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A SYSTEMATIC REVIEW AND META-ANALYSIS OF FUNCTIONAL VITAMIN B-12 STATUS AMONG ADULT VEGANS

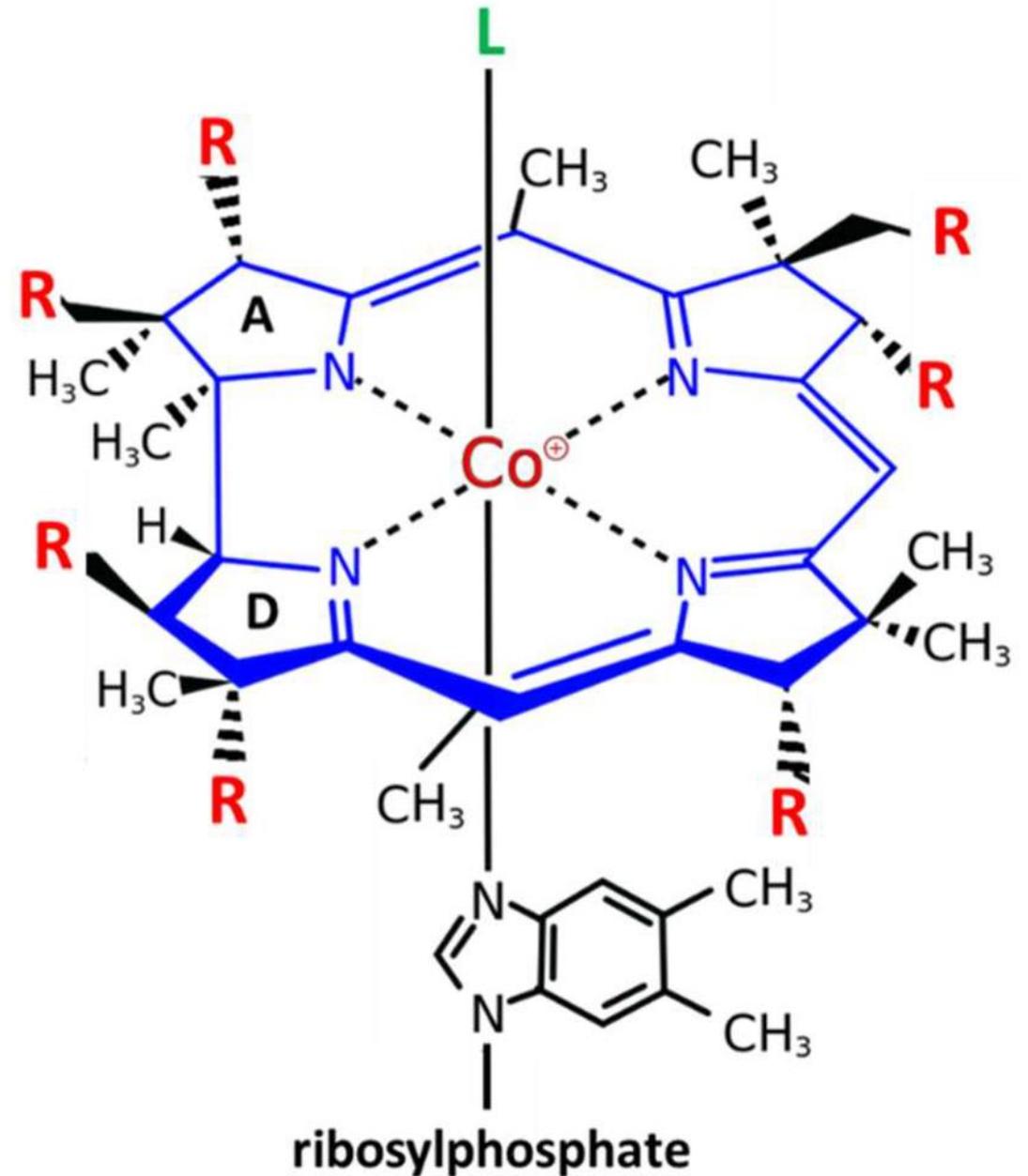
Authors: Ali Nicklewicz, Lucianna Hannibal, Martin Warren, Kouros R
Ahmadi. Pulished December 2024, journal on Nutrition Bulletin

