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Randomized Control Trials

The effect of vitamin B12-supplementation on actigraphy measured sleep pattern; a randomized control trial

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SUMMARY

Background: Vitamin B12 deficiency is common worldwide and has been associated with poor sleep. The effect of vitamin B12 supplementation on sleep in infants is not known.
Aims: To measure the effect of daily supplementation of vitamin B12 for one year on sleep in infants at risk of deficiency.
Methods: This was an individually randomized double-blind placebo-controlled trial in 600 infants in low-to middle-income neighborhoods in Bhaktapur, Nepal of daily supplementation of vitamin B12 for one year. Infants were included if they were 6–11 month year-old and with a length-for-age less than one z-score. Sleep was a predefined, secondary outcome, and was measured by actigraphy including sleep duration at night and total sleep duration (day and night), sleep onset latency (SOL), and wake after sleep onset (WASO). The effect of vitamin B12 on sleep was additionally assessed in predefined subgroups defined by stunting, underweight, vitamin B12 status, low birthweight, anemia and exclusive breastfeeding for 3 months.
Results: There was no effect of vitamin B12 supplementation on sleep duration at night, total sleep duration, or WASO. There was a small significant negative effect for SOL. None of the included subgroup analyses revealed effect modification on any of the sleep outcomes.
Conclusion: Overall, vitamin B12 supplementation did not have an effect on sleep in infants or for high-risk subgroups, with the exception of a small negative effect for SOL. The present study does not support vitamin B12 supplementation to improve sleep in infants.
Trial registration: clinicaltrials.gov: NCT02272842.
Universal trial number: U1111-1161-5187.

1. Introduction

Sleep is a key domain of development during the first years of life and fundamental for the physical, cognitive and emotional development of infants and children [1–3]. Known risk factors for sleep problems in children span from genetic factors [4] to parental behavior, as well as cultural influences [5–7]. Lately, the impact of nutrition on sleep has received increased attention. While an association between poor sleep and poor diet in young children has been suggested, the studies are mainly based on subjective reports of sleep and/or diet [8]. Although the evidence base is scarce and conflicting, there is support for a relationship between the concentration of specific circulating nutrients and sleep as indicated in a recent systematic review [9].

Vitamin B12 deficiency is common in South Asia and other low- and middle-income regions with low consumption of meat, animal milk, and fish [10,11]. Vitamin B12 deficiency has been associated

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with sleep problems such as short sleep duration and insomnia in adults [12,13]. The systematic review mentioned above, was not able to reveal any consistent association between vitamin B12 and sleep [9]. Possible biological pathways from vitamin B12 deficiency to sleep problems could be through the suggested link with neurodevelopment and *vice versa* [14,15]. Vitamin B12 is also involved in melatonin synthesis which is a key hormone in sleep regulation, and this may be another possible mechanism linking vitamin B12 to sleep [16].

To our knowledge and based on the recent review on the literature [8], there are no RCTs on the effect of vitamin B12 on sleep. The aim of the present study was to assess the effect of daily supplementation of vitamin B12 for one year in marginally stunted Nepalese infants on sleep parameters including sleep duration, sleep onset latency and wake after sleep onset.

2. Methods and study design

Details on the background and study design have previously been published [17], and the study is registered at Clinicaltrials.com (NCT02272842). The main outcomes of the study were neurodevelopment, growth and hemoglobin concentration [18]. Sleep was a pre-defined secondary outcome [17].

The study was conducted from April 2015 until February 2018 and enrolled 600 infants 6–11 months old with a length-for-age less than one z-score. Infants with acute illness, severe systemic illness requiring hospitalization, severe malnutrition (weight for length z-score <−3), who had ongoing infections that required medical treatment, or were taking B vitamins at the time of enrollment were not included. In cases of severe malnutrition, anemia, or infections, children received treatment and were screened again for eligibility after recovery.

We randomized the infants in a 1:1 ratio in blocks of 8 using a computer-generated randomization list. Randomization was concealed, and the study double−masked as the participants were only linked to the intervention through the identity number printed on the supplement labels. The list that linked this identity number to the randomization code was kept with the producers of the supplements and the independent scientist who generated it. None of the investigators had access to this list until the data collection and cleaning for the primary outcomes were completed.

