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ARTÍCULO ORIGINAL

Correlation between malaria incidence and prevalence of soil-transmitted helminths in Colombia: An ecologic evaluation

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Introduction. Recent studies have suggested an association between the soil-transmitted helminth infections and malaria incidence. However, published evidence is still insufficient and diverging. Since 1977, new ecologic studies have not been carried out to explore this association. Ecologic studies could explore this correlation on a population level, assessing its potential importance on public health.
Objectives. The aim of this evaluation is to explore the association between soil-transmitted helminths prevalence and malaria incidence, at an ecologic level in Colombia.
Materials and methods. Using data from the National Health Survey, which was carried out in 1980 in Colombia, we calculated Spearman correlation coefficients between the prevalence of: *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm, with the 1980 malaria incidence data of the same year provided from the Colombian Malaria National Eradication Service. A robust regression analysis with least trimmed squares was performed.
Results. Falciparum malaria incidence and *Ascaris lumbricoides* prevalence had a low correlation (R^2 = 0.086) but this correlation was stronger into the clusters of towns with prevalence of *Ascaris lumbricoides* infection above 30% were only included (R^2 = 0.916).
Conclusion. This work showed an ecologic correlation in Colombia between malaria incidence and soil-transmitted helminths prevalence. This could suggest that either there is an association between these two groups of parasites, or could be explained by the presence of common structural determinants for both diseases.

Key words: malaria/epidemiology, helminthes, epidemiologic factors, ecological studies, Colombia.

Correlación entre la incidencia de malaria y la prevalencia de las geohelmintiasis en Colombia: enfoque ecológico

Introducción. Los estudios recientes han sugerido una asociación entre las geohelmintiasis y la incidencia de malaria, sin embargo, la evidencia publicada es escasa y divergente. Desde 1977 no se han realizado nuevos estudios ecológicos para explorar esta asociación. Los estudios ecológicos podrían explorar dicha correlación en la población, midiendo su impacto potencial en salud pública.
Objetivo. Explorar la asociación entre la prevalencia de geohelmintiasis y la incidencia de malaria desde el punto de vista ecológico, en Colombia.
Materiales y métodos. Usando datos provenientes de la Encuesta Nacional de Salud, llevada a cabo en 1980, se estimaron coeficientes de correlación de Spearman a nivel departamental, entre las prevalencias de *Ascaris lumbricoides*, *Trichuris trichiura* y *Uncinaria* sp. con la incidencia de malaria para el mismo año suministrada por el Servicio de Erradicación de Malaria. A todos los datos, se les aplicó un método sólido de regresión con mínimos cuadrados ajustados.
Resultados. La incidencia de malaria por *Plasmodium falciparum* y la prevalencia de *A. lumbricoides* tuvieron una correlación baja (R^2=0,086). No obstante, dicha correlación se hizo más fuerte cuando se incluyó solamente el grupo de poblaciones con prevalencias de *A. lumbricoides* mayores de 30% (R^2=0,916).
Conclusión. Este trabajo evidenció una correlación ecológica en Colombia entre la incidencia de malaria y la prevalencia de geohelmintiasis. Esto podría justificar la existencia de una asociación entre estos dos grupos de parásitos o explicarse por la presencia de factores determinantes estructurales comunes a ambas enfermedades.

Palabras clave: malaria/epidemiología, helmintos, factores epidemiológicos, estudios ecológicos, Colombia.

Malaria and soil-transmitted helminth (STH) infections are widespread worldwide; the first is considered the most important tropical disease, causing about 500 million cases and more than one million deaths per year (1). Furthermore, more than 2 billion people are infected with at least one geohelminth species (2) mainly school-age children from developing countries. The burden and spread of both diseases overlap extensively as a result of similar social and environmental conditions determining their occurrence (3). Therefore, an unknown but probably significant amount of people are infected with both groups of parasites (4).

