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

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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 a 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 use 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 I^2 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. Arch Endocrinol Metab. 2015;59(1):13-22

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) recomends daily iodine intake of 50 µg for newborns, 90 µg for children between 13 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 America, identified Brazil (with 17 sentinel sites and a total of 1,563 school children evaluated) as a country of excessive iodine consumption, with a mean urinary iodine excretion (UIE) concentration of 360 µg/L (15,16). Consequently, 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). Notwithstanding, the Brazilian Endocrine Society (SBEM) have strongly diverged on this reduction (http://www.tireoide.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 systematize and analyze all studies which assessed the prevalence of IDD in Brazil through UIE analysis in order 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 because we wanted to reach all studies conducted in the country. The search strategy used controlled vocabulary supplemented with keywords describing the following 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 investigated 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 Brazilian journals. Duplicate publication was checked and, if necessary, the corresponding author was contacted. After this, reviews of iodine status methods were collected 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 included 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 methodology, evaluation and data analysis.

Study selection

Inclusion criteria were defined as follow: a) the language in which the article was published was English or Portuguese; b) the main purpose of the article: assessment 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. Experimental 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 databases were excluded.

Diagnosis of iodine deficiency disorders

The WHO recommendations regarding IDD assessment 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 interconverted to allow comparison between studies (Table 1). The studies selected for the meta-analysis had UIE generally, UIE was determined by the colorimetric ceric arsenite method based on the Sandell-Kolthoff (S-K) reaction, 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 1. Summary from studies conducted in Brazil in the between 1985-2013

Study	Population	Methodology	Outcomes	Study Quality	Conclusions
Alves and cols. (22) Cross-sectional study Year of study: 1985-1990 Year of publication: 2005	15,131 newborns 7,797 males, 7,328 females Location: Ribeirão Preto, SP	Umbilical cord blood for TSH and T4 dosage UIE sample 24 hours (S-K reaction) in 141 newborns	1/141 infants had TSH level equal to 19.4 µIU/mL. The UI ranged between 2.1 and 194 µg/L	5	Newborns were subjected to borderline IDD
Correa Filho and cols. (23) Cross-sectional study Year of study: 1994-1996 Year of publication: 2002	178,774 schoolchildren aged 6-14 years Location: 428 cities of all Brazilian states	UIE and table salt evaluation Palpation for goiter assessment	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	6	33% of schoolchildren had some degree of IDD and in 12%, UIE levels were less than 5 µg/dL, characterized severe deficiency
Esteves (24) Cross-sectional study Year of study: 1996 Year of publication: 1997	16,803 schoolchildren aged 6-14 years, both sexes Location: schods publics of 401 cities in all Brazilian states	UIE (adapted S-K method)	We observed IDD in 85 cities, moderate DDI (≥ 25 and < 50 µg/L) in Cocos in Bahia, and Almas, Arraias and Paraná in Tocantins, and to mild (values ≥ 50 and < 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	4	Mild to moderate IDD in 30% of the cities
Barca and cols. (25) Cohort Year of study: 1998 Year of publication: 2001	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	TSH, FT4, Tg, anti-Tg and anti-TPO antibodies. Thyroid ultrasound UIE (S-K reaction)	The median UI excretion was 167.8 µg/L	7	Adequate iodine nutritional status. No correlation with TPP
Nimer and cols. (26) Cross-sectional study Year of study: 1996 Year of publication: 2002	280 schoolchildren Location: two elementary schools, one private and one public of Ouro Preto, Minas Gerais	UIE (adapted S-K. method) Measure levels iodine of salt	The concentration levels of UI were normal in 92.2% of private school students and 42.6% of public school children	4	Iodine status was drastically different between private and public school students
Pretell and cols. (16) Cross-sectional study Year of study: 1998-2000 Year of publication: 2004	1,563 schoolchildren Location: 17 sentinel sites distributed in 8 states (PA, MA, TO, GO, MT, MS, MG and ES*)	UIE by Pino and cols. method (26) Table salt Thyroid ultrasounds	UIE was < 50 µg/L in 2.3%, 29.1% of 200-299 µg/L and 70.6% with UI > 300 µg/L. The median UI concentrations of 360 µg/L	7	Iodine excess was more prevalent
Saab (27) Cross-sectional study Year of study: 1998-2000 Year of publication: 2000	1,000 school children Location: Mato Grosso do Sul	UIE (S-K reaction). TSH and FT4, Tg, anti-Tg and anti-TPO antibodies Assessment of goiter by palpation Thyroid ultrasound	Had UI lower than 50 µg/dL. The total number of samples with values below UI 5 µg/dL. In 95.2% UI > 10 µg/dL, 22.1% > 30 µg/dL	6	Goiter prevalence was low. UIE was above the recommended iodine content in salt was adequate
Marino and cols.** (28) Year of study: 2002-2003 Year of publication: 2009	13 adults aged 22-63 years Location: city of Santo André, SP	T3, T4, FT4, TSH, A-Tg, A-TPO, TSHR. UIE (S-K reaction)	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)	7	Iodine adequate sufficiency with an UIE mean of 262.31 µg/L
Duarte (29) Cross-sectional study Year of study: 2003-2007 Year of publication: 2007	964 school children Location: public schools in six cities in Sao Paulo (Taubaté, Registro, Ribeirão Preto, São José do Rio Preto, Araçatuba, Presidente Prudente)	Thyroid ultrasound UIE (S-K method modified)	UIE was < 100 µg/L in 1.5%, 21.6% of 100-299 and 76.7% with UIE > 300 µg/L	6	Excessive iodine intake in students from Sao Paulo

