Public Health Nutrition: 24(18), 6450–6465 doi:10.1017/S136898002100286X

Review Article

Prevalence of childhood anaemia in Brazil: still a serious health problem: a systematic review and meta-analysis

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Submitted 26 November 2020: Final revision received 7 June 2021: Accepted 28 June 2021: First published online 2 July 2021

Abstract

Objective: To estimate the prevalence of anaemia in Brazilian children up to 83·9 months old.

Design: Systematic review and meta-analysis, using databases PubMed, Scopus, SciELO, Lilacs, Google Scholar, Periódicos Capes, Arca, Biblioteca Virtual em Saúde, Microsoft Academic Search and Cochrane Library using search terms: anaemia, prevalence, child and Brazil. PROSPERO Registration number: CRD42020208818.

Setting: Cross-sectional, cohort, case–control and intervention studies published between 2007 and 2020 were searched, excluding those who assessed children with an illness or chronic condition. The main outcome was anaemia prevalence. Random effects models based on the inverse variance method were used to estimate pooled prevalence measures. Sensitivity analyses removed studies with high contribution to overall heterogeneity.

Participants: From 6790 first screened, 134 eligible studies were included, totalling 46 978 children aged zero to 83·9 months analysed, with adequate regions representativeness.

Results: Pooled prevalence of anaemia was 33 % (95 % CI 30, 35). Sensitivity analyses showed that withdrawal of studies that contributed to high heterogeneity did not influence national average prevalence.

Conclusions: Childhood anaemia is still a serious public health problem in Brazil, exposing 33 % of Brazilian children to the anaemia repercussions. The main limitation of the study is the estimation of national prevalence based on local surveys, but a large number of studies were included, with representation in all regions of the country, giving strength to the results. In Brazil, more public policies are needed to promote supplementation, fortification and access to healthy eating to reduce the high level of anaemia among children.

Keywords
Anaemia
Infant
Child
Preschool
Prevalence
Iron deficiency
Brazil

Anaemia is a disease that affects the production of erythrocytes and has as main characteristic the insufficient oxygenation capacity of tissues due to the lower amount of circulating Hb. This phenomenon can occur as a consequence of decreased production and/or increased loss of erythrocytes, with underlying and often overlapping causes[1]. This is a global public health problem that affects populations of different socio-economic levels and in all

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age groups, being more prevalent in poverty regions[2], where there is interaction of factors such as: (a) insufficient intake of Fe of adequate bioavailability (especially that from meat and offal); (b) diets rich in cereals composed of phytates, polyphenols and other ligands that impair intestinal absorption of Fe and (c) poor hygienic and sanitary conditions with parasitic diseases and frequent inflammatory processes[3].

The WHO considers anaemia as an indicator of nutritional and health poverty, which compromises quality of life and contributes to infant mortality. At population level, an anaemia prevalence >4·9 % is considered of public health significance, with a prevalence >40 % classified as a severe public health problem[4]. It is estimated that worldwide, the prevalence of anaemia among children in the preschool age group is 47·4 %, ranging from 21·7 % in Europe to 67·6 % in some countries of the African continent[5].

Chronic childhood anaemia is responsible for a number of well-documented physical, emotional and cognitive impairments, such as growth slowdown; pubertal retardation; impaired visual, auditory and memory functions; negative effects on cognitive development and behavioural disorders (appetite perversion, attention deficit hyperactivity, restless leg syndrome)[1,6–9]. In addition, the chronic effects of Fe deficiency can also compromise immunity, increasing the risk of infectious diseases and their complications[10].

Brazil nationwide data are not available due to the absence of research studies involving population Hb dosage. Some authors, such as Jordão *et al.*[11], Iglesias Vásquez *et al.*[12] and Ferreira *et al.*[13], have used statistical strategies to estimate national prevalence based on local studies. Currently, surveys of anaemia prevalence conducted in specific localities, of local scope, are rarely published in journals indexed in the most relevant databases and are usually published in smaller journals, although official and with peer review process. Therefore, in order to comprehensively estimate the national prevalence, it is necessary to include in the review the local data published in these journals of lesser expression.

The present study proposes to estimate the Brazilian prevalence of anaemia among infants and preschoolers through a systematic review study with meta-analysis, with the inclusion of data obtained in articles published in official scientific journals, which have International Standard Serial Number and meet the criteria described in the methodology.

Methods

Study design and search strategy

This meta-analysis was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[14]. Studies on the prevalence of anaemia were researched in Brazilian children from birth to 83·9 months, published between January 2007 and July 2020, in the databases PubMed, Scopus, SciELO, Lilacs, Google Scholar, *Periódicos Capes*, Arca, *Biblioteca Virtual em Saúde*, Microsoft Academic Search and Cochrane Library.

The choice was made to evaluate the studies published after 2007 in order to be able to verify and update the prevalence estimated in a meta-analysis by Jordão *et al.*[11], who reviewed studies published between 1996 and 2007. We chose the age group to achieve greater comparability with other studies, since most surveys related to the prevalence of anaemia in Brazil have included children under the age of 7 years.

The terms that used for searching were: 'anaemia' 'iron deficiency anaemia' and 'prevalence' and 'child' and 'Brazil'. These terms in Portuguese were also used: 'anaemia', 'anaemia ferropriva' and 'prevalência' and 'criança' and 'Brasil'. Additional eligible studies on the prevalence of anaemia in childhood were sought by reviewing the reference lists of identified articles and searching relevant journals related to our research topic. No language restrictions were adopted during the search.

The choice to carry out a meta-analysis was made due to the fact that there are a large number of local surveys of anaemia prevalence in Brazil, but that these could only be used to estimate national prevalence through appropriate statistical methods. Although meta-analyses are often criticised for combining heterogeneous data, in the present study, this would have little chance of occurring because data on the prevalence of anaemia were obtained through standardised methods and cut-off points, enabling studies to be analysed together. Additionally, as described (at page 98) by Grant and Booth[15], "small or inconclusive studies lacking in statistical significance can nevertheless make a contribution to the larger picture and such compilations are time efficient for decision makers, particularly when compared with the time taken to review scattered individual studies".

Study selection and eligibility criteria

Two reviewers independently screened titles and abstracts and critically reviewed the full texts of all selected studies on the basis of the inclusion and exclusion criteria. Any disagreement that arose between reviewers was resolved through discussion and involvement of a third reviewer.

