NUTRITION REVIEWS

Lead Article

Systematic review using meta-analyses to estimate dose-response relationships between iodine intake and biomarkers of iodine status in different population groups

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The objective of this systematic review was to identify studies investigating iodine intake and biomarkers of iodine status, to assess the data of the selected studies, and to estimate dose-response relationships using meta-analysis. All randomized controlled trials, prospective cohort studies, nested case-control studies, and cross-sectional studies that supplied or measured dietary iodine and measured iodine biomarkers were included. The overall pooled regression coefficient (β) and the standard error of β were calculated by random-effects meta-analysis on a double-log scale, using the calculated intake-status regression coefficient (β) for each individual study. The results of pooled randomized controlled trials indicated that the doubling of dietary iodine intake increased urinary iodine concentrations by 14% in children and adolescents, by 57% in adults and the elderly, and by 81% in pregnant women. The dose-response relationship between iodine intake and biomarkers of iodine status indicated a 12% decrease in thyroid-stimulating hormone and a 31% decrease in thyroglobulin in pregnant women. The model of dose-response quantification used to describe the relationship between iodine intake and biomarkers of iodine status may be useful for providing complementary evidence to support recommendations for iodine intake in different population groups.

INTRODUCTION

Adequate intake of iodine is essential for thyroid hormone synthesis and, consequently, for normal development and metabolism.[1,2] The main dietary sources of iodine are iodized salt, saltwater fish, seaweed, and grains (if grown in iodine-replete soils).[3,4] Iodate obtained through the diet is almost completely absorbed. Absorption depends mainly on the level of dietary iodine intake rather than on the chemical form of iodine or the composition of the diet. Iodine deficiencies, therefore, are due primarily to insufficient intake of the nutrient.[5,6] The World Health Organization (WHO), the International Council for the Control of Iodine Deficiency Disorders (ICCIDD), and the United Nations Children's Fund (UNICEF) recommend iodine intakes of 90 µg/day for preschool children, 150 µg/day for adults, and 250 µg/day for pregnant and lactating women.[7,8] Approximately 44%

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of the European population have mild iodine deficiency, and iodine intakes in other industrialized countries, including the United States and Australia, have decreased in recent years.[7,9]

In order to include the evidence on iodine status and iodine deficiency disorders in the process of developing recommendations for iodine intake, it is essential to know the daily iodine intake level necessary to maintain or achieve optimal values of iodine biomarkers in blood and urine.[10,11] In a previous systematic review undertaken within the European Micronutrient Recommendations Aligned (EURRECA) Network of Excellence,[12] four biomarkers were found to be useful for determining the iodine status of individuals in various population groups: urinary iodine (UI), serum or dried whole-blood spot thyroglobulin (Tg), serum thyroxine (T4), and serum thyroid-stimulating hormone (TSH).

The aim of this systematic review was to identify and examine studies investigating iodine intake and biomarkers of iodine status and to combine these studies in a meta-analysis to estimate the dose-response relationships between iodine intake and iodine status.

METHODS

This research was conducted within the framework of the EURRECA Network of Excellence.

Study selection

The search included randomized controlled trials (RCTs), prospective cohort studies, nested case-control studies, and cross-sectional studies. RCTs had to involve an iodine intervention (iodine supplementation given as iodized salt (potassium iodide, potassium iodate, or sodium iodide), iodized oil (orally or by injection), iodized water, iodine tablets, or iodine-enriched food or milk formula), and observational studies had to evaluate dietary iodine intake using a validated food frequency questionnaire, a dietary history method or a 24-h recall method for at least 3 days, or WHO criteria for assessing iodine intake (see below). In addition, only studies that measured iodine status with the most robust and sensitive biomarkers were included, i.e., UI, serum Tg, and serum TSH. Studies were excluded if the intervention period was less than 2 weeks (for RCTs) or if they were performed in patient populations. In addition, commentaries, reviews, or duplicate publications from the same study were excluded. Studies in which iodine was administered in combination with another dietary or other lifestyle intervention were also excluded. Studies that reported insufficient data or had insufficient data obtainable from the authors to estimate β and the standard error (SE) of β (SE[β]) for the assumed linear relationship on the $\log_e$-$\log_e$ scale were also excluded.[13]

The assessment of iodine intake using the WHO-specific criteria for calculating iodine intake in epidemiological settings was accepted in the absence of standard dietary assessment methods.[6] This method of population intake assessment is based on the measurement of the median UI concentration and uses the following formula to calculate daily iodine intake: UI (μg/L) $\times$ 0.0235 $\times$ body weight (kg). A median UI concentration of 100 μg/L corresponds to an average iodine intake of 150 μg/day.[14] If the WHO method had not been used and an estimate of intake was needed, median daily iodine intake was estimated from the median UI concentration by the method of the Institute of Medicine,[15] which assumes that 92% of dietary iodine is excreted in the urine and calculates a 24-h urine volume in children by using body weight and age-specific median urine volumes for 7- to 15-year-old children.[16]

Search strategy

Ovid Medline, Embase (OvidSP; both available at http://www.ovid.com), and the Cochrane Central Register of Controlled Trials (CENTRAL) database (available at http://www.thecochranelibrary.com) were searched from inception to February 2010 for relevant studies using the following search terms: "study designs in humans" AND "iodine" AND ("intake" OR status"). Database alerts were checked from February 2010 until December 2011. Details about the search terms used for all databases can be found in the Supporting Information for this article, available online (Table S1). Additionally, 15 reviews were scrutinized[17–31] in duplicate to search for additional potentially relevant studies. Moreover, the reference lists of the RCTs and the observational studies were also checked. Search results from the three databases were pooled and duplicates removed. Each article was assessed for inclusion on the basis of review of the title and abstract (Figure 1). Full texts were assessed by four investigators to determine inclusion or exclusion, with independent duplicate assessment of a random sample of 50%. Disagreements among investigators were resolved through group discussion.

Data collection

Data were extracted by five investigators, with independent duplicate assessment of a random sample of 20% conducted by a second investigator. For RCTs, extracted data included population characteristics, source of iodine, dose of iodine in intervention and placebo groups, duration of the study, dietary intake of iodine, mode of delivery, duration of delivery, mean concentrations of UI, serum Tg and serum TSH at baseline and at the end of the

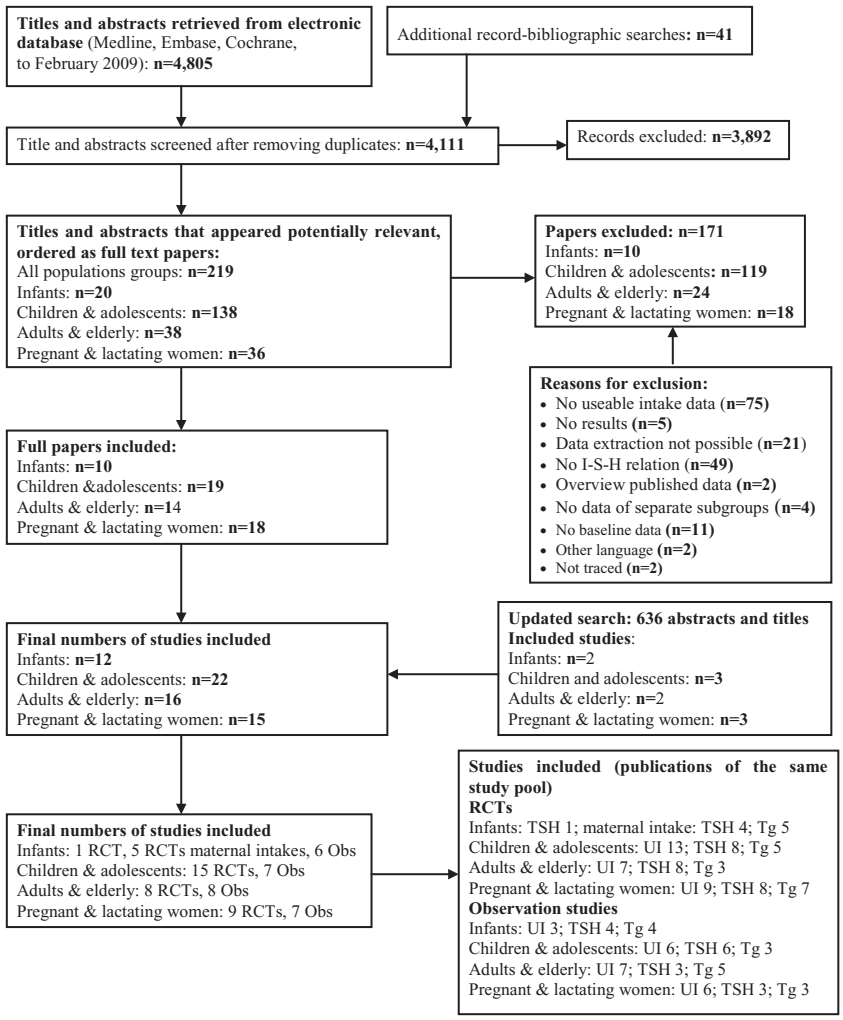

Figure 1 **Flow diagram for the identification of studies included in the systematic review of iodine intake and biomarkers of iodine status.**
Abbreviations: I-S-H, intake-status-health; Obs, observational studies in children and adolescents; RCT, randomized control trial; Tg, thyroglobulin; TSH, thyroid-stimulating hormone; UI, urinary iodine.

intervention period, and analytical methods used to assess iodine status. For the observational studies, extracted data included population characteristics, mean iodine intake and method used to estimate intake, concentrations of UI, serum Tg, and serum TSH, analytical methods used to assess iodine status, the association and type of association (Spearman's rank correlation coefficient, Pearson's correlation coefficient, linear regression coefficient) between iodine intake and iodine-related biomarkers, and information on any transformations applied to obtain the reported associations. Authors of papers were contacted to request missing data or to clarify methods and results.

