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Review Article

Spatial Distribution of Common Pathogenic Human Intestinal Protozoa in Iran: A Systematic Review

Mehdi MOHEBALI [1,2], Hossein KESHAVARZ [1,2], Mohammad Javad ABBASZADEH AFSHAR [2], Ahmad Ali HANAFI-BOJD [3], *Gholamreza HASSANPOUR [1,2]

1. *Center for Research of Endemic Parasites of Iran (CREPI), Tehran University of Medical Sciences, Tehran, Iran*
2. *Department of Medical Parasitology and Mycology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran*
3. *Department of Medical Entomology and Vector Control, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran*

***Corresponding Author:** Email: hassanpour@tums.ac.ir

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Abstract

Background: Pathogenic intestinal protozoa are considered as a serious public health problem in developing countries. This study aimed to elucidate the overall prevalence and spatial distribution of three common human pathogenic intestinal protozoan infections in Iran.

Methods: Six English and Persian databases were explored for published papers on the prevalence of *Entamoeba histolytica/dispar*, *Giardia lamblia,* and *Cryptosporidium* spp. in the general population of Iran from 2000 to 2015. All eligible data were collected using a pre-designed data extraction form, and the overall prevalence was estimated using a random-effects meta-analysis model. We used ArcMap for mapping the prevalence of the studied protozoa and clustering analysis.

Results: Altogether, 118 eligible papers from 24 provinces of Iran were included and analyzed. The weighted prevalence of *E. histolytica/dispar*, *G. lamblia*, and *Cryptosporidium* spp. infection among Iranian general population were calculated 1.3% (95% CI 1.1-1.5%), 10.6% (95% CI 9.6-11.5%) and 2% (95% CI 1.5-2.5%), respectively.

Conclusion: Our findings indicated human intestinal protozoan infections caused by *E. histolytica/dispar*, *G. lamblia,* and *Cryptosporidium* spp. have still public health importance in some parts of Iran.

Keywords: Pathogenic intestinal protozoa; Prevalence; Modeling; Human; Iran

Introduction

Pathogenic intestinal protozoa are a serious public health problem in developing countries. Despite the low mortality rate, the morbidity rate of these parasites is significant, particularly in developing countries (1).

Entamoeba histolytica, the causative agent of amoebiasis, has been reported to kill between 40,000 and 100,000 cases annually; thus, it is one of the most important parasitic diseases worldwide (2). The prevalence *of Giardia lamblia* has been estimated at 2–3% in developed and 20–30% in developing countries (3). *Cryptosporidium* spp. is another causal agent of diarrhea, primarily affecting immunocompromised patients such as HIV^+ individuals (4).

Despite the advancement in sanitation infrastructure, hygiene status, increased knowledge, attitude and, practice (KAP) during recent years (5), it

seems that the prevalence of intestinal parasites was reducing among Iranian people (6), although the results of some studies have been shown that the rate of these infections is still significant (7, 8).

During two recent decades, many studies have been carried out on the prevalence of human intestinal protozoan infections in different geographic areas of Iran using various diagnostic methods (9-15). Although many studies were performed on prevalence and risk factors of these infections in Iran, studies on the spatial distribution of intestinal protozoan infections are very limited.

Geographical information system (GIS) can prepare a geographical pattern of disease distribution and helps to develop early warning systems for early detection of infectious diseases (16).

We aimed to determine the spatial distribution of the most common human intestinal parasites infections in Iran using data available from 2000 to 2015.

Methods

Search strategy

To evaluate the epidemiological aspects of the pathogenic intestinal protozoa, i.e. *E. histolytica/dispar*, *G. lamblia, and Cryptosporidium* spp. among Iranian healthy population (peoples without gastrointestinal disorders and any underlying diseases), we planned a systematic review and meta-analysis according to the online literature screening of English (PubMed, Scopus, Web of Science and Embase) and Persian (SID and Magiran) databases for published papers from Jan 2000 to Nov 2015. We applied the medical subject heading (MeSH) terms and keywords as follows: "*Entamoeba histolytica*", "*Entamoeba dispar*", "Amoebiasis", "*Giardia lamblia*", "*Cryptosporidium* spp.", "Intestinal parasite infection", "Iran", "Epidemiology" and "Prevalence" alone or combined using "OR" and/or "AND". The reference list of selected full-text papers was also meticulously checked manually to find articles not retrieved by the database searching.

