Neonatal thyrotropin concentration and iodine nutrition status of mothers: a systematic review and meta-analysis[1]

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ABSTRACT

Background: Low maternal iodine intake disturbs the thyroid function of neonates transiently or permanently.

Objective: To our knowledge, we conducted one of the first systematic reviews and meta-analyses aimed at exploring the association of neonatal thyrotropin concentrations and iodine status of mothers during pregnancy and early postpartum periods.

Design: Data were collected through literature searches for studies published between 1969 and 2015 with the use of electronic databases. Mean or median maternal urinary iodine and neonatal thyrotropin concentrations, along with other relevant data, were extracted from eligible studies. The quality and risk of bias of each study was assessed.

Results: A random-effects model was used for the analysis. Of 110 studies identified, 25 trials were shown to be eligible for inclusion in the meta-analysis. Mean (95% CI) thyrotropin concentrations of neonates born to mothers with iodine deficiency were higher than in neonates born to mothers with iodine sufficiency during pregnancy in both heel blood samples [1.79 mIU/L (95% CI: 1.61, 1.97 mIU/L) compared with 1.75 mIU/L (95% CI: 1.68, 1.82 mIU/L), respectively] and cord blood samples [11.91 mIU/L (95% CI: 6.67, 17.14 mIU/L) compared with 6.15 mIU/L (95% CI: 4.30, 8.01 mIU/L), respectively]. There were no significant differences in neonatal thyrotropin concentrations of heel samples between mothers with iodine deficiency and those with sufficiency during the early postpartum period; however, the values of thyrotropin in cord samples of neonates born to mothers with iodine deficiency were significantly higher than in neonates born to mothers with iodine sufficiency [11.62 mIU/L (95% CI: 10.47, 12.77 mIU/L) compared with 7.40 mIU/L (95% CI: 6.21, 8.59 mIU/L)].

Conclusion: Our findings reveal that, compared with heel blood samples, neonatal thyrotropin in samples collected from the cord are more sensitive to the iodine status of mothers; however, further investigations are required in this regard. *Am J Clin Nutr* 2016;104:1628–38.

Keywords: iodine deficiency disorder, iodine nutrition, maternal urinary iodine, neonatal thyrotropin, pregnancy, postpartum, heel blood sample, cord blood sample

INTRODUCTION

On the basis of UNICEF estimations, currently >35 million newborns annually suffer from brain damage that is associated with iodine deficiency (1–3). In situations of iodine deficiency, even in its mild form, the production of thyroid hormones has been compromised, which causes increased thyroid-stimulating hormone (TSH) secretion. Therefore, an elevated TSH, also known as thyrotropin, is a sensitive indicator for iodine-nutrition insufficiency and, hence, an inadequate supply of thyroid hormones to the developing brain. However, neonatal thyrotropin concentrations have been shown to vary because of the influence of several prenatal and postnatal factors such as, e.g., the timing of blood sampling, type of TSH assay used, and season of birth. The WHO has proposed a frequency of neonatal TSH concentrations >5 mIU/L as <3% for the threshold for iodine sufficiency. Frequencies of 3–19.9%, 20–39.9%, and >40% may be observed in conditions of mild, moderate, and severe iodine deficiency, respectively (4–6).

It is well known that low maternal iodine intake disturbs the thyroid function of neonates transiently or permanently, although there have been controversial results regarding the association between neonatal TSH and maternal urinary iodine concentrations (UICs) (7). Data from newborn screenings in Turkey (8), Thailand (9), and Hong Kong (10) have shown that TSH was higher in neonates of mothers who had lower UICs. However, studies from Australia (11) and Denmark (12), which are countries with mild to borderline iodine deficiency, did not show the previously documented negative correlation between neonatal TSH and maternal UIC.

In contrast, there are limited data on the effects of maternal dietary iodine intake on neonatal thyroid function in a population chronically exposed to excess dietary iodine intake. A transient elevation of TSH was observed in some neonates born to Japanese mothers who consumed iodine-rich foods during pregnancy or in lactation such as seaweed and kelp; however, there was no direct relation between maternal UIC and neonatal TSH (13). In China, the TSH of neonates born to mothers living with long-term excessive iodine intake from drinking water was higher than in neonates born to mothers residing in areas with adequate

[1] Supported by a financial grant (no. 799) from the Research Institute of Endocrine Sciences, Shahid Beheshti University of Medical Sciences.

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Received February 3, 2016. Accepted for publication September 20, 2016.
First published online November 2, 2016; doi: 10.3945/ajcn.116.131953.

iodine intake (14). Moreover, both iodine fortification and supplementation for mothers residing in areas with iodine deficiency are usually associated with a decrease in neonatal TSH concentrations (15–17); however, studies have shown inconclusive results. For instance, in Australia and Denmark, neonates born to mothers who took iodine-containing supplements had a shift in distribution toward higher TSH concentrations (12, 18).

These findings raise the question of whether the neonatal TSH concentration truly reflects the iodine status of mothers who have higher iodine requirements. Hence, this systematic review and meta-analysis explores, for the first time to our knowledge, the association of the neonatal thyrotropin concentration and iodine status of mothers during pregnancy and early postpartum periods.

METHODS

Search strategy

We conducted a systematic literature search of all articles that were published between September 1969 and March 2015 with the use of electronic databases [i.e., MEDLINE/PubMed (National Library of Medicine; www.pubmed.com), Institute of Scientific Information Web of Science (www.webofscience.com), the Cochrane Library CENTRAL (www.cochrane.org), and Scopus (www.scopus.com)]. Additional searches were conducted with the use of relevant databases [i.e., the WHO (http://www.who.int/en/), International Council for the Control of Iodine Deficiency Disorders (http://www.iccidd.org/), and UNICEF (http://www.unicef.org/)]. Moreover, Internet searches were also carried out with general search engines (Google and Google Scholar). The key terms included in the search were as follows: iodine nutrition, lactating mothers, postpartum women, pregnant women, iodine and lactation, iodine and breastfeeding, iodine and pregnancy, urinary iodine, neonatal TSH screening, neonatal thyrotropin, congenital hypothyroidism screening program, neonatal thyroid function, and neonatal TSH. To further identify relevant papers, we also performed a manual search with the use of reference lists of original articles and relevant reviews.