Study	Population	Methodology	Outcomes	Study Quality	Conclusions
Soares and cols. (30) Cross-sectional study Year of study: 2003-2005 Year of publication: 2008	147 pregnant women Location: Public health care clinics of Porto Alegre, Rio Grande do Sul	Measurement of UIE (S-K reaction) and creatinina Thyroid ultrasound FT4 and Tg	Mean UI was 226 ± 87 µg/L and median UI 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	6	19.7% had insufficient iodine intake. No correlation between serum FT4, Tg and TV with UIE
Navarro and cols. (31) Cross-sectional study Year of study: 2004 Year of publication: 2010	145 schoolchildren, 79 from rural areas and 66 from urban area Location: Botucatu, Sao Paulo	UIE (S-K reaction) and table salt	IDD was detected in 3,4% and 3% of children from the rural and urban school, respectively. UI greater then 300 µg/L was detected in 62,3% and 90,9% of students from the rural and urban school, respectively	6	IDD is controlled in school children, with high prevalence of UIE excess
Camargo and cols. (32) Cross-sectional study Year of study: 2004 Year of publication: 2008	1,085 individuals aged 20-87 years Location: metropolitan area in Sao Paulo (houses randomly selected)	UIE (S-K method) and table salt Thyroid ultrasound TSH, TPOAb	UIE ≥ 300 in 45.6%, 14.1% had UIE greater than 400. The prevalence of CAT was 16,9%	8	High prevalence of iodine excess and CAT
Carvalho and cols. (33) Cross-sectional study Year of study: 2004 to 2007 Year of publication: 2012	828 schoolchildren Location: Botucatu, Sao Paulo	Determination of UIE casual urine sample (adapted S-K method)	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	6	High excessive iodine intake rate in school children
Vanacor and cols. (34) Cross-sectional study Year of study: 2005-2007 Year of publication: 2008	60 subjects Location: Hospital de Clínicas de Porto Alegre, Rio Grande do Sul	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	The UIE and sodium excretions were variable along the 24-hour period. The correlation between the total iodine and sodium excretions was very strong	4	The UIE 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
Pontes and Adan (35) Cross-sectional study Year of study: not described Year of publication: 2006	180 schoolchildren Location: public schools from Cabaceiras, Paraíba	Questionnaire nutritional UIE (Rapid Urinary Iodine Test®)	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	2	Goitrogenic foods are higerly consumed. One third of school children had low UI levels less than 100 µg/L
Alves and cols. (36) Cross-sectional study Year of study: 2007-2008 Year of publication: 2010	300 schoolchildren Location: public schools of different socioeconomic levels from Ribeirão Preto, Sao Paulo	UIE (S-K reaction) and table salt Thyroid ultrasound	100% of the urine samples had UI values greater than 100 µg/L, 59.5% of subjects had values above 300 µg/L	5	Iodine sufficiency in Ribeirão Preto school children population. UIE showed excess in 59,5%
Macedo and cols. (37) Cross-sectional study Year of study: 2008 Year of publication: 2012	475 children Location: Novo Cruzeiro, Minas Gerais	UIE (S-K reaction) and table salt	IDD prevalence was 34.4%, 23.5% (mild), 5.9 (moderate) and 5% (severe)	7	IDD prevalence of 34,4%
Macedo (38) Cross-sectional study Year of study: 2008 Year of publication: 2010	540 school children Location: Novo Cruzeiro, Minas Gerais	UIE (S-K method) and table salt	IDD prevalence was 38.9% (28.7% mild, 6.2% moderate and 4% severe)	8	High rate of IDD of 38,9%. Need to evaluated control as disease
Milhoransa and cols. (39). Cross-sectional study Year of study: 2009 Year of publication: 2010	47 healthy individuals, 22 men and 25 women, aged 18 years or older Location: Hospital de Clínicas de Porto Alegre, Rio Grande do Sul	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	2/14 women had 24-h UIE below 138 µg/24h in the three samples studied	6	UIE is adequate in the group of 14 people, however, the UIE two women suggests IDD