Study selection and data extraction

Pertinent to inclusion criteria, the cross-sectional studies based on parasitological methods that estimated the prevalence of *E. histolytica*, *G. lamblia,* and *Cryptosporidium* spp. infections among Iranian healthy population were included. Investigations that are written in a language other than English or Persian and without available full text, and hospital-based studies, as well as congress abstracts that were not published in valuable journals were excluded. Two reviewers assessed the eligibility of all explored papers. The discrepancies among studies were obviated by discussion and consensus. Afterward, data of interest were gathered using a pre-designed data extraction form based on the province, sample size, positive cases, method of examination, and year of publication. The current review was performed based on PRISMA (preferred reporting items for systematic review and meta-analysis) guideline (17).

Meta-analysis and Heterogeneity assessment

The prevalence and its standard error were calculated for each study. The random-effects model was used to the report of pooled prevalence with a 95% confidence interval (CI). STATA 14.1 (Stata Corp, College Station, TX, USA) was used for data analysis. In addition, the statistical heterogeneity was explored using the chi-squared test at 10% significant level. The I^2 statistic was used to quantify the amount of heterogeneity between the results of the included studies (18, 19).

Mapping and modeling

All data extracted from the reviewed papers were imported to ArcMap for mapping the prevalence of the studied protozoa. Clustering analysis was conducted using Anselin Local Moran's I statistic to identify statistically significant hot spots, cold spots, and spatial outliers.

The local Moran's I statistic of spatial association is given as:

$$I_i = \frac{x_i - \bar{X}}{S_i^2} \sum_{j=1, j\neq i}^{n} w_{i,j}(x_j - \bar{X})$$

Where x_i is an attribute for future I, X is the mean of the corresponding attribute, $w_{i,j}$ is the spatial weight between future i and j, and:

$$S_i^2 = \frac{\sum_{j=1, j\neq i}^{n} (x_j - \bar{X})^2}{n-1}$$

With n equating to the total number of features (http://pro.arcgis.com/en/pro-app/tool-reference/spatial-statistics/h-how-cluster-and-outlier-analysis-anselin-local-m.htm).

Results

Of the 2124 publications that were gathered for this systematic review, 118 records were qualified (Fig. 1). The results of qualified literature and details of each study are embedded in Excel sheet (As supplement but stored in the journal office) (10-13, 20-127). The random-effects model revealed that the weighted overall prevalence of *E. histolytica/dispar*, *G. lamblia* and, *Cryptosporidium* spp. infection among Iranian healthy population was 1.3 % (95% CI 1.1-1.5%), 10.6% (95% CI 9.6-11.5%) and 2% (95% CI 1.5-2.5%), respectively.

Mapping

The infection rate of the studied parasites in the general population of several provinces of Iran is shown in Figs. 2-4.

