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Hemoglobin Level and Risk of Anemia in Soil-Transmitted Helminths Infections among Children: A Systematic Review and Meta-analysis

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Abstract

BACKGROUND: Soil-transmitted helminthiasis (STH) is a Neglected Tropical Disease with almost 25% world population infected. Children were vulnerable to infection with morbidities affecting growth. STH infection alters children nutritional status which potentially causing anemia. Meta-analysis relating STH infections to hemoglobin (Hb) level and risk of anemia in children are limited.

AIM: The aim of this was to compare Hb levels and risk of anemia in children infected and uninfected with STH.

METHODS: Meta-analysis conducted from journals obtained from PubMed, ScienceDirect, WileyLibrary, Cochrane, EBSCO, ProQuest, DOAJ, and GoogleScholar from 2011 to 2021. Full-text cross-sectional studies on children with relevant topic are included, while unclear, inaccessible, or post interventional studies were excluded from the study. Articles were analyzed in Review Manager 5.4 in mean difference (MD) and odds ratio (OR) with confidence interval of 95%.

RESULTS: Out of 25,683 articles in the literature search, 29 were eligible for systematic review and meta-analysis. STH infection significantly decreases Hb level (MD −0.2 g/dL; p = 0.02) and increases risk of anemia (OR 1.83; p < 0.00001). Species analysis presented parallel result on *Trichuris trichiura* (MD −0.31 g/dL; p = 0.001 and OR 1.66; p = 0.009), Hookworm (MD −0.56 g/dL; p = 0.02 and OR 3.3; p < 0.00001), and multiple infection (MD −0.25g/dL; p = 0.03 and OR 4.49; p = 0.005). *Ascaris lumbricoides* did not show significance on Hb level but comparable for risk of anemia (MD −0.16 g/dL; p = 0.17 and OR 1.57; p = 0.001).

DISCUSSION: All STH infections exhibit lower Hb level and higher risk of anemia caused by lower nutrition absorption and occult bleeding in gastrointestinal tract. Hookworm and multiple infections have the highest risk of anemia. Proportion of anemia may vary in studies and influenced by sociodemographic characteristics, but higher proportions occur in STH infected.

CONCLUSION: Children infected with STH have lower Hb level and in risk of anemia compared to uninfected children; hence, further study is still needed to be conducted.

Introduction

Soil-transmitted helminthiasis (STH) is a parasitic infection which includes *Ascaris lumbricoides, Trichuris trichiura*, and Hookworm (*Ancylostoma duodenale* and *Necator americanus*) manifestation in human intestines with soil related in the transmission [1]. The WHO includes STH as one of the Neglected Tropical Disease (NTD) with barely one-fourth population in the world (1.5 billion) infected, with specifically estimated of 0.8–1.1 billion infected with *Ascaris lumbricoides*, 0.6–0.8 billion infected with *Trichuris trichiura*, and 0.5–0.7 billion with hookworms [2].

STH infections were common in tropical countries with low income and poor hygiene and sanitation. Countries in Subsahara, Latin America, Asia Pasific, and South East Asia were reported with the highest STH transmission and highest disability related to STH infections [3]. Children specifically in pre-school-aged children (PSAC) and school-aged children (SAC) have the highest risk of infection. More than 267 million PSAC and 568 SAC recorded to be infected with STH by 2020 [4].

STH is commonly asymptomatic and not life-threatening, but chronic infections affects long-term morbidities on children's growth and development. The pathophysiology of the infection relates to nutrition deficiency and anemia which may alter the rapid growth in childhood [5], [6]. Anemia itself stated as one of public health problem in the world by the WHO. PSAC and SAC were major groups in anemia prevalence with 47.3% (293 million) and 25.4% (305 million) each [7]. Children have a greater risk of anemia among other age, and since 1990–2013, there were more reports regarding anemia related to STH infection [8].