Associations between *Plasmodium sp*. and STH were firstly proposed in 1977, by casual findings on the Comoros Islands (5). Despite the importance of these suggestions, interest about this topic was scarce until the past ten years. There are only seven original studies published on the association between STH infections and non-complicated malaria incidence and their results are highly divergent. Two closed cohort analytical studies found a positive association between STH infections and malaria occurrence (6,7). A recent cross-sectional study carried out with 2.507 pregnant women in Uganda has found also found a positive association between some hookworm and malaria incidence (8). A case-control study found no association (9), and two randomized clinical trials (10,11), as well as the ecological study mentioned above (5), suggested a protection-inducing association. In perspective, studies about these associations are still limited, presenting many important methodological limitations and leading to different conclusions (12-15).

Colombia is a malaria endemic country, which in the recent years has reported about 100,000 annual cases, mostly caused by *P. vivax* (approximately 65%), by *P. falciparum* (34%), and by either *P. malariae* or mixed infections (less than 1% of reported cases) (16). According to the last nationwide survey, the prevalences of *Ascaris lumbricoides, Trichuris trichiura* and hookworm infections were high, 33.6%, 37.5% and 23% respectively, with an essentially rural distribution (17).

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Ecological studies allow assessing mainly correlations on a population level between health macro-determinants and their population effects. These studies have regained importance recently (18), allowing to obtain evidence of the differences between collective health determinants and individual disease causes (19). The main limitations of this kind of epidemiological designs are evidenced particularly when these studies are used to assess individual level associations, since these inferences could lead to the ecological fallacy. But, as we pretend to discuss in this article, the relationships between STH and malaria could occur in an individual as well as in a population level. Hence, this methodology could evaluate a potential ecological correlation or just explore with some limitations an individual association with ecological data.

The purpose of this study was to explore the above-mentioned association using a simple ecologic analysis of the distribution of both parasite groups in Colombia.

Materials and methods

Data from the National Health Survey (NHS), which was carried out between 1977 and 1980, were obtained from the original database provided by the National Institute of Health in Colombia. This survey assessed the health status in a national representative population sample including both children and adults, using single or collective questionnaires. Some towns considered as representatives of each department were included, analyzing a random sample of people selected in every town. The aggregate of those towns was used to calculate prevalences by department. Historically non-endemic towns for both illnesses were excluded to calculate geohelminthes prevalence in each department. Stool samples were taken from individuals and were studied to determine intestinal parasite infections using the Ritchie-Frick concentration method (20). The NHS included 19 of the 32 departments of the country, covering 52 towns and taking a total of 10,817 stool samples.

Malaria incidence records for 1980 were provided by the Ministry of Social Protection. Malaria incidence was expressed as annual parasitic index (API= malaria cases/population at risk x 1,000) for each department; annual *P. falciparum* index (AFI = *P. falciparum* cases/ population at risk x 1,000) and annual *P. vivax* index (AVI = *P. vivax* cases/population at risk x 1,000). Spearman's correlation coefficients were calculated between malaria incidence and soil-transmitted helminths prevalence on a department level, as data did not present a standard normal distribution. First we analyzed the data for all departments jointly and afterwards we calculated the correlation in departments with moderate (20-30%) and high (above 30%) prevalence of each helminth infection. Then, relationships were explored with ordinary least squares (OLS) regressions. However the residual analysis indicated that some of the observations were highly influential and residuals were not normally distributed. Therefore, a robust regression method with the Least Trimmed Squares (LTS) model was applied for all data. This was

