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Morbidity burden of imported chronic schistosomiasis among West African migrants

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SUMMARY

Background: Past exposure to schistosomiasis is frequent among migrants from endemic countries, and chronic untreated infection may lead to long-term morbidities.
Methods: We carried out a prospective population-based cross-sectional study among migrants from endemic Sub-Saharan countries living in Barcelona, Spain. Participants had not been previously diagnosed or treated for schistosomiasis. Clinical signs and symptoms were scrutinised through a systematic revision of electronic medical records and an on-site standardised questionnaire, and blood and urine samples were screened for *Schistosoma*.
Findings: We recruited 522 eligible participants, 74.3% males, mean age 42.7 years (SD=11.5, range 18–76), Overall, 46.4% were from Senegal and 23.6% from Gambia. They had lived in the European Union for a median of 16 years (IQR 10–21). The prevalence of a *Schistosoma*-positive serology was 35.8%. *S. haematobium* eggs were observed in urine samples in 6 (1.2%) participants. The most prevalent symptoms among *Schistosoma*-positive participants were chronic abdominal pain (68.8%, OR=1.79; 95%CI 1.2–2.6), eosinophilia (44.9%, OR=2.69; 95%CI 1.8–4.0) and specific symptoms associated with urinary schistosomiasis, like

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self-reported episodes of haematuria (37.2%; OR=2.47; 95%CI 1.6–3.8), dysuria (47.9%, OR=1.84; 95%CI=1.3–2.7) and current renal insufficiency (13.4%; OR=2.35; 95%CI=1.3–4.3). We found a significant prevalence of gender-specific genital signs and symptoms among females (mainly menstrual disorders) and males (erectile dysfunction and pelvic pain). Individuals typically presented with a multitude of interconnected symptoms, most commonly chronic abdominal pain, which are often disregarded.

Conclusions: Despite the lack of urine parasite identification, the high incidence of clinical signs and symptoms strongly correlated with a positive schistosomiasis serology suggests the existence of a heavy clinical burden among long-term West African migrants living for years/decades in the study region. More research is urgently required to determine whether these symptoms are the result of long-term sequelae or a persistent active Schistosoma infection.

Introduction

Schistosomiasis is caused by various species of blood trematodes (flukes) of the genus *Schistosoma*. The two main species of relevance to human health are *Schistosoma haematobium* and *Schistosoma mansoni*, highly endemic in most Sub-Saharan African countries.[1] Sub-Saharan Africa is the main hotspot for schistosomiasis, with roughly 90% of the global 229 million worldwide cases.[1,2] Adult worms may remain up to 40 years or more in the human body,[1,3–5] and after some weeks of infection deposit more than 300 eggs per day in the venous plexus of the bladder or urinary tract (*S. haematobium*), and mesenteric venules of the bowel or rectum (*S. mansoni*).[1] If untreated, chronic infection may lead to disease progression and severe complications, including renal insufficiency, liver fibrosis, *cor pulmonale*, or bladder cancer.[1,3] Long-term exposed people can develop, as well, a wide array of long-term and frequently non-specific clinical signs and symptoms and morbidities.[3] These conditions have been related to chronic inflammation and fibrosis driven by *Schistosoma* eggs and adult worms in the human body, including ectopic localisations outside the genitourinary and digestive systems.[1,3] Autopsy series have found eggs present throughout the human body, including the digestive, circulatory, neurologic, genital, and urinary systems.[6] The true global prevalence of schistosomiasis and morbidity associated with chronic infection may well exceed current estimates of 11 500 deaths (95% UI 10 100–13 300) and 1·64 million (1·04–2·64) DALYs.[2]

Europe receives a constant flow of migrants from schistosomiasis endemic countries - mainly from Sub-Saharan Africa - with an estimated 4 million residing in Europe in 2022.[7] The burden of chronic imported schistosomiasis has attracted limited attention in non-endemic countries, although serology-based prevalence estimates are as high as 24% in European migrants.[8] The unspecific clinical presentation and lack of a gold standard diagnostic test for chronic schistosomiasis is accompanied by low awareness, and the scarcity of systematic screening programs in European non-endemic countries, particularly among long-term residents. All of this strongly suggests that chronic schistosomiasis infection and/or associated long-term consequences are largely underestimated in non-endemic countries.

Our purpose was to estimate the prevalence of clinical signs and symptoms associated to a positive schistosomiasis test routinely available in primary care centres in Europe (serology and parasitology examination of urine) in individuals living in a European country (Spain) exposed to the infection many years before in their native countries.

Material and methods

Study design

Between April and November 2022, we carried out a prospective multi-centre population-based cross-sectional study among schistosomiasis-exposed individuals. The inclusion criteria were having been born in a schistosomiasis-endemic region of Sub-Saharan Africa, living in the study area at the time of the study, being over 18 years of age, not having been diagnosed and/or previously treated for schistosomiasis and, in the case of women, not being pregnant. The study site comprised two municipalities (Mataró and Granollers) which have the largest pockets of Sub-Saharan migrants, most of them communities from West African countries, in the North Metropolitan Barcelona health services district in Catalonia, Spain. This district serves around 1 300 000 inhabitants, of whom about 15% are immigrants from non-EU countries, with up to 20 000 coming from Sub-Saharan countries from which 36.5%, 23.0% Gambia and 12% are from Senegal, Gambia and Mali, respectively.[9] Participants were consecutively recruited in the referral Primary Health care centres, after a community-based awareness-raising campaign in the targeted communities. This campaign was carried out with the collaboration of cultural mediators and community leaders. Participants for this study presented themselves voluntarily at the recruiting centres and signed a consent form.

