

Vitamin B₁₂ — Complete briefing

Quick overview

Vitamin B₁₂ (cobalamin) is a water-soluble vitamin essential for DNA synthesis, red-blood-cell formation, myelin maintenance and two key enzymatic reactions (methylation/homocysteine metabolism and mitochondrial odd-chain fatty acid/propionate metabolism). Humans must obtain it from diet or supplements — it is not synthesised by the body. [Office of Dietary Supplements+1](#)

Chemical forms & pharmaceutical preparations

- **Common chemical forms:** cyanocobalamin (synthetic, stable), hydroxocobalamin (used IM, longer retention), methylcobalamin and adenosylcobalamin (coenzyme forms).
 - **Routes available:** oral (tablets/high-dose), sublingual, intranasal spray, intramuscular (IM) injections, intravenous (rare).
 - **ATC classification:** Vitamin B₁₂ group = **ATC B03BA** (B03 = antianemic preparations; B03BA = vitamin B₁₂ and analogues). Cyanocobalamin = **B03BA01**; hydroxocobalamin = **B03BA03**; mecobalamin (methylcobalamin) included in the group. [FHI+1](#)
-

Physiology & absorption (concise)

- Dietary B₁₂ in animal foods is released by gastric acid/pepsin, binds haptocorrin, then in the small intestine intrinsic factor (IF) — produced by parietal cells — is required for ileal uptake. Pancreatic insufficiency, achlorhydria, lack of IF (pernicious anemia), ileal disease/resection, or drugs that reduce acid (PPIs) impair absorption. Serum measurements can be misleading; **methylmalonic acid (MMA)** and **homocysteine** are useful functional markers. [Office of Dietary Supplements+1](#)
-

Dietary sources

- **Animal sources (richest):** liver, beef, lamb, oily fish (salmon, tuna), shellfish (clams), eggs, dairy.
 - **Fortified sources for vegetarians/vegans:** fortified nutritional yeast, fortified plant milks, fortified cereals. Plant foods naturally contain negligible/unstable B₁₂. [Verywell Health+1](#)
-

Recommended intakes (RDA / reference)

(typical values used by many agencies — age/stage specific):

- Infants 0–6 months: **0.4 µg**; 7–12 months: **0.5 µg**
 - Children 1–3 y: **0.9 µg**; 4–8 y: **1.2 µg**; 9–13 y: **1.8 µg**
 - Teens and adults: **2.4 µg/day**
 - Pregnancy: **2.6 µg/day**; Lactation: **2.8 µg/day**. [Office of Dietary Supplements](#)
-

Who is at risk of deficiency (key groups)

- Older adults (reduced gastric acid/absorption).
 - Strict vegans/veg* (no animal foods, no fortified products).
 - Pernicious anaemia / autoimmune gastritis (lack of intrinsic factor).
 - GI disorders (Crohn's disease, celiac), ileal resection/bypass.
 - Long-term **metformin** use (T2DM) and long-term **PPI/H2 blocker** use.
 - Chronic alcoholism, pancreatic insufficiency, tropical sprue, tapeworms.
 - Pregnancy & breastfeeding if mother deficient (risk to infant). [Office of Dietary Supplements+1](#)
-

Clinical consequences of deficiency

- **Hematologic:** megaloblastic (macrocytic) anemia, low reticulocyte count.
 - **Neurologic:** symmetric peripheral neuropathy, paresthesias, gait disturbance, loss of vibration/position sense; can progress to irreversible spinal cord (subacute combined degeneration) if untreated.
 - **Psychiatric/cognitive:** depression, memory impairment, cognitive decline in elderly (contribution complex).
 - **In pregnancy/infancy:** poor fetal neurodevelopment, developmental delay in infants breastfed by deficient mothers. [Office of Dietary Supplements](#)
-

Screening & diagnosis (practical)

- **Initial tests:** serum B₁₂ (total), complete blood count (CBC), MCV.
 - **If borderline/clinical suspicion:** measure **MMA** (more specific) and **homocysteine** (both rise in B₁₂ deficiency).
 - **If autoimmune cause suspected:** intrinsic-factor antibodies / parietal cell antibodies; consider endoscopy if autoimmune gastritis suspected. Follow national guidelines (e.g., NICE). [NICE+1](#)
-

Treatment & dosing — evidence & practical regimens

Principles: treat deficiency; route depends on cause/severity (neurological signs, absorption problems). High-dose oral therapy is effective for many patients; IM preferred for severe neurological involvement or when malabsorption is certain.