2.1. Intervention and co-interventions

All infants received daily oral supplements for 12 months with either 2 μg vitamin B12 (cyanocobalamin) (equal to approximately 2–3 recommended daily allowances (RDA)), or placebo. The vitamin B12 supplements and placebo were produced specifically for the trial and were identical in taste and appearance. The supplements were packed as sachets containing 20 g of a lipid-based paste produced by GC Rieber−Compact (http://www.gcrieber-compact.com/). To ensure that the effect of vitamin B12 was not limited by inadequate intake of other essential nutrients, both the placebo and vitamin B12 paste contained a base multi-micronutrient mixture with several other vitamins and minerals at approximately 1 RDA. Infants who developed diarrhea during the intervention period received zinc and oral rehydration solution. Those with moderate anemia (Hemoglobin 7–10 g/dL) were treated with peroral iron for at least 30 days. Infants with pneumonia, dysentery, or other illnesses were treated according to the most recent Integrated Management of Childhood Illness (IMCI) guidelines [19]. We found no adverse effects of vitamin B12 supplementation [18].

During weekly visits to the homes, mothers were asked about intake of the paste during the past 7 days. Fieldworker recorded the amount of paste given to the infants in detail (i.e., half, 1/3rd, 3/4th, or less), and counted the total number of empty paste sachets to verify the reported compliance.

2.2. Compliance

More than 94% of the prescribed doses were reportedly taken (94.3% in the vitamin B12 group and 94.0% in the placebo group). Of these, 86.3% and 84.7% of the vitamin B12 and placebo group, respectively, consumed the entire, prescribed doses.

2.3. Study setting

The study was conducted in Nepal, one of the worlds least developed countries, ranked as 143 of 189 countries on the Human Development Index. More specifically, the study was conducted in Bhaktapur municipality and surrounding peri-urban communities near the capital Kathmandu. Bhaktapur is one of the most densely populated municipalities in Nepal.

2.4. Background variables and subgroups

Socio-demographic information was collected at enrolment through interview. We used a composite WAMI index to indicate socio-economic status, using variables for water and sanitation access, household wealth (assets), and maternal education Psaki, Seidman [20]. Weight was measured with a portable electronic scale that measures to the nearest 0.01 kg, and length according to standard guidelines using an infantometers reading to the nearest mm. Weight-for-age, weight-for-length, and length-for-age z-scores were calculated using the WHO Child Growth Standards [21]. Underweight, stunting, and wasting were defined as z-scores below −2.

An infant was exclusively breastfed if it did not receive any other foods or drinks other than breastmilk (WHO). We dichotomized exclusive breastfeeding at three months or more. Low birthweight was defined as birthweight less than 2500 g. Anemia was defined as hemoglobin concentration <11 g/dL. A combined vitamin B12 indicator, namely 3cB12, was calculated according to the formula suggested by [22].

Sleep outcomes

Sleep/wake data was recorded using Philips Respironics Actiwatch 2 (Murrysville, PA). The device was placed on the infants' arm for 4 days and nights for baseline and end study. Parents received demonstrations and instructions by fieldworkers, including information to push the event button when their infant was put to sleep. The fieldworkers visited the families in their homes and checked if the actiwatch was applied properly or if there were any problems or concerns. On the 4th day of home visit, field workers removed the device and handed it over to the data manager who retrieved the data after checking the quality of the graph and other information. In case of a poor−quality graph or inadequate capture of sleep duration, the recording was repeated.

Actigraph data was further analyzed using Philips Actiware software, version 6.0.9. The scoring for sleep-wake counts is accomplished with the standard Actiware algorithm, a proprietary algorithm, which is a combination of a rule-based classification layer and a discriminant function analysis to predict the designation of an epoch as sleep or wake with some modifications: Epoch length for data collection was set to 30 s. Wake threshold setting was set to "High", with an activity count of 80. Sleep intervals were computed automatically, with sleep onset after 10 consecutive minutes below wake threshold value. Fragmented sleep intervals between 20:00–06:00 were merged. Minor

Table 1
Baseline characteristics in a study investigating the effect of daily vitamin B12 supplementation on neurodevelopment and growth in 600 Nepalese infants.