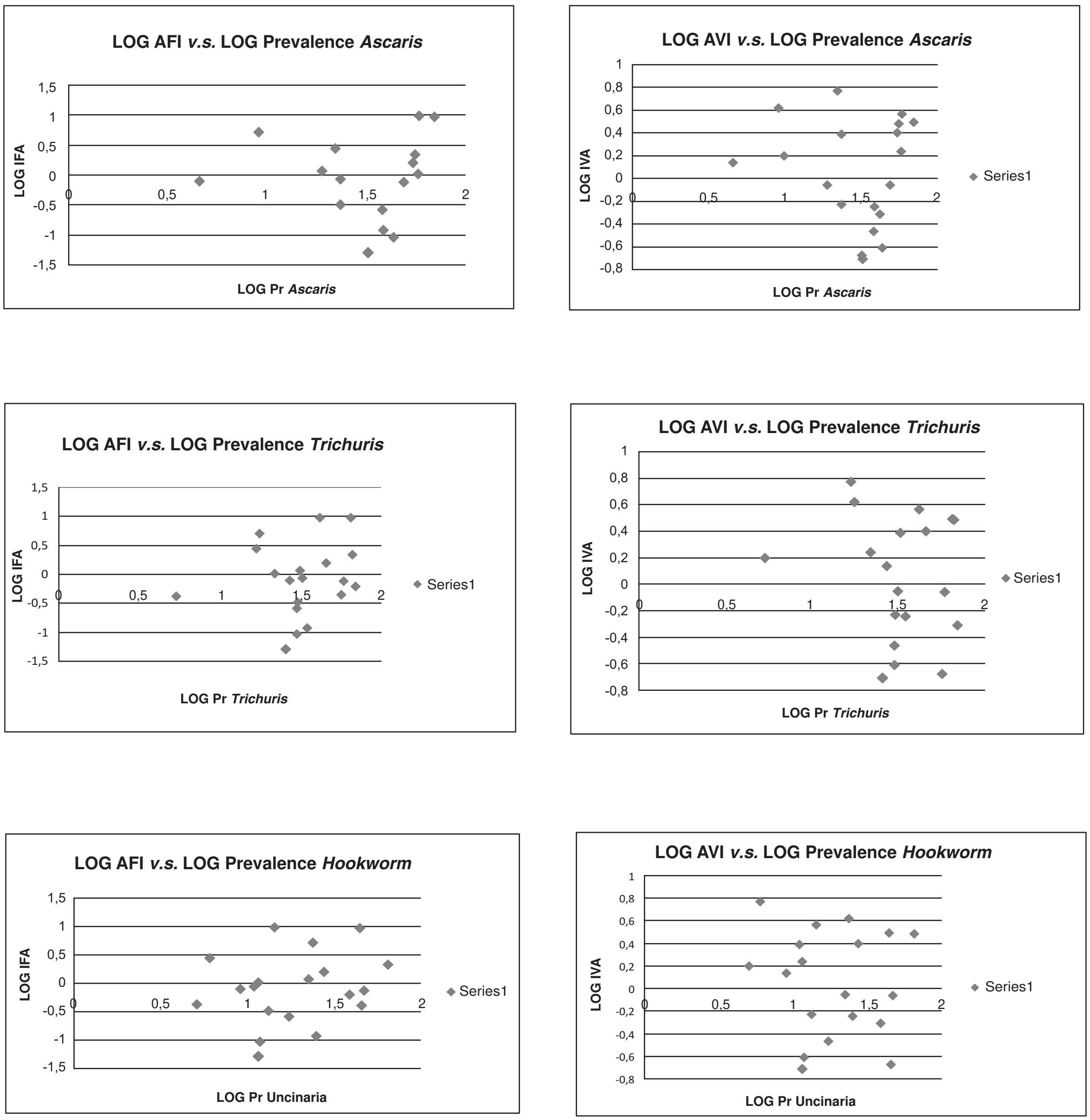

Figure 1. Scatterplots of LOG Malaria incidence (AVI and AFI) versus LOG of prevalence for each soil-transmitted helminth species.

a regression between the logarithms of malaria incidence (AVI or AFI index) against the logarithms of STH prevalence's.

