Iodine nutritional status in Brazil: a meta-analysis of all studies performed in the country pinpoints to an insufficient evaluation and heterogeneity

Renata de Oliveira Campos¹,², Iasmin dos Santos Barreto¹, Lorena Rejane de Jesus Maia³, Sara Cristina Lima Rebouças¹, Taisne Lima de Oliveira Cerqueira³, Clotilde Assis Oliveira³, Carlos Anfônio de Souza Teles Santos⁶, Carlos Maurício Cardeal Mendes⁵,⁶, Leonardo Sena Gomes Teixeira⁴, Helton Estrela Ramos¹,²

ABSTRACT

Objectives: Iodine deficiency disorder (IDD) is the result of an inadequate dietary intake of iodine, which physiological consequences are endemic goiter and thyroid dysfunction. The objective of this study was to analyze studies that assessed the status of Brazil's population iodine nutrition and IDD prevalence.

Materials and methods: Systematic review using PRISMA statement. Electronic database: PubMed, Medline, SciELO and Lilacs. Quality of studies: Newcastle-Ottawa Scale. Meta-analysis was carried out with R Core Team Statistical Software, version 3.1.0 (2014). The summary measure (WMD) and its confidence interval (CI) of 95% were calculated. The “Funnel plot” graph assessed publication bias and heterogeneity. Results: Seventeen papers were eligible: pregnant women (2), school children (9), adults/elderly (4) and preschool children/infants (2). Geographic distribution: North (1), Northeast (1), Midwest (2), Southeast (13), South (3). Twenty-three thousand two hundred seventy-two subjects were evaluated between 1997 and 2013 and all have used urinary iodine (UI) measurement. However, only 7 studies could be included in meta-analysis, all from Southeast region. The overall prevalence of IDD in school children in southeast region was 15.3% (95% CI, 13-35%), however this data had an important heterogeneity, expressed by the I² Statistic of 99.5%.

Conclusion: Only few studies have been performed and enrolled populations from south/southeast region of Brazil. The actual IDD prevalence analysis is complex because it was detected bias due influence of individual studies and very high heterogeneity. IDD might still be high in some areas but this remained unknown even after this meta-analysis evaluation. The generation of a national program for analysis of iodine status in all regions is urgently required.

Keywords
Iodine; hypothyroidism; iodine deficiency, Brazil

INTRODUCTION

Iodine is an essential micronutrient for the synthesis of thyroid hormones (TH), which are important for homeostasis and neurodevelopment (1-5). The World Health Organization (WHO) recommends daily iodine intake of 50 µg for infants, 90 µg for children between 1-12 months and 6 years, 120 µg for children (7-12 years), 150 µg for adults (after 12 years) and 250 µg for pregnant and lactating women (6-7). Iodine deficiency disorder (IDD) is the result of an inadequate dietary intake of iodine, whose physiological consequence is an abnormal function of the thyroid gland, hypothyroidism and endemic goiter (8). The harmful effects of IDD are even more severe in pregnant women, fetuses and children, being the worldwide most common cause of preventable mental retardation (6,7,9-11).

The Brazilian Government have been controlling salt iodization in the country, according to Federal Law 6,150, in partnership with the National Agency for Sanitary Surveillance (Anvisa) and the salt productive sector (12-14). In accordance with Resolution RDC nº 130 (2003), it was deemed fit, for human consumption, salt content that corresponded to 20-60 ppm of iodine concentration and this recommendation have
been prevailed for ten years (14). However, in the mean
time, data from the ThyroMobil Project in Latin Ameri-
can, identified Brazil (with 17 sentinel sites and a total of
1,563 school children evaluated) as a country of exces-
sive iodine consumption, with a mean urinary iodine
excretion (UIE) concentration of 360 µg/L (15,16). Con-
sequently, the levels of salt iodization were recently
reduced to 15 to 45 milligrams of iodine per kilogram
of product (http://www.in.gov.br) (17). Notwith-
standing, the Brazilian Endocrine Society (SBEM) have
strongly diverged on this reduction (http://www.tir-
eoide.org.br/reducao-de-iodo-no-sal/).

The fact is that there is not recent national survey
study about iodine content in table salt in households
from different regions of Brazil neither a continuous
monitoring of the overall population iodine status.
Therefore, given the above, this review aimed to sys-
tematize and analyze all studies which assessed the
prevalence of IDD in Brazil through UIE analysis in or-
der to describe the current available information about
iodine nutrition status.