Observational studies (cohort, case–control and cross-sectional studies) and clinical trials were included. In cohort, case–control and intervention studies, the prevalence of anaemia was obtained only at the beginning of the study (baseline). The data were considered only for children residing in Brazil. Inclusion criteria were studies that contained information about the children's age, city and region of the country, sample size, criteria for defining anaemia and specific method of laboratory evaluation of

https://doi.org/10.1017/S136898002100286X Published online by Cambridge University Press

blood Hb. The cut-off point for defining anaemia should be in accordance with the definitions of the WHO[16]. Although the authors' main interest was in Fe deficiency anaemia, all studies evaluating the prevalence of anaemia were included, even those in which there was no proof that the condition was effectively due to Fe deficiency. It is important to state that, in Brazil, the vast majority of cases of anaemia occur due to Fe deficiency[17]. Review studies, studies with secondary data, theses, dissertations, course completion papers, annals of scientific events and studies that evaluated the prevalence of anaemia in children with an illness or chronic condition, hospitalised or not were excluded.

Data extraction and risk of bias/quality assessment

Two authors independently extracted data on the year of the study and the region of the country, the study design, sample size, children's age group, prevalence and diagnostic criteria for anaemia. The Modified Newcastle–Ottawa quality assessment scale for observational studies (cohort, case–control and cross-sectional studies)[18,19] was used to assess the quality of the study for inclusion. The total score for the Modified Newcastle–Ottawa scale for observational studies is nine stars as a maximum for the overall scale with the minimum of zero. A study was considered of high quality if it reached 7 to 9, medium if it reached 4 to 6 and low if it reached 0 to 3.

For the evaluation of risk-of-bias (RoB) for the non-randomised clinical trials, the ROBINS-I tool (Risk of Bias in Non-randomized Studies-of Interventions) was used[20]. The evaluated criteria were divided into pre-intervention, intervention and post-intervention categories. The overall RoB judgement was individually analysed for each study and classified as low, moderate, serious, critical or no information. For randomised clinical trials, the RoB 2 tool (Revised Cochrane risk-of-bias tool for randomised trials)[21] was used, analysing five domains. The overall RoB judgement for each study was classified as low risk, some concerns or high risk.

All studies were included regardless of study quality, in order to obtain the largest possible national coverage of the prevalence of anaemia in childhood. In addition, although some tools are focused on the quality of the intervention, our objective was only to know the prevalence of anaemia in the baseline data. In this case, the representativeness of the sample was more important than the general quality of the intervention. Sensitivity analyses were undertaken to withdraw studies that contributed to high heterogeneity.

Data analysis and heterogeneity assessment

Meta-analysis on the prevalence of anaemia was carried out by using the 'meta' package[22] implemented in the R software version 3.6.2. Forest plots including 95 % CI calculated by the Clopper–Pearson exact method were used to describe the prevalence estimates for each study included in the meta-analysis[23]. Cochran's Q test, the between-study variance (tau^2) and I^2 statistics were used to assess heterogeneity[24]. Higher values of I^2 indicate a greater degree of heterogeneity among studies. Random effects models based on the inverse variance method were used to estimate pooled prevalence measures, taking into account the high heterogeneity observed between studies. Stratified analyses were performed by Brazilian regions, in order to assess geographic variations of the prevalence of anaemia. The contribution of each study to the overall prevalence measure and heterogeneity was assessed graphically by constructing a Baujat plot[25]. Sensitivity analyses removed studies with high contribution to overall heterogeneity, detected by the Baujat plots, in order to assess the possible effects of these studies on the pooled prevalence measures. The sensitivity analyses also assessed the possible effect of studies with sample size <100 and studies that are not cross-sectional on the pooled estimates[26]. An alternative funnel plot was used to explore the possibility of publication bias[27]. Alternative funnel plots are constructed using study size rather than 1/SE in y-axis, as recommended by Hunter *et al.*[27] in meta-analyses of proportion studies. Funnel plots are skewed and asymmetrical in the presence of publication bias and other biases.

The data presented are stratified by regions of Brazil and consolidated with the estimate of national prevalence. Brazil is divided into five geographic regions, being: North, Northeast, Midwest, Southeast and South. Data for the North and Midwest regions were grouped. This option was adopted due to some aspects described below: (1) fewer studies identified in these regions; (2) similar geographical and economic characteristics, such as the smaller number of large urban agglomerates, the presence of extensive areas of vegetation and watersheds, a smaller and less populous coastal strip, the presence of native indigenous populations and low migration and (3) and no studies were found regarding the metropolitan region of the Federal District, Brasília (located in the Midwest region), which could contribute to data asymmetry due to cosmopolitan characteristics similar to those observed in the metropolises of the South and Southeast regions.

Study registration

The protocol for this review was registered with PROSPERO: (no. CRD42020208818)

Results

The search of articles in the databases identified 6779 records from January 2007 to July 2020. An additional eleven articles were identified from reference lists and hand searches. Of these, 3128 records remained after the

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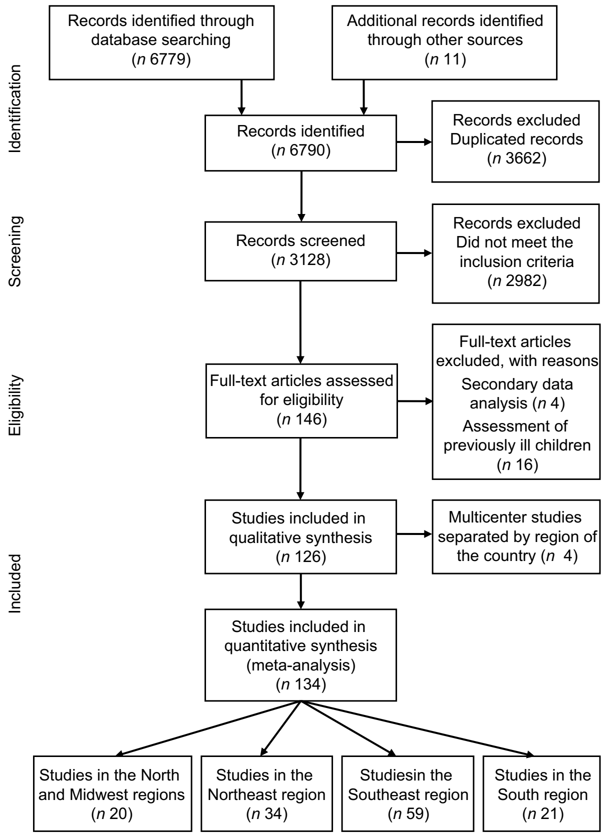

Fig. 1 Flow chart of the selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement

removal of duplicates (Fig. 1). Based on the title and screening of the abstract, 2982 records were removed due to not meeting the inclusion criteria. In total, 146 full-text articles were reviewed. In this full-text screening, twenty articles were excluded due to the analyses of secondary data and evaluation of previously ill children (Fig. 1). A total of 126 papers met the inclusion criteria and were included in the meta-analysis. As some of these articles were multicentre studies, the prevalence of anaemia was presented separately for each region where these studies were conducted. Therefore, the meta-analysis was conducted based on 126 papers and 134 studies, twenty from the North and Midwest regions[28–47], thirty-four from the Northeast region[29,38,39,48–76], fifty-nine from the Southeast region[55,77–134] and twenty-one from the Southern region[66,88,135–153].