Data collection and management

We screened eligible participants for past and present clinical schistosomiasis-related signs and symptoms, as classified in the International Classification of Diseases (11th Revision, Table S1),[10] and laboratory findings using three different sources of information. First, the prospective electronic clinical medical records database was examined by skilled study researchers. Second, a structured questionnaire was implemented by trained health personnel. We gathered socio-demographic data (age, sex, years of residence, country of origin or exposure, village of birth) and clinical information based on the clinical and syndromic presentations of long-term schistosomiasis, without any alternative aetiological diagnosis and results of abdominal ultrasonographies performed during the 5 years prior to enrolment. And third, two samples of whole blood for basic hemogram and biochemical determination, *Schistosoma* serology, and screening for concomitant infections (chronic hepatitis B virus (VHB), hepatitis C virus (HCV), HIV, and *Strongyloides stercoralis*). Renal insufficiency was defined as a glomerular filtrate rate reduction related to normal range for a young adult (90 mL/min/1.73 m2). A fresh urine sample was obtained as well. Additionally, an abdominal ultrasonography was offered to participants. Ultrasonographic images were evaluated according to WHO guidelines for schistosomiasis ultrasound morbidity assessment.[11] Data were introduced by two independent data managers into a standardised form using RedCap and double-checked by an independent clinician.

Laboratory procedures

We performed two qualitative diagnostic serological tests on serum samples, namely the ELISA for anti-schistosomiasis IgG

antibodies (Euroimmun, Lübeck, Germany) and *Schistosoma* in-vitro ICT (LDBIO Diagnostics, Lyon, France), which simultaneously detects both schistosomal IgM and IgG. For the ELISA, we used a spectrophotometer absorbance reading (450–620 nm). An optical density (OD) greater than 0.8 OD units was regarded as a positive result. Urine samples were processed by the sediMAX automatic sediment analyser with microscopy (77 Elektronika, Budapest, Hungary). For parasitological diagnosis, 10 mL were placed in a conical tube and centrifuged at 3000 rpm for 10 min. Subsequently, 20 µl were placed on a slide for ova and parasite examination by optic microscopy.

Statistical methods

Continuous variables were described as mean and Standard Deviation (SD) or median and Interquartile ranges (IQR) and categorical variables with proportions and 95% confidence intervals (CI). Bivariate analyses used the Chi-square test or Student's t-test for categorical or continuous variables, respectively, and McNemar test for paired categorical variables or their nonparametric counterparts when necessary (Fisher test and Wilcoxon test). Odds Ratios (OR) and corresponding 95%CI were estimated. A multivariate analysis was performed using logistic regression. For the network and cluster analysis, we regarded a working definition of chronic schistosomiasis when any schistosomiasis test was positive and clinical scores were over the estimated cut-off using the Youden (J) index. For this purpose, firstly, we calculated a clinical score for each participant, corresponding to the sum of the estimated OR value of each of the variables with a positive association with a p value ≤0.1 (included in Fig. 1a and b, see also Table S2). We performed then a Receiving Operating Characteristics analysis between schistosomiasis positivity and clinical score. Finally, we calculated the pairwise association between variables by means of Kendall's sb test. Bonferroni's method was used to account for multiple tests. Next, we built a network by connecting all variable pairs that had a significant association (corrected *p* value 0.1). Edges between any two variables were given a strength according to Kendall's sb value for the pair. Data were analysed using Stata v14.0 and R v3.1.4. Individuals with positive *Schistosoma* tests were georeferenced in the WGS84 reference system of the centroid of each municipality of origin using ArcGIS 10.8.1 geographic information systems (GIS) software.

Results

Participants

We enroled 529 participants, of whom 522 were eligible and had undergone a valid *Schistosoma* serology test. Five patients were excluded because they had received Praziquantel treatment in the past, and 2 women were pregnant. One hundred thirty-four (25.7%) were females, with a mean age of 42.7 years (SD=11.5, range 18–76). Participants had lived a median of 16 years in the European Union (EU) (IQR 10–21). Females were younger than males [40.5 (SD=9.4) vs. 43.5 (SD=12.0) years; p = 0.006] and had spent less time in the EU [median 14 years vs. 17 years (p = 0.002]. All participants were from a West African country. Among them, the most frequent origin were Senegal, with 242 participants (46.4%), Gambia (N = 123; 23.6%) and Mali [(N = 80; 15.3%). Overall, 187 (35.8%) had a positive *Schistosoma* serology [participants tested 'positive' by ELISA (N = 46; 24.6%) or ICT test (N = 63; 33.7%) alone or both (N = 76; 40.6%)]. Six participants (1.2%) had confirmed urine *S. haematobium* eggs by microscopy; four of them with a positive serology. Schistosoma-positive cases' origin was mostly aggregated in the main riversides of their country of origin (Fig. 2). A positive serology was significantly more frequent in men (38.4% vs 28.3%, p = 0.04). Chronic HBV infection (HBsAg positive) was detected in 67 out of 519 participants (12.9%), HCV serology in 10 out of 518 (1.9%) and HIV infection in 9 out of 519 (1.7%), including 2 new diagnoses. HIV infection tends to be associated with a schistosoma-positive test (p = 0.06). Table 1 shows full socio-demographic data and laboratory results.