MATERIALS AND METHODS

Research questions
(1) What is the overall prevalence of IDD in Brazil?;
(2) What is the prevalence of IDD in different areas
and population groups?; (3) Are there enough studies
to profile the population iodine nutrition status?; (4)
Are there differences related to IDD in individuals of
distinct ages, from one region to another, or in separate
areas of the same region?; (5) Are the published data
prevailing and have comprised all regions of Brazil?

Search strategy and data collection
This systematic review is reported in accordance with
the PRISMA (preferred reporting items for systematic
reviews and meta-analyses) statement (18,19). Analysis
of all studies conducted in Brazil in order to assess the
status of iodine nutrition in populations – retrieved from
the electronic database PubMed, Medline, SciELO and
Lilacs. We have not limited the period of the study be-
cause we wanted to reach all studies conducted in the
country. The search strategy used controlled vocabu-
lary supplemented with keywords describing the fol-
lowing concepts, not only limited to English language
publications, in the form of: “Iodine” and “Brazil” and
“Iodine deficiency” and “Brazil” and “Thyroid function
tests” and “Brazil”. Unpublished studies were also in-
vestigated in the largest thesis and doctoral dissertations
database of a Brazilian Agency (Capes). The searching
by hand has been conducted in the references of the
review papers and in a few non-indexed Medline Bra-
zilian journals. Duplicate publication was checked and,
if necessary, the corresponding author was contacted.
After this, reviews of iodine status methods were col-
llected in full text, the reference lists were checked and
the included study list was updated accordingly.

Quality assessment
Two reviewers working independently (R.O.C. and
H.E.R.) assessed the methodological quality of inclu-
ded observational studies using the Newcastle-Ottawa
Scale and adapted Newcastle-Ottawa Scale to evaluate
cross sectional studies (20). This instrument assesses
the protection against bias due subject selection meth-
odology, evaluation and data analysis.

Study selection
Inclusion criteria were defined as follow: a) the lan-
guage in which the article was published was English
or Portuguese; b) the main purpose of the article: as-
essment of iodine nutritional status of individuals; c)
primary studies conducted in Brazil; and d) description
of percentage of IDD, sufficiency and excess iodine,
according to the criteria established by WHO. Ex-
perimental animal studies, review articles, case reports,
studies investigating iodine nutrition in individuals
with thyroid disorders or chronic diseases, studies on
the iodine nutritional and duplicate articles in the data-
bases were excluded.

