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Impact of helminthiasis on gestational anemia in low- and middle-income countries: a systematic review and meta-analysis of more than 19,000 women

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SUMMARY

Intestinal helminthiasis are a common public health problem in developed and developing countries. It is thought that they can influence pregnancy by causing gestational anemia. The aim of this study was to determine if there is a relationship between helminth infection and gestational anemia. A structured review of scientific literature was conducted through active search in the electronic databases MEDLINE® and LILACS® until December 2021, following 2020 PRISMA statement. The studies were reviewed independently by two authors, extracting the most relevant information from each study. Cross-sectional studies, case-control and ecological studies were included, with no date or language limit. Randomized clinical trials were excluded. A total of 38 studies were included in the systematic review. The study populations of all studies belonged to low- and middle-income countries: 28 studies from Africa, 6 from Asia, 3 from Latin America and 1 from Oceania. Overall, the average prevalence of gestational anemia among the included studies was 40% (95% CI 34-46%). Hookworm was the predominant species detected in most studies (19/38; 50%), followed by *Ascaris lumbricoides* (15/38; 39.5%). Gestational anemia was positively associated with *A. lumbricoides* (OR 1.86, 95% CI 1.12-3.08) and hookworms (OR 3.09, 95% CI 1.99-4.78). Prevalence of malaria was not associated with the magnitude of the effect of hookworm on anemia risk during meta-regression (p=0.5182). The results of this review indicate that there is a statistically significant association between helminthiasis and gestational anemia. Although hookworm is the main species associated with the outcome, prevalence of malaria was not associated with the magnitude of the effect of hookworm on anemia risk. The impact of other species needs to be defined given the expected bias that arises from polyparasitism when defining comparison groups.

Keywords: Helminths, anemia, pregnancy, ascariasis, haemoglobin.

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INTRODUCTION

Anemia is the most common haematologic complication diagnosed during pregnancy [1]. It is a public health problem that affects developed and developing countries. The World Health Organization (WHO) states that, between 1993 and 2005, 41.8% [95% CI 39.9-43.8] (56 million) of pregnant women were affected by this condition [2]. Gestational anaemia (GA) has progressively decreased since 1995 (42.59%), with a global prevalence of 38.17% in 2011. In Latin America, countries such as Brazil (32%), Chile (25%), Ecuador (29%), and Colombia (30%) had prevalence below the average in 2011.

In Colombia, according to the National Survey of Nutritional Situation (Encuesta Nacional de la Situación Nutricional, ENSIN) 2010, one in every six pregnant women had anemia and 7.6% of women of fertile age had this haematological disorder [3].

Helminthiasis, specifically geohelminthiases caused by intestinal parasites, are the most common infections worldwide and they affect the poorest and most vulnerable populations. These infections are more common in women and children, and it is estimated that one in three people are infected; women of childbearing age, particularly pregnant women during the second and third trimesters and lactating women are at permanent risk [4, 5].

Helminthiasis affect a large part of the population and have a significant disease burden given their chronicity and association with malnutrition. Due to these associations, delays in physical and cognitive development can also be seen [6-8]. Surprisingly, there are not agreements upon screening guidelines for helminthiases in pregnant women in Colombia.

Several studies have shown that the prevalence of helminthiasis in pregnancy is considerable in countries of Latin America and Africa, and that it has a strong association with anemia in pregnant woman [6].

There are a few systematic reviews of the literature assessing the impact of these infections on pregnancy. This study sought to systematically collect and evaluate information regarding the association between intestinal helminthiases (IH), including several species, and GA from scientific databases.

MATERIALS AND METHODS

Study design

This review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [9]. The protocol of this systematic review was registered in the PROSPERO registry of systematic reviews (registration number: CRD42022312384). The primary outcome of this review was to estimate the association between intestinal helminthiasis (IH) and GA. Other outcomes were to determine the prevalence of GA and the helminths most frequently associated with GA.

Eligibility criteria

Women who were examined with a stool examination during their pregnancy and were also tested for anemia were included. Definition of anemia was based on the measurement of haemoglobin. Women whose anemic state was evaluated in the puerperium were excluded. Clinical trials were excluded. Studies comparing haemoglobin values as a continuous variable in regard to the infection status, but without definition of anemia status were neither included. Interventional studies that recruit women for iron supplementation were neither included.

Search strategy

In this study, an active search of information was done in two electronic databases MEDLINE® and LILACS®. Studies were selected from January 2000 to December 2021 using MeSH and DECS terms: *"anaemia"*, *"anemia"*, *"pregnancy"*, *"hemoglobin"*, *"helminths"*, *"helminth"*, *"helminthiasis"*, *"ascariasis"*, *"schistosomiasis"*, *"hookworm"* and *"trichuriasis"* without language restrictions. Studies that reported anemia during pregnancy as outcome measures and the detection of intestinal helminths by direct fecal microscopy as a variable of interest were included. The odds ratios (OR) with 95% confidence intervals (CI) to develop anaemia were estimated independently for each infection type using absolute numbers extracted from the publications. The available evidence and the internal validity of the evaluations were examined [10].