Clinical signs and symptoms screening results

We observed a median of clinical signs and symptoms (either by clinical records or questionnaire-based) by schistosomiasis positive serology vs. negative of 7 [(IQR 4–8) vs 5 (IQR 3–6); p < 0.001] among males and 10–11 [(IQR 7–13) vs 8 (IQR 6–11); p = 0.01] among females (Fig. 3). Among the 42 clinical items assessed trough the electronical clinical records, we found 17 analysed clinical items (including laboratory results), which were significantly associated with a positive schistosomiasis serology after adjusting for age and sex (Fig. 1a and Table S3). The most prevalent items among participants with a positive serology were chronic abdominal pain [52.7%; OR= 2.45 (CI 1.7–3.6)], chronic constipation [25.7%; OR= 2.26 (CI 1.4–3.6)] previous episodes of eosinophilia [44.9%; OR= 2.69 (CI 1.8–4.0)] and history of liver transaminase elevation [28.7%; OR= 2.56 (CI 1.6–4.0)]. We also found an association past episodes of laboratory-based haematuria [13.0%; OR= 1.95 (CI 1.1–3.6)], past episodes of renal insufficiency [17.9%; OR= 1.73 (CI 1.0–2.9)], and current renal insufficiency [13.4%; OR= 2.35 (CI 1.3–4.3)]. Other prevalent associated clinical findings were urticaria, epigastralgia, and bronchitis (Fig. 1a). The leading associated symptoms related to the genitourinary and reproductive systems among females were amenorrhoea and vulvar itching.[12] Among men, the leading specific symptoms were erectile dysfunction, genital pelvic pain, and ureteral discharge.[13] Fig. 4 shows the prevalence of signs and symptoms at enrolment among those with a positive serology test and Table S4 shows the cumulative prevalence of signs and symptoms recorded and the corresponding OR. Both male and female genital-associated findings have been analysed in detail in previous publications.[12,13]

Among the 32 items individually questioned in a one-to-one interview, we identified 7 self-reported clinical items significantly associated with schistosomiasis serology. The most prevalent were chronic abdominal pain [68.8%; OR 1.79 (CI 1.2–2.6)], 83.6% of which referred to an episode during the preceding 6 months, dysuria [47.9%; OR= 1.84 (CI 1.3–2.7)], 53.4% of which referred to an episode occurring within the prior 6 months, and episodes of haematuria [37.2%; OR= 2.47 (CI 1.6–3.8)], 63.8% of which referred to an episode during adulthood (Fig. 1b). The most frequently reported gender-specific signs or symptoms associated with a positive serology were vaginal flux and leucorrhoea among women[12] and pelvic pain, dyspareunia, and infertility among men.[13] Table S4 shows the cumulative prevalence of signs and symptoms obtained in the directed questionnaire and the corresponding OR. Most clinical items (23 over 32) were captured significantly more frequently through the directed questionnaire than with the structured electronic medical records review (Table S5).

Ultrasonography examination results

We had abdominal ultrasonography results from 211 participants (40.2% of the whole sample), from which 50.2% (N = 106) had a *Schistosoma*-positive test. 37.4% of the participants with a positive serology had some findings in the ultrasound scan. The most prevalent was diffuse echogenic liver images (n = 21; 19.8%), followed by prostate hypertrophy (n = 7; 8.5%) and unspecific chronic renal changes (n = 5; 4.7%). None of these findings was significantly associated with a serology-positive test (Table S6). However, individuals with a *Schistosoma* positive test and harbouring active HBV infection had a higher prevalence of ultrasonographic liver abnormalities [50% vs. 19.8%; p = 0.008 (OR=4.02; CI=1.2–12.8)].