Results

The correlation coefficients between malaria incidence (both by *P. falciparum* and *P. vivax)* and prevalence of soil-transmitted helminths are shown in table 1. Its representation is shown in figure 1. When all the departments were analyzed, a low correlation coefficient between malaria incidence (both by *P. falciparum* and *P. vivax)* and prevalence of *A. lumbricoides* was found. This correlation was stronger when only departments with moderate or high prevalence of *A. lumbricoides* were included (prevalences above 30%). High Spearman's correlation coefficients were observed only when the association between *A. lumbricoides* prevalence and malaria incidence was explored. These coefficients were stronger in departments with higher *A. lumbricoides* prevalence. In contrast, *T. trichiura* and hookworm prevalence presented low correlations with malaria incidence. A significant negative correlation between hookworm and AVI was found (-0.150; p=0.02). The robust regression coefficients are shown in table 2. These coefficients were mainly significant for *A. lumbricoides* and to a lesser extent for hookworm. It must be noted that the statistical relationship was not a linear one and the sign of the regression coefficient only identified the existing relationship between the lowest values of the dependent and independent variables.

Discussion

A positive correlation between malaria incidence and *A. lumbricoides* prevalence was mainly found in the departments with moderate and high STH prevalence (above 30%). No significant correlation was found between malaria incidence neither *Trichuris trichiura* nor hookworm prevalence's, despite the low regression coefficient for hookworm.

Table 1. Spearman's correlation coefficients between malaria incidence and prevalence of soil-transmitted helminths.

	All departments (n=19)		Departments with STH prevalence above 20% (n=15)		Departments with STH prevalence above 30% (n=12)	
Parasite	**AVI (p)**	**AFI (p)**	**AVI (p)**	**AFI (p)**	**AVI (p)**	**AFI (p)**
Ascaris lumbricoides	0.086	0.219	0.350 (0.20)	0.475	0.916	0.846
	(0.73)	(0.37)		(0.07)	(p <0.05)	(p <0.05)
Trichuris trichiura	-0.091	0.172	0.306 (0.25)	0.418	0.217	0.441
	(0.71)	(0.48)		(0.11)	(0.50)	(0.15)
Hookworm	-0.088	0.174	-0.150 (0.02)	0.017	0.200	0.200
	(0.72)	(0.48)		(0.70)	(0.75)	(0.75)

AVI: Annual Vivax Index; AFI: Annual Falciparum Index.

Table 2. Regression coefficients between log of STH prevalences, log annual Falciparum index (AFI) and log annual Vivax index (AVI) for 19 Colombian departments.

	Effect for AFI		Effect for AVI	
	Coefficient	**95%CI**	**Coefficient**	**95%CI**
Log *A. lumbricoides* prevalence	1.248	1.62, 4.12	1.842	0.8, 3.61
Log *T. trichiura* prevalence	-5.025	-10.86, 0.81	-4.850	-8.45,-1.25
Log hookworm prevalence	4.116	0.06, 8.17	3.315	0.82,5.82