Data collection

There were two delegated investigators (JZ and JA) to perform the search, one of them in charge of identifying records through database searching. The other investigator screened the identified records by title and abstract, removing those whose full text was not available, and determine eligible studies according to select criteria. Finally, both researchers did a qualitative synthesis of the included articles. Individual judgements about specific issues were discussed, including inadequate population, intervention, or publication type.

Data from the final included studies was extracted using a form designed in Kobo Toolbox [11]. This form included the following fields: first author, year of publication, geographic location, publication type, age, number of cases with anemia, number of cases with parasite infection in anaemic and non-anaemic subjects, prevalence of anemia, rates of infection for each helminth species (*i.e.* ascaris, schistosoma, hookworm and trichuris) as well as the general rate of intestinal parasite or helminth infection (when available), adjusted odds ratio for anemia/parasite infection. Information of other covariates that may influence associations was recorded: Human immunodeficiency virus (HIV) prevalence if (available), infection with *Plasmodium* (if available). Ferritin levels in parasitized and non-parasitized pregnant women and mean haemoglobin levels in parasite-infected and non-infected groups was extracted, but not analyzed due to few detected data.

Quality measure

The quality of the articles included in this study was evaluated using the "Strengthening the Reporting of Observational studies in Epidemiology" (STROBE) tool, which consists of a 22-item evaluation form, designed to examine the quality of every component of population-based descriptive and analytical observational studies [22].

Target population, sampling frame, random selection, census collects and response rate of the study, are the evaluated criteria for external validity, otherwise, case definition, data collection, study instrument, prevalence period and error calculation, are the evaluated criteria for internal validity of the article. The final score is calculated using a dichotomous method, in which, an affirmative answer for each item sums 1 point, while negative answer results in 0 points. The final grade is obtained out of a total of 22 and is considered as an adequate result for those studies that reach 60% of the criteria evaluated, which is, a score greater than 13.

Statistical analysis

The meta-analyses were conducted only for exposures (helminth type) assessed by three or more studies. OR for the association of GA presentation with:

a) helminthiasis
b) ascariasis
c) trichuriasis
d) hookworm infection
e) schistosomiasis.

Crude OR were calculated based on the number of subjects exposed or not and presenting or not the outcome [13]. Microsoft excel sheets were used for data synthesis [14]. For meta-analysis, pooled OR were calculated by using the inverse of variance method [15]. Heterogeneity of estimates across studies was assessed using the I^2 statistic in each analysis, as previously described [16]. A value of over 50% was indicative of significant heterogeneity and random-effects model was chosen; otherwise, a fixed-effect model was used. The Restricted Maximum-Likelihood method was used for $tauw^2$ estimation. Prevalence of GA was metanalyzed using the inverse variance method.

To handle with heterogeneity, different strategies were applied: subgroup analysis considering as geographical region, study type and crude/adjusted odds ratio) as group variables. Meta-regression (considering co-infection with plasmodium, year of publication) as covariates were considered. We additionally generated a contour improved funnel plot to visually examine asymmetry in the plot and give an explanation for the underlying cause, such as, time lag or pipeline bias [17]. All analyses were performed using R statistical software ver. 4.1.1. (2021-08-10) (R Core Team, R Foundation for Statistical Computing) with the "meta" package [18].

RESULTS

Three-hundred and four publications were identified through database search. After duplicate removal, we screened 128 articles and excluded 87 references based on title and abstract. Forty-one full-text publications were assessed for eligibility. Two studies were excluded in this phase due to unsatisfactory reporting of exposure status or inclusion of male individuals [19, 20]. Moreover, a study by Gyorkos et al was also excluded because it was a clinical trial [21]. As a result, data from 38 articles were eligible and assessed for quality evidence and synthesis [6, 7, 22-57]. The algorithm for the selection of the articles for the quantitative synthesis is shown in Figure 1. All included studies were considered of appropriate quality.

A summary of the included studies is presented in Table 1. Most studies had a cross-sectional design (n=29), 5 of them were prospective cohorts and 4 were case-control studies. The study populations of all studies belonged to low- and middle-income countries: 28 studies from Africa, 6 from Asia, 3 from Latin America and 1 from Oceania. Most studies did not report HIV status (21/38; 55%) or excluded HIV patients in the recruitment phase (11/38; 29%). HIV prevalence was 1-12% among the studies that did report HIV status (6/38; 16%).

We evaluated the prevalence of GA reported among the studies included in this review, which was high in most studies (Figure 2). Overall, the average prevalence of GA among the included studies was 40% (95% CI 34-46%). The lowest prevalence was reported by Demeke et al (7%, 95% CI 5-11%) in Ethiopia, whereas the highest was reported by Anchang-Kimbi (89%, CI 95% 84-92%) in Cameroon [25, 32]. Hookworm was the predominant species detected in most studies (19/38; 50%), followed by *Ascaris lumbricoides* (15/38; 39.5%).

Next, we analyzed the association between GA and parasitic infections. GA was strongly associated with infection by any helminth (OR 7.09, 95% CI 4.65-10.83; Figure 3-A). We also evaluated the relation between GA and infection by intestinal parasites (including both helminths and protozoa), which also showed a positive association (OR 4.34, 95% CI 2.66-7.10; Figure 3-B). Regarding the association with specific helminth species, GA was positively associated with *A. lumbricoides* (OR 1.86, 95% CI 1.12 - 3.08; Figure 3-C) and hookworm (OR 3.09, 95% CI 1.99-4.78; Figure 4-A). In addition, GA showed non-significant associations with *Schistosoma mansoni* (OR 1.36, 95% CI 0.85-2.17) and *Trichuris trichiura* (OR 1.33, 95% CI 0.84-2.10).

