exp Histamine H2 Antagonists/
57.	((histamine-2 or H2) adj3 (block* or antagonist*)).ti,ab,kf.
58.	(burimamide or cimetidine or ranitidine or metiamide or nizatidine or famotidine).ti,ab,kf.
59.	Anticonvulsants/
60.	(anticonvulsant* or anti convulsant*).ti,ab,kf.
61.	Phenobarbital/ or Phenytoin/ or Valproic Acid/
62.	(valproic acid or phenobarbital* or phenytoin*).ti,ab,kf.
63.	(Donnatal or Solfoton).ti,ab,kf.
64.	Nitrous Oxide/
65.	(nitrous oxide or laughing gas).ti,ab,kf.
66.	exp Bariatric Surgery/
67.	((gastric or bariatric or stomach) adj3 (surg* or procedure* or operation* or resection*)).ti,ab,kf.
68.	((Ileoceal or ileal or ileum or small bowel) adj3 (surg* or procedure* or operation* or resection*)).ti,ab,kf.
69.	ileectom*.ti,ab,kf.
70.	Aging/
71.	(increasing age or aging or elderly or old age or senior* or (older adj (person or people or patient* or adult* or grow*))).ti,ab,kf.
72.	((family or familial) adj2 histor*).ti,ab,kf.
73.	Autoimmune Diseases/ or Diabetes Mellitus, Type 1/ or Thyroiditis, Autoimmune/ or Sjogren's Syndrome/ or Vitiligo/
74.	((autoimmune or auto immune) adj3 (disease* or disorder* or condition*)).ti,ab,kf.
75.	(sjogren* or vitiligo or autoimmune thyroid*).ti,ab,kf.
76.	((diabet* or dm) adj4 (mellitus or type 1 or type1 or type i or type one)).ti,ab,kf.

77.	exp Gastritis/
78.	gastritis.ti,ab,kf.
79.	Celiac Disease/
80.	(coeliac* or celiac*).ti,ab,kf.
81.	Radiotherapy/ and (Pelvis/ or Abdomen/)
82.	((abdominal or abdomen or pelvic or pelvis or gynecolog* or gynaecolog* or bladder) adj3 (radiotherap* or radio therap* or radiation* or irradiation* or RT)).ti,ab,kf.
83.	or/28-82
84.	27 and 83
85.	Epidemiologic studies/
86.	Observational study/
87.	exp Cohort studies/
88.	(cohort adj (study or studies or analys* or data)).ti,ab.
89.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
90.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
91.	Controlled Before-After Studies/
92.	Historically Controlled Study/
93.	Interrupted Time Series Analysis/
94.	(before adj2 after adj2 (study or studies or data)).ti,ab.
95.	exp case control study/
96.	case control*.ti,ab.
97.	Cross-sectional studies/
98.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
99.	or/85-98
100.	Risk/
101.	Risk Assessment/
102.	Risk Factors/
103.	Proportional hazards models/
104.	Prevalence/
105.	Incidence/
106.	(risk* or prevalence* or incidence* or predict* or associat*).ti,ab.
107.	Logistic models/
108.	(logistic adj2 model).ti,ab.
109.	or/100-108
110.	exp Prognosis/
111.	Disease progression/
112.	(prognos* or predict*).ti,ab.
113.	(validat* or rule*).ti,ab.
114.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (model* or decision* or identif*)).ti,ab.
115.	(decision* and (model* or clinical*)).ti,ab.

116.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
117.	ROC curve/
118.	or/110-117
119.	Diagnosis/
120.	(diagnos* or identif*).ti,ab.
121.	or/119-120
122.	Meta-Analysis/
123.	Meta-Analysis as Topic/
124.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
125.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
126.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
127.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
128.	(search* adj4 literature).ab.
129.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
130.	cochrane.jw.
131.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
132.	or/122-131
133.	84 and (99 or 109 or 118 or 121 or 132)

1 **Embase (Ovid) search terms**

1.	exp B12 deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp macrocytic anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	intrinsic factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/

18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	exp vegetarian/ or vegan/ or exp vegetarian diet/
28.	(vegetarian* or vegan*).ti,ab,kf.
29.	exp malnutrition/
30.	(malnutrition or malnourish*).ti,ab,kf.
31.	((poor or restrict* or lack* or deficien*) adj3 (diet* or nutrit* or food* or intake)).ti,ab,kf.
32.	((picky or fussy) adj2 (eater* or eating)).ti,ab,kf.
33.	exp eating disorder/
34.	(bulimia or anorexia).ti,ab,kf.
35.	((eating or feeding or appetite or diet or food) adj3 (disorder* or aversion* or avoid* or selectiv*)).ti,ab,kf.
36.	social class/
37.	((socioeconomic* or socio-economic*) adj2 (level* or class* or context* or factor* or status*)).ti,ab,kf.
38.	learning disorder/ or intellectual impairment/
39.	((learning or intellectual) adj2 (difficult* or disabilit* or impairment* or disorder*)).ti,ab,kf.
40.	metformin/
41.	metformin*.ti,ab,kf.
42.	exp proton pump inhibitor/
43.	(dexlansoprazole or omeprazole or lansoprazole or esomeprazole or pantoprazole or rabeprazole).ti,ab,kf.
44.	proton pump inhibitor*.ti,ab,kf.
45.	PPI*.ti,ab,kf.
46.	colchicine/
47.	colchicine*.ti,ab,kf.
48.	exp contraceptive agent/
49.	((contraceptive* or combined) adj2 (agent* or pill* or oral or hormonal)).ti,ab,kf.
50.	(Microgynon or Marvelon or Yasmin or Logynon).ti,ab,kf.
51.	antibiotic agent/
52.	(antibacterial* or anti bacterial* or antibiotic* or anti biotic*).ti,ab,kf.
53.	exp sulfonamide/ or tetracycline/ or trimethoprim/ or minocycline/ or neomycin/ or cotrimoxazole/ or demeclocycline/ or exp quinolone derivative/ or exp macrolide/
54.	(sulfonamide* or tetracycline* or trimethoprim* or minocycline* or neomycin* or co-trimoxazole* or cotrimoxazole* or demeclocycline* or fluoroquinolone* or macrolide*).ti,ab,kf.
55.	exp histamine H2 receptor antagonist/

56.	(burimamide or cimetidine or ranitidine or metiamide or nizatidine or famotidine).ti,ab,kf.
57.	((histamine-2 or H2) adj3 (block* or antagonist*)).ti,ab,kf.
58.	anticonvulsive agent/
59.	(anticonvulsant* or anti convulsant*).ti,ab,kf.
60.	phenobarbital/ or phenytoin/ or valproic acid/
61.	(valproic acid or phenobarbital* or phenytoin*).ti,ab,kf.
62.	(Donnatal or Solfoton).ti,ab,kf.
63.	nitrous oxide/
64.	(nitrous oxide or laughing gas).ti,ab,kf.
65.	exp bariatric surgery/
66.	((gastric or bariatric or stomach) adj3 (surg* or procedure* or operation* or resection*)).ti,ab,kf.
67.	ileum resection/
68.	((Ileoceal or ileal or ileum or small bowel) adj3 (surg* or procedure* or operation* or resection*)).ti,ab,kf.
69.	ileectom*.ti,ab,kf.
70.	aging/
71.	(increasing age or aging or elderly or old age or senior* or (older adj (person or people or patient* or adult* or grow*))).ti,ab,kf.
72.	family history/
73.	((family or familial) adj2 histor*).ti,ab,kf.
74.	autoimmune disease/
75.	((autoimmune or auto immune) adj3 (disease* or disorder* or condition*)).ti,ab,kf.
76.	diabetes mellitus/ or autoimmune thyroiditis/ or Sjoegren syndrome/ or vitiligo/
77.	((diabet* or dm) adj4 (mellitus or type 1 or type1 or type i or type one)).ti,ab,kf.
78.	(sjogren* or vitiligo or autoimmune thyroid*).ti,ab,kf.
79.	exp gastritis/
80.	gastritis.ti,ab,kf.
81.	celiac disease/
82.	(coeliac* or celiac*).ti,ab,kf.
83.	abdominal radiotherapy/
84.	((abdominal or abdomen or pelvic or pelvis or gynecolog* or gynaecolog* or bladder) adj3 (radiotherap* or radio therap* or radiation* or irradiation* or RT)).ti,ab,kf.
85.	or/27-84
86.	26 and 85
87.	Clinical study/
88.	Observational study/
89.	Family study/
90.	Longitudinal study/
91.	Retrospective study/
92.	Prospective study/
93.	Cohort analysis/
94.	Follow-up/

95.	cohort*.ti,ab.
96.	94 and 95
97.	(cohort adj (study or studies or analys* or data)).ti,ab.
98.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
99.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
100.	(before adj2 after adj2 (study or studies or data)).ti,ab.
101.	exp case control study/
102.	case control*.ti,ab.
103.	cross-sectional study/
104.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
105.	or/87-93,96-104
106.	risk/
107.	risk assessment/
108.	risk factor/
109.	proportional hazards model/
110.	prevalence/
111.	incidence/
112.	(risk* or prevalence* or incidence* or predict* or associat*).ti,ab.
113.	statistical model/
114.	(logistic adj2 model).ti,ab.
115.	or/106-114
116.	prognosis/
117.	disease exacerbation/
118.	(prognos* or predict*).ti,ab.
119.	(validat* or rule*).ti,ab.
120.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (model* or decision* or identif*)).ti,ab.
121.	(decision* and (model* or clinical*)).ti,ab.
122.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
123.	ROC curve/
124.	or/116-123
125.	diagnosis/
126.	(diagnos* or identif*).ti,ab.
127.	or/125-126
128.	Systematic Review/
129.	Meta-Analysis/
130.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
131.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
132.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

133.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
134.	(search* adj4 literature).ab.
135.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
136.	cochrane.jw.
137.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
138.	or/128-137
139.	86 and (105 or 115 or 124 or 127 or 138)

B.2 What signs and symptoms are indicative of vitamin B12 deficiency?

B.2.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 11: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 14 December 2022	Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 14 December 2022	Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language

Medline (Ovid) search terms

1.	exp Vitamin B 12 Deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.

3.	exp Macrocytic Anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	Intrinsic Factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	Fatigue/ or Asthenia/
29.	(fatigue* or asthenia or aesthenia or tired* or weak* or weary or weariness or lassitude or debilit*).ti,ab,kf.
30.	((loss or less*) adj3 (strength or energ*)).ti,ab,kf.
31.	exp Headache Disorders/
32.	(headache* or head ache* or migraine*).ti,ab,kf.
33.	exp Anemia/
34.	(anaemi* or anemi*).ti,ab,kf.
35.	(macrocytosis or megalocytosis or macrocythemia or macrocyte* or megalocyte*).ti,ab,kf.
36.	((enlarged or large*) adj3 (erythrocyte* or red blood cell* or rbc*)).ti,ab,kf.
37.	Nervous System Diseases/ or Neurobehavioral Manifestations/
38.	((neurologic* or neuropsychological* or neuro psychological* or neuropsychiatric* or psychiatric* or neurobehavior* or neuro behavior* or neurobehaviour* or neuro behaviour*) adj3 (disorder* or dysfunction* or manifest* or complication* or sign* or symptom* or abnormal* or alter*)).ti,ab,kf.
39.	Peripheral Nervous System Diseases/
40.	neuropath*.ti,ab,kf.

41.	((peripheral nerv* or PNS) adj3 (disease* or disorder* or dysfunction*)).ti,ab,kf.
42.	exp Gait Disorders, Neurologic/
43.	((gait or standing or walking or ambulation or ambulatory or mobility or movement) adj3 (disorder* or dysfunction* or deviation* or trouble* or problem* or difficult* or instabilit* or unstable or abnormal* or poor or unsteady)).ti,ab,kf.
44.	Accidental Falls/
45.	(fall or falls or fell).ti,ab,kf.
46.	Cognition disorders/ or Cognitive dysfunction/ or Mood Disorders/
47.	(brain fog* or irritab*).ti,ab,kf.
48.	((mental* or cognit* or mood) adj3 (disorder* or dysfunction* or impair* or alter* or change* or disturb* or manifest* or decline or deteriorat*)).ti,ab,kf.
49.	Delirium/
50.	(delirium or delirious).ti,ab,kf.
51.	Dementia/
52.	(dementia* or amentia*).ti,ab,kf.
53.	Paresthesia/
54.	(paresthesia* or paraesthesia* or tingl* or (pins and needles)).ti,ab,kf.
55.	exp Ataxia/ or Proprioception/
56.	(ataxia or ataxic or pallhypesthesia or pallhypaesthesia or proprioception or vibrat*).ti,ab,kf.
57.	Depression/
58.	(depression or depressed or depressive).ti,ab,kf.
59.	Anxiety/
60.	(anxiety or anxious* or nervous*).ti,ab,kf.
61.	Psychotic Disorders/
62.	(psychosis or psychoses or psychotic).ti,ab,kf.
63.	exp Glossitis/
64.	(glossitis or glossitides or (tongue adj3 inflam*)).ti,ab,kf.
65.	Optic Nerve Diseases/ or Optic Atrophy/ or Optic Neuropathy, Ischemic/
66.	((optic* or ophthalm*) adj3 (atroph* or neuritis or disease* or dysfunction* or disorder* or impair* or damage* or manifest*)).ti,ab,kf.
67.	((vision or visual or sight) adj3 (blur* or loss or impair* or dysfunction* or disorder* or disturbance)).ti,ab,kf.
68.	or/28-67
69.	exp "signs and symptoms"/
70.	symptom assessment/
71.	diagnosis/ or prognosis/
72.	(clinical adj3 (manifestation* or feature* or finding* or aspect* or marker*)).ti,ab.
73.	(presenting or presents or presented or presentation*).ti,ab.
74.	(physical adj3 (manifestation* or characteristic* or feature* or finding*)).ti,ab.
75.	(sign or signs or symptom* or recogni* or identif* or complain*).ti,ab.
76.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,ab.
77.	or/69-76
78.	27 and (68 or 77)

79.	Epidemiologic studies/
80.	Observational study/
81.	exp Cohort studies/
82.	(cohort adj (study or studies or analys* or data)).ti,ab.
83.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
84.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
85.	Controlled Before-After Studies/
86.	Historically Controlled Study/
87.	Interrupted Time Series Analysis/
88.	(before adj2 after adj2 (study or studies or data)).ti,ab.
89.	exp case control study/
90.	case control*.ti,ab.
91.	Cross-sectional studies/
92.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
93.	or/79-92
94.	Meta-Analysis/
95.	Meta-Analysis as Topic/
96.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
97.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
98.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
99.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
100.	(search* adj4 literature).ab.
101.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
102.	cochrane.jw.
103.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
104.	or/94-103
105.	78 and (93 or 104)

1 **Embase (Ovid) search terms**

1.	exp B12 deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp macrocytic anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	intrinsic factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/

9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	fatigue/ or asthenia/
28.	(fatigue* or asthenia or aesthenia or tired* or weak* or weary or weariness or lassitude or debilit*).ti,ab,kf.
29.	((loss or less*) adj3 (strength or energ*)).ti,ab,kf.
30.	headache/ or migraine/
31.	(headache* or head ache* or migraine*).ti,ab,kf.
32.	exp anemia/
33.	(anaemi* or anemi*).ti,ab,kf.
34.	megalocytosis/
35.	(macrocytosis or megalocytosis or macrocythemia or macrocyte* or megalocyte*).ti,ab,kf.
36.	((enlarged or large*) adj3 (erythrocyte* or red blood cell* or rbc*)).ti,ab,kf.
37.	neurologic disease/
38.	((neurologic* or neuropsychological* or neuro psychological* or neuropsychiatric* or psychiatric* or neurobehavior* or neuro behavior* or neurobehaviour* or neuro behaviour*) adj3 (disorder* or dysfunction* or manifest* or complication* or sign* or symptom* or abnormal* or alter*)).ti,ab,kf.
39.	peripheral neuropathy/
40.	neuropath*.ti,ab,kf.
41.	((peripheral nerv* or PNS) adj3 (disease* or disorder* or dysfunction*)).ti,ab,kf.
42.	exp gait disorder/
43.	((gait or standing or walking or ambulation or ambulatory or mobility or movement) adj3 (disorder* or dysfunction* or deviation* or trouble* or problem* or difficult* or instabilit* or unstable or abnormal* or poor or unsteady)).ti,ab,kf.
44.	falling/
45.	(fall or falls or fell).ti,ab,kf.

46.	cognition/ or cognitive defect/ or mood disorder/
47.	(brain fog* or irritab*).ti,ab,kf.
48.	((mental* or cognit* or mood) adj3 (disorder* or dysfunction* or impair* or alter* or change* or disturb* or manifest* or decline or deteriorat*)).ti,ab,kf.
49.	delirium/
50.	(delirium or delirious).ti,ab,kf.
51.	dementia/
52.	(dementia* or amentia*).ti,ab,kf.
53.	exp paresthesia/
54.	(paresthesia* or paraesthesia* or tingl* or (pins and needles)).ti,ab,kf.
55.	ataxia/ or ataxic gait/ or proprioception/ or vibration sense/
56.	(ataxia or ataxic or pallhypesthesia or pallhypaesthesia or proprioception or vibrat*).ti,ab,kf.
57.	depression/
58.	(depression or depressed or depressive).ti,ab,kf.
59.	anxiety/
60.	(anxiety or anxious* or nervous*).ti,ab,kf.
61.	exp psychosis/
62.	(psychosis or psychoses or psychotic).ti,ab,kf.
63.	glossitis/
64.	(glossitis or glossitides or (tongue adj3 inflam*)).ti,ab,kf.
65.	optic nerve atrophy/
66.	((optic* or ophthalm*) adj3 (atroph* or neuritis or disease* or dysfunction* or disorder* or impair* or damage* or manifest*)).ti,ab,kf.
67.	((vision or visual or sight) adj3 (blur* or loss or impair* or dysfunction* or disorder* or disturbance)).ti,ab,kf.
68.	or/27-67
69.	symptom assessment/
70.	exp symptomatology/
71.	diagnosis/ or prognosis/
72.	(clinical adj3 (manifestation* or feature* or finding* or aspect* or marker*)).ti,ab.
73.	(presenting or presents or presented or presentation*).ti,ab.
74.	(physical adj3 (manifestation* or characteristic* or feature* or finding*)).ti,ab.
75.	(sign or signs or symptom* or recogni* or identif* or complain*).ti,ab.
76.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,ab.
77.	or/69-76
78.	26 and (68 or 77)
79.	Clinical study/
80.	Observational study/
81.	Family study/
82.	Longitudinal study/
83.	Retrospective study/
84.	Prospective study/
85.	Cohort analysis/

86.	Follow-up/
87.	cohort*.ti,ab.
88.	86 and 87
89.	(cohort adj (study or studies or analys* or data)).ti,ab.
90.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
91.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
92.	(before adj2 after adj2 (study or studies or data)).ti,ab.
93.	exp case control study/
94.	case control*.ti,ab.
95.	cross-sectional study/
96.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
97.	or/79-85,88-96
98.	Systematic Review/
99.	Meta-Analysis/
100.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
101.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
102.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
103.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
104.	(search* adj4 literature).ab.
105.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
106.	cochrane.jw.
107.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
108.	or/98-107
109.	78 and (97 or 108)