At present, there were plenty of local studies relating anemia and hemoglobin (Hb) levels in STH infections, but the results were vary and lots of bias may occur. At present, there were lack of broad systematic review and meta-analysis on Hb level and risk of anemia in children, except local meta-analysis or coinfections.

Aim

The aim of this study was to compare the Hb level and risk of anemia in infected with uninfected children with STH.

Methods

Study design and duration

This research was conducted as a systematic review and meta-analysis from the previous researches regarding STH infections relation to Hb level and risk of having anemia. This study was conducted in June up to November 2021 and was analyzing related journals published up to the literature search date.

Literature search

The literatures searching in this research was conducted in evidence of PRISMA Guideline in selecting eligible articles for systematic review and meta-analysis. We conducted a systematic search in certain search engines such as PubMed, Science Direct, Cochrane Library, Wiley Library, ProQuest, EBSCO, DOAJ, and Google Scholar. Search strategies applied were adapting Boolean logic association among keywords of PICO analysis of (Children OR Child OR Pediatric) AND (Soil-Transmitted Helminths OR Ascaris OR Trichuris OR Hookworm) AND (Anemia OR Hemoglobin OR Hemoglobin). Keywords were inserted in search entries every database, screened by filters available. Search results were, then, screened for title and abstract and relevant articles were, then, included for full-text read with careful selection based on inclusion and exclusion criteria of the articles. Selected articles were then presented as systematic review tables and further statistical calculation for meta-analysis.

Eligible study criteria

This systematic review and meta-analysis includes articles from observational or pre-clinical trial cross-sectional surveys providing data presenting Hb levels and case proportion of anemia among STH infected and uninfected children which were not mixed with other infection data. Studies included should presented researches conducted in human, written in English, and are accessible for full text. Articles published

previous that 10 years before the literature search and duplicates would be excluded. Unclear, biased data, or data presented in inaccessible supplements would also be excluded. Post-interventional and irrelevant data would not be considered for analysis.

Selected studies were assessed for analyzed for eligible methods of diagnosis with STH infections were confirmed by any presented STH infections of Kato-Katz, lugol, or iodine fecal microscopic examinations. Hb level was assessed with blood test from peripheral of vena puncture with automated spectrometry-based hemoglobinometer and anemia status which were grouped by the WHO Hb cut off value of anemia based on age and altitude.

Quality assessment and data extraction

Selected articles were then analysis for methodological quality using the Newcastle Ottawa Scale (NOS) assessment for sample selection, comparability, and outcome. Studies with very good and good quality assessment (NOS > 7) would be continued to data extraction for further review and analysis.

Data were extracted from the journals by two independent reviewer. Extracted data were mainly collected for authors' name, year of publication, country, number of sample, age, infection status (any type of STH, *Ascaris lumbricoides* only, *Trichuris trichiura* only, hookworm only, or multiple infections), Hb level (in mean and standard deviations), and number and proportion of anemia.

Data synthesis and analysis

Qualitative systematic review analysis was conducted with presentations of data in mean Hb level with standard deviation and number and percentage of anemia in every infection status groups. Quantitative meta-analysis were calculated and analyzed using Review Manger Version 5.4® (The Cochrane Collaboration, Oxford, UK). Numerical variables such as the Hb level were measured in mean differences (MD) and categorical variables such as proportion of anemia were measured in odds ratio (OR). Confidence interval of the statistic equation was 95% with α 5% and was considered as statistically significant with $p < 0.05$. Test of heterogeneity was used to assess data variability with $I^2 < 50\%$ analyzed with Fixed Effect Model and >50% analyzed in Random Effect Model.