	Vitamin B12 group ($n = 300$)		Placebo group ($n = 300$)	
	n	%	*n*	%
Infant characteristics				
Mean age of infant (months), mean ± SD	8.1 ± 1.7		8.0 ± 1.8	
Male infant	158	53	151	50
Low birth weight (<2500 g)[a]	56	19	59	20
Demographic features				
Mother's age, mean ± SD	27.1 ± 4.7		27.5 ± 4.6	
Father's age[b], mean ± SD	30.0 ± 7.1		30.6 ± 5.1	
Mothers who completed secondary school or above	197	65.7	180	60
Fathers who completed secondary school or above	199	66.3	189	63
Mothers who work	117	39.0	110	36.7
Fathers who work	286	95.3	280	93.3
Socio-economic status				
Family staying in joint family	143	47.7	149	49.7
Family residing in rented house	152	50.7	139	46.3
Number of rooms in use by the household (≤2)	163	54.3	174	58
Kitchen and bedroom in same room	148	49.3	150	50
Family having own land	138	46	144	48
Receiving remittance from abroad	30	10	27	9
Breastfeeding status				
Exclusive breastfeeding for 3 months or more	143	47.7	137	45.6
Nutritional status of infants				
Underweight (weight for age z-score ≤2)	62	20.7	50	16.6
Stunting (length for age z-score ≤2)	96	32.1	98	32.7
Wasting (weight for length z-score ≤2)				
Hemoglobin, g/dL, mean ± SD	10.6 ± .96		10.6 ± .91	
Anemia (hemoglobin <11 g/dL)	183	61	202	67.3
Sleep status in infants at baseline (actigraphy)				
Sleep duration night (mean hour: minutes, SD)	8:34	0:54	8:38	0:53
Sleep onset latency (mean, minutes: seconds, SD)	13:05	8:69	13:07	8:67
Wake after sleep onset (mean minutes, SD)	46:04	18:87	45:61	18:69

n: Number.
[a] Among 579 infants whose birth weights were recorded.
[b] Among 487 fathers who were available.

daytime sleep intervals were computed automatically, requiring minimum 30 min of length.

All cases were checked manually. When software output did not seem to match the actigraph measures, data was manually configured. If subject event markers were consistent, matched the infants' general pattern of sleep, measures of motion matched that of sleep, but the software did not record sleep, sleep intervals were added or prolonged. These configurations were also checked against sleep diaries. Sleep diaries were collected by field workers and included information on parent reported infant sleep.

A total of 10% of the data was scored by two assistants, which when compared showed an ICC of 0.99 between the two raters on sleep duration.

We used the following definition:

Sleep duration: Sleep duration during the night.

Sleep duration (total): Total sleep duration during night and day.

Sleep onset latency (SOL): The time required for sleep to start after initiating the intent to sleep.

Wake After Sleep Onset (WASO): The sum of wake time during the night.

2.5. Ethics

The study received ethical clearance from the Nepal Health Research Council (NHRC, #233/2014) and from the Regional Committee for Medical and Health Research Ethics (REC # 2014/1528) in Norway. After thorough information provided to parents, we obtained written informed consent or a thumbprint from those who were illiterate (in the presence of an impartial witness).

2.6. Statistical analysis

The sample size calculation was based on growth and neurodevelopment scores, as these were the main outcome of this study [18]. With a sample size of 300 infants per group and a 5% loss to follow up, we had 80 and 90% power to detect standardized effect sizes of 0.24 and 0.28, respectively.