BACKGROUND

COBALMINS: Methylcobalamin and 5-deoxyadenosylcobalamin

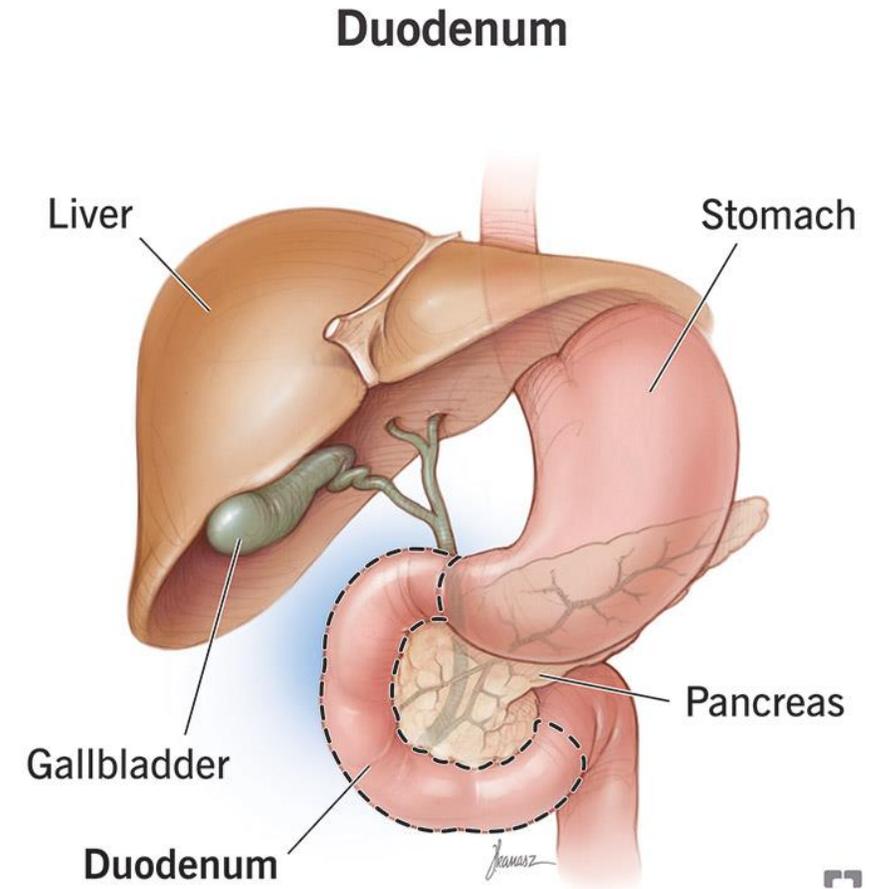
Critical nutrient require for DNA synthesis, red blood cell formation and neurological fxn.

- Synthesized by bacteria
 - Naturally found in animal products like meat, eggs, dairy.
 - Water-soluble
 - Acts as a cofactor for 2 enzymes: Methionine synthase and L-methylmalonyl-CoA mutaste
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- Methionine synthase → converts homocysteine to methionine
 - Supports formation of S-adenosylmethionine (SAM), the body's main methyl donor for DNA, RNA, proteins, and lipids.
 - L-methylmalonyl-CoA mutase → converts methylmalonyl-CoA to succinyl-CoA
 - Important for fatty acid and energy metabolism



VEGAN/VEGETARIAN

- 6% of U.S. adults are vegetarian; ~4% are vegan (numbers vary due to survey limitations). Plant-based diets are more common among younger adults.
- Health is the primary driver for adopting vegetarian, vegan, or plant-based diets; animal welfare also strongly influences food choices.
- Meat substitute growth has plateaued due to food inflation and concerns about ultra-processed foods, while milk alternatives continue to grow.
- Across vegans, vegetarians, and meat-reducers, the central goal is eating healthier, with ethical and environmental concerns as secondary factors.





<https://thefoodschool.com/vegan-vs-vegetarian/>

THE STUDY

- **Purpose** : The primary objective of this research was to determine if a vegan diet is associated with an increased risk of B12 deficiency when compared to vegetarian and omnivore diets.
- **Hypotheses**: Researchers proposed that vegans would show poorer B12 status across a full panel of biomarkers and also aimed to evaluate the impact of B12 supplementation.
- **Independent**: Dietary patterns (vegan, vegetarian, omnivore), and the use of vitamin B12 supplements
- **Dependent**: Biomarkers of B12 status > serum B12, holotranscobalamin (HoloTC), total homocysteine (tHcy), and methylmalonic acid (MMA).