Data synthesis for RCTs

If a study included two or three iodine-treated groups and one common control group, it was treated as two or three independent estimates in the analysis, and the control group was included more than once in the analysis. In order to check that this approach did not introduce bias to the results, a sensitivity analysis was carried out, removing all but one comparison from each study and re-running the analyses. The control group had to receive either a placebo or a low-dose iodine supplement (low dose had to be defined as providing a dose of <100 μg of iodine per day). In studies administering a single annual dose of iodized oil (mg/yr) and in which the control group received a certain amount of iodine supplementation, the time period for data extraction was selected as being after the lower dose was expected to be fully metabolized (i.e., no residual impact on iodine status) but while a potentially measurable impact on iodine status after the higher dose was still expected.[10] If dietary intake of iodine (on top of the intervention) was not reported, 100 μg/L/day of UI was imputed because this corresponds to the mean daily

iodine intake of RCTs that did report dietary iodine intake.[11,15] An intake-status regression coefficient (β) and the corresponding SE were calculated for each individual study for use in the meta-analyses.[13]

Risk of bias in individual studies

The overall risk of bias of each individual study was assessed using indicators of internal validity specific to RCTs, based on the guidance from the Cochrane Handbook.[32] To determine the validity of the included RCTs, the following were determined: 1) method of sequence generation and allocation concealment; 2) description of blinding and type of blinding; 3) number of participants at start, number of dropouts, and reasons for dropout; 4) potential funding bias; 5) dose check; 6) dietary intake data reported; 7) biomarker comparability and reproducibility; and 8) similarity of most and least exposed groups at baseline. To explore the variability in study results (heterogeneity), subgrouping analyses were used to investigate whether the effect of the type/matrix of the iodine provided (iodized salt, capsules of iodized oil, or potassium iodide tablets), the iodine dose and frequency (category I: single dose ≤500 mg/yr; single dose ≥501 mg/yr; category II: daily intake ≤150 μg; daily intake ≥151 μg), and the duration of the trial (in weeks) were variables that modified the association. A stratified meta-analysis for gender could not be performed because most of the studies included were performed in mixed-gender populations, and data were not available at the individual level or for gender subgroups.

Statistical data analyses

Data from RCTs were recalculated as an intake-status regression coefficient (β) and the corresponding SE(β) for each individual study, based on the assumption of a linear relationship on the $\log_e$-$\log_e$-scale (natural logarithm of intake versus natural logarithm of status).[13] Because of the double $\log_e$ transformation, the overall β represents the difference in the $\log_e$-transformed predicted value of biomarker for each one-unit difference in the $\log_e$-transformed value in iodine intake. The statistical transformations to obtain β and the SE(β)[13] were performed using GenStat version 13-SP2 (Hempstead, UK: VSN International Ltd.). Meta-analysis was carried out with RevMan 4.2 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) using a random-effects model with statistical significance defined as $P < 0.05$. Prespecified potential factors that could modify the association were explored using stratified random-effects meta-analyses. Heterogeneity (expressed as I^2) was used to assess the variability between studies.

RESULTS

The flow diagram of studies assessed and excluded at various stages of the review is presented in Figure 1. The electronic literature search of iodine intake or status yielded 4,805 references. Another 41 references were found by additional reference list searches. After removing duplicates, 4,111 titles and abstracts were screened, and of these, 219 studies appeared potentially relevant and were assessed as full-text papers. Fifty-eight papers for all population groups fulfilled the inclusion and exclusion criteria.[33–90] Of these, 33 were RCTs, in which sample sizes ranged from 30 to 646 participants.[33–65] Further details of included studies are presented in Table 1 and in the Supporting Information for this article, available online (Table S2). Three RCTs were judged to be at low risk of bias, three were judged to be at moderate risk of bias, and 27 were judged to be at a high risk of bias. The most common reasons for high risk of bias were inadequate information on study funding and lack of adequate sequence generation and/or allocation.

Thirty observational studies on iodine intake and status in different population groups were selected.[66–90] Five RCT intervention studies in pregnant women were included as observational studies in the infants of those women. Participants were infants (9 cross-sectional studies, 1 prospective cohort study, 1 nested case-control study), children and adolescents (2 cross-sectional studies, 5 prospective cohort studies), adults and elderly (6 cross-sectional studies, 2 prospective cohort studies), and pregnant and lactating women (4 cross-sectional studies, 2 prospective cohort studies). Two observational studies included both pregnant women and their infants as population groups but did not report the data required to obtain the β coefficients, and these data could not be obtained from the authors. The 30 observational studies included 28,326 subjects in total, with sample sizes ranging from 30 to 4,616 subjects (see Table S2, available in the Supporting Information online). Eleven studies were judged to have a moderate risk of bias, and 14 observational studies were judged to have a high risk of bias. The most common reasons for high risk of bias in observational studies were lack of adequate sequence generation and lack of allocation.

Iodine intake and urinary iodine

Evidence from RCTs in children and adolescents. Thirteen RCTs[33–45] that assessed iodine intake and UI in children and adolescents were identified. Two papers reported data for boys and girls separately,[33,34] two studies had two separate iodine intervention dose groups,[39,44] and two studies had three iodine-treated dose groups[35,41]; therefore, 21 estimates were included in the analysis. These 21

Table 1 **General characteristics of randomized controlled trials ($n = 33$) reporting the effect of dietary iodine intake on urinary iodine, thyroid-stimulating hormone, and thyroglobulin in different population groups.**

Reference	Country	Population characteristics No. included Age or age range	Study design and risk of bias Duration of follow-up for single dose or duration of daily supplementation	Iodine intake dose and characteristics of treatment groups	Iodine status biomarker	Analytic methods
Abuye et al. (1995)[33]	Ethiopia	Schoolchildren with severe ID; goiter rate = 69% $n = 147$ 4–16 yrs	RCT-2; high risk of bias Follow-up: 40 wks	Capsules, single dose (mg/day): 400 mg iodine vs 200 mg iodized oil Control group, low-dose iodine capsules: boys ($n = 34$), girls ($n = 33$) Intervention group, iodine capsules: boys ($n = 34$), girls ($n = 33$)	1. UI	1. Cloric acid digestion (Sandell-Kolthoff reaction)
Benmiloud et al. (1994)[35]	Algeria	Schoolchildren with severe ID in endemic goiter area $n = 182$ 6–11 yrs	RCT-2; high risk of bias Follow-up: 46 wks	Capsules, single dose (mg/day): 120 mg iodine vs 240 mg iodine vs 480 mg iodine vs 960 mg iodized oil Control group, low-dose iodine capsules: ($n = 36$) Intervention groups: I ($n = 36$), II ($n = 33$), III ($n = 28$)	1. UI 2. Tg 3. TSH	1. Automated Technicon AutoAnalyzer 2. RIA 3. RIA
Bautista et al. (1991)[34]	Bolivia	Schoolchildren with severe ID and goiter $n = 200$ 5–12 yrs	RCT-1; double-blind, high risk of bias Follow-up: 88 wks	Capsules, single dose (mg/day): I 475 mg iodized oil Placebo group: boys ($n = 44$), girls ($n = 50$) Intervention group: boys ($n = 45$), girls ($n = 50$)	1 UI 2. Tg 3. TSH	1. Acid digestion (Ce/As method) 2. RIA 3. RIA
Furnée et al. (2000)[36]	Malawi	Schoolchildren with severe ID $n = 230$ 5–12 yrsr	RCT-1; double-blind, high risk of bias Follow-up: 40 wks	Capsules, single dose (mg/day): I 490 mg iodized oil Placebo group: ($n = 33$) Intervention group: ($n = 197$)	1. UI	1. Chloric acid digestion (Sandell-Kolthoff reaction)
Gordon et al. (2009)[37]	New Zealand	Schoolchildren with mild ID $n = 184$ 10–13 yrs	RCT-1; double-blind, low risk of bias Length of daily intervention: 28 wks	Tablets: 150 µg I/day as KI Placebo group: ($n = 87$) Intervention group: ($n = 89$)	1. UI 2. Tg	1. Ammonium-persulfate method 2. RIA
Hintze et al. (1988)[39]	Germany	Schoolchildren in endemic goiter area with moderate ID and goiter vs no goiter $n = 334$ 10 yrs	RCT-1; high risk of bias Length of daily intervention: 192 wks	Iodized salt: 100 µg/day Control group, noniodized salt: ($n = 124$) Intervention group: ($n = 96$) Control group, noniodized salt, with goiter: ($n = 36$) Intervention group, with goiter: ($n = 30$)	1. UI	1. Automated Technicon AutoAnalyzer
Huda & Grantham-McGregor (2001)[38]	Bangladesh	Schoolchildren with severe ID and goiter $n = 305$ 10–13 yrs	RCT-1; double-blind, low risk of bias Follow-up: 16 wks	Capsules, single dose (mg/day): I 400 mg iodized oil Placebo group: ($n = 148$) Intervention group: ($n = 152$)	1. UI 2. TSH	1. Acid digestion (Ce/As method) 2. IRMA
Leisner et al. (1985)[60]	Germany	Schoolchildren in endemic goiter area $n = 195$ 5–17 yrs	RCT-1; high risk of bias Length of daily intervention: 8 mo	Tablets: 100 µg I/day as KI Control group: ($n = 21$) Intervention group: ($n = 66$)	1. TSH	1. RIA