Diagnosis of iodine deficiency disorders
The WHO recommendations regarding IDD assess-
ment have been followed by the selected studies. UIE
was measured using different methods and in a number
of different units that could not always be interconver-
ted to allow comparison between studies (Table 1).
The studies selected for the meta-analysis had UIE ge-
erally, UIE was determined by the colorimetric ceric ar-
senite method based on the Sandell-Kolthoff (S-K) re-
action, previously considered as the gold standard (21).
Normal reference range was considered 100-299 µg/l
for general population and 150-499 µg/l for pregnant
woman, according to WHO (8,9).
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Methodology</th>
<th>Outcomes</th>
<th>Study Quality</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alves and cols. (22)</td>
<td>15,131 newborns, 7,797 males, 7,328 females, Location: Ribeirão Preto, SP</td>
<td>Umbilical cord blood for TSH and T4 dosage, TSH sample 24 hours (S-K reaction) in 141 newborns</td>
<td>1/141 infants had TSH level equal to 19.4 μIU/mL. The UI ranged between 2.1 and 194 μg/L.</td>
<td>5</td>
<td>Newborns were subjected to borderline IDD</td>
</tr>
<tr>
<td>Correa Filho and cols. (23)</td>
<td>178,774 schoolchildren aged 6-14 years, Location: 428 cities of all Brazilian states</td>
<td>UE and table salt evaluation, Palpation for goiter assessment</td>
<td>7,702/16,803 were evaluated of urine samples collected for UI measurement. The median UI level was 14.0 µg/dL. The median UI level for the population in the states of AC, AM, and TO was equal to or below 9.0 µg/dL.</td>
<td>6</td>
<td>33% of schoolchildren had some degree of IDD and in 12%, UI levels were less than 5 µg/dL, characterized severe deficiency</td>
</tr>
<tr>
<td>Esteves (24)</td>
<td>16,803 schoolchildren aged 6-14 years, both sexes, Location: schools publics of 401 cities in all Brazilian states</td>
<td>TSH, FT4, Tg, anti-Tg and anti-TPO antibodies, Thyroid ultrasound, UIE (S-K reaction)</td>
<td>We observed IDD in 85 cities, moderate DDI (&gt; 25 and &lt; 50 µg/L) in Cocos in Bahia, and Almas, Arraias and Paraná in Tocantins, and to mild (values ≥ 50 and &lt; 100 µg/L). In the other 35 counties, median values were normal, but more than 10% of children had urine iodine levels below 25 µg/L.</td>
<td>4</td>
<td>Mild to moderate IDD in 30% of the cities</td>
</tr>
<tr>
<td>Barca and cols. (25)</td>
<td>800 pregnant women. 386 puerperal healthy women was followed-up regularly at 3, 6, 12 and 24 months, Location: public hospital in Sao Paulo, SP</td>
<td>TSH, FT4, Tg, anti-Tg and anti-TPO antibodies, Thyroid ultrasound, UIE (S-K reaction)</td>
<td>The median UI excretion was 167.8 µg/L. The concentration levels of UI were normal in 92.2% of private school students and 42.6% of public school children</td>
<td>7</td>
<td>Adequate iodine nutritional status. No correlation with TPP</td>
</tr>
<tr>
<td>Nimer and cols. (26)</td>
<td>280 schoolchildren, Location: public hospital in Sao Paulo,</td>
<td>Measure levels iodine of salt</td>
<td>The concentration levels of UI were normal in 92.2% of private school students and 42.6% of public school children</td>
<td>4</td>
<td>Iodine status was drastically different between private and public school students</td>
</tr>
<tr>
<td>Pretell and cols. (16)</td>
<td>1,563 schoolchildren, Location: 17 sentinel sites distributed in 8 states (PA, MA, TO, GO, MT, MS, MG and ES)</td>
<td>TSH, FT4, Tg, anti-Tg and anti-TPO antibodies, Thyroid ultrasound, UIE (S-K reaction)</td>
<td>UIE was &lt; 50 µg/L in 2.3%, 29.1% of 200-299 µg/L and 70.6% with UI &gt; 300 µg/L. The median UI concentrations of 360 µg/L.</td>
<td>7</td>
<td>Iodine excess was more prevalent</td>
</tr>
<tr>
<td>Saab (27)</td>
<td>1,000 school children, Location: Mato Grosso do Sul</td>
<td>Assessment of goiter by palpation, Thyroid ultrasound, UIE (S-K reaction)</td>
<td>Had UI lower than 50 µg/dL. The total number of samples with values below UI 5 µg/dL. In 95.2% UI &gt; 10 µg/dL, 22.1% &gt; 30 µg/dL.</td>
<td>6</td>
<td>Goiter prevalence was low. UIE was above the recommended iodine content in salt was adequate</td>
</tr>
<tr>
<td>Marino and cols. (28)</td>
<td>13 adults aged 22-63 years, Location: city of Santo André, SP</td>
<td>T3, T4, FT4, TSH, A-Tg, A-TPO, TSHR, UIE (S-K reaction)</td>
<td>2 subjects with deficiency (60 µg/L and 66 µg/L), 5 with excess (360-490 µg/L), 6 subjects with adequate UIE (150-295 µg/L)</td>
<td>7</td>
<td>Iodine adequate sufficiency with an UIE mean of 262.31 µg/L</td>
</tr>
<tr>
<td>Duarte (29)</td>
<td>964 school children, Location: public schools in six cities in Sao Paulo (Taubaté, Registro, Ribeirão Preto, São José do Rio Preto, Aracatuba, Presidente Prudente)</td>
<td>Thyroid ultrasound, UIE (S-K method modified)</td>
<td>UIE was &lt; 100 µg/L in 1.5%, 21.6% of 100-299 and 76.7% with UIE &gt; 300 µg/L.</td>
<td>6</td>
<td>Excessive iodine intake in students from Sao Paulo</td>
</tr>
</tbody>
</table>

