Methods of assessment of iodine status in humans: a systematic review[1–5]

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ABSTRACT

Background: Biomarkers of iodine status are required to study iodine deficiency disorders in different parts of the world and to evaluate the effects of fortification strategies.

Objective: The objective was to assess the usefulness of biomarkers of iodine status in humans by systematically reviewing intervention studies that altered iodine status.

Design: We performed a structured search for iodine intervention studies on Ovid MEDLINE, EMBASE (Ovid), and the Cochrane Library. Studies were assessed for inclusion and validity, with independent duplication. A random-effects meta-analysis was performed.

Results: Twenty-one intervention studies (12 randomized controlled trials, 3 controlled clinical trials, and 6 before-after studies) were included in the review. Urinary iodine (in children and adolescents and in those with low and moderate baseline iodine status), thyroglobulin (in children and adolescents but not in pregnant and lactating women), serum thyroxine (in children and adolescents, adults, women, and those with moderate baseline thyroxine status but not in pregnant and lactating women), and serum thyroid-stimulating hormone (in pregnant and lactating women but not in children and adolescents or those at moderate baseline status), but not triiodothyronine, proved to be useful biomarkers of iodine status.

Conclusions: Despite the high risk of bias of many of the included studies, the results suggested that urinary iodine, thyroglobin, serum thyroxine, and thyroid-stimulating hormone are useful biomarkers of iodine status, at least in some groups. High-quality controlled studies measuring relevant long-term outcomes are needed to address which biomarker is the most appropriate for assessing iodine intake in some population groups and settings. *Am J Clin Nutr* 2009;89(suppl):2052S–69S.

INTRODUCTION

Iodine is an essential micronutrient for normal growth and development. The human body contains ≈15–20 mg of iodine, of which 70–80% is concentrated in the thyroid gland. Iodine is primarily obtained through the diet, but it is also a component of some medications (1, 2).

Dietary iodine is converted into the iodide ion in the gut lumen, and >90% is rapidly absorbed in the upper small intestine. However, absorption can be reduced by the presence of goitrogens in some foods (including cabbage, broccoli, cassava, and lima beans) and by deficiency of other micronutrients, such as selenium (3, 4) or iron (5). Fifteen percent of ingested iodine is taken up by the thyroid gland within 24 h of ingestion, and the excess is excreted by the kidneys in urine (6).

The thyroid gland uses iodine for synthesis of the hormones thyroxine and triiodothyronine, which are essential for maintenance of the body's metabolic rate by controlling energy production and oxygen consumption in cells, for normal growth, and for neural and sexual development (7). Thyroglobulin, the most abundant thyroid protein, is a key precursor in the production of thyroid hormones. The synthesis and release of thyroid hormones are regulated by thyroid-stimulating hormone (TSH, or thyrotropin), which is released from the pituitary gland into the circulation. This regulation is subject to feedback inhibition.

Main sources of dietary iodine are iodized salt, saltwater fish, seaweed, and grains, although only trace amounts are present in the latter. The World Health Organization, International Council for the Control of Iodine Deficiency Disorders (ICCIDD), and UNICEF recommend daily iodine intakes of 90 μg/d for preschool children and 150 μg/d for adults, reaching 250 μg/d for pregnant and lactating women (8, 9). Despite remarkable progress in the control of iodine deficiency disorders, they remain a significant global public health problem (10). An estimated 200–300 million people worldwide show some degree of iodine deficiency disorders (9), especially in Asia and Africa but also in large parts of Eastern Europe (11). These epidemiologic findings are surprising, con-

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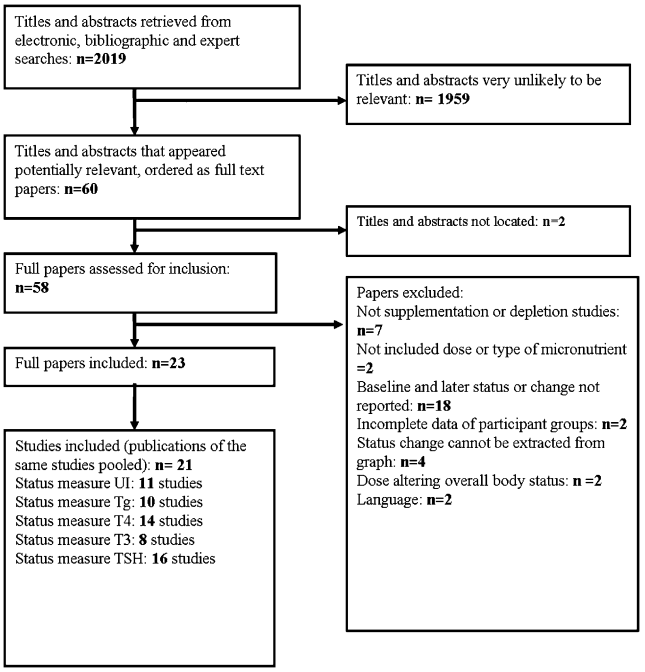

FIGURE 1. Flow diagram for systematic review of biomarkers of iodine status. UI, urinary iodine; Tg, thyroglobulin; T4, thyroxine; T3, triiodothyronine; TSH, thyroid-stimulating hormone.

sidering the very high efficiency of iodine recycling in human metabolism. Severe iodine deficiency within populations leads to endemic goiter, hypothyroidism, cretinism, decreased fertility rates, increased infant mortality, and mental retardation. In adults, iodine deficiency causes hypothyroidism and increased concentrations of TSH, causing hyperplasia of thyroid tissue, which results in goiter with iodine intakes <50 μg/d.

Iodine can be added to salt as potassium iodide, potassium iodate, or, less frequently, sodium iodide. Supplements vary in iodine content and form and may be available as potassium iodide tablets, prenatal multivitamin preparations, or iodized oil (12). Iodine bioavailability is probably influenced by encapsulation (tablets compared with gelatin capsules, coating substance, and the amount of pressure used to form the tablets) (13); however, only limited data are available. Although urinary iodine (UI) reflects short-term changes (a few days) in intake, thyroid function tests require $\geq$1 wk to respond (14, 15). Consequently, for optimal assessment of iodine status, the minimum duration of supplementation in intervention studies should be 2 wk.

This systematic review aimed to assess the usefulness of biomarkers of the status of iodine in humans by assessing the response of biomarkers in intervention studies in which iodine status was altered.

METHODS

Study selection

Included studies needed to meet all of the following criteria: *1*) involve a human intervention; *2*) be randomized or quasi-randomized controlled trials (RCTs), nonrandomized studies with a concurrent control group (controlled clinical trials; CCTs), or before-after (B/A) studies; *3*) report a change in iodine status over at $\geq$2 wk; *4*) involve participants from any population group, including children with goiter or populations from iodine-deficient geographical regions; *5*) involve supplementation given as iodized salt (potassium iodide, potassium iodate, or sodium iodide), iodized oil (given orally or by injection), iodized water, iodine tablets, or iodine-enriched food or milk formula; and *6*) include a control group that was given either a placebo (these studies were called RCT-1) or a low-dose iodine supplement (RCT-2). In single-dose studies in which the control group received a certain amount of iodine supplementation, the time period for data extraction was after the lower dose was expected to be fully metabolized, ie, when there was no residual impact on iodine status but while a potentially measurable impact on iodine status after the higher dose was still expected. For daily iodine supplementation, the low-dose arm had to provide a dose <100 μg iodine/d.

Search strategy

Ovid MEDLINE, EMBASE (Ovid; both at www.ovid.com), and the Cochrane Library CENTRAL database (www.thecochranelibrary.org) (from inception to September 2007) were searched for iodine intervention studies using text terms with appropriate truncation, and relevant indexing terms were exploded when relevant subterms needed to be included in the search. The search was not limited to English language publications and was in the form: [iodine terms] and [intervention study terms] and [human studies]. The full-structured Ovid MEDLINE search strategy can be found in Table S1 under ''Supplemental data'' in the online issue. Search strategies for the other databases were based on similar terms.

After an Ovid MEDLINE search, reviews of iodine status methods were collected in full text (11, 16, 17), the reference lists were checked (by DR-M and ZP), and the included study list was updated accordingly; the proceedings of nutrition conferences were also searched (18, 19). An expert in iodine metabolism (Michael Zimmermann, Swiss Federal Institute of Technology) was asked to check the included study list and to suggest any additional studies.

Data collection

The methodology of this review is based on the standard methodology developed for this set of reviews (20) and on methods used by the Cochrane Collaboration (21). Briefly, titles and abstracts were screened for inclusion independently by 3 reviewers (DR-M, ZP, and MG). The full text of the articles collected were screened for suitability with an inclusion/exclusion form used by a single reviewer with an independent duplicate assessment of a random sample of 50% by a second reviewer. Where the 2 reviewers disagreed, the study was discussed and a consensus decision reached where possible. If this was not possible, then a third reviewer was asked to arbitrate. Data were extracted onto a Microsoft Access (Microsoft Corp, Redmond, WA) database file by a single reviewer with independent duplicate assessment of a random sample of 30% by a second reviewer. The form was tested on 3 articles by each of the reviewers. If standard deviations were not reported, they were calculated or estimated by using methods described in the Cochrane Handbook (21).