Table 1 **Continued**

Reference	Country	Population characteristics No. included Age or age range	Study design and risk of bias Duration of follow-up for single dose or duration of daily supplementation	Iodine intake dose and characteristics of treatment groups	Iodine status biomarker	Analytic methods
Malone et al. (1996)[61]	Tanzania	Schoolchildren in endemic goiter area *n* = 152 6–17 yrs	RCT-1; high risk of bias Follow-up: 3 mo	Capsules, single dose (mg/day): I 480 mg iodized oil, oral vs i.m. Placebo group: (*n* = 58) Intervention groups: I (*n* = 73), II (*n* = 71)	1. TSH	1. IRMA
Tajtáková et al. (1998)[40]	Slovakia	Schoolchildren in endemic goiter area with mild ID *n* = 646 11 yrs	RCT-1; high risk of bias Length of daily intervention: 68 wks	Tablets: 1,530 µg I every 2 wks as KI Placebo group: (*n* = 305) Intervention group: (*n* = 341)	1. UI 2. Tg 3. TSH	1. Chloric acid digestion (Sandell-Kolthoff reaction) 2. RIA 3. TSH
Untoro et al. (2006)[41]	Indonesia	Schoolchildren in endemic goiter area *n* = 355 8–10 yrs	RCT-2; high risk of bias Follow-up: 12 mo	Capsules, single dose (mg/day): I 200 vs 400 vs 800 mg iodized oil, oral Placebo group: (*n* = 51) Intervention groups: I (*n* = 50), II (*n* = 51), II (*n* = 51)	1. UI	1. Chloric acid digestion (Sandell-Kolthoff reaction)
van den Briel et al. (2000)[42]	Benin	Schoolchildren with mild ID in endemic goiter area *n* = 198 7–10 yr	RCT-1; double-blind, high risk of bias Follow-up: 11 mo	Capsules, single dose (mg/day): I 540 mg iodized oil Placebo group: (*n* = 98) Intervention group: (*n* = 98)	1. UI 2. Tg 3. TSH	1. Chloric acid digestion (Sandell-Kolthoff reaction) 2. RIA 3. Immunoluminescence assay
van den Briel et al. (2001)[43]	Benin	School children with mild ID in endemic goiter area *n* = 198 7–10 yrs	RCT-1; double-blind, high risk of bias Follow-up: 11 mo	Capsules, single dose (mg/day): I 540 mg iodized oil Placebo group: (*n* = 98) Intervention group: (*n* = 98)	1. UI 2. Tg 3. TSH	1. Chloric acid digestion (Sandell-Kolthoff reaction) 2. RIA 3. Immunoluminescence assay
Zimmermann et al. (2006)[45]	Albania	Schoolchildren in endemic goiter area with mild ID *n* = 310 10–12 yrs	RCT-1; double-blind, low risk of bias Follow-up: 24 wks	Capsules, single dose (mg/day):I 400 mg iodized oil Placebo group: (*n* = 146) Intervention group: (*n* = 157)	1. UI 2. TSH	1. Ammonium persulfate method 2. RIA
Zhao et al. (1999)[44]	China	Schoolchildren in endemic goiter area with mild ID *n* = 205 8–10 yrs	RCT-1;. high risk of bias Follow-up: 24 wks	Capsules, single dose (mg/day): I 400 mg iodized oil + market salt Tablets: 200 µg I/day as KI Control group, distributed salt: (*n* = 69) Intervention group: I (*n* = 68), II (*n* = 68)	1. UI	1. Acid digestion (Ce/As method)
Gardner et al. (1988)[46]	United States	Adults in non ID area *n* = 30 22–40 yrs	RCT-2; high risk of bias Length of daily intervention: 2 wks	Tablets: I 500 vs 1,500 vs 4,500 µg I/day as KI in water Control group: low-dose KI tablets (*n* = 9) Intervention group: I (*n* = 9), II (*n* = 9)	1. UI 2. TSH	1. N/A 2. RIA
Elnagar et al. (1995)[47]	Sudan	Adults with goiter *n* = 117 ~21 yrs	RCT-2; high risk of bias Follow-up: 1 yr	Capsules, single dose (mg/day): I 200 vs 400 vs 800, iodized oil, oral Control group, low-dose iodine capsules: (*n* = 41) Intervention group: I (*n* = 37), II (*n* = 39)	1. UI 2. TSH	1. Automated Technicon AutoAnalyzer 2. RIA

Kahaly et al. (1997)[48]	Germany	Adults in endemic goiter area $n = 62$ 20–32 yrs	RCT-1; high risk of bias Length of daily intervention: 26 wks	Tablets: 200 µg I/day as KI Placebo group: ($n = 31$) Intervention group: ($n = 31$)	1. UI 2. TSH 3. Tg	1. Acid digestion (Ce/As method) 2. RIA 3. RIA
Kahaly et al. (1998)[49]	Germany	Adults in endemic goiter area $n = 62$ 19–50 yrs	RCT-1; high risk of bias Length of daily intervention: 26 wks	Tablets: 500 µg I/day as KI Placebo group: ($n = 31$) Intervention group: ($n = 31$)	1. UI 2. TSH 3. Tg	1 Acid digestion (Ce/As method) 2. RIA 3. RIA
Paul et al. (1988)[50]	United States	Adults in non ID area $n = 32$ 23–56 yrs	RCT-2; high risk of bias Length of daily intervention: 2 wks	Tablets: 250 vs 500 vs 1,500 I µg I/day as KI in water Control group, low-dose KI tablets: ($n = 9$) Intervention group: I ($n = 9$), II ($n = 9$)	1. UI 2. TSH	1. Ammonium persulfate method 2. RIA
Phillips et al. (1988)[51]	Zaire	Adults with severe ID in endemic goiter area $n = 38$ ~21 yrs	RCT-1; high risk of bias Length of daily intervention: 2 yrs	Capsules, single dose (mg/day): I 480 mg iodized oil, oral Control group: ($n = 19$) Intervention group: ($n = 19$)	1. UI	1. Ammonium persulfate method
Reinhardt et al. (1993)[62]	Germany	Healthy adults with mild ID $n = 24$ 23–42 yrs	RCT-1; high risk of bias Length of daily intervention: 4 wks	Tablets: 500 µg I/day as KI Placebo group: ($n = 16$) Intervention group: ($n = 8$)	1. TSH 2. Tg	1. IRMA 2. Immunoluminescence assay
Tonglet et al. (1992)[52]	Zaire	Adults with goiter $n = 75$ >15 yrs	RCT-2; high risk of bias Follow-up: 12 mo	Capsules, single dose (mg/day): I 470 vs 118 mg iodized oil, oral Intervention groups: I ($n = 22$), II ($n = 22$)	1. UI 2. TSH	1. Automated Technicon AutoAnalyzer 2. RIA
Antonangeli et al. (2002)[53]	Italy	Pregnant women with mild ID $n = 67$ 20–38 yrs	RCT-2; high risk of bias Length of daily intervention: 11 wks	Tablets: 200 µg iodide/day vs 50 µg iodide/day Control group, low-dose iodine capsules: ($n = 32$) Intervention group: ($n = 35$)	1. UI 2. TSH Measured: I: 29–33 wks gestation II: 3 mo postpartum	1. Automated Technicon AutoAnalyzer 2. IRMA
Glinoer et al. (1995)[54]	Belgium	Pregnant women with mild ID $n = 180$ N/A	RCT-1; high risk of bias Length of daily intervention: 30 wks	Tablets: 100 µg I/day as KI Placebo group: ($n = 60$) Intervention group: ($n = 60$)	1. UI 2. TSH 3. Tg Measured: I: 31.9 ± 0.2 wks gestation II: 40 ± 0.1 wks postpartum	1. Automated Technicon AutoAnalyzer 2. IRMA 3. IRMA
Liesenkotter et al. (1996)[55]	Germany	Pregnant women with mild ID $n = 108$ 21–40 yrs	RCT-1; high risk of bias Length of daily intervention: 30 wks	Tablets: 230 µg I/day as KI Intervention group: ($n = 38$) Control group: ($n = 70$)	1. UI 2. TSH 3. Tg Measured: 2–10 days postpartum	1. Ce/As method (Sandell-Kolthoff reaction) 2. DELFIA 3. RIA
Nohr & Laurberg (2000)[63]	Denmark	Pregnant women $n = 66$ 24–30 yr	RCT-1; moderate risk of bias Length of daily intervention: 14 wks	Multivitamin tablets: 150 µg I/day Control group: ($n = 24$) Intervention group: ($n = 42$)	1. TSH 2. Tg Measured: 35 wks gestation	1. Immunoluminescence assay 2. Immunoluminescence assay