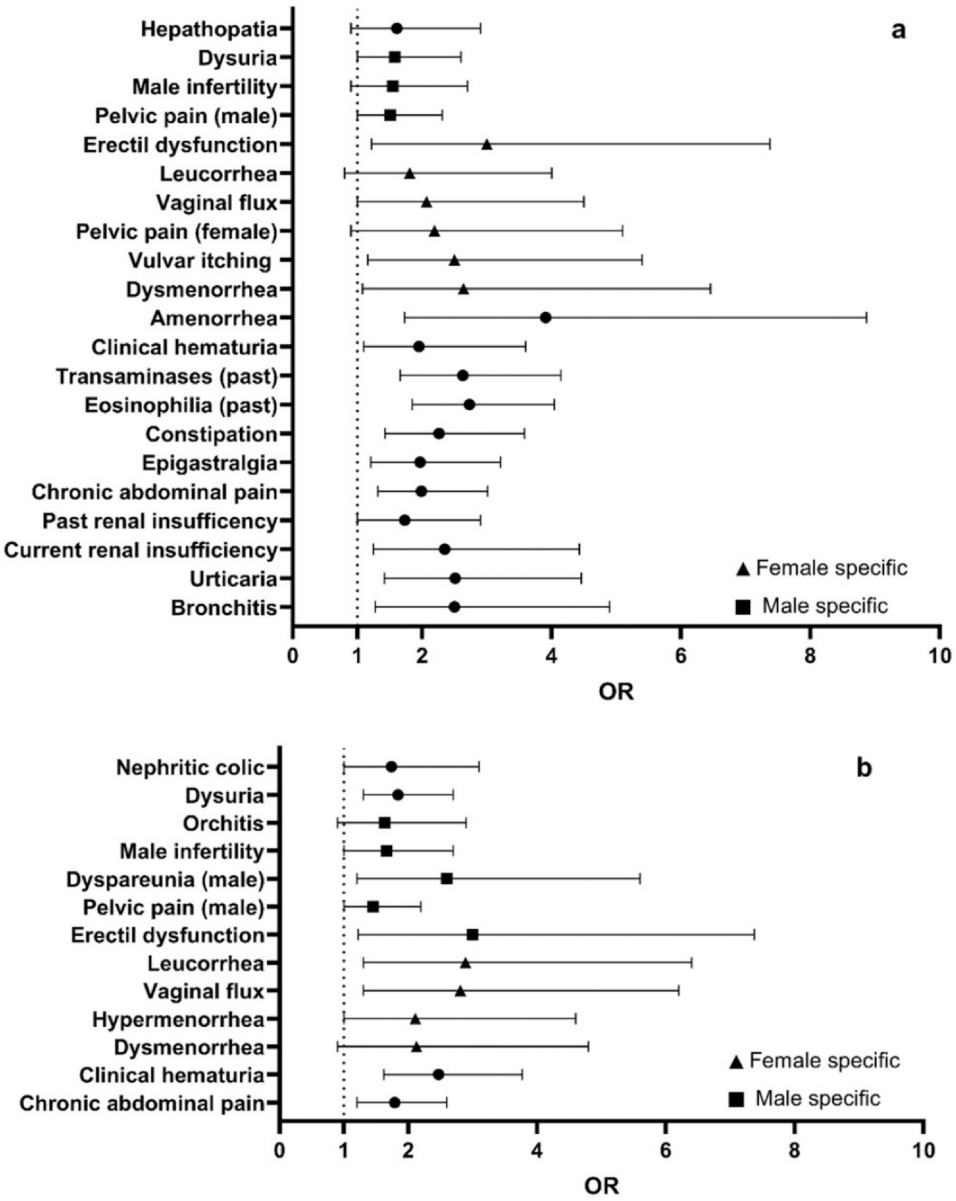

Fig. 1. a and b: Forest plot of variables associated with a positive *Schistosoma* serology after modelling collected through clinical records (a) and questionnaire based (b). We used for this analysis the weighted cumulative prevalence of history of signs and symptoms collected through either a directed questionnaire or the electronic medical history review, which were associated with Schistosomiasis positive test at analysis. Gender-specific signs and symptoms have been excluded.

Network analysis

The Youden was estimated to be of ≥ 12.3 score for females and ≥ 10.9 score for males. In total, 99 (19.0% of the whole sample) had both a clinical score above the estimated cut-off and a schistosomiasis-positive test. These individuals were regarded as the working case definition of chronic schistosomiasis for the network analysis. This analysis included 14 clinical items (nodes in terms of network graph theory), which resulted in 28 interrelationships (or edges; see Fig. 5 and corresponding footnote for an expanded explanation and interpretation). The network analysis confirmed a higher density of edges (higher strength) for the *Schistosoma* working case definition, followed by dysuria and abdominal pain (Fig. S1), and a higher centrality of abdominal pain. This analysis indicates that clinical signs and symptoms tend to present in clusters not randomly distributed, and around the working-case definition of schistosomiasis, with a leading role of dysuria and abdominal pain. Haematuria, dysuria, urinary tract infections and renal colic tend to be linked, whereas chronic abdominal pain appears associated with epigastralgia and constipation. The presence of liver disease is associated with increased transaminases and HBV infection.

Discussion

We found a prevalence of schistosomiasis positive serology at 35.8% among our sample of West African migrants higher than prior pooled values reported for Europe for Sub-Saharan African migrants (24%).[8] A positive *Schistosoma* serology was significantly associated with high cumulative or current prevalence of clinical signs and symptoms. In spite of this, urine *Schistosoma* eggs were only visible in four people with a positive serology. This supports the notion that a substantial proportion of this population might be suffering from long-term complications related to schistosomiasis infection acquired many years ago. Whether these people had just long-term sequelae or still have active, persistent infection is currently