Data synthesis

For each potential iodine status biomarker, we looked first at the overall effect on iodine status through meta-analysis of the

TABLE 1
Characteristics of included studies on the effect of iodine supplementation on assessment of iodine status[1]

Study	Population	Intervention and control	Outcomes reported	Methodology
Abuye et al, 1995 (22) Abuye_a (males) Abuye_b (females) Biomarker measured: UI	Country: Ethiopia Age range: 4–16 y Sex: male and female Participant group: 69.8% goiter rate in primary school children baseline iodine status: mean UIE 102–130 μg/L No. included: 147 Baseline biomarker status—UI: moderate	Short description of intervention: single oral dose 400 vs 200 mg I/iodized oil capsules Latest time point: 130 wk No. in intervention at latest time: 32 No. in control group at latest time: 34	Analytic methods—UI: catalytic action of iodide through the reduction of ceric ion by the oxidation of arsenite ion after acidic digestion (Ce/As method)	Study design: RCT-2 Study aim: to compare the efficacy of 2 different doses of oral iodized oil in the treatment and prophylaxis of goiter by age and sex among school children. Comments: 42 wk used as latest time point.
Antonangeli et al, 2002 (23) Biomarkers measured: UI, TSH, thyroglobulin	Country: Italy Age range: 20–38 y Sex: female Participant group: pregnant women living in marginally ID areas, enrolled from the 10th to the 16th week of gestation No. included: 87 Baseline biomarker status—UI: moderate; TSH: high; thyroglobulin: moderate	Short description of intervention: Potassium iodide 200 vs 50 μg/d Latest time point: 35 wk No. in intervention at latest time: 32 No. in control at latest time: 35	Analytic methods—UI: colorimetric method; TSH: ultrasensitive IRMA; thyroglobulin: IRMA	Study design: CCT Study aim: to assess the usefulness of iodine supplementation in the prevention of goiter in pregnant women living in marginally iodine-deficient areas. Comments: data are approximate and extracted from graph.
Azizi et al, 1996 (24) Biomarkers measured: T4, T3, TSH	Country: Iran Age range: 7–15 y Sex: male Participant group: boys, elevated serum TSH No. included: 32 Baseline biomarker status—T4: low; T3: moderate; TSH: high	Short description of intervention: single dose 480 mg iodine/iodized oil im. Latest time point: 52 wk No. in intervention at latest time: 32	Analytic methods—T4, T3, TSH: RIA diagnostic kits.	Study design: B/A Study aim: to investigate the effect of iodized oil administration on the thyroid status of male hypothyroid children and adolescents residing in an area of iodine deficiency.
Benmiloud et al, 1994 (37) Benmiloud_a (240 vs 120 mg I) Benmiloud_b (480 vs 120 mg I) Benmiloud_c (960 vs 120 mg I) Benmiloud_d (960 oral vs 960 mg I im) Biomarkers measured: UI, thyroglobulin, TSH	Country: Algeria Age range: 6–11 y Sex: mixed Participant group—children: goiter prevalence by 61%, cretinism prevalence 1.1% No. included: 182 Baseline biomarker status—UU: low; thyroglobulin: high; TSH: moderate	Short description of intervention: single oral dose 120, 240, 480, 960, mg iodine or 960 im iodized poppy-seed oil Latest time point: 395 d No. in intervention at latest time: 28 No. in control at latest time: 36	Analytic methods—UI: automated Technicon AutoAnalyzer (Technicon Corp, Tarrytown, NY); thyroglobulin, TSH: RIA diagnostic kits	Study design: RCT-2 Study aim: to develop better guidelines for iodized oil, using 5 indicators to study Algerian schoolchildren given one of several doses of iodized oil.
Contempre et al, 1996 (25) Biomarkers measured: UI, thyroglobulin, T4, T3, TSH	Country: Zaire Age range: 9–16 y Sex: mixed group Participant group: baseline iodine status median UI 19.42 μg/L, prevalence of goiter 43% No. included: 81 Baseline biomarker status—UI: not available; TSH: moderate; thyroglobulin: high; T4: moderate; T3: moderate	Short description of intervention: single oral dose 48 mg iodine/0.1 ml iodized oil Latest time point: 18 wk No. in intervention at latest time: 32	Analytic methods—UI: automated Technicon analyzer; thyroglobulin: IRMA; T4, T3, TSH: RIA diagnostic kits	Study design: B/A Study aim: to discusses the causes of the shortened response to iodine and the value of the serum thyroglobulin and low thyroid reserve

(Continued)

TABLE 1 (*Continued*)

Study	Population	Intervention and control	Outcomes reported	Methodology
Huda et al, 2001 (38) Biomarkers measured: UI, T4, TSH	Country: Bangladesh Age range: mean 9.8 ± 1.3 y Sex: mixed Participant group: children with poor nutritional status; high prevalence of goiter No. included: 305 Baseline biomarker status—UI: low; T4: moderate; TSH: moderate	Short description of intervention: single oral dose 400 mg iodine/ iodized oil vs placebo Latest time point: 4 mo No. in intervention at latest time: 122 No. in control at latest time: 126	Analytic methods—UI: ammonium persulfate by an adapted wet digestion method; T4: RIA diagnostic kits; TSH: immunoradiometric assay	Study design: RCT-1 Study aim: to present effects of iodized poppy-seed oil on cognitive and motor function and weight gain of iodine-deficient schoolchildren.
Liesenkötter et al, 1996 (26) Biomarkers measured: UI, thyroglobulin, T4, T3, TSH	Country: Germany Age range: 21–40 y Sex: female Participant group: pregnant women, with no clinical evidence of autoimmune thyroid disease; 14 had a history of goiter and 7 had goiter at first visit No. included: 108 Baseline biomarker status—UI: not available; thyroglobulin: moderate; T4: moderate; T3: moderate; TSH: moderate	Short description of intervention: 230 μg iodine/d in form potassium iodide vs control. Latest time point: 32 wk No. in intervention at latest time: 38 No. in control at latest time: 70	Analytic methods—UI: Ce/ As method; T4, T3, TSH: IRMAs; thyroglobulin: RIA diagnostic kits	Study design: RCT-1 Study aim: the effects of iodine supplementation on maternal and thyroid volume, thyroid function, and frequency of antibodies to thyroid peroxidase (TP0-ab).
Malone et al, 1996 (27) Biomarkers measured: T4, T3, TSH	Country: Tanzania Age range: 6–17 y Sex: mixed group Participant group: goiter children No. included: 202 Baseline biomarker status—T4: moderate; T3: moderate; TSH: moderate	Short description of intervention: iodine-1 single oral dose of iodized oil 480 mg iodine (n = 73); iodine-2 single im injection of iodized oil 480 mg iodine (n = 71); control-placebo capsule (n = 58). Latest time point: 12 wk No. in intervention at latest time: 73 No. in control at latest time: 58	Analytic methods—T4, T3: RIA diagnostic kits; TSH: hsTSH 1-step immuno-radiometric coated tube assay (IRMA)	Study design: RCT-1 Study aim: to compare methods of iodine supplementation, oral or im, for their effectiveness in reducing goiter and improving thyroid function over a 3-mo period.
Phillips and Osmond, 1989 (28) Biomarkers measured: UI, T4	Country: Zaire Age range: 15–44 y Sex: female Participant group: women of reproductive age from iodine deficiency region, who are the most important at-risk group No. included: 226 Baseline biomarker status—UI: not reported; T4: low	Short description of intervention: single oral or im dose of 960 mg iodine/ 2 ml iodized poppy-seed oil or no treated group. Latest time point: 96 wk No. in intervention at latest time: 130 No. in control at latest time: 96	Analytic methods—UI: ammonium persulfate method; T4: RIA determination with blood disc was carried out by the methods in use in neonatal screening	Study design: CCT Study aim: to compare single doses of oral with im iodized oil supplementation 2 y after administration in an unselected iodine-deficient population. Comments: at follow-up, 24 wk after oral supplementation of Lipidol in women of reproductive age, blood spot T4 levels showed a large, statistically significant increase with the same levels throughout 2-y period.

(Continued)

TABLE 1 (*Continued*)

Study	Population	Intervention and control	Outcomes reported	Methodology
Reinhardt et al, 1998 (29) Biomarkers measured: UI, thyroglobulin, T4, T3, TSH	Country: Germany Age range: 17–41 y Sex: female Participant group: all patients were euthyroid and had no known history of thyroid disease No. included: 70 Baseline biomarker status—UI: not available; thyroglobulin: moderate; T4: moderate; T3: moderate; TSH: moderate	Short description of intervention: 0 ($n = 56$), 50 ($n = 36$) or 250 ($n = 34$) μg potassium iodide/d Latest time point: 32 wk No. in intervention at latest time: 24 No. in control at latest time: 26	Analytic methods—UI: Ce/As method; thyroglobulin: RIA; T4, T3, TSH: immunoluminescence assay	Study design: RCT-2 Study aim: to evaluate the effect of iodine supplementation on postpartum thyroiditis and in thyroid volume decrease $\leq$8 mo postpartum in an area of mild iodine deficiency. Comments: thyroid hormone evaluated only at the beginning of the study in non-iodine-deficient subjects.
Reinhardt et al, 1993 (30) Biomarkers measured: UI, thyroglobulin, T4, T3, TSH	Country: Germany Age range: 23–42 y Sex: mixed Participant group: healthy and euthyroid, not obese, and not taking any medication No. included: 16 Baseline biomarker status—UI: not available; thyroglobulin: moderate; T4: moderate; T3: moderate; TSH: moderate	Short description of intervention: 500 μg iodine/d in form tablets vs placebo. Latest time point: 4 wk No. in intervention at latest time: 2 No. in control at latest time: 8	Analytic methods—UI: Ce/As method; thyroglobulin: IRMA; T4, T3: RIA diagnostic kits; TSH: IRMA	Study design: CCT Study aim: to study the effect of low-dose iodine supplementation on thyroid function before and after the short-term intake of a low-carbohydrate diet in normal subjects residing in an iodine-deficient area.
Rogahn et al, 2000 (31) Biomarkers measured: T4, T3, TSH	Country: United Kingdom Age range: infant born at $\leq$33 wk gestation Sex: mixed Participant group: premature infants (62 F, 59 M) from neonatal unit No. included: 121 Baseline biomarker status—T4: moderate; T3: moderate; TSH: moderate	Short description of intervention: 272 vs 68 μg iodine/L milk formula. Latest time point: 10 wk No. in intervention at latest time: 56 No. in control at latest time: 57	Analytic methods—T4, T3, TSH: Vitros ECi immunodiagnostic reagents (Ortho-Clinical Diagnostics, Amersham, United Kingdom)	Study design: RCT-2 Study aim: to investigate whether increases iodine intake from supplemented preterm formula improve thyroid hormone levels in preterm babies and hence improve neuro-developmental status.
Silva and Silva, 1981 (32) Biomarkers measured: UI, T4, T3, TSH	Country: Chile Age range: different gestational ages Sex: women Participant group: pregnant women from an iodine-deficient area, with differences in iodine intake No. included: 250 Baseline biomarker status—UI: not available; T4: moderate; T3: moderate; TSH: moderate	Short description of intervention: 10 drops daily of a 785-μg/mL KI solution $\approx$300 μg iodine/d or not treated Latest time point: 16 wk No. in intervention at latest time: 36 No. in control at latest time: 10	Analytic methods—UI: Ce/As method; T4, T3, TSH: by RIA diagnostic kits	Study design: RCT-1 Study aim: to analyze the relations between serum thyroid hormones and TSH concentrations in iodine-deficient pregnant women as well as their newborns.