Due to the predominant co-infection between malaria and helminthiasis, we consider this condition as a potential bias for the study. To address this situation, we also analyzed the malaria prevalence data reported among the included studies. Malaria prevalence was reported in 21 out of the 38 studies (55%), with no detected cases in two studies and a range of 2-53% among those with positive cases (average: 16%). Sixteen studies (42%) did not report malaria prevalence and in one study (3%) malaria was used as an exclusion criterion. Moreover, the protozoan parasite *Plas-*

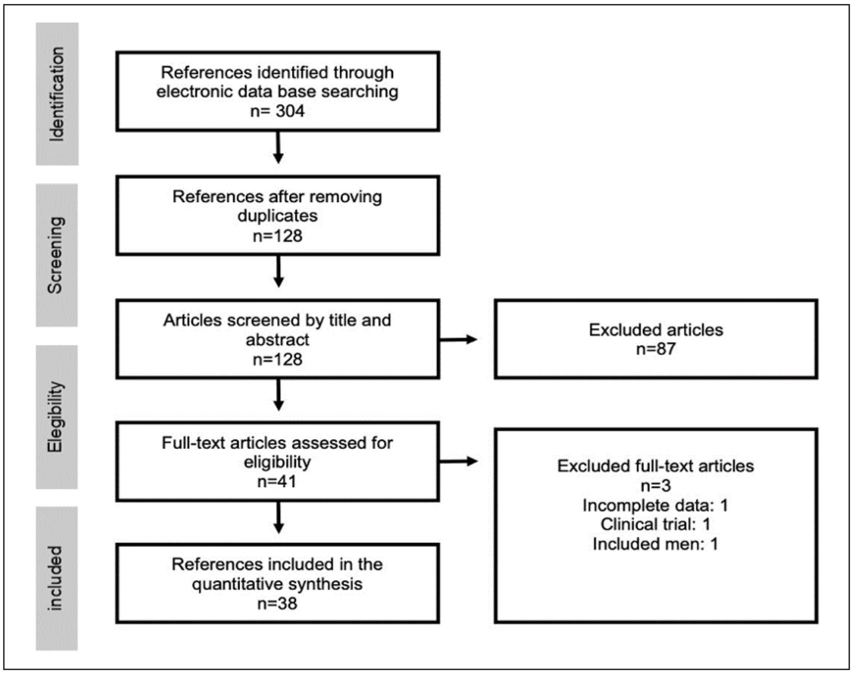


Figure 1 - Flowchart of studies included in the review.

Table 1 - Summary of the studies included in the meta-analysis of *anaemia* prevalence.

Author	*Year*	*Population*	*Prevalence of anaemia*	*Predominant helminth*	*Malaria status*	*HIV status*	*Ref.*
Aderoba	2015	Nigeria	26%	*Ascaris lumbricoides*	Excluded	8%	[6]
Agu	2013	Nigeria	40%	Hookworm	53%	NR	[22]
Ahenkora	2018	Ghana	63%	*Ascaris lumbricoides*	19%	Excluded	[23]
Aikawa	2006	Vietnam	43%	*Ascaris lumbricoides*	NR	NR	[24]
Anchang-Kimbi	2017	Cameroon	88%	*Schistosoma haematobium*	39%	NR	[25]
Argaw	2020	Ethiopia	29%	*Trichuris trichiura*	NR	NR	[26]
Ayoya	2006	Mali	63%	Hookworm	11%	NR	[27]
Baingana	2015	Uganda	29%	Hookworm	5%	Excluded	[28]
Berhe	2019	Ethiopia	25%	Hookworm	NR	NR	[29]
Bolka	2019	Ethiopia	32%	Hookworm	NR	NR	[30]
Bondevik	2000	Nepal	79%	*Ascaris lumbricoides*	NR	Excluded	[31]
Demeke	2021	Ethiopia	7%	Hookworm	NR	Excluded	[32]
Dreyfuss	2000	Nepal	67%	Hookworm	20%	NR	[33]
Ebuy	2017	Ethiopia	37%	Hookworm	7%	1%	[34]
Gari	2020	Ethiopia	38%	Hookworm	5%	Excluded	[35]
Gedefaw	2015	Ethiopia	40%	Hookworm	4%	NR	[36]
Getachew	2012	Ethiopia	54%	Hookworm	41%	NR	[37]
Hailu	2019	Ethiopia	11%	Hookworm	NR	NR	[38]
Kefiyalew	2014	Ethiopia	28%	*Ascaris lumbricoides*	3%	NR	[39]
Kumera	2018	Ethiopia	12%	Hookworm	NR	1%	[40]
Larocque	2005	Peru	47%	Hookworm	0%	NR	[41]
Lebso	2017	Ethiopia	23%	*Ascaris lumbricoides*	NR	NR	[42]
Lidstrom	2010	Bangladesh	28%	*Ascaris lumbricoides*	NR	NR	[43]
Melku	2014	Ethiopia	17%	*Ascaris lumbricoides*	5%	10%	[44]
Mengist	2017	Ethiopia	17%	Hookworm	NR	NR	[45]
Muhangi	2007	Uganda	40%	Hookworm	11%	12%	[46]
Ndyomugyenyi	2008	Uganda	21%	Hookworm	35%	NR	[47]
Ouédraogo	2012	Benin	68%	Hookworm	15%	Excluded	[48]
Phuanukoonnon	2015	New Guinea	8%	Hookworm	NR	NR	[49]
Puerto	2021	Colombia	42%	*Trichuris trichiura*	NR	Excluded	[50]
Rodriguez-Morales	2006	Venezuela	65%	*Ascaris lumbricoides*	0%	Excluded	[7]
Shah	2005	Nepal	59%	*Ascaris lumbricoides*	NR	NR	[51]
Shrinivas	2014	India	60%	*Ascaris lumbricoides*	NR	Excluded	[52]
Tay	2017	Ghana	66%	*Ascaris lumbricoides*	17%	NR	[53]
Tibambuya	2019	Ghana	31%	*Ascaris lumbricoides*	21%	Excluded	[54]
Tonga	2019	Cameroon	72%	*Schistosoma haematobium*	NR	2%	[55]
Tulu	2019	Ethiopia	33%	*Ascaris lumbricoides*	2%	Excluded	[56]
Wanyonyi	2018	Kenya	49%	*Ascaris lumbricoides*	22%	NR	[57]