One hundred and seven cross-sectional studies, eight cohort studies, one case–control study and eighteen intervention studies were included (see online Supplemental Table 1). The number of subjects per study ranged from 31 to 2376, with a mean age that ranged from 0 to 83·9 months. The Newcastle–Ottawa scale for observational studies was applied to 116 studies. Thirty-nine studies were classified as high quality, seventy-six as medium quality and one was classified as low quality of evidence. The ROBINS-I tool was used in nine studies. Five studies showed a moderate risk and four studies a serious RoB. The RoB 2 tool was used in nine studies, of which four were assessed as low RoB, four with some concerns and one with high risk (see online Supplemental Table 1).

In total, 46 978 children were included in the study, with an estimated national prevalence of 33 % of anaemia (Fig. 2). The prevalence measured was similar for the North/Midwest (36 %), Northeast (38 %) and South (35 %); however, they were lower in the Southeast region (28 %). Figures 3–6 show the results obtained according to the different regions.

One of the aspects that can be observed by the disposition of the studies in the graphs, which are presented according to the date of publication, is the fact that there seems to be no temporal trend, between 2007 and 2020, of changes in prevalence.

Figure 7 shows the contribution of each study to the overall effect size by Baujat plots, where the impact of excluding a study from the final analyses (vertical axis) is plotted against its contribution to the heterogeneity statistic (horizontal axis). For example, panel (a) of Fig. 7 shows that the studies by Leite *et al.* (2013)[39] and Cardoso *et al.* (2012)[31] have higher contribution to the overall heterogeneity and high influence to the overall result and, consequently, it is important to evaluate the effect of the removal of these studies in sensitivity analyses. The sensitivity analyses in Table 1 show that the removal of these studies did not significantly influence the average prevalence of each region, except in the South region.

The funnel plot for publication bias analyses considering the 134 studies is showed in Fig. 8. This graph seems to suggest that there is a reasonably symmetrical distribution of the logit transformed prevalence estimates around the pooled prevalence, indicating that this systematic review is not subject to a publication bias[26].

Discussion

Brazil is a country of continental dimensions and has faced successive political and economic crises. These facts, in a way, have interfered in the production of information and data related to health conditions of national scope. In the nutritional area, even relatively simple information, such as nutritional status obtained by anthropometry, is scarce in childhood and the last national survey that showed prevalence of malnutrition was conducted in 2008[154]. Regarding anaemia, there are virtually no national data that have been obtained by a study designed for this purpose, including representative sampling from all over the country. An attempt to estimate was made in 2006, in *Pesquisa Nacional de Demografia e Saúde da Criança e da Mulher* (PNDS 2006)[155], in which 3499 blood samples from children under 5 years of age using the dry drop technique were analysed, and Hb values below 11 g/dl were

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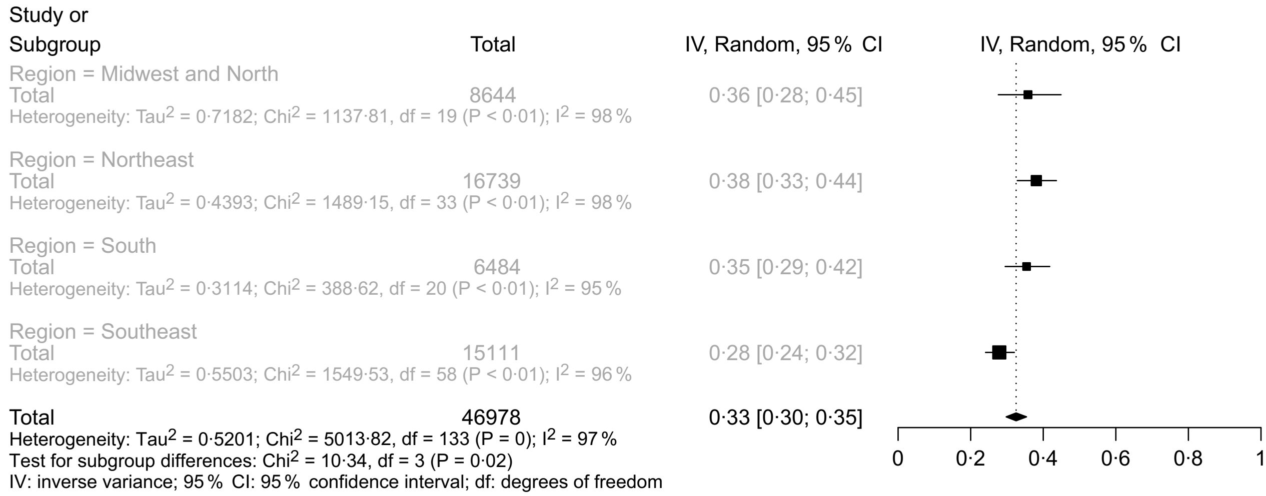

Fig. 2 Forest plot for meta-analysis of the prevalence of anaemia in all Brazilian regions