Study selection and data extraction

Two of the investigators conducted the search independently. Once the search was completed, the titles and abstracts of the studies identified were scanned to exclude studies that were obviously irrelevant. Full texts of the remaining studies were retrieved, and all relevant articles were identified. Criteria for inclusion of studies in the systematic review were as follows: all articles were human studies that included healthy pregnant women and postpartum mothers (during the first few weeks after delivery at the time of congenital hypothyroidism screening), and their healthy full-term neonates as target participants were also assessed; maternal UICs and neonatal thyrotropin concentrations were reported, and the type of blood sampling for neonatal thyrotropin was determined. Exclusion criteria were as follows: animal studies; non-English studies; studies in which mothers or infants had been exposed to environmental factors [i.e., perchlorate, tobacco smoking, and iodine overload (e.g., iodine containing contrast media, radioactive iodine, and povidone-iodine disinfection)] that can influence their iodine status and thyroid function; studies conducted in pregnant and postpartum women with thyroid diseases or in preterm and unhealthy infants; and any duplicate publications or any potentially relevant articles that lacked full texts.

Data from included studies were extracted by 2 investigators independently on standardized forms that were developed for this review, and if any discrepancies were shown, the studies were removed by consensus. The following data were extracted: first author; year of publication; country or location of study; number of mothers and infants; mean or median maternal UICs and neonatal thyrotropin concentrations or the percentage of neonate with TSH concentrations >5 mIU/L; type of sampling for the thyrotropin concentration (cord compared with heel); and correlation coefficients between maternal UICs and neonatal thyrotropin concentrations.

Quality assessment

We assessed study quality with the use of the Newcastle-Ottawa Scale and scored each study on the basis of 3 different points of view (i.e., the selection of the study samples, comparability of the groups, and ascertainment of the outcome of interest). Each study received 0, 1, and 2 stars for each criterion, and an overall quality score was calculated as the sum of individual stars. For descriptive purposes, we used the Newcastle-Ottawa scores 2–3, 4–6, and 7–10 as having low, moderate, and high quality, respectively.

Data synthesis

All medians, lower and upper CIs, minimums and maximums, IQRs, and sample sizes in each study were changed to means ± SDs or SEs for further calculations. According to the WHO/International Council for the Control of Iodine Deficiency Disorders/UNICEF criteria, median UICs <150 and ≥150 μg/L for pregnant women, and median UICs <100 and ≥100 μg/L for postpartum mothers were considered as iodine deficiency and sufficiency, respectively. In studies that were conducted in different regions of a country, with different iodine statuses, we included each region as a separate study. If studies reported neonatal thyrotropin in different surveys from a country, we included each survey as a separate study. If neonatal thyrotropin concentrations were reported in different types of blood sampling (heel or cord), they were included in our study as 2 separate studies. In studies in which the maternal UIC was assessed during pregnancy and early postpartum periods, we included each period (time point) as a separate study.

Statistical analysis

Means and 95% CIs of TSH were estimated in different subgroups on the basis of the mother's status (pregnant or breastfeeding) and type of blood sampling. The random-effects model was used because of the presence of heterogeneity, which was assessed with the use of Cochrane's Q statistics and I^2 (19). The presence of publication bias was also evaluated with the use of both Begg and Egger tests as well as funnel plots (20). A forest plot was used for showing means and 95% CIs of TSH in different subgroups. Stata 12.0 software (Stata Corp LP) was used for all analyses.

RESULTS

Study characteristics

The flowchart for this review is shown in **Figure 1**. We screened a total of 110 titles and abstracts after the electronic search. Of these articles, 59 studies appeared to be potentially relevant and were assessed as full-text articles for inclusion. Thirty-one potential studies were excluded because of a lack of inclusion criteria. The main reason for the exclusion of an article was that it did not report any data for the UIC in pregnant and postpartum women or neonatal thyrotropin concentrations. Further, one additional publication was included from the screening of reference lists, which yielding a total of 29 articles for inclusion in the current systematic review. Of these articles, 16 studies assessed UICs in pregnant women (**Table 1**), 10 studies reported the iodine nutrition status in mothers during the early postpartum periods (**Table 2**), and 3 studies measured maternal urinary iodine during both pregnancy and early postpartum periods. Sixteen studies reported on neonatal thyrotropin with the use of dried heel-prick blood spots, 11 studies assessed neonatal thyrotropin in cord blood samples, 1 study reported the use of 2 types of blood sampling, and only 1 study assessed the TSH of newborns with the use of a venous blood sample. Mean or median neonatal TSH was expressed in all studies, except in 3 studies in which the frequency of neonates with TSH concentrations >5 mIU/L was reported. After the exclusion of studies that reported neonatal TSH as a percentage (n = 3) and as a venous blood sample (n = 1), 25 studies were shown to be eligible for inclusion in the meta-analysis. Quality scores of studies included in the meta-analysis ranged from 6 to 8 (**Table 3**). The majority of studies received high-quality scores, and 8 studies were scored as being of moderate quality.

Neonatal TSH concentrations of heel samples of infants born to mothers with sufficient compared with deficient iodine nutrition

The forest plot with means and 95% CIs and the pooled estimates for means of neonatal TSH of heel blood samples of infants born to mothers with deficient and sufficient urinary iodine during pregnancy are illustrated in **Figure 2**. The plot