(Continued)

TABLE 1 (*Continued*)

Study	Population	Intervention and control	Outcomes reported	Methodology
Todd and Dunn, 1998 (39) Biomarkers measured: UI, DBS-thyroglobulin	Country: Zimbabwe Age range: 7–13 y Sex: mixed Participant group: goitrous and nongoitrous children No. included: 53 Baseline biomarker status—UI: low; DBS-thyroglobulin: moderate	Short description of intervention: 993 mg iodine single dose in form of potassium iodide. Latest time point: 13 mo No. in intervention at latest time: 47 No. in control at latest time: 53	Analytic methods—UI: Ce/As method	Study design: B/A Study aim: to address how often, and in what dose, potassium iodide solution should be given to achieve effective prophylaxis of iodine deficiency.
Tonglet et al, 1992 (33) Biomarkers measured: UI, T4, T3, TSH	Country: Zaire Mean age: 22 y Sex: mixed No. included: 125 Baseline biomarker status—UI: low; T4: moderate; T3: moderate; TSH: moderate	Short description of intervention: single oral dose 118 or 47 mg iodine/d iodized oil or placebo capsules Latest time point: 48 wk No. in intervention at latest time: 25 No. in control at latest time: 20	Analytic methods—UI: automated Technicon AutoAnalyzer (Technicon); T4, T3, TSH: RIA diagnostic kits	Study design: RCT-1 Study aim: to study efficacy of low doses of iodized oil in an area of severe iodine deficiency. Comments: data are approximate, extracted from graph.
van den Briel et al, 2001 (34) Biomarkers measured: UI, thyroglobulin, TSH	Country: Benin Age range: aged 7–10 y Sex: mixed Participant group: schoolchildren (168 boys, 30 girls) from an iodine-deficient area; 20–60% prevalence rates of goiter No. included: 198 Baseline biomarker status—UI: moderate; thyroglobulin: moderate; TSH: moderate	Short description of intervention: single oral dose 540 mg/ml iodized oil vs untreated Latest time point: 10 mo No. in intervention at latest time: 99 No. in control at latest time: 99	Analytic methods—UI: chloric acid digestion; thyroglobulin: RIA diagnostic kits; TSH: immunoluminescence assay	Study design: RCT-1 Study aim: to evaluate the suitability of indicators of iodine status and thyroid function, thyroglobulin, TSH, and free thyroxine (FT4) in serum, thyroid volume, and UI concentration in iodine-deficient schoolchildren. Comments: data are approximate, extracted from graph
Wijaya-Erhardt et al, 2007 (36) Biomarker measured: UI	Country: Indonesia Age range: 6–12 mo Sex: male Participant group: healthy infants No. included: 62 Baseline biomarker status—UI: moderate.	Short description of intervention: 118 μg iodine/d vs 59 μg iodine/d potassium food-like tablets. Latest time point: 23 wk No. in intervention at latest time: 31 No. in control at latest time: 31	Analytic methods—UI: ammonium persulfate	Study design: RCT-2 Study aim: to compare the efficacy of daily and weekly multiple micronutrient food-like tables (foodLETs; Roche Laboratories, Lima, Peru) on increasing iodine status among infants.
Zimmermann et al, 2000 (35) Biomarkers measured: UI, T4, TSH	Country: Côte d'Ivoire Age range: 6–12 y Sex: mixed Participant group: goitrous children in an area of severe iodine deficiency No. included: 109 Baseline biomarker status—UI: low; T4: moderate; TSH: moderate	Short description of intervention: single oral 200 mg iodine/0.4 ml iodized oil. Latest time point: 50 wk No. in intervention at latest time: 104	Analytic methods—UI: ammonium persulfate using a modification of the Sandell-Kolthoff reaction; T4, DBS, TSH: immunofluorimetric assays	Study design: B/A Study aim: to evaluate the efficacy and safety of a low dose of oral iodized oil (0.4 ml) in goitrous iodine-deficient children.

(Continued)

TABLE 1 (*Continued*)

Study	Population	Intervention and control	Outcomes reported	Methodology
Zimmermann et al, 2006 (16) Biomarkers measured: UI, DBS-thyroglobulin, T4, TSH	Country: Morocco Age range: 5–14 y Sex: mixed Participant group: schoolchildren from areas of long-term iodine sufficiency No. included: 86 Baseline biomarker status—UI: low; DBS-thyroglobulin: high; T4: moderate; TSH: moderate	Short description of intervention: 250 μg iodine/d of potassium iodate. Latest time point: 10 mo No. in intervention at latest time: 83	Analytic methods—UI: ammonium persulfate; DBS-thyroglobulin, TSH, T4: immunofluorimetric assays	Study design: B/A Study aim: to evaluate the standardized DBS-thyroglobulin assay and reference range in a longitudinal study of goitrous children before and after introduction of iodized salt.
Zimmermann et al, 2003 (17) Biomarkers measured: UI, DBS-thyroglobulin, T4, TSH	Country: Morocco Mean (SD) age: 10.2 ± 2.4 y Sex: mixed Participant group: severely iodine-deficient children; area of long-standing endemic goiter and severe iodine deficiency disorders No. included: 377 Baseline biomarker status: UI: low; DBS-thyroglobulin: moderate; T4: moderate; TSH: moderate	Short description of intervention: 250 μg iodine/d of potassium iodate. Latest time point: 52 wk No. in intervention at latest time: 377	Analytic methods—UI: ammonium persulfate; DBS-thyroglobulin, TSH, T4: immunofluorimetric assays	Study design: B/A Study aim: to optimize and validate a thyroglobulin assay on dried whole-blood spots and to evaluate thyroglobulin as an indicator of thyroid status in schoolchildren before and after the introduction of iodized salt.
Zimmermann et al, 2006 (40) Biomarkers measured: UI, T4, T3	Country: Albania Age range: 10–12 y Sex: mixed Participant group: iodine-deficient children No. included: 310 Baseline biomarker status—UI: low; T4: moderate; TSH: moderate	Short description of intervention: single oral dose 400 mg iodine/ iodized poppy-seed oil vs placebo Latest time point: 24 wk No. in intervention at latest time: 134 No. in control at latest time: 130	Analytic methods—UI: ammonium persulfate; DBS, TSH, T4: immunofluorimetric assays (DELFIA)	Study design: RCT-1 Study aim: to ascertain whether providing iodized oil to iodine-deficient Albanian school children would improved iodine and thyroid status and affect their cognitive and motor performance.

[1] UI, urinary iodine; UIE, urinary iodine excretion; B/A, before-after study; DBS, dried blood spot; Ce/As method, reduction of ceric ion by the oxidation of arsenite ion after acidic digestion method; DELFIA, immunofluorimetric assay; IRMA, immunoradiometric assay; RIA, radioimmunoassay; im, intramuscularly; KI, potassium iodide; RCT-1, randomized controlled trial with placebo; RCT-2, randomized controlled trial with low-dose iodine supplement; CCT, nonrandomized studies with a concurrent control group; T4, thyroxine; T3, triiodothyronine; TSH, thyroid-stimulating hormone; Abuye_ a, male group; Abuye_b, female group.

intervention group compared with the control group for all included studies that assessed the specified biomarker. For each iodine supplementation study, we chose the longest time point at the highest supplementation amount. Studies were subgrouped by type (RCTs, CCTs, or B/A studies) and meta-analysis was carried out with RevMan 4.2 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) by using a random-effects model. Tests for heterogeneity were carried out (I^2) to assess the variability between studies. We then addressed the secondary questions as described in the main methodology article in this supplement (20). Fixed-effect meta-analyses were used to check the effect of the duration of supplementation on biomarker response.

RESULTS

The flow diagram for this review appears in **Figure 1**. We screened 2019 titles and abstracts after the electronic and bibliographic searches. Of these, 60 appeared potentially relevant, and 58 were collected as full-text papers (2 could not be traced) and assessed for inclusion. Thirty-seven potential studies were excluded (for reasons, *see* Figure 1). Twenty-one studies fulfilled the inclusion criteria and reported on UI, thyroglobulin, thyroxine, triiodothyronine, and/or TSH (16, 17, 22–40). Overall, 3172 participants were included in studies with a duration of between 2 and 130 wk. Twelve of the studies were RCTs (7 RCT-1 and 5 RCT-2), 3 CCTs, and 6 B/A studies. Eleven of

TABLE 2
Validity of included studies[1]

Study	Randomization		Dropouts/reason	Compliance/method	Intervention/dose verification
	Randomized	Method			
Abuye et al, 1995 (22)	Yes	Stratified systematic sampling	None mentioned	None mentioned	Not relevant/standard pharmacologic preparation
Antonangeli et al, 2002 (23)	No	Not stated	Women with thyroid disease	None mentioned	Not mentioned
Azizi et al, 1996 (24)	No	Stratified by sex, age, diagnostic criteria	None mentioned	None mentioned	Not relevant/standard pharmacologic preparation
Benmiloud et al, 1994 (37)	Yes	Not stated	None mentioned	Thyroid size and change in size (ml; ultrasonography)	Not relevant/standard pharmacologic preparation
Contempre et al, 1996 (25)	No	Not stated	None mentioned	None mentioned	Not relevant/standard pharmacologic preparation
Huda et al, 2001 (38)	Yes	Not stated	11 in iodine group and 7 in placebo absent for testing	Height and weight measures. Cognitive and motor function test scores.	Not relevant/standard pharmacologic preparation
Liesenkötter et al, 1996 (26)	Yes	According to the days the women came to pregnancy care unit	None mentioned	Thyroid size (ultrasonography)	Not mentioned
Malone et al, 1996 (27)	Yes	Not stated	None mentioned	None mentioned	Not relevant/standard pharmacologic preparation
Phillips and Osmond, 1989 (28)	No	Not stated	None mentioned	Goiter rates using WHO classifications	Not relevant/standard pharmacologic preparation
Reinhardt et al, 1998 (29)	Yes	Not stated	14 women reevaluated by primary care physicians, 6 lost to follow-up. Women taking iodine medication during pregnancy excluded.	None mentioned	Not relevant/standard pharmacologic preparation
Reinhardt et al, 1993 (30)	No	Not stated	None mentioned	None mentioned	Not relevant/standard pharmacologic preparation
Rogahn et al, 2000 (31)	Yes	Randomized number tables	None mentioned	None mentioned	Standard milk formula
Silva and Silva, 1981 (32)	Yes	Not stated	None mentioned	None mentioned	Not relevant/standard pharmacologic preparation
Todd and Dunn, 1998 (39)	No	Not stated	None mentioned	Side effects, thyroid size, and height at 0 and 13 mo	Not reported
Tonglet et al, 1992 (33)	Yes	Subjects identified after random cluster sampling of 100 households in each village	Pregnant women	None mentioned	Not relevant/standard pharmacologic preparation
van den Briel et al, 2001 (34)	Yes	Stratified by school, class, sex, and matched for age and height	Left school or moved from area	None mentioned	Not relevant/standard pharmacologic preparation
Wijaya-Erhardt et al, 2007 (36)	Yes	Not stated	Moved or refused blood sample	None mentioned	Not relevant/standard pharmacologic preparation

(Continued)