Inter-rater reliability was examined using Intraclass Correlation (ICC). Continuous variables are expressed as mean and standard deviation (SD), and categorical variables as numbers and percentages. We compared the mean end study actigraphy measured sleep duration (night and total), sleep onset latency (SOL) and sleep after wake onset (WASO) between groups using the Students' t-test assuming equal variances. Subgroup analysis were performed by pre-defined status of stunting, underweight, and birthweight status; anemia, and whether or not the infant had been exclusively breastfed for the 3 first months of life. These are the same subgroup analyses as were performed in the paper reporting the primary outcome of the study [18]. The subgroup effects were analyzed in regression models adjusted for infant age at enrollment and the WAMI-score, and presented in forest plots (admetan function in Stata). Analyses was done in SPSS version 25 and in Stata version 16.

3. Results

Baseline characteristics by intervention and placebo groups for the 600 included infants are presented in Table 1. The mean age of the infants was 8 months at enrollment. One in every five infants was born with low birth weight and one third was stunted at

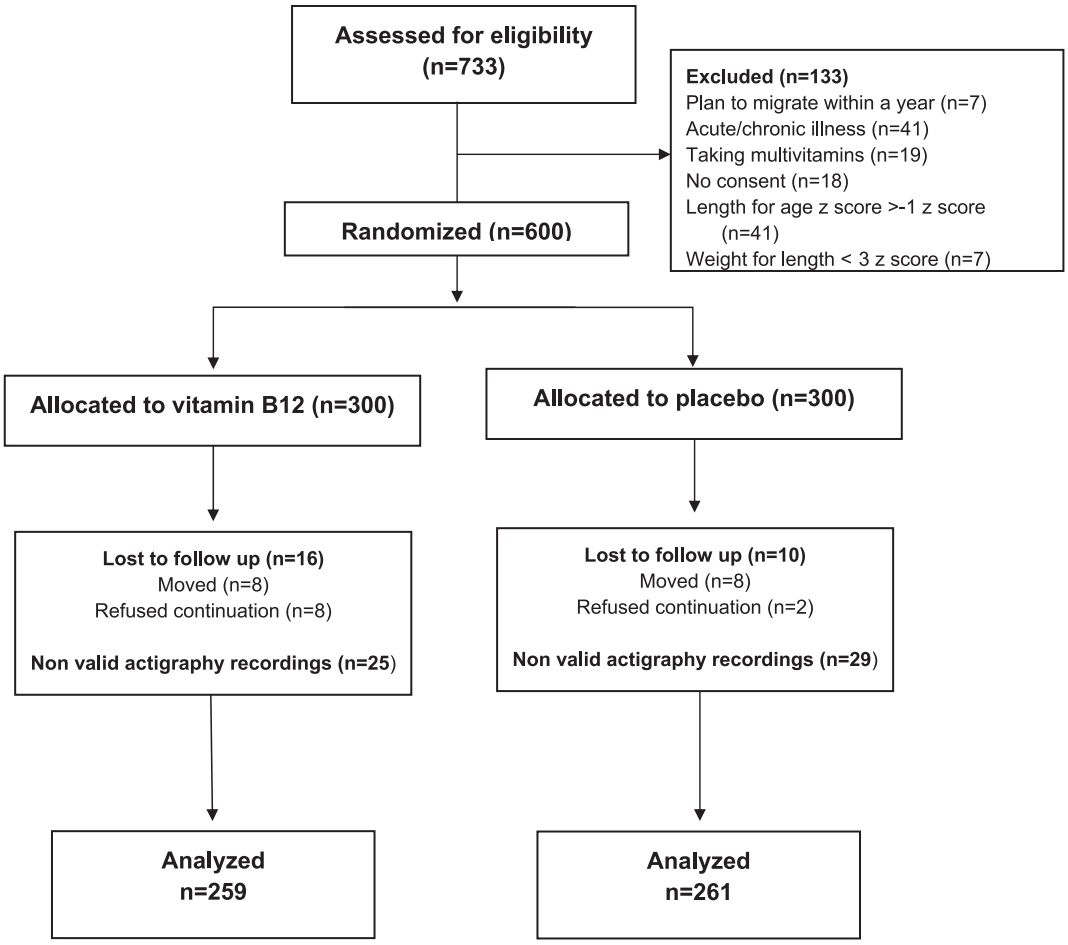

Fig. 1. Study participation and follow-up.