Received: 12 January 2024 | Revised: 23 September 2024 | Accepted: 25 September 2024

DOI: 10.1111/hbu.12712

Nutrition Bulletin 

REVIEW

A systematic review and meta-analysis of functional vitamin B12 status among adult vegans

Ali Niklewicz¹  | Luciana Hannibal² | Martin Warren³ | Kourosh R. Ahmadi¹

¹Department of Nutritional Sciences, School of Biosciences and Medicine, University of Surrey, Guildford, UK

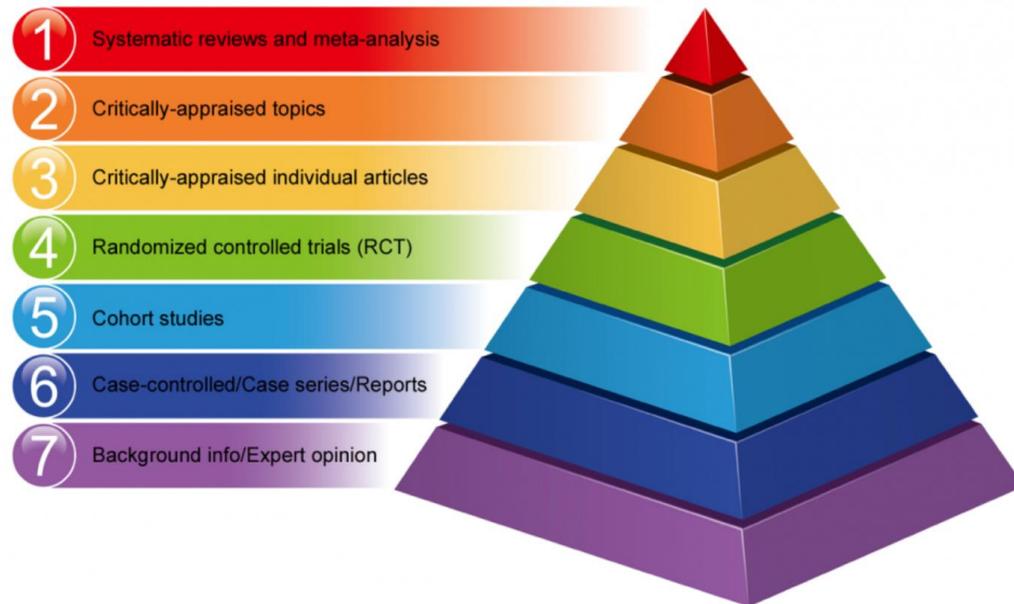
²Laboratory of Clinical Biochemistry and Metabolism, Department of General Paediatrics, Adolescent Medicine and Neonatology, Faculty of Medicine, Medical Centre, University of Freiburg, Freiburg, Germany

³Quadram Institute Bioscience, Norwich Research Park, Norwich, UK

Correspondence

Abstract

The dietary intake of vitamin B12 among unsupplemented vegans is notably lower compared to both vegetarians and omnivores. Prolonged low intakes of vitamin B12, such as seen in those adhering to a vegan diet, lead to physiological deficiency of vitamin B12 and an elevated risk of B12-related morbidity. However, while serum B12 serves as a conventional biomarker for assessing B12 status, its utility is limited given its sensitivity and specificity in ascribing physiological deficiency of B12 and the functional vitamin B12 status of those adhering to vegan diets is unclear. We conducted a systematic review and meta-analysis using data based on the full panel of biomarkers of vitamin B12 status to test whether adherence to a vegan diet is associated with an elevated risk of functional B12 deficiency.



Control/Confounding Variables: The study attempted to control for the effects of supplementation by conducting a specific subgroup analysis of supplemented versus unsupplemented individuals .

Study Design: systematic review and meta-analysis. It involved a comprehensive search of databases (such as PubMed, Scopus, and Web of Science) to find relevant peer-reviewed studies comparing B12 status across different dietary groups.

Study Subjects and Selection : The researchers initially identified 4,002 potential records . After applying inclusion and exclusion criteria, such as requiring adult participants and the measurement of at least one B12 biomarker, **19 studies** were included in the systematic review and **17 studies** were used in the meta-analysis .