Study	Population	Methodology	Outcomes	Study Quality	Conclusions
Lima and cols. (40) Cross-sectional study Year of study: 2009 Year of publication: 2013	33 infants (less than 6 months of age) and their mothers. Location: Guariba, Sao Paulo.	UIE and levels in the urine and maternal milk were assessed by ICP-MS Table salt	The median UIE value in the infants was 293 µg/L; the mean iodine concentration was 206 µg/L in the maternal milk and 39.9 mg I/kg in the salt	3	The median infant UIE was elevated due to the high iodine concentration present in the maternal milk. High iodine values were caused by high salt iodine levels, which should be reduced
Rates (41) Cross-sectional study Year of study: 2009 Year of publication: 2010	428 schoolchildren aged 10-19 years (63.3% female and 36.7%) Location: public schools of Vespasian, Minas Gerais	Anthropometry. UIE (S-K reaction)	4.4% with IDD, 28.7% with appropriate indices, 46.7% more than adequate and 20.1% excessive	6	The excessive concentrations of iodine in the urine were associated with female gender, adequate percentage of iodine in salt and overweight or obesity
Almeida (42) Cross-sectional study Year of study: 2011- 2012 Year of publication: 2013	125 newborns Location: Hospital Universitário Cassiano Antônio Moraes, Universidade Federal do Espírito Santo, Vitoria, ES	UIE (S-K reaction) TSH, FT4, Tg, anti-TPO, anti-TG and anti-TSH receptor (TRAb)	The average TSH was 1.74. The average FT4 was 1.99 ng/mL	6	All 125 neonates were euthyroid and had normal UIE
Ferreira (43) Case-control study Year of study: 2008-2009 Year of publication: 2011	191 pregnant women aged 18 years and gestational age up to 14 weeks Location: Health Center Street School Cuiabá and School Health Center of Avenida Dom Pedro, Ribeirão Preto, Sao Paulo	UIE (S-K reaction) TSH, FT4 and total T4	19 (9.9%) pregnant women had UIE > 250 µg/L, 63 (33%) had UIE in the normal range (150-250 µg/L), and 109 (57.1%) had UIE < 150 µg /L	6	IDD was detected in pregnant women, indicating the need for iodine replacement during prenatal period

* Additional data from Rossi and cols. 2001 (44).

** We included only control patients results.

Quality score: 0-3 points (low quality), 4-6 points (appropriate quality), 7-9 points (high quality).

CAT: chronic autoimmune thyroiditis; ICP-MS: inductively coupled plasma mass spectrometry; IDD: iodine deficiency disorders; S-K: Sandell-Kolthoff; UI: urinary iodine; UIE: urinary iodine excretion; TG: thyroglobulin; TSH: thyroid-stimulating hormone; TV: thyroid volume.

Statistical analysis

Statistical analyzes 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 I^2 Statistic and visual inspection of each "Forest plot". We have determined fixed and random model effects, but was systematically employed in cases where the I^2 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.

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

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 be not be analyzed by meta-analysis methodology. However, a high heterogeneity was immediately identified among the studies used for this meta-analysis ($p < 0.0001$, $I^2 = 99.5\%$) (Figure 2). After applying the I^2 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).

