

After 50 Higher Fracture Hazard was Linked to Vitamin B12 Deficiency

A recent retrospective study found an association between [vitamin B12 deficiency](#) and long-term fracture hazard in a propensity-matched cohort. However, the authors cautioned that this should not be interpreted as meaning that vitamin B12 deficiency causes or predicts fracture.



Study

The researchers used electronic health records from the TriNetX Global Collaborative Network, drawing on data from multiple [healthcare](#) organizations. After applying the initial eligibility criteria, the study included 115,735 patients with vitamin B12 deficiency and more than 1.76 million with concentrations in the normal range. All had undergone B12 testing between 2016 and 2023 and had at least one healthcare visit during the previous five years, helping the researchers capture relevant medical history.

Patients were grouped according to their B12 concentrations: [Deficiency](#) was defined as 199 pg/mL or less, borderline levels as 200–299 pg/mL, the normal reference range as 300–900 pg/mL, and high levels as above 900 pg/mL. Those with conflicting B12 measurements during the previous five years were excluded to keep the categories clearly separated.

To reduce the possibility that an existing or imminent fracture influenced B12 testing, the researchers used a one-year landmark design. Participants had to be alive and free of fracture, osteoporosis, and repeated falls when outcome follow-up began. These conditions were also exclusion criteria if recorded during the five years before the index measurement through the landmark period, although a single prior fall was permitted and accounted for in the matching process. Patients with several conditions that could affect bone health, as well as those with recent [critical illness](#), were also excluded.

The eligible patients were then matched according to a broad range of demographic characteristics, health conditions, [medications](#) and available laboratory measures, leaving 115,735 people in each of the B12-deficient and normal-B12 groups. From one year after the initial B12 measurement, the researchers tracked incident fractures across multiple parts of the body as the primary outcome.

The analysis went beyond fractures alone. Secondary outcomes included lower-limb and osteoporotic fractures, [osteoporosis](#) without fracture, all-cause falls, and repeated falls. Hyperhomocysteinemia served as a positive control, while lipoma was used as a negative control to help assess nonspecific associations and residual confounding.

Open wounds provided an additional comparison for whether greater exposure to [injury](#), rather than bone fragility, might partly explain the fracture findings. The researchers also carried out sensitivity and subgroup analyses to test how consistently the main association appeared under different analytical conditions.

Findings

Fractures occurred in 7.2% of the [B12-deficient patients](#) (8,362 individuals), versus 6% (6,962) of the reference group. The adjusted analysis found that the fracture hazard was 33% higher among patients who remained alive and under observation in the deficiency group.

Borderline and high vitamin B12 levels were also associated with increased fracture hazard, though the associations were weaker. This non-monotonic pattern argues against a simple deficiency-specific or dose-response relationship. These may support the coexistence of vitamin B12 abnormalities with conditions or factors other than those with a direct [biological link](#). In particular, the high-B12 association may reflect underlying morbidity, supplementation, or greater healthcare contact.

However, the analysis suggested non-proportionality of the [hazard rate](#) over the full period. Further testing using only the 1–5 years after the index measurement showed an increase in fracture hazard by 37%, without evidence of non-proportionality, and fracture-free probability was consistently lower in the deficiency group compared to controls throughout the follow-up.

Secondary outcomes were concordant with the primary outcome. Higher hazards of osteoporosis, osteoporotic fracture, [lower-limb fracture](#), all-cause falls, and repeated falls were found. The increase in hazard ranged from 22% for osteoporosis without fracture to 50% for repeated falls.

The authors suggest that these findings may mean that deficiency is linked to both poorer [bone health](#) and fall-related pathways that act together to eventually impact fracture risk.

Hyperhomocysteinemia was associated with a 41% higher hazard in the deficiency group, but not lipoma. Open wounds were associated with a 12% higher hazard. Conversely, high B12 levels were negatively linked to [hyperhomocysteinemia](#). None of these outcomes showed non-proportionality of hazards. However, these are exploratory findings as they do not rule out residual confounding.

The pattern persisted across all sensitivity analyses with similar direction and magnitude of association. A complementary multivariable analysis of the unmatched cohort also found an association between vitamin B12 deficiency and fracture after adjustment. Subgroup analyses suggested stronger associations with fracture among patients aged 50–65 years compared to those above 65, but not in other subgroups including sex, [obesity](#), or proton pump/metformin use. This was also considered an exploratory and hypothesis-generating finding.

The findings are [biologically plausible](#); however, they remain observational. The current study adds to previous knowledge by identifying associations between vitamin B12 levels and a wider range of outcomes, reducing the risk of reverse causation and adjusting for many known confounders.

Conclusion

The large multicenter study described an association between vitamin B12 status at baseline and subsequent fracture hazard in adults aged 50 years and above who underwent vitamin B12 testing, but without causality or predictive ability due to the study design. The primary outcome described fractures across multiple [anatomical sites](#) and was not restricted to fragility fractures resulting from bone fragility due to vitamin B12 deficiency.

However, it does not establish that deficiency causes or predicts fracture, or that [B12 supplementation](#) reduces the risk. This will require further prospective studies.

Source:

<https://www.news-medical.net/news/20261002/Vitamin-B12-deficiency-was-linked-to-higher-fracture-hazard-after-50.aspx>