TABLE 2 (*Continued*)

Study	Randomization		Dropouts/reason	Compliance/method	Intervention/dose verification
	Randomized	Method			
Zimmermann et al, 2000 (35)	No	Not stated	None mentioned	Goiter rates indirectly age-sex standardized using WHO classifications (ml, ultrasonography)	Not relevant/standard pharmacologic preparation
Zimmermann et al, 2006 (16)	No	Not stated	3: moved or absent on measurement days	None mentioned	Spectrophotometric measurement of iodine concentration using a modification of the Sandell-Kolthoff reaction
Zimmermann et al, 2003 (17)	No	Not stated	None mentioned	None mentioned	Reagent-grade potassium iodide was dry mixed into local salt by using a rotating drum mixer at a concentration of 25 μg iodine/g salt. No further dose verification reported.
Zimmermann et al, 2006 (40)	Yes	Computer-generated randomization	6 moved away, 12% refused blood sample	Cognitive and motor function tests	Not relevant/standard pharmacologic preparation

[1] WHO, World Health Organization.

the studies were conducted in Africa, 6 in Europe, 3 in Asia, and 1 in South America. Participants were infants (2 studies), children and adolescents (12 studies), or adults (7 studies). The iodine supplement was iodized oil in 11 studies (22, 24, 25, 27, 28, 33–35, 37, 38, 40), potassium iodide in 7 (23, 26, 29, 30, 32, 38, 39), potassium iodate in 2 (16, 17), and iodide-enriched milk formula in 1 study (31). Nine studies gave a daily dose of iodine (in μg/d) and 12 gave a single dose (in mg). For further details of the included studies, *see* **Table 1**.

Validity criteria are displayed in **Table 2**. Six of 12 RCTs had unclear randomization methods. Dropouts varied greatly from study to study, ranging from 7% to 60% (often increasing with

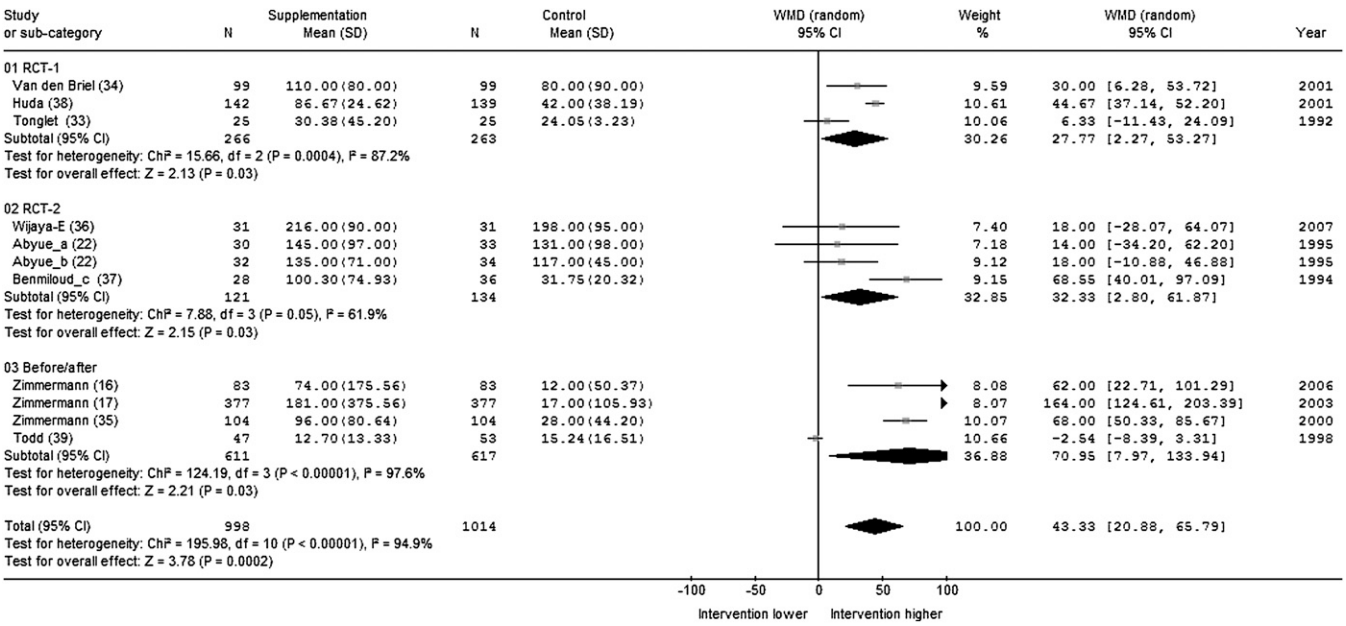

FIGURE 2. Primary analysis: urinary iodine (μg/L). WMD, weighted mean difference; RCT-1, randomized controlled trial with placebo; RCT-2, randomized controlled trial with low-dose iodine supplement; Abuye_a, male group; Abuye_b, female group; Benmiloud_c, 960 vs 120 mg I.

TABLE 3
Systematic review subgrouping results for urinary iodine[1]

Analysis	Mean effect, WMD (95% CI)	Study design			I^2	Biomarker useful?[2]
		RCT	CCT	Before/after		
	μg/L	*no. of studies included/no. of participants*			*%*	
All studies (primary outcome)	43.33 (20.88, 65.79)	7/784	N/A	4/617	94.9	Yes
Infants	18.00 (−28.07, 64.07)	1/62	N/A	N/A	N/A	Unclear
Children and adolescents	50.30 (24.22, 76.38)	5/772	N/A	4/617	95.9	Yes
Pregnant and lactating women	N/A	N/A	N/A	N/A	N/A	Unclear
Adults	6.33 (−11.43, 24.09)	1/50	N/A	N/A	N/A	Unclear
Postmenopausal women	N/A	N/A	N/A	N/A	N/A	Unclear
Elderly	N/A	N/A	N/A	N/A	N/A	Unclear
Low-income and immigrant groups	N/A	N/A	N/A	N/A	N/A	Unclear
Males	18.00 (−6.47, 42.47)	2/128	N/A	N/A	0	Unclear
Females	14.00 (−34.20, 62.20)	1/63	N/A	N/A	N/A	Unclear
Low status at baseline	55.18 (25.66, 84.71)	3/395	N/A	4/617	96.9	Yes
Moderate status	23.06 (7, 39.11)	4/389	N/A	N/A	0	Unclear
High status	N/A	N/A	N/A	N/A	N/A	Unclear
Supplement: iodized oil	37.32 (19.73, 54.92)	6/976	N/A	1/104	81.6	Yes
Supplement: potassium iodide or iodate	59.53 (16.30, 35.36)	1/62	N/A	3/513	96.1	Yes
Dose						
≤200 μg/d	7.86. (−8.7, 24.2)	2/113	N/A	N/A	0	Unclear
201–1000 μg/d	112.99 (13.03, 212.95)	N/A	N/A	2/460	92.30	Probably
≥1001 μg/d	N/A	N/A	N/A	N/A	N/A	Unclear
≤500 mg/single dose	41.87 (26.90, 56.85)	4/487	N/A	1/104	69.4	Yes
≥501 mg/single dose	30.22 (−11.43, 1.87)	2/262	N/A	1/100	93.0	No
Analytic methods						
With ammoniun persulfate	70.38 (37.72, 103.4)	2/343	N/A	3/564	90.0	Yes
With chloric acid	12.31 (−7.15, 31.77)	3/327	N/A	1/53	65.4	No
With automated Technicom Autoanalyzer	36.40 (−24,54, 97.34)	2/114	N/A	N/A	92.4	Unclear

[1] WMD, weighted mean difference; RCT, randomized controlled trial; CCT, nonrandomized trial with a concurrent control group; N/A, no available data.
[2] To claim that a biomarker was effective (ie, reflected a change in status) within a review, 3 conditions needed to be met: *1*) statistical significance within a forest plot (95% CI did not include 0 or $P < 0.05$), *2*) ≥3 studies contributing data, and *3*) ≥50 participants between the intervention and control arms contributing data. To claim that a biomarker was ineffective, 4 conditions had to be met: *1*) lack of statistical significance within a forest plot (95% CI included 0 or $P \geq 0.05$), *2*) ≥3 studies contributing data, *3*) ≥50 participants between the intervention and control arms contributing data, and *4*) study results were roughly similar (heterogeneity levels were acceptable so that I^2 <50%).

length of follow-up). Reasons for dropouts were given in only 7 studies, and compliance was discussed in 6 of the 21 studies. Only 3 studies reported checking the iodine content of the supplement. In 16 studies, iodine dose verification was not carried out because the supplement was a standard pharmacologic preparation.

Urinary iodine

Iodine excretion was measured using different methods and in a number of different units that could not always be interconverted to allow comparison between studies (Table 1). Eleven studies (16, 17, 22, 33–39) assessed change in UI status in response to iodine supplementation. Meta-analysis of the highest-dose arms, subgrouping by study design (3 RCT-1 studies, 4 RCT-2 studies, and 4 B/A studies), showed a statistically significant effect of supplementation on UI [weighted mean difference (WMD): 43.3 μg/L; 95% CI: 20.9, 65.8; 2012 participants; $I^2 = 95\%$, $P = 0.0002$], with each study design suggesting a statistically significant effect (*see* **Figure 2**). This suggested that UI is a useful biomarker of iodine status; because heterogeneity was high, subgroup analysis was performed to assess the usefulness of UI in infants (1 study), children and adolescents (9 studies), and adults (1 study). UI is clearly a useful marker of iodine status in children and adolescents (WMD: 50.3 μg/L; 95% CI: 24.2, 76.4; 1389 participants; $I^2 = 96\%$), but its usefulness in other groups is unclear due to the limited number of studies. This subgrouping did not explain the original heterogeneity of effect (**Table 3**).

There were enough studies and participants to conclude that UI is a useful biomarker in those with low (WMD: 55.2 μg/L; 95% CI: 25.7, 84.71; 7 studies; 1012 participants; $I^2 = 97\%$) (36, 38–40, 42, 43) and moderate iodine status at baseline (WMD: 23.1 μg/L, 95% CI 7.0–39.1, 4 studies, 389 participants, $I^2 = 0\%$) (23, 37, 41). There were no studies of participants with high baseline iodine status (Table 3).