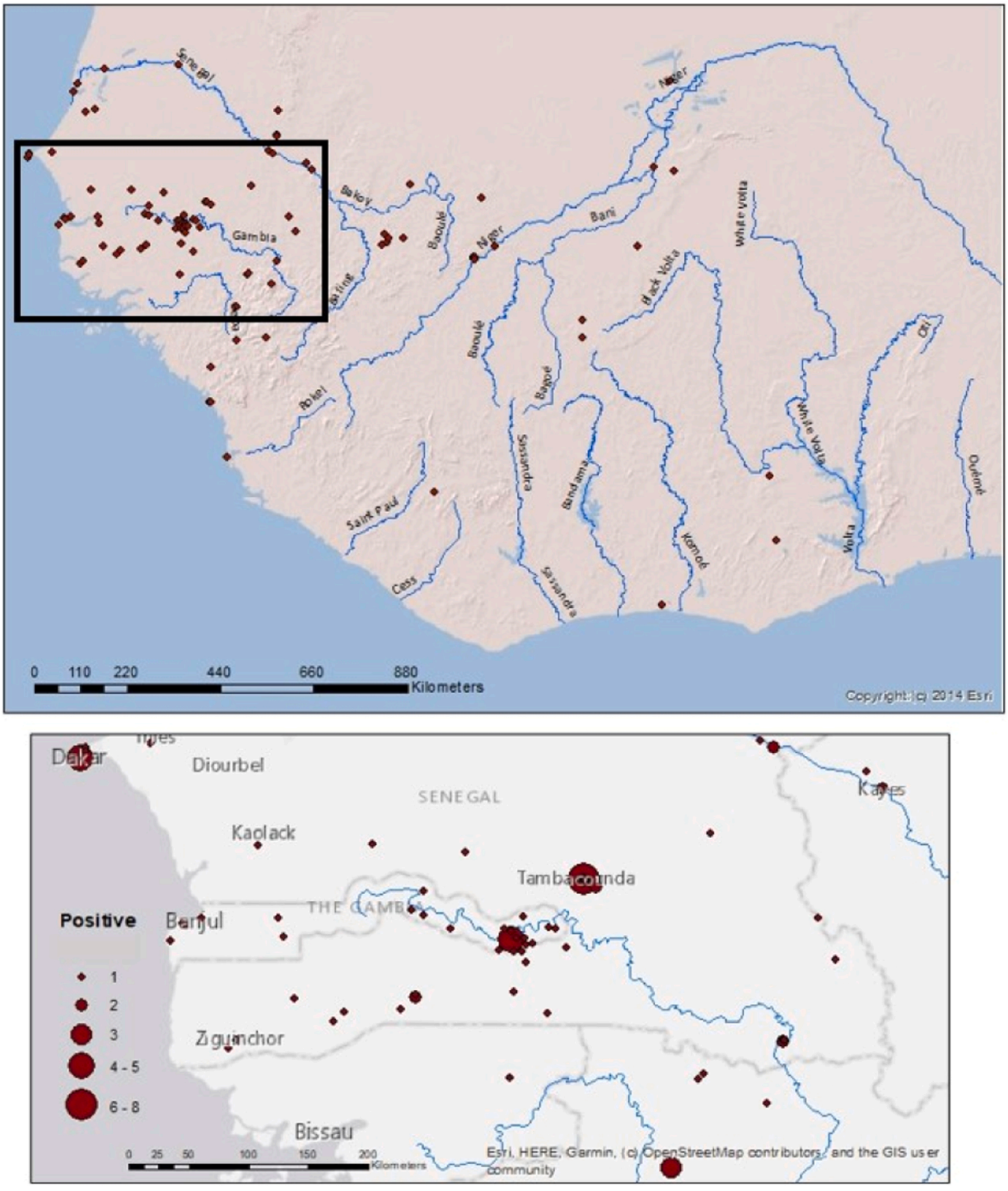

Fig. 2. Geo-localisation of the villages of origin of the study participants with a positive *Schistosoma* serology (N = 187).

unknown. This might be an emerging issue in Europe, which has not attracted enough attention.

To date, schistosomiasis-screening programs in non-endemic countries are directed at newly arrived migrants (less than 5 years).[14] In contrast, our sample represents a much longer-term resident population (median of 16 yrs.) compared to other published series.[15–18] Therefore, they constitute a specific population not examined before. Considering that around 4.000.000 sub-Saharan African migrants are currently living in Europe,[7] and 24–36% of them have a positive *Schistosoma* serology, chronic schistosomiasis could be common and might result in high associated costs to care and treatment of long-term complications.[18,19] Our results correspond to

Table 1
Socio-demographic features, schistosomiasis-positivity prevalence and laboratory results among the study sample.

		Total		Schistosoma positive		Schistosoma negative		
Variable	N[1]	N	%	N	%	N	%	*p-value*
Males	522	388	74.3	149	*38.4*	239	*61.6*	*0.04*
Females		134	25.7	38	*28.4*	96	*71.6*	
Age (m, DS)	520	42.7	(11.5)	42.9	(11.5)	42.6	*(11.5)*	*0.6*
18–25		41	7.9	14	*34.2*	27	*65.9*	*0.9*[2]
26–35		102	19.6	35	*34.3*	67	*65.7*	
36–45		191	36.7	68	*35.6*	123	*64.4*	
46–55		125	24.0	49	*39.2*	78	*60.8*	
> 55		61	11.7	21	*34.4*	40	*65.6*	
Country of origin	522							
Senegal		242	46.4	82	*33.8*	160	*66.2*	*0.4*
Gambia		123	23.6	38	*30.9*	85	*69.1*	*0.2*
Mali		80	15.3	35	*43.7*	45	*56.3*	*0.1*
Guinea Conakry		39	7.5	17	*43.6*	22	*56.4*	*0.3*
Mauritania		15	2.9	8	*53.3*	7	*46.7*	*0.2*
Ghana		10	1.9	3	*30.0*	7	*70.0*	*0.7*
Other countries[3]		13	2.5	4	*30.8*	9	*69.2*	*0.9*
Years living in EU (median, IQR)	521	16	(10–21)	16	(11–21)	16	(10–21)	*0.6*
< 5		61	11.7	20	*32.8*	41	*67.2*	*0.9*[2]
5 to 10		54	10.4	20	*37.0*	34	*63.0*	
10 to 15		95	18.2	32	*33.7*	63	*66.3*	
15 to 20		148	28.4	57	*38.5*	91	*61.5*	
> 20		163	31.3	57	*35.0*	106	*65.0*	
Return to the country of origin	500	393	79.1	147	*37.4*	246	*62.6*	*0.07*
< 5 years	497	348	70.0	132	*37.9*	216	*62.1*	*0.07*
> 5 years or never		149	30.0	44	*29.5*	105	*70.5*	
Swimming in wild waters[4]	386	69	17.9	23	33.3	46	*66.7*	*0.4*
Laboratory results[5,*]								
Eosinophilia (> 5%)	510	139	27.3	58	31.9	81	*24.7*	*0.08*
Haematuria	510	133	26.1	52	28.3	81	*24.9*	*0.4*
Anaemia	511	132	25.8	45	24.7	87	*26.4*	*0.7*
Glomerular filtrate < 90	514	153	29.8	61	33.2	92	*27.9*	*0.2*
Creatinine > 1.2	516	55	10.7	20	10.9	35	*10.5*	*0.9*
Alanin-amino-transferase > 50 U/L	515	14	2.7	7	3.8	7	*2.1*	*0.3*
Aspartate-amino-transferase > 50 U/L	515	13	2.5	4	2.2	9	*2.7*	*0.7*
Alcaline fosfatase > 120 U/L	516	26	5.0	6	3.3	20	*6.0*	*0.2*
Gamma-Glutamil-transferas > 55 U/L	515	64	12.4	29	15.8	35	*10.6*	*0.09*
Overall transaminases elevation	516	91	17.6	33	17.9	58	*17.5*	*0.9*
Other coinfections[*]								
HBV (AgS positive)	519	67	12.9	*24*	12.9	*43*	12.9	*0.9*
VHB anti-Core positive	516	403	78.1	*153*	83.2	*250*	75.3	*0.04*
VHB anti-AgS positive	468	246	52.6	*98*	59.0	*148*	49.3	*0.08*
HIV	519	9	1.7	*6*	3.2	*3*	0.9	*0.06*
HCV	518	10	1.9	*1*	0.5	*9*	2.7	*0.1*
Strongyloidiasis	506	38	7.5	*14*	7.6	*24*	7.5	*0.9*