**Table 1. Summary from studies conducted in Brazil in the between 1985-2013**
<table>
<thead>
<tr>
<th>Study</th>
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<th>Methodology</th>
<th>Outcomes</th>
<th>Study Quality</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soares and cols. (30)</td>
<td>147 pregnant women, Location: Public health care clinics of Porto Alegre, Rio Grande do Sul</td>
<td>Measurement of UIE (S-K reaction) and creatinina Thyroid ultrasound FT4 and Tg</td>
<td>Mean Ul was 226 ± 87 µg/L and median Ul was 224 µg/L. UIE levels ranged from 22 µg/L to 534 µg/L. Twenty-nine women (19.6%) had UI below 150 µg/L</td>
<td>6</td>
<td>19.7% had insufficient iodine intake. No correlation between serum FT4, Tg and TV with UIE</td>
</tr>
<tr>
<td>Navarro and cols. (31)</td>
<td>145 schoolchildren, 79 from rural areas and 66 from urban area, Location: Botucatu, Sao Paulo</td>
<td>UIE (S-K reaction) and table salt</td>
<td>IDD was detected in 3.4% and 3% of children from the rural and urban school, respectively. Ul greater than 300 µg/L was detected in 62.3% and 90.9% of students from the rural and urban school, respectively</td>
<td>6</td>
<td>IDD is controlled in school children, with high prevalence of UIE excess</td>
</tr>
<tr>
<td>Camargo and cols. (32)</td>
<td>1,085 individuals aged 20-87 years, Location: metropolitan area in Sao Paulo (houses randomly selected)</td>
<td>UIE (S-K method) and table salt Thyroid ultrasound TSH, TPOAb</td>
<td>UIE ≥ 300 in 45.6%, 14.1% had UIE greater than 400. The prevalence of CAT was 16.9%</td>
<td>8</td>
<td>High prevalence of iodine excess and CAT</td>
</tr>
<tr>
<td>Carvalho and cols. (33)</td>
<td>828 schoolchildren, Location: Botucatu, Sao Paulo</td>
<td>Determination of UIE casual urine sample (adapted S-K method)</td>
<td>Only 1.9% had low values of urinary iodine (100 µg/L), while 24.6% had UI excretion values between 200 and 300 µg/L, and 67.1% had values above 300 µg/L</td>
<td>6</td>
<td>High excessive iodine intake rate in school children</td>
</tr>
<tr>
<td>Vanacor and cols. (34)</td>
<td>60 subjects, Location: Hospital de Clinicas de Porto Alegre, Rio Grande do Sul</td>
<td>Four urine samples from each participant (completing 24 h -UIE) Dietary history UIE, creatine (Cr) and Na+ levels were measured in the 4 partial urine samples and in the 24h urine sample</td>
<td>The UI and sodium excretions were variable along the 24-hour period. The correlation between the total iodine and sodium excretions was very strong</td>
<td>4</td>
<td>The UI is variable during the daytime. Between lunch and dinner, it seems to better reflect the 24-hour UI. The casual urine sample collection in this period would probably be the best for the iodine nutritional status evaluation</td>
</tr>
<tr>
<td>Pontes and Adan (35)</td>
<td>180 schoolchildren, Location: public schools from Cabaceiras, Paraiba</td>
<td>Questionaire nutritional UIE (Rapid Urinary Iodine Test®)</td>
<td>31.6% of scholars used cassava in their meals with a frequency larger than three times a week. 33.3% scholars presented UIE ≤ 100 µg/L</td>
<td>2</td>
<td>Goitrogenic foods are higerly consumed. One third of school children had low UI levels less than 100 µg/L</td>
</tr>
<tr>
<td>Alves and cols. (36)</td>
<td>300 schoolchildren, Location: public schools of different socioeconomic levels from Ribeirão Preto, Sao Paulo</td>
<td>UIE (S-K reaction) and table salt Thyroid ultrasound</td>
<td>100% of the urine samples had UI values greater than 100 µg/L, 59.5% of subjects had values above 300 µg/L</td>
<td>5</td>
<td>Iodine sufficiency in Ribeirão Preto school children population, UIE showed excess in 59.5%</td>
</tr>
<tr>
<td>Macedo and cols. (37)</td>
<td>475 children, Location: Novo Cruzeiro, Minas Gerais</td>
<td>UIE (S-K reaction) and table salt</td>
<td>IDD prevalence was 34.4%, 23.5% (mild), 5.9 (moderate) and 5% (severe)</td>
<td>7</td>
<td>IDD prevalence of 34.4%</td>
</tr>
<tr>
<td>Macedo (38)</td>
<td>540 school children, Location: Novo Cruzeiro, Minas Gerais</td>
<td>UIE (S-K method) and table salt</td>
<td>IDD prevalence was 38.9% (28.7% mild, 6.2% moderate and 4% severe)</td>
<td>8</td>
<td>High rate of IDD of 38.9%. Need to evaluated control as disease</td>
</tr>
<tr>
<td>Milhoransa and cols. (39)</td>
<td>47 healthy individuals, 22 men and 25 women, aged 18 years or older, Location: Hospital de Clinicas de Porto Alegre, Rio Grande do Sul</td>
<td>UIE in 24h samples (S-K reaction) Evaluation of the content of creatinine, sodium, and 18 subjects with one, 15 with two, and 14 with three collections of urine samples/24h</td>
<td>2/14 women had 24-h UIE below 138 µg/24h in the three samples studied</td>
<td>6</td>
<td>UIE is adequate in the group of 14 people, however, the UIE two women suggests IDD</td>
</tr>
</tbody>
</table>
Arch Endocrinol Metab. 2015;59/1