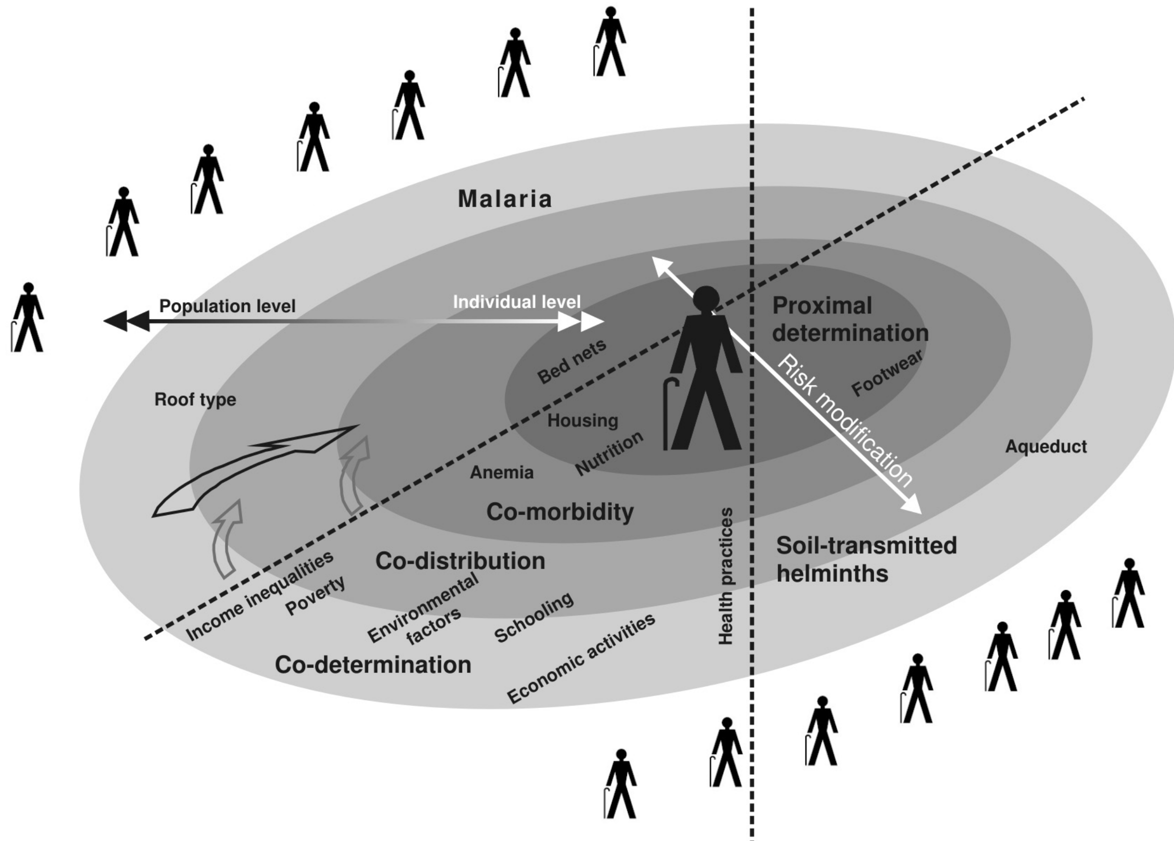

Figure 2. Links between malaria and soil transmitted helminth infections

A possible explanation for the results for *Ascaris* could be that higher helminth parasite loads could promote higher malaria parasitemias by producing greater immunomodulation from the host towards a Th2 type response, which may inhibit the Th1 type response, and, in consequence, cause a proliferation of malaria parasites (21-24). This is consistent with pathogenic mechanisms proposed by some authors (15).

Populations with higher STH prevalences usually also have higher malnutrition prevalences, which may interfere in the causal chain between malaria and geohelminth infections. Those correlations could be part of more complex links, at both individual and population levels, as will be explained later.

The findings of this study are consistent with the results of two cohort studies, which suggested soil-transmitted infections as a potential risk for malaria incidence (6,7), although a third analytical study published failed to find an association (9). In these three studies the geohelminth infections were studied jointly. On the other hand, two recent clinical trials reported a specific positive association between malaria incidence and *Ascaris lumbricoides* infections (10,11). Similar results were also found in the pioneer study carried out by Murray (5). This last study was also, as the present one, an ecological study, but it compared only two groups to evaluate the association and has many well recognized methodological limitations (12). The fact that the prevalence of *Ascaris lumbricoides* was correlated with malaria incidence in the present study is consistent with the three of the studies mentioned previously (5,10,11). The biological and epidemiological factors which can explain why the association seems more important for *Ascaris* are still unknown (13-15). In contrast, some of our results are consistent with a recent study carried out in Uganda with pregnant women, where the most common correlation found was between hookworm and malaria (8).