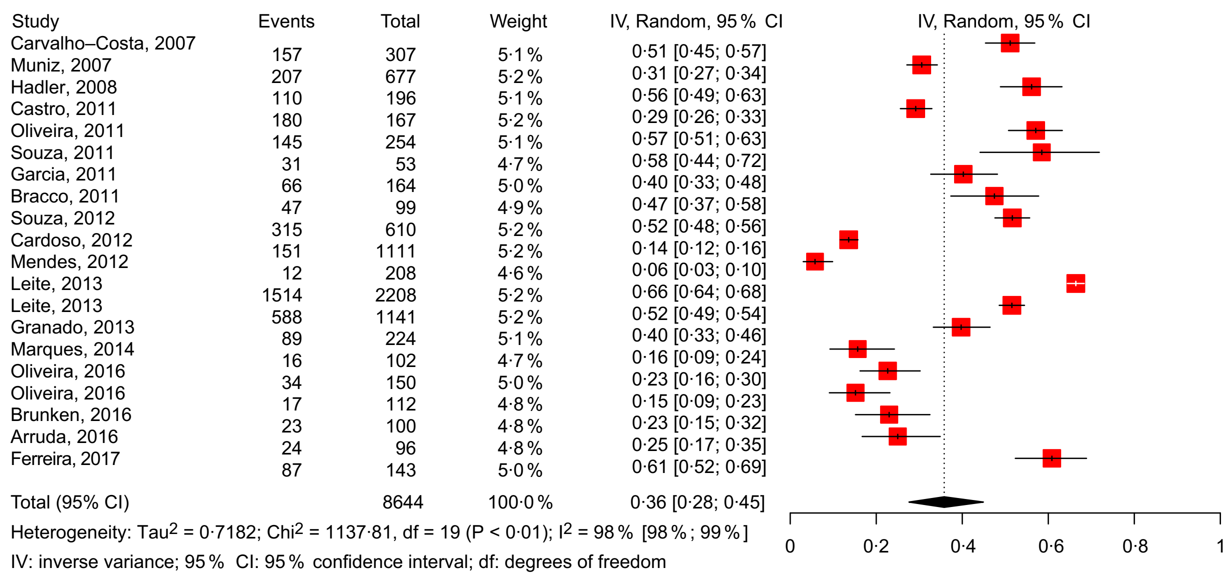

Fig. 3 (colour online) Forest plot for meta-analysis of the prevalence of anaemia in the Brazilian Midwest and North regions (ordered by year of publication)

considered as anaemia. However, a number of methodological limitations, including loss of samples and the fact that the dry drop method was not validated for children, led to the results of this study being questioned[156–158]. Additionally, these data are currently out dated in about 14 years[155].

For this reason, given the need to know the information about the prevalence of anaemia in the country as a whole and in its regions, in order to structure control measures, some authors have sought to estimate this information based on local studies[11–13]. One of the first initiatives in this sense appeared in the literature in 2009, by Jordão *et al.*[11], who reviewed fifty-three studies published between 1996 and 2007 and, through meta-analysis, estimated a national prevalence of 53 % of anaemia among children aged between zero and 5 years. Due to the large number of affected children, numerous attempts at fortification were tested in the country, especially studies by the Dutra-de-Oliveira group that sought to fortify drinking water with Fe, considering that to reach all children exposed to anaemia, it would be necessary to fortify food of widespread consumption[114,159,160]. An aspect that may be relevant for the prevalence has fallen, considering the data from Jordão *et al.*[11], and those in the present study refer to the possible impact of government initiatives to combat Fe deficiency. Because of a law published in 2002, from 2004, fortification of wheat and maize flours with Fe and folic acid became mandatory in Brazil[161] and, in 2005, the *Saúde de Ferro* programme was implemented, which added initiatives for universal supplementation of children up to 2 years old[162]. These two initiatives may have contributed to the decrease in prevalence

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Study	Events	Total	Weight	IV, Random, 95 % CI
Vieira, 2007	90	162	3·0 %	0·56 [0·48; 0·63]
Arcanjo, 2007	270	728	3·1 %	0·37 [0·34; 0·41]
Silva, 2008	388	827	3·1 %	0·47 [0·43; 0·50]
Pinheiro, 2008	33	104	2·8 %	0·32 [0·23; 0·42]
Ferreira, 2008	8	50	2·3 %	0·16 [0·07; 0·29]
Eickmann, 2008	50	76	2·8 %	0·66 [0·54; 0·76]
Vieira, 2010	300	666	3·1 %	0·45 [0·41; 0·49]
Oliveira, 2010	335	628	3·1 %	0·53 [0·49; 0·57]
Oliveira, 2010	269	502	3·1 %	0·54 [0·49; 0·58]
Oliveira, 2010	108	150	2·9 %	0·72 [0·64; 0·79]
Teixeira, 2010	215	330	3·0 %	0·65 [0·60; 0·70]
Carvalho, 2010	278	301	2·8 %	0·92 [0·89; 0·95]
Ferreira, 2011	249	973	3·1 %	0·26 [0·23; 0·28]
Leal, 2011	460	1403	3·1 %	0·33 [0·30; 0·35]
Santos, 2011	337	595	3·1 %	0·57 [0·53; 0·61]
Bracco, 2011	35	137	2·9 %	0·26 [0·18; 0·34]
Gondim, 2012	404	1108	3·1 %	0·36 [0·34; 0·39]
Pereira, 2012	57	99	2·9 %	0·58 [0·47; 0·67]
Leite, 2013	348	724	3·1 %	0·48 [0·44; 0·52]
Leite, 2013	497	1211	3·1 %	0·41 [0·38; 0·44]
Pedraza, 2013	37	240	2·9 %	0·15 [0·11; 0·21]
Vasconcelos, 2014	207	993	3·1 %	0·21 [0·18; 0·24]
Vasconcelos, 2014	432	777	3·1 %	0·56 [0·52; 0·59]
Cavalcanti, 2014	27	40	2·5 %	0·68 [0·51; 0·81]
Paula, 2014	331	945	3·1 %	0·35 [0·32; 0·38]
Lander, 2014	14	359	2·7 %	0·04 [0·02; 0·06]
Ferreira, 2015	11	55	2·5 %	0·20 [0·10; 0·33]
Duarte, 2015	22	92	2·8 %	0·24 [0·16; 0·34]
Matos, 2015	43	78	2·8 %	0·55 [0·43; 0·66]
Landim, 2016	48	262	3·0 %	0·18 [0·14; 0·24]
Pedraza, 2016	51	299	3·0 %	0·17 [0·13; 0·22]
Novaes, 2017	69	677	3·0 %	0·10 [0·08; 0·13]
Magalhães, 2018	98	366	3·0 %	0·27 [0·22; 0·32]
Vieira, 2018	214	782	3·1 %	0·27 [0·24; 0·31]
Total (95% CI)		16739	100·0 %	0·38 [0·33; 0·44]

Heterogeneity: $Tau^2 = 0·4393$; $Chi^2 = 1489·15$, df = 33 ($P < 0·01$); $I^2 = 98\,\%$ [97 %; 98 %]
IV: inverse variance; 95 % CI: 95 % confidence interval; df: degrees of freedom

