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REVIEW ARTICLE

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Elevated Vitamin B12, Risk of Cancer, and Mortality: A Systematic Review

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ABSTRACT

Vitamin B12 (B12) is a molecule involved in several biological. Abnormally high levels are frequently found, but their causes can be multiple, and consequences have not been clearly elucidated. The objective of this review was to summarize the current evidence on the associations of elevated B12 and the development of cancer, and all-cause mortality in adults. Six references looking at mortality and seven looking at cancer risk were included. The evidence suggests an association between elevated B12 with a higher risk of cancer, with risk ratios ranging 1,88 to 5,9. There was less consistent evidence linking vitamin B12 and mortality.

HIGHLIGHTS

- Elevated B12 levels exceeding 1000 pg/L, if sustained and unexplainable, warrant a comprehensive individual assessment of each patient. This evaluation should encompass various potential factors contributing to the elevation, aiming to effectively guide the diagnostic process of neoplastic diseases.
- Clinical longitudinal observational studies have suggested a potential link between heightened B12 levels and the risks of cancer and mortality. Nonetheless, these studies have been retrospective cohort studies, and lack a defined threshold point of B12 levels.
- Studies have documented a positive correlation between elevated levels of B12 and the incidence of lung, pancreatic, and liver cancers, as well as certain hematological neoplasms, particularly those related to the myeloid lineage. Conversely, a consistent negative association has been observed in the context of breast cancer. Findings concerning neoplasms of the lower gastrointestinal tract and prostate display contradictory outcomes.
- The diagnostic significance of elevated B12 levels among patients already diagnosed with cancer remains uncertain and could potentially be linked to reverse causality.

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Introduction

Vitamin B12 (cyanocobalamin) is a structurally complex, nonpolymeric biomolecule. It plays an essential role in several biological processes, including the synthesis and methylation of deoxyribonucleic acid (DNA) (1). Vitamin B12 (B12) is also a cofactor for two key enzymes in the conversion of homocysteine to methionine (2,3). In clinical practice, measurements of B12 levels usually seek a deficiency, considering the vitamin's roles in hematopoiesis and in some neurological functions (4). Incidental and paradoxical findings of elevated B12 are common in clinical practice, with a frequency of 1.2% to 18% of in-hospital patients (5–12).

Multiple causes of vitamin B12 hypervitaminosis have been described, including liver and kidney disease, exogenous administration, and solid or hematological neoplasms, among others (13–17). Previous observational studies have found an association between elevated B12 levels and increased risk of cancer or mortality.

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However, the findings are varied, preventing the clarification of this relationship and its clinical implication with this important biomarker (18–24).

If an association between elevated B12 levels and increased risk of cancer or mortality were to be demonstrated, the use of this marker could be considered as part of the screening, diagnostic or follow-up process to facilitate timely diagnosis and risk estimation. Since evidence for the association continues to be unclear, the purpose of this systematic review was to summarize up-to-date evidence in large cohort studies on the association of high B12 levels with the development or presence of cancer, as well as with all-cause mortality. Also, the review aimed to identify and describe the B12 values related to these effects and the populations that may benefit from active screening.

Methods

Study protocol and search strategy

This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (25). We carefully created a search strategy to find primary clinical studies that evaluated the association of elevated levels of B12 with risk of cancer or all-cause mortality. We searched up to May 15, 2023, in the electronic databases of MEDLINE (PubMed), SCOPUS, Web of Science, EMBASE, The Cochrane Library, and LILACS with no language restrictions (See Table S1 in the Supplementary Material). We also searched for similar studies published in nonindexed journals, references list of other studies, questioned experts in oncology and hematology, and resources such as grey literature and Google Scholar. No date limits neither language restriction was applied to the search strategy.