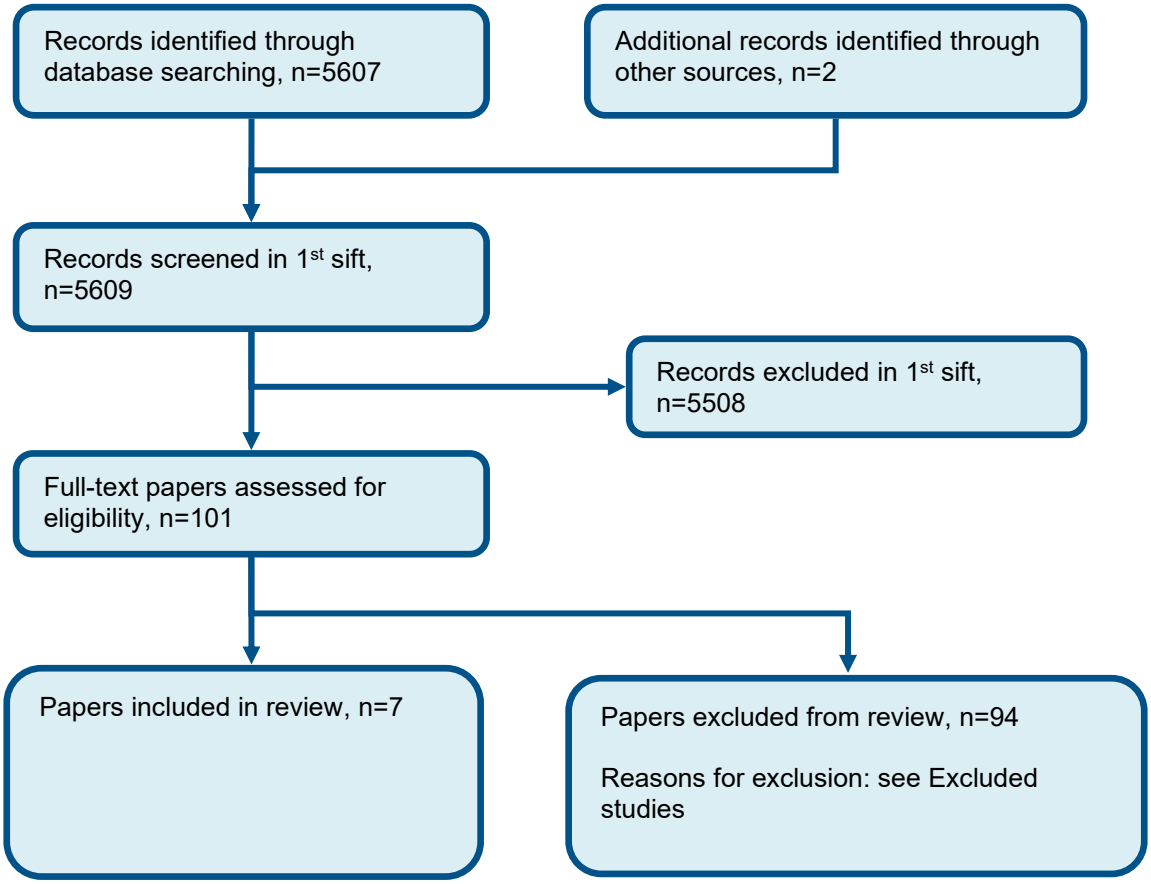
1

2

Appendix C Prognostic evidence study selection

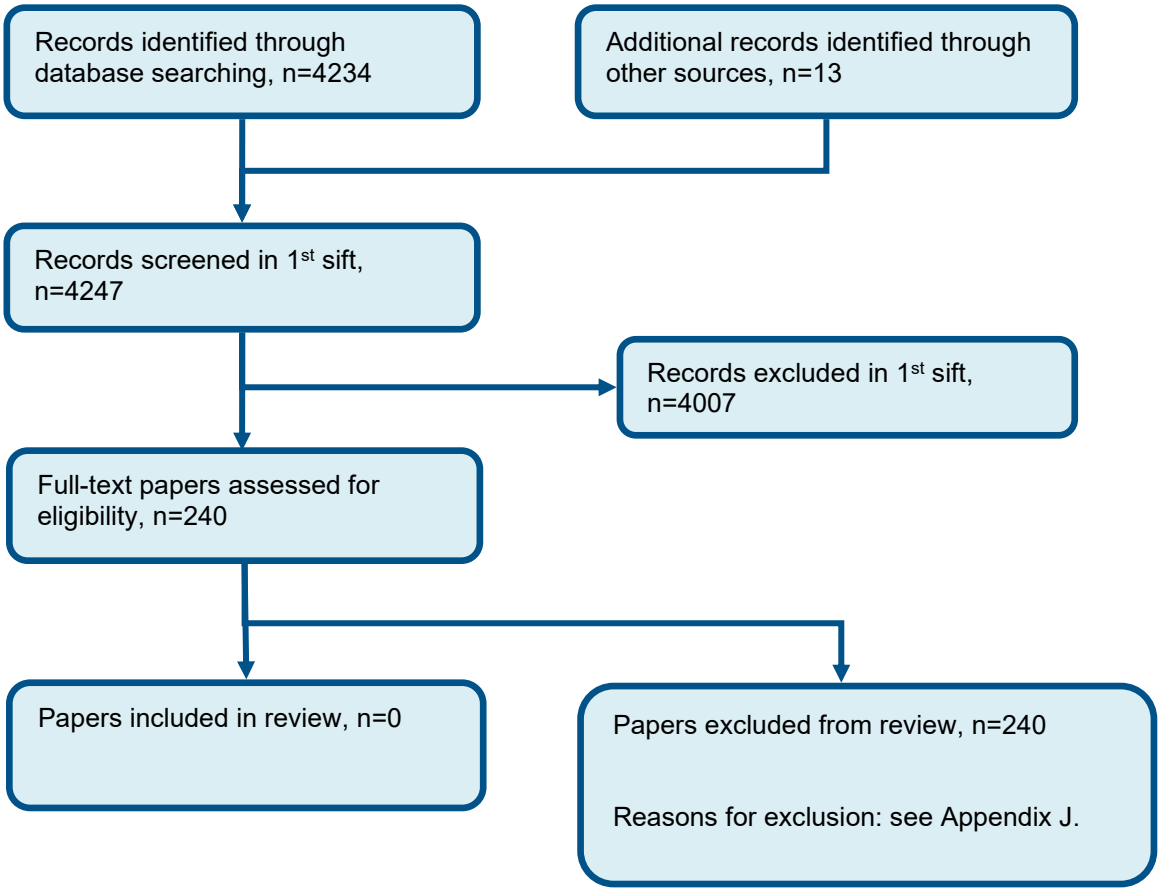
C.1 Risk factors for vitamin B12 deficiency

Figure 1: Flow chart of clinical study selection for the review of risk factors for vitamin B12 deficiency



C.2 Symptoms and signs of vitamin B12 deficiency

Figure 2: Flow chart of clinical study selection for the review of symptoms and signs of vitamin B12 deficiency



Appendix D Prognostic evidence

D.1 Risk factors for vitamin B12 deficiency

Aroda, 2016

Bibliographic Reference	Aroda, Vanita R; Edelstein, Sharon L; Goldberg, Ronald B; Knowler, William C; Marcovina, Santica M; Orchard, Trevor J; Bray, George A; Schade, David S; Temprosa, Marinella G; White, Neil H; Crandall, Jill P; Diabetes Prevention Program Research, Group; Long-term Metformin Use and Vitamin B12 Deficiency in the Diabetes Prevention Program Outcomes Study.; The Journal of clinical endocrinology and metabolism; 2016; vol. 101 (no. 4); 1754-61

Study details

Secondary publication of another included study- see primary study for details	NA
Trial name / registration number	Secondary analysis of the Diabetes Prevention Program Outcomes Study
Study type	Retrospective cohort study
Study location	USA
Study setting	27 study centers
Study dates	Enrolment began in July 1996 and ended in May 1999, randomised to metformin, lifestyle intervention or placebo and followed up at mean 3.2 years, then invited to participate in a follow up study in which those on metformin continued. Vitamin B12 measured at 5 (1 year into outcomes study) and 13 (9 years into outcomes study).
Sources of funding	The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health is the primary funding agency. Funding was also provided by the National Institute of Child Health and Human Development, the

	National Institute on Aging, the National Eye Institute, the National Heart, Lung, and Blood Institute, the Office of Research on Women's Health, the National Center for Minority Health and Human Disease, the Centers for Disease Control and Prevention, and the American Diabetes Association. Bristol-Myers Squibb and Parke-Davis provided additional funding and material support during the DPP, Lipha (Merck-Santé) provided medication, and LifeScan Inc donated materials during the DPP and DPPOS.
Recruitment / selection of participants	Participants enrolled in the DPP and DPPOS.
Inclusion criteria	Participants randomized to placebo (n = 902) or metformin (n = 898) during DPP who had available serum stored from either DPPOS years 1 or 9 measured for vitamin B12 levels. Eligibility criteria for enrolment in DPP: impaired glucose tolerance and fasting blood glucose of 95 to 125 mg/dL (≤125 mg/dL in American Indians) who were at least 25 years of age and had body mass index (BMI) of 24 kg/m2 or higher (≥22 kg/m2 in Asian Americans).
Exclusion criteria	Participants who had undergone bariatric surgery before collection of serum samples (n = 4 at DPPOS year 1, and n = 49 at year 9) were excluded.
Population subgroups	NA
Prognostic variable(s)	Metformin use
Confounders OR Stratification strategy	Age, sex, BMI, use of prescription proton pump inhibitors or prescription H2 blockers, diabetes status, weight change during DPP/DPPOS, and treatment arm.
Duration of follow-up	9 years
Indirectness	Serious population indirectness: prediabetes
Additional comments	NA

1

Characteristics

Study-level characteristics

Characteristic	Study (N = 1)
Number of participants Nominal	1800
% Female Nominal	67.6
Mean age (SD) Mean (SD)	51.2 (10)
Ethnicity Custom value	45.2% non-white

Outcomes

Study timepoints

- 9 year

Risk of vitamin B12 deficiency per year of metformin use

Outcome	DPPOS cohort vs DPPOS cohort, 9 year
Risk of vitamin B12 deficiency per year of metformin use Odds ratio/95% CI	1.13 (1.06 to 1.2)

Vitamin B12 deficiency (≤ 203 pg/mL). Adjusted for age, sex, baseline BMI, prescription acid suppression therapy, diabetes status, weight change at time of measurement, and treatment assignment.

Critical appraisal - QUIPS checklist

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Vitamin B12 status at baseline not reported; >10% last to follow up with no description of those missing from the analysis or attempts to follow up; measurement of metformin use included self-report; vitamin B12 deficiency based on serum level alone; not all confounders accounted for; model development strategy not reported.)*
Overall risk of bias and directness	Directness	Partially applicable *(Study population was people at risk of diabetes (impaired glucose tolerance).)*

Bermejo, 2013

Bibliographic Reference	Bermejo, Fernando; Algaba, Alicia; Guerra, Ivan; Chaparro, Maria; De-La-Poza, Gema; Valer, Paz; Piqueras, Belen; Bermejo, Andrea; Garcia-Alonso, Javier; Perez, Maria-Jose; Gisbert, Javier P; Should we monitor vitamin B12 and folate levels in Crohn's disease patients?.; Scandinavian journal of gastroenterology; 2013; vol. 48 (no. 11); 1272-7

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study location	Spain
Study setting	IBD outpatient clinic at two participant University Hospitals
Study dates	Recruitment period over two years
Sources of funding	Not reported
Recruitment / selection of participants	Consecutive
Inclusion criteria	Crohn's disease

Exclusion criteria	Receiving supplemental vitamin B12 and/or folate or if they had a known disease which causes vitamin deficiency other than CD (autoimmune atrophic gastritis); there were no cases of celiac disease, parasite infection or patients with strict vegetarian diet. None of the patients were pregnant. None of the patients reported a significant consumption of alcoholic drinks. Diagnoses of IBD were confirmed by routine clinical, radiological, endoscopic and histological criteria
Population subgroups	Duration since ileal resection not reported
Prognostic variable(s)	Ileal (or ileocolonic) resection
Confounders OR Stratification strategy	CD location (Montreal classification), disease activity (Harvey–Bradshaw index), duration of CD, age and gender, medications which could induce vitamin B12 deficiency (such as proton pump inhibitors, oral antidiabetics, neomycin, colchicine and cholestyramine) entered into univariate analysis and significant factors remained in multivariate analysis
Duration of follow-up	Unclear
Indirectness	Serious population indirectness: Crohn's disease
Additional comments	NA

Characteristics

Study-level characteristics

Characteristic	**Study (N = 1)**
Number of participants Nominal	180
% Female Nominal	53

Characteristic	Study (N = 1)
Mean age (SD) Mean (SD)	40 (13)

Outcomes

Risk of vitamin B12 deficiency with ileal resection

Outcome	Crohn's disease cohort vs Crohn's disease cohort, N2 = , N1 =
Risk of vitamin B12 deficiency with ileal (or ileocolonic) resection Odds ratio/95% CI	2.7 (1.2 to 6.7)

Serum levels below 200 pg/ml

Critical appraisal - QUIPS checklist

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(B12 status at baseline (prior to/at the time of resection) not reported; those receiving B12 supplements excluded; not all confounders considered; no information on missing data; significant results only reported in text.)*
Overall risk of bias and directness	Directness	Partially applicable *(Crohn's disease)*

de Jager, 2010

Bibliographic Reference	de Jager, Jolien; Kooy, Adriaan; Lehert, Philippe; Wulffele, Michiel G; van der Kolk, Jan; Bets, Daniel; Verburg, Joop; Donker, Ab J M; Stehouwer, Coen D A; Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial.; BMJ (Clinical research ed.); 2010; vol. 340; c2181

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	Hyperinsulinaemia: the Outcome of its Metabolic Effects (HOME) trial
Study location	The Netherlands
Study setting	three non-academic hospitals
Study dates	not reported
Sources of funding	Grants from Altana, Lifescan, Merck Santé, Merck Sharp & Dohme, and Novo Nordisk. The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Recruitment / selection of participants	Recruited from outpatient clinics, no further details.

Inclusion criteria	Aged 30-80 years with type 2 diabetes who were receiving treatment with insulin.
Exclusion criteria	5 cases in which there was a large discrepancy in vitamin B12 measurements.
Population subgroups	NA
Prognostic variable(s)	Metformin use
Confounders OR Stratification strategy	Study design means that confounding factors should be comparable between groups. There was a reported difference in age between groups (64±10 years *v* 59±11 years). Effects on B12 concentrations were adjusted for age, previous metformin treatment, duration of diabetes, gender, insulin dose, and smoking habits, but did not alter the results. Therefore, unadjusted HRs have been extracted.
Duration of follow-up	52 months
Indirectness	Serious population indirectness: adults with insulin treated diabetes
Additional comments	NA

Study arms

Metformin (N = 196)

850 mg metformin three times a day for 4.3 years

Placebo (N = 194)

Placebo three times a day for 4.3 years

Characteristics

Study-level characteristics

Characteristic	Study (N = 1)
Number of participants Nominal	390

Arm-level characteristics

Characteristic	Metformin (N = 196)	Placebo (N = 194)
% Female Nominal	69	50
Mean age (SD) (years) Mean (SD)	64 (10)	59 (11)

Outcomes

Study timepoints

- 52 month

Risk of vitamin B12 deficiency with metformin

Outcome	Metformin vs Placebo, 52 month, N2 = 194, N1 = 191
Risk of vitamin B12 deficiency with metformin (pmol/L) vitamin B-12 concentration below the value of 150 pmol/l Hazard ratio/95% CI	5.5 (1.6 to 19.1)

Critical appraisal - QUIPS checklist

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Those with vitamin B-12 concentrations < 150 pmol/l at baseline, interim analysis, or at both time points were excluded from analyses after 16 weeks; unclear measurement of adherence to metformin treatment; reported difference in age between groups, effects of which were investigated for B12 concentrations but not for deficiency outcome; high rate of missing outcome data at final visit)*
Overall risk of bias and directness	Directness	Partially applicable *(Insulin treated type 2 diabetes)*

Headstrom, 2008

Bibliographic Reference	Headstrom, Peggy D; Rulyak, Stephen J; Lee, Scott D; Prevalence of and risk factors for vitamin B(12) deficiency in patients with Crohn's disease.; Inflammatory bowel diseases; 2008; vol. 14 (no. 2); 217-23

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study location	USA
Study setting	Inflammatory Bowel Disease Center at a single University (medical record review)
Study dates	July 1, 2001 to August 1, 2005
Sources of funding	not reported
Recruitment / selection of participants	All patients with a diagnosis of CD who were evaluated in the Inflammatory Bowel Disease Center at the University between July 1, 2001 to August 1, 2005
Inclusion criteria	Diagnosis of CD confirmed by review of clinical, laboratory, endoscopic, histologic, and radiographic information.
Exclusion criteria	Previously diagnosed with B12 deficiency or receiving supplemental B12 at the time of initial visit; known cause of B12 deficiency other than inflammatory bowel disease; single visit to the center for a second opinion.

Population subgroups	no information on duration since surgery
Prognostic variable(s)	Prior ileal resection
Confounders OR Stratification strategy	Age, sex, race, duration of disease, disease location, and prior surgery.
Duration of follow-up	Unclear
Indirectness	Serious population indirectness: Crohn's disease
Additional comments	NA

Characteristics

Study-level characteristics

Characteristic	**Study (N = 1)**
Number of participants Nominal	201
% Female Nominal	56.2
Mean age (SD) Custom value	less than 20: 9%
Mean age (SD)	20-29: 28.9%

Characteristic	Study (N = 1)
Custom value	
Mean age (SD) Custom value	30-39: 22.9%
Mean age (SD) Custom value	40-49: 20.4%
Mean age (SD) Custom value	50-59: 13.9%
Mean age (SD) Custom value	60+: 5%
Ethnicity Custom value	93.5% White; 3.5% African-American; 3% other

Outcomes

Risk of vitamin B12 deficiency with ileal resection

Outcome	Crohn's disease cohort vs Crohn's disease cohort
Risk of vitamin B12 deficiency with prior ileal resection Odds ratio/95% CI	7.22 (1.97 to 26.51)

Values from 180 –223 pg/mL considered indeterminate and values <180 pg/mL considered deficient. For the primary analysis, B12 concentrations <224 pg/mL considered abnormal because practice is to offer replacement at this concentration.

Critical appraisal - QUIPS checklist

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Unclear duration between prognostic factor and outcome; adjusted for some but not all key confounders; limited information on measurement of prognostic and confounding factors; definition of deficiency based on serum values only and includes indeterminate range)*
Overall risk of bias and directness	Directness	Partially applicable *(Population: Crohn's disease)*

Lam, 2013

Bibliographic Reference	Lam, Jameson R; Schneider, Jennifer L; Zhao, Wei; Corley, Douglas A; Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency.; JAMA; 2013; vol. 310 (no. 22); 2435-42

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study location	USA
Study setting	Electronic database covering the Kaiser Permanente Northern California integrated healthcare system (3.3 million members)
Study dates	diagnosis of vitamin B12 deficiency between January 1997 and June 2011
Sources of funding	This project was supported by a Kaiser Permanente Community Benefit grant.
Recruitment / selection of participants	Case patients meeting the inclusion criteria and up to 10 matched control patients randomly selected.

Inclusion criteria	Cases were at least 18 years of age, had at least 1 year of membership prior to the index date, and had an initial diagnosis of vitamin B12 deficiency between January 1997 and June 2011. Controls were chosen from among all eligible adult members who lacked a diagnosis of vitamin B12 deficiency at the time of the case diagnosis.
Exclusion criteria	Case patients lacking matched controls, potential cases and controls with diagnoses known to directly cause vitamin B12 deficiency, and potential cases and controls who had taken PPIs or H2RAs for < 2 years.
Population subgroups	NA
Prognostic variable(s)	At least a 2-year supply of proton pump inhibitors or H2 receptor antagonists prior to the index date
Confounders OR Stratification strategy	Controls matched by sex, region of home facility, race/ ethnicity, year of birth within 1 year of the matched case, and membership duration (rounded to year) within 1 year. Conditions associated with vitamin B12 deficiency, other medications known to be associated with vitamin B12 deficiency or with the treatment of associated conditions, health service utilization, other commonly used medications, gastroesophageal reflux disease all entered into the original model but not significant.
Duration of follow-up	Unclear
Indirectness	No indirectness
Additional comments	Strongest association between PPI and deficiency among those < 30 years (OR, 8.12 [95% CI, 3.36-19.59]) and decreased with increasing age (OR, 1.04 [95% CI, 0.96-1.13] for ages ≥80 years)

Study arms

Cases (N = 25956)

diagnosis of B12 deficiency

Controls (N = 184199)

matched controls (by sex, region of home facility, race/ethnicity, year of birth within 1 year of the matched case, and membership duration (rounded to year) within 1 year)

Characteristics

Study-level characteristics

Characteristic	Study (N = 1)
Number of participants Nominal	210155

Arm-level characteristics

Characteristic	Cases (N = 25956)	Controls (N = 184199)
% Female Nominal	57.4	56.9
Mean age (SD) Custom value	2.9% less than 30, 6.2% 30-39, 9.8% 40-49, 13.9% 50-59, 18.5% 60-69, 24.8% 70-79, 20.2% 80-89, 3.7%	3.6% less than 30, 7.1% 30-39, 10.1% 40-49, 14.8% 50-59, 18.7% 60-69, 23.8% 70-79, 18.1% 80-89, 3%
Ethnicity Custom value	68.4% White, 10.1% Hispanic, 4.5% Black, 7.7% Asian/Pacific Islander, 4.8% multiracial, 4.5% other/u	69.4% White, 9% Hispanic, 4.3% Black, 7.8% Asian/Pacific Islander, 4.1% multiracial, 5.4% other/u

Outcomes

Risk of vitamin B12 deficiency

Outcome	Cases vs Controls
Risk of vitamin B12 deficiency with proton pump inhibitors Odds ratio/95% CI	1.65 (1.58 to 1.73)
Risk of vitamin B12 deficiency with H2RAs Odds ratio/95% CI	1.25 (1.17 to 1.34)

Vitamin B12 deficiency was defined as the presence of 1 of the following: the first diagnostic code for vitamin B12 deficiency, using International Classification of Diseases, Ninth Revision codes 281.0 (pernicious anaemia), 281.1 (other vitamin B12deficiency anaemia), 266.2 (specified at KPNC as vitamin B12 deficiency), or specific text diagnoses of vitamin B12 deficiency in the problem list; an abnormally low value for serum vitamin B12; or a new and at least 6-month supply of injectable vitamin B12 supplements. Sensitivity analyses were performed for the different case definitions.