Iodine deficiency in Brazil

**RESULTS**

**Studies characteristics**

In our investigation, a total of 1,252 records were identified (Figure 1). We have found only 24 studies published between 1997 and 2013 eligible for this systematic review (16,22-44) (Table 1). A total of 26,148 subjects were subscribed for UIE assessment between 1997 and 2013. The most widely carried out type of study was cross-section (n = 20) (86,9%). Two follow-up (cohort) and one case control study were also enclosed. The school environment was the place where the largest amount of data collection was performed, representing 13 studies (56,5%).

Seventeen/twenty-three studies received adequate qualification, by Prisma analysis, for quantitative synthesis (Tables 2 and 3): pregnant women (n = 2), school children (n = 9), adults/elderly (n = 4) and preschool children and/or infants (n = 2). The country distribution was very variable, with a clear shifting toward

**Statistical analysis**

Statistical analyses were performed using the R Core Team Statistical Software, version 3.1.0 (2014). The summary measure – weighted mean difference (WMD) – and its confidence interval (CI) of 95% were calculated. The heterogeneity was assessed initially through a hypothesis test for homogeneity, using the Cochran Q test (at a significance level of 5%), and subsequent application of the I² Statistic and visual inspection of each “Forest plot”. We have determined fixed and random model effects, but was systematically employed in cases where the I² Statistic found significant heterogeneity. As the available published data have been predominantly described in school children group, most of our data were achieved using this group. As we noted that only few studies could be selected for this investigation and the heterogeneity measured by the graph “Funnel plot” pointed to a possible publication bias, we decided to establish a cutoff of 15.3% (prevalence of overall meta-analysis) in WMD to independently calculate the IDD prevalence.
southeast region: North (n = 1), Northeast (n = 1), Midwest (n = 2), Southeast (n = 13) and South (n = 3) (Tables 2 and 3). Considering only the selected studies, 23,272 individuals had UIE being investigated. The main reasons for study exclusion were: incomplete or repeated results (n = 5), gold standard methodology for UIE measurement (S-K) (n = 2) and data that could not be compared because absence of similar evaluation coming from others studies (10).

**IDD prevalence in Southeast Brazil**

The studies were subgrouped according to the region and population group (school and/or preschool children, adults, elderly and pregnant women). The overall meta-analysis performed could include only 7 studies from the Southeast region (Figure 2) the others subgroups could not be analyzed by meta-analysis methodology. However, a high heterogeneity was immediately identified among the studies used for this meta-analysis (p < 0.0001, I² = 99.5%) (Figure 2). After applying the I² statistic and plot Forest visual inspection, it was noted that the studies should be analyzed separately because the large heterogeneity between then. The criteria for this separation was achieved by WMD random effect method calculation. Thus, the studies were divided by WMD average value less than 15.3% (Figure 3) showing IDD prevalence of 24% (95% CI, 13-35%); and higher than 15.3% showing IDD prevalence of 32% (95% CI, 25-39%) (Figure 3).