Eligibility criteria and data extraction

Studies were included if they were longitudinal analytic observational studies that quantified the association between vitamin B12 levels to the development any type of cancer or cause mortality in adults. Studies were excluded if they were conducted on animals, included pregnant women or included subjects on active multivitamin supplement intake that did not adjust their models for such a variable. The review also excluded studies assessing the association with cancer in subjects with known causes of elevated B12, such as sepsis, acute/chronic liver disease, and advanced chronic kidney disease. Abstracts, letters to the editors, conferences, and posters that did not mention the full data or original article were also excluded. Two independent groups of reviewers used Rayyan QRCI (26) for initial screened by title and abstract (Group 1, JM-C and LM-P. Group 2, SBA-G and AB-L), and then four reviewers (AV-P, MV-B, LM-P and SBA-G) selected articles by a full text revision. Any discrepancies were resolved by a third reviewer (AB-L). The authors extracted information on study design, authors, title, country, language, year of publication, participants characteristics, definition of elevated B12 levels, measurement units, categories, follow-up time, specific outcome, sample size, outcome measurement tool and sample size. They also recorded the most adjusted risk estimates with corresponding standard errors (SE) or 95% confidence intervals (CI).

Quality assessment

For each longitudinal observational study, three independent reviewers (MV-B, AV-P, and LM-P) in parallel assessed the risk of bias with the Newcastle-Ottawa Scale (NOS) (27). The reviewers critically evaluated each domain related to selection of study groups (up to 4 start points), comparability (up to 2 start points) and outcome assessment (up to 3 start points). The authors considered a low risk of bias at seven or more stars out of a possible nine, a moderate risk at four to six stars and high risk at 3 or less stars. Discrepancies were resolved by a third reviewer (AB-L or SBA-G).

Data analysis

We conducted a narrative description of characteristics of the included references. Studies were grouped and described by main outcomes: risk of cancer and mortality. We assessed whether the

results of studies appeared reasonable, considering effect sizes and cut-off levels of vitamin B12. We made no attempt to quantitatively summarize findings across the included studies due to heterogeneity in exposure and outcome variables. We then described findings across patients' clinical characteristics and age ranges for the studied outcomes (risk of cancer or mortality).

Results

The flowchart in Figure 1 presents details of the study selection process. The initial search identified 11,501 references. The selection process left 13 references with complete data for review (5,15,18,24,28–35). Of the 13 references, six assessed all-cause mortality outcome, and seven assessed the risk of developing cancer outcome. Table 1 shows the results of risk of bias assessments for the studies included. The risk of bias was low in eleven studies (5,18,23,24,29–31,33–36), moderate in one study (32), and high in one study (28) (Table S1). We describe findings according to the main clinical outcome below.

Risk of cancer

Evidence for an association between higher levels of vitamin B12 and any type of cancer was reported in seven cohort studies, their characteristics are presented in Table 1 (5,23,28–31,35). They included data from 1970 to 2015 about the incidence of cancer in 1,246,723 patients (58.6% females) with elevated B12. Five studies analyzed cohorts obtained from national information systems of patients and laboratories (5,28–31). One study by Lacombe *et al.* analyzed a prospective cohort from the Angers University Hospital Center in France (n = 688) (35), and another by Tamayo *et al.* evaluated a retrospective cohort from the University Clinical Hospital of Valladolid in Spain (n = 6710) (23). All studies were conducted in Europe, on adults from ages