Typical regimens used in practice / guidelines:

- **Emergency / neurological involvement:** IM hydroxocobalamin 1,000 µg (1 mg) IM alternate days or 1,000 µg daily for 1–2 weeks, then maintenance (e.g., 1,000 µg IM every 2 months or every 3 months depending on guideline). [BLMKICB Medicines Optimisation+1](#)
- **Non-neurological deficiency or dietary cause:** Oral cyanocobalamin **1,000–2,000 µg/day** for several weeks, then lower maintenance (e.g., 1,000 µg weekly or 50–150 µg/day depending on cause). High-dose oral ($\geq 1,000$ µg) overcomes malabsorption in many patients by passive diffusion. Randomized trials and reviews show **oral high-dose tablets can be as effective as IM injections** for haematological and neurological responses in many patients. [PMC+1](#)
- **Pregnancy:** treat clinically significant deficiency (IM hydroxocobalamin or oral high-dose cyanocobalamin); maternal repletion important for fetal/neonatal status. Evidence shows supplementation improves maternal B₁₂ concentrations but effects on perinatal outcomes need more robust data. [PubMed](#)

Safety: B₁₂ has very low toxicity; adverse effects are rare (local injection reactions, rare allergic reactions). Excess water-soluble B₁₂ is excreted. Still, monitor potassium in severe anemia during early treatment (risk of hypokalemia during haematologic recovery). [Notts APC](#)

Evidence for benefits by condition (summary of trials/reviews)

Cardiovascular disease

- B₁₂ (usually given with folic acid and B₆) lowers plasma homocysteine, but large RCTs (NORVIT, VISP, HOPE-2, SEARCH and others) **did not consistently show reductions in major cardiovascular events** despite homocysteine reduction. Some trials showed reduced stroke in subgroups, but overall evidence does **not** support routine B-vitamin therapy to prevent cardiovascular events in general populations. Clinical use remains targeted to deficiency correction, not primary CV prevention. [New England Journal of Medicine+1](#)

Diabetes (type 2) & diabetic neuropathy

- **Metformin** is associated with lower B₁₂ levels and increased risk of deficiency; systematic reviews support monitoring and supplementation in long-term metformin users. Evidence that B₁₂ supplementation improves diabetic peripheral neuropathy is mixed — some studies show symptomatic/functional improvement, but high-quality RCT evidence for clear neural recovery is limited. Correction of deficiency is recommended for patients with low B₁₂. [ScienceDirect+1](#)

Cancer

- Observational studies report **elevated plasma B₁₂** in some patients with cancer (likely marker of disease/altered metabolism rather than cause); randomized data do not show that B₁₂ supplementation increases cancer incidence, but the relationship is complex and causality is unclear. Elevated B₁₂ should prompt evaluation for underlying disease in some contexts. [PMC+1](#)

Nephrology (CKD)

- CKD patients often have altered B₁₂ metabolism and elevated homocysteine; trials lowering homocysteine with B vitamins in CKD reduced homocysteine but **did not consistently reduce cardiovascular risk**. Role of B₁₂ in CKD remains investigational re: outcomes; repletion is indicated in deficiency. [PubMed+1](#)

Pregnancy & gynecology

- Maternal B₁₂ deficiency is linked to poor fetal growth and neurodevelopmental risk. Systematic reviews find oral supplementation **raises maternal B₁₂** but evidence for

improved infant neurodevelopment outcomes is still limited/uncertain; nevertheless, correcting deficiency in pregnancy is standard clinical practice. [PubMed](#)

Pediatrics

- Infants depend on maternal B₁₂ (in utero and breast milk). Infants of deficient mothers — especially breastfed infants of vegan/vegetarian mothers without supplementation — can develop severe neurodevelopmental delay. Prompt diagnosis and treatment are critical. Pediatric dosing is lower; follow pediatric specialist guidance. [Office of Dietary Supplements](#)

Older adults & healthy individuals

- Older adults: decreased absorption → higher prevalence of deficiency/insufficiency; monitoring and low-threshold supplementation (or intramuscular therapy if pernicious anemia) is appropriate. For generally healthy, well-fed adults with normal dietary intake, routine supplementation is not necessary beyond recommended intakes. [Office of Dietary Supplements](#)

Key clinical trials & systematic reviews (selected, high-impact)