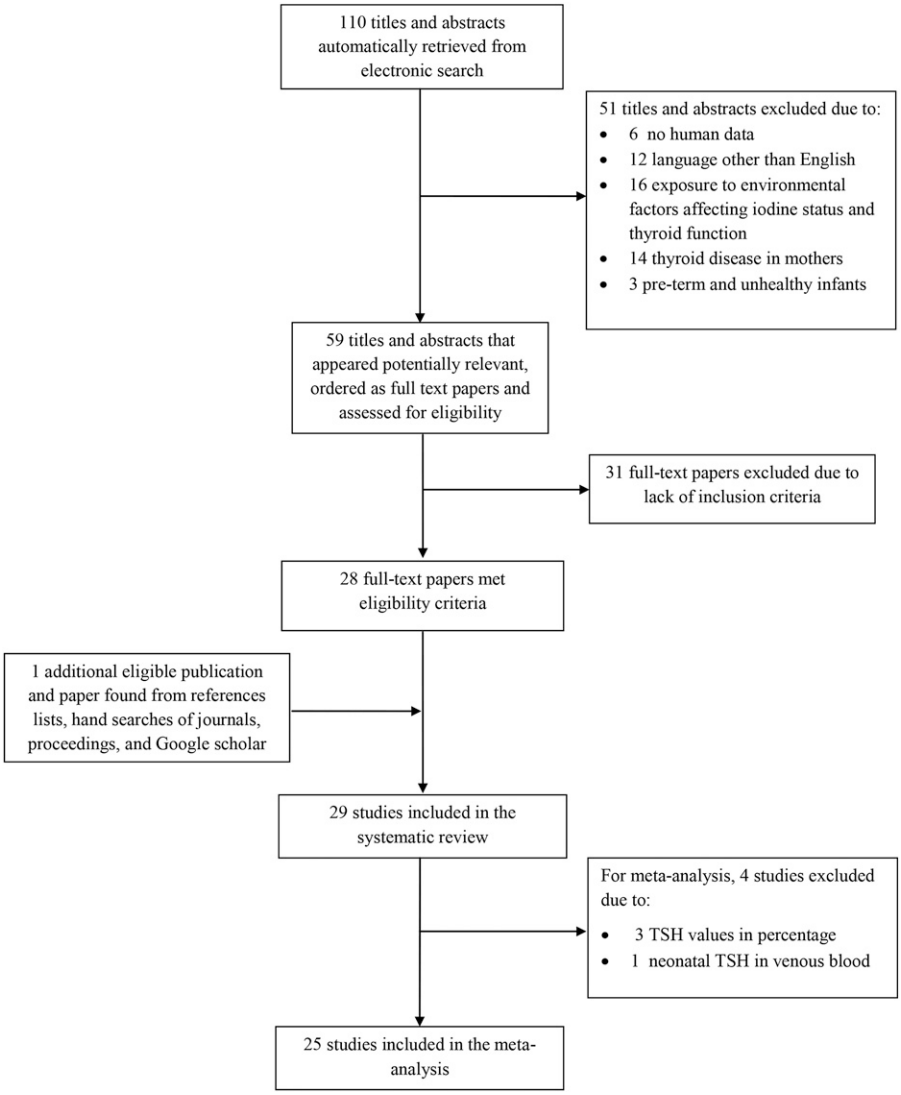

FIGURE 1 Flowchart for the selection of studies for the systematic review and meta-analysis. TSH, thyroid-stimulating hormone.

TABLE 1
Neonatal thyrotropin concentrations and maternal urinary iodine concentrations during pregnancy[1]

Study authors, year (ref)	Country	Neonates, *n*	Neonatal TSH, mIU/L	Type of sampling	Mothers, *n*	Maternal UIC, μg/L	Correlation
Travers et al., 2006 (22)	Australia	824	1.1 (1.60)[2]	Heel blood	815	85.0 (58.0)[2]	No
McElduff et al., 2002 (11)	Australia	84	1.8 (1.1–2.7)[2]	Heel blood	84	109.0 (65.0–168.0)[2]	Yes
Chen et al., 2015 (14)	China	210[3]	7.3 (5.5, 11.1)[4]	Cord blood	210	1241.0 (672.0, 1965.0)[4]	Yes
		174[3]	4.7 (3.9, 6.0)[4]	Cord blood	174	217.0 (146.0, 333.0)[4]	
Luton et al., 2011 (23)	France	72	7.7 ± 0.8[5]	Cord blood	102[6]	48.0 ± 2.0	NS
					63[6]	52.4 ± 4.0	
Copeland et al., 2002 (24)	Guatemala	141	58[7]	Cord blood	141	120.0 (99.0, 149.0)[8]	NS
Kung et al., 1997 (10)	Hong Kong	26[9]	18.4 (2.0, 45.0)[4]	Cord blood	253	124.0 (12.6, 260.7)[4]	NS
		142[9]	6.6 (1.7, 30.0)[4]	Cord blood			
Charoo et al., 2013 (25)	India	51	3.8 ± 1.4	Venous blood	51[6]	144.0 ± 17.6	NS
						133.5 ± 15.4	
						123.3 ± 14.8	
Chakraborty et al., 2006 (26)	India	267	4.1	Cord blood	267	144.0	NS
Azizi et al., 2011 (27)	Iran	52[9]	7.3 (5.3–11.3)[2]	Cord blood	52[6]	125.0 (55.0–143.0)[2]	No
						212.0 (150.0–488.0)[2]	
						97.0 (20.0–147.0)[2]	
		86[9]	7.5 (5.5–10.3)[2]	Cord blood	86[6]	213.0 (155.0–400.0)[2]	
						93.0 (22.0–147.0)[2]	
						227.0 (155.0–400.0)[2]	
Burns et al., 2008 (21)	Ireland	6406[10]	1.8 ± 2.6	Heel blood	36	52.0 ± 5.8	Yes
		5421[10]	1.6 ± 1.9	Heel blood	18	81.0 ± 12.2	
Fuse et al., 2011 (13)	Japan	711	2.5 (1.7–3.8)[2]	Heel blood	683	219.0 (124.0–436.0)[2]	No
Ojule and Osotimehin, 1998 (28)	Nigeria	105[3]	9.8 ± 1.6	Cord blood	105	144.7 ± 14.7	NS
		90[3]	4.2 ± 1.2	Cord blood	90	213.4 ± 10.0	
Costeira et al., 2009 (29)	Portugal	117	1.6 ± 1.2	Heel blood	136[6]	65.0 (28.0–100.0)[2]	No
					128[6]	57.0 (33.0–95.0)[2]	
					119[6]	70.0 (40.0–100.0)[2]	
Velasco et al., 2013 (30)	Spain	161[11]	12.2 ± 9.1	Cord blood	233	126.5 (133.9, 160.4)[8]	Yes
		227[11]	1.5 ± 1.3	Heel blood			NS
Aguayo et al., 2013 (31)	Spain	1868	2.9[7]	Heel blood	2104[6]	88.5 (16.0, 875.0)[4]	No
					1322[6]	140.0 (21.0, 880.0)[4]	
Marco et al., 2010 (32)	Spain	525	1.0 (0.7–1.6)[2]	Heel blood	525	164.0 (116.0–245.0)[2]	No
Zimmermann et al., 2005 (17)	Switzerland	259,035[10]	1.2 (0.8–1.9)[2]	Heel blood	511	138.0 (5.0, 1881.0)[4]	NS
		218,665[10]	1.2 (0.8–1.8)[2]	Heel blood	279	249.0 (8.0, 995.0)[4]	
Sukkhojaiwaratkul et al., 2014 (16)	Thailand	5181[10]	5.2 (0.01, 35.1)[4]	Cord blood	218	196.5 (11.5, 1174.0)[4]	NS
		8332[10]	7.3 (0.01, 87.7)[4]	Cord blood	270	161.0 (14.5, 1046.0)[4]	
Jaruratanasirikul et al., 2009 (9)	Thailand	236	2.4 ± 1.6	Heel blood	236[6]	75.5 (50.0, 105.0)[4]	No
						87.6 (50.0, 105.0)[4]	
						72.1 (50.0, 105.0)[4]	
Copeland et al., 2002 (24)	USA	243	82[7]	Cord blood	243	105.0 (90.0, 117.0)[8]	NS