Results

Figure 1 presented the literature search and selection process of the study. Twenty-five
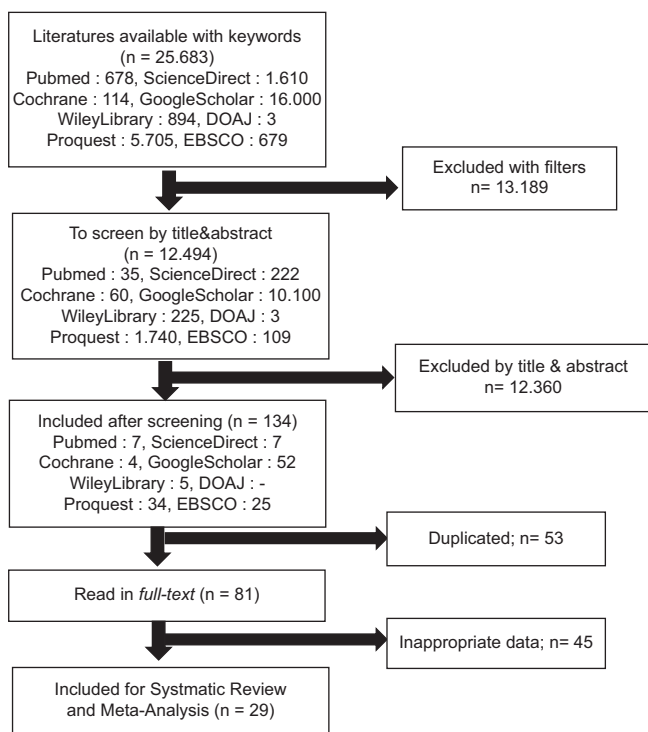
Figure 1: PRISMA flowchart of the study selection

thousand and six hundred eighty-three articles were identified in initial identification trough keyword search entry in search engines and were filtered in the database by selected criteria of publication year, language, human sample, study design, and type of article. Twelve thousand and four hundred ninety-four articles filtered articles were screened for title and abstract, but 9100 were inaccessible due to search engine limitations. Remaining 3394 articles were screened and only 134 included due to topic irrelevance. Articles were downloaded and checked for duplication using Mendeley® and 53 were duplicated.

From 81 articles read for full text, 16 excluded due to low NOS Score, 14 contained mixed data with other infections, ten were mixed with adult data, nine were not presenting either hb level or anemia, and nine other were irrelevant. Thirty-eight articles were available for systematic review, but only 29 has available raw data to be analyzed in Review Manager.

Hemoglobin level in infected and uninfected children

Fourteen reports were identified presenting data of mean Hb level in STH infected children and uninfected children. All reviewed articles compared Hb levels to non-infected children as control group. Any STH infection presented most records recorded for nine studies, while *Ascaris lumbricoides* had the most articles mentioning for seven articles. *Trichuris trichiura* and hookworm presented five and four journals mentioning, while multiple infection only three. Table 1 presented Hb level in any group presented in Mean and standard deviation. Overall STH infected individuals presented lower mean Hb level than control group, but individual reports of statistical significancies in each articles may vary or lacking. Lowest Hb level was reported in Any STH group with 10.3 g/dL (1.8) in Sumbele *et al.*, 2020. Highest Hb level was recorded from non-infected group for 13.6 g/dL (3.02) by Verhagen *et al.*, 213.

Figure 2 presented forest plot of Hb levels of subgroup comparison between STH infected and uninfected group. All five subgroups presented lower mean Hb level with negative MD to uninfected children. Only *Ascaris lumbricoides* infection failed to exert significance (p = 0.17) with MD −0.16 g/dL (−0.4, 0.07). Hookworm had the lowest Hb level with MD −0.56 g/dL (−1.04, −0.08, p < 0.05). Any STH, *Trichuris trichiura,* and multiple also had significance compared to uninfected with MD −0.2g/dL (−0.38, −0.03, p < 0.05), −0.3g/dL (−0.48, −0.14, p < 0.05), and −0.25 g/dL (−0.48, −0.02, p < 0.05), respectively. All mean Hb levels data were positive heterogenicity and analyzed in random effects.