**Table 2. Urinary iodine excretion in Brazilian population**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No of subjects</th>
<th>Region</th>
<th>Subgroup</th>
<th>Insufficient intake &lt; 100 µg/L</th>
<th>Sufficient intake ≥ 100 µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esteves</td>
<td>1997</td>
<td>4,231</td>
<td>North</td>
<td>School children</td>
<td>1,985</td>
<td>2,246</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6,553</td>
<td>Northeast</td>
<td></td>
<td>2,034</td>
<td>4,519</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2,186</td>
<td>Midwest</td>
<td></td>
<td>748</td>
<td>1,438</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2,165</td>
<td>Southeast</td>
<td></td>
<td>671</td>
<td>1,494</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,668</td>
<td>South</td>
<td></td>
<td>468</td>
<td>1,200</td>
</tr>
<tr>
<td>Saab</td>
<td>2000</td>
<td>1,000</td>
<td>Midwest</td>
<td>School children</td>
<td>48</td>
<td>952</td>
</tr>
<tr>
<td>Nimer and cols.</td>
<td>2002</td>
<td>280</td>
<td>Southeast</td>
<td>School children</td>
<td>72</td>
<td>208</td>
</tr>
<tr>
<td>Alves and cols.</td>
<td>2005</td>
<td>141</td>
<td>Southeast</td>
<td>Infants and preschoolers</td>
<td>87</td>
<td>54</td>
</tr>
<tr>
<td>Duarte</td>
<td>2007</td>
<td>964</td>
<td>Southeast</td>
<td>School children</td>
<td>15</td>
<td>949</td>
</tr>
<tr>
<td>Vanacor and cols.</td>
<td>2008</td>
<td>60</td>
<td>South</td>
<td>Adults</td>
<td>–</td>
<td>60</td>
</tr>
<tr>
<td>Camargo and cols.</td>
<td>2008</td>
<td>1,085</td>
<td>Southeast</td>
<td>Adults</td>
<td>85</td>
<td>1,000</td>
</tr>
<tr>
<td>Marino and cols.</td>
<td>2009</td>
<td>13</td>
<td>Southeast</td>
<td>Adults</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Rates</td>
<td>2010</td>
<td>428</td>
<td>Southeast</td>
<td>School children</td>
<td>19</td>
<td>409</td>
</tr>
<tr>
<td>Navarro and cols.</td>
<td>2010</td>
<td>145</td>
<td>Southeast</td>
<td>School children</td>
<td>5</td>
<td>140</td>
</tr>
<tr>
<td>Macedo</td>
<td>2010</td>
<td>540</td>
<td>Southeast</td>
<td>School children</td>
<td>217</td>
<td>323</td>
</tr>
<tr>
<td>Milhoransa and cols.</td>
<td>2010</td>
<td>47</td>
<td>South</td>
<td>Adults</td>
<td>–</td>
<td>47</td>
</tr>
<tr>
<td>Carvalho and cols.</td>
<td>2012</td>
<td>828</td>
<td>Southeast</td>
<td>School children</td>
<td>16</td>
<td>812</td>
</tr>
<tr>
<td>Macedo and cols.</td>
<td>2012</td>
<td>475</td>
<td>Southeast</td>
<td>Infants and preschoolers</td>
<td>166</td>
<td>309</td>
</tr>
<tr>
<td>Almeida</td>
<td>2013</td>
<td>125</td>
<td>Southeast</td>
<td>Infants</td>
<td>–</td>
<td>125</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>22,934</td>
<td></td>
<td></td>
<td>6,638</td>
<td>16,296</td>
</tr>
</tbody>
</table>

No: number of subjects evaluated; µg/L: micrograms per liter.

*Figure 1. Study selection process.*
Table 3. Urinary Iodine Excretion in Brazilian Pregnant Women

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No of subjects</th>
<th>Region</th>
<th>Insufficient intake &lt; 150 µg/L</th>
<th>Sufficient intake ≥ 150 µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soares and cols.</td>
<td>2008</td>
<td>147</td>
<td>South</td>
<td>29</td>
<td>118</td>
</tr>
<tr>
<td>Ferreira</td>
<td>2011</td>
<td>191</td>
<td>Southeast</td>
<td>109</td>
<td>82</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>338</td>
<td></td>
<td>138</td>
<td>200</td>
</tr>
</tbody>
</table>

No: number of subjects; µg/L: micrograms per liter.

Study Events Total Proportion 95% CI W (fixed) W (random)

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Total</th>
<th>Proportion</th>
<th>95% CI</th>
<th>W (fixed)</th>
<th>W (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esteves, 1997</td>
<td>671</td>
<td>2165</td>
<td>0.310</td>
<td>[0.290; 0.330]</td>
<td>7.5%</td>
<td>14.4%</td>
</tr>
<tr>
<td>Nimer and cols., 2002</td>
<td>72</td>
<td>280</td>
<td>0.257</td>
<td>[0.207; 0.313]</td>
<td>1.1%</td>
<td>13.8%</td>
</tr>
<tr>
<td>Duarte, 2007</td>
<td>15</td>
<td>964</td>
<td>0.016</td>
<td>[0.009; 0.026]</td>
<td>46.6%</td>
<td>14.5%</td>
</tr>
<tr>
<td>Rates, 2010</td>
<td>19</td>
<td>428</td>
<td>0.044</td>
<td>[0.027; 0.068]</td>
<td>7.5%</td>
<td>14.4%</td>
</tr>
<tr>
<td>Navarro and cols., 2010</td>
<td>5</td>
<td>145</td>
<td>0.034</td>
<td>[0.011; 0.079]</td>
<td>3.2%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Macedo, 2010</td>
<td>217</td>
<td>540</td>
<td>0.402</td>
<td>[0.360; 0.445]</td>
<td>1.7%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Canhão and cols., 2012</td>
<td>16</td>
<td>828</td>
<td>0.019</td>
<td>[0.011; 0.031]</td>
<td>32.4%</td>
<td>14.5%</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>1015</td>
<td>5350</td>
<td>0.051</td>
<td>[0.045; 0.056]</td>
<td>100%</td>
<td>–</td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
<td></td>
<td>0.153</td>
<td>[0.069; 0.237]</td>
<td>–</td>
<td>100%</td>
</tr>
</tbody>
</table>

Proportion of iodine insufficient intake - region 4

Heterogeneity: I² = 99.5%, tau-squared = 0.0127, Q = 1142, df = 6, p < 0.0001

CI: confidence interval; W: weighted.