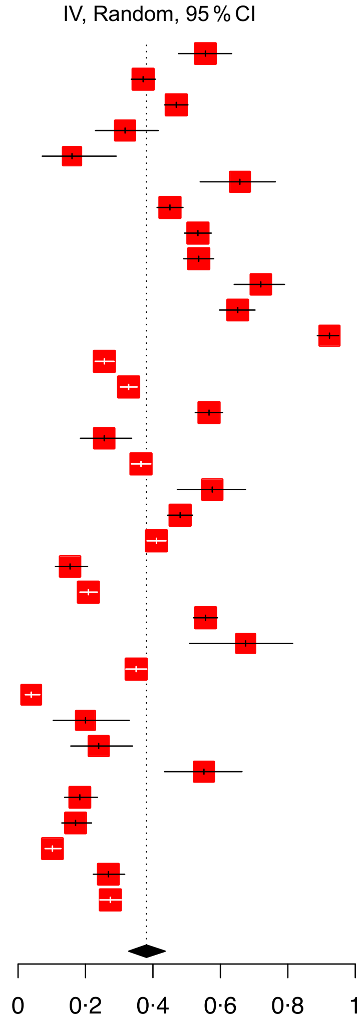

Fig. 4 (colour online) Forest plot for meta-analysis of the prevalence of anaemia in the Brazilian Northeast region (ordered by year of publication)

observed in these two studies of similar methodology, but covering sequential periods. On the other hand, our meta-analysis showed that, at least between 2007 and 2020, there seems to have been no trend of change in prevalence. The results are found, as can be seen in the graphs referring to the regions, scattered over the years, not seeing a propensity to fall or increase in numbers.

More recently, Iglesias Vásquez *et al.*[12] found a prevalence of 39·6 % of anaemia among preschool children and schoolchildren in Latin America, reviewing eighteen studies published between 2000 and 2014. And, Ferreira *et al.*[13] reviewed thirty-seven studies published between 2007 and 2019 involving 17 741 Brazilian children aged 6–60 months and found, through meta-analysis, a general prevalence of 40·4 % of anaemia. The article by Ferreira *et al.*[13] aimed to describe the prevalence of anaemia in different scenarios (health services, populations subject to social inequalities and population-based studies), including thirty-seven studies with children aged 6–60 months. Our analysis included 134 studies, with children from a wider age group and also differed by describing the prevalence according to the regions of the country. These regional inequalities have not been studied in previous meta-analyses[13].

The present study, when compared with the three mentioned above[11–13], who evaluated similar age groups, found a lowest prevalence. However, considering that the number of studies included was quite high, it is possible that our data are better able to reflect the real situation. In any case, the figures are extremely high in view of the recognised repercussions of anaemia[163–165] and the situation demonstrated has the potential to compromise the growth and development of about 1/3 of the country's children.

Fe deficiency has been shown to compromise thyroid function and negatively influence growth[166–169]. According to Pivina *et al.*, Fe deficiency can cause changes in neurotransmitter homoeostasis, decrease myelin production, impair synaptogenesis and decrease basal ganglia function, negatively affecting cognitive functions and psychomotor development, and is also frequent