[1] . N of participants with data available;
[2] . Chi-square test for trend;
[3] . Includes Guinea Bissau (N = 6; 1.2%) Nigeria (N = 1; 0.2%), Burkina-Faso (N = 1; 0.2%), Ivory Coast (N = 1; 0.2%), Cameroon (N = 1; 0.2%), Togo (N = 1; 0.2%), Sierra Leone (N = 1; 0.2%); missing (N = 1; 0.2%)
[4] . Among those who reported to have swimming in wild water upon their return to an endemic country during the last 5 years prior to enrolment (N = 329).
[5] Laboratory test results at enrolment.
[*] Data of laboratory results are displayed in prevalence between individuals schistosomiasis positive and negative test and should be read in rows to compare the results.

migrants from West African countries, which are the region of origin of the majority of sub-Saharan immigrants in Spain and neighbouring European countries such as Italy[16] and France,[17] where similar findings could be expected.

The network analysis shows that patients present with interrelated clinical signs and symptoms. Chronic abdominal pain plays a central role, with a high prevalence of 68.8% of individuals with a positive serology. Among them, 83.6% refer to current episodes of abdominal pain. Chronic abdominal pain is interrelated to all other symptoms, more particularly with epigastralgia and constipation. Symptoms related to the urinary system tract, such as haematuria, dysuria, urinary tract infections and renal colic, are interrelated as well, with a prominent role of dysuria. Overall, 47.9% of *Schistosoma*-positive individuals refer episodes of dysuria. Among them, 53.4% reported a recent episode.

This multi-systemic involvement might be related with the ubiquitous presence of eggs' and the corresponding inflammation and fibrosis processes in the body.[6] Our systematic evaluation of electronic medical records has unexpectedly revealed that these symptoms have rarely prompted an investigation to rule out schistosomiasis.

The physio-pathological pathways could be diverse. The association of bronchitis, eosinophilia and urticarial with *Schistosoma* positive tests might be due to a persistent immune Th-2 response induced by eggs.[20] Clinical chronic bronchitis and pulmonary involvement could be caused by the chronic presence of granulomatous lesions in the lung parenchyma.[21]

Constipation could be a symptom of chronic inflammation of the colonic mucosa resulting from a granulomatous reaction to *S. mansoni* eggs deposited in bowel walls.[22] Renal system involvement might correspond to late manifestations to both *S. haematobium* infection[23] due to obstructive uropathy and, more probably, to *S. mansoni* infection due to long-term effect of unnoticed schistosomiasis-associated glomerulonephritis, which can last for years.[24] Schistosomiasis-associated glomerulonephritis has been described in 10–12% in autopsy studies, more frequently associated to a

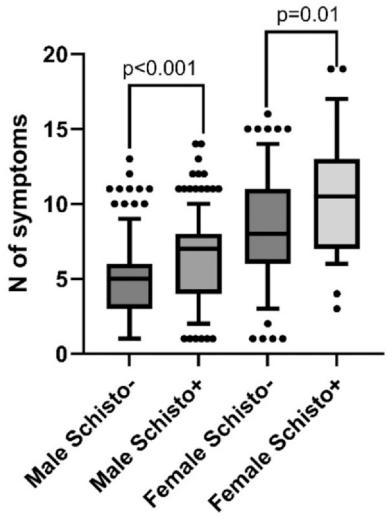

Fig. 3. Box plot of cumulative number of clinical signs and symptoms stratified by positive and negative schistosoma test results and sex.

chronic hepatosplenic form due to *S. mansoni*.[24] Subclinical glomerulonephritis is not uncommon in the chronic forms of schistosomiasis, but the true incidence of this complication is unknown. The final consequence, renal insufficiency, is a characteristic long-term complication. Despite all this, schistosomiasis was not regarded, again, as a potential cause of chronic renal failure in our study sample.