Table 1 **Continued**

Reference	Country	Population characteristics No. included Age or age range	Study design and risk of bias Duration of follow-up for single dose or duration of daily supplementation	Iodine intake dose and characteristics of treatment groups	Iodine status biomarker	Analytic methods
Nohr et al. (2000)[64]	Denmark	Lactating women *n* = 144 24–30 yrs	RCT-1; moderate risk of bias Length of daily intervention: 30 wks	Multivitamin tablets: 150 µg I/day Control group: (*n* = 954) Intervention group: (*n* = 49)	1. TSH 2. Tg Measured: 5 days postpartum	1. Immunoluminescence assay 2. Immunoluminescence assay
Pedersen et al. (1993)[56]	Denmark	Pregnant women with mild ID *n* = 54 24–29 yrs	RCT-1; high risk of bias Length of daily intervention: 30 wks	Tablets: I 200 µg/day as KI Control group: (*n* = 28) Intervention group: (*n* = 28)	1. UI 2. TSH 3. Tg Measured: I: 37 wks gestation II: 2–10 days postpartum	1. Acid digestion (Ce/As method) 2. RIA 3. Immunoluminescence assay
Reinhard et al. (1998)[57]	Germany	Lactating women with mild ID *n* = 70 17–41 yrs	RCT-2; high risk of bias Length of daily intervention: 32 wks	Tablets: 50 µg iodine/day vs 250 µg I/day Control group: (*n* = 34) Intervention group: (*n* = 36)	1. UI 2. TSH 3. Tg Measured: 5 days postpartum	1. Acid digestion (Ce/As method) 2. Immunoluminescence assay 3. Immunoluminescence assay
Romano et al. (1991)[58]	Italy	Pregnant women in endemic goiter area with mild ID *n* = 35 21 yrs	RCT-1; high risk of bias Length of daily intervention: 36 wks	Iodized salt (120–180 µg I/day) Control group: (*n* = 18) Intervention group: (*n* = 17)	1. UI Measured: third trimester of pregnancy	1. Riley & Gochman method (Technicon AutoAnalyzer)
Silva & Silva (1981)[59]	Chile	Pregnant women with moderate ID *n* = 46 17–41 yrs	RCT-1; high risk of bias Tablets: I 300 µg/day as KI Length of daily intervention: 4–16 wks	Tablets: I 300 µg/day as KI Control group: (*n* = 10) Intervention group: (*n* = 36)	1. UI 2. TSH Measured: different gestational ages	1. Acid digestion (Ce/As metrhod) 2. RIA
Rogahn et al. (2000)[65]	United Kingdom	Premature infants *n* = 62 females, N = 59 males <33 wks of gestation	RCT-2; moderate risk of bias Length of daily intervention: 40 wks	272 vs 68 µg I/L milk formula Control group, lower I: (*n* = 60) Intervention group, higher I: (*n* = 61)	1. TSH 2. Tg	1. chemoluminescence assay 2. chemoluminescence assay

Abbreviations: Ce/As method, reduction of ceric ion by the oxidation of arsenite ion after acidic digestion method; DBS, dried blood spot; DELFIA, immunofluorometric assay; I, iodine; i.m., intramuscularly; IRMA, immunoradiometric assay; KI, potassium iodide; N/A: no answer; RCT-1, randomized controlled trial with placebo; RCT-2, randomized controlled trial with low-dose iodine supplement; RIA, radioimmunoassay; Tg, thyroglobulin, TSH, thyroid-stimulating hormone; UI, urinary iodine; UIE, urinary iodine excretion.
Criteria by WHO/UNICEF/ICCIDD[6,7] were used to classify the severity of IDD in the population. For thyroid volumes and goiter, the classification is based on the prevalence of the condition: mild, 5–19.9%; moderate, 20–29.9%; and severe, >30%. For the median urinary iodine, the classification is as follows: mild, 50–99 µg/L; moderate µg/L, 20–49 µg/L; and severe, <20 µg/L.

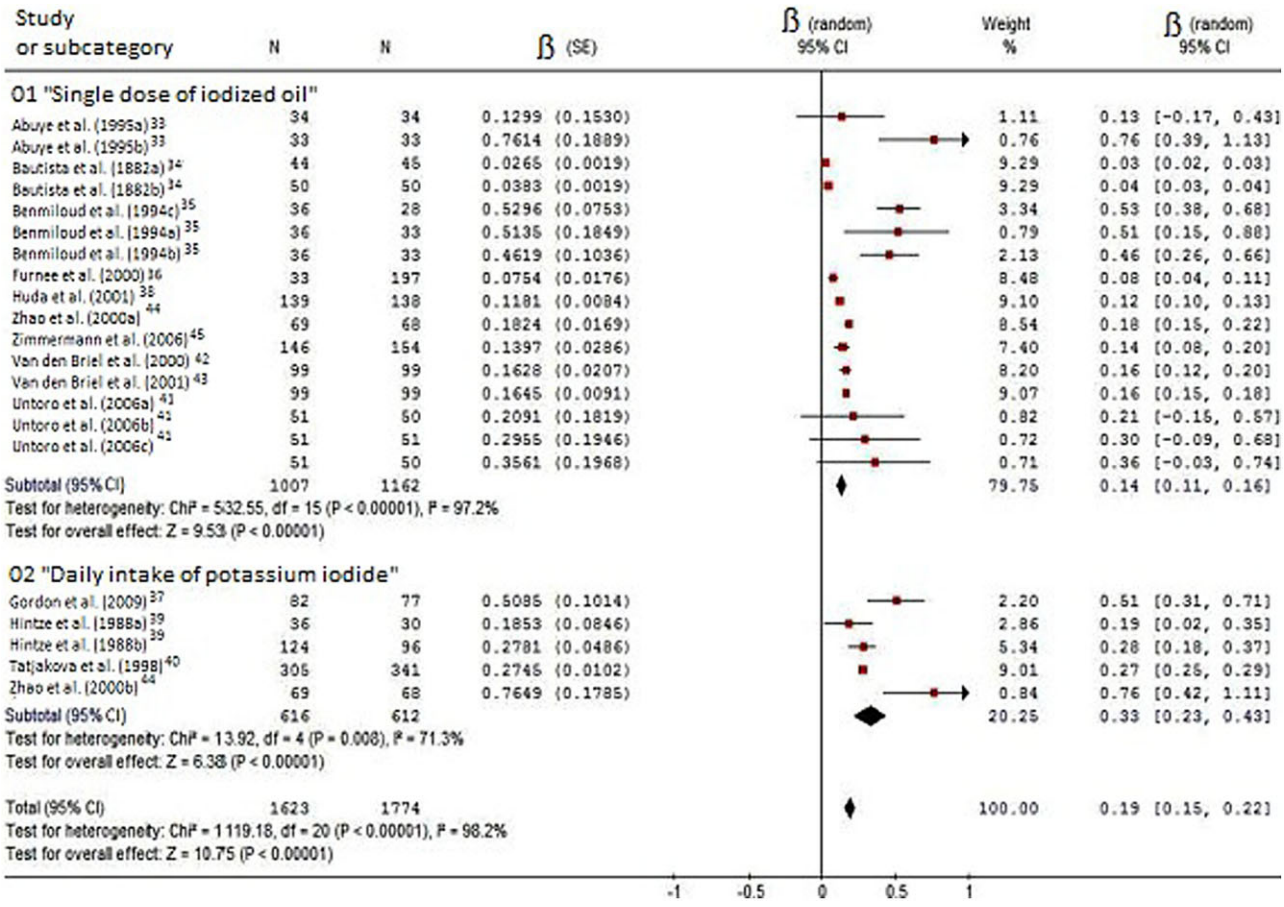

Figure 2 **Primary analysis of urinary iodine (μg/L) in children and adolescents.** β (random) values represent the regression coefficients for the linear association between log-transformed iodine intake and log-transformed urinary iodine excretion.
Abbreviations: CI, confidence interval; df, degrees of freedom; SE, standard error.

estimates included a total of 3,397 participants with an age range of 4 to 16 years (Table 1). The median duration of the included studies was 12 weeks (range, 2–192 weeks). In four RCTs,[37,39,40,44] iodine supplements were given in the form of potassium iodide, in doses that ranged from 100 to 1,500 μg/day. Iodized oil supplementation was used in 10 RCTs,[33–36,38,41–45] with doses ranging from 120 to 960 mg/day.

Combining the 21 estimates of RCTs provided an overall pooled β coefficient of 0.19 (95%CI: 0.15–0.22; 3,397 participants, $I^2 = 98\%$) (Figure 2, Table 2). Therefore, an overall β of 0.19 means that, for every doubling in iodine intake, the difference in UI concentration increases 2^{β}-fold or by 14%, since $2^{0.19} = 1.14$. A stratified meta-analysis on the basis of 16 RCT estimates using a single dose of iodized oil yielded an overall β of 0.14 (95%CI: 0.11–0.16; $I^2 = 97\%$). A stratified meta-analysis on five RCT estimates using a daily dose of potassium iodide yielded an overall β of 0.33 (95%CI: 0.23–0.43; $I^2 = 71\%$) (see Table 2 and Figure 2). This means that children who receive an annual dose of iodized oil of 1,000 mg/yr have a UI excretion that is $2^{0.14}$ (1.10-fold) or 10% higher than that in children who receive an annual dose of 500 mg/yr. However, in studies that investigated a daily dose of potassium iodide, the difference in UI concentration is 2^{β} (i.e., $2^{0.33} = 1.26$), or 26%. Thus, children with an iodine intake of 150 μg/day have a UI concentration that is 26% higher than that in children who have a iodine intake of 75 μg/day.