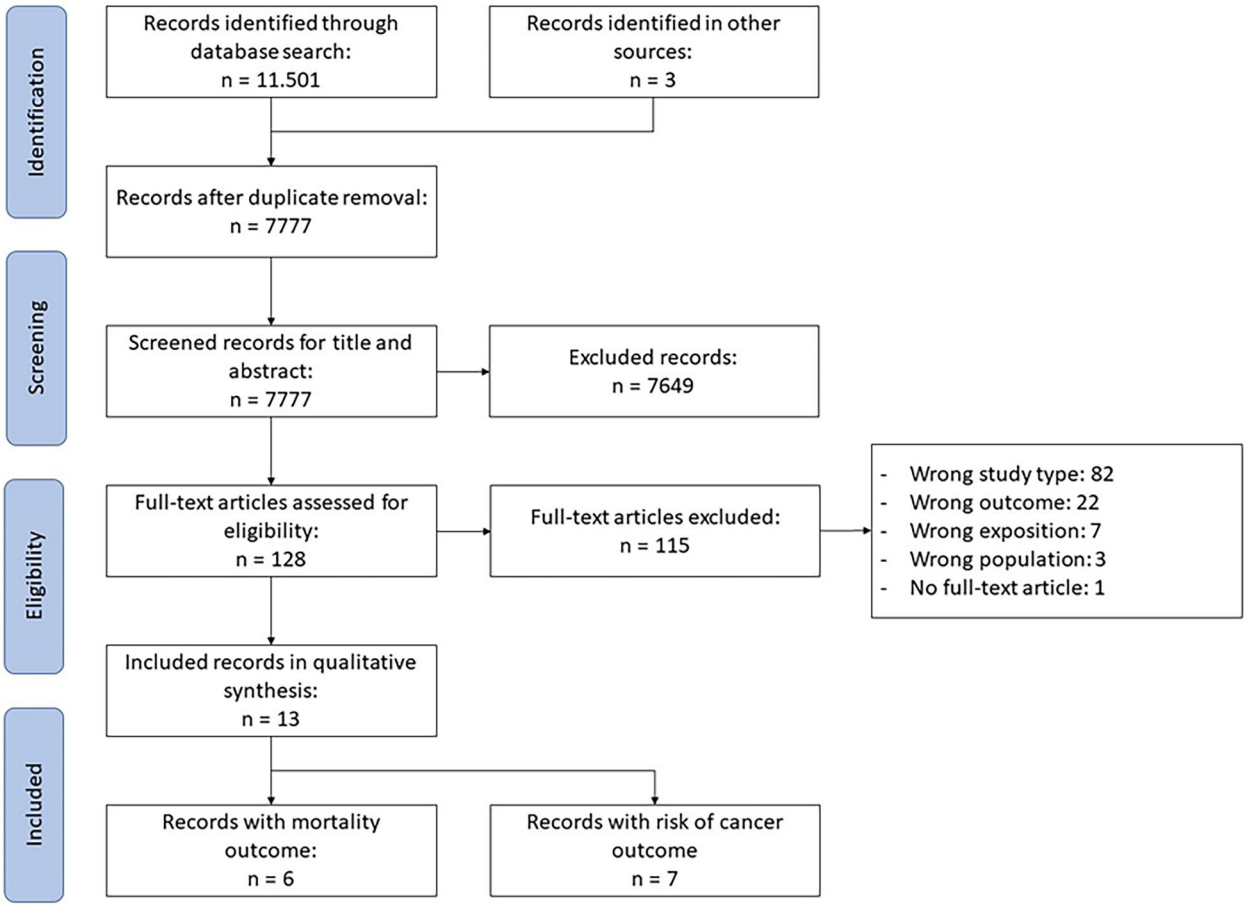


Figure 1. Study selection process.

Table 1. Characterization of included studies.