Subgrouping by type of supplementation showed statistically significant effects in both groups and did not reduce heterogeneity (Table 3). Subgrouping by daily dose generally reduced the number of studies in each category to <3, but there was sufficient evidence to suggest that UI appeared to be a useful biomarker of iodine status in those given a <500-mg single-dose of iodine but not in larger single-dose studies. Ordering by duration of supplementation did not suggest a significant effect of time on UI response (Figure S1 under "Supplemental data" in the online supplement). The analytic techniques used to determine UI appeared to influence the data, with analysis using ammonium persulfate seemingly associated with significant effects on UI but

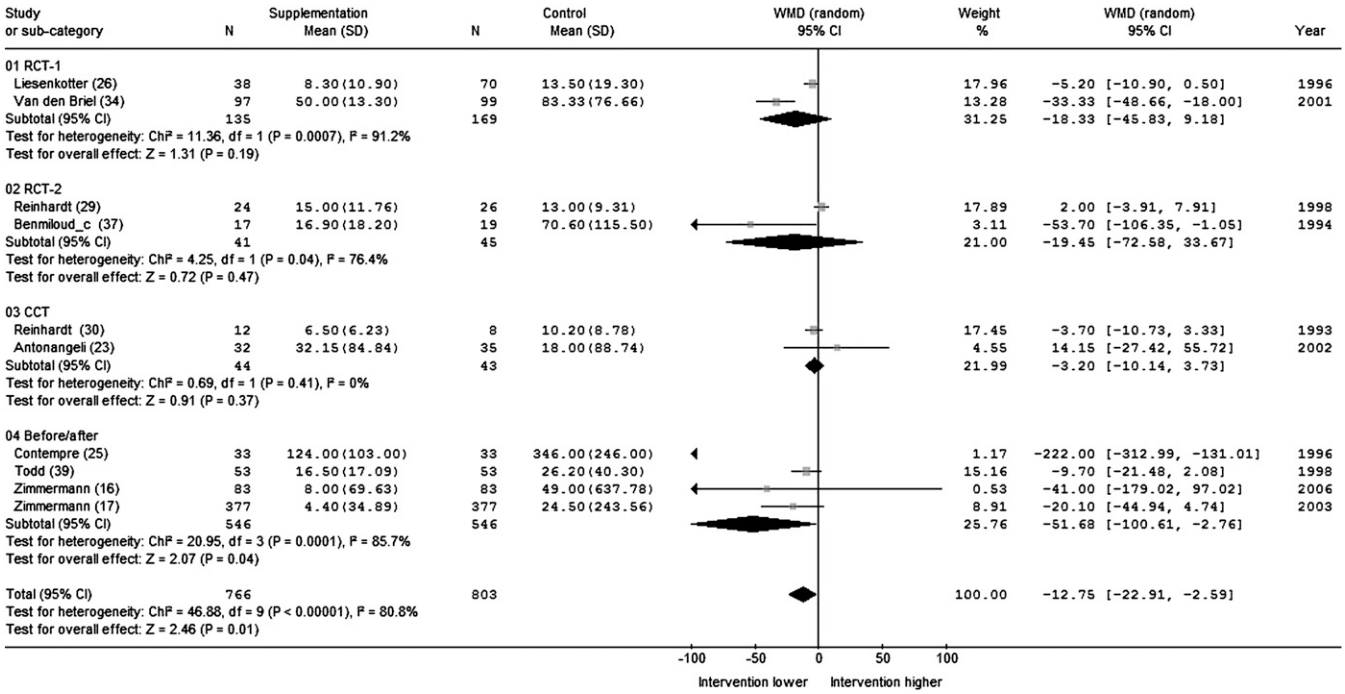

FIGURE 3. Primary analysis: serum/dried blood spot–thyroglobulin (ng/L). WMD, weighted mean difference; RCT-1, randomized controlled trial with placebo; RCT-2, randomized controlled trial with low-dose iodine supplement; CCT, nonrandomized studies with a concurrent control group; Benmiloud_c, 960 vs 120 mg I.

not analysis with chloric acid. There were insufficient studies using an automated technicom analyzer to be sure of its effect.

Overall, UI appears to be an effective biomarker of iodine status in children and adolescents, in those with low-to-moderate baseline iodine status, in those supplemented with iodized oil and potassium iodide or iodate, and in those given a single dose of <500 mg iodine, whereas UI may not be a good marker of status in those given higher (>500 mg) single doses of iodine. However, the data were dependent on the analytic technique used, with responses in UI shown when analysis was performed with ammonium persulfate but not with chloric acid.

Serum thyroglobulin

Ten studies (16, 17, 23, 25, 26, 29, 30, 34, 37, 39) including 1569 participants showed a significant reduction of serum thyroglobulin concentration in response to iodine supplementation (WMD: −12.8 ng/L; 95% CI: −22.9, −2.6, $I^2 = 81\%$, $P = 0.01$), although there was significant heterogeneity in the data. Subgrouping by RCTs, CCTs, and B/A studies did not reduce heterogeneity greatly or suggest statistically significant effects in any but the B/A studies (**Figure 3**). There was a significant decrease in thyroglobulin concentration in children and adolescents (WMD: −39.72 ng/L; 95% CI: −66.82, −12.62; 6 studies; 1324 participants; $I^2 = 81\%$, $P = 0.004$). The evidence was unclear for other population subgroups except for pregnant and lactating women, for whom there was evidence that the marker was not effective (WMD: −1.29 ng/L; 95% CI: −7.67, 5.08; $I^2 = 43.0\%$; *see* **Table 4**). It appeared to be ineffective in adult women (WMD: −1.2 ng/L; 95% CI:−7.7, 5.1; 3 studies; 217 women; $I^2 = 43.0\%$), but there was not enough evidence to assess effectiveness in adult males. Thyroglobulin concentration was not altered in response to supplementation in those with moderate thyroglobulin baseline status (WMD: −3.5; 95% CI: −7.9, 1.0; 6 studies; 648 participants; $I^2 = 29\%$) but was altered in those of high status (WMD: −81.5, 95% CI: −150.7, −12.4; 4 studies; 348 participants; $I^2 = 82\%$), with no studies in those of low baseline status. Ordering studies by duration of supplementation did not suggest an important time effect on thyroglobulin (*see* Figure S2 under "Supplemental data" in the online supplement). Subgrouping by supplementation type suggested that thyroglobulin is an effective biomarker of iodized oil supplementation (WMD: −90.23 ng/L; 95% CI: −170.8, −9.65; 3 studies; 265 participants; $I^2 = 88\%$) but not of potassium iodate or iodide (WMD: −2.51 ng/L; 95% CI: −5.53, 0.51; 7 studies; 758 participants; $I^2 = 1\%$). Dose data were confusing, with clear effects in the 201- to 1000-μg/d subgroup, lack of effect in the ≤200-μg/d subgroup and the >501-mg single-dose group, and unclear effects in other groups (Table 4). Studies using immunofluoroimetric analytic methods showed a significant effect on thyroglobulin, whereas radioimmunoassay and immunoradiometric methods did not.

Thyroglobulin does appear to be a useful marker of iodine status in children and adolescents, but there was little evidence of its usefulness in other groups, and it does not appear to be useful during pregnancy and lactation. Subgrouping did not clarify the sources of heterogeneity in effect size, but the biomarker may be more effective in populations with high baseline thyroglobulin concentrations.

Serum thyroxine

Fourteen studies assessed the effect of iodine supplementation on thyroxine (16, 17, 24–32, 35, 38, 40). Iodine supplementation

TABLE 4
Subgrouping results for serum thyroglobulin[1]

Analysis	Mean effect, WMD (95% CI)	Study design			I^2	Biomarker useful?[2]
		RCT	CCT	Before/after		
	ng/L	*no. of studies included/no. of participants*			*%*	
All studies (primary outcome)	−12.75 (−22.91, −2.59)	4/390	2/87	4/546	80.8	Yes
Infants	N/A	N/A	N/A	N/A	N/A	Unclear
Children and adolescents	−39.72 (−66.82, −12.62)	2/232	N/A	4/546	81	Yes
Pregnant and lactating women	−1.29 (−7.67, 5.08)	3/158	N/A	1/67	43.0	No
Adults	−3.70 (−10.73, 3.33)	N/A	N/A	1/20	N/A	Unclear
Postmenopausal women	N/A	N/A	N/A	N/A	N/A	Unclear
Elderly	N/A	N/A	N/A	N/A	N/A	Unclear
Low-income and immigrant groups	N/A	N/A	N/A	N/A	N/A	Unclear
Males	N/A	N/A	N/A	N/A	N/A	Unclear
Females	−1.29 (−7.67, 5.08)	2/150	1/67	N/A	43.0	No
Low status at baseline	N/A	N/A	N/A	N/A	N/A	Unclear
Moderate status	−3.47 (−7.93, 0.98)	2/158	2/87	2/403	29.3	No
High status	−81.53 (−150.71, −12.36)	2/232	N/A	2/116	81.7	Yes
Supplement: iodized oil	−90.23 (−170.80, −9.65)	2/232	N/A	1/33	87.8	Yes
Supplement: potassium iodide or iodate	−2.51 (−5.53, 0.51)	2/158	2/87	3/513	0.7	No
Dose						
≤200 μg/d	−10.0 (−21.71, 1.72)	1/62	2/55	N/A	66.2	No
201–1000 μg/d	−14.19 (−24.20, −4.17)	2/166	N/A	3/513	59.4	Yes
≥1001 μg/d	−6.50 (−17.69, 4.69)	N/A	N/A	1/53	N/A	Unclear
≤500 mg/single dose	−222.00 (−312.99, −131.01)	N/A	N/A	1/33	N/A	Unclear
≥501 mg/single dose	−25.25 (−47.16, 3.35)	2/262	N/A	1/53	73.0	No
Analytic methods						
Radioimunoassay	−9.90 (−23.3, 3.52)	3/354	N/A	N/A	89.0	No
Immunoradiometric	−52.95 (−130.37–24.46)	N/A	2/87	1/33	91.2	No
Immunofluorimetric	−13.76 (−24.72, −2.80)	1/36	N/A	3/513	2.0	Yes

[1] WMD, weighted mean difference; RCT, randomized controlled trial; CCT, nonrandomized study with a concurrent control group; N/A, no available data.
[2] For explanation of terms, *see* Table 3, footnote *2*.

appears to increase thyroxine concentrations (WMD: 10.7; 95% CI: 6.6, 14.7; 14 studies; 2459 participants; $I^2 = 83\%$), and the effect was similar regardless of the study methodology (**Figure 4**). There was evidence that thyroxine is a good marker of iodine supplementation in children and adolescents (WMD: 14.0; 95% CI: 7.4, 20.5; 8 studies; 1275 participants; $I^2 = 93\%$) and adults (WMD: 12.8; 95% CI: 2.3, 23.1; 3 studies; 260 participants; $I^2 = 85\%$) but not in pregnant and lactating women (WMD: 21.3; 95% CI: −0.8, 43.4; 3 studies; 204 participants; $I^2 = 68\%$), with too few studies in other groups to judge with any certainty (**Table 5**). Thyroxine appears to be an effective biomarker in women (WMD: 19.9; 95% CI: 7.7, 32.1; 4 studies; 430 participants; $I^2 = 52\%$), but there were insufficient studies to evaluate the data in men.