Evidence from RCTs in adults and the elderly. Seven RCTs[46–52] on iodine intake and UI in adults and the elderly (646 participants) were included in the review. Four studies[46,47,50,52] had two groups treated with different doses of iodine; therefore, 11 estimates were included in the analysis. Combining the seven RCTs in one meta-analysis provided an overall pooled β coefficient of 0.65 (95%CI: 0.39–0.90; $I^2 = 98\%$), which corresponded to a $2^{0.65}$ or 1.57-fold increase in UI (Table 2 and Figure 3). A stratified analysis yielded an overall β of 0.07 (95%CI:

Table 2 **Stratification of the systematic review, along with results of subgrouping meta-analyses for urinary iodine, serum thyroid-stimulating hormone, and serum thyroglobulin (RCTs for all population groups).**

Population group	Urinary iodine					Serum thyroid-stimulating hormone					Serum thyroglobulin				
	No. of estimates of RCT/no. of participants	β value	Lower limit 95%CI	Upper limit 95%CI	I^2	No. of estimates of RCT/no. of participants	β value	Lower limit 95%CI	Upper limit 95%CI	I^2	No. of estimates of RCT/no. participants	β value	Lower limit 95%CI	Upper limit 95%CI	I^2
Children and adolescents[a]															
Single dose of iodized oil (200–500 mg)[33–38,41–44]	16/2,169	0.14	0.11	0.16	97%	8/1,039	0.02	0.01	0.09	0%	5/498	−0.04	−0.10	0.03	91%
Daily dose of potassium iodide (100–200 μg)[37–40,44]	5/1,228	0.33	0.23	0.43	71%	3/184	−0.14	−0.34	0.06	92%	3/261	0.00	−0.24	−0.24	85%
Combined analysis		0.19	0.15	0.22	98%		−0.00	−0.02	0.03	70%		−0.02	−0.08	0.03	88%
Adults and elderly[b]															
Single dose of iodized oil (200–500 mg)[47,51,52]	5/446	0.07	0.03	0.10	14%	4/408	−0.08	−0.15	−0.01	0%					
Daily dose of potassium iodide (250–1,500 μg)[46,48–50]	6/200	0.98	0.64	1.32	94%	7/224	0.11	0.06	0.16	0%	3/144	−0.23	−0.50	0.03	59%
Combined analysis		0.65	0.39	0.90	98%		0.03	−0.05	0.12	60%					
Pregnant and lactating women[c,d]															
Daily dose of potassium iodide: (100–300 μg)[53–59]															
Pregnancy	7/430	0.86	0.62	1.10	78%	6/461	−0.18	−0.36	0.00	78%	5/415	−0.54	−0.78	−0.32	48%
After delivery	4/291	0.27	−0.04	0.58	78%	5/335	0.02	−0.39	0.44	95%	5/434	−0.38	−0.82	−1.08	89%
Combined analysis		0.62	0.38	0.86	88%		−0.13	−0.27	0.11	90%		−0.60	−0.70	−0.49	86%

Abbreviations: CI, confidence interval; RCT, randomized controlled trial.

[a] For every doubling in iodine intake, the difference in UI increases 2β-fold or by 14% in the case of the exponentiated value of 0.19 = 1.14.

[b] For every doubling in iodine intake, the difference in UI increases 2β-fold or by 57% in the case of the exponentiated value of 0.65 = 1.57.

[c] For every doubling in iodine intake, the difference in UI increases 2β-fold or by 52% in the case of the exponentiated value of 0.62 = 1.57.

[d] For every doubling in iodine intake, the difference in thyroglobulin decreased 2β-fold or by 31% in the case of the exponentiated value of −0.60 = 1.57.

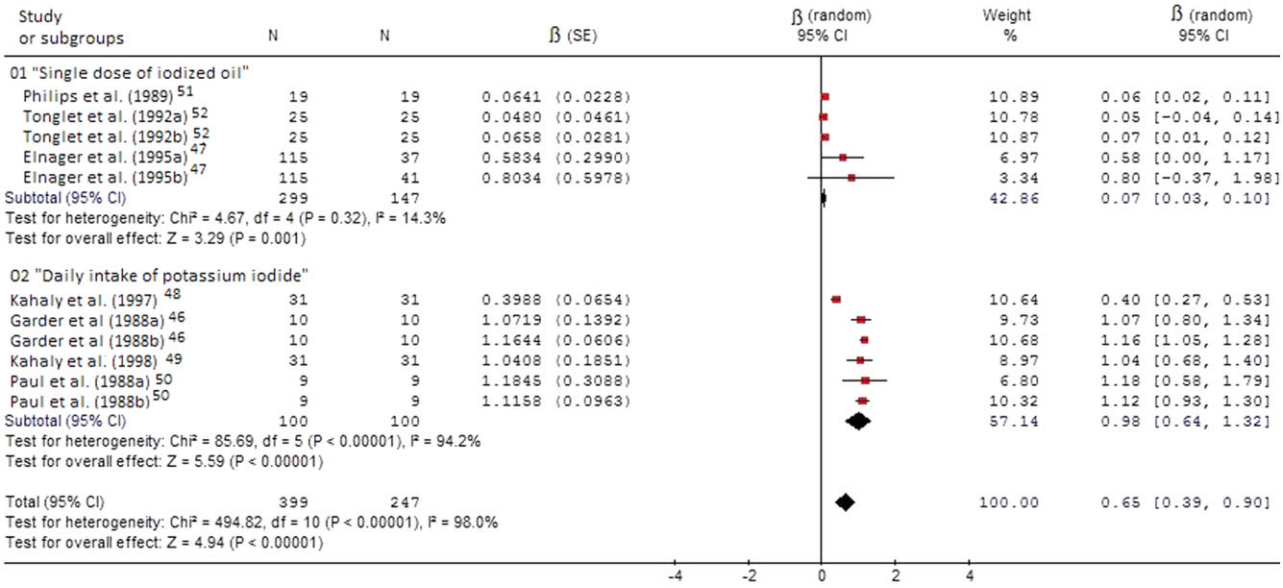

Figure 3 **Primary analysis of urinary iodine (µg/L) in adults and the elderly.** β (random) values represent the regression coefficients for the linear association between log-transformed iodine intake and log-transformed urinary iodine excretion. *Abbreviations*: CI, confidence interval; df, degrees of freedom; SE, standard error.

0.03–0.10; 446 participants, $I^2 = 14.3\%$) for studies using a single dose of iodized oil (5 estimates of RCTs) and an overall β of 0.98 (95%CI: 0.64–1.32; 200 participants, $I^2 = 94\%$) for studies using a daily dose of iodine (6 estimates of RCTs), i.e., a 1.05- and 1.97-fold increase in UI, respectively (Table 2). Thus, a subject with an annual intake of iodized oil of 1,000 mg/yr will have a UI excretion that is 5% higher (predicted UI <158 µg/L) than a person who has an iodine intake of 500 mg/yr (predicted UI <150 µg/L) given as a single dose of iodized oil.

Evidence from RCTs in pregnant and lactating women. Seven RCTs[53–59] that assessed the daily dose of potassium iodide intake and UI in pregnant and lactating women (470 participants) were included in the review. Combining the seven RCTs in one meta-analysis provided an overall pooled β coefficient of 0.62 (95%CI: 0.38–0.86; $I^2 = 88.1\%$), which corresponded to a $2^{0.62} = 1.52$-fold increase in UI (Table 2 and Figure 4). In the subgroup of pregnant women, the pooled β was 0.86 (95%CI: 0.62–1.10; 430 participants, $I^2 = 78\%$) (6 estimates of RCTs), whereas it was 0.27 (95%CI: −0.04–0.58; 291 participants $I^2 = 78\%$, $P = 0.09$) in the subgroup of women in the postnatal period (4 estimates of RCTs), i.e., a 1.84- and 1.20-fold increase in UI, respectively (Table 2 and Figure 4). Thus, in pregnant women with an iodine intake of 200 µg/day in the form of potassium iodide, the UI concentration was 81% higher than in pregnant women with an iodine intake of 100 µg/day, and in the postnatal period, it was 20% higher.

Observational evidence in all population groups. Twenty-two observational studies of iodine intake and UI were included.[66–79,81–86,88,89] Participants were infants (2 cross-sectional studies, 1 nested case control study), children and adolescents (2 cross-sectional studies, 5 prospective cohort studies), adults and elderly (6 cross-sectional studies, 1 prospective cohort study), and pregnant and lactating women (4 cross-sectional studies, 1 prospective cohort study) (see Table S2, available in the Supporting Information online). One study presented data for two population groups: pregnant women and their infants. The included observational studies reported iodine intake and iodine biomarker concentrations per category of iodine deficiency. Since these studies did not report the association or correlation between intake and status, it was not possible to estimate the β or the SE(β) for a dose-response meta-analysis. A brief summary of the key results of these observational studies is shown in Table 3.

