Vitamin B₁₂ is an essential water soluble micronutrient found substantially in non vegetarian sources. It serves as a cofactor for two enzymes, cystolic methionine synthase and mitochondrial methylmalonyl CoA mutase. Methylcobalamin is required for synthesis of methionine from homocysteine catalyzed by the enzyme methionine synthase. This reaction regenerates tetrahydrofolate from methyl tetrahydrofolate, which is essential for nucleic acid synthesis. Additionally, adenosylcobalamin is a vitamin B₁₂ cofactor of methylmalonyl-CoA mutase, that converts methylmalonyl-CoA to succinyl-CoA, an anaplerotic reaction that feeds in succinyl-CoA to citric acid cycle and for synthesis of heme (1). Therefore, vitamin B₁₂ is particularly important in cellular metabolism, via its role in methylation processes involving DNA synthesis and energy production in the mitochondria (2). It is also the building block of cell membrane and myelin sheath protecting the nerves, which if altered affects the correct nerve transmission (3). Thus, the clinical manifestations of vitamin B₁₂ deficiency are heterogenous, including neuropathy (autonomic dizziness on standing, peripheral-absent reflexes, diminished vibration or soft touch sensation, tingling sensation of limbs or limb weakness), cognitive deficits (dementia and or other psychiatric symptoms) and hematological disorder, involving increased mean corpuscular red cell volume and anemia due to alteration in erythropoiesis (3, 4). The role of vitamin B₁₂ deficiency in hyperhomocysteinemia and the promotion of atherosclerosis have also been substantiated (4). Therefore, inadequate vitamin B₁₂ intake and deficiency can lead to serious clinical consequences.

In India, vitamin B₁₂ deficiency is a common nutritional problem, owing to dietary limitation to a strict vegan diet and often unrecognised due to subtle clinical manifestations. Moreover, malabsorption due to gastric atrophy (5), ileal disease, pernicious anaemia, nutrient-drug interactions and infections involving parasite and Helicobacter pylori also predispose human beings to vitamin B₁₂ deficiency (6). Epidemiologic data shows that prevalence of vitamin B₁₂ deficiency ranges between 25% to almost 86% among children, 21–41% among adolescents, and 11–90% among the elderly (7). With more than 50% of population across all age groups (51.1%, 56.2% and 61.7% for children, young adults and elderly respectively) reported to have low serum/plasma vitamin B₁₂ levels (5, 8), deficiency of vitamin B₁₂ is an issue of public health concern in India. Furthermore, with a host of factors affecting the intake and absorption of Vitamin B₁₂ an early diagnosis and treatment of vitamin B₁₂ deficiency is essential.

Although substantial data has been published emphasizing on the contribution of vitamin B₁₂ towards clinical manifestations and metabolic disorders, there is no national data regarding the extent of vitamin B₁₂ deficiency among Indian population. This review aims to summarise the limited data on the vitamin B₁₂ levels in Indian population with respect to age, gender and
dietary habits. Additionally, the purpose of this review is to determine if there is sufficient data to ascertain the national prevalence of vitamin B12 deficiency, and thus their potential public health importance.

**MATERIALS AND METHODS**

A systematic literature search was carried out using PubMed for selected peer reviewed articles in English from 2000 to 2019. To identify relevant literature, a title search using combinations of the following key words was used, ‘vitamin B12 prevalence’, ‘healthy Indians’, ‘vitamin B12 deficiency’, ‘cobalamin status’, ‘vitamin B12 status and India.’ Following the literature search, the titles and abstracts of the manuscripts were screened to assess the eligibility of identified studies. Inclusion criteria consisted of studies that assessed serum vitamin B12 concentration in apparently healthy Indian adult and elderly population. Case control studies, case reports, randomised control trials, reviews and meta-analysis were excluded. Figure 1 shows the flow chart of the selection process. The literature search yielded 771 articles. A total of 14 studies that matched the selection criteria were included in the review. Vitamin B12 level was expressed in pmol/L in this review and any values expressed in pg/mL was converted to pmol/L, using the conversion factor of 0.738 (9).