Risk of anemia in STH infected children

Table 2 presented compilations of proportion of anemia between STH infected and uninfected children. Almost all presented more proportions of anemia in infected groups, whether single or multiple infections occur. Non-specific any type of STH infection presented the most number of studies included with 20 articles analyzed, followed by *Ascaris* and hookworm with 12 articles and *Trichuris* with nine articles. Only

Table 1: Hemoglobin level in soil-transmitted helminthiasis infected and uninfected children

Author, year	Number of sample	Age (year)	Any STH		*Ascaris lumbricoides*		*Trichuris trichiura*		Hookworm		Multiple infection		Not infected	
			n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Abanyie *et al.*, 2013 [9]	690	1–5			72	10.1 (1.5)							77	10.1 (1.4)
Cho *et al.*, 2021 [10]	2018	8.3 (2.5)	369	12.4 (2.2)	304	12.37 (2.18)	17	12.45 (1.76)	41	12.01 (2.54)			1649	13.2 (2.0)
De Gier *et al.*, 2016 [11]	510	7.5±0.9			118	12.11 (0.732)	67	11.69 (0.75)	9	11.74 (0.84)	215	11.81 (0.77)	101	12.2 (0.587)
Liu *et al.*, 2015 [12]	2179	10.58 (0.87)	912	12.54 (1.31)									1267	12.68 (1.19)
Matangila *et al.*, 2014 [13]	616	8 (7.5–9.5)			92	11.45 (1.13)	120	11.5 (1.22)					365	11.6 (1.26)
Müller *et al.*, 2016 [14]	934	9–12			248	12.4 (0.964)	207	11.95 (0.844)			156	11.95 (0.83)	635	12.31 (0.964)
Muñoz-Antoli *et al.*, 2018 [15]	341	8.53 (2.68)	185	11.41 (1.31)	11	11.7 (1.13)	95	11.7 (1.25)	7	12.1 (1.14)			156	11.72 (1.26)
Sanchez *et al.*, 2013 [16]	320	7–12	232	12.95 (0.77)							103	12.93 (0.71)	88	12.91 (0.74)
Staudacher *et al.*, 2015[17]	301	4.9–17.10	115	13.3 (1)									186	13.4 (1.2)
Staudacher *et al.*, 2016[17]	321	4.9–17.11	43	12.8 (1.3)									278	13.2 (1.1)
Sumbele *et al.*, 2020 [18]	401	4–14	3	10.3 (1.8)									195	10.8 (1.3)
Suraweera *et al.*, 2018 [19]	233	1–12	64	12.3 (0.8)									169	12.1 (0.8)
Verhagen *et al.*, 2013 [20]	390	4–16			104	13.5 (2.08)			111	12.8 (1.88)			286	13.6 (3.02)
Wijaya *et al.*, 2021 [21]	384	5–14	138	12.27 (0.99)									246	12.59 (0.73)

STH: Soil-transmitted helminthiasis, SD: Standard deviation.

seven studies presented proportion of anemia and was measurable to uninfected groups. Most prevalence of anemia was found in the STH infected groups in Tandoh *et al.* with barely 70% of infected children that were also anemia. Only some of the included studies exert contradictive result with lower proportions of anemia in infected group in contrast to uninfected group such as Djuardi *et al.* and Suraweera *et al.,* but most did not show statistical significance.

Forest plot analysis on Figure 3 of the anemia proportion also provided significance and relation that infected by STH was a risk factor of having anemia in childhood. All subgroup analysis whether non-specific test, specific to single species of STH, or multiple infection were all exerts OR > 1. Children with multiple infection were at the greatest risk for anemia with OR 4.49 (1.58, 12.75, p < 0.05). Greatest risk of anemia in single infection was possible in hookworm infected children with OR 3.3 (1.98, 5.49, p < 0.05), while *Ascaris lumbricoides* had OR 1.57 (1.2, 2.07, p < 0.05) and *Trichuris trichiura* with OR 1.66 (1.13, 2.43, p < 0.05). Overall any type of STH infection would risk children to be anemic for 2.05 (1.52, 2.76, p < 0.05) more likely than uninfected children.