Critical appraisal - QUIPS checklist

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Unclear duration of follow up; medication duration <2 years and OTC medications not included in the analysis; not all key confounders considered/measurable due to study design; analytical strategy described, but results not fully reported)*
Overall risk of bias and directness	Directness	Directly applicable

Shivaprasad, 2020

Bibliographic Reference	Shivaprasad, Channabasappa; Gautham, Kolla; Ramdas, Barure; Gopaldatta, Kolli S; Nishchitha, Krishnamurthy; Metformin Usage Index and assessment of vitamin B12 deficiency among metformin and non-metformin users with type 2 diabetes mellitus.; Acta diabetologica; 2020; vol. 57 (no. 9); 1073-1080

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study type	Retrospective cohort study
Study location	India
Study setting	Outpatient clinic of the Department of Endocrinology, single centre
Study dates	January 2018 to November 2019.
Sources of funding	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for the profit sectors.
Recruitment / selection of participants	Consecutive patients meeting the inclusion criteria.

Inclusion criteria	≥20 and ≤65 years of age; T2D diagnosed as per the American Diabetes Association criteria; had not consumed any vitamin B12-containing supplement within the past 6 months
Exclusion criteria	Diagnosed with type 1 diabetes mellitus; secondary causes of diabetes; newly diagnosed with T2D (<3 months); received vitamin B12 supplementation or proton-pump inhibitors over the last 6 months; hypothyroidism, pernicious anaemia, inflammatory bowel disease, and other causes of malabsorption; alcohol use disorder; undergone surgical interventions including gastrectomy and colectomy.
Population subgroups	NA
Prognostic variable(s)	Metformin (metformin usage index - product of the dose of metformin (mg) used and its duration divided by 1000) Age
Confounders OR Stratification strategy	Age, MUI, duration, BMI, and HbA1c (gender also considered in univariate analysis).
Duration of follow-up	Unclear
Indirectness	Serious population indirectness: type 2 diabetes
Additional comments	NA

Characteristics

Study-level characteristics

Characteristic	**Study (N = 1)**
Number of participants Nominal	2887

Characteristic	Study (N = 1)
% Female Nominal	33.9
Mean age (SD) Mean (SD)	48.9 (8.8)

Outcomes

Risk of vitamin B12 deficiency (absolute and borderline)

Outcome	Type 2 diabetes cohort vs Type 2 diabetes cohort
Risk of vitamin B12 deficiency with MUI <5 Odds ratio/95% CI	1.37 (0.88 to 2.16)
Risk of vitamin B12 deficiency with MUI more than 5 Odds ratio/95% CI	3.56 (2.29 to 5.51)
Risk of vitamin B12 deficiency with MUI >10 Odds ratio/95% CI	5.12 (3.12 to 8.38)
Risk of vitamin B12 deficiency with MUI >15 Odds ratio/95% CI	6.74 (4.39 to 10.4)

Absolute deficiency <200 pg/ml, borderline deficiency 200–300 pg/ml, and normal levels>300 pg/ml.

Critical appraisal - QUIPS checklist

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Vitamin B12 status at baseline (prior to risk factors) not reported and those receiving supplements were excluded; unclear measurement of metformin use (based on clinical records - no further detail); no information on missing data; unclear whether borderline deficiency is included in deficiency outcome (appears so))*
Overall risk of bias and directness	Directness	Partially applicable *(Study population: type 2 diabetes)*

Ward, 2015

Bibliographic Reference	Ward, M.G.; Kariyawasam, V.C.; Mogan, S.B.; Patel, K.P.; Pantelidou, M.; Sobczynska-Malefora, A.; Porte, F.; Griffin, N.; Anderson, S. H. C; Sanderson, J.D.; Harrington, D.J.; Irving, P.M.; Prevalence and risk factors for functional b12 deficiency in patients with Crohn's disease; Inflammatory bowel diseases; 2015; vol. 21 (no. 12); 2839-47

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study location	UK
Study setting	IBD service, single centre
Study dates	January 2012 to March 2013
Sources of funding	Not reported
Recruitment / selection of participants	All patients with Crohn's disease who had holoTC measured between January 2012 and March 2013, identified retrospectively by review of the electronic patient record.
Inclusion criteria	Crohn's disease who had holoTC measured between January 2012 and March 2013.

Exclusion criteria	Receiving vitamin B12 replacement or with a history of vitamin B12 deficiency unrelated to IBD or those who had undergone previous gastrectomy or IBD-unclassified.
Population subgroups	Duration since procedure: not reported
Prognostic variable(s)	Ileal resection
Confounders OR Stratification strategy	Age, gender, smoking status, disease phenotype, current treatment with immunomodulators (thiopurines, methotrexate, or tioguanine) or anti–tumour necrosis factor agents (infliximab or adalimumab), disease duration, ileal resection length (0, 1–20, and .20 cm), and disease activity were entered into a forward stepwise model. Variables with P < 0.1 were initially entered into the model, and variables with P < 0.05 were retained in the model.
Duration of follow-up	Unclear
Indirectness	Serious population indirectness: ileal resection as a risk factor for deficiency in people with Crohn's disease only.
Additional comments	NA

Characteristics

Study-level characteristics

Characteristic	**Study (N = 1)**
Number of participants Nominal	381
% Female Nominal	49
Mean age (SD)	35 (29 to 47)

Characteristic	Study (N = 1)
Median (IQR)	

Outcomes

Risk of vitamin B12 deficiency with ileal resection

Outcome	Crohn's disease cohort vs Crohn's disease cohort
Risk of vitamin B12 deficiency with ileal resection 0-20cm vs. none n=292 included in the multivariate analysis Odds ratio/95% CI	3 (1.5 to 6)
Risk of vitamin B12 deficiency with ileal resection >20cm n=292 included in the multivariate analysis Odds ratio/95% CI	6.7 (3 to 15)

A value <25 pmol/L was defined as B12 deficiency and >50 pmol/L considered replete. Values between 25 and 50 pmol/L were classified as intermediate and underwent MMA analysis, subject to an estimated glomerular filtration rate of >60 mL.min-1.1.73 m-2, using liquid chromatography–tandem mass spectrometry with electrospray ionization as previously described. MMA values >280 nmol/L confirmed B12 deficiency in patients <65 years old, or >360 nmol/L in patients >65 years old. Serum B12 was measured using the ARCHITECT assay (Abbott Diagnostics). Patients with values <107 pmol/L were defined as B12 deficient as per local laboratory ranges. A separate analysis was performed using the National Health and Nutrition Evaluation Survey serum B12 cut-off for diagnosing B12 deficiency of <147 pmol/L.

Critical appraisal - QUIPS checklist

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(vitamin B12 status at baseline not reported, although history of diagnosed deficiency excluded; retrospective chart review with unclear duration between prognostic factor and outcome; not all key confounders measured/adjusted for)*
Overall risk of bias and directness	Directness	Partially applicable *(Study population: Crohn's disease)*

D.2 Symptoms and signs of vitamin B12 deficiency

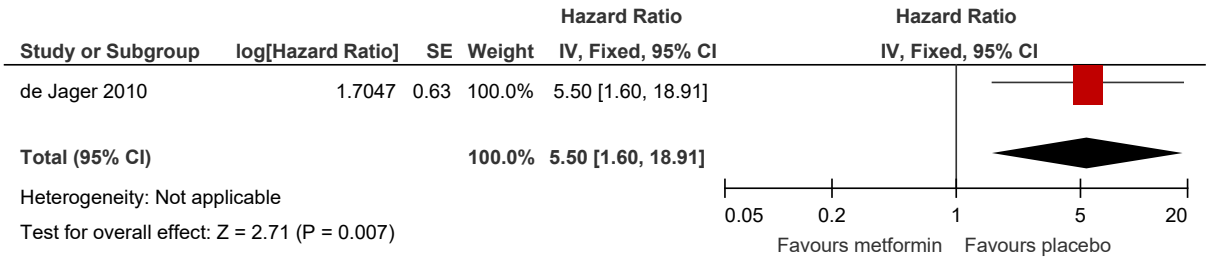
No evidence identified.

Appendix E Forest plots

E.1 Risk factors for vitamin B12 deficiency

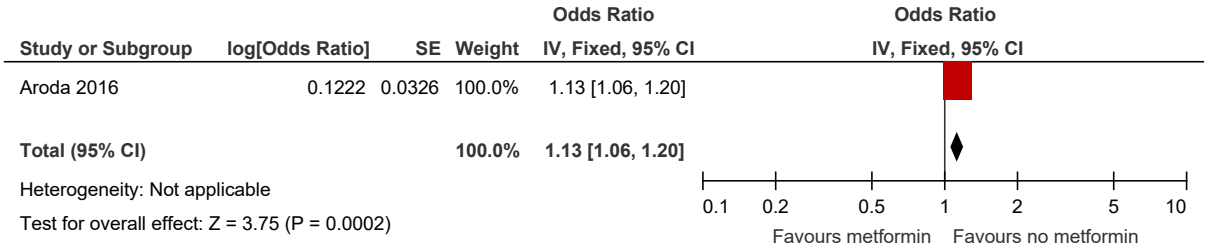
E.1.1 Metformin (randomised controlled trials)

Figure 3: Metformin use for predicting vitamin B12 deficiency (<150 pmol/l)



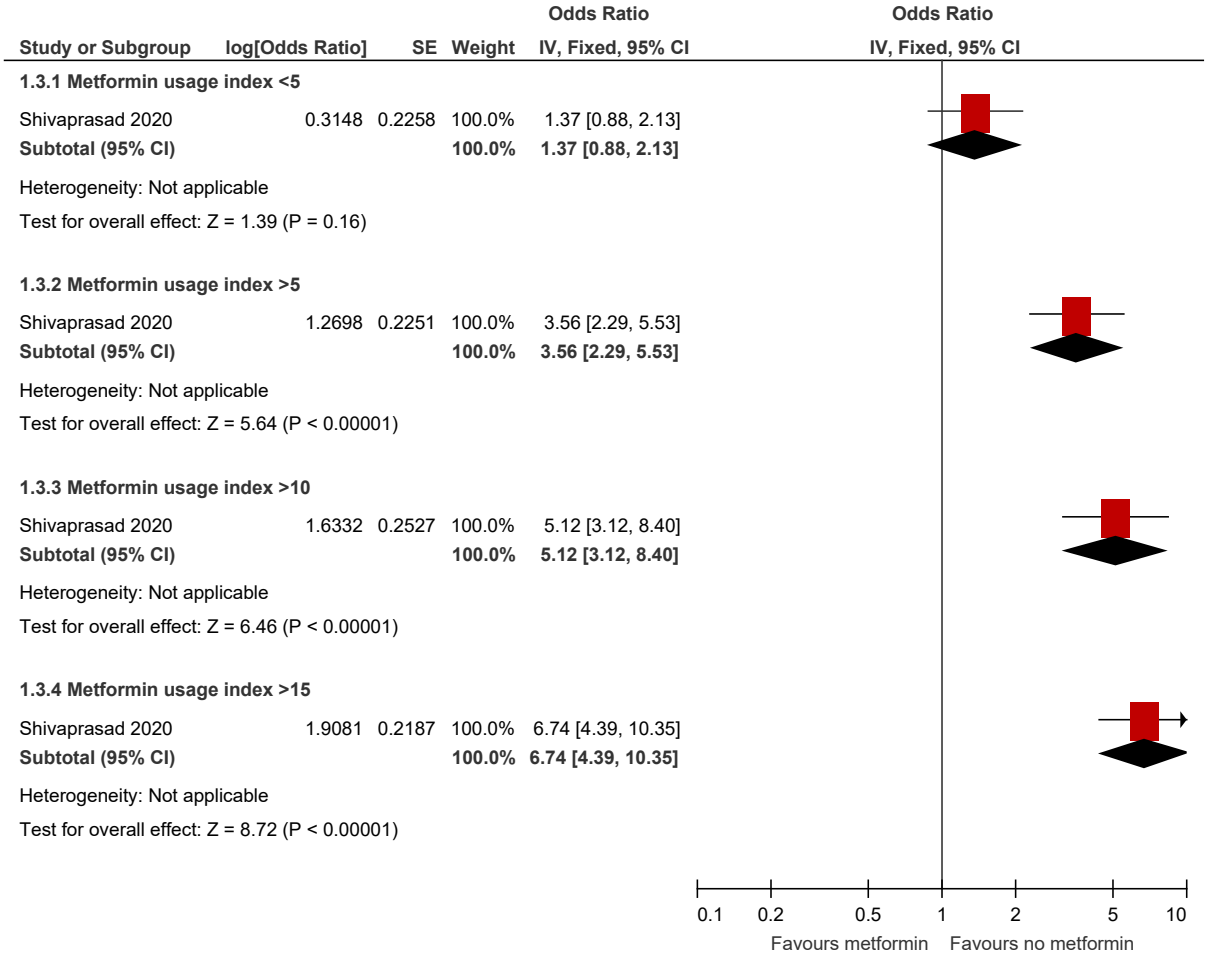
E.1.2 Metformin (prospective cohort studies)

Figure 4: Metformin use per year for predicting vitamin B12 deficiency (≤ 203 pg/mL)



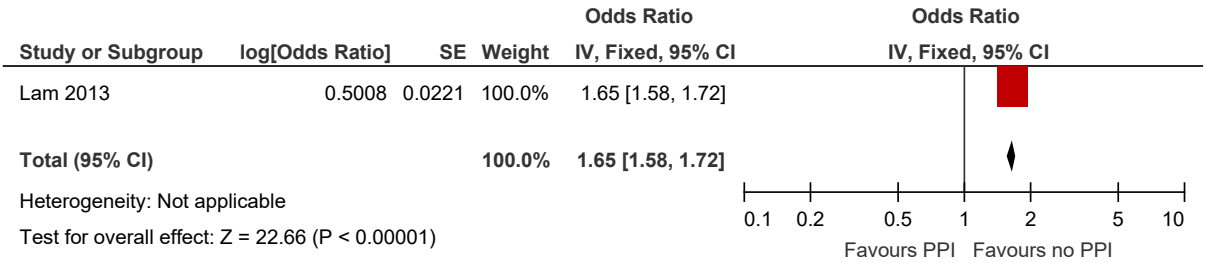
E.1.31 Metformin (retrospective cohort studies)

Figure 5: Metformin (metformin usage index) for predicting vitamin B12 deficiency (<200 pg/ml or borderline deficiency 200–300 pg/ml)



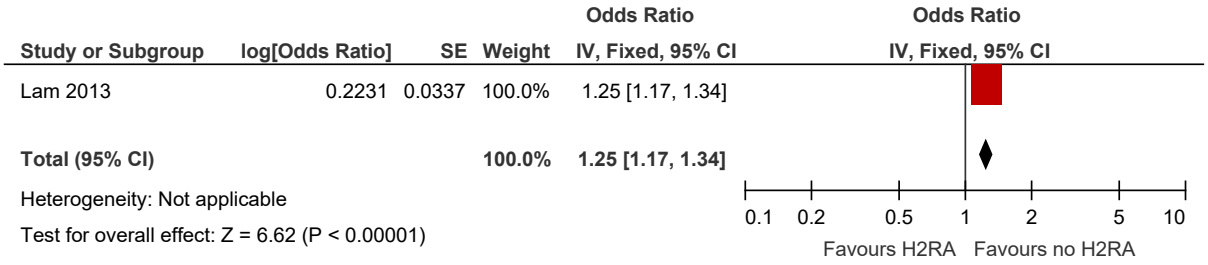
E.1.42 Proton pump inhibitors (case-control studies)

Figure 6: Proton pump inhibitor (at least a 2-year supply prior to the index date) for predicting vitamin B12 deficiency (diagnostic code for deficiency/specific text diagnoses/low serum B12/new at least 6-month supply of injectable B12)



E.1.51 H2 antagonists (case-control studies)

Figure 7: H2 antagonists (at least a 2-year supply prior to the index date) for predicting vitamin B12 deficiency (diagnostic code for deficiency/specific text diagnoses/low serum B12/new at least 6-month supply of injectable B12)



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E.1.63 Ileal resection (retrospective cohort studies)

Figure 8: Previous ileal or ileocolonic resection for predicting vitamin B12 deficiency (< 200 pg/ml)

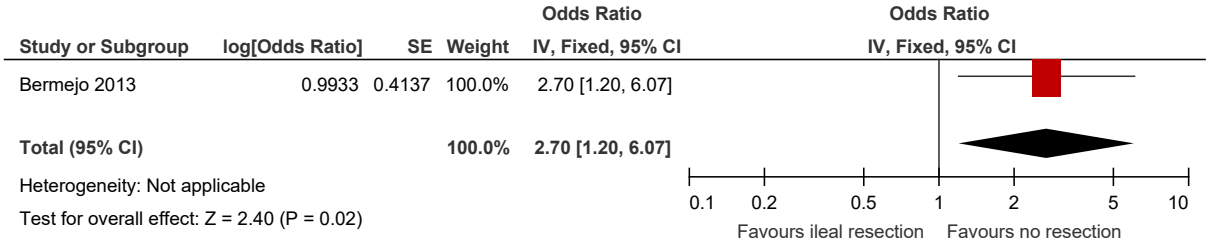

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Figure 9: Prior ileal resection for predicting vitamin B12 deficiency (<25 pmol/L Values 25-50 pmol/L underwent MMA analysis. See study details)

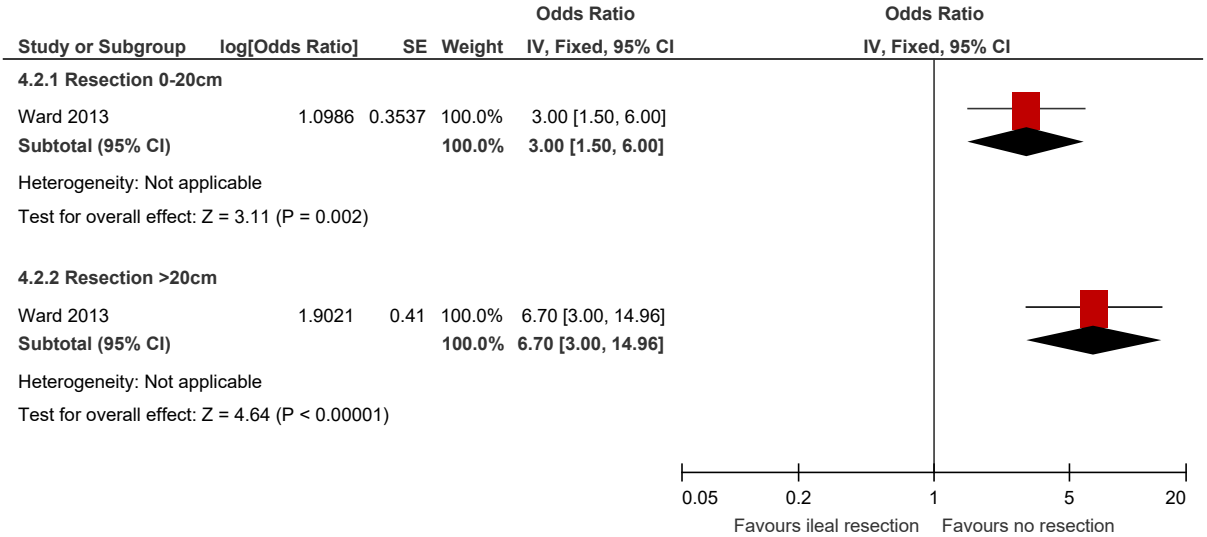

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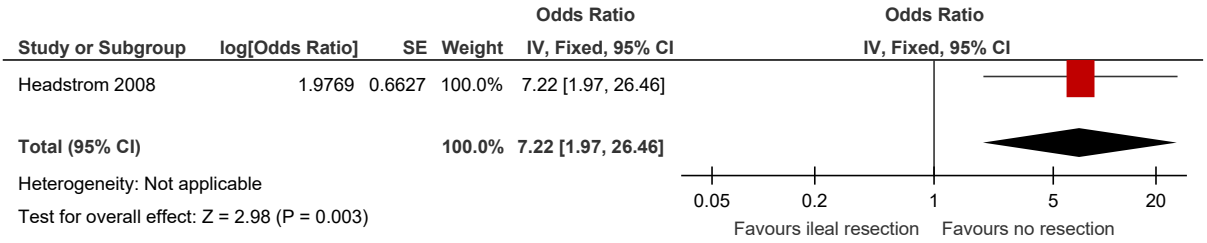
Figure 10: Prior ileal resection for predicting vitamin B12 deficiency (<224 pg/mL)



2 E.2 Symptoms and signs of vitamin B12 deficiency

3 No evidence identified.

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Appendix F GRADE tables

F.1 Risk factors for vitamin B12 deficiency

Table 12: Clinical evidence profile: metformin (randomised controlled trials)

Quality assessment							Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Pooled effect (95% CI)	
Metformin use for predicting vitamin B12 deficiency (<150 pmol/l) (insulin treated type 2 diabetes)								
1	randomised studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	HR: 5.5 (1.6 to 18.91)	VERY LOW

[1] Downgraded by two increments due to very high risk of bias (those with vitamin B-12 concentrations < 150 pmol/l at baseline, interim analysis, or at both time points were excluded from analyses after 16 weeks; unclear measurement of adherence to metformin treatment; reported difference in age between groups, effects of which were investigated for B12 concentrations but not for deficiency outcome; high rate of missing outcome data at final visit)

[2] Downgraded by 1 increment due to serious population indirectness (applicability limited to those with insulin treated type 2 diabetes).