Iodine intake and thyroid-stimulating hormone

Evidence from RCTs in children and adolescents. Eight RCTs[34–36,42–45,60,61] that assessed iodine intake and TSH concentration in children and adolescents were included. One study reported data for boys and girls separately,[40] and one study had three groups treated with different doses of iodine,[35] so 11 estimates with a total of 1,223 participants were included. The overall pooled β coefficient was 0.00 (95%CI: −0.02–0.03; $I^2 = 70\%$, $P = 0.88$)

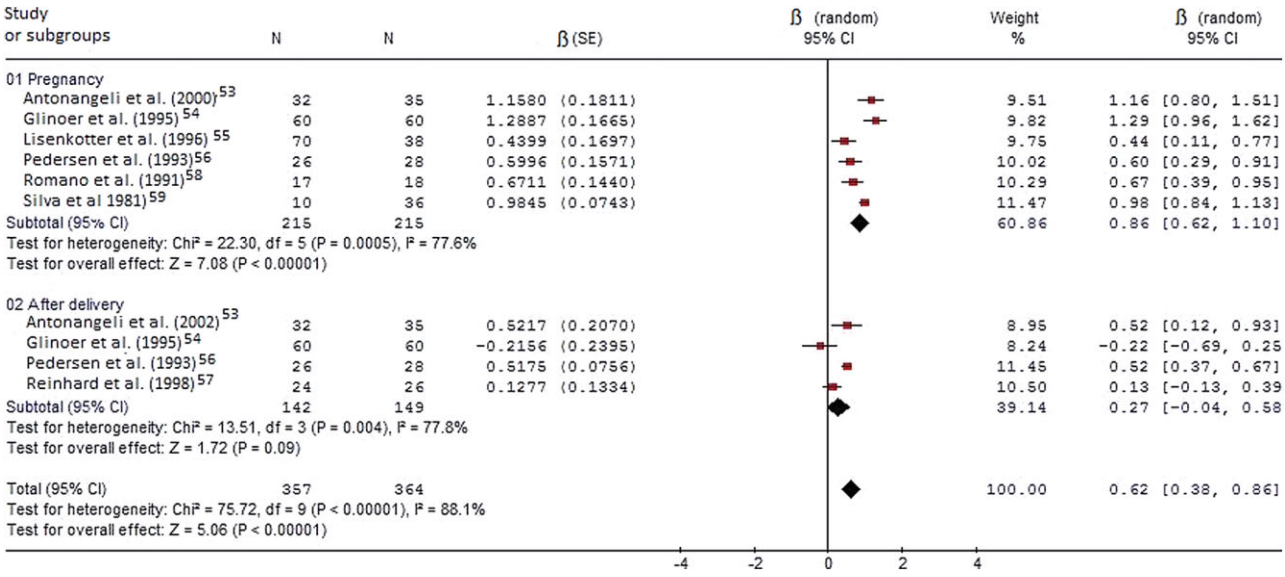

Figure 4 **Primary analysis of urinary iodine (μg/L) in pregnancy and lactating women.** β (random) values represent the regression coefficients for the linear association between log-transformed iodine intake and log -transformed urinary iodine excretion.
Abbreviations: CI, confidence interval; df, degrees of freedom; SE, standard error.

(Table 2). A stratified meta-analysis yielded an overall β of 0.02 (95%CI: 0.01–0.03; $I^2 = 0\%$) using a single dose of iodized oil (8 estimates of RCTs, 1,039 participants) and an overall β of −0.14 (95%CI: −0.34–0.06; $I^2 = 92\%$) for a daily dose of iodine (3 estimates of RCTs; 184 participants) (Table 2). An overall β of 0.02 means that, for every doubling in iodine intake, the difference in TSH concentration increases by 1%. An annual dose of iodized oil of 1,000 mg iodine/yr translates to a TSH concentration that is 1% higher than that in a child with an iodine intake of 500 mg in a single dose.

Evidence from RCTs in adults and the elderly. Seven RCTs[46–50,52,62] on iodine intake and TSH in adults and elderly (632 participants) were included in this review. Four studies[46,47,50,52] had two groups treated with different doses of iodine; therefore, 11 estimates were included in the analysis. Combining the estimates provided an overall pooled β coefficient of 0.03 (95%CI: −0.05–0.12; $I^2 = 60\%$) (Table 2). A stratified analysis yielded an overall β of −0.08 (95%CI: −0.15 to −0.01; $I^2 = 0\%$) using a single dose of iodized oil (4 estimates of RCTs, 408 participants) and of 0.11 (95%CI: 0.06–0.16; $I^2 = 0\%$) for the daily doses of iodine (7 estimates of RCTs, 224 participants) (Table 1 and 2). Thus, the TSH concentration is decreased by 5% in subjects who receive an annual dose of iodized oil and is increased by 8% in persons who receive a daily dose of iodine in the form of potassium iodide.

Evidence from RCTs in pregnant and lactating women. Seven RCTs[53–56,58,59] on iodine intake and TSH concentration in pregnant and lactating women (511 participants) were included in this review. Combining the seven RCTs in one meta-analysis resulted in an overall pooled β coefficient of −0.13 (95%CI: −0.27–0.01; $I^2 = 90\%$) (Table 2). In the subgroup of pregnant women, the pooled β was −0.18 (95%CI: −0.36–0.00; $I^2 = 77\%$, $P < 0.05$) (6 estimates of RCTs, 461 participants) during pregnancy and 0.02 (95%CI: −0.39–0.44; $I^2 = 95.8\%$, $P = 0.91$) in the postnatal period (5 estimates of RCTs, 335 participants) (Table 2). Therefore, daily intake of iodine as potassium iodide, with an overall β of −0.18, results in a decrease in TSH concentration of 12% for every doubling in iodine intake in pregnant women.

Observational evidence in all population groups. Nineteen observational studies of iodine intake and TSH (see Table S2, available in the Supporting Information online) were selected for inclusion.[66–68,70–72,75] Participants were infants (7 cross-sectional study, 1 prospective cohort study), children and adolescents (2 cross-sectional studies, 4 prospective cohort studies), adults and elderly (3 cross-sectional studies), and pregnant and lactating women (2 cross-sectional studies) (see Table S2, available in the Supporting Information online). The 19 observational studies included a total of 8,288 participants, with sample sizes ranging from 20 to 1,584 subjects. Since no correlations between iodine intake and status were presented by these studies, a meta-analysis was not possible. A brief summary of iodine intake and TSH levels in different population groups in the observational studies is included in Table 3.

Table 3 **A brief summary of key association of low, adequate, and excess iodine intake and urinary iodine, thyroid-stimulating hormone, and thyroglobulin in 30 observational studies.**

Reference	Population group	Severity of ID[a]	Iodine intake	Results
Simescu et al. (2002)[67]; Zimmermann et al. (2000)[68]	Schoolchildren	Mild	200 mg/single dose; yes vs no supplement use	UI 130 μg/L vs UI <40 μg/L
Ojule & Osotimehin (1998)[90]; Zimmermann et al. (2005)[71]; Zimmermann et al. (2006)[72]	Schoolchildren	Mild	Adequate vs more-than-adequate vs excess intake of iodized salt (>300 μg/day)	UI <130 μg/L vs UI >200 μg/L vs UI >700 μg/L
Zimmermann et al. (2003)[69]; Zimmermann et al. (2004)[70]; Zimmermann et al. (2006)[72]	Schoolchildren	Severe	250 μg/day; yes vs no supplement use	UI <180 μg/L vs UI <20 μg/L
Torheim et al. (2005)[77]	Adults	Severe	Iodization of salt: <25 ppm vs 25–70 ppm vs >70 ppm	UI from 34 μg/L to 40 μg/L to 70 μg/L
	Adults	Mild	Before vs after bread fortification; yes vs no supplement use	UI <70 μg/L vs UI >100 μg/L vs UI >200 μg/L
Teng et al. (2006)[76]; Andersen et al. (2009)[78]; Laurberg et al. (1998)[79]; Squatrito et al. (1981)[75]	Adults	Mild Moderate	Low (40–60 μg/day), adequate (>100 μg/day), more-than-adequate (>200 μg/day), or higher (>300 μg/day) intake	UI 30–40 μg/L vs UI 130–160 μg/L vs UI 350 μg/L vs UI >600 μg/L
Mian et al. (2009)[81]; Mezosi et al. (2000)[82]; Velasco et al. (2009)[86]	Pregnant women	Moderate	150 vs 300 μg/day; yes vs no supplement use	UI <100–130 μg/L vs UI 200 μg/L vs UI <20 μg/L
Mian et al. (2009)[81]; Mezosi et al. (2000)[82]; Zimmermann et al. (2005)[84]	Pregnant women	Moderate[31,32] in areas of non ID[34]	Iodized salt intake: 105 μg/day vs 190 μg/day	UI <60 μg/L vs UI >100 μg/L UI from 115 μg/L to 141 μg/L
Simescu et al. (2002)[67]; Zimmermann et al. (2005)[84]	Schoolchildren	Mild	200 mg/single dose; yes vs no supplement use	TSH unchanged and TSH ↓ 0.2 mU/L
Ojule & Osotimehin (1998)[90]	Schoolchildren	Mild	Adequate iodized salt intake: >100 μg/day	TSH ↓ 0.5 mU/L
Zimmermann et al. (2003)[69]; Zimmermann et al. (2004)[70]; Zimmermann et al. (2006)[72]	Schoolchildren	Severe	250 μg/day; yes vs no supplement use	TSH ↑ 0.2–0.4 mU/L after 20-wk intervention TSH ↓ 0.2 mU/L vs baseline after 48-wk intervention
Andersen et al. (2009)[78]; Guan et al. (2008)[80]; Squatrito et al. (1981)[75]	Adults	Mild	More-than-adequate (>200–299 μg/day) or higher (>300 μg/day) intake	TSH at baseline 0.9–1.1 mU/L TSH ↑ 0.2–0.8 mU/L vs TSH ↑ 0.2–0.8 mU/L
Squatrito et al. (1981)[75]	Adults	Moderate	Adequate intake: >100 μg/day	TSH at baseline <5 mU/L, TSH ↓ 0.8 mU/L
Velasco et al. (2009)[86]; Moleti et al. (2008)[83]	Pregnant women	Moderate	300 μg/day; yes vs no supplement use Iodized salt intake: 190 μg/day vs 105 μg/day	TSH ↓ 0.5 mU/L TSH ↑ 0.3 mU/L
Simescu et al. (2002)[67]	Schoolchildren	Mild	200 mg/single dose of iodized oil; yes vs no supplement use	Tg ↓ 3.8 ng/L
Zimmermann et al. (2004)[70]; Zimmermann et al. (2006)[72]	Schoolchildren	Severe	250 μg/day; yes vs no supplement use	Tg ↓ 18–36 ng/L after 20 wks
Teng et al. (2006)[76]; Andersen et al. (2009)[78]; Rasmussen et al. (2002)[73]; Squatrito et al. (1981)[75]	Adults	Mild	Adequate (>100 μg/day) vs more-than-adequate (>200 μg/day) intake	Tg at baseline 6–15 ng/L Tg ↓ 4 ng/L adequate vs ↓ 1.7–7 ng/L >adequate intake
Laurberg et al. (1998)[79]	Adults	Moderate	Adequate intake: >100 μg/day	Tg ↑ 6 0.3 ng/L
Velasco et al. (2009)[86]; Moleti et al. (2008)[83]	Pregnant women	Moderate	300 μg/day; yes vs no supplement use Iodized salt:intake; 190 μg/day vs 105 μg/day	Tg ↓ 5.5 ng/L Tg ↓ 4.8.5 ng/L