[1] NS, not stated; ref, reference; TSH, thyroid-stimulating hormone; UIC, urinary iodine concentration.
[2] Median; IQR in parentheses.
[3] Results from different regions of a country with different iodine statuses.
[4] Median; minimum, maximum in parentheses.
[5] Mean ± SD (all such values).
[6] Results from different stages of pregnancy.
[7] Percentage of TSH concentrations >5 mIU/L.
[8] Median; 95% CI in parentheses.
[9] Results from neonates born to mothers with different iodine statuses.
[10] Results from different surveys of a country.
[11] Results from different types of blood sampling.

revealed substantial heterogeneity between study-specific estimates (test for heterogeneity: I^2= 93.4% and 99.8%, respectively; $P < 0.001$ for both), and hence, the random-effects model was considered to provide a more-appropriate estimate. There was no publication bias in these subgroups. Mean thyrotropin concentrations of neonates born to mothers with iodine deficiency were higher than in neonates born to mothers with iodine sufficiency during pregnancy; however, when 95% CIs were compared, no significant difference was observed between the 2 iodine statuses [1.79 mIU/L (95% CI: 1.61, 1.97 mIU/L) compared with 1.75 mIU/L (95% CI: 1.68, 1.82 mIU/L)]. In **Figure 3**, the forest plot shows studies with means and 95% CIs and the pooled estimates for means of TSH concentrations of neonates born to mothers with different iodine statuses during the early postpartum period. Study-specific estimates exhibited substantial heterogeneity between studies (I^2 = 97.5% and

TABLE 2
Neonatal thyrotropin concentrations and maternal urinary iodine values during early postpartum[1]

Study authors, year (ref)	Country	Neonates, *n*	Neonatal TSH, mIU/L	Type of sampling	Mothers, *n*	Maternal UIC, μg/L	Correlation
Chan et al., 2003 (18)	Australia	50	1.5 (0.2, 21.0)[2]	Heel blood	50	46.0 (4.0, 140.0)[2]	No
Copeland et al., 2002 (24)	Bangladesh	208	84[3]	Cord blood	208	96.0 (81.0, 111.0)[4]	NS
Tahirović et al., 2009 (33)	Bosnia and Herzegovina	47	3.0 (0.7, 12.0)[2]	Heel blood	47	134.0 (12.0, 3360.0)[2]	NS
Hashemipour et al., 2010 (34)	Iran	179	5.4 (4.0, 22.0)[2]	Heel blood	179	130.0 (20.0, 400.0)[2]	No
Ordookhani et al., 2007 (35)	Iran	48	7.1 (1.5, 18.2)[2]	Cord blood	48	107.0 (20.0, 710.0)[2]	No
Fuse et al., 2011 (13)	Japan	711	2.5 (1.7–3.8)[5]	Heel blood	533	135.0 (78.0–262.0)	No
Sullivan et al., 1997 (36)	Malaysia	195	52[3]	Cord blood	194	33.0	NS
Fuse et al., 2003 (37)	Mongolia	138	3.1 ± 2.4[6]	Heel blood	138	107.0 (9.0, 840.0)[2]	No
Costeira et al., 2009 (29)	Portugal	117	1.6 ± 1.2[6]	Heel blood	88[7]	35.0 (15.0–98.0)	No
					105[7]	50.0 (28.0–84.0)	
					73[7]	40.0 (20.0–83.0)	
Rajatanavin, 2007 (38)	Thailand	1023[8]	5.8 (2.2, 2.5)[4]	Heel blood	1023	85.0	No
		181[8]	5.7 (2.2, 2.5)[4]		181	249.0	
		203[8]	6.5 (2.2, 2.5)[4]		203	106.0	
Yaman et al., 2013 (39)	Turkey	116	7.2 ± 5.7[6]	Heel blood	116	84.0	NS
Kurtoglu et al., 2004 (40)	Turkey	70	7.4 (1.1, 30.5)[2]	Cord blood	70	30.2 (3.2, 171.5)[2]	NS
Simsek et al., 2005 (8)	Turkey	5210[9]	5.5 ± 0.2[10]	Heel blood	57	48.8 ± 8.7[10]	NS
		6140[9]	4.9 ± 0.2[10]		68	55.4 ± 6.1[10]	
		7256[9]	3.9 ± 0.05[10]		65	71.6 ± 9.8[10]	

[1] NS, not stated; ref, reference; TSH, thyroid-stimulating hormone; UIC, urinary iodine concentration.
[2] Median; minimum, maximum in parentheses.
[3] Percentage of TSH > 5mIU/L.
[4] Median; 95% CI in parentheses.
[5] Median; IQR in parentheses (all such values).
[6] Mean ± SD.
[7] Results from different times of postpartum.
[8] Results from different surveys of a country.
[9] Results from different regions of a country.
[10] Mean ± SEM.

99.2%, respectively; $P < 0.001$ for both); no publication bias was shown in these subgroups. Mean thyrotropin concentrations of neonates born to mothers with iodine deficiency and of neonates born to mothers with iodine sufficiency during the early postpartum period were 3.37 mIU/L (95% CI: 2.71, 4.02 mIU/L) and 3.85 mIU/L (95% CI: 2.76, 4.94 mIU/L), respectively. A comparison of 95% CIs showed that none of these values were significant. Taken together, in iodine-deficient mothers who were either pregnant or postpartum, mean newborn TSH concentrations of heel samples ranged between 1.79 mIU/L (95% CI: 1.61, 1.97 mIU/L) and 3.37 mIU/L (95% CI: 2.71, 4.02 mIU/L), whereas these values in iodine-sufficient mothers ranged between 1.75 mIU/L (95% CI: 1.68, 1.82 mIU/L) and 3.85 mIU/L (95% CI: 2.76, 4.94 mIU/L).