Author	Country	*n*	Female, *n* (%)	Age in years (SD, IQR)	B12	Follow-up length	Risk of bias (NOS)
Risk of cancer							
Arendt et al., 2013 (29)	Denmark	333,667	198,182 (59)	Median 55.1 (40.2–69.2)	200-600 pmol/L 601-800 >800	Median, 3.5 years	* * * * * * * * *
Ryg et al., 2013 (30)	Denmark	40,391	24,695 (61)	Median 61 (44–77)	< 1,200 pmol/L >1,200	Mean, 2 years	* * * * - * * *
Essen et al., 2019 (31)	Sweden	Prostate: 8,783 Breast: 19,775	Prostate: 0 (0) Breast: 19,775 (100)	Prostate: mean 60.4 Breast: mean 55.7	< 150 pmol/L 150-650 >650	Prostate: Mean, 12.7 y Breast: Mean 14.3 y	* * * * * * * * *
Arendt et al., 2019 (5)	United Kingdom	757,185	484,570 (64)	Median, 55.8	150-600 pmol/L 601-800 800-1,000 >1,000	Median, 2.8 years	* * * * * * * *
Gavars et al., 2019 (28)	Latvia	79,524	Not specified	Not specified	< 568 pmol/L *converted 568-1,254 pmol/L *converted >1,254 pmol/L	Not specified	* * * - -
Lacombe et al., 2021 (35)	France	688	432 (63)	Median, 79 (64-86)	<1,000 ng/L >1,000 in one sample >1,000 in two samples	Median, 3.2 years	* * * * * * * * *
Tamayo et al., 2023 (23)	Spain	6710	4137 (21,7)	Median, 69 (24)	<197 pmol/L 197-771 >771	Median, 5 years	* * * * * * * * *
Mortality							
Zeitlin et al.,1997 (32)	United States	440	282 (64.1)	Mean, 79	N/A pg/mL	9 years	* * * - *
Callaghan et al., 2014 (33)	United States	1,684	677 (40.2)	Median, 67.7 (55.4–78.1)	>1,000 pmol/L	90 days	* * * * * * * * *
Arendt et al., 2016 (34)	Denmark	87,005	44,139 (50.7)	Mean, 71	200-600 pmol/L 601-800 >800	13 years	* * * * * * * * *
Chen et al., 2021 (24)	Japan	3,050	1,718 (56.3)	Mean, 60 (12)	≤276 pmol/L 277-388 ≥389	Median 10.2 years	* * * * * * *
Xu et al., 2021 (18)	China	2,086	1,178 (56.5)	Mean, 87.74 (11.74)	<203 ng/mL 204-740 >740	Mean 3.34 years	* * * * * * * * *
Liu et al., 2022 (22)	United States	4860	2470 (50,8%)	Media, 57.8 (0.3)	<369.1 369.1-506.0 506.1-703.4 >703.5	NA	* * * * * * * * *

NOS: Newcastle-Ottawa Scale described according to following levels:.
1 level: Selection of Study Groups.
2 level: Comparability.
3 level: Outcome Assessment.

18 to 99. Age distribution was similar for all studies (5,29–31) except for the one by Lacombe et al., which included older patients (35). None of the studies included patients from Africa or South America.

Statistical analyses grouped patients by basal serum levels of B12. Cut-off points and methods to define them, however, were clinically heterogeneous. All studies established the reference values of the clinical laboratory as their B12 cut-off points (5,23,28–31,35) (Table 1). The study by Lacombe *et al.* collected a second sample of B12 in all patients and then compared patients with persistently elevated B12 (in the two samples), non-persistent elevated B12 (only in the first sample) with the control group (no B12 elevation in any sample) (35). The type of neoplasm assessed in the studies was also heterogeneous. Arendt *et al.* (2013), Ryg *et al.*, Arendt *et al.* (2019), Gavars *et al.*, and Lacombe *et al.* assessed

all types of cancer, and made subgroup analysis by type of cancer (5,29,30,35). On the other hand, Essen *et al.* assessed only breast and prostate cancer (31) and Tamayo *et al. e*valuated hematological neoplasms (23). Most of the studies performed age-adjusted and comorbidity-adjusted analyses to calculate risk measures, such as hazard ratio (HR), odds ratio (OR), standardized morbidity ratio (SMR), and standardized incidence ratio (SIR) (Table 2). The study by Gavars *et al.* was the only one not including data on age or comorbidities or adjusting analyses for possible confounders (28). The control groups used by each study were also heterogeneous, with some studies using patients with low B12, and others using patients with B12 in the middle or normal range. Studies had similar follow-up times, around three years, except for the one by Essen *et al.* that extended for more than 10 years (31). The study by Gavars *et al.* did not specify the follow-up time nor was it clear about the timing of cancer diagnosis in relation to B12 sample-taking (28).

Studies assessing all types of cancer (5,28–30,35) showed a statistically significant association between elevated B12 and cancer incidence (Table 2). In the study by Ryg *et al.*, the association was significant until 1-year follow-up, stronger during the first 6 months, and absent in lengthier periods (30). The study by Essen *et al.* on prostate and breast cancer showed no statistically significant associations (31). The study by Lacombe *et al.* found an association between persistently elevated B12 and the risk of cancer (HR 5.9, 95%CI 2.79–12.45) and found no association with non-persistently elevated B12 (HR 1.52, 95%CI 0.7–3.3) (35). When evaluating the risk of hematological cancer, the study by Tamayo *et al* found an association between a previously elevated B12 and risk of cancer, mostly diagnosed within the first three years from the sample (OR 1.97, 95% CI 1.05–3.67) (23).