Table 13: Clinical evidence summary: metformin (prospective cohort studies)

Quality assessment							Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Pooled effect (95% CI)	
Metformin use per year for predicting vitamin B12 deficiency (≤ 203 pg/mL) (impaired glucose tolerance)								
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	Adjusted OR: 1.13 (1.06 to 1.2)	VERY LOW

[1] Downgraded by two increments due to very high risk of bias (vitamin B12 status at baseline not reported; >10% last to follow up with no description of those missing from the analysis or attempts to follow up; measurement of metformin use included self-report; vitamin B12 deficiency based on serum level alone; not all confounders accounted for; model development strategy not reported)

[2] Downgraded by 1 increment due to serious population indirectness (applicability limited to those with impaired glucose tolerance).

Table 14: Clinical evidence summary: metformin (retrospective cohort studies)

Quality assessment							Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Pooled effect (95% CI)	
Metformin (metformin usage index <5) for predicting vitamin B12 deficiency (<200 pg/ml or borderline deficiency 200–300 pg/ml (type 2 diabetes)								
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	Adjusted OR: 1.37 (0.88 to 2.13)	VERY LOW
Metformin (metformin usage index >5) for predicting vitamin B12 deficiency (<200 pg/ml or borderline deficiency 200–300 pg/ml) (type 2 diabetes)								
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	Adjusted OR: 3.56 (2.29 to 5.53)	VERY LOW
Metformin (metformin usage index >10) for predicting vitamin B12 deficiency (<200 pg/ml or borderline deficiency 200–300 pg/ml) (type 2 diabetes)								
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	Adjusted OR: 5.12 (3.12 to 8.4)	VERY LOW
Metformin (metformin usage index >15) for predicting vitamin B12 deficiency (<200 pg/ml or borderline deficiency 200–300 pg/ml) (type 2 diabetes)								
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	Adjusted OR: 6.74 (4.39 to 10.35)	VERY LOW

[1] Downgraded by two increments due to very high risk of bias (vitamin B12 status at baseline (prior to risk factors) not reported and those receiving supplements were excluded; unclear measurement of metformin use (based on clinical records - no further detail); no information on missing data; unclear whether borderline deficiency is included in deficiency outcome (appears so))
[2] Downgraded by one increment due to serious population indirectness (applicability limited to those with type 2 diabetes)
[3] Downgraded by one increment due to imprecision if the confidence interval crossed the null line

Table 15: Clinical evidence summary: proton pump inhibitors (case control studies)

Quality assessment	Effect	Quality

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Pooled effect (95% CI)	
Proton pump inhibitor (at least a 2-year supply prior to the index date) for predicting vitamin B12 deficiency (diagnostic code for deficiency/specific text diagnoses/low serum B12/new at least 6-month supply of injectable B12) (B12 deficiency cases and matched controls from an electronic database)								
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	OR: 1.65 (1.58 to 1.72)	LOW

[1] Downgraded by two increments due to very high risk of bias (unclear duration of follow up; medication duration <2 years and OTC medications not included in the analysis; not all key confounders considered/measurable due to study design; analytical strategy described, but results not fully reported)

Table 16: Clinical evidence summary: H2 receptor antagonists (case control studies)

Quality assessment							Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Pooled effect (95% CI)	
H2 receptor antagonists (at least a 2-year supply prior to the index date) for predicting vitamin B12 deficiency (diagnostic code for deficiency/specific text diagnoses/low serum B12/new at least 6-month supply of injectable B12) (B12 deficiency cases and matched controls from an electronic database)								
1	cohort studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	OR: 1.25 (1.17 to 1.34)	LOW

[1] Downgraded by two increments due to very high risk of bias (unclear duration of follow up; medication duration <2 years and OTC medications not included in the analysis; not all key confounders considered/measurable due to study design; analytical strategy described, but results not fully reported)

Table 17: Clinical evidence summary: Ileal resection (retrospective cohort studies)

Quality assessment							Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Pooled effect (95% CI)	
Previous ileal or ileocolonic resection for predicting vitamin B12 deficiency (< 200 pg/ml) (Crohn's disease)								

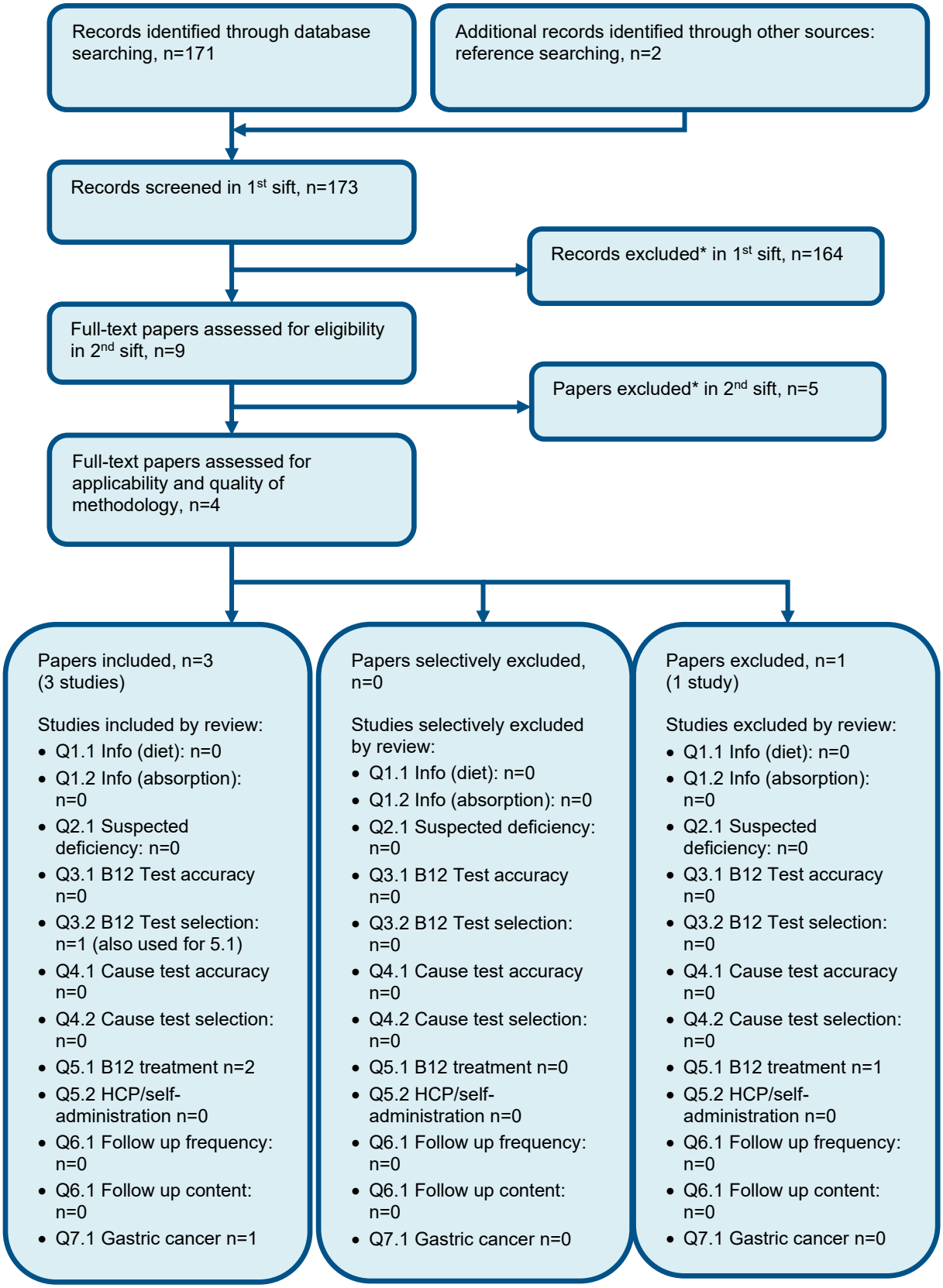
1	cohort studies	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	Adjusted OR: 2.7 (1.2 to 6.07)	VERY LOW
Prior ileal resection 0-20cm for predicting vitamin B12 deficiency (<25 pmol/L Values 25-50 pmol/L underwent MMA analysis. See study details) (Crohn's disease)								
1	cohort studies	serious[3]	no serious inconsistency	serious[2]	no serious imprecision	none	Adjusted OR: 3 (1.5 to 6)	LOW
Prior ileal resection >20cm for predicting vitamin B12 deficiency (<25 pmol/L Values 25-50 pmol/L underwent MMA analysis. See study details) (Crohn's disease)								
1	cohort studies	serious[3]	no serious inconsistency	serious[2]	no serious imprecision	none	Adjusted OR: 6.7 (3 to 14.96)	LOW
Prior ileal resection for predicting vitamin B12 deficiency (<224 pg/mL) (Crohn's disease)								
1	cohort studies	very serious[4]	no serious inconsistency	serious[2]	no serious imprecision	none	Adjusted OR: 7.22 (1.97 to 26.46)	VERY LOW

[1] Downgraded by two increments due to very high risk of bias (B12 status at baseline (prior to/at the time of resection) not reported; those receiving B12 supplements excluded; not all confounders considered; no information on missing data; significant results only reported in text)
[2] Downgraded by one increment due to serious population indirectness (applicability limited to those with Crohn's disease)
[3] Downgraded by one increment due to high risk of bias (vitamin B12 status at baseline not reported, although history of diagnosed deficiency excluded; retrospective chart review with unclear duration between prognostic factor and outcome; not all key confounders measured/adjusted for)
[4] Downgraded by two increments due to very high risk of bias (unclear duration between prognostic factor and outcome; adjusted for some but not all key confounders; limited information on measurement of prognostic and confounding factors; definition of deficiency based on serum values only and includes indeterminate range)

F.2 Symptoms and signs of vitamin B12 deficiency

No evidence identified.

1 Appendix G Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

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Appendix H – Economic evidence tables

No economic evidence identified (prognostic/diagnostic review).

1 Appendix I Health economic model

2 There was no original economic modelling undertaken for this review question.

3 Appendix J Excluded studies

4 J.1 Clinical studies

J.1.15 Risk factors for vitamin B12 deficiency

6 **Table 18: Studies excluded from the clinical review**

Study	Code [Reason]
Alhaji, Jwaher Haji (2022) Vitamin B12 Deficiency in Patients with Diabetes on Metformin: Arab Countries. Nutrients 14(10)	- Review article but not a systematic review
Alharbi, Turki J, Tourkmani, Ayla M, Abdelhay, Osama et al. (2018) The association of metformin use with vitamin B12 deficiency and peripheral neuropathy in Saudi individuals with type 2 diabetes mellitus. PloS one 13(10): e0204420	- Study design not relevant to this review protocol
Arora, S., Singh, B., Gupta, V.K. et al. (2011) Burden of vitamin B12 deficiency in urban population in Delhi, India: A hospital based study. International Journal of Pharma and Bio Sciences 2(1): 521-528	- Full text paper not available
Atabi, D.F., Qasim, A.H., Mohammed, S.A.K. et al. (2021) Association of metformin use with vitamin b12 deficiency in iraqi patients with type ii diabetes mellitus. Indian Journal of Forensic Medicine and Toxicology 15(3): 4728-4733	- Data not reported in an extractable format or a format that can be analysed
Awad, N.A., Alsaady, Z.A., Albayati, M.A.M. et al. (2022) Correlation study of metformin drug with vit.B12 and folic acid in women suffer of type 2 diabetic disease. Journal of Pharmaceutical Negative Results 13(3): 308-312	- Data not reported in an extractable format or a format that can be analysed
Battat, Robert, Kopylov, Uri, Szilagyi, Andrew et al. (2014) Vitamin B12 deficiency in inflammatory bowel disease: prevalence, risk	- Systematic review used as source of primary studies

Study	Code [Reason]
factors, evaluation, and management. Inflammatory bowel diseases 20(6): 1120-8	
Bilici, Ahmet, Sonkaya, Alper, Ercan, Serif et al. (2015) The changing of serum vitamin B12 and homocysteine levels after gastrectomy in patients with gastric cancer: do they associate with clinicopathological factors?. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine 36(2): 823-8	- No relevant outcomes
Bledsoe, Adam C, King, Katherine S, Larson, Joseph J et al. (2019) Micronutrient Deficiencies Are Common in Contemporary Celiac Disease Despite Lack of Overt Malabsorption Symptoms. Mayo Clinic proceedings 94(7): 1253-1260	- Data not reported in an extractable format or a format that can be analysed
Bussen, S and Bussen, D (2012) Serum Folate and Cobalamin Levels in Women Using Combined Contraceptive Vaginal Ring. Geburtshilfe und Frauenheilkunde 72(2): 149-153	- Data not reported in an extractable format or a format that can be analysed
Buyukgol, Huseyin and Gunes, Muzaffer (2020) The Effects of Antiepileptic Medications on Lipid Profile, Thyroid Panel, and Vitamin Level. Cureus 12(10): e11005	- Data not reported in an extractable format or a format that can be analysed
Carmel, R., Cairo, K., Bondareff, W. et al. (1996) Spouses of demented patients with low cobalamin levels: A new risk group for cobalamin deficiency. European Journal of Haematology 57(1): 62-67	- Data not reported in an extractable format or a format that can be analysed
Carmel, R; Aurangzeb, I; Qian, D (2001) Associations of food-cobalamin malabsorption with ethnic origin, age, Helicobacter pylori infection, and serum markers of gastritis. The American journal of gastroenterology 96(1): 63-70	- Data not reported in an extractable format or a format that can be analysed
Castillo-Lancellotti, C., Margozzini, P., Valdivia, G. et al. (2013) Serum folate and vitamin B12 in older people. Results from the Chilean national health survey 2009-2010. Revista Medica de Chile 141(9): 1107-1116	- Study not reported in English

Study	Code [Reason]
Chapman, L E; Darling, A L; Brown, J E (2016) Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes & metabolism 42(5): 316-327	- Systematic review used as source of primary studies
Chapman, L.E.; Darling, A.L.; Brown, J.E. (2015) The association between the biguanide drug metformin and vitamin B12 deficiency in diabetic patients: A systematic review. Proceedings of the Nutrition Society 74(oce1)	- Conference abstract
Clarke, Robert, Grimley Evans, J, Schneede, J et al. (2004) Vitamin B12 and folate deficiency in later life. Age and ageing 33(1): 34-41	- Data not reported in an extractable format or a format that can be analysed
Cotter, P.E. and O'Keeffe, S.T. (2011) Use of proton pump inhibitors is not associated with Vitamin B12 deficiency and in older hospital patients: A case control study. European Geriatric Medicine 2(4): 253-255	- Study design not relevant to this review protocol
Crandall, J.P., Edelstein, S.L., Aroda, V. et al. (2013) Vitamin B12 deficiency in the diabetes prevention program outcome study (DPPOS). Diabetes 62(suppl1): a309	- Conference abstract
Crane, M.G., Sample, C., Patchett, S. et al. (1994) Vitamin B12 studies in total vegetarians (vegans). Journal of Nutritional Medicine 4(4): 419-430	- Data not reported in an extractable format or a format that can be analysed
Elsborg, L; Lung, V; Bastrup-Madsen, P (1976) Serum vitamin B12 levels in the aged. Acta medica Scandinavica 200(4): 309-14	- Study design not relevant to this review protocol
Force, R W and Nahata, M C (1992) Effect of histamine H2-receptor antagonists on vitamin B12 absorption. The Annals of pharmacotherapy 26(10): 1283-6	- Review article but not a systematic review
Force, Rex W, Meeker, Angela D, Cady, Paul S et al. (2003) Ambulatory care increased vitamin B12 requirement associated with chronic acid suppression therapy. The Annals of pharmacotherapy 37(4): 490-3	- No relevant outcomes

Study	Code [Reason]
Gorjipour, Fazel, Asadi, Yasin, K Osguei, Nushin et al. (2013) Serum level of homocysteine, folate and vitamin-B12 in epileptic patients under carbamazepine and sodium valproate treatment: a systematic review and meta-analysis. Iranian Red Crescent medical journal 15(3): 249-53	- Systematic review used as source of primary studies
Greibe, Eva, Trolle, Birgitta, Bor, Mustafa V et al. (2013) Metformin lowers serum cobalamin without changing other markers of cobalamin status: a study on women with polycystic ovary syndrome. Nutrients 5(7): 2475-82	- Data not reported in an extractable format or a format that can be analysed
Gumurdulu, Yuksel, Serin, Ender, Ozer, Birol et al. (2003) Predictors of vitamin B12 deficiency: age and Helicobacter pylori load of antral mucosa. The Turkish journal of gastroenterology : the official journal of Turkish Society of Gastroenterology 14(1): 44-9	- Study design not relevant to this review protocol
Gupta, Anil K; Damji, Alkarim; Uppaluri, Aparna (2004) Vitamin B12 deficiency. Prevalence among South Asians at a Toronto clinic. Canadian family physician Medecin de famille canadien 50: 743-7	- No adjustment for key confounders
Hartman, Brenda, Donnelly-VanderLoo, Mary, Watson, Tiffany et al. (2016) Proton-pump inhibitor therapy and vitamin B12 status in an inpatient hospital setting. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 41(10): 1071-1076	- Study design not relevant to this review protocol
Hemminki, Kari, Li, Xinjun, Sundquist, Jan et al. (2009) Familial associations of rheumatoid arthritis with autoimmune diseases and related conditions. Arthritis and rheumatism 60(3): 661-8	- Study design not relevant to this review protocol
Hendrawati, Y D, Andrajati, R, Supardi, S et al. (2018) THE RISK OF COBALAMIN DEFICIENCY SYMPTOMS RELATED TO LONG-TERM METFORMIN USE IN T2DM PATIENTS. Acta endocrinologica (Bucharest, Romania : 2005) 14(1): 49-54	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
Herrmann, W., Schorr, H., Purschwitz, K. et al. (2001) Total homocysteine, vitamin b12, and total antioxidant status in vegetarians. Clinical Chemistry 47(6i): 1094-1101	- Data not reported in an extractable format or a format that can be analysed
Hitzhusen, J C, Taplin, M E, Stephenson, W P et al. (1986) Vitamin B12 levels and age. American journal of clinical pathology 85(1): 32-6	- Data not reported in an extractable format or a format that can be analysed
Huang, Shaozhong, Ma, Jiayi, Zhu, Mingming et al. (2017) Status of serum vitamin B12 and folate in patients with inflammatory bowel disease in China. Intestinal research 15(1): 103-108	- Data not reported in an extractable format or a format that can be analysed
Humphrey, M.L.; Barkhordari, N.; Kaakeh, Y. (2012) Effects of omeprazole on vitamin and mineral absorption and metabolism. Journal of Pharmacy Technology 28(6): 243-248	- Review article but not a systematic review
Javanainen, Mervi, Pekkarinen, Tuula, Mustonen, Harri et al. (2018) Two-Year Nutrition Data in Terms of Vitamin D, Vitamin B12, and Albumin After Bariatric Surgery and Long-term Fracture Data Compared with Conservatively Treated Obese Patients: a Retrospective Cohort Study. Obesity surgery 28(9): 2968-2975	- No relevant outcomes
Jayashri, Ramamoorthy, Venkatesan, Ulagamathesan, Rohan, Menon et al. (2018) Prevalence of vitamin B12 deficiency in South Indians with different grades of glucose tolerance. Acta diabetologica 55(12): 1283-1293	- Study design not relevant to this review protocol
Johnson, M A, Hausman, D B, Davey, A et al. (2010) Vitamin B12 deficiency in African American and white octogenarians and centenarians in Georgia. The journal of nutrition, health & aging 14(5): 339-45	- Study design not relevant to this review protocol
Ju, H.J., Seo, J.M., Kim, S.H. et al. (2022) 32632 Comorbidities in patients with vitiligo: A systematic review and meta-analysis. Journal of the American Academy of Dermatology 87(3supplement): ab150	- Conference abstract