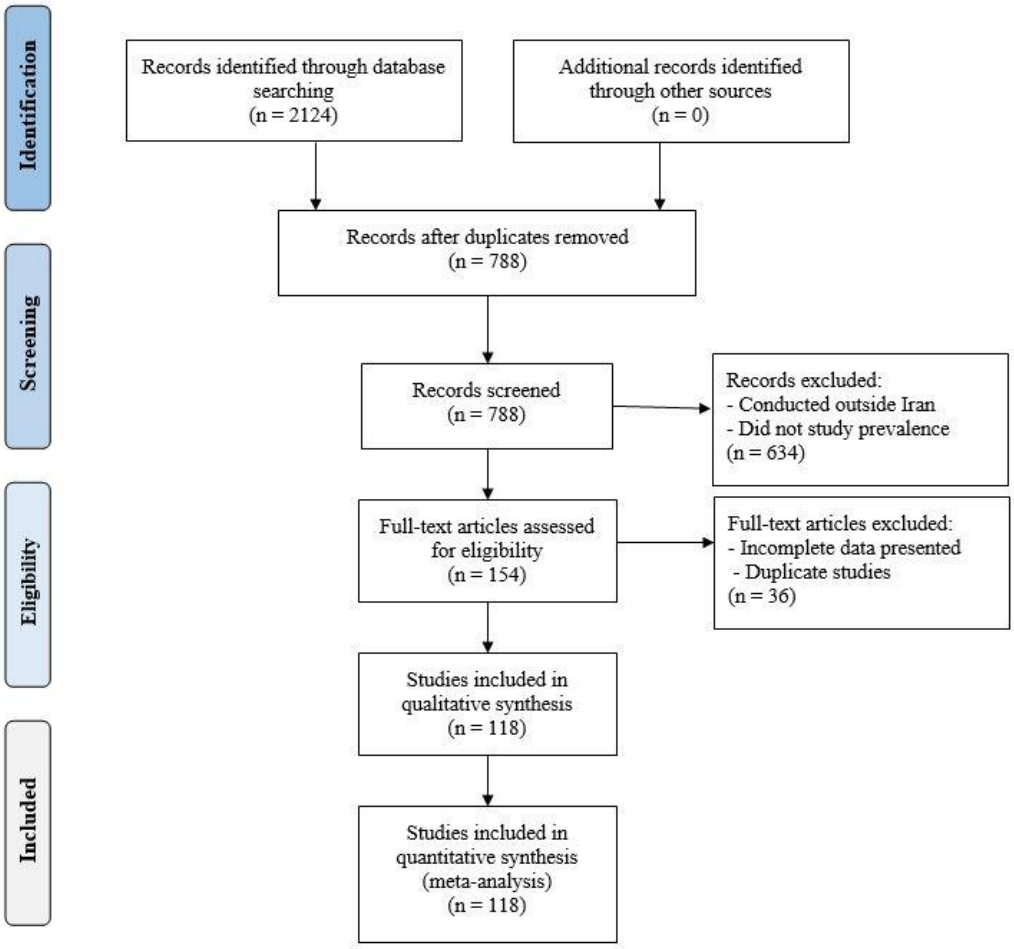

Fig. 1: PRISMA flow diagram

Fig. 2: Pooled prevalence of *Entamoeba histolytica/dispar* infection in the Iranian general population at the provincial scale, 2000-2015

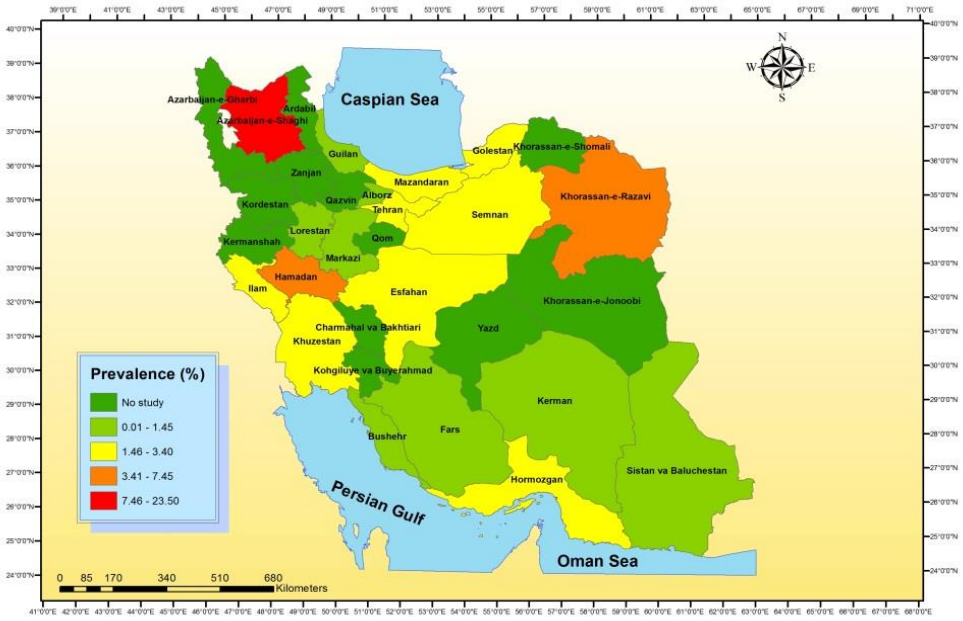

Fig. 3: Pooled prevalence of *Giardia lamblia* infection in the Iranian general population at the provincial scale, 2000-2015