**RESULT**

Table 1 lists vitamin B12 status of Indian adult and elderly population. The data covers several states, including Pune, Bangalore, Tamil Nadu, Hyderabad, Delhi and Lucknow, with most of studies from West and South India. All the studies reviewed included the assessment of serum/plasma vitamin B12 levels. From these, 9 reported serum/plasma Homocysteine (Hcy) levels and only 2 reported Methylmalonic Acid (MMA) levels as biomarkers for assessing vitamin B12. Various forms of Immunoassay involving chemiluminescence, electro chemiluminescence, radio immunoassay and ELISA were used to measure plasma/serum vitamin B12 levels. The threshold used to define normal from deficient values for the blood concentration of vitamin B12 differ widely. However, Institute of Medicine (1998) (10) recommended 120–180 pmol/L (170 to 250 pg/mL) plasma vitamin B12 as a depletion range, which may vary with the assay method used. Since no standard threshold exists, various researcher-defined cut offs were used to define vitamin B12 deficiency, ranging from <138 pmol/L (11) to <156 pmol/L (12). Most of the authors reported mean or median values of vitamin B12 and homocysteine levels. Such a disparity in the laboratory methods used for assessment, low specificity of available biomarkers of vitamin B12 levels and no consensus regarding the cuts offs used to define low vitamin B12 status, makes it difficult to draw conclusions on the prevalence of vitamin B12 deficiency. However, this review does indicate the extent of vitamin B12 deficiency in adult and elderly population in India.

**Vitamin B12 and age**

Due to wide age ranges used in the studies exclusion
| AUTHOR, YEAR | LOCATION | PARTICIPANTS (n, SEX) | ASSAY METHOD | % DEFICIENCY (Cut off for Vitamin B12 Deficiency) | DIETARY HABIT | MEAN (SD) | MEAN (SD) Hcy (µmol/L) | MEAN (SD) MMA (µmol/L) |
|--------------|----------|-----------------------|--------------|-----------------------------------------------|---------------|-----------|------------------------|------------------------|
| Sucharita et al, 2013 (8) | Bangalore | 14 (M) 19–34 y<sup>a</sup> <br> 24.0 (6.0) | Chemiluminescent Immuno assay | 78.5% (<148 pmol/L) | All non-vegetarian (% not mentioned) | 130.5 (34.9) | 13.4 (8.0) | 0.45 (0.17) |
| Agrawal et al, 2015 (13) | Tamil Nadu And Uttar Pradesh | 639 (M/F) 20–35 y: 81 <br> 36–45 y: 122 <br> 46–55 y: 176 <br> 56–65 y: 168 <br> 66–75 y: 92 | ELISA | — | — | 20–35 y: 9.11 (2.74) | 20–35 y: 9.62 (1.93) |
| Sucharita et al, 2016 (5) | Bangalore | 20–40 y: 32 (M) 21.0 (2.0) <br> >60 y: 47 (M: 18, F: 29) 65.0 (7.0) | Chemiluminescent Assay | 20–40 y: 56.2% (<148 pmol/L) | Mostly non-vegetarian, but less frequently consumed | 20–40 y: 150.7 (62.3) | >60 y: 175.4 (180.5) | — |
| Haroon et al, 2012 (19) | Lucknow | 151 (M: 51, F: 100) 20–40 y: 26 (5.0) <br> M: 26 (4.0) <br> F: 26 (5.0) | Radio Immuno Assay | T: 71% M: 75% F: 76% (<148 pmol/L) | Vegetarian: 77% <br> M (veg): 71% <br> F (veg): 81% | T: 103.3 (53.1, 169.7)<sup>bc</sup> (n=131) <br> M: 103.3 (53.1) <br> F: 103.3 (53.1, 167.7)<sup>bc</sup> | T: 18 (14.3, 22.5)<sup>bc</sup> (n=131) <br> M: 18 (14.3) <br> F: 16 (13.25)<sup>bc</sup> | 68% <br> M: 90% <br> F: 60% (<150 µmol/L) |
| Sivaprasad et al, 2016 (16) | Hyderabad and Telangana | 630 (M/F) 21–40 y: 240 <br> 41–60 y: 184 <br> >60 y: 206 | Radio Immuno Assay | T: 33.7% 21–40 y: 44.6% <br> 41–60 y: 38.7% <br> >60 y: 27.9% | — | 21–40 y: 190.4 (7.9)<sup>a</sup> (n=89) | 21–40 y: 17.4 (1.3) (n=89) |