Neonatal TSH concentrations of cord samples of offspring born to mothers with sufficient compared with deficient iodine nutrition

Figure 4 shows a forest plot of studies with means and 95% CIs and pooled estimates for mean neonatal TSH concentrations of cord samples of offspring born to mothers with deficient urinary iodine and of offspring born to mothers with sufficient urinary iodine. There was significant heterogeneity between studies that were conducted in pregnant women (I^2 = 100% and 99.8%, respectively; $P < 0.001$ for both). We showed no publication bias in these subgroups. The mean thyrotropin value of newborns born to mothers with iodine deficiency was higher than in newborns born to mothers with iodine sufficiency during pregnancy; however, a comparison of 95% CIs showed no significant difference between the iodine status of these 2 groups of mothers [11.91 mIU/L (95% CI: 6.67, 17.14 mIU/L) compared with 6.15 mIU/L (95% CI: 4.30, 8.01 mIU/L), respectively]. As shown in **Figure 5**, mean neonatal thyrotropin concentrations of offspring born to mothers with iodine deficiency was significantly higher than in offspring born to mothers with iodine sufficiency during the early postpartum period [11.62 mIU/L (95% CI: 10.47, 12.77 mIU/L) compared with 7.40 mIU/L (95% CI: 6.21, 8.59 mIU/L), respectively]; however, because of the small sample size of the study in each group of iodine status, the results may have been inconclusive. Generally, in iodine-deficient mothers who were either pregnant or postpartum, newborn TSH concentrations of cord samples ranged between 11.62 mIU/L (95% CI: 10.47, 12.77 mIU/L) and 11.91 mIU/L (95% CI: 6.67, 17.14 mIU/L), whereas, newborn TSH concentrations of cord samples in iodine-sufficient mothers ranged between 6.15 mIU/L (95% CI: 4.30, 8.01 mIU/L) and 7.40 mIU/L (95% CI: 6.21, 8.59 mIU/L).

Neonatal TSH concentrations of heel samples compared with cord samples of newborns born to mothers with sufficient and deficient iodine nutrition

A summary of pooled estimates of TSH concentrations of neonates born to mothers with different iodine statuses by type of

TABLE 3
Quality assessment of all studies included in the meta-analysis[1]

	Selection				Comparability	Outcome		
Study authors, year (ref)	Representativeness of the sample	Sample size	Nonrespondents	Ascertainment of exposure	On the basis of the design and analysis	Assessment of outcome	Statistical test	Newcastle-Ottawa scale[2]
Azizi et al., 2011 (27)	*	*	—	**	*	**	*	8
Burns et al., 2008 (21)	—	—	—	**	*	**	*	6
Chakraborty et al., 2006 (26)	*	*	—	**	*	**	*	8
Chan et al., 2003 (41)	—	—	—	**	*	**	*	6
Chen et al., 2015 (14)	*	*	—	**	*	**	*	8
Costeira et al., 2009 (29)	*	*	—	**	*	**	*	8
Fuse et al., 2003 (37)	*	*	—	**	*	**	*	8
Fuse et al., 2011 (13)	*	*	—	**	*	**	*	8
Hashemipour et al., 2010 (34)	*	*	—	**	—	**	*	7
Jaruratanasirikul et al., 2009 (9)	*	*	—	**	—	**	*	7
Kung et al., 1997 (10)	*	*	—	**	*	**	*	8
Kurtoglu et al., 2004 (40)	—	—	—	**	*	**	*	6
Luton et al., 2011 (23)	—	—	—	**	*	**	*	6
Marco et al., 2010 (32)	*	*	—	**	*	**	*	8
McElduff et al., 2002 (11)	—	—	—	**	*	**	*	6
Ojule and Osotimehin, 1998 (28)	—	—	—	**	*	**	*	6
Ordookhani et al., 2007 (35)	—	—	—	**	*	**	*	6
Rajatanavin, 2007 (38)	*	*	—	**	*	**	*	8
Simsek et al., 2005 (8)	*	*	—	**	*	**	*	8
Sukkhojaiwaratkul et al., 2014 (16)	*	*	—	**	*	**	*	8
Tahirović et al., 2009 (33)	—	—	—	**	*	**	*	6
Travers et al., 2006 (22)	*	*	—	**	*	**	*	8
Velasco et al., 2013 (30)	*	*	—	**	*	**	*	8
Yaman et al., 2013 (39)	—	—	—	**	*	**	*	6
Zimmermann et al., 2005 (17)	*	*	—	**	*	**	*	8

[1] The asterisks denote the score(s) for each criterion. One asterisk denotes a score of 1, and 2 asterisks denote a score of 2. ref, reference.
[2] Scores 2–3, 4–6, and 7–10 were considered as being of low, moderate, and high qualities, respectively.