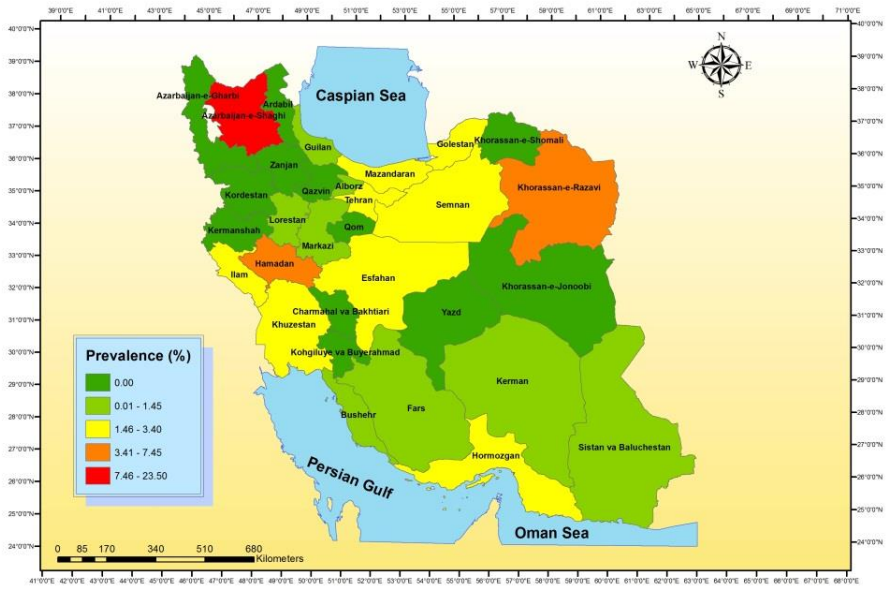

Fig. 4: Pooled prevalence of *Cryptosporidium* spp. infection in the Iranian general population at the provincial scale, 2000-2015

Modeling

Figs 5-7 show the spatial association observed in the data. The areas shaded in red had positive spatial autocorrelation while those shaded in blue had negative spatial autocorrelation of giardiasis rates. A high-low cluster was occurred in East Azerbaijan Province regarding *E. histolytica/dispar* parasite (Fig. 5), while for *G. lamblia* there was no significant cluster in different provinces of Iran (Fig. 6). Finally, for *Cryptosporidium* spp.**,** there was a high-high cluster in the Ilam province, and two high-low clusters in Razavi Khorasan and East Azerbaijan provinces (Fig. 7).

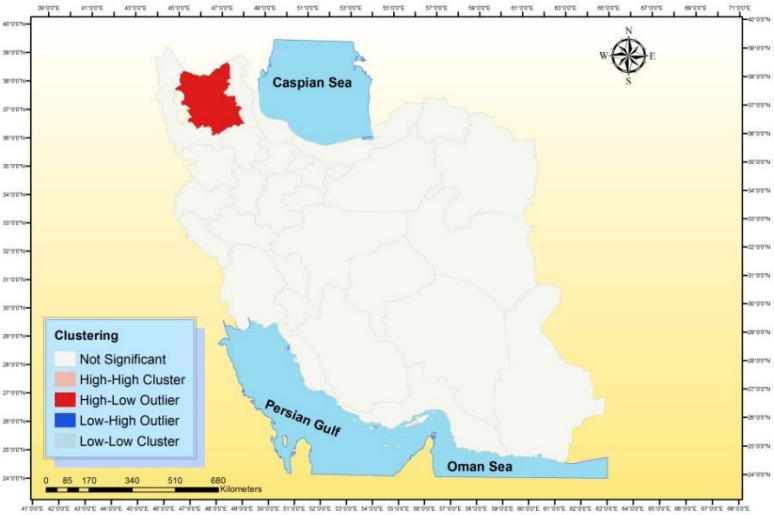

Fig. 5: Moran scatterplot of *Entamoeba histolytica/dispar*, represents the distribution of local Moran's I values, at the provincial scale, Iran, 2000-2015