METHODS

The researchers focused on four specific biomarkers to measure B12 status:

- **Serum B12:** Total B12 in the blood .
- **HoloTC (Active B12):** The portion of B12 available for cellular use .
- **tHcy and MMA:** Metabolic markers that increase when B12 is deficient, indicating **functional deficiency** . The meta-analysis calculated the **mean difference (MD)** in these markers between the different dietary groups to provide a pooled estimate of the effect .

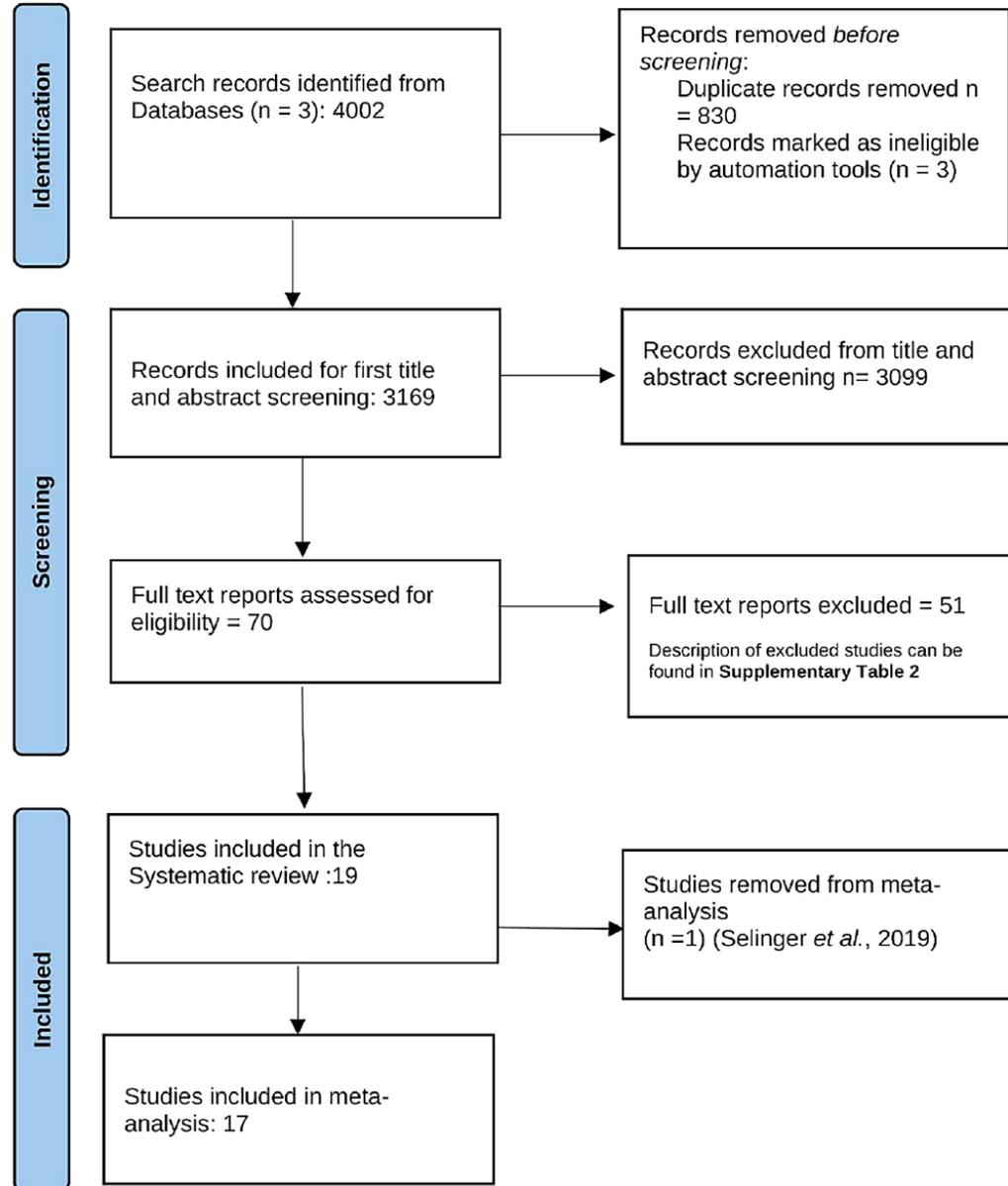
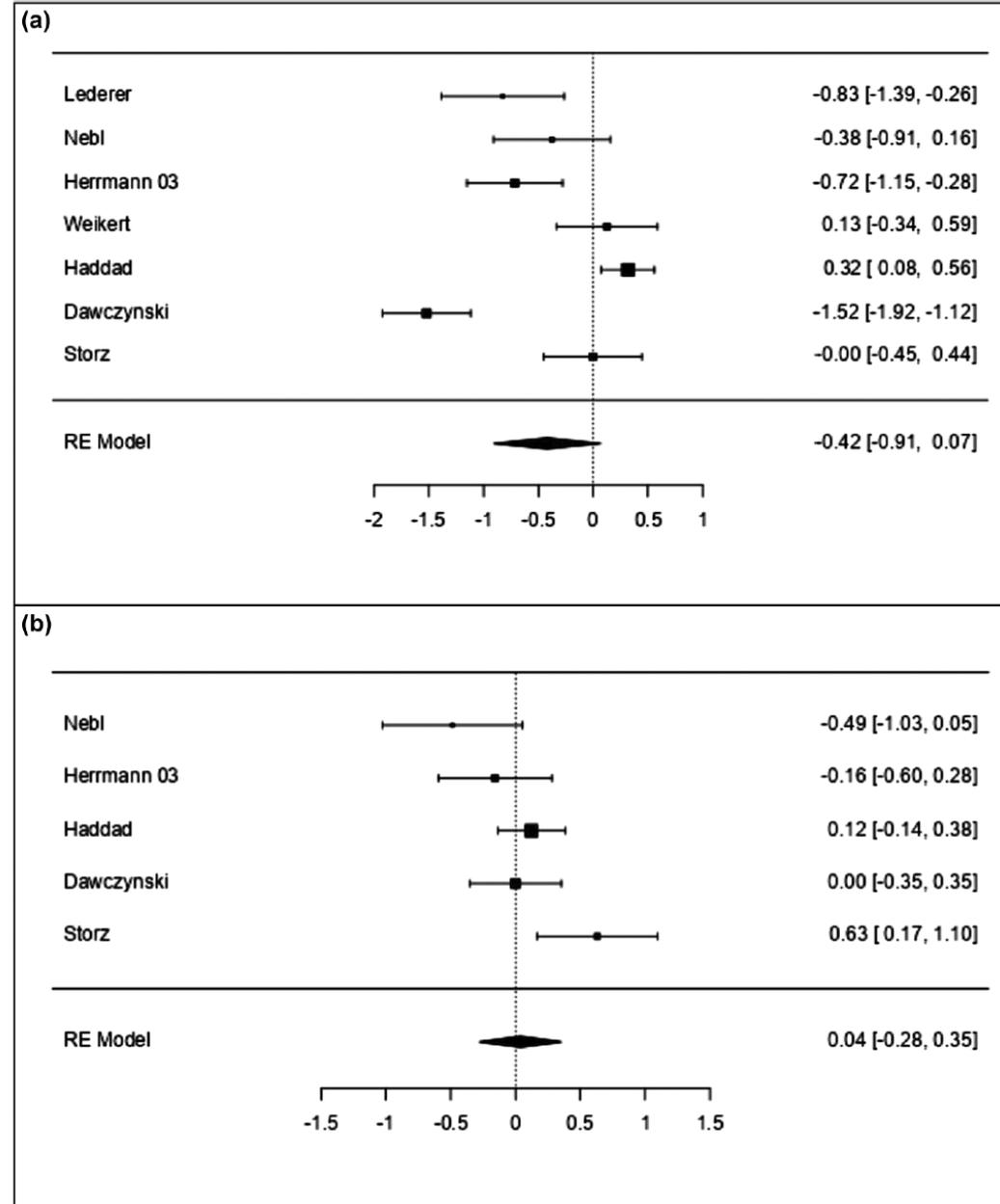