Table 1. Vitamin B<sub>12</sub> status in adults and elderly Indian population (8).
| AUTHOR, YEAR | LOCATION | PARTICIPANTS (n, SEX) | ASSAY METHOD | % DEFICIENCY | DIETARY HABIT | MEAN (SD) | MEAN (SD) Hcy (μmol/L) | MEAN (SD) MMA (μmol/L) |
|--------------|----------|-----------------------|--------------|--------------|--------------|-----------|------------------------|------------------------|
| Shalini et al, 2018 | Hyderabad and Telangana | 300 (M: 144, F: 156) | Radio Immuno Assay | T: 35.5% | vegetarian: 24.3% | T: 235.2 (10.0) | — | — |
| | | 21–40 y: 101 | 21–40: 41.2% | M: 29.0 (25.5, 33.3) | M: 22.6 (13.9, 52.0) |
| | | 41–60 y: 104 | 41–60: 39.4% | F: 28.2 (27, 32.5) | F: 14.2 (9.9, 24.4) |
| | | >60 y: 95 | >60: 23.4% | M: 45.7% | M: 92% |
| Naik et al, 2018 | Pune | 119 (M: 46, F: 73) | Immuno assay | M: 77% | vegetarian: 100% | M: 146 (84, 244) | — | — |
| | | M: 29.0 (25.5, 33.3) | M: 22.6 (13.9, 52.0) | F: 28.2 (27, 32.5) | F: 14.2 (9.9, 24.4) |
| | | F: 50% | F: 50% | F: 164 (100, 288) | F: 164 (100, 288) |
| | | (<150 pmol/L) | (<150 pmol/L) | (148 pmol/L) | (148 pmol/L) |
| Refsum et al, 2001 | Pune | 63 (M/F) | Micro Biological Assay | 46% | Vegetarian: 27% | 160d | 19,7d | 0.40d |
| | | 44d | (<150 pmol/L) | (<150 pmol/L) | (>15,0 μmol/L) |
| | | | | | (138 pmol/L) |
| Yajnik et al, 2006 | Pune | 441 (M) | Radio Immune Assay | T: 67% | R (veg): 41% | R: 119 (73, 171) | — | — |
| | | (R: 149, S: 142, U: 150) | R: 68% | S (veg): 11% | S: 145 (90, 241) |
| | | 30–50 y | U: 81% | U (veg): 44% | U: 89 (58, 133) |
| | | R: 37 (34, 43) | U: 81% | (<150 pmol/L) | (<150 pmol/L) |
| | | S: 36 (33, 42) | U: 81% | (<150 pmol/L) | (<150 pmol/L) |
| | | U: 41 (36, 46) | U: 81% | (<150 pmol/L) | (<150 pmol/L) |
| | | | | | (138 pmol/L) |
| Ingole et al, 2015 | Pune | 84 (M: 55, F: 29) | Standard laboratory method | 33.3% | Veg: 47.5% | — | — | — |
| | | 32.3d | HIG: 31.2% | Non veg: 20.4% | MIG: 27.0% |
| | | | | | LIG: 71.4% |