Participants with a moderate thyroxine concentration at baseline responded to iodine supplementation (WMD: 9.9; 95% CI: 5.6, 14.2; 12 studies; 1494 participants; $I^2 = 84\%$), but there were insufficient studies in those with low or high baseline status to draw any conclusion. Iodized oil taken orally and potassium iodide or iodate resulted in statistically significant thyroxine changes ($P < 0.0001$), whereas there were insufficient studies to assess the effects of intramuscular iodized oil and supplemented infant formula (Table 5).

A single dose (≤500 mg iodine) resulted in significant effects on thyroxine (WMD: 10.5; 95% CI: 2.7, 18.3; 6 studies; 825 participants; $I^2 = 90\%$, $P = 0.008$), whereas a moderate daily dose (201–1000 μg/d) did not (WMD: 6.8; 95% CI: −3.0, 16.6; 7 studies; 821 participants; $I^2 = 93\%$), and there were insufficient studies to assess other dose groups. Ordering studies by duration had no clear effect on the size of the thyroxine response (Figure S3 under "Supplemental data" in the online supplement). Studies where thyroxine was assayed with both radioimmuno- and immunofluorimetric assays resulted in significant effects on thyroxine (Table 5).

Overall, serum thyroxine appears to be a useful marker of iodine status in children and adolescents, adults, women, and those at moderate thyroxine status at baseline, where iodized oil, potassium iodate, or iodide are used for supplementation, where a single dose of <500 mg is given, and where either radioimmuno- or immunofluorimetric assays are used. It is not a useful biomarker in pregnant and lactating women or with moderate daily supplementation. The significant heterogeneity seen in the overall analysis of the usefulness of thyroxine is modulated by separating out female only studies, supplementation with potassium iodide or iodate, and use of radioimmunoassay kits.

Serum triiodothyronine

Eight studies assessed the effect of iodine supplementation on triiodothyronine (24–27, 29–32). There was little evidence for a statistically significant effect of changed iodine status on triiodothyronine (WMD: −0.17 nmol/L; 95% CI: −0.36, 0.031;

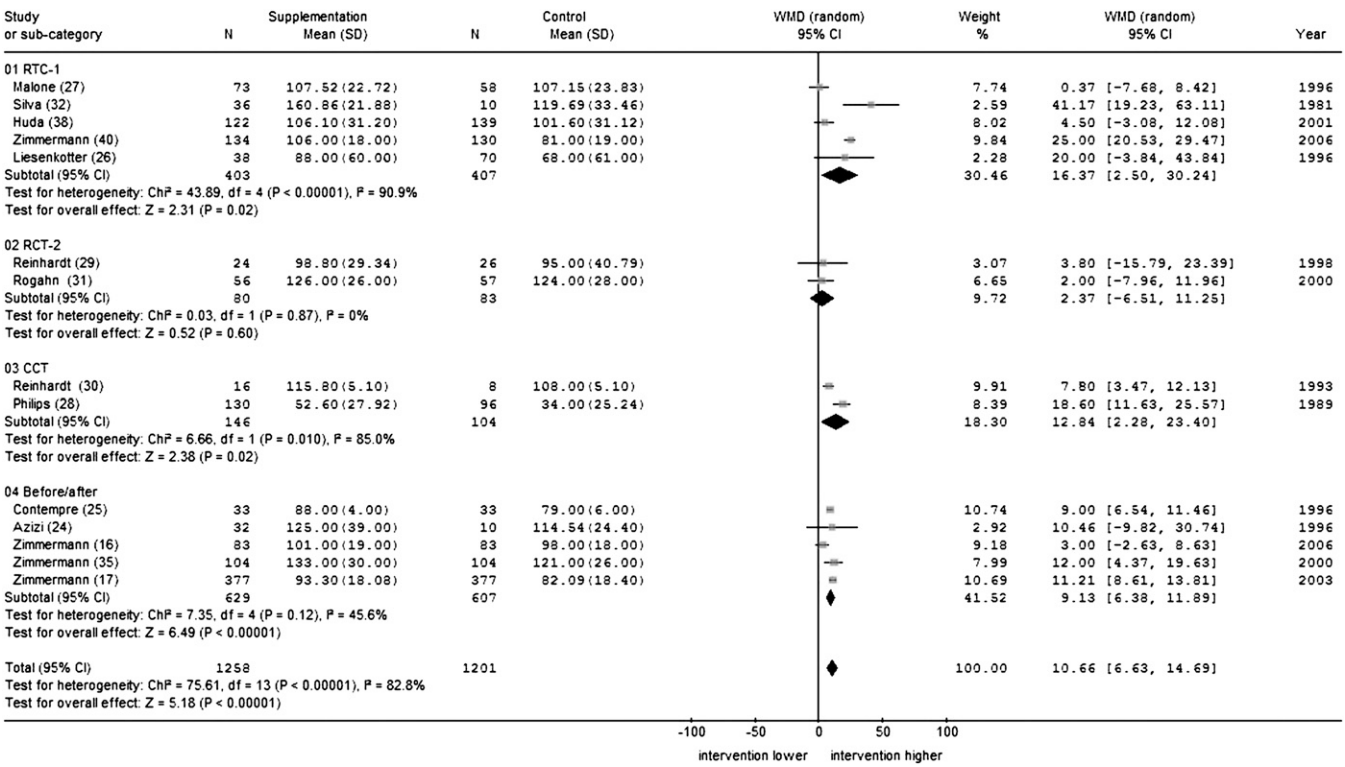

FIGURE 4. Primary analysis: serum thyroxine (nmol/L). WMD, weighted mean difference; RCT-1, randomized controlled trial with placebo; RCT-2, randomized controlled trial with low-dose iodine supplement; CCT, nonrandomized study with a concurrent control group.

8 studies; 625 participants; $I^2 = 86\%$) (**Figure 5**). There were sufficient data to indicate that triiodothyronine is not a useful biomarker of iodine status in children and adolescents, pregnant and lactating women, females, and individuals with moderate triiodothyronine status at baseline. Studies involving potassium iodide or iodate supplementation in which participants consume either a moderate daily iodine dose (201–1000 μg/d) or a $\leq$500-mg single dose or in which samples were analyzed by using either radioimmuno- or immunofluorimetric assays also indicate that triiodothyronine is not a useful biomarker (**Table 6**). In all other subgroupings, there were insufficient studies to assess the effect clearly. There was no evidence of an effect of duration on effect size (Figure S4 under ''Supplemental data'' in the online supplement). Overall, there is no evidence that triiodothyronine is a useful biomarker for iodine status.

Serum thyroid-stimulating hormone

Sixteen studies assessed the effect of iodine intake on serum TSH (16, 17, 23, 24, 26, 27, 29–35, 37–40), which, overall, appeared to be a useful biomarker of iodine status (WMD: −3.00 mU/L; 95% CI: −4.59, −1.40; 16 studies; 1848 participants; $I^2 = 99.4\%$). However, the analysis demonstrated a high degree of heterogeneity in the data, which can probably be explained by high baseline TSH status in participants from 2 of the included studies (23, 24). Consequently, subgroup analysis was undertaken in an attempt to identify other possible sources of variability. RCT-1 studies showed a statistically significant effect on TSH (WMD: −0.33 mU/L; 95% CI: −0.58, −0.08; 7 studies; 968 participants; $I^2 = 29\%$, $P < 0.01$), but none of the other methodology subgroups showed statistically significant effects in their own right (**Figure 6**). There appeared to be statistically significant reductions in TSH for pregnant and lactating women (WMD: −8.8 mU/L; 95% CI: −14.9, −2.7; 4 studies; 184 participants; $I^2 = 100\%$, $P = 0.005$) but not for children and adolescents (WMD: −0.26 mU/L; 95% CI: −0.78, 0.25; 9 studies; 1479 participants; $I^2 = 81\%$), with insufficient data in other participant groups to assess effectiveness. TSH appeared to be a good marker of iodine status in females (data for pregnant and lactating women), but there was insufficient evidence in men (**Table 7**).

There was evidence that TSH was not an effective marker in those with moderate TSH status at baseline (WMD: −0.15 mU/L; 95% CI: −0.4, −0.01; 14 studies; 1781 participants; $I^2 = 67\%$), and there was insufficient evidence from those with low or high baseline status. TSH responded to supplementation with intramuscular iodized oil (WMD: −3.38 mU/L; 95% CI: −6.69, −0.07; 3 studies; 205 participants; $I^2 = 95\%$) and potassium iodide or iodate (WMD: −5.07 mU/L; 95% CI: −8.57, −1.57; 7 studies; 658 participants; $I^2 = 100\%$) but not with oral iodized oil (WMD: −0.18 mU/L; 95% CI: −0.39, 0.03; 7 studies; 947 participants; $I^2 = 11\%$) (unclear with supplemented infant formula). There was evidence that a moderate dose of daily iodine supplementation (201–1000 μg/d) did result in reductions in TSH (WMD: −5.0 mU/L; 95% CI: −8.9, −1.1; 7 studies; 751 participants; $I^2 = 100\%$), but a single dose of <500 mg did not (WMD: −0.4 mU/L; 95% CI: −0.9, 0.2; 8 studies; 882 participants; $I^2 = 85\%$), and results from other dose groups were unclear. Ordering the meta-analyses by duration of supplementation did not suggest any strong effect of duration on TSH response (Figure S5 under ''Supplemental data'' in the online supplement).