Abbreviations: IDD, iodine deficiency disorder; Tg, thyroglobulin; TSH, thyroid-stimulating hormone; UI, urinary iodine; ↑, increase; ↓, decrease.

[a] Criteria by WHO/UNICEF/ICCIDD[6] were used to classify the severity of IDD in the population. For thyroid volumes and goiter, the classification is based on the prevalence of the condition: mild, 5–19.9%; moderate, 20–29.9%; and severe, >30%. For the median UI, the classification is as follows: mild, 50–99 μg/L; moderate, 20–49 μg/L; and severe, <20 μg/L.

Iodine intake and thyroglobulin

Evidence from RCTs in children and adolescents. Five RCTs[35,37,40,42,43] that assessed iodine intake and Tg were included. One study[40] reported data for boys and girls separately, and one study[35] had three different iodine-treated groups; therefore, eight estimates were included in the analysis. Combining the five RCTs (760 participants) provided an overall pooled β coefficient of −0.02 (95%CI: −0.08–0.03; $I^2 = 88\%$, $P = 0.41$) (Table 2). A stratified meta-analysis yielded an overall β of −0.04 (95%CI: −0.10–0.03; $I^2 = 91\%$) when based on studies using a single dose of iodized oil (5 estimates of RCTs, 498 participants) and an overall β of 0.00 (95%CI: −0.24–0.24; $I^2 = 85\%$) when based on studies using a daily dose of potassium iodide (3 estimates of RCTs, 261 participants) (Table 2).

Evidence from RCTs in adults and the elderly. Three RCTs[48,49,62] on iodine intake and Tg concentration were included (114 participants). Combining the three estimates of RCTs in one meta-analysis yielded an overall pooled β of −0.23 (95%CI: −0.50–0.03; $I^2 = 59\%$, 144 participants) (Table 2).

Evidence from RCTs in pregnant and lactating women. Seven RCTs[53–57,63,64] on iodine intake and Tg concentrations in pregnant and lactating women (849 participants) were included. Combining the seven RCTs in one meta-analysis yielded an overall pooled β coefficient of −0.60 (95%CI: −0.70 to −0.49; $I^2 = 85\%$) (Table 2). In the subgroup of pregnant women, the pooled β was −0.54 (95%CI: −0.76 to −0.32; $I^2 = 48\%$) (5 estimates of RCTs, 415 participants), whereas it was −0.38 (95%CI: −0.82–0.05; $I^2 = 89\%$, $P < 0.09$) in the subgroup of women in the postnatal period (5 estimates of RCTs, 415 participants) (Table 2). Therefore, daily iodine intake as potassium iodide, with an overall β of −0.54, results in a decrease in Tg concentration of 31% for every doubling in iodine intake. Thus, in pregnant women with an iodine intake of 200 μg/day, the Tg concentration is 31% lower than that in pregnant women with an iodine intake of 100 μg/day. This corresponds to predicted Tg levels of 10 ng/L and 15 ng/L in pregnant women with intakes of 200 μg/day and 100 μg/day, respectively.

Observational evidence in all population groups. Twenty observational studies of iodine intake and Tg were selected for inclusion (see Table S2, available in the Supporting Information online).[53–56,59,69–73,75,76,78–80,83,86–89] Participants were infants (6 cross-sectional studies, 1 prospective cohort study, 1 nested case control study), children and adolescents (3 prospective cohort studies), adults and elderly (4 cross-sectional studies, 2 prospective cohort studies), and pregnant and lactating women (3 cross-sectional studies). In regions of mild iodine deficiency, four observational studies in adults with baseline Tg levels of 6–15 ng/L showed a decrease in Tg of 4 ng/L when the intake of iodine was adequate (>100 μg/day) and a decrease in the range of 1.7–7 ng/L when the intake of iodine was more than adequate (>200 μg/day)[73,75,76,79]

A brief summary of levels of iodine intake and TSH levels in different population groups is included in Table 3.

Summary evidence: iodine intake, urinary iodine, thyroid-stimulating hormone, and thyroglobulin in infants

Seven studies[54–59,63,85,86] that reported prenatal iodine intake in relation to iodine biomarkers in infants were included (see Table S2 available in Supporting Information online). Only four of these studies, however, investigated the association between iodine intake and status, which is not sufficient to justify a meta-analysis. Cord blood Tg levels were significantly lower in neonates treated prenatally with 100–200 μg of iodine per day from approximately 14–17 weeks of gestation to term compared with levels in nontreated neonates.[54,56,63] Three studies showed that TSH levels were unaltered in infants treated prenatally with 100–230 μg of iodine per day,[55,56,59] and three studies[54,63,86] (100–300 μg of iodine per day, respectively) described higher TSH levels in the cord blood of neonates born to iodine-treated mothers. UI in neonates, reported in only two studies,[85,86] was higher in infants when mothers were supplemented with iodine during pregnancy. Kurtoglu et al.[89] found no correlation between iodine content in breast milk and UI but found a positive correlation between TSH and estimated dietary intake of iodine.[87,88] TSH, as an indicator of iodine deficiency in infants, was higher in neonates from areas of moderate iodine deficiency than in neonates from areas of adequate iodine intake.[90] An RCT by Roghan et al.[63] did not confirm that increased iodine intake (272 μg/L versus 68 μg/L in milk formula) in preterm infants would improve circulating concentrations of thyroid hormones (Table 1).

DISCUSSION

This review is the first dose-response meta-analysis on the relationship between iodine intake and biomarkers of iodine excretion and status. RCTs that examined iodine supplementation showed a significant effect of supplementation on all markers of iodine status, and this effect was particularly strong for UI and TSH across all population groups. The dose-response relationship was much stronger for potassium iodide than for other types of

iodine supplements. RCTs that investigated a daily potassium iodide supplement showed an increase in UI concentration in adults (97%), pregnant women (81%), and children (26%). RCTs that investigated serum TSH concentrations in pregnant women showed that doubling the iodine intake as potassium iodide significantly decreased the serum TSH concentration by 12%. This dose-response effect on TSH hormone levels is reflected by the guidance of the Technical Consultation, which proposed an increase in the current Food and Agriculture Organization of the United Nations (FAO)/WHO recommended nutrient intake for iodine during pregnancy from 200 μg/day to 250 μg/day to prevent maternal subclinical hypothyroidism (an increased concentration of TSH in the second trimester).[27,31] In adults, doubling the iodine intake significantly increases the serum TSH concentration by 8% ($P < 0.005$). The dose-response relationship between serum Tg and iodine intake indicates a decrease of 31% in pregnant women (with daily intake) for every doubling of the daily iodine intake. It should be emphasized that serum Tg represents a very sensitive index of thyroid hyperstimulation and reflects iodine deficiency.[11]

Several assumptions were needed to conduct the meta-analyses presented here. For six RCTs, independence of estimates was assumed when two or three intervention groups were compared with the same placebo group. Another option for handling studies with multiple intervention groups would have been to use only one of the intervention groups. A sensitivity study using only one intervention group for each study (the group with the most common dosage) showed similar results (data not shown). Therefore, as much information as possible was included in the current meta-analysis. A further potential limitation that should be considered in interpreting the results is that, in some included studies, the control groups were not given placebo but instead were given a low dose of iodine supplement. Iodine intervention studies are often carried out in areas of severe iodine deficiency, and therefore an RCT with a placebo group receiving no iodine at all would be ethically unfeasible. However, a low-dose control group would reduce, rather than exaggerate, the differences between the intervention and control groups. For RCTs in which there was no indication of habitual iodine intake (above that given as a supplement), an average intake value (100 μg/day) based on median urinary excretion was assigned to the population so that total iodine intake could be compared. Though this introduces a potential source of error, it was agreed that this was a less erroneous way of dealing with the data than to ignore habitual intake entirely and compare only supplemented doses. Iodine intake is difficult to determine by dietary assessment because the iodine content of foods is variable, and reliable values are not always available in food composition tables. No studies on the relevance of dietary assessment methods for iodine intake in infants, children, and adolescents were identified.[91]

These meta-analyses required transformations of the intake and biomarker data to a common scale, as the studies included had diverse ways of presenting the data and the relationship between intake of iodine and biomarkers of iodine status in urine and blood. Such differences between studies are a challenge when trying to quantitatively summarize the data using conventional methods of meta-analysis. A linear relationship on the double-$\log_e$ scale permitted the pooling of β coefficients and the presentation of these as a dose-response relationship between iodine intake and UI excretion, serum TSH, and serum Tg. As compared with a standard meta-analysis of mean differences between subjects with high versus low exposure, a linear relationship on the double-$\log_e$ scale allows biomarker status levels to be modeled as a nonlinear but monotonic concave function of iodine doses, which is believed to be a more likely shape. The RCTs included in the present meta-analyses differ in follow-up time, study population, supplemental forms of iodine, dose and dose frequency of iodine, and the analytical laboratory methods used to measure UI, serum TSH, and serum Tg. Although these factors were coupled with each study's specific aims and study design, they interfered with the comparison of results and contributed to the large between-study heterogeneity. In the stratified analyses for supplemental forms of iodine, a reduction in the between-study heterogeneity was observed only for the association with the UI concentration in adults (Table 2).