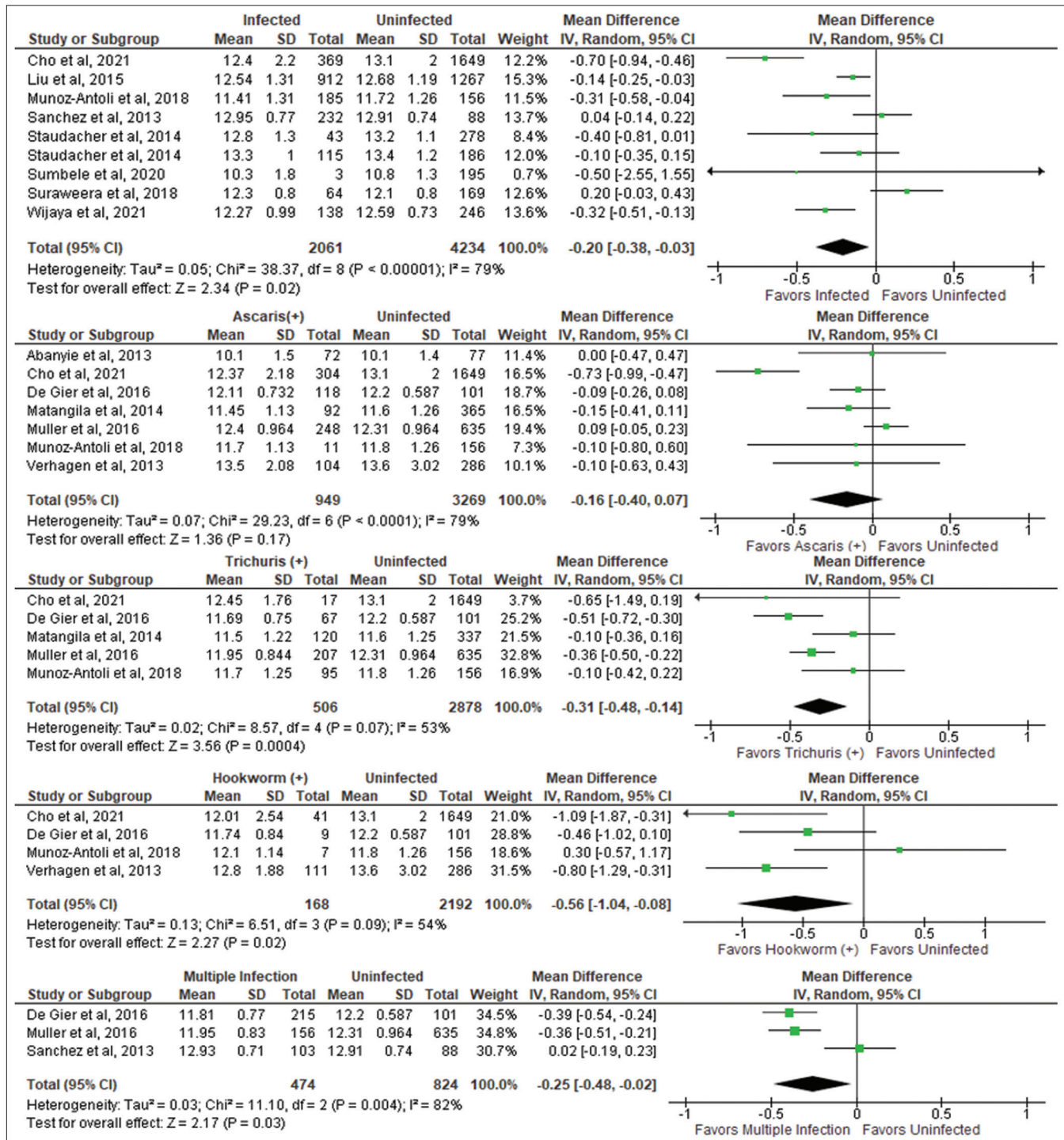Figure 2: Subgroup forest plot of hemoglobin mean differences of soil-transmitted helminthiasis infected and uninfected children