Study	Code [Reason]
Jung, S B, Nagaraja, V, Kapur, A et al. (2015) Association between vitamin B12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis. Internal medicine journal 45(4): 409-16	- Systematic review used as source of primary studies
Kacharava, Tinatin, Giorgadze, Elene, Janjgava, Shota et al. (2022) Correlation between Vitamin B12 Deficiency and Autoimmune Thyroid Diseases. Endocrine, metabolic & immune disorders drug targets	- Study design not relevant to this review protocol
Kancherla, Vijaya, Elliott, John L Jr, Patel, Birju B et al. (2017) Long-term Metformin Therapy and Monitoring for Vitamin B12 Deficiency Among Older Veterans. Journal of the American Geriatrics Society 65(5): 1061-1066	- Data not reported in an extractable format or a format that can be analysed
Khattab, Rabie, Albannawi, Mayar, Alhajjmohammed, Dua'a et al. (2022) Metformin-Induced Vitamin B12 Deficiency among Type 2 Diabetes Mellitus' Patients: A Systematic Review. Current diabetes reviews	- Systematic review used as source of primary studies
Knapik, Joseph J, Farina, Emily K, Fulgoni, Victor L 3rd et al. (2021) Clinically-diagnosed vitamin deficiencies and disorders in the entire United States military population, 1997-2015. Nutrition journal 20(1): 55	- No adjustment for key confounders
Koebnick, Corinna, Hoffmann, Ingrid, Dagnelie, Pieter C et al. (2004) Long-term ovo-lacto vegetarian diet impairs vitamin B-12 status in pregnant women. The Journal of nutrition 134(12): 3319-26	- No adjustment for key confounders
Koenig, Victoria, Stanga, Zeno, Zerlauth, Manfred et al. (2014) Prevalence of vitamin B(12) depletion and deficiency in Liechtenstein. Public health nutrition 17(2): 241-7	- Study design not relevant to this review protocol
Kos, Elizabeth, Liszek, Mary Jo, Emanuele, Mary Ann et al. (2012) Effect of metformin therapy on vitamin D and vitamin B12 levels in patients with type 2 diabetes mellitus. Endocrine practice : official journal of the American College	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
of Endocrinology and the American Association of Clinical Endocrinologists 18(2): 179-84	
Krajewski, W, Kucharska, M, Pilacik, B et al. (2007) Impaired vitamin B12 metabolic status in healthcare workers occupationally exposed to nitrous oxide. British journal of anaesthesia 99(6): 812-8	- Data not reported in an extractable format or a format that can be analysed
Lachner, C, Martin, C, John, D et al. (2014) Older adult psychiatric inpatients with non-cognitive disorders should be screened for vitamin B12 deficiency. The journal of nutrition, health & aging 18(2): 209-12	- Data not reported in an extractable format or a format that can be analysed
Li, Xinjun, Thomsen, Hauke, Sundquist, Kristina et al. (2021) Familial Risks between Pernicious Anemia and Other Autoimmune Diseases in the Population of Sweden. Autoimmune diseases 2021: 8815297	- Data not reported in an extractable format or a format that can be analysed
Liebman, M.F., Brien, W., Parulekar, W.R. et al. (2014) Vitamin B12 (Vit B12) biochemical (BCH) deficiency (DEF) in non-diabetic breast cancer (BC) patients on NCIC CTG MA.32: A phase III randomized adjuvant BC trial comparing metformin (Met) to placebo (Pl). Journal of Clinical Oncology 32(15suppl1)	- Conference abstract
Lindblad, A.J. and Sadowski, C.A. (2008) Safety of proton pump inhibitors in community-dwelling older adults. Journal of Pharmacy Technology 24(4): 213-218	- Systematic review used as source of primary studies
Linder, Lauren; Tamboue, Cynthia; Clements, Jennifer N (2017) Drug-Induced Vitamin B12 Deficiency: A Focus on Proton Pump Inhibitors and Histamine-2 Antagonists. Journal of pharmacy practice 30(6): 639-642	- Review article but not a systematic review
Linnebank, Michael, Moskau, Susanna, Semmler, Alexander et al. (2011) Antiepileptic drugs interact with folate and vitamin B12 serum levels. Annals of neurology 69(2): 352-9	- Data not reported in an extractable format or a format that can be analysed
Liu, Q., Li, S., Quan, H. et al. (2014) Vitamin B12 status in metformin treated patients: A	- Duplicate reference

Study	Code [Reason]
systematic review. Diabetes/Metabolism Research and Reviews 30(suppl3): 50-51	
Liu, Qilin, Li, Sheyu, Quan, Heng et al. (2014) Vitamin B12 status in metformin treated patients: systematic review. PloS one 9(6): e100379	- Systematic review used as source of primary studies
Madanchi, Matiar, Fagagnini, Stefania, Fournier, Nicolas et al. (2018) The Relevance of Vitamin and Iron Deficiency in Patients with Inflammatory Bowel Diseases in Patients of the Swiss IBD Cohort. Inflammatory bowel diseases 24(8): 1768-1779	- Data not reported in an extractable format or a format that can be analysed
Martin, Darby, Thaker, Jeet, Shreve, Maria et al. (2021) Assessment of vitamin B12 deficiency and B12 screening trends for patients on metformin: a retrospective cohort case review. BMJ nutrition, prevention & health 4(1): 30-35	- Study design not relevant to this review protocol
Mastroianni, Antonio, Ciniselli, Chiara Maura, Panella, Rossella et al. (2019) Monitoring Vitamin B12 in Women Treated with Metformin for Primary Prevention of Breast Cancer and Age-Related Chronic Diseases. Nutrients 11(5)	- No adjustment for key confounders
McArthur, Jennifer O, Tang, HoMan, Petocz, Peter et al. (2013) Biological variability and impact of oral contraceptives on vitamins B(6), B(12) and folate status in women of reproductive age. Nutrients 5(9): 3634-45	- Data not reported in an extractable format or a format that can be analysed
Mearns, Gael Janine and Rush, Elaine Carolyn (2017) Screening for inadequate dietary vitamin B-12 intake in South Asian women using a nutrient-specific, semi-quantitative food frequency questionnaire. Asia Pacific journal of clinical nutrition 26(6): 1119-1124	- No adjustment for key confounders
Meziere, Anthony, Audureau, Etienne, Vairelles, Stephane et al. (2014) B12 deficiency increases with age in hospitalized patients: a study on 14,904 samples. The journals of gerontology. Series A, Biological sciences and medical sciences 69(12): 1576-85	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
Mintzer, Scott; Skidmore, Christopher T; Sperling, Michael R (2012) B-vitamin deficiency in patients treated with antiepileptic drugs. Epilepsy & behavior : E&B 24(3): 341-4	- Data not reported in an extractable format or a format that can be analysed
Mitchell, S L and Rockwood, K (2001) The association between antiulcer medication and initiation of cobalamin replacement in older persons. Journal of clinical epidemiology 54(5): 531-4	- No relevant outcomes
Moratalla-Navarro, F., Moreno, V., Lopez-Simarro, F. et al. (2021) MorbiNet Study: Hypothyroidism Comorbidity Networks in the Adult General Population. Journal of Clinical Endocrinology and Metabolism 106(3): e1179-e1190	- No relevant outcomes
Mumtaz, H., Ghafoor, B., Saghir, H. et al. (2022) Association of Vitamin B12 deficiency with long-term PPIs use: A cohort study. Annals of Medicine and Surgery 82: 104762	- No adjustment for key confounders
Neufingerl, Nicole and Eilander, Ans (2021) Nutrient Intake and Status in Adults Consuming Plant-Based Diets Compared to Meat-Eaters: A Systematic Review. Nutrients 14(1)	- Systematic review used as source of primary studies
Niafar, Mitra, Hai, Faizi, Porhomayon, Jahan et al. (2015) The role of metformin on vitamin B12 deficiency: a meta-analysis review. Internal and emergency medicine 10(1): 93-102	- Systematic review used as source of primary studies
Nilsson-Ehle, H, Jagenburg, R, Landahl, S et al. (1991) Serum cobalamins in the elderly: a longitudinal study of a representative population sample from age 70 to 81. European journal of haematology 47(1): 10-6	- Data not reported in an extractable format or a format that can be analysed
Out, M., Kooy, A., Lehert, P. et al. (2015) Metformin, methylmalonic acid and the risk of neuropathy: A randomised placebo-controlled trial. Diabetologia 58(1suppl1): 110-s111	- Full text paper not available
Out, Mattijs, Kooy, Adriaan, Lehert, Philippe et al. (2018) Long-term treatment with metformin in	- No relevant outcomes

Study	Code [Reason]
type 2 diabetes and methylmalonic acid: Post hoc analysis of a randomized controlled 4.3year trial. Journal of diabetes and its complications 32(2): 171-178	
Pfisterer, Kaylen J, Sharratt, Mike T, Heckman, George G et al. (2016) Vitamin B12 status in older adults living in Ontario long-term care homes: prevalence and incidence of deficiency with supplementation as a protective factor. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 41(2): 219-22	- Study design not relevant to this review protocol
Polonen, S., Tiihonen, M., Nykanen, I. et al. (2019) Incidence of prescription vitamin B12 use in relation to diagnosis of Alzheimer's disease among community-dwelling persons. Journal of Public Health (Germany) 27(6): 775-779	- No relevant outcomes
Porter, Kirsty M, Hoey, Leane, Hughes, Catherine F et al. (2021) Associations of atrophic gastritis and proton-pump inhibitor drug use with vitamin B-12 status, and the impact of fortified foods, in older adults. The American journal of clinical nutrition 114(4): 1286-1294	- Data not reported in an extractable format or a format that can be analysed
Porter, Kirsty M, Ward, Mary, Hughes, Catherine F et al. (2019) Hyperglycemia and Metformin Use Are Associated With B Vitamin Deficiency and Cognitive Dysfunction in Older Adults. The Journal of clinical endocrinology and metabolism 104(10): 4837-4847	- Study design not relevant to this review protocol
Prasad, A S, Lei, K Y, Moghissi, K S et al. (1976) Effect of oral contraceptives on nutrients. III. Vitamins B6, B12, and folic acid. American journal of obstetrics and gynecology 125(8): 1063-9	- Study design not relevant to this review protocol
Presse, N., Kergoat, M.-J., Dorais, M. et al. (2016) Time trends of vitamin B12 deficiency in older adults: A population-based cohort study. Pharmacoepidemiology and Drug Safety 25(supplement3): 373	- Conference abstract

Study	Code [Reason]
Qorraj-Bytyqi, Hasime, Hoxha, Rexhep, Sadiku, Shemsedin et al. (2018) Proton Pump Inhibitors Intake and Iron and Vitamin B12 Status: A Prospective Comparative Study with a Follow up of 12 Months. Open access Macedonian journal of medical sciences 6(3): 442-446	- Data not reported in an extractable format or a format that can be analysed
Reinstatler, Lael, Qi, Yan Ping, Williamson, Rebecca S et al. (2012) Association of biochemical B12 deficiency with metformin therapy and vitamin B12 supplements: the National Health and Nutrition Examination Survey, 1999-2006. Diabetes care 35(2): 327-33	- Study design not relevant to this review protocol
Rezaei, Shahabeddin, Shab-Bidar, Sakineh, Abdulahi Abdurahman, Ahmed et al. (2017) Oxcarbazepine administration and the serum levels of homocysteine, vitamin B12 and folate in epileptic patients: A systematic review and meta-analysis. Seizure 45: 87-94	- Systematic review used as source of primary studies
Sagar, M, Janczewska, I, Ljungdahl, A et al. (1999) Effect of CYP2C19 polymorphism on serum levels of vitamin B12 in patients on long-term omeprazole treatment. Alimentary pharmacology & therapeutics 13(4): 453-8	- Data not reported in an extractable format or a format that can be analysed
Singh, A K, Kumar, A, Karmakar, D et al. (2013) Association of B12 deficiency and clinical neuropathy with metformin use in type 2 diabetes patients. Journal of postgraduate medicine 59(4): 253-7	- Study design not relevant to this review protocol
Solomon, L R (2015) Functional cobalamin (vitamin B12) deficiency: role of advanced age and disorders associated with increased oxidative stress. European journal of clinical nutrition 69(6): 687-92	- No relevant outcomes
Staubli, Georg, Baumgartner, Matthias, Sass, Jorn Oliver et al. (2016) Laughing Gas in a Pediatric Emergency Department-Fun for All Participants: Vitamin B12 Status Among Medical Staff Working With Nitrous Oxide. Pediatric emergency care 32(12): 827-829	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
Termanini, B, Gibril, F, Sutliff, V E et al. (1998) Effect of long-term gastric acid suppressive therapy on serum vitamin B12 levels in patients with Zollinger-Ellison syndrome. The American journal of medicine 104(5): 422-30	- Data not reported in an extractable format or a format that can be analysed
Ting, Rose Zhao-Wei, Szeto, Cheuk Chun, Chan, Michael Ho-Ming et al. (2006) Risk factors of vitamin B(12) deficiency in patients receiving metformin. Archives of internal medicine 166(18): 1975-9	- Study design not relevant to this review protocol
Valuck, Robert J and Ruscin, J Mark (2004) A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults. Journal of clinical epidemiology 57(4): 422-8	- Study design not relevant to this review protocol
Vistad, Ingvild, Kristensen, Gunnar B, Fossa, Sophie D et al. (2009) Intestinal malabsorption in long-term survivors of cervical cancer treated with radiotherapy. International journal of radiation oncology, biology, physics 73(4): 1141-7	- Data not reported in an extractable format or a format that can be analysed
Ward, M.G., Kariyawasam, V.C., Mogan, S.B. et al. (2013) Prevalence and risk factors for functional b12 deficiency in patients with Crohn's disease. Journal of Gastroenterology and Hepatology 28(suppl2): 101	- Conference abstract
Wile, Daryl J and Toth, Cory (2010) Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. Diabetes care 33(1): 156-61	- Data not reported in an extractable format or a format that can be analysed
Wong, Chit Wai, Leung, Chi Shing, Leung, Chung Ping et al. (2018) Association of metformin use with vitamin B12 deficiency in the institutionalized elderly. Archives of gerontology and geriatrics 79: 57-62	- Study design not relevant to this review protocol
Wulffele, M G, Kooy, A, Lehert, P et al. (2003) Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes	- Secondary publication of an included study that does not provide any additional relevant information

Study	Code [Reason]
mellitus: a randomized, placebo-controlled trial. Journal of internal medicine 254(5): 455-63	
Xu, Yubin, Zhang, Na, Xu, Shanshan et al. (2019) Effects of phenytoin on serum levels of homocysteine, vitamin B12, folate in patients with epilepsy: A systematic review and meta-analysis (PRISMA-compliant article). Medicine 98(12): e14844	- Systematic review used as source of primary studies
Yang, W., Cai, X., Wu, H. et al. (2018) Associations between metformin use and the risks of vitamin B12 deficiency, anaemia and neuropathy in patients with diabetes: A meta-analysis. Diabetologia 61(supplement1): 342-s343	- Conference abstract
Yang, Wenjia, Cai, Xiaoling, Wu, Haiya et al. (2019) Associations between metformin use and vitamin B12 levels, anemia, and neuropathy in patients with diabetes: a meta-analysis. Journal of diabetes 11(9): 729-743	- Systematic review used as source of primary studies
Zhou, H, Wang, N, Huang, H et al. (2015) Effect observation of anti epileptic drugs on serum folic acid and vitamin B12 of epileptic patients. Minerva medica 106(4): 215-9	- Data not reported in an extractable format or a format that can be analysed

J.1.22 Symptoms and signs of vitamin B12 deficiency

Table 19: Studies excluded from the clinical review

Study	Code [Reason]
Aamir, R., Virk, S.T., Zahra, T. et al. (2018) Vitamin b12 deficiency and its co-relation with symptoms. Rawal Medical Journal 43(4): 615-618	- Data not reported in an extractable format or a format that can be analysed
Aaron, S, Kumar, Sudhir, Vijayan, J et al. (2005) Clinical and laboratory features and response to treatment in patients presenting with vitamin B12 deficiency-related neurological syndromes. Neurology India 53(1): 55-59	- Population not relevant to this review protocol
Abbas, Zaigham, Raza, Sajjad, Yakoob, Javed et al. (2013) Varied presentation of celiac disease in Pakistani adults. Journal of the	- No relevant signs/symptoms reported

Study	Code [Reason]
College of Physicians and Surgeons--Pakistan : JCPSP 23(7): 522-4	
Abdelkader, Nadia Abdelaaty, Zaky, Doaa Zakaria, Afifi, Hossam et al. (2014) Neuropathies in hepatitis C-related liver cirrhosis. Indian journal of gastroenterology : official journal of the Indian Society of Gastroenterology 33(6): 554-9	- Vitamin B12 deficiency not investigated
Abrahamsen, J.F., Monsen, A.-L.B., Ranhoff, A.H. et al. (2020) No association between subnormal serum vitamin B12 and anemia in older nursing home patients. European Geriatric Medicine 11(2): 247-254	- Population not relevant to this review protocol
Abu-Shanab, Amer, Zihlif, Malek, Rbeihat, Momen N et al. (2021) Vitamin B12 Deficiency Among the Healthy Jordanian Adult Population: Diagnostic Levels, Symptomology and Risk Factors. Endocrine, metabolic & immune disorders drug targets 21(6): 1107-1114	- Population not relevant to this review protocol
Adhikari, P.M., Chowta, M.N., Ramapuram, J.T. et al. (2016) Effect of Vitamin B12 and folic acid supplementation on neuropsychiatric symptoms and immune response in HIV-positive patients. Journal of Neurosciences in Rural Practice 7(3): 362-367	- Data not reported in an extractable format or a format that can be analysed
Agarwal, Rachna, Chhillar, Neelam, Kushwaha, Suman et al. (2010) Role of vitamin B(12), folate, and thyroid stimulating hormone in dementia: A hospital-based study in north Indian population. Annals of Indian Academy of Neurology 13(4): 257-62	- Data not reported in an extractable format or a format that can be analysed
Ahmed, F, Khan, M R, Banu, C P et al. (2008) The coexistence of other micronutrient deficiencies in anaemic adolescent schoolgirls in rural Bangladesh. European journal of clinical nutrition 62(3): 365-72	- Data not reported in an extractable format or a format that can be analysed
Ahmed, Marwan A; Muntingh, George; Rheeder, Paul (2016) Vitamin B12 deficiency in metformin-treated type-2 diabetes patients, prevalence and association with peripheral neuropathy. BMC pharmacology & toxicology 17(1): 44	- Population not relevant to this review protocol
Allain, T J, Gomo, Z, Wilson, A O et al. (1997) Anaemia, macrocytosis, vitamin B12 and folate levels in elderly Zimbabweans. The Central African journal of medicine 43(11): 325-8	- Full text paper not available
Alves, Jose Miguel, Seabra, Mafalda, Braz, Luis et al. (2020) Optic neuropathy: A 15-year retrospective observational study. Multiple sclerosis and related disorders 44: 102337	- Vitamin B12 deficiency not investigated
Andersen, Mathilde Horn, Kruse, Alexandra, Frederiksen, Hanne Winther et al. (2020) Health	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
status of refugees newly resettled in Denmark. Danish medical journal 67(12)	
Andersen-Ranberg, K; Vasegaard, L; Jeune, B (2001) Dementia is not inevitable: a population-based study of Danish centenarians. The journals of gerontology. Series B, Psychological sciences and social sciences 56(3): p152-9	- Data not reported in an extractable format or a format that can be analysed
Areekul, S.; Ratanabanangkoon, K.; Hathirat, P. (1978) Vitamin B12 and vitamin B12 binding proteins in iron deficiency anaemia. Southeast Asian Journal of Tropical Medicine and Public Health 9(4): 510-515	- Vitamin B12 deficiency not defined
Arican, P., Bozkurt, O., Cavusoglu, D. et al. (2020) Various neurological symptoms with vitamin b12 deficiency and posttreatment evaluation. Journal of Pediatric Neurosciences 15(4): 365-369	- Population not relevant to this review protocol
Arora, H.; Srivastava, N.; Bala, K. (2016) Prevalence of vitamin D/B12 deficiency among urban populations complaining pain of lower limb and generalize weakness. Asian Journal of Pharmaceutical and Clinical Research 9(3)	- Population not relevant to this review protocol
Ata, Fateen, Bint I Bilal, Ammara, Javed, Saad et al. (2020) Optic neuropathy as a presenting feature of vitamin B-12 deficiency: A systematic review of literature and a case report. Annals of medicine and surgery (2012) 60: 316-322	- Study design not relevant to this review protocol
Aydin, Hilal; Bucak, Ibrahim Hakan; Geyik, Mehmet (2021) Vitamin B12 and folic acid levels in pediatric migraine patients. Acta neurologica Belgica 121(6): 1741-1744	- Data not reported in an extractable format or a format that can be analysed
Bandyopadhyay, D.; Choudhury, J.R.; Mukherjee, K. (2021) Vitamin B12 deficiency in Eastern India: A hospital based cross-sectional study. Journal of Clinical and Diagnostic Research 15(4): bc01-bc04	- Data not reported in an extractable format or a format that can be analysed
Bao, L., Li, Q., Chen, H. et al. (2020) Clinical, electrophysiological and radiological features of nitrous oxide-induced neurological disorders. Neuropsychiatric Disease and Treatment 16: 977-984	- Data not reported in an extractable format or a format that can be analysed
Bao, Zhe-Xuan; Yang, Xiao-Wen; Fang, Dong-Dong (2021) Lingual Linear Lesions: A Clinical Sign Strongly Suggestive of Severe Vitamin B12 Deficiency. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition 36(5): 1041-1048	- Data not reported in an extractable format or a format that can be analysed
Baz, Rachid, Alemany, Carlos, Green, Ralph et al. (2004) Prevalence of vitamin B12 deficiency	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
in patients with plasma cell dyscrasias: a retrospective review. Cancer 101(4): 790-5	
Bednarska-Makaruk, Malgorzata, Graban, Alla, Sobczynska-Malefora, Agata et al. (2016) Homocysteine metabolism and the associations of global DNA methylation with selected gene polymorphisms and nutritional factors in patients with dementia. Experimental gerontology 81: 83-91	- Data not reported in an extractable format or a format that can be analysed
Bisbe, E: Castillo, J: Sáez M, Santiveri X, Ruíz A et al. (2008) Prevalence of preoperative anemia and hematinic deficiencies in patients scheduled for elective major orthopedic surgery. Transfusion Alternatives in Transfusion Medicine 10: 166-173.	- Population not relevant to this review protocol
Bjelland, Ingvar, Tell, Grethe S, Vollset, Stein Emil et al. (2003) Folate, vitamin B12, homocysteine, and the MTHFR 677C->T polymorphism in anxiety and depression: the Hordaland Homocysteine Study. Archives of general psychiatry 60(6): 618-26	- Data not reported in an extractable format or a format that can be analysed
Bjorkegren, K and Svardsudd, K (2003) Reported symptoms and clinical findings in relation to serum cobalamin, folate, methylmalonic acid and total homocysteine among elderly Swedes: a population-based study. Journal of internal medicine 254(4): 343-52	- Population not relevant to this review protocol
Bonetti, Francesco, Brombo, Gloria, Magon, Stefania et al. (2015) Cognitive Status According to Homocysteine and B-Group Vitamins in Elderly Adults. Journal of the American Geriatrics Society 63(6): 1158-63	- Vitamin B12 deficiency not investigated
Boston, Paul F, McKirdy, Stuart J, Al-Turki, Maha A et al. (2020) Vitamin B12 and folate levels in progression of Alzheimer's disease - a short report. International journal of psychiatry in clinical practice 24(1): 68-70	- Data not reported in an extractable format or a format that can be analysed
Bouaziz, Noomen, Ayedi, Imen, Sidhom, Oussama et al. (2010) Plasma homocysteine in schizophrenia: determinants and clinical correlations in Tunisian patients free from antipsychotics. Psychiatry research 179(1): 24-9	- Unadjusted OR reported
Boumenna, Tahani, Scott, Tammy M, Lee, Jong-Soo et al. (2021) Folate, vitamin B-12, and cognitive function in the Boston Puerto Rican Health Study. The American journal of clinical nutrition 113(1): 179-186	- Data not reported in an extractable format or a format that can be analysed
Brito Noronha, Mafalda, Almeida Cunha, Nathalie, Agra Araujo, Daniela et al. (2015) UNDERNUTRITION, SERUM VITAMIN B12, FOLIC ACID AND DEPRESSIVE SYMPTOMS	- Population not relevant to this review protocol