Liver enzimes elevation with dominance of GGT, indicates the involvement of the hepatic system, a well-described complication of *S. mansoni* ranging from focal granulomas to extensive fibrosis of the liver with portal hypertension.[25] According to previous observations,[26] we found as well a significantly higher level of liver transaminases history among patients with HBV (HBsAg +) and a *Schistosoma* positive serology (N = 24) compared with those with simple HBV infection (N = 42 or simple *Schistosoma* positive test [N = 160 (62.5% vs 17.1%/23.8%; p < 0.001), which indicates an interaction between both infections. Finally, the gender-specific manifestations of the genitourinary tract involvement of schistosomiasis among males and females are considered full entities in their own (namely Female Genital Schistosomiasis and Male Genital Schistosomiasis), which has been analysed separately in detail in previous publications.[12,13]

Considering these findings, it is a matter of concern that healthcare providers overlooked the frequent recorded history of haematuria (13.4% of individuals with a *Schistosoma* positive test), the most characteristic symptom of urinary *S. haematobium* infection. This represents missed opportunities to screen the infection and prevent long-term consequences. The reasons behind might be the lack of awareness of health professionals about imported schistosomiasis, together with the absence of adequate diagnostic tests. Indeed, the lack of *Schistosoma* eggs in urine exams, usually finalises the diagnostic work-up to rule out schistosomiasis. Barriers to access to health care among migrant populations[27] might have

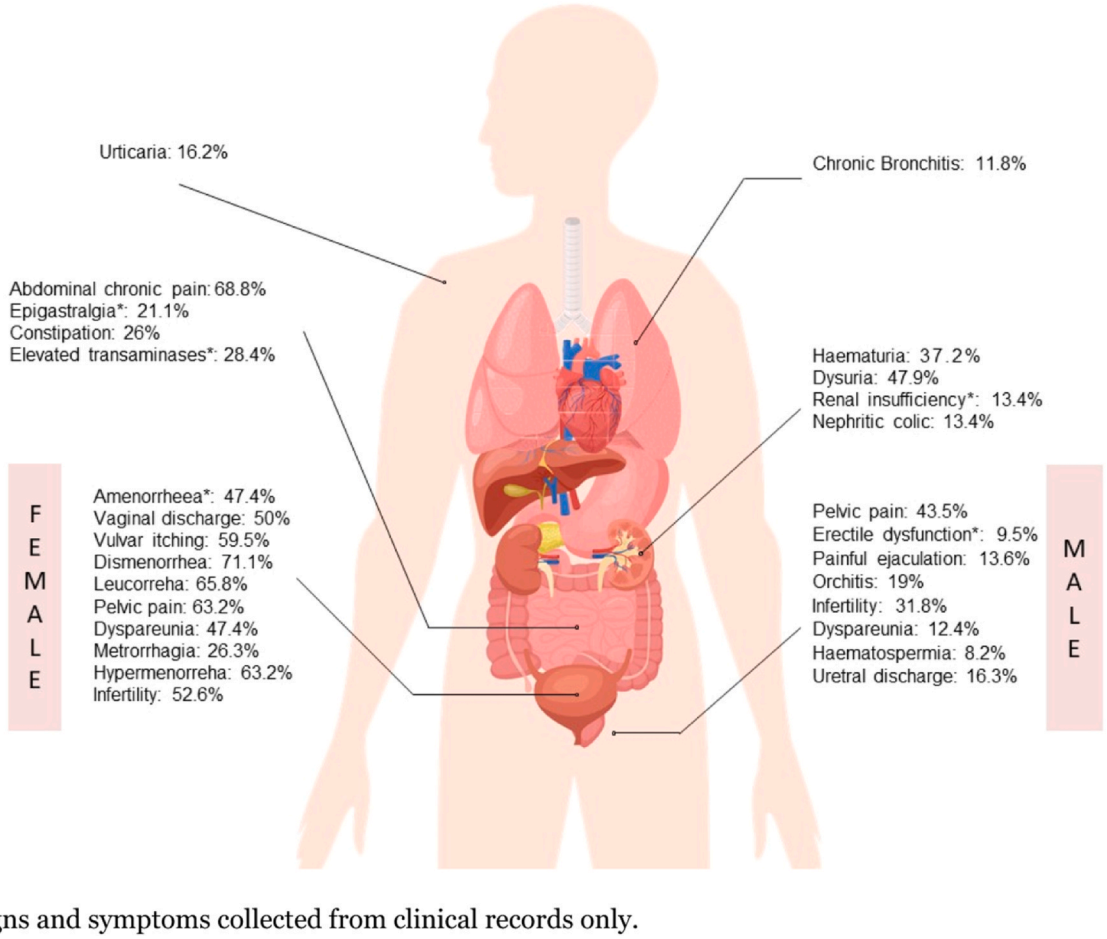

Fig. 4. Graphical representation of referred clinical signs and symptoms among patients with positive schistosomiasis serology at the moment of recruitment (n = 187). *Signs and symptoms collected from clinical records only.