The study by Arendt *et al.* (2019) analyzed the association between elevated B12 and cancer by type of neoplasm. They found an association between elevated B12 and the development of gastric, hepatic, pancreatic, and pulmonary cancer, as well as myeloid hematologic neoplasms. They found no statistically significant association for prostate, colon, and rectal cancer (5). The study by Arendt *et al.* (2013) divided neoplasms into four groups (29): (1) Related to tobacco and alcohol use (oropharyngeal, pulmonary, esophageal, pancreatic, hepatic, colonic/rectal, kidney, and bladder cancer). (2) Hematological. (3) Related to the immune system (cervical, anal, penile, melanoma skin cancer, and non-melanoma skin cancer). (4) Related to hormone-influx (prostate, breast, uterine, ovarian, and testicular). They found an association between elevated B12 and hematological and tobacco/alcohol-related neoplasms. For hormone influx-related

Table 2. Risk of cancer and levels of vitamin B12 in adults.

Author	Outcome	Measure of association	Control group	Estimated risk
Arendt et al., 2013 (29)	All-type cancer	SIR	Cancer incidence expected in the general population	Total: 2.38 (2.22–2.56) <1 year: 6.27 (5.7–6.88) >1 year 1.24 (1.1–1.39)
Ryg et al., 2013 (30)	All-type cancer	SMR	Low vitamin B12	0-6 months: 15.1 (10.4–21.1) 1 year: 3.7 (1.4–8.1) 1-2 years: 2 (0.6–4.6) 2-3 years: 2.7 (0.9–6.3) >3 years: 1.4 (0.4–3.2)
Essen et al., 2019 (31)	Prostate cancer Breast cancer	HR (95%CI)	Normal vitamin B12	Prostate: 0.99 (0.61–1.62) Breast: 0.81 (0.53–1.24)
Arendt et al., 2019 (5)	All-type cancer	RR (95%Ci)	Low vitamin B12	800–1.000 pmol/L: 1.88 (1.64–2.15) > 1.000 pmol/L: 2.42 (2.11–2.77)
Gavars et al., 2019 (28)	All-type cancer	OR (95%CI)	Normal vitamin B12	2.8 (2.4–3.4)
Lacombe et al., 2021 (35)	Solid neoplasm	HR (95%CI)	Normal vitamin B12	Persistently elevated B12: 5.9 (2.79–12.45) non-persistently elevated B12: 1.52 (0.70–3.30)
Tamayo et al., 2023 (23)	Hematological neoplasm	OR (95 % CI)	Normal B12	5 years: 1.975 (1.056–3.679)

*SIR: Standardized incidence ratio. SMR: Standardized morbidity ratios. HR: Hazard Ratio. RR: Relative Risk. OR: Odds Ratio. CI: confidence interval.

Table 3. Risk of mortality, measures of association.

Author	Outcome	Measure of association	Estimated Risk
Zeitlin et al., 1997 (32)	All-cause mortality, cardiovascular morbidity	OR	1.001 ($p = 0.041$)
Callaghan et al., 2014 (33)	Mortality at 30 and 90 days in critical care patients	OR (95%CI)	30 days: 1.18 (0.81–1.72) 90 days: 1.20 (0.84–1.71)
Arendt et al., 2016 (34)	Survival probability at 30, 90, and 365 days after diagnosis of cancer	Mortality Risk Ratios (95% CI)	30 days: 2.7 (2.4–3.1) 90 days: 2.4 (2.1–2.7) 365 days: 1.9 (1.7–2.2)
Chen et al., 2021 (24)	All-cause mortality	HR (95%CI)	1.3 (0.95–1,76)
Xu et al., 2021 (18)	All-cause mortality	HR (95%CI)	1.3 (1.03–1,64)
Liu et al., 2022 (22)	All-cause mortality	HR (95%CI)	Third quartile 1.37 (1.1–1.7) Fourth quartile 1.29 (1.06–1.58)

SIR: standardized incidence ratio. SMR: standardized morbidity ratios. HR: hazard ratio. RR: relative risk. OR: odds ratio. CI: confidence interval.

neoplasms, there was an association in the first year of follow-up, but not in the lengthier periods. There was no relationship between elevated B12 and immune system-related cancers.