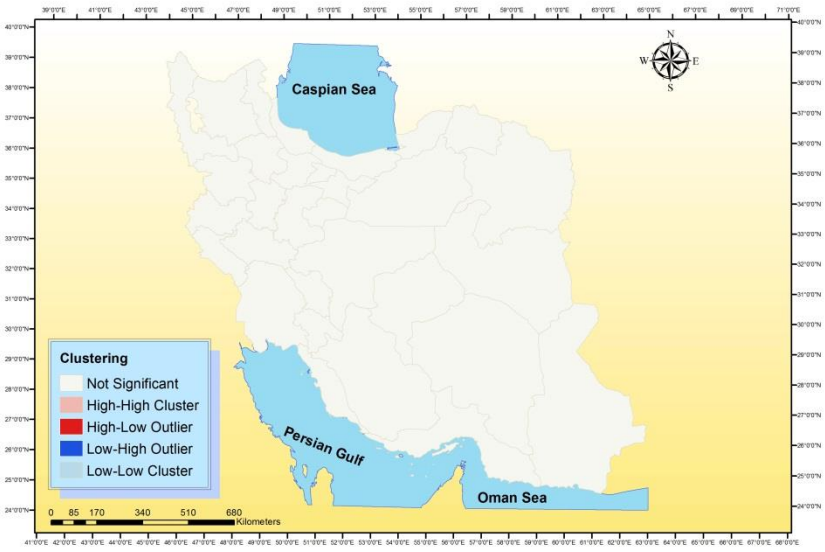

Fig. 6: Moran scatterplot of *Giardia lamblia***,** represents the distribution of local Moran's I values, at the provincial scale, Iran, 2000-2015

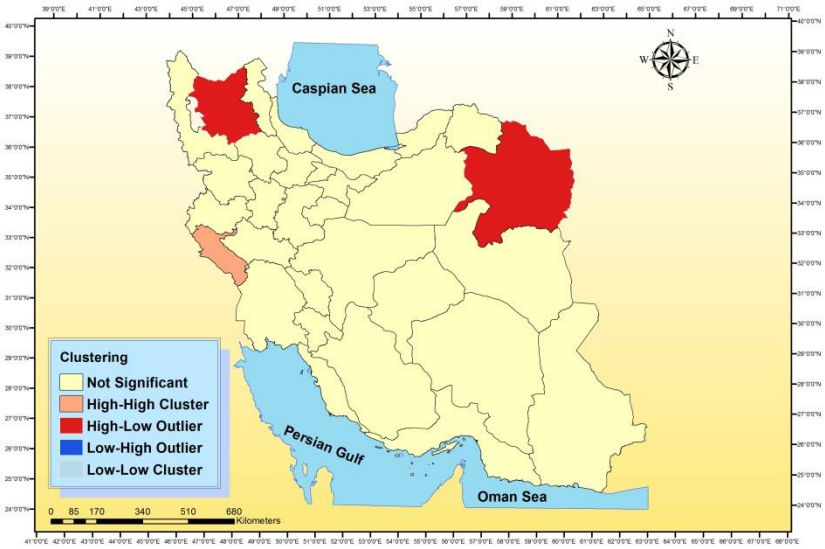

Fig. 7: Moran scatterplot of *Cryptosporidium* spp.**,** represents the distribution of local Moran's I values, at the provincial scale, Iran, 2000-2015

Discussion

There are many published articles on the prevalence of human intestinal protozoa using various laboratory methods in different parts of Iran. This was the first comprehensive systematic review that presented a new epidemiological concept of the most three important pathogenic intestinal protozoan infections, including *E. histolytica/dispar*, *G. lamblia*, and *Cryptosporidium* spp. in Iran. This review showed the four types of spatial association using the pooled prevalence of men-

tioned protozoan infections and their hot spots in provinces of Iran.

One of the most important pathogenic intestinal parasites is *E. histolytica,* which is estimated to infect about 50 million people worldwide and kills more than 55 individuals each year. Referring to recent study, almost 90% of intestinal amoebic infections were caused by *E. dispar* (128). *E. dispar* is a new species of *Entamoeba* that is similar to *E. histolytica* and morphologically differentiation of them is impossible. Improved methods such as molecular and biochemical assays need to differentiate both species (129). Hence, in this study, the agent of amoebiasis infection reported as *E. histolytica/dispar*.