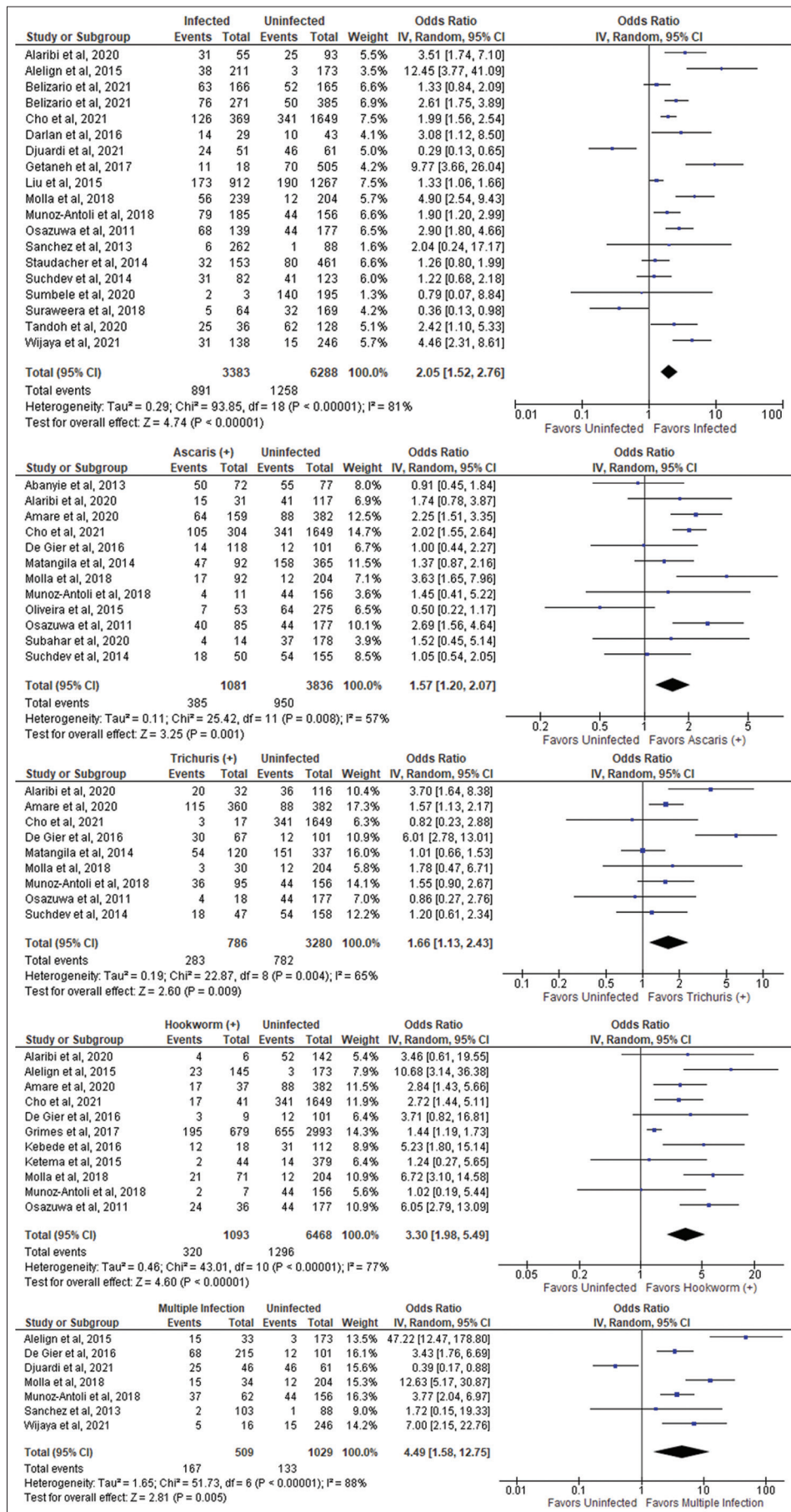
Figure 3: _Subgroup forest plot for risk of anemia in soil-transmitted helminthiasis infected and uninfected children_