Study	Code [Reason]
IN OLDER ADULTS. Nutricion hospitalaria 32(1): 354-61	
Budge, Marc M, de Jager, Celeste, Hogervorst, Eva et al. (2002) Total plasma homocysteine, age, systolic blood pressure, and cognitive performance in older people. Journal of the American Geriatrics Society 50(12): 2014-8	- No relevant signs/symptoms reported
Cahill, V, McCorry, D, Soryal, I et al. (2017) Newer anti-epileptic drugs, vitamin status and neuropathy: A cross-sectional analysis. Revue neurologique 173(12): 62-66	- Data not reported in an extractable format or a format that can be analysed
Calik, Mustafa, Aktas, Mehmet Salih, Cecen, Emre et al. (2018) The association between serum vitamin B12 deficiency and tension-type headache in Turkish children. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 39(6): 1009-1014	- Population not relevant to this review protocol
Calis, Job Cj, Phiri, Kamija S, Faragher, E Brian et al. (2016) Severe anemia in Malawian children. Malawi medical journal : the journal of Medical Association of Malawi 28(3): 99-107	- Population not relevant to this review protocol
Callaghan, Brian C, Kerber, Kevin A, Lisabeth, Lynda L et al. (2014) Role of neurologists and diagnostic tests on the management of distal symmetric polyneuropathy. JAMA neurology 71(9): 1143-9	- Vitamin B12 deficiency not investigated
Campbell, A K, Jagust, W J, Mungas, D M et al. (2005) Low erythrocyte folate, but not plasma vitamin B-12 or homocysteine,is associated with dementia in elderly Latinos. The journal of nutrition, health & aging 9(1): 39-43	- Vitamin B12 deficiency not defined
Campelo, M.D.G.L.C., Campelo, C.L.D.C., Medeiros, J.L.A. et al. (2017) Peripheral polyneuropathy in idiopathic Parkinson's disease with oral levodopa: Prevalence and associated factors. Revista Brasileira de Neurologia e Psiquiatria 21(2): 88-99	- Data not reported in an extractable format or a format that can be analysed
Carmel, R, Gott, P S, Waters, C H et al. (1995) The frequently low cobalamin levels in dementia usually signify treatable metabolic, neurologic and electrophysiologic abnormalities. European journal of haematology 54(4): 245-53	- Data not reported in an extractable format or a format that can be analysed
Castillo-Lancellotti, Cecilia, Margozzini, Paula, Valdivia, Gonzalo et al. (2015) Serum folate, vitamin B12 and cognitive impairment in Chilean older adults. Public health nutrition 18(14): 2600-8	- Vitamin B12 deficiency not defined
Castro, Luisa and Goldani, Luciano Z (2009) Iron, folate and vitamin B12 parameters in HIV-1	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
infected patients with anaemia in southern Brazil. Tropical doctor 39(2): 83-5	
Cebi, Merve; Metin, Baris; Tarhan, Nevzat (2022) The association between vitamin B12 and plasma homocysteine levels with episodic memory and the volume of memory related brain structures in middle-aged individuals: a retrospective correlational study. Brain structure & function 227(6): 2103-2109	- Data not reported in an extractable format or a format that can be analysed
Cecchetti, Luca, Lettieri, Giada, Handjaras, Giacomo et al. (2019) Brain Hemodynamic Intermediate Phenotype Links Vitamin B12 to Cognitive Profile of Healthy and Mild Cognitive Impaired Subjects. Neural plasticity 2019: 6874805	- Data not reported in an extractable format or a format that can be analysed
Celik, E.; Anik, A.; Ayanoglu, M. (2021) Neutrophil-lymphocyte ratio and serum ferritin, folate, vitamin b12 and 25-hydroxyvitamin D levels in children and adolescents with primary headaches. Meandros Medical and Dental Journal 22(2): 203-209	- Unadjusted OR reported
Chan, J CW, Liu, H SY, Kho, B CS et al. (1998) Megaloblastic anaemia in Chinese patients: a review of 52 cases. Hong Kong medical journal = Xianggang yi xue za zhi 4(3): 269-274	- Population not relevant to this review protocol
Chaudhary, Himanshi, Verma, Savita, Bhatia, Prateek et al. (2020) Infantile Tremor Syndrome or a Neurocutaneous Infantile B12 Deficiency (NIB) Syndrome?. Indian journal of pediatrics 87(3): 179-184	- No relevant signs/symptoms reported
Chen, H, Sui, Q, Chen, Y et al. (2015) Impact of haematologic deficiencies on recurrent aphthous ulceration: a meta-analysis. British dental journal 218(4): e8	- No relevant signs/symptoms reported
Chen, Hui, Liu, Shuai, Ji, Lu et al. (2015) Associations between Alzheimer's disease and blood homocysteine, vitamin B12, and folate: a case-control study. Current Alzheimer research 12(1): 88-94	- Population not relevant to this review protocol
Chen, Hui, Liu, Shuai, Zheng, Miaoyan et al. (2016) Factors Associated with Frontotemporal Dementia in China: A Cross-Sectional Study. Archives of medical research 47(5): 388-393	- Vitamin B12 deficiency not defined
Chen, Jen-Yin, Chu, Chin-Chen, Lin, Yung-Song et al. (2011) Nutrient deficiencies as a risk factor in Taiwanese patients with postherpetic neuralgia. The British journal of nutrition 106(5): 700-7	- No relevant signs/symptoms reported
Chen, Shaw-Ji, Chao, Yu-Lin, Chen, Chuan-Yu et al. (2012) Prevalence of autoimmune diseases in in-patients with schizophrenia: nationwide population-based study. The British	- Unadjusted OR reported

Study	Code [Reason]
journal of psychiatry : the journal of mental science 200(5): 374-80	
Chhabra, A., Chandar, V., Gupta, A. et al. (2012) Megaloblastic anaemia in hospitalised children. Journal, Indian Academy of Clinical Medicine 13(3): 195-197	- Full text paper not available
Chiang, Chun-Pin, Chang, Julia Yu-Fong, Wang, Yi-Ping et al. (2018) Significantly higher frequencies of anemia, hematinic deficiencies, hyperhomocysteinemia, and serum gastric parietal cell antibody positivity in atrophic glossitis patients. Journal of the Formosan Medical Association = Taiwan yi zhi 117(12): 1065-1071	- Data not reported in an extractable format or a format that can be analysed
Chiang, Chun-Pin, Chang, Julia Yu-Fong, Wang, Yi-Ping et al. (2019) Anemia, hematinic deficiencies, and hyperhomocysteinemia in gastric parietal cell antibody-positive and -negative atrophic glossitis patients. Journal of the Formosan Medical Association = Taiwan yi zhi 118(2): 565-571	- Data not reported in an extractable format or a format that can be analysed
Chiang, Chun-Pin, Wu, Yu-Hsueh, Yu-Fong Chang, Julia et al. (2020) Hematinic deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody positivity in atrophic glossitis patients with normocytosis. Journal of the Formosan Medical Association = Taiwan yi zhi 119(6): 1109-1115	- Data not reported in an extractable format or a format that can be analysed
Christine, Chadwick W, Auinger, Peggy, Joslin, Amelia et al. (2018) Vitamin B12 and Homocysteine Levels Predict Different Outcomes in Early Parkinson's Disease. Movement disorders : official journal of the Movement Disorder Society 33(5): 762-770	- Data not reported in an extractable format or a format that can be analysed
Chui, C H, Lau, F Y, Wong, R et al. (2001) Vitamin B12 deficiency--need for a new guideline. Nutrition (Burbank, Los Angeles County, Calif.) 17(1112): 917-20	- Full text paper not available
Clarke, R, Smith, A D, Jobst, K A et al. (1998) Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Archives of neurology 55(11): 1449-55	- Vitamin B12 deficiency not defined
Clarke, Robert, Birks, Jacqueline, Nexo, Ebba et al. (2007) Low vitamin B-12 status and risk of cognitive decline in older adults. The American journal of clinical nutrition 86(5): 1384-91	- Data not reported in an extractable format or a format that can be analysed
Clarke, Robert, Sherliker, Paul, Hin, Harold et al. (2008) Folate and vitamin B12 status in relation to cognitive impairment and anaemia in the setting of voluntary fortification in the UK. The British journal of nutrition 100(5): 1054-9	- Vitamin B12 deficiency not defined

Study	Code [Reason]
Clement, Louise, Boylan, Mallory, Miller, Virginia G et al. (2007) Serum levels of folate and cobalamin are lower in depressed than in nondepressed hemodialysis subjects. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation 17(5): 343-9	- Data not reported in an extractable format or a format that can be analysed
Crystal, H A, Ortof, E, Frishman, W H et al. (1994) Serum vitamin B12 levels and incidence of dementia in a healthy elderly population: a report from the Bronx Longitudinal Aging Study. Journal of the American Geriatrics Society 42(9): 933-6	- No relevant signs/symptoms reported
Cunha, U G (1990) An investigation of dementia among elderly outpatients. Acta psychiatrica Scandinavica 82(3): 261-3	- Data not reported in an extractable format or a format that can be analysed
Cunha, U G, Rocha, F L, Peixoto, J M et al. (1995) Vitamin B12 deficiency and dementia. International psychogeriatrics 7(1): 85-8	- Data not reported in an extractable format or a format that can be analysed
da Rosa, M I, Beck, W O, Colonetti, T et al. (2019) Association of vitamin D and vitamin B12 with cognitive impairment in elderly aged 80 years or older: a cross-sectional study. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association 32(4): 518-524	- Vitamin B12 deficiency not defined
de Greef, B T A, Hoeijmakers, J G J, Gorissen-Brouwers, C M L et al. (2018) Associated conditions in small fiber neuropathy - a large cohort study and review of the literature. European journal of neurology 25(2): 348-355	- Data not reported in an extractable format or a format that can be analysed
De Koning, E.J., Van Der Zwaluw, N.L., Van Wijngaarden, J.P. et al. (2015) Effects of B-vitamin supplementation on depressive symptoms and health-related quality of life in older adults with elevated homocysteine levels. European Journal of Epidemiology 30(8): 828-829	- Full text paper not available
de Wilde, Martijn C, Vellas, Bruno, Girault, Elodie et al. (2017) Lower brain and blood nutrient status in Alzheimer's disease: Results from meta-analyses. Alzheimer's & dementia (New York, N. Y.) 3(3): 416-431	- Vitamin B12 deficiency not defined
Demir, Recep, Saritemur, Murat, Ozel, Lutfi et al. (2015) Red cell distribution width identifies cerebral venous sinus thrombosis in patients with headache. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 21(4): 354-8	- Vitamin B12 deficiency not investigated
den Elzen, Wendy P J, van der Weele, Gerda M, Gussekloo, Jacobijn et al. (2010) Subnormal	- Systematic review used as source of primary studies

Study	Code [Reason]
vitamin B12 concentrations and anaemia in older people: a systematic review. BMC geriatrics 10: 42	
den Elzen, Wendy P J, Westendorp, Rudi G J, Frolich, Marijke et al. (2008) Vitamin B12 and folate and the risk of anemia in old age: the Leiden 85-Plus Study. Archives of internal medicine 168(20): 2238-44	- Population not relevant to this review protocol
Diaz, Monica M, Custodio, Nilton, Montesinos, Rosa et al. (2021) Thyroid Dysfunction, Vitamin B12, and Folic Acid Deficiencies Are Not Associated With Cognitive Impairment in Older Adults in Lima, Peru. Frontiers in public health 9: 676518	- Data not reported in an extractable format or a format that can be analysed
Dileep Satya, K, Attri, Savita Verma, Sharawat, Indar Kumar et al. (2021) Plasma and Urinary Amino Acid Profile in Children with Infantile Tremor Syndrome. Journal of tropical pediatrics 67(3)	- Data not reported in an extractable format or a format that can be analysed
Dimopoulos, N., Piperi, C., Salonicioti, A. et al. (2007) Correlation of folate, vitamin B12 and homocysteine plasma levels with depression in an elderly Greek population. Clinical Biochemistry 40(910): 604-608	- Data not reported in an extractable format or a format that can be analysed
Doets, Esmee L, Ueland, Per M, Tell, Grethe S et al. (2014) Interactions between plasma concentrations of folate and markers of vitamin B(12) status with cognitive performance in elderly people not exposed to folic acid fortification: the Hordaland Health Study. The British journal of nutrition 111(6): 1085-95	- Data not reported in an extractable format or a format that can be analysed
Dong, Bao and Wu, Rongrong (2020) Plasma homocysteine, folate and vitamin B12 levels in Parkinson's disease in China: A meta-analysis. Clinical neurology and neurosurgery 188: 105587	- Vitamin B12 deficiency not defined
Duman Tuba, T., Aktas, G., Atak Burcin, M. et al. (2019) A systematic analysis of the patients with anemia in a university clinic. Gaceta Medica de Bilbao 116(4): 151-157	- Population not relevant to this review protocol
Duman, Tuba Taslamacioglu, Aktas, Gulali, Meryem Atak, Burcin et al. (2020) General characteristics of anemia in postmenopausal women and elderly men. The aging male : the official journal of the International Society for the Study of the Aging Male 23(5): 780-784	- Data not reported in an extractable format or a format that can be analysed
Eastley, R; Wilcock, G K; Bucks, R S (2000) Vitamin B12 deficiency in dementia and cognitive impairment: the effects of treatment on neuropsychological function. International journal of geriatric psychiatry 15(3): 226-33	- Study design not relevant to this review protocol

Study	Code [Reason]
Eid, H.F., Abdel Mawla, S.M., Hussin, H.A. et al. (2013) Methyl tetrahydrofolate reductase polymorphism , folic acid, B12 in a sample of patients with depressive and anxiety symptoms. European Psychiatry 28(suppl1)	- Full text paper not available
Elias, Merrill F, Robbins, Michael A, Budge, Marc M et al. (2006) Homocysteine, folate, and vitamins B6 and B12 blood levels in relation to cognitive performance: the Maine-Syracuse study. Psychosomatic medicine 68(4): 547-54	- Data not reported in an extractable format or a format that can be analysed
Ellinson, M; Thomas, J; Patterson, A (2004) A critical evaluation of the relationship between serum vitamin B, folate and total homocysteine with cognitive impairment in the elderly. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association 17(4): 371-7	- Vitamin B12 deficiency not defined
Elsborg, L.; Hansen, T.; Rafaelsen, O.J. (1979) Vitamin B12 concentrations in psychiatric patients. Acta Psychiatrica Scandinavica 59(2): 145-152	- Data not reported in an extractable format or a format that can be analysed
Engelborghs, Sebastiaan, Vloeberghs, Ellen, Maertens, Karen et al. (2004) Correlations between cognitive, behavioural and psychological findings and levels of vitamin B12 and folate in patients with dementia. International journal of geriatric psychiatry 19(4): 365-70	- Data not reported in an extractable format or a format that can be analysed
Enko, D., Meinitzer, A., Brandmayr, W. et al. (2018) Association between increased plasma levels of homocysteine and depression observed in individuals with primary lactose malabsorption. PLoS ONE 13(8): e0202567	- Data not reported in an extractable format or a format that can be analysed
Eren, E., Yegin, A., Yilmaz, N. et al. (2010) Serum total homocystein, folate and vitamin B12 levels and their correlation with antipsychotic drug doses in adult male patients with chronic schizophrenia. Clinical laboratory 56(1112): 513-518	- Data not reported in an extractable format or a format that can be analysed
Esnafoglu E and Ozturan DD (2020) The relationship of severity of depression with homocysteine, folate, vitamin B12, and vitamin D levels in children and adolescents. Child and adolescent mental health 25(4): 249-255	- Vitamin B12 deficiency not defined
Fakkar, N.F.H., Marzouk, D., Allam, M.F. et al. (2022) Association between vitamin B12 level and clinical peripheral neuropathy in type 2 diabetic patients on metformin therapy. Egyptian Journal of Neurology, Psychiatry and Neurosurgery 58(1): 46	- Data not reported in an extractable format or a format that can be analysed
Falasca, Katia, Di Nicola, Marta, Di Martino, Giuseppe et al. (2019) The impact of	- No relevant signs/symptoms reported

Study	Code [Reason]
homocysteine, B12, and D vitamins levels on functional neurocognitive performance in HIV-positive subjects. BMC infectious diseases 19(1): 105	
Farhad, Khosro, Traub, Rebecca, Ruzhansky, Katherine M et al. (2016) Causes of neuropathy in patients referred as "idiopathic neuropathy". Muscle & nerve 53(6): 856-61	- Full text paper not available
Fateen, T., Kashif, Z., Ali, S.S. et al. (2022) Vitamin B 12 deficiency .The predominant cause of macrocytic anemia in pediatric population visiting Children hospital Lahore. Pakistan Journal of Medical and Health Sciences 16(3): 242-244	- No relevant signs/symptoms reported
Faux, Noel G, Ellis, Kathryn A, Porter, Lorine et al. (2011) Homocysteine, vitamin B12, and folic acid levels in Alzheimer's disease, mild cognitive impairment, and healthy elderly: baseline characteristics in subjects of the Australian Imaging Biomarker Lifestyle study. Journal of Alzheimer's disease : JAD 27(4): 909-22	- Data not reported in an extractable format or a format that can be analysed
Feng, Lei, Ng, Tze-Pin, Chuah, Lisa et al. (2006) Homocysteine, folate, and vitamin B-12 and cognitive performance in older Chinese adults: findings from the Singapore Longitudinal Ageing Study. The American journal of clinical nutrition 84(6): 1506-12	- Vitamin B12 deficiency not investigated
Field, E A, Speechley, J A, Rugman, F R et al. (1995) Oral signs and symptoms in patients with undiagnosed vitamin B12 deficiency. Journal of oral pathology & medicine : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology 24(10): 468-70	- Population not relevant to this review protocol
Franques, Jerome, Chiche, Laurent, De Paula, Andre Maues et al. (2019) Characteristics of patients with vitamin B12-responsive neuropathy: a case series with systematic repeated electrophysiological assessment. Neurological research 41(6): 569-576	- Population not relevant to this review protocol
Gallagher, Damien, Kiss, Alex, Lanctot, Krista L et al. (2018) Toward Prevention of Mild Cognitive Impairment in Older Adults With Depression: An Observational Study of Potentially Modifiable Risk Factors. The Journal of clinical psychiatry 80(1)	- Unadjusted OR reported
Gao, Han, Li, Weishuai, Ren, Jing et al. (2021) Clinical and MRI Differences Between Patients With Subacute Combined Degeneration of the Spinal Cord Related vs. Unrelated to Recreational Nitrous Oxide Use: A Retrospective Study. Frontiers in neurology 12: 626174	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
Garcia, Angeles A, Haron, Yafa, Evans, Lisa R et al. (2004) Metabolic markers of cobalamin deficiency and cognitive function in normal older adults. Journal of the American Geriatrics Society 52(1): 66-71	- Data not reported in an extractable format or a format that can be analysed
Garrod, Marjorie G, Green, Ralph, Allen, Lindsay H et al. (2008) Fraction of total plasma vitamin B12 bound to transcobalamin correlates with cognitive function in elderly Latinos with depressive symptoms. Clinical chemistry 54(7): 1210-7	- Data not reported in an extractable format or a format that can be analysed
Gautam, Piyush, Sharma, Nivedita, Chaudhary, Sanjeev et al. (2017) Infantile Tremor Syndrome in Modern Times. Journal of pediatric neurosciences 12(3): 232-236	- Population not relevant to this review protocol
Gonmei, Z., Dwivedi, S., Toteja, G.S. et al. (2018) Anemia and vitamin B12 deficiency in elderly. Asian Journal of Pharmaceutical and Clinical Research 11(1): 402-404	- No relevant signs/symptoms reported
Gowda, Vykuntaraju K, Kolli, Vinyasa, Benakappa, Asha et al. (2018) Case Series of Infantile Tremor Syndrome in Tertiary Care Paediatric Centre from Southern India. Journal of tropical pediatrics 64(4): 284-288	- Population not relevant to this review protocol
Gulacti, U., Lok, U., Hatipoglu, S. et al. (2014) Assessment of vitamin B12 and folic acid deficiency in emergency department as a cause of acute presentation of dizziness. Acta Medica Mediterranea 30(4): 771-774	- Population not relevant to this review protocol
Guzelcan, Yener and van Loon, Peter (2009) Vitamin B12 status in patients of Turkish and Dutch descent with depression: a comparative cross-sectional study. Annals of general psychiatry 8: 18	- Data not reported in an extractable format or a format that can be analysed
Hagnelius, Nils-Olof, Wahlund, Lars-Olof, Schneede, Jorn et al. (2012) Blood Concentrations of Homocysteine and Methylmalonic Acid among Demented and Non-Demented Swedish Elderly with and without Home Care Services and Vitamin B(12) Prescriptions. Dementia and geriatric cognitive disorders extra 2(1): 387-99	- Vitamin B12 deficiency not investigated
Hassan, M.J., Rehman, M., Imteyaz, S.P. et al. (2020) Clinical and hematological profile in geriatric patients with special emphasis on morphological and etiological classification of anemia in these patients-A pilot Study. JK Science 22(4): 187-192	- Vitamin B12 deficiency not investigated
Health Quality, Ontario (2013) Vitamin B12 and cognitive function: an evidence-based analysis. Ontario health technology assessment series 13(23): 1-45	- No relevant signs/symptoms reported