Figure 2. Overall meta-analysis of studies from the Southeast.

Proportion of iodine insufficient intake - region 4 < 0.153

Heterogeneity: I² = 63.3%, tau-squared < 0.0001, Q = 8.2, df = 3, p = 0.0425

CI: confidence interval; W: weighted.

Figure 3. Meta-analysis of studies from the Southeast with IDD prevalence of less than 15.3.

DISCUSSION

This unprecedented systematic review showed the prevalence of IDD measured in populational studies conducted in Brazil and aimed to answer our main question: What is the overall prevalence of IDD in Brazil? However, the vast majority of surveys (94, 1%) were conducted in the South (4/17) and Southeast (13/17) regions. Consequently, a comprehensive conclusion about the real IDD prevalence in the country cannot be achieved. While the Southeast region has been recognized as an iodine sufficient area, differences were also detected between states from the same region (Minas Gerais vs. São Paulo). In São Paulo, there is a rising concern regarding the excessive iodine exposure and predisposition to thyroid autoimmune diseases (Table 2) (29,33,36,40). In contrary, in the state of Minas Gerais, few studies have reported increased IDD prevalence, especially in children and adolescents from low-income populations (Table 2) (37,38). Macedo evaluated 540 children from schools in the municipality of Novo Cruzeiro (Minas Gerais) and observed IDD prevalence of 40% (38). This might be related to low salt intake, decay of iodine in salt due the storage form and/or expiration date and reduced education level...
(38). Limitations of the number of studies conducted in all regions of Brazil and the possibility of ‘publication bias’ identified in our investigation ($I^2 = 99.5\%$; $p < 0.0001$), made impossible to conduct a meta-analysis for the entire country or particular region (Figure 2). Our quantitative analysis rejected 17 studies because lack of urinary iodine (UI) standardization and similar surveys conducted in the same area.

In our study, only a supplementary central questions (What is the prevalence of IDD in different areas and population groups?) could be partially addressed. The IDD prevalence rate predicted in school children from Southeast region diverged between 24% (95% CI, 13-35%) and 32% (95% CI, 25-39%), using different analysis methodology (Figure 3). Therefore, we have diagnosed a tremendous heterogeneity available of data. We have demonstrated that the higher rate of 32% of IDD prevalence, was clearly influenced by two individual studies performed by Esteves (24) and Macedo (38) (Figure 4). Thus, we assumed that the calculated IDD prevalence of 15.3% (95% CI, 6-23%) after biased studies exclusion is the one that could better represents the studies developed in this area, pinpointing to a possible compelling iodine deficiency.

The very few studies ($N = 2$) executed in North and Northeast regions, did not fit the inclusion criteria for the meta-analysis (Table 1) (24,35). Pontes and Adan (35) assessed the iodine nutritional status and cassava consumption of 180 school children in the city of Cabaceiras/Paraiba (northeast region). The high rate of cassava flour utilization (31.6%), associated with in elevated rate (33.3%) of IDD prevalence in school children. Nonetheless, in this study, the gold standard method for UI evaluation was not used (35). In another survey conducted in north/northeast region, Esteves identified in Bahia, the city of Cocos had low UI level, with median of 44 μg/L (24). Almas, Arraias and Paranâ (Tocantins) had median UI of 33 μg/L, 34 μg/L and 26 μg/L, respectively (24). Therefore, a limitation of the data collected in our review is that the greater number of studies was based only on school survey data, without any enough available information about other population groups. In summary, targeting other essential questions, our review shows that there