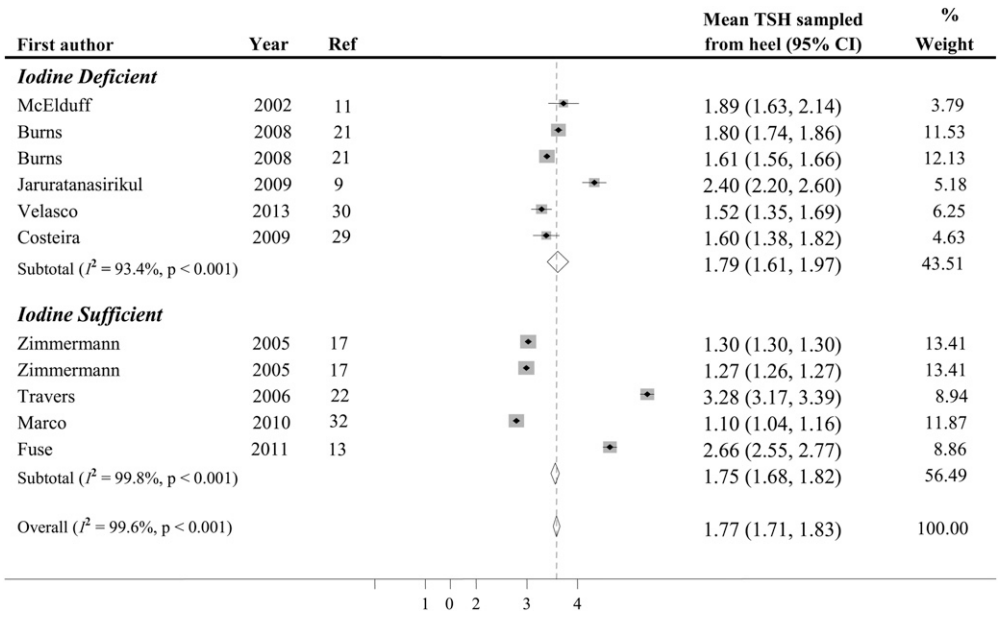

FIGURE 2 Means (95% CIs) and pooled estimates for means of neonatal TSH of heel blood samples of infants born to mothers with different iodine statuses during pregnancy. The subgroup analysis was based on maternal iodine status during pregnancy. Open diamonds represent pooled estimates for each subgroup and the overall estimate for the neonatal TSH of heel blood samples. Solid diamonds represent point estimates of studies (horizontal lines represent 95% CIs), and sizes of squares are proportional to the percentages of weight of studies. I^2 values refer to the statistical heterogeneity within each subgroup and combined studies. A random-effects model was used to calculate weighted mean differences and 95% CIs. Ref, reference; TSH, thyroid-stimulating hormone.

blood sampling is given in **Table 4**. In the analysis that was stratified by the type of blood sampling, the pooled (95% CI) neonatal TSH concentrations of heel and cord samples of newborns born to mothers with iodine sufficiency during pregnancy were 1.75 mIU/L (95% CI: 1.68, 1.82 mIU/L) and 6.15 mIU/L (95% CI: 4.30, 8.01 mIU/L), respectively; however, in neonates born to mothers with iodine sufficiency during the early postpartum period, these values were 3.85 mIU/L (95% CI: 2.76, 4.94 mIU/L) and 7.40 mIU/L (95% CI: 6.21, 8.59 mIU/L), respectively. The weighted (95% CI) neonatal TSH concentrations of heel and cord samples of offspring born to mothers with iodine deficiency during pregnancy were 1.79 mIU/L (95% CI: 1.61,

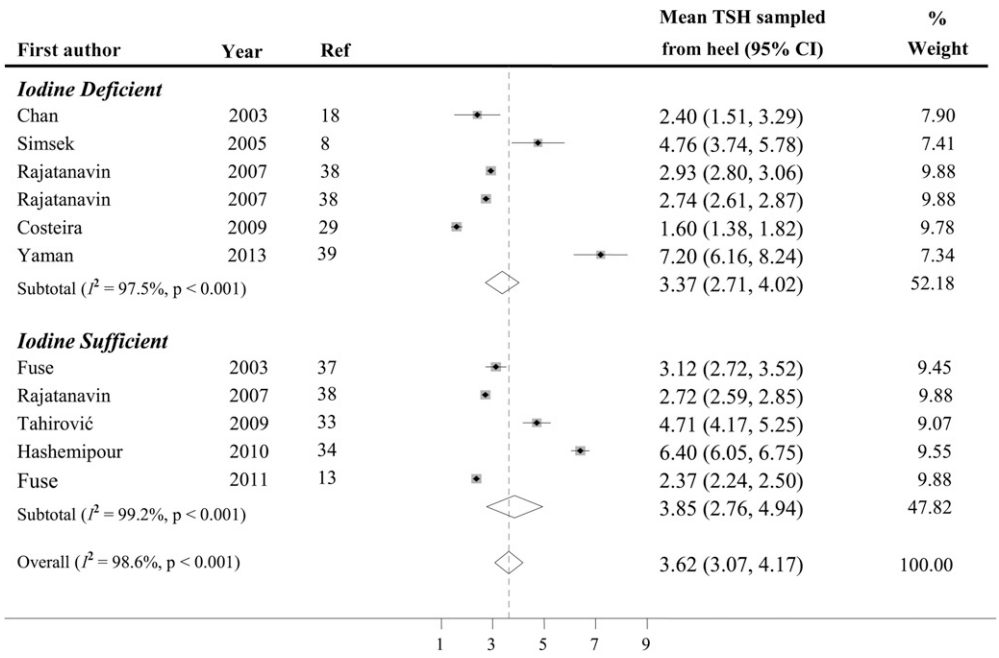

FIGURE 3 Means (95% CIs) and pooled estimates for means of neonatal TSH of heel blood samples of infants born to mothers with different iodine statuses during the early period of postpartum. A subgroup analysis was based on maternal iodine status during the early period of postpartum. Open diamonds represent pooled estimates for each subgroup and the overall estimate for the neonatal TSH of heel blood samples. Solid diamonds represent point estimates of studies (horizontal lines represent 95% CIs), and sizes of squares are proportional to the percentages of weight of studies. I^2 values refer to the statistical heterogeneity within each subgroup and combined studies. A random-effects model was used to calculate weighted mean differences and 95% CIs. Ref, reference; TSH, thyroid-stimulating hormone.