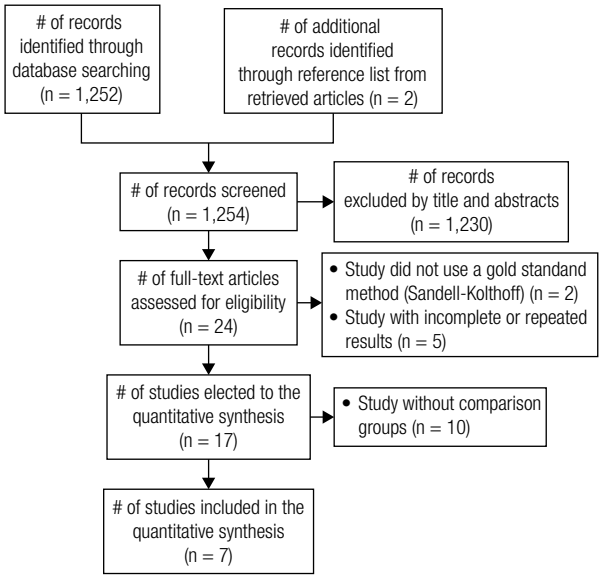


Figure 1. Study selection process.

Table 2. Urinary iodine excretion in Brazilian population

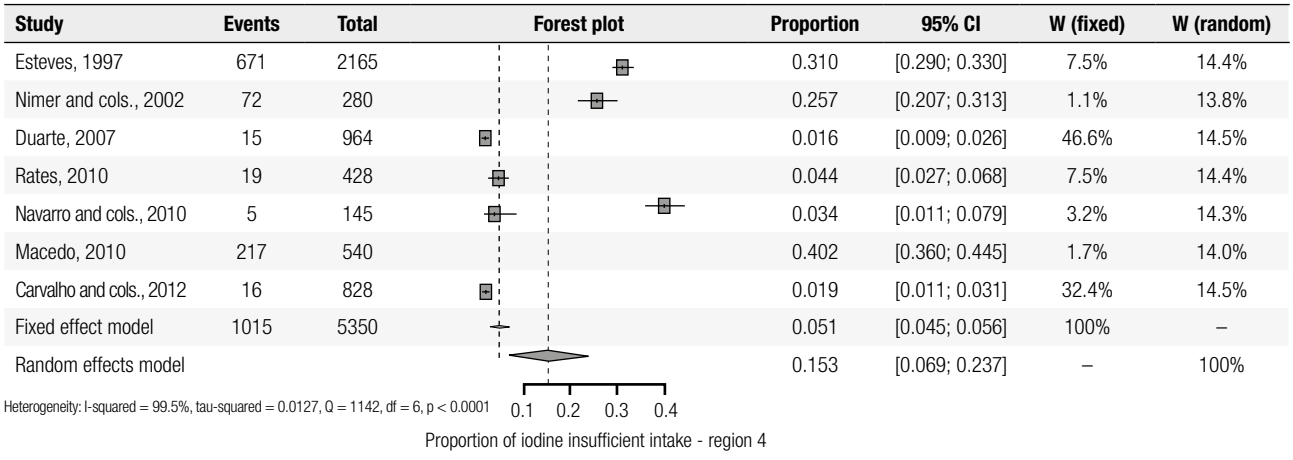
Study	Year	No of subjects	Region	Subgroup	Insufficient intake	Sufficient intake
					< 100 µg/L	≥ 100 µg/L
Esteves	1997	4,231	North	School children	1,985	2,246
		6,553	Northeast		2,034	4,519
		2,186	Midwest		748	1,438
		2,165	Southeast		671	1,494
		1,668	South		468	1,200
Saab	2000	1,000	Midwest	School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