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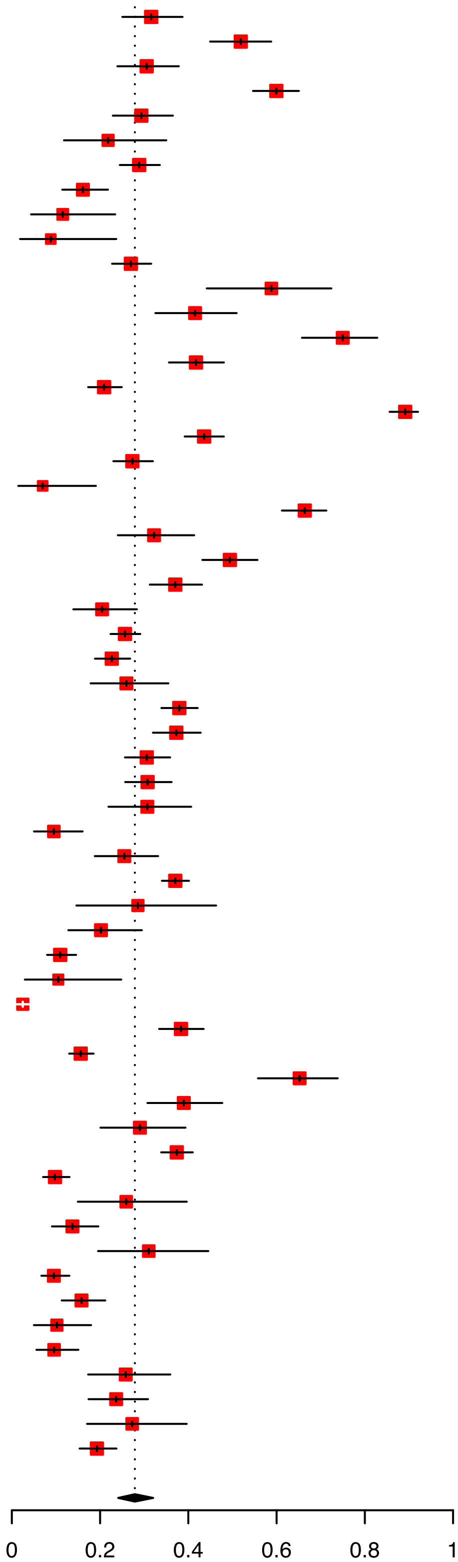
Study	Events	Total	Weight	IV, Random, 95 % CI
Souto, 2007	60	190	1·8 %	0·32 [0·25; 0·39]
Konstantyner, 2007	110	212	1·8 %	0·52 [0·45; 0·59]
Modesto, 2007	55	180	1·8 %	0·31 [0·24; 0·38]
Compri, 2007	214	357	1·8 %	0·60 [0·55; 0·65]
Nogueira–de–Almeida, 2007	54	184	1·8 %	0·29 [0·23; 0·36]
Prieto, 2008	12	55	1·5 %	0·22 [0·12; 0·35]
Rocha, 2008	116	402	1·8 %	0·29 [0·24; 0·34]
Camillo, 2008	34	211	1·7 %	0·16 [0·11; 0·22]
Biscegli, 2008	6	52	1·4 %	0·12 [0·04; 0·23]
Oliveira, 2008	3	34	1·1 %	0·09 [0·02; 0·24]
Carvalho, 2008	109	404	1·8 %	0·27 [0·23; 0·32]
Gomes, 2008	30	51	1·6 %	0·59 [0·44; 0·72]
Shibukawa, 2008	49	118	1·7 %	0·42 [0·33; 0·51]
Coutinho, 2008	81	108	1·7 %	0·75 [0·66; 0·83]
Fujimori, 2008	106	254	1·8 %	0·42 [0·36; 0·48]
Costa, 2009	96	459	1·8 %	0·21 [0·17; 0·25]
Bagni, 2009	345	387	1·8 %	0·89 [0·86; 0·92]
Konstantyner, 2009	217	498	1·8 %	0·44 [0·39; 0·48]
Sá, 2009	109	399	1·8 %	0·27 [0·23; 0·32]
Ferreira, 2009	3	43	1·1 %	0·07 [0·01; 0·19]
Jordão, 2009	235	354	1·8 %	0·66 [0·61; 0·71]
Reis, 2010	39	121	1·7 %	0·32 [0·24; 0·41]
Righ, 2010	128	259	1·8 %	0·49 [0·43; 0·56]
Oliveira, 2010	100	270	1·8 %	0·37 [0·31; 0·43]
Santos, 2010	27	132	1·7 %	0·20 [0·14; 0·28]
Costa, 2011	171	667	1·8 %	0·26 [0·22; 0·29]
Cotta, 2011	101	446	1·8 %	0·23 [0·19; 0·27]
Netto, 2011	27	104	1·7 %	0·26 [0·18; 0·35]
Pessoa, 2011	211	556	1·8 %	0·38 [0·34; 0·42]
Capanema, 2011	120	322	1·8 %	0·37 [0·32; 0·43]
Azeredo, 2011	100	327	1·8 %	0·31 [0·26; 0·36]
Rocha, 2012	96	312	1·8 %	0·31 [0·26; 0·36]
Netto, 2012	31	101	1·7 %	0·31 [0·22; 0·41]
Mendes, 2012	12	126	1·6 %	0·10 [0·05; 0·16]
Nogueira–de–Almeida, 2013	39	153	1·7 %	0·25 [0·19; 0·33]
Oliveira, 2013	363	980	1·8 %	0·37 [0·34; 0·40]
Dias, 2013	10	35	1·5 %	0·29 [0·15; 0·46]
Coutinho, 2013	20	99	1·7 %	0·20 [0·13; 0·29]
Correa, 2013	41	374	1·8 %	0·11 [0·08; 0·15]
Pereira, 2013	4	38	1·2 %	0·11 [0·03; 0·25]
Castro, 2013	9	363	1·5 %	0·02 [0·01; 0·05]
Oliveira, 2014	143	373	1·8 %	0·38 [0·33; 0·43]
Saraiva, 2014	108	692	1·8 %	0·16 [0·13; 0·19]
Barreto, 2014	75	115	1·7 %	0·65 [0·56; 0·74]
Stulbach, 2014	53	136	1·7 %	0·39 [0·31; 0·48]
Silva, 2015	27	93	1·7 %	0·29 [0·20; 0·39]
Lisbôa, 2015	271	725	1·8 %	0·37 [0·34; 0·41]
Clarke, 2015	40	409	1·8 %	0·10 [0·07; 0·13]
Vaz–Tostes, 2015	14	54	1·6 %	0·26 [0·15; 0·40]
Fonseca, 2016	25	182	1·7 %	0·14 [0·09; 0·20]
Freitas, 2016	18	58	1·6 %	0·31 [0·20; 0·45]
André, 2017	34	357	1·7 %	0·10 [0·07; 0·13]
Nobre, 2017	36	228	1·7 %	0·16 [0·11; 0·21]
Lucia, 2017	10	98	1·5 %	0·10 [0·05; 0·18]
Man, 2017	16	167	1·6 %	0·10 [0·06; 0·15]
Mendes, 2017	24	93	1·7 %	0·26 [0·17; 0·36]
Silva, 2019	39	165	1·7 %	0·24 [0·17; 0·31]
Siqueira, 2019	18	66	1·6 %	0·27 [0·17; 0·40]
Rocha, 2020	70	363	1·8 %	0·19 [0·15; 0·24]
Total (95 % C I)		15111	100·0%	0·28 [0·24; 0·32]

IV, Random, 95 % CI



Heterogeneity: $Tau^2 = 0.5503$; $Chi^2 = 1549.53$, df = 58 (P < 0.01); $I^2 = 96\%$ [96 %; 97 %]

IV: inverse variance; 95 % CI: 95% confidence interval; df: degrees of freedom

Fig. 5 (colour online) Forest plot for meta-analysis of the prevalence of anaemia in the Brazilian Southeast region (ordered by year of publication)

https://doi.org/10.1017/S136898002100286X Published online by Cambridge University Press

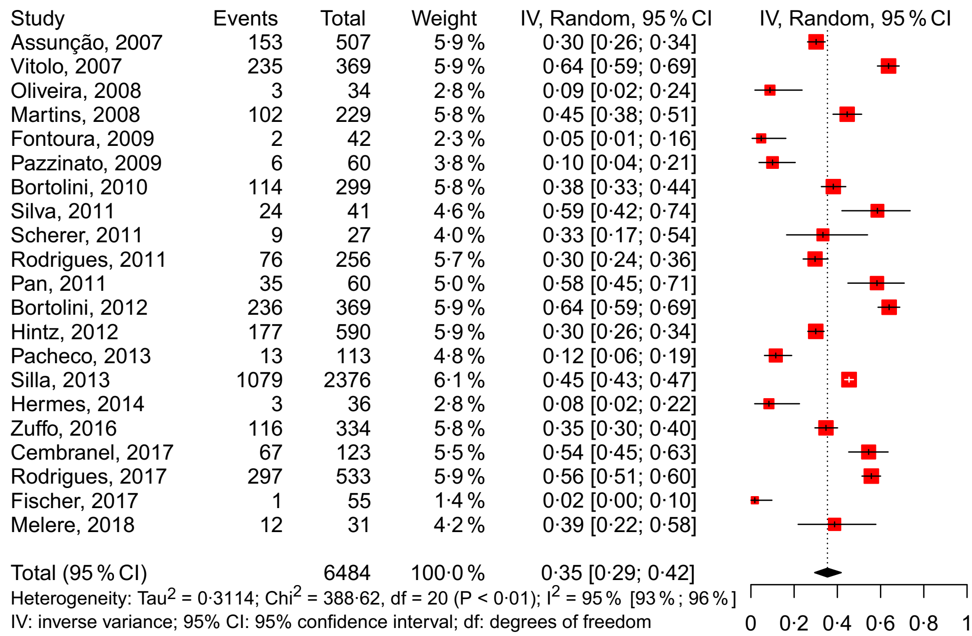


Fig. 6 (colour online) Forest plot for meta-analysis of the prevalence of anaemia in the Brazilian South region (ordered by year of publication)