Study	Events	Total	Weight (common)	Weight (random)	IV, Fixed + Random, 95% CI
Aderoba (2015)	46	178	0.9%	2.6%	0.26 [0.20; 0.33]
Agu (2013)	90	226	1.4%	2.6%	0.40 [0.33; 0.47]
Ahenkora (2018)	253	400	2.3%	2.7%	0.63 [0.58; 0.68]
Aikawa (2004)	189	439	2.7%	2.7%	0.43 [0.38; 0.48]
Anchang-Kimbi (2017)	222	250	0.6%	2.5%	0.89 [0.84; 0.92]
Argaw (2020)	107	373	1.9%	2.6%	0.29 [0.24; 0.34]
Ayoya (2006)	62	131	0.8%	2.6%	0.47 [0.39; 0.56]
Baingana (2014)	44	151	0.8%	2.6%	0.29 [0.22; 0.37]
Berhe (2019)	150	600	2.8%	2.7%	0.25 [0.22; 0.29]
Bolka (2019)	110	349	1.9%	2.6%	0.32 [0.27; 0.37]
Bondevik (2000)	308	390	1.6%	2.6%	0.79 [0.75; 0.83]
Demeke (2021)	21	281	0.5%	2.5%	0.07 [0.05; 0.11]
Dreyfuss (2000)	244	334	1.6%	2.6%	0.73 [0.68; 0.78]
Ebuy (2017)	88	264	1.5%	2.6%	0.33 [0.28; 0.39]
Gari (2020)	145	384	2.3%	2.7%	0.38 [0.33; 0.43]
Gedefaw (2015)	145	363	2.2%	2.7%	0.40 [0.35; 0.45]
Getachew (2012)	209	388	2.4%	2.7%	0.54 [0.49; 0.59]
Hailu (2019)	79	743	1.8%	2.6%	0.11 [0.09; 0.13]
Kefiyalew (2014)	72	258	1.3%	2.6%	0.28 [0.23; 0.34]
Kumera (2018)	116	234	1.5%	2.6%	0.50 [0.43; 0.56]
Larocque (2005)	495	1041	6.5%	2.7%	0.48 [0.44; 0.51]
Lebso (2017)	117	504	2.2%	2.7%	0.23 [0.20; 0.27]
Lindstrom (2010)	201	740	3.7%	2.7%	0.27 [0.24; 0.31]
Melku (2014)	50	302	1.0%	2.6%	0.17 [0.13; 0.21]
Mengist (2017)	65	372	1.3%	2.6%	0.17 [0.14; 0.22]
Muhangi (2007)	995	2498	14.9%	2.7%	0.40 [0.38; 0.42]
Ndyomugyenyi (2008)	171	832	3.4%	2.7%	0.21 [0.18; 0.23]
Ouedraogo (2012)	686	1005	5.4%	2.7%	0.68 [0.65; 0.71]
Phuanukoonnon (2015)	16	201	0.4%	2.4%	0.08 [0.05; 0.13]
Puerto (2021)	387	930	5.6%	2.7%	0.42 [0.38; 0.45]
Rodriguez-Morales (2005)	676	1038	5.9%	2.7%	0.65 [0.62; 0.68]
Shah (2005)	66	112	0.7%	2.5%	0.59 [0.49; 0.68]
Shriniva (2014)	302	500	3.0%	2.7%	0.60 [0.56; 0.65]
Tay (2017)	249	375	2.1%	2.7%	0.66 [0.61; 0.71]
Tibambuya (2019)	118	378	2.0%	2.7%	0.31 [0.27; 0.36]
Tonga (2019)	202	282	1.4%	2.6%	0.72 [0.66; 0.77]
Tulu (2019)	191	573	3.2%	2.7%	0.33 [0.29; 0.37]
Wanyonyi (2018)	367	750	4.7%	2.7%	0.49 [0.45; 0.53]
Total (fixed effect, 95% CI)		**19169**	**100.0%**	**--**	**0.43 [0.42; 0.44]**
Total (random effects, 95% CI)			**--**	**100.0%**	**0.40 [0.34; 0.46]**