Table 1. (Continued)
| AUTHOR, YEAR   | LOCATION | PARTICIPANTS (n, SEX) | MEAN (SD) | DIETARY HABIT   | % DEFICIENCY | MEAN (SD) Hcy (μmol/L) | MEAN (SD) MMA (μmol/L) |
|---------------|----------|-----------------------|-----------|-----------------|--------------|------------------------|------------------------|
| Naik et al, 2011 (18) | Pune | 587 (M: 441, F: 146) | M: 38.0 (34.0, 44.0) | F: 34.0 (29.0, 39.0) | Radio Immuno Assay | M: 67.0% F: 60.9% (<150 pmol/L) | M (veg): 33% F (veg): 37% | — |
| Gupta et al, 2016 (12) | Western India | 250 (M: 140, F: 110) | 48.5 | Electro Chemi Luminescence | 28% | M: 35.7% F: 18.2% | vegetarian: 78.8% mixed diet: 21.2% | — |
| Mittal et al, 2017 (20) | Delhi | 100 (F) | Mean age: Not given | Chemi Luminescence immune assay method | 46% | M: 35.2% F: 18.8% (<148 pmol/L) | vegetarian: 29% non vegetarian: 71% | 159.4 (117.7, 205.5)bc |
| Shobha et al, 2011 (15) | Bangalore | 175 (M: 91, F: 84) | 66.3 (6.8) | Electro Chemi luminescence method | T: 16% M: 22% F: 9.5% | M: 35.2% F: 18.8% (<148 pmol/L) | vegetarian: 57% non vegetarian: 76% | 306.9 (180.9, 598.8)bc |

Table 1. (Continued)
of adult and elderly population became difficult, therefore, data on vitamin B12 status in adults and elderly could not be tabulated separately. The age ranges included in Table 1 are from 19 to 75 y with most authors reporting either age range or mean age. The mean vitamin B12 levels reported were between 130.5 (34.9) pmol/L (8) and 272.2 (39.2) pmol/L (13) in adults: 142.7 (32.3) pmol/L (13) and 269.4 (12.0) pmol/L (14) in elderly. Considerable heterogeneity was reported in the proportion of adults and elderly deficient in Vitamin B12 (33.3% (11) vs 78.5% (8) and 16.1% (15) vs 61.7% (5) in adult and elderly, respectively). The proportion of participants deficient or sufficient in plasma/serum vitamin B12 levels were reported on the basis of different cutoffs and thus no comparisons could be made. However, an increasing trend in the homocysteine level with age was reported irrespective of demographic characteristics, which is known to increase with age (13).

**Vitamin B12 and gender**

Vitamin B12 deficiency varied by sex across several studies, with higher prevalence of vitamin B12 deficiency in men than women (44% vs 29% (16), 45.7% vs 26.4% (14), 77% vs 50% (12, 15, 17, 18) respectively. Females had higher mean and median plasma vitamin B12 levels as compared to males (14, 17–19). Moreover, women had lower plasma homocysteine levels than men. Thus, reporting lower prevalence of hyperhomocysteinemia (60% vs 90% (19), 50% vs 92% (17), 3.6% vs 20.9% (15) when compared to men. Interestingly, an inverse relation of plasma homocysteine to vitamin B12 levels was reported in both gender (17–19) suggesting to role of B12 in homocysteine metabolism, where an insufficient supply of vitamin B12 impairs cellular processing leading to accumulation of homocysteine, which then enters circulation resulting in hyperhomocysteinemia (I).

**Vitamin B12 and diet**

Use of vitamin B12 supplements was either absent or not reported in majority of the studies. Only 1 study reported consumption of vitamin B12 supplements by 35% of the elderly (15). Most of the studies defined vegetarians inclusive of lactovegetarian and mixed diet including ovo vegetarian and non vegetarian (12, 16, 18, 20). Due to diverse religions, ethnic, and socioeconomic heterogeneity, the percentage of population following a vegetarian diet ranged from 11% (21) to 100% (17). Vitamin B12 deficiency was higher in vegetarian (54% vs 31% (16), 47.5% vs 20.4% (11), 72.4% vs 35.2% (12, 15, 19)) than those on a mixed or non vegetarian diet irrespective of demographic characteristics, age or type of vegetarian diet, indicating that dietary vitamin B12 deficiency is a severe problem in Indian population. However, in study population with more than 70% participants following a mixed or non-vegetarian diet, the proportion of vitamin B12 deficiency varied from 11.8% (15) to 78.5% (8), based on varying cut offs. Therefore, inspite of following a non vegetarian diet, low frequency of consumption of non vegetarian foods have been reported in Indian population (5, 22).