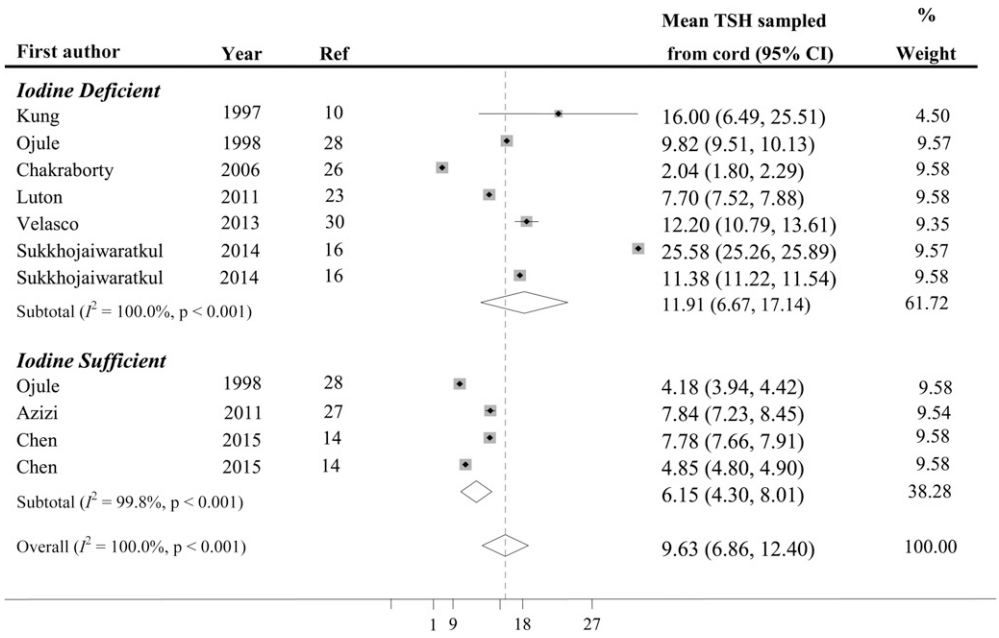

FIGURE 4 Means (95% CIs) and pooled estimates for means of neonatal TSH of cord blood samples of offspring born to mothers with different iodine statuses during pregnancy. The subgroup analysis was based on maternal iodine status during pregnancy. Open diamonds represent pooled estimates for each subgroup and the overall estimate for the neonatal TSH of cord blood samples. Solid diamonds represent point estimates of studies (horizontal lines represent 95% CIs), and sizes of squares are proportional to the percentages of weight of studies. I^2 values refer to the statistical heterogeneity within each subgroup and combined studies. A random-effects model was used to calculate weighted mean differences and 95% CIs. Ref, reference; TSH, thyroid-stimulating hormone.

1.97 mIU/L) and 11.91 mIU/L (95% CI: 6.67, 17.14 mIU/L), respectively. However, these values in neonates born to mothers with iodine deficiency during the early postpartum period were 3.37 mIU/L (95% CI: 2.71, 4.02 mIU/L) and 11.62 mIU/L (95% CI: 10.47, 12.77 mIU/L), respectively. In both pregnant and postpartum women, significant differences were shown between thyrotropin concentrations of heel and cord samples.

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis to be conducted on the maternal iodine nutrition status and neonatal thyrotropin concentration. In the current study, meta-analyses of available studies indicated that thyrotropin concentrations of heel and cord samples in neonates born to mothers with iodine deficiency were higher than in neonates born to mothers with iodine sufficiency during pregnancy;

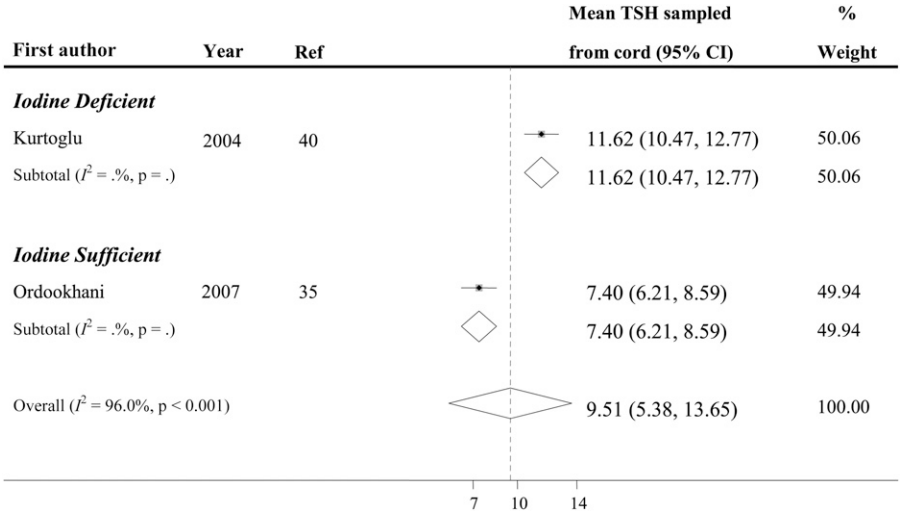

FIGURE 5 Means (95% CIs) and pooled estimates for means of neonatal TSH of cord blood samples of offspring born to mothers with different iodine statuses during the early period of postpartum. The subgroup analysis was based on maternal iodine status during the early period of postpartum. Open diamonds represent pooled estimates for each subgroup and the overall estimate for the neonatal TSH of cord blood samples. Solid diamonds represent point estimates of studies (horizontal lines represent 95% CIs), and sizes of squares are proportional to the percentages of weight of studies. I^2 values refer to the statistical heterogeneity within combined studies. Assessment of heterogeneity within different subgroups was not possible because of only one study being included in each group of iodine status. A random-effects model was used to calculate weighted mean differences and 95% CIs. Ref, reference; TSH, thyroid-stimulating hormone.

TABLE 4
Summary of pooled estimates of neonatal thyrotropin born to mothers with different iodine statuses by type of blood sampling[1]

	Neonatal thyrotropin concentration, mIU/L	
	Heel sample	Cord sample
Pregnant women		
Iodine sufficient	1.75 (1.68, 1.82)	6.15 (4.30, 8.01)
Iodine deficient	1.79 (1.61, 1.97)	11.91 (6.67, 17.14)
Postpartum mothers		
Iodine sufficient	3.85 (2.76, 4.94)	7.40 (6.21, 8.59)
Iodine deficient	3.37 (2.71, 4.02)	11.62 (10.47, 12.77)

[1] All values are pooled means; 95% CI in parentheses.

however, no significant difference was observed between the 2 iodine statuses. Although only 2 studies were conducted in postpartum mothers that reported the neonatal thyrotropin in cord blood samples, the values of cord samples in newborns born to mothers with iodine deficiency were significantly higher than in newborns born to mothers with iodine sufficiency.

Effects of maternal inadequate iodine intakes compared with excessive iodine intakes on neonatal thyrotropin concentrations

The neonatal thyroid gland has a lower iodine content and higher iodine turnover than in thyroid glands of adults; hence, in infants born to mothers with an inadequate iodine status, the decrease of thyroid hormone production is much faster in the neonate than in the mother (7, 21). However, there is not enough evidence to confirm the higher sensitivity of thyroid function to iodine deficiency in full-term infants compared with in their mothers (42). In contrast, excessive iodine intake has an inhibitory effect on the thyroid gland, indicating that the fetal thyroid is more susceptible to this inhibitory effect than are adult glands, thereby resulting in hyperthyrotropinemia in newborns; e.g., in Japan and China, a transient elevation of TSH was reported in some neonates born to mothers who were chronically exposed to high doses of iodine mainly from foods and drinking water (13, 14).