Heterogeneity: $Tau^2 = 0.5954$; $Chi^2 = 2302.45$, df = 37 (P = 0); $I^2 = 98\%$

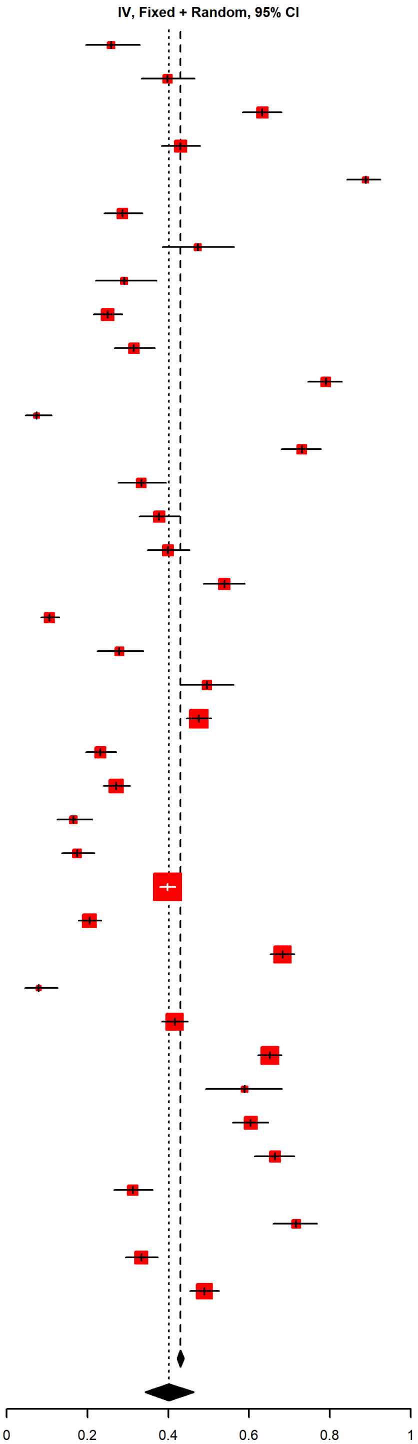


Figure 2 - Forest plot of the prevalence of *anaemia* among the studies included in the review.