Mortality

Associations between higher B12 and mortality were assessed in six studies (18,24,32–34,22). They included 94,313 patients, mostly adults older than 65 years (54%) (Table 1). The study by Arendt *et al.* was the only one including pediatric population, with no effects of B12 discriminated for such patients (34). Only one study assessed in-hospital mortality in critical care (33), and one other assessed mortality in a cancer population (34). The remaining studies were conducted in outpatients (18,24,32,22) assessing all-cause mortality. The Danish cohort had the largest sample size (34). Four studies divided their population by terciles according to B12 levels, with different cut-off points used in each study. One article analyzed B12 as a continuous variable (32) and the remaining article conducted one analysis using it as a continuous variable and another using the variable divided into quartiles (22). In general, the high-elevation category was higher than 700 pmol/L (18,33,34,22), except for the article by Chen et al. (24) Follow-up length to assess the outcome was at minimum 90 days in the cohort analyzing mortality in the intensive care unit (ICU) (33), and at maximum 10 years, with an average of 9 years (18,24,32,34).

Statistical methods to assess risk of mortality were Kaplan–Meier curves with Cox regression analysis (18,24,32–34,22). Five studies assessed all-cause mortality in outpatients with result adjustment by demographic variables and comorbidities (18,24,32,34,22). In the ICU cohort, multivariate logistic regression analysis with four models compared the risk of death in subjects with elevated B12 to those with low B12, adjusted by demographic variables, other confounders, and liver function (33).

In the ICU cohort, 30-day and 90-day mortality was higher for the group with elevated B12. However, when they adjusted for liver function the association was lost (33). The cohort by Arendt et al (34) showed a significant association between higher B21 and mortality among cancer patients at 30 days, 90 days and one year follow-up and Liu et al. (22) demonstrated a significant association between the two upper quartiles of B12 and all-cause mortality in a diabetic patient's cohort (Table 3). In the secondary outcomes, a specific association was found with cardiovascular mortality both at the highest and lowest levels of B12 (HR 2.32, 95% CI 1.60–3.25 and HR 1.79, 95% CI 1.19–2.71, respectively). Zeitlin et al (32) found a 10% increase in mortality and incidence of coronary heart disease for every 100 pg increase in B12. In the study by Chen et al. all-cause mortality of patients with elevated B12 was slightly higher without reaching statistical significance (24) (Table 3).

Discussion

This is the first systematic review that synthesizes the existing literature on the association between elevated B12 and risk of cancer or mortality. While various causes of elevated B12 levels have been described, a discernible positive correlation appears to exist between high B12 levels and the risk of cancer incidence. The study by Lacombe et al. showed a strong association with

persistently elevated B12, as opposed to transiently elevated B12 levels (35). This distinction holds potential clinical significance, given the existence of alternative causes contributing to isolated elevation. We did not find any other studies or literature assessing the differences between persistent or transient B12 elevation. Results in the study by Lacombe suggest the hypothesis that elevated B12 is clinically relevant when it persists (28). However, further prospective studies focused on this subject are required.

In the studies included in our revision analyses by subgroups showed an association with all types of neoplasms including hematological. Several authors of previous publications have described such an association (7,14). Though the mechanism is not clear, an increase in transport proteins (36) and excessive synthesis of B12 by the tumor (9) have been described, but there may be differences in the mechanism in each type of cancer. For example, levels of vitamins in peripheral tissues are associated with the DNA methylation status, and it has been demonstrated that methylation is directly related to carcinogenesis. The role of DNA methylation is distinct for each type of cancer, with a greater effect observed in neoplasms such as colorectal and hematological cancers but is also described in others such as prostate cancer (37).