FIGURE 1 Prisma flow diagram of the systematic review and meta-analysis. Prisma flow diagram of the step-by-step process of obtaining the studies used for the systematic review and meta-analysis. An initial 1894 articles were retrieved from three databases: Web of Science, Pubmed and Scopus. Duplicates were removed using the Zotero software. The remaining articles were screened by AN and KA, and discrepancies were resolved through discussion. A total of 17 studies were used in the meta-analysis.

FIGURE 3 Forest plots illustrating the standardised mean difference effect of holotranscobalamin (HoloTC) status using the random-effects model with outliers removed. Subfigures 3a and 3b show the standardised mean difference between the vegans and omnivores ($p=0.093$, $I^2=89.7\%$) and between vegans and vegetarians ($p=0.814$, $I^2=68.8\%$). (a) Comparison of HoloTC status between vegan (left) and omnivorous (right) participants. (b) Comparison of HoloTC status between vegan (left) and vegetarian (right) participants.



Study	Study design	Country	Number of participants <i>n</i>			Mean age	
			VG	OMV	LOV	VG	OMV
Mann 1999	Cross-sectional	Australia	18	18	43	33 (± 7.7)	34.2 (± 9.4)
Krajovica 2000	Case-control	Slovakia	32	59	62	41.5 (1.8)	
Hermann 2001	Case-control	Germany	7	44	34	22	23
Bissoli 2002	Cross-sectional	Italy	31	29	14	45.8 (15.8)	43.8 (17.3)
Herrmann 2003	Case-control	Germany and the Netherlands	29	79	66		
Waldman 2004	Cross-sectional	Germany	86		45	43.8 \pm 15.6	
Majchrzak 2006	Cross-sectional	Austria	42	40	36	30.7 \pm 9.9	38.4 \pm 14.8
Gilsing 2010	Cross-sectional	UK	232	226	231	27.5 (11)	30.5 (10.5)
Elorrine 2016	Case-control	Finland	22	21		33	35
Siebert 2017	RCT	Spain	76			29.4 (± 7.1)	
Gallego- Nabron 2019	Cross-sectional	Spain	54		49		
Lederer 2019	RCT	Germany	26	27		33.2	29.9
Nebi 2019	Cross-sectional	Germany	28	27	26	27.5 \pm 4.24	27.4 \pm 4.0

TABLE 2 Overall mean (SD) values for each biomarker in each of the dietary groups.

Diet group	Serum B12 (pmol/L)			HoloTC (pmol/L)			MMA (nmol/L)			tHcy (μ mol/L)		
	<i>N</i> ^a	Mean	SD	<i>N</i>	Mean	SD	<i>N</i>	Mean	SD	<i>N</i>	Mean	SD
Vegan	17	249.4	87.8	7	62.9	33.9	9	269	263	15	13.4	7.8
Vegetarian	14	252	85.7	5	60.6	36.6	7	213.7	173.2	12	12.5	5.2
Omnivore	13	384.9	109.6	7	75.5	28.6	7	180.5	89.0	11	9.7	3.8
Vegan supplement users ^b	4	276.9	154.1	3	43	30.47	4	340.1	429.2	2	11.4	5.2
Vegan non-supplement users	4	183.9	85.7	3	26	26	4	484.5	678.9	3	14.4	9.8

Note: The data presents the number of studies included for each biomarker to produce a combined mean (SD) concentration. The data show that in general, the vegan group has the lowest serum B12 and holotranscobalamin (HoloTC) concentration and the highest methylmalonic acid (MMA) and total homocysteine (tHcy) compared to vegetarian and omnivorous groups. The vegetarian group has slightly lower Holo-TC concentrations than the vegan group; however, both are in the range of normal B12 status. Vegan supplement users had higher vitamin B12 and HoloTC concentrations and lower MMA and tHcy concentrations than the non-supplement users, based on 4 studies. Values in bold highlight values outside the normal range relating to the primary outcomes for low vitamin B12 status defined as: Serum B12 (<180 pmol/L), HoloTC (<50 pmol/L), tHcy (\geq 13 μ mol/L, and MMA) (>260 nmol/L) in vegan participants.

^aNumber of studies included.

^bIncludes both vitamin B12 supplements or multivitamins containing vitamin B12.

LOV	Total	Sex (female %)			Biomarkers	Duration on a vegan diet	Quality of evidence
		VG	OMV	LOV			
34.9 ± 9		0	0	0	Serum B12, tHcy	Not stated	Poor
		69			Serum B12, tHcy	Not stated	Poor
22		71			Serum B12, MMA, tHcy	Minimum 1 year	Poor
48.5 (14.5)		39	38	57	Serum B12, tHcy	Minimum 5 years	Moderate
	37	55			Serum B12, HoloTC, MMA, tHcy	Minimum 1 year	Poor
44.6 ± 15		59		64	Serum B12, tHcy	Minimum 1 year	Poor
34.2 ± 13.6		50	72	72	Serum B12, tHcy	Among vegetarians and vegans were 67% who had been following diet at least 5 years, 25%–31% 1–5 years and 8%–2% 1 year.	Moderate
27 (9)		0	0	0	Serum B12	38% of vegans on diet <7 years	Good
		73	52		Serum B12, tHcy	The average duration of a vegan diet = is 8.6 years.	Poor
		68			Serum B12, HoloTC, MMA, tHcy	Not stated	Poor
	30.3 (7.7)	78			Serum B12, MMA, THcy	Not stated	Poor
		69	56		Serum B12, HoloTC, MMA, tHcy	4 weeks	Poor
27.6 ± 4.31		64	59	62	Serum B12, HoloTC, MMA, tHcy	0.5-1 year-21% 1-2 years- 14% 2-3 years- 25% >3 years- 39%	Moderate