To our knowledge, this is the first study in Colombia to establish an ecological correlation between malaria incidence and soil-transmitted helminth infections. This association was evaluated at the population level using the last available data for all Colombian departments studied. The results suggest that the prevalence of *Ascaris lumbricoides* seems to have a significant positive correlation with malaria incidence. However, this study has some limitations. Confounding has a potentially important role in previous observations as well as in this study, because adjustment for environmental and socioeconomic variables was not done due to lack of information. Despite this, we did not find a significant correlation between malaria incidence and *T. trichiura* or hookworm prevalence.

An important limitation of this study is the low sample size compared to the large territorial extension of the departments, producing high internal heterogeneity as observation units with few data points. Using a small sample size, there are increased probabilities of occurrence for both type I and type II errors. The first one, having a lower *p* value, leads to a false rejection of the null hypothesis; the second one, with higher *p* values, leads to a false acceptance of the null hypothesis (25). These two problems could potentially increase the influence of confounding factors as well as of random bias. Other modifying factors, such as geographical differences, could affect comparability between populations, especially when comparing towns in the coastal areas with those ones in the mountain zones. This implies that the ecological risk of acquiring both diseases may not be the same in all cases. The fact that some of the previous studies did not strictly control for confounding variables may allow confounding to operate in single level studies as it does in ecological ones (26). Given the characteristics of ecologic studies as hypotheses generators, we cannot go far beyond in concluding about this particular aspect. Consequently, considering these variables in further single level studies could help to unravel the role that confounding may play on this association. Taking into account that *A. lumbricoides* share common social and environmental determinants with all the soil-transmitted helminths, this particular finding suggests that the association can be explained by specific characteristics of *Ascaris lumbricoides* and not by confounding factors.

STH and malaria links could be explained by highly related, conceptually different phenomena (figure 2). Firstly, co-determination defined as the existence of common determinants of their occurrence, not only environmental but also behavioral, cultural and socioeconomic (for example: housing characteristics) representing mainly an epidemiologic problem. Secondly and highly related with the previous one, the co-distribution or overlapping given by the sharing of key environmental factors for the transmission of both groups of parasites, represents mainly a biological problem. It is possible to think that overlapping could be a part or an effect of co-determination but co-distribution could be better explained as a biological phenomenon in which some parasites share hosts with some specific characteristics within specific environments. Thirdly, co-morbidity, is defined as the effect exerted by co-distribution and co-determination on a particular human being. Lastly, the biological association (also called *risk modification*) which by immunological hypotheses is presumed between both parasites, whereby a parasite (one of the STH) increases the probabilities of success of another (*Plasmodium sp*). This last issue is the most controversial one and has had the most attention in recent years.

Both the results of this study and that factor could also be explained by population phenomena. Overlapping and co-determination are mainly population phenomena with individual effects although certainly they also represent some equivalent common causes on an individual level. Some co-determinants could be individual, others ecological and some could work at both levels (26). Co-morbidity is originated from a population event but has a clinical individual representation. In contrast, *risk modification* is strictly an individual problem, although it could have ecologic impacts.

The results of this study may reflect the four factors at the same time, but it was not possible to establish this clearly, although this approach at least indicates the existence of one of them.

The importance of undertaking similar studies on this subject is related to design limitations which are present in single level studies, i.e., single level studies may not be useful to estimate the outcomes of a determined exposure if it has slight changes within an area or region (27). Besides, convenience inherent to ecologic inference levels for public policies, community intervention formulations and etiologic research is another encouraging issue, since disease determinants are not the same at the individual and ecologic levels (19).

Since soil-transmitted helminth infections are tool ready diseases and malaria is one of the ‘big three’, integrating soil-transmitted helminths control into partnership programs could reduce the burden of both diseases, reducing the number of disability-adjusted life years (DALYs) and improving the outcomes of their natural history (28). Either this association does in fact exist or it can be explained by common determinants. In both cases these results highlight the need for developing integrated control programs focused on the social determinants rather than on the diseases, which presents the most important challenge for the control of the neglected tropical diseases.

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Conflict of interest

No conflict of interest

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