Study	Code [Reason]
Hin, Harold, Clarke, Robert, Sherliker, Paul et al. (2006) Clinical relevance of low serum vitamin B12 concentrations in older people: the Banbury B12 study. Age and ageing 35(4): 416-22	- Vitamin B12 deficiency not defined
Honzik, Tomas, Adamovicova, Miriam, Smolka, Vratislav et al. (2010) Clinical presentation and metabolic consequences in 40 breastfed infants with nutritional vitamin B12 deficiency--what have we learned?. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society 14(6): 488-95	- Population not relevant to this review protocol
Hope, S., Naerland, T., Hoiland, A.L. et al. (2020) Higher vitamin B12 levels in neurodevelopmental disorders than in healthy controls and schizophrenia: A comparison among participants between 2 and 53 years. FASEB Journal 34(6): 8114-8124	- Data not reported in an extractable format or a format that can be analysed
Huijts, M., Duits, A., Staals, J. et al. (2012) Association of vitamin B12 deficiency with fatigue and depression after lacunar stroke. PLoS ONE 7(1): e30519	- Unadjusted OR reported
Hvas AM and Nexo E (2005) Holotranscobalamin--a first choice assay for diagnosing early vitamin B deficiency?. Journal of internal medicine 257(3): 289-298	- Population not relevant to this review protocol
Ipcioglu, Osman Metin, Ozcan, Omer, Gultepe, Mustafa et al. (2008) Reduced urinary excretion of homocysteine could be the reason of elevated plasma homocysteine in patients with psychiatric illnesses. Clinical biochemistry 41(1011): 831-5	- Data not reported in an extractable format or a format that can be analysed
Iqbal, Saira Perwaiz; Kakepoto, Ghulam Nabi; Iqbal, Saleem Perwaiz (2009) Vitamin B12 deficiency--a major cause of megaloblastic anaemia in patients attending a tertiary care hospital. Journal of Ayub Medical College, Abbottabad : JAMC 21(3): 92-4	- Data not reported in an extractable format or a format that can be analysed
Irevall, T; Axelsson, I; Naumburg, E (2017) B12 deficiency is common in infants and is accompanied by serious neurological symptoms. Acta paediatrica (Oslo, Norway : 1992) 106(1): 101-104	- No relevant signs/symptoms reported
Islam, M N, Khan, R K, Rahman, M M et al. (2013) Etiological pattern of demented patients attending in a tertiary hospital. Mymensingh medical journal : MMJ 22(3): 496-503	- Full text paper not available
Islam, M., Arooj, A., Aziz, M. et al. (2019) Different causes of anaemia in elderly patients. Medical Forum Monthly 30(5): 108-112	- Population not relevant to this review protocol
Jain, M.; Joag, G.G.; Kshirsagar, V.Y. (2020) Prevalence of folic acid and vitamin b12	- Population not relevant to this review protocol

Study	Code [Reason]
deficiency in anemic adolescents. International Journal of Research in Pharmaceutical Sciences 11(3): 4630-4635	
Jain, Rahul, Singh, Archana, Mittal, Medha et al. (2015) Vitamin B12 deficiency in children: a treatable cause of neurodevelopmental delay. Journal of child neurology 30(5): 641-3	- Data not reported in an extractable format or a format that can be analysed
Jatoi, Shazia, Hafeez, Abdul, Riaz, Syeda Urooj et al. (2020) Low Vitamin B12 Levels: An Underestimated Cause Of Minimal Cognitive Impairment And Dementia. Cureus 12(2): e6976	- Data not reported in an extractable format or a format that can be analysed
Jiang, Bo, Chen, Yumei, Yao, Guoen et al. (2014) Effects of differences in serum total homocysteine, folate, and vitamin B12 on cognitive impairment in stroke patients. BMC neurology 14: 217	- Data not reported in an extractable format or a format that can be analysed
Johannsen, P, Ostergaard, K, Christensen, J E et al. (1995) Methylmalonic acid in serum from patients with neurological symptoms consistent with cobalamin deficiency. European journal of neurology 2(4): 357-62	- Population not relevant to this review protocol
Johnson MA, Hawthorne NA, Brackett WR et al. (2003) Hyperhomocysteinemia and vitamin B-12 deficiency in elderly using Title IIIc nutrition services. The American journal of clinical nutrition 77(1): 211-220	- Data not reported in an extractable format or a format that can be analysed
Joosten E, Pelemans W, Hiele M et al. (1990) [Vitamin B12 (cobalamin)-deficiency in the elderly]. Nederlands tijdschrift voor geneeskunde 134(13): 652-656	- Study not reported in English
Kamburoglu, Gunhal, Gumus, Koray, Kadayifcilar, Sibel et al. (2006) Plasma homocysteine, vitamin B12 and folate levels in age-related macular degeneration. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 244(5): 565-9	- No relevant signs/symptoms reported
Karatoprak, E.; Sozen, G.; Yilmaz, K. (2021) How often do neurological disorders lead to dizziness in childhood?. Turkish Archives of Pediatrics 56(3): 249-253	- Data not reported in an extractable format or a format that can be analysed
Karnaze, D S and Carmel, R (1987) Low serum cobalamin levels in primary degenerative dementia. Do some patients harbor atypical cobalamin deficiency states?. Archives of internal medicine 147(3): 429-31	- Population not relevant to this review protocol
Kaur, Navjyot, Nair, Velu, Sharma, Sanjeevan et al. (2018) A descriptive study of clinico-hematological profile of megaloblastic anemia in	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
a tertiary care hospital. Medical journal, Armed Forces India 74(4): 365-370	
Kemperman, R F J, Veurink, M, van der Wal, T et al. (2006) Low essential fatty acid and B-vitamin status in a subgroup of patients with schizophrenia and its response to dietary supplementation. Prostaglandins, leukotrienes, and essential fatty acids 74(2): 75-85	- Data not reported in an extractable format or a format that can be analysed
Kevere, Laura, Purvina, Santa, Bauze, Daiga et al. (2014) Homocysteine and MTHFR C677T polymorphism in children and adolescents with psychotic and mood disorders. Nordic journal of psychiatry 68(2): 129-36	- Vitamin B12 deficiency not investigated
Khan, M.; Memon, S.I.; Memon, A. (2018) Vitamin B12 deficiency in megaloblastic anemia in rural population of tando. Medical Forum Monthly 29(10): 31-34	- Population not relevant to this review protocol
Khan, Sara and Zhou, Lan (2012) Characterization of non-length-dependent small-fiber sensory neuropathy. Muscle & nerve 45(1): 86-91	- Data not reported in an extractable format or a format that can be analysed
Khanduri, Uma and Sharma, Archna (2007) Megaloblastic anaemia: prevalence and causative factors. The National medical journal of India 20(4): 172-5	- Data not reported in an extractable format or a format that can be analysed
Khattak, M.B., Ullah, A., Ali, N. et al. (2017) Frequency of vitamin B12 in patients with diabetic peripheral neuropathy. Medical Forum Monthly 28(10): 12-15	- Population not relevant to this review protocol
Kim, Ggotpin, Kim, Hyesook, Kim, Ki Nam et al. (2013) Relationship of cognitive function with B vitamin status, homocysteine, and tissue factor pathway inhibitor in cognitively impaired elderly: a cross-sectional survey. Journal of Alzheimer's disease : JAD 33(3): 853-62	- Vitamin B12 deficiency not defined
Kim, Hyun and Lee, Kang Joon (2014) Serum homocysteine levels are correlated with behavioral and psychological symptoms of Alzheimer's disease. Neuropsychiatric disease and treatment 10: 1887-96	- Data not reported in an extractable format or a format that can be analysed
Kim, Sunghee, Choi, Bo Youl, Nam, Jung Hyun et al. (2019) Cognitive impairment is associated with elevated serum homocysteine levels among older adults. European journal of nutrition 58(1): 399-408	- Population not relevant to this review protocol
Kivelä SL; Pahkala K; Eronen A (1989) Depression in the aged: relation to folate and vitamins C and B12. Biological psychiatry 26(2): 210-213	- Population not relevant to this review protocol
Knopman, David S, Petersen, Ronald C, Cha, Ruth H et al. (2006) Incidence and causes of	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
nondegenerative nonvascular dementia: a population-based study. Archives of neurology 63(2): 218-21	
Kocer, B., Guven, H., Conkbayir, I. et al. (2016) The Effect of Hyperhomocysteinemia on Motor Symptoms, Cognitive Status, and Vascular Risk in Patients with Parkinson's Disease. Parkinson's Disease 2016: 1589747	- Vitamin B12 deficiency not investigated
Kwok, T, Cheng, G, Woo, J et al. (2002) Independent effect of vitamin B12 deficiency on hematological status in older Chinese vegetarian women. American journal of hematology 70(3): 186-90	- Full text paper not available
Lachner, C, Martin, C, John, D et al. (2014) Older adult psychiatric inpatients with non-cognitive disorders should be screened for vitamin B12 deficiency. The journal of nutrition, health & aging 18(2): 209-12	- Data not reported in an extractable format or a format that can be analysed
Lerner, Vladimir, Kanevsky, Michael, Dwolatzky, Tzvi et al. (2006) Vitamin B12 and folate serum levels in newly admitted psychiatric patients. Clinical nutrition (Edinburgh, Scotland) 25(1): 60-7	- Data not reported in an extractable format or a format that can be analysed
Levitt, A J and Karlinsky, H (1992) Folate, vitamin B12 and cognitive impairment in patients with Alzheimer's disease. Acta psychiatrica Scandinavica 86(4): 301-5	- Data not reported in an extractable format or a format that can be analysed
Li, Ling, Cao, Dongfeng, Desmond, Renee et al. (2008) Cognitive performance and plasma levels of homocysteine, vitamin B12, folate and lipids in patients with Alzheimer disease. Dementia and geriatric cognitive disorders 26(4): 384-90	- Data not reported in an extractable format or a format that can be analysed
Li, Siying, Zhang, Qingxi, Gao, Yuyuan et al. (2021) Serum Folate, Vitamin B12 Levels, and Systemic Immune-Inflammation Index Correlate With Motor Performance in Parkinson's Disease: A Cross-Sectional Study. Frontiers in neurology 12: 665075	- Data not reported in an extractable format or a format that can be analysed
Liampas, I, Papathanasiou, S, Tsikritsis, N et al. (2021) Nutrient Status in Patients with Frequent Episodic Tension-Type Headache: A Case-Control Study. Revue neurologique 177(10): 1283-1293	- Data not reported in an extractable format or a format that can be analysed
Lildballe, Dorte L, Fedosov, Sergey, Sherliker, Paul et al. (2011) Association of cognitive impairment with combinations of vitamin B12-related parameters. Clinical chemistry 57(10): 1436-43	- Vitamin B12 deficiency not defined
Lippi G, Montagnana M, Targher G et al. (2009) Vitamin B12, folate, and anemia in old age. Archives of internal medicine 169(7): 716	- Not a peer-reviewed publication

Study	Code [Reason]
Loikas S, Koskinen P, Irjala K et al. (2007) Vitamin B12 deficiency in the aged: a population-based study. Age and ageing 36(2): 177-183	- Population not relevant to this review protocol
Luthra, Nijee S, Marcus, Ariane H, Hills, Nancy K et al. (2020) Vitamin B12 measurements across neurodegenerative disorders. Journal of clinical movement disorders 7: 3	- Data not reported in an extractable format or a format that can be analysed
Lyu, N., Xing, G., Yang, J. et al. (2021) Comparison of inflammatory, nutrient, and neurohormonal indicators in patients with schizophrenia, bipolar disorder and major depressive disorder. Journal of Psychiatric Research 137: 401-408	- Vitamin B12 deficiency not defined
Ma, Fei, Wu, Tianfeng, Zhao, Jiangang et al. (2017) Plasma Homocysteine and Serum Folate and Vitamin B12 Levels in Mild Cognitive Impairment and Alzheimer's Disease: A Case-Control Study. Nutrients 9(7)	- Vitamin B12 deficiency not defined
Malaguarnera, Mariano, Ferri, Raffaele, Bella, Rita et al. (2004) Homocysteine, vitamin B12 and folate in vascular dementia and in Alzheimer disease. Clinical chemistry and laboratory medicine 42(9): 1032-5	- Data not reported in an extractable format or a format that can be analysed
Manavifar, Lida, Nemati Karimooy, Habibollah, Jamali, Jamshid et al. (2013) Homocysteine, Cobalamin and Folate Status and their Relations to Neurocognitive and Psychological Markers in Elderly in Northeasten of Iran. Iranian journal of basic medical sciences 16(6): 772-80	- Data not reported in an extractable format or a format that can be analysed
Martinis, I., Vrca1, A., Bevanda, M. et al. (2021) NUTRITIONAL ASSESSMENT OE PATIENTS with PRIMARY PROGRESSIVE DEMENTIA at the TIME OE DIAGNOSIS. Psychiatria Danubina 33: 226-235	- Population not relevant to this review protocol
Mathukumalli, N.L., Kandadai, M.R., Shaik, J.A. et al. (2020) Serum B12, homocysteine levels, and their effect on peripheral neuropathy in Parkinson's disease: Indian cohort. Annals of Indian Academy of Neurology 23(1): 48-53	- Data not reported in an extractable format or a format that can be analysed
McLennan WJ, Andrews GR, Macleod C et al. (1973) Anaemia in the elderly. The Quarterly journal of medicine 42(165): 1-13	- Not a peer-reviewed publication
Merola, A, Zibetti, M, Rizzone, M G et al. (2014) Prospective assessment of peripheral neuropathy in Duodopa-treated parkinsonian patients. Acta neurologica Scandinavica 129(1): e1-5	- Population not relevant to this review protocol
Metz, J, Bell, A H, Flicker, L et al. (1996) The significance of subnormal serum vitamin B12 concentration in older people: a case control	- Population not relevant to this review protocol