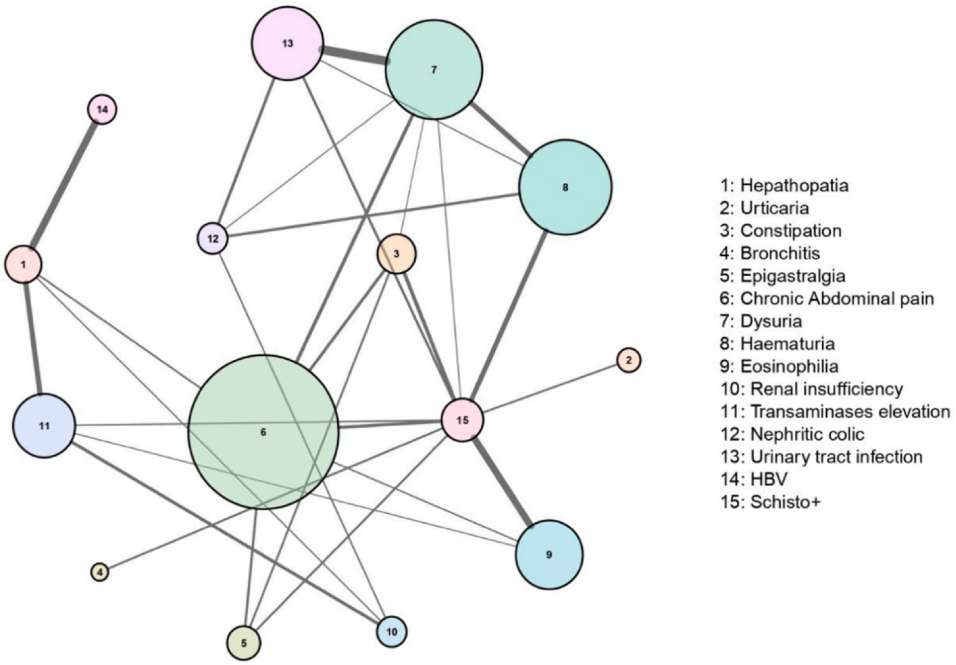

Fig. 5. Network analysis results. Every clinical item is a node. The size of the node correlates with the number of individuals with the given condition. An edge between nodes (variables), indicates a statistically significant association between them. The thickness of the edges indicates the strength of the association, which correlates with the number of times that both items appear together in the data set. A more central situation of the node indicates a higher centrality score, which can be interpreted as a higher influence (higher density of connections) over the network. In Fig. S1 we show the centrality scores of the network calculations for each of the variables examined. Note that the working case definition should not be considered a diagnostic criteria for chronic schistosomiasis which cannot be performed with the lack of reliable microbiological identification of parasites. We used for this analysis the weighted cumulative prevalence of history of signs and symptoms collected through either a directed questionnaire and the electronic medical history review, which were associated to Schistosomiasis positive test at analysis. Gender-specific signs and symptoms have been excluded.

had influence to the delayed diagnostic. We emphasise the need for an in-depth review of each patient's clinical history, and the use of a structured questionnaire as a screening tool for chronic schistosomiasis-associated signs and symptoms.

The limitation of serology-based methods could further support the use of clinical criteria for diagnosis. With this regard, the use of a clinical score as we developed for a working definition of clinical chronic schistosomiasis, could be a valuable screening tool, which needs further assessment.

An additional question arises about the significance of patients with clinical signs but without a positive serology. We cannot rule out that some of these participants still could have chronic schistosomiasis due to the limited sensitivity and specificity of available serological-based methods is well known, especially for *S. haematobium* infections.[28,29]

Our results showed substantial discordances between ICT and ELISA serology (Fig. S2). This suggests a higher sensitivity of ICT compared to ELISA, as previously noted.[30] Accordingly, we suggest the implementation of a two-step serological screening using ICT first, followed by ELISA testing only for those with a negative ICT result. A PZQ empiric pro-active treatment should be assessed in this scenario and could result in considerable cost savings to the health system.[19]

Our study did not include performance of PCR test or circulating antigen in blood or urine or confirm the serology results with a Western Blot, which might increase the specificity of the diagnosis. However, the value of PCR, or antigen determination has not been stablished for chronic or very long-lasting schistosomiasis.

The close to significant association with HIV infection is consistent with previous observations of schistosomiasis as risk factor for HIV acquisition.[31] The interaction between HIV and/or HBV with schistosomiasis deserves attention in populations with a high prevalence of these infections. Based on our findings, testing for HBV and HIV should be encouraged in all patients with suspected schistosomiasis.

The higher prevalence of schistosomiasis-positive tests among males than females has been consistently found in previous studies and is attributed to behavioural factors with higher rates of exposure to *Schistosoma*.[32] The association with return to the country of origin may be confounded by this fact (males tended to return to the country of origin more frequently in our study sample, 74.6% vs. 57.6% $p < 0.001$). A risk of reinfection cannot be excluded.

Finally, participants with *S. haematobium* eggs in their urine (N = 6) represent a risk for local transmission of *Schistosomiasis*, as has occurred elsewhere in Europe.[33]

Our study has limitations. We cannot ascertain the fraction of signs, symptoms and clinical features attributable to active persistent schistosomiasis infection due to the lack of a true gold standard diagnose and the limited sensitivity/specificity of the serology.[28,29] Secondly, patients with more prominent symptoms could well have been overrepresented due to the voluntary recruitment methodology. Additionally, we did not perform microscopic analyses of faeces to check for *S. mansoni* eggs, but we presumed a low yield. Finally, we should note that some small communities from Senegal and Gambia are certainly overrepresented in our study sample, which could be particularly highly exposed to schistosomiasis. Therefore, the generalisation of our results should be confirmed in similar studies in other settings with important pockets of Sub-Saharan migrant population in Europe.

In summary, chronic schistosomiasis associated with persistent symptoms may be more common than previously believed. Current public health guidelines should be expanded to include long-term migrants in systematic schistosomiasis screening in migrants in spite of long periods of residence in non-endemic ones. Additional studies are urgently needed to develop appropriate diagnostic tools to identify/confirm the presence of persistent active infection in

long-lasting chronic schistosomiasis, determine its true prevalence and further characterise its clinical spectrum.

Ethical statement

Consent form to participate was obtained from all individuals included in the study. The study was approved by the ethics boards of the Jordi Gol Foundation, the board with competence over the region (Permit No. 22/063-P). Adequate treatment and clinical follow-up were offered to all participants according to standards of care.

Authorship statement

All listed authors contributed to the work according to the ICMJE criteria: substantial contributions to the conception of the work, data acquisition, analysis, interpretation, drafting the article or reviewing and final approval of the version to be published. All authors are accountable for all aspects of the work related to their accuracy or integrity.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106234.

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