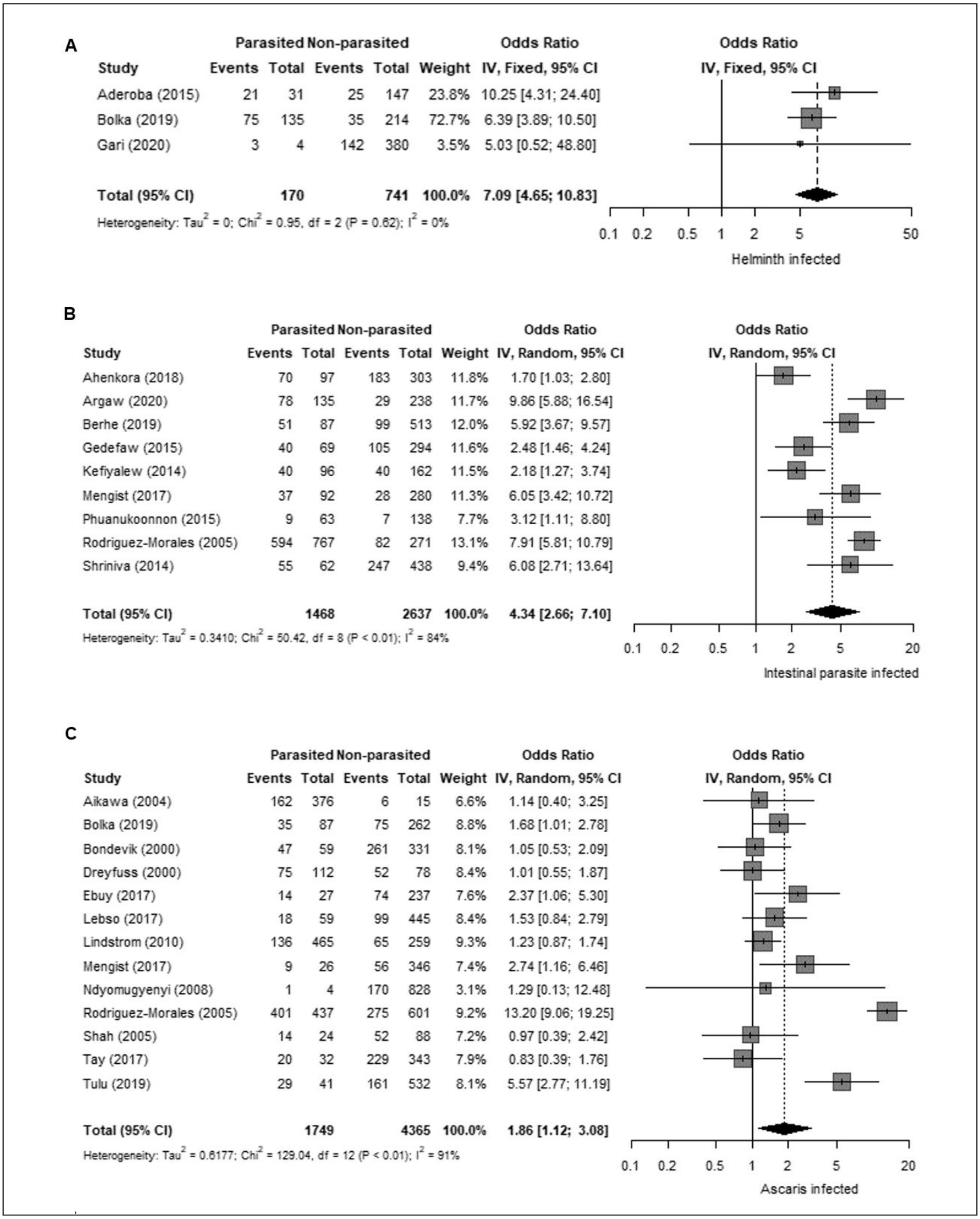
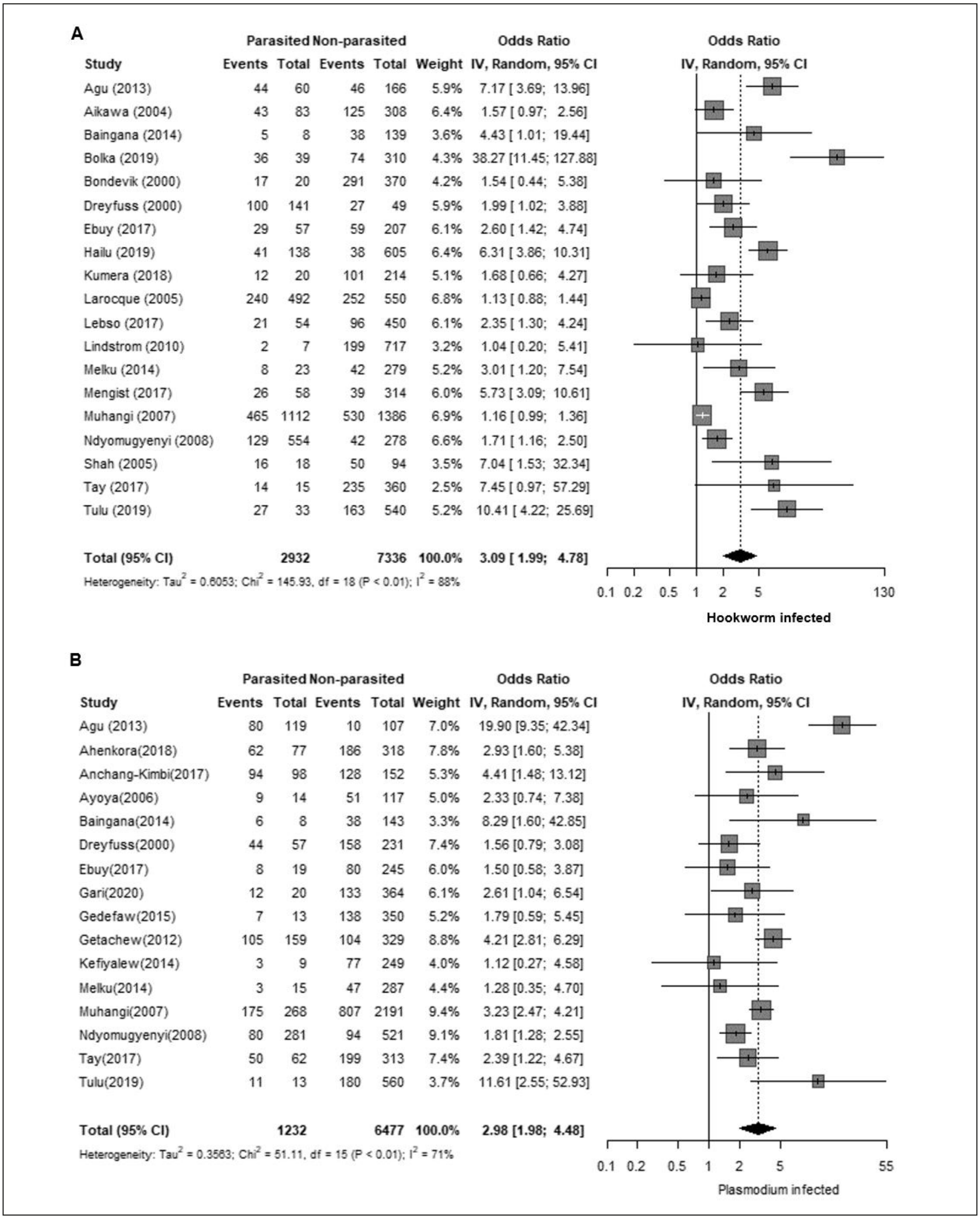


Figure 3 - A. Association between gestational *anaemia* and any helminth. B. Association between gestational *anaemia* and intestinal parasites. C. Association between gestational anaemia and *Ascaris lumbricoides*.