TABLE 5
Subgrouping results for serum thyroxine[1]

Analysis	Mean effect, WMD (95% CI)	Study design			I^2	Biomarker useful?[2]
		RCT	CCT	Before/after		
	nmol/L	*no. of studies included/no. of participants*			%	
All studies (primary outcome)	10.66 (6.63, 14.69)	7/873	2/250	5/629	90.9	Yes
Infants	2.00 (−7.96, 11.96)	1/113	N/A	N/A	N/A	Unclear
Children and adolescents	13.95 (7.41, 20.49)	3/656	N/A	5/619	93.2	Yes
Pregnant and lactating women	21.27 (−0.83, 43.37)	3/204	N/A	N/A	67.8	No
Adults	12.84 (2.28, 23.14)	N/A	2/250	1/10	85	Yes
Postmenopausal women	N/A	N/A	N/A	N/A	N/A	Unclear
Elderly	N/A	N/A	N/A	N/A	N/A	Unclear
Low-income and immigrant groups	N/A	N/A	N/A	N/A	N/A	Unclear
Males	10.46 (−9.82, 30.74)	N/A	N/A	1/32	N/A	Unclear
Females	19.91 (7.74, 32.08)	3/204	1/226	N/A	52.1	Yes
Low status at baseline	41.25 (−4.21, 86.70)	N/A	1/226	1/32	96.4	Unclear
Moderate status	9.92 (5.62–14.22)	7/873	1/24	4/597	84,4	Yes
High status	N/A	N/A	N/A	N/A	N/A	Unclear
Supplement: iodized oil	11.76 (4.89, 18.62)	3/656	1/226	3/169	88.8	Yes
Supplement: iodized oil (im)	16.95 (−9.58, 43.48)	1/129	1/168	N/A	93.7	Unclear
Supplement: potassium iodide or iodate	9.71 (4.28, 15.13)	3/280	1/24	2/460	69.6	Yes
Milk formula for preterm infants	2.00 (−7.96, 11.96)	1/113	N/A	N/A	N/A	Unclear
Dose						
≤200 μg/d	−15.39 (−83.98, 53.20)	2/178	N/A	N/A	96.8	Unclear
201–1000 μg/d	6.77 (−3.03, 16.57)	4/337	1/24	2/460	92.5	No
≥1001 μg/d	N/A	N/A	N/A	N/A	N/A	Unclear
≤500 mg/single dose	10.51 (2.73, 18.29)	3/656	N/A	3/169	89.9	Yes
≥501 mg/single dose	18.60 (11.63, 25.57)	N/A	1/226	N/A	N/A	Unclear
Analytic methods						
Radioimunoassay	7.78 (3.13, 12.34)	3/438	1/24	2/65	63.5	Yes
Immunofluorimetric	12.17 (5.87, 18.47)	4/535	1/226	3/564	86.0	Yes

[1] WMD, weighted mean difference; RCT, randomized controlled trial; CCT, nonrandomized trial with a concurrent control group; im, intramuscularly; N/A, no available data.

[2] For explanation of terms, *see* Table 3, footnote *2*.

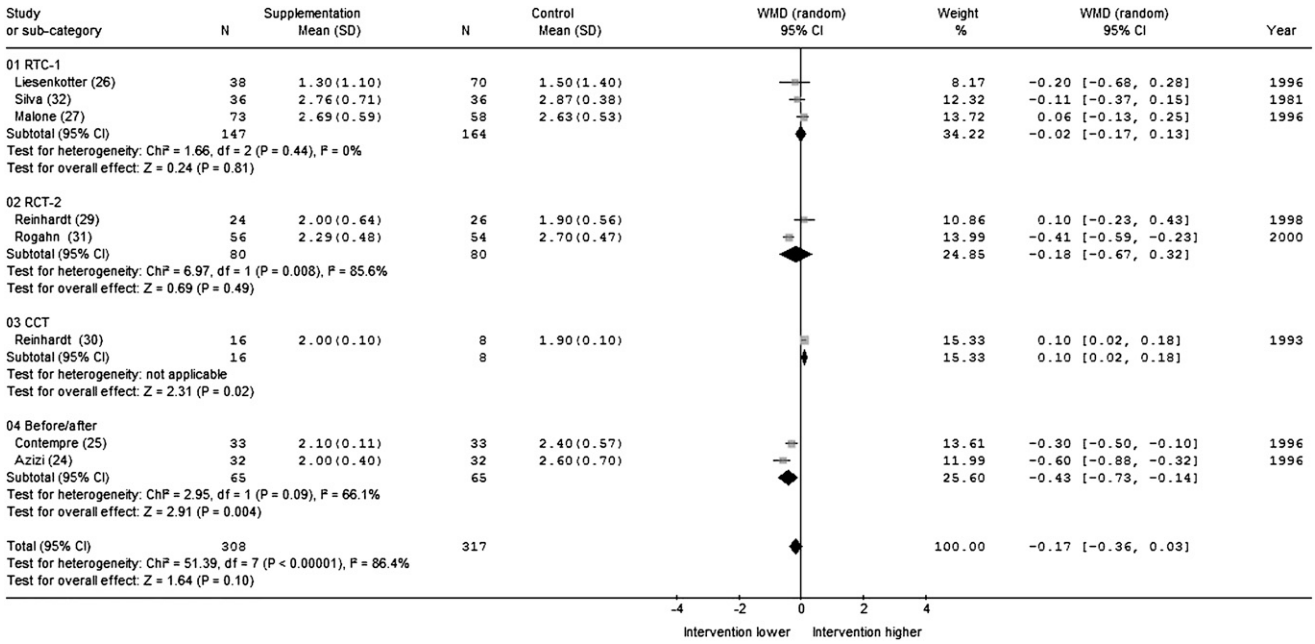

FIGURE 5. Primary analysis: serum triiodothyronine (nmol/L). WMD, weighted mean difference; RCT-1, randomized controlled trial with placebo; RCT-2, randomized controlled trial with low-dose iodine supplement; CCT, nonrandomized study with a concurrent control group.

TABLE 6
Subgrouping results for serum triiodothyronine[1]

Analysis	Mean effect, WMD (95% CI)	Study design			I^2	Biomarker useful?[2]
		RCT	CCT	Before/after		
	nmol/L	*no. of studies included/no. of participants*			%	
All studies (primary outcome)	−0.17 (−0.36, 0.03)	5/4.71	1/24	2/65	86.3	No
Infants	−0.41 (−0.59, −0.23)	1/110	N/A	N/A	N/A	Unclear
Children and adolescents	−0.27 (−0.62, 0.09)	1/131	N/A			No
				2/55	86.9	
Pregnant and lactating women	−0.05 (−0.25, 0.13)	3/230	N/A	N/A	0	No
Adults	0.1 (−0.02, 0.18)	N/A	1/24	N/A	N/A	Unclear
Postmenopausal women	N/A	N/A	N/A	N/A	N/A	Unclear
The elderly	N/A	N/A	N/A	N/A	N/A	Unclear
Low-income and immigrant groups	N/A	N/A	N/A	N/A	N/A	Unclear
Males	−0.60 (−0.88, 0.32)	N/A	N/A	1/32	N/A	Unclear
Females	−0.06 (−0.25, 0.13)	3/230	N/A	N/A	0	No
Low status at baseline	N/A	N/A	N/A	N/A	N/A	Unclear
Moderate status	−0.17 (−0.36, 0.03)	5/471	1/24	2/65	86.3	No
High status	N/A	N/A	N/A	N/A	N/A	Unclear
Supplement: iodized oil	−0.12 (−0.47, 0.22)	1/131	N/A	1/33	82.8	Unclear
Supplement: iodized oil (im)	−0.38 (−0.79, 0.04)	1/129	N/A	1/32	83.9	Unclear
Supplement: potassium iodide or iodate	0.05 (−0.06, 0.16)	3/230	1/24	N/A	14.7	No
Milk formula for preterm infants	−0.41 (−0.59, −0.23)	1/110	N/A	N/A	N/A	Unclear
Dose						
≤200 μg/d	−0.30 (−1.45, 2.05)	2/175	N/A	N/A	88.3	Unclear
201–1000 μg/d	0.04 (−0.59, 0.66)	4/346	1/24	N/A	87.8	No
≥1001 μg/d	N/A	N/A	N/A	N/A	N/A	Unclear
≤500 mg/single dose	−0.27 (−0.62, 0.08)	1/131	N/A	2/65	86.9	No
≥501 mg/single dose	N/A	N/A	N/A	N/A	N/A	Unclear
Analytic methods						
Radioimunoassay	−0.15 (−0.39, 0.08)	2/203	1/24	2/65	92.8	No
Immunofluorimetric	−0.19 (−0.54, 0.15)	3/268	N/A	N/A	71.9	No

[1] WMD, weighted mean difference; RCT, randomized controlled trial; CCT, nonrandomized trial with a concurrent control group; im, intramuscularly; N/A, no available data.
[2] For explanation of terms, *see* Table 3, footnote *2*.

Use of both immunoradiometric (WMD: −8.4 mU/L; 95% CI: −15.3, −1.4; 4 studies; 438 participants; $I^2 = 100\%$, $P = 0.02$) and immunofluorimetric assays (WMD: −0.20 mU/L; 95% CI: −0.37, −0.02; 6 studies; 992 participants; $I^2 = 0\%$, $P = 003$) led to significant effects of iodine on TSH, but the 2 forms of assay gave very different results. The radioimmunoassay did not appear to be effective (WMD: −2.3 mU/L; 95% CI: −4.7, 0.1; 4 studies; 192 participants; $I^2 = 94\%$) (Table 7).

Overall, TSH appears to be a good marker of iodine status and to be useful in pregnant and lactating women and females; with intramuscular iodized oil, potassium iodide, or iodate; with a moderate daily iodine dose; and when using immunoradiometric and immunofluorimetric assays. It does not appear to be useful in children and adolescents, in persons with moderate TSH baseline status who take oral iodized oil supplements or a single dose of <500 mg iodine, and when using radioimmunoassays for sample analysis. There was little indication of which factors might reduce the heterogeneity among studies.

DISCUSSION

Our meta-analyses have demonstrated that UI (in children and adolescents and in those with low and moderate baseline iodine status), serum thyroglobulin (in children and adolescents but not in pregnant and lactating women), serum thyroxine (in children and adolescents, adults, women, and those with moderate baseline thyroxine status but not in pregnant and lactating women), and TSH (in pregnant and lactating women and adult females but not in children and adolescents or those at moderate baseline TSH status) all seem to be useful biomarkers of iodine status. However, there was no evidence that triiodothyronine is a useful biomarker for iodine status.

Overall analysis of all the included studies confirmed UI as an effective biomarker reflecting changes in iodine status in response to iodine administration in certain circumstances. Serum thyroglobulin is a promising new biomarker for monitoring thyroid function (14, 40). However, its sensitivity in population subgroups other than children and adolescents was unclear because of small numbers of participants in most subgroups, and results were also inconsistent in pregnant and lactating women (23, 26, 32). Two intervention studies (16, 17) used the novel dried blood spot thyroglobulin assay and showed its sensitivity to iodine status. It reflected improvements in thyroid function within 42–52 wk of iodine repletion and seemed to be a valid iodine deficiency disorder indicator in that it detected changes in thyroid function in response to changes in iodine supply, which was not shown with UI (33, 35).