TABLE 3 Overall effect and heterogeneity of the results with outliers removed. A mean difference analysis for each biomarker was carried out using the SMD (standard mean difference) as the outcome measure. The degree of heterogeneity was estimated using I^2 statistic.

Variables	Overall effect			Heterogeneity			
	SMD [95%, CI]	Z	p	I^2	Tau ²	Std. err.	p
Vegan versus omnivore							
Serum vitamin B12 ^{a,b}	-0.72 [-1.26, -0.18]	-2.60	0.01	93%	0.76	0.37	<0.001
HoloTC	-0.42 [-0.91, 0.07]	-1.68	0.09	89.7%	0.384	0.25	<0.001
MMA	0.28 [-0.01, 0.57]	1.90	0.06	70.7%	0.113	0.09	0.003
HCY	0.57 [0.26, 0.89]	3.57	<0.001	81.74%	0.238	0.13	<0.001
Vegan versus vegetarian							
Serum vitamin B12 ^{a,b,c}	-0.25 [-0.40, -0.10]	-3.27	0.001	31.8%	0.02	0.03	0.16
HoloTC ^c	0.04 [-0.28, 0.35]	0.236	0.81	68.8%	0.09	0.09	0.03
MMA	-0.05 [-0.29, 0.20]	-0.38	0.71	66.05%	0.07	0.06	0.01
HCY	0.24 [0.09, 0.39]	3.09	0.002	41.78%	0.03	0.03	0.05
Supplemented vegan versus non supplemented vegan							
Serum vitamin B12	0.73 [0.39, 1.09]	4.16	0.001	16%	0.021	0.104	0.38
HoloTC	0.49 [0.13, 0.85]	2.64	0.01	0	0	0.112	0.61
MMA	-0.33 [-0.64, -0.03]	-2.14	0.03	0%	0	0.081	0.75
tHcy	-0.41 [-0.87, 0.05]	-1.76	0.08	42%	0.069	0.164	0.18

Note: Significant *p*-values are identified in bold. Results were considered significant with a *p* < 0.05. Degree of heterogeneity based on the I^2 statistics was classified as (i) non important if <25%, (ii) moderate if 25–50, (iii) substantial if 51–75 and, (iv) considerable if >75%.

Abbreviations: HCY, homocysteine; Hcy, total homocysteine; HoloTC, holotranscobalamin; MMA, methylmalonic acid.

^aStudy Krajovika removed as outlier.

^bStudy Gislign removed as outlier.

^cStudy Storz removed as outlier.

KEY FINDINGS

- **Lower B12 status vs. omnivores:** Vegans have significantly lower serum B12 and higher homocysteine levels, indicating functional deficiency.
- **More affected than vegetarians:** Vegans show lower serum B12 and higher homocysteine than vegetarians, though MMA and HoloTC are similar.
- **Supplementation is critical:** B12 supplementation significantly improves all B12 biomarkers in vegans.
- **Functional markers matter:** Serum B12 alone may miss deficiency; homocysteine and MMA reveal hidden insufficiency.



CONCLUSION

Adhering to a vegan diet is associated with an elevated risk of functional vitamin B12 deficiency compared to omnivorous or vegetarian diets (Niklewicz).

Limitation: Standard serum B12 tests often fail to capture true physiological status; a full panel including functional biomarkers (tHcy, MMA, HoloTC) is necessary for accurate assessment

Key comparisons: Vegans vs. Omnivores: Significantly lower serum B12 and higher total homocysteine (tHcy) (Niklewicz).

Vegans vs. Vegetarians: Vegans exhibit poorer B12 status and higher metabolic deficiency markers

Primary Intervention: B12 supplementation is highly effective, leading to significant improvements across all status biomarkers in vegans.