Table 2: Number and proportion of soil-transmitted helminthiasis infected and uninfected children with anemia

Author, year	Number of sample	Age (year)	Any STH n (total)	Percentage	Ascaris lumbricoides n (total)	Percentage	Trichuris trichiura n (total)	Percentage	Hookworm n (total)	Percentage	Multiple Infection n (total)	Percentage	Not Infected n (total)	Percentage
Abanyie et al., 2013 [9]	690	1–5	50 (72)	69.4									55 (77)	71.4
Alaribi et al., 2020 [22]	148	< 12	31 (55)	56.36	15 (31)	48.4	20 (32)	62.5	4 (6)	66.7			25 (93)	26.88
Alelign et al., 2015 [23]	384	5–14	38 (211)	18.01					23 (145)	15.86	15 (33)	45.45	3 (173)	1.73
Hailu Amare and Lindtjørn, 2020 [24]	861	11.4 (1.9)			64 (159)	40.25	115 (360)	31.94	17 (37)	45.94			88 (382)	23.04
Belizario et al., 2021[25]	331	3–6	63 (166)	38									52 (165)	31.5
Belizario et al., 2021[25]	656	6–12	76 (271)	28									50 (385)	13
Cho et al., 2021 [10]	2018	8.3 (2.5)	126 (369)	34.1	105 (304)	34.54	3 (17)	17.65	17 (41)	41.46			341 (1649)	20.7
Darlan et al., 2018 [26]	72	7–10	14 (29)	48.28									10 (43)	23.26
De Gier et al., 2016 [11]	510	7.5 (0.9)			14 (118)	11.9	30 (67)	44.8	3 (9)	33.3	68 (215)	31.6	12 (101)	11.9
Djuardi et al., 2021 [27]	393	1–5	24 (51)	47.1							25 (46)	54.3	46 (61)	75.4
Getaneh et al., 2017 [28]	542	6–14	11 (18)	61									70 (505)	13.9
Grimes et al., 2017 [29]	3672	11.8 (2.1)							195 (679)	29			655 (2993)	22
Kebede et al., 2016 [30]	130	0–19							12 (18)	66.7			31 (112)	27.7
Ketema et al., 2015 [31]	423	5–14							2 (44)	4.55			14 (379)	4.48
Liu et al., 2015 [12]	2179	10.58 (0.87)	173 (912)	19									190 (1267)	15
Matangila et al., 2014 [13]	616	8 (7.5–9.5)			47 (92)	51.1	54 (120)	45					158 (365)	43.2
Molla and Mamo, 2018 [32]	443	6–15	56 (239)	23.4	17 (92)	18.48	3 (30)	10	21 (71)	29.58	15 (34)	44.12	12 (204)	5.9
Muñoz-Antoli et al., 2018 [15]	341	8.53 (2.68)	79 (185)	42.7	4 (11)	36.3	36 (95)	37.9	2 (7)	28.5	37 (62)	59.68	44 (156)	28.2
Oliveira et al., 2015 [33]	328	5–12			7 (53)	13.2							64 (275)	23.3
Osazuwa et al., 2011 [34]	316	1–15	68 (139)	48.92	40 (85)	47.06	4 (18)	22.22	24 (36)	66.67			44 (177)	24.86
Sanchez et al., 2013 [16]	320	7–12	6 (262)	1.9							2 (103)	1.7	1 (88)	1.1
Staudacher et al., 2014 [17]	622	4.9–17.9	32 (153)	20.92									80 (461)	17.35
Subahar et al., 2020 [35]	188	6–18			4 (14)	28.57							37 (178)	20.79
Suchdev et al., 2014 [6]	205	3.2 (0.08)	31 (82)	37.9	18 (50)	35.6	18 (47)	38					41 (123)	33.6
Sumbele et al., 2020 [36]	401	4–14	2 (3)	66.7									140 (195)	71.8
Suraweera et al., 2018 [19]	233	1–12	5 (64)	7.8									32 (169)	18.9
Tandoh et al., 2020 [37]	86	9–12	25 (36)	69.4									61 (128)	48.4
Wijaya et al., 2021 [21]	384	5–14	38 (211)	18.01					23 (145)	15.86	15 (33)	45.45	15 (246)	6.1