Accordingly, some of the results of the included studies were different regarding the association to specific types of cancer. Essen *et al.* did not show any association between elevated B12 and prostate or breast cancer (31). Likewise, in their analysis by subgroups, the 2019 study by Arendt *et al.* did not find an association between elevated B12 and prostate or rectal cancer. On the contrary, a previous systematic review of case-control studies with 47% heterogeneity found a positive association of circulating B12 with a higher risk of prostate cancer, with a 10% higher probability per each 100 pmol/L increase in B12 levels (21). A case-control study by Hultdin et al found that the highest quartile of plasma B12 was associated with an almost threefold increase in the risk of prostate cancer (OR 2.96; 95% CI 1.58, 5.55) (20) The EPIC study in Europe found that a doubling concentration of B12 was associated with a higher risk of advanced prostate cancer (OR 1.69, 95%CI 1.05-2.72), but had no association with the risk of localized disease (19). However, other studies did not show such an association (38–40). Some authors have concluded that mechanisms of reverse causation were more possible than a causal role (37). Differences in the design of the studies may account for the opposite results, but the complexity of B12 metabolism and its interactions with other vitamins or alcohol consumption hinder proper risk assessment.

Regarding breast cancer, the previous existing evidence appears to be more consistent with an absence of association or even a negative association with elevated levels of B12 (41). Zhang et al. showed that high plasma B12 levels with a cut-off point of 571.7 pg/mL were associated with a statistically significant lower risk of breast cancer among premenopausal women (RR 0.36, 95% CI 0.15–0.86), but not among postmenopausal women (RR 1.08, 95% CI 0.7-1.67) (42).

Conversely, the cohort examined by Arendt et al. in 2019 included in our review, revealed a compelling association between elevated plasma B12 levels and the susceptibility to upper gastrointestinal tract, liver, and pancreatic cancers within a population cohort in the United Kingdom, encompassing a broad spectrum of ages (5). Other case-control studies have presented similar findings, with positive association in patients with liver cancer and chronic hepatitis C, in a Chinese population (43,44). However, a confounder in hepatic cancer is the frequent coexistence with known causes of B12 like liver cirrhosis. On the other hand, there could be confounding factors due to indication, as the blood sample was obtained after the diagnosis of the disease. Consequently, Jammal et al. demonstrated an association of high levels of B12 not only with hepatocellular carcinoma but also with other liver diseases such as cirrhosis or hepatitis (8). Other studies have even dismissed the utility of B12-associated proteins as markers for hepatocellular carcinoma because they are equally associated with other liver diseases (45).

The evidence for stomach, colon, and rectal cancers is heterogeneous, with most studies finding an absence of association or a negative association. On the contrary, our review found a

positive association in Arendt et al (2013) and Lacombe et al (29,35), but not in Arendt et al (2019) (5). A previous systematic review did not find an association between dietary vitamin B12 intake and the risk of gastric cancer, with some potential differences observed in Helicobacter pylori-positive patients (46). Other studies did not find associations with the risk of colorectal cancer (47). However, most of these previous studies specifically evaluate vitamin B12 from diet, which could explain the difference in the results of our review.

The literature for lung cancer seems to support the positive association with high B12. A nested case-control study found a positive association of elevated B12 concentrations and overall lung cancer and by histological subtype, also observed in genetically determined high B12 levels (48). Another case-control study assessed the risk for solid cancer in patients with B12 > 1000 ng/L adjusting for confounding factors and found elevated risk for multiple solid cancers with and without metastases, with a 2.89 OR for lung cancer (95% CI 1.14-7.35) (6). These findings are consistent with our revision in the study by Arendt et al, with a strong association for lung cancer in the highest B12 quartile (5).

For hematological disorders, it's been described the presence of high levels of B12, mostly in myeloproliferative disorders including chronic myelomonocytic leukemia, myelodysplastic syndromes and acute leukemias (17). In our search, this is consistent with the findings in three of the included studies, with the predominance of acute myeloid leukemias and myelodysplastic syndromes, and it has been linked to the release of haptocorrin by tumor granulocytes and their precursors (5,17,23,30).