Table 2
Effect of daily vitamin B12 supplementation for one year starting in infancy on the sleep measured by actigraphy among infants in Bhaktapur, Nepal.

Sleep variables End study	Vitamin B12 group (n = 259)		Placebo group (n = 261)		Mean difference	
	Mean	SD	Mean	SD	95 %CI	
Sleep duration (night), minutes	522.51	(56.88)	518.53	51.82	3.99	−5.3,9,-13.36
Sleep Onset Latency (SOL)	14.99	10.58	13.24	7.97	−1.75[a]	−3.56, −0.13
Wake after Sleep Onset (WASO)	42.81	16.48	42.58	16.48	0.23	−3.05, −2.59
Sleep duration (total), minutes	588.43	53.21	589.37	58.50	−0.94	−10.57, −8.69

[a] $p < .029$.

enrollment. At baseline, the mean sleep duration at night for the total sample was 8:36 h, with a mean SOL of 13 min and WASO of 46 min.

Of the 600 enrolled infants, 259 infants were in the intervention group and 261 in the placebo group at end study. The attrition was due to 16 families of infants that moved, 10 that refused continuation and 45 had invalid actigraphy scores. For details see trial flowchart, Fig. 1.

Vitamin B12 supplementation had no effect on sleep duration during the night, total sleep duration (night and day) or on WASO (Table 2). There was a longer SOL in the intervention group compared to the control groups. The adjusted effects of the intervention on sleep duration by various subgroups are shown in Fig. 1. The subgroups included low/normal B12, stunted/not stunted, underweight/not underweight, low birthweight/normal birthweight, anemia/no anemia, exclusive breastfed 3 months/not exclusive breastfed 3 months. These analyses did not reveal any variable that modified the effect on sleep duration.

4. Discussion

In the present randomized placebo-controlled trial in infants, there was no effect of daily supplementation of vitamin B12 for one year in infants at risk of deficiency on sleep duration or wake after sleep onset. The only exception was a longer sleep onset latency in the intervention group compared to the placebo. No effect on sleep duration was observed in any of the sub-group analyses. Fig. 2.

The present study is unique. Not only is it the first RCT on the effect of vitamin B12 supplementation on sleep, we are also not aware of any other study of this magnitude that has described the sleep pattern in infants from a low-income country. Based on the lack of measurable effect of the intervention on sleep and the

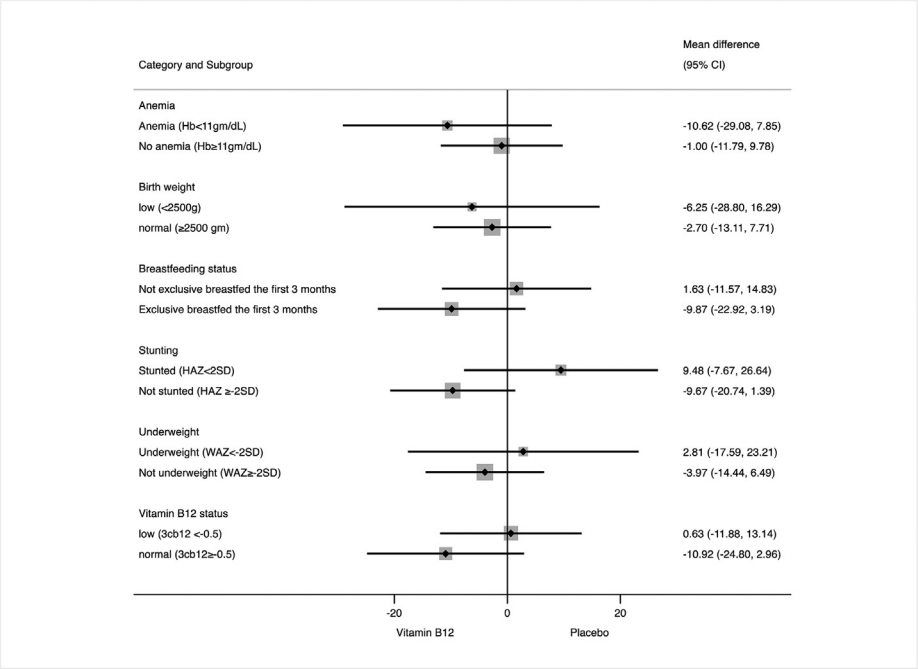

Fig. 2. The effect of vitamin B12 supplementation on sleep duration at night in predefined subgroups.