The prevalence rate of intestinal infection caused by *E. histolytica/dispar* was reported from 1-40% associated with various geographical areas of the world. Referring to a systematic review and meta-analysis study that was carried out on 71 eligible articles in 25 provinces of Iran, the pooled prevalence of *E. histolytica/dispar* infection was calculated by about 1% (28). In our study, *E. histolytica/dispar* infection among Iranian healthy population was calculated 1.3% (95% CI 1.1-1.5%) which is similar to the results of Karambaigi et al (130).

The reason for these differences may be associated with the hot and dry climate in most parts of Iran and poor sanitary conditions and no integration and implementation of amoebic detection in primary health care (PHC) network of Iran. Fig. 2 showed that the highest prevalence of *E. histolytica/dispar* infection in the Iranian healthy population is from south Khorasan Province in northeastern Iran, where the climate is hot and dry, and the sanitation measures are limited.

Cryptosporidiosis is an important cause of human morbidity and mortality worldwide (131). Kalantari et al estimated the pooled prevalence of *Cryptosporidium* infections among children and immunocompromised patients in Iran through a systematic review and meta-analysis (132). The estimated prevalences of *Cryptosporidium* infections obtained in the mentioned study were 3.8% and 8% among children and immunosuppressed patients, respectively. In this study, the estimated prevalence of *Cryptosporidium* spp. infection among Iranian healthy population was obtained 2% (95% CI 1.5-2.5%) that is lower than prevalence rate 6% in Iranian children and immunosuppressive patients reported by Kalantari et al Children and immunocompromised patients consider as the high-risk groups for *Cryptosporidium* infection in the world. East Azerbaijan province in northwestern Iran showed the highest level of the *Cryptosporidium* spp. prevalence (Fig. 4).

G. lamblia is a human pathogen protozoan with a worldwide distribution. The prevalence of *Giardia* infection is higher in countries with limited sanitation, and this disease was listed as the 'WHO Neglected Diseases Initiative' in 2004. *Giardia* infection has been the most widespread intestinal parasites of humans in Iran, particularly in children under the ages of primary school and food handlers (133). Several studies were carried out on *Giardia* infection in different parts of Iran, during the last decades, which documented various infections rates between 1.4–39.5% (134). Referring to a systematic review, altogether, 4788 people who referred to health centers in the Mazandaran province of northern Iran during 2015, the overall prevalence of *Giardia* infection was estimated at 4.6% that was significantly higher among 5-9 yr ages compared to other older groups (134).

In this study, the pooled prevalence of *G. lamblia* infection among the healthy population lived in different parts of Iran was estimated at 10.6% (95% CI 9.6-11.5%). It appears that differences between the prevalence of the infection should be caused by many factors such as the target population under study, sampling methods, seasonal variation, source of drinking water, processing of stool specimens, and different diagnostic tests. Fig. 3 showed the highest prevalence of *Giardia* infection in the Iranian healthy population was reported from Razavi Khorasan and East Azerbaijan provinces in the northeastern and northwestern Iran, respectively. It should be noted that these two important provinces of Iran attract a great number of pilgrims, tourists, immigrants, and foreign refugees annually. Travelers' diarrhea is a more prevalent event among tour-

ists, and *G. lamblia* is one of the principal causative agents of diarrhea.

The strengths of this study was a large number of eligible studies, covering large populations and different provinces with geographical characteristics, presentation of pooled prevalence of simultaneous three prevalent intestinal protozoan infections, utilization of distribution models of the infection rates and identification of their hot spots in Iran. Moreover, this study has some limitations such as significant heterogeneity of studies and an underestimation of the true prevalence due to lacking data for some provinces.

Conclusion

This review provided a comprehensive view of the pooled prevalence as well as specific spatial and temporal patterns of the most important pathogenic intestinal protozoan infections in various geographical zones of Iran. These pieces of evidence can be considered and implemented for the control of the diseases by decision-makers.

We suggested additional investigations to further clarify other epidemiological aspects of the three pathogenic intestinal protozoan infections in Iran using molecular methods to prepare an appropriate guideline for the more appropriate control strategies of the infections.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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