Public Health Priority: Targeted strategies and clear supplementation guidelines are critical, especially for women of childbearing age

LIMITATIONS

- **Methodological heterogeneity:** Study-level data, varied assays, and assumptions converting medians to means may affect accuracy.
- **Limited study pool & publication bias:** Few included studies (17–19) and funnel plots suggest possible overestimation of effects.
- **Risk of bias:** Most studies rated moderate–poor quality with inadequate control for confounders.
- **Restricted generalisability:** Participants were Caucasian adults; older adults and other populations were excluded.
- **Population gaps:** Vegan diet duration not accounted for; no data on pregnant or lactating vegan women.

FOLLOW-UP STUDY

Optimal Vitamin B12 Dosing for Pregnant Vegan Women: A Randomized Controlled Trial.

The purpose of this study is to determine the optimal daily dose of oral vitamin B12 (cyanocobalamin) required to maintain functional B12 adequacy throughout pregnancy in vegan women. Currently, there is a lack of expert consensus on effective dosing for this high-risk group (Brady, 2017).

Hypothesis: A higher daily dose (e.g., 100 μg) will be significantly more effective at preventing functional deficiency (as indicated by elevated MMA and tHcy) in the third trimester than the standard recommended daily allowance (RDA) of approximately 4.5 μg .

Study Design: double-blind, randomized controlled trial (RCT). This design is a significant step forward from the predominantly observational studies (cross-sectional and case-control) analyzed previously.

Subjects: healthy pregnant women in their first trimester who adhere to a strict vegan diet for at least two years. 150 participants randomized into 3 groups of 50. Recruitment through prenatal clinics and plant-based organizations. Exclusion criteria include pre-existing renal ds. Or medications that interfere with B12 absorption.

Methods: 3 different daily oral doses (independent variable) on the full panel of B12 biomarkers (dependent variable). Data collection: Supplement compliance will be tracked via digital pill-bottle caps. Dietary B12 intake from fortified foods will be monitored using monthly 3-day weighed food records to control for confounding dietary sources

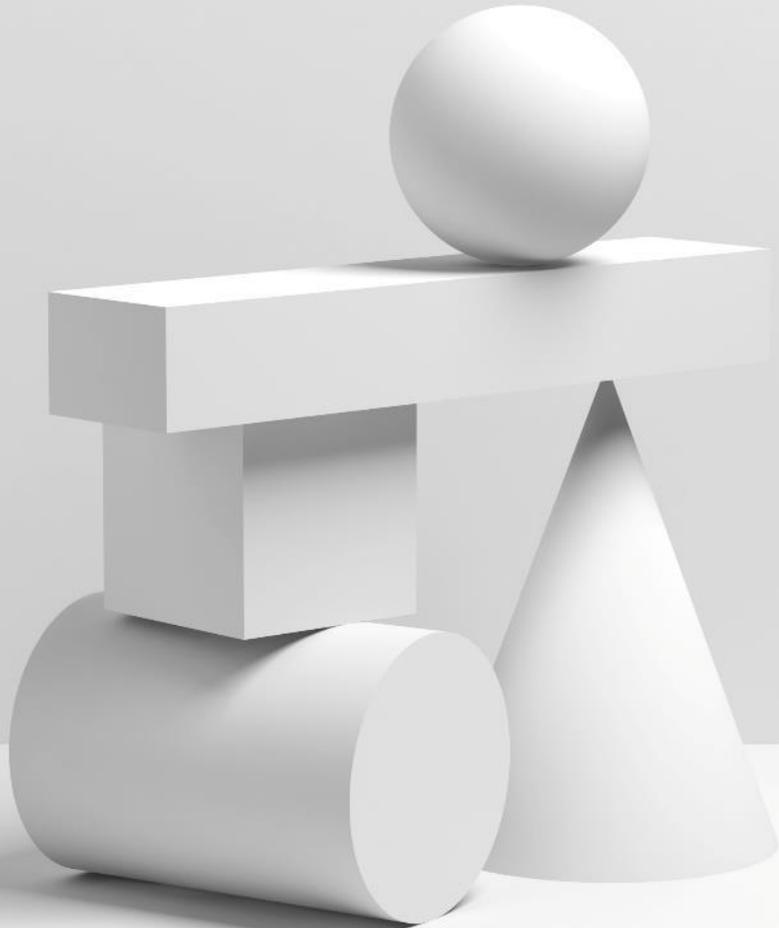
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Q & A

Panel discussion session