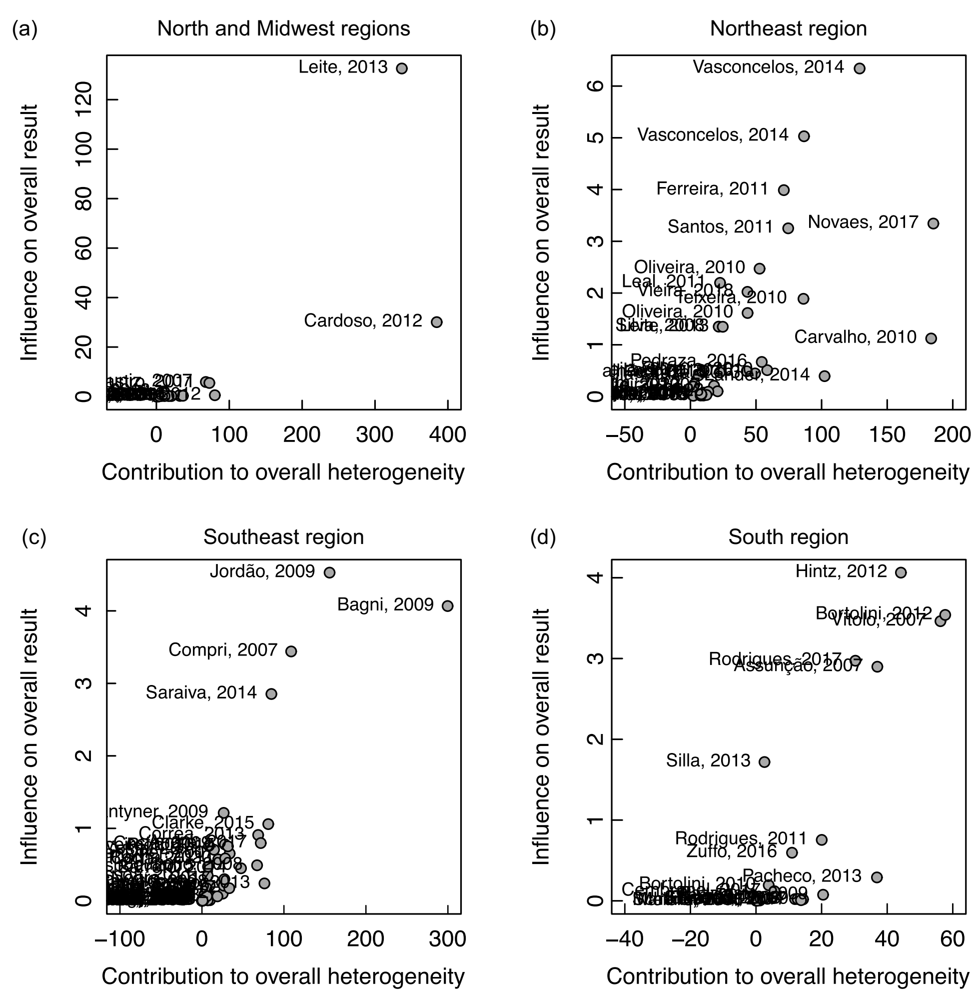


Fig. 7 Contribution of each study to the overall effect size by Baujat plots

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Table 1 Sensitivity analyses table

	Studies	Prevalence	95 % CI	I^2 (%)	Cochran's *Q*
North and Midwest regions					
Removal of studies with sample size <100	17	34·6	25·9, 44·6	98·6	1118·01
Removal of two studies with high contribution to overall heterogeneity	18	36·1	29·8, 43·1	95·6	385·14
Removal of studies that are not cross-sectional	17	35·5	26·6, 45·5	98·5	1094·48
All studies	20	35·8	27·6, 44·9	98·3	1137·81
Northeast region					
Removal of studies with sample size <100	27	37·1	31·4, 43·1	98·2	1407·95
Removal of two studies with high contribution to overall heterogeneity	32	37·3	32·6, 42·3	97·2	1119·81
Removal of studies that are not cross-sectional	27	37·6	31·7, 43·8	98·1	1337·50
All studies	34	38·1	32·8, 43·6	97·8	1489·15
Southeast region					
Removal of studies with sample size <100	45	29·8	25·3, 36·6	97·0	1647·47
Removal of two studies with high contribution to overall heterogeneity	57	26·4	23·1, 29·9	94·8	1076·43
Removal of studies that are not cross-sectional	49	27·0	23·3, 31·0	95·8	1133·22
All studies	59	27·9	24·1, 32·0	96·3	1549·53
South region					
Removal of studies with sample size <100	12	41·3	34·2, 48·7	96·4	305·14
Removal of six studies with high contribution to overall heterogeneity	15	33·8	27·7, 40·4	88·7	124·11
Removal of studies that are not cross-sectional	17	30·4	24·7, 56·8	92·3	209·04
All studies	21	35·4	29·5, 41·8	94·9	388·62
Brazil					
Removal of studies with sample size <100	101	33·8	30·7, 37·1	97·9	4713·40
Removal of all studies with high contribution to overall heterogeneity in each region	122	31·9	29·4, 34·4	96·1	3105·42
Removal of studies that are not cross-sectional	110	31·1	28·2, 34·1	97·4	4170·68
All studies	134	32·5	29·8, 35·4	97·3	5013·82

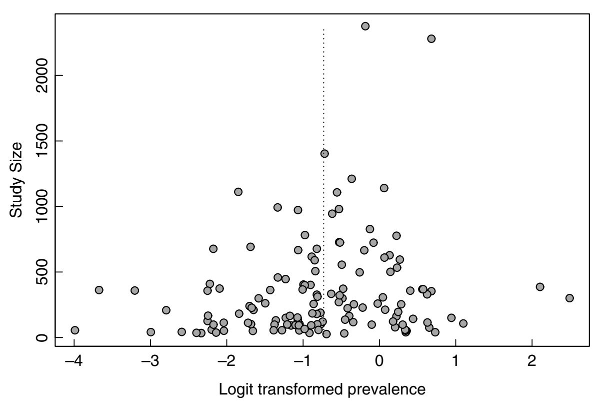

Fig. 8 Funnel plot for publication bias analyses considering the 134 studies. The dashed vertical line refers to the position of the pooled prevalence in Brazil

comorbidity in autism and attention deficit hyperactivity disorder[170]. Several studies have proven that Fe deficiency anaemia in childhood due to its negative effects mainly on myelogenesis and synaptogenesis[9] is associated with changes in development and motor skills and worse cognitive performance in varying degrees (results identified through assessments performed with the Denver II scale), which certainly compromises the learning and, consequently, the permanent intellectual future of these children[163,170–173]. Fe deficiency, interfering in the production and action of cytokines, reducing the phagocytic capacity of neutrophils and macrophages[174] and compromising the production of T lymphocytes, particularly CD4 + Th1 subpopulations[175], has been associated with changes that compromise the proper functioning of both the innate and adaptive immune systems[176,177], increasing susceptibility to infections by intracellular microorganisms. Among the various roles played by Fe in the body should be mentioned the modulating function of the innate immune response[178] which is impaired when the levels of this metal are decreased, predisposing the body to infection[179,180].