STH: Soil transmitted helminthiasis.

Discussion

Meta-analysis result of all parameters in this study presented trends of Hb level decrease and increase risk of anemia than that uninfected children groups. Most of analysis was comparable in statistic. This result was also in line to another meta-analysis which was limited in India by Salam and Fareed, in 2019, which pooled that mean Hb was lower than anemia cut off value and risk of anemia at OR 2.8 (2.4–3.4) and still limited at not specific at each species analysis [38]. Lower Hb level and risk of anemia were also synergy to a meta-analysis in Africa which analyzed an increased

risk of anemia in malaria patients coinfected with STH than without STH coinfection for 2.2 times. Children were also at higher risk in comparison to other age groups, in which OR was 2.72 (1.11, 6.7) and Hb level reduction was −1.1 g/dL [39].

Hb level reduction in STH infection was explained from certain mechanism of nutrition absorption deficiency and blood lost [38]. Nutrition absorption alteration was common in *Ascaris lumbricoides* infection affection iron (Fe) absorption followed with other nutrients such as zinc (Zn), protein, folate, vitamin B6, and B12 [40]. One of the symptoms in STH infection causing abdominal discomfort caused lost in appetite which leads to less food and nutrient intake [41]. Blood lost was common due to occult bleeding in *Trichuris trichiura* and hookworm infection, in which biological activity of the parasite caused penetration and disruption in intestinal mucosal epithelium. This was also related to hyaluronidase enzyme responsible in degrading mucosal layer [42].

Almost all included articles in this study presented similar results in Hb level reduction and risk of anemia. Some of those failed to show significance in comparison to uninfected groups such as Sanchez *et al*. All included studies were cross-sectional that direct causative relation was not clear enough. Endemic area might also interfere due to malnutrition, sociodemographic factors, and climate in study area which may be related to nutritional status and Hb level among subjects [16]. Population with high number or stunting and underweight could also be contrast to other studies as subjects may be at high risk even without any other risk factors such as infections. Daily food intake problems might vary the results as some groups with food intake problem may be a greater risk specific to certain nutrients essential in blood formation which may cause anemia even without any STH infections [25], [43]. Poverty and living in rural communities were the most common factors related to less differences between infected and uninfected groups [42], [44].

As far as, the literature searches were done that the authors could not find other similar meta-analysis to this research specially with species subgroup analysis with broad inclusion in children populations. Some limitation were recorded in this study due to inability to access all publication from all countries and some parameter and subgroup analysis were consisted of small number of references.

Conclusion

STH infection whether single of multiple infection, *Ascaris lumbricoides, Trichuris trichiura*, or hookworm infection were all causes decrease in Hb level and increase risk to be anemia in children compared to uninfected children. Multiple infection and hookworm infection had the highest risk among other STH species. Other further meta-analysis with broader population and preventive programs to avoid further cases of STH infection and anemia related to STH infections will still needed to be conducted.

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