The overall results of the meta-analysis showed a significant increase in thyroxine concentration after supplementation; however, there were many differences both between and within

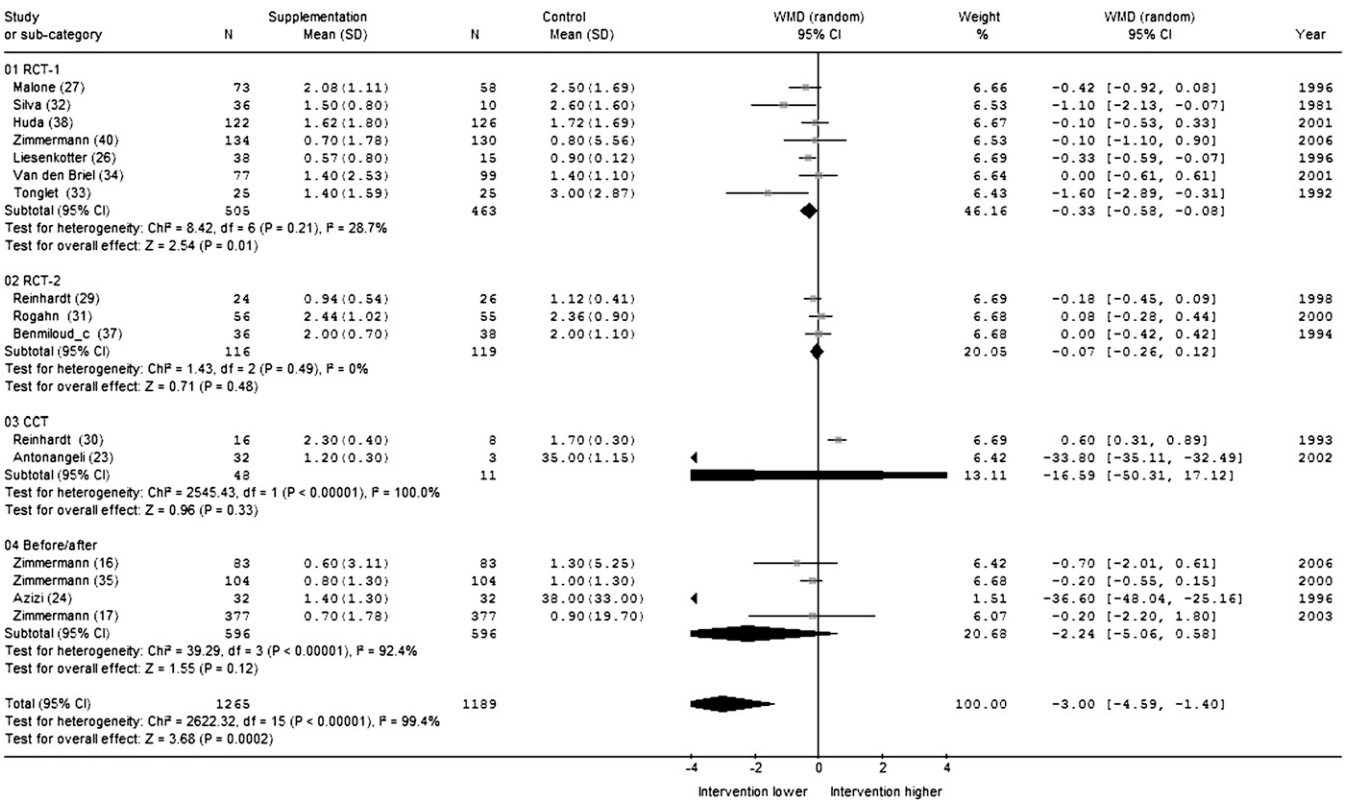

FIGURE 6. Primary analysis: serum thyroid-stimulating hormone (mU/L). WMD, weighted mean difference; RCT-1, randomized controlled trial with placebo; RCT-2, randomized controlled trial with low-dose iodine supplement; CCT, nonrandomized study with a concurrent control group.

the population subgroups studied. A significant increase in serum thyroxine concentrations after supplementation was shown in the moderate thyroxine baseline status group. Many children had goiter due to iodine deficiency even when their baseline thyroxine concentrations were within the normal range. It is generally accepted that thyroxine is usually not recommended for monitoring iodine status because of its lack of sensitivity; however, the results of this review suggested that it may be a useful biomarker in children and adolescents, females, and those with low-to-moderate iodine status.

Random-effect analysis, which included all the studies, presented TSH as an effective biomarker for assessing change in iodine status. Methods for determining TSH concentrations either from dried blood spots on filter paper or from serum are well established and widely available. Serum TSH is measured by very sensitive and highly specific competitive radioimmuno-, immunoradiometric, and immunofluorimetric assay methods, which are available as commercial kits. However, in the case of serum triiodothyronine, random-effects analysis did not show any statistically significant change after supplementation; hence, it cannot be considered as a suitable biomarker of iodine status.

Supplementation with iodized oil in studies measuring UI, thyroglobulin, and thyroxine demonstrated a significant change in status. Iodized oil, when given to children, showed statistically significant changes in 4 of the biomarkers analyzed, which proved the strong effectiveness of this form of supplementation in this particular population subgroup. Further research is needed on the effect of the oral and the intramuscular administration routes. Some studies concluded that iodized oil injection improved thyroid function and could be used for effective treatment of goiter in children and adolescents (24, 27), but others suggested that orally administered iodized oil is cheaper and simpler to use and provides effective iodine prophylaxis for $\leq$2 y after a single dose (28, 34).

Our systematic review included 21 studies, which combined studies of different durations that assessed various doses with various supplemental forms of iodine administered as daily supplements or as single doses in different population subgroups (including schoolchildren, pregnant women, and iodine-deficient adults). These factors, coupled with each study's specific aims and study design, made comparison between the results somewhat complex. None of the included studies fulfilled all the ideal quality criteria (Table 2); eg, there was imbalance in the randomization process for some of the studies.

Cost-effectiveness was not assessed in any of the included interventions, but it is an important factor that needs to be addressed. For example, spot urine samples are relatively easy and inexpensive to obtain, which makes UI a suitable assessment method for iodine status in developing countries, compared with thyroxine and triiodothyronine methods, which are expensive and complex. The choice of the most appropriate indicators to assess iodine status depends on several factors, including their performance, available resources, the age or life stage of the subjects, dietary patterns, the iodine status of the study group, and the study objectives (18).

Because 90% of ingested iodine is excreted in the urine, UI is a widely used method of assessment of iodine status and intake (42). In this review, we found that UI is useful indicator of iodine status along with thyroglobulin concentrations. In the literature, thyroglobulin is described as a promising new

TABLE 7
Subgrouping results for serum thyroid-stimulating hormone[1]

Analysis	Mean effect WMD (95% CI)	Study design			I^2	Biomarker useful?[2]
		RCT	CCT	Before/after		
	mU/L	*no. of studies included/no. of participants*			%	
All studies (primary outcome)	−3.00 (−4.59, −1.40)	10/1193	2/59	4/596	99.4	Yes
Infants	0.09 (−0.28, 0.44)	1/111	N/A	N/A	N/A	Unclear
Children and adolescents	−0.26 (−0.78, 0.25)	5/883	N/A	4/596	80.8	No
Pregnant and lactating women	−8.80 (−14.94, −2.65)	3/149	1/35	N/A	99.9	Yes
Adults	−0.41 (−2.56–1.74)	1/50	1/24	N/A	90.7	Unclear
Postmenopausal women	N/A	N/A	N/A	N/A	N/A	Unclear
Elderly	N/A	N/A	N/A	N/A	N/A	Unclear
Low-income and immigrant groups	N/A	N/A	N/A	N/A	N/A	Unclear
Males	−33.60 (−48.04 to −25.16)	N/A	N/A	1/32	N/A	Unclear
Females	−8.80 (−14.94, −2.65)	3/149	1/35	N/A	99.9	Yes
Low status at baseline	N/A	N/A	N/A	N/A	N/A	Unclear
Moderate status	−0.15 (−0.38, 0.08)	10/1193	1/24	3/564	66.7	No
High status	−33.84 (−35.13, −32.54)	N/A	1/35	1/32	0	Unclear
Supplement: iodized oil	−0.18 (−0.39, 0.03)	6/843	N/A	1/104	11.4	No
Supplement: iodized oil (im)	−3.38 (−6.69, −0.07)	2/173	N/A	1/32	94.7	Yes
Supplement: potassium iodide or iodate	−5.07 (−8.57, 1.57)	3/139	2/59	2/460	99.8	Yes
Milk formula for preterm infants	0.08 (−0.28, 0.44)	1/111	N/A	N/A	N/A	Unclear
Dose						
≤200 μg/d	0.04 (−0.40, 0.32)	2/163	N/A	N/A	47.1	Unclear
201–1000 μg/d	−4.97 (−8.85, −1.09)	3/232	2/59	2/460	99.8	Yes
≥1001 μg/d	N/A	N/A	N/A	N/A	N/A	Unclear
≤500 mg/single dose	−0.35 (−0.92, 0.22)	6/746	N/A	2/136	84.9	No
≥501 mg/single dose	−0.12 (−0.39, 0.15)	1/74	N/A	1/104	0	Unclear
Analytic methods						
Radioimunoassay	−2.25 (−4.65, 0.13)	3/160	N/A	1/32	93.6	No
Immunoradiometric	−8.38 (−15.33, −1.43)	2/379	2/59	N/A	99.9	Yes
Immunofluorimetric	−0.20 (−0.37 to −0.02)	3/428	N/A	3/564	0	Yes
Immunoluminescence	−0.15 (−0.40–0.09)	2/226	N/A	N/A	0	Unclear

[1] WMD, weighted mean difference; RCT, randomized controlled trial; CCT, nonrandomized trial with a concurrent control group; im, intramuscularly; N/A, no available data.
[2] For explanation of terms, *see* Table 3, footnote *2*.

biomarker for monitoring thyroid function (14, 15), which seems to correlate with UI concentrations (9, 14, 41, 43). It is also suggested that thyroid hormones are relatively insensitive markers of status, although TSH is a sensitive biomarker in newborns (14, 15, 44). In contrast, the current review showed that TSH responded significantly to iodine supplementation in the meta-analysis of included studies, although its effectiveness in infants was unclear. The analysis of thyroxine concentration also indicated its potential as a status biomarker. The results for triiodothyronine were in accordance with the literature and showed its ineffectiveness as a useful biomarker of iodine status.

To fully assess the validity of biomarkers of iodine status, RCTs that measure relevant long-term outcomes that specifically investigate iodine supplementation in various population groups in a range of settings need to be undertaken. It is essential that the studies use supplements of known iodine content and appropriate analytic techniques for assessing biomarkers over ≥2 time points. However, interventions have often been carried out in areas with a high prevalence of iodine deficiency, which makes placebo-controlled groups ethically unfeasible. (Other articles in this supplement to the Journal include references 20 and 45–51.)

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