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

Table 3. Urinary Iodine Excretion in Brazilian Pregnant Women

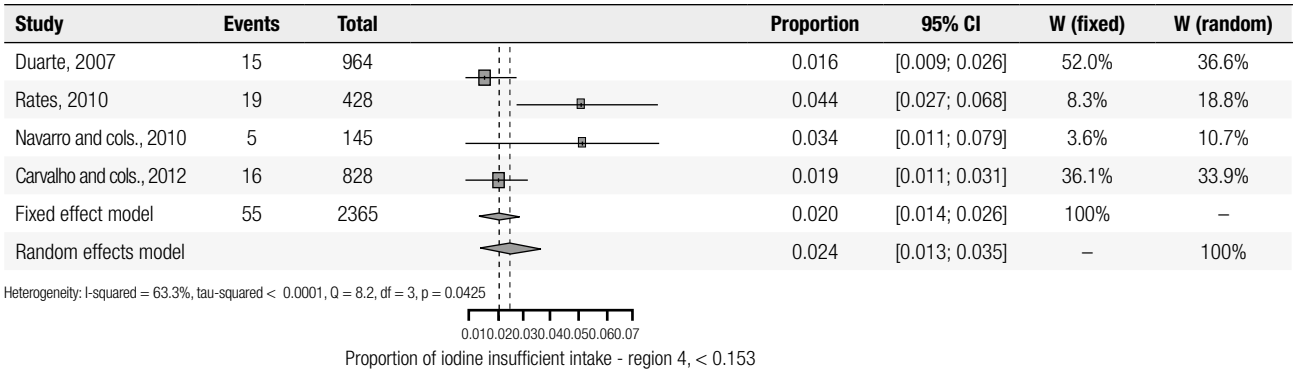
Study	Year	No of subjects	Region	Insufficient intake	Sufficient intake
				< 150 µg/L	≥ 150 µg/L
Soares and cols.	2008	147	South	29	118
Ferreira	2011	191	Southeast	109	82
Total	–	338	–	138	200

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



CI: confidence interval; W: weighted.

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



CI: confidence interval; W: weighted.

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

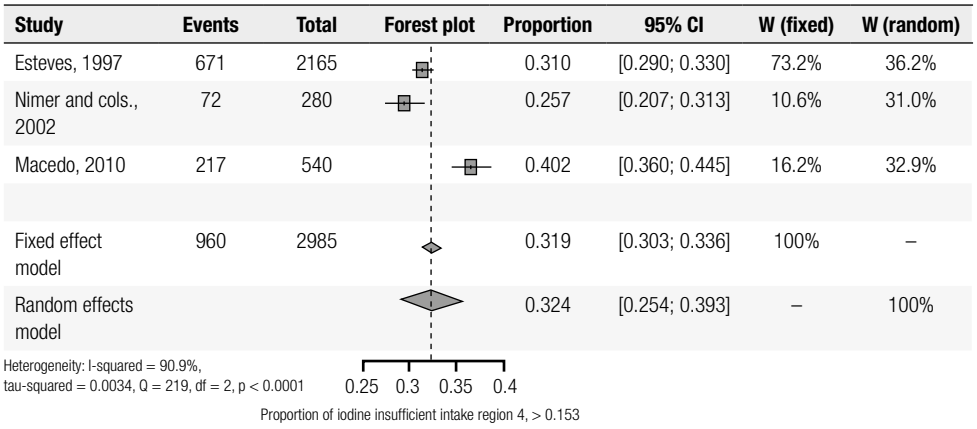
DISCUSSION

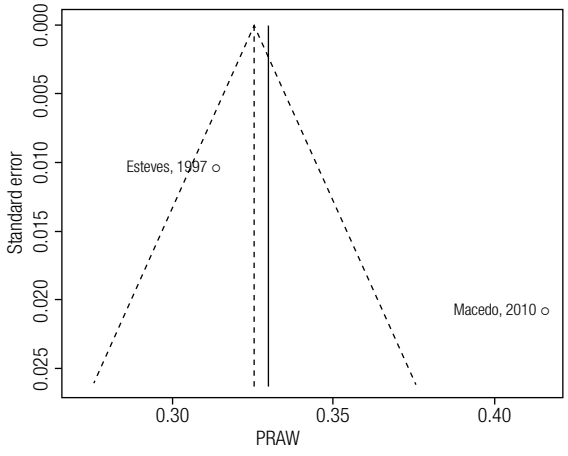
This unprecedented systematic review showed the prevalence of IDD measured in populational studies conducted in Brazil and aimed to answer our main question: What is the overall prevalence of IDD in Brazil?. However, the vast majority of surveys (94, 1%) were conducted in the South (4/17) and Southeast (13/17) regions. Consequently, a comprehensive conclusion about the real IDD prevalence in the country can not be acchieved. 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 predictied 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 Paraná (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





CI: confidence interval; W: weighted.

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 iodination 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 coustolering 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 goitrogens 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.

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