A

	Parasited		Non-parasited			Odds Ratio
Study	Events	Total	Events	Total	Weight	IV, Random, 95% CI
Agu (2013)	44	60	46	166	5.9%	7.17 [3.69; 13.96]
Aikawa (2004)	43	83	125	308	6.4%	1.57 [0.97; 2.56]
Baingana (2014)	5	8	38	139	3.6%	4.43 [1.01; 19.44]
Bolka (2019)	36	39	74	310	4.3%	38.27 [11.45; 127.88]
Bondevik (2000)	17	20	291	370	4.2%	1.54 [0.44; 5.38]
Dreyfuss (2000)	100	141	27	49	5.9%	1.99 [1.02; 3.88]
Ebuy (2017)	29	57	59	207	6.1%	2.60 [1.42; 4.74]
Hailu (2019)	41	138	38	605	6.4%	6.31 [3.86; 10.31]
Kumera (2018)	12	20	101	214	5.1%	1.68 [0.66; 4.27]
Larocque (2005)	240	492	252	550	6.8%	1.13 [0.88; 1.44]
Lebso (2017)	21	54	96	450	6.1%	2.35 [1.30; 4.24]
Lindstrom (2010)	2	7	199	717	3.2%	1.04 [0.20; 5.41]
Melku (2014)	8	23	42	279	5.2%	3.01 [1.20; 7.54]
Mengist (2017)	26	58	39	314	6.0%	5.73 [3.09; 10.61]
Muhangi (2007)	465	1112	530	1386	6.9%	1.16 [0.99; 1.36]
Ndyomugyenyi (2008)	129	554	42	278	6.6%	1.71 [1.16; 2.50]
Shah (2005)	16	18	50	94	3.5%	7.04 [1.53; 32.34]
Tay (2017)	14	15	235	360	2.5%	7.45 [0.97; 57.29]
Tulu (2019)	27	33	163	540	5.2%	10.41 [4.22; 25.69]
Total (95% CI)		**2932**		**7336**	**100.0%**	**3.09 [1.99; 4.78]**

Heterogeneity: $Tau^2 = 0.6053$; $Chi^2 = 145.93$, df = 18 ($P < 0.01$); $I^2 = 88\%$

B

	Parasited		Non-parasited			Odds Ratio
Study	Events	Total	Events	Total	Weight	IV, Random, 95% CI
Agu (2013)	80	119	10	107	7.0%	19.90 [9.35; 42.34]
Ahenkora(2018)	62	77	186	318	7.8%	2.93 [1.60; 5.38]
Anchang-Kimbi(2017)	94	98	128	152	5.3%	4.41 [1.48; 13.12]
Ayoya(2006)	9	14	51	117	5.0%	2.33 [0.74; 7.38]
Baingana(2014)	6	8	38	143	3.3%	8.29 [1.60; 42.85]
Dreyfuss(2000)	44	57	158	231	7.4%	1.56 [0.79; 3.08]
Ebuy(2017)	8	19	80	245	6.0%	1.50 [0.58; 3.87]
Gari(2020)	12	20	133	364	6.1%	2.61 [1.04; 6.54]
Gedefaw(2015)	7	13	138	350	5.2%	1.79 [0.59; 5.45]
Getachew(2012)	105	159	104	329	8.8%	4.21 [2.81; 6.29]
Kefiyalew(2014)	3	9	77	249	4.0%	1.12 [0.27; 4.58]
Melku(2014)	3	15	47	287	4.4%	1.28 [0.35; 4.70]
Muhangi(2007)	175	268	807	2191	9.4%	3.23 [2.47; 4.21]
Ndyomugyenyi(2008)	80	281	94	521	9.1%	1.81 [1.28; 2.55]
Tay(2017)	50	62	199	313	7.4%	2.39 [1.22; 4.67]
Tulu(2019)	11	13	180	560	3.7%	11.61 [2.55; 52.93]
Total (95% CI)		**1232**		**6477**	**100.0%**	**2.98 [1.98; 4.48]**

Heterogeneity: $Tau^2 = 0.3563$; $Chi^2 = 51.11$, df = 15 ($P < 0.01$); $I^2 = 71\%$

Figure 4 - A. Association between gestational *anaemia* and Hookworm. B. Association between gestational *anaemia* and Plasmodium.

Table 2 - Subgroups and meta-regression analysis of the factors associated with risk of bias.

Covariate	*Coefficient*	*SE*	*p-value*	*Model*
Year of publication	0.0200	0.0331	0.5586	Ascaris
Year of publication	0.0831	0.0255	0.0046	Hookworm
Malaria	1.0478	1.5502	0.5182	Hookworm

modium, the causal agent of malaria, showed a positive association with GA (OR 2.98, 95% CI 1.98-4.48; Figure 4-B).