Historically, Brazil has been unable to effectively reduce its prevalence of Fe deficiency anaemia. Some factors can be listed as possibly responsible for this fact, and one of them dates back to the first year of life, when the use of unmodified cows' milk is used by 62·4 % of babies aged 0–5 months and 74·6 % of those between 6 and 12 months, when the child is weaned[181]. Due to the fact that it has little amount of low bioavailability Fe and the chelating potential of milk Ca; and leading to micro haemorrhages in the intestinal mucosa, cows' milk contributes decisively to the installation and maintenance of Fe deficiency[182,183]. Many babies are not able to satisfactorily make up their reserves during the gestational period and even during breast-feeding because the prevalence of anaemia among pregnant and lactating women is also high in the country[184]. It should also be remembered the low use of fortified foods during the feeding introduction period in Brazilian children[185].

Another aspect concerns the consumption of Fe of inadequate bioavailability, associated with low-cost foods and low nutritional density, characteristic of the poorest countries, in which good sources of Fe, especially meat and fortified foods, have a higher cost[133]. Additionally, the diet based on plant protein sources predisposes to the intake of Fe-chelators nutrients, such as phytate, and is usually poor in absorption stimulating nutrients such as vitamin C[186,187]. A recent survey published in 2020 conducted by the Brazilian government showed that food insecurity in the country increased by 33·3 % compared with 2004 and 62·2 % compared with 2013, leading to a significant portion of the population being exposed to inadequate and insufficient micronutrient nutrition[188]. The same research showed that in the North and Northeast regions, less than half of the households in these regions had full and regular access to food and that the general sewage network was present only in about half of the households with moderate and severe food insecurity and, in both cases, the existence of a fossa not connected to the health network was quite relevant (43 %)[188]; data from the present study found the highest prevalence of anaemia in these two regions. The issue of basic sanitation of very low coverage in the country can also contribute to the difficulty of controlling anaemia, as it provides a greater amount of infectious diseases and intestinal parasitosis[189]. At the other end of this issue, it is verified that the prevalence of anaemia has shown a slight fall in southeast Brazil in the last 10 years (Fig. 5), which can be explained by the better socio-economic conditions of this region in relation to the others. The Southeast region has the highest Human Development Index[190] and the highest rates of access to basic sanitation in the country[191]; in addition, with the exception of the South region, the Southeast has the lowest rates of food insecurity in Brazil[188].

Some aspects may have interfered in the results of the present study. There is a tendency for research on a given disease to focus on areas where it is most prevalent. Thus, it is likely that some results, especially those with abnormally high prevalence of anaemia, have been obtained exactly in regions where high results would already be expected. Similarly, areas with more socio-economically privileged populations may have been less investigated than the poorer ones. The data in Figs. 2–6 show that an asymmetric arrangement of the points was observed, demonstrating that this fact must have actually occurred[192]. For this to be avoided, it would be necessary to study with national sampling, which is not available in Brazil, justifying the search for results that are obtained in another way.

Joint analyses of cross-sectional and longitudinal studies may include bias in the results. However, as shown in Table 1, the impact of the separation of these studies was not relevant for the final results. Similarly, the sample size was also quite different in each of the studies. However, Table 1 shows that the exclusion of studies with low sample size did not alter the prevalence of anaemia in the regions, except in the South region, in which, withdrawing studies with sample size smaller than 100, the prevalence increases from 35·4 to 41·3 %. The careful analyses of the individual studies considered showed the existence of outliers, which can be verified in Fig. 7. As can be seen in Table 1, the withdrawal of these surveys practically does not alter the results.

The present study has some limitations. The first, and more importantly, refers to the fact that, considering that local prevalence studies are rarely published in the most important scientific journals, in so that the survey could be made feasible, it was necessary to also seek data in journals of lesser expression. This method may have led to the inclusion of data with a lower degree of reliability, even taking care to include only articles in which quality was verified. Another limitation concerns the fact that almost all studies that seek to determine the prevalence of Fe deficiency anaemia do not include criteria that prove that there is nutritional deficiency. Therefore, the results presented here may include anaemia for causes other than deficiency of Fe food intake. However, knowing that in low- and middle-income countries, the vast majority of cases have nutritional origin and, taking into account that studies with children with an illness condition were not included, this limitation can be considered of little relevant impact. Five studies did not report the Hb cut-off point used to define anaemia, and it was not possible to obtain this information by direct contact with the authors. However, the methodology reported that internationally accepted criteria were used, so that the cut-off points suggested by the WHO were considered to have been used. Finally, it should also be noted that not all studies used the same method of laboratory evaluation, including surveys with different analyses techniques, even with portable methodologies.

Conclusion

Our meta-analysis of 134 studies revealed a high prevalence of anaemia among Brazilian preschool children. Although the comparison with previous similar studies suggests a reduction in prevalence, the numbers are still very high, placing approximately one-third of Brazilian children at risk of damage to physical and psychosocial health. There is an urgent need for the Brazilian government to conduct a nationwide survey of Fe deficiency, using appropriate biomarkers, in order to confirm whether the prevalence is really so high and, if so, implement appropriate public health strategies.

Acknowledgements

Acknowledgements: None. *Financial support:* This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. *Conflict of interest:* There are no conflicts of interest. *Authorship:* C.A.N.-d.-A.: Substantial contributions to the

conception or design of the work; or the acquisition, analysis or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; figures, study design; data collection; data interpretation; data analyses. F.d.V.U.: Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; figures, study design; data collection; data interpretation. 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J.A.L.: Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; literature search; data analysis; data interpretation. *Ethics of human subject participation:* This study was conducted according to the guidelines laid down in the Declaration of Helsinki.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S136898002100286X

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https://doi.org/10.1017/S136898002100286X Published online by Cambridge University Press

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Public Health Nutrition

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