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Total</th>
<th>Forest plot</th>
<th>Proportion</th>
<th>95% CI</th>
<th>W (fixed)</th>
<th>W (random)</th>
</tr>
</thead>
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<tr>
<td>Esteves, 1997</td>
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<td></td>
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<td>[0.290; 0.330]</td>
<td>73.2%</td>
<td>36.2%</td>
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<tr>
<td>Nimer and cols., 2002</td>
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<td>280</td>
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<td>[0.207; 0.313]</td>
<td>10.6%</td>
<td>31.0%</td>
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<tr>
<td>Macedo, 2010</td>
<td>217</td>
<td>540</td>
<td></td>
<td>0.402</td>
<td>[0.360; 0.445]</td>
<td>16.2%</td>
<td>32.9%</td>
</tr>
<tr>
<td><strong>Fixed effect model</strong></td>
<td>960</td>
<td>2985</td>
<td></td>
<td>0.319</td>
<td>[0.303; 0.336]</td>
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<td>–</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.324</td>
<td>[0.254; 0.393]</td>
<td>–</td>
<td>100%</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 90.9\%$, $tau^2 = 0.0034$, $Q = 219$, df = 2, $p < 0.0001$. 

Figure 4. Meta-analysis of studies from the Southeast with IDD prevalence of greater than 15.3.
are not enough studies to profile the population iodine nutrition status in Brazil; and perhaps we might find huge differences related to IDD in individuals of distinct ages, from one region to another, or even in separate areas of the same region. In the manner that the available published data have not considered all country regions and was mostly concentrated in southeast.

The guidelines of the Brazilian Control Program for Iodine Deficiency Disorders (Pro-Iodo), recommended observation in schoolchildren between 6-14 years-old, as the child population is high vulnerable (5,8). Only few studies have analyzed pregnant women (25,30,43). Interesting, Ferreira evaluated 191 pregnant women in Ribeirao Preto, Sao Paulo, and found a very high IDD prevalence (57%) and an average UI of 144.4 μg/L (43). It is important to remark that all surveys were conducted when the level of salt iodization were still of 20-40 ppm (ref). Therefore, it is not known if the impact of salt iodization reduction on the health of pregnant and lactating women in Brazil, since this group has a greater need for iodine and previous studies pointed to higher susceptibility for IDD (45). Considering the IDD neurological potential damage during childhood development, the establishment of preventive evaluation for pregnant women and children might be essential (4).

Macedo and cols. (37) when assessing infants and preschoolers in Minas Gerais found a IDD prevalence of 34.4% (37). Therefore, this group of individuals (children until the fifth year of life) might be also extremely vulnerable for IDD (37). In contrast, Lima and cols. (40) have recently used Inductively Coupled Plasma Mass Spectrometry (ICP-MS) to measure iodine content in breast milk and urine from children during the first six months of life in the state of São Paulo and the data revealed a high average concentration of iodine in breast milk (206 μg/L) and urine (293 μg/L) (40).

Therefore, it seems that only considering the risk of excessive iodine intake, based on studies from southeast region, Brazil has changed the contents of this micronutrient in salt traded domestically to 15-45 ppm. However, after adoption of this measure, it would be necessary to monitor the novel iodine nutritional status of the population. Indeed, we hypothesized that the recommended iodination could be modified based on the data about salt intake and UI concentration found for individual area coutoulering Brazil each region, especially in a country of continental dimensions with vast differences in socio-demographic, geographic and climate aspects.

The main challenge is to adequate salt iodization and to promote educational and nutritional programs in order to strengthen the IDD or excessive control related to excessive consumption of iodine. Ideally, periodic monitoring of iodine nutritional status of the population in different states would be essential, especially less studied is essential to establishment of the proper individual range of salt iodization. The actual IDD prevalence analysis is complex, because publication bias high heterogeneity between studied. IDD might still be high in some areas but this remained unknown even after this meta-analysis evaluation.

In conclusion, nutritional status of iodine in Brazil has improved over the past few years, in general, in order to control the supply of iodine and reducing the rate of endemic goiter. However, concern about iodine optimal nutrition persists in all regions of the country, especially, after the reduction in the levels of salt iodization (15-45 ppm).

We hypothesized that changes in diet, differences in goiitrogens consumption (including cassava), geographical and social demographic characteristics, road construction/commercial negotiation and processed foods availability may explain the coexistence of IDD and excessive intake iodine in different areas of the country. Most studies have been conducted many years ago and the generation of a national program for the analysis of the actual situation iodine in all regions is an urgently needed crucial for establishing the specific salt iodization needed for each region.

Acknowledgments: this study was made possible through financial support from the State of Bahia Research Foundation (Fapesb-PET 0002/2013; Edict 29/2012). We gratefully acknowledge the contribution of Coordination of Improvement of Higher Education (Capes) by awarding scholarship to R.O.C. The researchers who kindly gave papers and/or theses for this meta-analysis.

Disclosure: no potential conflict of interest relevant to this article was reported.

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