To assess risk of bias, we performed meta-regression between hookworm *orAscaris lumbricoides* OD and malaria prevalence or year of publication as covariates (Table 2). However, only six studies reported simultaneously Ascaris risk estimates and malaria prevalence, which precluded meta-regression analysis for this pair of variables. Year of publication was associated with the magnitude of the effect of hookworm on anemia risk. This covariate was not associated with Ascaris OR. Prevalence of malaria was not associated with the magnitude of the effect of hookworm on anemia risk.

Furthermore, asymmetry in funnel plots of hookworms and plasmodium were observed during meta-analyses. *Ascaris lumbricoides* and *Trichuris trichuria* in opposition showed a symmetric figure plot, which corresponds to no intervention effect in most of studies.

DISCUSSION

Intestinal helminthiasis continue to be a public health problem in areas with low socioeconomic status and in the most vulnerable groups of children and pregnant women [58, 59]. Although the management of these infections depends primarily on the improvement of health services and hygiene conditions in the population, it is important to actively treat populations at risk to reduce their impact on health and the transgenerational cycle of this disease. No clear guidelines exist on the management of intestinal parasitosis in pregnancy, especially in the most affected areas in the world. This can be due to a couple of reasons such as the adoption of protocols from developed countries where these infections are not frequent and also the lack of attention that has been placed on some intestinal parasitosis in populations other than children under 5 years of age. Current recommendations on deworming in pregnancy are not clear due to the lack of studies to determine their consequences. There is a small quantity of meta-regression analysis of literature on evaluating the impact of helminthiases on GA. In this systematic review and meta-analysis, a significant association between IH and GA in pregnant women was found.

As the review shows, IH are a common problem in tropical countries. This is partially explained by the climatic conditions favoring the life cycle of the parasites. Furthermore, the absence of effective hygienic measures (*i.e.*, correct sanitary handling of stools) favor the transmission of the infection and the economic constraints of the affected countries contribute to the problem.

Only three studies in Latin America have evaluated the impact of these infections in pregnancy [7, 41, 50]. Two of them showed a high prevalence of helminth infection during pregnancy and its association with GA. Interestingly, despite having data about the impact of intestinal helminthiasis in pre-kinder population from the National Survey of Parasitism, there is no data regarding the prevalence of this infection in the gestational age in Colombia [60]. Thereby, national studies are needed to evaluate if this problem is similar to neighboring countries.

A. lumbricoides is the most common helminthiasis on the planet and it is estimated that almost two billion humans are infected by this parasite. The disease burden of the infection is driven by its high prevalence. However, it is estimated that its effect on health is lower than other infections such as hookworm infection (*Necator americanus* or *Anchylostoma duodenalis*) which cause blood loss and have a stronger association with anemia and nutritional deficiencies. This review showed that geohelminthiases, specifically hookworm infection, are associated with GA. However, since polyparasitism is common, evaluating each helminth infection individually could lead to result bias because control groups (non-infected) could include individuals infected with different species [61]. Fur-

thermore, we have to consider that hookworm is the predominant helminth in most of the studies that evaluated the relationship between IH and the outcome in this meta-analysis. Conducting studies in populations where these helminths are more common (*e.g.*, Colombia) will help clarify the association between each helminth infection and anemia. It will be important to define if pregnant women with helminth infections require treatment due to the potential negative effects of an untreated infection on fetal development [62]. In addition, it is important to note that infection with multiple parasites has an additive effect on health outcome. Although hookworm is the main species associated with the outcome, the impact of other species needs to be defined with better epidemiological studies given the expected bias that arises from polyparasitism when defining comparison groups. Moreover, year of publication was associated with the magnitude of the effect of hookworm on anemia risk (p-value 0.0046); recent publications show a larger effect than previous ones. This could be attributed to better quality of study design and increase sensitivity of instruments that measure parasitic infection.
Meanwhile the most common parasitic co-infection in the world is malaria and helminths, we found prevalence of malaria was not associated with the magnitude of the effect of hookworm on anemia risk (p-value 0.5182); contrasting in the results showed in a study in children, which reported higher mean haemoglobin concentration in co-infected group with *P. falciparum* and *S. haematobium* than those with only malaria infection, and also a study, which reported that the odds of anemia were higher in children who were co-infected with malaria and helminths than those infected with Plasmodium alone [63, 64]. These different findings are consistent with the proposed mechanism that modulates anemia during parasitic co-infection [65]. However, target population was variable in most of studies. This is the first study on pregnant women that shows a negative association between prevalence of malaria and anemia risk during co-infection, supporting that single helminthic infestation is associated with the outcome of (GA), as shown in *A. lumbricoides* (OR 1.86, 95% CI 1.12-3.08) and hookworms (OR 3.09, 95% CI 1.99-4.78).
Another bias of the results is the heterogeneity of the cut off points to define anemia as each study used different haemoglobin levels relevant for their target population. Nonetheless, we consider that the risk of this variability is lower than choosing a fixed haemoglobin cut off point as it varies depending on the target population (*e.g.*, oxygen concentration varies based on altitude) [66].
In conclusion, the results of this review indicate that there is a statistically significant association between intestinal parasitosis (helminthiasis) and (GA). Although hookworm is the main species associated with the outcome, prevalence of malaria was not associated with the magnitude of the effect of hookworm on anemia risk. The impact of other species needs to be defined given the expected bias that arises from polyparasitism when defining comparison groups.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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