Study	Code [Reason]
study. Journal of the American Geriatrics Society 44(11): 1355-61	
Misiak, Blazej, Laczmanski, Lukasz, Sloka, Natalia Kinga et al. (2016) Metabolic dysregulation in first-episode schizophrenia patients with respect to genetic variation in one-carbon metabolism. Psychiatry research 238: 60-67	- Vitamin B12 deficiency not investigated
Mojica, C.V., Yu, J.M.F., Ampil, E.R. et al. (2021) Demographic and Clinical Profile of Patients with Mild Cognitive Impairment Seen at St. Luke's Medical Center-Global City Memory Service. Dementia and Geriatric Cognitive Disorders 50(4): 387-393	- Data not reported in an extractable format or a format that can be analysed
Monji, Akira, Yanagimoto, Kazuyuki, Maekawa, Toshihiko et al. (2005) Plasma folate and homocysteine levels may be related to interictal "schizophrenia-like" psychosis in patients with epilepsy. Journal of clinical psychopharmacology 25(1): 3-5	- Data not reported in an extractable format or a format that can be analysed
Mooney KM, Young IS, Patterson CC et al. (2004) Vitamin B12 status in elderly subjects with low haemoglobin. Proc Nutr Soc 63: 77A	- Conference abstract
Moore, Eileen, Mander, Alastair, Ames, David et al. (2012) Cognitive impairment and vitamin B12: a review. International psychogeriatrics 24(4): 541-56	- Review article but not a systematic review
Morris, Martha Savaria, Jacques, Paul F, Rosenberg, Irwin H et al. (2007) Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. The American journal of clinical nutrition 85(1): 193-200	- Population not relevant to this review protocol
Munipalli, Bala, Strothers, Shelby, Rivera, Fernando et al. (2022) Association of Vitamin B12, Vitamin D, and Thyroid-Stimulating Hormone With Fatigue and Neurologic Symptoms in Patients With Fibromyalgia. Mayo Clinic proceedings. Innovations, quality & outcomes 6(4): 381-387	- Population not relevant to this review protocol
Mwanda, O W and Dave, P (1999) Megaloblastic marrow in macrocytic anaemias at Kenyatta National and M P Shah Hospitals, Nairobi. East African medical journal 76(11): 610-4	- Data not reported in an extractable format or a format that can be analysed
Nagga, K, Rajani, R, Mardh, E et al. (2003) Cobalamin, folate, methylmalonic acid, homocysteine, and gastritis markers in dementia. Dementia and geriatric cognitive disorders 16(4): 269-75	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
Nardin, Rachel A; Amick, Amy N H; Raynor, Elizabeth M (2007) Vitamin B(12) and methylmalonic acid levels in patients presenting with polyneuropathy. Muscle & nerve 36(4): 532-5	- Data not reported in an extractable format or a format that can be analysed
Nazir, I., Usman, M., Nazir, S. et al. (2021) Relation of serum Vitamin B12 and red cell folate levels to age and cognition in healthy individuals of different age groups: A cross sectional study. Pakistan Journal of Medical and Health Sciences 15(1): 178-182	- No relevant signs/symptoms reported
Ng, Tze-Pin, Feng, Lei, Niti, Mathew et al. (2009) Folate, vitamin B12, homocysteine, and depressive symptoms in a population sample of older Chinese adults. Journal of the American Geriatrics Society 57(5): 871-6	- Population not relevant to this review protocol
NiChroinin, D., Quinn, D., Martin, A. et al. (2013) Exploration of the association between vitamin B12 and cognitive impairment in older patients. Irish Journal of Medical Science 182(suppl6): 268	- Full text paper not available
Nizamani, G.S., Memon, I.A., Memon, A. et al. (2014) Vitamin B12 deficiency with megaloblastic anemia: An experience at tertiary care hospital of sindh. Journal of the Liaquat University of Medical and Health Sciences 13(1): 13-17	- Population not relevant to this review protocol
O'Leary, Fiona; Allman-Farinelli, Margaret; Samman, Samir (2012) Vitamin B12 status, cognitive decline and dementia: a systematic review of prospective cohort studies. The British journal of nutrition 108(11): 1948-61	- Vitamin B12 deficiency not defined
Oosterhuis, W P, Niessen, R W, Bossuyt, P M et al. (2000) Diagnostic value of the mean corpuscular volume in the detection of vitamin B12 deficiency. Scandinavian journal of clinical and laboratory investigation 60(1): 9-18	- No relevant signs/symptoms reported
Ozen, Serkan; Ozer, Murat Atabey; Akdemir, Mehmet Orcun (2017) Vitamin B12 deficiency evaluation and treatment in severe dry eye disease with neuropathic ocular pain. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 255(6): 1173-1177	- Data not reported in an extractable format or a format that can be analysed
Paciullo, Francesco, Menduno, Paola Santina, Tucci, Davide et al. (2022) Vitamin B12 levels in patients with retinal vein occlusion and their relation with clinical outcome: a retrospective study. Internal and emergency medicine 17(4): 1065-1071	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
Papakostas, George I, Petersen, Timothy, Mischoulon, David et al. (2004) Serum folate, vitamin B12, and homocysteine in major depressive disorder, Part 2: predictors of relapse during the continuation phase of pharmacotherapy. The Journal of clinical psychiatry 65(8): 1096-8	- Population not relevant to this review protocol
Park, Jin-Sung, Park, Donghwi, Ko, Pan-Woo et al. (2017) Serum methylmalonic acid correlates with neuropathic pain in idiopathic Parkinson's disease. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 38(10): 1799-1804	- Data not reported in an extractable format or a format that can be analysed
Pattnaik, Jogamaya, Kayal, Smita, Dubashi, Biswajit et al. (2020) Profile of anemia in acute lymphoblastic leukemia patients on maintenance therapy and the effect of micronutrient supplementation. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 28(2): 731-738	- Data not reported in an extractable format or a format that can be analysed
Paul, M.L., Khan, R.K., Khan, Z.H. et al. (2014) Clinical patterns of polyneuropathy attending in a tertiary level of hospital. Journal of Medicine (Bangladesh) 15(1): 3-8	- Vitamin B12 deficiency not investigated
Paulus, Michelle C, Wijnhoven, Anjali M, Maessen, Gerdinique C et al. (2021) Does vitamin B12 deficiency explain psychiatric symptoms in recreational nitrous oxide users? A narrative review. Clinical toxicology (Philadelphia, Pa.) 59(11): 947-955	- Study design not relevant to this review protocol
Penninx, B W, Guralnik, J M, Ferrucci, L et al. (2000) Vitamin B(12) deficiency and depression in physically disabled older women: epidemiologic evidence from the Women's Health and Aging Study. The American journal of psychiatry 157(5): 715-21	- Population not relevant to this review protocol
Petridou, Eleni Th, Kousoulis, Antonis A, Michelakos, Theodoros et al. (2016) Folate and B12 serum levels in association with depression in the aged: a systematic review and meta-analysis. Aging & mental health 20(9): 965-73	- Systematic review used as source of primary studies
Pinazo-Duran, M.D., Santander-Trentini, F., Lleo-Perez, A. et al. (2015) Differential profiles of miRNAs, homocystein, vitamin B12/folate levels and oxidative stress parameters in diabetic retinopathy. Investigative Ophthalmology and Visual Science 56(7): 5199	- Full text paper not available
Politis, Antonis, Olgiati, Paolo, Malitas, Petros et al. (2010) Vitamin B12 levels in Alzheimer's disease: association with clinical features and	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
cytokine production. Journal of Alzheimer's disease : JAD 19(2): 481-8	
Postiglione, A, Milan, G, Ruocco, A et al. (2001) Plasma folate, vitamin B(12), and total homocysteine and homozygosity for the C677T mutation of the 5,10-methylene tetrahydrofolate reductase gene in patients with Alzheimer's dementia. A case-control study. Gerontology 47(6): 324-9	- Data not reported in an extractable format or a format that can be analysed
Prades, Nuria, Varela, Eva, Flamarique, Itziar et al. (2022) Water-soluble vitamin insufficiency, deficiency and supplementation in children and adolescents with a psychiatric disorder: a systematic review and meta-analysis. Nutritional neuroscience: 1-23	- Systematic review used as source of primary studies
Prakash, Rashmi; Aggarwal, Nitin; Jose, Nimmi (2019) A Cross-Sectional Study of Serum Folate and Vitamin B12 Levels in Psychiatric Inpatients. The primary care companion for CNS disorders 21(5)	- Data not reported in an extractable format or a format that can be analysed
Prayurahong B, Tungtrongchitr R, Chanjanakijskul S et al. (1993) Vitamin B12, folic acid and haematological status in elderly Thais. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 76(2): 71-78	- Data not reported in an extractable format or a format that can be analysed
Prodan, C I, Cowan, L D, Stoner, J A et al. (2009) Cumulative incidence of vitamin B12 deficiency in patients with Alzheimer disease. Journal of the neurological sciences 284(12): 144-8	- Study design not relevant to this review protocol
Quadri, Pierluigi, Fragiacomo, Claudia, Pezzati, Rita et al. (2005) Homocysteine and B vitamins in mild cognitive impairment and dementia. Clinical chemistry and laboratory medicine 43(10): 1096-100	- Vitamin B12 deficiency not defined
Rajabally, Yusuf A and Martey, Jean (2013) Levodopa, vitamins, ageing and the neuropathy of Parkinson's disease. Journal of neurology 260(11): 2844-8	- Data not reported in an extractable format or a format that can be analysed
Rajabally, Yusuf A and Martey, Jean (2011) Neuropathy in Parkinson disease: prevalence and determinants. Neurology 77(22): 1947-50	- Vitamin B12 deficiency not defined
Ravaglia, G, Forti, P, Maioli, F et al. (2000) Elevated plasma homocysteine levels in centenarians are not associated with cognitive impairment. Mechanisms of ageing and development 121(13): 251-61	- Data not reported in an extractable format or a format that can be analysed
Regland, B, Gottfries, C G, Oreland, L et al. (1988) Low B12 levels related to high activity of platelet MAO in patients with dementia	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
disorders. A retrospective study. Acta psychiatrica Scandinavica 78(4): 451-7	
Reif, Andreas; Pfuhlmann, Bruno; Lesch, Klaus-Peter (2005) Homocysteinemia as well as methylenetetrahydrofolate reductase polymorphism are associated with affective psychoses. Progress in neuro-psychopharmacology & biological psychiatry 29(7): 1162-8	- Data not reported in an extractable format or a format that can be analysed
Renvall, M J, Spindler, A A, Ramsdell, J W et al. (1989) Nutritional status of free-living Alzheimer's patients. The American journal of the medical sciences 298(1): 20-7	- Data not reported in an extractable format or a format that can be analysed
Robinson, D J, O'Luanaigh, C, Tehee, E et al. (2011) Associations between holotranscobalamin, vitamin B12, homocysteine and depressive symptoms in community-dwelling elders. International journal of geriatric psychiatry 26(3): 307-13	- Data not reported in an extractable format or a format that can be analysed
Rochtchina, Elena, Wang, Jie Jin, Flood, Victoria M et al. (2007) Elevated serum homocysteine, low serum vitamin B12, folate, and age-related macular degeneration: the Blue Mountains Eye Study. American journal of ophthalmology 143(2): 344-6	- Data not reported in an extractable format or a format that can be analysed
Rodriguez-Oroz, Maria C, Lage, Pablo Martinez, Sanchez-Mut, Jose et al. (2009) Homocysteine and cognitive impairment in Parkinson's disease: a biochemical, neuroimaging, and genetic study. Movement disorders : official journal of the Movement Disorder Society 24(10): 1437-44	- Data not reported in an extractable format or a format that can be analysed
Roos, D (1974) Neurological symptoms and signs in a selected group of partially gastrectomized patients with particular reference to B12 deficiency. Acta neurologica Scandinavica 50(6): 719-52	- Population not relevant to this review protocol
Sabeen, S. and Holroyd, S. (2009) Vitamin B12 and psychiatric illness. Annals of Long-Term Care 17(3): 32-36	- Review article but not a systematic review
Sachdev, Perminder S, Parslow, Ruth A, Lux, Ora et al. (2005) Relationship of homocysteine, folic acid and vitamin B12 with depression in a middle-aged community sample. Psychological medicine 35(4): 529-38	- Vitamin B12 deficiency not defined
Salah, N, El Hamid, F Abd, Abdelghaffar, S et al. (2005) Prevalence and type of anaemia in young Egyptian patients with type 1 diabetes mellitus. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit 11(56): 959-67	- No relevant signs/symptoms reported

Study	Code [Reason]
Sarbay, H. and Ay, Y. (2018) Evaluation of children with macrocytosis: Clinical study. Pan African Medical Journal 31: 54	- No relevant signs/symptoms reported
Sarode, R, Garewal, G, Marwaha, N et al. (1989) Pancytopenia in nutritional megaloblastic anaemia. A study from north-west India. Tropical and geographical medicine 41(4): 331-6	- Full text paper not available
Sashindran, V K; Aggarwal, Vivek; Khera, Anurag (2022) Prevalence of Vitamin B12 deficiency in elderly population (>60 years) presenting with dementia to outpatient department. Medical journal, Armed Forces India 78(1): 94-98	- Population not relevant to this review protocol
Satyanarayana, Alleboena, Balakrishna, Nagalla, Pitla, Sujatha et al. (2011) Status of B-vitamins and homocysteine in diabetic retinopathy: association with vitamin-B12 deficiency and hyperhomocysteinemia. PloS one 6(11): e26747	- Data not reported in an extractable format or a format that can be analysed
Schrempf, Wiebke, Eulitz, Marco, Neumeister, Volker et al. (2011) Utility of measuring vitamin B12 and its active fraction, holotranscobalamin, in neurological vitamin B12 deficiency syndromes. Journal of neurology 258(3): 393-401	- Data not reported in an extractable format or a format that can be analysed
Serin, Hepsen Mine and Arslan, Elif Acar (2019) Neurological symptoms of vitamin B12 deficiency: analysis of pediatric patients. Acta clinica Croatica 58(2): 295-302	- Data not reported in an extractable format or a format that can be analysed
Sharif, N., Rahman, S., Suleman, S. et al. (2019) Vitamin B12 deficiency among patients with megaloblastic anemia. Journal of Medical Sciences (Peshawar) 27(2): 103-106	- Population not relevant to this review protocol
Shrestha, Lochana, Shrestha, Bikal, Gautam, Keyoor et al. (2022) Plasma Vitamin B-12 Levels and Risk of Alzheimer's Disease: A Case-Control Study. Gerontology & geriatric medicine 8: 23337214211057715	- Population not relevant to this review protocol
Soh, Yunsoo; Lee, Do Hun; Won, Chang Won (2020) Association between Vitamin B12 levels and cognitive function in the elderly Korean population. Medicine 99(30): e21371	- Data not reported in an extractable format or a format that can be analysed
Soni, Ravi M, Tiwari, Sarvada C, Mahdi, Abbas A et al. (2019) Serum Homocysteine and Behavioral and Psychological Symptoms of Dementia: Is There Any Correlation in Alzheimer's Disease?. Annals of neurosciences 25(3): 152-159	- Data not reported in an extractable format or a format that can be analysed
Srivastav, Khushboo, Saxena, Sandeep, Mahdi, Abbas A et al. (2016) Increased serum level of homocysteine correlates with retinal nerve fiber	- Vitamin B12 deficiency not defined

Study	Code [Reason]
layer thinning in diabetic retinopathy. Molecular vision 22: 1352-1360	
Ssonko, Michael; Ddungu, Henry; Musisi, Seggane (2014) Low serum vitamin B12 levels among psychiatric patients admitted in Butabika mental hospital in Uganda. BMC research notes 7: 90	- Unadjusted OR reported
Stott, D J, Langhorne, P, Hendry, A et al. (1997) Prevalence and haemopoietic effects of low serum vitamin B12 levels in geriatric medical patients. The British journal of nutrition 78(1): 57-63	- Data not reported in an extractable format or a format that can be analysed
Teunisse, S, Bollen, A E, van Gool, W A et al. (1996) Dementia and subnormal levels of vitamin B12: effects of replacement therapy on dementia. Journal of neurology 243(7): 522-9	- Study design not relevant to this review protocol
Thomas, Deena, Chandra, Jagdish, Sharma, Sunita et al. (2015) Determinants of Nutritional Anemia in Adolescents. Indian pediatrics 52(10): 867-9	- Unadjusted OR reported
Tiemeier H, van Tuijl HR, Hofman A et al. (2002) Vitamin B12, folate, and homocysteine in depression: the Rotterdam Study. The American journal of psychiatry 159(12): 2099-2101	- Population not relevant to this review protocol
Togha, Mansoureh, Razeghi Jahromi, Soodeh, Ghorbani, Zeinab et al. (2019) Serum Vitamin B12 and Methylmalonic Acid Status in Migraineurs: A Case-Control Study. Headache 59(9): 1492-1503	- Vitamin B12 deficiency not defined
Tsuchimine S, Saito M, Kaneko S et al. (2015) Decreased serum levels of polyunsaturated fatty acids and folate, but not brain-derived neurotrophic factor, in childhood and adolescent females with depression. Psychiatry research 225(1-2): 187-190	- Vitamin B12 deficiency not investigated
Turkoglu, S.A., Ogun, M.N., Micoogullari, E. et al. (2017) The relationship between total standardized mini mental state examination (SMMSE) and subscores and D vitamin, Folate and B12 levels in patients with cognitive dysfunction. Biomedical Research (India) 28(22): 9894-9897	- Population not relevant to this review protocol
Ulusoy, S.I.; Horasanli, B.; Kulaksizoglu, S. (2021) The relationship between vitamin B12 and vitamin D levels and subjective cognitive complaints in patientswithfirstepisodemajordepressivedisorder. Dusunen Adam - The Journal of Psychiatry and Neurological Sciences 34(1): 64-72	- Data not reported in an extractable format or a format that can be analysed
Uygun, S.D., Goker, Z., Kara, F.K. et al. (2021) P.311 Evaluation of serum vitamin B12, folate and ferritin levels in children and adolescents	- Full text paper not available

Study	Code [Reason]
with anxiety disorders. European Neuropsychopharmacology 44(supplement1): 46-s47	
Vahdat Shariatpanahi, Maryam, Velayati, Aynaz, Jamalian, Seyed Ali et al. (2019) The relationship between serum cobalamin, folic acid, and homocysteine and the risk of post-cardiac surgery delirium. Neuropsychiatric disease and treatment 15: 1413-1419	- Unadjusted OR reported
van Wijngaarden J., P., van der Zwaluw N., L., Dhonukshe-Rutten R. A., M. et al. (2013) The Vitamin B12 Biomarkers Homocysteine and Methylmalonic Acid Are Associated With Cognitive Performance in a Dutch Elderly Population. Journal of Psychophysiology 27(suppl1): 42-43	- Vitamin B12 deficiency not investigated
Villa, Paola, Bosco, Paolo, Ferri, Raffaele et al. (2009) Fasting and post-methionine homocysteine levels in Alzheimers disease and vascular dementia. International journal for vitamin and nutrition research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Journal international de vitaminologie et de nutrition 79(3): 166-72	- Data not reported in an extractable format or a format that can be analysed
Vogiatzoglou, Anna, Smith, A David, Nurk, Eha et al. (2013) Cognitive function in an elderly population: interaction between vitamin B12 status, depression, and apolipoprotein E epsilon4: the Hordaland Homocysteine Study. Psychosomatic medicine 75(1): 20-9	- Data not reported in an extractable format or a format that can be analysed
Wang, Yu-Hui, Yan, Fang, Zhang, Wen-Bo et al. (2009) An investigation of vitamin B12 deficiency in elderly inpatients in neurology department. Neuroscience bulletin 25(4): 209-15	- No relevant signs/symptoms reported
Warendorf, Janna K, van Doormaal, Perry T C, Vrancken, Alexander F J E et al. (2021) Clinical relevance of testing for metabolic vitamin B12 deficiency in patients with polyneuropathy. Nutritional neuroscience: 1-11	- No relevant signs/symptoms reported
Werder, Steven F (2010) Cobalamin deficiency, hyperhomocysteinemia, and dementia. Neuropsychiatric disease and treatment 6: 159-95	- Study design not relevant to this review protocol
Witte, Klaus K A, Desilva, Ramesh, Chattopadhyay, Sudipta et al. (2004) Are hematinic deficiencies the cause of anemia in chronic heart failure?. American heart journal 147(5): 924-30	- Data not reported in an extractable format or a format that can be analysed
Xie, Yi, Feng, Hongliang, Peng, Sisi et al. (2017) Association of plasma homocysteine, vitamin B12 and folate levels with cognitive function in	- Vitamin B12 deficiency not defined

Study	Code [Reason]
Parkinson's disease: A meta-analysis. Neuroscience letters 636: 190-195	
Yahya, Y., Jamal, A., Nasir, S. et al. (2022) Are We Under-estimating the Frequency of Vitamin B12 Deficiency in Pediatric Population?. Pakistan Paediatric Journal 46(2): 130-135	- Population not relevant to this review protocol
Yazici, A.B., Akcay Ciner, O., Yazici, E. et al. (2019) Comparison of vitamin B12, vitamin D and folic acid blood levels in patients with schizophrenia, drug addiction and controls. Journal of Clinical Neuroscience 65: 11-16	- Population not relevant to this review protocol
Yilmaz, Sanem, Serdaroglu, Gul, Tekgul, Hasan et al. (2016) Different Neurologic Aspects of Nutritional B12 Deficiency in Infancy. Journal of child neurology 31(5): 565-8	- Data not reported in an extractable format or a format that can be analysed

J.2 Health Economic studies

None.

Appendix K Recommendations for research – full details

K.1 Recommendation for research

Which medicines increase the risk of vitamin B12 deficiency?

K.1.1 Why this is important

No evidence was identified for the prognostic value of nitrous oxide, colchicine, the contraceptive pill, antibiotics or anticonvulsants as risk factors for vitamin B12 deficiency. Of particular concern is the lack of evidence for nitrous oxide, given that recreational use is a significant public health issue. Research on the effects of nitrous oxide use, particularly use of large amounts and chronic use, is greatly needed. Further research is also needed to understand the association between use of other medicines and vitamin B12 deficiency. Better awareness regarding when to suspect vitamin B12 deficiency may reduce delayed and missed diagnosis and help reduce complications associated with vitamin B12 deficiency.

K.1.2 Rationale for the recommendation for research

Importance to 'patients' or the population	Better awareness regarding when to suspect vitamin B12 deficiency may reduce delayed and missed diagnosis and help reduce complications associated with vitamin B12 deficiency. For some people, a change or cessation of certain medications may be appropriate.
Relevance to NICE guidance	This guideline raises awareness of medications that might be associated with an increased risk of vitamin B12 deficiency. Further evidence is

	needed to quantify the potential increase in risk at different doses and durations of use.
Relevance to the NHS	The outcome may lead to an increase in the number of people suspected of and having investigations for vitamin B12 deficiency, which may lead to an increase in the number diagnosed and treated. If people have any medications topped, there may be an increase in prescriptions for alternative medications.
National priorities	Not applicable.
Current evidence base	No evidence was identified for the prognostic value of nitrous oxide, colchicine, the contraceptive pill, antibiotics or anticonvulsants as risk factors for vitamin B12 deficiency.
Equality considerations	None known.

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K.1.32 Modified PICO table

Population	General population
Exposure	Medications: • nitrous oxide (prescription and recreational) • colchicine • the contraceptive pill • antibiotics (sulfonamides, tetracyclines, trimethoprim, minocycline, neomycin, co-trimoxazole, demeclocycline, fluoroquinolones, macrolides) • anticonvulsants (valproic acid, phenobarbital (Donnatal®, Solfoton®), phenytoin) Stratify by: • dose • duration
Confounding factors	Age and sex as a minimum
Outcome	Diagnosis of vitamin B12 deficiency at any time point reported in the study
Study design	Prospective cohort studies with multivariate analysis
Timeframe	Long term
Additional information	None

3

4 K.2 Recommendation for research

5 Which dietary factors increase the risk of vitamin B12 deficiency?

K.2.11 Why this is important

Anyone not getting enough B12 in their body can get a deficiency, but no evidence was identified on which dietary factors increase the risk. Further research is needed to identify which groups of people are at risk of low dietary intake. In addition, information about vegetarian and vegan diets may be outdated, as dietary trends have changed in recent years, the choice of vegetarian and vegan food products has vastly increased, and many foods are now fortified with vitamin B12. Better awareness regarding when to suspect vitamin B12 deficiency may reduce delayed and missed diagnosis and help reduce complications associated with vitamin B12 deficiency.

K.2.20 Rationale for the recommendation for research

Importance to 'patients' or the population	Better awareness regarding when to suspect vitamin B12 deficiency may reduce delayed and missed diagnosis and help reduce complications associated with vitamin B12 deficiency.
Relevance to NICE guidance	This guideline raises awareness of dietary factors that might be associated with an increased risk of vitamin B12 deficiency. Further evidence is needed to quantify the potential increase in risk for different dietary factors.
Relevance to the NHS	The outcome may lead to an increase in the number of people suspected of and having investigations for vitamin B12 deficiency, which may lead to an increase in the number diagnosed and treated.
National priorities	Not applicable.
Current evidence base	No evidence was identified for the prognostic value of dietary factors as risk factors for vitamin B12 deficiency.
Equality considerations	The recommendation addresses inequalities related to age, disability, pregnancy and maternity, religion and belief as these groups may have reduced ability or energy to buy or prepare food.

K.2.32 Modified PICO table

Population	General population
Exposure	Dietary risk factors: • vegetarianism • veganism • restrictive diets including eating disorders • socioeconomic status • learning difficulties
Confounding factors	Age and sex as a minimum
Outcome	Diagnosis of vitamin B12 deficiency at any time point reported in the study

Study design	Prospective cohort studies with multivariate analysis
Timeframe	Long term
Additional information	None