**DISCUSSION**

Vitamin B12 plays an important role in DNA synthesis and cellular energy production (23). Its deficiency is associated with hematologic, neurologic and psychiatric manifestation (4). With several health implications associated with vitamin B12 deficiency and homocysteinemia has increasingly linked to vascular disease, leading to atherosclerosis and cardiovascular morbidity (24) there is a need to draw attention towards vitamin B12 status among populations. This review, therefore, is conducted to determine vitamin B12 status either assessed by mean or median serum/plasma vitamin B12 or proportion deficiency based on varied cutoffs. In the absence of an accepted definition of vitamin B12 deficiency, a comparison of deficiency prevalence was cumbersome considering the wide range of vitamin B12 values defined by authors as indicative of Vitamin B12 deficiency. Role of metabolites related to vitamin B12 activity such as homocysteine (Hcy) and methylmalonic acid (MMA), which are more sensitive markers of vitamin B12 deficiency at a tissue level (8) makes interpretation of vitamin B12 status more challenging. However, this review is indicative of the extent of vitamin B12 deficiency among adults and elderly in India.

It is observed that vitamin B12 status is influenced by gender and dietary habits in the studied population. The difference in vitamin B12 status between Indian males and females have been reported by several authors, with higher vitamin B12 levels in females than males (16, 18, 25). Similar sex differences in the vitamin B12 and homocysteine levels have been observed worldwide (25–27). Hyperhomocysteinemia is more common among males than females presumably due to larger muscle mass and greater creatine phosphate synthesis in men (28), lowering effect of estrogens in women (29) and differences in vitamin status (30) and homocysteine formation between sexes (25, 28). High prevalence of poor vitamin B12 status as reported may also be attributed to a combination of factors related to vegetarianism due to religious and cultural beliefs and low purchasing power of the people (8). The main source of dietary vitamin B12 is animal food. In India, diets are very low in vitamin B12 since the animal protein in the diet mainly comes from the milk, occasional eggs and very rarely meat (16). Apart from nutritional deficiency, inherited or acquired defects inhibit B12 absorption which enhance the vitamin B12 deficiency. These include parasitic and helicobacter pylori infection, tropical sprue, lack of intrinsic factor and malabsorption syndrome caused by gastrointestinal malfunction (5, 31).

Altogether, this review demonstrates the problem of low levels of plasma/serum vitamin B12 in Indian population, emphasizing the need for more research based cut offs values and assessment of vitamin B12 status. The issue of adequate vitamin B12 intake and status should be taken up by public health policy makers and stakeholders to identify conditions that predispose to vitamin B12 deficiency and plan strategies involving for-
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tification and supplementation to prevent vitamin B12 deficiency.

Limitation

This review was based on studies that used serum vitamin B12 deficiency as marker of vitamin B12 status. Serum vitamin B12 in combination with other biomarkers such as methylmalonic acid or homocysteine is a better indicator of the prevalence of deficiency. However, many studies have not reported methylmalonic acid or homocysteine levels. Secondly, the different cut-offs used to define deficiency, variety in the laboratory methods used for assessment of plasma vitamin B12 levels and the heterogeneity in results make it very difficult to draw clear conclusions on the extent of vitamin B12 deficiency in Indian population. Lastly, most of the studies are conducted in western and southern India. India is a country with diverse culture and dietary habits. Therefore, more literature is required from other parts of the country to draw clearer conclusions.

Disclosure of state of COI

The authors declare no conflict of interest.

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