Effects of iodized salt fortification compared with maternal iodine supplementation on neonatal thyrotropin concentrations

A nationwide survey in Switzerland showed that a 25% increase in the content of iodized salt (from 15 to 20 parts per million) markedly improved the iodine status in pregnant women with an improvement that was reflected in the frequency of neonate TSH concentrations >5 mIU/L from 2.9% to 1.7% between the years 1992–1998 and 1999–2004 (17). A similar pattern was observed in the Islamic Republic of Iran, which was previously known as an area of iodine deficiency (43), where the production and nationwide consumption of iodized salt containing 20–40 parts per million iodine began in 1990 and was legislated for household consumption by 1994 (44, 45). The assessment of transient neonatal hypothyroidism in Tehran and Damavand (2 cities in the Tehran province) in 1998 and 2000 indicated that hyperthyrotropinemia significantly decreased from 5% to 1.6% after salt-iodization programs (15, 46).

Different studies have shown that, in populations with mild to moderate iodine deficiency, children of mothers who took iodine-containing supplements had higher cord blood TSH values, which was an observation that was not consistent with previously documented direct associations between iodine deficiency and neonatal thyrotropin TSH values (12, 47, 48). In Denmark, cord TSH concentrations >10 mIU/L were observed in 41% of newborns whose mothers were supplemented with 150 μg iodine/d during pregnancy, whereas TSH concentrations >10 mIU/L were present in only 31% of control neonates (12). Consistently, in Thailand after iodine supplementation during pregnancy, the percentage of neonates who had cord blood TSH concentrations >10 mIU/L was 11.7%, whereas the maternal median UIC was 170.6 μg/L (16). However, a clinical trial that was conducted in Belgium on iodine supplementation in pregnant women showed no differences in TSH concentrations of neonates born to women who had received iodine supplements and in neonates born to women who had did not received iodine supplements (49).

Thyrotropin as a reliable indicator for monitoring iodine status during pregnancy and early postpartum periods

The application of neonatal TSH values in the determination of iodine status at population levels has been successful in some countries (8–10); however, some regions have reported conflicting or uncertain data (11, 12, 50). It is assumed that the thyroid of newborns is very sensitive to iodine status, and even mild iodine deficiency during pregnancy will cause an increase in neonatal TSH secretion. Our results revealed that thyrotropin concentrations of neonates born to mothers with iodine deficiency were higher (but not significantly) than in neonates born to mothers with iodine sufficiency during pregnancy in both heel blood samples (mean: 1.79 compared with 1.75 mIU/L, respectively) and cord blood samples (mean: 11.91 compared with 6.15 mIU/L, respectively). Although there were small sample sizes of studies with cord blood samples in mothers during the early postpartum period, neonates born to mothers with iodine deficiency had significantly higher thyrotropin concentrations than did neonates who were born to mothers with iodine sufficiency (11.62 compared with 7.40 mIU/L, respectively). In Switzerland, a significant decrease in the frequency of neonatal TSH concentrations >5 mIU/L was associated with an increase in the median UIC in pregnant women (from 138.0 to 249.1 μg/L) (17). In a study conducted in Australian lactating mothers, a median UIC <50 μg/L was consistent with the percentage of neonatal TSH concentrations >5 mIU/L of > 3% (18). Our findings confirmed that, in conditions of iodine deficiency, neonatal thyrotropin concentrations tend to be elevated, although higher values of TSH do not necessarily reflect an increase in the proportion of TSH concentrations >5 mIU/L. For instance, the national neonatal screening programs in Ireland have shown that the shift to the right in the distribution of TSH values was not accompanied by the presence of a large number of concentrations >5 mIU/L (21).

However, the discrepancy between neonatal TSH and maternal UIC has been reported in the literature, which has suggested that the percentage of TSH concentrations >5 mIU/L may not be sensitive enough to evaluate iodine status, especially when iodine deficiency is mild (51). A study from Australia showed that

only 2.2% of neonates had TSH concentrations >5 mIU/L despite a median UIC of 85.0 μg/L in pregnant women (52). Similarly, the percentage of TSH concentrations >5 mIU/L in infants born to mildly iodine-deficient mothers in Belgium between 2009 and 2011 was unexpectedly low and fluctuated between 2.6% and 3.3% (50). Even in France, which is considered an area of moderate iodine deficiency, low maternal UIC was not accompanied by high concentrations of cord blood TSH (53).

The main strength of this research is that, to our knowledge, it is the first systematic review and meta-analysis to investigate the effect of maternal iodine status on neonatal thyrotropin concentrations in both cord and heel blood samples. However, the small sample sizes of studies in certain subgroups of maternal iodine status may not have provided reliable estimations of neonatal thyrotropin. In the current study, we excluded studies that reported the use of a povidone iodine application; however, the exposure of mothers or infants to povidone iodine has not been mentioned in some studies. Another potential limitation was related to several influential factors, such as, e.g., the mode of delivery, the TSH assay methodology, gestational age, season of birth, sex of the newborn, and birth weight, that could have possibly been the source of heterogeneity that was observed across the studies included; however, we could not determine the source of heterogeneity with the use of a meta-regression analysis because of the small sample sizes of studies within different subgroups; last, because of the limited number of studies, we were also not able to include the previously mentioned influential issues in the analysis, which makes the interpretation of our results difficult.

In conclusion, although neonatal thyrotropin constitutes an index of monitoring the iodine status in populations and intervention programs, it can be influenced by several prenatal and postnatal factors of which maternal iodine status plays the crucial role. The findings of our meta-analysis reveal that, compared with iodine sufficiency, iodine deficiency during pregnancy results in higher values of neonatal thyrotropin in both heel and cord blood samples. Also, in conditions of iodine deficiency during early postpartum, a significant increase in TSH values of cord blood samples can be observed; however, caution is needed in interpreting this data because of the limited number of studies on cord blood samples in neonates born to mothers with different iodine statuses during the early postpartum period. It seems that, despite this limitation, neonatal thyrotropin in samples collected from cord blood is more sensitive to the iodine status of mothers. To confirm these findings, the sensitivity of neonatal TSH at different degrees of iodine deficiency needs to be assessed in subsequent studies. Furthermore, future meta-analyses on neonatal thyrotropin in different subgroups of influential factors are warranted.

We thank Niloofar Shiva for the critical editing of English grammar and syntax of the manuscript.

The authors' responsibilities were as follows—PN: contributed to the design and data analysis; PM and FA: contributed to the design of the study; AK: contributed to the statistical analysis; and all authors: contributed to the writing, reading, and final approval of the manuscript. None of the authors reported a conflict of interest related to the study.

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