inconsistent reports of the association between vitamin B12 status and sleep, it is reasonable to believe that poor vitamin B12 status does not limit sleep in infants [9]. The reported compliance was excellent and vitamin B12 supplementation substantially improved infant B12 status as measured by direct and indirect biomarkers [18]. Thus, lack of a biological effect does not explain the null findings that we observed here. The reason for poor sleep is multifaceted and it is also a possibility that the effect of vitamin B12 could have been overshadowed by other factors limiting sleep. Examples of possible factors is the high rate of premature born infants in the study, the high poverty rate and infections that may have impacted the health in general and sleep in particular.

One reason for the lack of effect could be that the main trial did not find an improvement in neurodevelopment, one of the possible mechanisms for an effect on sleep [18]. We did not investigate to what extent vitamin B12 had an effect on melatonin production, one of the possible biological pathways for which vitamin B12 can affect sleep [16]. Methodological issues could also be of importance. It could be that higher doses of vitamin B12 interventions earlier during critical periods of neurodevelopment, for instance during pregnancy, could have given a different outcome. This should be investigated in future studies. The reason for the observed longer sleep onset latency among the intervention group is not clear. The hypothesis was that sleep would be improved by the intervention. Given that there are no clear mechanisms that may account for this result, this can be a spurious finding which could be further explored in future studies. The small difference of only a couple of minutes is probably not clinically meaningful.

The importance of addressing sleep and finding effective interventions to improve sleep is underlined by the very short sleep duration in the presence study, which was on average 8 h and 26 min. This is far below the expert recommendations in this age group [23]. For the age range in the present study, less than 10 h is not recommended, while 12–15 h is the recommended range. The short sleep duration observed in this study is in line with the duration that has previously been observed in other Asian countries [24]. This is especially concerning given the known association between sleep duration and mental and physical health and development in infants [25,26].

The strength of the present study is the randomized placebo-controlled design. It addresses a knowledge gap by the combination of a strict RCT design and objective measures of sleep that has been called for in the literature [8]. The use of an objective measure of sleep supported by the close follow-up from field workers of the actigraphy is an advantage. Further, the actigraphy has been carefully scored and quality controlled, and obtained good reliability across scorers. Still, there are some issues regarding the use of actigraphy for assessing wake time in young infants. Brief movements could be the results of adults moving the infant, or bed sharing for instance. Polysomnography would have given additional information on physiological sleep and would also serve as an important validation of the actigraphy rated sleep outcomes. However, this was not feasible in the current study. Another limitation is that the study was designed to assess the effect of vitamin B12 supplementation on growth and neurodevelopment; thus, no a priori power calculations was conducted to ensure sufficient power for the sleep outcomes. The generalizability may also be limited due to the demographically restricted high-risk sample.

In the present study we demonstrate that short sleep duration among infants could be a public health concern. However, our finding does not support vitamin B12 supplementation for improving sleep in infants with suboptimal vitamin B12 status. Other factors than vitamin B12 deficiency that should be targeted to improve infant sleep. These factors could be related to parental strategies, or the infant's physical health status in general, but may also be related to other nutrients.

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Author contribution

Mari Hysing: Conceptualization, formal analysis, writing original draft, review and editing. Tor Strand: Conceptualization, investigation, writing-review and editing. Ram K. Chandyo, Manjeswori Ulak and Suman Ranjitkar: investigation, data collection, writing-review and editing. Catherine Schwinger writing-review and editing. Merina Shrestha: writing-review and editing. Ingrid Kvestad, formal analysis, writing-review and editing.

Conflict of interest

None reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.11.040.

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