In addition to the evidence from RCTs, data from 30 observational studies were identified and extracted, but they were too heterogeneous to combine in a meta-analysis (see Table S2 available in Supporting Information online). A basic comparison of data from supplemented pregnant women in regions of moderate iodine deficiency shows similarities between the results of RCT meta-analyses and the observational studies. In observational studies, pregnant women with an iodine intake of 150 μg/day had a UI concentration of 100 μg/L to 130 μg/L. In women with intakes of 300 μg/day, the UI concentration was doubled to 200 μg/L. The pooled β from comparable RCTs suggested that UI concentrations were 81% higher in pregnant women supplemented with 300 μg/day versus 150 μg/day. Review analyses of all included observational studies indicated that recommended values for iodine intake should be specific for each individual country due to differences in the prevalence of iodine deficiency.

A recently published paper by Zimmermann and Andersson[9] estimates the prevalence of iodine deficiency

in Europe in 2010 on the basis of a systematic review to update the WHO Vitamin and Mineral Nutrition Information System database.[92] The studies included in the present meta-analysis were checked against the WHO database (http://www.who.int/vmnis/iodine/data/en/index.html). Most of the RCTs[33–36,38,39,41–45] included in meta-analyses and relevant cross-selection studies[55,58,59,73–77,79,82,84,89] in the review presented here represent additional references included in the WHO database. Certain studies included here[37,40,44,46–54,56,57,60,72,78,80,81,83,85–90] are not included in the WHO database, probably because they had a low number of participants that would not be sufficient to accurately assess iodine intake in the country. The process of monitoring the prevention of iodine deficiency disorders should include the assessment of iodine status. As demonstrated by the meta-analyses in this review, UI may be the best indicator of WHO-UNICEF-ICCIDD iodine program effectiveness. Assessment of iodine status is necessary to identify iodine deficiency within a nation or region. In some countries, however, implementation of a salt iodization program may not be feasible in all areas. Results from the meta-analyses of RCTs presented here suggest that single-dose iodine supplementation is a good option in areas of severe iodine deficiency where universal salt iodization cannot be rapidly implemented. Overall, analysis of the included studies confirmed UI as an effective biomarker that reflects changes in iodine status and dose response to iodine intake.

The amount of iodine needed to prevent iodine deficiency disorders and to maintain body stores, as well as to reduce the risk of iodine deficiency disorders, is the basis for establishing micronutrient recommendations. This meta-analysis was designed to quantify the dose-response relationship between iodine intake and biomarkers of iodine status. This information is useful for establishing the dose of iodine to recommend for different population groups, especially pregnant women and infants, since fetuses and infants have increased sensitivity to the effects of iodine deficiency during periods of rapid and new growth and are at higher risk of brain damage from iodine deficiency. Healthy women maintain iodine stores of 15–20 mg in the thyroid[1]; during pregnancy, these significant iodine stores can be used to help meet the approximate 50% increase in maternal iodine requirement.

This meta-analyses model for RCTs was carried out within the context of the EURRECA project as a means to provide additional evidence to support reference values for iodine and to contribute evidence to substantiate the daily dose of iodine necessary to maintain normal UI levels or optimal levels of biomarkers for iodine status.[91] The focus of the EURRECA work was micronutrient deficiencies; therefore, less emphasis has been placed on intakes at the upper end of the normal range and into excess intakes. In some areas of the world, however, higher intakes are an important issue to be considered in establishing the best practice for the usefulness (or adequacy) of biomarkers in assessing intake within a population. Higher intakes are also a key area of concern when setting reference values, as tolerable upper limits are often established in order to prevent the toxicity issues associated with excess intakes. Although iodine is largely the focus of deficiency research at present, it is important that intakes at the other end of the spectrum are not ignored. Perhaps more important in the context of population monitoring is understanding how the relationship between intake and status evolves as populations move from deficiency to adequacy, and how to monitor these changes using the most appropriate biomarkers. The vast majority of studies that were included in this review were conducted in populations with some degree of iodine deficiency (see Table 1 and Table S2, available in the Supporting Information online). Populations were typically classified as having endemic goiter or severe or mild iodine deficiency, with very few deemed to have adequate iodine status and none identified within the higher range of intake/status. This makes interpretation of the intake-status relationship at higher concentrations difficult within the context of this study and perhaps highlights a limitation of this review as well as a gap in the current knowledge. Future research on the relationships between iodine intake, iodine status, and health in infants and the elderly is particularly important, as iodine requirements and health effects in these population groups are presently lacking.[91]

The relationship of UI to iodine intake is relevant to establish dietary requirements for iodine, but as an indicator of iodine intake, the median UI concentration reflects short-term intake and does not provide direct information about thyroid function and longer-term iodine exposure. Serum TSH and Tg concentrations primarily indicate thyroid function, which is largely dependent on iodine intake, as a means of detecting functional iodine deficiency. Serum Tg is easier to assess than thyroid volume measurement. However, reference ranges for tests of thyroid hormones (TSH, free T4, Tg) are wide, making it difficult to use such tests to assess iodine status. 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, but it is inadvisable to rely on a single biomarker to clearly identify iodine deficiency within a population. As the results of this review indicate, certain biomarkers are more reliable and useful in particular population groups, but the aim of this review was not to assess the usefulness or limitations of these markers. This work was previously undertaken within the context of EURRECA and was used to inform the selection of biomarkers for the current

review.[11,12] The previous systematic review found that all of the following appear to be useful biomarkers of iodine status: 1) UI in children and adolescents as well as in general populations with low or moderate baseline iodine status, 2) serum Tg in children and adolescents, and 3) TSH in pregnant and lactating women and in adult females, but not in children and adolescents or in those with moderate baseline TSH status.[12] Normal levels of serum Tg are geographically sensitive, because they are affected by the availability of iodide. In countries where iodine intake is adequate, the reference serum level for Tg in Tg-antibody-negative euthyroid populations is approximately 3–40 ng/mL, using analytical standards.[93] Both the mean level of Tg in a population and the upper reference limit of Tg can be increased relative to the degree of iodine deficiency in iodine-deficient countries. The meta-analyses presented here showed a dose-response effect between iodine intake and decreased serum Tg and in pregnant women, a finding that is relevant for programs that aim to eliminate iodine deficiency disorders.

CONCLUSION

The principal aim of this review was to use the meta-analyses model to provide an estimate of the dose-response relationship between iodine intake and biomarkers of iodine status. The dose-response regression indicated that, in the dose range of 120–500 μg/day, doubling the daily intake of potassium iodide increased the UI by 1.97-fold (97%) in adults, by 1.81-fold (81%) in pregnant women, and, though less strong, by 1.26-fold (26%) in children. For TSH concentrations, the data indicated a 1.08-fold (8%) increase for every doubling of intake in the adult population and a 0.88-fold decrease in pregnant women. Pooled estimates obtained for Tg indicated a 31% decrease in this biomarker in pregnant women when the daily dose of iodine was doubled. Further RCTs are required to examine target serum and urinary biomarker concentrations in relation to thyroid function, a broader range of intakes of iodine within the population groups, and interindividual variability. The model of dose-response used to describe the relationship between iodine intake and status in this review may, in the future, have applications for setting iodine requirements in different population groups.

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The authors' responsibilities were as follows: DRM approved and screened the literature search, extracted data and assessed validity, conducted meta-analyses, tabulated the data, interpreted the data, designed the study, and wrote the manuscript. OWS and CD performed statistical transformations to derive coherent single-study estimates. AA, JT, GOP, and TP screened the results of the literature search and extracted the data. RC performed the electronic literature search, provided advice, and contributed to the writing of the manuscript. CD, MG, and MGu contributed to the writing of the manuscript. AC, LdG, and PvV designed the study and provided advice. All authors contributed to the subsequent drafts of the manuscript and approved the submitted version.

Declaration of interest. The authors have no relevant interests to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 **Search terms used and results for the Embase , Medline, and Cochrane databases.**
Table S2 **General characteristics of observational studies ($n = 30$) reporting the effect of dietary iodine intake on UI, TSH, and Tg in different population groups.**