Regarding mortality, although evaluating this outcome is challenging considering the study designs, there also seems to be an association with elevated B12 and higher all-cause mortality in the included studies. Among evaluated studies on mortality, most patients are older adults, who are at higher risk of comorbidities, which may bias results. All the included studies evaluated different populations and outcomes, from ICU patients, cardiovascular mortality or cancer mortality. Therefore, comparing their results is difficult and could lead to wrong assumptions. Some previous studies have shown an association between elevated B12 and increased mortality in patients with and without a history of cancer (49). Several underlying physiological mechanisms account for the association. These include hepatic cellular exchange (due to chronic or acute liver disease), increased haptocorrin high-regulation, increased transcobalamin synthesis, and change of affinity of the B12 transport proteins. These mechanisms are also present in conditions like chronic kidney disease, hematological diseases, infections, and cancer, all of them known possible causes of death. However, there's not a physiological mechanism directly associated with the increased mortality related to high levels of B12 (13,50).

The study by Arendt *et al*. 2016 assessing cancer population showed that elevated B12 before diagnosis was also associated with higher mortality risk at 30, 90, and 365 days (34). That was the case for hematological and solid cancers, mainly breast, prostate, and gastrointestinal (34). This finding suggests that elevated B12 relates to more advanced and more aggressive cancers. Case-control studies have previously documented this finding with higher B12 levels in more advanced stages, suggesting that B12 levels may depend on tumor size or extension (6).

This review is constrained by limitations inherent in the available evidence, rendering it difficult to extrapolate the findings or formulate recommendations. In any case, there is a clinical necessity to synthesize the available evidence. In doing so, it becomes possible to propose more robust studies in the future that can elucidate the described uncertainties and eventually allow the formulation of recommendations. Another limitation to the comparison and summary of the evidence for both assessed outcomes is the heterogeneity of the cut-off points used in each study to define elevated B12 levels. There is no global consensus on the superior normal limit of B12 and most of the studies used the laboratory cut-off points, which come from the distribution of the results in their specific population and can be different in diverse scenarios (5,29,31). On the other hand, some studies used cut-off points higher than the usual laboratory range to include

patients with a significant elevation (30,33,35). These methodological differences between each study make it challenging to compare and summarize the evidence. Indeed, due to the varying cut-off levels used in each study, there is a gray area between 700–1000 pmol/L where it becomes difficult to assume associations. Conversely, levels exceeding 1000 pmol/L consistently fall within the upper range across most studies, making them more reliably considered. Further studies are needed to define the cut-off point from which an elevation of B12 becomes clinically significant. A patient-level metanalysis allowing reclassification of patients with the same cut-off levels could also help to summarize the available evidence.

While our search strategy aimed to include the entirety of available literature, we specifically included only longitudinal studies characterized by a higher quality of evidence. Heterogeneity is more significant in studies assessing mortality, but it is also present in those assessing the risk of cancer. Also, not all studies included data on variables that may increase vitamin B12 levels, which are confounders. Not all studies defined the laboratory technique for B12 measurement and information on B12 supplement intake is also limited. Though most of the studies attempt to control intake, it is not possible to completely rule out self-medication. Few studies included pediatric population, and those that did reported no discriminated analysis for this population, nor did they specify the number of patients or their age ranges. This review highlights knowledge gaps that could be addressed in forthcoming longitudinal studies specifically formulated and designed to elucidate the association between elevated vitamin B12 levels and oncological outcomes.

The strengths of this systematic review include that most of the included studies were qualified as having low risk of bias. Even these are observational studies, they included large longitudinal cohorts and measures were taken to achieve adequate bias control through subgroup analysis. The review was rigorous and followed all the steps required by a systematic review, with a proper description of exposure and outcome. Accordingly, the review provides a proper summary of the available evidence and allows further studies to fill the gap in the evidence.

Conclusions

Based on longitudinal observational evidence, very elevated B12 levels may suggest an association with some types of solid and hematological cancer even in sub-clinical state, especially when high values persist over time, so an additional measurement may contribute to the diagnostic process, which is feasible, considering that it is a non-invasive and widely available diagnostic test. Further prospective studies for specific types of cancer will precisely determine clinically relevant cut-off points and potential indications for directed studies and subsequent measurements. Results of studies addressing mortality are heterogeneous, addressing different populations and outcomes, so discriminating the effect of vitamin B12 elevation on the risk of mortality is difficult.

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Author contributions

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