- **NORVIT & HOPE-2 (2006)** — randomized trials lowering homocysteine with folic acid + B₁₂: **reduced homocysteine but no consistent reduction in major CV events**; some stroke subgroup signals. [New England Journal of Medicine+1](#)
- **VISP (2004)** — high-dose B-vitamin formula after ischemic stroke: **no reduction** in recurrent stroke over 2 years. [PubMed](#)
- **Cochrane / RCTs (oral vs IM)** — high-dose oral B₁₂ (1,000–2,000 µg/day) **as effective** as IM for haematological and neurological responses in many patients (limited sample sizes; more large trials desirable). [PubMed+1](#)
- **Systematic reviews on metformin** — support monitoring and supplementing B₁₂ in long-term metformin users. [ScienceDirect](#)

Laboratory thresholds (practical)

- **Serum B₁₂**: values vary by lab. Common cutoffs: <200 pg/mL (≈148 pmol/L) often considered deficient; 200–300 pg/mL borderline/insufficient. Functional testing (MMA, homocysteine) clarifies borderline cases. Prevalence estimates vary; adult deficiency ~3–4% in some surveys, insufficiency higher. [Office of Dietary Supplements](#)

Dosing quick-reference (clinical/practical)

- **Prevention (adult, dietary):** meet RDA (2.4 µg/day) via diet/fortified foods; vegans should use fortified foods or supplements (e.g., 25–100 µg/day OTC or a periodic high-dose).
 - **Mild deficiency / dietary cause (adult):** oral cyanocobalamin **1000 µg/day** for several weeks, then maintenance (e.g., 1000 µg weekly or 50–150 µg/day).
 - **Severe deficiency / neurological signs:** IM hydroxocobalamin **1000 µg** alternate days x1–2 weeks (or 3×/week for 2 weeks per local guideline) → maintenance 1000 µg IM every 2–3 months. Exact regimen varies by guideline — follow local protocols (NICE/NHS/tertiary guidance). [BLMKICB Medicines Optimisation+1](#)
-

Drug interactions & special notes

- **Metformin** reduces B₁₂ absorption — monitor levels in long-term users. [ScienceDirect](#)
 - Long-term **PPI/H2 blocker** use can increase risk (reduced gastric acid). [RES Systems Portal](#)
 - **Nitrous oxide** (anesthetic/recreational) oxidises B₁₂ and can precipitate acute neurological B₁₂ inactivation — treat promptly if neurologic signs. [Knowledge NoW](#)
-

Practical guidance for clinicians & industry (Alcardia perspective)

1. **Screening policy:** consider B₁₂ testing for older adults, long-term metformin users, strict vegans, post-gastric surgery patients, unexplained macrocytic anemia or neuropathy. Use MMA/homocysteine to clarify borderline cases. [Office of Dietary Supplements](#)
 2. **Product positioning:** offer both **high-dose oral cyanocobalamin (1,000 µg)** tablets for maintenance/deficiency corrected by oral route and **hydroxocobalamin IM** for severe cases or confirmed malabsorption. Ensure clear labeling on indication, dosing, and monitoring. [PMC+1](#)
 3. **Patient education:** emphasize that vegans need reliable fortified sources or supplements, and metformin users should be monitored. Explain that B₁₂ is generally safe and essential, but large-scale supplementation for CV prevention is not supported. [JAMA Network+1](#)
-

Gaps/uncertainties & research needs

- Whether B₁₂ supplementation reduces long-term cardiovascular events or cognitive decline in specific high-risk subgroups remains uncertain (trial data mixed).
- Optimal strategies for screening and population-level fortification policy vary by region and need further evaluation. Recent guideline updates (e.g., NICE 2024) call for clearer diagnostic and management pathways. [NICE+1](#)

Selected key references (for clinicians / regulatory dossiers)

1. NIH Office of Dietary Supplements — Vitamin B₁₂ Fact Sheet (health professional & consumer). [Office of Dietary Supplements+1](#)
2. NICE guideline: *Vitamin B12 deficiency in over 16s: diagnosis and management* (2024). [NICE](#)
3. NORVIT / HOPE-2 / VISP trials (effects of homocysteine lowering on CVD) — NEJM, JAMA and primary trial reports. [New England Journal of Medicine+1](#)
4. Systematic reviews and RCTs comparing oral vs IM B₁₂ (Vidal-Alaball, Cochrane/2005; later reviews). [PubMed+1](#)
5. Systematic review: B₁₂ and metformin-associated deficiency. [ScienceDirect](#)
6. Pregnancy supplementation reviews (Cochrane / PubMed 2024). [PubMed](#)